Sulfonylureas and the risk of ventricular arrhythmias among people with type 2 diabetes

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ABSTRACT

Sulfonylureas have been an effective and inexpensive oral antihyperglycemic agent used in the management of type 2 diabetes for several decades. However, some studies have found that their use may be associated with an increased risk of cardiovascular death. A potential mechanism behind this risk is hypoglycemia-induced ventricular arrhythmia (VA). Several studies have explored the relationship between sulfonylureas and the risk of arrhythmic endpoints (including VA, cardiac arrest, and sudden cardiac death), but this literature has provided conflicting results regarding this potential adverse drug effect. Thus, my thesis had two primary objectives. The first was to synthesize the existing evidence regarding the use of sulfonylureas and risk of VA among people with type 2 diabetes, and the second was to determine whether the use of sulfonylureas is associated with an increased risk of VA among people with type 2 diabetes.

In the first manuscript, I systematically reviewed observational studies reporting VA, cardiac arrest, or sudden cardiac death outcomes among people with type 2 diabetes using a sulfonylurea. I searched 5 databases from inception to July 8, 2021 for studies comparing sulfonylureas and other therapies or intra-class comparisons. Two independent reviewers screened articles, extracted data, and assessed study quality using the Cochrane Collaboration's Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Our systematic review included 17 studies. Two higher-quality studies reported head-to-head comparisons between sulfonylureas and other therapies; these studies were consistent in reporting an increased risk of VA with sulfonylureas. Sulfonylureas were associated with an increased risk of VA relative to dipeptidyl peptidase (DPP)-4 inhibitors (adjusted hazard ratio [aHR]: 1.52, 95% confidence interval [CI]: 1.28-1.82) and an increased risk of VA relative to metformin (aHR: 1.52, 95% CI: 1.10-2.13). A high risk of bias across the existing literature motivated the need for an additional real-world safety study.

In the second manuscript, I report our original retrospective, population-based cohort study that used the United Kingdom's Clinical Practice Research Datalink (CPRD). I constructed a cohort of individuals initiating a sulfonylurea or metformin as their first-ever antihyperglycemic drug. The primary outcome was fatal or non-fatal VA. Patients were followed from cohort entry until an outcome, discontinuation of their cohort entry medication, initiation of another

antihyperglycemic drug, end of the study period, or administrative censoring. I used Cox proportional hazards models with inverse probability of treatment weighting to estimate the aHR and corresponding bootstrap 95% CIs for VA, comparing new users of a sulfonylurea with new users of metformin. The study cohort included 599,520 first-time users (93,638 sulfonylurea and 506,883 metformin). There were 279 VA events among sulfonylurea users during a median follow-up of 0.50 years (crude incidence rate per 10,000 person-years [IR]: 25.5, 95% CI: 22.7-28.7). Among metformin users, there were 1,537 VA events during a median follow-up of 0.70 years (IR: 18.5, 95% CI: 17.6-19.5). Compared with the use of metformin, sulfonylurea use was associated with an increased risk of VA (aHR: 1.42, 95% CI: 1.16-1.67). This finding was robust to several sensitivity analyses.

In this thesis, I found that the use of sulfonylurea monotherapy as an initial treatment for type 2 diabetes was associated with an increased risk of VA relative to the use of metformin monotherapy. This increased risk should be considered when prescribing sulfonylureas as an initial treatment for type 2 diabetes.

RÉSUMÉ

Les sulfonylurées sont des agent antihyperglycémique oraux efficaces et économiques utilisés dans le traitement du diabète de type 2 depuis plusieurs décennies. Mais, certaines études ont trouvé que leur utilisation pouvait être associée à un risque accru de décès cardiovasculaire. Un mécanisme potentiel est l'arythmie ventriculaire (AV) induite par l'hypoglycémie. Ainsi, ma thèse comporte deux objectifs principaux. Le premier est de synthétiser les preuves existantes concernant l'utilisation des sulfonylurées et le risque de AV chez les personnes atteintes de diabète de type 2, et le second est de déterminer si l'utilisation des sulfonylurées est associée à un risque accru de AV chez les personnes atteintes de diabète de type 2.

Dans le premier article, j'ai passé en revue de manière systématique les études d'observation rapportant les résultats de l'AV, de l'arrêt cardiaque ou de la mort cardiaque subite chez les personnes utilisant une sulfonylurée pour contrôler le diabète de type 2. J'ai recherché des études rapportant des comparaisons entre les sulfonylurées et d'autres thérapies ou des comparaisons intra-classes de sulfonylurées. Deux examinateurs indépendants ont sélectionné les articles, extrait les données et évalué la qualité des études à l'aide de l'outil ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) de la Collaboration Cochrane. Les deux études de qualité supérieure rapportaient des comparaisons directes entre les sulfonylurées et d'autres thérapies ; ces études étaient cohérentes dans leur rapport d'un risque accru d'AV avec les sulfonylurées. Les sulfonylurées étaient associées à un risque accru d'AV par rapport aux inhibiteurs de la dipeptidyl peptidase-4 (rapport de risque ajusté [RRa]: 1,52, intervalle de confiance [IC] à 95%: 1,28-1,82) et à un risque accru d'AV par rapport à la metformine (RRa : 1,52, IC à 95%: 1,10-2,13). Un risque élevé de biais dans la littérature existante a motivé la nécessité d'une étude supplémentaire sur la sécurité dans le monde réel.

Dans le second article, je rapporte notre première étude de cohorte rétrospective, basée sur la population, qui a utilisé le Clinical Practice Research Datalink du Royaume-Uni. J'ai construit une cohorte de personnes ayant commencé à prendre une sulfonylurée ou de la metformine comme premier médicament antihyperglycémique. L'issue primaire était l'AV fatale ou non fatale. Les patients ont été suivis à partir de l'entrée dans la cohorte jusqu'à ce qu'ils obtiennent un évènement, l'arrêt de leur médicament d'entrée dans la cohorte, l'initiation d'un autre

médicament antidiabétique, la fin de la période d'étude ou la censure administrative. J'ai utilisé des modèles de risques proportionnels de Cox avec pondération de la probabilité inverse du traitement pour estimer l'aHR et les IC 95% en bootstrap correspondants pour la AV, en comparant les nouveaux utilisateurs d'une sulfonylurée aux nouveaux utilisateurs de metformine. La cohorte d'étude comprenait 599 520 nouveaux utilisateurs (93 638 de la sulfonylurée et 506 883 de la metformine). Il y a eu 279 événements AV parmi les utilisateurs de sulfonylurée pendant un suivi médian de 0,50 an (taux d'incidence brut pour 10 000 personnes-années [IR]: 25,5, IC 95%: 22,7-28,7). Parmi les utilisateurs de metformine, 1 537 événements AV ont été enregistrés au cours d'un suivi médian de 0,70 an (IR: 18,5, IC 95%: 17,6-19,5). Par rapport à l'utilisation de la metformine, l'utilisation d'une sulfonylurée était associée à un risque accru d'AV (aHR : 1,42, IC 95% : 1,16-1,67). Ce résultat était robuste à plusieurs analyses de sensibilité.

Dans cette thèse, j'ai constaté que l'utilisation d'une sulfonylurée en monothérapie comme traitement initial du diabète de type 2 était associée à un risque accru d'AV par rapport à l'utilisation de la metformine en monothérapie. Ce risque accru doit être pris en compte lors de la prescription de sulfonylurées comme traitement initial du diabète de type 2.

PREFACE

This thesis includes an introduction of the thesis topic, a manuscript describing a systematic review of the existing observational literature, a transition section, a detailed description of the methods used in my original pharmacoepidemiologic study, the manuscript describing this study, a thesis discussion, and overall thesis conclusions.

CONTRIBUTION OF AUTHORS

Nehal Islam, BSc

I authored the entirety of my thesis. I led the systematic review and was involved at every stage of the knowledge synthesis, including developing the protocol, conducting the search, screening studies, quality assessment, interpreting results and drafting the manuscript. I also led the original pharmacoepidemiology study, including developing the protocol submitted to the Independent Scientific Advisory Committee (ISAC) of the Clinical Practice Research Datalink. I contributed to the study design, created the operational variable definitions, participated in statistical analyses, interpreted results, and drafted the manuscript.

Kristian B. Filion, PhD

Dr. Filion supervised my thesis. He conceived of the thesis topic and contributed to both the systematic review and pharmacoepidemiologic study. He regularly provided insight on study design, analytical approach, interpretation of results, and reviewed both manuscripts and my thesis for important intellectual content.

Antonios Douros, MD PhD

Dr. Douros was a member of my thesis committee. He provided his clinical expertise, reviewed analytical methods, and provided insight for the development of both manuscripts. He reviewed the entirety of my thesis for important intellectual content.

Oriana H.Y. Yu, MD MSc

Dr. Yu was a member of my thesis committee. She provided her clinical expertise and insight for the design and interpretation of both manuscripts. She reviewed the entirety of my thesis and provided her clinical expertise and insight for important intellectual content.

Pauline Reynier, MSc

Pauline Reynier was the statistical analyst for this project. She provided important insight with respect to the application of statistical methods for the original pharmacoepidemiologic study. She performed data management and the more complex statistical modelling. She also assisted with interpreting data, developing the protocol for the study, reviewed the manuscript, translated the abstract into French.

Henok T. Ayele, PhD

Dr. Ayele collaborated on the systematic review, where he served as the second reviewer. He provided insight and valuable feedback for the protocol, screened studies for inclusion, extracted data, assessed study quality, and reviewed the manuscript for intellectual content.

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Finally, I would like to thank my funding sources for enabling me to devote time to my Master's thesis. I received a stipend from Dr. Filion and was awarded the Nyman Award from the Faculty of Medicine and Health Sciences, McGill University.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

Supplemental Tables

Supplemental Figures

ABBREVIATIONS

ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease Preterax And Diamicron MR Controlled Evaluation
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BNF	British National Formulary
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes
CHF	Congestive Heart Failure
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular Disease
DM+D	Dictionary of Medicines and Devices
DPP-4	Dipeptidyl Peptidase-4
GLP-1	Glucagon-Like Peptide-1
GP	General Practitioners
HbA1c	Glycated Hemoglobin A1c (HbA1c)
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD-10	International Classification of Diseases, 10th Revision
IPCW	Inverse Probability of Censoring Weighting
IPTW	Inverse Probability of Treatment Weighting
IR	Incidence Rate
MACE	Major Adverse Cardiovascular Event
MCMC	Markov Chain Monte Carlo
MI	Myocardial Infarction
NHS	National Health Service
ONS	Office for National Statistics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT	Randomized Controlled Trial
ROBINS-I	Risk Of Bias In Non-Randomized Studies of Interventions
SCA	Cardiac Arrest
SCD	Sudden Cardiac Death
SGLT-2	Sodium-Glucose Cotransporter 2
SUR	Sulfonylurea Receptor
TOSCA.IT	Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial
TZD	Thiazolidinedione
UGDP	University Group Diabetes Program
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
VA	Ventricular Arrhythmia
VA CSDM	Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Chapter 1: Background

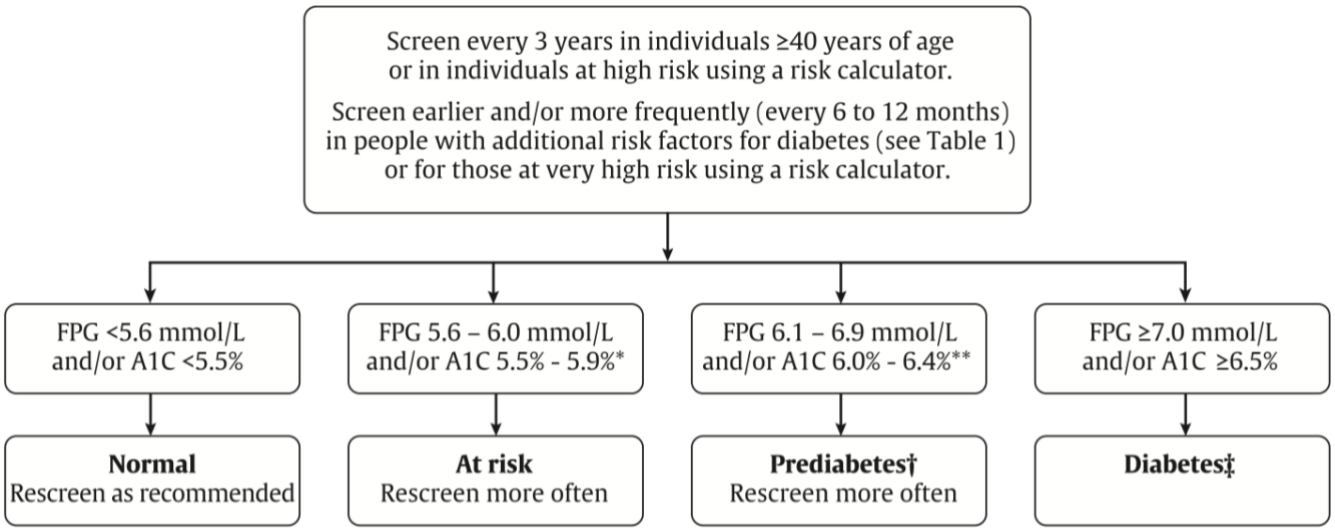
1.1 Type 2 Diabetes

Type 2 diabetes mellitus is a chronic metabolic disorder among the most prevalent diseases in the world today, affecting 7.8% of Canadians and 9.3% of adults globally[1]. It is characterized by a deficiency in the secretion of insulin and/or diminished tissue response to insulin. Canada had an estimated 11 million individuals with type 2 diabetes or pre-diabetes in 2019, representing a substantial human, health, and economic burden[2]. Type 2 diabetes is one of the top 10 leading causes of hospitalization and medical resource usage[3]. Importantly, the cost of treating this disease has increased substantially over the last decade. In Canada, the cost of treating type 2 diabetes increased from $14 billion in 2008 to just under $30 billion in 2019. The economic burden to individuals with type 2 diabetes living in countries without publicly funded medical care and prescription drug coverage programs can be substantial. The past decade's increasing prevalence is partly attributed to the obesity epidemic, an increase in type 2 diabetes among children and adolescents, and prolonged survival among individuals with type 2 diabetes[4 5].

1.1.1 Pathophysiology of Type 2 Diabetes

The exact cause of type 2 diabetes is unknown. Our current understanding of type 2 diabetes implicates genetic and lifestyle factors, including obesity and lower levels of physical activity[6 7]. The pathophysiology of type 2 diabetes can be explained by two irregular processes: insufficient insulin production by pancreatic beta cells and insulin resistance[8 9]. Among individuals with type 2 diabetes, insulin secretion by beta cells is inadequate for maintaining normal levels of blood glucose, leading to prolonged periods of hyperglycemia[10]. Beta cell dysfunction and dysregulation with insulin-sensitive tissues is particularly a concern for individuals with obesity[11]. Another hallmark of type 2 diabetes, insulin resistance, is characterized by the failure of insulin-target tissues such as muscles, liver, and fat tissue to react to normal insulin levels over time. These two abnormalities can coexist among people with type 2 diabetes, manifesting in varying levels of insulin resistance and deficiencies in insulin secretion[12]. During the early stages, pancreatic beta cells can compensate for glucose uptake deficiencies by secreting elevated amounts of insulin[13]. Regardless of this innate mechanism, persistent insulin resistance can lead to a prolonged state of hyperglycemia.

A diagnosis for type 2 diabetes requires a patient to be in an ongoing hyperglycemic state, as measured by laboratory tests such as a repeated fasting plasma glucose test (FPG), random blood sugar test (RBS), oral glucose tolerance test (OGTT), or a glycosylated hemoglobin (HbA1c) measure (which provides an average level over the previous 2 to 3 months)[14]. Since HbA1c testing is less vulnerable to the day-to-day fluctuations in blood glucose levels, it is considered more practical and commonly recommended in treatment guidelines[15 16]. The ranges of FPG and HbA1c recommended by Diabetes Canada for diagnosing type 2 diabetes are presented in **Figure 1.1**.



If both FPG and A1C are available, but discordant, use the test that appears furthest to the right side of the algorithm.

*Consider 75 g OGTT if ≥1 risk factors; ** Consider 75 g OGTT (see Tables 3 and 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10 for interpretation of 75 g OGTT).

†Prediabetes = IFG or A1C 6.0 to 6.4% (see Table 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

‡In the presence of symptoms of hyperglycemia, a single test result in the diabetes range is sufficient to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. If results of two different tests are available and both are above the diagnostic cut points the diagnosis of diabetes is confirmed.

A1C, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose

Figure 1.1. Diabetes Canada treatment guidelines for the management of hyperglycemia in patients with type 2 diabetes. Reproduced with permission from the Canadian Journal of Diabetes[17].

1.1.2 Microvascular and Macrovascular Complications of Type 2 Diabetes

People with type 2 diabetes are at risk for a broad range of diabetes-related complications and comorbidities including severe vascular complications. They can be classified as either micro-vascular or macro-vascular complications[18-20]. Microvascular complications include retinopathy, nephropathy, and neuropathy[21]. These complications may lead to increased mortality and can often substantially reduce well-being and quality of life due to increased medical care and invasive procedures. For instance, individuals with poorly controlled type 2 diabetes who develop neuropathy may experience infections requiring amputation. In addition, retinopathy and nephropathy may lead to blindness and dialysis, respectively. The consequences of macrovascular complications are more severe, including cardiovascular disease (CVD), including myocardial infarction (MI), unstable angina, heart failure, cerebrovascular disease (including ischemic stroke and transient ischemic attacks), and peripheral artery disease[22]. Macrovascular complications often arise due to the narrowing of the arterial vessel lumen[19]. This narrowing is primarily caused by plaque buildup in the walls of the coronary artery leading to atherosclerosis, hardening of the arteries. Type 2 diabetes is associated with a two- to a six-fold increase in CVD risk, accounting for 65 to 75% of all deaths among individuals with type 2 diabetes[23 24]. Compared with the general population, individuals with type 2 diabetes develop earlier and more severe forms of CVD. Despite dramatic reductions over the last 20 years in CVD mortality among the general population and among individuals with type 2 diabetes, the growing prevalence of type 2 diabetes is a concern[25-27]. CVD is accountable for the largest proportion of health care use among people with type 2 diabetes[28]. Macrovascular complications are also responsible for a large proportion of morbidity and mortality among those with type 2 diabetes[29]. Some of the other harmful complications commonly faced by individuals with type 2 diabetes include cirrhosis from hepatic steatosis, cancer, fractures, erectile dysfunction, and cognitive defects[30-32].

1.1.3 Clinical Management of Type 2 Diabetes

Individuals newly diagnosed with type 2 diabetes are often initially prescribed glycemic management in the form of diet and exercise[33]. Lifestyle modification may dramatically reduce type 2 diabetes complications by increasing insulin sensitivity and improving glycemic control[34]

[35]. However, commitment to lifestyle programs is often low and occasionally insufficient despite adherence to a lifestyle program, making subsequent pharmacological therapy a common practice among individuals with diabetes[36].

Although pharmacologic type 2 diabetes management is commonly used worldwide, the type and course of treatment intensification recommended by guidelines vary by region. Navigating the labyrinthian clinical opinions on standard type 2 diabetes management is challenging, leading to different guidelines. In addition to both short and long-term safety, type 2 diabetes management guidelines must consider the cost, availability, and effectiveness of recommended treatments[37]. Type 2 diabetes care must be tailored to a patient's individual needs to ensure maximal safety and effectiveness. The early initiation of pharmacologic therapy is associated with improved glycemic control in addition to a lower likelihood of long-term complications[38]. There are six classes of antihyperglycemic agents currently available in Canada[15]. These therapies differ in their mechanisms of action, contraindications, benefits regarding glycemic control and other endpoints (e.g., body weight, CVD prevention), safety profiles, and costs. Drugs are grouped into first- second- and third-line therapies based on these factors. Pharmacological treatment involves an escalating sequence of more intensive treatment if glycemic control is not achieved with the preceding therapy[39].

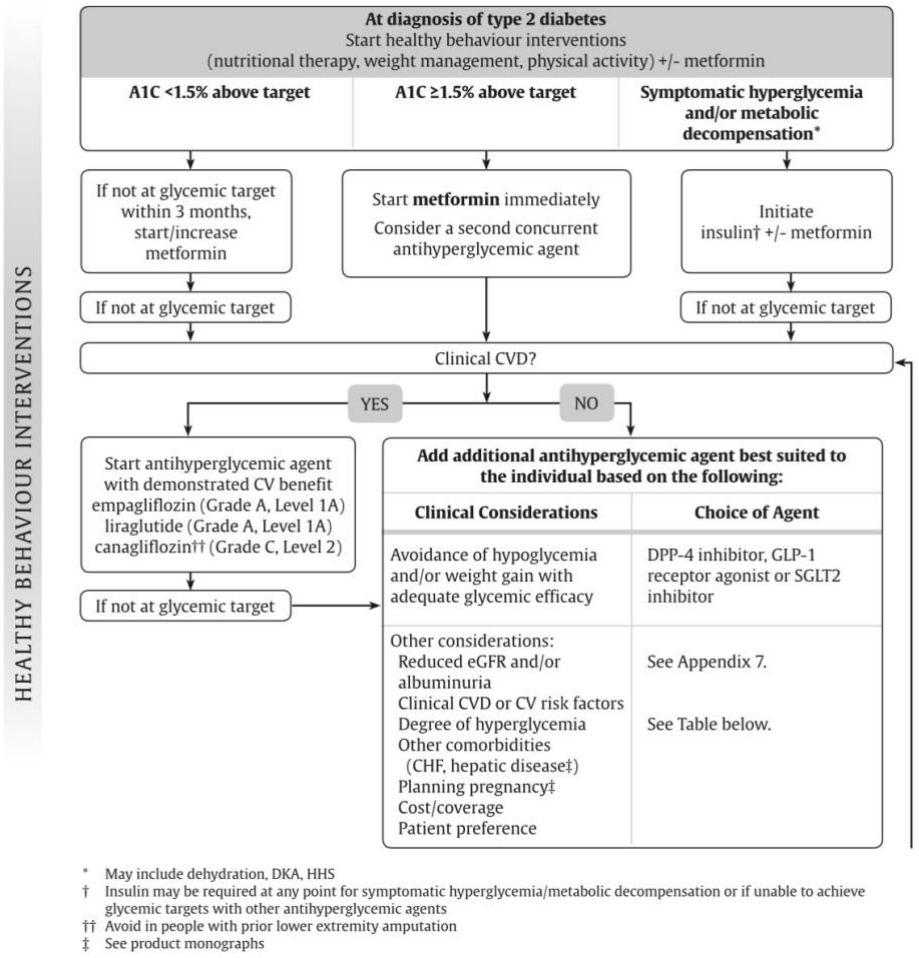


Figure 1.2. Diabetes Canada treatment guidelines for the management of hyperglycemia in patients with type 2 diabetes. Reproduced with permission from the Canadian Journal of Diabetes[15].

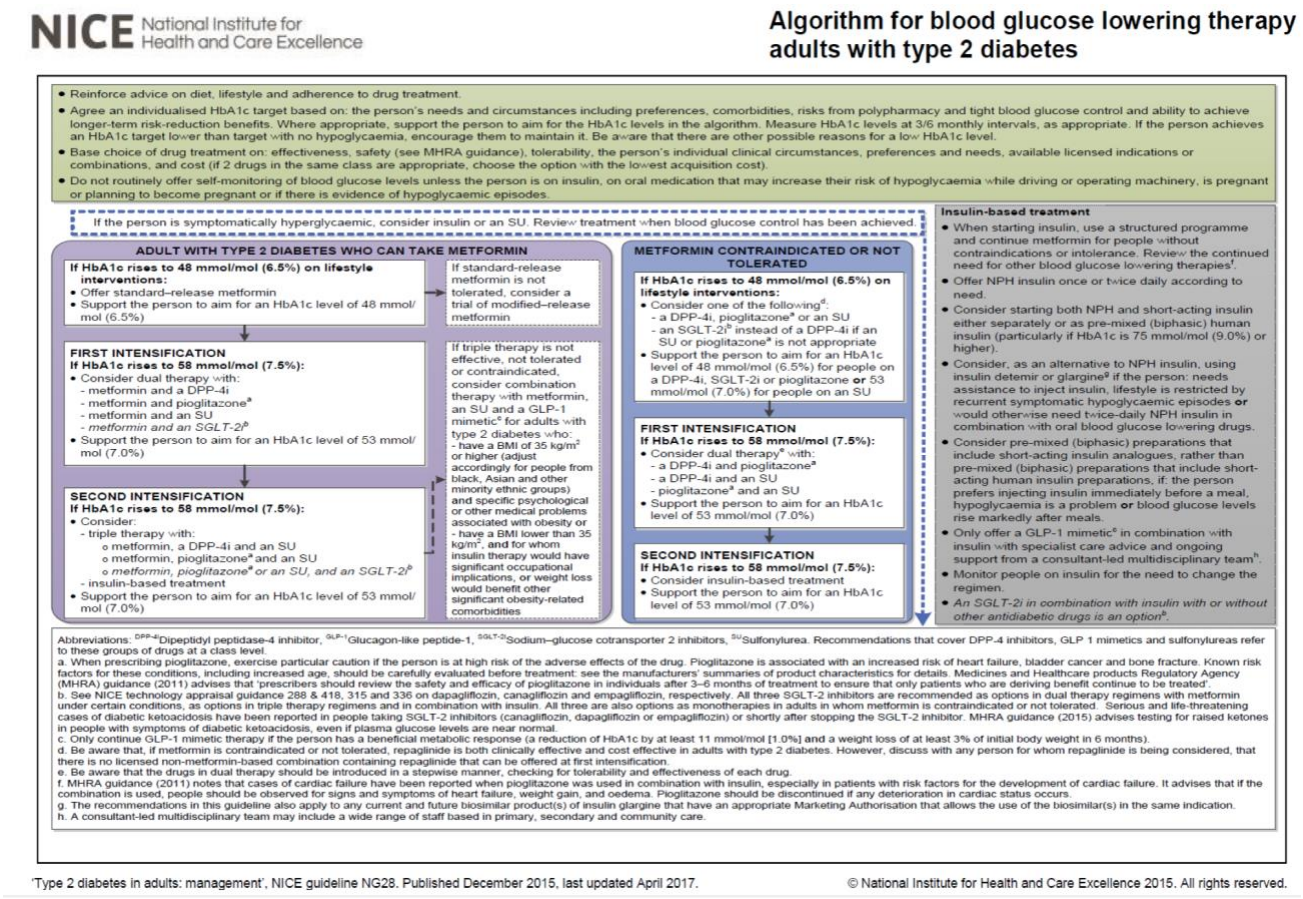


Figure 1.3. National Institute for Health and Care Excellence (NICE) United Kingdom treatment algorithm for the management of hyperglycemia in patients with type 2 diabetes. Reproduced with permission from NICE. NICE [2015] Type 2 diabetes in adults: management. Available from *www.nice.org.uk/guidance/ng28*. NICE guidance is prepared for the National Health Service in England. All NICE guidance is subject to regular review and may be updated or withdrawn. NICE accepts no responsibility for the use of its content in this product/publication.

1.1.3.1 First-line Therapies for Type 2 Diabetes

First-line therapies are prescribed when attempts for lifestyle modification are insufficient to meet treatment targets. One of the challenges of type 2 diabetes management is that it requires pharmacotherapy to lower blood glucose, limit cardiovascular risk factors, and have a reasonable safety profile regarding an individual's existing comorbidities[40]. Varying opinions exist regarding the relative safety and effectiveness of antihyperglycemic drugs, contributing to an array of guideline recommendations[31 37 41]. Metformin and sulfonylureas, two oral antihyperglycemic agents, are the most frequently prescribed first-line pharmacotherapies that are initiated following lifestyle modification[42].

1.1.3.1.1 Metformin

Metformin is a member of the biguanide drug class, along with phenformin and buformin. They were first approved in Europe in 1959, with approval in Canada occurring in 1973. However, the US Food and Drug Administration (FDA) did not approve metformin until 1995[43]. This delayed approval was partly due to the FDA's hesitance after phenformin and buformin were removed from the market due to associations with lactic acidosis[44]. Metformin has since been widely accepted as the first-line treatment of choice for type 2 diabetes[15]. This shift was fueled in part by the results of the United Kingdom (UK) Prospective Diabetes Study (UKPDS), which found that patients randomized to metformin had fewer hypoglycemic attacks and type 2 diabetes-related complications than those randomized to sulfonylureas [45]. When used as first-line treatment, metformin can be expected to safely lower HbA1c levels by 1-2%[43]. Metformin works by suppressing hepatic glucose production and decreasing insulin resistance[46 47]. Since it does not directly affect insulin secretion, it is considered to have a low risk of hypoglycemia. Some of the adverse effects of metformin include rare yet dangerous lactic acidosis among patients with renal disease and mild gastrointestinal-related complications that may have implications for adherence[48 49]. Metformin is also contraindicated in individuals with liver dysfunction (including liver disease, alcohol abuse), kidney dysfunction (glomerular filtration rate <30 mL/min/1.73 m^2), and cardiac dysfunction (e.g., heart failure, hemodynamic instability). Nevertheless, metformin is generally considered well-tolerated, particularly for patients with obesity[46].

Metformin is also relatively inexpensive, contributing to its popularity as the first-line therapy of choice[50].

1.1.3.1.2 Sulfonylureas

First-generation sulfonylureas were approved in Europe starting in 1956. These early sulfonylureas were not approved in the US; the US FDA approved second-generation sulfonylurea starting in 1985[43]. Similar to metformin, sulfonylureas have also been shown to reduce HbA1c levels by 1-2%[51 52]. Historically, they were a common choice for first-line therapy given their low cost and widespread availability. Although they continue to be widely prescribed, dispensing of sulfonylureas as a first-line treatment has waned in favour of metformin over time. According to a long-term U.S. drug utilization study, the number of patients initiating therapy with a sulfonylurea decreased from 20% in 2005 to 8% in 2016[42], with the use of metformin increasing from 60% to 77% during this period. Sulfonylureas are now typically used as second-line therapy or for individuals with a contraindication to metformin, severe hyperglycemia, an inherited monogenic form of diabetes known as maturity-onset diabetes of the young, or as add-on therapy to metformin[53-55]. The reduction in use as a first-line therapy is partly due to their association with several potential adverse effects, including an increased risk of hypoglycemia, cardiovascular events, and mortality[56-60].

A sulfonyl group is common to each sulfonylurea molecule. By binding to potassium adenosine triphosphate (ATP) channels in the beta-cell plasma membrane, they force potassium channels to close and calcium channels to open, allowing cytoplasmic calcium levels to rise. This process stimulates insulin secretion[61 62]. Therefore, sulfonylureas are only useful among patients with partial rather than complete beta-cell dysfunction. Sulfonylureas are typically grouped into 1st, 2nd, and 3rd generation molecules. Common first-generation drugs include chlorpropamide and tolbutamide. Second-generation drugs include glyburide (glibenclamide), glipizide, and gliclazide. Glimepiride is referred to either as a 2nd or 3rd generation sulfonylurea. Although sulfonylureas are typically assumed to have a broad class-effect in some clinical and research settings, there is increasing evidence that there are numerous differences among members of the sulfonylurea drug class in their mechanisms, specificity, and adverse effects. For instance, gliclazide and glipizide are commonly grouped due to their specificity for pancreatic SUR1

receptors. By contrast, the pancreas specificity of glimepiride and glyburide is lower, having an affinity for SUR2 on cardiac myocytes and vascular smooth muscle cells[63].

1.1.3.2 Other Pharmacologic Therapies for Type 2 Diabetes

1.1.3.2.1 Incretin-based drugs

Incretin-based drugs, which include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, were first introduced to the US market in 2005. Both of these drug classes involve similar mechanisms[64]. GLP-1 is a peptide hormone produced from the proglucagon gene in L cells of the small intestine. In response to nutrient intake, the hormone stimulates glucose-dependent insulin release from the pancreatic islets[65]. DPP-4 enzymes rapidly degrade endogenous GLP-1. Also, GLP-1 slows gastric emptying, suppresses appetite, reduces plasma glucagon, and stimulates glucose disposal. GLP-1 receptor agonists are injectable drugs that mimic the GLP-1 molecule, increasing the bioavailability of the GLP-1 hormone. DPP-4 inhibitors are oral drugs that slow the degradation of intrinsic GLP-1 molecules by making DPP-4 mediated degradation of GLP-1 thermodynamically unfavourable. Therefore, both GLP-1 receptor agonists and DPP-4 inhibitors improve glycemic control by maintaining prolonged glucose-dependent insulin release. GLP-1 receptor agonists can be expected to reduce HbA1c levels by 1%, while DPP-4 inhibitors may reduce levels by 0.8%[43].

A recent meta-analysis of RCTs comparing GLP-1 receptor agonists to placebo found that randomization to GLP-1 receptor agonists was associated with improved glycaemic control and reduced body weight [66]. They have also been described to have cardioprotective actions and CVD benefits[67]. However, all GLP-1 receptor agonists were found to have a greater risk of adverse gastrointestinal symptoms than placebo[66]. There are safety concerns with mixed evidence for an increased risk of acute pancreatitis and pancreatic cancer[68 69]. Furthermore, they are costly relative to metformin, and there have been little to no long-term comparative safety studies on type 2 diabetes complications. They are now recommended as second-line agents and to be used for individuals with a history of CVD or renal disease[15].

DPP-4 inhibitors are rarely considered for initial therapy. They are occasionally offered to patients with contraindications to metformin, patients with chronic kidney disease, and patients

at high risk for hypoglycemia[64]. Relative to GLP-1 receptor agonists, DPP-4 inhibitors have similar to more modest effects on HbA1c levels[70]. Patients using a DPP-4 inhibitor can expect a 0.5 to 0.8% reduction in HbA1c with monotherapy[71]. Like GLP-1 receptor agonists, their high cost impedes their accessibility as a first-line therapy option.

1.1.3.2.2 SGLT-2 Inhibitors

The most recently approved class of antihyperglycemic drugs is the sodium-glucose cotransporter 2 (SGLT-2) inhibitors, the first of which was approved in the US in 2013[72]. SGLT-2 is a transport molecule expressed in the proximal renal tubule, mediating glucose's reabsorption in excreted urine. SGLT-2 inhibitors hinder the ability of SGLT-2 to reabsorb glucose following excretion. People with type 2 diabetes using an SGLT-2 inhibitor can expect a 0.5 to 0.7% reduction in HbA1c with SGLT-2 inhibitor monotherapy. There have now been several cardiovascular outcome trials and observational studies studying this class[73-79]. Early studies have also identified potential risks, including increased risks of genitourinary tract infections, acute kidney injury and diabetic ketoacidosis, amputations, and fractures[73-79]. Their modest improvements in glycemic levels, cost, and sparse long-term safety data will need to be reconciled before they can be adopted as initial therapy. Given the CVD benefits associated with their use, they may eventually be suitable for use as first-line treatment[80].

1.1.3.2.3 Thiazolidinediones

The thiazolidinedione (TZD) class is controversial and no longer commonly prescribed. The FDA first approved troglitazone in 1997, followed by pioglitazone and rosiglitazone in 1999[81]. This class increases sensitivity to insulin by binding to and activating the peroxisome proliferator activator receptor-γ and activating it, thus increasing glucose uptake in adipose, muscle, and liver tissues[81]. TZDs were recommended for use in those with renal impairments, were generally well tolerated in older adults compared to metformin, and were found to lower HbA1c levels by 1.0-1.5%.

The safety of all three individual TZDs is concerning. In 2000, troglitazone was withdrawn from the market after being found to cause liver damage[82]. In 2010, the FDA restricted the use of rosiglitazone following a meta-analysis that suggested that it is associated with adverse

cardiovascular events[83 84]. Finally, pioglitazone is suspected of being associated with an increased risk of bladder cancer and thus is limited in its use[85-87]. The safety of TZDs has had important implications for the regulatory approval process of all antihyperglycemic agents; the adverse cardiovascular events associated with the use of rosiglitazone were especially influential in the US FDA's decision to draft new guidance in 2008 requiring large cardiovascular outcomes trials for all new type 2 diabetes therapies[88].

1.1.3.2.4 Insulin

Insulin is typically used as the last line of therapy for the management of type 2 diabetes. Injectable insulin is often offered to patients when first- and second-line antihyperglycemic agents fail to maintain adequate glucose control[14]. They are also recommended for initial therapy for patients with severe hyperglycemia on presentation (HbA1c > 10%) or an uncertain diagnosis between types 1 and 2 diabetes[37 89]. Among insulin therapies, there is substantial variability in their time to and duration of action. Patients with residual beta-cell function may be treated with an intermediate-acting to long-acting insulin that controls blood glucose between meals. Patients with little to no beta-cell function may be dispensed a rapid-action dose to be taken before meals. Combinations of these therapies mentioned above are also available, demanding tailored consultation between prescribing clinicians and patients[90]. Many individuals eventually require the addition of exogenous insulin to maintain adequate glycemic control. Insulin therapy is associated with weight gain and hypoglycemia, both of which are risk factors for cardiovascular disease[91 92]. Furthermore, frequent injections, titrations, and close-monitoring are inconveniences that may impact a patient's quality of life[93].

1.2 Ventricular Arrhythmia

The heart is responsible for pumping blood to the rest of the body. On average, the heart beats 72 times per minute, circulating 5 L of blood per minute to ensure the body's metabolic needs are met[94]. Deviations from this regular rate, an arrhythmia, can compromise cardiac output by altering the period available for the heart to fill and ensure adequate blood circulation[95].

Arrhythmias are a cardiac dysfunction manifesting as disruptions to the rate of the heart's electromechanical activity[96]. Under normal conditions, action potentials reaching myocardial

cells dictate the cardiac cycle's frequency and duration. Based on these signals, ion channels modify the relative ionic concentrations across the membrane, establishing an electrochemical membrane potential. Changes in these ions' concentrations can contribute to a dangerous altered function of conductive cells in the heart[97]. For instance, dysregulation in K+ and Ca+ ion concentrations can change cardiac electrical activity by depolarizing the resting potential, potentially leading to cardiac arrest.

Ventricular arrhythmias (VA) originate in the heart's two lower chambers (the left and right ventricles), and supraventricular arrhythmias originate in the structures above the ventricles that comprise the heart's upper two chambers (the left and right atriums). The three major forms of VAs correspond to the relative dysregulation in the rate or rhythm of ventricular contractions. Bradycardia is a slow heart rate (fewer than 60 beats per minute). Tachycardia is a rapid heart rate (typically defined by the heart beating faster than 100 beats per minute). Fibrillations are the most serious form of arrhythmia; individual heart-muscle fibre contractions produce rapid, uncoordinated beats. Arrhythmias disrupt the carefully orchestrated pumping and filling phases of the heart, leading to insufficient time to adequately fill the heart. This inadequate delivery of oxygenated blood can cause cell death due to lack of oxygen, a process known as ischemia. Arrhythmias may manifest very quickly. The disorganized electrical activity in the heart's muscle contributes to inconsistent contractions of the heart's ventricles, causing the heart to be unable to pump blood and thus leading to sudden cardiac death. The estimated global annual burden of sudden cardiac death is estimated to be between 4 to 5 million cases per year, of which VAs are the largest contributor[98 99]. Therefore, preventing VAs may reduce the number of sudden cardiac deaths.

The symptoms and type of VA vary depending on a patient's clinical status and other comorbidities[100]. Patients may report feeling palpitations, chest pains, or abrupt loss of consciousness. There is often not much time for patients with sustained ventricular tachycardia before they are at substantial risk of subsequent cardiac arrest and hemodynamic collapse[101]. Changes in electrocardiogram (ECG) patterns can help identify these irregularities in the heart's conduction system[97]. For example, a prolonged QT interval indicates a repolarization abnormality associated with VAs. In a patient with normal heart function, the QRS duration is 120 milliseconds[102]. A QRS interval longer than 140 milliseconds strongly suggests ventricular

tachycardia. Patients with a heart rate above 200 beats per minute require immediate intervention[103]. Treatment for VA depends on the hemodynamic stability of the patient. If the patient is hemodynamically stable, treatment may consist of the initiation of an anti-arrhythmic drug such as intravenous lidocaine, procainamide, or amiodarone. Regardless of pharmacologic therapy, it is important to identify any abrupt hemodynamic stability changes through blood pressure measurements and other clinical parameters including capillary refill time [104 105]. Patients who are hemodynamically compromised (systolic blood pressure less than 80 mmHg) may require cardioversion.

Many factors can contribute to an increased risk of VA, including patient sex, advanced age, underlying heart disease, and drugs with a known risk of arrhythmias. There have been increasingly more non-cardiac drugs that have been identified as having higher risks of arrhythmias[106]. Drug-induced QT interval prolongation precedes torsade de point, a deadly rhythm associated with fatal VAs. Furthermore, given that hypoglycemia is known to affect cardiac repolarization, drugs associated with an increased risk of hypoglycemia may also induce VAs[107], and it is particularly important to assess the arrhythmic safety of drugs commonly used by individuals with type 2 diabetes.

1.3 Sulfonylurea and Cardiovascular Safety

Although there have been several studies on the cardiovascular safety of sulfonylureas, their arrhythmic safety remains relatively unknown. The existing literature reports mechanisms by which sulfonylureas may promote or impair VAs[108 109]. Individual sulfonylureas also have different extra-pancreatic actions, requiring the consideration of molecule-specific pharmacodynamics rather than class effects only. For example, differences in the potential arrhythmic effects among sulfonylurea molecules may be due to differences in pancreatic K_{ATP} channel selectivity.

Sulfonylureas induce the release of insulin by closing K_{ATP} on pancreatic B cells[62]. Some sulfonylureas, including glyburide, bind similar ATP-sensitive potassium channels in cardiomyocytes and vascular smooth muscles[110 111]. The three known subtypes of the Sulfonylurea Receptor (SUR)/K_{ATP} channel complex include the SUR1 (found in pancreatic beta

cells and neuronal cells), SUR 2 (found in cardiac and skeletal muscle cells), and SUR 2B (found in vascular smooth muscle cells) receptors[112]. The *opening* of SUR 2/ K_{ATP} and SUR 2B/ K_{ATP} channels contribute to ischemic preconditioning, an endogenous cardioprotective mechanism[113]. Decreased myocardial contraction, reduced cellular oxygen demand, reduced infarct size, decreased vascular resistance, and an increase in blood flow are all associated with this innate self-protective mechanism[114]. Therefore, ischemic preconditioning may help the myocardium anticipate and prepare for a subsequent ischemic insult[115]. Within 24 hours of an acute myocardial infarction, individuals appear to have a lower risk of life-threatening VAs associated with reperfusion. In binding to and *closing* cardiac SUR/ K_{ATP} channels, sulfonylureas may diminish ischemic preconditioning's protection. This may leave individuals at greater risk of severe tissue damage during myocardial ischemia, infarction, or subsequent VAs [116-119]. Individuals with diabetes are believed to have attenuated ischemic preconditioning[120]. Thus, any further antagonism may instigate severe deleterious results.

Alternatively, hypoglycemia (i.e., HbA1c < 4mmol/L) may mediate the relationship between sulfonylurea use and VAs[121]. The increased risk of hypoglycemia among sulfonylurea users has been detailed in several RCTs, described in section 1.3.1. An observational study reported a 4.5-fold increase in the risk of severe hypoglycemia among sulfonylurea users relative to metformin[122]. Therefore, the strong association between sulfonylureas and the risk of hypoglycemia may induce VA. Hypoglycemia may contribute to critical electrocardiographic changes, including altered ST-segment, T-wave morphology, and a prolonged QT interval[123-125]. Additionally, hypoglycemia induced increases in myoplasmic calcium concentrations, which are associated with myocardial apoptosis, the process by which myocardial cells die[126]. Both QT interval prolongation via action potential prolongation and increasing myoplasmic calcium concentrations can have synergistic deleterious effects. Given the known arrhythmic risks strongly associated with hypoglycemia, drugs related to hypoglycemia should be carefully scrutinized for any potential increased risks of arrhythmias.

1.3.1 Evidence from Randomized Controlled Trials

RCTs studying sulfonylureas have primarily explored glycemic control. To date, the primary cardiovascular safety endpoints of existing RCTs have been commonly restricted to ischemic

cardiovascular endpoints such as MI and ischemic stroke. While some RCTs have identified adverse cardiovascular events, there is some evidence that sulfonylureas may have a cardioprotective effect in animal models[58 127-129]. In the following paragraphs, I describe the RCTs that have assessed the cardiovascular safety of sulfonylureas. The characteristics and the findings of the trials are summarized in **Table 1.1**.

1.3.1.1 UGDP

The University Group Diabetes Program (UGDP) study was an interventional trial of 1027 individuals newly diagnosed with type 2 diabetes. It was designed to compare the efficacy of antihyperglycemic drugs (variable dose insulin, fixed dose insulin, tolbutamide, phenformin) and diet alone to prevent diabetes-related vascular complications[125]. Patients randomized to tolbutamide, a first-generation sulfonylurea, experienced an increased risk of cardiovascular mortality relative to those randomized to placebo (12.7% vs 4.9%; relative risk: 2.59, 95% confidence interval (CI): 1.88 to 3.56). Lack of biological rationale in addition to swift criticism of methodological and statistical shortcomings such as skewed distributions for sex brought doubt to the study findings[130 131]. Also, study participants were randomized to a first-generation sulfonylurea, the effects of which cannot be easily extrapolated to the second- and third-generation sulfonylureas used today.

1.3.1.2 Veterans Affairs CSDM

The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM) was a feasibility trial of 153 men comparing the risk of cardiovascular mortality and morbidity with standard and intensive glycemic therapy[132]. Standard therapy consisted of once-daily injections of insulin. Failure to reach glycemic targets resulted in intensification with either evening insulin injection with daytime glipizide, two injections of insulin alone, or three or more injections of insulin[133]. The study results were inconclusive, finding neither an increased nor decreased risk of cardiovascular endpoints among the intensive and standard treatment arms (32% vs 20%; RR: 1.56, 95% CI: 0.90-2.70). The 61 incident cardiovascular events occurred amongst 16 patients randomized to the standard of care arm 24 patients randomized to the intensive treatment arm[132]. Participants in the intensive arm were also

more likely to experience mild to moderate hypoglycemic events. Furthermore, this was a feasibility trial with limited power to detect differences in specific cardiovascular endpoints between treatment groups. Therefore, the trial supports the need for a trial with long-term follow-up powered to assess specific cardiovascular endpoints.

1.3.1.3 UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) was a large, randomized controlled trial designed to examine the risk of developing microvascular and macrovascular complications among people with type 2 diabetes randomly assigned to either conventional lifestyle modification, insulin, or a physician-dictated sulfonylurea use[134]. Of the 1573 patients randomized to a sulfonylurea, 788 received chlorpropamide, 615 received glyburide, and 170 received glipizide. Patients with persistent hypoglycemia were secondarily allocated to intensification with metformin or insulin[134 135]. Patients in the intensive group experienced more hypoglycemic episodes than those in the conventional group. Due to concerns regarding hypoglycemia caused by sulfonylurea use, patients recruited in the last eight centers receiving a sulfonylurea underwent treatment intensification to insulin earlier. In the intention-to-treat (ITT) analysis, the proportion of major hypoglycemic episodes per year was 0.7% with lifestyle modification, 1.0% with chlorpropamide, 1.4% with glyburide, and 1.8% with insulin. There were 3 composite outcomes: diabetes-related endpoints (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal MI, angina, heart failure, stroke. renal failure, vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction), diabetes-related death (death from MI, stroke. peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia, and sudden death), all-cause mortality. Compared to the conventional group, the intensive group had a numerically lower risk for all 3 endpoints (diabetes-related endpoints RR: 0.88, 95% CI: 0.79-0.99; diabetes-related death RR: 0.90, 95% CI: 0.73-1.11; all-cause mortality RR: 0.94, 95% CI: 0.80-1.10). There were no differences for any of the three composite endpoints between the three intensive agents (chlorpropamide, glyburide, or insulin). Although this study appeared to dismiss concerns brought forth by the UGDP study, a subsequent sub-study among a small sample of overweight patients found that adding metformin to sulfonylurea therapy was associated with a higher risk of diabetes-related

death than those receiving only sulfonylurea monotherapy. The authors attributed this to type 1 error[136]. Nonetheless, the increased hypoglycemic events among sulfonylureas was concerning.

1.3.1.4 ADVANCE

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial randomized over 10,000 patients to gliclazide (standard control group), gliclazide in combination with a blood pressure lowering perindopril/indapamide (intensive control group), or usual care using a factorial design[137]. Participants in the usual care arm could receive treatment using a sulfonylurea other than gliclazide based on local guidelines. The primary outcome was a composite of macrovascular (MI, stroke, or cardiovascular death) and microvascular (retinopathy or nephropathy) events[138]. Secondary outcomes included heart failure, hospitalization, all-cause mortality, and dementia. Their study found no differences in the rate of macrovascular events between the two groups (HR: 0.94, 95% CI: 0.84-1.06) or secondary outcomes, including sudden death between the intensive control group and standard control group (HR: 0.93, 95% CI: 0.83-1.06)[139]. The study reported hospitalization as being more frequent in the intensive control group. Notably, the rate of severe hypoglycemia was markedly greater in the intensive-control group than in the standard-control group (HR: 1.86, 95% CI: 1.42-2.40)[140].

1.3.1.5 TOSCA.IT

Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT) was a multicentre pragmatic clinical trial. The intervention arm was comprised of patients randomized to intensify metformin therapy with one of glimepiride, glipizide, or glyburide. Metformin add-on with pioglitazone, a thiazolidinedione, was the comparator[141]. The primary outcome was a composite of the first occurrence of all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularization. The secondary outcome was a composite of ischaemic cardiovascular disease, including sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, leg amputation above the ankle, and any revascularization of the coronary, leg, or carotid arteries. At the Data and Safety Monitoring Board's suggestion, heart failure was added as a stand-alone secondary outcome during the trial[142]. Patients

randomized to pioglitazone had a similar risk of experiencing the primary outcome relative to those randomized to sulfonylureas (HR: 0.96, 95% CI: 0.74-1.26). TOSCA.IT was ended early due to futility and reported a low rate of cardiovascular events.

1.3.1.6 CAROLINA

The recently completed Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) non-inferiority trial randomized 6042 participants to receive either linagliptin (a DPP-4 inhibitor) or glimepiride[143 144]. The primary endpoint was time to the first 3-point major adverse cardiovascular event (3P-MACE) occurrence (cardiovascular death, non-fatal MI (excluding silent MI), or nonfatal stroke). Secondary endpoints included individual components of 3P-MACE and 4-point Major Adverse Cardiovascular Events (4P-MACE) occurrence (cardiovascular death (including fatal stroke and fatal MI), non-fatal stroke, non-fatal MI (excluding silent MI), or hospitalisation for unstable angina pectoris). No difference was observed in all-cause mortality between patients randomized to linagliptin versus glimepiride (HR: 0.82, 95% CI: 0.66-1.03) or cardiovascular death (HR: 1.00, 95% CI: 0.81-1.24)[143]. Although this finding suggests a possible protective effect with linagliptin, the results were ultimately inconclusive due to wide 95% CIs. Furthermore, the cardiovascular safety of sulfonylurea molecules other than glimepiride remains a concern.

Although RCTs generally produce higher-quality evidence than observational studies, RCTs often have smaller sample sizes and highly selected patient populations. Moreover, RCTs have a relatively smaller study population and shorter follow-up, resulting in less precision and often compromising the feasibility of studying rare endpoints. Practically, RCTs are expensive and time demanding. These factors contribute to resources for RCTs being allocated for newly emerging therapies such as SGLT-2 inhibitors instead of legacy therapies including sulfonylureas.

1.3.2 Evidence from Observational Studies

Several observational studies have examined the association between the use of sulfonylureas and the risk of cardiovascular events. In 2009, Pantalone and colleagues conducted a head-to-head comparison of antihyperglycemic drugs including sulfonylureas, metformin or

thiazolidinediones (pioglitazone, rosiglitazone)[145]. This retrospective cohort study used clinical data at the Cleveland Clinic. The three primary outcomes were coronary artery disease (CAD), congestive heart failure (CHF), and all-cause mortality. Thiazolidinediones and metformin were both associated with lower mortality than sulfonylureas (Pioglitazone: HR: 0.59, 95% CI: 0.43-0.81; Rosiglitazone: HR: 0.73, 95% CI: 0.51-1.02; Metformin: HR: 0.54, 95% CI: 0.46-0.64). These findings are consistent with those from a study by Johnson and colleagues using Saskatchewan Health databases, which had also found metformin therapy was associated with a decreased all-cause mortality compared to sulfonylurea monotherapy (HR: 0.60, 95% CI: 0.49-0.74)[146]. Unfortunately, both Pantalone's and Johnson's studies have substantial methodological limitations, including time-lag bias and immortal time bias[56].

In 2012, Roumie and colleagues conducted a retrospective cohort study on the comparative effectiveness of sulfonylurea versus metformin by using the National Veterans Health administrative database[147]. The primary outcome was a composite of acute MI, stroke, or death. The investigators found an increased risk of cardiovascular events or death among incident sulfonylurea monotherapy users (aHR: 1.15, 95% CI: 1.07-1.25). These results were consistent relative to metformin for both glyburide (aHR: 1.26, 95% CI: 1.16-1.37) and glipizide (aHR: 1.15, 95% CI: 1.06 - 1.25)[147]. Furthermore, the results were robust to numerous pre-specified sensitivity analyses.

In 2017, Azoulay and Suissa conducted a methodological review with meta-regression on the cardiovascular safety and risk of death among patients taking sulfonylureas relative to other antihyperglycemic drugs[56]. Of the 20 observational studies, only 6 studies, including Roumie and colleagues' 2012 study, were deemed to have no major design-related biases (exposure misclassification, time-lag bias, selection bias, immortal time bias). The majority of these studies reported that sulfonylureas were associated with an increased risk of adverse cardiovascular events and mortality, with all studies using metformin as an active comparator.

Recently, our group conducted a matched population-based cohort study using data from the UK's Clinical Practice Research Datalink (CPRD) Gold with linkage to Hospital Episode Statistics hospitalization data and Office for National Statistics (ONS) vital statistics data[57]. We found that the use of sulfonylureas as a first-line treatment for type 2 diabetes was not associated

with an increased risk of MI but was associated with increased risks of ischaemic stroke (aHR: 1.25, 95% CI: 1.00-1.56), cardiovascular death (aHR: 1.25, 95% CI: 1.06-1.47), and all-cause mortality (aHR: 1.60, 95% CI: 1.45-1.76) relative to metformin[57]. Sulfonylureas were associated with an additional 2.0 ischaemic strokes and 3.5 cardiovascular deaths per 1000 patients per year. While this study identified an increased risk of cardiovascular death with sulfonylureas compared with metformin, the underlying cause of this increased risk remains unclear.

1.4 Sulfonylureas and Arrhythmic Safety

The existing knowledge available on the arrhythmic safety of these agents is sparse. Major trials including CAROLINA, TOSCA.IT and ADVANCE did not report VAs or their sequela (sudden cardiac death or cardiac arrest) as primary or secondary endpoints[137 141 143]. This can be explained, in part, by the incidence of arrhythmic events in this population and the corresponding need for a large sample size to assess this endpoint. Therefore, observational studies represent the most feasible approach to assessing this potential adverse drug reaction.

1.5 Original Thesis Work

1.5.1 Thesis Objectives

This thesis contains two primary objectives:

1. To synthesize the existing evidence regarding the use of sulfonylureas and risk of VA among people with type 2 diabetes via systematic review of observational studies.
2. To determine whether the use of sulfonylureas, when used as first-line therapy and compared with the use of metformin, is associated with an increased risk of VA among people with type 2 diabetes.

1.5.2 Thesis Overview

Chapter 2 includes the first manuscript of my thesis, a systematic review of the existing observational literature investigating the arrhythmic safety of sulfonylureas relative to other therapies used for type 2 diabetes. Chapter 3 provides a detailed description of the methods used in the enclosed database study. Chapter 4 describes a retrospective cohort study that uses an

active comparator, new user design to assess the arrhythmic effects of sulfonylureas. Chapter 5 discusses the main findings and implications of this thesis, as well as directions for future research. Finally, Chapter 6 provides some overall conclusions for this thesis.

1.6 REFERENCES

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice* 2019;157 doi: 10.1016/j.diabres.2019.107843
2. New diabetes rates released with urgent plea for governments to implement national diabetes strategy 2020 [accessed August 18, 2020.
3. Bilandzic A, Rosella L. The cost of diabetes in Canada over 10 years: applying attributable health care costs to a diabetes incidence prediction model. *Health Promot Chronic Dis Prev Can* 2017;37(2):49-53. doi: 10.24095/hpcdp.37.2.03
4. Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009. *JAMA* 2014;311(17):1778-86. doi: 10.1001/jama.2014.3201
5. D'Adamo E, Caprio S. Type 2 Diabetes in Youth: Epidemiology and Pathophysiology. *Diabetes Care* 2011;34(Supplement 2):S161-S65. doi: 10.2337/dc11-s212
6. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. *Nature reviews endocrinology* 2012;8(4):228-36.
7. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *New England Journal of Medicine* 2009;360(2):129-39. doi: 10.1056/NEJMoa0808431
8. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *The Lancet* 2011;378(9786):169-81. doi: https://doi.org/10.1016/S0140-6736(11)60614-4
9. Robertson RP. Antagonist: diabetes and insulin resistance--philosophy, science, and the multiplier hypothesis. *J Lab Clin Med* 1995;125(5):560-4; discussion 65. [published Online First: 1995/05/01]

10. Kahn CR. Banting Lecture. Insulin action, diabetogenes, and the cause of type II diabetes. *Diabetes* 1994;43(8):1066-84. doi: 10.2337/diab.43.8.1066 [published Online First: 1994/08/01]
11. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab Syndr Obes* 2014;7:587-91. doi: 10.2147/dmso.S67400 [published Online First: 2014/12/17]
12. Kahn S. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003;46(1):3-19.
13. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. Sequence of events leading to non-insulin-dependent diabetes mellitus. *J Clin Invest* 1994;94(5):1714-21. doi: 10.1172/jci117518 [published Online First: 1994/11/01]
14. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35 Suppl 1(Suppl 1):S64-71. doi: 10.2337/dc12-s064 [published Online First: 2012/01/04]
15. Lipscombe L, Booth G, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. *Can J Diabetes* 2018;42 Suppl 1:S88-s103. doi: 10.1016/j.jcjd.2017.10.034 [published Online First: 2018/04/14]
16. John WG. Use of HbA1c in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011. *Diabet Med* 2012;29(11):1350-7. doi: 10.1111/j.1464-5491.2012.03762.x [published Online First: 2012/09/11]
17. Ekoe JM, Goldenberg R, Katz P. Screening for Diabetes in Adults. *Can J Diabetes* 2018;42 Suppl 1:S16-s19. doi: 10.1016/j.jcjd.2017.10.004 [published Online First: 2018/04/14]
18. Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *The American journal of medicine* 2010;123(3):S3-S11.
19. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clinical diabetes* 2008;26(2):77-82.
20. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S135-s51. doi: 10.2337/dc20-S011 [published Online First: 2019/12/22]
21. Cheng AY, Leiter LA. Glucose lowering and cardiovascular disease: what do we know and what should we do? *European Journal of Cardiovascular Prevention & Rehabilitation* 2010;17(1_suppl):s25-s31.

22. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clinical diabetes* 2011;29(3):116-22.
23. Clark CM, Perry RC. Type 2 diabetes and macrovascular disease: epidemiology and etiology. *The American heart journal* 1999;138(5):S330-S33.
24. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 1996;39(12):1577-83.
25. Holden SE, Currie CJ. Mortality risk with sulphonylureas compared to metformin. *Diabetes, Obesity and Metabolism* 2014;16(10):885-90. doi: 10.1111/dom.12280
26. Mensah GA, Wei GS, Sorlie PD, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circulation research* 2017;120(2):366-80. doi: 10.1161/CIRCRESAHA.116.309115
27. Htay T, Soe K, Lopez-Perez A, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *Curr Cardiol Rep* 2019;21(6):45. doi: 10.1007/s11886-019-1133-9 [published Online First: 2019/04/24]
28. Economic Costs of Diabetes in the U.S. in 2002. *Diabetes Care* 2003;26(3):917-32. doi: 10.2337/diacare.26.3.917
29. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100(10):1134-46. doi: 10.1161/01.cir.100.10.1134 [published Online First: 1999/09/08]
30. Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329(14):977-86. doi: 10.1056/nejm199309303291401 [published Online First: 1993/09/30]
31. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S61-s70. doi: 10.2337/dc19-S006 [published Online First: 2018/12/19]
32. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S37-s47. doi: 10.2337/dc20-S004 [published Online First: 2019/12/22]

33. Pillay J, Armstrong MJ, Butalia S, et al. Behavioral Programs for Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-analysis. *Ann Intern Med* 2015;163(11):848-60. doi: 10.7326/m15-1400 [published Online First: 2015/09/29]
34. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369(2):145-54. doi: 10.1056/NEJMoa1212914 [published Online First: 2013/06/26]
35. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346(6):393-403. doi: 10.1056/NEJMoa012512 [published Online First: 2002/02/08]
36. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7(5):344-55. doi: 10.1016/s2213-8587(19)30068-3 [published Online First: 2019/03/11]
37. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S90-s102. doi: 10.2337/dc19-S009 [published Online First: 2018/12/19]
38. Colagiuri S, Cull CA, Holman RR. Are Lower Fasting Plasma Glucose Levels at Diagnosis of Type 2 Diabetes Associated With Improved Outcomes? *UK Prospective Diabetes Study 61* 2002;25(8):1410-17. doi: 10.2337/diacare.25.8.1410
39. Nathan DM, Buse JB, Davidson MB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes* 2006;29(8):1963-72. doi: 10.2337/dc06-9912
40. Rawshani A, Rawshani A, Franzén S, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2018;379(7):633-44. doi: 10.1056/NEJMoa1800256 [published Online First: 2018/08/16]
41. Anonymous. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetesd2021. *Diabetes Care* 2021;44(SUPPLIMENTRY 1):S111-S24. doi: http://dx.doi.org/10.2337/dc21-S009

42. Montvida O, Shaw J, Atherton JJ, et al. Long-term Trends in Antidiabetes Drug Usage in the U.S.: Real-world Evidence in Patients Newly Diagnosed With Type 2 Diabetes. *Diabetes Care* 2018;41(1):69-78. doi: 10.2337/dc17-1414
43. Quianzon CCL, Cheikh IE. History of current non-insulin medications for diabetes mellitus. *Journal of Community Hospital Internal Medicine Perspectives* 2012;2(3):19081. doi: 10.3402/jchimp.v2i3.19081
44. Gan SC, Barr J, Arieff AI, et al. Biguanide-Associated Lactic Acidosis: Case Report and Review of the Literature. *Archives of Internal Medicine* 1992;152(11):2333-36. doi: 10.1001/archinte.1992.00400230129023
45. Bailey CJ. Metformin: historical overview. *Diabetologia* 2017;60(9):1566-76. doi: 10.1007/s00125-017-4318-z
46. DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 1991;73(6):1294-301. doi: 10.1210/jcem-73-6-1294 [published Online First: 1991/12/01]
47. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia* 2017;60(9):1577-85. doi: 10.1007/s00125-017-4342-z [published Online First: 2017/08/05]
48. Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998;338(4):265-6. doi: 10.1056/nejm199801223380415 [published Online First: 1998/01/24]
49. Goergen SK, Rumbold G, Compton G, et al. Systematic review of current guidelines, and their evidence base, on risk of lactic acidosis after administration of contrast medium for patients receiving metformin. *Radiology* 2010;254(1):261-9. doi: 10.1148/radiol.09090690 [published Online First: 2009/12/25]
50. Qaseem A, Barry MJ, Humphrey LL, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med* 2017;166(4):279-90. doi: 10.7326/m16-1860 [published Online First: 2017/01/06]
51. Hirst JA, Farmer AJ, Dyar A, et al. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia* 2013;56(5):973-84. doi: 10.1007/s00125-013-2856-6 [published Online First: 2013/03/16]

52. Hermann LS, Scherstén B, Bitzén PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. *Diabetes Care* 1994;17(10):1100-9. doi: 10.2337/diacare.17.10.1100 [published Online First: 1994/10/01]
53. Davidson MB. Successful treatment of markedly symptomatic patients with type II diabetes mellitus using high doses of sulfonylurea agents. *West J Med* 1992;157(2):199-200. [published Online First: 1992/08/01]
54. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006;355(5):467-77. doi: 10.1056/NEJMoa061759 [published Online First: 2006/08/04]
55. Abrahamson MJ. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? Yes, they continue to serve us well! *Diabetes Care* 2015;38(1):166-9. doi: 10.2337/dc14-1945 [published Online First: 2014/12/30]
56. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;40(5):706-14. doi: 10.2337/dc16-1943 [published Online First: 2017/04/22]
57. Filion KB, Douros A, Azoulay L, et al. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: A population-based cohort study. *Br J Clin Pharmacol* 2019;85(10):2378-89. doi: 10.1111/bcp.14056 [published Online First: 2019/07/06]
58. Varvaki Rados D, Catani Pinto L, Reck Remonti L, et al. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. *PLoS Med* 2016;13(4):e1001992. doi: 10.1371/journal.pmed.1001992 [published Online First: 2016/04/14]
59. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999;33(1):119-24. doi: 10.1016/s0735-1097(98)00557-9 [published Online First: 1999/02/06]
60. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI

(Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *Bmj* 1997;314(7093):1512-5. doi: 10.1136/bmj.314.7093.1512 [published Online First: 1997/05/24]

61. Bressler R, Johnson DG. Pharmacological regulation of blood glucose levels in non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997;157(8):836-48. [published Online First: 1997/04/28]
62. Aguilar-Bryan L, Nichols CG, Wechsler SW, et al. Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science* 1995;268(5209):423-6. doi: 10.1126/science.7716547 [published Online First: 1995/04/21]
63. Middleton TL, Wong J, Molyneaux L, et al. Cardiac Effects of Sulfonylurea-Related Hypoglycemia. *Diabetes Care* 2017;40(5):663-70. doi: 10.2337/dc16-1972 [published Online First: 2017/02/23]
64. Koliaki C, Doupis J. Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus. *Diabetes Ther* 2011;2(2):101-21. doi: 10.1007/s13300-011-0002-3 [published Online First: 2011/12/01]
65. Lee YS, Jun HS. Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. *Metabolism* 2014;63(1):9-19. doi: 10.1016/j.metabol.2013.09.010 [published Online First: 2013/10/22]
66. Htike ZZ, Zaccardi F, Papamargaritis D, et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab* 2017;19(4):524-36. doi: 10.1111/dom.12849 [published Online First: 2016/12/17]
67. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012;33(2):187-215. doi: 10.1210/er.2011-1052 [published Online First: 2012/02/11]
68. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *New England Journal of Medicine* 2014;370(9):794-97.
69. Azoulay L, Filion KB, Platt RW, et al. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. *BMJ* 2016;352:i581. doi: 10.1136/bmj.i581
70. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *Jama* 2007;298(2):194-206. doi: 10.1001/jama.298.2.194 [published Online First: 2007/07/12]

71. Craddy P, Palin HJ, Johnson KI. Comparative effectiveness of dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. *Diabetes Ther* 2014;5(1):1-41. doi: 10.1007/s13300-014-0061-3 [published Online First: 2014/03/26]

72. SGLT2 Inhibitors (Gliflozins) [Available from: http://www.diabetes.co.uk/diabetes-medication/sglt2-inhibitors.html] accessed 07/2017.

73. Dave CV, Schneeweiss S, Kim D, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med* 2019;171(4):248-56. doi: 10.7326/m18-3136 [published Online First: 2019/07/30]

74. Douros A, Lix LM, Fralick M, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis : A Multicenter Cohort Study. *Ann Intern Med* 2020;173(6):417-25. doi: 10.7326/m20-0289 [published Online First: 2020/07/28]

75. Nadkarni GN, Ferrandino R, Chang A, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. *Diabetes Care* 2017;40(11):1479-85. doi: 10.2337/dc17-1011 [published Online First: 2017/08/23]

76. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. *Jama* 2018;319(15):1580-91. doi: 10.1001/jama.2018.3024 [published Online First: 2018/04/21]

77. Zhou Z, Jardine M, Perkovic V, et al. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. *Diabetologia* 2019;62(10):1854-67. doi: 10.1007/s00125-019-4955-5 [published Online First: 2019/08/11]

78. Abrahami D, Douros A, Yin H, et al. Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of Fractures Among Patients With Type 2 Diabetes. *Diabetes Care* 2019;42(9):e150-e52. doi: 10.2337/dc19-0849 [published Online First: 2019/07/13]

79. Yu OHY, Dell'Aniello S, Shah BR, et al. Sodium–Glucose Cotransporter 2 Inhibitors and the Risk of Below-Knee Amputation: A Multicenter Observational Study. *Diabetes Care* 2020;43(10):2444-52.

80. Fralick M, Schneeweiss S, Redelmeier DA, et al. Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2

diabetes: An observational study using data from routine care. *Diabetes Obes Metab* 2021 doi: 10.1111/dom.14474 [published Online First: 2021/06/26]

81. Yki-Järvinen H. Thiazolidinediones. *New England Journal of Medicine* 2004;351(11):1106-18. doi: 10.1056/NEJMra041001
82. Watkins PB, Whitcomb RW. Hepatic dysfunction associated with troglitazone. *N Engl J Med* 1998;338(13):916-7. doi: 10.1056/nejm199803263381314 [published Online First: 1998/03/28]
83. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356(24):2457-71. doi: 10.1056/NEJMoa072761 [published Online First: 2007/05/23]
84. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010;170(14):1191-201. doi: 10.1001/archinternmed.2010.207 [published Online First: 2010/07/27]
85. Filipova E, Uzunova K, Kalinov K, et al. Pioglitazone and the Risk of Bladder Cancer: A Meta-Analysis. *Diabetes Ther* 2017;8(4):705-26. doi: 10.1007/s13300-017-0273-4 [published Online First: 2017/06/18]
86. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *Bmj* 2012;344:e3645. doi: 10.1136/bmj.e3645 [published Online First: 2012/06/02]
87. Tuccori M, Filion KB, Yin H, et al. Pioglitazone use and risk of bladder cancer: population based cohort study. *Bmj* 2016;352:i1541. doi: 10.1136/bmj.i1541 [published Online First: 2016/04/01]
88. Regier EE, Venkat MV, Close KL. More Than 7 Years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications. *Clin Diabetes* 2016;34(4):173-80. doi: 10.2337/cd16-0005 [published Online First: 2016/10/22]
89. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care* 2004;27(5):1028-32. doi: 10.2337/diacare.27.5.1028 [published Online First: 2004/04/28]

90. Wallia A, Molitch ME. Insulin therapy for type 2 diabetes mellitus. *Jama* 2014;311(22):2315-25. doi: 10.1001/jama.2014.5951 [published Online First: 2014/06/11]
91. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med* 2005;22(6):749-55. doi: 10.1111/j.1464-5491.2005.01501.x [published Online First: 2005/05/25]
92. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367(4):319-28. doi: 10.1056/NEJMoa1203858 [published Online First: 2012/06/13]
93. Frid AH, Kreugel G, Grassi G, et al. New Insulin Delivery Recommendations. *Mayo Clin Proc* 2016;91(9):1231-55. doi: 10.1016/j.mayocp.2016.06.010 [published Online First: 2016/09/07]
94. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man1. *Cardiovascular Research* 1970;4(2):160-67. doi: 10.1093/cvr/4.2.160
95. SAMET P. Hemodynamic Sequelae of Cardiac Arrhythmias. *Circulation* 1973;47(2):399-407. doi: doi:10.1161/01.CIR.47.2.399
96. Bastiaenen R, Behr ER. Early repolarisation: controversies and clinical implications. *Heart* 2012;98(11):841-47. doi: 10.1136/heartjnl-2011-301347
97. Martin CA, Matthews GDK, Huang CLH. Sudden cardiac death and inherited channelopathy: the basic electrophysiology of the myocyte and myocardium in ion channel disease. *Heart* 2012;98(7):536-43. doi: 10.1136/heartjnl-2011-300953
98. Chugh SS, Reinier K, Teodorescu C, et al. Epidemiology of Sudden Cardiac Death: Clinical and Research Implications. *Progress in Cardiovascular Diseases* 2008;51(3):213-28. doi: https://doi.org/10.1016/j.pcad.2008.06.003
99. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *The Journal of Clinical Investigation* 2005;115(9):2305-15. doi: 10.1172/JCI26381
100. Bigger JT, Dresdale RJ, Heissenbuttel RH, et al. Ventricular arrhythmias in ischemic heart disease: Mechanism, prevalence, significance, and management. *Progress in Cardiovascular Diseases* 1977;19(4):255-300. doi: https://doi.org/10.1016/0033-0620(77)90005-6

101. Markman TM, Nazarian S. Treatment of ventricular arrhythmias: What's New? *Trends in Cardiovascular Medicine* 2019;29(5):249-61. doi: https://doi.org/10.1016/j.tcm.2018.09.014

102. Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991;83(5):1649-59. doi: 10.1161/01.cir.83.5.1649 [published Online First: 1991/05/01]

103. Vereckei A, Duray G, Szénási G, et al. Application of a new algorithm in the differential diagnosis of wide QRS complex tachycardia. *Eur Heart J* 2007;28(5):589-600. doi: 10.1093/eurheartj/ehl473 [published Online First: 2007/02/03]

104. Kaiser E, Darrieux FC, Barbosa SA, et al. Differential diagnosis of wide QRS tachycardias: comparison of two electrocardiographic algorithms. *Europace* 2015;17(9):1422-7. doi: 10.1093/europace/euu354 [published Online First: 2015/01/21]

105. Sevransky J. Clinical assessment of hemodynamically unstable patients. *Curr Opin Crit Care* 2009;15(3):234-8. doi: 10.1097/MCC.0b013e32832b70e5 [published Online First: 2009/04/24]

106. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf* 2012;3(5):241-53. doi: 10.1177/2042098612454283 [published Online First: 2012/10/01]

107. Leonard CE, Hennessy S, Han X, et al. Pro- and Antiarrhythmic Actions of Sulfonylureas: Mechanistic and Clinical Evidence. *Trends in Endocrinology & Metabolism* 2017;28(8):561-86. doi: https://doi.org/10.1016/j.tem.2017.04.003

108. Wilde AA. Role of ATP-sensitive K+ channel current in ischemic arrhythmias. *Cardiovascular drugs and therapy* 1993;7(3):521-26.

109. Wilde AA, Janse MJ. Electrophysiological effects of ATP sensitive potassium channel modulation: implications for arrhythmogenesis. *Cardiovascular research* 1994;28(1):16-24.

110. Inagaki N, Gonoi T, Iv JPC, et al. A family of sulfonylurea receptors determines the pharmacological properties of ATP-sensitive K+ channels. *Neuron* 1996;16(5):1011-17.

111. Panten U, Schwanstecher M, Schwanstecher C. Sulfonylurea receptors and mechanism of sulfonylurea action. *Experimental and clinical endocrinology & diabetes* 1996;104(01):1-9.

112. Fosset M, De Weille J, Green R, et al. Antidiabetic sulfonylureas control action potential properties in heart cells via high affinity receptors that are linked to ATP-dependent K+ channels. *Journal of Biological Chemistry* 1988;263(17):7933-36.
113. Engler RL, Yellon DM. Sulfonylurea KATP blockade in type II diabetes and preconditioning in cardiovascular disease: time for reconsideration. *Circulation* 1996;94(9):2297-301.
114. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74(5):1124-36.
115. Gross G. ATP-sensitive potassium channels and myocardial preconditioning. *Basic research in cardiology* 1995;90(2):85-88.
116. Grover GJ. Protective effects of ATP-sensitive potassium-channel openers in experimental myocardial ischemia. *Journal of cardiovascular pharmacology* 1994;24:S18-S27.
117. Grover GJ, Sleph PG, Dzwonczyk S. Role of myocardial ATP-sensitive potassium channels in mediating preconditioning in the dog heart and their possible interaction with adenosine A1-receptors. *Circulation* 1992;86(4):1310-16.
118. Terzic A, Tung RT, Inanobe A, et al. G proteins activate ATP-sensitive K+ channels by antagonizing ATP-dependent gating. *Neuron* 1994;12(4):885-93.
119. Escande D, Cavero I. K+ channel openers and 'natural'cardioprotection. *Trends in pharmacological sciences* 1992;13:269-72.
120. Ashcroft FM, Gribble FM. Tissue-specific effects of sulfonylureas: Lessons from studies of cloned KATP channels. *Journal of Diabetes and its Complications* 2000;14(4):192-96. doi: https://doi.org/10.1016/S1056-8727(00)00081-7
121. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 2010;53(8):1552-61. doi: 10.1007/s00125-010-1752-6
122. Yu O, Azoulay L, Yin H, et al. Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia. *Am J Med* 2018;131(3):317.e11-17.e22. doi: 10.1016/j.amjmed.2017.09.044 [published Online First: 2017/10/17]
123. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014;10(12):711-22. doi: 10.1038/nrendo.2014.170 [published Online First: 2014/10/08]

124. Khan SG, Huda MS. Hypoglycemia and Cardiac Arrhythmia; Mechanisms, Evidence Base a nd Current Recommendations. *Curr Diabetes Rev* 2017;13(6):590-97. doi: 10.2174/1573399812666161201155941 [published Online First: 2016/12/03]
125. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;19:Suppl:789-830. [published Online First: 1970/01/01]
126. Brady PA, Zhang S, López J, et al. Dual effect of glyburide, an antagonist of KATP channels, on metabolic inhibition-induced Ca2+ loading in cardiomyocytes. *European journal of pharmacology* 1996;308(3):343-49.
127. Bril A, Laville M-P, Gout B. Effects of glibenclamide on ventricular arrhythmias and cardiac function in ischaemia and reperfusion in isolated rat heart. *Cardiovascular research* 1992;26(11):1069-76.
128. Kantor PF, Coetzee WA, Carmeliet EE, et al. Reduction of ischemic K+ loss and arrhythmias in rat hearts. Effect of glibenclamide, a sulfonylurea. *Circulation Research* 1990;66(2):478-85.
129. Leibowitz G, Cerasi E. Sulphonylurea treatment of NIDDM patients with cardiovascular disease: a mixed blessing? *Diabetologia* 1996;39(5):503-14.
130. Seltzer HS. A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). *Diabetes* 1972;21(9):976-9. doi: 10.2337/diab.21.9.976 [published Online First: 1972/09/01]
131. Kilo C, Miller JP, Williamson JR. The Achilles heel of the University Group Diabetes Program. *Jama* 1980;243(5):450-7. [published Online First: 1980/02/01]
132. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular Events and Correlates in the Veterans Affairs Diabetes Feasibility Trial: Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. *Archives of Internal Medicine* 1997;157(2):181-88. doi: 10.1001/archinte.1997.00440230053007
133. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM): results of the feasibility trial. *Diabetes care* 1995;18(8):1113-23.
134. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK

Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837-53. [published Online First: 1998/09/22]

135. Group UPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet* 1998;352(9131):854-65.
136. Kerner W. The UK Prospective Diabetes Study. *Lancet* 1998;352(9144):1934. doi: 10.1016/s0140-6736(05)60427-8 [published Online First: 1998/12/24]
137. Patel A, Chalmers J, Poulter N. ADVANCE: action in diabetes and vascular disease. *J Hum Hypertens* 2005;19 Suppl 1:S27-32. doi: 10.1038/sj.jhh.1001890 [published Online First: 2005/08/03]
138. Study rationale and design of ADVANCE: action in diabetes and vascular disease--preterax and diamicron MR controlled evaluation. *Diabetologia* 2001;44(9):1118-20. doi: 10.1007/s001250100612 [published Online First: 2001/10/13]
139. Chalmers J, Kengne AP, Joshi R, et al. New insights from ADVANCE. *J Hypertens Suppl* 2007;25(1):S23-30. doi: 10.1097/01.hjh.0000271506.69949.46 [published Online First: 2007/12/06]
140. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358(24):2560-72. doi: 10.1056/NEJMoa0802987 [published Online First: 2008/06/10]
141. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 2017;5(11):887-97. doi: 10.1016/s2213-8587(17)30317-0 [published Online First: 2017/09/18]
142. Packer M. Are physicians neglecting the risk of heart failure in diabetic patients who are receiving sulfonylureas? Lessons from the TOSCA. IT trial. *European Journal of Heart Failure* 2018;20(1):49-51.
143. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *Jama* 2019;322(12):1155-66. doi: 10.1001/jama.2019.13772 [published Online First: 2019/09/20]

144. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular outcome trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA®). *Diabetes and Vascular Disease Research* 2015;12(3):164-74.
145. Pantalone KM, Kattan MW, Yu C, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. *Acta diabetologica* 2009;46(2):145-54.
146. Johnson JA, Majumdar SR, Simpson SH, et al. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes care* 2002;25(12):2244-48.
147. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2012;157(9):601-10. doi: 10.7326/0003-4819-157-9-201211060-00003 [published Online First: 2012/11/07]

Table 1.1. RCTs of sulfonylureas and cardiovascular outcomes.

Year	Trial	Follow-Up Duration	Population (n)	Treatments	Outcome
1970	University Group Diabetes Program (UGDP)[1]	8.5 years	n=1027 Patients diagnosed with diabetes (≤ 1 year)	Diet and exercise (placebo) versus Insulin (variable dose) insulin (fixed dose) tolbutamide phenformin	No benefit observed on micro- and macro-vascular complications. Cardiovascular deaths (total of 61 deaths): 4.9% (10/205) placebo; 12.7% (26/204) tolbutamide; 6.2% (13/210) fixed dose insulin; 5.9% (12/204) variable dose insulin Tolbutamide treated experienced a significantly higher CV mortality rate compared to placebo group (RR: 2.59, 95% CI: 1.88-3.56) Increased risk for CV mortality of approximately 1% per year for tolbutamide.
1997	Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM) [2]	Mean: 27 month (Range 18-25 months)	n=153 Men with prevalent type 2 disease and with suboptimal control on insulin or oral agents. Mean age=60 ± 6.0 years Mean duration of diabetes=7.8 ± 4.0 years.	Standard treatment (i.e., AM insulin) versus Intensive" treatment (PM insulin + daytime glypizide, increasing number of insulin injection as needed to maintain glycemic targets)	16/78 (20%) in standard group had at least 1 new CVD event compared to 24/75 (32%) in intensive group (RR: 1.56, 95% CI: 0.90-2.70) Overall 6/10 (60%) of deaths were attributable to CVD

1998	United Kingdom Prospective Diabetes Study (UKPDS 33) [3]	Median: 10 years for analysis of endpoints; 11.1 years for analysis of conventional versus intensive therapies	n=4209 patients with newly treated type 2 DM Mean age=53.3 years ± 8.6 Male/Female=2359/1508	Conventional treatment (diet and exercise to maintain FBG<15 mmol/L + sulfonylurea or insulin if FBG > 15 mmol/L or symptoms of hyperglycemia occurred) versus Intensive treatment (to maintain FBG<6.0) (sulfonylureas or insulin adjusted to maintain FBG < 6.0mmol/L with combination therapy as needed)	Sudden death (glyburide vs. conventional) (RR: 0.67, 95% CI: 0.21-2.16) Hypoglycemia (per protocol) diet=0.1% chlorpropamide=0.4% glyburide=0.6% insulin=2.3%
1998	United Kingdom Prospective Diabetes Study (UKPDS 34) [134]	Median: 10.7 years	n=1704 overweight patients with newly treated type 2 diabetes Male/Female=784/920	Conventional treatment (see above) versus Intensive treatment (see above) versus Metformin	Sulfonylurea + Metformin versus Sulfonylurea (RR: 1.96, 95% CI: 1.02-9.75)
2008	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [4]	Median: 5 years	n=11,140 Intensive glucose control (n=5571)	Intensive glycemic strategy using sulfonylurea gliclazide versus standard glycemic strategy targeting HbA1c	MACE 10.0% vs. 10.6% (HR: 0.94, 95% CI: 0.84-1.06) Severe hypoglycemia (blood glucose level ≤50 mg/dl or presence of typical

			Standard glucose control (n=5569)	defined by local guidelines	symptoms and signs of hypoglycemia without other apparent cause): 2.7% vs. 1.5% (HR: 1.86, 95% CI: 1.42-2.40)
2017	Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) [5]	Median: 4.8 years	n=3028 patients pioglitazone + metformin: n=1535 sulfonylurea + metformin (n=1493)	Pioglitazone + Metformin versus Sulfonylurea + Metformin	Primary composite outcome (all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation) Metformin plus pioglitazone versus Metformin plus sulfonylurea (RR: 0.96, 95% CI: 0.74-1.26)
2019	CAROLINA[6 7]	Median: 6.3 year	n=6042 Linagliptin (n=3023) Glimepiride (n=3010)	Linagliptin versus Glimepiride	Cardiovascular death, nonfatal MI, or nonfatal stroke (3P-MACE) (HR: 0.98, 95% CI: 0.84-.14) ≥1 Investigator-reported episode of hypoglycemia Linagliptin n (%): 320 (10.6), 2.3/100 py Glimepiride n (%): 1132 (37.7), 11.1/100 py

Chapter 2: Systematic Review

2.1 Preface to the systematic review

Given the large number of patients using sulfonylureas and the increased risk of cardiovascular events among people with type 2 diabetes, there is an urgent need to assess the arrhythmic safety of sulfonylureas. A precursory search suggested limited existing literature with substantial heterogeneity. Therefore, we anticipated this to be a systematic review rather than a meta-analysis to determine whether the use of sulfonylureas by people with type 2 diabetes is associated with increased risks of ventricular arrhythmias. To our knowledge, this is the first systematic review to examine the arrhythmic safety of sulfonylureas among people with type 2 diabetes while thoroughly assessing the risk of bias of the included studies. The results of this systematic review were reported using best practices reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist.

2.2 Sulfonylureas and the risk of ventricular arrhythmias among people with type 2 diabetes: a systematic review of observational studies

Short title: Sulfonylureas and Arrhythmias

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Keywords: Sulfonylureas, Diabetes, Arrhythmias, Systematic Review

2.2.1 ABSTRACT

Background: Sulfonylureas are associated with an increased risk of cardiovascular death among patients with type 2 diabetes. A potential mechanism involves sulfonylurea-induced ventricular arrhythmias (VA).

Objective: To determine whether the use of sulfonylureas, compared to the use of other antihyperglycemic drugs, is associated with the risk of VA (including ventricular tachycardia, ventricular fibrillation, and premature ventricular complexes), cardiac arrest and sudden cardiac death among patients with type 2 diabetes.

Methods: We systematically searched MEDLINE, EMBASE, CINAHL Plus, CENTRAL, and ClinicalTrials.gov from inception to July 2021 for observational studies reporting comparisons of sulfonylureas versus other antihyperglycemic therapies or intra-class comparisons of sulfonylureas among patients with type 2 diabetes. Two independent reviewers screened potentially relevant articles, extracted data, and assessed study quality.

Results: Our systematic review included 17 studies (1,607,612 patients). Per ROBINS-I, there were few high-quality studies (risk of bias: 2 moderate; 4 serious; 11 critical). All studies at a moderate or serious risk of bias reporting comparisons with other therapies were consistent with an increased risk of VA. Sulfonylureas were associated with a higher risk of arrhythmia versus dipeptidyl peptidase-4 inhibitors (adjusted hazard ratio [aHR]: 1.52, 95% confidence interval [CI]: 1.27-1.80) and of VA versus metformin (aHR: 1.52, 95% CI: 1.10-2.13). One moderate quality study reporting an intra-class comparison of glimepiride or glyburide versus glipizide reported inconsistent results for a composite of cardiac arrest/VA in analyses of US Medicaid claims (glimepiride: aHR=1.17, 95% CI: 0.96-1.42; glyburide: aHR=0.87, 95% CI: 0.74-1.03) and Optum claims data (glimepiride: aHR = 0.84, 95% CI: 0.65-1.08; glyburide: aHR = 1.11, 95% CI: 0.86-1.42).

Conclusions: Our systematic review suggests that among higher-quality observational studies, sulfonylurea therapy is associated with an increased risk of VA. However, we identified few methodologically rigorous studies, underscoring the need for additional real-world safety studies.

2.2.2 INTRODUCTION

The cardiovascular safety of sulfonylureas is controversial. It was first queried in the University Group Diabetes Program trial[1], in which the investigators reported an increased risk of sudden cardiac death among patients randomized to the sulfonylurea tolbutamide relative to those randomized to diet or insulin[1]. Subsequent studies have since produced disparate results regarding the cardiovascular safety of sulfonylureas[2]. While higher-quality studies have identified an increased risk of all-cause mortality and cardiovascular mortality associated with sulfonylureas, the underlying cause of this increased risk remains unclear[3-6].

One possible explanation for the observed increased risks of all-cause and cardiovascular death is an increased risk of hypoglycemia-induced ventricular arrhythmias (VA)[5 7 8]. Moreover, some studies suggest that some sulfonylureas such as glipizide inhibit re-entrant arrhythmias associated with myocardial ischemia and myocardial infarction (MI)[2]. The arrhythmic effects of sulfonylureas have been examined in several observational studies but these studies have produced heterogeneous results, and there is a need to better understand this literature and its heterogeneity. Given the large number of patients using sulfonylureas, the previously reported increased risk of cardiovascular death associated with their use, and the increased cardiovascular risk among patients with type 2 diabetes, there is an urgent need to address this important drug safety issue[9]. We therefore conducted a systematic review of observational studies examining the association between sulfonylurea use and the risk of VA among patients with type 2 diabetes.

2.2.3 METHODS

This review was conducted following a pre-specified protocol (PROSPERO #CRD42020219919) and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist[10 11].

2.2.3.1 Search Strategy

We searched Medline (OVID), EMBASE + EMBASE Classic (OVID), CINAHL Plus, and CENTRAL (Cochrane Library) databases from inception to November 5, 2020, with the search updated on July 8, 2021. Our strategy included the use of Medical Subject Headings (MeSH)

terms in MEDLINE, EMTREE terms in EMBASE, CINAHL headings for CINAHL, and keywords in all included databases for sulfonylureas and their known molecular formulations. We did not impose restrictions on language, geographic location, or study design in our search strategy. Furthermore, we conducted a hand search of references in the included studies, previous reviews, Google Scholar and ClinicalTrials.gov to identify any additional relevant studies not captured by our initial database search. The search strategies used in each database are reported in detail in **Table S1**.

2.2.3.2 Inclusion and Exclusion Criteria

We included observational studies (cohort or case-control studies) examining the association between sulfonylureas and the risk of arrhythmias among people with type 2 diabetes. The sulfonylurea group could have received any drug from the sulfonylurea class, with no requirement for the exact formulation or dose to be reported. The allowed comparators included other antihyperglycemic drugs or intra-class comparisons of sulfonylureas. In addition, we included studies that used non-use of a sulfonylurea as a comparator. Included studies were those that reported any VA (including ventricular tachycardia, ventricular fibrillation, and premature ventricular complexes; our primary endpoint), cardiac arrest, or sudden cardiac death. Studies that reported composite outcomes, including any one of these outcomes, were also included. We required that studies report at least one effect measure for an outcome of interest (odds ratio, hazard ratio, incidence rate ratio, risk ratio) or sufficient data to calculate one.

We excluded randomized controlled trials (RCTs), cross-sectional studies, previous reviews, meta-analyses, case reports, case series, conference abstracts, letters-to-the-editor, editorials, and commentaries. Conference abstracts were excluded as their results are often preliminary, and they provide insufficient information for adequate quality assessment. Case reports and case series were excluded due to the lack of a comparator group. Cross-sectional studies were excluded due to difficulties in establishing temporality.

Citations retrieved by the electronic search were imported and managed on EndNote X9. Duplicate records were removed, and the remaining records were uploaded to Rayyan (https://rayyan.qcri.org), a cloud-based systematic review management tool for reviewers to

assess study eligibility. Two reviewers (NI and HTA) independently screened titles and abstracts to identify potentially relevant articles. Any study identified as potentially relevant by either reviewer proceeded to full-text review. Both reviewers independently assessed each full-text record against the inclusion and exclusion criteria to define the final set of included studies. Disagreements regarding inclusion following the full-text review were resolved by either consensus or consulting a third reviewer (KBF).

2.2.3.3 Data Extraction

Data were independently extracted by both reviewers using a pre-specified, pilot-tested data extraction form. Disagreements were resolved by either consensus or by consulting a third reviewer. The fields of the data extraction form included entries on basic study information (study authors, geographic location, data source, citation, journal), study design characteristics (study design, study period, sample size, follow-up time), cohort characteristics (inclusion/exclusion criteria, age/demographic, comorbidities), exposure drug information (sulfonylurea molecule, dose, formulation, exposure definition), comparator drug information (specific antihyperglycemic drug, dose, formulation, exposure definition), outcomes (both crude and adjusted effect measures), and study quality variables.

2.2.3.4 Quality Assessment

Both reviewers independently assessed study quality using the Cochrane Collaboration's Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[12]. The studies were evaluated for each of the seven domains: bias due to confounding; bias in the selection of study participants (including immortal time bias); bias in the classification of interventions; bias due to departure from intended interventions; bias due to missing data; bias in the measurement of outcomes; and bias in the selection of the reported results. We then assigned each study an overall low, moderate, serious, or critical risk of bias, with the overall risk determined by the highest risk in any individual domain. Given the potential residual confounding inherent in any observational study, the highest quality a study could be assigned was a moderate risk of bias due to confounding. To be ascribed a moderate risk of bias, we required effect measures to account (by design or analytically) for the following pre-specified minimum set of confounders: age, sex,

body mass index (BMI), smoking, diabetes severity, drugs with known arrhythmic effects, and previous cardiovascular events (stroke, MI, arrhythmias). Outcomes with no consideration for confounding were ascribed a critical risk of bias.

We also evaluated the included studies for biases that are particularly frequent in the pharmacoepidemiologic literature, including time-lag bias and a depletion of susceptibles[13]. Time-lag bias may emerge from the comparison of treatments used at different stages of a disease[13 14]. Comparisons with treatments prescribed at an earlier stage (i.e., lifestyle modification) or later stage (i.e., insulin) can induce intractable confounding by disease severity. A depletion of susceptibles may occur if studies exclude individuals with a previous history of the event of interest or a high case fatality rate[15]. Any increased risk of VA associated with treatment would lead to a rapid increase in the incidence rate of arrhythmia close to treatment initiation, followed by a gradual decrease in incidence rate over time as those already vulnerable to cardiovascular challenges experience the event and are censored due to death. Thus, the most susceptible patients to the adverse event of interest will no longer be recorded and bias results. Restriction of the study cohort to new users of the drugs under investigation will prevent the inclusion of prevalent users and thus avoid this potential bias.

2.2.4 RESULTS

Our search identified 3641 studies, of which 3465 were excluded during the title and abstract screening (**Figure 2.1**). The reasons for their exclusions are described in **Appendix S1**. The remaining 176 studies underwent a full-text review. A total of 17 studies were included.

2.2.4.1 Study Characteristics

All 17 included studies were cohort studies, including a total of 1,607,612 patients (**Table 2.1**). The studies included data from Australia, Canada, France, Germany, Hungary, Israel, Italy, the Netherlands, the United Kingdom (UK) and the United States (US). Comparator therapies included other oral antihyperglycemic drugs (n=3), insulin (n=1), non-sulfonylurea use (n=10), and intra-class comparisons of sulfonylureas (n=3). The follow-up durations ranged from 1 day to 20 years.

Four studies used an as-treated exposure definition (patients were considered continuously exposed until drug discontinuation), and 13 studies used an intention-to-treat approach (patients' exposure was determined by their treatment at cohort entry). While all studies included patients using a sulfonylurea, 2 studies considered patients newly initiating pharmacotherapy with a sulfonylurea, 3 considered prevalent users of a sulfonylurea, and 12 considered both new and prevalent users of a sulfonylurea. There was one study that considered new users of a sulfonylurea following previous use of metformin.

The definition of VA was also heterogeneous (**Table 2.2**). The included studies had a broad spectrum of definitions including ventricular fibrillation, ventricular tachycardia, premature ventricular complexes, and unspecified arrhythmia. Due to sparse data, we were unable to explore the different types of arrhythmia in further detail.

2.2.4.2 Quality Assessment

After applying the ROBINS-I tool, 2 studies were assigned a moderate risk of bias[16 17], 4 studies were assigned a serious risk of bias,[18-21] and 11 studies were assigned a critical risk of bias[19 22-31] (**Table 2.3**). The domain 'risk of bias due to confounding' was one of the ROBINS-I domains most responsible for the overall risk of bias. Of 17 studies, 9 did not account for the pre-specified confounders described above[19 22-24 26-31]. Diabetes severity and BMI were the confounders most frequently not accounted for. Another domain contributing to an increased risk of bias was 'bias in selection of participants into the study'. Selection bias most frequently occurred in two ways in the included studies. A total of 11 studies examined sulfonylurea use following hospitalization (often for a cardiovascular event). Those who survived this initial event and were included in the study are likely to be systematically different from those who did not have this initial event and did not survive this initial hospitalization. This hospitalization is said to be 'a collider', and conditioning on its occurrence can result in selection bias. In such studies, observed incidence of VA may be underestimated since patients not surviving to hospitalization no longer enter the study cohort defined at hospitalization, though the magnitude of this bias is difficult to predict. Selection bias can also occur due to informative censoring in the 4 studies that used an as-treated exposure definition if drug discontinuation was related to the occurrence of cardiovascular events. None of the included studies used statistical approaches to address informative censoring

such as inverse probability of censoring weights. Finally, several studies did not describe a pre-specified study protocol, increasing the overall risk of bias due to a potential 'bias in selection of reported results'.

2.2.4.2.1 Time Lag Bias

Time-lag bias likely occurred in 10 included studies[19 21-24 26-29 31 32]. For example, one study compared the risk of VA between sulfonylurea users and insulin users[25]. Sulfonylureas are typically prescribed as first or second-line treatment for type 2 diabetes, whereas insulin is typically prescribed as last-line therapy. Given that diabetes is a disease commonly associated with poor cardiovascular outcomes, such a comparison favors the sulfonylurea group, resulting in spuriously protective associations or biasing increased risks downward. Not surprisingly, when compared with insulin, sulfonylureas appeared to be protective for VA (crude odds ratio [OR]: 0.89, 95% CI: 0.72-1.09)[25].

2.2.4.2.2 Depletion of Susceptibles Bias

A depletion of susceptible patients (prevalent user bias) likely occurred in 12 included studies[18-20 22-28 31 32]. For example, one study that may be at risk of a depletion of susceptibles defined a cohort of individuals who have survived an acute MI[25]. Exposure status included prevalent users and was collected at cohort entry following admission and recorded as either sulfonylurea or insulin use. Relative to insulin, sulfonylurea use was not associated with cardiac arrest and VA (cardiac arrest: OR = 0.96, 95% CI: 0.91-1.02; VA: OR = 0.89, 95% CI: 0.72-1.09). Patients who are susceptible to the potential arrhythmic effects of a drug and thus experience a fatal arrhythmic event shortly after treatment initiation would no longer be included in the study. Thus, any potential arrhythmic effect of sulfonylureas may be underestimated. Given the high case fatality rate of VA and cardiac arrest, depletion of susceptibles because of the inclusion of prevalent users is particularly important.

2.2.4.3 Sulfonylureas and Ventricular Arrhythmia

Sixteen studies examined the association between sulfonylurea use and the risk of VA, reporting heterogeneous results. However, both studies with reported adjusted estimates for head-to-head comparisons of sulfonylureas with other oral antihyperglycemic drugs consistently reported an

increased risk of VA. In a study at moderate risk of bias using the UK's Clinical Practice Research Datalink, sulfonylureas were associated with a higher risk of cardiac arrhythmias (including atrial fibrillation, atrioventricular block, ventricular and supraventricular tachycardias, cardiac arrest, and other unspecified conduction disorders) versus dipeptidyl peptidase-4 (DPP-4) inhibitors (adjusted hazard ratio [aHR]: 1.51, 95% CI: 1.27-1.80)[17]. In another study, this one at a serious risk of bias, the investigators used the IBM MarketScan Medicare Supplemental Database and reported an increased risk of ventricular tachycardia and ventricular fibrillation among patients using sulfonylurea monotherapy (aHR: 1.52, 95% CI: 1.10-2.13) relative to metformin[21]. However, this study included sulfonylurea users who may have previously undergone therapy using another antihyperglycemic drug and were likely to be at risk for other biases including left censoring and outcome misclassification. Among the 10 studies comparing sulfonylurea use with non-sulfonylurea use, the risk of VA varied from substantially decreased (OR: 0.31, 95% CI: 0.12-0.78)[33] to higher (OR: 3.71, 95% CI: 0.85-16.20)[34]. A total of two studies reported intra-sulfonylurea class comparisons for VA. One study reported an imprecise increased risk of VA with gliclazide relative to glyburide (OR: 1.20, 95% CI: 0.60-2.30)[18]. Another study reported no VA events among glyburide users relative to first-generation sulfonylureas including tolbutamide and carbutamide (OR: 0.00, 95% CI: 0.00-0.19)[35].

2.2.4.4 Sulfonylureas and Cardiac Arrest

Three studies compared the risk of cardiac arrest among sulfonylureas[17 25]. A study at critical risk of bias identified no difference in the unadjusted risk of cardiac arrest among users of sulfonylureas relative to insulin following admission to a hospital for acute MI (OR: 0.96, 95% CI: 0.91-1.02)[25]. A Danish case-control study that used a prospectively collected out-of-hospital cardiac arrest registry reported a decreased risk of cardiac arrest among sulfonylurea users relative to metformin (aOR: 0.6, 95% CI: 0.4-0.9). However, this study is likely to have immortal time bias and other important pharmacoepidemiologic biases, making it difficult to interpret[20]. Finally, one study at a moderate risk of bias reported discrepant results for a composite of cardiac arrest/VA with glimepiride or glyburide versus glipizide; the analysis of Medicaid claims data suggested an increased risk of cardiac arrest/VA with glimepiride (aHR: 1.17, 95% CI: 0.96-1.42) and a lower risk with glyburide (aHR: 0.87, 95% CI: 0.74-1.03); these

trends were not observed in the analysis of Optum claims data (glimepiride = aHR: 0.84, 95% CI: 0.65-1.08; glyburide = aHR: 1.11, 95% CI: 0.86-1.42)[16].

2.2.4.5 Sulfonylureas and Sudden Cardiac Death

No studies reported sudden cardiac death as an individual endpoint. One study at a moderate risk of bias using US Medicaid claims data conducted an intra-class comparison, reporting an increased risk for a composite endpoint of sudden cardiac death and fatal VA among glimepiride users (aHR = 1.33, 95% CI: 1.02-1.75 and no association among glyburide users (aHR = 0.91, 95% CI: 0.72-1.20), both relative to glipizide[16].

2.2.5 DISCUSSION

Our objective was to determine whether the use of sulfonylureas, compared to the use of other antihyperglycemic drugs, is associated with the risk of VA, cardiac arrest, and sudden cardiac death among patients with type 2 diabetes via systematic review of observational studies. Overall, we identified 17 studies that met our inclusion criteria. Across all studies, associations of VA varied from a lower unadjusted risk to a higher unadjusted risk. Many of these studies were at a substantial risk of bias from common pharmacoepidemiologic biases. Four of the five higher-quality studies suggest a higher risk of VA for sulfonylureas versus other therapies. Intra-class comparisons of sulfonylureas and VA were inconclusive, with estimates varying across studies and data sources. In addition, two of the three studies that examined cardiac arrest had important methodological limitations, with the third study reporting heterogenous results across its two included data sources. Few studies reported sudden cardiac death as an outcome.

Several of the included studies are at risk of bias, including confounding, selection bias, time-lag bias, and depletion of susceptibles. Using the ROBINS-I tool, 2 studies were assigned a moderate risk of bias, 5 studies were assigned a serious risk of bias, and 10 studies were assigned a critical risk of bias. A potential limitation observed in all studies with a serious or critical risk of bias was confounding. The majority of included studies were also at risk of time-lag bias. A total of 2 studies adjusted for a minimum set of confounders, both using propensity score-based approaches. Finally, a major limitation was the inclusion of prevalent users following an acute MI. The inclusion of prevalent users may result in a depletion of susceptibles, while conditioning

on surviving the acute MI may result in selection bias. Restricting inclusion to incident new-users of sulfonylureas and an appropriate comparator is needed to avoid these issues.

The heterogeneity amongst all included studies may reflect different pharmacodynamic and pharmacokinetic properties within the sulfonylurea drug class. Many of the studies compared sulfonylureas as a class to either non-use of sulfonylureas or another antihyperglycemic drug. The pancreas specificity of glimepiride and glyburide is lower; they may also bind to sulfonylurea receptors on cardiac myocytes and vascular smooth muscle cells[7]. Therefore, there is a possibility of extra-pancreatic effects among these sulfonylurea molecules. Subsequent observational studies should report the comparative safety of sulfonylureas against other oral antihyperglycemic drugs and explore potential molecule-specific effects.

A subsequent well-powered RCT or prospective observational study examining this issue is unlikely. Large RCTs including CAROLINA, TOSCA.IT, and ADVANCE have not reported VA as an endpoint[36-39]. Practically, RCTs are expensive and lengthy to conduct. Furthermore, with sulfonylureas off-patent, such trials are unlikely to be funded by their manufacturers. These factors contribute to resources for RCTs being allocated for newly developed therapies such as sodium-glucose transport protein 2 (SGLT-2) inhibitors instead of well-established therapies including sulfonylureas. A retrospective cohort study using a methodologically rigorous design could address this gap in the literature reporting the comparative safety of sulfonylureas for VA relative to antihyperglycemic agents used at a similar stage of type 2 diabetes. This study should abide by reporting guidelines suggested by RECORD-PE and give ample consideration for critical biases due to confounding, selection bias, time-related biases, and prevalent user bias present in the existing literature[40]. The use of an active comparator, new user design with a comparator used at a similar stage of type 2 diabetes management would avoid many of these issues[41]. Future studies should also carefully consider relevant outcomes, including VA and important sequelae such as cardiac arrest and sudden cardiac death. VA has been described to be challenging to detect in administrative health records[42]. Therefore, possible approaches include case validation or supplementing with more detailed databases that will capture some events that are not captured by administrative databases.

Our study has many strengths. First, it was conducted following a pre-specified, registered protocol. Second, we implemented a comprehensive literature search across 5 databases and double-screened all abstracts and full-texts for eligibility. Third, we undertook a comprehensive investigation of methodological biases using ROBINS-I to evaluate the quality of the included studies. This tool enabled us to discuss the existing literature's vulnerabilities to different biases such as confounding and selection bias. Fourth, this systematic review and its critical assessment of the existing literature identified important knowledge gaps for future research.

Our review also has limitations. First, the methodological heterogeneity among included studies made it inappropriate to pool results across studies via meta-analysis for any outcomes. Second, this review is vulnerable to the limitations of the included studies. Third, we were limited in our ability to directly compare results across studies given that these studies used a range of comparators and were of varying methodological rigour. Fourth, given the limited number of higher-quality studies that we identified, we were only able to draw modest substantive conclusions regarding the associations of interest. Finally, publication bias is possible due to potentially eligible studies not having been published and thus indexed in the searched databases.

2.2.6 CONCLUSIONS

Several observational studies have investigated the association between sulfonylureas and the risk of VA, cardiac arrest and sudden cardiac death, though the lower overall quality of the literature causes it challenging to interpret. Many of the existing studies are at risk of conclusion altering biases, including time lag bias and a depletion of susceptibles (prevalent user bias). Our systematic review suggests that among higher-quality observational studies, sulfonylurea therapy is associated with an increased risk of VA. Given the existence of few methodologically rigorous studies, we underscore the need for additional real-world safety studies of this drug safety issue.

2.2.7 ACKNOWLEDGEMENTS

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support awards from the FRQS. KBF is also supported by a William Dawson Scholar award from McGill University.

2.2.8 DISCLOSURES

This systematic review was presented at the International Society for Pharmacoepidemiology's (ISPE) 37th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2021 All Access).

HTA is an employee of Merck. He contributed to this study during his post-doctoral training at McGill University. The other authors have no relationships to disclose.

2.2.9 AUTHORS' CONTRIBUTIONS

KBF conceived the study. NI contributed to the study design, performed the search and the data extraction, assessed the quality of the studies, and drafted the manuscript. HTA contributed to the study design, performed the search and the data extraction, and reviewed the manuscript for important intellectual content. OHYY and AD provided clinical expertise and reviewed the manuscript for important intellectual content. KBF supervised the study and reviewed the manuscript for important intellectual content.

2.2.10 REFERENCES

1. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;19:Suppl:789-830.
2. Wheeler S, Moore K, Forsberg CW, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. *Diabetologia* 2013;56(9):1934-43. doi: 10.1007/s00125-013-2958-1 [published Online First: 2013/06/26]
3. Azoulay L, Schneider-Lindner V, Dell'aniello S, et al. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case-control study. *Pharmacoepidemiol Drug Saf* 2010;19(4):335-42. doi: 10.1002/pds.1834 [published Online First: 2010/01/07]
4. Filion KB, Douros A, Azoulay L, et al. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: A population-based cohort study. *Br J Clin Pharmacol* 2019;85(10):2378-89. doi: 10.1111/bcp.14056 [published Online First: 2019/07/06]
5. Gulliford M, Latinovic R. Mortality in type 2 diabetic subjects prescribed metformin and sulphonylurea drugs in combination: cohort study. *Diabetes Metab Res Rev* 2004;20(3):239-45. doi: 10.1002/dmrr.457 [published Online First: 2004/05/11]
6. Middleton TL, Wong J, Molyneaux L, et al. Cardiac Effects of Sulfonylurea-Related Hypoglycemia. *Diabetes Care* 2017;40(5):663-70. doi: 10.2337/dc16-1972 [published Online First: 2017/02/23]
7. Douros A, Dell'Aniello S, Yu OHY, et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *Bmj* 2018;362:k2693. doi: 10.1136/bmj.k2693 [published Online First: 2018/07/20]
8. Leonard CE, Hennessy S, Han X, et al. Pro- and Antiarrhythmic Actions of Sulfonylureas: Mechanistic and Clinical Evidence. *Trends in Endocrinology & Metabolism* 2017;28(8):561-86. doi: https://doi.org/10.1016/j.tem.2017.04.003

9. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ Open* 2018;8(7):e022768. doi: 10.1136/bmjopen-2018-022768
10. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000;283(15):2008-12. doi: 10.1001/jama.283.15.2008 [published Online First: 2000/05/02]
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
12. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj* 2016;355:i4919. doi: 10.1136/bmj.i4919 [published Online First: 2016/10/14]
13. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiology and Drug Safety* 2020;29(9):1101-10. doi: 10.1002/pds.5083
14. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care* 2012;35(12):2665-73. doi: 10.2337/dc12-0788 [published Online First: 2012/11/23]
15. Miettinen OS, Caro JJ. Principles of nonexperimental assessment of excess risk, with special reference to adverse drug reactions. *J Clin Epidemiol* 1989;42(4):325-31. doi: 10.1016/0895-4356(89)90037-1 [published Online First: 1989/01/01]
16. Dhopeshwarkar N, Brensinger CM, Bilker WB, et al. Risk of sudden cardiac arrest and ventricular arrhythmia with sulfonylureas: An experience with conceptual replication in two independent populations. *Sci* 2020;10(1):10070. doi: https://dx.doi.org/10.1038/s41598-020-66668-5
17. Gamble JM, Thomas JM, Twells LK, et al. Comparative effectiveness of incretin-based therapies and the risk of death and cardiovascular events in 38,233 metformin monotherapy users. *Medicine (Baltimore)* 2016;95(26):e3995. doi: 10.1097/MD.0000000000003995 [published Online First: 2016/07/02]
18. Davis TM, Parsons RW, Broadhurst RJ, et al. Arrhythmias and mortality after myocardial infarction in diabetic patients. Relationship to diabetes treatment. *Diabetes Care* 1998;21(4):637-40.

19. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1999;33(1):119-24.
20. Eroglu TE, Jia L, Blom MT, et al. Sulfonylurea antidiabetics are associated with lower risk of out-of-hospital cardiac arrest: Real-world data from a population-based study. *British Journal of Clinical Pharmacology* 2021
21. Ostropolets A, Elias PA, Reyes MV, et al. Metformin Is Associated With a Lower Risk of Atrial Fibrillation and Ventricular Arrhythmias Compared With Sulfonylureas: An Observational Study. *Circulation: Arrhythmia and Electrophysiology* 2021;14(3):e009115.
22. Aronson D, Mittleman MA, Burger AJ. Effects of sulfonylurea hypoglycemic agents and adenosine triphosphate dependent potassium channel antagonists on ventricular arrhythmias in patients with decompensated heart failure. *Pacing Clin Electrophysiol* 2003;26(5):1254-61.
23. Danchin N, Charpentier G, Ledru F, et al. Role of previous treatment with sulfonylureas in diabetic patients with acute myocardial infarction: results from a nationwide French registry. *Diabetes Metab Res Rev* 2005;21(2):143-9.
24. Halkin A, Roth A, Jonas M, et al. Sulfonylureas are not associated with increased mortality in diabetics treated with thrombolysis for acute myocardial infarction. *Journal of Thrombosis and Thrombolysis* 2001;12(2):177-84. doi: 10.1023/A:1012979622945
25. Jollis JG, Simpson RJ, Jr., Cascio WE, et al. Relation between sulfonylurea therapy, complications, and outcome for elderly patients with acute myocardial infarction. *American Heart Journal* 1999;138(5):S376-S80.
26. Klamann A, Sarfert P, Launhardt V, et al. Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). *Eur Heart J* 2000;21(3):220-9.
27. Lichstein E, Kuhn LA, Goldberg E, et al. Diabetic treatment and primary ventricular fibrillation in acute myocardial infarction. *Am J Cardiol* 1976;38(1):100-2. doi: 10.1016/0002-9149(76)90069-2 [published Online First: 1976/07/01]

28. Lomuscio A, Vergani D, Marano L, et al. Effects of glibenclamide on ventricular fibrillation in non-insulin-dependent diabetics with acute myocardial infarction. *Coron Artery Dis* 1994;5(9):767-71.
29. Pogatsa G, Koltai MZ, Balkanyi I, et al. The effect of various hypoglycaemic sulphonylureas on the cardiotoxicity of glycosides and arrhythmogenic activity due to myocardial ischaemia. *Acta Physiol Hung* 1988;71(2):243-50.
30. Pogatsa G, Koltai MZ, Jermendy G, et al. The effect of sulphonylurea therapy on the outcome of coronary heart diseases in diabetic patients. *Acta Med Hung* 1992;49(1-2):39-51.
31. Rana JS, Mukamal KJ, Nesto RW, et al. Effect of diabetes mellitus and its treatment on ventricular arrhythmias complicating acute myocardial infarction. *Diabet Med* 2005;22(5):576-82.
32. Zeller M, Danchin N, Simon D, et al. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010;95(11):4993-5002. doi: https://dx.doi.org/10.1210/jc.2010-0449
33. Aronson D, Mittleman MA, Burger AJ. Effects of sulfonylurea hypoglycemic agents and adenosine triphosphate dependent potassium channel antagonists on ventricular arrhythmias in patients with decompensated heart failure. *PACE - Pacing and Clinical Electrophysiology* 2003;26(5):1254-61. doi: 10.1046/j.1460-9592.2003.t01-1-00177.x
34. Pogatsa G, Koltai MZ, Balkanyi I, et al. The effect of various hypoglycaemic sulphonylureas on the cardiotoxicity of glycosides and arrhythmogenic activity due to myocardial ischaemia. *Acta Physiologica Hungarica* 1988;71(2):243-50.
35. Pogatsa G, Koltai MZ, Jermendy G, et al. The effect of sulphonylurea therapy on the outcome of coronary heart diseases in diabetic patients. *Acta Med Hung* 1992;49(1-2):39-51. [published Online First: 1992/01/01]
36. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *Jama* 2019;322(12):1155-66. doi: 10.1001/jama.2019.13772 [published Online First: 2019/09/20]

37. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular outcome trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA®). *Diabetes and Vascular Disease Research* 2015;12(3):164-74.
38. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 2017;5(11):887-97. doi: 10.1016/s2213-8587(17)30317-0 [published Online First: 2017/09/18]
39. Patel A, Chalmers J, Poulter N. ADVANCE: action in diabetes and vascular disease. *J Hum Hypertens* 2005;19 Suppl 1:S27-32. doi: 10.1038/sj.jhh.1001890 [published Online First: 2005/08/03]
40. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports* 2015;2(4):221-28.
41. Hennessy S, Leonard CE, Palumbo CM, et al. Diagnostic codes for sudden cardiac death and ventricular arrhythmia functioned poorly to identify outpatient events in EPIC's General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2008;17(12):1131-6. doi: 10.1002/pds.1632 [published Online First: 2008/07/10]

Table 2.1. Study characteristics of comparative studies evaluating arrhythmic effects of sulfonylureas

Study	Study Design	Exposure Definition	n	Data origin	Study Period	Patient Population	Effect Measure
Aronson 2003	Post-hoc RCT analysis	ITT - Use at cohort entry	255	USA	1998-1999	Post decompensated CHF	aOR
Danchin 2005	Prospective cohort	ITT - Use at cohort entry	2320	France	2000	Post-Acute MI	OR
Davis 1998	Retrospective cohort	ITT - 28 days use at cohort entry	5715	Australia	1984-1993	Post-Acute MI	aOR
Dhopeshwarkar 2020	Retrospective cohort	AT - Use at cohort entry	491940	USA	1999-2012	Insurance Claims & USA Medicaid	aHR
Eroglu 2021	Retrospective cohort	ITT – 90 day exposure assessment window	916	The Netherlands	2005-2011	Cardiac Arrest Registry	aOR
Gamble 2016	Retrospective cohort	AT - Use at cohort entry	38233	UK	2000-2016	UK General Practice	aHR
Garratt 1999	Retrospective cohort	ITT - Use at cohort entry	185	USA	2007-2012	Post-Acute MI	OR†
Halkin 2001	Post-hoc RCT analysis	ITT - Ever-use at cohort entry	245	Israel	1985-1994	Post-Acute MI	OR†
Jollis 1999	Retrospective cohort	ITT - Use at cohort entry	207419	USA	1985-1994	Post-Acute MI	OR†
Klamann 2000	Retrospective cohort	ITT - Ever-use at cohort entry	602	Germany	1991-1997	Post-Acute MI	OR†
Lichstein 1976	Retrospective cohort	ITT - Ever-use at cohort entry	265	USA	1971-1974	Post-Acute MI	OR†
Lomuscio 1994	Retrospective cohort	ITT - 1 month use at cohort entry	232	Italy	Not Reported	Post-Acute MI	OR
Ostropelets 2021	Retrospective Cohort	AT – Use at cohort entry	232269	USA	2010-2018	Insurance Claims	aHR
Pogatsa 1988	Prospective cross-over cohort	AT - 3 months use at cohort entry	557	Hungary	Not Reported	Digitalized Patients	OR†
Pogatsa 1992	Retrospective cohort	ITT - Use at cohort entry	1040	Hungary	1967-1991	Outpatient Clinic	OR†
Rana 2005	Prospective cohort	ITT - Use at cohort entry	3882	USA	1989-1996	Post-Acute MI	aOR
Zeller 2010	Prospective cohort	ITT - Use at cohort entry	1310	France	2005	Post-Acute MI	OR†

Abbreviations: aOR: Adjusted odds ratio; AT: As Treated; CHF: Congestive heart failure; †: Hand-calculated odds ratio; HR: Hazards ratio; ITT: Intention to treat; MI: Myocardial infarction; OR: Crude Odds ratio;

Table 2.2. Effect estimates of ventricular arrhythmia and cardiac arrest in comparative studies evaluating the association between sulfonylureas and the risk of ventricular arrhythmias.

Study	Sulfonylurea	Comparator	Sulfonylurea (n)	Comparator (n)	Outcome	Effect Measure	Point Estimate	95% CI	Risk of Bias[a]
Sulfonylurea versus non-sulfonylurea use									
Aronson 2003	Sulfonylurea	Non Sulfonylurea Use	34	66	PVC	aOR	0.31	0.12-0.78	Critical
Danchin 2005	Sulfonylurea	Non Sulfonylurea Use	215	272	VF	OR	0.38	0.14-1.06	Critical
Garratt 1999	Sulfonylurea	Non Sulfonylurea Use	67	118	VT and/or VF	hOR	1.31	0.66-2.62	Critical
Halkin 2001	Sulfonylurea	Non Sulfonylurea Use	120	17	VT and/or VF	hOR	0.30	0.08-1.08	Critical
Klamann 2000	Glyburide	Non Sulfonylurea Use	76	89	VA	hOR	1.69	0.56-5.13	Critical
Lichstein 1976	Sulfonylurea	Non Sulfonylurea Use	151	60	Primary VF	hOR	1.84	0.39-8.70	Critical
Lomuscio 1994	Glyburide	Non Sulfonylurea Use	106	126	VT and/or VF	OR	0.40	0.16-0.99	Critical
Pogatsa 1988	Sulfonylurea	Non Sulfonylurea Use	80	66	PVC	hOR	3.71	0.85-16.20	Critical
Rana 2005	1st Generation Sulfonylurea	Non Sulfonylurea Use	62	3068	VA	aOR	0.91	0.39-2.51	Critical
Zeller 2010	Sulfonylurea	Non Sulfonylurea Use	459	295	VT	hOR	1.56	0.54-4.47	Serious
Sulfonylurea versus other therapies									
Eroglu 2021	Sulfonylurea	Metformin	215	385	SCA	aOR	0.6	0.4-0.9	Serious
Gamble 2016	Sulfonylurea	DPP-4 Inhibitors	25916	6213	All Arrhythmia	aHR	1.52	1.28-1.82	Moderate
Jollis 1999	Sulfonylurea	Insulin	25035	18935	VT	hOR	0.89	0.72-1.09	Critical
Jollis 1999	Sulfonylurea	Insulin	25035	18935	SCA	hOR	0.96	0.91-1.02	Critical
Gamble 2016	Sulfonylurea	DPP-4 Inhibitors	25916	6213	All Arrhythmia	aHR	1.52	1.28-1.82	Moderate
Ostropelets 2021	Sulfonylurea	Metformin	136,144	96,125	VT and/or VF	aHR	1.52	1.10-2.13	Serious
Sulfonylurea intra-class comparison									
Eroglu 2021	Glyburide	Glimepiride	41	222	SCA	aOR	1.3	0.6-2.7	Serious
Eroglu 2021	Gliclazide	Glimepiride	117	222	SCA	aOR	0.5	0.3-0.9	Serious
Eroglu 2021	Tolbutamide	Glimepiride	148	222	SCA	aOR	0.6	0.3-1	Serious
Davis 1998	Gliclazide	Glyburide	111	110	VT	aOR	1.20	0.6-2.3	Serious
Dhopeshwarkar 2020[b]	Glimepiride	Glipizide	124,354	268,094	SCA/VA	aHR	1.17	0.96-1.42	Moderate
Dhopeshwarkar 2020[b]	Glyburide	Glipizide	231,958	268,094	SCA/VA	aHR	0.87	0.74-1.03	Moderate
Dhopeshwarkar 2020[b]	Glyburide	Glipizide	231,958	268,094	SCD/Fatal VA	aHR	0.91	0.72-1.2	Moderate
Dhopeshwarkar 2020[b]	Glimepiride	Glipizide	124,354	268,094	SCD/Fatal VA	aHR	1.33	1.02-1.75	Moderate

Dhopeshwarkar 2020[c]	Glimepiride	Glipizide	59246	206,034	SCA/VA	aHR	0.84	0.65-1.08	Moderate
Dhopeshwarkar 2020[c]	Glyburide	Glipizide	134,677	206,034	SCA/VA	aHR	1.11	0.86-1.42	Moderate
Pogatsa 1992	Glyburide	1st Generation Sulfonylurea	144	227	PVC	hOR	0.00	0.00-0.19	Critical

Abbreviations: aOR: Adjusted odds ratio; CI: Confidence Interval; DPP-4 Inhibitors: Dipeptidyl Peptidase-4 Inhibitors; hOR: Hand-calculated odds ratio; HR:Hazards ratio; MI: Myocardial infarction; OR: Odds ratio; PVC: Premature Ventricular Complexes; SCA: Cardiac arrest; SCD: Sudden cardiac death; VA: Ventricular Arrhythmia; VF: Ventricular fibrillation; VT: Ventricular Tachycardia;

[a]Risk of Bias according to overall assessment derived from seven domains of Risk of Bias in Non-Randomized Studies of Intervention tool (ROBINS-I)

[b]Dhopeshwarkar 2020: Medicaid Claims analysis

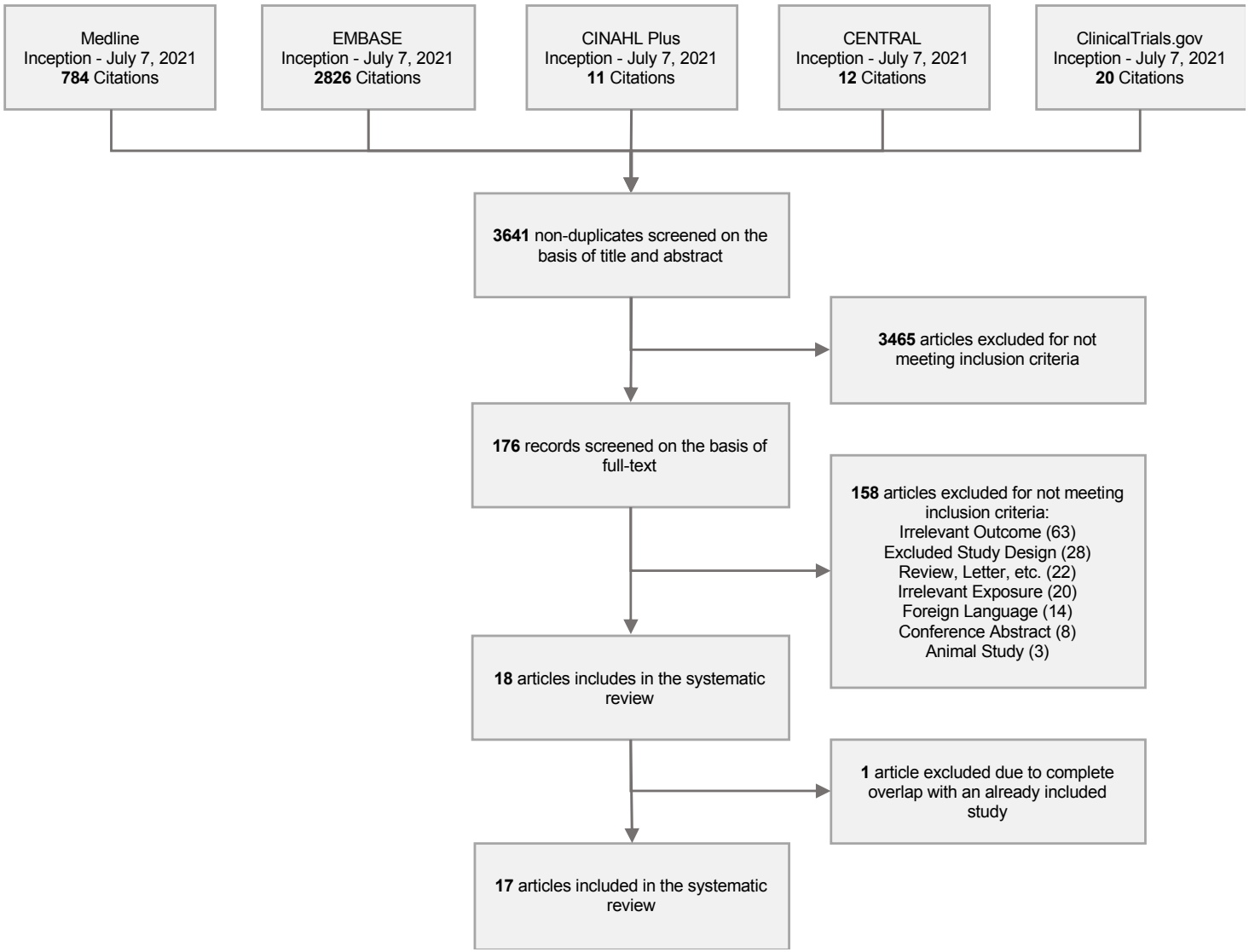
[c]Dhopeshwarkar 2020: Optum Clinformatics analysis

Table 2.3. ROBINS-I quality assessment and assessment of additional biases of observational studies examining the association between sulfonylureas and the risk of ventricular arrhythmias.

Study	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall	Time-Lag Bias	Depletion of Susceptibles
Aronson 2003	Critical	Low	Serious	NI	Low	Moderate	Low	Critical	X	X
Danchin 2005	Critical	Critical	Critical	Moderate	NI	Low	Serious	Critical	X	X
Davis 1998	Serious	Serious	Serious	NI	NI	Moderate	Serious	Serious		X
Dhopeshwarkar 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate		
Eroglu 2021	Serious	Serious	Moderate	Moderate	Moderate	Low	Low	Serious		X
Gamble 2016	Moderate	Low	Low	Low	Low	Low	Low	Moderate		
Garratt 1999	Serious	Serious	Moderate	Low	NI	Moderate	Serious	Serious	X	X
Halkin 2001	Critical	Serious	Serious	NI	Low	Moderate	Low	Critical	X	X
Jollis 1999	Serious	Critical	Serious	NI	Serious	Low	Serious	Critical		X
Klamann 2000	Critical	Critical	Serious	NI	Low	Low	Serious	Critical	X	X
Lichstein 1976	Critical	Serious	Moderate	NI	Low	Low	Serious	Critical	X	X
Lomuscio 1994	Critical	Critical	Serious	NI	NI	Moderate	Low	Critical	X	X
Ostropelets 2021	Serious	Serious	Moderate	Moderate	Low	Low	Low	Serious	X	
Pogatsa 1988	Critical	Serious	Moderate	Low	Low	Moderate	Serious	Critical	X	
Pogatsa 1992	Critical	Low	Moderate	Low	Low	Moderate	Serious	Critical		
Rana 2005	Serious	Critical	Serious	NI	Serious	Low	Low	Critical	X	X
Zeller 2010	Serious	Moderate	Moderate	NI	Low	Low	Moderate	Serious	X	X

2.2.11 FIGURE LEGEND

Figure 2.1 PRISMA flow diagram describing systematic literature search for observational studies examining the association between sulfonylureas as therapy for type 2 diabetes and the risk of ventricular arrhythmia, cardiac arrest, or sudden cardiac death



Supplemental Table 2.2.1 Targeted search strategy for the selection of studies

Database	Search Strategy
OVID Medline & OVID Embase + Embase Classic	1. (sulfonylurea* or sulphonylurea* or sulphonyl urea* or sulfonyl urea*).mp. or exp Sulfonylurea Compounds/ 2. (glimepiride* or glibenclamide* or glyburide* or glibornuride* or gliclazide* or glipizide* or gliquidone* or glisozepide* or glyclopyramide* or acetohexamide* or carbutamide* or chlorpropamide* or glycyclamide* or tolcyclamide* or metahexamide* or tolazamide* or tolbutamide*).mp. 3. (arrhythm* or arrythm*).mp. or exp Arrhythmias, Cardiac/ 4. tachycardia*.mp. or exp Tachycardia, Ventricular/ 5. tachyarrhythmia*.mp. 6. (dysrhythm* or dysrhythm* or dysrrhythm* or dysrrythm*).mp. 7. sudden cardiac death.mp. or exp death, sudden/ 8. Heart rate*.mp. or exp heart rate/ 9. Fibrillation*.mp. or exp Ventricular Fibrillation/ 10. (sudden cardiac arrest or cardiac arrest or heart arrest).mp. or exp Heart Arrest/ 11. ventricular dysfunction*.mp. or exp Ventricular Dysfunction/ 12. angiopath*.mp. or exp Diabetic Angiopathies/ 13. 1 or 2 14. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 15. (diabet* or t2dm or dm or hyperglycem*).mp. or exp Diabetes Mellitus, Type 2/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 16. 13 and 14 and 15
CINAHL Plus	1. (MH "Sulfonylurea Compounds+") OR "Sulfonylurea" OR "Sulphonylurea" 2. (MH "Arrhythmia, Ventricular+") OR "ventricular arrhythmia" 3. "sudden cardiac death" OR (MH "Death, Sudden, Cardiac" 4. (MH "Heart Arrest+") OR "sudden cardiac arrest" 5. S1 AND (S2 OR S3 OR S4)
CENTRAL (Cochrane Library)	1. (sulfonylurea* OR sulphonylurea*) AND (ventricular arrhythmia* OR sudden NEXT cardiac NEXT death OR cardiac NEXT arrest)
U.S. National Library of Medicine ClinicalTrial.gov	**Intervention/Treatment:** sulfonylurea OR sulphonylurea **Outcome Measure:** arrhythmia OR death OR arrest

Chapter 3: Transition

Our systematic review identified 17 observational studies examining the association between sulfonylurea use and arrhythmic events among patients with type 2 diabetes. I found that many of the studies had important methodological limitations and are at serious or critical risk of bias, including confounding, selection bias, time-lag bias, and a depletion of susceptibles. Consequently, there remains a need for large, methodologically-rigorous, population-based studies examining this issue to improve our understanding of the arrhythmic safety profile of this drug class that is commonly used for the management of type 2 diabetes.

To help fulfil this need, I designed an original research study described in the subsequent chapters of this thesis. I used the Clinical Practice Research Database (CPRD) linked to Hospital Episode Statistics Admitted Patient Care (HES) and Office for National Statistics Vital Statistics (ONS) databases to define a cohort of individuals initiating type 2 diabetes pharmacotherapy with either sulfonylurea or metformin monotherapy. I used an active comparator, new user design with an as-treated exposure definition to examine the risk of VA among patients initiating pharmacotherapy with a sulfonylurea relative to metformin. Our choice of study design allowed us to minimize the risk of time-lag bias by establishing a cohort of new users of these drugs in addition to the comparison of the most commonly used first-line therapies for type 2 diabetes. A detailed discussion of the methods of this study is found in Chapter 4, and the manuscript describing the study is found in Chapter 5.

Chapter 4: Detailed Description of Methods Used in Pharmacoepidemiologic Study

This chapter provides a detailed description of the methods used in our Clinical Practice Research Datalink (CPRD) cohort study described in Chapter 5. This chapter includes descriptions of the CPRD, cohort creation, and outcome and covariate definitions. Furthermore, I describe choices I made to minimize potential biases through inverse probability of treatment weighting (IPTW) and multiple imputation. In addition, I describe sensitivity analysis to explore the robustness of study results.

4.1 Data Source

I used the CPRD Aurum as the data source for this study[1]. Many observational studies now use large databases that contain administrative health records[2]. The CPRD is a United Kingdom (UK) database of anonymized medical records collected from in a primary care setting[3]. This database was first established in 1987 as the Value Added Medical Products dataset. It was later rebranded the General Practice Research Database in 1993 and later as the CPRD in 2012.

The CPRD's purpose has primarily remained the same, providing access to medical records for research purposes. For many years, CPRD GOLD was the main product offered by the CPRD[3]. However, starting in 2018, the CPRD introduced access to CPRD Aurum[4]. This new offering includes data from the EMIS health record management software. In contrast, CPRD GOLD collects patient records entered by general practitioners using the Vision software system[5]. Despite this change in platform, data are derived from a substantially similar UK patient group and have been found to have similar correctness for commonly studied diseases such as type 2 diabetes, hyperlipidemia, and anemia diagnoses[6]. Over time, practices have been shifting from Vision to EMIS, resulting in a substantial increase in the size of CPRD Aurum in recent years. The CPRD is one of the most commonly used data sources for medical research; it has been the data source for over 2800 publications[1].

CPRD Aurum contains comprehensive data on demographics, diagnoses, prescriptions, and referrals on over 40 million patients from 1,491 general practices in the UK, representing 20% of

UK's population[4 7]. A total of 98% of the UK population is registered with a general practitioner, and visits are reimbursed by the National Health Service (NHS)[8]. General practitioners (GPs) are designated the primary point of contact for all non-emergency medical visits, which are then either managed in primary care or referred to secondary care as necessary[3]. Thus, GPs are known as the gatekeepers of the UK's healthcare system and are responsible for prescribing and renewing prescriptions for their patients. GPs are encouraged through prompts and financial incentives to routinely report data from primary care practices in England, allowing the CPRD to hold high-quality data on diagnoses, symptoms, prescriptions, referrals, and laboratory tests (i.e., HbA1c)[3]. The CPRD has been validated for representativeness relative to UK census data[9]. Patients recorded in the CPRD were found to have similar age, sex, and ethnicity distributions to the general population[4].

The CPRD GOLD and Aurum can also be linked with several National Health Service data holdings such as secondary care datasets, including Hospital Episode Statistics (HES) Admitted Patient Care hospitalization data and Office for National Statistics (ONS) vital statistics[10 11]. HES contain hospitalization data, allowing researchers to collect data dimensions, including emergency and planned hospital admissions. ONS vital statistics include the date and coded cause of death for the population based on the death certificate. Together, these linked data offer a more comprehensive record of a patient's healthcare service usage. HES use the International Classification of Diseases, 10th Revision (ICD-10) and the Office of Population, Censuses and Surveys' Classification of Surgical Operations and Procedures (OPCS) coding systems. Causes of death recorded in ONS were recorded using ICD-9 codes until 2000 and ICD-10 codes 2001 onwards.

Routinely collected data from primary care including diagnoses, symptoms, prescriptions, referrals and laboratory tests are recorded in both CPRD products by GPs through documentation in the electronic health system for each patient visit. In CPRD Aurum, data on diagnosis and procedures use a combination of SNOMED CT (UK edition), Read Version 2, and local EMIS Web codes[4 5]. The Read code system is a hierarchical clinical classification system consisting of five-character alphanumeric codes that is specific to the UK. Although the hierarchical organization system is convenient for referencing, their inter-code dependencies limit their

flexibility[5]. Starting in April 2018, GP practices started shifting to SNOMED CT in place of Read Codes. Rather than a hierarchical system as in Read codes, SNOMED codes have a unique 'concept ID' indexed to clinical terms, which do not contain any implicit meaning. SNOMED codes' benefits include consistency of clinical terms across different care settings, more flexible data maintenance, and improved user experience. In some circumstances, SNOMED codes can also be indexed to their corresponding hierarchical arranged Read codes. Prescriptions in the CPRD Aurum are coded using the Dictionary of Medicines and Devices (DM+D). Each product code is also associated with the British National Formulary (BNF) chapter to which the product belongs and a unique product code specific to the CPRD. Although prescription data issued by the GPs are generally reliable, there are certain limitations. For example, information on dispensing, products prescribed by a specialist, and over-the-counter medication use are not recorded.

Data from the CPRD have been used for many pharmacoepidemiologic studies. Consequently, there have been many efforts to establish sets of codes validated for the CPRD[12]. Some systematic reviews have established validated definitions for CPRD GOLD but not for the more recently released CPRD Aurum[12]. Although there are certain repositories where code lists for previously published electronic medical record studies are made available, less commonly studied exposures and outcomes do not generally have standardized definitions[13 14]. Furthermore, the validity of definitions may vary depending on the specific variable of interest. The impact of missing data and outcome misclassification requires important consideration and rigorous sensitivity analyses. Nevertheless, data from the CPRD have been demonstrated to have high validity for both prescriptions and diagnoses. Prescription drugs that are prescribed on a long-term basis with refills are especially noted to have high validity[15]. A meta-analysis of 212 publications reporting validation analyses for CPRD GOLD confirmed 89% of computerized diagnoses[16].

4.2 Study Population

For this retrospective cohort study, I used an active comparator, new-user design. I included all patients who received a prescription for either metformin or a sulfonylurea as their first-ever

antihyperglycemic drug between April 1, 1998 and December 30, 2019[17]. Patients entered the study cohort on the date of their first prescription for a sulfonylurea or metformin. I then excluded patients with: 1) age <18 years; 2) database history <365 days (to exclude prevalent users and to ensure sufficient observation time for the assessment of comorbidities); 3) a previous prescription for an antihyperglycemic drug; 4) a prescription for both metformin and a sulfonylurea or a prescription for any antihyperglycemic drug other than metformin or a sulfonylurea on the day of cohort entry; 5) a previous diagnosis of polycystic ovary syndrome (other indication for metformin use); 6) a diagnosis of gestational diabetes in the year before cohort entry; and 7) no recorded follow-up. Patients were followed from cohort entry until an event or censoring due to study drug discontinuation, initiation of another antihyperglycemic drug, death, departure from the CPRD, end of linkage to HES or ONS, or end of the study period (December 30, 2019), whichever occurred first.

4.3 Definitions

4.3.1 Exposure

I used an as-treated exposure definition in the primary and secondary analyses. Patients analyzed using an as-treated approach accrue exposure time during the duration of the prescription and subsequent refills. The end of the prescription is usually estimated using an algorithm including the days' supply and a grace period to account for less than perfect adherence. Conditioning on patients who stay on treatment may induce selection bias due to informative censoring. To examine this potential issue, I used inverse probability of censoring weighting (IPCW) in a sensitivity analysis. An intention-to-treat analysis, which classifies exposure according to the therapy receive at cohort entry, can offer some reassurance regarding the potential consequences of informative censoring due to drug discontinuation, effect measures obtained using this approach are at higher risk of bias due to increasing misclassification of exposure over time[18]. For this reason, it is often recommended to truncate follow-up time for analyses that use an intention-to-treat approach (e.g., a maximum follow-up of 6 months or 1 year).

Patients in the primary analysis were classified according to their cohort-entry-defining antihyperglycemic medication in one of two mutually exclusive exposure categories: 1) current

use of sulfonylureas; 2) current use of metformin (the reference category). Patients were considered continuously exposed if one prescription overlapped the date of the next prescription, using a 30-day grace period in the event of non-overlapping prescriptions. The as-treated approach was chosen as the primary approach because the outcomes of interest were acute cardiovascular events. To test this assumption, I did a sensitivity analysis using an intention-to-treat exposure definition. In this analysis, patients were followed from cohort entry until the occurrence of an outcome, death from any cause, one year of follow-up (to avoid the exposure misclassification and dilution of effect that is inherent to an intention-to-treat analysis), or end of the study period (December 30, 2019), whichever occurred first. Exposure was time-fixed, and patients were not allowed to change their exposure (e.g., metformin to sulfonylurea or vice versa). Such switching may be an indicator for diabetes severity or could be related to an adverse drug effect. Switches within sulfonylureas (e.g., glyburide to glimepiride) were permitted in the primary analysis. In molecule-specific secondary analyses, patients were not permitted to switch their initial drug (e.g., glyburide to glimepiride) and were censored at the time of switching from one sulfonylurea to another. The remaining secondary analyses used the same exposure definition as the primary analysis.

4.3.2 Outcome

Our primary outcome was time to first VA (fatal and non-fatal), including ventricular tachycardia, ventricular fibrillation, and ventricular flutter. Our secondary endpoints included cardiac arrest and fatal VA. Arrhythmias have been reported to be difficult to capture in administrative data[13]. I measured outcomes based on recorded diagnoses in CPRD Aurum, HES, or ONS. I identified records with the corresponding SNOMED codes in CPRD Aurum for patients with a diagnosis of VA. Events were defined by ICD-10 codes I47.0, I47.2, I49.0, I49.01, I49.02, or I49.3 in HES (in the primary or secondary position) or in ONS (where these codes were listed as the underlying cause of death). Until 2000, ICD-9 codes were used in ONS. Therefore, fatal VA events were additionally identified with ICD-9 codes 427.1, 427.4, 427.41, or 427.42 in ONS. The event date was the date of diagnosis for CPRD-defined events, the date of admission for HES-defined events, and the date of death for ONS-defined events. Diagnostic codes in the CPRD and HES for VA/sudden cardiac death have been reported to have a positive predictive value of 93%[13].

Secondary outcomes were cardiac arrest and fatal VA. For cardiac arrest, an event was defined by an ICD-10 code for cardiac arrest (I46.x, I46.1, I46.2, I46.8, I46.9) in either the primary or secondary position in the HES. For fatal VA, I identified records in ONS with the corresponding ICD-10 code (I47.0, I47.2, I49.0, I49.01, I49.02, I49.3) or ICD-9 code (427.1, 427.4, 427.41, 427.42) listed as the cause of death.

4.3.3 Variable Definitions

A major undertaking of this study was creating variable definitions for exposure, outcomes, covariates, and laboratory data. Developing a valid set of operational variable definitions using diagnostic and product codes is essential to limit misclassification. Our group has had substantial experience developing and maintaining definitions for variables in previous studies using CPRD GOLD. Conventionally, group members can adapt previously developed definitions. However, diagnoses in CPRD Aurum are recorded using SNOMED codes rather than Read codes. For this reason, I defined most variables used in this thesis. To do so, I implemented a systematic process using existing CPRD GOLD definitions to develop CPRD Aurum definitions. First, I created operational variable definitions by systematically searching the CPRD code browser to identify all relevant SNOMED codes. I then cross-referenced the Read codes associated with the SNOMED codes with the existing CPRD GOLD definitions to ensure consensus between these definitions. After identifying all applicable Read codes or product codes in the code browser, I compiled them to finalize the variable definition. Variable definitions for outcome variables were constructed in a similar manner using ICD-10 codes. Any discrepancies were resolved by consulting a member of the research group.

Drug definitions were created by searching the CPRD code browser for British National Formulary category, generic drug names, and trade names. Drugs in the UK are occasionally marketed under different trade names than those in North America. To supplement my initial search of trade names for products available in the UK, I compiled and searched trade names from previously developed definitions.

4.4 Statistical Analysis

4.4.1 Primary Analysis

My primary analysis was to compare the rates of VA among patients using sulfonylurea monotherapy versus metformin monotherapy as initial treatment for type 2 diabetes. I compared the baseline characteristics of exposure groups using traditional descriptive statistics. Discrete data was presented as counts with percentages, and continuous data was presented as means with standard deviations or, in the case of skewed distributions, as medians with inter-quartile ranges. I then used standardized differences to compare characteristics across groups, with standardized differences greater than 0.1 considered to be important. Crude incidence rates and corresponding 95% confidence intervals (CIs) for the primary and secondary endpoints were estimated overall and by exposure group using Poisson regression. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs of the association between VA and current use of sulfonylurea versus metformin with follow-up duration as the underlying time axis. The Cox proportional hazards model assumes the proportionality of hazards among both exposure groups. This assumption may be tested by including an interaction term between time and exposure in the Cox proportional hazards model. Analyses with non-proportional hazards may be repeated with follow-up time stratified by quartile based on the distribution of the exposure cohort. To ensure the exchangeability between the sulfonylurea and metformin treatment groups, I used IPTW using a propensity score. The included covariates are listed in the manuscript. A more thorough discussion of IPTW is provided below.

4.4.2 Secondary Analyses

I conducted 7 secondary analyses. First, I used a Cox proportional hazards model to assess the potential presence of a duration-response relationship between hospitalization for VA and sulfonylurea monotherapy versus metformin monotherapy as initial treatment for type 2 diabetes by stratifying person-time into the following duration categories: 0-6 months, 6 months-1 year, 1-2 years, more than 2 years. Second, since sulfonylurea drugs vary in their pharmacology and potentially in their cardiotoxic risk, I applied the Cox proportional hazards models for sulfonylurea molecule (glyburide, gliclazide, glipizide, and glimepiride; used in monotherapy) versus metformin monotherapy. Patients were censored at the time of switching from one sulfonylurea to another. In addition, I grouped sulfonylurea molecules by pancreatic sulfonylurea

receptor specificity, applying the Cox proportional hazards model for both pancreas-specific molecules (gliclazide and glipizide) and non-pancreas-specific molecules (glimepiride and glyburide) used in monotherapy versus metformin monotherapy. In this analysis, patients were permitted to switch within the pancreas-specific molecule group or within the non-pancreas-specific molecule group but were censored at the time of switching from one group to another. Third, I applied the Cox proportional hazard models to determine whether demographic characteristics (age, sex), baseline history of cardiovascular disease (CVD), and level of glycemic control (last HbA1c measure before cohort entry) modified the association between current use sulfonylureas, relative to metformin, and VA. Finally, I repeated our primary analysis for the outcomes of cardiac arrest and fatal VA.

4.4.3 Inverse Probability of Treatment Weights

Sulfonylureas are now commonly indicated for more advanced forms of diabetes relative to our chosen comparator, metformin[19]. However, they have historically been indicated as first-line therapy. Furthermore, sulfonylureas are also used as second-line therapy or for individuals with a contraindication to metformin (individuals with liver, cardiac or kidney dysfunction), severe hyperglycemia, an inherited monogenic form of diabetes known as maturity-onset diabetes of the young, or as add-on therapy to metformin[20-24]. These important differences in their indication may confound the relationship between sulfonylurea use versus metformin use and the risk of arrhythmias. In well-done randomized controlled trials (RCTs), randomization ensures exchangeability on important measured and unmeasured confounders. However, observational studies must rely on design and analytical strategies to reduce potential confounding[25].

I used IPTW using a propensity score to increase exchangeability between the sulfonylurea and metformin treatment groups. I used a logistic model to estimate the probability of a patient receiving a treatment relative to a comparator conditional on identified covariates, creating a propensity score[26 27]. Although individuals with the same propensity score likely have different values for baseline covariates, they are assumed to have the same probability of treatment conditional on the aggregate score. This propensity score can then be used for IPTW, stratification, or matching to increase exchangeability between the treatment groups and thus help reduce bias due to measured cofounders[26].

Using IPTW, I created a pseudo-population balanced on key covariates according to the observed probability of treatment received conditional to baseline covariates[28 29]. Therefore, the distribution of baseline covariates in the sulfonylurea and metformin monotherapy groups in the IPTW pseudo-population was assumed to be exchangeable on measured confounders[30]. However, the creation of this pseudo-population may result in biased estimates of standard error due to a larger pseudo-population than subjects included in the study[31]. Using a variance-based bootstrap estimator will estimate the least biased estimates of the confidence intervals relative to a model-based variance estimator or a robust sandwich-type estimator.

4.4.4 Multiple Imputation

Observational studies using administrative data must carefully consider missing data[25]. Most variables in the CPRD are assumed not to have missing data as they are binary variables present when a relevant code is there and assumed to be absent when a relevant code is not there. Those with missing data are smoking, BMI, race, laboratory test results, and other clinical measures (e.g., blood pressure). Restricting inclusion to observations with no missing data (i.e., a complete case analysis) for key clinical measures may induce selection bias since missing data can systematically differ depending on the exposure[32]. Multiple imputation is a commonly used method of dealing with data assumed to be missing at random[33 34]. This assumption specifies that missing data is randomly missing conditional on other variables known about the observation in the dataset. However, simply imputing a single missing value based on existing covariates does not adequately consider this value's uncertainty. Therefore, I used multiple imputation, which was first described by Rubin in 1977, to impute incomplete data (i.e., missing values for HbA1c, BMI, and smoking)[33 34].

I imputed missing data using a Markov Chain Monte Carlo model (MCMC)[35]. A Markov chain is a sequence of random variables in which each element's distribution depends on the distribution of the preceding variables. This approach generates potential values for the missing parameter from multidimensional probability distributions via Markov chains. The MCMC approach continues until the distribution of possible missing values stabilizes to a standard

distribution. I then estimated propensity scores for the 5 imputed datasets. I used Rubin's rules to combine the treatment effect estimates from the imputed datasets to obtain an overall estimate[36].

4.4.5 Sensitivity Analyses

Observational studies must often make assumptions of varying strength to estimate causal effects. Following the design stage, sensitivity analyses allow the opportunity to demonstrate if the results are robust to changes in methods, values of unmeasured variables, biases, and other assumptions. An effect measure that is robust to changes in these assumptions increases confidence in a causal effect. Therefore, I pre-specified 15 sensitivity analyses to appraise the strength of our results. Our sensitivity analysis included the following:

1. Databases such as the CPRD have data on drug prescriptions but do not report if patients filled and used these medications. I explored the potential for exposure misclassification by repeating the primary analysis while varying the grace period for non-overlapping prescriptions to 0 and 60 days.
2. Given the diminishing relevance of first-generation sulfonylureas such as tolbutamide, I repeated our primary analysis while restricting inclusion to patients who initiated a second- or third-generation sulfonylurea or metformin.
3. Our study defines a cohort of individuals in the CPRD using sulfonylurea or metformin monotherapy following a series of exclusions. However, I did not restrict our study cohort to those diagnosed with type 2 diabetes (I excluded those with other indications for their use). To test the assumption that our cohort was using these oral hypoglycemic agents to manage type 2 diabetes, I restricted the study population to patients at least 40 years of age to increase the likelihood of a diagnosis of type 2 diabetes.
4. I excluded patients with a previous diagnosis of cardiac arrest or ventricular arrhythmia at any time before cohort entry to help restrict to incident events as opposed to recurring events.
5. To examine potential outcome misclassification, I restricted HES-defined events to those with a relevant ICD-10 code listed in the primary position.
6. I restricted events in our primary analysis to events recorded in HES or ONS.
7. I further restricted events in our primary analysis to VA events listed in HES. This sensitivity analysis excluded VA events identified in the CPRD and non-hospitalized fatal VAs identified in ONS only.

8. I censored follow-up at the occurrence of pregnancy since pregnant women have particular indications for antihyperglycemic management and thus may contribute to low overlap in the propensity score.
9. I censored follow-up at the prescription of a drug with a known risk of torsade de pointes or QT interval prolongation to help explore the potential contribution of competing risks from concurrent medications for our primary analysis[37].
10. To help explore informative censoring, I repeated the analyses using an intention-to-treat approach with a maximum follow-up of 1 year.
11. To further examine the impact of informative censoring due to drug discontinuation and all-cause mortality (competing risks), I applied two IPCW models to account for censoring due to drug discontinuation and all-cause mortality. These two models were applied by taking the product of the IPTW and IPCW weights. Weights greater than ten were truncated to avoid extremely influential observations.
12. I repeated my primary analysis after truncating IPTW weights greater than ten to avoid patients being assigned extreme weights.
13. To help adjust for residual confounding following the application of truncated IPTW weights in sensitivity analysis 12, I directly adjusted for unbalanced variables in our Cox proportional hazards model. Unbalanced variables were identified as those with standardized differences greater than 0.1 between the sulfonylurea and metformin monotherapy groups.
14. Instead of IPTW, we used a greedy matching algorithm to match each sulfonylurea user with one metformin user by the propensity score (logit calliper: propensity score of 0.05).
15. I calculated an E-value to assess the strength of the unmeasured confounding necessary to explain the observed findings for the association of sulfonylurea use and ventricular arrhythmias[38]. Unmeasured confounding is an inherent concern in non-randomized studies. Since they are, by definition, unmeasured and thus impossible to directly account for in the analysis, sensitivity analysis must be defined to characterize the degree to which results are vulnerable to bias. The E-Value is an approach introduced by Vanderweele and Peng in 2017[39]. The E-value represents the minimum strength of association required for an unmeasured confounder to explain away a specific treatment-outcome association given adjustment for measured confounders in design or analysis[40]. Rather than identify the degree to which our effect measure is confounded, this value helped us identify the magnitude of the

confounder associations required to be equal to the observed treatment-outcome association. A larger E-value implies that a severe confounder would be required to explain away an association[40].

4.5 REFERENCES

1. Primary care data for public health research: CPRD; [Available from: https://cprd.com/primary-care accessed Dec 17, 2020 2020.
2. Ghosh RE, Crellin E, Beatty S, et al. How Clinical Practice Research Datalink data are used to support pharmacovigilance. *Therapeutic advances in drug safety* 2019;10:2042098619854010-10. doi: 10.1177/2042098619854010
3. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *International journal of epidemiology* 2015;44(3):827-36.
4. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical practice research datalink (cprd) aurum. *International journal of epidemiology* 2019;48(6):1740-40g.
5. Booth H, Dedman D, Wolf A, et al. CPRD Aurum Frequently asked questions (FAQs): The CPRD; [updated April 20, 2019. 2.0:[Available from: https://www.cprd.com/sites/default/files/CPRD%20Aurum%20FAQs%20v2.0_2.pdf.
6. Persson R, Vasilakis-Scaramozza C, Hagberg KW, et al. CPRD Aurum database: Assessment of data quality and completeness of three important comorbidities. *Pharmacoepidemiology and Drug Safety*;n/a(n/a) doi: 10.1002/pds.5135
7. Datalink CPR. CPRD Aurum June 2021 (Version 2021.06.001) [Data set]. June 2021.
8. Ray D, Rouebuck C, Smith O. Delivering linked datasets to support health and care delivery and research: NHS Digital; 2018 [accessed Dec 17, 2020.
9. Mathur R, Bhaskaran K, Chaturvedi N, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2014;36(4):684-92. doi: 10.1093/pubmed/fdt116 [published Online First: 2013/12/11]
10. Herbert A, Wijlaars L, Zylbersztejn A, et al. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;46(4):1093-93i. doi: 10.1093/ije/dyx015 [published Online First: 2017/03/25]
11. Gallagher AM, Dedman D, Padmanabhan S, et al. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. *Pharmacoepidemiol Drug Saf* 2019;28(5):563-69. doi: 10.1002/pds.4747 [published Online First: 2019/03/26]

12. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;60(572):e128-36. doi: 10.3399/bjgp10X483562 [published Online First: 2010/03/06]
13. Hennessy S, Leonard CE, Palumbo CM, et al. Diagnostic codes for sudden cardiac death and ventricular arrhythmia functioned poorly to identify outpatient events in EPIC's General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2008;17(12):1131-6. doi: 10.1002/pds.1632 [published Online First: 2008/07/10]
14. Springate DA, Kontopantelis E, Ashcroft DM, et al. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PLoS One* 2014;9(6):e99825. doi: 10.1371/journal.pone.0099825 [published Online First: 2014/06/19]
15. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the General Practice Research Database. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 2003;23(5):686-89. doi: https://doi.org/10.1592/phco.23.5.686.32205
16. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69(1):4-14. doi: 10.1111/j.1365-2125.2009.03537.x [published Online First: 2010/01/19]
17. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports* 2015;2(4):221-28.
18. Stürmer T, Wang T, Golightly YM, et al. Methodological considerations when analysing and interpreting real-world data. *Rheumatology* 2019;59(1):14-25. doi: 10.1093/rheumatology/kez320
19. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S90-s102. doi: 10.2337/dc19-S009 [published Online First: 2018/12/19]
20. Davidson MB. Successful treatment of markedly symptomatic patients with type II diabetes mellitus using high doses of sulfonylurea agents. *West J Med* 1992;157(2):199-200. [published Online First: 1992/08/01]

21. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006;355(5):467-77. doi: 10.1056/NEJMoa061759 [published Online First: 2006/08/04]
22. Abrahamson MJ. Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with type 2 diabetes? Yes, they continue to serve us well! *Diabetes Care* 2015;38(1):166-9. doi: 10.2337/dc14-1945 [published Online First: 2014/12/30]
23. Yu O, Azoulay L, Yin H, et al. Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia. *Am J Med* 2018;131(3):317.e11-17.e22. doi: 10.1016/j.amjmed.2017.09.044 [published Online First: 2017/10/17]
24. Association AD. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2020. *Diabetes Care* 2020;43(Supplement 1):S193-S202.
25. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359(9302):248-52. doi: 10.1016/s0140-6736(02)07451-2 [published Online First: 2002/01/29]
26. Deb S, Austin PC, Tu JV, et al. A review of propensity-score methods and their use in cardiovascular research. *Canadian Journal of Cardiology* 2016;32(2):259-65.
27. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.
28. Robins JM, Hernán MÁ, Brumback B. Marginal Structural Models and Causal Inference in Epidemiology. *Epidemiology* 2000;11(5):550-60.
29. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research* 2011;46(3):399-424.
30. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *American journal of epidemiology* 2008;168(6):656-64.
31. Schafer JL. Analysis of incomplete multivariate data: CRC press 1997.
32. An overview of multiple imputation. Proceedings of the survey research methods section of the American statistical association; 1988. Citeseer.
33. Multiple imputations in sample surveys-a phenomenological Bayesian approach to nonresponse. Proceedings of the survey research methods section of the American Statistical Association; 1978. American Statistical Association.

34. Yuan YC. Multiple imputation for missing data: Concepts and new development (Version 9.0). *SAS Institute Inc, Rockville, MD* 2010;49(1-11):12.
35. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. doi: 10.1136/bmj.b2393
36. Wooseley R, Heise C, Komera K. QTdrugs List 1822 Innovation Park Dr., Oro Valley, AZ 85755: AZCERT, Inc. ; [Available from: http://www.crediblemeds.org/ accessed Jan 15 2020.
37. VanderWeele;, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Annals of Internal Medicine* 2017;167(4):268-74. doi: 10.7326/m16-2607 %m 28693043
38. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Annals of internal medicine* 2017;167(4):268-74.
39. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. *JAMA* 2019;321(6):602-03. doi: 10.1001/jama.2018.21554

Chapter 5: Pharmacoepidemiologic Study

5.1 Preface to Pharmacoepidemiologic Study

Our systematic review determined that most of the existing literature in this area has important methodological limitations, underscoring the need for additional, methodologically rigorous, comparative drug safety studies that examine the association between sulfonylureas and the risk of VA. Our subsequent population-based study addressed this knowledge gap. Important, this study had some important methodological features that overcame the limitations of this existing literature: (1) it used an active comparator new-user design to establish a cohort of individuals initiating first-line pharmacotherapy therapy for type 2 diabetes; (2) it used metformin as the active comparator as it is the most frequently prescribed first-line therapy in the UK, ensuring that results are clinically relevant; (3) it compared two drugs being used as first-line therapy, reducing the risk of time-lag bias; (4) it used IPTW by propensity score to reduce potential confounding; (5) it included extensive sensitivity analyses to examine the robustness of results to various biases common in observational pharmacoepidemiologic studies.

5.2 Sulfonylureas versus metformin and the risk of ventricular arrhythmias among people with type 2 diabetes: a population-based cohort study

Short Title: Sulfonylureas and Ventricular Arrhythmias

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5.2.1 ABSTRACT

Background: Previous studies of sulfonylureas and the risk of ventricular arrhythmias (VA) have produced conflicting results. Our objective was to determine whether the use of sulfonylurea monotherapy, compared with metformin monotherapy, is associated with an increased risk of VA among patients initiating pharmacotherapy for type 2 diabetes.

Methods: We conducted a retrospective, population-based cohort study using the United Kingdom's Clinical Practice Research Datalink linked to Hospital Episode Statistics and the Office for National Statistics. The cohort included patients initiating a sulfonylurea or metformin as their first-ever antihyperglycemic drug. The primary outcome was VA. We used a Cox proportional hazards models with inverse probability of treatment weighting to estimate the adjusted hazard ratio (aHR) and a corresponding bootstrap 95% confidence interval (CI) for VA, comparing new users of a sulfonylurea with new users of metformin.

Results: The cohort included 93,638 new users of sulfonylurea and 506,883 new users of metformin. A total of 279 VA events occurred among sulfonylurea users (incidence rate per 10,000 person-years [IR]: 25.5, 95% CI: 22.7-28.7) and 1,537 VA events occurred among metformin users (incidence rate per 10,000 person-years: 18.5, 95% CI: 17.6-19.5). Compared to metformin, sulfonylureas were associated with an increased risk of VA (aHR: 1.42, 95% CI: 1.16-1.67). They were also associated with an increased risk of cardiac arrest (aHR: 1.63, 95% CI: 1.34-2.02).

Conclusions: Sulfonylureas are associated with an increased risk of VA when used as first-line therapy for type 2 diabetes. This increased risk should be considered when prescribing sulfonylureas as an initial treatment for type 2 diabetes.

5.2.2 INTRODUCTION

Sulfonylureas are a frequently used yet controversial antihyperglycemic treatment used to manage type 2 diabetes. While they are typically recommended as second-line therapy, they are also used as first-line pharmacological treatment, particularly among patients who are intolerant to or with contraindications to metformin[1,2]. Indeed, a drug utilization study showed 15% of patients who initiated treatment for type 2 diabetes between 2000 and 2017 in the United Kingdom did so using a sulfonylurea[3].

The cardiovascular safety of sulfonylureas is controversial, with several studies identifying higher rates of all-cause and cardiovascular mortality among patients using sulfonylureas[4-7]. The University Group Diabetes Program trial first reported an increased risk of sudden cardiac death among patients randomized to the first-generation sulfonylurea, tolbutamide, relative to those randomized to diet or insulin[8]. While sulfonylureas do not appear to be associated with an increased risk of MI, subsequent studies have found sulfonylureas to be associated with increased risks of ischaemic stroke, cardiovascular death, and all-cause mortality relative to metformin users[6,9]. The underlying cause of this increased risk of cardiovascular death remains unclear.

One possible cause of this increased risk of cardiovascular death is an increased risk of ventricular arrhythmias (VA). Sulfonylureas are known to substantially increase the risk of hypoglycemia relative to other oral antihyperglycemic drugs[10]. Hypoglycemia has been associated with increased risks of ventricular tachycardia and sudden cardiac death[11-16]. While several observational studies have investigated the association between sulfonylureas and the risk of VA, many of these studies had important limitations, including time-lag bias and depletion of susceptibles (prevalent user bias)[17]. Consequently, the effect of sulfonylureas on the risk of VA remains unclear. Our objective was therefore to determine if sulfonylureas, relative to metformin, are associated with the risk of VA when used as monotherapy for the initial treatment of type 2 diabetes.

5.2.3 METHODS

5.2.3.1 Data Sources

We conducted a retrospective, population-based cohort study using an active comparator, new-user design and data from the United Kingdom's (UK) Clinical Practice Research Datalink (CPRD) Aurum[18 19]. The CPRD contains de-identified longitudinal primary care data on demographics, lifestyle measures (e.g., smoking, alcohol consumption), diagnoses, prescriptions, laboratory tests (e.g., glycated hemoglobin A1c [HbA1c]) and referrals for over 40 million patients from 1,491 general practices in the UK. Patients included in the CPRD are consistent with UK census data regarding distributions of age, sex, and ethnicity[20]. Diagnoses and procedures recorded in the CPRD use a combination of SNOMED CT (UK edition), Read Version 2, and local EMIS Web codes. Prescriptions written by general practitioners are automatically recorded using a coded drug dictionary based on the British National Formulary product dictionary. We linked the CPRD to the Hospital Episodes Statistics (HES) repository, which contains information on all inpatient and outpatient hospital admissions, primary and secondary diagnoses, and procedures received during the hospital stay[21]. In addition to HES, we linked data with the Office for National Statistics (ONS) database, which contains UK citizens' electronic death certificates. HES diagnoses are recorded using the 10th revision of the International Classification of Diseases (ICD-10) coding system. ONS diagnoses have been recorded using the ICD-10 coding system since 2001; the 9th revision of the International Classification of Diseases (ICD-9) coding system was used prior to this point. Linkage with HES and ONS data is available for approximately 94% of patients in CPRD Aurum. The CPRD has been validated for representativeness relative to UK census data[18 20].

This study's protocol was approved by the CPRD's Independent Scientific Advisory Committee (ISAC) (protocol #20_000298) and the Research Ethics Board of the Jewish General Hospital in Montreal, Canada. The protocol was made available to journal reviewers.

5.2.3.2 Study Population

We included all patients who received a prescription for either metformin or a sulfonylurea as their first-ever antihyperglycemic drug between April 1, 1998 and December 30, 2019[19]. Patients entered the study cohort on the date of this first prescription. We then excluded patients with: 1) age <18 years; 2) database history <365 days (to exclude prevalent users and to ensure sufficient

observation time for the assessment of comorbidities); 3) a previous prescription for an antihyperglycemic drug; 4) a prescription for both metformin and a sulfonylurea or a prescription for any antihyperglycemic drug other than metformin or a sulfonylurea on the day of cohort entry; 5) a previous diagnosis of polycystic ovary syndrome (another indication for metformin use); 6) a diagnosis of gestational diabetes in the year before cohort entry; and 7) no recorded follow-up. Patients were followed from cohort entry until an event (defined below) or censoring due to study drug discontinuation, initiation of another antihyperglycemic drug, death, departure from the CPRD, end of linkage to HES or ONS, or the end of the study period (December 30, 2019), whichever occurred first.

5.2.3.3 Exposure

Exposure was defined as current use of sulfonylurea monotherapy or metformin monotherapy. We modelled exposure as 'current use' using a time-fixed, as-treated definition in which patients were followed from cohort entry until sulfonylurea or metformin monotherapy discontinuation, defined by a treatment gap of greater than 30 days between the end of one prescription and the start of the next prescription within the same drug class or the initiation of another antihyperglycemic drug. This 30-day grace period was used to account for non-adherence and the biological half-life of the medication. Switches within sulfonylureas (e.g., glyburide to glimepiride) were permitted in our primary analysis. Metformin monotherapy was chosen as the reference group was it is the most frequently used first-line therapy and has no known arrhythmic effects. In addition, by comparing two classes used as first-line therapy, this approach reduces the possibility of time-lag bias, a severe form of confounding by disease severity[17].

5.2.3.4 Outcome

Our primary outcome was time to a first VA, including fatal and non-fatal events. We identified records with the corresponding SNOMED codes in CPRD Aurum, ICD-10 codes in HES (primary or secondary position) and ICD-10 or ICD-9 codes in ONS. The event date was defined by the date of diagnosis for CPRD-defined events, the date of hospital admission for HES-defined events, and the date of death for ONS-defined events. Although VA would usually be treated in a hospital setting, we included CPRD identified events as a previous validation study

showed using all available databases improved validity[22]. We had two secondary outcomes. The first was cardiac arrest, defined by a relevant ICD-10 code in either the primary or secondary position in HES. The second was fatal VA, defined as death recorded in ONS for which VA was listed as the underlying cause of death.

5.2.3.5 Potential Confounders

We assessed the following potential confounders at cohort entry: calendar year, demographic characteristics, lifestyle variables, comorbidities, proxies for overall health, laboratory test values and prescription drugs. The specific confounders are described in detail in **Supplemental Table 5.1.** Comorbidities were measured at any time before cohort entry. Lifestyle variables were measured up to five years before cohort entry. Proxies for health and prescription drug use were measured in the year before cohort entry. Missing baseline data for smoking, body mass index (BMI) and HbA1c were imputed using multiple imputation using the Markov Chain Monte Carlo approach[23]. We imputed five datasets and combined results using Rubin's rules[24]. Age, BMI, HbA1c and duration of type 2 diabetes were treated as continuous variables and modelled flexibly using restricted quadratic splines.

5.2.3.6 Statistical Analysis

To minimize potential confounding, we estimated a propensity score using a logistic model with the use of sulfonylureas as the dependent variable and the potential confounders listed above as independent variables. We compared the baseline characteristics of exposure groups using traditional descriptive statistics and standardized differences, both before and after inverse probability of treatment weighting (IPTW). IPTW is an approach in which the study population is re-weighted by the inverse of the propensity score to generate a pseudo-population balanced on the included covariates[25 26]. Standardized differences greater than 0.1 were considered important. Crude incidence rates and corresponding 95% CIs for the primary and secondary endpoints were estimated overall and by exposure group using Poisson regression. We used Cox proportional hazards models to estimate crude and adjusted hazard ratios (HRs) of the association between VA and current use of sulfonylurea versus metformin with follow-up

duration as the underlying time axis. Standard errors and 95% CIs were estimated using a variance-based bootstrap estimator by drawing 500 samples.

We conducted 7 secondary analyses. First, we assessed for the potential presence of a duration-response relationship (0-6 months; 6 months-1 year; 1-2 years; >2 years) in the association between sulfonylurea monotherapy use and VA. Second, we examined whether age (≤65 or >65), sex, history of cardiovascular disease (CVD), and HbA1c level modified the association of interest. Third, since sulfonylurea drugs vary in their pharmacology and potentially in their cardiotoxic risk, we repeated our primary analysis for each sulfonylurea molecule (glyburide, gliclazide, glipizide, and glimepiride; used in monotherapy) versus metformin monotherapy. We also grouped sulfonylurea molecules by pancreas sulfonylurea receptor specificity, subclassifying sulfonylureas as pancreas-specific molecules (gliclazide and glipizide) and non-pancreas-specific molecules (glimepiride and glyburide). Finally, we repeated our primary analysis for our two secondary endpoints: cardiac arrest and fatal VA. Propensity scores were re-estimated for each outcome. In addition, we conducted 15 sensitivity analyses to examine the robustness of our results; these analyses are described in the **Supplementary Methods**.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

5.2.4 RESULTS

Our cohort included 92,638 initiators of sulfonylurea monotherapy and 506,882 initiators of metformin monotherapy (**Figure 5.1**). These patients had median follow-up durations of 0.50 (IQR [interquartile range]: 0.20-1.48) years and 0.70 (IQR: 0.24-2.06) years, respectively. Overall, there were a total of 1,816 incident VA events in the cohort, generating a crude incidence rate (IR) of 19.3 per 10,000 person-years (95% CI: 18.5-20.2) (**Table 5.2**). A total of 279 events occurred in 109,220 person-years among sulfonylurea users (IR: 25.5 per 10,000 person-years, 95% CI: 22.7-28.7) and 1,537 VA events in 830,008 person-years among metformin users (IR: 18.5 per 10,000 person-years, 95% CI: 17.6-19.5).

Table 5.1 presents baseline characteristics for sulfonylurea and metformin users before and after IPTW. Before IPTW and compared to metformin users, sulfonylurea users were more likely to be older, to have a lower BMI, and to have a longer duration of type 2 diabetes. In addition, they were more frequently prescribed non-antihyperglycemic medications and were more frequently hospitalized in the previous year. Metformin users were more likely to have an alcohol-related disorder, hyperlipidemia, hypertension, and depression, to have an elevated HbA1c, and to have been prescribed angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and statins in the year before cohort entry. After weighting, all baseline characteristics were well balanced between groups, with no standardized difference exceeding 0.08.

The primary results for the outcomes of VA, cardiac arrest, and fatal VA are shown in **Table 5.2**. Compared with metformin monotherapy, sulfonylurea monotherapy was associated with an increased risk of VA (aHR: 1.42, 95% CI: 1.16-1.67). Sulfonylureas were also associated with a large increased risk of cardiac arrest (aHR: 1.63, 95% CI: 1.30-1.96) and may be associated with an increased risk of fatal VA relative to metformin (aHR: 1.84, 95% CI: 0.89-3.81) (**Table 5.2**). The results of the secondary analyses are shown in **Table 5.3** and **Supplemental Tables 5.2-5.9**. There was strong evidence of a duration-response relationship, with sulfonylureas associated with the largest risk of VA during the 0-6 months following cohort entry (aHR: 1.88, 95% CI: 1.68-2.11) (**Figure 5.2**; **Supplemental Table 5.2**). We also found that the risk of VA with sulfonylureas was greater among women than among men (**Supplemental Table 5.3**). Although an increased risk of VA was observed in both age strata, a greater increased risk with sulfonylureas was observed among patients aged 65 years or less (**Supplemental Table 5.4**). We found an increased risk of VA among patients with a history of CVD; the aHR among patients with no history of CVD was consistent with a null result (**Supplemental Table 5.5**). In contrast, the association did not vary with baseline HbA1c level (**Supplemental Table 5.6**). Our molecule-specific analysis suggested an increased risk of VA with gliclazide (aHR: 1.50, 95% CI: 1.39-1.63) and glimepiride (aHR: 1.07, 95% CI: 0.89-1.30); these trends were not observed with glyburide (aHR: 0.47, 95% CI: 0.36-0.61) or glipizide (aHR: 0.91, 95% CI: 0.69-1.20) (**Supplemental Table 5.7**). We identified an increased risk of VA with pancreas-specific sulfonylureas (glipizide or gliclazide) (aHR: 1.44, 95% CI: 1.33-1.56) but a numerically

decreased risk with non-pancreas-specific sulfonylureas (glyburide or glimepiride) (aHR: 0.89, 95% CI: 0.77-1.03) (**Supplemental Table 5.8**).

5.2.4.1 Sensitivity Analyses

The results of our sensitivity analyses were consistent with those of our primary analyses (**Supplemental Table 5.9**). Our primary analysis produced an E-value of 2.19.

5.2.5 DISCUSSION

In our population-based cohort study of people with type 2 diabetes, use of sulfonylureas as first-line treatment was associated with a 40% relative increase in the risk of VA compared with metformin. The risk was greatest in the first 6 months of sulfonylurea use. We also found sulfonylurea users aged 65 or less years, females, and patients with a history of CVD to be at greater risk of sulfonylurea-associated VA than those aged 66+ years, males, and those without a history of CVD, respectively. Gliclazide and glimepiride, pancreas-specific and non-pancreas-specific molecules respectively, were both associated with a higher risk of VA. Sulfonylureas were also associated with an increased risk of cardiac arrest. We observed a small number of fatal VA events and sparse data prevented the definitive assessment of this endpoint. Our finding of an increased risk of VA was robust to several sensitivity analyses.

The results of our study support the current American Diabetes Association recommendations for using metformin as a first-line treatment for type 2 diabetes[1]. This recommendation is based on metformin's effectiveness, relatively low cost, and overall favourable safety profile relative to other commonly used antihyperglycemic drugs. However, 21.4% to 73% of patients with type 2 diabetes are intolerant to metformin or have contraindications to its use[27]. Sulfonylureas have often been used as first-line therapy in these patients given their effectiveness, low cost, and physicians clinical experience with their use[28]. However, they have previously been associated with increased risks of ischemic stroke, cardiovascular death, and all-cause mortality, and they have a substantially higher risk of hypoglycemia[6 17 29-31]. Given these safety concerns and the results of the present study, alternative therapeutic options should be considered for patients unable to use metformin. For example, SGLT-2 inhibitors have a favourable cardiovascular safety profile[32]. Although there are some concerns with several adverse events associated with

their use, including acute kidney injury, diabetic ketoacidosis, fractures, and genital tract infections[32-40], SGLT-2 inhibitors may represent a more favourable treatment alternative among those who are intolerant to metformin or for whom metformin is contraindicated.

In the existing literature, one study compared the risk of VA/cardiac arrest among users of the second-generation sulfonylureas glimepiride, glyburide, and glipizide[41]. The investigators updated their earlier study by repeating their analysis in two different claims databases, Medicaid claims (1999-2012) and Optum Clinformatics commercial claims (2000-2016). Associations with VA/cardiac arrest for both glimepiride and glyburide, both relative to the use of glipizide, were inconsistent across these two databases. The analysis using Medicaid claims suggested a numerically increased risk of VA/cardiac arrest with glimepiride (aHR: 1.17, 95% CI: 0.96-1.42) and a numerically decreased risk with glyburide (aHR: 0.87, 95% CI: 0.74-1.03). In contrast, the analysis using Optum Clinformatics commercials claims suggested a numerically lower risk of VA/cardiac arrest with glimepiride (aHR: 0.84, 95% CI: 0.65-1.08) and a numerically higher risk with glyburide (aHR: 1.11, 95% CI: 0.86-1.42). In another study, which used the IBM MarketScan Medicare Supplemental Database, investigators reported a large increased risk of ventricular tachycardia and ventricular fibrillation among patients using sulfonylurea monotherapy (aHR: 1.52, 95% CI: 1.10-2.13) relative to metformin[42]. However, this study included sulfonylurea users who may have previously undergone therapy using another antihyperglycemic drug and was likely affected by other biases including left censoring and outcome misclassification. Left censoring may arise in this data source as it only includes individuals aged 65+ years with employer-sponsored Medicare supplemental coverage. While the findings need to be interpreted with caution, they nonetheless appear concordant with the results of the present study. Our study includes a population of those initiating first-line type 2 diabetes treatment with sulfonylurea compared with those initially treated with metformin monotherapy in a real-world setting with a greater incidence of events and higher generalizability than what has been observed in previous studies. Furthermore, with our use of IPTW and the availability of clinical data in the CPRD, it likely has reduced residual confounding relative to previous studies in this area.

The potential mechanism between the use of sulfonylureas and the risk of VA is not well understood[13]. There are two main mechanisms that have been hypothesized to explain the association between sulfonylureas and the risk of VA. The first hypothesis is sulfonylureas may hypoglycemia-induced VA. We previously found a 4.5 -fold increased risk of severe hypoglycemia[43]. The second potential mechanism hypothesizes some sulfonylureas (including glyburide and glimepiride) having extra-pancreatic effects and potentially inhibiting the heart's innate protective ischemic preconditioning[13]. Our finding of the largest risk of VA with gliclazide, a pancreas-specific sulfonylurea, is inconsistent with this hypothesis. Future studies should examine the potential mediating role of hypoglycemia in inducing VA.

Our study had several strengths. First, our study used a large, population-based data source that generated 939,228 person-years of follow-up, allowing for both generalizable results and the estimation of precise treatment effects. Second, we used an active-comparator, new-user design to reduce biases associated with the inclusion of prevalent users. Third, we used an active comparator used at a similar point in the management of type 2 diabetes, reducing potential confounding and avoiding time-lag bias[44]. In addition, we used IPTW to adjust for several potential confounders, further reducing potential residual confounding. Finally, the results remained consistent across several sensitivity analyses, suggesting that our findings are robust.

Our study had several potential limitations. First, there is the potential for outcome misclassification. To reduce this potential misclassification, we used linked data including hospitalization and vital statistics records. In addition, our results were robust to 3 sensitivity analyses that used more strict outcome definitions. It is also unlikely that such misclassification is differential between exposure groups. Second, prescriptions recorded in the CPRD represent those issued by the general practitioner and thus do not state whether a patient had adhered to the prescribed treatment regimen. This creates the potential for exposure misclassification. However, we expect few patients to not fill their prescriptions given the consequences of hyperglycemia and the affordability of these treatments in the UK under the National Health Service. Our results were robust to sensitivity analyses varying the duration of the exposure grace period and that used an intention-to-treat analysis. Third, as with all observational studies, residual confounding due to unobserved or poorly-measured covariates is possible. However, we employed rigorous

statistical methods and conducted multiple sensitivity analyses to address confounding and assess its potential impact on our proposed study using an E-value, which suggested that confounding is an unlikely explanation for the observed results. Fourth, we estimated the association between sulfonylurea use relative to metformin use. Consequently, we could not distinguish the potentially harmful effects of sulfonylureas versus the protective effects of metformin. We had selected metformin as the reference group as it is not believed to be associated with cardiac arrhythmias. Nonetheless, this remains a potential limitation that should be considered when interpreting our study's results.

5.2.6 CONCLUSION

Our large population-based study suggests that, compared with the use of metformin, the use of a sulfonylurea is associated with an increased risk of VA among patients initiating first-line therapy for type 2 diabetes. This elevated risk was greatest in the 6 months following the initiation of sulfonylureas. Compared with metformin, sulfonylureas were also associated with an increased risk of cardiac arrest and may be associated with an increased risk of fatal VA. The increased risk of VA associated with the use of sulfonylureas should be considered by physicians and patients when considering the potential benefits and risks of different options of initial pharmacological treatment for type 2 diabetes.

5.2.7 ACKNOWLEDGEMENTS

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5.2.8 DISCLOSURES

None to declare.

5.2.9 AUTHORS' CONTRIBUTIONS

NI, with support from KBF, designed the study, interpreted data, and wrote and revised the manuscript. PR contributed to the study design, performed data management, and conduct the

statistical analyses. OHYY and AD provided clinical expertise and reviewed the study design and manuscript for important intellectual content. All authors contributed to protocol development, interpretation of the data, and provided critical revisions to the manuscript. KBF conceived the question, supervised the study, and is the guarantor.

5.2.10 REFERENCES

1. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S61-s70. doi: 10.2337/dc19-S006 [published Online First: 2018/12/19]
2. Lipscombe L, Booth G, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. *Can J Diabetes* 2018;42 Suppl 1:S88-s103. doi: 10.1016/j.jcjd.2017.10.034 [published Online First: 2018/04/14]
3. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ Open* 2018;8(7):e022768. doi: 10.1136/bmjopen-2018-022768
4. Wheeler S, Moore K, Forsberg CW, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. *Diabetologia* 2013;56(9):1934-43. doi: 10.1007/s00125-013-2958-1 [published Online First: 2013/06/26]
5. Azoulay L, Schneider-Lindner V, Dell'aniello S, et al. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case-control study. *Pharmacoepidemiol Drug Saf* 2010;19(4):335-42. doi: 10.1002/pds.1834 [published Online First: 2010/01/07]
6. Filion KB, Douros A, Azoulay L, et al. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: A population-based cohort study. *Br J Clin Pharmacol* 2019;85(10):2378-89. doi: 10.1111/bcp.14056 [published Online First: 2019/07/06]
7. Gulliford M, Latinovic R. Mortality in type 2 diabetic subjects prescribed metformin and sulphonylurea drugs in combination: cohort study. *Diabetes Metab Res Rev* 2004;20(3):239-45. doi: 10.1002/dmrr.457 [published Online First: 2004/05/11]
8. Meinert CL, Knatterud GL, Prout TE, et al. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;19:Suppl:789-830. [published Online First: 1970/01/01]
9. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2012;157(9):601-10. doi: 10.7326/0003-4819-157-9-201211060-00003 [published Online First: 2012/11/07]

10. Group UPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet* 1998;352(9131):854-65.
11. Jungen C, Scherschel K, Flenner F, et al. Increased arrhythmia susceptibility in type 2 diabetic mice related to dysregulation of ventricular sympathetic innervation. *Am J Physiol Heart Circ Physiol* 2019;317(6):H1328-h41. doi: 10.1152/ajpheart.00249.2019 [published Online First: 2019/10/19]
12. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 2010;53(8):1552-61. doi: 10.1007/s00125-010-1752-6
13. Leonard CE, Hennessy S, Han X, et al. Pro- and Antiarrhythmic Actions of Sulfonylureas: Mechanistic and Clinical Evidence. *Trends in Endocrinology & Metabolism* 2017;28(8):561-86. doi: https://doi.org/10.1016/j.tem.2017.04.003
14. Ashcroft FM, Gribble FM. Tissue-specific effects of sulfonylureas: Lessons from studies of cloned KATP channels. *Journal of Diabetes and its Complications* 2000;14(4):192-96. doi: https://doi.org/10.1016/S1056-8727(00)00081-7
15. Valensi P, Slama G. Review: Sulphonylureas and cardiovascular risk: facts and controversies. *The British Journal of Diabetes & Vascular Disease* 2006;6(4):159-65. doi: 10.1177/14746514060060040301
16. Riveline JP, Danchin N, Ledru F, et al. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. *Diabetes & Metabolism* 2003;29(3):207-22. doi: https://doi.org/10.1016/S1262-3636(07)70030-7
17. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;40(5):706-14. doi: 10.2337/dc16-1943 [published Online First: 2017/04/22]
18. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical practice research datalink (cprd) aurum. *International journal of epidemiology* 2019;48(6):1740-40g.
19. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports* 2015;2(4):221-28.

20. Mathur R, Bhaskaran K, Chaturvedi N, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2014;36(4):684-92. doi: 10.1093/pubmed/fdt116 [published Online First: 2013/12/11]
21. Herbert A, Wijlaars L, Zylbersztejn A, et al. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017;46(4):1093-93i. doi: 10.1093/ije/dyx015 [published Online First: 2017/03/25]
22. Hennessy S, Leonard CE, Palumbo CM, et al. Diagnostic codes for sudden cardiac death and ventricular arrhythmia functioned poorly to identify outpatient events in EPIC's General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2008;17(12):1131-6. doi: 10.1002/pds.1632 [published Online First: 2008/07/10]
23. Yuan YC. Multiple imputation for missing data: Concepts and new development (Version 9.0). *SAS Institute Inc, Rockville, MD* 2010;49(1-11):12.
24. An overview of multiple imputation. Proceedings of the survey research methods section of the American statistical association; 1988. Citeseer.
25. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.
26. Rosenbaum PR. Model-based direct adjustment. *Journal of the American Statistical Association* 1987;82(398):387-94.
27. Salber GJ, Wang YB, Lynch JT, et al. Metformin Use in Practice: Compliance With Guidelines for Patients With Diabetes and Preserved Renal Function. *Clin Diabetes* 2017;35(3):154-61. doi: 10.2337/cd15-0045 [published Online First: 2017/08/02]
28. Montvida O, Shaw J, Atherton JJ, et al. Long-term Trends in Antidiabetes Drug Usage in the U.S.: Real-world Evidence in Patients Newly Diagnosed With Type 2 Diabetes. *Diabetes Care* 2018;41(1):69-78. doi: 10.2337/dc17-1414
29. Varvaki Rados D, Catani Pinto L, Reck Remonti L, et al. The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials. *PLoS Med* 2016;13(4):e1001992. doi: 10.1371/journal.pmed.1001992 [published Online First: 2016/04/14]
30. Garratt KN, Brady PA, Hassinger NL, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J*

Am Coll Cardiol 1999;33(1):119-24. doi: 10.1016/s0735-1097(98)00557-9 [published Online First: 1999/02/06]

31. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *Bmj* 1997;314(7093):1512-5. doi: 10.1136/bmj.314.7093.1512 [published Online First: 1997/05/24]
32. Fralick M, Schneeweiss S, Redelmeier DA, et al. Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: An observational study using data from routine care. *Diabetes Obes Metab* 2021 doi: 10.1111/dom.14474 [published Online First: 2021/06/26]
33. Dave CV, Schneeweiss S, Kim D, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med* 2019;171(4):248-56. doi: 10.7326/m18-3136 [published Online First: 2019/07/30]
34. Douros A, Lix LM, Fralick M, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis : A Multicenter Cohort Study. *Ann Intern Med* 2020;173(6):417-25. doi: 10.7326/m20-0289 [published Online First: 2020/07/28]
35. Nadkarni GN, Ferrandino R, Chang A, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. *Diabetes Care* 2017;40(11):1479-85. doi: 10.2337/dc17-1011 [published Online First: 2017/08/23]
36. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. *Jama* 2018;319(15):1580-91. doi: 10.1001/jama.2018.3024 [published Online First: 2018/04/21]
37. Zhou Z, Jardine M, Perkovic V, et al. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. *Diabetologia* 2019;62(10):1854-67. doi: 10.1007/s00125-019-4955-5 [published Online First: 2019/08/11]
38. Abrahami D, Douros A, Yin H, et al. Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of Fractures Among Patients With Type 2 Diabetes. *Diabetes Care* 2019;42(9):e150-e52. doi: 10.2337/dc19-0849 [published Online First: 2019/07/13]

39. Yu OHY, Dell'Aniello S, Shah BR, et al. Sodium–Glucose Cotransporter 2 Inhibitors and the Risk of Below-Knee Amputation: A Multicenter Observational Study. *Diabetes Care* 2020;43(10):2444-52.
40. Puckrin R, Saltiel MP, Reynier P, et al. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018;55(5):503-14. doi: 10.1007/s00592-018-1116-0 [published Online First: 2018/02/28]
41. Dhopeshwarkar N, Brensinger CM, Bilker WB, et al. Risk of sudden cardiac arrest and ventricular arrhythmia with sulfonylureas: An experience with conceptual replication in two independent populations. *Scientific Reports* 2020;10(1):10070. doi: 10.1038/s41598-020-66668-5
42. Ostropolets A, Elias PA, Reyes MV, et al. Metformin Is Associated With a Lower Risk of Atrial Fibrillation and Ventricular Arrhythmias Compared With Sulfonylureas: An Observational Study. *Circulation: Arrhythmia and Electrophysiology* 2021;14(3):e009115.
43. Yu O, Azoulay L, Yin H, et al. Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia. *Am J Med* 2018;131(3):317.e11-17.e22. doi: 10.1016/j.amjmed.2017.09.044 [published Online First: 2017/10/17]

Table 5.1 Characteristics of sulfonylurea and metformin users before and after inverse probability of treatment weighting.

Characteristics***	Before Weighting			After Weighting[bcd]		
	Metformin	Sulfonylurea	SD[a]	Metformin	Sulfonylurea	SD[a]
Total	506,882	93,638		605,013	545,284	
Age, years (mean, SD)	59.0 (13.9)	64.7 (14.2)	0.40	60.0 (15.5)	59.8 (35.5)	0.01
Male, n (%)	278,123 (54.9)	52,860 (57.1)	0.04	334,166 (55.2)	304,285 (55.8)	0.01
Alcohol related disorders, n (%)	65,314 (12.9)	8,066 (8.7)	0.13	73,733.0 (12.2)	65,237 (12.0)	0.01
Smoking status, n (%)						
Ever	297,472 (58.7)	40,298 (43.5)	0.06*	377,661 (62.4)	342,692 (62.8)	0.01
Never	171,117 (33.8)	26,461 (28.6)		227,352 (37.6)	202,592 (37.2)	
Missing	38,293 (7.6)	25,879 (27.9)	0.55	0 (0.0)	0 (0.0)	---
BMI, n (%)						
< 25 kg/m^2	40,898 (8.1)	19,331 (20.9)	0.55*	78,553 (13.0)	75,535 (13.9)	0.03
25-29.9 kg/m^2	132,239 (26.1)	25,049 (27.0)	0.20*	187,326 (31.0)	169,348 (31.1)	0.00
≥30.0 kg/m^2	275,744 (54.4)	19,638 (21.2)	0.65*	339,134 (56.1)	300,401 (55.1)	0.02
Missing	58,001 (11.4)	28,620 (30.9)	0.49	0 (0.0)	0 (0.0)	---
HbA1c (%), n (%)	8.3 (1.9)	8.9 (2.4)	0.31	8 (2.2)	8.8 (5.2)	0.08
≤ 7%	108,272 (21.4)	9,446 (10.2)	0.19*	143,674 (23.7)	110,433 (20.3)	0.08
7.1-8.0%	131,625 (26.0)	11,867 (12.8)	0.20*	167,085 (27.6)	129,360 (23.7)	0.09
> 8.0%	170,081 (33.6)	29,452 (31.8)	0.34*	294,254 (48.6)	305,491 (56.0)	0.15
Missing	96,904 (19.1)	41,873 (45.2)	0.58	0 (0.0)	0 (0.0)	---
Medical History, n (%)						
Cardiomyopathy/left ventricular hypertrophy/heart failure	40,231 (7.9)	10,177 (11.0)	0.10	52,373 (8.7)	50,293 (9.2)	0.02
Cerebrovascular disease	36,019 (7.1)	9,138 (9.9)	0.10	46,598 (7.7)	44,312 (8.1)	0.02
Depression	123,984 (24.5)	15,070 (16.3)	0.20	140,063 (23.2)	130,123 (23.9)	0.02
Epilepsy	9,661 (1.9)	1,681 (1.8)	0.01	11,591 (1.9)	11,519 (2.1)	0.01

Hepatic disease	22,067 (4.4)	3,042 (3.3)	0.06	25,421 (4.2)	22,964 (4.2)	0.00
History of arrhythmia or conductions disorders	40,569 (8.0)	9,357 (10.1)	0.07	51,242 (8.5)	49,932 (9.2)	0.02
History of insertion of a pacemaker or defibrillator	4,987 (1.0)	1,196 (1.3)	0.03	6,372 (1.1)	6,538 (1.2)	0.01
Hyperlipidemia	145,963 (28.8)	18,099 (19.5)	0.22	164,862 (27.2)	145,635 (26.7)	0.01
Hypertension	276,126 (54.5)	44,154 (47.7)	0.14	322,830 (53.4)	286,921 (52.6)	0.01
Hypocalcemia	0 (0.0)	0 (0.0)	---	0 (0.0)	0 (0.0)	---
Hypokalemia	1,854 (0.4)	465 (0.5)	0.02	2,429 (0.4)	2,367 (0.4)	0.01
Hypomagnesemia	83 (0.0)	29 (0.0)	0.01	127 (0.0)	115.6 (0.0)	0.00
Ischemic heart disease	100,706 (19.9)	22,085 (23.8)	0.10	125,192 (20.7)	115,258 (21.1)	0.01
Peripheral vascular disease	22,080 (4.4)	5,714 (6.2)	0.08	28,579 (4.7)	27,588 (5.1)	0.02
Renal disease	37,450 (7.4)	8,187 (8.8)	0.05	46,928.7 (7.8)	48,093 (8.8)	0.04
Valvular heart disease	13,710 (2.7)	3,228 (3.5)	0.05	17,380.6 (2.9)	16,894 (3.1)	0.01
Drugs, n (%)						
Aspirin	120,321 (23.7)	24,572 (26.5)	0.06	146,915 (24.3)	134,284 (24.6)	0.01
Acetaminophen	157,536 (31.1)	30,712 (33.2)	0.04	191,669 (31.7)	178,963 (32.8)	0.02
Anti-arrhythmic drugs	27,265 (5.4)	6,225 (6.7)	0.06	34,336 (5.7)	32,119 (5.9)	0.01
Antihypertensive medications	299,810 (59.1)	50,912 (55.0)	0.08	353,505 (58.4)	314,529 (57.7)	0.02
Beta-blockers	115,477 (22.8)	22,704 (24.5)	0.04	137,888 (22.8)	138,206 (25.3)	0.06
Thiazide diuretics	95,823 (18.9)	16,688 (18.0)	0.02	114,101 (18.9)	99,083 (18.2)	0.02
Calcium-channel blockers	134,384 (26.5)	20,980 (22.6)	0.09	156,420 (25.9)	137,231 (25.2)	0.02
Angiotensin receptor blockers	55,146 (10.9)	6,062 (6.5)	0.15	62,233 (10.3)	52,811 (9.7)	0.02
Angiotensin-converting enzyme inhibitors	162,838 (32.1)	24,342 (26.3)	0.13	189,667 (31.3)	160,199 (29.4)	0.04
Clopidogrel	16,615 (3.3)	2,531 (2.7)	0.03	19,447 (3.2)	18,692 (3.4)	0.01
Digoxin	13,704 (2.7)	6,727 (7.3)	0.21	21,966 (3.6)	21,578 (4.0)	0.02
Direct oral anticoagulants	4,806 (0.9)	415 (0.4)	0.06	5,238 (0.9)	4,818 (0.9)	0.00
Fibrates	6,819 (1.3)	1,265 (1.4)	0.00	8,177 (1.4)	7,372 (1.4)	0.00

Nonsteroidal anti-inflammatory drugs	133,592 (26.4)	21,573 (23.3)	0.07	156,565 (25.9)	140,339 (25.7)	0.00
Opioids	149,040 (29.4)	27,777 (30.0)	0.01	179,856 (29.7)	167,795 (30.8)	0.02
Statins	264,797 (52.2)	26,903 (29.0)	0.49	292,193 (48.3)	247,835 (45.5)	0.06
Warfarin	20,101 (4.0)	5,555 (6.0)	0.09	26,652 (4.4)	26,789 (4.9)	0.02
Drugs with a known risk of prolonging the QT interval	86,297 (17.0)	15,810 (17.1)	0.00	104,080 (17.2)	100,991 (18.5)	0.03
Induce CYP2C9	3,523 (0.7)	940 (1.0)	0.03	4,609 (0.8)	4,537 (0.8)	0.01
Inhibit CYP2C9	100,263 (19.8)	16,882 (18.2)	0.04	118,754 (19.6)	111,687 (20.5)	0.02
Duration of diabetes type 2 (years), Mean (SD)	2.3 (5.6)	3.2 (10.3)	0.10*	2.4 (7.5)	2.4 (16.2)	0.01
Missing	28,541 (5.6)	8,135 (8.8)	0.12	0 (0.0)	0 (0.0)	---
Number of hospitalization episodes of care, n (%)						
0, n (%)	443,558 (87.5)	68,458 (73.9)	0.35	512,365 (84.7)	449,591 (82.5)	0.06
1, n (%)	46,181 (9.1)	14,787 (16.0)	0.21	63,036 (10.4)	65,510 (12.0)	0.05
2+, n (%)	17,143 (3.4)	9,393 (10.1)	0.27	29,613 (4.9)	30,183 (5.5)	0.03
Number of unique non-antihyperglycemic prescription drugs, mean (SD)	8.9 (7.2)	9.4 (8.2)	0.06	9.1 (8.2)	9.6 (18.9)	0.03

Abbreviations: SD, Standardized Difference;

[a]Standard difference was calculated excluding patients with missing data.

[b]The weight is the inverse probability weight using a propensity score

[c]All variables included in this table were included in the propensity score used for IPTW

[d]Missing values for BMI, HbA1c, and smoking were imputed using multiple imputation

Table 5.2 Hazard ratios (95% confidence intervals) for ventricular arrhythmias, fatal ventricular arrhythmias, and cardiac arrest for sulfonylurea use versus metformin use among people with type 2 diabetes.

Exposure	No. of events	Person-years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)
Ventricular Arrhythmia				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	279	109,220	25.5 (22.7-28.7)	1.42 (1.16-1.67) [c]
Fatal Ventricular Arrhythmia				
Metformin	14	832,388	0.17 (0.10-0.28)	1.00 (Reference)
Sulfonylurea	6	109,505	0.55 (0.25-1.22)	1.84 (0.89-3.81) [b]
Cardiac Arrest				
Metformin	1,121	832,004	13.5 (12.7-14.3)	1.00 (Reference)
Sulfonylurea	303	109,467	27.7 (24.7-31.0)	1.63 (1.30-1.96) [c]

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using a Cox proportional hazards model.
[c]Confidence intervals were estimated using variance-based non-parametric bootstrapping with 500 samples.

Table 5.3 Hazard ratios (95% confidence intervals) for ventricular arrhythmias for sulfonylurea use versus metformin use among people with type 2 diabetes from subgroup analyses.

Strata	Subgroup	Adjusted HR[a] (95% CI)
Duration of Exposure		
	0 - 6 months	1.88 (1.68-2.11) [c]
	6 months - 1 year	1.02 (0.84-1.25) [c]
	1 - 2 years	1.27 (1.02-1.59) [c]
	More than 2 years	1.19 (1.04-1.36) [c]
Sex		
	Male	1.27 (0.97-1.57) [b]
	Female	1.80 (1.25-2.35) [b]
Age, years		
	≤65	1.52 (1.004-2.04) [b]
	>65	1.22 (0.97-1.47) [b]
History of CVD		
	Yes	1.54 (1.43-1.66) [c]
	No	1.03 (0.80-1.32) [c]
HbA1c		
	≤ 7%	1.52 (1.31-1.77) [c]
	7.1-8.0%	1.52 (1.33-1.74) [c]
	> 8.0%	1.45 (1.28-1.65) [c]
	Missing	1.48 (1.20-1.82) [c]
Pancreas-Specific Molecule		
	Yes (glipizide, gliclazide)	1.44 (1.33-1.56) [c]
	No (glimepiride, glyburide)	0.89 (0.77-1.03) [c]
Sulfonylurea Molecule[d]		
	Glyburide	0.47 (0.36-0.61) [c]
	Glipizide	0.91 (0.69-1.20) [c]
	Gliclazide	1.50 (1.39-1.63) [c]
	Glimepiride	1.07 (0.89 -1.30) [c]

[a]All Hazard Ratios for sulfonylureas relative to metformin.
[b]Confidence intervals were estimated using variance-based non-parametric bootstrapping with 500 samples.
[c]Confidence intervals were estimated using the Cox proportional hazards model.
[d]IPTW truncated to 10 when ≥ 10.

5.2.11 FIGURE LEGEND

Figure 5.1

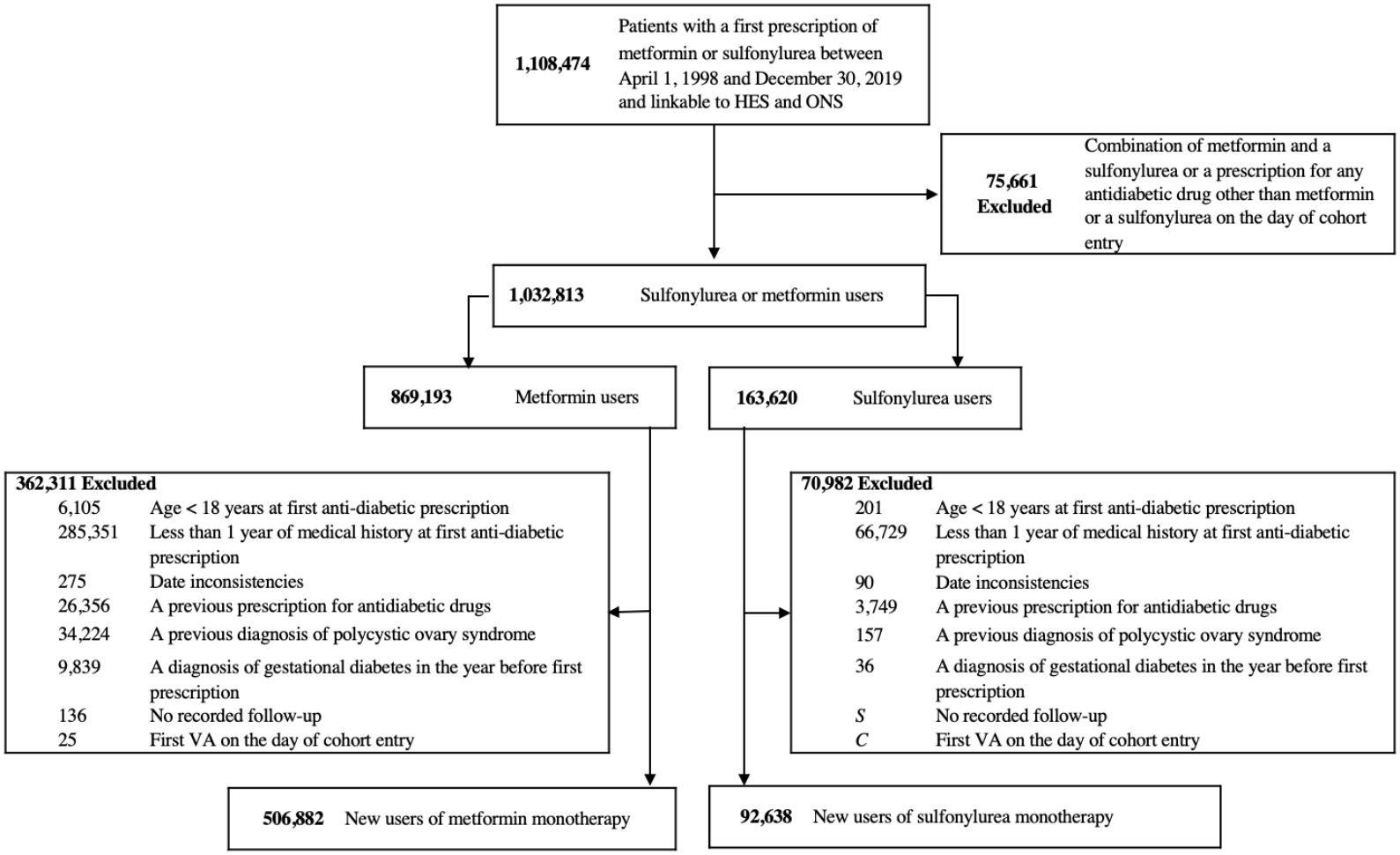
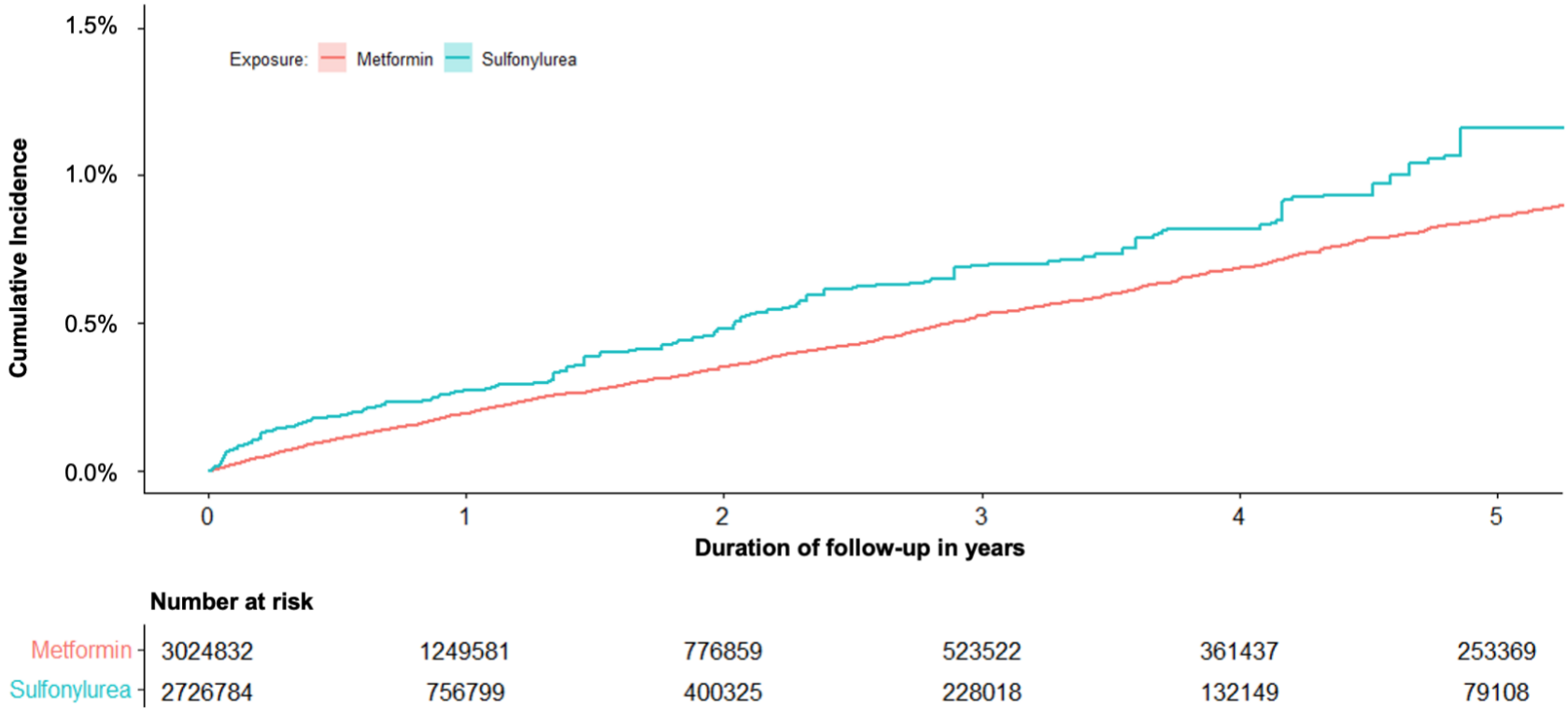

1,108,474
Patients with a first prescription of metformin or sulfonylurea between April 1, 1998 and December 30, 2019 and linkable to HES and ONS
75,661 Excluded
Combination of metformin and a sulfonylurea or a prescription for any antidiabetic drug other than metformin or a sulfonylurea on the day of cohort entry
1,032,813 Sulfonylurea or metformin users
869,193 Metformin users
163,620 Sulfonylurea users
362,311 Excluded
6,105 Age < 18 years at first anti-diabetic prescription
285,351 Less than 1 year of medical history at first anti-diabetic prescription
275 Date inconsistencies
26,356 A previous prescription for antidiabetic drugs
34,224 A previous diagnosis of polycystic ovary syndrome
9,839 A diagnosis of gestational diabetes in the year before first prescription
136 No recorded follow-up
25 First VA on the day of cohort entry
70,982 Excluded
201 Age < 18 years at first anti-diabetic prescription
66,729 Less than 1 year of medical history at first anti-diabetic prescription
90 Date inconsistencies
3,749 A previous prescription for antidiabetic drugs
157 A previous diagnosis of polycystic ovary syndrome
36 A diagnosis of gestational diabetes in the year before first prescription
S No recorded follow-up
C First VA on the day of cohort entry
506,882 New users of metformin monotherapy
92,638 New users of sulfonylurea monotherapy

Figure 5.2 Cumulative incidence of ventricular arrhythmia with the use of sulfonylurea and metformin monotherapy in primary IPTW weighted analysis



***Supplementary Methods**: Sensitivity Analysis*

We pre-specified 15 sensitivity analyses to assess the robustness of our results. First, we explored the potential for exposure misclassification by repeating the primary analysis while varying the grace period for non-overlapping prescriptions to 0 and 60 days. Second, given the diminishing relevance of first-generation sulfonylureas such as tolbutamide, we repeated our primary analysis while restricting sulfonylurea use to second- or third-generation sulfonylureas. Third, we restricted the study population to patients aged 40+ years to increase the likelihood of included patients having type 2 diabetes. Fourth, we excluded patients with a diagnosis of VA or cardiac arrest at any time before cohort entry to help isolate the rate of incident events as opposed to recurring events. Fifth, to examine potential outcome misclassification, we restricted HES-defined events to those with a relevant ICD-10 code listed in the primary position. Sixth, we restricted events in our primary analysis to those recorded in HES or ONS. Seventh, we further restricted events to VA events identified in HES, excluding those identified in the CPRD or ONS only. Eighth, we censored follow-up at the occurrence of pregnancy since pregnant women have particular indications for antihyperglycemic management and thus may contribute to low overlap in the propensity score. Ninth, we censored follow-up at the prescription of a drug with a known risk of torsade de pointes or QT interval prolongation to help minimize the potential contribution of competing risks from concurrent medications for our primary analysis. Tenth, to help explore informative censoring, we repeated the analyses using an intention-to-treat approach with a maximum follow-up of 1 year. Eleventh, to further assess informative censoring due to competing risks and drug discontinuation related to drug side-effects, we applied two inverse probability of censoring weighting (IPCW) models for all-cause mortality and for drug discontinuation. Twelfth, we truncated IPTW weights greater than ten to minimize the potential effects of extreme weights. Thirteenth, to reduce potential residual confounding following truncated IPTW weighting, we directly adjusted for unbalanced variables in our Cox proportional hazards model. Fourteenth, we repeated our primary analysis by 1:1 matching on the propensity with a greedy matching algorithm using a caliper of 0.05 on the logit scale. Finally, we calculated an E-value to assess the strength of the unmeasured confounding necessary to explain the results of the primary analysis

Supplemental Table 5.1 Covariates and period of assessment for variables included in the propensity score.

Category	Covariates	Period of Assessment
Time	Calendar Year at Cohort Entry	Cohort Entry
Demographic Characteristics	Age[b], Sex	Cohort Entry
Lifestyle Variables	Smoking[a], Body Mass Index[a], Alcohol-related Disorders	5 Years Before Cohort Entry
Comorbidities	A Previous History of Arrhythmia or Conductions Disorders, Previous Insertion of a Pacemaker or Defibrillator, Hyperlipidemia, Hypertension, Depression, Epilepsy, Cardiomyopathy/Left Ventricular Hypertrophy/ Heart Failure, Cerebrovascular Disease, Ischemic Heart Disease, Peripheral Vascular Disease, Valvular Heart Disease, Hepatic Disease, Renal Disease, Hypokalemia, Hypocalcemia, Hypomagnesemia	Any Time Before Cohort Entry
Proxies for Overall Health	Number of Hospitalizations, Number of Non-antihyperglycemic Prescription Drugs Used in the Year Before Cohort Entry[b]	1 Year Before Cohort Entry
Laboratory Test Values	HbA1c[a]	Last Measure Before Cohort Entry
Duration of Diabetes †	Time Since the First Diagnosis of Type 2 Diabetes and Cohort Entry[b]	N/A
Prescription Drugs	Aspirin, Acetaminophen, Anti-arrhythmic Drugs, Antihypertensive Medications (Beta-blockers, Thiazide Diuretics, Calcium-channel Blockers, Angiotensin Receptor Blockers, and Angiotensin-converting Enzyme Inhibitors), Clopidogrel, Digoxin, Direct Oral Anticoagulants, Fibrates, Nonsteroidal Anti-inflammatory Drugs, Opioids, Statins, Warfarin, Drugs with a known risk of torsade de pointes and QT interval prolongation, Drugs known to induce or inhibit CYP2C9	1 Year Before Cohort Entry

[a]We used multiple imputation to impute missing baseline data for BMI, HbA1c, and smoking
[b]We treated number of non-antihyperglycemic drugs, duration of type 2 diabetes, age, HbA1c continuously in our propensity score using restricted quadratic splines.

Supplemental Table 5.2. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Duration stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)
0-6 months				
Metformin	433	197,369	21.9 (20.0-24.1)	1.00 (Reference)
Sulfonylurea	131	33,170	39.5 (33.3-46.9)	1.88 (1.68-2.11) [b]
6 months-1 year				
Metformin	217	123,446	17.6 (15.4-20.1)	1.00 (Reference)
Sulfonylurea	44	19,058	23.1 (17.2-31.0)	1.02 (0.84-1.25) [b]
1-2 years				
Metformin	256	165,169	15.5 (13.7-17.5)	1.00 (Reference)
Sulfonylurea	41	23,301	17.6 (13.0-23.9)	1.27 (1.02-1.59) [b]
More than 2 years				
Metformin	631	344,024	18.3 (17.0-19.8)	1.00 (Reference)
Sulfonylurea	63	33,692	18.7 (14.6-23.9)	1.19 (1.04-1.36) [b]

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using the Cox proportional hazards model.

Supplemental Table 5.3. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Sex stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)[b]
Male				
Metformin	1,089	457,599	23.8 (22.4-25.3)	1.00 (Reference)
Sulfonylurea	191	62,792	30.4 (26.4-35.1)	1.27 (0.97-1.57)
Female				
Metformin	448	372,409	12.0 (11.0-13.2)	1.00 (Reference)
Sulfonylurea	88	46,428	19.0 (15.4-23.4)	1.80 (1.25-2.35)

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using variance-based non-parametric bootstrapping with 500 samples.

Supplemental Table 5.4. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Age stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)[b]
Age ≤65 years				
Metformin	695	510,118	13.6 (12.7-14.7)	1.00 (Reference)
Sulfonylurea	81	44,611	18.2 (14.6-22.6)	1.52 (1.004-2.04)
Age >65 years				
Metformin	842	319,890	26.3 (24.6-28.2)	1.00 (Reference)
Sulfonylurea	198	64,609	30.7 (26.7-35.2)	1.22 (0.97-1.47)

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using variance-based non-parametric bootstrapping with 500 samples.

Supplemental Table 5.5. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (CVD stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)
History of CVD				
Metformin	1,221	444,251	27.5 (26.0-29.1)	1.00 (Reference)
Sulfonylurea	235	47,352	49.6 (43.7-56.4)	1.54 (1.43-1.66)[b]
No History of CVD				
Metformin	316	385,757	8.2 (7.3-9.2)	1.00 (Reference)
Sulfonylurea	44	61,869	7.1 (5.3-9.6)	1.03 (0.80-1.32)[b]

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using the Cox proportional hazards model.

Supplemental Table 5.6. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (HbA1c stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)
≤ 7%				
Metformin	418	169,305	24.7 (22.4-27.2)	1.00 (Reference)
Sulfonylurea	45	10,120	44.5 (33.2-59.6)	1.52 (1.31-1.77) [b]
7.1-8.0%				
Metformin	438	237,218	18.5 (16.8-20.3)	1.00 (Reference)
Sulfonylurea	54	17,436	31.0 (23.7-40.4)	1.52 (1.33-1.74) [b]
> 8.0%				
Metformin	447	260,076	17.2 (15.7-18.8)	1.00 (Reference)
Sulfonylurea	90	34,518	26.1 (21.21-33.0)	1.45 (1.28-1.65) [b]
Missing				
Metformin	234	163,409	14.3 (12.6-16.3)	1.00 (Reference)
Sulfonylurea	90	47,147	19.1 (15.5-23.5)	1.48 (1.20-1.82) [b]

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using the Cox proportional hazards model.

Supplemental Table 5.7. Hazard Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Sulfonylurea molecule stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI) [bc]
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea				
Glyburide	6	6,759	8.8 (4.0-19.8)	0.47 (0.36-0.61)
Glipizide	5	2,971	16.8 (7.0-40.4)	0.91 (0.69-1.20)
Gliclazide	241	87,126	27.7 (24.4-31.4)	1.50 (1.39-1.63)
Glimepiride	11	5,524	19.9 (11.0-36.0)	1.07 (0.89 -1.30)

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using the Cox proportional hazards model.
[c]IPTW truncated to 10 when ≥ 10.

Supplemental Table 5.8. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Pancreas specificity stratified analysis)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][a]	Adjusted HR (95% CI)
Pancreas-specific Molecules				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Glipizide and Gliclazide	246	90,375	27.2 (24.0-30.8)	1.44 (1.33-1.56) [b]
Non-Pancreas-specific Molecules				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Glimepiride and Glyburide	17	12,350	13.8 (8.6-22.1)	0.89 (0.77-1.03) [b]

[a]Confidence intervals were estimated using a Poisson model.
[b]Confidence intervals were estimated using the Cox proportional hazards model.

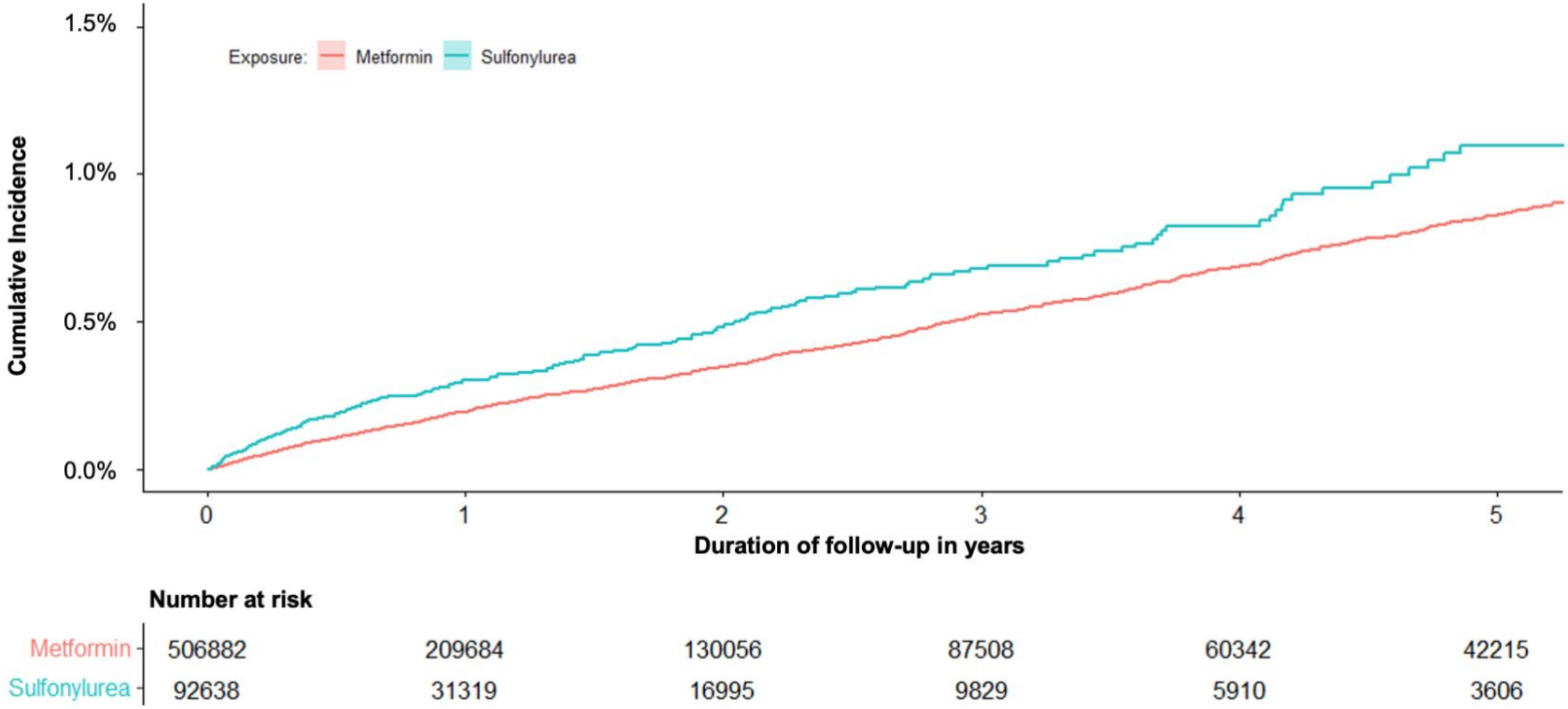
Supplemental Table 5.9. Hazard ratios (95% confidence intervals) for the association between sulfonylurea versus metformin and the risk of ventricular arrhythmia (Sensitivity analyses)

Exposure	Events	Person-Years	Incidence rate (95% CI) [per 10,000 PY][b]	Adjusted HR (95% CI)
Grace Period = 0 Days				
Metformin	401	231,354	17.3 (15.7-19.1)	1.00 (Reference)
Sulfonylurea	101	30,152	33.5 (27.6-40.7)	2.37 (1.57-3.16)[d]
Grace Period = 60 Days				
Metformin	2,284	1,171,508	19.5 (18.7-20.3)	1.00 (Reference)
Sulfonylurea	387	157,043	24.6 (22.3-27.2)	1.33 (1.12-1.54)[d]
Events listed in the primary position of HES				
Metformin	235	832,084	2.82 (2.49-3.21)	1.00 (Reference)
Sulfonylurea	49	109,461	4.48 (3.38-5.92)	1.44 (0.88-2.01)[d]
Events listed in HES or ONS (excluding events listed in the CPRD)				
Metformin	667	831,634	8.02 (7.43-8.65)	1.00 (Reference)
Sulfonylurea	135	109,406	12.34 (10.4-14.6)	1.72 (1.28-2.16)[d]
Events listed in HES				
Metformin	660	831,634	7.9 (7.4-8.6)	1.00 (Reference)
Sulfonylurea	130	109,406	11.9 (10.0-14.1)	1.71 (1.53-1.92)[c]
Restricting cohort to patients aged 40<				
Metformin	1,514	785,091	19.3 (18.3-20.3)	1.00 (Reference)
Sulfonylurea	274	106,060	25.8 (23.0-29.1)	1.41 (1.31-1.52)[c]
Inverse Probability of Censoring Weighting due to all-cause mortality[af]				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	279	109,220	25.5 (22.7-28.7)	1.47 (1.26-1.68)[d]
Inverse Probability of Censoring Weighting due to discontinuation of the assigned drug at cohort entry[af]				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	279	109,220	25.5 (22.7-28.7)	1.26 (1.20-1.32)[c]
Maximum follow-up of 1 year				

Metformin	651	321,390	20.3 (18.8-21.9)	1.00 (Reference)
Sulfonylurea	175	52,314	33.5 (28.9-38.8)	1.61 (1.21-2.01) [d]
Restricting to initiation of a 2nd or 3rd generation sulfonylurea				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	266	104,652	25.4 (22.5-28.7)	1.42 (1.31-1.53) [c]
Censoring at pregnancy				
Metformin	1,536	826,859	18.6 (17.7-19.5)	1.00 (Reference)
Sulfonylurea	279	109,177	25.6 (22.7-28.7)	1.41 (1.15-1.67) [d]
Censoring at initiation of a drug with a known risk of arrhythmias				
Metformin	1,079	661,795	16.3 (15.4-17.3)	1.00 (Reference)
Sulfonylurea	206	90,479	22.8 (19.9-26.1)	1.48 (1.35-1.62) [c]
Excluding patients with a history of VA/SCA				
Metformin	1,263	821,969	15.4 (14.5-16.2)	1.00 (Reference)
Sulfonylurea	215	108,101	19.9 (17.4-22.7)	1.33 (1.22-1.44) [c]
IPTW truncated to 10 when ≥ 10				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	279	109,220	25.5 (22.7-28.7)	1.46 (1.24-1.68) [d]
IPTW truncated to 10 when ≥ 10 and direct adjustment for unbalanced variables[g]				
Metformin	1,537	830,008	18.5 (17.6-19.5)	1.00 (Reference)
Sulfonylurea	279	109,220	25.5 (22.7-28.7)	1.57 (1.45-1.70) [d]
Matching on the propensity score				
Metformin	301	160,855	18.71 (16.71-20.95)	1.00 (Reference)
Sulfonylurea	279	109,220	25.54 (22.72-28.72)	1.34 (1.03-1.76) [ce]

[a]The weight is obtained by multiplying IPTW and IPCW and truncating to 10 when ≥ 10.
[b]Confidence intervals were estimated using a Poisson model.
[c]Confidence intervals were estimated using the Cox proportional hazards model.
[d]Confidence intervals were estimated using variance-based non-parametric bootstrapping with 500 samples.
[e]Matched using a greedy algorithm (logit calliper: propensity score of 0.05).
[f]IPTW and IPCW truncated to 10 when ≥ 10.
[g]Unbalanced variables were those with SD > 10% (Year cohort entry ; BMI; Number of hospitalizations; HbA1c in continuous with splines; statins).

Supplemental Figure 5.1 Cumulative incidence of ventricular arrhythmia with the use of sulfonylurea and metformin monotherapy in primary (non-IPTW) crude analysis



Chapter 6: Discussion

6.1 Summary

My thesis investigates the association between the use of sulfonylureas in the management of type 2 diabetes and the risk of VA. To investigate this association, I systematically reviewed the existing literature and then designed, conducted, and reported a methodologically rigorous drug safety study. Our systematic review found that, among the studies that have reported endpoints relevant to VA, the results are inconsistent. However, this existing literature has several important methodological limitations. Indeed, our quality assessment identified several of these studies as having a high risk of bias, with time-lag bias and prevalent user bias frequently occurring in this literature. However, higher-quality studies identified in our systematic review suggested a higher risk of VA with sulfonylurea relative to other commonly-used antihyperglycemic therapies including metformin and DPP-4 inhibitors. Our population-based study found that the use of sulfonylureas is associated with a 40% higher relative risk of VA compared to the use of metformin. There was also evidence of a strong duration-response relationship, with the highest risk occurring during the first six months after treatment initiation. This early elevated risk magnifies my concerns regarding the potential consequences of previous studies inclusion of prevalent users and the corresponding depletion of susceptibles. Subgroup analyses revealed that the risk of sulonylurea-associated VA was higher among females and patients with a history of CVD than among males and those without a history of CVD, respectively. Finally, my findings remained highly consistent across several sensitivity analyses meant to address possible sources of bias. The findings of our study suggest that sulfonylurea use as initial therapy is associated with an increased risk of VA. Although our CPRD study had limitations, we encourage physicians and patients to consider this increased risk when determining the most appropriate drug class as an initial therapy for type 2 diabetes.

The first-generation sulfonylurea, tolbutamide, has been marketed since the 1950s[1]. While first-generation sulfonylurea drugs were associated with several safety concerns, second-generation sulfonylurea drugs were deemed safer, with a lower likelihood of adverse effects including hypoglycemia. Since the release of the UKPDS results, several RCTs and observational studies evaluating the cardiovascular effects of sulfonylureas have been published[2]. Many of these

studies have studied outcomes including post-MI death, cardiovascular death, and all-cause mortality[3-6]. Arrhythmic safety has been understudied as an endpoint.

Few of the major RCTs examining sulfonylureas have incorporated VA as an outcome. Subsequent RCTs are likely to focus on drugs that are newly marketed and less well-studied. While RCTs are the gold standard for evaluating efficacy and provide some information regarding safety, they are typically limited by small sample sizes and highly selected patient populations[7]. Moreover, RCTs have a relatively smaller study population with lower statistical power and shorter follow-up, which will likely compromise the feasibility of studying rare endpoints. Furthermore, given the lower incidence rate of VA, a trial to conclusively address this issue would likely be cost-prohibitive because of the size and duration required. Thus, large population-based observational studies represent the most feasible approach to generating critical evidence regarding these treatments' real-world, long-term safety.

6.2 Biological Mechanisms

Despite our study adding important evidence regarding the arrhythmic safety of sulfonylureas, the mechanism behind the observed increased risk of VA is unclear. Sulfonylureas act on the pancreatic beta cells, leading to increased insulin secretion, which lowers glycemia. Some hypotheses suggest sulfonylurea molecules that bind to cardiac sulfonylurea receptors, including glyburide and glimepiride, inhibit ischemic preconditioning and thus make the heart more vulnerable to subsequent arrhythmias[8]. Our study suggests a higher risk of VA among the pancreas-specific molecules, which is inconsistent with this potential mechanism. Alternatively, severe hypoglycemia-induced VA may be a potential mechanism that explains the observed increased risk of VA[9 10]. Sulfonylureas have a considerably higher risk of hypoglycemia relative to other oral antihyperglycemic medications [9]. Our previous study found a 4.5-fold increased risk of severe hypoglycemia (defined as hospitalization for hypoglycemia) among sulfonylurea monotherapy users relative to metformin monotherapy (HR: 4.53, 95% CI: 2.76–7.45)[11]. The increased risk of hypoglycemia is especially troubling since hypoglycemia has arrhythmia-promoting characteristics, including prolonged QT intervals[9 10]. Hypoglycemia is also associated with increased myoplasmic calcium concentrations, a process that may promote myocardial cell apoptosis and necrosis[12]. Despite the rare incidence of severe hypoglycemia in our previous

CPRD study, mild or moderate hypoglycemia may be sufficient to mediate this association between sulfonylurea use and VA[11 13]. Given these effects, there is biological plausibility for severe hypoglycemia-induced VA and sudden cardiac arrest. Therefore, a subsequent study should examine the potential role of hypoglycemia mediating the association between sulfonylurea and VA.

6.3 Clinical Implications

Despite the introduction of newer therapies for managing type 2 diabetes that have more favourable safety profiles, the use of sulfonylureas has endured. Newer drugs such as SGLT-2 inhibitors are now available[14]. This new drug class uses mechanisms distinct from those of sulfonylureas, and the literature suggests CVD benefits associated with their use. Fralick and colleagues' propensity score matched cohort study found a numerically decreased risk of a composite of heart failure, MI or stroke among patients initiating type 2 diabetes pharmacotherapy with an SGLT-2 relative to metformin (HR: 0.82, 95% CI: 0.58-1.15)[14]. Although there exist some concerns regarding the occurrence of several adverse events associated with their use, including acute kidney injury, diabetic ketoacidosis, fractures and genital tract infections, their relatively favourable cardiovascular safety profile makes them a promising alternative first-line therapy[14-22]. However, given the prevalence of type 2 diabetes, it would likely be cost prohibitive to use SGLT-2 inhibitors for all patients in many jurisdictions. One option may be recommending SGLT-2 inhibitors to those who are intolerant to metformin or for whom metformin is contraindicated (e.g., people with severe renal disease) given their potential benefits and the increased risk of VA with sulfonylureas.

6.4 Overall Limitations

While I observed an association between the use of sulfonylureas and an increased risk of VA and results were consistent across several sensitivity analyses, I cannot exclude the possibility of bias. Our choice of using an active comparator new user design helped prevent many common biases, including prevalent user bias and confounding present among studies included in our systematic review. While confounding is a common concern among observational studies, our study took several steps, including using a high-quality dataset that includes lifestyle variables

such as smoking and BMI that are not typically available in many datasets and the use of IPTW. There is still the possibility of bias due to missing data on comorbidities. We observed a substantial proportion of sulfonylurea users with missing data for BMI and smoking relative to metformin. This may bias effect estimates due to residual confounding. However, we used multiple imputations to help reduce this potential source of bias. Outcome misclassification is another potential source of bias. Ideally, outcome definitions should be validated in the same data source adopted for the study. To our knowledge, the outcome of VA has not been validated in CPRD Aurum. Bias attributable to outcome misclassification for relative effect measures (including a hazards ratio) will depend on whether misclassification is likely to be differential between exposure groups. Higher specificity definitions are generally preferred for ratio measures, as higher specificity will generate unbiased estimates[23]. Thus, we used a definition validated for the CPRD GOLD (formerly GPRD) and HES. Additionally, we applied more strict definitions for VA to explore outcome misclassification in sensitivity analyses.

6.5 Future Directions

Future directions include replicating this study in other high-quality datasets. Although we were underpowered for our secondary outcome of fatal VA, the cause of this increased risk may partly be due to an increased risk of fatal VA. This association should be reviewed and replicated in other well-conducted studies. More person-time for specific endpoints such as fatal VA and replication of our study will ensure results are robust to methodological choices and study populations. Our study used the active-comparator new user design[24]. This approach aligns treatment initiation with the start of follow-up, limiting time-varying hazards and precludes the risk of bias from prevalent users. However, the active-comparator new user design excludes a large proportion of patients. This has implications for clinical relevance and generalizability, particularly for patients who are now initiating a second-line drug following a more commonly used first-line therapy. One option would be repeating the study with a prevalent new-user design[25]. Proposed by Suissa and colleagues, the prevalent new-user design allows patients to be on the comparator treatment before initiating the treatment of interest and matches these switchers to patients not switching with a similar history of comparator drug use[26]. Our group has previously used this design to assess whether adding or switching to sulfonylureas is associated with an increased risk of MI, ischaemic stroke, cardiovascular death, all-cause

mortality, and severe hypoglycemia, compared with remaining on metformin monotherapy in patients with type 2 diabetes[27]. However, the potential gains in clinical relevance and sample size will depend on the specific treatment patterns. Our study was conducted over a period during which sulfonylureas were still commonly indicated as first-line therapy. Interest in evaluating the risk among patients switching to a drug of interest from a comparator is not the same clinical question as initiating a drug of interest or the comparator. The study of switching is also more prone to the potential consequences of confounding as such switching is often informative. Another potential area of study is to examine potential mediation by the occurrence of hypoglycemia on the association between sulfonylurea versus metformin and the risk of VA.

6.6 Summary

Although the arrhythmic safety of sulfonylureas will require continued surveillance, our study and several other high-quality studies identified by our systematic review suggest an increased risk of VA. Furthermore, the associations between sulfonylureas and increased risks of all-cause mortality and cardiovascular death are concerning and suggest the need for the reconsideration of their use for initial type 2 diabetes therapy[28-30]. More recently marked therapies with more favourable safety profiles represent potential alternatives to sulfonylureas, particularly among patients who are intolerant to metformin and among those with contraindications to it. Overall, my thesis suggests sulfonylureas, relative to metformin, are associated with an increased risk of VA among patients initiating therapy for type 2 diabetes.

6.7 REFERENCES

1. White JR. A Brief History of the Development of Diabetes Medications. *Diabetes Spectrum* 2014;27(2):82-86. doi: 10.2337/diaspect.27.2.82
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):837-53. [published Online First: 1998/09/22]
3. Patel A, Chalmers J, Poulter N. ADVANCE: action in diabetes and vascular disease. *J Hum Hypertens* 2005;19 Suppl 1:S27-32. doi: 10.1038/sj.jhh.1001890 [published Online First: 2005/08/03]
4. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *Jama* 2019;322(12):1155-66. doi: 10.1001/jama.2019.13772 [published Online First: 2019/09/20]
5. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular outcome trial of LINAgliptin versus glimepiride in type 2 diabetes (CAROLINA®). *Diabetes and Vascular Disease Research* 2015;12(3):164-74.
6. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 2017;5(11):887-97. doi: 10.1016/s2213-8587(17)30317-0 [published Online First: 2017/09/18]
7. Rogers JR, Liu C, Hripcsak G, et al. Comparison of Clinical Characteristics Between Clinical Trial Participants and Nonparticipants Using Electronic Health Record Data. *JAMA Network Open* 2021;4(4):e214732-e32. doi: 10.1001/jamanetworkopen.2021.4732
8. Leonard CE, Hennessy S, Han X, et al. Pro- and Antiarrhythmic Actions of Sulfonylureas: Mechanistic and Clinical Evidence. *Trends in Endocrinology & Metabolism* 2017;28(8):561-86. doi: https://doi.org/10.1016/j.tem.2017.04.003
9. Nordin C. The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence. *Diabetologia* 2010;53(8):1552-61. doi: 10.1007/s00125-010-1752-6

10. Nordin C. The proarrhythmic effect of hypoglycemia: evidence for increased risk from ischemia and bradycardia. *Acta Diabetologica* 2014;51(1):5-14. doi: 10.1007/s00592-013-0528-0
11. Yu O, Azoulay L, Yin H, et al. Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia. *Am J Med* 2018;131(3):317.e11-17.e22. doi: 10.1016/j.amjmed.2017.09.044 [published Online First: 2017/10/17]
12. Arad M, Seidman CE, Seidman JG. AMP-activated protein kinase in the heart: role during health and disease. *Circ Res* 2007;100(4):474-88. doi: 10.1161/01.Res.0000258446.23525.37 [published Online First: 2007/03/03]
13. Stahn A, Pistrosch F, Ganz X, et al. Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemias and silent arrhythmias. *Diabetes Care* 2014;37(2):516-20. doi: 10.2337/dc13-0600 [published Online First: 2013/09/18]
14. Fralick M, Schneeweiss S, Redelmeier DA, et al. Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: An observational study using data from routine care. *Diabetes Obes Metab* 2021 doi: 10.1111/dom.14474 [published Online First: 2021/06/26]
15. Dave CV, Schneeweiss S, Kim D, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med* 2019;171(4):248-56. doi: 10.7326/m18-3136 [published Online First: 2019/07/30]
16. Douros A, Lix LM, Fralick M, et al. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis : A Multicenter Cohort Study. *Ann Intern Med* 2020;173(6):417-25. doi: 10.7326/m20-0289 [published Online First: 2020/07/28]
17. Nadkarni GN, Ferrandino R, Chang A, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. *Diabetes Care* 2017;40(11):1479-85. doi: 10.2337/dc17-1011 [published Online First: 2017/08/23]
18. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis. *Jama* 2018;319(15):1580-91. doi: 10.1001/jama.2018.3024 [published Online First: 2018/04/21]

19. Zhou Z, Jardine M, Perkovic V, et al. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. *Diabetologia* 2019;62(10):1854-67. doi: 10.1007/s00125-019-4955-5 [published Online First: 2019/08/11]
20. Abrahami D, Douros A, Yin H, et al. Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of Fractures Among Patients With Type 2 Diabetes. *Diabetes Care* 2019;42(9):e150-e52. doi: 10.2337/dc19-0849 [published Online First: 2019/07/13]
21. Yu OHY, Dell'Aniello S, Shah BR, et al. Sodium–Glucose Cotransporter 2 Inhibitors and the Risk of Below-Knee Amputation: A Multicenter Observational Study. *Diabetes Care* 2020;43(10):2444-52.
22. Puckrin R, Saltiel MP, Reynier P, et al. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018;55(5):503-14. doi: 10.1007/s00592-018-1116-0 [published Online First: 2018/02/28]
23. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. *J Clin Epidemiol* 2012;65(3):343-49.e2. doi: 10.1016/j.jclinepi.2011.09.002 [published Online First: 2011/12/27]
24. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports* 2015;2(4):221-28.
25. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiology and drug safety* 2017;26(4):459-68.
26. Douros A, Dell'Aniello S, Yu OHY, et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *Bmj* 2018;362:k2693. doi: 10.1136/bmj.k2693 [published Online First: 2018/07/20]
27. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2012;157(9):601-10. doi: 10.7326/0003-4819-157-9-201211060-00003 [published Online First: 2012/11/07]

28. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;40(5):706-14. doi: 10.2337/dc16-1943 [published Online First: 2017/04/22]
29. Filion KB, Douros A, Azoulay L, et al. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: A population-based cohort study. *Br J Clin Pharmacol* 2019;85(10):2378-89. doi: 10.1111/bcp.14056 [published Online First: 2019/07/06]

Chapter 7: Conclusions

While there have been several studies on the overall cardiovascular safety profile of sulfonylureas, the possible association between sulfonylureas and the risk of VA has remained poorly understood. To address this knowledge gap, I first synthesized the existing literature in this literature. Our systematic review suggests that sulfonylurea therapy is associated with an increased risk of VA among higher-quality observational studies. However, the existing literature had several limitations, underscoring the need for an additional real-world safety study in this area. I therefore designed a population-based comparative drug safety study to evaluate the risk of VA among people initiating type 2 diabetes therapy with a sulfonylurea. We established a cohort of patients initiating either a sulfonylurea or metformin as their first-ever pharmacotherapy to treat type 2 diabetes. In this study, patients initiating therapy with a sulfonylurea had a 40% increased risk of VA relative to those initiating therapy with metformin.

My thesis contributes substantial information concerning the cardiovascular safety profile of sulfonylureas. Future research should aim to replicate these results in other high-quality datasets and alternative study designs. In addition, these studies should perform mediation analysis to understand better the potential mediating role of hypoglycemia in the association between sulfonylureas and VA. Clinicians should be aware of the potential risk of VA associated with sulfonylurea use, especially when considering the most appropriate treatment among individuals with type 2 diabetes.