Interaction between sulfonylureas and warfarin and the risk of severe hypoglycemia: a prevalent new-user study design

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Contents

1. ABSTRACT

Background

Sulfonylureas (SUs) are antidiabetic drugs used in the management of type 2 diabetes. SUs can cause hypoglycemia, and the risk of this adverse effect can further be elevated due to interactions between SUs and other drugs such as the anticoagulant warfarin. Prior observational studies have suggested that concomitant use of SUs and warfarin is associated with an increased risk of severe hypoglycemia compared to use of SUs alone. However, these studies may have been affected by confounding and other biases.

Objective

To assess the association between concomitant use of SUs and warfarin and the risk of severe hypoglycemia compared to use of SUs alone, using the recently developed prevalent new-user design (PNU).

Methods

Using the United Kingdom's Clinical Practice Research Datalink Aurum linked to hospitalization and vital statistics data, we assembled a base cohort of all patients initiating treatment with SUs from 1998 to 2020. Out of this base cohort, we identified those adding-on warfarin while on a SU. For each co-exposed patient, we defined an exposure set of SU users who had the same number of prior SU prescriptions but did not add-on warfarin (comparators). Within each exposure set, we then matched each co-exposed patient to up to five comparators on i) calendar year, ii) number of prior insulin prescriptions, and iii) closest time-conditional propensity score (TCPS). Co-exposed patients and matched comparators comprised the study cohort and were followed using an as-treated approach. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of severe hypoglycemia associated with concomitant use of SUs

and warfarin compared to use of SU alone. Secondary analyses stratified by age, sex, and renal disease, after repeating the matching process within each stratum. Sensitivity analyses assessed the potential impact of information bias, selection bias and residual confounding.

Results

The study cohort included 17,890 patients co-exposed to SUs and warfarin and 88,749 matched comparators using SU alone. After matching, patient characteristics were well balanced between groups. During 121,076 person-years of follow-up, 2,210 events of severe hypoglycemia occurred (incidence rate, 18 per 1,000 person-years). Compared to use of SUs alone, concomitant use of SUs and warfarin was not associated with the risk of severe hypoglycemia (HR, 1.04; 95% CI, 0.92 to 1.17). Stratification by demographics and renal disease suggested no effect measure modification. Sensitivity analyses were consistent with the primary analyses (HRs ranging from 1.02 to 1.15; all not statistically significant).

Discussion

Our study showed that concomitant use of SUs and warfarin was not associated with the risk of severe hypoglycemia compared to use of SUs alone. The findings suggest that this interaction does not result in a clinically apparent excess in the risk of severe hypoglycemia. They also suggest that the prevalent new user design can be used for the assessment of clinical effects of drug-drug interactions.

Conclusion

The interaction between SUs and warfarin does not seem to cause an excess in the risk of severe hypoglycemia.

2. RESUME

Contexte

Les sulfonylurées (SUs) sont des médicaments antidiabétiques utilisés dans le traitement du diabète de type 2. Les SUs peuvent causer l'hypoglycémie, et le risque de cet effet indésirable peut être encore plus élevé en raison des interactions entre les SUs et d'autres médicaments tels que l'anticoagulant warfarine. Des études observationnelles ont suggéré que l'utilisation concomitante de SUs et de warfarine est associée à un risque accru d'hypoglycémie grave par rapport à l'utilisation de SUs seuls. Cependant, ces études peuvent avoir été affectées par le biais de confusion et d'autres biais.

Objectif

Évaluer l'association entre l'utilisation concomitante des Suss et de la warfarine, et le risque d'hypoglycémie grave par rapport à l'utilisation des SUss seulement, à l'aide du devis « prevalent new-user » récemment mis au point.

Méthodes

En utilisant les données de la « Clinical Practice Research Datalink » du Royaume-Uni liées aux données sur l'hospitalisation et les statistiques de l'état civil, nous avons réuni une cohorte de base de tous les patients ayant commencé un traitement avec SUs de 1998 à 2020. Pour chaque patient co-exposé à la warfarine, nous avons défini un ensemble d'exposition de patients ayant reçu le même nombre d'ordonnances antérieures de SU, mais n'ayant pas ajouté de warfarine (comparateurs). Dans chaque série d'exposition, nous avons ensuite apparié chaque patient co-exposé à un maximum de cinq comparateurs pour i) l'année civile, ii) le nombre d'ordonnances d'insuline antérieures et iii) le score de propension conditionnel temporel le plus près (« time-conditional propensity scores »). Les patients co-exposés et les comparateurs appariés ont été

suivis selon une approche sous- traitement. Nous avons utilisé des modèles de risques proportionnels de Cox pour estimer les rapports de risque (hazard ratio [HR]) et les intervalles de confiance (confidence intervals [CIs]) à 95% de l'hypoglycémie sévère associée à l'utilisation concomitante de SU et de warfarine par rapport à l'utilisation de SU seulement. Dea analyses secondaires stratifiées selon l'âge, le sexe et l'insuffisance rénale, après avoir répété le processus d'appariement dans chaque strate ont été effectuées. Les analyses de sensibilité ont évalué l'impact potentiel des biais d'information, de sélection et de confusion résiduelle.

Résultats

La cohorte de l'étude comprenait 17 890 patients co-exposés aux SUs et à la warfarine et 88 749 comparateurs appariés utilisant SUs seulement. Après l'appariement, les caractéristiques des patients étaient bien équilibrées entre les groupes. Au cours de 121 076 années-personnes de suivi, 2 210 événements d'hypoglycémie sévère se sont produits (taux d'incidence, 18 pour 1 000 années-personnes). Comparativement à l'utilisation du SUs seul, l'utilisation concomitante du SUs et de la warfarine n'était pas associée au risque d'hypoglycémie sévère (HR, 1,04; 95% CI, 0.92 à 1.17). La stratification selon les caractéristiques démographiques et l'insuffisance rénale n'a laissé entendre aucune modification des mesures d'effet. Les résultats des analyses de sensibilité étaient semblables a ceux des analyses principales.

Discussion

Notre étude a montré que l'utilisation concomitante de SUs et de warfarine n'était pas associée au risque d'hypoglycémie sévère par rapport à l'utilisation de SUs seulement. Les résultats suggèrent que cette interaction n'entraîne pas un excès cliniquement apparent du risque d'hypoglycémie sévère. Ils suggèrent également que le devis « prevalent new-user » récemment mis au point peut être utilisée pour l'évaluation des effets cliniques des interactions médicamenteuses.

Conclusion

L'interaction entre le SUs et la warfarine ne semble pas causer d'excès dans le risque d'hypoglycémie sévère.

3. PREFACE

This thesis is a traditional thesis. The Introduction contains the background and the rationale for the cohort study that assessed the risk of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin. It also contains a critical appraisal of the previous studies in the area. The Methods contain the applied methodology including an introduction to the prevalent new-user design. The Results contain all the study findings. The Discussion and the Conclusions contain a critical appraisal of the study findings. The conducted study will soon be submitted for publication in a peer-reviewed journal.

4. INTRODUCTION

4.1 Diabetes mellitus

Diabetes mellitus is a chronic disease characterized by persistent high blood sugar (=glucose) levels. In healthy individuals, when blood glucose levels increase after food intake, the pancreatic β-cells release insulin, a hormone that regulates blood glucose by stimulating its intake in different tissues. However, in individuals with diabetes mellitus, blood glucose levels remain high as a result of insufficient insulin production, defective insulin action, or both[1].

There are two main types of diabetes mellitus. Type 1 diabetes is an autoimmune disease most commonly diagnosed in childhood or adolescence. In type 1 diabetes, the pancreatic β-cells are destroyed by the immune system, resulting in insufficient insulin production[2]. Type 2 diabetes mainly occurs among adults. Important risk factors include inadequate physical activity, older age, smoking, overweight, and family history of diabetes mellitus. In type 2 diabetes, tissues in the periphery develop resistance to the effects of insulin, and this resistance is further aggravated by the progressive decrease of insulin secretion[2]. **Table 1** summarizes the main differences between type 1 and type 2 diabetes. The current study focused on type 2 diabetes. Type 2 diabetes currently affects 462 million individuals globally, corresponding to 1 in 16 (6.3%) of the world's population[3]. In Canada, the prevalence is even higher: type 2 diabetes affects 3.1 million individuals or 8.4% of the population[4,5].

Table 1. Comparison of Type 1 and Type 2 diabetes mellitus

	Type 1 diabetes	**Type 2 diabetes**
Onset	Primarily during childhood or adolescence	Primarily in adults
Weight at onset	Often normal weight	Often overweight or obese
Pathophysiology	Absolute insulin deficiency due to autoimmune destruction of pancreatic beta cells	Relative insulin deficiency due to peripheral insulin resistance
Treatment	Insulin	Healthy diet, physical activity, treatment with non-insulin antidiabetic drugs or insulin
Acute complications	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state

4.2 Complications of diabetes mellitus

4.2.1 Acute complications of diabetes mellitus: Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two acute complications of diabetes mellitus. Both complications are related to chronic hyperglycemia[6]. In diabetes mellitus, insulin deficiency leads to increased levels of counter-regulatory hormones such as glucagon that stimulate the production of glucose in the liver[7]. However, the utilization of glucose in peripheral tissues remains low, potentially further exacerbating hyperglycemia.

In DKA, hyperglycemia leads to an increased breakdown of triglycerides with accompanying fatty acid release and their conversion in ketone bodies[7]. High blood ketone levels (hyperketonemia) can then lead to acidosis and DKA[7]. In HHS, the main characteristic is not hyperketonemia, which is absent because ketogenesis is suppressed by insulin,[7] but dehydration due to osmotic diuresis. Patients with untreated or newly diagnosed type 1 diabetes are more likely to develop hyperketonemia and DKA due to the underlying absolute insulin deficiency. Indeed, the prevalence of DKA at the time point of diagnosis of type 1 diabetes can be as high as 58%[8].

HHS can be observed among patients with type 2 diabetes, especially those with additional risk factors such as infection or cardiovascular disease, or those using certain medications such as steroids or diuretics[7]. HHS has a high mortality ranging between 10% and 50%[7]. Fortunately, with increasing availability of glucose lowering drugs, HHS has become less prevalent nowadays, with an incidence of less than 1 per 1000 person-years among patients with diabetes mellitus[7].

4.2.2 Long-term complications of diabetes mellitus

Long-term complications of diabetes mellitus can occur when tissues and organs are damaged due to long-time exposure to hyperglycemia[9]. Generally, long-term complications can be classified into microvascular and macrovascular complications.

Microvascular complications

Microvascular complications refer to the complications related to smaller blood vessels; the most common are retinopathy, neuropathy and nephropathy[9]. In diabetic retinopathy, hyperglycemia promotes the polyol pathway (a two-step process that converts glucose to fructose through the mediator sorbitol) and leads to increased sorbitol accumulation in the lens and retina[10]. Retinopathy affects more than one third of individuals with diabetes[11], and it is one of the leading cause of blindness[12]. Insulin and other glucose-lowering drugs can prevent or delay the onset of diabetic retinopathy[13].

Diabetic nephropathy is defined as the deterioration of kidney function of individuals with diabetes. The pathophysiology of diabetic nephropathy is related to the damage of the glomeruli in the kidneys due to hyperglycemia[14]. Diabetic nephropathy affects 20~40% of patients with diabetes,[15] and it is one of the leading causes of end-stage renal disease,[16] the final and permanent

stage of kidney function loss requiring dialysis or kidney transplantation[15]. Glucose-lowering treatments can prevent diabetic nephropathy and its progression[15].

Diabetic neuropathy is a group of heterogeneous disorders that affect the nervous system and have diverse clinical manifestations[13,17]. Diabetic neuropathy is a result of long-time exposure to hyperglycemia through the mechanisms of polyol accumulation and oxidative stress, which are similar to those leading to diabetic retinopathy. The prevalence of diabetic neuropathy is up to 51% among patients with diabetes[18]. Glucose-lowering treatments can prevent or slow the progression of diabetic neuropathy[13].

Macrovascular complications

Macrovascular complications refer to the complications affecting larger blood vessels. Unlike microvascular complications, where long-term hyperglycemia is the main factor leading to tissue and organ damage, the pathophysiology of macrovascular complications is not restricted to elevated blood glucose levels[14]. The main mechanism of macrovascular complications is atherosclerosis[14]. Indeed, insulin resistance and altered glucose metabolism are related to an overproduction of reactive oxygen species, which increases the risk of atherosclerosis[14]. Atherosclerosis can then affect different blood vessels such as coronary arteries (leading to coronary heart disease including myocardial infarction), peripheral arteries (leading to peripheral artery disease), and cerebral arteries (leading to cerebrovascular disease including ischemic stroke).

Macrovascular complications caused by atherosclerosis have become the leading cause of mortality for patients with diabetes mellitus[19]. Of note, although glucose-lowering treatments can effectively prevent or delay the onset of microvascular complications, they have been less effective in reducing the risk of macrovascular complications[14]. Indeed, only certain compounds belonging

to newer antidiabetic drug classes such as sodium-glucose co-transporter 2 inhibitors or glucagon-like peptide-1 receptor agonists have demonstrated the ability to reduce the risk of cardiovascular events in randomized controlled trials[19].

Table 2. Prevalence and incidence of complications of diabetes mellitus

Complications	Prevalence	Incidence
Diabetic ketoacidosis	40.6% at the time point of diagnosis of type 1 diabetes[8]	4.6~8.0 per 1000 person-years among patients with type 1 diabetes[7]
Hyperosmolar hyperglycemic state	Unknown[20]	<1 per 1000 person-years among patients with type 2 diabetes[7]
Diabetic retinopathy	35%[11]	38.3 per 1,000 person-years among patients with type 2 diabetes [21]
Diabetic nephropathy	20%~40%[15]	3 per 1000 person-years[22]
Diabetic neuropathy	6%~51%[18]	6 per 100 person-years[23]
Cardiovascular disease	32%[24] in type 2 diabetes	15-25 per 1000 person-years among patients with type 2 diabetes[25,26]

4.3 Pharmacologic approaches for the treatment of diabetes mellitus

In 1922, insulin was first extracted from dog pancreas to be used as treatment for type 1 diabetes[27]. Exogenous insulin compensates for absolute insulin deficiency in type 1 diabetes, leading to a strong improvement in survival in this population[28]. Insulin is also used in the treatment of type 2 diabetes, because it can lower blood glucose levels effectively and achieve normoglycemia in a short time. In 1978, the first recombinant DNA human insulin was produced by expressing chemically synthesized cDNA in Escherichia coli[27].

Following the development of insulin, many non-insulin glucose-lowering medications were discovered. **Table 3** shows an overview of commonly used glucose-lowering medications. Sulfonylureas were the first group of non-insulin antidiabetic drugs to obtain regulatory approval[29]. In 1937, the hypoglycemic activity of synthetic sulfur compounds was observed[27,30], and a few

years later, it was noticed that typhoid patients treated with the antibiotic p-amino-sulfonamide-isopropylthiodiazole developed hypoglycemia[27,30] and that aryl sulfonylurea compounds stimulate insulin secretion in pancreatic β-cells[27,30]. In 1956, the first sulfonylurea, tolbutamide, was marketed in Germany. Later, chlorpropamide, acetohexamide, and tolazamide were introduced commercially, and this group of drugs was labeled as first-generation sulfonylureas[27,30]. In 1984, more potent, second-generation sulfonylureas, glyburide and glipizide, were introduced in the United States (US)[27,30]. First-generation sulfonylureas are rarely used today because they are less potent and thus need to be administrated in higher doses[31].

Table 3. Overview of commonly used glucose-lowering medications

Class	Common agents	Administration [32,33]	Mechanism [27,30]	Hypoglycemia[32]	Weight gain[32]	HbA1c reduction (%)[33]	Half-life[33]	Metabolism[33]	Cost[32]
Biguanides	Metformin	Oral	Hepatic glucose production↓ intestinal glucose absorption↓ insulin sensitivity↑	No	Mild loss	1-2	5h	Unmetabolized, renal excretion	Low
Sulfonylureas	Glimepiride Glipizide Glyburide Gliclazide	Oral	Pancreatic insulin secretion↑	Yes	Gain	1-2	5-8h[34] 2-4h[34] 7-10h[35] 10h[34]	Liver	Low
TZDs	Pioglitazone	Oral	Insulin sensitivity↑	No	Gain	0.5-1.4	8-9h[36]	Liver	Low
DPP-4i	Sitagliptin Saxagliptin Vidagliptin Linagliptin Alogliptin	Oral	GLP-1 levels↑	No	Neutral	0.4-0.8[37]	3->200h[38]	Kidneys	High
SGLT2i	Canagliflozin Dapagliflozin Empagliflozin	Oral	Urinary glucose excretion↑	No	Loss	0.7-1.0[37]	8-16h[39]	Liver[39]	High
GLP-1 RAs	Semaglutide Liraglutide Exenatide Dulaglutide	Parenteral	Insulin secretion↑ satiety↑ delayed gastric emptying	No	Loss	0.5-1.5	< 2min[40]	Kidney[41]	High
Insulin	Human insulin, Analogs	Parenteral	Cell intake of glucose↑; Liver storage of glucose↑	Yes	Gain	1-2.5	Variable	Liver and kidney	Low, High

Abbreviations: HbA1c, hemoglobin A1c; TZDs, thiazolidinediones; DPP-4i, dipeptidyl peptidase 4 inhibitors; SGLT2i, sodium-glucose co-transporter 2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists.

Sulfonylureas lower blood glucose by stimulating insulin secretion in the pancreas. The mechanism is shown in **Figure 1**. Under physiologic conditions, blood glucose enters the beta cells in the pancreas through the glucose cell surface transporter GLUT2, leading to increased intracellular adenosine triphosphate (ATP) levels and the closing of ATP-dependent potassium (K^+) channels. Decreased K^+ efflux results in depolarization and the opening of voltage-gated calcium (Ca^{2+}) channels. The accompanying increase in Ca^{2+} levels subsequently triggers the secretion of insulin.

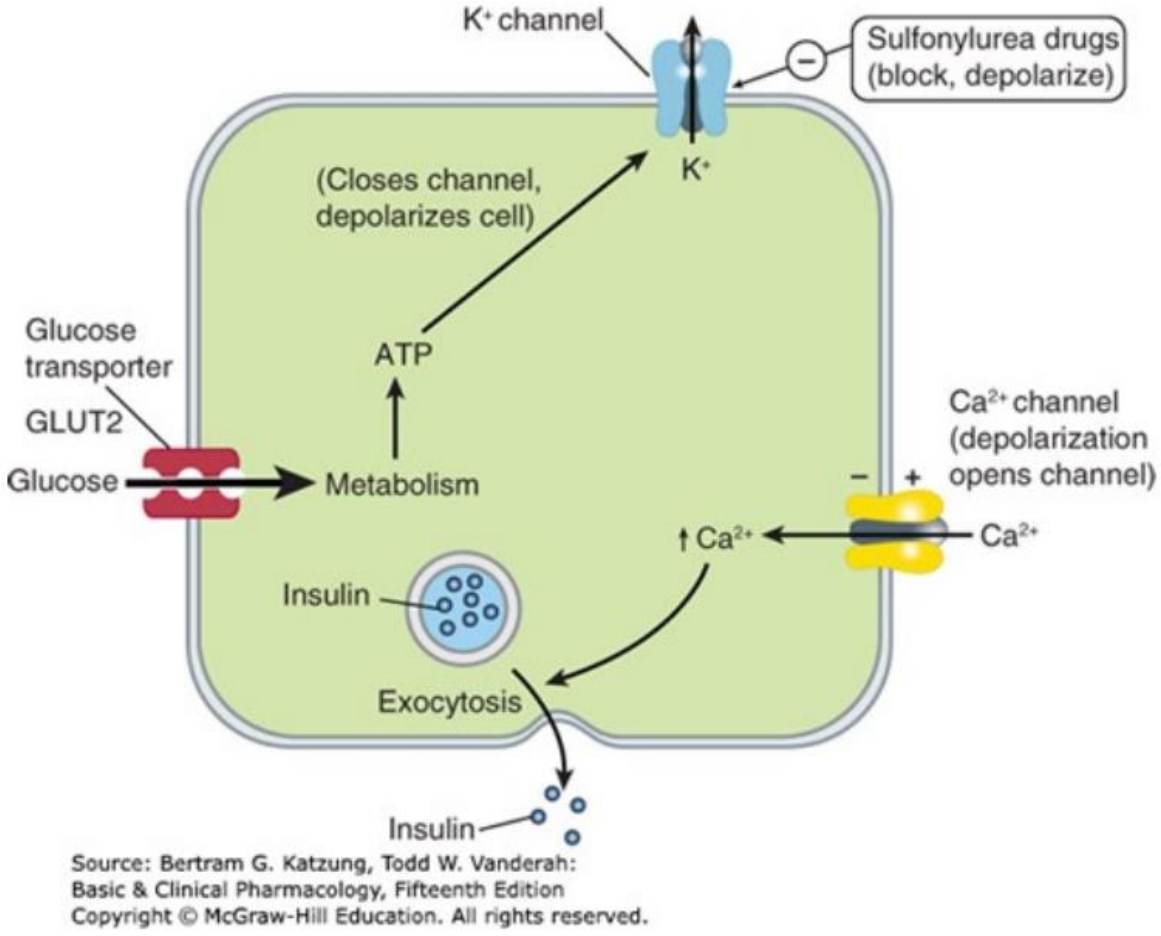

Figure 1. Mechanism of insulin secretion.
Abbreviations: GLUT2, glucose transporter 2; ATP, adenosine triphosphate.

Sulfonylureas bind to specific sulfonylurea receptors on the surface of beta cells. Binding of sulfonylureas results in the activation of the cascade described above involving the closing of ATP-dependent K^+ channels, the opening of voltage-gated Ca^{2+} channels, and the secretion of insulin. Sulfonylureas are highly efficacious in lowering blood glucose levels, reducing hemoglobin A1c(HbA1c) levels by 1–2% among patients with type 2 diabetes[30].

Today, sulfonylureas are mostly used as second-line or third-line treatments for type 2 diabetes[32,42]. Because of their efficacy and low cost, sulfonylureas are one of the most commonly prescribed antidiabetic drugs after treatment failure with the monotherapy of first-line drug metformin[29,43]. Indeed, 41.4% of treated type 2 diabetes patients use sulfonylureas as a part of their therapeutic regime[44]. Importantly, sulfonylureas are also approved for patients with severe kidney disease[45], when decreased renal function is often a contraindication for therapeutic alternatives such as metformin[46]. Data from the Clinical Practice Research Datalink (CPRD), a primary care database from the United Kingdom (UK) show that 58% of patients with an estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2 initiate antidiabetic pharmacotherapy with a sulfonylurea[47].

4.4 Pharmacokinetics and safety of sulfonylureas

Sulfonylureas are mainly metabolized by the enzymes cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 in the liver. The metabolites are then excreted by the kidneys and/or the biliary tract. Sulfonylurea metabolites can be pharmacologically inactive, weakly active, or moderately active. Together with variations in the plasma half-life of the original compounds, the pharmacologic activity of metabolites accounts for the intra-class differences in the duration of

action of sulfonylureas[48]. A summary of pharmacokinetic characteristics of different sulfonylureas is presented in **Table 4**.

Sulfonylureas are considered to be generally safe because idiosyncratic reactions such as exfoliative dermatitis and photosensitivity are rarely reported[34]. Moreover, most of the adverse drug reactions related to sulfonylurea use are dose-related[34]. Regarding such dose-related adverse drug reactions, second-generation sulfonylureas are considered to be safer than first-generation sulfonylureas[34]. The reason is the higher affinity of second-generation sulfonylureas to the sulfonylurea receptors of beta cells, making possible the lowering of blood glucose levels using much lower doses than with first-generation sulfonylureas.

The most common dose-related adverse effect of sulfonylureas is hypoglycemia. As shown in **Figure 1**, the mechanism based on which sulfonylureas stimulate insulin secretion is independent of the actual blood glucose levels. Therefore, sulfonylureas can stimulate insulin secretion even when glucose levels are below the normal threshold for glucose-stimulated insulin release[48]. As a result, sulfonylurea-induced hypoglycemia may occur in different settings including aggressive sulfonylurea treatment, lower glucose intake by the individual through nutrition, or decreased metabolism or excretion of sulfonylureas.

Table 4. Summary of pharmacokinetic characteristics of second-generation sulfonylureas

Molecules	% of metabolic clearance via CYP2C9[49]	Duration of action ($t_{1/2}$)[34]	Activity of metabolites ($t_{1/2}$)[34]	Elimination[34]
Gliclazide	30-40	10h	Inactive	65% via urine
Glimepiride	>80	5-8h	Active 3-6h	80% via urine
Glipizide	Not reported	2-4h	Inactive	70% via urine
Glyburide (Glibenclamide)	20-30	5-7h	Active 10h	50% via bile

Abbreviation: CYP2C9, cytochrome P-450 2C9.

4.5 Risk factors for sulfonylurea-induced hypoglycemia

Several factors can affect the risk of sulfonylurea-induced hypoglycemia. Of note, these risk factors can be either modifiable or non-modifiable. In general, modifiable risk factors of adverse drug effects are more interesting from a drug safety perspective, given that controlling for them can decrease the risk of toxicity. **Table 5** summarizes some major modifiable and non-modifiable risk factors of sulfonylurea-induced hypoglycemia.

Table 5. Major modifiable and non-modifiable risk factors of sulfonylurea-induced hypoglycemia

Behavioral factors[48]	**Interacting drugs**[31]	**Comorbidities**
Irregular eating habits, alcohol consumption, glycemic control	Fluconazole, ketoconazole, miconazole, fibrates, salicylates, ACE inhibitors, phenylbutazone, azapropazone, H_2 blockers, magnesium salts, sulfonamides, chloramphenicol, DPP-4 inhibitors, GLP-1 RAs	Decreased kidney and liver function

Abbreviations: HbA1c, hemoglobin A1c; ACE, angiotensin-converting enzyme; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide-1 receptor agonists.

Age and certain comorbidities are non-modifiable risk factors of sulfonylurea-induced hypoglycemia. For example, advanced age increases the risk of this adverse effect because of the accompanying decrease in organ function of the kidneys and the liver, which can reduce the patient's ability to metabolize and eliminate sulfonylueras[48]. For the same reason, chronic kidney and liver disease are further risk factors of sulfonylurea-induced hypoglycemia.

Modifiable risk factors of sulfonylurea-induced hypoglycemia include behavioral and lifestyle aspects such as irregular eating habits and alcohol consumption[48]. However, another category of modifiable risk factors of this adverse drug effect includes certain drug-drug

interactions involving sulfonylureas. Of note, drug-drug interactions are generally considered to be modifiable risk factors of drug toxicity because the risk can be reduced by using alternative drugs instead of the interacting compounds. Examples of drugs interacting with sulfonylureas to increase their risk of hypoglycemia are azole antifungal agents and the lipid-lowering agent gemfibrozil. Indeed, these drugs are strong inhibitors of CYP2C9 in the liver, and their concomitant use with sulfonylureas can inhibit the metabolism of sulfonylureas and possibly increase the risk of sulfonylurea-induced hypoglycemia[48]. However, the clinical relevance of these interactions is probably limited, given that the aforementioned drugs are not commonly used together with sulfonylureas.

Sulfonylureas may also interact with warfarin, a commonly used oral anticoagulant. Oral anticoagulants are used in the prevention of ischemic stroke in patients with atrial fibrillation but also in the prevention and treatment of thrombosis. Because atrial fibrillation shares some common antecedents with type 2 diabetes (e.g., arterial hypertension, obesity, atherosclerosis)[50], the concurrence of atrial fibrillation and diabetes mellitus is common: atrial fibrillation occurs in 15% of patients with type 2 diabetes mellitus[51], while diabetes mellitus occurs in 20% of patients with atrial fibrillation[52]. Moreover, diabetes mellitus is a risk factor for stroke in patients with atrial fibrillation.[53]. Therefore, oral anticoagulation is common among patients with diabetes mellitus, and concomitant use of sulfonylureas and warfarin is not rare in clinical practice (roughly 1% of sulfonylurea users[54]).

Two pharmacokinetic mechanisms have been proposed for the sulfonylurea-warfarin drug-drug interaction, with both potentially leading to elevated plasma levels of sulfonylureas and an increase in their risk of hypoglycemia. First, warfarin is mainly metabolized in the liver by the CYP2C9 enzyme. Since warfarin and sulfonylureas are both CYP2C9 substrates, concomitant use

of these drugs could lead to reduced CYP2C9-mediated metabolism and elevated sulfonylurea levels[55]. Of note, sulfonylureas with a strong CYP2C9 involvement such as glimepiride could have a higher risk of interaction with warfarin based on this mechanism[49]. Second, warfarin may displace sulfonylureas from their protein binding sites in the blood, resulting in an increase of the unbound, that is pharmacologically active, sulfonylurea fraction[56].

4.6 Observational studies on the sulfonylurea-warfarin interaction

To date, there have been four observational studies that have assessed the potential association between the concomitant use of sulfonylureas and warfarin and the risk of hypoglycemia.

4.6.1 Romley et al. 2015

The first study[57] was a retrospective cohort study based on Medicare administrative data in the US. The study assessed the risk of severe hypoglycemia associated with concomitant use of the sulfonylureas glipizide or glimepiride and warfarin compared with the use of these sulfonylureas alone. The analytical time unit was a person-quarter, that is a three-month period. Initially, all person-quarters with a pharmacy claim for either glipizide or glimepiride were identified. Then, person-quarters with an additional pharmacy claim for warfarin were labeled as person-quarters of concomitant use, and other person-quarters without such claims were labeled as person-quarters of sulfonylurea use alone. Person-quarters without a pharmacy claim of the sulfonylureas of interest were excluded from the analysis. Finally, multivariable logistic regression estimated odds ratios (OR) and 95% confidence intervals (CIs) of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin compared with sulfonylurea use alone. The

statistical analysis was adjusted for age, sex, race, and comorbidities. The study reported that concomitant use of sulfonylureas and warfarin was associated with a 22% increased risk of severe hypoglycemia compared with use of sulfonylureas alone (OR, 1.22; 95% CI, 1.05 to 1.42).

Several important biases could have limited the validity of the study findings. First, the assumption that an entire person-quarter was co-exposed if a prescription for warfarin and a prescription for a sulfonylurea occurred anytime during the three-month period probably introduced exposure misclassification. The entire person-quarter would be misclassified as co-exposed if the prescriptions for warfarin and for the sulfonylurea did not overlap. Moreover, parts of the person-quarter would be misclassified as co-exposed even if there was an overlap of prescriptions, but the duration of the overlap was shorter than the duration of the person-quarter.

Second, the exact timing of the hypoglycemic event during a person-quarter is unknown. Therefore, for individuals with overlapping prescriptions for sulfonylureas and warfarin and the outcome in the same quarter, it is difficult to determine whether the overlapping prescriptions actually preceded the outcome. As a result, reverse causation is possible. Of note, even if concomitant use of sulfonylureas and warfarin is not likely to be a direct result of hypoglycemia, it could be an indirect result of hospital admission or discharge that was related to hypoglycemia.

Third, the study included a mix of new users and prevalent users of sulfonylureas. As compared to new users of sulfonylureas, prevalent users of sulfonylureas may have a lower risk of hypoglycemia because they have tolerated the drug for a certain period of time, a phenomenon known as depletion of susceptibles[58]. If co-exposed person-quarters have, on average, more new sulfonylureas users and less prevalent sulfonylurea users than the not co-exposed person-quarters, an artificially increased risk of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin can be observed even in the absence of a true effect.

Finally, comorbidities were measured "at time of first appearance in the sample". Given that patients may develop comorbidities during follow-up, time-dependent confounding is possible. If certain comorbidities are associated with warfarin addition and increase the risk of hypoglycemia, the onset of these comorbidities during follow-up could potentially result in an overestimation of the effect.

4.6.2 Nam et al. 2019

The study by Nam et al.[59] assessed the potential association between concomitant use of sulfonylureas and warfarin and the risk of severe hypoglycemia using a self-controlled case series. The data source was administrative healthcare data from Medicare in the US. Only individuals who experienced severe hypoglycemia were included. The observation period was defined as continuous use of sulfonylureas. The exposure risk period was defined as time of concurrent use with warfarin. Conditional Poisson regression yielded the outcome occurrence rate ratio (RR), defined as the rate of severe hypoglycemia during time of concurrent use versus the rate of severe hypoglycemia during time of sulfonylureas use alone. Metformin was used as a negative control object drug given the absence of known pharmacologic mechanisms by which metformin could interact with warfarin.

This study reported that concomitant use of glimepiride with warfarin was associated with a 47% increased rate of severe hypoglycemia compared with glimepiride use alone (RR, 1.47; 95% CI, 1.07 to 2.02). The RRs for two other sulfonylureas were also elevated but not statistically significant (glipizide: RR, 1.20; 95% CI, 0.98 to 1.46 / glyburide: RR, 1.09; 95% CI, 0.88 to 1.35). Surprisingly, there was also a 73% increased rate associated with concomitant use of metformin with warfarin compared with metformin use alone (RR, 1.73; 95% CI, 1.38 to 2.16). While the

authors attributed these unexpected findings post-hoc to an assumed intrinsic hypoglycemic effect of warfarin, the lack of any published cases of warfarin-related hypoglycemia after more than half a century of warfarin experience in clinical practice makes such an explanation unlikely[60].

This study had several potential limitations. First, severe hypoglycemia is a well-known adverse effect of sulfonylurea use. Hence, sulfonylurea use is likely to be stopped (either temporarily or permanently) after such events. If patients discontinue sulfonylureas because of severe hypoglycemia, outcome-dependent censoring (censoring of patients due to the occurrence of the outcome) can be introduced. While the direction of the bias may depend on the specific utilization patterns of a given cohort, there are several clinical scenarios where the bias can lead to an overestimation of the risk. Such clinical scenarios include the avoidance of a future initiation of warfarin while on a sulfonylurea following the hypoglycemic event (assuming the prescribing physician was aware of the potential interaction) or the stopping of concomitant use of sulfonylureas and warfarin due to the hypoglycemic event.

Second, the risk of sulfonylurea-induced hypoglycemia may decrease with longer durations of sulfonylurea use (depletion of susceptibles[58]). In this study, continuous sulfonylurea use defined the observation period, while the addition of warfarin on sulfonylureas defined the exposure risk period. The exposure risk period could have a lower susceptibility than the observation period before exposure, but a higher susceptibility than the observation period after the exposure. However, a difference in occurrence rate of severe hypoglycemia will be observed during time of concurrent use versus time of sulfonylureas use alone, even in the absence of a true effect.

Finally, the authors adjusted for several drugs known to interact with sulfonylureas but without intrinsic hypoglycemic risk. However, the adjustment for covariates that are only (or

mostly) associated with the exposure (and not with the outcome), so-called 'instrumental variables', has been shown to potentially increase bias[61].

4.6.3 Alwafi et al. 2022

Alwafi et al.[62] conducted a retrospective cohort study using patient records from IQVIA Medical Research Data and The Health Improvement Network in the UK. Patients were defined as co-exposed if they had a sulfonylurea prescription overlapping with a new warfarin prescription or vice versa. Individuals were censored if they stopped the relevant medications (either concomitant use of sulfonylureas and warfarin or sulfonylurea use alone). Patients with a prescription for a direct oral anticoagulant (DOAC) at any time during study period (that is also after cohort entry) were excluded from the analysis. Propensity score matching was used for confounding control. A Cox proportional hazards model was used to estimate the risk of hypoglycemia, which was defined as any hypoglycemia recorded by the general practitioner. The study reported an increased risk of hypoglycemia associated with concurrent use of warfarin and sulfonylureas when compared to sulfonylurea use alone (hazard ratio [HR] 1.38; 95% CI 1.10 to 1.75).

This study had some important limitations. First, while the date of cohort entry (time zero) for the co-exposed group was the first overlap of sulfonylureas and warfarin among patients with type 2 diabetes, the respective date for the comparator group was the date of the first prescription for a sulfonylurea among patients with type 2 diabetes. This may lead to prevalent user bias. Indeed, at the time of cohort entry, patients in the comparator group were new users of sulfonylureas, while co-exposed patients were a mix of prevalent and new users of sulfonylureas. This bias could result

in an underestimation of the HR because prevalent users of sulfonylureas may have a lower risk of sulfonylurea-induced hypoglycemia due to depletion of susceptibles.

Second, the potential exclusion of patients with a DOAC prescription even after cohort entry would do not only limit the external validity of the results but may also cause selection bias. This bias can be introduced due to the potential association of DOAC use both with the exposure (warfarin use or not among users of sulfonylureas) and with the outcome. The latter association is possible considering that a reason for patients switching from warfarin to DOACs is high disease severity, which can in turn be associated with the risk of hypoglycemia.

Third, outcome misclassification and thus information bias is possible. Especially for very mild hypoglycemic events, it may be unclear if the recorded date in the data source reflects the actual date of the event or the date of the reporting to the treating physician. Of note, this type of information bias could be either differential or non-differential between exposure groups.

Fourth, the definition of the outcome based exclusively on outpatient diagnoses can also lead to detection bias, given that patients on warfarin visit their physicians more often due to the need for dose adjustments. Thus, they are more likely to report a hypoglycemic event, which could then lead to an overestimation of the incidence rate in the co-exposed group and thus to an overestimation of the true effect.

Finally, similar to the study by Nam et al., the inclusion of several medications that interact with sulfonylureas but do not have an intrinsic hypoglycemic risk in the propensity score may have introduced bias because they are potential instrumental variables.

4.6.4 Dimakos et al. 2022

Dimakos et al[54] studied the sulfonylurea-warfarin interaction in a retrospective cohort study based on the UK Clinical Practice Research Datalink (CPRD). This study used a time-varying exposure definition to compare current concomitant use of sulfonylureas and warfarin with current use of sulfonylureas. Time-dependent Cox proportional hazards models were used to estimate the risk of severe hypoglycemia. The study reported a 25% increase in the risk of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin compared with sulfonylurea use alone (HR 1.25; 95% CI 1.16 to 1.35). The study also estimated the risk using antiplatelet agents (HR 1.20; 95% CI 1.11 to 1.30) and DOACs (HR 1.01; 95% CI 0.67 to 1.52) as negative control precipitants. These analyses led to an attenuation or even disappearance of the risk.

This study had some potential limitations. First, covariates were measured at cohort entry, which was defined as the first prescription of a sulfonylurea. However, patient characteristics may change during follow-up. If certain characteristics are related to the indication of warfarin use and also affect the risk of severe hypoglycemia, they could introduce time-dependent confounding. Reassuringly, a sensitivity analysis using a marginal structural Cox proportional hazards model found results that were consistent with those of the primary analysis.

Second, when using DOACs as an active comparator, the study cohort was restricted to January 1st, 2011, when the first DOAC was approved in the UK for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation, onwards. The rationale was to ensure that patients are eligible to contribute person-time to either exposure group (sulfonylureas and warfarin versus sulfonylureas and DOACs). While this approach guaranteed compliance to the positivity assumption, it limited the sample size and thus the precision of the findings.

Finally, time-varying exposure definition could potentially lead to depletion of susceptibles. According to this exposure definition, patients in the cohort are allowed to contribute multiple episodes of concomitant use during follow-up. If the risk of an adverse effect due to a drug-drug interaction does not remain constant over time but decreases after the most susceptible individuals have experienced it and their follow-up has been censored, considering more than one episode of concomitant use per patient could potentially dilute the effect.

Table 6. Main characteristics and biases in the previous four observational studies

	Romley 2015[57]	**Nam 2019**[59]	**Alwafi 2022**[62]	**Dimakos 2022**[54]
Study design	Retrospective cohort study	Self-controlled case series	Retrospective cohort study	Retrospective cohort study
Exposure definition	Time-varying	Time-varying	As treated	Time-varying
Outcome	Severe hypoglycemia	Severe hypoglycemia	Hypoglycemia	Severe hypoglycemia
Risk (versus SU use alone)	OR 1.22 (95% CI 1.05 to 1.42)	RR 1.47 (95% CI 1.07 to 2.02)	HR 1.38 (95% CI 1.10 to 1.75)	HR 1.25 (95% CI, 1.16 to 1.35)
Bias				
Prevalent user bias	Yes	Yes	Yes	No
Reverse causality	Possible (hospital discharge leading to warfarin or SU prescription)	Severe hypoglycemia cause not concurrent use of sulfonylureas and warfarin	No	No
Exposure misclassification	Yes (within each person-quarter)	No	No	No
Outcome detection bias	No	No	Possible	No
Selection bias	Possible (exclusion of person-quarters without SU prescription)	Possible (outcome-dependent censoring)	Possible (informative censoring, exclusion of patients using DOACs after cohort entry)	No
Time dependent confounding	Possible	No (adjustment for time-dependent covariates)	Possible	Possible but consistent results with marginal structural Cox model
Adjustment for IV	No	Yes	Yes	No
Confounding by indication	Possible	Possible	Possible	Possible (attenuation of increased risk with use of control precipitant)

Abbreviations: SU, sulfonylureas, OR, odds ratio; RR, rate ratio; HR, hazard ratio; CI, confidence interval, IV, instrumental variable; DOACs, direct oral anticoagulants.

4.7 Summary of previous studies

The previous four observational studies applied various study designs: self-controlled case series[59], cohort study with a time-fixed exposure definition[62], cohort study with a time-varying exposure definition and 3-month periods as time unit[57], and cohort study with a time-varying exposure definition and 1-day periods as time unit[54]. Each design has strengths and limitations, with the latter mostly including different types of selection bias[57,59,62] and confounding. In general, the cohort approach with a time-varying exposure definition and 1-day periods as time unit (see Dimakos et al. 2022[54]) but also a case-control analysis nested within an underlying cohort, an approach very similar to the cohort approach with a time-varying exposure definition,[63] have the advantage of minimizing selection bias. However, both approaches can introduce time-dependent confounding and may potentially miss effects with a small size due to depletion of susceptibles. To overcome these limitations, we propose the use of the recently developed prevalent new-user design to study the safety of the potential interaction between sulfonylureas and warfarin.

5. METHODS

5.1 Data Source

We used data from the UK CPRD Aurum, which is a primary care database that contains electronic medical records of 60 million individuals collected from 2,000 practices in the UK[64]. This represents 10% of general practitioner practices and 13% of the population of England. In the UK, specialists and other healthcare providers are required to report back to the general practitioner, who serves as the gatekeeper of the healthcare system[65]. The CPRD population has been shown to be a representative sample of the general UK population in terms of important variables such as age, sex, region, deprivation, and ethnicity.[65] The CPRD contain rich information including demographic characteristics, medical diagnoses (based on the Read coding system), and drug prescription data (based on the British National Formulary). It also contains lifestyle variables (e.g., smoking habits, alcohol consumption), anthropometric variables (e.g., body mass index [BMI]), clinical measures (e.g., blood pressure), and laboratory test results (e.g., HbA1c, serum creatinine). CPRD data have been validated extensively[66,67]. Regarding type 2 diabetes, Read codes for this condition have shown a sensitivity of 99% and a specificity ranging from 94-98%[66].

The HES includes information on hospital admissions, medical procedures, and discharge diagnoses coded by the International Classification of Diseases, 10th Revision (ICD-10)[65]. The ONS contains the electronic death certificates including the date and the underlying cause of death of people who died in England and Wales[65]. The linkages are currently available for roughly 93% of CPRD practices in England [65]. Linked data are available from April 1, 1997 to present. Linkage between the CPRD and the HES and the ONS has been well validated and the linked population has been shown to be representative of the larger CPRD population[68,69].

5.2 Base cohort

First, we assembled a base cohort that included all patients initiating treatment with second-generation sulfonylureas in the CPRD between April 1, 1998 and June 30, 2020. For our study, we considered glibenclamide (also known as glyburide), glimepiride, gliclazide, and glipizide, compounds that account for >99% of the prescriptions for second-generation sulfonylureas in the CPRD. We excluded i) patients younger than 18 years, ii) patients with less than 365 days of recorded history in the CPRD (to have a sufficient look-back period for the application of inclusion and exclusion criteria and for the measurement of covariates), and iii) patients with previous use of first-generation sulfonylureas, meglitinides or insulin. The rationale for the latter exclusion criterion was that the mechanism of drug-induced hypoglycemia for first-generation sulfonylureas, meglitinides, and insulin is very similar to the one of second-generation sulfonylureas[70]. Thus, prior use of these medications may introduce depletion of susceptibles[58]. The date of base cohort entry was defined as the date of the first prescription for a second-generation sulfonylurea.

5.3 Prevalent new-user design and study cohort

Out of the base cohort, we assembled a study cohort using the prevalent new-user design[71]. The prevalent new-user design is an extension of the active-comparator new-user design[72]. It was first introduced in 2017 for the assessment of comparative drug effects in settings where a newer drug needs to be compared to an older drug[71]. Since then, this design has also been used in settings where there is no adequate active compactor available[73]. In the following two sections, we will briefly describe the rationale for using the prevalent new-user design in the aforementioned settings. Then, we will show how we used it to assemble the study cohort in the setting of a drug-drug interaction study.

5.3.1 Prevalent new-user cohort design for comparative drug effects

The prevalent new-user design was first used to assess the risk of heart failure associated with the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as compared with the use of sulfonylureas[71]. GLP-1 RAs entered the market in 2007, while sulfonylureas were first approved in the 1950s. Treatment switches between older antidiabetic drugs such as sulfonylureas and newer antidiabetic drugs such as GLP-1 RAs are common in the pharmacotherapy of type 2 diabetes treatment switches between older antidiabetic drugs such as sulfonylureas and newer antidiabetic drugs such as GLP-1 RAs are common in the pharmacotherapy of type 2 diabetes. If an incident new-user cohort design was used, about 75% of GLP-1 RA users would be excluded due to history of sulfonylurea use[71]. However, GLP-1 RA users with a history of sulfonylurea use comprise a clinically relevant population and represent a significant number of type 2 diabetes patients.

To overcome this limitation of the new-user design, and to enhance external validity and potentially statistical power, a prevalent new-user cohort design was used. A base cohort was assembled including all users of antidiabetic drugs between 2000 and 2014. For each GLP-1 RA user, a time-based exposure set was defined by all patients in the base cohort who were exposed to a sulfonylurea for the same duration of treated diabetes as the GLP-1 RA user when starting treatment with GLP-1 RAs. An alternative method is to define a prescription-based exposure set by all patients in the base cohort with the same number of prior sulfonylurea prescriptions as GLP-1 RA users at the time point of GLP-1 RA initiation (the number of prior sulfonylurea prescription could be 0 when both GLP-1 RA users and sulfonylureas users are incident new users). Within each time-based or prescription-based exposure set, a sulfonylurea user with very similar characteristics (same calendar year and closest time-conditional propensity score) as the GLP-1 RA user was identified as a comparator[71]. The risk of heart failure among GLP-1 RA users was

compared with the risk among the matched comparators from either time-based or prescription-based exposure sets.

5.3.2 Prevalent new-user design in the absence of an active comparator

Another setting where the prevalent new-user design can be applied is when an appropriate active comparator is lacking. In this case, users of the drug of interest need to be compared to non-users. Using a traditional new-user design, new users are defined as patients who initiated the drug of interest during a defined chronological time, with treatment initiation defining the date of cohort entry ('time-zero'). However, the definition of the date of cohort entry among non-users is not as straightforward and may introduce time-related biases such as immortal time-bias and time-lag bias[74]. The application of a prevalent new-user design can minimize or eliminate these biases by matching patients initiating the drug of interest to patients who had the opportunity to get exposed but did not either on the duration of disease in a time-base exposure set or the number of physician visits in a 'prescription'-based exposure set.

Of note, some of the non-users may become new users of the drug of interest later during follow-up, and they are censored according to the as-treated approach. However, this censoring can be informative and thus introduces selection bias. In the setting of using the prevalent new-user design to assess the effectiveness of proton pump inhibitors in reducing mortality among patients with idiopathic pulmonary fibrosis, Tran et al. compared three different approaches (study based on never users, marginal structural Cox proportional hazards model, and inverse probability of censoring weighting) in addressing this bias[73]. The results suggested that the use of a marginal structural Cox proportional hazards model combined with inverse probability of censoring weighting produced the most robust findings[73].

5.3.3 Study cohort

Out of the base cohort of new users of second-generation sulfonylureas (from now on sulfonylureas for simplicity), we identified those adding on warfarin while on a sulfonylurea during the study period ("co-exposed"). Patients with a warfarin prescription in the past three months were excluded. For each co-exposed patient, we defined a prescription-based exposure set[71] based on the number of prior sulfonylurea prescriptions. To minimize the loss of co-exposed patients due to lack of potential matches, while assuring that all patients in the exposure set have a similar history of sulfonylurea use, we created 10 different groups of prior sulfonylurea prescriptions based on the distribution of this variable in the cohort: 0, 1, 2-3, 4-7, 8-13, 14-22, 23-34, 35-52, 53-87, and >88. Thus, each exposure set included one co-exposed patient and all other patients from the base cohort who were currently on sulfonylureas, did not add-on warfarin, and had the same or a very similar number of prior sulfonylurea prescriptions as the co-exposed patient (**Figure 2**).

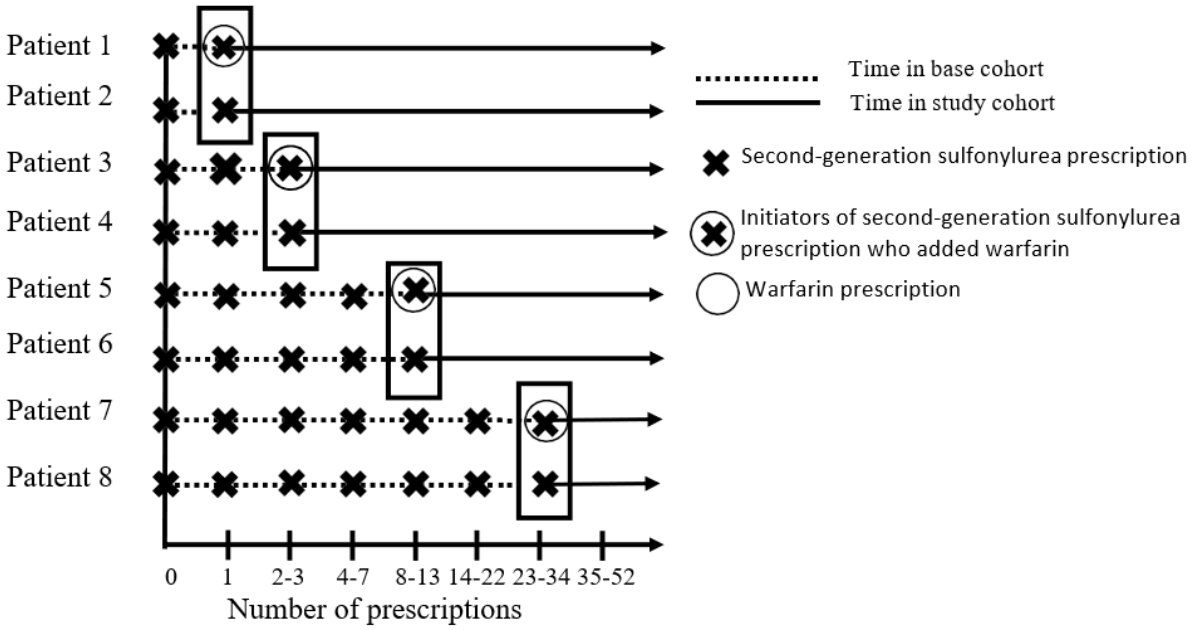

Figure 2. Illustration of the prevalent new-user study design
The figure shows how initiators of second-generation sulfonylureas who add warfarin are matched to initiators of second-generation sulfonylureas who do not add warfarin based on prescription-based exposure sets.

Within each exposure set, we matched the co-exposed patient to up to five comparator patients on i) calendar year, ii) number of prior insulin prescriptions (≤1, 2-4, or >4) and iii) closest time-conditional propensity score (TCPS) (see below). For matching on TPCS, we used a caliper width of 0.2 standard deviations of the TCPS on the logarithmic scale. To maximize study power, we matched with replacement, that means we allowed comparators to be matched to more than one co-exposed patients. The date of the matched set defined the date of study cohort entry. Of note, matched patients from the comparator group were allowed to switch to the co-exposed group upon addition of warfarin later during follow-up. Patients were followed until the earliest of the following: treatment discontinuation (see below), treatment switch (see below), occurrence of the study outcome (see below), end of registration with the general practice in the CPRD, or end of

the study period (June 30th, 2020). Patients in both groups were allowed to switch between different sulfonylureas.

5.4 Time-conditional propensity scores

Using logistic regression, we calculated TCPS. Time-conditional refers to the estimation of the propensity score based on the patient characteristics measured at the time of the prescription-based exposure sets - that is, conditional on the time of the exposure set. The TCPS predicted the probability (or propensity) of adding-on warfarin versus not adding-on warfarin on the basis of pre-specified covariates. We included the following pre-specified covariates in the TCPS: calendar year, age, sex, smoking status, body mass index category and important comorbidities including alcohol-related disorders, arterial hypertension, congestive heart failure, hyperlipidemia, chronic kidney disease, cognitive dysfunction, and acute infection. We also included markers of diabetes severity including diabetes duration, HbA1c levels, number of non-sulfonylurea antidiabetic drugs, microvascular diabetic complications (nephropathy, retinopathy, neuropathy), macrovascular diabetic complications (ischemic stroke or transient ischemic attack, myocardial infarction, peripheral vascular disease), other diabetic complications, severe hypoglycemia during time in base cohort, and severe hypoglycemia before base cohort entry. Moreover, we included the use of medications that have been associated with the risk of hypoglycemia (fluoroquinolones, tramadol, lithium). Finally, we included the number of prior hospitalizations as a proxy of overall health. Details regarding the definition of covariates and their time period of measurement can be found in **Table 7**.

5.5 Exposure definition

We used an as-treated exposure definition, in which patients were considered continuously exposed to the drug(s) of interest if the duration of one prescription overlapped with the date of the next prescription. In case of non-overlapping successive prescriptions, we allowed for a 30-day grace period between successive prescriptions. Thus, treatment discontinuation was defined by a gap exceeding prescription duration plus grace period. For the comparator group, addition of warfarin was considered treatment switch; hence, the follow-up of these patients in the comparator group was censored.

5.6 Outcome definition

The study outcome was severe hypoglycemia, which was defined as hospitalization with hypoglycemia (diagnostic code anywhere in the hospitalization record in the HES) or death due to hypoglycemia (underlying cause of death in the ONS). The date of hospital admission or death defined the date of the event. We used the following three ICD-10 codes to define hypoglycemia: E16.0 ("drug-induced hypoglycemia without coma"), E16.1 ("other hypoglycemia"), and E16.2 (hypoglycemia, unspecified). The specificity of these codes has been shown to be high (>90%)[75].

Table 7. List of covariates for time-conditional propensity scores

Covariate	Definition	Time-period of measurement	Type of covariate
Year of study cohort entry	Calendar year	At study cohort entry	Categorical
Age	-	At study cohort entry	Continuous; flexible modelling using restricted cubic splines with five interior knots[76]
Sex	Sex at birth	At study cohort entry	Binary (male, female)
Smoking status	Diagnostic Read codes	Last measurement before study cohort entry	Categorical (current, former, never, unknown)
Body mass index category	Weight/height^2	Last measurement before study cohort entry	Categorical (<25 kg/m^2, 25-29 kg/m^2, ≥30 kg/m^2, unknown)
Comorbidities			
Alcohol-related disorders	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Arterial hypertension	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Congestive heart failure	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Hyperlipidemia	Diagnostic Read and ICD codes, Product codes of antihyperlipidemic drugs	Ever before study cohort entry	Binary
Chronic kidney disease	See below[a]	Ever before study cohort entry	Binary
Cognitive dysfunction	Diagnostic Read and ICD codes, Product codes of antidementia drugs	Ever before study cohort entry	Binary
Acute infection	Diagnostic Read and ICD codes	Three months before study cohort entry	Binary
Markers of diabetic severity			
Diabetes duration	See below[b]	See below[b]	Continuous; flexible modelling using restricted cubic splines with five interior knots[76]
HbA1c level	Laboratory test result	Last measurement before study cohort entry	Categorical (<7%, 7-8%, >8%, unknown)
Number of non-sulfonylurea antidiabetic drugs	Product codes	Year before study cohort entry	Binary (0, ≥1)
Diabetic nephropathy	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary

Covariate	Definition	Time-period of measurement	Type of covariate
Diabetic neuropathy	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Diabetic retinopathy	Diagnostic Read and ICD codes, OPCS codes	Ever before study cohort entry	Binary
Myocardial infarction	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Ischemic stroke/TIA	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Peripheral vascular disease	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
Other diabetic complications	Diagnostic Read and ICD codes	Ever before study cohort entry	Binary
History of severe hypoglycemia	Diagnostic Read and ICD codes	During time in base cohort	Binary
History of severe hypoglycemia	Diagnostic Read and ICD codes	Ever before base cohort entry	Binary
Prior use of drugs			
Quinolones	Product codes	One year before study cohort entry	Binary
Tramadol	Product codes	One year before study cohort entry	Binary
Lithium	Product codes	Year before study cohort entry	Binary
Proxy of overall health			
Number of hospitalizations	Administrative data	Year before study cohort entry	Binary (0, ≥1)

Abbreviations: ICD, International Classification of Diseases; OPCS, operating procedure code supplement; TIA, transient ischemic attack; HbA1c, hemoglobin A1c; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration.

[a] Chronic kidney disease was defined as i) a diagnosis of chronic kidney disease (diagnostic Read and ICD codes), ii) kidney transplantation (diagnostic Read and ICD codes, OPCS codes), iii) at least two sessions of dialysis (diagnostic Read and ICD codes, OPCS codes), iv) at least two values for GFR/eGFR <90 mL/min per 1.73m^2 and recorded at least three months apart, v) at least one session of dialysis and one value GFR/eGFR <90 mL/min per 1.73m^2, recorded at least three months apart, vi) at least two diagnoses for unspecified renal failure and recorded at least three months apart, vii) at least one diagnosis for unspecified renal failure, and one session of dialysis or one value GFR/eGFR <90 mL/min per 1.73m^2, recorded at least three months apart. For eGFR, we used either eGFR values or calculated it indirectly based on serum creatinine values and using the CKD-EPI formula.

[b] Duration of diabetes was defined as the time period between the first diagnosis of type 2 diabetes (diagnostic Read or ICD codes) or the first HbA1c >6.5%, or the first prescription for an antidiabetic drug and study cohort entry.

5.7 Primary analysis

Our primary aim was to compare the risk of severe hypoglycemia of patients adding warfarin on sulfonylureas, compared with sulfonylureas users not adding warfarin. To this end, we first calculated the incidence rates of severe hypoglycemia before and after matching overall and in each of the two exposure groups. We further used a Cox proportional hazards model to estimate the HR and 95% CIs of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin, as compared to use of sulfonylureas alone. To account for variance potentially resulting from matching with replacement, we used a robust sandwich estimator.

5.8 Secondary analyses

We also conducted four pre-specified secondary analyses. First, we stratified the analyses by sex (male, female), age (<65 years, ≥65 years) and history of renal disease. Second, we assessed a potential duration-response relation by modelling concomitant use of sulfonylureas and warfarin as a continuous variable flexibly using splines with up to five interior knots[76].

5.9 Sensitivity analyses

We conducted eight sensitivity analyses to address the potential impact of different sources of bias. First, we used an intention to treat exposure definition, thereby limiting follow-up to 1 year. According to this approach, co-exposed patients were not censored upon discontinuation of concomitant use, and comparator patients were not censored upon discontinuation of sulfonylureas or addition of warfarin. The rationale was to assess the potential impact of informative censoring due to the as-treated approach. Second, we used inverse probability of censoring weights. This is another approach to assess the potential impact of informative censoring[73]. Third, we matched

without replacement, thus not allowing matched comparators to be matched again to co-exposed patients in future exposure sets. Fourth, we used alternate 15-day and 60-day grace periods between successive, non-overlapping prescriptions to assess the potential impact of exposure misclassification. Fifth, we restricted the outcome definition to hospitalization codes of hypoglycemia in primary position only to account for potential outcome misclassification. Sixth, we additionally censored upon initiation of insulin during follow-up to eliminate potential time-dependent confounding due to differential use of insulin after cohort entry. Finally, we excluded patients with severe hypoglycemia prior to study cohort entry.

5.10 Supplementary analyses

In supplementary analyses, we used time-based exposure sets instead of prescription-based exposure sets. The construction of time-based exposure sets was based on the time since the first prescription for a second-generation sulfonylurea. When using time-based exposure sets, we tried three different matching approaches: (i) up to five matches with replacement (as in the primary analysis), (ii) up to five matches without replacement, and (iii) “closest match” without replacement.

5.11 Ethics

The cohort was obtained from the CPRD, and it was stored and analyzed at the Centre for Clinical Epidemiology of the Jewish General Hospital (JGH) in Montreal, Quebec, Canada. The study protocol has been approved by the JGH's Research Ethics Board and the Independent Scientific Advisory Committee of the CPRD (protocol 20_195R).

6. RESULTS

Overall, there were 325,549 patients initiating sulfonylurea use between 1998 and 2020 (**Figure 3**). After sulfonylurea initiation, 18,104 patients added-on warfarin (from now on "co-exposed group" for simplicity) at some point during the study period creating an equal number of exposure sets (**Figure 4**). **Table 8** shows the baseline characteristics of each co-exposed patient and a random comparator within the prescription-based exposure set created by the co-exposed patient, matched on year of cohort entry and number of prior insulin prescriptions. As expected, co-exposed patients were older, more likely to have cardiovascular comorbidities, and more likely to have been hospitalized than comparators. On the other hand, comparators were more likely to have poorly controlled diabetes (HbA1c >8%). After TCPS matching, the study cohort included 17,890 co-exposed patients and 88,749 comparators. The study cohort was formed by matching each co-exposed patient with up to 5 comparators within the same prescription-based exposure set on closest TCPS, year of cohort entry, and number of prior insulin prescriptions. All characteristics were well-balanced after matching (**Table 8**).

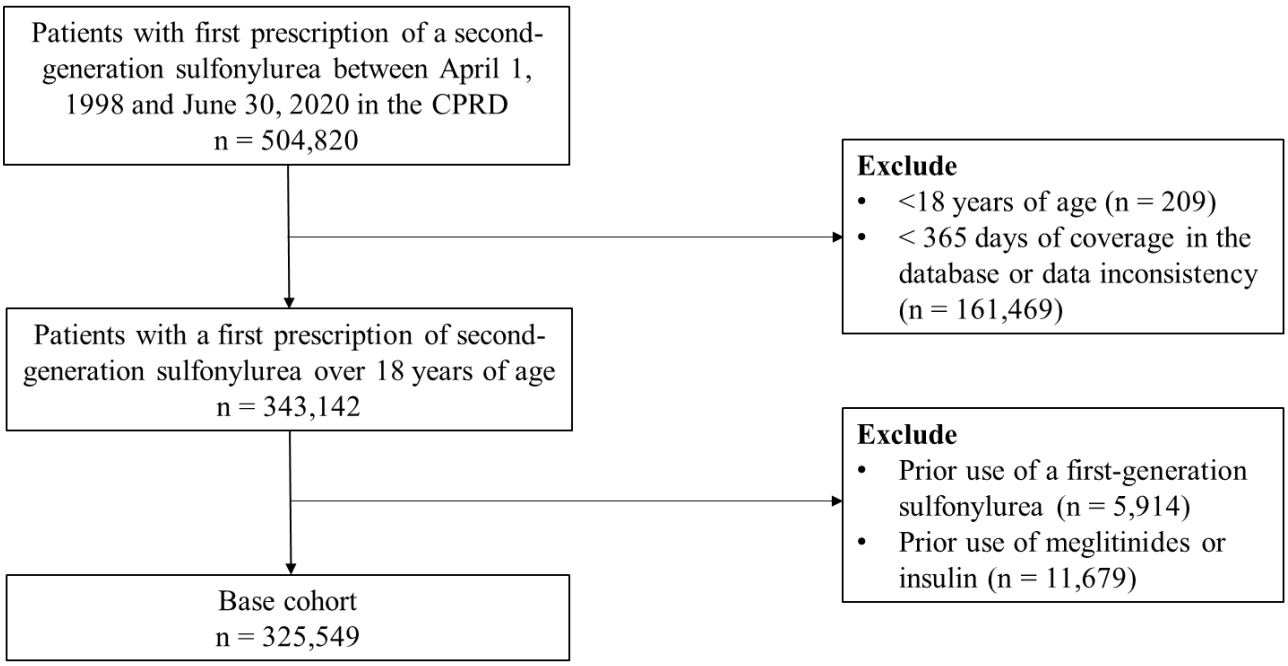

Figure 3. Construction of the base cohort
Abbreviations: CPRD, Clinical Practice Research Datalink.

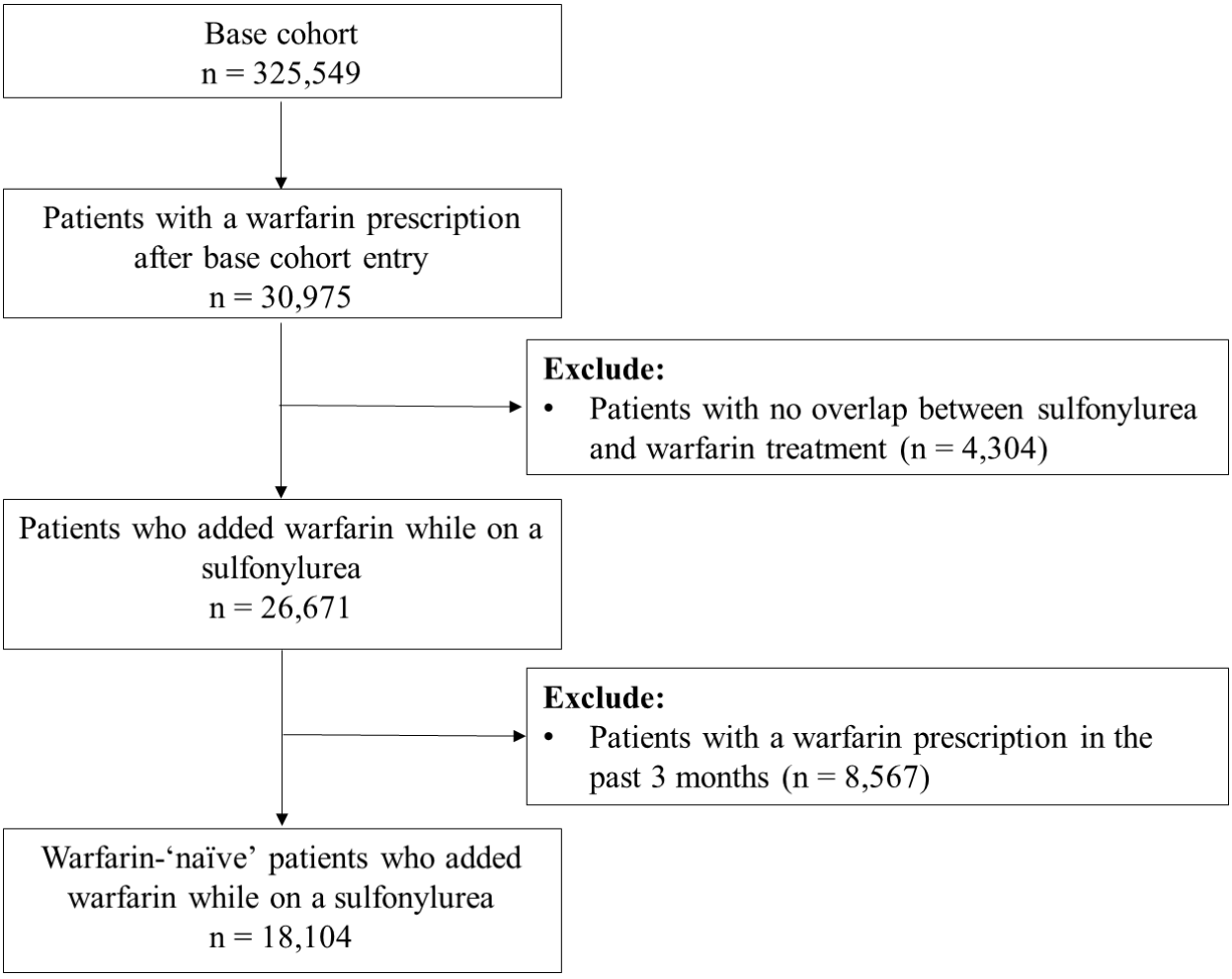

Figure 4. Identification of 'co-exposed' patients.

6.1 Primary analysis

Before TCPS matching, 347 events of severe hypoglycemia were observed among 18,070 person-years in the co-exposed group during follow-up, generating a crude incidence rate of 19.2 per 1,000 person-years; 190 events of severe hypoglycemia were observed among 22,554 person-years in the comparator group, generating a crude incidence rate of 8.4 per 1000 person-year. The crude HR was 2.32 (95% CI, 1.93 to 2.78).

After TCPS matching, 337 events of severe hypoglycemia were observed among 17,941 person-years in the co-exposed group during follow-up, generating an incidence rate of 18.8 per 1,000 person-years; 1,873 events of severe hypoglycemia were observed among 103,135 person-years in the comparator group, generating an incidence rate of 18.2 per 1000 person-years. Compared to use of sulfonylureas alone, concomitant use of sulfonylureas and warfarin was not associated with the risk of severe hypoglycemia (HR, 1.04; 95% CI, 0.92 to 1.17) (**Table 9**).

6.2 Secondary analyses

In our secondary analyses, we did not observe any signs of major effect measure modification (**Table 9**, **Figure 5**). Indeed, there was no duration response relation between continuous concomitant use of sulfonylureas and warfarin and the risk of severe hypoglycemia, with the HR ranging from 0.95 to 1.04 during the first 24 months (**Figure 4**). Moreover, stratifying by age, sex, or renal disease did not modify the association between concomitant use of sulfonylureas and warfarin and the risk of severe hypoglycemia (**Table 9**). The crude incidence rates and HRs, that is before TCPS matching, are summarized in **Table 10**.

6.3 Sensitivity analyses

The results remained robust in all sensitivity analyses (**Table 11**). Indeed, accounting for the potential impact of information bias (alternate grace periods, stricter outcome definition), selection bias (intention-to-treat, inverse probability of censoring weights), residual confounding (exclusion of patients with prior severe hypoglycemia), and time-dependent confounding (censoring upon insulin initiation during follow-up) led to no major changes in the HRs, that ranged from 1.02 to 1.15 (all not statistically significant).

6.4 Supplementary analyses

In the three supplementary analyses using time-based exposure sets, we observed a more heterogeneous picture regarding the risk of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin, as compared with use of sulfonylureas alone. When matching with replacement with an 1:5 ratio, the HR (95% CI) was 1.24 (1.08 to 1.42). When matching without replacement with an up to 1:5 ratio, the HR (95% CI) was 1.26 (1.10 to 1.44). Finally, when matching without replacement with an 1:1 ratio, the HR (95% CI) was 1.09 (0.93 to 1.30). The baseline characteristics for the three supplementary analyses are presented in **Tables 12-14**, while the results regarding the risk of severe hypoglycemia associated with concomitant use of sulfonylureas and warfarin are presented in detail in **Table 15**.

Table 8. Baseline characteristics of SU users adding warfarin or not before and after TCPS matching

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=18,082)	SU users not adding warfarin* (N=18,082)	SMD	SU users adding warfarin (N=17,890)	SU users not adding warfarin** (N=88,749)	SMD
Age in years, mean (SD)	72.57 (10.12)	65.00 (13.09)	0.647	72.53 (10.13)	72.91 (9.77)	-0.038
Female sex	7,050 (39.0%)	7,731 (42.8%)	-0.077	6,985 (39.0%)	34,371 (38.7%)	0.006
Smoking Status						
Current	1,813 (10.0%)	2,669 (14.8%)	-0.144	1,803 (10.1%)	8,779 (9.9%)	0.006
Former	7,273 (40.2%)	5,293 (29.3%)	0.232	7,161 (40.0%)	36,196 (40.8%)	-0.015
Never	8,317 (46.0%)	9,429 (52.2%)	-0.123	8,253 (46.1%)	40,483 (45.6%)	0.010
Unknown	679 (3.8%)	691 (3.8%)	-0.003	673 (3.8%)	3,291 (3.7%)	0.003
Body mass index in kg/m^2						
<25	2,524 (14.0%)	2,944 (16.3%)	-0.065	2,509 (14.0%)	12,741 (14.4%)	-0.010
25-29	5,740 (31.7%)	6,247 (34.6%)	-0.060	5,695 (31.8%)	28,278 (31.9%)	-0.001
≥30	8,943 (49.5%)	8,131 (45.0%)	0.090	8,822 (49.3%)	43,467 (49.0%)	0.007
Unknown	875 (4.8%)	760 (4.2%)	0.031	864 (4.8%)	4,263 (4.8%)	0.001
Comorbidities						
Alcohol-related disorder	4,097 (22.7%)	3,845 (21.3%)	0.034	4,052 (22.7%)	20,420 (23.0%)	-0.009
Arterial hypertension	14,325 (79.2%)	11,801 (65.3%)	0.316	14,160 (79.2%)	70,877 (79.9%)	-0.018
Congestive heart failure	6,633 (36.7%)	1,335 (7.4%)	0.756	6,462 (36.1%)	29,529 (33.3%)	0.060
Hyperlipidemia	14,523 (80.3%)	13,738 (76.0%)	0.105	14,362 (80.3%)	71,369 (80.4%)	-0.004
Chronic kidney disease	10,940 (60.5%)	9,372 (51.8%)	0.175	10,814 (60.5%)	53,835 (60.7%)	-0.004
Cognitive dysfunction	383 (2.1%)	281 (1.6%)	0.042	381 (2.1%)	2,065 (2.3%)	-0.014
Acute infection	2,147 (11.9%)	890 (4.9%)	0.253	2,092 (11.7%)	9,742 (11.0%)	0.022
Markers of diabetic severity						
Nephropathy	690 (3.8%)	435 (2.4%)	0.081	684 (3.8%)	3,403 (3.8%)	-0.001
Neuropathy	1,254 (6.9%)	926 (5.1%)	0.077	1,245 (7.0%)	6,200 (7.0%)	-0.001
Retinopathy	5,108 (28.3%)	5,231 (28.9%)	-0.015	5,079 (28.4%)	25,369 (28.6%)	-0.004
Myocardial infarction	5,456 (30.2%)	2,423 (13.4%)	0.415	5,354 (29.9%)	26,186 (29.5%)	0.009
Ischemic stroke/TIA	3,325 (18.4%)	1,355 (7.5%)	0.329	3,234 (18.1%)	15,750 (17.8%)	0.009

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=18,082)	SU users not adding warfarin* (N=18,082)	SMD	SU users adding warfarin (N=17,890)	SU users not adding warfarin** (N=88,749)	SMD
Peripheral vascular disease	2,925 (16.2%)	1,305 (7.2%)	0.282	2,854 (16.0%)	13,831 (15.6%)	0.010
Other diabetic complications	9,166 (50.7%)	9,398 (52.0%)	-0.026	9,101 (50.9%)	45,187 (50.9%)	-0.001
Prior severe hypoglycemia[a]	421 (2.3%)	256 (1.4%)	0.067	416 (2.3%)	2,146 (2.4%)	-0.006
Prior severe hypoglycemia[b]	58 (0.3%)	23 (0.1%)	0.040	56 (0.3%)	294 (0.3%)	-0.004
Hemoglobin A1c level						
<7%	5,498 (30.4%)	4,911 (27.2%)	0.072	5,471 (30.6%)	27,615 (31.1%)	-0.012
7-8%	5,259 (29.1%)	4,961 (27.4%)	0.036	5,212 (29.1%)	25,902 (29.2%)	-0.001
>8%	4,325 (23.9%)	5,620 (31.1%)	-0.161	4,281 (23.9%)	20,925 (23.6%)	0.008
Unknown	3,000 (16.6%)	2,590 (14.3%)	0.063	2,926 (16.4%)	14,307 (16.1%)	0.007
Diabetes duration in years, mean (IQR)	6.55 (2.95-10.69)	6.82 (3.53-10.93)	-0.027	6.60 (3.00-10.73)	6.35 (3.02-10.71)	-0.008
Non-SU antidiabetic drugs						
0	5,863 (32.4%)	4,797 (26.5%)	0.129	5,800 (32.4%)	28,904 (32.6%)	-0.003
≥1	12,219 (67.6%)	13,285 (73.5%)	-0.129	12,090 (67.6%)	59,845 (67.4%)	0.003
Comedications						
Quinolones	866 (4.8%)	552 (3.1%)	0.090	850 (4.8%)	4,363 (4.9%)	-0.008
Tramadol	1,585 (8.8%)	1,034 (5.7%)	0.118	1,559 (8.7%)	7,927 (8.9%)	-0.008
Lithium	30 (0.2%)	51 (0.3%)	-0.023	30 (0.2%)	139 (0.2%)	0.002
Hospitalizations						
0	8,919 (49.3%)	15,255 (84.4%)	-0.802	8,909 (49.8%)	43,869 (49.4%)	0.007
≥1	9,163 (50.7%)	2,827 (15.6%)	0.802	8,981 (50.2%)	44,880 (50.6%)	-0.007

Abbreviations: SU, second-generation sulfonylureas; TCPS, time-conditional propensity score; SMD, standardized mean difference; SD, standard deviation; TIA, transient ischemic attack.

* Randomly selected SU user not adding warfarin from the exposure set defined by the SU user adding warfarin with the same number of prior SU prescriptions.

** Matching was conducted up to 1:5 on calendar year, number of prior sulfonylurea prescriptions, number of prior insulin prescriptions, and TCPS.

[a] History of severe hypoglycemia during time in base cohort.
[b] History of severe hypoglycemia before base cohort entry.

Table 9. Risk of severe hypoglycemia associated with concomitant use of SU and warfarin after TCPS matching (primary and secondary analyses)

Cohort	N Patients	N Events	N Person-years	IR per 1000 person-years	HR (95% CI)
Primary analysis					
SU users adding warfarin	17,890	337	17,941	18.78	1.04 (0.92 to 1.17)
Matched SU users not adding warfarin	88,749	1,873	103,135	18.16	1.00 (reference)
Female sex					
SU users adding warfarin	6,988	146	6,687	21.83	1.16 (0.97 to 1.40)
Matched SU users not adding warfarin	34,869	774	40,615	19.06	1.00 (reference)
Male sex					
SU users adding warfarin	10,915	191	11,253	16.97	0.99 (0.84 to 1.16)
Matched SU users not adding warfarin	54,514	1,078	63,092	17.09	1.00 (reference)
Age <65 years					
SU users adding warfarin	3,618	23	3,681	6.25	0.96 (0.61 to 1.52)
Matched SU users not adding warfarin	18,035	153	22,414	6.83	1.00 (reference)
Age ≥65 years					
SU users adding warfarin	14,284	314	14,264	22.01	1.04 (0.92 to 1.18)
Matched SU users not adding warfarin	71,169	1,723	81,259	21.20	1.00 (reference)
Patients without renal disease					
SU users adding warfarin	7,086	82	7,119	11.52	1.15 (0.90 to 1.47)
Matched SU users not adding warfarin	35,340	455	42,456	10.72	1.00 (reference)
Patients with renal disease					
SU users adding warfarin	10,822	255	10,816	23.58	1.01 (0.87 to 1.16)
Matched SU users not adding warfarin	54,025	1,433	61,509	23.30	1.00 (reference)

Abbreviations: IR, incidence rate; CI, confidence interval; SU, sulfonylurea; HR, hazard ratio; TCPS, time-conditional propensity score.

Table 10. Crude IRs and HRs of severe hypoglycemia associated with concomitant use of SU and warfarin before TCPS matching

Cohort	N Patients	N Events	N Person-years	IR per 1,000 person-years	HR (95% CI)
Primary analysis					
SU users adding warfarin	18,082	347	18,070	19.20	2.32 (1.93 to 2.78)
Matched SU users not adding warfarin	18,082	190	22,554	8.42	1.00 (reference)
Female sex					
SU users adding warfarin	7,050	147	6,736	21.82	2.59 (1.98 to 3.40)
Matched SU users not adding warfarin	7,731	86	9,771	8.80	1.00 (reference)
Male sex					
SU users adding warfarin	11,032	200	11,334	17.65	2.17 (1.70 to 2.77)
Matched SU users not adding warfarin	10,351	104	12,783	8.14	1.00 (reference)
Age <65 years					
SU users adding warfarin	3,626	23	3,683	6.24	2.09 (1.22 to 3.60)
Matched SU users not adding warfarin	8,530	34	10,722	3.17	1.00 (reference)
Age ≥65 years					
SU users adding warfarin	14,456	324	14,387	22.52	1.73 (1.43 to 2.11)
Matched SU users not adding warfarin	9,552	156	11,832	13.18	1.00 (reference)
Patients without renal disease					
SU users adding warfarin	7,142	82	7,155	11.46	2.61 (1.82 to 3.75)
Matched SU users not adding warfarin	8,710	54	11,125	4.85	1.00 (reference)
Patients with renal disease					
SU users adding warfarin	10,940	265	10,915	24.28	2.04 (1.66 to 2.51)
Matched SU users not adding warfarin	9,372	136	11,429	11.90	1.00 (reference)

Abbreviations: IR, incidence rate; CI, confidence interval; SU, sulfonylurea; HR, hazard ratio; TCPS, time-conditional propensity score.

Table 11. Risk of severe hypoglycemia associated with concomitant use of SU and warfarin (sensitivity analyses)

	N Patients	N Events	N Person-years	IR per 1000 person-years	HR (95% CI*)
Intention-to-treat					
SU users adding warfarin	17,890	315	16,835	18.71	1.06 (0.93 to 1.20)
Matched SU users not adding warfarin	88,749	1,482	83,954	17.65	1.00 (reference)
IPCW					
SU users adding warfarin	17,884	340	17,900	18.99	1.03 (0.91 to 1.17)
Matched SU users not adding warfarin	88,785	1,898	103,010	18.43	1.00 (reference)
No replacement					
SU users adding warfarin	17,840	336	17,893	18.78	1.02 (0.88 to 1.18)
Matched SU users not adding warfarin	17,840	396	21,576	18.35	1.00 (reference)
15-day grace period					
SU users adding warfarin	17,890	211	10,671	19.77	1.04 (0.89 to 1.22)
Matched SU users not adding warfarin	88,749	1,033	54,265	19.04	1.00 (reference)
60-day grace period					
SU users adding warfarin	17,890	569	31,092	18.30	1.04 (0.95 to 1.15)
Matched SU users not adding warfarin	88,749	3,452	193,250	17.86	1.00 (reference)
Stricter outcome definition					
SU users adding warfarin	17,890	139	18,000	7.72	1.15 (0.94 to 1.39)
Matched SU users not adding warfarin	88,749	699	103,744	6.74	1.00 (reference)
Censoring upon insulin initiation					
SU users adding warfarin	17,890	282	16,585	17.00	1.04 (0.91 to 1.19)
Matched SU users not adding warfarin	88,749	1,557	95,724	16.27	1.00 (reference)
Exclude prior severe hypoglycemia					
SU users adding warfarin	17,470	306	17,682	17.31	1.03 (0.91 to 1.17)
Matched SU users not adding warfarin	86,630	1,728	101,361	17.05	1.00 (reference)

Abbreviations: CI, confidence interval; SU, sulfonylurea; HR, hazard ratio; IPCW, inverse probability of censoring weight.

Table 12. Baseline characteristics of SU users adding warfarin or not before and after TCPS matching (time-based exposure sets; 1:5 with replacement)

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,745)	SU users not adding warfarin** (N=70,317)	SMD
Age in years, mean (SD)	72.60 (10.08)	64.37 (13.04)	0.706	72.38 (10.09)	72.51 (9.71)	-0.013
Female sex	6,953 (39.1%)	7,494 (42.2%)		6,245 (39.7%)	28,159 (40.0%)	-0.008
Smoking status						
Current	1,773 (10.0%)	2,808 (15.8%)	-0.174	1,609 (10.2%)	7,140 (10.2%)	0.002
Former	7,145 (40.2%)	5,107 (28.7%)	0.243	6,154 (39.1%)	27,508 (39.1%)	-0.001
Never	8,185 (46.1%)	9,152 (51.5%)	-0.109	7,378 (46.9%)	32,847 (46.7%)	0.003
Unknown	668 (3.8%)	704 (4.0%)	-0.010	604 (3.8%)	2,822 (4.0%)	-0.009
Body mass index in kg/m^2						
<25	2,482 (14.0%)	2,839 (16.0%)	-0.056	2,258 (14.3%)	10,075 (14.3%)	0.000
25-29	5,620 (31.6%)	5,955 (33.5%)	-0.040	5,060 (32.1%)	22,379 (31.8%)	0.007
≥30	8,810 (49.6%)	8,118 (45.7%)	0.078	7,653 (48.6%)	34,241 (48.7%)	-0.002
Unknown	859 (4.8%)	859 (4.8%)	0.000	774 (4.9%)	3,622 (5.2%)	-0.011
Comorbidities						
Alcohol-related disorder	4,034 (22.7%)	3,691 (20.8%)	0.047	3,506 (22.3%)	15,452 (22.0%)	0.007
Arterial hypertension	14,080 (79.2%)	11,412 (64.2%)	0.338	12,396 (78.7%)	55,434 (78.8%)	-0.002
Congestive heart failure	6,505 (36.6%)	1,333 (7.5%)	0.750	5,060 (32.1%)	18,103 (25.7%)	0.141
Hyperlipidemia	14,263 (80.3%)	13,445 (75.7%)	0.111	12,554 (79.7%)	55,376 (78.8%)	0.024
Chronic kidney disease	10,733 (60.4%)	8,897 (50.1%)	0.209	9,319 (59.2%)	40,623 (57.8%)	0.029
Cognitive dysfunction	378 (2.1%)	240 (1.4%)	0.060	321 (2.0%)	1,410 (2.0%)	0.002
Acute infection	2,097 (11.8%)	804 (4.5%)	0.268	1,655 (10.5%)	6,179 (8.8%)	0.058
Markers of diabetic severity						
Nephropathy	681 (3.8%)	379 (2.1%)	0.100	545 (3.5%)	2,146 (3.1%)	0.023
Neuropathy	1,245 (7.0%)	844 (4.8%)	0.096	1,047 (6.7%)	4,324 (6.2%)	0.020
Retinopathy	5,053 (28.4%)	4,853 (27.3%)	0.025	4,383 (27.8%)	18,860 (26.8%)	0.023
Myocardial infarction	5,353 (30.1%)	2,426 (13.7%)	0.406	4,480 (28.5%)	18,197 (25.9%)	0.058

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,745)	SU users not adding warfarin** (N=70,317)	SMD
Ischemic stroke/TIA	3,272 (18.4%)	1,319 (7.4%)	0.332	2,698 (17.1%)	10,692 (15.2%)	0.052
Peripheral vascular disease	2,873 (16.2%)	1,216 (6.8%)	0.296	2,388 (15.2%)	9,435 (13.4%)	0.050
Other diabetic complications	9,007 (50.7%)	8,997 (50.6%)	0.001	7,886 (50.1%)	34,454 (49.0%)	0.022
Prior severe hypoglycemia[a]	419 (2.4%)	209 (1.2%)	0.090	336 (2.1%)	1,256 (1.8%)	0.025
Prior severe hypoglycemia[b]	56 (0.3%)	50 (0.3%)	0.007	50 (0.3%)	221 (0.3%)	0.002
Hemoglobin A1c level						
<7%	5,421 (30.5%)	4,509 (25.4%)	0.115	4,911 (31.2%)	22,117 (31.5%)	-0.006
7-8%	5,198 (29.3%)	4,921 (27.7%)	0.035	4,586 (29.1%)	20,673 (29.4%)	-0.006
>8%	4,247 (23.9%)	5,486 (30.9%)	-0.157	3,674 (23.3%)	15,972 (22.7%)	0.015
Unknown	2,905 (16.4%)	2,855 (16.1%)	0.008	2,574 (16.4%)	11,555 (16.4%)	-0.002
Diabetes duration in years, mean (IQR)	6.60 (2.98-10.72)	6.14 (2.92-10.10)	-0.027	6.53 (3.01-10.54)	6.20 (2.85-10.26)	0.019
Non-SU antidiabetic drugs						
0	5,792 (32.6%)	4,641 (26.1%)	0.142	5,230 (33.2%)	23,636 (33.6%)	-0.008
≥1	11,979 (67.4%)	13,130 (73.9%)	-0.142	10,515 (66.8%)	46,681 (66.4%)	0.008
Comedications						
Quinolones	853 (4.8%)	509 (2.9%)	0.101	739 (4.7%)	3,173 (4.5%)	0.009
Tramadol	1,555 (8.8%)	1,087 (6.1%)	0.100	1,348 (8.6%)	5,922 (8.4%)	0.005
Lithium	29 (0.2%)	45 (0.3%)	-0.020	28 (0.2%)	126 (0.2%)	0.000
Hospitalizations						
0	8,765 (49.3%)	14,956 (84.2%)	-0.796	8,337 (52.9%)	39,473 (56.1%)	-0.064
≥1	9,006 (50.7%)	2,815 (15.8%)	0.796	7,408 (47.1%)	30,844 (43.9%)	0.064

Abbreviations: SU, second-generation sulfonylureas; TCPS, time-conditional propensity score; SMD, standardized mean difference; SD, standard deviation; TIA, transient ischemic attack.

* Randomly selected SU user not adding warfarin from the exposure set defined by the SU user adding warfarin with the same duration of prior SU prescriptions.

** Matching was conducted up to 1:5 on calendar year, number of months since the first sulfonylurea prescription, number of insulin prescriptions, and TCPS.
[a] History of severe hypoglycemia during time in base cohort.
[b] History of severe hypoglycemia before base cohort entry.

Table 13. Baseline characteristics of SU users adding warfarin or not before and after TCPS matching (time-based exposure sets; 1:5 without replacement)

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,422)	SU users not adding warfarin** (N=61,323)	SMD
Age in years, mean (SD)	72.60 (10.08)	64.37 (13.04)	0.706	72.31 (10.11)	71.52 (10.08)	0.078
Female sex	6,953 (39.1%)	7,494 (42.2%)		6,130 (39.8%)	25,108 (40.9%)	-0.024
Smoking Status						
Current	1,773 (10.0%)	2,808 (15.8%)	-0.174	1,582 (10.3%)	6,587 (10.7%)	-0.016
Former	7,145 (40.2%)	5,107 (28.7%)	0.243	6,003 (38.9%)	23,363 (38.1%)	0.017
Never	8,185 (46.1%)	9,152 (51.5%)	-0.109	7,245 (47.0%)	28,782 (46.9%)	0.001
Unknown	668 (3.8%)	704 (4.0%)	-0.010	592 (3.8%)	2,591 (4.2%)	-0.020
Body mass index in kg/m^2					(%)	
<25	2,482 (14.0%)	2,839 (16.0%)	-0.056	2,203 (14.3%)	8,721 (14.2%)	0.002
25-29	5,620 (31.6%)	5,955 (33.5%)	-0.040	4,958 (32.2%)	19,438 (31.7%)	0.010
≥30	8,810 (49.6%)	8,118 (45.7%)	0.078	7,502 (48.6%)	29,799 (48.6%)	0.001
Unknown	859 (4.8%)	859 (4.8%)	0.000	759 (4.9%)	3,365 (5.5%)	-0.026
Comorbidities						
Alcohol-related disorder	4,034 (22.7%)	3,691 (20.8%)	0.047	3,417 (22.2%)	13,314 (21.7%)	0.011
Arterial hypertension	14,080 (79.2%)	11,412 (64.2%)	0.338	12,130 (78.7%)	47,128 (76.9%)	0.043
Congestive heart failure	6,505 (36.6%)	1,333 (7.5%)	0.750	4,821 (31.3%)	12,655 (20.6%)	0.244
Hyperlipidemia	14,263 (80.3%)	13,445 (75.7%)	0.111	12,293 (79.7%)	47,842 (78.0%)	0.041
Chronic kidney disease	10,733 (60.4%)	8,897 (50.1%)	0.209	9,104 (59.0%)	34,698 (56.6%)	0.050
Cognitive dysfunction	378 (2.1%)	240 (1.4%)	0.060	311 (2.0%)	1,241 (2.0%)	0.000
Acute infection	2,097 (11.8%)	804 (4.5%)	0.268	1,601 (10.4%)	5,357 (8.7%)	0.056
Markers of diabetic severity						
Nephropathy	681 (3.8%)	379 (2.1%)	0.100	525 (3.4%)	1,756 (2.9%)	0.031
Neuropathy	1,245 (7.0%)	844 (4.8%)	0.096	1,018 (6.6%)	3,595 (5.9%)	0.031
Retinopathy	5,053 (28.4%)	4,853 (27.3%)	0.025	4,293 (27.8%)	16,095 (26.3%)	0.036
Myocardial infarction	5,353 (30.1%)	2,426 (13.7%)	0.406	4,359 (28.3%)	14,244 (23.2%)	0.115

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,422)	SU users not adding warfarin** (N=61,323)	SMD
Ischemic stroke/TIA	3,272 (18.4%)	1,319 (7.4%)	0.332	2,612 (16.9%)	8,488 (13.8%)	0.086
Peripheral vascular disease	2,873 (16.2%)	1,216 (6.8%)	0.296	2,319 (15.0%)	7,450 (12.2%)	0.084
Other diabetic complications	9,007 (50.7%)	8,997 (50.6%)	0.001	7,721 (50.1%)	29,828 (48.6%)	0.028
Prior severe hypoglycemia[a]	419 (2.4%)	209 (1.2%)	0.090	320 (2.1%)	1,030 (1.7%)	0.029
Prior severe hypoglycemia[b]	56 (0.3%)	50 (0.3%)	0.007	48 (0.3%)	195 (0.3%)	-0.002
Hemoglobin A1c level						
<7%	5,421 (30.5%)	4,509 (25.4%)	0.115	4,818 (31.2%)	18,249 (29.8%)	0.032
7-8%	5,198 (29.3%)	4,921 (27.7%)	0.035	4,496 (29.2%)	18,032 (29.4%)	-0.005
>8%	4,247 (23.9%)	5,486 (30.9%)	-0.157	3,582 (23.2%)	14,568 (23.8%)	-0.013
Unknown	2,905 (16.4%)	2,855 (16.1%)	0.008	2,526 (16.4%)	10,474 (17.1%)	-0.019
Diabetes duration in years, mean (IQR)	6.60 (2.98-10.72)	6.14 (2.92-10.10)	-0.027	6.51 (3.00 - 10.51)	6.05 (2.74 - 10.09)	0.033
Non-SU antidiabetic drugs						
0	5,792 (32.6%)	4,641 (26.1%)	0.142	5,113 (33.2%)	19,815 (32.3%)	0.018
≥1	11,979 (67.4%)	13,130 (73.9%)	-0.142	10,309 (66.9%)	41,508 (67.7%)	-0.018
Comedications						
Quinolones	853 (4.8%)	509 (2.9%)	0.101	724 (4.7%)	2,616 (4.3%)	0.020
Tramadol	1,555 (8.8%)	1,087 (6.1%)	0.100	1,323 (8.6%)	5,037 (8.2%)	0.013
Lithium	29 (0.2%)	45 (0.3%)	-0.020	27 (0.2%)	123 (0.2%)	-0.005
Hospitalizations						
0	8,765 (49.3%)	14,956 (84.2%)	-0.796	8,260 (53.6%)	34,813 (56.8%)	-0.065
≥1	9,006 (50.7%)	2,815 (15.8%)	0.796	7,162 (46.4%)	26,510 (43.2%)	0.065

Abbreviations: SU, second-generation sulfonylureas; TCPS, time-conditional propensity score; SMD, standardized mean difference; SD, standard deviation; TIA, transient ischemic attack.

* Randomly selected SU user not adding warfarin from the exposure set defined by the SU user adding warfarin with the same duration of prior SU prescriptions.

** Matching was conducted up to 1:5 on calendar year, number of months since the first sulfonylurea prescription, number of insulin prescriptions, and TCPS.
[a] History of severe hypoglycemia during time in base cohort.
[b] History of severe hypoglycemia before base cohort entry.

Table 14. Baseline characteristics of SU users adding warfarin or not before and after TCPS matching (time-based exposure sets; 1:1 without replacement)

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,422)	SU users not adding warfarin** (N=15,422)	SMD
Age in years, mean (SD)	72.60 (10.08)	64.37 (13.04)	0.706	72.31 (10.11)	72.40 (9.90)	-0.009
Female sex	6,953(39.1%)	7,494 (42.2%)		6,130 (39.8%)	6,207 (40.3%)	-0.010
Smoking Status						
Current	1,773 (10.0%)	2,808 (15.8%)	-0.174	1,582 (10.3%)	1,617 (10.5%)	-0.008
Former	7,145 (40.2%)	5,107 (28.7%)	0.243	6,003 (38.9%)	6,029 (39.1%)	-0.003
Never	8,185 (46.1%)	9,152 (51.5%)	-0.109	7,245 (47.0%)	7,176 (46.5%)	0.009
Unknown	668 (3.8%)	704 (4.0%)	-0.010	592 (3.8%)	600 (3.9%)	-0.003
Body mass index in kg/m^2						
<25	2,482 (14.0%)	2,839 (16.0%)	-0.056	2,203 (14.3%)	2,200 (14.3%)	0.000
25-29	5,620 (31.6%)	5,955 (33.5%)	-0.040	4,958 (32.2%)	4,793 (31.1%)	0.023
≥30	8,810 (49.6%)	8,118 (45.7%)	0.078	7,502 (48.6%)	7,601 (49.3%)	-0.013
Unknown	859 (4.8%)	859 (4.8%)	0.000	759 (4.9%)	828 (5.4%)	-0.020
Comorbidities						
Alcohol-related disorder	4,034 (22.7%)	3,691 (20.8%)	0.047	3,417 (22.2%)	3,475 (22.5%)	-0.009
Arterial hypertension	14,080 (79.2%)	11,412 (64.2%)	0.338	12,130 (78.7%)	12,222 (79.3%)	-0.015
Congestive heart failure	6,505 (36.6%)	1,333 (7.5%)	0.750	4,821 (31.3%)	4,476 (29.0%)	0.049
Hyperlipidemia	14,263 (80.3%)	13,445 (75.7%)	0.111	12,293 (79.7%)	12,314 (79.9%)	-0.003
Chronic kidney disease	10,733 (60.4%)	8,897 (50.1%)	0.209	9,104 (59.0%)	9,094 (59.0%)	0.001
Cognitive dysfunction	378 (2.1%)	240 (1.4%)	0.060	311 (2.0%)	334 (2.2%)	-0.010
Acute infection	2,097 (11.8%)	804 (4.5%)	0.268	1,601 (10.4%)	1,512 (9.8%)	0.019
Markers of diabetic severity						
Nephropathy	681 (3.8%)	379 (2.1%)	0.100	525 (3.4%)	516 (3.4%)	0.003
Neuropathy	1,245 (7.0%)	844 (4.8%)	0.096	1,018 (6.6%)	1,071 (6.9%)	-0.014
Retinopathy	5,053 (28.4%)	4,853 (27.3%)	0.025	4,293 (27.8%)	4,256 (27.6%)	0.005
Myocardial infarction	5,353 (30.1%)	2,426 (13.7%)	0.406	4,359 (28.3%)	4,144 (26.9%)	0.031

Characteristic	Before TCPS matching			After TCPS matching		
	SU users adding warfarin (N=17,771)	SU users not adding warfarin* (N=17,771)	SMD	SU users adding warfarin (N=15,422)	SU users not adding warfarin** (N=15,422)	SMD
Ischemic stroke/TIA	3,272 (18.4%)	1,319 (7.4%)	0.332	2,612 (16.9%)	2,489 (16.1%)	0.022
Peripheral vascular disease	2,873 (16.2%)	1,216 (6.8%)	0.296	2,319 (15.0%)	2,204 (14.3%)	0.021
Other diabetic complications	9,007 (50.7%)	8,997 (50.6%)	0.001	7,721 (50.1%)	7,691 (49.9%)	0.004
Prior severe hypoglycemia[a]	419 (2.4%)	209 (1.2%)	0.090	320 (2.1%)	326 (2.1%)	-0.003
Prior severe hypoglycemia[b]	56 (0.3%)	50 (0.3%)	0.007	48 (0.3%)	51 (0.3%)	-0.004
Hemoglobin A1c level						
<7%	5,421 (30.5%)	4,509 (25.4%)	0.115	4,818 (31.2%)	4,765 (30.9%)	0.007
7-8%	5,198 (29.3%)	4,921 (27.7%)	0.035	4,496 (29.2%)	4,597 (29.8%)	-0.014
>8%	4,247 (23.9%)	5,486 (30.9%)	-0.157	3,582 (23.2%)	3,601 (23.4%)	-0.003
Unknown	2,905 (16.4%)	2,855 (16.1%)	0.008	2,526 (16.4%)	2,459 (15.9%)	0.012
Diabetes duration in years, mean (IQR)	6.60 (2.98-10.72)	6.14 (2.92-10.10)	-0.027	6.51 (3.00 - 10.51)	6.43 (3.00 - 10.52)	0.004
Non-SU antidiabetic drugs						
0	5,792 (32.6%)	4,641 (26.1%)	0.142	5,113 (33.2%)	4,966 (32.2%)	0.020
≥1	11,979 (67.4%)	13,130 (73.9%)	-0.142	10,309 (66.9%)	10,456 (67.8%)	-0.020
Comedications						
Quinolones	853 (4.8%)	509 (2.9%)	0.101	724 (4.7%)	690 (4.5%)	0.011
Tramadol	1,555 (8.8%)	1,087 (6.1%)	0.100	1,323 (8.6%)	1,342 (8.7%)	-0.004
Lithium	29 (0.2%)	45 (0.3%)	-0.020	27 (0.2%)	40 (0.3%)	-0.017
Hospitalizations						
0	8,765 (49.3%)	14,956 (84.2%)	-0.796	8,260 (53.6%)	8,022 (52.0%)	0.031
≥1	9,006 (50.7%)	2,815 (15.8%)	0.796	7,162 (46.4%)	7,400 (48.0%)	-0.031

Abbreviations: SU, second-generation sulfonylureas; TCPS, time-conditional propensity score; SMD, standardized mean difference; SD, standard deviation; TIA, transient ischemic attack.

* Randomly selected SU user not adding warfarin from the exposure set defined by the SU user adding warfarin with the same duration of prior SU prescriptions.

** Matching was conducted 1:1 on calendar year, number of months since the first sulfonylurea prescription, number of insulin prescriptions, and TCPS.
[a] History of severe hypoglycemia during time in base cohort.
[b] History of severe hypoglycemia before base cohort entry.

Table 15. Risk of severe hypoglycemia associated with concomitant use of SU and warfarin after TCPS matching (time-based exposure sets)

	N Patients	N Events	N Person-years	IR per 1,000 person-years	HR (95% CI)
Up to 5 matches, with replacement					
SU users adding warfarin	15,745	286	16,110	17.75	1.24 (1.08 to 1.42)
Matched SU users not adding warfarin	70,317	1,159	82,793	14.00	1.00 (reference)
Up to 5 matches, without replacement					
SU users adding warfarin	15,745	278	15,825	17.57	1.26 (1.10 to 1.44)
Matched SU users not adding warfarin	61,323	1,071	80,963	13.23	1.00 (reference)
Best match, without replacement					
SU users adding warfarin	15,422	278	15,825	17.57	1.09 (0.93 to 1.30)
Matched SU users not adding warfarin	15,422	301	18,342	16.41	1.00 (reference)

Abbreviations: IR, incidence rate; CI, confidence interval; SU, sulfonylurea; HR, hazard ratio; TCPS, time-conditional propensity score.

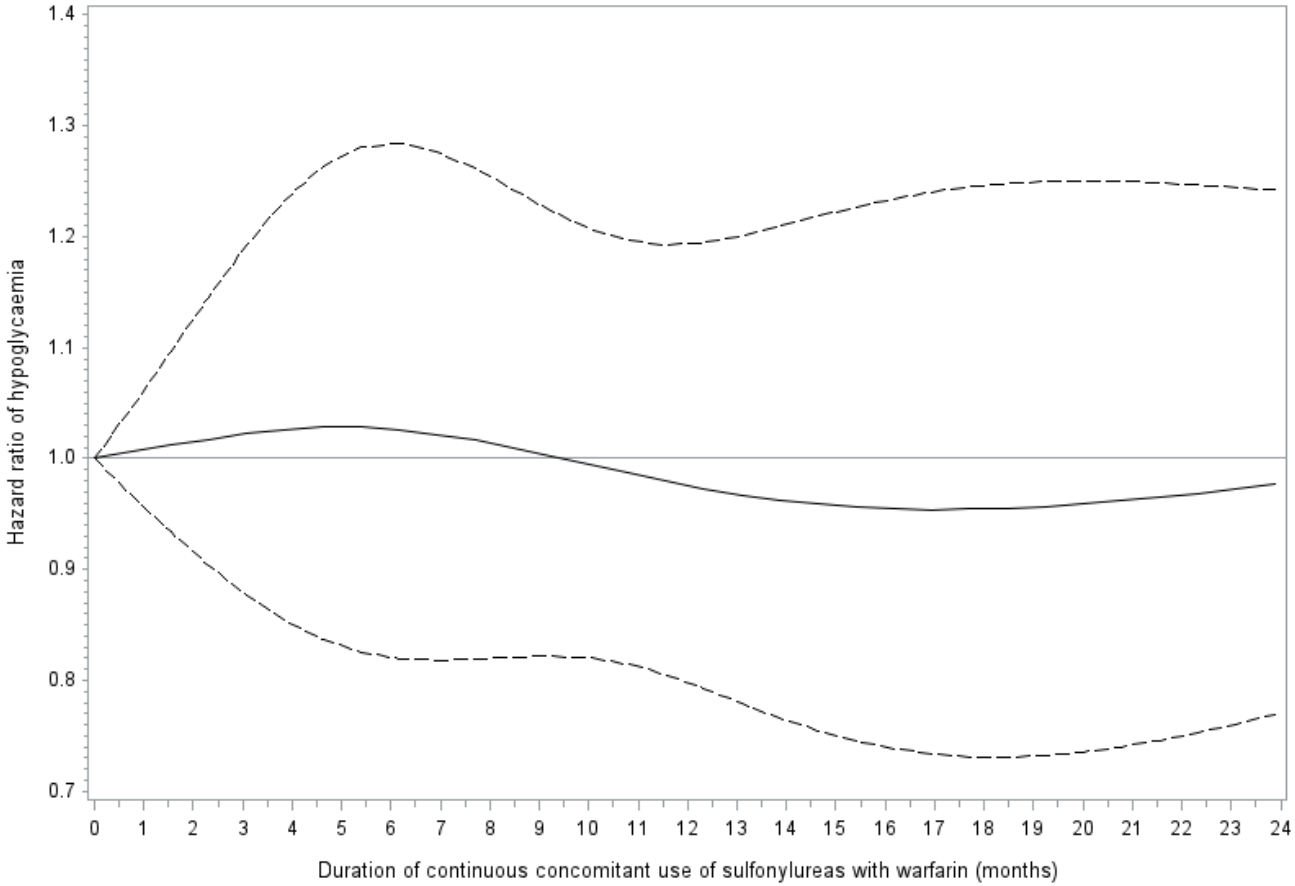

Figure 5. Duration-response relation between continuous concomitant use of sulfonylureas and warfarin and the risk of severe hypoglycemia.

7. DISCUSSION

Our study analysis included 17,890 patients co-exposed to sulfonylureas and warfarin and 88,749 comparators using sulfonylureas alone. Compared to use of sulfonylureas alone, concomitant use of sulfonylureas and warfarin was not associated with the risk of severe hypoglycemia (incidence rates 18.8 vs 18.2 per 1,000 person-years; HR, 1.04; 95% CI 0.92 to 1.17). Stratifying by duration of continuous concomitant use, age, sex, or renal disease did not modify the association. Moreover, the results remained robust in all sensitivity analyses that addressed different potential sources of bias. However, a small increase in the risk was observed in supplementary analyses using time-based exposure sets instead of the prescription-based exposed sets that were used in the primary analysis.

Two pharmacokinetic mechanisms have been proposed for the potential interaction between sulfonylureas and warfarin. First, since warfarin and sulfonylureas are both substrates of the enzyme CYP2C9, concomitant use of these drugs could result in reduced CYP2C9-mediated metabolism and potentially elevated systemic levels of sulfonylureas[55]. Second, warfarin can displace sulfonylureas from plasma proteins, which could then result in an increase in the systemic levels of the unbound, that is the pharmacologically active, sulfonylurea fraction[56]. However, the clinical relevance of these two suggested mechanisms is not clear. Moreover, even if these mechanisms were to lead to an increase in the systemic levels of sulfonylureas sufficient enough to cause an increase in the risk of sulfonylurea-induced severe hypoglycemia, strong effects seem unlikely.

Overall, our study findings do not necessarily support those from previous observational studies in the area. Indeed, most of the previous studies suggested an increased risk of severe hypoglycemia due to concomitant use of sulfonylureas and warfarin, with some of them suggesting

even strong increases in the risk (up to 47%). However, several methodological biases including mostly information bias due to exposure and outcome misclassification as well as different forms of selection bias and confounding possibly contributed to these findings. That being said, the study by Dimakos et al. also alluded to an absence of an increased risk of severe hypoglycemia due to concomitant use of sulfonylureas and warfarin[54]. In that study, the use of DOACs as a negative control precipitant led to a null association, suggesting that the moderate increase in the risk observed in the primary analysis was probably due to residual confounding.

Interestingly, using time-based exposure sets in supplementary analyses led to a slightly different picture regarding the hypoglycemic potential of the interaction between sulfonylureas and warfarin. In two of the three analyses (the ones matching 1:5 with or without replacement), a moderate increase in the risk was observed. On the other hand, in the analysis using the best available match within the time-based exposure set and without replacement, the findings were consistent with those of the primary analysis (no increased risk). Overall, these results seem to suggest that prescription-based exposure sets may provide better confounding control than time-based exposure sets, at least in this particular setting. This notion is further supported by the fact that imbalances in covariates between exposure groups after TCPS matching were more pronounced with the time-based approach.

Our study has several strengths. First, the application of the prevalent new-user design addressed several limitations of previous observational studies in the area. For example, prevalent user bias due to prior sulfonylurea use was minimized because each sulfonylurea user adding warfarin was matched to a sulfonylurea user not adding warfarin on the number of sulfonylurea prescriptions before study cohort entry. Moreover, the use of exposure sets provided a well-defined ‘time zero’ both for co-exposed and comparator patients, thus eliminating immortal-time bias.

Second, the use of a large study cohort allowed the calculation of relatively precise effect estimates for a rare adverse drug effect such as severe hypoglycemia. Finally, the use of hospitalization or death to define hypoglycemia and the exclusive consideration of diagnostic codes that explicitly refer to hypoglycemia likely maximized the validity of our outcome definition.

This study also has some limitations. First, residual confounding cannot be excluded in the absence of randomization. To alleviate this bias, we matched on TCPS that included many potential confounders including several markers of diabetes disease severity. Second, as in all studies based on data sources without available information on inpatient medication use, immeasurable time bias is possible[77]. However, both sulfonylureas and warfarin are not commonly used during hospitalization given the existence of therapeutic alternatives (insulin instead of sulfonylureas, low-molecular weight heparin instead of warfarin) that are more appropriate for the inpatient setting. Third, informative censoring due to the as-treated exposure definition is also possible. That being said, the use of an intention-to-treat exposure definition and also of inverse probability of censoring weights led to highly consistent findings. Therefore, the potential impact of this bias should be negligible. Fourth, in our study, potential differences due to the intra-class pharmacological heterogeneity among sulfonylureas were not considered. Finally, the generalizability of our findings is not necessarily guaranteed when it comes to milder forms hypoglycemia that are treated in the outpatient setting (and are also not fatal).

8. CONCLUSIONS

Our study showed that the concomitant use of sulfonylureas and warfarin is not associated with an increased risk of severe hypoglycemia, as compared to use of sulfonylureas alone. These results are in line with the absence of a strong pharmacologic rationale for this potential drug-drug interaction. They are also in line with the notion that the small-to-moderate increases in the risk of severe hypoglycemia reported in previous observational studies were rather due to methodological biases and did not necessarily reflect a true effect.

Overall, our findings should provide some reassurance to treating physicians and patients regarding the safety of the concomitant use of sulfonylureas and warfarin, two commonly used drug classes. Our findings also support the application of the recently developed prevalent new-user design when it comes to the assessment of the clinical effects of drug-drug interactions. Further research is needed to corroborate the potentially better performance of prescription-based exposure sets over time-based exposure sets regarding confounding control. Future studies could also assess the applicability of the design in settings where both drugs are used for the same medical condition, rendering confounding by indication a stronger concern than in the current example.

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