Sulfonylureas and the Risk of Ventricular Arrhythmias Among People with Type 2 Diabetes: A Systematic Review of Observational Studies

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Word Count: 3585; **Tables**: 3; **Figures**: 2; **Supplemental Tables**: 1; **Supplemental Figures**: 0

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CONFLICT OF INTEREST:
HTA is an employee of Merck. He contributed to this study during his post-doctoral training at McGill University. All other authors declared no competing interests for this work.

FUNDING:
Not applicable.

Keywords: Sulfonylureas, Diabetes, Arrhythmias, Systematic Review

ABSTRACT

Previous studies have suggested an association between sulfonylureas and an increased risk of cardiovascular death among patients with type 2 diabetes. A potential mechanism involves sulfonylurea-induced ventricular arrhythmias (VA). We conducted a systematic review of observational studies to determine whether the use of sulfonylureas, compared to the use of other antihyperglycemic drugs, is associated with the risk of VA (ventricular tachycardia, ventricular fibrillation, and premature ventricular complexes), cardiac arrest, and sudden cardiac death among patients with type 2 diabetes. Two independent reviewers searched MEDLINE, EMBASE, CINAHL Plus, CENTRAL, and ClinicalTrials.gov from inception to July 2021 for observational studies comparing sulfonylureas versus other antihyperglycemic therapies or intra-class comparisons of sulfonylureas. Our systematic review included 17 studies (1,607,612 patients). Per ROBINS-I, there were few high-quality studies (2 studies at moderate risk of bias; 4 at serious risk; 11 at critical risk). All studies at a moderate or serious risk of bias reporting comparisons with other therapies were consistent with an increased risk of VA. Sulfonylureas were associated with a higher risk of arrhythmia versus dipeptidyl peptidase-4 inhibitors (adjusted hazard ratio [aHR]: 1.52, 95% confidence interval [CI]: 1.27-1.80) and of VA versus metformin (aHR: 1.52, 95% CI: 1.10-2.13). One moderate quality study reported inconsistent results for a composite of cardiac arrest/VA in analyses of US Medicaid claims and Optum claims data. Our systematic review suggests that, among higher-quality observational studies, sulfonylureas are associated with an increased risk of VA. However, we identified few methodologically rigorous studies, underscoring the need for additional real-world studies.

INTRODUCTION

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

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

METHODS

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

Search Strategy

We searched Medline (OVID), EMBASE + EMBASE Classic (OVID), CINAHL Plus, and CENTRAL (Cochrane Library) databases from inception to November 5, 2020, with the search updated on July 8, 2021. Our strategy included the use of Medical Subject Headings (MeSH) terms in MEDLINE, EMTREE terms in EMBASE, CINAHL headings for CINAHL, and keywords in all included databases for sulfonylureas and their known molecular formulations. We did not impose restrictions on language, geographic location, or study design in our search strategy. Furthermore, we conducted a hand search of reference lists of the included studies, previous reviews, Google Scholar, and ClinicalTrials.gov to identify any additional relevant studies not captured by our initial database search. The search strategies used in each database are reported in detail in **Table S1**.

Inclusion and Exclusion Criteria

We included observational studies (cohort or case-control studies) examining the association between sulfonylureas and the risk of arrhythmias among people with type 2 diabetes. The sulfonylurea group could have received any drug from the sulfonylurea class, with no requirement for the exact formulation or dose to be reported. The allowed comparators included

other antihyperglycemic drugs or intra-class comparisons of sulfonylureas. In addition, we included studies that used non-use of a sulfonylurea as a comparator. Included studies were those that reported any VA (including ventricular tachycardia, ventricular fibrillation, and premature ventricular complexes; our primary endpoint), cardiac arrest, or sudden cardiac death. Studies that reported composite outcomes that included any one of these outcomes were also included. We required that studies report at least one effect measure for an outcome of interest (odds ratio, hazard ratio, incidence rate ratio, risk ratio) or sufficient data to calculate one.

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

Citations retrieved by the electronic search were imported and managed in EndNote X9. Duplicate records were removed, and the remaining records were uploaded to Rayyan (https://rayyan.qcri.org), a cloud-based systematic review management tool for reviewers to assess study eligibility. Two reviewers (NI and HTA) independently screened titles and abstracts to identify potentially relevant articles. Any study identified as potentially relevant by either reviewer proceeded to full-text review. Both reviewers independently assessed each full-text record against the inclusion and exclusion criteria to define the final set of included studies.

Disagreements regarding inclusion following the full-text review were resolved by either consensus or consulting a third reviewer (KBF).

Data Extraction

Data were independently extracted by both reviewers using a pre-specified, pilot-tested data extraction form. Disagreements were resolved by either consensus or by consulting a third reviewer (KBF). The fields of the data extraction form included entries on basic study information (study authors, geographic location, data source, citation, journal), study design characteristics (study design, study period, sample size, follow-up duration), cohort characteristics (inclusion/exclusion criteria, age/demographic, comorbidities), exposure drug information (sulfonylurea molecule, dose, formulation, exposure definition), comparator drug information (specific antihyperglycemic drug, dose, formulation, exposure definition), outcomes (both crude and adjusted effect measures with corresponding 95% confidence intervals [CI]), and study quality variables.

Quality Assessment

Both reviewers independently assessed study quality using the Cochrane Collaboration's Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool(12). The ROBINS-I instrument is a transparent and structured assessment tool containing signaling questions in seven domains: bias due to confounding; bias in the selection of study participants; bias in the classification of interventions; bias due to departure from intended interventions; bias due to missing data; bias in the measurement of outcomes; and bias in the selection of the reported

results. Using a series of signalling questions, users may make domain-level risk of bias assessments consisting of: low risk; moderate risk; serious risk; and critical risk of bias. More details about this instrument are available on the website (http://www.riskofbias.info).

Immortal time bias was considered as part of the bias in the selection of study participants or as part of the bias in the classification of intervention depending on whether the bias was the result of the exclusion or misclassification of immortal person-time. We then assigned each study an overall risk of bias, with the overall risk determined by the highest risk in any individual domain. Given the potential residual confounding inherent in any observational study, the highest quality a study could be assigned was a moderate risk of bias due to confounding. To be ascribed a moderate risk of bias, we required effect measures to account (by design or analytically) for the following pre-specified minimum set of confounders: age, sex, body mass index (BMI), smoking, diabetes severity (e.g., defined by either level of glycemic control or duration of diabetes), drugs with known arrhythmic effects, and previous cardiovascular events (stroke, MI, arrhythmias). Effect estimates derived with no consideration for confounding were ascribed a critical risk of bias.

We also evaluated the included studies for frequent biases in the pharmacoepidemiologic literature that are not stand-alone domains in ROBINS-I, including time-lag bias (a form of severe confounding by disease severity) and a depletion of susceptibles (a type of selection bias) (13). Time-lag bias may emerge from the comparison of treatments used at different stages of a disease(13, 14). Comparisons with treatments prescribed at an earlier stage (i.e., lifestyle modification) or later stage (i.e., insulin) can induce intractable confounding by disease severity.

A depletion of susceptibles may occur if studies include prevalent users and 1) exclude individuals with a previous history of the event of interest; or 2) the event has a high case fatality rate(15). In such situations, the most susceptible patients to the adverse event of interest will no longer be recorded and bias results. Restriction of the study cohort to new users of the drugs under investigation will prevent the inclusion of prevalent users and thus avoid this potential bias.

RESULTS

Our search identified 3641 studies, of which 3465 were excluded during the title and abstract screening (**Figure 2**). The reasons for their exclusions are described in **Appendix S1**. The remaining 176 studies underwent a full-text review. A total of 17 studies were included.

Study Characteristics

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

Four studies used an as-treated exposure definition in which patients were considered continuously exposed to the drug that defined cohort entry until drug discontinuation. Thirteen studies used an intention-to-treat approach in which patients' exposure was determined by their

treatment at cohort entry regardless of use during follow-up. While all studies included patients using a sulfonylurea, 2 studies included patients newly initiating pharmacotherapy with a sulfonylurea, 3 included prevalent users of a sulfonylurea, and 12 included both new and prevalent users of a sulfonylurea. There was one study that considered new users of a sulfonylurea following previous use of metformin.

The definition of VA was also heterogeneous (**Table 2**). The included studies used a broad spectrum of definitions including ventricular fibrillation, ventricular tachycardia, premature ventricular complexes, and unspecified arrhythmia. Due to sparse data, we were unable to explore the different types of arrhythmia in further detail.

Quality Assessment

After applying the ROBINS-I tool, 2 studies were assigned a moderate risk of bias(16, 17), 4 studies were assigned a serious risk of bias,(18-21) and 11 studies were assigned a critical risk of bias(19, 22-31) (**Table 3**). The domain 'risk of bias due to confounding' was one of the ROBINS-I domains most responsible for the overall risk of bias. Of 17 studies, 9 did not account for the pre-specified confounders described above(19, 22-24, 26-31). Diabetes severity and BMI were the confounders most frequently not accounted for. Another domain contributing to an increased risk of bias was 'bias in selection of participants into the study'. Selection bias most frequently occurred in two ways in the included studies. A total of 11 studies examined sulfonylurea use following hospitalization (often for a cardiovascular event). Those who survived this initial event and were included in the study are likely to be systematically different from those who did not have this initial event and did not survive this initial hospitalization. This

hospitalization is said to be ‘a collider’, and conditioning on its occurrence can result in selection bias. In such studies, observed incidence of VA may be underestimated since patients not surviving to hospitalization no longer enter the study cohort defined at hospitalization. Inclusion in such studies is restricted to one stratum of the population (those who were hospitalized for a cardiac event), which can introduce bias if use of sulfonylureas and increased arrhythmic risk are both associated with hospitalization for myocardial infarction. Importantly the magnitude of this bias is often difficult to predict. Selection bias can also occur due to informative censoring in the 4 studies that used an as-treated exposure definition if drug discontinuation was related to the occurrence of cardiovascular events or poor glycemic control, a risk factor for cardiovascular events. While this analysis has certain strengths, none of the included studies used statistical approaches to address potential informative censoring such as inverse probability of censoring weighting. Finally, several studies did not describe a pre-specified study protocol, increasing the overall risk of bias due to a potential ‘bias in selection of reported results’.

Time Lag Bias

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

Depletion of Susceptibles Bias

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

Sulfonylureas and VA

Sixteen studies examined the association between sulfonylurea use and the risk of VA, reporting heterogeneous results. However, both studies with reported adjusted estimates for head-to-head comparisons of sulfonylureas versus other oral antihyperglycemic drugs consistently reported an increased risk of VA. In a study at moderate risk of bias conducted using the UK's Clinical Practice Research Datalink, sulfonylureas were associated with a higher risk of cardiac arrhythmias (including atrial fibrillation, atrioventricular block, ventricular and supraventricular tachycardias, cardiac arrest, and other unspecified conduction disorders) versus dipeptidyl peptidase-4 (DPP-4) inhibitors (adjusted hazard ratio [aHR]: 1.51, 95% CI: 1.27-1.80)(17). In another study, this one at a serious risk of bias, the investigators used the IBM MarketScan

Medicare Supplemental Database and reported an increased risk of ventricular tachycardia and ventricular fibrillation among patients using sulfonylurea monotherapy (aHR: 1.52, 95% CI: 1.10-2.13) relative to metformin(21). However, this study included sulfonylurea users who may have previously undergone therapy using another antihyperglycemic drug (resulting in potential time-lag bias). In addition, this study may have been affected by left censoring and outcome misclassification. Among the 10 studies comparing sulfonylurea use with non-sulfonylurea use, the risk of VA varied from substantially decreased (OR: 0.31, 95% CI: 0.12-0.78)(33) to higher (OR: 3.71, 95% CI: 0.85-16.20)(34). A total of two studies reported intra-sulfonylurea class comparisons for VA. One study had inconclusive results due to wide 95% CIs for the risk of VA with gliclazide relative to glyburide (OR: 1.20, 95% CI: 0.60-2.30)(18). Another study reported no VA events among glyburide users, who were compared to users of first-generation sulfonylureas including tolbutamide and carbutamide (OR: 0.00, 95% CI: 0.00-0.19)(35).

Sulfonylureas and Cardiac Arrest

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

Medicaid claims data suggested an increased risk of cardiac arrest/VA with glimepiride (aHR: 1.17, 95% CI: 0.96-1.42) and a lower risk with glyburide (aHR: 0.87, 95% CI: 0.74-1.03); these trends were not observed in the analysis of Optum claims data (glimepiride = aHR: 0.84, 95% CI: 0.65-1.08; glyburide = aHR: 1.11, 95% CI: 0.86-1.42)(16).

Sulfonylureas and Sudden Cardiac Death

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

DISCUSSION

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

Several of the included studies had important methodological limitations, including confounding, selection bias, time-lag bias, and depletion of susceptibles. Using the ROBINS-I tool, 2 studies were assigned a moderate risk of bias, 5 studies were assigned a serious risk of bias, and 10 studies were assigned a critical risk of bias. A potential limitation observed in studies with a serious or critical risk of bias was confounding. The majority of included studies were also at risk of time-lag bias. A total of 2 studies adjusted for the pre-defined minimum set of confounders, both using propensity score-based approaches. Finally, a major limitation was the inclusion of prevalent users following an acute MI. The inclusion of prevalent users may result in a depletion of susceptibles, while conditioning on surviving the acute MI may result in selection bias. Restricting inclusion to new users of sulfonylureas and an appropriate comparator is needed to avoid these issues.

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

There are no existing RCTs designed to examine the arrhythmic safety of sulfonylureas. A subsequent well-powered RCT or prospective observational study examining this issue is unlikely. Large RCTs including CAROLINA, TOSCA.IT, and ADVANCE have not reported VA as an endpoint(36-39). Practically, RCTs are expensive and lengthy to conduct. Furthermore, with sulfonylureas off-patent, such trials are unlikely to be funded by their manufacturers. These factors contribute to resources for RCTs being allocated for newly developed therapies such as sodium-glucose transport protein 2 (SGLT-2) inhibitors instead of well-established therapies including sulfonylureas. A retrospective cohort study using a methodologically rigorous design could address this knowledge gap in the literature by comparing the safety of sulfonylureas with respect to VA relative to antihyperglycemic agents used at a similar stage of type 2 diabetes. This study should abide by reporting guidelines suggested by RECORD-PE and give ample consideration for critical biases due to confounding, selection bias, time-related biases, and prevalent user bias present in the existing literature(40). The use of an active comparator, new user design with a comparator used at a similar stage of type 2 diabetes management would avoid many of these issues(41). Future studies should also carefully consider relevant outcomes, including VA and important sequelae such as cardiac arrest and sudden cardiac death. VA has been described to be challenging to detect in administrative health records(42). Therefore, possible approaches include case validation or supplementing with more detailed databases that will capture some events that are not captured by administrative databases.

Our study has many strengths. First, it was conducted following a pre-specified, registered protocol. Second, we implemented a comprehensive literature search across 5 databases and double-screened all abstracts and full-texts for eligibility. Third, we undertook a comprehensive

investigation of methodological biases using ROBINS-I to evaluate the quality of the included studies. This tool enabled us to discuss the existing literature's vulnerabilities to different biases such as confounding and selection bias. Fourth, this systematic review and its critical assessment of the existing literature identified important knowledge gaps for future research.

Our review also has limitations. First, the methodological heterogeneity among included studies made it inappropriate to pool results across studies via meta-analysis for any outcomes. Second, this review is vulnerable to the limitations of the included studies. Third, we were limited in our ability to directly compare results across studies given that these studies used a range of comparators and were of varying methodological rigour. Fourth, **Table 2** and our discussion were limited to the exposure definition (either intention-to-treat or as-treated) used in the primary analysis. However, an alternative exposure definition used in a sensitivity analysis was considered in the quality assessment. Fifth, given the limited number of higher-quality studies that we identified, we were only able to draw modest substantive conclusions regarding the associations of interest. Sixth, our systematic review was restricted to observational studies. Finally, publication bias is possible due to potentially eligible studies not having been published and thus indexed in the searched databases.

CONCLUSIONS

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

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Sulfonylurea use is associated with an increased risk of cardiovascular death among people with type 2 diabetes. A potential mechanism behind this risk includes hypoglycemia-induced ventricular arrhythmias.

What question did this study address?

Are sulfonylureas associated with an increased risk of ventricular arrhythmia, cardiac arrest, or sudden cardiac death?

What does this study add to our knowledge?

Our systematic review suggests that among higher-quality observational studies, sulfonylurea therapy is associated with an increased risk of VA. Many of the existing studies are at risk of conclusion-altering biases, including time lag bias and a depletion of susceptibles (prevalent user bias).

How might this change clinical pharmacology or translational science?

Several observational studies have investigated the association between sulfonylureas and the risk of VA, cardiac arrest, and sudden cardiac death, although the lower overall quality of the literature renders it challenging to interpret. Given the existence of few methodologically rigorous studies, we underscore the need for additional real-world safety studies of this drug safety issue.

ACKNOWLEDGEMENTS

NI holds the Nyman award from the Faculty of Medicine and Health Sciences, McGill University. HTA was supported by a post-doctoral fellowship from the *Fonds de recherche du Québec – santé* (FRQS; Quebec Foundation for Research – Health). OHYY, AD, and KBF hold salary support awards from the FRQS. KBF is also supported by a William Dawson Scholar award from McGill University.

AUTHORS' CONTRIBUTIONS

N.I, wrote the manuscript; N.I. and K.B.F. designed the research; N.I. and H.T.A. performed the research; N.I, H.T.A., O.H.Y.Y, A.D. and K.B.F. analyzed the data.

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram describing systematic literature search for observational studies examining the association between sulfonylureas as therapy for type 2 diabetes and the risk of ventricular arrhythmia, cardiac arrest, or sudden cardiac death

Figure 2. Forest plot of comparative studies evaluating the arrhythmic effects of sulfonylureas by ROBINS-I defined risk of bias. [a]Dhopeshwarkar 2020: Medicaid Claims analysis. [b]Dhopeshwarkar 2020: Optum Clinformatics analysis. **Abbreviations**: ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions