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Safety of add-on sulfonylurea therapy in patients with type 2 diabetes using metformin: a population-based real-world study

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ABSTRACT

Introduction Metformin is the initial oral antihyperglycemic agent (OHA) of choice for most patients with type 2 diabetes (T2D). However, more than one agent is often required for optimal glucose control. As the choice of preferred second OHAs is less well defined, we sought to compare the real-world safety of sulfonylureas to other OHAs as add-on therapy to metformin in patients with T2D.

Research design and methods This retrospective cohort study included adults in Manitoba, Canada with T2D from 2006 to 2017. Using a new-user design, we divided patients who started on metformin into two groups: add-on therapy with a sulfonylurea and add-on therapy with a different OHA. Outcomes included all-cause mortality, cardiovascular events, and major hypoglycemic episodes. We calculated propensity scores and applied inverse probability of treatment weights to each individual. We compared groups using Cox proportional hazards regression and explored differences in HRs between pre-2008 (acarbose, meglitinides, and thiazolidinediones) and post-2008 (dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose linked transporter-2 inhibitors) OHAs.

Results Our cohort included 32 576 individuals (28 077 metformin plus sulfonylurea and 4499 metformin plus 'other'). Patients newly prescribed a sulfonylurea in the setting of metformin had a higher risk of all-cause mortality (HR 1.44, 95% CI 1.12 to 1.84, p=0.005) and major hypoglycemic episodes (HR 2.78, 95% CI 1.66 to 4.66, p<0.001) than those prescribed an 'other' OHA. No differences in cardiovascular events were observed (HR 0.99, 95% CI 0.81 to 1.22, p=0.92). In subgroup analyses, mortality and cardiovascular event risk was higher in patients prescribed sulfonylureas versus post-2008 OHAs.

Conclusions Sulfonylureas as add-on therapy to metformin are associated with increased risk of all-cause mortality and major hypoglycemic episodes compared with 'other' OHAs. Post hoc analysis suggests newer OHAs may be preferred to sulfonylureas as second-line therapy for glycemic control.

Significance of this study

What is already known about this subject?

- Current guidelines recommend metformin as initial therapy in most patients with type 2 diabetes.
- The optimal choice of a second oral antihyperglycemic agent (OHA) in addition to metformin is less well defined, and as a result significant practice variation exists.
- Many observational studies have compared dipeptidyl peptidase-4 inhibitors with sulfonylureas when in combination with metformin and most have found lower risks of mortality and cardiovascular disease.
- However, comparisons between sulfonylureas and other OHAs in this setting are much less common.

What are the new findings?

- Patients prescribed sulfonylureas as add-on therapy to metformin had increased risk of all-cause mortality compared with those prescribed other add-on OHAs.
- Patients prescribed sulfonylureas as add-on therapy to metformin had increased risk of major hypoglycemic episodes compared with those prescribed other add-on OHAs.
- Post hoc analysis suggests newer OHAs may have lower risk of cardiovascular events compared with sulfonylureas when used as second-line therapy for glycemic control.

How might these results change the focus of research or clinical practice?

- Our study findings would suggest that in all patients with T2D, sulfonylureas are a harmful second agent for combotherapy with metformin and should not be recommended.
- Guideline statements may want to incorporate real-world effectiveness trials in their updated statements concerning second-line agent preference.
- Formal economic analyses incorporating these expected outcome differences are needed to inform policy.

INTRODUCTION

Proper glycemic control is a key component of type 2 diabetes (T2D) management, as it has been shown to reduce the incidence of microvascular and macrovascular complications.[1] Some patients with T2D have adequate glycemic control with lifestyle modification alone, but most require the addition of oral antihyperglycemic agents (OHAs) and/or

insulin. To date, at least seven different classes of OHAs have become available for the management of T2D, each with different mechanisms of action, side effects, and risk/benefit profiles. Current guidelines recommend metformin as initial therapy in most patients and suggest tailoring the choice of a second agent based on degree of hyperglycemia, risk of hypoglycemia, comorbidities (including obesity, cardiovascular disease, chronic kidney disease and hepatitis), patient preference, and access to treatment.[2 3]

The optimal choice of a second OHA in addition to metformin is less well defined, and as a result significant practice variation exists. Sulfonylureas have been used as an OHA medication for over 60 years. They stimulate pancreatic insulin secretion, and in clinical trials have been shown to reduce glycosylated hemoglobin (A1c) by 1%–2%.[4] It is well known that sulfonylureas increase the risk of hypoglycemia when compared with other oral agents,[5] but they remain widely prescribed as a second-line OHA added to metformin due to their low costs.

Since 2008, several new classes of OHAs, dipeptidyl peptidase-4 inhibitors (DPP4), glucagon-like peptide-1 (GLP1) receptor agonists, and sodium-glucose linked transporter-2 (SGLT2) inhibitors, have been approved for use in patients with T2D. In addition to demonstrating efficacy for short-term glycemic end points,[6–8] these classes of OHAs have also been shown to be either neutral or substantially effective in reducing the risk of a composite cardiovascular outcome consisting of cardiovascular death, myocardial infarction, and stroke compared with placebo in randomized controlled trials.[9–14] In these trials, newer OHAs were most often used as a second or third agent alongside metformin, but how they perform against sulfonylureas when used specifically as a second-line OHA is less well known.

Many observational studies have compared DPP4 inhibitors with sulfonylureas when in combination with metformin and most have found lower risks of mortality and cardiovascular disease.[15–19] However, comparisons between sulfonylureas and other OHAs in this setting are much less common. In this observational, population-wide study, we set out to compare all-cause mortality, cardiovascular events, and major hypoglycemic episodes in patients using metformin who were newly prescribed sulfonylureas compared with other OHAs (older and newer agents) in a real-world setting.

METHODS

Data sources

Data were obtained from eight population-wide, anonymized administrative health databases in Manitoba, a Canadian province of 1.3 million people with universal single-payer health insurance. Databases analyzed include the Canadian Institute for Health Information Hospital Discharge Abstracts (hospital admissions), Diabetes Education Resource for Children and Adolescents (type of diabetes), Diagnostic Services of Manitoba (laboratory test results), Drug Program Information Network (complete record of all outpatient drug prescriptions in Manitoba), Emergency Admission, Discharge, and Transfer/Emergency Department Information System (emergency room visits), Manitoba Health Insurance Registry (demographics and coverage dates), and Medical Claims/Services (physician claims). These databases are housed at the Repository at the Manitoba Centre for Health Policy at the University of Manitoba and cleaned according to published data quality framework.[20–22] The de-identified information in each database can be linked to a unique individual through a scrambled personal health identification number. The databases and time periods used for data extraction are listed in online supplemental table 1.

Study design and population

The study period for this retrospective cohort study was from April 1, 2006 to March 31, 2017. Eligible patients were those who met one of the following criteria: at least one hospitalization with a diabetes diagnosis, at least two physician claims with a diabetes diagnosis, or at least one prescription for an OHA or insulin. We excluded patients with gestational or type 1 diabetes, and those who were under 18 years of age or had <1 year of history in the health insurance registry at the index date. A wash-in period of 365 days without use of any antihyperglycemic agents with the exception of metformin was required prior to filling a prescription for a new OHA. Patients needed to have evidence of metformin use at the time of their new OHA prescription. Individuals who were simultaneously prescribed two or more additional add-on OHAs on the index date were not eligible. The index date was defined as the date an individual filled an incident prescription. No restrictions were applied on the length of time on metformin treatment before add-on therapy.

OHAs were identified through their anatomic therapeutic chemical (ATC) code and date of dispensation. Online supplemental table 2 lists all of the OHAs available in our databases during the study period. Subjects were divided into two exposure groups: metformin plus sulfonylurea users (chloropropamide, gliclazide, glimepiride, glyburide, or tolbutamide) versus metformin plus 'other' OHA users (acarbose, DPP4 inhibitors, GLP1 receptor agonists, meglitinides, SGLT2 inhibitors, and thiazolidinediones (TZDs)).

Patients were followed from the index date until either the date of an outcome or the earliest censoring event. Censoring events consisted of one of: (1) a switch to or addition of insulin; (2) discontinuation of metformin or the index OHA (defined as a failure to refill before a 90-day grace period); (3) termination of insurance coverage due to migration out of province or death; (4) the end of the study period; (5) a switch to or addition of a sulfonylurea for those in the metformin plus 'other' group; or (6) a switch to or addition of another OHA in the metformin plus sulfonylurea group. We identified the days of supply for each prescription and counted

that as the number of days with the drug in-hand while accounting for early refills, meaning that if an individual refilled a prescription before the end of their supply the excess number of days left over was carried over to the new prescription.

Outcomes

Our primary outcomes were all-cause mortality, hospitalization for fatal and non-fatal cardiovascular events, and major hypoglycemic episodes (see specific case definitions in online supplemental table 3). All-cause mortality was determined using date of death in the Manitoba Health Insurance Registry Database. A cardiovascular event was defined as the composite of acute myocardial infarction, heart failure, stroke (ischemic or hemorrhagic), or unstable angina. We only included hospitalizations for the composite outcome that was a primary discharge diagnosis and excluded International Classification of Diseases (ICD) codes that were explicitly associated with recurrent events.[23–28] Major hypoglycemic episodes were defined as a presentation to the emergency room or admission to hospital with a primary or underlying diagnosis of hypoglycemia,[29] or a blood glucose level of 3.5 mmol/L or lower.[30]

Covariates

We collected demographics, comorbidities, and drug prescription data on patients. We obtained the postal code of an individual's residence from the health insurance registry and linked it to the most recent Canada Census data to obtain neighborhood level median income in order to estimate socioeconomic status. A single physician claim or hospitalization prior to the index date was used to identify comorbidities with a look-back period of at least 3 years (see online supplemental table 4 for ICD codes for comorbidities). We used physician claims to determine if an individual used chronic dialysis at baseline according to a validated algorithm,[31] however, there were no individuals on dialysis at the index date. We checked prescriptions up to 1 year prior to the index date for selective concomitant medications indicative of the comorbidities collected. One dispensed prescription was required for an individual to be considered a user of the medication (see online supplemental table 5 for ATC codes of medications). We also derived a nominal variable (<1 year; 1–3 years; ≥3 years) based on the number of years prior an individual was adherent on metformin before they added a second OHA. We used the same criteria for adherence to metformin as we did with the index OHA.

Data analysis

All analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). Descriptive statistics were reported for both cohorts and stratified by OHA exposure group. Categorical variables were reported as frequency and percentage. Continuous variables were reported as means plus SD or as median and IQR depending on the distribution.

We calculated the predicted probability of being assigned a sulfonylurea (propensity score) using binary logistic regression based on baseline covariates for pairwise comparisons in our cohorts. We used a non-parsimonious approach in our propensity score models. Age, sex, socioeconomic status, index fiscal year, time spent on metformin, and the concomitant medications and comorbidities we collected at baseline were included as covariates.

We evaluated the performance of the propensity score models with C statistics and the rescaled maximum R^2. We assessed for multicollinearity among covariates by creating a linear regression model where the propensity score was the dependent variable. We considered variance inflation >10 as our threshold to remove a covariate from the final propensity score model. We used the propensity score to calculate a stabilized inverse probability of treatment weight (IPTW)[32] and applied the weight to each individual. We diagnosed balance pre-IPTW and post-IPTW by calculating a standardized mean difference (SMD) to compare the distribution of baseline covariates between treatment groups. An SMD with a magnitude of 0.10 or less was considered to be balanced.[33]

We then constructed a series of Cox proportional hazards regression models to analyze time to event for each of the proposed safety outcomes comparing those newly prescribed sulfonylureas versus 'other' OHAs while adjusting for a stabilized IPTW. The proportional hazards assumption was assessed by the Kolmogorov-type supremum test.[34] The assumption was met for all Cox proportional hazards regression models. We reported HRs with 95% CIs and p values for each of the safety outcomes. We also reported cumulative incidence functions for each of the safety outcomes using Kaplan-Meier estimates and compared the results for each OHA group using the log-rank test.

Sensitivity and subgroup analysis

As a sensitivity analysis, we log-transformed the propensity score and matched new sulfonylureas users to 'other' OHA 1:1 based on their nearest neighbor within a caliper distance of 0.2 SD of the logit of the propensity score.[35 36] We conducted survival analysis with Cox proportional hazards regression models in that cohort as well and accounted for matching by stratifying by matched pairs. To address the issue of informative censoring bias, we also investigated a scenario where we did not censor for adding other antidiabetic drugs including insulin to the existing regimen to see if the results would be significantly changed. We limited our follow-up to 2 years in this intention-to-treat analysis to reduce the risk of exposure misclassification. As a final sensitivity analysis, we limited the grace period between prescriptions to 30 days before censoring due to discontinuation.

As a post hoc subgroup analysis, we divided our 'other' OHAs into two groups reflecting the era of when they

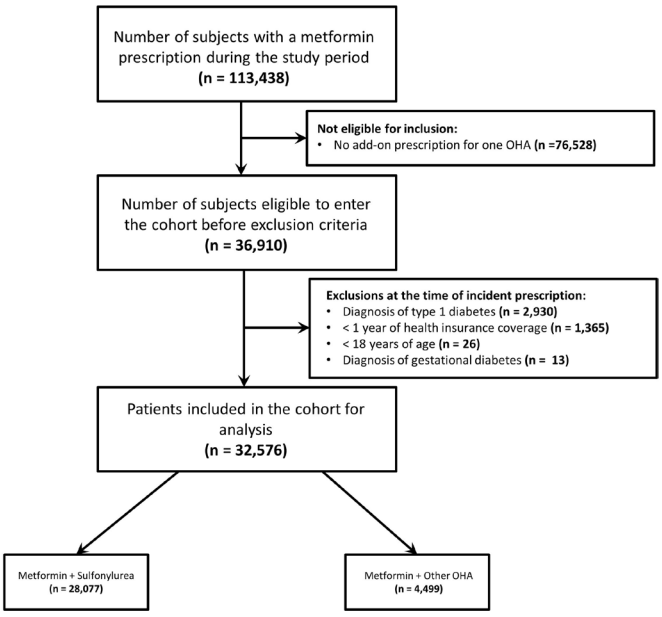

Figure 1 Cohort selection. OHA, oral antihyperglycemic agent.

became available for prescription. Acarbose, meglitinides, and TZDs comprised the pre-2008 group and DPP4 inhibitors, GLP1 receptor agonists, and SGLT2 inhibitors comprised the post-2008 group. We chose 2008 as a cut-off as it corresponded to use of distinct classes of OHAs with a reduced overlap period. We performed additional Cox proportional hazards regression models comparing sulfonylureas with each subgroup for all of our outcomes while adjusting for stabilized IPTW.

RESULTS

Study population

We identified 32 576 metformin users with T2D who had an incident OHA prescription between April 1, 2006 and March 31, 2017 (figure 1). Of those, 28 077 were newly prescribed a sulfonylurea and 4499 were prescribed an 'other' OHA. Prior to matching, the 'other' OHA group included patients prescribed DPP4 inhibitors (36.2%), TZDs (27.4%), SGLT2 inhibitors (20.8%), meglitinides (9.4%), GLP1 receptor agonists (4.0%), and acarbose (2.2%). Among patients prescribed a sulfonylurea, 18 800 (67.0%) were prescribed gliclazide, 9139 (32.5%) were prescribed glyburide, and 138 (0.5%) were prescribed a different sulfonylurea. At baseline, both groups had similar demographics and comorbidity and medication profiles. However, patients in the sulfonylurea group were more likely to be of lower socioeconomic status, have filled their prescription in an earlier era, and spent less time on metformin before add-on therapy (table 1).

Propensity score analysis

The logistic regression model used to derive the propensity score achieved a C statistic of 0.68 and R^2 of 8.5% and there was no evidence of multicollinearity. Groups were well balanced on IPTW (table 2). Mean age in the sulfonylurea group was 56.4±14.0 years whereas the 'other' group had a mean age of 56.8±13.3 years. Both groups weighted by IPTW were 44% female. All other baseline characteristics were balanced (SMD <0.1). The 1:1 propensity matching algorithm matched 4499 combotherapy sulfonylurea users to all 4499 combotherapy 'other' OHA users. After propensity matching, the sulfonylurea and 'other' combotherapy groups were similar in age, gender, socioeconomic status, comorbid conditions, and baseline medications (online supplemental table 6).

Cox regression models

There were a total of 838 deaths, 836 cardiovascular events, 359 major hypoglycemic episodes, and a mean follow-up time of 1.7±1.9 years (median: 0.9, IQR: 0.4, 2.3) in the metformin plus sulfonylurea group and 44 deaths, 78 cardiovascular events, 9 major hypoglycemic episodes and a mean follow-up time of 1.2±1.4 years (median: 0.7, IQR: 0.3, 1.5) in the metformin plus 'other' group. After adjusting for IPTW, new users of sulfonylureas had a higher risk of all-cause mortality (HR 1.44, 95% CI 1.12 to 1.84; p=0.005) and major hypoglycemic episodes (HR 2.78, 95% CI 1.66 to 4.66; p<0.001) when compared with 'other' OHAs combined with metformin (table 3). Sulfonylurea use was not associated with a higher risk for cardiovascular events (HR 0.99, 95% CI 0.81 to 1.22; p=0.92) compared with 'other' OHAs. Findings were qualitatively unchanged in the propensity-matched analysis, when the grace period for discontinuation was limited to 30 days, and when adding additional antidiabetic drug(s) to the existing regimen was not considered a censoring event where 7805 subjects (24.0%) were originally censored for that reason.

Subgroup analyses

There were clear differences in HRs when the 'other' OHAs were divided into classes approved before and after 2008 (table 3). Patients who were prescribed sulfonylureas compared with pre-2008 'other' OHAs (70.3% TZDs, 24.1% meglitinides, 5.6% acarbose) were at lower risk of cardiovascular events (HR 0.74, 95% CI 0.57 to 0.95; p=0.019) and were not associated with an increased risk of all-cause mortality (HR 0.87, 95% CI 0.66 to 1.15; p=0.32). By contrast, when compared with post-2008 'other' OHAs (59.3% DPP4 inhibitors, 34.1% SGLT2 inhibitors, 6.6% GLP1 receptor agonists), sulfonylureas were associated with a higher risk of cardiovascular events (HR 1.40, 95% CI 1.01 to 1.89; p=0.041) and a higher risk of death (HR 3.33, 95% CI 2.02 to 5.49; p<0.001). There were an insufficient number of major hypoglycemic episodes to conduct a pre-2008/post-2008 analysis for this outcome.

DISCUSSION

In this observational cohort study of 32 576 patients with T2D using metformin, we found that patients newly prescribed a sulfonylurea had a 40% higher risk

Table 1 Baseline characteristics by combotherapy group (full cohort)

Characteristic	Sulfonylurea (n=28 077)	'Other' (n=4499)	SMD
Demographics			
Age (years)	56.4±14.1	56.3±12.6	0.007
Sex (% female)	12 240 (43.6%)	2010 (44.7%)	0.022
Geographic/Socioeconomic status			
Rural/Income quintile 1	3576 (12.7%)	275 (6.1%)	0.228
Rural/Income quintile 2	2616 (9.3%)	279 (6.2%)	0.117
Rural/Income quintile 3	2205 (7.9%)	287 (6.4%)	0.057
Rural/Income quintile 4	2081 (7.4%)	313 (7.0%)	0.017
Rural/Income quintile 5	1684 (6.0%)	328 (7.3%)	0.052
Urban/Income quintile 1	4175 (14.9%)	508 (11.3%)	0.106
Urban/Income quintile 2	3520 (12.5%)	625 (13.9%)	0.04
Urban/Income quintile 3	3127 (11.1%)	611 (13.6%)	0.074
Urban/Income quintile 4	2752 (9.8%)	643 (14.3%)	0.138
Urban/Income quintile 5	2020 (7.2%)	607 (13.5%)	0.208
Unknown	321 (1.1%)	23 (0.5%)	0.07
Baseline comorbidities			
Alcohol abuse	1151 (4.1%)	75 (1.7%)	0.146
Amputation	107 (0.4%)	9 (0.2%)	0.034
Asthma	3900 (13.9%)	695 (15.4%)	0.044
CKD	793 (2.8%)	100 (2.2%)	0.038
COPD	2858 (10.2%)	382 (8.5%)	0.058
Cardiovascular disease	7332 (26.1%)	1066 (23.7%)	0.056
Dementia	916 (3.3%)	92 (2.0%)	0.076
Hypertension	17 943 (63.9%)	3006 (66.8%)	0.061
Hyperlipidemia	9668 (34.4%)	1769 (39.3%)	0.101
Liver disease	1617 (5.8%)	284 (6.3%)	0.023
Malignancy	2858 (10.2%)	453 (10.1%)	0.004
Microvascular disease	6178 (22.0%)	997 (22.2%)	0.004
Obesity	1878 (6.7%)	364 (8.1%)	0.054
Baseline medication use			
ACE inhibitors	11 491 (40.9%)	1753 (39.0%)	0.04
Anticoagulants	1227 (4.4%)	173 (3.8%)	0.026
Antiplatelets	5559 (19.8%)	661 (14.7%)	0.135
ARBs	5461 (19.5%)	1085 (24.1%)	0.113
Beta-blockers	5882 (20.9%)	903 (20.1%)	0.022
CCBs	5388 (19.2%)	881 (19.6%)	0.01
Digoxin	627 (2.2%)	77 (1.7%)	0.038
Direct vasodilators	52 (0.2%)	9 (0.2%)	0.003
Loop diuretics	2257 (8.0%)	307 (6.8%)	0.046
Potassium-sparing diuretics	448 (1.6%)	76 (1.7%)	0.007
Thiazide diuretics	4147 (14.8%)	615 (13.7%)	0.032
Statins	13 785 (49.1%)	2432 (54.1%)	0.099
Other lipid-lowering medications	1756 (6.3%)	335 (7.4%)	0.047
Index fiscal year			

Continued

Table 1 Continued

Characteristic	Sulfonylurea (n=28 077)	'Other' (n=4499)	SMD
2006/07	2321 (8.3%)	584 (13.0%)	0.153
2007/08	2090 (7.4%)	375 (8.3%)	0.033
2008/09	2223 (7.9%)	263 (5.8%)	0.082
2009/10	2490 (8.9%)	295 (6.6%)	0.087
2010/11	2714 (9.7%)	247 (5.5%)	0.158
2011/12	2865 (10.2%)	253 (5.6%)	0.17
2012/13	2638 (9.4%)	297 (6.6%)	0.103
2013/14	2762 (9.8%)	271 (6.0%)	0.141
2014/15	2848 (10.1%)	468 (10.4%)	0.009
2015/16	2899 (10.3%)	853 (19.0%)	0.246
2016/17	2227 (7.9%)	593 (13.2%)	0.171
Time on metformin before add-on therapy			
≥3 years	6976 (24.8%)	1339 (29.8%)	0.111
1–3 years	5892 (21.0%)	1146 (25.5%)	0.106
<1 year	15 209 (55.6%)	2014 (44.8%)	0.189

ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

of all-cause mortality and, a nearly threefold higher risk of major hypoglycemic episodes compared with those prescribed 'other' OHAs as a second-line agent. There were no differences in risk of cardiovascular events between the two groups, however, a post hoc analysis found new sulfonylurea users had a 40% higher risk of cardiovascular events versus those prescribed newer OHAs. Taken together, these results raise real-world safety concerns with the use of sulfonylureas compared with newer OHAs.

Our study findings are consistent with recent retrospective studies from the UK, Sweden, Taiwan, and Korea that evaluated the safety of sulfonylureas compared with DPP4 inhibitors when added on to metformin.[15–19] In two cohort studies using the UK Clinical Practice Research Datalink, investigators noted an increased risk of cardiovascular-related and all-cause mortality in patients prescribed sulfonylureas. Similarly, in three independent analyses from Sweden, Taiwan, and Korea, an increased risk of mortality, cardiovascular events, and hypoglycemia was noted in patients prescribed sulfonylureas. Compared with these studies however, our study population was more racially diverse. We also used IPTW analysis, which requires fewer distributional assumptions about underlying data, avoids potential residual confounding from stratification on a fixed number of strata, and allowed us to capture more people than propensity matching.[37] Additionally, we included a broader definition of severe hypoglycemia by using emergency room visits and lab values, and collected more information on comorbid conditions and baseline medications to add to the propensity score.

Our study also included patients on novel OHAs other than DPP4 inhibitors. While study numbers were not large enough to allow analysis of individual medication classes, DPP4 inhibitors represented a plurality of the OHAs in the 'other' group and therefore had the greatest influence in their comparison with sulfonylureas in our study. Currently, studies directly comparing sulfonylureas to OHAs other than DPP4 inhibitors as add-on therapy to metformin are limited. A recent study in the UK Clinical Practice Research Datalink[38] compared cardiovascular outcomes with add-on therapy and found a lower risk of cardiovascular disease or cardiovascular death with TZDs compared with sulfonylureas. This contrasts with our results when 'other' OHAs are stratified by era and may be due to the fact that unlike our study, the UK investigators did not include heart failure among the possible cardiovascular outcomes. This may bias results in favor of TZDs as TZDs have been independently associated with heart failure due to fluid retention.[39]

Ekström *et al*[40] studied add-on OHAs comparing sulfonylureas to TZDs, meglitinide, DPP4 inhibitors, GLP1 receptor agonists, acarbose, as well as insulin, in a Swedish population. Similar to our study, they calculated a stabilized IPTW and used it in weighted Cox models to analyze comparative risk mortality and cardiovascular events. However, they did not examine the risk of major hypoglycemic episodes, they could not include patients using SGLT2 inhibitors, and the sample for each OHA class they used for comparison was at least 36% smaller than our group of all other OHAs combined. Additionally, this study excluded patients who were on metformin for fewer than 180 days prior to add-on therapy and who

Table 2 Baseline characteristics by combotherapy group (weighted cohort)

Characteristic	Sulfonylurea (n=28077)	'Other' (n=4499)	SMD
Demographics			
Age (years)	56.4±14.0	56.8±13.3	0.029
Sex (% female)	43.80%	44.00%	0.004
Geographic/ Socioeconomic status			
Rural/Income quintile 1	11.80%	11.50%	0.008
Rural/Income quintile 2	8.90%	9.50%	0.017
Rural/Income quintile 3	7.60%	7.60%	0.001
Rural/Income quintile 4	7.30%	7.40%	0.003
Rural/Income quintile 5	6.20%	6.10%	0.001
Urban/Income quintile 1	14.40%	14.20%	0.005
Urban/Income quintile 2	12.70%	12.40%	0.008
Urban/Income quintile 3	11.50%	11.40%	0.002
Urban/Income quintile 4	10.40%	10.40%	<0.001
Urban/Income quintile 5	8.10%	8.30%	0.007
Unknown	1.10%	1.10%	0.005
Baseline comorbidities			
Alcohol abuse	3.80%	3.70%	<0.001
Amputation	0.40%	0.40%	<0.001
Asthma	14.10%	13.20%	0.02
CKD	2.80%	3.00%	0.013
COPD	10.00%	9.70%	0.008
Cardiovascular disease	25.80%	26.20%	0.009
Dementia	3.10%	3.20%	0.004
Hypertension	64.30%	65.10%	0.013
Hyperlipidemia	35.10%	35.10%	<0.001
Liver disease	5.80%	6.00%	0.005
Malignancy	10.20%	10.60%	0.01
Microvascular disease	22.00%	22.10%	0.001
Obesity	6.90%	6.40%	0.016
Baseline medication use			
ACE inhibitors	40.70%	40.90%	0.004
Anticoagulants	4.30%	4.50%	0.009
Antiplatelets	19.10%	18.90%	0.005
ARBs	20.10%	20.60%	0.009
Beta-blockers	20.80%	21.40%	0.012
CCBs	19.30%	19.90%	0.014
Digoxin	2.20%	2.20%	0.004
Direct vasodilators	0.20%	0.20%	0.002
Loop diuretics	7.90%	8.30%	0.012
Potassium-sparing diuretics	1.60%	1.60%	0.001
Thiazide diuretics	14.60%	14.70%	0.001
Statins	49.80%	49.90%	0.002
Other lipid-lowering medications	6.40%	6.20%	0.006
Index fiscal year			
2006/07	9.00%	9.80%	0.025
2007/08	7.60%	8.00%	0.013
2008/09	7.60%	7.70%	<0.001
2009/10	8.50%	8.90%	0.01
2010/11	9.10%	8.70%	0.012
2011/12	9.60%	9.20%	0.011
2012/13	9.00%	9.00%	<0.001
2013/14	9.30%	8.80%	0.014
2014/15	10.20%	10.10%	0.003
2015/16	11.50%	11.20%	0.009
2016/17	8.70%	8.60%	<0.001
Time on metformin before add-on therapy			
≥3 years	25.50%	25.90%	0.006
1–3 years	21.60%	21.80%	0.003
<1 year	52.90%	52.40%	0.008

ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

had fewer than 180 days follow-up on the add-on therapy itself. This may have produced different results than what would have occurred had this criteria not been applied, as patients who initiated add-on therapy prior to 180 days may have been systematically more likely to be prescribed a sulfonylurea and those who stopped their combotherapy regimen before 180 days may be more likely to be using another OHA as seen in our data.

In our study, prescriptions for sulfonylureas as add-on therapy to metformin increased every fiscal year, and represented 77% of all add-on OHA prescriptions in the most recent fiscal year. Reasons for this may include physician familiarity with the medication given its long history and its preeminence in previous guidelines,[41] as well as cost associated with some of the other OHAs which may be prohibitive to patients and not universally reimbursed by private drug plans.[42] Currently, sulfonylureas are listed in all Canadian provincial drug formularies for coverage in public drug plans, which is not the case for any other OHA other than metformin. Additionally, sulfonylureas are effective medications in terms of lowering A1c with meta-analyses showing A1c reductions between 0.9% and 1.62%, as add-on therapy to metformin.[43] This reduction

Table 3 HRs with 95% CIs and p values of Cox proportional hazards regression models for sulfonylurea versus other OHAs

	Outcomes					
	All-cause mortality		Cardiovascular events		Major hypoglycemic episodes	
Model type	HR (95% CI)	P value	HR (95% CI)	P values	HR (95% CI)	P values
Unadjusted	2.23 (1.65 to 3.03)	<0.001	1.29 (1.02 to 1.63)	0.031	4.72 (2.43 to 9.15)	<0.001
IPTW	1.44 (1.12 to 1.84)	0.005	0.99 (0.81 to 1.22)	0.92	2.78 (1.66 to 4.66)	<0.001
Propensity matched	2.25 (1.39 to 3.64)	<0.001	0.78 (0.52 to 1.19)	0.25	3.50 (1.15 to 10.63)	0.027
IPTW (no censoring for insulin or additional OHAs)	1.35 (1.03 to 1.77)	0.028	1.00 (0.79 to 1.26)	1.00	2.88 (1.62 to 5.10)	<0.001
IPTW (censoring after 30-day grace period)	1.73 (1.26 to 2.34)	<0.001	1.11 (0.86 to 1.42)	0.42	3.75 (1.90 to 7.39)	<0.001
Stratified by era using IPTW						
Sulfonylurea versus pre-2008 OHAs	0.87 (0.66 to 1.15)	0.32	0.74 (0.57 to 0.95)	0.019		
Sulfonylurea versus post-2008 OHAs	3.33 (2.02 to 5.49)	<0.001	1.40 (1.01 to 1.93)	0.041		

IPTW, inverse probability of treatment weight; OHA, oral antihyperglycemic agent.

is not necessarily unique to sulfonylureas, however, as shown in a recent systematic review which found no statistically significant difference in A1c reduction between sulfonylureas and DPP4 inhibitors as combotherapy agents (mean pooled 0.6% reduction with DPP4 vs 0.7% at 52 weeks with sulfonylureas).[44]

The evidence showing increased cardiovascular risks with sulfonylureas may be particularly relevant for patients with established cardiovascular disease or increased cardiovascular risk factors, as oral agents that provide a cardiovascular benefit are now available. Since 2008, the United States Food and Drug Administration has required that new OHAs demonstrate cardiovascular safety prior to approval, and as a result newer agents including the GLP1 receptor agonists liraglutide and semiglutide, and the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin have been shown to have cardiovascular benefits in large, well-conducted randomized controlled trials which are congruent with our findings.[10–14 45] Current guidelines suggest that in patients with clinical cardiovascular disease in whom glycemic targets are not met, an OHA with cardiovascular benefit should be added.[2 3] Our study findings would suggest that in all patients with T2D, sulfonylureas are a harmful second agent for combotherapy with metformin and should not be recommended.

Sulfonylureas are insulin secretagogues, a class of drugs that bind to sulfonylurea receptors on pancreatic beta-cells and stimulate insulin release. It has been posited that sulfonylureas are associated with weight gain and major hypoglycemia episodes through this mechanism since the insulin secretion is independent of plasma glucose concentrations.[46] The insulin is released by inhibiting ATP-sensitive potassium channels, which impair ischemic preconditioning and increases infarct size.[47] The increased risk for hypoglycemia and weight gain, and inhibition of ischemic preconditioning may explain why an increase in all-cause mortality was observed among sulfonylurea users.[48–50] While no OHA is without its own side-effect profile, sulfonylureas certainly appear to carry greater risk of important safety outcomes including mortality and hypoglycemia without the benefit seen in large randomized controlled trials with newer agents such as GLP1 receptor agonists and SGLT2 inhibitors.

Our study has several strengths. First, we used large administrative databases that contained population-level data since every member of the cohort was covered under the same universal health insurance program. This allowed us to capture all possible exposures and outcomes in our study population. Furthermore, most observational studies that compare the safety of combotherapy regimens in patients with T2D use propensity score matching to account for confounding which leads to eliminating individuals from the analysis, whereas our study conducted our primary analysis using stabilized IPTW and as a result no individuals in our cohort were excluded from analysis. Finally, <1% of individuals in our cohort were lost to follow-up and therefore any missed events during the study period would be minimal.

Our study also has limitations. First, our results may not be generalizable to patients who need more than two OHAs for optimal glycemic control. Second, despite controlling for many factors, we could not fully control for important clinical variables such as blood pressure, body mass index, diabetes duration, and laboratory results. Nevertheless, many of the characteristics we collected at baseline were representative of these variables. Residual confounding is also always possible in observational studies. However, the fact that we observed harm with sulfonylurea use when compared with newer OHAs, and no difference when compared with older OHAs would argue against residual confounding, which would not be affected by era. Finally, our study numbers precluded the ability to analyze sulfonylureas compared with each subgroup of 'other' OHAs separately and findings from the subgroup analyses we did undertake were post hoc, which may reduce the strength of their evidence.

CONCLUSIONS

In conclusion, patients prescribed sulfonylureas as add-on therapy to metformin had increased risk of all-cause mortality and major hypoglycemic events compared with those prescribed other add-on OHAs. Post hoc analysis suggests that newer OHAs may be preferred to sulfonylureas as second-line therapy for glycemic control. Guidelines statements may want to incorporate real-world effectiveness trials in their updated statements concerning second-line agent preference. Formal economic analyses incorporating these expected outcomes differences are needed to inform policy.

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Contributors NT contributed to the conception and design of the work and interpretation of data and is responsible for the overall content as the guarantor. RHW contributed to the acquisition, statistical analysis, and interpretation of data. IH, PK, CR, and KKC contributed to the interpretation of the data. All authors contributed to the drafting of the work and critical revision of important intellectual content, final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Ethics approval This study received ethics approval from the University of Manitoba Health Research Ethics Board (ethics file number HS19580).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data used in this article were derived from administrative health and social data as a secondary use. The data were provided under specific data sharing agreements only for approved use at Manitoba Centre for Health Policy (MCHP). The original source data is not owned by the researchers or MCHP and as such cannot be provided to a public repository. The original data source and approval for use has been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies.

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Supplementary Table 1: Databases

Database	Years
Diabetes Education Resource for Children and Adolescents (DERCA)	1986 to 2015‡
Diagnostic Services of Manitoba (DSM)	2006 to 2016‡
Drug Program Information Network (DPIN)	2002/03 to 2016/17†
Emergency Department - Admission, Discharge, and Transfer (ADT) & Information System (EDIS)	2003 to 2015‡
Hospital Discharge Abstracts (CIHI-DAD)	2002/03 to 2016/17†
Manitoba Health Insurance Registry	2002/03 to 2016/17†
Medical Claims (MHSC)	2002/03 to 2016/17†

† Fiscal year: April 1 - March 31.

‡ Calendar Year: January 1 - December 31.

Supplementary Table 2: Exposures

OHA Category	OHA Name	ATC Code
Biguanides (Metformin)	Metformin	A10BA
Sulfonylureas	Chloropropamide, Gliclazide, Glimepiride, Glyburide, Tolbutamide	A10BB
Metformin + TZD	Metformin + Rosiglitazone	A10BD03
Metformin + DPP4 inhibitors	Metformin + (Linagliptin, Saxagliptin, Sitagliptin)	A10BD07, A10BD10, A10BD11
Metformin + SGLT2 inhibitors	Metformin + Dapagliflozin	A10BD15
Alpha-glucosidase inhibitors	Acarbose	A10BF
TZDs	Pioglitazone, Rosiglitazone	A10BG
DPP4 inhibitors	Linagliptin, Saxagliptin, Sitagliptin	A10BH
GLP1 receptor agonists	Dulaglutide, Exenatide, Liraglutide	A10BJ
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin	A10BK
Meglitinides	Nateglinide, Repaglinide	A10BX02, A10BX03

† ATC - anatomical therapeutic chemical; DPP4 - dipeptidyl peptidase-4; GLP1 - glucagon like peptide-1; OHA - oral antihyperglycemic agent; SGLT2 - sodium-glucose linked transporter-2; TZD - thiazolidinedione.

Supplementary Table 3: Safety outcomes

Outcome	Case definition
All-cause mortality	• Date of death as recorded in the MB Health Insurance Registry.
Cardiovascular event	
Acute MI	• Date of hospitalization where the reason code for the main diagnosis has a prefix of 410 (ICD-9) or I21 (ICD-10).
Heart Failure	• Date of hospitalization where the reason code for the main diagnosis has a prefix of 428 (ICD-9) or I50 (ICD-10).
Stroke	• Date of hospitalization where the reason code for the main diagnosis has a prefix of 430, 431, 432, 433, 434, 436 (ICD-9) or I60, I61, I62, I63 or I64 (ICD-10).
Unstable Angina	• Date of hospitalization where the reason code for the main diagnosis has a prefix of 411 (ICD-9) or I20.0 (ICD-10).
Major hypoglycemic event	• First of the following occurrences: o Date of hospitalization where the reason code for any diagnosis has a prefix of 251.0, 251.1, 251.2 (ICD-9) or E11.63, E13.63, E14.63, E15, E16.0, E16.1 or E16.2 (ICD-10) **or** o Date of Emergency Department visit where the reason for the visit is coded as "Hypoglycemia" **or** o Date of laboratory test where blood glucose is < 3.5 mmol/L.

† ICD - international classification of diseases; MB - Manitoba; MI - myocardial infarction.

Supplementary Table 4: Baseline comorbidities

Hospital/Physician Claims	ICD-9 Codes	ICD-10 Codes
Alcohol use	291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 780.0, 977.3, V11.3	F10, K70, X45, X65, Y15, Y90-Y91
Amputation of lower extremity	84.1	1VC.91, 1VC.93, 1VG.93, 1VQ93, 1WA.93, 1WE.93, 1WJ.93, 1WL.93
Asthma	493	J45
Cancer	140-172, 174-209.3, 209.7	C00 – C99
Cardiovascular disease	402.01, 402.11, 402.91, 410, 411, 413, 414.0, 420-434, 436, 440, 441, 444, V12.5	G45, I20.0, I20.1, I20.8, I20.9, I21-I23, I25.1, I25.2, I50-I51, I60-I64, I70-I79, Z95
	00.61, 00.63, 00.66, 17.55, 36.06, 36.07, 36.1, 38.11, 38.12, 39.28	1IJ.50, 1IJ.57, 1IJ.76, 1JE.50, 1JE.51, 1JE.57, 1JE.76
CKD	585, 586	N18-N19
COPD	491, 492, 496	J41-J44
Dementia	290.0 , 290.1, 290.2, 290.3, 290.4, 290.8, 290.9, 291.2, 292.82, 294.0, 294.1, 294.2, 294.8, 331.0 , 331.1, 331.2, 331.7, 331.8, 331.9, 797	F00-F03, F05.1, G30, G31.1
HIV/AIDS	042, 043, 044, 795.71, V08, 079.53	B20-24, B97.35, R75, Z21
Hyperlipidemia	272.0-272.2, 272.4	E78.0-E78.2, E78.4-E78.5
Hypertension	401, 402.00, 402.1, 402.10, 402.90, 403-405	I10-I13, I15
Liver disease	570-573	K70-K77
Microvascular disease	250.40, 250.43, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 337.0, 337.1, 354, 355, 362, 583.81, 681.1, 6826.6, 682.7, 682.9	E11.2-E11.4, E11.7, E13.2-13.4, E13.7, E14.2-E14.4, E14.7, G57, G59.0 G63.2, G99.0, H35.0-HE35.2, H36.0, N08.3
Obesity	278.0, 793.91, V85.3, V85.4, 783.1	E66.01, E66.2, E66.3, E66.9

† CKD – chronic kidney disease; COPD - chronic obstructive pulmonary disease; HIV/AIDS - human immunodeficiency virus infection and acquired immune deficiency syndrome; ICD - international classification of diseases; PVD - peripheral vascular disease

Supplementary Table 5: Baseline medications

Medication Class	ATC Code
ACE inhibitors	C09A, C09B
Anticoagulants	B01AA01, B01AA03, B01AE07, B01AF
Anti-platelets	B01AC
ARBs	C09C, C09D (excluding C09DX04)
Beta-blockers	C07
CCBs	C08
Digoxin	C01AA05
Direct Vasodilators	C02D
Loop diuretics	C03C
Potassium sparing diuretics	C03D
Thiazide diuretics	C03A
Statins	C10AA
Other lipid lowering medications	C10 (excluding C10AA)

† ACE - Angiotensin-converting enzyme; ARB - Angiotensin II receptor blocker; ATC - anatomical therapeutic chemical; CCB - calcium channel blocker.

Supplementary Table 6: Post-match baseline characteristics by combotherapy group

Characteristic	Sulfonylurea (n = 4,498)	'Other' (n = 4,498)	SMD
Demographics			
Age (years)	56.7 ± 13.6	56.3 ± 12.6	0.031
Sex (% female)	1,984 (44.1%)	2,010 (44.7%)	0.012
Geographic/Socioeconomic Status			
Rural/Income Quintile 1	282 (6.3%)	275 (6.1%)	0.007
Rural/Income Quintile 2	284 (6.3%)	279 (6.2%)	0.005
Rural/Income Quintile 3	311 (6.9%)	287 (6.4%)	0.021
Rural/Income Quintile 4	298 (6.6%)	313 (7.0%)	0.013
Rural/Income Quintile 5	332 (7.4%)	328 (7.3%)	0.003
Urban/Income Quintile 1	496 (11.0%)	508 (11.3%)	0.008
Urban/Income Quintile 2	620 (13.8%)	625 (13.9%)	0.003
Urban/Income Quintile 3	619 (13.8%)	611 (13.6%)	0.005
Urban/Income Quintile 4	619 (13.8%)	643 (14.3%)	0.015
Urban/Income Quintile 5	608 (13.5%)	606 (13.5%)	0.001
Unknown	29 (0.5%)	23 (0.5%)	0.018
Baseline Comorbidities			
Alcohol abuse	82 (1.8%)	75 (1.7%)	0.012
Amputation	10 (0.2%)	9 (0.2%)	0.005
Asthma	690 (15.3%)	694 (15.4%)	0.002
CKD	100 (2.2%)	107 (2.4%)	0.010
COPD	366 (8.1%)	382 (8.5%)	0.013
Cardiovascular disease	1,090 (24.2%)	1,066 (23.7%)	0.012
Dementia	110 (2.4%)	92 (2.0%)	0.027
Hypertension	3,011 (66.9%)	3,005 (66.8%)	0.003
Hyperlipidemia	1,725 (38.4%)	1,768 (39.3%)	0.013
Liver disease	278 (6.2%)	284 (6.3%)	0.006
Malignancy	494 (11.0%)	453 (10.1%)	0.030
Microvascular disease	986 (21.7%)	996 (22.2%)	0.005
Obesity	350 (7.8%)	364 (8.1%)	0.012
Baseline Medication Use			
ACE inhibitors	1,756 (39.0%)	1,753 (39.0%)	0.001
Anticoagulants	156 (3.5%)	173 (3.8%)	0.020
Anti-platelets	676 (15.0%)	661 (14.7%)	0.009
ARBs	1,121 (23.5%)	1,084 (24.1%)	0.019
Beta blockers	894 (19.9%)	902 (20.1%)	0.004
CCBs	858 (19.1%)	881 (19.6%)	0.013
Digoxin	76 (1.7%)	77 (1.7%)	0.002
Direct Vasodilators	9 (0.2%)	9 (0.2%)	0.000
Loop diuretics	319 (7.1%)	307 (6.8%)	0.010
Potassium sparing diuretics	79 (1.8%)	76 (1.7%)	0.005
Thiazide diuretics	599 (13.3%)	615 (13.7%)	0.010
Statins	2,407 (53.5%)	2,431 (54.0%)	0.011
Other lipid lowering medications	340 (7.6%)	335 (7.4%)	0.004

Index Fiscal Year			
2006/07	581 (12.9%)	584 (13.0%)	0.002
2007/08	395 (8.8%)	375 (8.3%)	0.016
2008/09	259 (5.8%)	263 (5.8%)	0.004
2009/10	312 (6.9%)	295 (6.6%)	0.015
2010/11	227 (5.0%)	247 (5.5%)	0.020
2011/12	245(5.4%)	253 (5.6%)	0.008
2012/13	283 (6.3%)	297 (6.6%)	0.013
2013/14	258 (5.7%)	271 (6.0%)	0.012
2014/15	462 (10.3%)	468 (10.4%)	0.004
2015/16	857 (19.1%)	852 (18.9%)	0.003
2016/17	619 (13.8%)	593 (13.2%)	0.017
Time on metformin before add-on therapy			
≥ 3 years	1,314 (29.2%)	1,339 (29.8%)	0.012
1 - 3 years	1,168 (26.0%)	1,145 (25.5%)	0.012
< 1 year	2,016 (44.8%)	2,014 (44.8%)	<0.001

† ACE - Angiotensin-converting enzyme; ARB - Angiotensin II receptor blocker; CCB - calcium channel blocker; COPD - chronic obstructive pulmonary disease; PVD - peripheral vascular disease; SMD - standardized mean difference.