Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study

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ABSTRACT

OBJECTIVE
To assess whether adding or switching to sulfonylureas is associated with an increased risk of myocardial infarction, ischaemic stroke, cardiovascular death, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy in patients with type 2 diabetes.

DESIGN
Population based cohort study.

SETTING
General practices contributing data to the UK Clinical Practice Research Datalink.

PARTICIPANTS
Patients with type 2 diabetes initiating metformin monotherapy between 1998 and 2013.

MAIN OUTCOME MEASURES
Using the prevalent new-user cohort design we matched 1:1 patients adding or switching to sulfonylureas with those remaining on metformin monotherapy on high-dimensional propensity score, haemoglobin A1c, and number of previous metformin prescriptions. The two groups were compared using Cox proportional hazards models to estimate adjusted hazard ratios and 95% confidence intervals for the study outcomes.

RESULTS
Among 77 138 metformin initiators, 25 699 added or switched to sulfonylureas during the study period. During a mean follow-up of 1.1 years, sulfonylureas were associated with an increased risk of myocardial infarction (incidence rate 7.8 v 6.2 per 1000 person years, hazard ratio 1.26, 95% confidence interval 1.01 to 1.56), all cause mortality (27.3 v 21.5, 1.28, 1.15 to 1.44), and severe hypoglycaemia (5.5 v 0.7, 7.60, 4.64 to 12.44) compared with continuing metformin monotherapy. There was a trend towards increased risks of ischaemic stroke (6.7 v 5.5, 1.24, 0.99 to 1.56) and cardiovascular death (9.4 v 8.1, 1.18, 0.98 to 1.43). Compared with adding sulfonylureas, switching to sulfonylureas was associated with an increased risk of myocardial infarction (hazard ratio 1.51, 95% confidence interval, 1.03 to 2.24) and all-cause mortality (1.23, 1.00 to 1.50). No differences were observed for ischaemic stroke, cardiovascular death, or severe hypoglycaemia.

CONCLUSIONS
Sulfonylureas as second line drugs are associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy. Continuing metformin when introducing sulfonylureas appears to be safer than switching.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Sulfonylureas are widely used second line oral antidiabetic drugs

Previous studies have assessed their cardiovascular and hypoglycaemic safety as first line drugs or in comparison with other second line antidiabetic drugs

WHAT THIS STUDY ADDS

Sulfonylureas as second line drugs are associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with remaining on metformin monotherapy

Continuation of metformin when introducing sulfonylureas is safer than switching

Introduction

Sulfonylureas are oral antidiabetic drugs recommended as second line treatment in patients with type 2 diabetes.[1] Despite the recent approval of several new drugs, sulfonylureas remain the most commonly prescribed antidiabetic drugs after treatment failure with the first line drug metformin.[2] The safety of sulfonylureas with respect to adverse cardiovascular and hypoglycaemic events has been studied extensively.[3] [4] However, studies focusing specifically on their cardiovascular and hypoglycaemic safety as a second line drug in patients with poorly controlled diabetes in need of adding or switching to other drugs, are sparse and limited.

The randomised controlled trials evaluating sulfonylureas as second line drugs were underpowered to assess cardiovascular complications of diabetes or severe hypoglycaemia, which may contribute to the development of adverse cardiovascular events.[5] [6] In clinical practice, most observational studies assessing these outcomes compared sulfonylureas with other second line antidiabetic drugs such as dipeptidyl peptidase-4 inhibitors or insulin.[7-9] Thus, the specific risk of supplementing treatment with sulfonylureas compared with staying on metformin monotherapy has rarely been investigated, and several of the respective observational studies had method limitations such as selection bias,[10] [11] exposure misclassification,[12] and residual confounding.[10] [12]

Metformin is associated with a decreased risk of cardiovascular events and low rates of hypoglycaemia.[13] Supplementing treatment with sulfonylureas, a potentially cardiotoxic class with

high risk of hypoglycaemic events,[3] [14] may outweigh the benefits of metformin. Thus, the objective of our population based study was to assess whether the use of second line sulfonylureas, after metformin, is associated with increased risks of myocardial infarction, ischaemic stroke, cardiovascular death, all cause mortality, and severe hypoglycaemia in patients with type 2 diabetes, compared with continuation of metformin monotherapy.

Methods
Data sources
We used the UK Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases. The CPRD is a large primary care database which contains the medical records for over 14 million people registered at over 680 general practices.[15] Diagnoses and procedures are recorded using the Read code classification. Drugs prescribed by general practitioners are coded based on the UK Prescription Pricing Authority dictionary. The CPRD contains information on anthropometric variables such as body mass index, and lifestyle variables such as smoking and alcohol use. CPRD data have been previously validated and shown to be of high quality.[16] The HES contains all inpatient and outpatient hospital admission information, including primary and secondary diagnoses (coded using ICD-10 (international classification of diseases, 10th revision), and hospital procedures (coded using the Office of Population Censuses and Surveys classification of interventions and procedures, 4th version (OPCS-4)). The ONS database contains the electronic death certificates of all UK residents and includes the underlying cause of death (coded using ICD-9 and ICD-10). HES and ONS data can be linked to the CPRD since 1 April 1997, and are limited to general practices in England that have consented to the linkage scheme (currently representing 75% of all practices in England).[16]

Base cohort
The methods have been previously reported.[17] We first formed a base cohort of patients newly treated with metformin in monotherapy for type 2 diabetes between 1 April 1998 and 31 March 2013, with follow-up until 31 March 2014. Base cohort entry was defined by the date of the first metformin prescription. We excluded all patients aged under 40, those with less than one year of medical history in the CPRD before cohort entry, and women with a diagnosis of polycystic ovary syndrome at any time before cohort entry. We also excluded patients prescribed any antidiabetic drugs at any time before base cohort entry. Patients with a history of cardiovascular disease at cohort entry were included.

Study cohort
The study cohort was formed by identifying all subjects from the base cohort of metformin initiators who subsequently added or switched to a sulfonylurea as second line treatment. Patients who added or switched to other antidiabetic drugs were censored. For each patient adding or switching to a sulfonylurea, we identified a matched reference patient who also was a metformin initiator but remained on metformin, using a prevalent new-user design.[18] The potential reference patients were selected from the corresponding exposure sets, namely from the metformin initiators in the base cohort who received a metformin prescription within three months of the date the exposed patients added or switched to a sulfonylurea, and who received the same number of metformin prescriptions during the time in the base cohort as the exposed subjects (see efigure 1, supplementary materials). Thus, the number of metformin prescriptions between base cohort entry (monotherapy initiation) and study cohort entry (adding or switching to a sulfonylurea or matched continuation) was inherently a matching covariate. Moreover, exposed and reference subjects were matched on haemoglobin A1c level (≤7%, 7.1-8%, >8%, or unknown) at study cohort entry. Finally, exposed and reference subjects were matched on high-dimensional propensity score.[19] The high-dimensional propensity score method empirically selects covariates based on their prevalence and potential for confounding. For each member of each matched set, we identified all available information from seven data dimensions (five dimensions from the CPRD: drug prescriptions, procedures, diagnoses, disease history, and administrative information; two dimensions form the HES: diagnoses and procedures) in the one year period before the date of the matched set. We then applied conditional logistic regression to estimate the propensity of receiving a sulfonylurea drug, thereby considering the 500 most likely confounders. Patients with non-overlapping high-dimensional propensity scores were trimmed from the cohort. The high-dimensional propensity score procedure was repeated for each outcome, since this method calculates a bias term that accounts for the association with a specific outcome. Matched metformin patients could add or switch to sulfonylureas later during follow-up. In this case, the follow-up for the metformin monotherapy group was censored at the point of adding or switching to sulfonylureas. Then, the patient was included as a sulfonylurea user from that point onwards and could be potentially matched to a metformin patient.

Patients meeting the study inclusion criteria were followed until the earliest of the following events: treatment discontinuation, occurrence of one of the study outcomes, end of registration with the general practice, or end of the study period (31 March 2014). Treatment discontinuation was defined either by the absence of a new prescription by the end of a 60 day period (30 days prescription duration plus 30 days grace period) or by the addition or the switch to another, non-sulfonylurea antidiabetic drug. For the metformin initiators adding or switching to sulfonylureas, further switches within the sulfonylurea class were permitted.

Study outcomes

We considered five outcomes: hospital admission for myocardial infarction, hospital admission for ischaemic stroke, cardiovascular death, all cause mortality, and severe hypoglycaemia. Hospital admission for myocardial infarction (ICD-9 codes 410.x, ICD-10 codes I21.x) and ischaemic stroke (ICD-9 codes 433.x, 434.x, or 436.x; ICD-10 codes I63.x or I64.x) were identified using the HES and ONS. The diagnostic codes to identify myocardial infarction in HES have been shown to be highly valid (>90%).[20] The validity of stroke diagnoses in administrative data are also high (>80%).[21] Cardiovascular death (ICD-9 codes 390.x-398.x, 401.x-405.x, 410.x-417.x, 420.x-429.x (except 427.5), 430.x-438.x, or 440.x-447.x; ICD-10 codes I00.x-I77.x (except I46.9)) was identified in ONS, and all cause mortality was identified from all three databases, with the date of death defined by the earliest recording of death in any database. Severe hypoglycaemia (ICD-10 codes E16.0, E16.1, E16.2) was identified in HES.

Statistical analysis

We used descriptive statistics to summarise the characteristics of the patients in the matched groups. Potential imbalances after matching among covariates were assessed using standardised mean differences. Incidence of each outcome was calculated based on the Poisson distribution and expressed as number of events per 1000 person years. Moreover, we constructed a Cox proportional hazards regression model for each outcome that estimated the hazard ratio and the 95% confidence intervals for sulfonylurea versus metformin. To maximise comparability between the two groups, the models for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were additionally adjusted for age, sex, deciles of high-dimensional propensity score, and history of the respective outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke). The model for all cause mortality was additionally adjusted for age, sex, and deciles of high-dimensional propensity score.

Secondary analyses

We conducted three secondary analyses. Firstly, we assessed the risk of the study outcomes separately for addition of sulfonylureas to metformin and for switching to sulfonylureas from metformin. For this analysis, we used a time dependent exposure definition subcategorising the person time of sulfonylurea use, which resulted in three mutually exclusive categories: current use of metformin only (reference), current use of sulfonylureas only, and concomitant current use of metformin and sulfonylureas. Thus, the same patient could contribute person time to different exposure categories. Secondly, to assess a duration-response relation between adding or switching to sulfonylureas and the risk of each study outcome, drug use was further categorised according to three predefined

durations (≤3 months, 3.1-12 months, >12 months). Thirdly, given the pharmacologic heterogeneity observed among different sulfonylureas, the risk of each study outcome was assessed separately for two groups of sulfonylureas classified by duration of action and pancreas specificity. The first group included pancreas non-specific, long acting drugs (ie, glyburide and glimepiride). The second group included pancreas specific, short acting drugs (ie, gliclazide, glipizide, and tolbutamide).[17 22-25] This analysis was based on the first sulfonylurea added or switched to. Switches among sulfonylureas of the same group were allowed during follow-up.

Sensitivity analyses

We performed four sensitivity analyses to assess the robustness of our findings. Firstly, to assess possible exposure misclassification, we repeated the analyses using a 60 day grace period between non-overlapping successive prescriptions. Secondly, the analyses for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were repeated after excluding patients with a history of the outcome (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke) in the year before cohort entry. Thirdly, to assess the potential impact of residual confounding, we repeated the primary analysis after additionally adjusting for covariates with a standardised mean difference >5%. Finally, to assess the potential impact of unmeasured confounding, we conducted a post-hoc sensitivity analysis using the approach proposed by Ding and VanderWeele (described in eMethods 1, supplementary material).[26]

Negative control analysis

To further assess the validity of our findings, we conducted an additional analysis using a negative control outcome.[27] We compared metformin initiators who added or switched to sulfonylureas with metformin initiators who stayed on metformin monotherapy regarding the risk of diabetic retinopathy (identified using Read codes from the CPRD and ICD-10 codes from the HES), since no differential effects between metformin and sulfonylureas have been reported for this outcome.[28] For this analysis, we additionally excluded all patients with previous retinopathy in order to assess incident disease.

Ancillary analysis

In an ancillary analysis, we compared head-to-head patients adding sulfonylureas to metformin with patients switching to sulfonylureas from metformin. For this analysis, we defined addition of sulfonylureas as a metformin prescription in the first month after the first sulfonylurea prescription. Switching to sulfonylureas was defined by the absence of a metformin prescription in the same period. Next, we performed a multivariable logistic regression to estimate the probability (propensity score) of switching to sulfonylureas versus adding sulfonylureas conditional on all covariates

listed in the manuscript. We then trimmed patients with non-overlapping propensity score distributions. The remaining patients were followed from one month after the initial sulfonylurea prescription until they added or switched to a non-metformin, non-sulfonylurea antidiabetic drug or experienced one of the study outcomes, whichever occurred earlier. Patients adding sulfonylureas were additionally censored at metformin or sulfonylurea discontinuation, and patients switching to sulfonylureas were additionally censored in case of metformin re-initiation or sulfonylurea discontinuation. The hazard ratio of the study outcomes was estimated using a Cox proportional hazards model adjusted for age, sex, history of the outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke), propensity score deciles, and for covariates with a standardised mean difference >5%. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Figure 1 shows that the base cohort included 77 138 patients with a first prescription for metformin between 1 April 1998 and 31 March 2013. A total of 25 699 patients added or switched to sulfonylureas during follow-up. For the analysis on all cause mortality, 2107 (8%) of these patients were trimmed from the cohort due to non-overlapping high-dimensional propensity score distributions or absence of eligible matches. Figure 1 shows that the study cohort for this outcome was 23 592 patients who added or switched to sulfonylureas and 23 592 matched patients who remained on metformin monotherapy. The size of the study cohorts for the other four outcomes was similar.

The mean follow-up was 1.1 (SD 1.4) years, generating a total of 244 150 patient years. During follow-up, there were 337 myocardial infarctions (incidence rate 6.9 per 1000 patient years, 95% confidence interval 6.2 to 7.7), 299 ischaemic strokes (6.1, 5.5 to 6.9), 429 cardiovascular deaths (8.7, 7.9 to 9.6), 1190 deaths from any cause (24.4, 23.0 to 25.8), and 150 severe hypoglycaemic events (3.1, 2.6 to 3.6). The most frequent causes of death were cancer (31%), cardiovascular diseases (31%), and respiratory diseases (10%). Table 1 shows the baseline characteristics of the matched cohorts for the analysis on all cause mortality. Corresponding tables for the other outcomes (myocardial infarction, ischaemic stroke, cardiovascular death, and severe

hypoglycaemia) were practically identical (see eTables 1-4, supplementary materials). After high-dimensional propensity score matching, patients adding or switching to sulfonylureas had a similar baseline profile to those remaining on metformin monotherapy.

Table 2 and eFigures 2-6 (supplementary materials) show the results for the five outcomes. Compared with the use of metformin monotherapy, adding or switching to sulfonylureas was associated with an increased risk of myocardial infarction (7.8 v 6.2 per 1000 person years, hazard ratio 1.26, 95% confidence interval 1.01 to 1.56), all cause mortality (27.3 v 21.5, 1.28, 1.15 to 1.44), and severe hypoglycaemia (5.5 v 0.7, 7.60, 4.64 to 12.44). There was also a trend towards increased risks of ischaemic stroke (6.7 v 5.5, 1.24, 0.99 to 1.56) and cardiovascular death (9.4 v 8.1, 1.18, 0.98 to 1.43).

Separately comparing adding and switching to sulfonylureas suggested that the increase in the risk was driven by the switching and not the addition for myocardial infarction, cardiovascular death, and all cause mortality, but not for ischaemic stroke or severe hypoglycaemia (see eTable 5, supplementary materials). The analyses based on different durations of use yielded higher point estimates for all five outcomes for shorter durations of use and especially for the ≤3 months category (see eTables 6-10, supplementary materials). Classifying sulfonylureas based on important pharmacologic properties provided similar point estimates for the two sulfonylurea groups (see eTable 11, supplementary materials).

Figure 2 shows that the results of the primary analysis remained consistent in the sensitivity analyses (see full detail in eTables 12-14, supplementary materials). For myocardial infarction, the extension of the grace period to 60 days led to a dilution of the hazard ratio, resulting in a non-statistically significant association (hazard ratio 1.12, 95% confidence interval 0.94 to 1.32). Based on a post-hoc analysis, the findings of the primary analysis on myocardial infarction, all cause mortality, and severe hypoglycaemia are unlikely to be the result of an unmeasured confounder under most plausible exposure-confounder and confounder-outcome associations (see eTables 15-17, supplementary materials). Finally, we observed no difference in the risk among patients taking sulfonylureas and metformin regarding the negative control outcome of diabetic retinopathy (incidence rate 41.4 v 40.4 per 1000 person years, hazard ratio 1.02, 95% confidence interval 0.92 to 1.14).

Table 3 shows the results of the head-to-head comparison between patients adding sulfonylureas and patients switching to sulfonylureas (baseline characteristics for the five outcomes are presented in eTables 18-22, supplementary materials). Compared with adding sulfonylureas, switching to sulfonylureas was associated with an increased risk of myocardial infarction (hazard ratio 1.51, 95% confidence interval 1.03 to 2.24) and a borderline increased risk of all cause mortality (1.23, 1.00 to 1.50). No differences in risk were observed for ischaemic stroke (0.88, 0.58
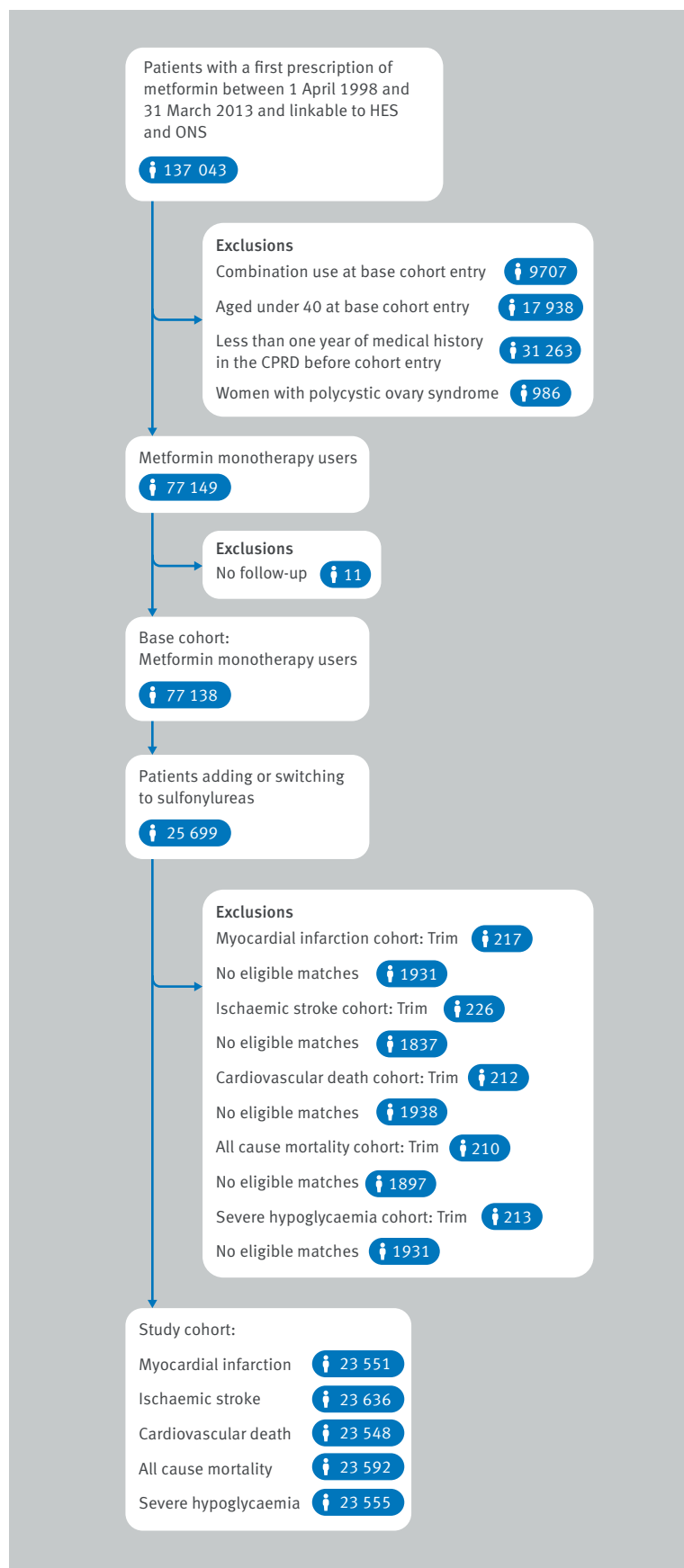
Fig 1 | Flowchart showing the base and study cohorts. HES=Hospital Episode Statistics; ONS=Office for National Statistics; CPRD=Clinical Practice Research Datalink.

to 1.33), cardiovascular death (1.22, 0.87 to 1.71), or severe hypoglycaemia (1.06, 0.65 to 1.71).

Discussion

Our study assessed the cardiovascular and hypoglycaemic risk associated with the use of sulfonylureas as second line drugs. Among metformin initiators, adding or switching to sulfonylureas was associated with an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia, compared with patients remaining on metformin. Moreover, there was a trend towards increased risks of ischaemic stroke and cardiovascular death. Importantly, the observed associations with myocardial infarction and all cause mortality were driven by the switching to sulfonylureas and not the addition of sulfonylureas. The results of the primary analysis remained consistent in sensitivity analyses, as well as after classifying sulfonylureas in two different groups based on important pharmacologic properties.

Comparison with other studies

Numerous observational studies have evaluated the safety of sulfonylureas as first line drugs.[3] However, their results cannot be directly extrapolated to patients having failed initial monotherapy with metformin, since these patients probably have progressive disease and are thus at a higher risk of adverse cardiovascular and hypoglycaemic events. Most of the studies evaluating the safety of sulfonylureas as second line drugs used other second to third line drugs as comparators.[7-9] Thus, no conclusions can be drawn on the risk of adding or switching to sulfonylureas, which have been associated with an increased risk of cardiovascular and hypoglycaemic events,[3 14] as compared with remaining on monotherapy with metformin, a drug with potential cardioprotective properties and low risk of hypoglycaemia.[13] Moreover, among the few studies assessing the latter risk, several featured method limitations such as selection bias owing to the inclusion of prevalent users,[10 11] exposure misclassification,[12] and confounding.[10 12] For our study, we used the recently developed prevalent new-user design.[18] To emulate the randomised controlled trial, this design identifies (at the doctor visit that led to the patient on metformin adding or being switched to sulfonylureas) a comparable patient with the same history of metformin use and of other characteristics, but who on that visit continued on metformin. Thus, we could specifically address the question of how supplementing treatment with sulfonylureas performs in patients for who metformin monotherapy has failed.

This is the first observational study assessing the risk of myocardial infarction associated with sulfonylureas as second line treatment. Several potential mechanisms could account for the increase in the risk compared with patients remaining on metformin monotherapy. Firstly, sulfonylureas are associated with weight gain, which is an important risk factor for myocardial infarction.[25] Secondly, hypoglycaemia is implicated

Table 1 | Characteristics of users of sulfonylureas as second line treatment and metformin as first line treatment in patients with type 2 diabetes (all cause mortality study cohort).* Values are numbers (percentages) unless stated otherwise

Characteristic	Sulfonylureas (n=23 592)	Metformin (n=23 592)	Standardised mean difference (%)
Mean (SD) age (years)	64 (12)	64 (12)	3.6
Women	10 269 (43.5)	10 018 (42.5)	2.2
Mean (SD) diabetes duration (years)	3.5 (3.6)	3.4 (3.5)	2.8
Alcohol related disorders	1284 (5.4)	1274 (5.4)	0.2
Smoking status:			
Ever	12 944 (54.9)	12 810 (54.3)	1.1
Never	10 435 (44.2)	10 559 (44.8)	−1.1
Unknown	213 (0.9)	223 (0.9)	−0.4
Body mass index (kg/m^2):			
<25	2694 (11.4)	2182 (9.2)	7.1
25-30	7914 (33.5)	7559 (32.0)	3.2
≥30	12 554 (53.2)	13 425 (56.9)	−7.4
Unknown	430 (1.8)	426 (1.8)	0.1
Mean (SD) haemoglobin A1c (%)	8.7 (1.7)	8.4 (1.5)	
Haemoglobin A1c (%):			
≤7	2028 (8.6)	2028 (8.6)	†
7.1-8.0	7106 (30.1)	7106 (30.1)	†
>8	12 439 (52.7)	12 439 (52.7)	†
Unknown	2019 (8.6)	2019 (8.6)	†
Medical history:			
Heart failure	1623 (6.9)	1413 (6.0)	3.6
Arterial hypertension	15 089 (64.0)	14 804 (62.8)	2.5
Coronary artery disease	5174 (21.9)	4994 (21.2)	1.9
Atrial fibrillation or flutter	2217 (9.4)	2052 (8.7)	2.4
Hyperlipidaemia	7424 (31.5)	7212 (30.6)	1.9
Chronic obstructive pulmonary disease	3396 (14.4)	3275 (13.9)	1.5
Cancer	2328 (9.9)	2211 (9.4)	1.7
Anaemia	399 (1.7)	360 (1.5)	1.3
Thyroid disease	2526 (10.7)	2396 (10.2)	1.8
Severe hypoglycaemia	35 (0.1)	18 (0.0)	2.2
Myocardial infarction	1190 (5.0)	1020 (4.3)	3.4
Ischaemic stroke	434 (1.8)	385 (1.6)	1.6
Drugs:			
Angiotensin converting enzyme inhibitors	10 523 (44.6)	10 037 (42.5)	4.2
Angiotensin II receptor blockers	3300 (14.0)	3108 (13.2)	2.4
Beta-blockers	6163 (26.1)	5751 (24.4)	4.0
Calcium channel blockers	6751 (28.6)	6366 (27.0)	3.6
Diuretics	8410 (35.6)	7924 (33.6)	4.3
Cardiac glycosides	1069 (4.5)	962 (4.1)	2.2
Nitrates	1453 (6.2)	1348 (5.7)	1.9
Statins	16 402 (69.5)	15 800 (67.0)	5.5
Acetylsalicylic acid	9187 (38.9)	8886 (37.7)	2.6
Clopidogrel	875 (3.7)	693 (2.9)	4.3
Warfarin	1368 (5.8)	1228 (5.2)	2.6
Paracetamol	8350 (35.4)	7845 (33.3)	4.5
Non-steroidal anti-inflammatory drugs	4987 (21.1)	4981 (21.1)	0.1
Opioids	7544 (32.0)	7019 (29.8)	4.8
Diabetic complications:			
Neuropathy	3040 (12.9)	2888 (12.2)	1.9
Peripheral vascular disease	1439 (6.1)	1297 (5.5)	2.6
Nephropathy	3082 (13.1)	2561 (10.9)	6.8
Retinopathy	5566 (23.6)	5433 (23.0)	1.3

*The two groups were matched 1:1 on high-dimensional propensity score, level of haemoglobin A1c, and number of metformin prescriptions before the first sulfonylurea prescription. Slight differences exist in the populations for each outcome due to trimming.
†Matching variable.

in the development of arrhythmias and cardiac ischaemia,[29] so the hypoglycaemic propensity of sulfonylureas could contribute to the increased risk of myocardial infarction. The higher estimates observed for shorter durations of use argue for an involvement of short term mechanisms such as arrhythmias and

Table 2 | Crude and adjusted hazard ratios for the association between the use of sulfonylureas as second line treatment and the risk of the study outcomes

Exposure	No of patients	No of events	Person years	Incidence rate (95% CI) per 1000 person years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Myocardial infarction						
Metformin	23 551	152	24 673	6.2 (5.3 to 7.2)	Reference	Reference
Sulfonylureas	23 551	185	23 858	7.8 (6.7 to 9.0)	1.25 (1.01 to 1.55)	1.26 (1.01 to 1.56)
Ischaemic stroke						
Metformin	23 636	137	24 791	5.5 (4.7 to 6.5)	Reference	Reference
Sulfonylureas	23 636	162	24 015	6.7 (5.8 to 7.9)	1.22 (0.97 to 1.53)	1.24 (0.99 to 1.56)
Cardiovascular death						
Metformin	23 548	203	25 176	8.1 (7.0 to 9.3)	Reference	Reference
Sulfonylureas	23 548	226	24 011	9.4 (8.3 to 10.7)	1.17 (0.97 to 1.41)	1.18 (0.98 to 1.43)
All cause mortality						
Metformin	23 592	533	24 742	21.5 (19.8 to 23.5)	Reference	Reference
Sulfonylureas	23 592	657	24 060	27.3 (25.3 to 29.5)	1.27 (1.13 to 1.42)	1.28 (1.15 to 1.44)
Severe hypoglycaemia						
Metformin	23 555	18	24 905	0.7 (0.5 to 1.1)	Reference	Reference
Sulfonylureas	23 555	132	23 919	5.5 (4.7 to 6.5)	7.59 (4.64 to 12.43)	7.60 (4.64 to 12.44)

*The models for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were adjusted for age, sex, deciles of high-dimensional propensity score, and history of the respective outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke). The model for all cause mortality was adjusted for age, sex, and deciles of high-dimensional propensity score.

against long term mechanisms such as weight gain. Moreover, the similar estimates obtained for the two sulfonylurea groups classified by pancreas specificity indicate that this pharmacodynamic property does not necessarily translate into improved clinical outcomes.[17] Finally, the absence of an increased risk of myocardial infarction associated with the addition of sulfonylureas to metformin (ie, in case of metformin continuation) alludes to the established beneficial effects of the biguanide in this regard.[13] Interestingly, metformin was recently shown to also positively

modify the cardiovascular effects of a newer class of antidiabetic drugs, dipeptidyl peptidase-4 inhibitors.[30]

Our results on all cause mortality support a previous study showing an increased risk associated with using sulfonylureas only, but not with concomitant use of sulfonylureas and metformin, when compared with using metformin only.[31] Again, the absence of an increased risk associated with the addition of sulfonylureas to metformin could reflect the beneficial effects of the biguanide.[13] Moreover, our higher point estimates for shorter durations of use indicate that

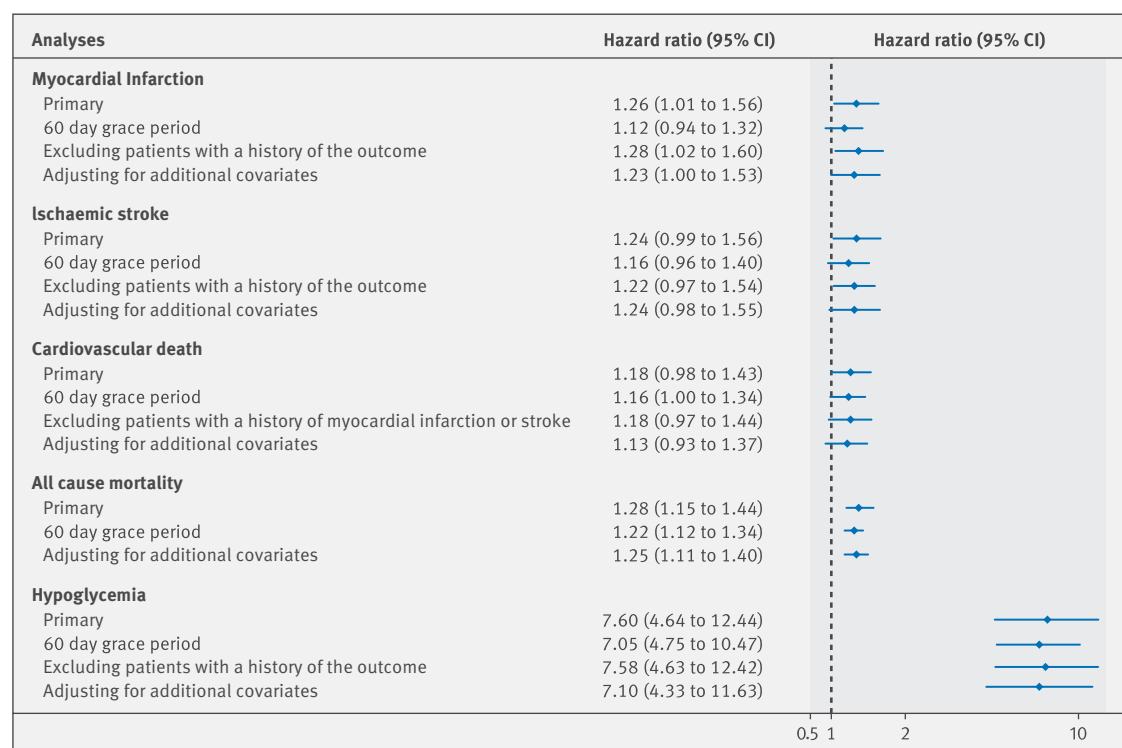| Analyses	Hazard ratio (95% CI)
Myocardial Infarction	
Primary	1.26 (1.01 to 1.56)
60 day grace period	1.12 (0.94 to 1.32)
Excluding patients with a history of the outcome	1.28 (1.02 to 1.60)
Adjusting for additional covariates	1.23 (1.00 to 1.53)
Ischaemic stroke	
Primary	1.24 (0.99 to 1.56)
60 day grace period	1.16 (0.96 to 1.40)
Excluding patients with a history of the outcome	1.22 (0.97 to 1.54)
Adjusting for additional covariates	1.24 (0.98 to 1.55)
Cardiovascular death	
Primary	1.18 (0.98 to 1.43)
60 day grace period	1.16 (1.00 to 1.34)
Excluding patients with a history of myocardial infarction or stroke	1.18 (0.97 to 1.44)
Adjusting for additional covariates	1.13 (0.93 to 1.37)
All cause mortality	
Primary	1.28 (1.15 to 1.44)
60 day grace period	1.22 (1.12 to 1.34)
Adjusting for additional covariates	1.25 (1.11 to 1.40)
Hypoglycemia	
Primary	7.60 (4.64 to 12.44)
60 day grace period	7.05 (4.75 to 10.47)
Excluding patients with a history of the outcome	7.58 (4.63 to 12.42)
Adjusting for additional covariates	7.10 (4.33 to 11.63)

Fig 2 | Forest plot summarising the primary analysis and all sensitivity analyses

Table 3 | Crude and adjusted hazard ratios for the association between switching versus adding sulfonylureas and the risk of the study outcomes

Exposure	No of patients	No of events	Person years	Incidence rate (95% CI) per 1000 person years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Myocardial infarction						
Adding sulfonylureas	13 203	57	11 442	5.0 (3.8 to 6.5)	Reference	Reference
Switching to sulfonylureas	9759	68	5138	13.2 (10.4 to 16.8)	2.65 (1.86 to 3.78)	1.51 (1.03 to 2.24)
Ischaemic stroke						
Adding sulfonylureas	13 300	63	11 542	5.5 (4.3 to 7.0)	Reference	Reference
Switching to sulfonylureas	9771	46	5185	8.9 (6.6 to 11.8)	1.60 (1.09 to 2.34)	0.88 (0.58 to 1.33)
Cardiovascular death						
Adding sulfonylureas	13 217	75	11 464	6.5 (5.2 to 8.2)	Reference	Reference
Switching to sulfonylureas	9779	93	5204	17.9 (14.6 to 21.9)	2.70 (1.99 to 3.66)	1.22 (0.87 to 1.71)
All cause mortality						
Adding sulfonylureas	13 242	217	11 504	18.9 (16.5 to 21.5)	Reference	Reference
Switching to sulfonylureas	9800	256	5216	49.1 (43.4 to 55.5)	2.57 (2.14 to 3.08)	1.23 (1.00 to 1.50)
Severe hypoglycaemia						
Adding sulfonylureas	13 215	39	11 440	3.4 (2.5 to 4.7)	Reference	Reference
Switching to sulfonylureas	9770	45	5177	8.7 (6.5 to 11.6)	2.61 (1.70 to 4.01)	1.06 (0.65 to 1.71)

*The models for myocardial infarction, ischaemic stroke, cardiovascular death, and severe hypoglycaemia were adjusted for age, sex, deciles of propensity score, history of the respective outcome in the year before cohort entry (or, for the case of cardiovascular death, history of myocardial infarction or ischaemic stroke), body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy. The model for all cause mortality was adjusted for age, sex, deciles propensity score, body mass index category, diuretics, statins, paracetamol, opioids, and nephropathy.

short term mechanisms such as arrhythmias or seizures and falls potentially induced by severe hypoglycaemia could be involved in the increased risk of mortality.

Our results on severe hypoglycaemia are concordant with a recently published observational study showing an increased risk for second line sulfonylureas.[11] The similar estimates we obtained for the two groups of sulfonylureas classified by the duration of action argue against an effect of this pharmacokinetic property on the risk of severe hypoglycaemia in the setting of second line treatment. This contrasts with our recent findings on the safety of sulfonylureas as first line drugs,[17] and underscores the importance of diabetes severity as a possible effect modifier on the risk of adverse events.

Strengths and weaknesses of our study

Our study has several strengths. Firstly, the population based design, the inclusion of patients with previous events, and the few exclusion criteria make its results highly generalisable. Secondly, the large sample size allowed the calculation of precise estimates even for rare outcomes such as severe hypoglycaemia. Thirdly, our separate analysis of pancreas specific, short acting and pancreas non-specific, long acting sulfonylureas could account for the high pharmacologic heterogeneity observed within this drug class.[25]

Our study also has some limitations. Firstly, owing to its observational nature there is the potential for residual confounding. However, we went to great lengths to minimise this potential bias by matching on high-dimensional propensity score, the number of previous metformin prescriptions, and haemoglobin A1c level. Moreover, we observed no difference in the risk regarding our negative control outcome, diabetic retinopathy. Secondly, owing to the relatively short duration of follow-up, we were not able to assess long term risk differences between the two groups. However, the length of follow-up reflects real world use

of second line sulfonylureas.[7] Thirdly, since metformin use is contraindicated in patients with severe kidney disease and decompensated heart failure,[32] we cannot exclude that such conditions leading to metformin discontinuation and switching to sulfonylureas may also account for the observed increased risks. Finally, drug dose was not considered in our analyses. Thus, the increased risks observed in patients switching to sulfonylureas compared with patients adding sulfonylureas could also result from the potentially higher sulfonylurea doses in the former group.

Conclusions

Our study showed an increased risk of myocardial infarction, all cause mortality, and severe hypoglycaemia associated with the use of second line sulfonylureas compared with remaining on metformin monotherapy. The associations with myocardial infarction and all cause mortality were driven by the switching to sulfonylureas and not the addition of sulfonylureas. Thus, in line with current recommendations on the treatment of type 2 diabetes,[1] continuing metformin when introducing sulfonylureas is safer than switching.

management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. SS has received research grants and has participated in advisory board meetings or as a speaker at conferences for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Merck, and Novartis. No other potential conflicts of interest relevant to this article were reported.

Ethical approval: The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 14_019AMn) and by the Research Ethics Board of the Jewish General Hospital, Montréal, Canada.

Data sharing: No additional data are available.

Transparency: The manuscripts guarantor (SS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix: Supplementary materials