Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study

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ABSTRACT

OBJECTIVE

To determine the association between use of sulphonylureas and risk of hypoglycaemia in relation to renal function and sulphonylurea metabolic group compared with use of metformin.

DESIGN

Population based cohort study using routinely collected data from general practices in England.

SETTING

Clinical Practice Research Datalink (CPRD) database, 2004-12.

PARTICIPANTS

120 803 new users of a non-insulin antidiabetic agent with at least one prescription and aged 18 years or more. The first prescription defined start of follow-up. Patients were followed until the end of data collection, a record for hypoglycaemia, or a blood glucose level of less than 3.0 mmol/L.

MAIN OUTCOME MEASURES

Associations between sulphonylurea dose, renal impairment, type of sulphonylurea used, and risk of hypoglycaemia, were determined using Cox proportional hazard models. Adjustments were made for age, sex, lifestyle, comorbidity, and drug use.

RESULTS

The risk of hypoglycaemia in current users of sulphonylureas only was significantly increased compared with current users of metformin only (adjusted hazard ratio 2.50, 95% confidence interval 2.23 to 2.82). The higher risk in current users of sulphonylureas only was further increased in patients with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 (4.96, 3.76 to 6.55). The risk of hypoglycaemia was also significantly higher in patients with a high sulphonylurea dose (3.12, 2.68 to 3.62) and in current users of glibenclamide (7.48, 4.89 to 11.44). Gliclazide, the sulphonylurea of first choice, showed a similar risk of hypoglycaemia compared with other sulphonylureas.

CONCLUSIONS

Sulphonylurea treatment in patients with a renal function of less than 30 mL/min/1.73 m^2 should be considered with caution. Moreover, an increased risk of hypoglycaemic events was observed among all users of sulphonylureas. This contrasts with several guidelines that recommend gliclazide as first choice sulphonylurea, and therefore requires further investigation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypoglycaemia is a well known side effect of treatment with sulphonylureas

Gliclazide is the first choice sulphonylurea for type 2 diabetes in many countries as it is associated with a lower risk of hypoglycaemia

Data on the incidence of hypoglycaemia in sulphonylurea treated patients with impaired renal function are sparse and conflicting

WHAT THIS STUDY ADDS

The risk of a hypoglycaemic event is significantly increased in sulphonylurea only users with severe renal impairment receiving general care

The risk of hypoglycaemia did not differ between users of sulphonylureas with active metabolites and users of sulphonylureas with inactive metabolites

Our study does not confirm current guidelines that suggest the superiority of gliclazide to other sulphonylureas in reducing the risk of hypoglycaemia

Introduction

In the 21st century, type 2 diabetes has reached epidemic proportions globally.[1] It currently affects over 310 million people worldwide, and in 2014, 4.9 million deaths were attributable to diabetes related complications.[1 2] Strict glycaemic control is critically important in people with type 2 diabetes. Sulphonylureas play a pivotal role in glycaemic control by stimulating insulin secretion, thereby suppressing glucose production and stimulating the utilisation of glucose.[3] As a direct extension of their mechanism of action, however, the risk of hypoglycaemia is increased, and this risk may be further increased in patients with renal impairment, which is a common comorbidity associated with type 2 diabetes.

It is well established that metabolites can accumulate as the glomerular filtration rate falls. In people with type 2 diabetes, hypoglycaemia is more common among those who use long acting sulphonylureas with renally excreted active metabolites (eg, glibenclamide and glimepiride).[4-7] Use of these sulphonylureas might therefore further increase the risk of hypoglycaemia in patients with renal impairment. In contrast, tolbutamide, glipizide, and gliclazide are mainly excreted as unchanged drug or inactive metabolites with minimal hypoglycaemic effect.[7] As gliclazide is associated with a low risk of hypoglycaemia, it is the first choice sulphonylurea in many countries.[8 9]

Studies have shown that incidence rates of hypoglycaemia in sulphonylurea users without renal impairment range from 0.2 to 1.8 events per 100 person years.[10-13] For patients with renal impairment, however, the literature is sparse and conflicting. Although one study[14] did not find an association in glibenclamide users, three others[15-17] suggested an increased risk of hypoglycaemia among sulphonylurea users with renal

impairment. No study has compared the risk of hypoglycaemia between the two groups of sulphonylureas—those with active metabolites and those with inactive metabolites—in patients with renal impairment.

Therefore, we evaluated the association between current use of sulphonylureas only and the risk of hypoglycaemia according to renal function and sulphonylurea metabolite group, compared with current use of metformin only.

Methods

Data sources

Data for this study were derived from the Clinical Practice Research Datalink (CPRD), which contains computerised medical records for more than 11 million patients from 674 practices in the United Kingdom. CPRD currently holds data on 7% of the UK population and is generalisable to the UK population.[18] Data since 1987 include patients' personal characteristics, medical history, laboratory test results, details of prescriptions, specialist referrals, hospital admissions, and major outcomes, with ongoing data collection. Read codes, a hierarchical coding system, are used to define symptoms, diagnoses, referrals, and laboratory or diagnostic tests and results. Read codes are entered by the general practitioner and undergo quality checks before entry into CPRD. Diagnoses in CPRD have been validated in a wide range of diseases, including diabetes and hypoglycaemia, showing a high validity.[19 20]

Study population

We included all patients aged 18 years or more with at least one prescription for a non-insulin antidiabetic agent during the period of valid CPRD data collection. For this study, data collection began in April 2004, the introduction of the Quality and Outcomes Framework, and ended in August 2012. We defined the index date as the date of the first prescription, after the start of valid data collection. In the CPRD, the date that a practice became "up to research standard" (ie, practice has medical, laboratory, and drug recording of sufficient quality for at minimum one year) largely determines the valid data collection. Therefore, all patients had a minimum of one year of high quality data collection before the index date. We applied a new user design by excluding all patients with a history of non-insulin antidiabetic agent or insulin prescriptions, or the outcome of interest, before the index date.

Use of non-insulin antidiabetic agents

Use of non-insulin antidiabetic agents was assessed in a time dependent manner. We divided follow-up in 90 day intervals, starting on the first date of an eligible prescription (ie, the index date). Use of non-insulin antidiabetic agents was assessed at the start of each 90 day time interval, and classified according to the time since the most recent prescription: current use (1-90 days), recent use (91-180 days), or past use (>180 days). As a result, participants can move between these groups during follow-up.

We further stratified current users of sulphonylureas only according to their most recent prescribed defined daily dose (low, medium, and high), most recent renal function (≥60, 30-59, and <30 mL/min/1.73 m^2 or receiving dialysis), and sulphonylurea metabolite group (active versus inactive). Dosage equivalents were calculated using the World Health Organization's defined daily dosages.[21] When written instructions on dosage were missing, we assigned the median value of all prescriptions. Most recent renal function was evaluated using laboratory test data (estimated glomerular filtration rate (eGFR) (modification of diet in renal disease, MDRD) where possible) and CPRD Read codes (stages of chronic kidney disease). To obtain renal function, we considered data up to one year before the start of a 90 day interval. When multiple eGFR values were reported on one day, we used the mean value. In the event of a CPRD Read code and laboratory test result being recorded on the same day, we prioritised CPRD Read codes.

Outcomes

We followed patients from the index date to the end of data collection, date of transfer out of the practice area, date the practice stopped delivering data, date of death, or a first ever hypoglycaemic event; whichever occurred first. According to the methods of Bruderer et al,[22] we defined a first ever hypoglycaemic event as the first Read code recording for hypoglycaemia or a laboratory test result indicating a blood glucose level of less than 3.0 mmol/L. When multiple blood glucose levels were recorded on the same day, we used the lowest value. Patients were excluded if they had a history of a hypoglycaemic event before their index date.

Potential confounders

We assessed the presence of risk factors for hypoglycaemia during follow-up by reviewing computerised medical records for any record of a risk factor before the start of an interval. Several potential confounders were determined at baseline: sex, smoking status (non-smoker, current smoker, former smoker, or unknown), and body mass index (<25.0, 25.0–29.9, ≥30 kg/m^2, or unknown). Other confounders considered in this study were determined time dependently at the start of each new interval; alcohol use, the most recent haemoglobin $A1_c$ record in the past year, chronic liver disease, cardiovascular disease, congestive heart failure, or cognitive impairment or dementia. In addition, we considered use of any of the following drugs in the previous six months of an interval as a potential confounder: oral anticoagulants, statins, antipsychotics or antidepressants, corticosteroids, antihypertensives (including loop diuretics, thiazide diuretics, renin-angiotensin-aldosterone system inhibitors (angiotensin converting enzyme inhibitors or angiotensin receptor blockers), calcium channel blockers, and β blockers[23]), and non-steroidal anti-inflammatory drugs. Confounders are factors associated with hypoglycaemia and the exposure of interest (sulphonylurea use or renal function) and we selected them based on the literature.

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We entered confounders into the final model if they independently changed the β coefficient for current sulphonylurea use by at least 5% or when inclusion was supported by clinical evidence, or both.

Data analysis

We identified and summarised incidence rates as events per 1000 person years. The primary analysis was to estimate the risk of hypoglycaemia in current users of sulphonylureas only compared with current users of metformin only in relation to renal function. This analysis was further stratified by prescribed daily dose, sulphonylurea metabolite (active versus inactive), and specific sulphonylurea. We used Cox regression analysis (SAS 9.2. PHREG procedure) in all analyses.

Sensitivity analyses

Additional sensitivity analyses were requested during peer review, and the following post hoc analyses were completed: stratification of current users of metformin only by renal function, and stratification of current users of sulphonylureas only by daily dose and haemoglobin $A1_c$ level: low (<7%) versus high (≥7%).

Patient involvement

Patients were not involved in the development of the research question, outcome measures, design, or implementation of the study. Patients were not asked to advise, interpret, or disseminate results. However, we plan on sharing our findings with the European Diabetes Association.

Results

Table 1 shows the baseline characteristics of all 120 803 patients (see supplementary appendix for stratification by drugs at the index date). The mean duration of follow-up was 3.7 years. The mean age of all users was 67.4 years, and 47.2% (n=57 065) were women. No substantial differences were observed in age and sex distribution across drug use groups (see supplementary appendix A). However, the proportion of patients with a high body mass index (≥30) was considerably lower in sulphonylurea users (26.8%; n=3544) compared with metformin users (57.1%; n=52 496) or other non-insulin antidiabetic agents (57.9%; n=3628). More sulphonylurea users had lower renal function than metformin users or users of other non-insulin antidiabetic agents. Similarly, cardiovascular diseases were more prevalent in sulphonylurea users compared with the other groups.

We identified a 2.5-fold increased risk of a hypoglycaemic event among current users of sulphonylureas only compared with current users of metformin only (adjusted hazard ratio 2.50, 95% confidence interval 2.23 to 2.82), adjusted for use of other non-insulin antidiabetic agents (table 2). The risk was further increased among patients who used sulphonylureas and metformin concomitantly. When current sulphonylurea use was stratified by prescribed daily dose, a more than threefold increased risk of hypoglycaemic events was found among users of the highest daily dose (3.12, 2.68 to 3.62) compared with users of metformin only.

Table 3 shows that the risk of hypoglycaemic events also increased with reduced renal function. Patients with an eGFR of less than 30 mL/min/1.73 m^2 using sulphonylureas only had a fivefold increased risk compared with users of metformin only (4.96, 3.76 to 6.55), whereas this risk was noticeably lower among patients with an eGFR of 30-59 mL/min/1.73 m^2 (2.69, 2.25 to 3.20) or ≥60 mL/min/1.73 m^2 (2.04, 1.73 to 2.41).

No substantial differences in risk were observed between sulphonylureas with active metabolites and those with inactive metabolites, with hazard ratios estimating a similar twofold to threefold increase in risk (tables 3 and 4). It seems that the risk of hypoglycaemic events was highest among current users of sulphonylureas with active metabolites. As there were fewer outcomes, however, this analysis had limited power. Particularly, there were insufficient numbers of current users of sulphonylureas with active metabolites and an eGFR less than 30 mL/min/1.73 m^2 to make a valid comparison in patients with chronic kidney disease stage 4 or 5.

When we stratified further to individual sulphonylureas, our results showed that use of glibenclamide was associated with the highest risk of hypoglycaemic events (7.48, 4.89 to 11.44) compared with current use of metformin (table 4). Gliclazide use, often recommended as the first choice sulphonylurea, did not coincide with a significantly lower risk, as it appeared to be similar to the risk of glimepiride, glipizide, and tolbutamide.

Sensitivity analyses

In a post hoc analysis we compared current users of metformin only with renal impairment to current users of sulphonylureas only with renal impairment (see supplementary appendix B). Compared with users of metformin only with low renal function, users of sulphonylureas only with low renal function had a fourfold increase in risk for a hypoglycaemic event (4.12, 2.72 to 6.25). When current use of sulphonylureas only was stratified by daily dose and high or low haemoglobin $A1_c$ values (see supplementary appendix C), we identified that patients with a high daily dose (>10 mg glibenclamide equivalents) and low haemoglobin $A1_c$ value (<7%) had an increased risk of hypoglycaemic events (4.88, 3.40 to 6.99).

Discussion

Compared with current use of metformin only, current use of sulphonylureas only was associated with an increased risk of hypoglycaemic events, and this risk was increased in patients with a high prescribed daily dose and stage 4 or 5 chronic kidney disease. We also identified a similar risk of hypoglycaemia between current users of sulphonylureas with active or inactive metabolites. Interestingly, gliclazide is the first choice sulphonylurea in many countries, as it is associated with lower rates of hypoglycaemia, yet in our study we did not observe a decreased risk compared with glimepiride, glipizide, and tolbutamide. This could greatly

Table 1 | Baseline characteristics of users of non-insulin antidiabetic agents. Values are numbers (percentages) unless stated otherwise

Characteristics	Users of non-insulin antidiabetes agents (n=120 803)
Mean (SD) follow-up time	3.65 (2.4)
Women	57 065 (47.2)
Mean (SD) age (years)	67.4 (16.0)
Age group (years):	
18-29	2127 (1.8)
30-39	4014 (3.3)
40-49	10 157 (8.4)
50-59	19 319 (16.0)
60-69	27 815 (23.0)
70-79	29 042 (24.0)
≥80	28 329 (23.5)
Most recent renal function in past year (mL/min/1.73 m^2):	
<30	734 (0.6)
30-59	19 070 (15.8)
≥60	60 025 (49.7)
Unknown	40 974 (33.9)
Mean (SD) haemoglobin A1$_c$ (%)	8.32 (1.86)
Unknown	57 850 (47.9)
Smoking status:	
Current smoker	22 007 (18.2)
Former smoker	49 598 (41.1)
Never smoker	48 328 (40.0)
Unknown	870 (0.7)
Alcohol use:	
Yes	77 880 (64.5)
No	35 427 (29.3)
Unknown	7496 (6.2)
Body mass index:	
<20.0	1670 (1.4)
20.0-24.9	14 759 (12.2)
25.0-29.9	36 907 (30.6)
≥30.0	63 770 (52.8)
Unknown	3697 (3.1)
History of disease:	
Asthma or COPD	18 698 (15.5)
Cardiovascular disease	18 863 (15.6)
Chronic liver disease	321 (0.3)
Cognitive impairment or dementia	1767 (1.5)
Drug use in past six months:	
Thiazide diuretics	20 689 (17.1)
RAAS inhibitors	43 611 (36.1)
Loop diuretics	10 918 (9.0)
β blockers	20 843 (17.3)
Calcium channel blockers	23 963 (19.8)
Typical antipsychotics	1079 (0.9)
Atypical antipsychotics	1693 (1.4)
SSRIs	9159 (7.6)
SNRIs	1491 (1.2)
Tricyclic antidepressants	7276 (6.0)
Monoamine oxidase inhibitors	22 (0.02)
NSAIDs	15 471 (12.8)
Statins	50 925 (42.2)
Corticosteroids (systemic)	6185 (5.1)
Oral anticoagulants	4620 (3.8)
Trimethoprim	4838 (4.0)

COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs; RAAS=renin-angiotensin-aldosterone system; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin-norepinephrine reuptake inhibitors.

influence the treatment decision making process of doctors and should be investigated further.

We found a 2.5-fold increased risk of hypoglycaemic events in current users of sulphonylureas only compared with current users of metformin only. This is consistent with the UK Prospective Diabetes Study and the studies by Ben Salem et al and Bodmer et al.[24-26] Results also confirmed an increased risk when sulphonylureas were used in combination with metformin or with other non-insulin antidiabetic agents,[26] and also among patients receiving a high sulphonylurea dose.

Our study provides an important addition to the existing literature by providing new information about the role of renal function and different sulphonylureas on risk of hypoglycaemic events. When patients were stratified by renal function, an eGFR of less than 30 mL/min/1.73 m^2 was associated with a significantly increased risk of a hypoglycaemic event in users of sulphonylureas only, suggesting that impaired renal function is a risk factor for hypoglycaemia. Schloot et al[17] reported similar results for risk of severe hypoglycaemia (requiring third party assistance). However, results were not generalisable to general care, as the study population consisted of patients treated in specialised diabetes centres. Therefore, our study is the first with real life data on the rates of hypoglycaemic events in patients with renal impairment during routine sulphonylurea treatment in general clinical practice.

Remarkably, the results showed no difference between current users of sulphonylureas with active metabolites and those with inactive metabolites. Because of the mechanism of action, we expected sulphonylureas with active metabolites to show an increased risk, yet found no conclusive evidence of this. However, it is noteworthy that among sulphonylurea users with renal impairment most hypoglycaemic events were among those receiving sulphonylureas with inactive metabolites, limiting comparisons with active metabolites. Moreover, among sulphonylureas with active metabolites, the risk of hypoglycaemic events was lower in current users of glimepiride compared with current users of glibenclamide (twofold *v* 7.5-fold increase); however, we were unable to stratify this by renal function. Several underlying mechanisms might explain the difference between glibenclamide and glimepiride. The active metabolite of glimepiride has less hypoglycaemic effect than the parent drug,[7] and glimepiride is known to exhibit a higher exchange rate and lower binding affinity to the pancreatic β cells than glibenclamide.[27 28] Thus, although not affecting treatment efficacy, smaller amounts of insulin are secreted in the fasting state or postprandially with use of glimepiride compared with glibenclamide.[29 30]

While unexpected, one of our most interesting findings is that gliclazide may not be accompanied by a lower risk of hypoglycaemia compared with other sulphonylureas. Gliclazide is a sulphonylurea of first choice in many countries, including the UK, the Netherlands, and Canada, as it is assumed to be associated with a lower risk of hypoglycaemia and lower mortality and morbidity compared with other sulphonylureas.[8 9] A meta-analysis of 25 randomised controlled trials found a lower proportion of glicalazide users at risk of hypoglycaemia (0.1%) compared with users of other sulphonylureas (0.9-15.5%).[9] However, as is often the case, participants in randomised controlled trials may not be

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Table 2 | Risk of hypoglycaemia in participants with diabetic using non-insulin antidiabetic agents (NIAAs), sulphonylurea only users stratified by most recent prescribed daily dose

	Risk of hypoglycaemia				
Drug use	No of events	Person years	Incident rate	Adjusted hazard ratio (95% CI)*	Fully adjusted hazard ratio (95% CI)†
Metformin only use					
Current	836	205 351	4.1	Reference	Reference
Recent	20	21 584	0.9	0.37 (0.24 to 0.57)	0.36 (0.23 to 0.55)
Past	47	673 009	0.1	0.18 (0.14 to 0.24)	0.18 (0.14 to 0.25)
Sulphonylurea only use					
Current‡:	457	33 829	13.5	3.30 (2.94 to 3.69)	2.50 (2.23 to 2.82)
Low dose	146	15 236	9.6	2.68 (2.35 to 3.06)	2.03 (1.77 to 2.32)
Medium dose	109	8988	12.1	2.81 (2.43 to 3.24)	2.16 (1.86 to 2.50)
High dose	102	4386	23.3	4.18 (3.61 to 4.84)	3.12 (2.68 to 3.62)
Unknown§	100	3808	26.3	5.88 (5.02 to 6.87)	4.60 (3.92 to 5.40)
Recent	17	3734	4.6	1.53 (0.95 to 2.48)	1.09 (0.67 to 1.76)
Past	43	78 383	0.6	0.74 (0.55 to 1.01)	0.56 (0.41 to 0.76)
Metformin and sulphonylurea use					
Current	1043	74 847	13.9	3.24 (2.95 to 3.56)	3.06 (2.79 to 3.37)
Recent	16	6187	2.6	1.15 (0.68 to 1.97)	1.05 (0.62 to 1.78)
Past	58	447 723	0.1	0.44 (0.34 to 0.58)	0.40 (0.30 to 0.52)
Metformin and other NIAA use					
Current	124	19 652	6.3	1.26 (1.00 to 1.59)	1.28 (1.02 to 1.61)
Recent	<6	594	6.7	0.80 (0.23 to 2.84)	0.83 (0.23 to 2.92)
Past	<6	3850	0.1	0.17 (0.06 to 0.45)	0.17 (0.06 to 0.47)
Sulphonylurea and other NIAA use					
Current	82	4830	17.0	3.69 (2.83 to 4.80)	3.12 (2.39 to 4.06)
Recent	<6	425	4.7	1.25 (0.25 to 6.18)	1.05 (0.21 to 5.20)
Past	<6	7822	0.4	0.52 (0.17 to 1.62)	0.41 (0.13 to 1.30)
Other NIAA use¶					
Current	32	4700	6.8	0.88 (0.74 to 1.04)	0.93 (0.79 to 1.10)
Recent	<6	357	5.6	1.45 (0.64 to 3.25)	1.44 (0.64 to 3.20)
Past	<6	876	1.1	1.37 (1.21 to 1.56)	1.37 (1.21 to 1.55)

Current use=in previous 90 days from start of a 90 day interval; recent use=between 91 and 180 days from start of a 90 day interval; past use=more than 180 days from start of a 90 day interval. All analyses adjusted for current, recent, past use of all drug use groups.
*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, alcohol use, smoking status, cardiovascular disease, chronic heart failure, and use of loop diuretics.
‡Sulphonylurea only use stratified by most recent dose: low dose, <5 mg glibenclamide equivalents; medium dose, 5-10 mg glibenclamide equivalents; high dose, >10 mg glibenclamide equivalents.
§Patients only received one prescription; a minimum of two are required to estimate the prescribed daily dose.
¶Other than sulphonylurea and metformin use.

representative of the general population with type 2 diabetes receiving sulphonylureas in clinical practice (eg, age, general state of health, and comorbidities, including renal impairment). Results from two observational studies suggest that severe hypoglycaemic events are uncommon among gliclazide users,[31 32] although the number of patients in these studies was relatively low (800 and 1397, respectivly). Thus, although in contrast with the findings of previous studies,[8 9] the results of this large real world cohort suggest that gliclazide may not be superior to other sulphonylureas. This result could greatly impact the current clinical decision making for diabetes care, and should therefore be further assessed, particularly in relation to renal function.

In addition to those already mentioned, the study has some limitations. Firstly, we were unable to identify patients with mild hypoglycaemia that was corrected at home with glucose. Consequently, we expect our results may be an underestimation of the overall incidence of hypoglycaemia. We excluded patients with a history of a hypoglycaemic event before the index date, as this is risk factor for a second event and these patients may have experienced in home management. While this may have resulted in an underestimation of hypoglycaemia, we do not believe the misclassification of mild outcomes to be differential between metformin users and sulphonylurea users. Moreover, non-differential misclassification would result in masking the true effect (bias towards the null) leading to insignificant findings. As we found a significant association, we do not believe our main conclusions are influenced by the potential non-differential misclassification of outcome. A second, and similar, limitation was the inability to distinguish severe hypoglycaemia from mild hypoglycaemia. In light of this, we completed a post hoc analysis using CPRD Read codes for admission to hospital or visit to an emergency room as a proxy indicator of severity (data not shown). However, there were few cases where the hypoglycaemic event date and the date of hospital admission or emergency room visit were identical. As we cannot confirm the reason for hospital admission, it presumably led to misclassification, in particular for identifying severe cases. We therefore encourage future research to examine further the differences between severe and mild hypoglycaemic events in sulphonylurea users with renal impairment.

Table 3 | Risk of hypoglycaemia in current users of sulphonylureas only compared with current users of metformin only; current sulphonylurea only users stratified by renal function and active versus inactive metabolites

	Risk of hypoglycaemia				
NIAA use	No of events	Person years	Incident rate	Adjusted hazard ratio (95% CI)*	Fully adjusted hazard ratio (95% CI)†
Current metformin only	836	205 351	4.1	Reference	Reference
Current sulphonylurea only	457	33 829	13.5	3.30 (2.94 to 3.69)	2.50 (2.23 to 2.82)
Renal function <30 mL/min/1.73 m^2:	56	1702	32.9	7.98 (6.08 to 10.46)	4.96 (3.76 to 6.55)
Sulphonylureas with active metabolites	<6	110	9.7	2.24 (0.32 to 15.94)	1.48 (0.21 to 10.52)
Sulphonylureas with inactive metabolites	55	1517	36.3	8.41 (6.40 to 11.05)	5.20 (3.94 to 6.88)
Renal function 30-59 mL/min/1.73 m^2:	156	10 143	15.4	3.79 (3.19 to 4.49)	2.69 (2.25 to 3.20)
Sulphonylureas with active metabolites	17	906	18.8	4.65 (2.88 to 7.52)	3.48 (2.15 to 5.64)
Sulphonylureas with inactive metabolites	138	8837	15.6	3.68 (3.08 to 4.41)	2.60 (2.16 to 3.13)
Renal function ≥60 mL/min/1.73 m^2:	174	16 711	10.5	2.52 (2.14 to 2.97)	2.04 (1.73 to 2.41)
Sulphonylureas with active metabolites	19	1562	12.7	2.91 (1.85 to 4.59)	2.46 (1.56 to 3.88)
Sulphonylureas with inactive metabolites	155	14 466	10.7	2.48 (2.09 to 2.95)	2.01 (1.69 to 2.39)
Unknown	71	5274	13.5	3.32 (2.60 to 4.23)	2.63 (2.06 to 3.36)

NIAA=non-insulin antidiabetic agent. Current use=in previous 90 days from start of a 90 day interval.
Results are corrected for all other possible combinations of NIAA use (see table 2).
*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, alcohol use, smoking status, cardiovascular disease, chronic heart failure and use of loop diuretics.

Table 4 | Risk of hypoglycaemia in current users of sulphonylureas only compared with current users of metformin only; current sulphonylurea only users stratified by type of sulphonylurea

	Risk of hypoglycaemia				
NIAA use	No of events	Person years	Incident rate	Adjusted hazard ratio (95% CI)*	Fully adjusted hazard ratio (95% CI)†
Current metformin only use	836	205 351	4.1	Reference	Reference
Current sulphonylurea only use	457	33 829	13.5	3.30 (2.94 to 3.69)	2.50 (2.23 to 2.82)
Sulphonylureas with active metabolites:	50	3241	15.4	3.60 (2.70 to 4.78)	2.91 (2.18 to 3.87)
Glimepiride	28	2629	10.7	2.46 (1.69 to 3.59)	1.97 (1.35 to 2.87)
Glibenclamide	22	610	36.1	8.76 (5.73 to 13.39)	7.48 (4.89 to 11.44)
Sulphonylurea with inactive metabolites:	406	29 141	13.9	3.26 (2.90 to 3.67)	2.46 (2.18 to 2.78)
Glipizide	14	1273	11.0	2.61 (1.54 to 4.43)	2.11 (1.24 to 3.58)
Tolbutamide	<6	410	7.3	1.75 (0.56 to 5.42)	1.24 (0.40 to 3.87)
Gliclazide	389	27 433	14.2	3.32 (2.94 to 3.74)	2.50 (2.21 to 2.83)
Combination of metabolites	<6	64	15.7	3.75 (0.53 to 26.68)	2.65 (0.37 to 18.86)

NIAA=non-insulin antidiabetic agent.
Results are corrected for all other possible combinations of NIAA use (see table 2). Current use=in previous 90 days from start of a 90 day interval.
*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, alcohol use, smoking status, cardiovascular disease, chronic heart failure, and use of loop diuretics.

A third limitation was that two prescriptions are required to estimate the prescribed daily dose. A patient had to have sufficient follow-up time in the database before an event (or censoring) to estimate the given daily dose (at least six months), otherwise the dose was reported as unknown. However, there was no indication that doses were selectively missing in one of the three groups (low, medium, or high dose). Similarly, there is the potential that missing data on lifestyle factors, such as body mass index and smoking, may have introduced bias. Missing data can be dealt with in many ways, including, as in our analysis, the use of an indicator variable for "missingness." Another option is the so called complete case analysis, where only patients with complete information on all confounders are included. Both methods were examined, and results and interpretation were similar (data not shown). Fourthly, although there were many hypoglycaemic events in our database, we did not have adequate statistical power to stratify current sulphonylurea only users by type of sulphonylurea, renal function, and average prescribed daily dose. Similarly, the number of events (<6) in the sulphonylurea group with active metabolites and chronic kidney disease stage 4 or 5 was low. This may explain the absence of the expected higher risk of hypoglycaemic events in this group. Fifthly, there is the potential for off-label use of metformin in women of reproductive age with polycystic ovarian syndrome; however, in a sensitivity analysis excluding all affected women (n=82) at baseline (data not shown), results were unchanged.

Finally, there is the potential for residual confounding. While participants of randomised controlled trials are highly selected and randomly allocated to one of the treatment options, this is not the case in general practice. Indeed, our data show that metformin users were characterised by higher body mass index and renal clearance compared with sulphonylurea users at baseline, although this is not unexpected. To tackle this, we adjusted or stratified our analysis by the most important

clinical risk factors (body mass index, renal function, and age), yet we acknowledge that we were unable to correct for all potential confounders, such as autonomic neuropathy, exercise,[33] and amount of alcohol consumption.[34]

A major strength of this study is the long follow-up period in a large database, representative of the total UK population. As information is present for a wide range of confounding factors, such as smoking status, body mass index, and comorbidities, we were able statistically to adjust our results for several potentially important confounders. We were also able to classify drug use and covariates in a time varying classification. Although we were unable to identify severity, the evaluation of hypoglycaemia using Read codes results in a lower chance of overestimating the risk of hypoglycaemic events compared with glucose levels. Additionally, we excluded patients with a history of hypoglycaemic events, as a previous episode of hypoglycaemia is known to increase the risk of a second event.[35] Finally, we employed a new user design, which eliminates the influence of previous treatment.

Conclusions

The findings of this large observational study suggest that the risk of hypoglycaemia is significantly increased in current users of sulphonylureas only with severe renal impairment compared with users of metformin only. Moreover, the results of this study provide evidence that the use of high sulphonylurea doses should be considered with caution in patients with renal impairment. Interestingly, we did not find evidence of superiority of gliclazide to other sulphonylureas in reducing the risk of hypoglycaemia compared with metformin users. Since current guidelines suggest gliclazide as the first choice in many countries, the findings of this study provide grounds for further investigation as they may have a substantial impact on current clinical decision making in diabetes care.

Contributors: JvD initiated the study, did the literature review, and wrote the first draft of the paper. AMB led the statistical analysis. JvD, MCGJB, FdV, and AMB were responsible for the study concept and design and participated in the interpretation of data. All authors critically revised the paper for important intellectual content and approved the final version to be published. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. FdV and AMB supervised the study and are the guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: HGML receives no direct funding or donations from private parties, including the pharmaceutical industry. Research funding from public-private partnerships, ie, IMI and TI Pharma (www.tipharma.nl), has been accepted under the condition that no company specific product or company related study is conducted. He has received unrestricted research funding from the public sources, ie, the Netherlands Organisation of Health Research and Development (ZonMW), the EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board (MEB), the National Health Care Institute (ZIN), and the Dutch Ministry of Health. Other authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was reviewed and approved by the independent scientific committee of the Clinical Research Practice Datalink (reference 16_016R), which is responsible for reviewing protocols for scientific quality.

Data sharing: No additional data available.

Transparency: The lead author (FdV) affirms that this 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. The study hypothesis originated before inspection of the data.

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Appendix: Supplementary information