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Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia

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A nested case-control analysis

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OBJECTIVE — Lactic acidosis has been associated with use of metformin. Hypoglycemia is a major concern using sulfonylureas. The aim of this study was to compare the risk of lactic acidosis and hypoglycemia among patients with type 2 diabetes using oral antidiabetes drugs.

RESEARCH DESIGN AND METHODS — This study is a nested case-control analysis using the U.K.-based General Practice Research Database to identify patients with type 2 diabetes who used oral antidiabetes drugs. Within the study population, all incident cases of lactic acidosis and hypoglycemia were identified, and hypoglycemia case subjects were matched to up to four control patients based on age, sex, practice, and calendar time.

RESULTS — Among the study population of 50,048 type 2 diabetic subjects, six cases of lactic acidosis during current use of oral antidiabetes drugs were identified, yielding a crude incidence rate of 3.3 cases per 100,000 person-years among metformin users and 4.8 cases per 100,000 person-years among users of sulfonylureas. Relevant comorbidities known as risk factors for lactic acidosis could be identified in all case subjects. A total of 2,025 case subjects with hypoglycemia and 7,278 matched control subjects were identified. Use of sulfonylureas was associated with a materially elevated risk of hypoglycemia. The adjusted odds ratio for current use of sulfonylureas was 2.79 (95% CI 2.23–3.50) compared with current metformin use.

CONCLUSIONS — Lactic acidosis during current use of oral antidiabetes drugs was very rare and was associated with concurrent comorbidity. Hypoglycemic episodes were substantially more common among sulfonylurea users than among users of metformin.

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Metformin plays a pivotal role in the treatment of patients with type 2 diabetes (1). Metformin decreases basal glucose output by suppressing gluconeogenesis and glycogenolysis in liver and increasing glucose disposal in muscle tissue. As the most worrisome complication, lactic acidosis (pH <7.37 and/or plasma lactate levels >4 mmol/l) continues to be discussed in the literature (2) even though the absolute risk appears to be low, with incidence rates of lactic acidosis associated with metformin use ranging from 1 to 16.7 cases per 100,000 patient-years (3,4). Salpeter et al. (5) identified all trials and cohort studies conducted between 1959 and 2002 and did not find a single case of lactic acidosis in 36,893 person-years of metformin exposure. Lalau and Race (6) analyzed 49 cases of lactic acidosis associated with metformin use; overall mortality was not correlated with plasma lactate concentrations. Interestingly, plasma metformin concentrations were, on average, three times higher in patients who survived. All case subjects with lactic acidosis had, in addition to metformin use, acute or chronic comorbidities predisposing to lactic acidosis. These data suggest that lactic acidosis may be coincidental rather than causally associated with metformin use.

Metformin alone is not (7,8) or only rarely (1) associated with hypoglycemia (defined as symptoms and signs of hypoglycemia and/or plasma glucose levels <3.3 mmol/l and clinical response to glucose administration). According to a recent review (9), the reported risks of hypoglycemia for metformin users varied between 0 and 21%. Since metformin does not directly stimulate insulin secretion, hypoglycemia risk may be lower than for that of other oral antidiabetes drugs. However, hypoglycemia in patients using metformin may occur in association with strenuous physical activity or fasting.

Hypoglycemia is a major concern for users of sulfonylureas. Magnitude and severity of sulfonylurea-induced hypoglycemia range widely across studies (1,9,10). In an observational study (11), the annual risk for a first hypoglycemia diagnosis associated with sulfonylurea use was 1.8% (1,800 per 100,000 person-years); long-acting formulations, renal impairment, older age, and incidental use of sulfonylureas were associated with a higher hypoglycemia risk. Despite many reports on the risk of hypoglycemia in patients using oral antidiabetes drugs, direct comparisons between drug classes in the same study population are rare (9). Furthermore, the definition of hypoglycemia varies considerably across previous studies, and a comparison of their results is therefore difficult (7). Additionally, no previous study quantified both the risk of developing lactic acidosis and hypoglyce-

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Table 1—*Oral antidiabetes drug use in seven case subjects with lactic acidosis*

Case no.	Age (years)/ sex	Use of oral antidiabetes drugs	Approximate duration of metformin use prior to diagnosis (months)	Time between last metformin prescription and diagnosis (days)	Relevant comorbidities and outcome (died or survived)
1	83/female	Metformin, glibenclamide	57	21	Acute renal failure, acute heart failure (hypertensive heart disease) (died)
2	63/female	Metformin, gliclazide	11	13	Acute seizure, stable hypertensive heart disease, nonexacerbated chronic obstructive pulmonary disease (survived)
3	70/female	Gliclazide	—	—	Urosepsis (survived)
4	74/male	Metformin, gliclazide	11	106*	Stable hypertensive heart disease, nonexacerbated chronic obstructive pulmonary disease (survived)
5	82/female	Metformin	29	52	Acute gastroenteritis with hypovolemia (died)
6	42/female	Metformin, pioglitazone	82	7	Stable hypertensive heart disease, liver cirrhosis (survived)
7	70/male	Metformin, gliclazide	32	36	Acute heart failure (hypertensive heart disease) (survived)

*Patient no. 4 was classified as a "past metformin user" because the tablet supply of the last metformin prescription prior to the index date was likely to not last up to or beyond the index date (for details, see text).

mia among users of sulfonylureas or metformin in the same study population. Therefore, we conducted an observational study to compare the risk of lactic acidosis and hypoglycemia among users of metformin, sulfonylureas, or other oral antidiabetes drugs.

RESEARCH DESIGN AND METHODS

— Data were derived from the U.K.-based General Practice Research Database (GPRD) (12,13). Briefly, this database was established around 1987 and currently encompasses ~5 million people who are enrolled with selected general practitioners (GPs), covering ~50 million person-years of follow-up. The patients enrolled in the GPRD are representative of the U.K. with regard to age, sex, geographic distribution, and annual turnover rate. GPs have been trained to record medical information, including demographic data, medical diagnoses, hospitalizations, deaths, and drug prescriptions, using standard software and standard coding systems. The GPs generate prescriptions directly with the computer; this information is automatically transcribed into the computer record. It contains the name of the preparation, instructions for use, route of administration, dose, and number of tablets for each prescription. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality (14,15). The GPRD has been the source of many observational studies, including research on diabetes and antidiabetes drugs (11,16). The study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research.

We identified in the GPRD all subjects who received at least one prescription for a sulfonylurea (glibenclamide, gliclazide, glipizide, glimepiride, glibornuride, gliquidone, tolbutamide, chlorpropamide, tolazamide, or acetohexamide), a biguanide (metformin), a thiazolidinedione (pioglitazone, rosiglitazone, or troglitazone), an α-glucosidase inhibitor (acarbose), or a prandial glucose regulator (repaglinide or nateglinide), with or without concomitant insulin use, and who were between the ages of 30 and 79 years between 1994 and 2005. We did not include type 1 diabetic subjects with insulin-dependent diabetes who had never used oral antidiabetes drugs. We excluded all patients with <3 years of recorded history in the database before the first prescription for an antidiabetes drug, as well as all patients with alcoholism, a history of cancer (except nonmelanoma skin cancer), and women with a diagnosis of gestational diabetes at any time in their record.

Case definition and control selection

Within this diabetic study population, we identified all patients between age 30 and 89 years with a first-time diagnosis of lactic acidosis or hypoglycemia after the first prescription for an oral antidiabetes drug. The date of this first diagnosis of interest will be referred to as the index date. We manually reviewed all case subjects with a recorded hypoglycemia diagnosis, blinded to any exposure of interest, and classified them into "mild to moderate" if they were diagnosed and treated by the GP or "severe" if they had to be hospitalized and/or died at the index date. We sent for original medical records in the U.K. for all potential lactic acidosis cases. Within the study population, we identified at random up to four control patients per hypoglycemia case subject, matched to case subjects with regard to age (same year of birth), sex, general practice, and index date (i.e., the date of the hypoglycemia diagnosis of the case).

Statistical analysis

We assessed from the computer records exposure to oral antidiabetes drugs and insulin before the index date in case and control subjects. We classified users of antidiabetes drugs according to the drug class (insulin, sulfonylureas, metformin, thiazolidinediones, prandial glucose regulators, or α-glucosidase inhibitors), the

Table 2—*Characteristics and comorbidities of hypoglycemia case* (n = 2,025) *and control* (n = 7,278) *subjects*

Parameter	Case subjects	Control subjects	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	*P* value
Age (years)			—	—	—
<50	262 (12.9)	747 (10.6)			
50–59	356 (17.6)	1,304 (17.9)	—	—	—
60–69	592 (29.2)	2,234 (30.7)	—	—	—
70–79	649 (32.1)	2,384 (32.8)	—	—	—
≥80	166 (8.2)	582 (8.0)	—	—	—
Sex			—	—	—
Male	969 (47.9)	3,523 (48.4)			
Female	1,056 (52.2)	3,755 (51.6)	—	—	—
Smoking					
Nonsmoker	1,031 (50.9)	3,692 (50.7)	1.0 (reference)	1.0 (reference)	—
Current smoker	297 (14.7)	1,257 (17.3)	0.84 (0.72–0.97)	0.75 (0.63–0.89)	0.001
Past smoker	607 (30.0)	1,950 (26.8)	1.17 (1.03–1.32)	1.04 (0.91–1.20)	0.58
Unknown	90 (4.4)	379 (5.2)	0.78 (0.59–1.02)	0.82 (0.59–1.14)	0.24
BMI (kg/m^2)					
<25.0	346 (17.1)	1,052 (14.5)	1.0 (ref.)	1.0 (ref.)	—
25.0–29.9	712 (35.1)	2,527 (34.7)	0.87 (0.75–1.01)	0.87 (0.73–1.04)	0.13
≥30.0	840 (41.5)	3,179 (43.7)	0.81 (0.69–0.94)	0.68 (0.57–0.82)	<0.0001
Unknown	127 (6.3)	520 (7.1)	0.74 (0.58–0.94)	0.78 (0.58–1.05)	0.10
Renal failure	157 (7.8)	339 (4.7)	1.76 (1.44–2.15)	1.58 (1.25–2.00)	<0.001
Diabetic retinopathy	41 (2.0)	123 (1.7)	1.19 (0.82–1.71)	1.07 (0.70–1.62)	0.77
Diabetic neuropathy	57 (2.8)	120 (1.7)	1.91 (1.35–2.69)	1.25 (0.83–1.87)	0.29
Ischemic heart disease/congestive heart failure	654 (32.3)	2,132 (29.3)	1.21 (1.08–1.36)	0.84 (0.72–0.98)	0.02
Stroke/transient ischemic attack	248 (12.3)	706 (9.7)	1.36 (1.16–1.59)	1.13 (0.93–1.36)	0.21
Hypotension	69 (3.4)	165 (2.3)	1.57 (1.16–2.11)	1.02 (0.72–1.44)	0.91
Hypertension	1,056 (52.2)	3,772 (51.8)	1.06 (0.95–1.17)	0.95 (0.82–1.10)	0.47
Hyperlipidemia	547 (28.4)	1,910 (26.2)	1.15 (1.02–1.29)	1.00 (0.87–1.14)	0.94
Depression/suicide ideas	545 (26.9)	1,468 (20.2)	1.46 (1.30–1.65)	1.13 (0.95–1.33)	0.17

Data are *n* (%), unless otherwise indicated. *Adjusted for all the variables displayed in the table plus for use of oral antidiabetes drugs, insulin, antihypertensive drugs, lipid-lowering agents, diuretics, inhaled and systemic corticosteroids, anticonvulsants, antidepressants, neuroleptics, benzodiazepines, stomach acid–reducing drugs, and analgesics.

timing of exposure (current use, if the last prescription for a drug of interest was recorded <60 days; or past use, if it was recorded ≥60 days before the index date), and the duration of use, based on the number of prescriptions before the index date (none, 1–4, 5–14, or ≥15 prescriptions). We assessed crude incidence rates, in person-years, of the outcomes of interest for current metformin and sulfonylurea use, based on the number of users of these drugs in the study population, their total number of recorded prescriptions, and the average number of tablets per prescription.

We conducted conditional logistic regression analyses using SAS 9.1 (SAS Institute, Cary, NC) to compare the exposure prevalence between hypoglycemic case subjects and control subjects. Risk estimates are presented as odds ratios with 95% CIs. *P* values are two-sided and considered statistically significant if <0.05. In one model, we compared metformin users with nonusers of metformin and adjusted for use of sulfonylureas; other oral antidiabetes drugs; insulin; smoking status (none, current, past, or unknown); BMI (<25, 25–29.9, or ≥30 kg/m^2); a variety of diagnosed comorbidities potentially associated with an altered hypoglycemia risk such as renal failure, diabetic neuropathy, diabetic retinopathy, congestive heart failure, ischemic heart disease, stroke/transient ischemic attack, hypotension, hypertension, hyperlipidemia, depression, and/or suicidal ideation; and the use of various antihypertensives, diuretics, antiarrhythmic drugs, lipid-lowering agents, inhaled or systemic corticosteroids, stomach acid–reducing drugs, analgesics, antiepileptic drugs, benzodiazepines, antipsychotics, or antidepressants. In a second model, we compared users of sulfonylureas with nonusers of sulfonylureas and adjusted for metformin use and all other variables displayed above. In a further model, we directly compared the risk of developing hypoglycemia between current metformin users and current sulfonylurea users and adjusted for use of other antidiabetes agents.

RESULTS — The study population encompassed 50,048 patients who received at least one prescription for at least one study drug. The mean ± SD age of subjects of the study population was 60.7 ± 11.7 years, and 54.8% were women.

Lactic acidosis

We identified 14 patients with a recorded code for lactic acidosis. After manual review of the medical records, we excluded seven patients because they had ketoacidosis, respiratory acidosis, or nonacidotic hyperosmolar dysfunction. Five patients were current metformin users, one patient (no. 4) was classified as a past metformin user, and one was a current gliclazide user (Table 1). Among six case

Table 3—*Hypoglycemia risk by antidiabetes drug class and by duration of use among case (n = 2,025) and control (n = 7,278) subjects*

Exposure	Cases subjects	Controls subjects	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	*P* value
Insulin (no use)	1,421 (70.2)	6,382 (87.7)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	86 (4.3)	87 (1.2)	4.54 (3.28–6.26)	6.26 (4.35–9.02)	<0.0001
Current 5–14 Rx	107 (5.3)	154 (2.1)	2.20 (2.46–4.17)	5.46 (4.00–7.45)	<0.0001
Current ≥15 Rx	325 (16.1)	352 (4.8)	4.46 (3.76–5.29)	7.56 (6.04–9.45)	<0.0001
Sulfonylureas (no use)	312 (15.4)	2,162 (29.7)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	313 (15.5)	358 (4.9)	6.85 (5.54–8.47)	10.8 (8.48–13.8)	<0.0001
Current 5–14 Rx	229 (11.3)	714 (9.8)	2.33 (1.91–2.85)	3.31 (2.64–4.14)	<0.0001
Current ≥15 Rx	579 (28.6)	1,758 (24.2)	2.48 (2.11–2.91)	3.18 (2.64–3.84)	<0.0001
Metformin (no use)	604 (29.8)	2,279 (31.3)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	150 (7.4)	397 (5.5)	1.49 (1.20–1.85)	2.32 (1.79–3.01)	<0.0001
Current 5–14 Rx	242 (12.0)	877 (12.1)	1.12 (0.94–1.33)	1.74 (1.42–2.14)	<0.0001
Current ≥15 Rx	534 (26.4)	1,889 (26.0)	1.19 (1.03–1.38)	1.36 (1.14–1.62)	<0.001
Thiazolidinediones (no use)	1,827 (90.2)	6,743 (92.7)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	38 (1.9)	98 (1.4)	1.52 (1.03–2.34)	1.67 (1.08–2.59)	0.02
Current ≥5 Rx	83 (4.1)	239 (3.3)	1.41 (1.08–1.84)	1.44 (1.06–1.96)	0.02
Prandial glucose inhibitors (no use)	1,982 (97.9)	7,154 (98.3)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	5 (0.3)	11 (0.2)	1.69 (0.55–5.21)	3.01 (0.89–10.1)	0.08
Current ≥5 Rx	14 (0.7)	37 (0.5)	1.43 (0.76–2.70)	2.36 (1.13–4.92)	0.02
Acarbose (no use)	1,895 (93.6)	6,907 (94.9)	1.0 (reference)	1.0 (reference)	—
Current 1–4 Rx	6 (0.3)	15 (0.2)	1.24 (0.47–3.28)	0.88 (0.30–2.62)	0.82
Current ≥5 Rx	24 (1.2)	84 (1.2)	0.99 (0.62–1.58)	0.90 (0.54–1.51)	0.70

Data are *n* (%), unless otherwise indicated. *Adjusted for each other, insulin, antihypertensive drugs, lipid-lowering agents, diuretics, inhaled and systemic corticosteroids, anticonvulsants, antidepressants, neuroleptics, benzodiazepines, stomach acid–reducing drugs, and analgesics. Rx, prescription.

subjects with current use of oral antidiabetes drugs, five suffered from acute worsening of known risk factors for lactic acidosis, namely acute heart failure, urosepsis, hypovolaemia, seizure, or acute renal failure. Two of seven patients died (nos. 1 and 5). Based on the number of metformin users, prescriptions, and average number of tablets per metformin prescription, we assessed a crude incidence rate of lactic acidosis in metfomin users of ~3.3 per 100,000 person-years. The crude incidence rate of lactic acidosis during current use of sulfonylureas was ~4.8 per 100,000 person-years. Due to the small case number, no formal analyses were conducted.

Hypoglycemia

Within the study population, we identified 2,025 case subjects with recorded hypoglycemia and 7,278 matched control subjects. Based on a manual computer record review, we classified 73 of 2,025 (3.6%) as severe hypoglycemic episodes, defined as leading to an emergency hospitalization and/or to death. Based on a crude person-time assessment, the incidence rates for current users of metformin or sulfonylureas were 60 per 100,000 and 110 per 100,000 person-years, respectively (Table 2). The odds ratio of developing hypoglycemia in association with current metformin use was 1.42 (95% CI 1.22–1.64) and with current use of a sulfonylurea drug 3.73 (3.16–4.42), compared with nonuse of the respective drug classes and adjusted for each other, current use of insulin, other oral antidiabetes drugs, smoking, BMI, comorbidities, and various comedication (Table 3).

To exclude the possibility of residual confounding by insulin use, we ran an analysis in which we directly compared the risk of developing hypoglycemia in current sulfonylurea users to the risk in current metformin users in the absence of any insulin exposure. Among patients who did not use insulin, the adjusted odds ratio for current use of a sulfonylurea drug was 2.79 (95% CI 2.23–3.50) compared with the reference group of current metformin users (Table 4). We further stratified this model by sex and age (<70 vs. ≥70 years); the adjusted odds ratios for current sulfonylurea use versus current metformin use (in the absence of insulin) for male and female subjects were 2.42 (1.75–3.35) and 3.05 (2.21–4.21), respectively, and for subjects aged <70 vs. ≥70 years were 2.71 (2.04–3.61) and 3.30 (2.18–5.00), respectively.

We also intended to formally analyze 73 case subjects with severe hypoglycemia and their 266 matched control subjects, but the numbers were too small for a meaningful model. Of 73 case subjects, 35 were on insulin (26 were on insulin only and 9 used insulin in combination with an oral antidiabetes drug), 22 used sulfonylureas only, 3 metformin only, 11 a combination of sulfonylureas and metformin, and 2 were past users of antidiabetes drugs. Among 22 users of sulfonlyureas only, 16 used gliclazide, 5 glibenclamide, and 1 glimepiride, and 17 used a high dose and 5 a low dose.

CONCLUSIONS — In our study, 5 of 50,048 type 2 diabetic patients (1 per 10,000 subjects) developed lactic acidosis while exposed to metformin, of whom only 1 patient used metformin alone, whereas 4 patients used metformin and another oral antidiabetes agent concomitantly. In only one patient on metformin, no acute deterioration of a medical condition known to be a risk factor for lactic acidosis could be identified. However, in addition to hypertensive heart disease, this patient suffered from liver cirrhosis, which is associated with impaired clearance of lactic acid and thereby predisposes to lactic acidosis. One case subject was exposed to a sulfonylurea only. The

Table 4—*Hypoglycemia risk by current exposure to sulfonylurea drugs, metformin, and/or insulin among case (n = 2,025) and control (n = 7,278) subjects*

Exposure to antidiabetes drugs							
Sulfonylurea	Metformin	Insulin	Cases subjects	Control subjects	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	*P* value
Current	No	No	392 (19.4)	1,213 (16.7)	2.86 (2.31–3.55)	2.79 (2.23–3.50)	<0.0001
No	Current	No	151 (7.5)	1,383 (19.0)	1.0 (reference)	1.0 (reference)	—
No	No	Current	7 (0.4)	4 (0.1)	14.9 (4.1–54.5)	16.5 (4.2–65.0)	<0.0001
Current	Current	No	526 (26.0)	1,194 (16.4)	4.07 (3.33–4.98)	4.04 (3.27–4.98)	<0.0001
Current	No	Current	17 (0.8)	3 (0.04)	50.5 (14.4–176)	39.9 (11.2–142)	<0.0001
No	Current	Current	53 (2.6)	54 (0.7)	8.72 (5.63–13.5)	8.73 (5.49–13.9)	<0.0001
Current	Current	Current	19 (0.9)	22 (0.3)	8.61 (4.47–16.6)	8.86 (4.47–17.6)	<0.0001

Data are n (%) unless otherwise indicated. *Adjusted for use of other oral antidiabetes drugs, insulin, antihypertensive drugs, lipid-lowering agents, diuretics, inhaled and systemic corticosteroids, anticonvulsants, antidepressants, neuroleptics, benzodiazepines, stomach acid–reducing drugs, and analgesics.

case group was too small for formal analysis, but the crude incidence rates were 3.3 and 4.8 per 100,000 person-years for current users of metformin or of sulfonylureas, respectively. Thus, there was no greater risk of lactic acidosis among metformin users compared with users of other oral antidiabetes drugs (3,17).

The term "metformin-associated lactic acidosis" describes a temporal relationship of metformin use and the occurrence of lactic acidosis. Sometimes, this term is used to suggest causality, which could only be proven by a positive rechallenge and elimination of contributing factors. The vast majority of metformin-associated lactic acidosis cases in the literature describe patients who had predisposing medical conditions, such as acute heart failure, hypovolemia due to abdominal infection or bleeding, sepsis, exacerbated chronic obstructive pulmonary disease, or liver cirrhosis (2,18). Numerous case reports have associated metformin with lactic acidosis in patients with acute renal failure or severely impaired renal function (19). However, no correlation between lactate serum concentrations, metformin serum concentrations, and mortality have been reported (6,19). Although debated (2,20), impaired renal function is considered to be a risk factor for the development of metformin-associated lactic acidosis. Interestingly, similar incidence rates for lactic acidosis with or without metformin use have been reported in diabetic patients (3,5). These findings suggest that diabetes, rather than metformin, may be a leading risk factor for lactic acidosis.

In our study population, 2,025 of 50,048 (4.1%) patients experienced a first episode of hypoglycemia under treatment with oral antidiabetes drugs. As expected, use of insulin was an important risk factor for hypoglycemia, as was use of sulfonylureas (adjusted odds ratio 3.73). In contrast, metformin (odds ratio 1.42) was associated with only a small relative risk elevation, as reported previously (1,9). The proportion of patients developing documented hypoglycemia in our study population was similar to previous studies (9,11), although reported frequencies varied substantially (0–73,000 per 100,000 person-years) (7,11,21). In our study, hypoglycemia had to be severe enough to lead to a GP or hospital visit, while minor events may have been missed. Thus, our findings may be based on hypoglycemic episodes of moderate to high severity; randomized trials with prespecified protocols and intensive follow-up may produce higher absolute risks for hypoglycemic events.

In our study population, renal failure was an independent risk factor for hypoglycemia, while obesity (BMI $\geq$30 kg/m^2) was inversely related with the risk of developing hypoglycemia, probably due to increased insulin resistance and poorer diabetes control in obese patients. As previously observed (22), sex did not predispose to hypoglycemia. Interestingly, current smokers had a decreased risk of hypoglycemia compared with nonsmokers in our study. These results differ from the findings of a recent study in type 1 diabetic subjects that reported a higher risk of hypoglycemia in smokers (23). Particularly for sulfonylurea users, the risk of developing hypoglycemia was substantially higher in the early phase of therapy. Similar findings were reported before, with elevated risk for incidental sulfonylurea use compared with continuous use (11). Possible explanations include worsening of glycemic control over time, better patient education to avoid hypoglycemia over time, or reduced awareness of hypoglycemia in long-standing diabetes.

Long-acting sulfonylureas were associated with a higher risk of hypoglycemic episodes than short-acting sulfonylureas (7,11). In our study, the odds ratios for all hypoglycemic events were closely similar for most sulfonylureas (data not shown). Among the 19 case subjects with severe hypoglycemia who used a sulfonylurea drug, gliclazide was highly represented, with 16 case subjects, while 5 patients used glibenclamide. We were not able to conduct formal multivariate comparisons of the hypoglycemia risk during current use of these drugs because of the small number of case subjects.

In conclusion, we identified seven cases of lactic acidosis, among whom five subjects were current users of metformin. In these five case subjects, chronic diseases and an acute deterioration of the clinical situation preceded lactic acidosis. This supports the previous notion that metformin-associated lactic acidosis is rare and is observed in association with an acutely worsening clinical condition. The risk for moderate to severe hypoglycemia was approximately threefold for users of sulfonylureas, particularly in the early phase of therapy, compared with metformin users. Considering morbidity of severe hypoglycemia and the low absolute risk of lactic acidosis associated with metformin use, clinicians must carefully ensure that risks outweigh benefits when withholding metformin from patients with type 2 diabetes.

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