



Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events

Diabetes Care 2017;40:1506–1513 | <https://doi.org/10.2337/dc17-0595>

Antonios Douros,^{1,2,3} Hui Yin,¹
 Oriana Hoi Yun Yu,^{1,4} Kristian B. Filion,^{1,2,5}
 Laurent Azoulay,^{1,2,6} and Samy Suissa^{1,2,5}

OBJECTIVE

Sulfonylureas have been associated with an increased risk of cardiovascular adverse events and hypoglycemia, but it is unclear if these risks vary with different agents. We assessed whether the risks of acute myocardial infarction, ischemic stroke, cardiovascular death, all-cause mortality, and severe hypoglycemia differ between sulfonylureas grouped according to pancreas specificity and duration of action.

RESEARCH DESIGN AND METHODS

Using the U.K. Clinical Practice Research Datalink, linked with the Hospital Episodes Statistics and the Office for National Statistics databases, we conducted a cohort study among patients with type 2 diabetes initiating monotherapy with sulfonylureas between 1998 and 2013. Adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models, comparing use of pancreas-nonspecific, long-acting sulfonylureas (glyburide/glimepiride) to pancreas-specific, short-acting sulfonylureas (gliclazide/glipizide/tolbutamide).

RESULTS

The cohort included 17,604 sulfonylurea initiators (mean [SD] follow-up 1.2 [1.5] years). Compared with specific, short-acting sulfonylureas (15,741 initiators), non-specific, long-acting sulfonylureas (1,863 initiators) were not associated with an increased risk of acute myocardial infarction (HR 0.86; CI 0.55–1.34), ischemic stroke (HR 0.92; CI 0.59–1.45), cardiovascular death (HR 1.01; CI 0.72–1.40), or all-cause mortality (HR 0.81; CI 0.66–1.003), but with an increased risk of severe hypoglycemia (HR 2.83; CI 1.64–4.88).

CONCLUSIONS

The nonspecific, long-acting sulfonylureas glyburide and glimepiride do not have an increased risk of cardiovascular adverse events compared with the specific, short-acting sulfonylureas gliclazide, glipizide, and tolbutamide. However, nonspecific, long-acting sulfonylureas glyburide and glimepiride have an increased risk of severe hypoglycemia.

Despite the recent approval of several novel groups of antidiabetic drugs, sulfonylureas remain a cornerstone in the treatment of type 2 diabetes (1). However, concerns remain regarding their association with cardiovascular and hypoglycemic adverse events. Although these events have been investigated in several observational studies, their findings have been contradictory, in part because of important methodological

¹Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada

²Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

³Institute of Clinical Pharmacology and Toxicology, Charité - Universitätsmedizin Berlin, Berlin, Germany

⁴Division of Endocrinology, Jewish General Hospital, Montreal, Quebec, Canada

⁵Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Quebec, Canada

⁶Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada

Corresponding author: Samy Suissa, samy.suissa@mcgill.ca.

Received 24 March 2017 and accepted 11 August 2017.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0595/-/DC1>.

This article is featured in a podcast available at <http://www.diabetesjournals.org/content/diabetes-core-update-podcasts>.

© 2017 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

shortcomings, including exposure misclassification, time-lag bias, and selection bias (2). Furthermore, few studies have examined the risk of cardiovascular and hypoglycemic adverse events with individual sulfonylureas, as these differ in their pharmacodynamic and pharmacokinetic properties (3). Indeed, some sulfonylureas such as glyburide and glimepiride lack selectivity for pancreatic β -cells, allowing them to bind to other receptors, including those on cardiomyocytes and vascular smooth muscle cells. In the case of glyburide, such binding has been suggested to inhibit ischemic preconditioning (4–7). Moreover, other sulfonylureas such as chlorpropamide, glyburide, and glimepiride yield pharmacologically active metabolites, which could prolong the duration of action and result in an increased risk of hypoglycemia (3).

Thus, the objective of this population-based study was to determine whether the risk of acute myocardial infarction (AMI), ischemic stroke, cardiovascular death, all-cause mortality, and severe hypoglycemia is different among sulfonylureas grouped according to their specificity to the pancreatic β -cells and duration of action.

RESEARCH DESIGN AND METHODS

Data Sources

This study was conducted using the U.K. Clinical Practice Datalink (CPRD) linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases. The CPRD is a large primary care database containing the medical records for >14 million people enrolled in >680 general practices (8). Medical diagnoses and procedures are recorded using the Read code classification, and drugs prescribed by general practitioners are coded based on the U.K. Prescription Pricing Authority dictionary. The CPRD contains information on anthropometric variables (such as BMI) and lifestyle variables (such as smoking and alcohol use), and its data have been previously validated and shown to be of high quality (9). The HES contains all inpatient and day-case hospital admission information, including primary and secondary diagnoses (coded using the ICD-10) and hospital-related procedures (coded using the Office of Population Censuses and Surveys classification of interventions and procedures, version 4). The ONS contains the electronic death certificates of all citizens living in the U.K. and was used to identify

the underlying cause of death (coded using the ICD-9 and ICD-10 classifications) for all patients who died during follow-up. The linkage of the HES and ONS to the CPRD is possible from 1 April 1997 onward and is limited to English general practices that have consented to the linkage scheme (currently representing 75% of all English practices) (9).

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

Study Population

The cohort consisted of patients newly treated for type 2 diabetes with sulfonylureas in monotherapy between 1 April 1998 and 31 March 2013, with follow-up until 31 March 2014. Cohort entry was defined by the date of the first sulfonylurea prescription. We excluded all patients <40 years of age, as well as those with <1 year of medical history in the CPRD before cohort entry. We also excluded patients prescribed other antidiabetic drugs at any time before cohort entry. Because this study aimed to be representative of real-world practice, patients with a history of cardiovascular disease at cohort entry were not excluded.

Patients meeting the study inclusion criteria were followed until the earliest of the following events: treatment discontinuation, add-on, or switch (defined in detail in EXPOSURE DEFINITION), occurrence of one of the study outcomes (defined in detail in STUDY OUTCOMES), death from any cause, end of registration with the general practice, or end of the study period (31 March 2014).

Exposure Definition

Patients were classified into two groups based on the sulfonylurea they initiated: pancreas nonspecific, long-acting sulfonylureas (glyburide and glimepiride), and pancreas-specific, short-acting sulfonylureas (tolbutamide, gliclazide, and glipizide; reference group) (3,5–7). Other compounds such as chlorpropamide or gliquidone were excluded because of the low number of exposed patients (less than five). We used an as-treated exposure definition in which patients were considered continuously exposed if the duration of one prescription overlapped with the date of the subsequent prescription. In the event of nonoverlap, we allowed for a 30-day grace period between

two successive prescriptions. Termination of treatment was therefore defined by either the absence of a new prescription by the end of a 30-day grace period, a switch to a different sulfonylurea group, or an add-on or switch to another antidiabetic drug, whichever came first. Switches within the same group of sulfonylureas (e.g., glyburide to glimepiride or vice versa) were permitted.

Study Outcomes

We considered five outcomes: hospitalization for AMI, hospitalization for ischemic stroke, cardiovascular death, all-cause mortality, and hospitalization for hypoglycemia. Hospitalization for AMI and ischemic stroke were identified using the HES and the ONS databases (AMI ICD-9 codes: 410.x; ICD-10 codes: I21.x; ischemic stroke ICD-9 codes: 433.x, 434.x, and 436.x; ICD-10 codes: I63.x and I64.x; in primary or secondary position). The diagnostic codes to identify AMI in HES have been shown to be highly valid (>90%) (10), whereas the validity of stroke diagnoses in administrative data is also high (>80%) (11). Cardiovascular death was identified in the ONS (underlying cause of 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, 440.x–447.x; and ICD-10 codes: I00.x–I77.x [except I46.9]), and all-cause mortality was identified from all three databases. Hospitalization for hypoglycemia was identified in HES (ICD-10 code: E16.2; in primary or secondary position).

High-Dimensional Propensity Score

For each patient, we used multivariable logistic regression to calculate a high-dimensional propensity score (hdPS); this method empirically selects covariates based on their prevalence and potential for confounding (12). The hdPS defined the probability of being exposed to non-specific, long-acting sulfonylureas as compared with specific, short-acting sulfonylureas, conditional on several predefined and 500 empirically identified covariates measured at cohort entry.

We identified the empirical covariates from seven data dimensions (five dimensions from the CPRD: drug prescriptions, procedures, diagnoses, disease history, and administrative information; and two dimensions from the HES: diagnoses and procedures), whereas the predefined covariates were age, sex, calendar year, duration of diabetes prior to cohort entry (defined as the time since a first diagnosis of type 2 diabetes or an elevated glycated

hemoglobin A_{1c} [HbA_{1c}] level [$>7.0\%$ or 53 mmol/mol], whichever appeared first in the medical record), alcohol-related disorders (based on diagnoses for alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and failure and other related disorders), smoking status (ever, never, or unknown), BMI category (<25 , $25\text{--}30$, or $\geq 30\text{ kg/m}^2$ or unknown), HbA_{1c} level ($\leq 7\%$ or $\leq 53\text{ mmol/mol}$, $7.1\text{--}8.0\%$ or $54\text{--}64\text{ mmol/mol}$, $>8\%$ or $>64\text{ mmol/mol}$, or unknown), heart failure, arterial hypertension, thyroid disease, cerebrovascular disease including transient ischemic attack, atrial fibrillation or flutter, cancer, chronic obstructive pulmonary disease, coronary artery disease, hyperlipidemia, previous coronary revascularization, previous myocardial infarction, angina pectoris, anemia, and diabetic complications (neuropathy, peripheral vascular disease, nephropathy, and retinopathy). We also included the number of hospitalizations in the year prior to cohort entry (0, 1, 2, 3, or ≥ 4).

In addition, prescriptions for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium-channel blockers, thiazide, loop or other diuretics, digoxin, statins, fibrates, clopidogrel, warfarin, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, opioid analgesics, acetaminophen, and nitrates in the year prior to cohort entry were assessed. We also assessed the overall number of nonantidiabetic drugs in the year prior to cohort entry (0, 1, 2, 3, and ≥ 4). The hdPS procedure was repeated for each outcome, because this method calculates a bias term that accounts for the association with a specific outcome. Patients in nonoverlapping regions of the hdPS were trimmed from the analysis.

Statistical Analysis

We used descriptive statistics to summarize the characteristics of the patients in the cohort. Crude incidence rates of each outcome were calculated with 95% CIs based on the Poisson distribution and expressed as number of events per 1,000 patients per year. Moreover, we conducted five separate analyses using Cox proportional hazards regression models that provided estimates of the hazard ratio (HR) and the 95% CIs for each outcome. The models for AMI, ischemic stroke, and cardiovascular death were adjusted for hdPS deciles as

well as for history of the respective outcome (or, in the case of cardiovascular death, history of AMI or ischemic stroke). The model for all-cause mortality was adjusted for hdPS deciles. The model for severe hypoglycemia was adjusted for hdPS quintiles. We also conducted a post hoc secondary analysis assessing the risks of all study outcomes separately for each of the two pancreas nonspecific, long-acting sulfonylureas (i.e., glyburide and glimepiride), given the previously reported pharmacologic differences between the two compounds regarding their effect on ischemic preconditioning and their risk of hypoglycemia (13).

Sensitivity Analyses

We conducted four sensitivity analyses to assess the robustness of our findings. First, to assess possible exposure misclassification, we repeated the analyses using a 60-day grace period between nonoverlapping successive prescriptions. Second, to assess potential informative censoring in the as-treated approach (i.e., to account for the possibility that censoring was related to the outcome), we repeated the analyses using an intention-to-treat approach with a maximum follow-up of 1 year. In the intention-to-treat approach, patients are assumed to be continuously exposed to their initial treatment for the whole duration of follow-up, regardless of any switching or discontinuation that occurs. Third, a sensitivity analysis was conducted after excluding patients receiving tolbutamide, because this first-generation sulfonylurea was shown to be associated with increased mortality (14). Finally, the analyses for AMI, ischemic stroke, cardiovascular death, and severe hypoglycemia were repeated after excluding patients with a history of these events. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>).

RESULTS

The cohort included 1,863 patients newly treated with nonspecific, long-acting sulfonylureas (917 glyburide and 946 glimepiride users) and 15,741 patients newly treated with specific, short-acting sulfonylureas (14,412 gliclazide, 775 glipizide, and 554 tolbutamide users) (Fig. 1). The mean (SD) follow-up was 1.2 (1.6) years,

generating a total of 104,011 patient-years. During this follow-up, there were 245 AMI events (incidence rate: 11.8 per 1,000/year; 95% CI 10.4–13.4), 237 ischemic stroke events (incidence rate: 11.4 per 1,000/year; 95% CI 10.0–13.0), 458 cardiovascular deaths (incidence rate: 21.9 per 1,000/year; 95% CI 19.9–24.0), 1,332 deaths from any cause (incidence rate: 64.2 per 1,000/year; 95% CI 60.8–67.7), and 87 severe hypoglycemic events (incidence rate: 4.2 per 1,000/year; 95% CI 3.4–5.2). The most frequent causes of death were cancer (34%), cardiovascular diseases (34%), respiratory diseases (14%), and gastrointestinal diseases (5%).

Table 1 presents the baseline characteristics of the two treatment groups prior to trimming nonoverlapping hdPS distributions. Patients newly treated with nonspecific, long-acting sulfonylureas were similar compared with patients newly treated with specific, short-acting sulfonylureas. However, they were less likely to have a history of nephropathy or to have been hospitalized prior to cohort entry. Overall, initiators of sulfonylurea treatment were predominantly male (57%), had a mean age of 68 years, and a mean duration of nonpharmacologically treated diabetes of 1.6 years. The most common comorbidities were arterial hypertension (56%), coronary artery disease (29%), and hyperlipidemia (20%), whereas the most common comedications were acetaminophen (34%), statins (33%), and acetylsalicylic acid (31%).

Table 2 shows the results for the five outcomes. Compared with the use of specific, short-acting sulfonylureas, use of nonspecific, long-acting sulfonylureas was not associated with an increased risk of AMI (9.1 vs. 12.1 per 1,000/year; adjusted HR 0.86; 95% CI 0.55–1.34), ischemic stroke (9.1 vs. 11.7 per 1,000/year; adjusted HR 0.92; 95% CI 0.59–1.45), cardiovascular death (16.8 vs. 22.5 per 1,000/year; adjusted HR 1.01; 95% CI 0.72–1.40), or all-cause mortality (40.6 vs. 67.3 per 1,000/year; adjusted HR 0.81; 95% CI 0.66–1.003). However, use of nonspecific, long-acting sulfonylureas was associated with an increased risk of severe hypoglycemia (7.4 vs. 3.8 per 1,000/year; adjusted HR 2.83; 95% CI 1.64–4.88). In the secondary analysis assessing the risks of the study outcomes separately for each of the two pancreas-nonspecific, long-acting sulfonylureas (i.e., glyburide and glimepiride), we observed no major

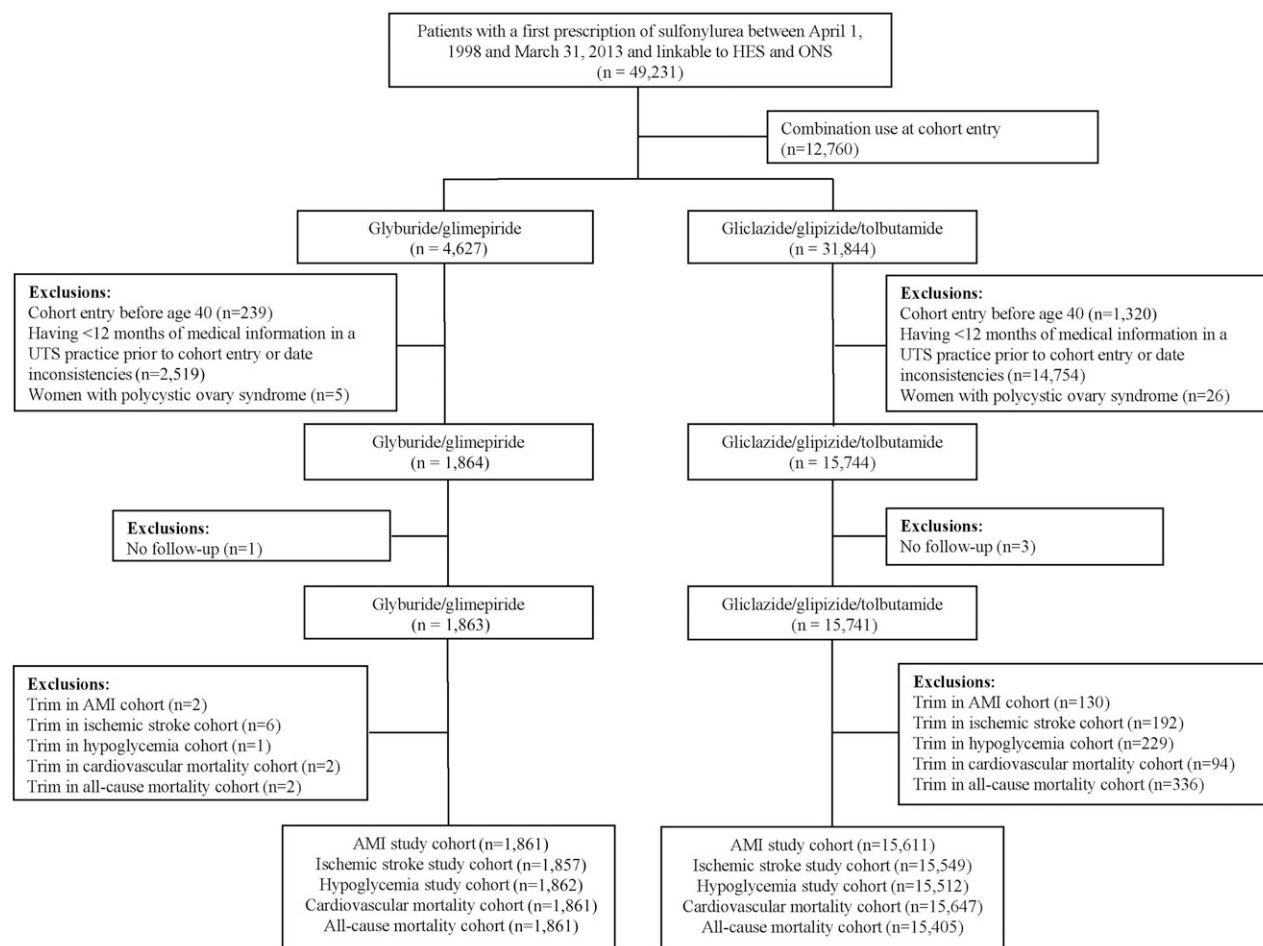


Figure 1—Study flow chart of patients initiating sulfonylureas between 1998 and 2013. UTS, up to standard.

differences between the two compounds (Supplementary Table 1).

The results of the primary analysis remained consistent in the sensitivity analyses (summarized in Fig. 2 and presented in Supplementary Tables 2–5). Indeed, no associations were observed with AMI, ischemic stroke, cardiovascular death, and all-cause mortality, whereas an increased risk was observed for severe hypoglycemia (Supplementary Tables 2–4). For the severe hypoglycemia outcome, the intention-to-treat approach led to a dilution of the HR, resulting in a nonstatistically significant association (HR 1.51; 95% CI 0.73–3.12) (Supplementary Table 5).

CONCLUSIONS

To our knowledge, this is the first observational study comparing major cardiovascular adverse events and severe hypoglycemia among different sulfonylureas grouped based on their specificity to pancreatic β -cells and duration of action. In comparison with the use of

specific, short-acting sulfonylureas, the use of nonspecific, long-acting sulfonylureas was not associated with an increased risk of AMI, ischemic stroke, cardiovascular death, and all-cause mortality. In contrast, these sulfonylureas were associated with an increased risk of severe hypoglycemia. Moreover, a secondary analysis showed no major differences in the risks of the study outcomes between the two pancreas nonspecific, long-acting sulfonylureas (i.e., glyburide and glimepiride), suggesting a similar risk profile. Overall, the findings of the primary analysis remained consistent in several sensitivity analyses.

Our findings on AMI, ischemic stroke, cardiovascular death, and all-cause mortality add new information to a field characterized by an abundance of studies that have generated contradicting results (13,15–17). To date, several observational studies have suggested that individual sulfonylureas, and particularly glyburide, possess an increased cardiovascular risk

as compared with others (15,17,18). However, methodological limitations, including exposure misclassification, time-lag bias, and selection bias, could affect the validity of these results (2). Our findings indicate that the binding of glyburide and glimepiride to cardiac and vascular structures, as reported in several preclinical studies (5), does not necessarily translate into an increased risk of ischemic adverse events or cardiovascular death as compared with other pancreas specific sulfonylureas. Possible explanations include reduced sulfonylurea concentrations on site (i.e., in cardiomyocytes or vascular smooth cells), thus alleviating the consequences of receptor binding or the existence of competing factors in the cardiovascular system, such as the impact of certain sulfonylureas on atherosclerosis or weight gain (5,19,20).

Our findings on hypoglycemia are concordant with those of previous clinical trials and observational studies (21,22). They also support the hypothesis that

Table 1—Characteristics of users of pancreas-nonspecific, long-acting sulfonylureas (glyburide and glimepiride) and pancreas-specific, short-acting sulfonylureas (gliclazide, glipizide, and tolbutamide) in patients with type 2 diabetes

Characteristics	Treatment group	
	Pancreas-nonspecific, long-acting sulfonylureas	Pancreas-specific, short-acting sulfonylureas
Total	1,863	15,741
Age (years), mean (SD)	66.8 (12.2)	68.4 (12.5)
Male, <i>n</i> (%)	1,093 (58.7)	9,025 (57.3)
Diabetes duration (years), mean (SD)	1.7 (3.6)	1.6 (3.4)
Alcohol-related disorders, <i>n</i> (%)	41 (2.2)	468 (3.0)
Smoking status, <i>n</i> (%)		
Ever	930 (49.9)	8,175 (51.9)
Never	783 (42.0)	6,474 (41.1)
Unknown	150 (8.1)	1,092 (6.9)
BMI, <i>n</i> (%)		
<25 kg/m ²	507 (27.2)	4,602 (29.2)
25–29 kg/m ²	665 (35.7)	5,563 (35.3)
≥30.0 kg/m ²	475 (25.5)	3,682 (23.4)
Unknown	216 (11.6)	1,894 (12.0)
HbA _{1c} (%), <i>n</i> (%)		
≤7 (≤53 mmol/mol)	191 (10.3)	1,411 (9.0)
7.1–8.0 (54–64 mmol/mol)	269 (14.4)	2,296 (14.6)
>8 (>64 mmol/mol)	609 (32.7)	5,186 (32.9)
Unknown	794 (42.6)	6,848 (43.5)
Medical history, <i>n</i> (%)		
Congestive heart failure	154 (8.3)	1,789 (11.4)
Arterial hypertension	1,031 (55.3)	8,848 (56.2)
Thyroid disease	136 (7.3)	1,390 (8.8)
Cerebrovascular disease	197 (10.6)	1,811 (11.5)
Atrial fibrillation or flutter	191 (10.3)	2,121 (13.5)
Cancer	223 (12.0)	2,505 (15.9)
Chronic obstructive pulmonary disease	273 (14.7)	2,306 (14.7)
Coronary artery disease	489 (26.3)	4,681 (29.7)
Hyperlipidemia	321 (17.2)	3,113 (19.8)
Previous coronary revascularization	70 (3.8)	734 (4.7)
Previous myocardial infarction	175 (9.4)	1,664 (10.6)
Angina pectoris	266 (14.3)	2,266 (14.4)
Anemia	261 (14.0)	2,935 (18.7)
Drugs, <i>n</i> (%)		
ACE inhibitors	525 (28.2)	4,596 (29.2)
Angiotensin II receptor blockers	99 (5.3)	1,117 (7.1)
β-Blockers	468 (25.1)	3,931 (25.0)
Calcium-channel blockers	392 (21.0)	3,675 (23.4)
Thiazide diuretics	381 (20.5)	3,251 (20.7)
Loop diuretics	322 (17.3)	3,298 (21.0)
Other diuretics	79 (4.2)	897 (5.7)
Digoxin	149 (8.0)	1,495 (9.5)
Statins	545 (29.3)	5,335 (33.9)
Fibrates	28 (1.5)	210 (1.3)
Clopidogrel	29 (1.6)	516 (3.3)
Warfarin	107 (5.7)	1,199 (7.6)
Acetylsalicylic acid	561 (30.1)	4,994 (31.7)
Nonsteroidal anti-inflammatory drugs	243 (13.0)	1,946 (12.4)
Opioid analgesics	542 (29.1)	4,788 (30.4)
Acetaminophen	600 (32.2)	5,444 (34.6)
Nitrates	222 (11.9)	2,076 (13.2)
Diabetic complications, <i>n</i> (%)		
Neuropathy	52 (2.8)	624 (4.0)
Peripheral vascular disease	106 (5.7)	981 (6.2)
Nephropathy	119 (6.4)	1,944 (12.4)
Retinopathy	167 (9.0)	1,509 (9.6)

Continued on p. 1511

Table 1—Continued

Characteristics	Treatment group	
	Pancreas-nonspecific, long-acting sulfonylureas	Pancreas-specific, short-acting sulfonylureas
Number of unique nonantidiabetic drugs, mean (SD)	7.1 (5.7)	8.1 (6.3)
0, n (%)	128 (6.9)	828 (5.3)
1, n (%)	110 (5.9)	890 (5.7)
2, n (%)	149 (8.0)	1,090 (6.9)
3, n (%)	175 (9.4)	1,243 (7.9)
≥4, n (%)	1,301 (69.8)	11,690 (74.3)
Number of hospitalization episodes of care, mean (SD)	0.3 (0.7)	0.5 (1.2)
0, n (%)	1,515 (81.3)	11,095 (70.5)
1, n (%)	239 (12.8)	3,010 (19.1)
2, n (%)	66 (3.5)	973 (6.2)
3, n (%)	24 (1.3)	359 (2.3)
≥4, n (%)	19 (1.0)	304 (1.9)

pharmacologically active metabolites resulting in longer durations of action can increase the hypoglycemic risk of sulfonylureas (3). A recent CPRD-based study by van Dalem et al. (23) compared long-acting with short-acting sulfonylureas but did not show a difference in hypoglycemic risk. However, in contrast to our study, their outcome definition was based on outpatient diagnoses rather than events leading to hospitalization. As their outcome definition likely included a mix of both mild and severe cases of hypoglycemia, direct comparison between the two studies is challenging. Moreover, the inclusion of mild hypoglycemia as their outcome definition may have introduced misclassification in the timing of the

outcome, resulting in a dilution of the association (24). Indeed, as mild hypoglycemia is generally self-managed by patients, it is possible that the date of the hypoglycemic event recorded is inaccurate.

Hypoglycemia has been implicated as a risk factor for cardiovascular adverse events and all-cause mortality in patients with diabetes (25). The Veterans Affairs Diabetes Trial (VADT) found severe hypoglycemia to be a predictor of both cardiovascular death and all-cause mortality (26). The Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) trial also indicated that severe hypoglycemia could contribute to cardiovascular adverse events (27). In our study, the increased

hypoglycemic risk associated with pancreas-nonspecific, long-acting sulfonylureas was not accompanied by an increased cardiovascular or mortality risk, arguing against a major contribution of hypoglycemia in sulfonylurea-related cardiovascular disease or mortality. However, the much lower incidence rate of hypoglycemia in our study cohort relative to the rates of the other outcomes could have masked its true impact, thus hampering definite conclusions.

Our study has a number of strengths. First, it is one of the first studies to group sulfonylureas based on important pharmacodynamic (i.e., specificity to pancreatic β -cells) and pharmacokinetic (i.e., duration of action) properties, thus

Table 2—HRs for all outcomes associated with pancreas-nonspecific, long-acting sulfonylureas (glyburide and glimepiride) compared with pancreas-specific, short-acting sulfonylureas (gliclazide, glipizide, and tolbutamide) in patients with type 2 diabetes

Exposure	Number of patients	Number of events	Person-years	Incidence rate (95% CI) (per 1,000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
AMI						
Specific, short-acting sulfonylureas	15,611	223	18,361	12.1 (10.6–13.8)	1.00 (reference)	1.00 (reference)
Nonspecific, long-acting sulfonylureas	1,861	22	2,422	9.1 (5.7–13.8)	0.76 (0.49–1.17)	0.86 (0.55–1.34)
Ischemic stroke						
Specific, short-acting sulfonylureas	15,549	215	18,316	11.7 (10.2–13.4)	1.00 (reference)	1.00 (reference)
Nonspecific, long-acting sulfonylureas	1,857	22	2,420	9.1 (5.7–13.8)	0.78 (0.50–1.21)	0.92 (0.59–1.45)
Severe hypoglycemia						
Specific, short-acting sulfonylureas	15,512	69	18,358	3.8 (2.9–4.8)	1.00 (reference)	1.00 (reference)
Nonspecific, long-acting sulfonylureas	1,862	18	2,435	7.4 (4.4–11.7)	1.97 (1.17–3.31)	2.83 (1.64–4.88)
Cardiovascular death						
Specific, short-acting sulfonylureas	15,647	417	18,498	22.5 (20.4–24.8)	1.00 (reference)	1.00 (reference)
Nonspecific, long-acting sulfonylureas	1,861	41	2,441	16.8 (12.1–22.8)	0.75 (0.55–1.04)	1.01 (0.72–1.40)
All-cause mortality						
Specific, short-acting sulfonylureas	15,405	1,233	18,320	67.3 (63.6–71.2)	1.00 (reference)	1.00 (reference)
Nonspecific, long-acting sulfonylureas	1,861	99	2,440	40.6 (33.0–49.4)	0.62 (0.50–0.76)	0.81 (0.66–1.00)

*Adjusted for hdPS deciles and history of the outcomes for the AMI and ischemic stroke models; adjusted for hdPS quintiles for the severe hypoglycemia model; adjusted for hdPS deciles and history of AMI or ischemic stroke for the cardiovascular death model; adjusted for hdPS deciles for the all-cause mortality model.

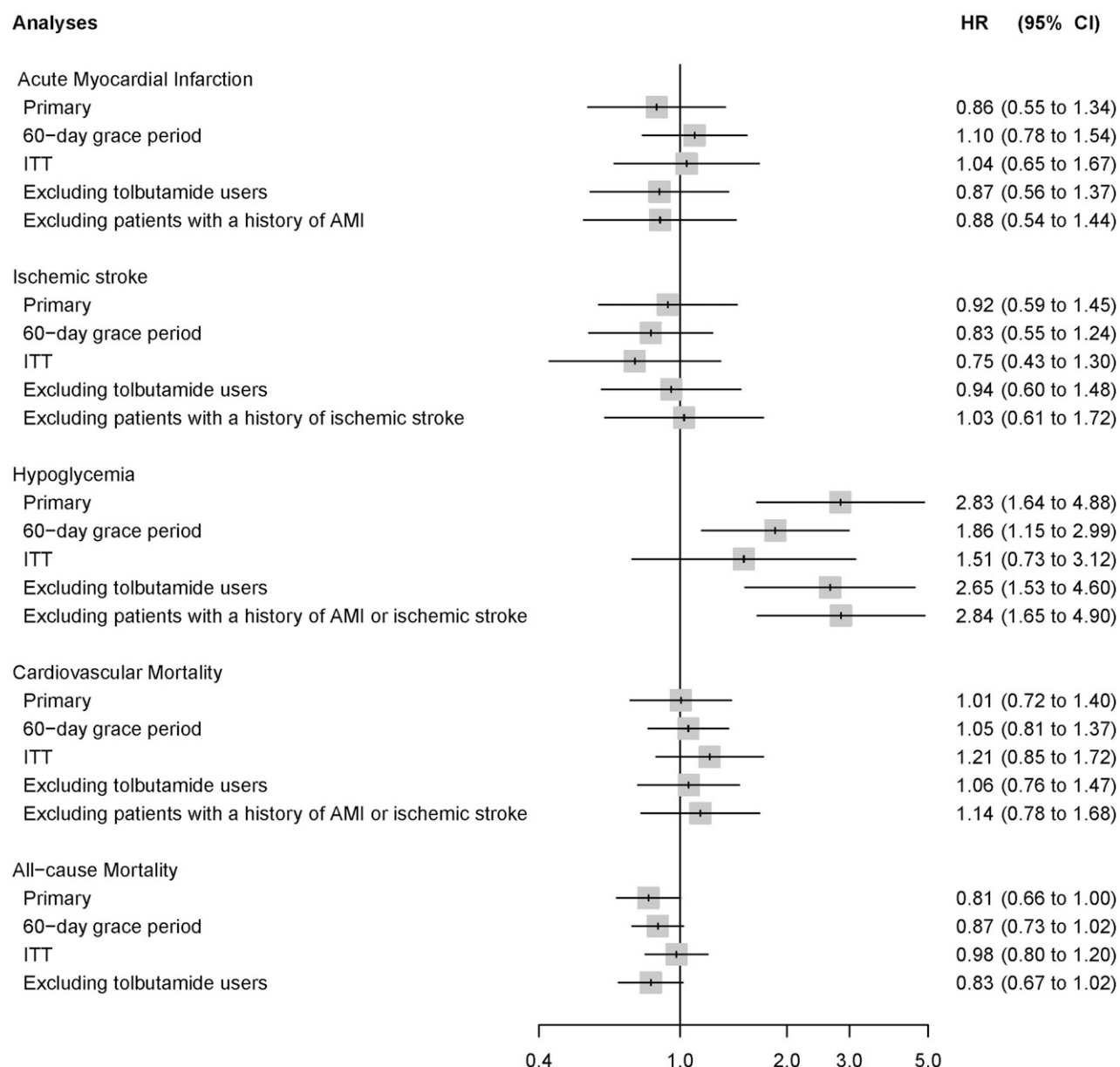


Figure 2—Forest plot with HRs for all outcomes associated with pancreas-nonspecific, long-acting sulfonylureas (glyburide and glimepiride) compared with pancreas-specific, short-acting sulfonylureas (glizalide, glipizide, and tolbutamide), in the primary analysis and all sensitivity analyses. ITT, intention-to-treat.

accounting, at least partly, for the high pharmacologic heterogeneity of this drug class. This classification does not consider the varying effects of the two pancreas-nonspecific sulfonylureas (i.e., glyburide and glimepiride) on ischemic preconditioning (13). However, we did consider this phenomenon in a secondary analysis, in which the risks of all study outcomes were assessed separately for glyburide and glimepiride, and found a similar risk profile. Second, the population-based design, the inclusion of patients with previous events, and the few exclusion criteria make its results highly

generalizable. Third, the definition of hypoglycemia was based on solely hospitalization-associated events, which likely maximized the specificity of this outcome definition.

Our study also has some limitations. First, because of its observational nature, there is potential for residual confounding. However, the application of a new user design with an active comparator and the use of robust statistical adjustment such as the hdPS likely minimized this potential bias. Second, the result for hypoglycemia in our sensitivity analysis using an intention-to-treat approach was

attenuated and no longer statistically significant. Although a dilution of the effect is a potential limitation of such analyses, the existence of informative censoring in our primary analysis cannot be ruled out. Third, the results of this study are generalizable to the use of sulfonylureas as first-line treatment; further research is needed to evaluate the safety of sulfonylureas when used as second- or third-line treatment. Fourth, because of the relatively short follow-up of the study, it is not possible to exclude long-term differences in risks in cardiovascular and mortality outcomes between the two groups.

In summary, our population-based cohort study showed no difference in the risk of major cardiovascular adverse events, cardiovascular death, and all-cause mortality between pancreas-nonspecific and pancreas-specific sulfonylureas, thereby contradicting previous studies and arguing that the clinical implications of the lack of pancreas specificity of certain sulfonylureas may have been overstated (28,29). Finally, it corroborates the previously reported increased risk of severe hypoglycemia associated with long-acting sulfonylureas as compared with short-acting compounds.

Funding. A.D. is the recipient of a Research Fellowship from the German Research Foundation (Deutsche Forschungsgemeinschaft). K.B.F. holds a Canadian Institutes of Health Research New Investigator Award. L.A. holds a Chercheur Boursier award from Fonds de recherche du Québec-Santé and is the recipient of a William Dawson Scholar award. S.S. is the recipient of the James McGill Professorship award.

Duality of Interest. This research was funded in part by grants from the Canadian Institutes of Health Research, the Canadian Foundation for Innovation, and Boehringer Ingelheim. S.S. 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.

The sponsors were not directly involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Author Contributions. A.D., H.Y., O.H.Y.Y., K.B.F., L.A., and S.S. contributed to study concept and design, analyzed and interpreted the data, and critically revised the manuscript. A.D. drafted the manuscript. A.D., H.Y., and L.A. conducted the statistical analysis. S.S. acquired the data, obtained funding, and supervised the study. S.S. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016; 39(Suppl. 1):S52–S59
2. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care* 2017; 40:706–714
3. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs* 2005;65:385–411
4. Riveline JP, Danchin N, Ledru F, Varroud-Vial M, Charpentier G. Sulfonylureas and cardiovascular effects: from experimental data to clinical use. Available data in humans and clinical applications. *Diabetes Metab* 2003;29:207–222
5. Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. *Diabetes Obes Metab* 2012; 14:130–138
6. Gribble FM, Reimann F. Pharmacological modulation of K(ATP) channels. *Biochem Soc Trans* 2002;30:333–339
7. Gribble FM, Reimann F. Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 2003; 46:875–891
8. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097–1099
9. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69: 4–14
10. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* 2013;346: f2350
11. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl. 1):100–128
12. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;20:512–522
13. Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. *Diabetes Care* 2010;33:1224–1229
14. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;19(Suppl.):789–830
15. Abdelmoneim AS, Eurich DT, Senthilvelan A, Qiu W, Simpson SH. Dose-response relationship between sulfonylureas and major adverse cardiovascular events in elderly patients with type 2 diabetes. *Pharmacoepidemiol Drug Saf* 2016;25: 1186–1195
16. Horsdal HT, Johnsen SP, Søndergaard F, et al. Sulfonylureas and prognosis after myocardial infarction in patients with diabetes: a population-based follow-up study. *Diabetes Metab Res Rev* 2009;25:515–522
17. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015;3:43–51
18. Johnsen SP, Monster TB, Olsen ML, et al. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther* 2006;13:134–140
19. Koshihara K, Nomura M, Nakaya Y, Ito S. Efficacy of glimepiride on insulin resistance, adipocytokines, and atherosclerosis. *J Med Invest* 2006; 53:87–94
20. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2015;100:363–370
21. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 2004; 34:535–542
22. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc* 1996;44: 751–755
23. van Dalem J, Brouwers MC, Stehouwer CD, et al. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. *BMJ* 2016;354:i3625
24. Csiszmadyi I, Collet J-P, Biovin J-F. *Pharmacoepidemiology*. Strom BL, Ed. London, England, John Wiley & Sons, 2006, p. 791–809
25. Paty BW. The role of hypoglycemia in cardiovascular outcomes in diabetes. *Can J Diabetes* 2015;39(Suppl. 5):S155–S159
26. Duckworth W, Abirra C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
27. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–1418
28. Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. *Eur Heart J* 2015;36:2288–2296
29. Abdelmoneim AS, Eurich DT, Gamble JM, et al. Risk of acute coronary events associated with glyburide compared with gliclazide use in patients with type 2 diabetes: a nested case-control study. *Diabetes Obes Metab* 2014;16: 22–29