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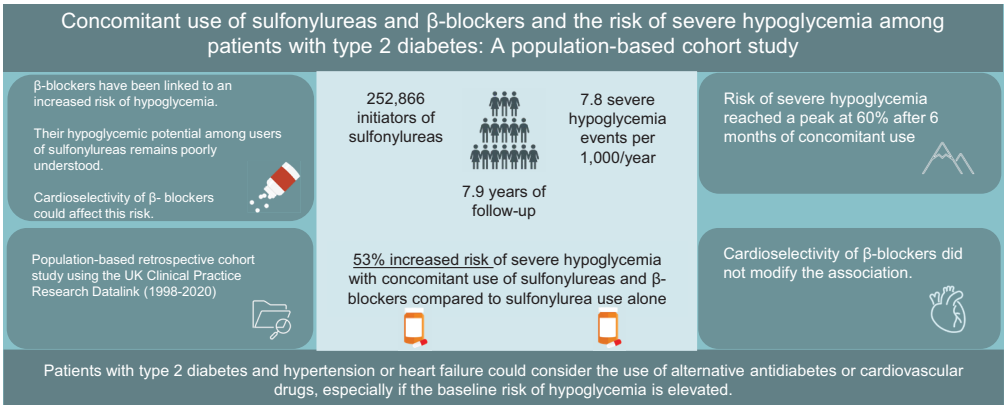

ARTICLE HIGHLIGHTS

- Our population-based cohort study showed that concomitant use of sulfonylureas and β-blockers was associated with a 53% increase in the risk of severe hypoglycemia compared with the use of sulfonylureas alone.
- The risk of severe hypoglycemia increased with increasing duration of continuous concomitant use of sulfonylureas and β-blockers, reaching a peak of 60% after roughly 6 months and decreasing afterward.
- Cardioselectivity of β-blockers, age, and sex did not seem to play a major role in this regard.

Concomitant Use of Sulfonylureas and β-Blockers and the Risk of Severe Hypoglycemia Among Patients With Type 2 Diabetes: A Population-Based Cohort Study

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OBJECTIVE

The hypoglycemic potential of β-blockers among users of sulfonylureas, drugs that strongly increase the risk of this potentially fatal adverse effect, is not well understood. Our population-based cohort study assessed the potential association between concomitant use of sulfonylureas and β-blockers versus use of sulfonylureas alone and the risk of severe hypoglycemia.

RESEARCH DESIGN AND METHODS

Using the U.K. Clinical Practice Research Datalink Aurum, we included patients initiating sulfonylureas between 1998 and 2020, excluding those with β-blocker use in the past 6 months. Time-dependent Cox models estimated hazard ratios (HRs) with 95% CIs of severe hypoglycemia (hospitalization with or death resulting from hypoglycemia; ICD-10 codes E16.0, E16.1, and E16.2) associated with current concomitant use of sulfonylureas and β-blockers compared with current sulfonylurea use alone, adjusted for baseline confounders. We also compared current concomitant use of sulfonylureas and non-cardioselective versus cardioselective β-blockers.

RESULTS

Our cohort included 252,869 initiators of sulfonylureas (mean age 61.3 years; 43% female). Median follow-up was 7.9 years. The crude incidence rate of severe hypoglycemia was 7.8 per 1,000 per year. Concomitant use of sulfonylureas and β-blockers was associated with an increased risk of severe hypoglycemia compared with sulfonylurea use alone (HR 1.53; 95% CI 1.42–1.65). There was no difference in the risk between concomitant use of sulfonylureas and noncardioselective β-blockers and concomitant use of sulfonylureas and cardioselective β-blockers (HR 0.95; 95% CI 0.74–1.24).

CONCLUSIONS

β-blockers could further increase the risk of severe hypoglycemia when used concurrently with sulfonylureas. β-blocker cardioselectivity did not seem to play a major role in this regard.

β-Blockers have well-established beneficial effects in the treatment of cardiovascular diseases, including hypertension, heart failure, and cardiac arrhythmias (1). However, use of β-blockers has also been associated with an increased risk of hypoglycemia, a

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potentially fatal adverse effect (2,3). Indeed, β-blockers can lower blood glucose levels. They also blunt early symptoms of hypoglycemia, which could delay its diagnosis and lead to more severe outcomes (4).

Although the absolute risk of β-blocker–induced hypoglycemia is low among patients without diabetes (5), this risk could become clinically relevant for patients with diabetes who concomitantly use other medications that increase the risk of hypoglycemia, such as sulfonylureas. Moreover, given that hypertension is a common comorbidity among patients with diabetes, roughly 30% of this patient population is treated with β-blockers (6).

To date, two observational studies have evaluated the effects of β-blockers on the risk of hypoglycemia in patients receiving sulfonylureas (7,8). The first study assessed all β-blockers together (7), whereas the second study stratified them based on their cardioselectivity (8), given that noncardioselective compounds may possess higher hypoglycemic potential as a result of stronger β-2 blockade in the liver and augmented inhibition of glycogenolysis and glucogenesis (9,10). However, the two studies were not able to generate conclusive findings, as suggested by the wide 95% CIs (7,8). Moreover, both studies had several methodological limitations, such as misclassification of exposure and important confounding resulting from lack of adjustment for markers of diabetes severity (7,8).

Given the scarcity and limitations of the available evidence, more research is needed to address this clinically important question. To this end, we conducted a population-based cohort study to assess the potential association between concomitant use of sulfonylureas and β-blockers versus sulfonylureas alone and the risk of severe hypoglycemia and whether cardioselectivity of β-blockers modifies this association.

RESEARCH DESIGN AND METHODS

Data Source

We conducted a retrospective cohort study using the U.K. Clinical Practice Research Datalink (CPRD) Aurum database linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases. The CPRD is a large primary care database that contains the records of 40 million patients (14 million patients currently registered) who are seen across 1,370 practices (15% of U.K. practices), and has been shown to be representative of the U.K. population (11,12). In the U.K., specialists and other health care providers are required to report back to general practitioners, who serve as gatekeepers of the health care system (12). In the CPRD, diagnoses are recorded using a combination of SNOMED Clinical Terms (a structured clinical vocabulary for use in an electronic health records), Read codes (a hierarchical coding system containing >80,000 terms capturing the many aspects of a patient's health status), and local EMIS Web codes (a coding system including clinical events, online test requests, test results, and prescriptions), all of which are coding systems with greater granularity than the ICD (12,13). Moreover, all prescriptions issued by general practitioners are recorded in the CPRD. The CPRD also contains clinical measures such as blood pressure, laboratory test results (e.g., hemoglobin A_{1c} [HbA_{1c}]), anthropometric measures (e.g., BMI), and lifestyle variables (e.g., smoking and alcohol use), all of which are recorded by general practitioners. The HES database includes information on hospital admissions, procedures, and discharge diagnoses coded using the ICD-10. Finally, the ONS database contains vital statistics data, which are considered the gold standard for mortality data in the U.K., and the date, place, and underlying cause of death of citizens in the U.K. (coded using ICD-10 during the study period of this project). The linkage between the CPRD, HES, and ONS databases is currently available for 90% of CPRD Aurum practices in the U.K. (11). The study protocol, including all proposed analyses, was approved before the beginning of data analysis by the Independent Scientific Advisory Committee (ISAC) of the CPRD (protocol 20_195R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

Study Population

We assembled a study cohort that included all patients who received a second-generation sulfonylurea (i.e., glibenclamide, glimepiride, gliclazide, or glipizide; compounds accounting for 99% of second-generation sulfonylureas in the CPRD) between 1 April 1998 and 30 June 2020. The date of the first prescription in the CPRD for a second-generation sulfonylurea during the study period defined entry into the study cohort. We excluded patients aged <18 years, patients with <365 days of medical history recorded in the CPRD before the date of cohort entry, and patients with a previous prescription for a second-generation sulfonylurea. We also excluded patients with a previous prescription for a first-generation sulfonylurea (e.g., tolbutamide), meglitinide, or insulin (at any time before cohort entry) because their mechanisms of drug-induced hypoglycemia are identical or similar to those of second-generation sulfonylureas. Patients with use of β-blockers in the 6 months before cohort entry were also excluded to minimize selection bias resulting from the depletion-of-susceptibles phenomenon (14). Patients who entered the study cohort were followed until the occurrence of the study outcome (defined below), non–hypoglycemia-related death, end of registration with the general practice, or end of study period (30 June 2020), whichever occurred first.

Exposure Definition

For the primary objective, we used a time-varying exposure definition, in which each person-day of the follow-up period was classified into one of four mutually exclusive categories, all of which may or may not have included concomitant treatment with metformin, given its very low risk of hypoglycemia (15): *1*) current concomitant use of sulfonylureas and β-blockers without other nonmetformin antidiabetic drugs, including insulin (i.e., concomitant use of sulfonylureas and β-blockers); *2*) current use of sulfonylureas without β-blockers and without other nonmetformin antidiabetic drugs, including insulin (i.e., use of sulfonylureas alone); *3*) current use of sulfonylureas with other nonmetformin antidiabetic drugs, including insulin (with or without β-blockers); and *4*) no current use of sulfonylureas (with or without β-blockers and with or without nonmetformin antidiabetic drugs, including insulin). Patients were allowed to contribute person-time to different exposure categories during follow-up. For example, concomitant users of sulfonylureas and β-blockers were followed (not censored) upon discontinuation of β-blockers, but then started contributing person-time to the use-of-sulfonylureas-alone exposure category. Patients were considered continuously exposed if the duration of one

prescription overlapped with the date of the next prescription, allowing for a 30-day grace period between nonoverlapping successive prescriptions. Concomitant use was defined as an overlap in prescriptions of drugs of interest on the same day. This exposure definition was chosen because of its ability to reflect the dynamic nature of antidiabetic treatment and to maximize study power. A detailed illustration of the exposure definition can be found in Supplementary Fig. 1.

Because the primary objective of the study was to assess the risk of sulfonylurea-induced hypoglycemia associated with concomitant use of β-blockers, concomitant use of sulfonylureas and β-blockers was compared with the use of sulfonylureas alone, with the latter group being the reference category. All person-time (i.e., person-time from all four exposure categories) was considered in the time-dependent model but not presented in the study.

For the secondary objective, we subclassified current use of sulfonylureas without nonmetformin antidiabetic drugs by β-blocker cardioselectivity: *1*) current concomitant use of sulfonylureas and noncardioselective β-blockers (i.e., propranolol, carvedilol, sotalol, or labetalol); and *2*) current concomitant use of sulfonylureas and cardioselective β-blockers (i.e., acebutolol, atenolol, bisoprolol, metoprolol, nebivolol, or esmolol). The secondary objective explored the role of cardioselectivity of β-blockers in sulfonylurea-induced hypoglycemia, whereas concomitant use of sulfonylureas and non-cardioselective β-blockers was compared with concomitant of sulfonylureas and cardioselective β-blockers, with the latter group serving as the reference category.

Outcome Definition

The outcome of interest was severe hypoglycemia. Severe hypoglycemia was defined as hospitalization with hypoglycemia or death resulting from hypoglycemia. Emergency department visits not resulting in admission were not considered. To this end, we identified the ICD-10 diagnostic codes E16.0 (drug-induced hypoglycemia without coma), E16.1 (other hypoglycemia), and E16.2 (hypoglycemia, unspecified) in the HES (codes in primary or nonprimary positions) and ONS databases (codes as the underlying cause of death only). The date of hospital admission or death defined the event date. These ICD-10 codes were chosen because they specifically refer to hypoglycemia and have shown excellent positive predictive values (94–100%) when used in the primary position only. Algorithms including these codes but also other, less specific, diabetes-related ICD-10 codes showed a positive predictive value of 54% when used in any position (16). Our decision to include the ICD-10 codes in any position in hospitalization data was based on an attempt to balance the feasibility of the secondary objective while ensuring the validity of the primary objective.

Covariates

To minimize potential confounding, we included the following variables, measured at cohort entry, in the Cox proportional hazards model: calendar year, age (modeled flexibly as a continuous variable using restricted cubic splines to account for potential nonlinear association with the outcome) (17), sex, BMI category ($<$25, 25–29, or $\geq$30 kg/m^2 or unknown; last measurement before cohort entry), and smoking (current, former, never, or unknown). We also adjusted for alcohol-related disorders (e.g., alcoholism, alcoholic hepatitis, liver cirrhosis, or liver failure), hypertension, hyperlipidemia, congestive heart failure, chronic kidney disease, cognitive impairment (all measured before cohort entry), and acute infection (measured in the 3 months before cohort entry) (18–21). Moreover, we adjusted for markers of severity of diabetes, including diabetes duration (time between the first diagnosis of type 2 diabetes, first HbA_{1c} value $>$6.5%, or first prescription for an antidiabetic drug and cohort entry; modeled flexibly using restricted cubic splines [17]), HbA_{1c} level ($<$7, 7–8, or $>$8% or unknown; last measurement before cohort entry), number of non-sulfonylurea antidiabetic drugs in the year before cohort entry, microvascular complications (nephropathy, neuropathy, or retinopathy), macrovascular diabetic complications (myocardial infarction, ischemic stroke, or peripheral vascular disease/transient ischemic attack), other complications of diabetes (e.g., cataracts, glaucoma, or skin ulcer), and history of severe hypoglycemia (all measured before cohort entry) (21). In addition, we adjusted for the use of drugs previously linked to hypoglycemia (i.e., quinolones or tramadol) in the year before cohort entry. Finally, we adjusted for the number of hospitalizations in the year before cohort entry as a proxy for overall health.

Statistical Analyses

For the primary objective, we used time-dependent Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% CIs of severe hypoglycemia associated with current concomitant use of sulfonylureas and β-blockers compared with current use of sulfonylureas alone. For the secondary objective, we used time-dependent Cox proportional hazards models to estimate adjusted HRs and 95% CIs associated with current concomitant use of sulfonylureas and non-cardioselective β-blockers compared with current concomitant use of sulfonylureas and cardioselective β-blockers. All analyses were adjusted for the covariates listed previously at baseline.

Secondary Analyses

We conducted three secondary analyses. We stratified by age ($<$65 vs. $\geq$65 years) and sex. In addition, we assessed a potential duration-response relation between current concomitant use of sulfonylureas and β-blockers and the risk of severe hypoglycemia, by modeling the duration of current concomitant use as a continuous variable using restricted cubic splines with five interior knots (17).

Sensitivity Analyses

We also conducted seven prespecified sensitivity analyses to address different potential sources of bias. First, to assess potential exposure misclassification, we repeated the primary analyses using 15- and 60-day grace periods. Second, we used a stricter outcome definition considering only diagnostic codes of hypoglycemia in the primary position of hospitalization data. Third, we used an active comparator (i.e., current concomitant use of sulfonylureas and thiazide diuretics) to assess the potential impact of residual confounding. Thiazide diuretics were chosen as the control precipitant of the active comparator, given that they share common indications with β-blockers while having no intrinsic risk of hypoglycemia and no interaction potential with sulfonylureas (22). Fourth, we repeated the primary analysis after excluding patients with prior severe hypoglycemia. Fifth, to assess the potential impact of time-dependent confounding, we used a marginal

structural Cox proportional hazards model. In this analysis, we considered five time-dependent covariates (i.e., alcohol-related disorders, infection, HbA_{1c} level, tramadol use, and quinolone use) that may have simultaneously been confounders and intermediate variables (23). They were updated every 30 days. Extreme weights were not truncated. Sixth, we conducted an analysis accounting for the competing risk of death resulting from any cause using the Fine and Gray subdistribution hazards model (24).

Finally, we conducted five post hoc sensitivity analyses. First, we assessed the potential impact of unmeasured confounding using the approach of Ding and VanderWeele (25). The advantage of this approach is that no assumptions regarding the nature of the unmeasured confounder or confounders (e.g., having an unmeasured confounder that is binary, having no interaction between the effects of the exposure and the confounder on the outcome, or having only one unmeasured confounder) are required. Second, we used multiple imputation for variables with missing values (i.e., HbA_{1c}, BMI, and smoking) instead of the unknown indicator approach in the primary analysis (26,27). To this end, we initially fitted an ordinal logistic regression model to impute variables with missing information with explanatory variables and cumulative hazard (28) and one of the exposure groups (at cohort entry), along with all confounders considered in the primary analysis. Then, we used multiple imputation methods for variables with missing information, and then combined the results of 10 imputations using Rubin rules (29). Third, we additionally adjusted our models for liver disease. Finally, we conducted two additional analyses modifying the specifications of the marginal structural Cox proportional hazards model: *1*) additionally truncating extreme weights using the 99th percentile as cutoff; and *2*) additionally truncating extreme weights using the 99th percentile as cutoff and including three common indications for β-blocker use (i.e., hypertension, heart failure, and myocardial infarction) as time-dependent covariates. All analyses were conducted with SAS 9.4 software (SAS Institute, Cary, NC) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study cohort included 252,869 patients who initiated treatment with a second-generation sulfonylurea between April 1998 and June 2020 (Fig. 1). During a median (interquartile range [IQR]) follow-up of 7.9 (3.9–12.4) years, there were 16,857 events of severe hypoglycemia, generating a crude incidence rate of 7.8 (95% CI, 7.6–7.9) per 1,000 person-years. Median (IQR) duration of follow-up for the two exposure categories of interest was 1.1 (0.3–3.0) for concomitant use of sulfonylureas and β-blockers and 1.9 (0.5–4.4) for sulfonylureas alone. During follow-up, 29,754 patients were coexposed to sulfonylureas and β-blockers. Of those, a majority (26,347; 88.5%) were treated with non-cardioselective β-blockers. Table 1 presents patient characteristics at cohort entry stratified based on the potential coexposure of sulfonylureas and β-blockers during the first 6 months after cohort entry. Overall, patient characteristics were similar between groups. As expected, sulfonylurea users coexposed to β-blockers were more likely to have a diagnosis of hypertension or congestive heart failure and a history of myocardial infarction. They were also more likely to have been hospitalized in the year before cohort entry. Sulfonylurea users not coexposed to β-blockers were more likely to have used non-sulfonylurea antidiabetic drugs and to have a history of diabetic complications, such as cataracts, glaucoma, or skin ulcer.

Table 2 shows that when compared with use of sulfonylureas alone, concomitant use of sulfonylureas and β-blockers was associated with a 53% relative increase in the risk of severe hypoglycemia (crude incidence rate 13.52 vs. 5.76 per 1,000 person-years; adjusted HR 1.53; 95% CI 1.42–1.65). The head-to-head comparison between non-cardioselective and cardioselective β-blockers among sulfonylurea users suggests that the risk of severe hypoglycemia did not vary by β-blocker cardioselectivity (crude incidence rate 11.39 vs. 13.69 per 1,000 person-years; adjusted HR 0.95; 95% CI 0.74–1.24).

We did not observe major effect measure modification by age or sex (Supplementary Table 1). Supplementary Figure 2 shows that the risk of severe hypoglycemia increased with increasing duration of continuous concomitant use of sulfonylureas and β-blockers, reaching a peak at an HR of 1.60 after roughly 6 months and decreasing afterward. Finally, the results of the sensitivity analyses were overall consistent with those of the primary analysis, with the respective HRs ranging from 1.31 to 1.69 (Supplementary Table 2). The results of the primary and sensitivity analyses are summarized in Fig. 2. Finally, the post hoc sensitivity analysis based on the approach of Ding and VanderWeele (25) suggested that unmeasured confounding was unlikely to fully explain the results of the primary analysis under most plausible confounder-exposure and confounder-outcome associations (Supplementary Table 3).

CONCLUSIONS

Our population-based cohort study of >200,000 patients who initiated sulfonylurea therapy revealed an increased risk of severe

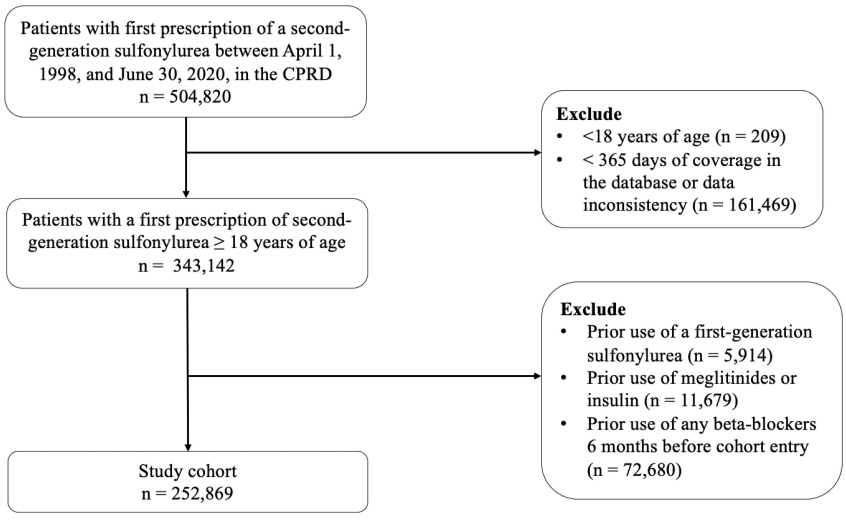

Figure 1—Flowchart demonstrating construction of the study cohort.

Table 1—Patient characteristics at cohort entry stratified by coexposure to β-blockers

Characteristic*	Sulfonylurea users: Coexposed to β-blockers (*n* = 4,233)	Sulfonylurea users: Not coexposed to β-blockers (*n* = 242,788)	Standardized difference
Age, years, mean (SD)	64.6 (12.5)	61.3 (13.8)	0.250
Female sex	1,774 (41.9)	105,168 (43.3)	0.030
BMI, kg/m^2			
<25	604 (14.3)	36,466 (15.0)	−0.021
25–29	1,293 (30.6)	74,236 (30.6)	−0.001
≥30	1,748 (43.5)	107,505 (44.3)	−0.060
Unknown	451 (10.7)	24,578 (10.1)	0.116
Smoking status			
Current	670 (15.8)	42,403 (17.4)	−0.044
Former	1,269 (30.0)	61,613 (27.9)	0.047
Never	1,843 (43.5)	114,451 (47.1)	−0.072
Unknown	451 (10.7)	18,318 (7.5)	0.108
Comorbidities			
Alcohol-related disorders	710 (16.8)	44,163 (18.2)	−0.037
Hypertension	2,706 (63.9)	118,117 (48.7)	0.312
Hyperlipidemia	2,378 (56.2)	138,981 (57.2)	−0.021
Congestive heart failure	547 (12.9)	13,067 (5.4)	0.264
Chronic kidney disease	2,123 (50.2)	126,171 (52.0)	−0.036
Cognitive impairment	41 (1.0)	3,197 (1.3)	−0.033
Acute infection	333 (7.9)	15,143 (6.2)	0.064
Markers of diabetic severity			
Diabetes duration, years, median (IQR)	2.16 (0.18–6.08)	2.60 (0.36–6.08)	−0.016
HbA_{1c} level, %			
<7	542 (12.8)	27,875 (11.5)	0.040
7–8	751 (17.7)	47,297 (19.5)	−0.045
>8	1,224 (28.9)	78,872 (32.5)	−0.077
Unknown	1,716 (40.5)	88,741 (36.6)	0.082
N of nonsulfonylurea antidiabetic drugs			
0	1,987 (46.9)	86,507 (35.6)	0.231
≥1	2,246 (53.1)	156,278 (64.4)	−0.231
Microvascular complications			
Diabetic nephropathy	68 (1.6)	2,303 (1.0)	0.059
Diabetic neuropathy	87 (2.1)	5,016 (2.1)	−0.001
Diabetic retinopathy	524 (12.4)	32,383 (13.3)	−0.029
Macrovascular complications			
Myocardial infarction	757 (17.9)	15,849 (6.5)	0.352
Ischemic stroke/TIA	362 (8.6)	14,241 (5.9)	0.104
Diabetic PVD or PVD	266 (6.3)	11,400 (4.7)	0.069
Other diabetic complications	1,149 (27.1)	89,297 (36.8)	−0.208
History of severe hypoglycemia	15 (0.4)	1,002 (0.4)	−0.010
Prior use of drugs			
Quinolones	117 (2.8)	6,774 (2.8)	−0.002
Tramadol	235 (5.6)	12,478 (5.1)	0.018
Proxy of overall health			
N of hospitalizations			
0	3,137 (74.1)	205,039 (84.5)	−0.257
≥1	1,096 (25.9)	37,746 (15.6)	0.257

All values are *n* (%) unless indicated otherwise. PVD, peripheral vascular disease; TIA, transient ischemic attack. *Measured within the first 6 months after cohort entry.

hypoglycemia associated with concomitant use of sulfonylureas and β-blockers, when compared with use of sulfonylureas alone. Cardioselectivity of β-blockers, age, and sex did not modify this association. Moreover, the results were robust across multiple sensitivity analyses addressing different potential sources of bias.

To date, two observational studies assessed the risk of hypoglycemia associated with concomitant use of sulfonylureas and β-blockers (7,8). The first study, a case-control study using Pennsylvania Medicaid data, reported no increased risk of hypoglycemia (odds ratio 1.1; 95% CI, 0.5–2.6) (7). However, the wide 95% CIs suggest that the number of cases was not sufficient to generate conclusive findings. The second study, a cohort study using Tennessee Medicaid data, reported only separate estimates for cardioselective β-blockers (relative risk 0.86; 95% CI, 0.36–1.33) and non-cardioselective β-blockers (relative risk 0.25; 95% CI 0.05–1.24) (8). Similar to the first study, this study also did not have the required statistical power. Importantly, both studies also had several methodological limitations, including information bias resulting from misclassification of exposure and important residual confounding resulting from lack of adjustment for markers of diabetes severity, such as diabetes duration, HbA_{1c} level, and history of diabetic complications (7,8).

Our study showed a 53% increase in the risk of severe hypoglycemia associated with concomitant use of sulfonylureas and β-blockers, compared with use of sulfonylureas alone. These results are congruent with pharmacological data supporting a pharmacodynamic interaction between these two drug classes (30). β-Blockers can lower blood glucose levels by suppressing glycogenolysis and inhibiting hepatic glucose production. In some cases, this mechanism may suffice to independently cause hypoglycemia (31). More importantly, however, it can also delay hypoglycemic recovery time and prolong the duration of sulfonylurea-induced hypoglycemia (4). In addition, β-blockers may mask initial hypoglycemic symptoms, such as tachycardia, thus leading to silent (asymptomatic) hypoglycemia and potentially to delayed treatment and more severe outcomes (2,30). Of note, all these potential mechanisms seem to operate at the acute to subacute level. Therefore, the observed duration-response pattern with a relatively early peak in the risk of severe hypoglycemia within the first months of concomitant use of sulfonylureas and β-blockers is also consistent with available pharmacological data. The subsequent decline could be interpreted in the context of the depletion-of-susceptibles phenomenon.

Cardioselectivity of β-blockers did not modify the association with the risk of severe hypoglycemia comparable between

Table 2—Crude and adjusted HRs of severe hypoglycemia associated with current concomitant use of sulfonylureas and β-blockers versus sulfonylureas alone

Exposure*	*N* of events	*N* of person-years	Incidence rate†	HR (95% CI) Crude	HR (95% CI) Adjusted‡
Primary objective					
Sulfonylureas and β-blockers	846	62,584	13.52	1.78 (1.65–1.92)	1.53 (1.42–1.65)
Sulfonylureas alone	4,297	745,915	5.76	1.00 (reference)	1.00 (reference)
Secondary objective					
Sulfonylureas and non-cardioselective β-blockers	62	5,442	11.39	0.89 (0.68–1.15)	0.95 (0.74–1.24)
Sulfonylureas and cardioselective β-blockers	781	57,066	13.69	1.00 (reference)	1.00 (reference)

*All person-time was considered in the model but not presented in the table (i.e., current use of a sulfonylurea with other nonmetformin antidiabetic drugs, with or without β-blockers, and no current use of a sulfonylurea (with or without β-blockers, with or without nonmetformin antidiabetic drugs). †Per 1,000 person-years. ‡All of the following variables were included in the Cox proportional hazards model: calendar year, age, sex, BMI, smoking, alcohol-related disorders, hypertension, hyperlipidemia, congestive heart failure, chronic kidney disease, cognitive impairment, acute infection, diabetes duration, HbA_{1c} level, *n* of non-sulfonylurea antidiabetic drugs, microvascular diabetic complications (nephropathy, neuropathy, retinopathy), macrovascular diabetic complications (myocardial infarction, ischemic stroke, peripheral vascular disease), other complications of diabetes (e.g., cataracts, glaucoma, skin ulcer), history of severe hypoglycemia, quinolones, tramadol, and *n* of prior hospitalizations.

the use of non-cardioselective and cardioselective compounds among patients treated with sulfonylureas. To date, available literature on the role of cardioselectivity in this regard has been inconsistent. On one hand, there is pharmacological rationale in favor of a higher hypoglycemic potential with non-cardioselective β-blockers. Indeed, the action of non-cardioselective compounds on the extracardiac β-2 adrenergic receptors in the liver is expected to be stronger than that of cardioselective compounds, which could then lead to enhanced inhibition of glycogenolysis and gluconeogenesis (10). On the other hand, previous small clinical studies have not been able to corroborate this pharmacological hypothesis (3,8,32). Overall, our findings suggest that the clinical implications of this aspect of intraclass pharmacological heterogeneity of β-blockers are probably limited.

Our study has several strengths. First, the large sample size allowed for the calculation of precise effect estimates in primary and secondary analyses. Therefore, we were able to assess the hypoglycemic risk of the interaction between sulfonylureas and β-blockers and whether cardioselectivity of β-blockers, age, or sex modify the association. Second, the population-based design, the inclusion of patients with previous events, and the use of few exclusion criteria during the construction of the study cohort make the results highly generalizable. Finally, using a time-varying exposure definition, we were able to depict the dynamic nature of pharmacotherapy for diabetes over time and avoid time-related biases.

This study also has some limitations. First, residual confounding resulting from unmeasured variables, such as physical activity or frailty, cannot be excluded. However, we adjusted for many potential confounders in our statistical models, including several markers of diabetes severity. Moreover, we used an active comparator (i.e., concomitant use of sulfonylureas and thiazide diuretics) in a sensitivity analysis, which yielded findings that were consistent with those of the primary analysis. That being said, effect estimates in the marginal structural Cox proportional hazards model analyses were slightly lower, suggesting that time-dependent confounding may have accounted, partly, for the increase in risk. Second, the CPRD records issued prescriptions but not dispensed medications, which could allow for exposure misclassification. However, the use of alternate grace periods did not change the results. Third, outcome misclassification is also possible given the varying validity of diagnostic codes and the inability to consider laboratory values upon hospitalization, such as capillary blood glucose, for the definition of severe hypoglycemia. Indeed, algorithms based on ICD-10 diagnostic codes showed a positive predictive value of 54% when used in any position in hospitalization data (as was the case in our study) (16).

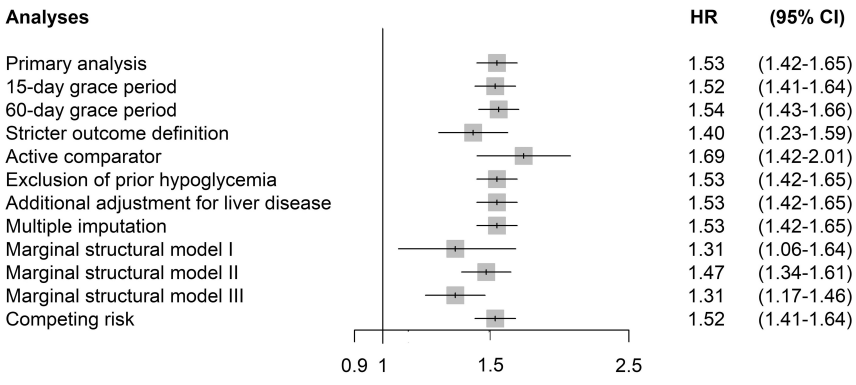

Figure 2—Forest plot summarizing the results of primary analysis and sensitivity analyses for the association between concomitant use of sulfonylureas and β-blockers and the risk of severe hypoglycemia. Marginal structural model I: alcohol-related disorders, infection, HbA_{1c} level, tramadol use, and quinolone use as time-varying covariates (update every 30 days); no truncation of extreme weights. Marginal structural model II: alcohol-related disorders, infection, HbA_{1c} level, tramadol use, and quinolone use as time-varying covariates (update every 30 days); truncation of extreme weights (99th percentile as cutoff). Marginal structural model III: alcohol-related disorders, infection, HbA_{1c} level, tramadol use, quinolone use, hypertension, congestive heart failure, and myocardial infarction as time-varying covariates (update every 30 days); truncation of extreme weights (99th percentile as cutoff).

Reassuringly, the sensitivity analysis using a strict outcome definition (codes in primary position only in hospitalization data) yielded findings that were consistent with those of the primary analysis. Last, our outcome definition did not include nonsevere events or severe events that were treated in the outpatient setting. Therefore, the generalizability of our findings to these forms of hypoglycemia is unclear.

In summary, we found an increased risk of severe hypoglycemia associated with concomitant use of sulfonylureas and β-blockers compared with use of sulfonylureas alone. Cardioselectivity of β-blockers did not modify this association. These findings are important, given the common concomitant use of these medications, the clinical importance of severe hypoglycemia, and the costs associated with this adverse event (33). Therefore, patients with type 2 diabetes and hypertension or heart failure should be cautious regarding the concomitant use of sulfonylureas and β-blockers and should consider the use of alternative antidiabetic (e.g., sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists) or cardiovascular drugs (e.g., diuretics or inhibitors of the renin angiotensin system), especially if the baseline risk of hypoglycemia is elevated.

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