



Comparative Safety of Sulfonylureas and the Risk of Sudden Cardiac Arrest and Ventricular Arrhythmia

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OBJECTIVE

To examine the association between individual antidiabetic sulfonylureas and outpatient-originating sudden cardiac arrest and ventricular arrhythmia (SCA/VA).

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study using 1999–2010 U.S. Medicaid claims from five large states. Exposures were determined by incident use of glyburide, glimepiride, or glipizide. Glipizide served as the reference exposure, as its effects are believed to be highly pancreas specific. Outcomes were ascertained by a validated ICD-9–based algorithm indicative of SCA/VA (positive predictive value ~85%). Potential confounding was addressed by adjustment for multinomial high-dimensional propensity scores included as continuous variables in a Cox proportional hazards model.

RESULTS

Of sulfonylurea users under study ($N = 519,272$), 60.3% were female and 34.9% non-Hispanic Caucasian, and the median age was 58.0 years. In 176,889 person-years of sulfonylurea exposure, we identified 632 SCA/VA events (50.5% were immediately fatal) for a crude incidence rate of 3.6 per 1,000 person-years. Compared with glipizide, propensity score-adjusted hazard ratios for SCA/VA were 0.82 (95% CI 0.69–0.98) for glyburide and 1.10 (0.89–1.36) for glimepiride. Numerous secondary analyses showed a very similar effect estimate for glyburide; yet, not all CIs excluded the null.

CONCLUSIONS

Glyburide may be associated with a lower risk of SCA/VA than glipizide, consistent with a very small clinical trial suggesting that glyburide may reduce ventricular tachycardia and isolated ventricular premature complexes. This potential benefit must be contextualized by considering putative effects of different sulfonylureas on other cardiovascular end points, cerebrovascular end points, all-cause death, and hypoglycemia.

Sudden cardiac arrest (SCA) is the sudden cessation of cardiac activity in which the affected individual becomes unresponsive, with no normal breathing or signs of circulation (1). Coronary heart disease is the most common pathology underlying SCA (2). Despite advances in coronary heart disease treatment, SCA kills as many as 450,000 persons annually in the U.S. (3), ~100,000 of whom have diabetes mellitus (DM) (4). The pathophysiology of SCA is complex, typically requiring an underlying substrate plus a transient event that induces electric instability and a ventricular arrhythmia (VA) followed by hemodynamic collapse (5). In fact, ventricular tachycardia or fibrillation is the

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initial electrocardiogram rhythm in 75–84% of SCA events (6–8). Because of this close relationship between SCA and VA, these clinical entities are often studied together.

In the setting of DM, incidence rates of SCA are 3.2 and 13.8 per 1,000 person-years (p-y) in persons without and persons with clinically recognized heart disease (9)—indicative that DM confers a two- to fourfold risk of SCA (4). This may be due to a combination of atherosclerotic, thrombotic, neural, and other factors (10,11). The relative importance of these determinants is unknown, although recent opinion has emphasized the roles of coronary artery disease, myocardial dysfunction, and electrical abnormalities (9) while downplaying the role of cardiac autonomic dysfunction (12). Antidiabetes drugs have also been implicated (13). The ongoing DM epidemic, coupled with an increasing rate of SCA in persons with DM (14), represents a major and growing public health concern.

Studies conducted in animals and humans have demonstrated that some second-generation sulfonylureas—the most commonly used dual-therapy add-on to metformin in type 2 DM (15,16) and agents that have long since supplanted first-generation predecessors (17)—act on the myocardium (11). In particular, glyburide and glimepiride potentially block cardiac ion channels such as the K_{ATP} channel (18). Myocardial K_{ATP} channel antagonism may attenuate or abolish ischemic preconditioning and prevent action potential duration shortening, leading to propagation of delayed afterdepolarizations, yet prevention of re-entrant arrhythmias (19). Interestingly, the loss of ischemic preconditioning has frequently been demonstrated with glyburide but not glimepiride use (11). Further, extrapancreatic effects of some sulfonylureas may include human ether-a-go-go-related gene (hERG) channel inhibition leading to electrocardiographic QT interval prolongation. These diverse actions might be expected to either propagate or prevent VAs. In contrast, glipizide is highly selective for blocking the pancreatic β -cell K_{ATP} channel (20). Sulfonylureas also may differ with respect to hypoglycemia risk (21), which may influence VAs and SCA (22).

Recent meta-analyses (23–28) and clinical trials (29–32) have reinvigorated the longstanding debate of sulfonylureas' cardiovascular effects and potential associations with all-cause and cardiovascular death

(33,34). Yet, there has been little specific focus on serious arrhythmogenicity like SCA and VA. Major ongoing trials such as Glycemia Reduction Approaches in Diabetes (GRADE) and Cardiovascular Outcome Trial of Linagliptin Versus Glimperide in Type 2 Diabetes (CAROLINA) will not provide data on these end points. The recently completed Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention (TOSCA.IT) trial in fact examined SCA, but only as part of a composite secondary outcome, and did not elucidate differences in risk among individual sulfonylureas; see Supplementary Table 1 for further detail on these trials. Given this, the comparative safety of glyburide, glimepiride, and glipizide with regard to risk of serious arrhythmic events in persons with DM is unknown. This knowledge gap motivated our comparative safety study elucidating SCA and VA risk among users of second-generation sulfonylureas.

RESEARCH DESIGN AND METHODS

Overview and Study Population

We conducted a high-dimensional propensity score (hdPS)-adjusted, incident user cohort study to examine the risk of SCA/VA among users of individual sulfonylureas. The study included adults aged 30–75 years. Younger persons were excluded because SCA/VA is extremely rare in such individuals and unlikely to be due to prescription drugs (35); older persons were excluded to minimize potential confounding by significant competing comorbidities that may mimic SCA/VA. The cohort consisted exclusively of person-time exposed to a second-generation sulfonylurea: glimepiride, glipizide, or glyburide. Data included demographic, enrollment, and health care claims from the U.S. Medicaid programs of California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2010. These states comprise ~40% of the national Medicaid population, with the 12-year data set recording the experience of nearly 65 million cumulative enrollees and >200 million p-y of observation. Because a substantive proportion of Medicaid beneficiaries are co-enrolled in the U.S. Medicare program, we also obtained Medicare claims to ascertain a more complete picture of enrollees' health care (36,37). We linked these data sets to the U.S. Social Security Administration Death Master File to supplement dates of death with those provided by the U.S. Centers for Medicare and Medicaid Services.

Defining the Study Cohort

Persons under study were apparent incident users of a sulfonylurea, i.e., had a 12-month baseline period devoid of a first- or second-generation sulfonylurea dispensing prior to their first second-generation sulfonylurea dispensing of interest. Cohort entry occurred upon incident use of a second-generation sulfonylurea.

The following events occurring during the baseline period served to exclude observations from study: 1) interruption in Medicaid enrollment; 2) SCA or VA diagnosis in an emergency department, inpatient, or ambulatory setting—broader than the outcome definition described below, to ensure the study of incident events; and 3) pregnancy, as such persons treated with a sulfonylurea almost exclusively receive glyburide (38) and their inclusion would create unwanted areas of nonoverlap in propensity score (PS) distributions (39). Persons with excluded observations could later be eligible for inclusion if the inclusion criteria were subsequently met; yet, once a person was included, she or he could not contribute second or later observations.

Follow-up began at cohort entry and continued until the first occurrence of the following: 1) outcome of interest (defined below), 2) SCA or VA diagnosis not meeting the outcome definition, 3) death, 4) >15-day gap in therapy for the cohort-defining sulfonylurea, 5) dispensing of a sulfonylurea different than that upon cohort entry (i.e., indicative of switching within pharmacologic class), 6) dispensing of a drug with a known risk of torsade de pointes (TdP) (40), 7) disenrollment from Medicaid, or 8) the end of the data set. Follow-up time occurring during a period of hospitalization was excluded, although hospitalization did not serve as a censoring event. This exclusion served to minimize immeasurable time bias (41).

Exposure and Covariate Ascertainment

Exposure was defined by the second-generation sulfonylurea dispensed on the day of cohort entry, i.e., glimepiride, glipizide, or glyburide. We were unable to study gliclazide, as it is not marketed in the U.S. First-generation sulfonylureas were excluded from study because of scant use. For minimization of the potential for selection bias and confounding by indication and other unmeasured subject characteristics (42), no sulfonylurea-unexposed persons were included for study. Glipizide

was selected as the active comparator referent since it 1) is >100 times more selective for pancreatic than for cardiac K_{ATP} channels (20), 2) does not impact ischemic preconditioning (43), and 3) does not inhibit hERG (44). Therefore, glipizide is expected to have no direct effect on myocardial contractility. Further, glipizide may have the lowest risk of serious hypoglycemia among second-generation sulfonylureas (21) and is very commonly used.

Potential confounders included prespecified variables and those identified via empiric methods, both of which informed the PS. Prespecified variables included demographics, baseline measures of intensity of health care utilization (e.g., numbers of prescription drugs used, visits to health care providers, and hospitalizations) (45), baseline drug exposures, and baseline comorbidities. Empiric covariates included those identified during baseline via a high-dimensional approach (46,47), which ranks and selects potential confounders (or proxies thereof) based on their empirical associations with exposure and outcome. (See specifications in Supplementary Table 2.)

Outcome Ascertainment

The outcome of primary interest was an incident outpatient-originating SCA/VA event precipitating hospital presentation—consistent with our aim to study the serious arrhythmogenic effects of sulfonylureas in an ambulatory population. The rationale for using a composite outcome is that SCA events are generally considered undocumented arrhythmias (i.e., sudden and presumed arrhythmic) (48).

Outcomes were identified in emergency department or hospital claims having at least one discharge diagnosis code of interest (Supplementary Table 3) in the principal or first-listed position (indicative of the reason for presentation/admission). This algorithm—validated against primary medical records in a Medicaid population—has a positive predictive value (PPV) of ~85% for identifying outpatient-originating SCA/VA not due to extrinsic (i.e., traumatic) causes (49). The rationale for not using death certificate causes of death is that they have a poor PPV for identifying sudden death (50). The rationale for not studying inpatient-originating SCA/VA is that 1) sulfonylureas are rarely used in the inpatient setting, 2) arrhythmogenic events occurring during hospitalizations

are often attributable to causes other than ambulatory drug exposures, and 3) U.S. Centers for Medicare and Medicaid Services data, like most claims data sets, do not record inpatient drug exposures.

The outcome of secondary interest included the subset of primary events that were fatal, i.e., sudden cardiac death (SCD) or fatal VA. Operationally, this subanalysis was limited to persons dying the day of or the day after their event.

Statistical Analysis

We calculated descriptive statistics for baseline variables, incidence rates, and unadjusted association measures, the latter via Cox proportional hazards models. We used an hdPS approach—a dimension-reducing method to measure proxies for important confounder constructs (51)—to reduce the impact of measured potential confounders. However, as we wished to compare multiple sulfonylurea drugs with a common active comparator, matching on PS was impractical, and the hdPS algorithm has thus far been developed only for pairwise comparisons (47,51). We therefore used pairwise hdPS to identify potential confounders for each sulfonylurea of interest versus glipizide and included all such empirically identified variables (plus prespecified variables) in a multinomial PS model. We first used the hdPS program (47,51) to identify the 200 most prevalent diagnosis, procedure, and drug codes (excluding drug codes indicative of sulfonylurea dispensing) in each of nine data dimensions; to assess their associations with the sulfonylurea of interest versus glipizide; and to assess their associations with the outcome. We then used these associations to select the top 500 codes with the largest potential for causing confounding. Because of the large number of variables in the final multinomial PS model, empirically identified covariates did not include measures of frequency (i.e., sporadic or frequent) as generated by the hdPS program. Then, the union of all confounders arising from the two sets of 500 hdPS-identified variables (one for each sulfonylurea of interest versus glipizide) was included in the multinomial PS. Prespecified covariates included in the multinomial PS model are presented in Supplementary Table 4; we assessed conditional differences in these covariates by exposure group using weighted conditional standardized differences (52). The multinomial PSs were modeled using

multinomial logistic regression (53), generating for each subject the predicted probability of receiving each sulfonylurea. These PSs were then included in the outcome model as continuous covariates (54), along with a covariate for calendar year of cohort entry. PS-adjusted hazard ratios (HRs) and 95% CIs were calculated via Cox proportional hazards regression. Proportional hazards assumptions were examined via inclusion of an interaction term of exposure by survival time. We calculated the number needed to treat from the Cox proportional hazards regression model using an approach described by Austin (55).

Numerous prespecified and post hoc secondary analyses (Supplementary Table 5) were conducted to assess the robustness of our primary findings. Primary and secondary analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC). The research described herein was approved by the institutional review board of the University of Pennsylvania.

RESULTS

Cohort Characteristics and Outcome Frequency

We identified 519,272 incident users of a second-generation sulfonylurea; their baseline characteristics are presented in Table 1. Overall, users were predominantly female (60.3%) and Caucasian (34.9%), with a median age of 58.0 years. Large proportions of users had preexisting hypertension (58.9%), dyslipidemia (42.6%), depression (24.3%), and ischemic heart disease (21.9%). A small proportion had a preexisting cardiac conduction disorder (2.0%), implantable cardioverter-defibrillator/pacemaker use (1.0%), or a serious hypoglycemic episode (2.3%).

These individuals contributed 176,889 p-y of follow-up, during which we identified 632 SCA/VA outcomes (unadjusted incidence rate 3.6/1,000 p-y [95% CI 3.3–3.9]), 319 (50.5%) of which were fatal. See Fig. 1 for the Kaplan-Meier time-to-event plot. In the secondary analysis limited to the first 30 days of follow-up, we identified 221 SCA/VA outcomes during 38,180 p-y of follow-up (unadjusted incidence rate 5.8/1,000 p-y [5.1–6.6]). Corresponding crude incidence rates for SCD/fatal VA were 1.8/1,000 p-y (95% CI 1.6–2.0) and 3.1/1,000 p-y (2.6–3.7), respectively. These incidence rates are

Table 1—Characteristics of second-generation sulfonylurea users

	Second-generation sulfonylurea				
	Glipizide	Glimepiride	WCSD*	Glyburide	WCSD*
Users, N	219,604	97,520		202,148	
p-y of follow-up among all users, sum	75,606	32,984		68,299	
Days of follow-up per user, median (5th, 95th percentile)	55 (1, 464)	61 (1, 445)		56 (1, 446)	
Proportion of follow-up time covered by days' supply of given sulfonylurea dispensings, median (5th, 95th percentile)	88.6 (67.4, 100.0)	90.4 (67.4, 100.0)		86.8 (67.4, 100.0)	
Demographics					
Age in years at cohort entry, continuous, median (Q1–Q3)	57.8 (48.0–67.0)	58.8 (49.0–67.5)	0.05	57.8 (47.9–67.2)	0.06
Female sex, %	60.1	61.7	0.01	59.7	0.01
Race, %					
White	34.0	42.3	0.09	32.4	0.01
Black	20.8	15.1	0.05	18.3	0.03
Hispanic/Latino	23.8	18.8	0.07	25.3	0.01
Other/unknown	21.5	23.8	0.06	24.0	0.01
State of residence, %					
CA	42.6	41.7	0.07	49.6	0.08
FL	12.8	9.3	0.07	10.7	0.07
NY	27.8	27.5	0.04	26.7	0.06
OH	8.0	13.6	0.11	7.6	0.05
PA	9.0	7.9	0.05	5.5	0.07
Calendar year of cohort entry, %					
2000	7.7	6.2	0.02	7.3	0.05
2001	8.6	5.9	0.06	10.7	0.05
2002	8.8	7.0	0.04	10.7	0.04
2003	8.8	7.9	0.02	9.9	0.01
2004	7.1	7.4	0.01	8.0	0.01
2005	9.4	9.1	0.03	10.1	0.01
2006	13.9	12.8	0.04	13.1	0.01
2007	9.1	10.5	0.03	8.3	0.01
2008	7.6	9.1	0.04	6.7	0.02
2009	8.7	10.7	0.05	7.0	0.03
2010	10.2	13.3	0.09	8.2	0.05
Medicare enrolled, yes, %	50.3	52.4	0.03	47.7	0.06
Nursing home residence ever during baseline, yes, %	7.3	5.9	0.03	5.3	0.02
Health care use intensity measures in baseline period, median (Q1–Q3)**					
# prescriptions dispensed, total	34 (7–75)	49 (17–91)	0.04	30 (6–70)	0.01
# prescriptions dispensed, by unique drug	11 (4–18)	14 (7–21)	0.07	10 (4–18)	0.04
# outpatient diagnosis codes, total	29 (10–72)	37 (15–82)	0.03	26 (9–62)	0.05
# outpatient diagnosis codes, by unique code	11 (5–21)	14 (7–24)	0.07	11 (5–20)	0.09
# outpatient CPT-4/HCPCS px codes, total	34 (12–79)	44 (18–92)	0.06	31 (11–70)	0.10
# outpatient CPT-4/HCPCS px codes, by unique code	21 (8–40)	26 (12–45)	0.06	20 (8–37)	0.09
Other investigator-predefined covariates in baseline period, %					
Disorders of lipid metabolism	41.1	51.8	0.08	39.7	0.05
Rheumatic heart disease, chronic	2.5	2.7	0.02	2.2	0.01
Hypertensive disease	58.7	64.4	0.07	56.5	0.06
Ischemic heart disease	21.9	25.2	0.05	20.1	0.05
Conduction disorders	2.1	2.1	0.01	1.8	0.01
Heart failure/cardiomyopathy	14.2	14.7	0.02	12.1	0.02
Cardiomegaly	6.6	6.8	0.02	5.5	0.01
Congenital anomalies of the heart, other	1.4	1.6	0.02	1.4	0.02
Implantable cardioverter defibrillator/pacemaker use	1.1	1.3	0.01	0.9	<0.01
Kidney disease	17.5	18.9	0.03	13.5	0.03
Depression	24.2	28.2	0.03	22.5	0.01
Obesity	11.6	12.9	0.03	10.3	0.02
Tobacco use	8.6	8.8	0.01	7.2	0.02
Alcohol abuse	4.0	3.0	0.01	3.6	0.01
Hypoglycemia, serious	2.3	2.3	0.01	2.2	0.01
Type 2 DM†§	94.7	94.1	0.03	94.8	<0.01

Continued on p. 5

Table 1—Continued

	Second-generation sulfonylurea				
	Glipizide	Glimepiride	WCSD*	Glyburide	WCSD*
Other investigator-predefined covariates, 30 days prior to cohort entry, %†					
Antidiabetes drug§					
α-Glucosidase inhibitor	0.3	0.4	0.03	0.3	<0.01
Amylin analog	0.0	0.0	0.02	0.0	<0.01
Dipeptidyl peptidase-4 inhibitor	0.8	2.1	0.11	0.5	0.03
Glucagon-like peptide 1 receptor agonist	0.1	0.5	0.06	0.1	0.01
Insulin	7.3	10.3	0.10	6.6	0.03
Metformin	20.6	25.4	0.11	18.3	0.06
Meglitinide	0.8	1.9	0.10	0.8	0.01
Sodium–glucose cotransporter 2 inhibitor§§	—	—	—	—	—
Thiazolidinedione	7.6	12.9	0.17	6.7	0.04
CYP2C9 inhibitor	5.0	5.0	0.01	4.8	0.01
CYP3A4 inhibitor	4.8	5.1	0.01	4.6	<0.01
CYP2C9 inducer	1.0	1.0	0.01	0.9	<0.01
CYP3A4 inducer	5.8	8.9	0.04	5.3	<0.01
Drug with known risk of TdPll	8.9	10.3	0.02	7.9	0.01
Drug with known, possible, or conditional risk of TdPll	38.9	43.6	0.04	35.9	0.01
≥5 prescription dispensings for unique drugs, a potential indicator of polypharmacy§	38.8	47.3	0.17	35.6	0.07

CPT-4, Current Procedural Terminology-4; CYP, hepatic cytochrome P450; HCPCS, Healthcare Common Procedure Coding System; px, procedure; Q, quartile; WCSD, weighted conditional standardized difference. *Versus glipizide. **The following health care use covariates were excluded from presentation in the table, as their median values were 0 for each sulfonylurea: # inpatient ICD-9 diagnosis codes, # unique inpatient ICD-9 diagnosis codes, # inpatient ICD-9 procedure codes, # unique inpatient ICD-9 procedure codes, # inpatient Current Procedural Terminology-4/Healthcare Common Procedure Coding System procedure codes, # unique inpatient CPT-4/HCPCS procedure codes, # outpatient ICD-9 procedure codes, # unique outpatient ICD-9 procedure codes, # other setting ICD-9 diagnosis codes, # unique other setting ICD-9 diagnosis codes, # other setting ICD-9 procedure codes, and # unique other setting ICD-9 procedure codes. †Antimicrobial drugs within each category were examined within 14 (rather than 30) days prior to cohort entry; these agents are typically prescribed for acute rather than chronic conditions. ‡Defined by ratio of type 1 (ICD-9 250.X1 or 250.X3) to type 2 (ICD-9 250.X0 or 250.X2) codes ≤0.5, ascertained during baseline and on cohort entry date (78,79). §Predefined covariate not forced into PS; therefore, standardized differences are presented in the WCSD columns. §§Not marketed during years of study. ||Per CredibleMeds.

similar to prior findings in persons with DM (56).

Measures of Association: Primary Analysis

The multinomial PS model included 537 covariates—99 predefined (Supplementary Table 4) and 438 empirically identified by the hdPS algorithm (Supplementary Table 6). Crude HRs are presented in Table 2; PS-adjusted HRs are presented in Table 2 and Fig. 2. Notably, glyburide was associated with a lower rate of SCA/VA than glipizide (adjusted HR 0.82 [95% CI 0.69–0.98]).

Measures of Association: Secondary Analyses

Secondary analyses (Supplementary Table 5) had point estimates (Table 3) very similar to the primary finding for glyburide (vs. glipizide) and SCA/VA. The following four analyses had 95% CIs excluding the null value: exclusion of empirical covariates from the PS thought to be instrumental variables (adjusted HR 0.82 [95% CI 0.68–0.98]), exclusion of persons with an any-claim type, or any-position

diagnosis of SCA or VA ever prior to cohort entry (0.82 [0.68–0.99]), censoring follow-up time upon a pregnancy diagnosis (0.88 [0.68–0.98]), and exclusion of persons with baseline enrollment in Medicaid managed care (0.65 [0.46–0.92]). The following three analyses had 95% CIs including the null value: limiting maximum follow-up time to 30 days (adjusted HR 0.82 [0.60–1.12]), decreasing the permissible grace period between contiguous sulfonylurea dispensings (0.83 [0.68–1.02]), and increasing the permissible grace period between contiguous sulfonylurea dispensings (0.88 [0.75–1.03]). No obvious trends were identified in dose-response relationship analyses (Supplementary Fig. 1). No effect modification analyses met the traditional threshold for statistical significance (Table 3).

Results for the secondary outcome, SCD/fatal VA, were similar for both follow-up periods (i.e., overall [Fig. 2] and within the first 30 days); adjusted HRs for glyburide (vs. glipizide) were 0.89 (95% CI 0.69–1.14) and 0.79 (0.52–1.21), respectively. Results from secondary

analyses of the secondary outcome are detailed in Table 3.

CONCLUSIONS

This comparative safety study examined the risk of serious arrhythmia among users of different sulfonylureas, providing data on a clinically and biologically relevant end point that will not be forthcoming from ongoing clinical trials designed and powered to examine major adverse cardiovascular events (including cardiovascular death) and related composites. We found that glyburide was associated with an 18% reduction (95% CI 2–31) in SCA/VA risk compared with glipizide, a sulfonylurea thought to have no direct action on the myocardium. This result was broadly consistent across numerous preplanned and post hoc secondary analyses, although not all such findings met the traditional threshold for statistical significance. If this association represents a true causal effect, one SCA/VA event would be prevented for every 1,804 (840–9,482) patients treated with glyburide (vs. glipizide) for 1 year. This number needed to treat

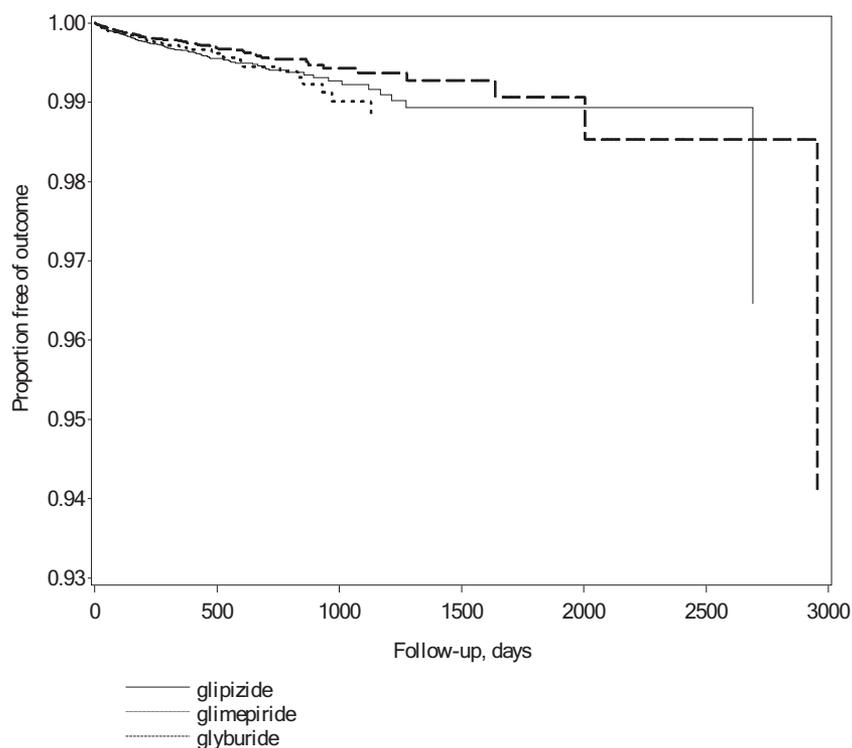


Figure 1—Time-to-event plot for SCA/VA by sulfonylurea. Solid black line, glipizide; dotted black line, glimepiride; dashed black line, glyburide.

reflects a very modest effect size. This could partly explain, for example, why trials like Bypass Angioplasty Revascularization Investigation 2 Diabetes (32) had large

differences in sulfonylurea use between study arms and yet no differences in survival.

Our findings are important for several reasons. Persons with type 2 DM are

inherently at an increased baseline risk for sudden death, driven by complex interplay among putative mechanisms such as silent myocardial ischemia, autonomic dysfunction, QT interval prolongation, increased QT dispersion, hypoglycemia, hypercoagulable states, cardiomyopathy, and a decreased ventilatory response (4). Further, the public health impact is substantive; each day nearly 275 persons with DM die of a sudden death in the U.S. alone. Therefore, an important goal is to reduce SCA risk among persons with DM by risk factor reduction and tailoring of prescription therapies (9). Our results demonstrate that clinicians may be able to tailor sulfonylurea therapy to minimize the risk of SCA/VA in their patients with type 2 DM.

Our findings extend those of small experimental studies in persons with type 2 DM. In 80 digoxin-treated persons with type 2 DM, Pogátsa et al. (57) demonstrated an explicit antiarrhythmic effect of glyburide, evidenced by a reduction in ventricular ectopic beats. In 19 persons with type 2 DM, Cacciapuoti et al. (58) demonstrated that glyburide reduced both the frequency of ventricular premature complexes and episodes of nonsustained ventricular tachycardia during transient myocardial ischemia. Lomuscio et al. (59) found glyburide to reduce

Table 2—Outcomes and measures of association for the primary analysis

	Second-generation sulfonylurea		
	Glipizide	Glimepiride	Glyburide
Outcomes during follow-up period			
SCA/VA outcomes, <i>N</i>	304	127	201
SCA outcomes	211 (69.4)	94 (74.0)	146 (72.6)
Ventricular arrhythmia outcomes	72 (23.7)	*	35 (17.4)
Both outcomes (contemporaneously)	21 (6.9)	*	20 (10.0)
SCA/VA outcomes immediately preceded by hospitalization for acute ischemic event	*	*	*
SCA/VA outcomes immediately preceded by emergency department presentation or hospitalization for hypoglycemia	*	*	*
Measure of SCA/VA occurrence, incidence rate (95% CI)			
Unadjusted, per 1,000 p-y	4.0 (3.6–4.5)	3.9 (3.2–4.6)	2.9 (2.6–3.4)
Age and sex standardized, per 1,000 p-y**	4.3 (3.8–4.9)	4.0 (3.3–4.7)	3.2 (2.7–3.6)
Relative measures of association for SCA/VA, HR (95% CI)§			
Unadjusted†	1.00 (reference)	0.95 (0.77–1.17)	0.73 (0.61–0.87)
hdPS adjusted‡ (also see ■ in Fig. 2)	1.00 (reference)	1.10 (0.89–1.36)	0.82 (0.69–0.98)

Data are *N* (%) unless otherwise indicated. *Omitted in compliance with Centers for Medicare and Medicaid Services data privacy policy (i.e., cell count <11 or allows back calculation of a cell in which count <11). **Direct standardization using age-by-sex distribution of sulfonylurea users identified in 2006–2010 National Ambulatory Medical Care Survey (Centers for Disease Control and Prevention, Atlanta, GA). †Test for nonproportional hazards, $P = 0.73$; did not meet the traditional threshold for statistical significance. ‡Test for nonproportional hazards, $P = 0.75$; did not meet the traditional threshold for statistical significance. §After hdPS adjustment, the HR for glimepiride moved away from the null value of 1.0. This may seem counterintuitive, since glimepiride users have more comorbidities compared with users of glyburide and glipizide (see Table 1). Yet, by the nature of this, glimepiride users may have more negative risk factors for SCA/VA. For example, given that more glimepiride users had hypertension and a lipid disorder, they may have been more likely to receive antihyperlipidemic and antihypertensive drugs, thereby reducing cardiovascular disease risk. Glimepiride users were also more likely to have an implantable cardioverter defibrillator/pacemaker. Finally, increased use of ambulatory care services among glimepiride users could suggest more extensive preventive care. Therefore, adjustment for such negative risk factors might be expected to increase the HR.

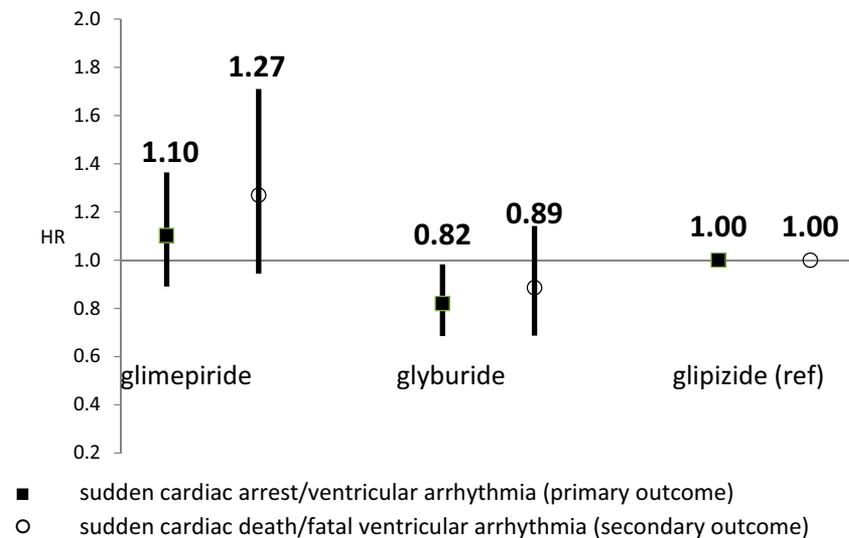


Figure 2—hdPS-adjusted HRs for association between sulfonylurea exposure and primary and secondary outcomes. Model includes adjustment for PS and calendar year of cohort entry. ref, reference. (A high-quality color representation of this figure is available in the online issue.)

ventricular fibrillation during acute ischemic events in 106 persons with type 2 DM. In 19 patients with type 2 DM and heart failure, Aronson et al. (60) found that glyburide reduced mean hourly paired ventricular ectopic beats, mean hourly repetitive ventricular beats, and the daily frequency of ventricular tachycardia. To our knowledge, the only epidemiologic study other than our own was a cohort study of 745 persons with type 2 DM post-myocardial infarction (MI) within an Australian cardiovascular registry that found numerically lower yet nonsignificant differences in rates of ventricular tachycardia (multivariate odds ratio [OR] 0.83) and ventricular fibrillation (OR 0.53) with glyburide versus gliclazide (61). Our study is nearly 700 times larger, examined SCA and VA, was not limited to the post-MI setting, and more adequately addressed confounding (i.e., adjusted for 537 predefined and hdPS-identified covariates vs. 10 predefined covariates). Use of hdPS methods results in improved effect estimates compared with adjustment limited to predefined covariates when benchmarked against results expected from randomized trials (46).

At first glance, despite being buttressed by the studies discussed above, our findings may seem counterintuitive and therefore unexpected. Glyburide has putative proarrhythmogenic effects that may be mediated by 1) serious hypoglycemia, 2) increased cardiac excitability, and/or 3) attenuated or abolished ischemic

preconditioning. Regarding the first, hypoglycemia has been associated with QT prolongation (4), with glyburide carrying the greatest risk of serious hypoglycemia among second-generation sulfonylureas (21). Regarding the second, glyburide has been shown to inhibit hERG, prolong the QT interval, and increase QT dispersion (62–64). Despite this, glyburide is not considered to have TdP risk (40). Regarding the third, glyburide's blockade of cardiac K_{ATP} channels may drastically minimize the body's natural protective response to limit infarct size and reduce myocardial stunning in the setting of acute ischemia; this antagonism may propagate arrhythmias caused by delayed afterdepolarizations (19). Yet, this blockade may also prevent re-entrant arrhythmias (via prevented shortening of the action potential duration) (19), a major cause of fatal early arrhythmias (65). Interestingly, recent reviews have suggested that the multiple facets of ischemic preconditioning are not coupled, such that the mechanisms that minimize infarct size may be distinct from those influencing arrhythmia (66,67). Therefore, even if glyburide's blockade of cardiac K_{ATP} channels completely abolishes ischemic preconditioning, there may be no attenuation of its ability to reduce ventricular fibrillation (68). Our findings may be consistent with this mechanism.

Our study has notable strengths. It is the first population-based study to examine the association between individual

sulfonylureas and SCA/VA. Such results will not be forthcoming from ongoing trials, and a trial is unlikely to be conducted in the future (43,69). Further, our algorithm to identify the outcome of interest was developed and validated in the population used within and has a very good PPV. Finally, our use of an active comparator reference exposure, hdPS methods, and secondary analyses served to mitigate confounding.

Our study also has limitations. First, despite our cohort building, confounder identification, and statistical modeling approaches, there may still be differences among users of individual sulfonylureas that account for the associations with SCA/VA described herein. Second, we did not have access to biosamples and were therefore unable to examine genetic determinants of SCA/VA risk. Third, information on family history of diseases was underascertained, as such information was captured only if diagnostically coded. Fourth, we lacked data on direct adherence to sulfonylurea therapy. To address this, we conducted secondary analyses in which we modified the allowable grace period between contiguous prescriptions. Fifth is the potential for incomplete ascertainment of SCA/VA and SCD/fatal VA outcomes. For example, because this study relied solely upon emergency department and inpatient diagnoses, it would have missed fatal events that did not result in presentation to a hospital. However, prior work suggests that 69–80% of persons experiencing an out-of-hospital cardiac arrest (70,71) and up to 88% of persons experiencing a witnessed ventricular tachycardia survive to hospital admission (72), although literature estimates do vary by year and patient age (73). Furthermore, trends suggest that survival until hospital admission among such persons is increasing over time (74). An approach by which out-of-hospital events could be captured, via use of death certificate diagnoses alone, has been shown to have a poor PPV for identifying SCA/VA (50,75,76). Sixth, while point estimates from primary and secondary analyses were generally congruous, findings from some secondary analyses no longer met the traditional threshold for statistical significance; this could result from loss of power and/or indicate no differences in SCA/VA hazards among sulfonylureas under study. Seventh, our study did not simultaneously consider other major clinical outcomes

Table 3—Summary of findings from prespecified and post hoc secondary analyses

Analysis*	Results†
Limiting maximum follow-up time to 30 days	<i>N</i> = 519,272; glyburide aHRs 0.82 (95% CI 0.60–1.12) and 0.79 (0.52–1.21) for SCA/VA and SCD/fatal VA, respectively, and glimepiride, aHRs 1.38 (0.98–1.95) and 1.39 (0.86–2.22) for SCA/VA and SCD/fatal VA
Decreasing permissible grace period between contiguous sulfonylurea dispensings from 15 days to 7 days	<i>N</i> = 519,272; glyburide aHRs 0.83 (0.68–1.02) and 0.88 (0.66–1.16) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 1.10 (0.87–1.40) and 1.26 (0.90–1.75) for SCA/VA and SCD/fatal VA
Increasing permissible grace period between contiguous sulfonylurea dispensings from 15 days to 30 days**	<i>N</i> = 519,272; glyburide aHRs 0.88 (0.75–1.03) and 0.88 (0.68–1.13) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 1.06 (0.87–1.29) and 1.27 (0.94–1.71) for SCA/VA and SCD/fatal VA
Exclusion of persons with baseline enrollment in Medicaid managed care	<i>N</i> = 282,466; glyburide aHRs 0.65 (0.46–0.92) and 0.78 (0.37–1.61) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 0.88 (0.60–1.30) and 1.67 (0.79–3.52) for SCA/VA and SCD/fatal VA
Exclusion of persons with an any-claim type, or any-position diagnosis of SCA or VA ever prior to cohort entry**	<i>N</i> = 510,981; glyburide aHRs 0.82 (0.68–0.99) and 0.91 (0.70–1.18) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 1.13 (0.91–1.40) and 1.36 (1.00–1.84) for SCA/VA and SCD/fatal VA
Censoring follow-up time upon a pregnancy diagnosis**	<i>N</i> = 519,272; glyburide aHRs 0.88 (0.68–0.98) and 0.88 (0.69–1.14) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 1.11 (0.89–1.37) and 1.27 (0.94–1.71) for SCA/VA and SCD/fatal VA
Exclusion of empirical covariates from the PS thought to be strong correlates of exposure but not associated with the outcome	<i>N</i> = 519,272; glyburide aHRs 0.82 (0.68–0.98) and 0.88 (0.68–1.13) for SCA/VA and SCD/fatal VA, respectively, and glimepiride aHRs 1.10 (0.89–1.36) and 1.25 (0.93–1.68) for SCA/VA and SCD/fatal VA
Limiting outcomes to fatal events	<i>N</i> = 519,272; glyburide aHR 0.89 (0.69–1.14) for SCD/fatal VA, and glimepiride aHR 1.27 (0.94–1.71) for SCD/fatal VA
Examining sulfonylurea dose-response relationships and limiting maximum follow-up time to 90 days	See Supplementary Fig. 1
Examining effect modification by drugs that inhibit hepatic CYP450-based metabolism of sulfonylureas	
CYP2C9 inhibitors	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.75), stratified results are not presented
CYP3A4 inhibitors	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.26), stratified results are not presented
Examining effect modification by drugs that have a “known risk of TdP”	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.65), stratified results are not presented
Examining effect modification by drugs that have a “known,” “possible,” or “conditional risk of TdP”	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.17), stratified results are not presented
Age-group	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.28), stratified results are not presented
Sex	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.93), stratified results are not presented
Race	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.29), stratified results are not presented
Nursing home residence	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.64), stratified results are not presented
Ischemic heart disease	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.77), stratified results are not presented
Conduction disorders	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.97), stratified results are not presented
Heart failure/cardiomyopathy	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.38), stratified results are not presented
Kidney disease**	As the <i>P</i> value for the interaction term was nonsignificant (<i>P</i> = 0.77), stratified results are not presented

aHR, PS-adjusted HR; CYP, hepatic cytochrome P450; *N*, number of sulfonylurea users under study. *Rationale detailed in Supplementary Table 5. **Post hoc analysis. †Comparison vs. glipizide.

relevant to type 2 DM, such as nonarrhythmic cardiovascular end points (e.g., MI), cerebrovascular end points, all-cause death, and serious hypoglycemia. Finally, our results may not be generalizable beyond a U.S. Medicaid population. Nevertheless, this population was specifically

chosen because of its inherent vulnerability and inclusion of large numbers of women and minorities—groups typically understudied. Further, biological associations identified in Medicaid populations are often replicated in commercially insured populations and vice versa (77).

Conclusion

This nonexperimental comparative safety study is the first to examine differences in the rate of SCA/VA among users of different sulfonylureas, the most commonly used second-line pharmacologic therapy for type 2 DM. Data on this topic are of

public health import and are severely lacking; it will not be investigated by GRADE or CAROLINA, and was only examined as a component of a composite secondary outcome by TOSCA.IT. We found that glyburide may be associated with an 18% reduction in SCA/VA risk compared with glipizide. This finding is consistent with small clinical studies in humans demonstrating antiarrhythmic properties of glyburide, particularly in settings of acute ischemia. A clinician with a desire to treat a patient with type 2 DM with a sulfonylurea may wish to consider glyburide's potential ability to reduce the risk of serious arrhythmia—surely to be considered along with its increased rate of serious hypoglycemia versus other sulfonylureas and its debated effects on other cardiovascular end points (including cardiovascular death), cerebrovascular end points, and all-cause death.

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Author Contributions. C.E.L. formulated the research question. C.E.L. and S.H. designed the study. C.M.B. and W.B.B. analyzed data. C.M.B., W.B.B., and J.J.G. provided analytic tools. C.E.L., C.M.B., C.L.A., W.B.B., D.M.B., R.D., J.H.F., J.J.G., M.J.M., and S.H. were involved in data interpretation. C.E.L. drafted the manuscript. C.E.L., C.M.B., C.L.A., W.B.B., D.M.B., R.D., J.H.F., J.J.G., and S.H. critically revised the manuscript. S.H. secured funding for the study and acquired data. C.E.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the

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