Sulfonylurea is associated with higher risks of ventricular arrhythmia or sudden cardiac death compared to metformin: a population-based cohort study

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Abstract

Background: Commonly prescribed diabetic medications such as metformin and sulfonylurea may be associated with different arrhythmogenic risks. This study compared the risk of ventricular arrhythmia or sudden cardiac death (VA/SCD) between metformin and sulfonylurea in patients with type 2 diabetes.

Methods: Patients aged 40 years or older who were diagnosed with type-2 diabetes mellitus or prescribed anti-diabetic agents in Hong Kong between 1st January 2009 and 31st December 2009 were included and followed up till 31st December 2019. Patients prescribed with both metformin and sulfonylurea or had prior myocardial infarction were excluded. The study outcome was a composite of VA/SCD. Metformin users and sulfonylurea users were matched at a 1:1 ratio by propensity score matching.

Results: The study cohort consisted of 5756 metformin users (48.00% male, age 68±11 years, mean follow-up 5.04±2.57 years) and 5756 sulfonylurea users (50.30% male, age 69±11 years, mean follow-up 5.04±2.54 years). Sulfonylurea was associated with higher risk of VA/SCD than metformin (hazard ratio 1.84 [1.56 - 2.16], p<0.001). Such difference was consistently observed in subgroup analyses stratifying for insulin usage or known coronary heart disease.

Conclusion: Sulfonylurea use is associated with higher risk of VA/SCD than metformin in patients with type 2 diabetes.

Introduction

Type 2 diabetes mellitus is a highly prevalent condition worldwide, with 1 in 11 adults suffering from it globally. Every year, type 2 diabetes mellitus alone causes over 1 million deaths, making it the ninth leading cause of mortality (1). Cardiovascular complications are significantly associated with death among type 2 diabetes patients (2), with ventricular arrhythmia and sudden cardiac death (VA/SCD) as the most common macrovascular complications (3). Siscovick and colleagues estimated the incidence rate of sudden cardiac arrest to be 3.15 per 1000 diabetic patients without prior clinically-recognized heart disease; and the incident rate was 13.80 per 1000 diabetic patients with clinically-recognized heart disease, 3.84 and 2.31 times higher when compared with non-diabetic patients respectively (4). The elevated risk can be attributed to a poor glycemic control and other risk factors such as dyslipidemia and nephropathy (4).

Metformin and sulfonylurea were frequently prescribed because of their effective glycemic control and low cost even though their cardiovascular risks continue to be debated (5). The choice of antidiabetic medications on atrial fibrillation has been well documented (6, 7), yet not many studies investigated the effect of such medications on the risk of VA/SCD, let alone the comparison between metformin and sulfonylurea use. There is a need for the above investigation as sudden cardiac death, the most devastating manifestation of VA, is the leading cause of death among type 2 diabetes patients with cardiovascular complications (8).

Therefore, this study aimed to compare the risk of developing VA/SCD between metformin and sulfonylurea users.

Methods

Data Source

This study has been approved by The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. This was a population-based retrospective cohort study. Data was extracted from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic database storing patient healthcare records managed by the Hong Kong Hospital Authority, which manages 42 hospitals, 47 Specialist Out-patient Clinics, and 73 General Out-patient Clinics; serving a population of 7 million. This database has previously been used for cohort studies by other teams in Hong Kong (9, 10). Informed consent was not required from patients as the data used in this study were anonymized.

Study Cohort

Patients who fulfilled all of the following inclusion criteria were included: 1) aged 40 years or older; 2) had documented diagnosis of type 2 diabetes mellitus under the International Classification of Diseases, Ninth Revision (ICD-9) coding system, or prescribed anti-diabetic agents between January 1st, 2009, to December 31st, 2009. Patients who were prescribed both metformin and sulfonylurea or had past medical history of myocardial infarction , as identified using ICD-9 codes, were excluded from the study.

Outcomes

The primary outcome of the study is a composite of ventricular arrhythmia and sudden cardiac death (VA/SCD), as identified using ICD-9 codes. A diagnosis of VA/SCD was made based on clinical judgment by the treating physician and was then coded according to the ICD-9 system into CDARS. VA/SCD episodes where a MI occurred within 1 week before or after the VA/SCD episode were considered AMI-related and thus excluded. Patients were followed up till December 31st 2019.

Propensity Score Matching

To ensure comparability of the cohorts, propensity score matching was performed with the baseline demographics of gender, age, and duration since type 2 diabetes diagnosis; prior comorbidities including peripheral vascular disease, ischemic stroke, atrial fibrillation, heart failure, prior VA/SCD, intracranial hemorrhage, coronary heart disease, hypertension and chronic obstructive pulmonary disease; baseline medication use including ACE inhibitors, beta blockers, calcium channel blockers, diuretics, and use of diabetic medications including insulin, thiazolidinediones, dipeptidyl-peptidase 4 (DPP4) inhibitors and glucagon-like peptide (GLP-1) agonists; and laboratory tests including serum levels of high density lipoprotein, low density lipoprotein, triglycerides, and HbA1c. The ICD-9 codes used for classification of the corresponding medical conditions are available in Supplementary Table 1.

Imputation was not performed as patients with missing data were excluded during the generation of the matched cohort. Patients with use of either metformin or sulfonylurea were matched on a 1:1 ratio on the propensity score which was derived from logistic regression using the nearest-neighbor matching algorithm. To assess the balance of covariates, the standardized mean difference (SMD), which is the difference in means or proportions over the pooled standard deviation (SD) was used for categorical covariates, while the variance ratio (VR), which is the ratio of variance between the treatment and control groups was used for both categorical and continuous covariates. A caliper width of 0.2 was chosen as it is considered as the optimal caliper width for estimating mean differences (11). Covariates were considered balanced in both groups when the standardized mean difference was less than 0.1, and when the VR lied between the range of 0.5 and 2.0 (12, 13).

Statistical Analysis

Continuous variables were presented as the mean (Standard deviation [SD]) and categorical variables were presented as frequency (%). Hazard ratios (HRs), along with 95% CIs and P-values were reported accordingly with the Cox proportional hazards regression model. Kaplan-Meier curves were plotted against the time-to-event for VA/SCD stratified by either metformin or sulfonylurea use. The log-rank test was performed to investigate the statistical significance between metformin and sulfonylurea groups. Incidence rates for VA/SCD were presented as incidence per 1000 person-years along with 95% CIs. Subgroup analyses were conducted to investigate the risk of VA/SCD by users versus nonusers of insulin and patients with versus without prior coronary heart disease, and by different types of sulfonylurea. Sensitivity analysis was performed by excluding patients with prior cardiomyopathy or valvular disease. Computed E-values for HRs were computed to assess the effects of any unmeasured confounding on our study. The E-value is defined as the minimum strength of association that an unmeasured confounder would require to have with both the outcome and treatment to fully explain away a specific association between the treatment and outcome, conditional on the measured covariates (14). In this study, a large E-value implies that an unmeasured confounder must be very strong to explain away the effect of sulfonylurea over metformin use in the risk of developing VA/SCD.

All significance tests were two-tailed and considered significant when $P < 0.05$. No imputation was performed for missing data. Statistical analyses were conducted using RStudio 1.4.1717 (RStudio, Boston, Massachusetts).

Results

The steps for the selection of patients for this study cohort are shown in **Figure 1**. In total, 261,308 patients fulfilled the inclusion criteria. After excluding patients with missing data, the study cohort consisted of 15,158 patients (46.7% male, mean baseline age: 68 ± 11 years old), where 8,542 (22.41%) patients received metformin and 6,616 (17.35%) patients received sulfonylurea. After 1:1 propensity score matching, the final study cohort consisted of 5,756 metformin users and 5,756 matched sulfonylurea users. The baseline and clinical characteristics of the study population before and after propensity score matching were shown in **Table 1**. A Love plot summarizing covariate balances before and after propensity score matching is provided in **Supplementary Figure 1**. SMD values were less than 0.1 and VR values were within 0.5-2.0, indicating a good balance in baseline characteristics between the two cohorts; the only exception was age, which had a SMD of 1.1, but the VR value was 1.07 which was very close to 1.0, indicative of good balance (15).

The main and subgroup analysis of VA/SCD risk were presented in **Table 2**. The mean follow-up duration was 5.08±2.56 years for the metformin cohort, and 5.01±2.54 years for the sulfonylurea cohort. During the study period, 229 metformin users and 415 sulfonylurea users exhibited episodes of VA/SCD. Cox proportional hazards model analyses over the entire follow-up showed that sulfonylurea use was associated with an overall higher risk of VA/SCD than metformin use (HR: 1.84 [95% CI, 1.56 - 2.16], p<0.001), as visualized by the Kaplan-Meier curves in **Figure 2**.

Subgroup analyses were performed by sulfonylurea type, concurrent use of insulin, and the presence of coronary heart disease **(Table 2)**; sensitivity analysis was performed by excluding patients with either valvular heart disease or cardiomyopathy **(Table 3)**. Baseline characteristics of the subgroups are summarized in **Supplementary Tables 2 to 4**. Sulfonylurea was consistently associated with a higher risk of VA/SCD in patients without a history of valvular heart disease or cardiomyopathy (HR: 1.87 [1.57-2.23], p<0.001), and in both insulin users (HR: 1.65 [1.21 - 2.24], p=0.001) and non-users (HR: 1.89 [1.56 - 2.29], p<0.001). Similarly, sulfonylurea use was associated with higher risks of VA/SCD across those with (HR: 1.67 [1.17 - 2.38], p=0.004) and without (HR: 1.86 [1.55 - 2.23], p<0.001) coronary heart disease. The corresponding E-values for the point estimates of sulfonylurea versus metformin among the overall cohort, among patients without prior cardiomyopathy or valvular disease, those with insulin use, without insulin use, with coronary heart disease, and without coronary heart disease in the HR scale were 3.08, 3.15, 2.69, 3.19, 2.72, and 3.12 respectively.

The risk of VA/SCD between individual types of sulfonylurea are shown in **Table 3**. Both tolbutamide (HR: 5.01 [3.20-7.83], p<0.001) and glicazide (HR: 1.75 [1.46-2.10], p<0.001) were significantly associated with a higher risk of VA/SCD. The corresponding E-values were 9.49 and 2.90 respectively.

Discussion

The main finding of this study is that sulfonylurea users have a higher risk of ventricular arrhythmia and sudden cardiac death than metformin users. These results were consistent irrespective of severity of diabetes or history of coronary heart disease.

Mechanism underlying the observations

It is hypothesized that sulfonylurea may inhibit the delayed rectifier potassium channel, leading to prolonged QT interval (16). A trial conducted in 30 type 2 diabetes patients found that patients randomized to glyburide were associated with an increase in corrected QT interval (QTc) compared to patients randomized to metformin (17). Sulfonylurea carries a high risk of hypoglycemia compared to other antidiabetic medications (18), in turn prolonging action potentials in myocardial tissue by blocking potassium channels at the cellular level (19). Multiple studies found that severe hypoglycemia, a major concern of sulfonylurea, increased the risk of VA/SCD (20-22). However, sulfonylurea may also have anti-arrhythmic effects by inhibiting reentrant arrhythmias by a mechanism known as ischemic preconditioning (IPC), and thus reducing the risk of developing cardiac arrest (16), but it has been suggested that the effects of IPC are abolished in type 2 diabetes (23). Metformin has pleotropic effects with many cardiovascular benefits as shown in basic science studies (24, 25); it was found to be associated with a decreased QTc in animal models (26, 27), but no decrease in ventricular arrhythmic outcomes were reflected in clinical trials (28).

Comparison with previous observational studies

Two recent observational studies have investigated the association between metformin and sulfonylurea use and risk of VA/SCD (29, 30). Ostropolets and colleagues found that diabetic patients on metformin monotherapy had a reduced risk of VA compared to sulfonylurea monotherapy (29). However, patients with a history of atrial fibrillation, ventricular tachycardia and ventricular fibrillation were excluded from their study, so their results may not be generalizable to patients with prior arrhythmic conditions. Moreover, younger type 2 diabetes patients were not captured as only patients above the age of 50 were included in their study, which may lead to biased results. A recent systematic review has shown that type 2 diabetes is increasingly diagnosed in patients under the age of 50 in many countries worldwide (31). Our study included type 2 diabetes patients aged 40 or above, which may be more generalizable to a larger population.

Conversely, Eroglu and colleagues found that sulfonylurea antidiabetics were associated with a lower risk of developing out-of-hospital cardiac arrest (30). However, their study did not match cases and controls by duration of diabetes, which is a risk factor for ventricular arrhythmias (4). The duration of diabetes was accounted for during propensity score matching in our study. Moreover, age was not evenly distributed in their study groups, as patients on sulfonylurea drugs alone were older (mean age: 75.2, SD: 9.7) than those on metformin alone (mean age: 69.6, SD: 10.1). Finally, their sample size was small for both patients on sulfonylurea alone (N=215) and patients on metformin alone (N=385), while our study included 5756 metformin users and 5756 sulfonylurea users after matching.

Implications of subgroup and sensitivity analyses

Sensitivity analysis was performed by excluding patients with a history of cardiomyopathy or valvular heart disease, as cardiomyopathies are a common cause of SCD (32, 33); a systematic review identified cardiomyopathies as one of the top causes of SCD in Chinese patients (34). Similarly, studies have found associations of aortic valve disease and mitral valve prolapse with VA/SCD (35-38). It was found that the risk for sulfonylurea compared to metformin to develop VA/SCD was similar in both sensitivity and overall analysis.

Common complications of type 2 diabetes include coronary artery disease and myopathy (39), which are risk factors for developing VA/SCD (40). The risk for these complications increases with the duration and severity of type 2 diabetes, which is consistent with the underlying low-grade inflammation and glycation (41, 42). As such, it was possible that the risk of VA/SCD increases with the duration and severity of diabetes, and the influence from medication-related effects may become less important accordingly. To better elucidate drug-related effects and minimize confounding by the above factors, we performed a subgroup analysis using insulin usage as a surrogate of diabetic duration and severity. We found that sulfonylurea was consistently associated with greater risk of developing VA/SCD than metformin regardless of diabetes severity, suggesting that the differences between these two drugs are clinically important in diabetic patients regardless of their condition's severity and duration.

Myocardial ischemia in coronary heart disease alters metabolic and electrical processes in the heart, altering the propagation and conduction of resting and acting membrane potentials, leading to cardiac arrhythmias (43). We performed subgroup analyses to explore if coronary heart disease would be a dominant risk factor for VA/SCD such that the differences in arrhythmogenicity between sulfonylurea and metformin would be considered relatively insignificant. The results of the subgroup analyses found the risk of developing VA/SCD was consistently higher in metformin users compared to sulfonylurea users even in patients with coronary heart disease. This further suggested that the differences in arrhythmogenicity between the two drugs were significant and clinically important regardless of patients' inherent risks for VA/SCD.

Subgroup analyses were performed to investigate the risk of VA/SCD among individual types of sulfonylurea. Only glicazide and tolbutamide users were statistically significant for the risk of VA/SCD when compared to metformin. Tolbutamide users were at a higher risk of VA/SCD, but this may be attributed to a higher usage of pro-arrhythmic calcium channel blockers and beta blockers in the subgroup (44).

Clinical implications

Our study has important clinical implications. Although the use of sulfonylurea has decreased in recent years, it remains a commonly prescribed antidiabetic agent, second to metformin (45, 46). Diabetic nephropathy is a common complication

among type 2 diabetes patients with a prevalence of 31.6% in Hong Kong (47). When metformin is contraindicated, such as in patients with severe kidney impairment, sulfonylurea is a viable alternative (48, 49). The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines recommends patients with an estimated glomerular filtration rate of ≤30 mL/min/1.73 m^2 to discontinue metformin therapy (48, 50) However, in practice, the risk of developing VA/SCD by antidiabetic choice is often neglected. Aside from increased mortality risk, VA/SCD necessitates further therapy such as the use of implantable cardioverter-defibrillators and antiarrhythmic agents and thereby imposes more healthcare burden (51, 52). Patient adherence to metformin may be difficult due to the common side effect of gastrointestinal disturbance (53), but this can be avoided with alternative formulations such as extended-release metformin (54). Given the findings of our study, there exists a compelling case to move away from prescribing sulfonylurea for glycemic control.

Study limitations

This study has limitations. As this study was retrospective in nature, the effect of unmeasured confounders on the risk of developing VA/SCD cannot be ruled out. For instance, smoking status and alcohol consumption are not recorded by CDARS. Nonetheless, we have included multiple significant risk factors in the propensity score matching. Furthermore, the E-value suggested that the observed association of the higher VA/SCD risk in sulfonylurea over metformin users would only be insignificant if an unmeasured risk factor exists with an HR of 2.69 to 3.12, which is realistically unlikely.

Recent studies have shown that the risk of VA/SCD differed by choice of sulfonylurea (55-58). Further research comparing risk of VA/SCD between different drugs of the sulfonylurea class is warranted, such that clinicians can avoid choosing sulfonylurea with high arrhythmogenic risk.

To conclude, this study found that among patients diagnosed with type 2 diabetes, use of sulfonylurea was associated with higher risk of developing VA/SCD compared to use of metformin. The increased risk was consistent in patients with severe diabetes and in those with a history of coronary heart disease. Hence, the use of sulfonylurea should be reconsidered in patients at risk of VA/SCD. Further studies are warranted to study the risk of VA/SCD in different drugs of the sulfonylurea class.

Abbreviations

ACE: Angiotensin-converting enzyme

CI: Confidence interval

CDARS: Clinical Data Analysis and Reporting System

DPP4: Dipeptidyl-peptidase 4

GLP-1: Glucagon-like peptide 1

HR: Hazard ratio

ICD-9: International Classification of Diseases, Ninth Revision

IPC: Ischemic preconditioning

KDIGO: Kidney Disease: Improving Global Outcomes

QTc: Corrected QT interval

SCD: Sudden cardiac death

SD: Standard deviation

SMD: Standardized mean difference

T2DM: Type-2 diabetes mellitus

VA: Ventricular arrhythmia

VR: Variance ratio

Declarations

Ethics approval and consent to participate

This study has been approved by The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee. Study data was anonymized in this study; thus consent of study patients was not acquired.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

None.

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None.

Author’s contributions

T.T.L.L., J.S.K.C., and G.T. conceived the initial study. T.T.T.L. performed data analyses. T.T.T.L., J.M.H.H., Y.H.A.L., D.I.S., Y.K.L.S. and J.S.K.C. wrote the manuscript, which was reviewed, edited and approved by all the coauthors. G.T. is the guarantor of this work, and as such, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Tables

Table 1

Baseline characteristics before and after 1:1 propensity score matching.

Characteristics	Before matching		After matching			
	Metformin (N=8,542)	Sulfonylurea (N=6,616)	Metformin (N=5,756)	Sulfonylurea (N=5,756)	SMD	VR
Demographics						
Male , N (%)	3585 (42.0%)	3488 (52.7%)	2762 (48.0%)	2893 (50.3%)	0.02	-
Baseline age, years	65.18±11.22	70.66±10.90	68.27±10.50	69.48±10.84	0.11	1.07
Follow up duration since type 2 diabetes diagnosis, years	5.08±2.56	5.01±2.54	5.04±2.57	5.04±2.54	<0.01	0.98
Comorbidities						
Peripheral vascular disease, N (%)	24 (0.3%)	11 (0.2%)	10 (0.2%)	9 (0.2%)	<0.01	-
Ischemic stroke, N (%)	359 (4.2%)	466 (7.0%)	311 (5.4%)	357 (6.2%)	<0.01	-
Atrial fibrillation, N (%)	278 (3.3%)	495 (7.5%)	261 (4.5%)	337 (5.9%)	0.01	-
Heart failure, N (%)	298 (3.5%)	723 (10.9%)	291 (5.1%)	437 (7.6%)	0.03	-
Prior VA/SCD, N (%)	0 (0.0%)	3 (0.0%)	0 (0.0%)	0 (0.0%)	<0.01	-
Intracranial hemorrhage, N (%)	106 (1.2%)	146 (2.2%)	96 (1.7%)	105 (1.8%)	<0.01	-
Coronary heart disease, N (%)	1015 (11.9%)	1257 (19.0%)	838 (14.6%)	967 (16.8%)	0.02	-
Hypertension, N (%)	2802 (32.8%)	3085 (46.6%)	2259 (39.2%)	2448 (42.5%)	0.03	-
Chronic obstructive pulmonary disease, N (%)	25 (0.3%)	35 (0.5%)	22 (0.4%)	21 (0.4%)	<0.01	-
Medications						
ACE inhibitors, N (%)	4891 (57.3%)	3740 (56.5%)	3087 (53.6%)	3181 (55.3%)	0.02	-
Beta blockers, N (%)	3509 (41.1%)	2859 (43.2%)	2480 (43.1%)	2478 (43.1%)	<0.01	-
Calcium channel blockers, N (%)	3648 (42.7%)	3365 (50.9%)	2696 (46.8%)	2807 (48.8%)	0.02	-
Diuretics, N (%)	1683 (19.7%)	1992 (30.1%)	1371 (23.8%)	1531 (26.6%)	0.03	-
Insulin, N (%)	2648 (31.0%)	949 (14.3%)	863 (15.0%)	919 (16.0%)	<0.01	-
Thiazolidinediones, N (%)	132 (1.5%)	110 (1.7%)	74 (1.3%)	92 (1.6%)	<0.01	-
DPP4 inhibitors, N (%)	18 (0.2%)	1 (0.0%)	1 (0.0%)	1 (0.0%)	<0.01	-
GLP-1 agonists, N (%)	5 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.01	-
Glicazide, N(%)	-	4144 (62.6%)	-	3514 (61.0%)	-	-
Glipizide, N(%)	-	236 (3.6%)	-	194 (3.4%)	-	-
Tolbutamide, N(%)	-	248 (3.7%)	-	196 (3.4%)	-	-
Glibenclamide, N(%)	-	561 (8.5%)	-	502 (8.7%)	-	-
Glimepiride, N(%)	-	63 (1.0%)	-	55 (1.0%)	-	-

Laboratory tests						
Cholesterol, mmol/L	4.82±0.99	4.75±1.09	4.81±0.96	4.78±1.09	0.03	1.28
High density lipoprotein, mmol/L	1.22±0.33	1.19±0.36	1.21±0.31	1.19±0.36	0.04	1.33
Low density lipoprotein, mmol/L	2.89±0.87	2.90±0.93	2.91±0.87	2.91±0.93	<0.01	1.15
Triglyceride, mmol/L	1.75±1.33	1.65±1.39	1.70±1.11	1.67±1.45	0.03	1.71
HbA1c, %	7.47±1.45	7.45±1.43	7.45±1.44	7.44±1.43	<0.01	0.98

Continuous variables were expressed as mean ± standard deviation. SMD <0.1 / VR >0.5 & <2.0 indicated good balance in matching. SMD: Standardized mean difference; VR: Variance Ratio; VA/SCD: Ventricular arrhythmia or sudden cardiac death; DPP4: dipeptidyl-peptidase 4; GLP-1: glucagon-like peptide 1.

Table 2

Main, subgroup and sensitivity analysis of VA/SCD risk in sulfonylurea over metformin users.

Sulfonylurea versus metformin	HR (95% CI, P value)	Metformin users			Sulfonylurea users			E-value (HR)
		Cohort size	Number of events	Follow up person-years/incidence per 1,000 person-years (95% CI)	Cohort size	Number of events	Follow up person-years/incidence per 1,000 person-years (95% CI)	
Overall	1.84 (1.56-2.16, p<0.001)	5756	229	29007/7.89 (6.91-8.99)	5756	415	28983/14.32 (12.97-15.76)	3.08
Without history of valvular heart disease/cardiomyopathy	1.87 (1.57-2.23, p<0.001)	5329	196	26854/7.30 (6.31-8.40)	5222	355	26380/13.46 (12.09-14.93)	3.15
Insulin use								
Insulin users only	1.65 (1.21-2.24, p=0.001)	863	65	4436/14.65 (11.31-18.68)	919	112	4702/23.82 (19.61-28.67)	2.69
Without insulin use	1.89 (1.56-2.29, p<0.001)	4893	164	24571/6.67 (5.69-7.78)	4837	303	24281/12.48 (11.11-13.97)	3.19
Coronary heart disease								
Without coronary heart disease	1.86 (1.55-2.23, p<0.001)	4918	182	24691/7.37 (6.34-8.52)	4789	326	23972/13.60 (12.16-15.16)	2.72
With coronary heart disease only	1.67 (1.17-2.38, p=0.004)	838	47	4315/10.89 (8.00-14.48)	967	89	5011/17.76 (14.26-21.86)	3.12

VA/SCD: Ventricular arrhythmia or sudden cardiac death

A large E-value implies that any unmeasured confounder must be strong to explain away the effect of sulfonylurea over metformin use in the risk of developing VA/SCD.

Table 3

Subgroup analysis of VA/SCD risk by individual sulfonylurea.

Sulfonylurea versus metformin	HR (95% CI, P value)	Cohort size	Number of events	Follow up person-years/incidence per 1,000 person-years	E-value (HR)
Glicazide	1.75 (1.46-2.10, p<0.001)	3411	235	17158/13.70 (12.00-15.56)	2.90
Glipizide	1.66 (0.85-3.23, p=0.136)	138	9	713/12.62 (5.77-23.96)	2.71
Tolbutamide	5.01 (3.20-7.83, p<0.001)	115	21	578/36.33 (22.49-55.54)	9.49
Glibenclamide	0.75 (0.44-1.28, p=0.293)	467	14	2390/5.86 (3.20-9.83)	2.00
Glimepiride	0.64 (0.09-4.53, p=0.652)	39	1	192/5.21 (0.13-29.02)	2.50

VA/SCD: Ventricular arrhythmia or sudden cardiac death

A large E-value implies that any unmeasured confounder must be strong to explain away the effect of sulfonylurea over metformin use in the risk of developing VA/SCD.

Figures

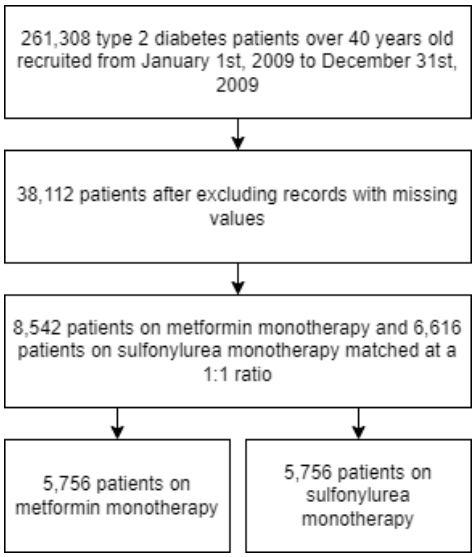

Figure 1

The steps for the selection of patients for this study cohort

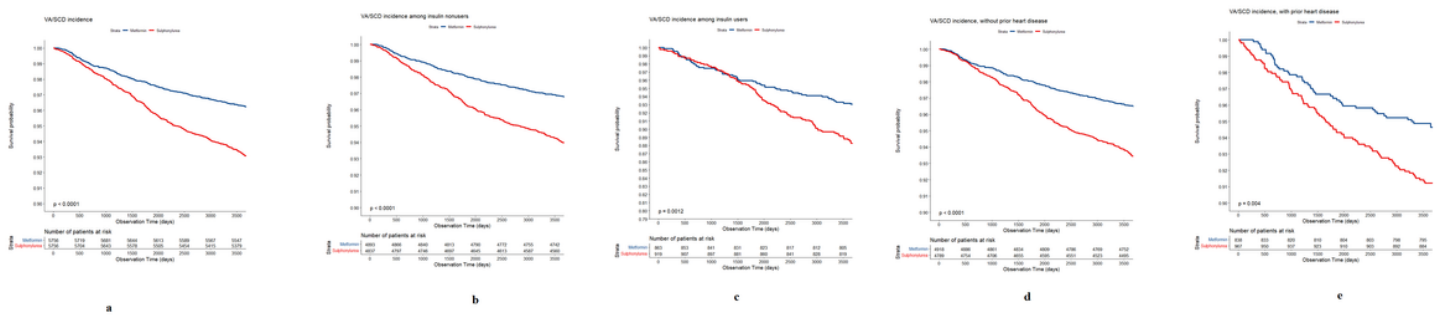

Figure 2

Kaplan-Meier survival curves of VA/SCD stratified by metformin versus sulfonylurea from main and subgroup analysis.

Blue= Metformin; Red= Sulfonylurea

VA/SCD: Ventricular arrhythmia or sudden cardiac death

Supplementary Files

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