Metformin versus sulphonylureas for new onset atrial fibrillation and stroke in type 2 diabetes mellitus: a population-based study

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Abstract

Background To compare the rates of incident atrial fibrillation (AF), stroke, cardiovascular mortality, and all-cause mortality between metformin and sulphonylurea users in type 2 diabetes mellitus. **Methods** This was a retrospective population-based cohort study of type 2 diabetes mellitus patients receiving either sulphonylurea or metformin monotherapy between January 1 st, 2000 and December 31 st, 2019. The primary outcome was new-onset AF or stroke. Secondary outcomes were cardiovascular, non-cardiovascular and all-cause mortality. Propensity score matching (1:2 ratio) between sulphonylurea and metformin users was performed, based on demographics, CHA-DS-VASc score, Charlson comorbidity index, past comorbidities, and medication use. Cox regression was used to identify significant risk factors. Competing risk analysis was conducted using cause-specific and subdistribution hazard models. Sensitivity analysis using propensity score stratification, high dimensional propensity score and inverse probability of treatment weighting were conducted. **Results** A total of 36228 sulphonylurea users and 72456 metformin users were included in the propensity score-matched cohort. Multivariable Cox regression showed that sulphonylurea users had higher risks of incident AF (hazard ratio [HR]: 2.89, 95% confidence interval [CI]: 2.75-2.77; $P<0.0001$), stroke (HR: 3.23, 95% CI: 3.01-3.45; $P<0.0001$), cardiovascular mortality (HR: 3.60, 95% CI: 2.62-4.81; $P<0.0001$), and all-cause mortality (HR: 4.35, 95% CI: 3.16-4.75; $P<0.0001$) compared to metformin users. Similarly significant results were observed using cause-specific and subdistribution hazard models. Sensitivity analysis using other propensity score techniques also yielded higher risks in sulphonylurea users. **Conclusions** Sulphonylurea use was associated with higher risks of incident AF, stroke, cardiovascular mortality and all-cause mortality compared to metformin.

Background

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic disorders around the world which leads to significant morbidity and mortality [1]. It is predicted that by 2040, T2DM would have a global prevalence of 600 million people [2, 3]. T2DM is associated with multisystem complications including atrial fibrillation (AF) and stroke [4]. The manifestations of metabolic syndrome transform the epicardial adipose tissue to cause fibrosis, resulting in atrial remodelling [5]. Furthermore, the sympathetic activity is also increased in T2DM patients [6]. Hence, it has been reported that T2DM patients has a 40% increase in AF risk [7, 8]. Besides, The T2DM insulin resistance state leads to endothelium-dependent vasodilation impairment [9]. The T2DM induced hyperglycemia also damages the vessels by reducing the endothelium-derived NO via inhibiting the phosphatidylinositol 3 kinase pathway. This leads to increase inflammation and formation of foam cells [10]. As such, the T2DM patients also have an increased risk of stroke incidences due to the direct or indirect diabetic-induced changes in the cerebral vessels.

Glycaemic control is essential to reduce the occurrence of AF and stroke in patients with T2DM [8, 11]. Yet, studies investigating the risk of new-onset AF and stroke in diabetic patients on different diabetes medications are scarce. Metformin is the first-line antidiabetic drug treatment recommended by international guidelines, given its high efficacy and safety in ameliorating metabolic controls [12]. Metformin has been reported to reduce stroke severity, cardiovascular caused mortality, and all-cause mortality among T2DM patients [13]. On the other hand, sulphonylurea is also another commonly prescribed antidiabetic agent for patients who are refractory to metformin [14]. Sulphonylurea suspected to be associated with increases the risk of hypoglycaemic events, which raises the risk of adverse cardiovascular events and mortality [15]. However, some studies indicated that sulphonylurea does not increase all-cause mortality or cardiovascular mortality compared to metformin [16]. The following study aims to compare the outcomes of new-onset AF and stroke between metformin and sulphonylurea users amongst T2DM patients in order to provide insights on the cardiovascular effects of antidiabetic medication.

Methods

Study design and population

This retrospective population-based cohort study received approval from The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. The inclusion criteria were patients with T2DM between January 1st, 2000 to December 31st, 2019. Patients who received both sulphonylureas and metformin on follow-up, did not receive either sulphonylureas or metformin, and those with prior AF or stroke were excluded. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS). This territory-wide database centralizes patient information from affiliated local hospitals to establish comprehensive clinical and medical data, including demographics, past comorbidities, medications, and laboratory data. CHA-DS-VASc score and Charlson comorbidity index were also calculated. The detailed standard ICD-9 codes to identify prior comorbidities and outcomes of new-onset AF or stroke are shown in **Supplementary Table 1**.

Different variability measures of fasting blood glucose and HbA1c were calculated, including standard deviation (SD), absolute successive variability score, percentage successive variability score, normalized score, normalized absolute successive variability score, normalized percentage successive variability score, coefficient of variation, SD/initial value, and variability independent of mean. The detailed definitions of the calculations of these variability measures were provided in **Supplementary Table 2**.

Statistical analysis and outcomes

The study outcomes were new-onset AF, new-onset stroke, cardiovascular mortality and all-cause mortality after the initiation of sulphonylurea or metformin. Patients were followed up to the endpoints of new-onset AF/stroke, mortality or the study end (December 31st, 2019). Hong Kong Death Registry, an official government registry that registered death records of the Hong Kong population, provided the mortality data. There was no adjudication of the outcomes, as this relied on the ICD-9 coding or record in the death registry. However, the coding was performed by the clinicians or administrative staff, who were not involved in the mode development.

Descriptive statistics were used to summarise the characteristics of the patient cohort. Mean (standard deviation [SD]) are utilised to depict the continuous variables and presented count (%) were applied to illustrate categorical variables. A standardised mean difference (SMD) of no more than 0.2 between the

treatment groups post-weighting was deemed insignificant. Propensity score matching with a 1:2 ratio was used to create the control cohort of sulphonylureas vs. metformin drug use based on demographics, CHA-DS-VASc score, Charlson comorbidity index, past comorbidities, and medication history.

Univariate Cox regression was used to determine the significant risk factors and uncover the exposure effects of metformin and sulphonylurea on the adverse outcomes. Multivariate Cox regression models were employed with adjustments based on the significant confounding elements. Hazard ratios (HRs) with corresponding 95% confidence interval (CI) and P value were reported. Cause-specific hazard models and subdistribution hazard models were conducted to further discern possible competing risks.

Other matching approaches are also tried to identify the treatment effects of metformin versus sulphonylureas. This includes propensity score stratification [17], propensity score matching with inverse probability weighting [18], and high-dimensional propensity score approach [19]. PS stratification splits the dataset into several strata on the basis of the individual's PS alone without reference to the treatment group. The treatment effect is then estimated within each stratum, and an overall estimated treatment effect is calculated by taking a weighted average across each strata. Inverse probability weighting uses the whole dataset but reweights individuals to increase the weights of those who received unexpected exposures. It effectively generates a pseudopopulation with near-perfect covariate balance between treatment groups. IPW applies weights corresponding to $1/PS$ for patients in the treated cohort and $[1/(1 - PS)]$ for those in the control cohort. The high-dimensional propensity score (HDPS) is an automated data-driven or empirical approach to deriving variables from administrative data for inclusion in propensity score models.

The two-tailed significance tests were regarded as significant if the P values were less than 0.05. There was no imputation performed for missing data. No blinding was performed for the predictor as the values were obtained from the electronic health records automatically. Data were analysed using RStudio software (Version: 1.1.456) and Python (Version: 3.6).

Results

Baseline characteristics

Initially, the cohort comprised of 273876 T2DM patients. Upon excluding patients that match the exclusion criteria (8809 patients with both medication use, 79186 without either medication use, and 10946 patients with prior diagnosis of AF or stroke) yields a study cohort of 174935 patients (Fig. 1). The cohort involved 46.61% males and had initial drug exposure at a mean age of 64.5 years old (SD: 12.2) after a mean follow-up duration of 3535.1 days (SD: 1250.4). Of these, 36228 (20.7%) patients received sulphonylurea and 138707 (79.3%) received metformin. Amongst this cohort, 50304 patients exhibited 10925 new-onset AF (IR = 0.26%) and 15233 new-onset stroke (9.7%), 450 cardiovascular caused mortality (incidence ratio (IR) = 0.26%), non-cardiovascular mortality and all-cause mortality (IR = 38.75%). The comparisons of the baseline and clinical characteristics between T2DM patients with sulphonylurea and metformin monotherapy before and after propensity score matching are shown in **Table 1**. The baseline and clinical characteristics of type 2 diabetes patients stratified by new-onset AF or stroke outcomes are detailed in **Supplementary Tables 3 and 4**, respectively. The two groups showed a similar density of propensity scores after matching (**Supplementary Fig. 1**). No significant baseline and clinical characteristics differences were observed between the two groups of patients.

Outcome Predictors

Compared to metformin monotherapy users, the sulphonylurea monotherapy users had higher rates of new onset AF (before: 15.54% vs. 3.81%, SMD = 0.40; after: 15.54% vs. 5.44%, SMD = 0.33), stroke (before: 21.33% vs. 5.41%, SMD = 0.48; after: 21.33% vs. 6.8%, SMD = 0.43), and all-cause mortality (before: 71.94% vs. 17.47%, SMD = 1.31; after: 71.94% vs. 24.7%, SMD = 1.07) after 1:2 propensity score matching. Kaplan-Meier survival curves of new-onset AF, new-onset stroke, cardiovascular mortality, and all-cause mortality, after 1:2 propensity score matching, stratified by sulphonylurea and metformin use, shows that metformin users are less likely to experience these adverse outcomes (Fig. 2 and Fig. 3)

Significant univariate predictors for all-cause mortality, cardiovascular mortality, new onset AF and new onset stroke after 1:2 propensity score matching are shown in **Table 2**. Compared with metformin monotherapy, sulphonylurea monotherapy demonstrated adverse medication effects on cardiovascular mortality (HR: 3.78 [3.05, 4.68], P value < 0.0001), all-cause mortality (HR: 4.25 [4.17, 4.34], P value < 0.0001), new onset AF (HR: 2.84[2.73, 2.96], P value < 0.0001), and new onset stroke (HR: 3.18[3.07, 3.3], P value < 0.0001). The trend remains the same after propensity score matching and adjusting for significant demographics, CHA-DS-VASc score, past comorbidities, and non-sulphonylurea/metformin medications in the multivariate Cox model. The trend that sulphonylurea are associated with higher risks of new-onset AF, new-onset stroke, cardiovascular mortality and all cause mortality are consistent after matching via different approaches (**Table 3**).

Competing risk analysis

Cause-specific and subdistribution hazard models demonstrates that sulphonylurea users have an increased risk for cardiovascular mortality, all-cause mortality, new-onset AF and new-onset stroke in comparison to metformin users (HR > 1, P value < 0.0001) (**Table 3**). Correspondingly, the unbiased estimates of the cumulative incidence functions with competing risk analysis for cardiovascular mortality, all-cause mortality, new-onset AF and new-onset stroke stratified by sulphonylurea and metformin use before and after 1:2 propensity score matching were presented in Fig. 4.

Discussion

The main finding for the present study is that in comparison to metformin users, sulphonylurea users have a higher risk of new-onset AF, new-onset stroke, cardiovascular mortality, and all-cause mortality.

Metformin and sulphonylurea are two of the most prescribed drugs for initial diabetic control. However, it was uncertain if the two drugs would have different clinical outcomes. In accord with the previous data, our data revealed that sulphonylurea would be more perilous to heart failure and cardiovascular mortality [20]. This is partly explained by the fact that metformin enhances insulin sensitivity while sulphonylurea acts by increasing endogenous insulin levels. As such, metformin can help with weight reduction, and causes fewer hypoglycemic events compared to sulphonylurea [21, 22]. Besides increased cardiovascular mortality, the raise in all-cause mortality amongst sulphonylurea users may be due to drug-induced hyperinsulinemia. This is consistent with the findings in several studies from different part of the world [23–25]. It has been proposed that hyperinsulinaemia would raise the risk of cancers risks by increasing mitogenesis [26]. There are reports demonstrating an increased risk of cancer in patients on sulphonylurea in comparison to metformin users [27]. Besides, sulphonylurea was also shown to increase risks of serious pneumonia, renal function decline and dementia [28–30].

An abundance of evidence suggested strong associations between T2DM and AF occurrences [31]. This is not only because AF and T2DM have mutual risk factors such as atherosclerosis and hypertension; T2DM is also an independent risk factor for AF occurrence, as shown in the Framingham study [32]. Reasonable glycemic control would, therefore, reduce the AF onset as well as lessen the mortality rate among the patients with AF. As with our investigations, metformin has been demonstrated to bring down the risk of AF and ventricular arrhythmias compared to sulphonylureas [33]. Metformin has antioxidant effects and anti-inflammatory effects that reduce atrial fibrosis and remodeling [34, 35]. Meanwhile, the impact of sulphonylurea on the AF onset was less well investigated. The sulphonylurea-induced potassium channel blockade is hypothesized to inhibit the ischemic preconditioning, shorten the action potential duration and increase the cardiac excitability, resulting in AF [36].

Metformin was also exemplified to have a lower risk of stroke onset compared to sulphonylurea. In fact, metformin can reduce stroke onset independent of its glycemic control [37]. Metformin activation of the glial cells AMPK have neuroprotective effects [38]. Similar to its effect on AF, metformin also demonstrates extra anti-inflammatory by activating the nuclear factor erythroid 2-related factor (Nrf2) pathways in neurons. It also has antioxidant effects by increasing glutathione and catalase levels [39]. In contrast, sulphonylurea-induced hypoglycemia contributes to stroke occurrence. Hypoglycemic events have been reported to increase stroke risk via pathways such as increased platelet activation, thrombotic and atherosclerotic cytokine release, and inflammation [40, 41]. Furthermore, sulphonylurea stimulates the release of atherogenic C-peptide [42]. Therefore, it is expectable that metformin has a more protective effect than sulphonylurea in terms of AF and stroke.

Limitations

There are some limitations in this study that should be acknowledged. Firstly, the data is from a single locality, hence external validation is needed to explore the applicability of findings onto other populations. Secondly, important clinical factors, such as smoking history and physical activity are not routinely coded into the local health database, which are significant predictors for diabetes and the primary outcomes. Finally, this study only shows the association between metformin and reducing AF and stroke outcomes but cannot elucidate causal relationships. There is a need for further studies to investigate the mechanism of how metformin exerts those additional protective effects compared to sulphonylurea.

Conclusions

Compared to metformin users, sulphonylurea use was significantly associated with higher risks of new onset AF, new onset stroke, cardiovascular mortality, and all-cause mortality.

Declarations

Ethics approval and consent to participate: This retrospective population-based cohort study received approval from The Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee

Consent for publication: All authors have read and approved submission of the manuscript which has not been published and is not being considered for publication elsewhere in whole or part in any language.

Availability of data and materials: The data will be available upon requests to the corresponding authors

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Authors' contributions:

JD, GZ, CC, OHIC: data analysis, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

SL, KSKL, WTW, TL, AKCW, SHC: project planning, data acquisition, data interpretation, critical revision of manuscript

QZ, GT: study conception, study supervision, project planning, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

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Tables

Table 1. Baseline and clinical characteristics of type-2 diabetes patients on sulphonylurea vs. metformin medications before and after 1:2 propensity score matching.

* for SMD 0.2

Characteristics	Before matching			After 1:2 matching	
	Sulphonylurea (N=36228) Mean(SD);Max;N or Count(%)	Metformin (N=138707) Mean(SD);Max;N or Count(%)	SMD	Sulphonylurea (N=36228) Mean(SD);Max;N or Count(%)	Metformin (N=72456) Mean(SD);Max;N or Count(%)
Outcomes					
Mortality	26065(71.94%)	24239(17.47%)	1.31*	26065(71.94%)	17899(24.70%)
Cardiovascular mortality	251(0.69%)	208(0.14%)	0.08	251(0.69%)	126(0.17%)
AF	5633(15.54%)	5292(3.81%)	0.40*	5633(15.54%)	3947(5.44%)
Stroke	7728(21.33%)	7505(5.41%)	0.48*	7728(21.33%)	4932(6.80%)
Demographics					
Male gender	17522(48.36%)	64026(46.15%)	0.04	17522(48.36%)	34983(48.28%)
Female gender	18706(51.63%)	74681(53.84%)	0.04	18706(51.63%)	37473(51.71%)
Baseline age, years	71.3(10.9);105.1;n=36228	63.0(11.9);104.1;n=138707	0.72*	71.3(10.9);105.1;n=36228	71.1(10.7);99.5;n=72456
<50	1350(3.72%)	19379(13.97%)	0.37*	1350(3.72%)	2699(3.72%)
[50-60]	4738(13.07%)	38069(27.44%)	0.36*	4738(13.07%)	9462(13.05%)
[60-70]	8094(22.34%)	37957(27.36%)	0.12	8094(22.34%)	16212(22.37%)
[70-80]	13724(37.88%)	32263(23.25%)	0.32*	13724(37.88%)	27557(38.03%)
>80	8325(22.97%)	11052(7.96%)	0.42*	8325(22.97%)	16526(22.80%)
Past comorbidities					
CHA-DS-VASc score	2.1(1.3);7.0;n=36228	1.6(1.3);7.0;n=138707	0.44*	2.1(1.3);7.0;n=36228	2.1(1.3);7.0;n=72456
Charlson score	2.9(1.3);15.0;n=36228	2.2(1.6);16.0;n=138707	0.45*	2.9(1.3);15.0;n=36228	2.9(1.4);15.0;n=72456
Systemic embolism	9(0.02%)	46(0.03%)	0	9(0.02%)	18(0.02%)
Hypertension	9804(27.06%)	25562(18.42%)	0.21*	9804(27.06%)	19429(26.81%)
Heart failure	869(2.39%)	2657(1.91%)	0.03	869(2.39%)	1723(2.37%)
Coronary heart disease	4015(11.08%)	10055(7.24%)	0.13	4015(11.08%)	7847(10.83%)
Hemiplegia or paraplegia	63(0.17%)	110(0.07%)	0.03	63(0.17%)	126(0.17%)
Renal diseases	148(0.40%)	1798(1.29%)	0.1	148(0.40%)	290(0.40%)
Neurological diabetic complication	66(0.18%)	402(0.28%)	0.02	66(0.18%)	131(0.18%)
Osteoporosis	15(0.04%)	53(0.03%)	<0.01	15(0.04%)	30(0.04%)
Ophthalmical diabetic complication	189(0.52%)	1466(1.05%)	0.06	189(0.52%)	376(0.51%)
Liver diseases	56(0.15%)	280(0.20%)	0.01	56(0.15%)	112(0.15%)
Ventricular tachycardia/fibrillation	127(0.35%)	455(0.32%)	<0.01	127(0.35%)	250(0.34%)
Dementia	180(0.49%)	575(0.41%)	0.01	180(0.49%)	357(0.49%)
Anemia	1534(4.23%)	3925(2.82%)	0.08	1534(4.23%)	2985(4.11%)
AMI	499(1.37%)	1946(1.40%)	<0.01	499(1.37%)	995(1.37%)
COPD	587(1.62%)	1650(1.18%)	0.04	587(1.62%)	1161(1.60%)
IHD	2224(6.13%)	7533(5.43%)	0.03	2224(6.13%)	4428(6.11%)
PVD	156(0.43%)	640(0.46%)	<0.01	156(0.43%)	310(0.42%)
Gastrointestinal bleeding	625(1.72%)	2157(1.55%)	0.01	625(1.72%)	1234(1.70%)
Malignancy	218(0.60%)	755(0.54%)	0.01	218(0.60%)	436(0.60%)
Obesity	113(0.31%)	1046(0.75%)	0.06	113(0.31%)	226(0.31%)

Medications					
Number of diabetes mellitus drugs	1.8(0.6);6.0;n=36228	1.8(0.6);6.0;n=138707	0.03	1.8(0.6);6.0;n=36228	1.8(0.5);5.0;n=72456
Number of cardiovascular drugs	1.9(1.2);5.0;n=36228	1.6(1.2);5.0;n=138707	0.25*	1.9(1.2);5.0;n=36228	1.9(1.2);5.0;n=72456
ACEI/ARB	18529(51.14%)	65870(47.48%)	0.07	18529(51.14%)	37451(51.68%)
Beta blockers	14309(39.49%)	45613(32.88%)	0.14	14309(39.49%)	28559(39.41%)
Calcium channel blockers	18428(50.86%)	53427(38.51%)	0.25*	18428(50.86%)	36821(50.81%)
Diuretics	8083(22.31%)	22413(16.15%)	0.16	8083(22.31%)	15739(21.72%)
Statins	8605(23.75%)	30530(22.01%)	0.04	8605(23.75%)	17046(23.52%)
Antidiabetic drugs	8288(22.87%)	13678(9.86%)	0.36*	8288(22.87%)	14755(20.36%)
Lipid-lowering drugs	40(0.11%)	527(0.37%)	0.05	40(0.11%)	80(0.11%)
Gliclazide	1402(3.86%)	9344(6.73%)	0.13	1402(3.86%)	2761(3.81%)
Nitrates	15(0.04%)	240(0.17%)	0.04	15(0.04%)	30(0.04%)
Antihypertensive drugs	17(0.04%)	249(0.17%)	0.04	17(0.04%)	34(0.04%)
Anticoagulants	1(0.00%)	45(0.03%)	0.02	1(0.00%)	2(0.00%)
Antiplatelets	22(0.06%)	423(0.30%)	0.06	22(0.06%)	44(0.06%)
Laboratory tests					
Lymphocyte, x10 ⁹ /L	1.9(0.9);14.7;n=2772	2.0(0.9);47.2;n=8884	0.09	1.9(0.9);14.7;n=2772	1.8(0.8);14.7;n=4924
Neutrophil, x10 ⁹ /L	5.6(2.9);37.2;n=2772	5.3(2.7);41.1;n=8884	0.07	5.6(2.9);37.2;n=2772	5.4(2.7);41.1;n=4924
Platelet, x10 ⁹ /L	254.3(88.3);1560.0;n=2912	263.1(82.1);1098.0;n=8525	0.1	254.3(88.3);1560.0;n=2912	261.0(88.4);1080.0;n=5262
Potassium, mmol/L	4.2(0.5);8.0;n=20729	4.2(0.5);14.6;n=72334	0.04	4.2(0.5);8.0;n=20729	4.2(0.5);8.0;n=40019
Albumin, g/L	38.4(5.2);53.9;n=5916	39.5(4.8);55.0;n=18556	0.2*	38.4(5.2);53.9;n=5916	39.1(5.0);52.0;n=10279
Sodium, mmol/L	139.4(3.3);153.0;n=20740	139.5(3.0);160.3;n=72377	0.04	139.4(3.3);153.0;n=20740	139.5(3.2);153.0;n=40022
Urea, mmol/L	6.5(2.8);56.3;n=17896	6.0(2.4);61.3;n=63368	0.21*	6.5(2.8);56.3;n=17896	6.3(2.6);61.3;n=35235
Creatinine, umol/L	92.4(35.3);783.0;n=18011	84.6(30.2);1019.0;n=63689	0.24*	92.4(35.3);783.0;n=18011	90.3(32.3);1014.0;n=35432
Total protein, g/L	74.3(7.0);104.6;n=5900	74.7(6.4);109.2;n=18517	0.06	74.3(7.0);104.6;n=5900	74.5(6.7);109.2;n=10241
Alkaline phosphatase, U/L	78.9(41.8);2503.0;n=16786	75.0(31.9);3273.0;n=57204	0.1	78.9(41.8);2503.0;n=16786	75.6(35.4);1721.0;n=31235
Aspartate transaminase, U/L	32.6(53.2);777.0;n=1540	32.1(93.7);4994.0;n=4895	0.01	32.6(53.2);777.0;n=1540	33.5(151.9);4994.0;n=2702
Alanine transaminase, U/L	24.5(24.6);874.0;n=13870	26.7(23.1);870.0;n=45855	0.09	24.5(24.6);874.0;n=13870	23.9(21.2);870.0;n=25311
Bilirubin, umol/L	11.2(10.6);145.0;n=831	12.7(13.6);346.7;n=2142	0.13	11.2(10.6);145.0;n=831	12.7(11.0);157.0;n=1208
Triglyceride, mmol/L	1.7(1.1);46.4;n=23778	1.8(1.4);90.8;n=89917	0.06	1.7(1.1);46.4;n=23778	1.7(1.1);41.3;n=47366
LDL, mmol/L	2.9(0.9);10.5;n=14474	2.9(0.9);10.5;n=53250	0.06	2.9(0.9);10.5;n=14474	2.9(0.8);9.7;n=28923
Total cholesterol, mmol/L	4.8(1.0);12.9;n=23835	4.8(1.0);20.1;n=90076	0.09	4.8(1.0);12.9;n=23835	4.8(1.0);15.3;n=47480
HDL, mmol/L	1.2(0.3);4.2;n=21130	1.2(0.3);4.7;n=81686	0.01	1.2(0.3);4.2;n=21130	1.2(0.3);3.9;n=42479
HbA1c, g/dL	12.4(1.9);18.3;n=3088	12.8(1.8);18.6;n=10127	0.21*	12.4(1.9);18.3;n=3088	12.3(1.8);18.4;n=5635
Glucose, mmol/L	9.5(4.2);50.4;n=7970	9.1(4.4);64.3;n=14151	0.09	9.5(4.2);50.4;n=7970	8.9(4.1);64.1;n=12652
NLR	4.0(5.3);108.0;n=2772	3.5(3.9);68.5;n=8884	0.11	4.0(5.3);108.0;n=2772	3.8(4.0);49.0;n=4924
Fasting blood glucose, mmol/L	7.8(2.6);36.3;n=15751	7.7(2.6);67.2;n=58145	0.01	7.8(2.6);36.3;n=15751	7.8(2.6);33.1;n=31839
HbA1c, %	7.4(1.4);20.8;n=16681	7.4(1.5);21.9;n=59591	<0.01	7.4(1.4);20.8;n=16681	7.4(1.4);18.5;n=33126
Variability measurements					
<i>Glucose</i>					

Absolute successive variability score (glucose)	57.9(20.6);96.8;n=15752	56.8(20.9);96.6;n=58148	0.06	57.9(20.6);96.8;n=15752	56.3(21.2);96.6;n=31839
Percentage successive variability score (glucose)	50.2(21.6);96.0;n=15752	48.9(21.6);96.2;n=58148	0.06	50.2(21.6);96.0;n=15752	48.8(21.9);96.2;n=31839
SD of glucose	1.7(1.2);13.1;n=15752	1.7(1.2);30.4;n=58148	0.02	1.7(1.2);13.1;n=15752	1.6(1.2);24.9;n=31839
Mean glucose, mmol/L	8.1(1.8);24.1;n=15752	8.3(1.9);29.0;n=58148	0.07	8.1(1.8);24.1;n=15752	8.0(1.7);22.7;n=31839
Normalized absolute successive variability score (glucose)	7.3(2.8);20.1;n=15752	7.0(2.7);20.7;n=58148	0.09	7.3(2.8);20.1;n=15752	7.2(2.8);20.7;n=31839
Normalized percentage successive variability score (glucose)	6.4(3.0);21.2;n=15752	6.1(3.0);22.2;n=58148	0.09	6.4(3.0);21.2;n=15752	6.3(3.1);22.2;n=31839
SD/Initial (glucose)	23.4(20.4);418.2;n=15751	23.2(19.9);475.4;n=58148	0.01	23.4(20.4);418.2;n=15751	22.4(19.9);378.8;n=31839
Coefficient of variation (glucose)	20.2(12.2);110.9;n=15752	20.2(12.4);174.8;n=58148	0.01	20.2(12.2);110.9;n=15752	19.5(12.3);135.0;n=31839
Variability independent of mean (glucose)	31.8(19.6);188.5;n=15752	31.8(19.9);323.1;n=58148	<0.01	31.8(19.6);188.5;n=15752	30.6(19.7);227.8;n=31839
<i>HbA1c</i>					
Absolute successive variability score (HbA1c)	37.6(21.9);92.3;n=16935	37.0(21.5);93.3;n=60447	0.03	37.6(21.9);92.3;n=16935	36.1(21.9);90.9;n=33644
Percentage successive variability score (HbA1c)	28.4(20.4);90.9;n=16935	27.5(19.9);90.9;n=60447	0.04	28.4(20.4);90.9;n=16935	26.8(20.0);90.0;n=33644
SD of HbA1c	0.9(0.7);8.0;n=16934	0.9(0.7);19.3;n=60440	0.02	0.9(0.7);8.0;n=16934	0.9(0.7);18.5;n=33637
Mean HbA1c, %	7.7(1.1);19.0;n=16935	7.8(1.2);20.3;n=60447	0.08	7.7(1.1);19.0;n=16935	7.6(1.1);20.3;n=33644
Normalized absolute successive variability score (HbA1c)	4.8(2.7);15.4;n=16935	4.7(2.7);14.6;n=60447	0.05	4.8(2.7);15.4;n=16935	4.6(2.7);14.3;n=33644
Normalized percentage successive variability score (HbA1c)	3.6(2.6);15.4;n=16935	3.5(2.5);16.2;n=60447	0.06	3.6(2.6);15.4;n=16935	3.5(2.6);13.4;n=33644
SD/Initial (HbA1c)	12.2(9.9);121.4;n=16686	12.4(10.6);296.4;n=59678	0.01	12.2(9.9);121.4;n=16686	11.7(9.9);253.2;n=33191
Coefficient of variation (HbA1c)	11.3(7.7);74.5;n=16934	11.4(8.1);166.2;n=60440	0.01	11.3(7.7);74.5;n=16934	10.8(7.7);137.8;n=33637
Variability independent of mean (HbA1c)	16.0(11.1);109.8;n=16934	16.2(11.6);252.1;n=60440	0.01	16.0(11.1);109.8;n=16934	15.3(11.1);214.2;n=33637
<i>Lipids</i>					
SD of LDL	0.5(0.4);3.4;n=6357	0.5(0.3);5.1;n=23852	0.04	0.5(0.4);3.4;n=6357	0.5(0.3);3.0;n=12390
SD of HDL	0.1(0.1);1.2;n=13898	0.1(0.1);1.6;n=54920	0.07	0.1(0.1);1.2;n=13898	0.1(0.1);1.2;n=28779
SD of TC	0.6(0.4);8.3;n=16259	0.6(0.4);11.8;n=62537	0.02	0.6(0.4);8.3;n=16259	0.6(0.4);6.3;n=32886
SD of TG	0.6(0.9);28.0;n=16167	0.6(1.1);35.1;n=62344	0.06	0.6(0.9);28.0;n=16167	0.6(0.8);32.3;n=32815

AF: atrial fibrillation, HF: heart failure, MI: myocardial infarction, COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease, PVD: peripheral vascular disease, TIA: transient ischemic attack, ACEI: angiotensin-converting-enzyme inhibitors, ARB: angiotensin II receptor blockers, LDL: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, TG: triglycerides, SD: standard deviation.

Table 2. HRs (and 95% CIs) of sulphonylurea vs. metformin from univariate Cox models, multivariate Cox models, cause-specific and subdistribution hazard models for cardiovascular mortality, non-cardiovascular mortality, new onset HF and new onset MI before and after 1:2 propensity score matching.

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$

Model	Outcome	Sulphonylurea vs. Metformin (Before matching) HR [95% CI]	P value	Sulphonylurea vs. Metformin (After 1:2 matching) HR [95% CI]	P value
Univariate Cox model	New onset AF	3.81[3.67, 3.96]	<0.0001***	2.84[2.73, 2.96]	<0.0001***
	New onset stroke	3.73[3.62, 3.85]	<0.0001***	3.18[3.07, 3.3]	<0.0001***
	Cardiovascular mortality	4.23[3.52, 5.09]	<0.0001***	3.78[3.05, 4.68]	<0.0001***
	All-cause mortality	6.44[6.33-6.55]	<0.0001***	4.25[4.17-4.34]	<0.0001***
Multivariate Cox model [#]	New onset AF	2.60[2.51, 2.79]	<0.0001***	2.89[2.75, 2.77]	<0.0001***
	New onset stroke	3.1[2.5, 3.4]	<0.0001***	3.23[3.01, 3.45]	<0.0001***
	Cardiovascular mortality	2.42[1.93, 2.98]	<0.0001***	3.60[2.62, 4.81]	<0.0001***
	All-cause mortality	4.10[3.88, 4.35]	<0.0001***	4.35[3.16, 4.75]	<0.0001***
Cause-specific hazard model	New onset AF	5.58[5.34, 5.84]	<0.0001***	4.04[3.85, 4.24]	<0.0001***
	New onset stroke	5.93[5.73, 6.13]	<0.0001***	4.79[4.62, 4.97]	<0.0001***
	Cardiovascular mortality	6.73[5.58, 8.12]	<0.0001***	5.71[4.6, 7.09]	<0.0001***
	All-cause mortality	7.09[6.94, 7.23]	<0.0001***	4.77[4.67, 4.88]	<0.0001***
Subdistribution hazard model	New onset AF	4.98[4.1, 6.02]	<0.0001***	4.21[3.02, 5.11]	<0.0001***
	New onset stroke	4.85[3.25, 5.43]	<0.0001***	3.55[2.87, 4.53]	<0.0001***
	Cardiovascular mortality	5.43[4.44, 7.09]	<0.0001***	5.09[3.65, 6.88]	<0.0001***
	All-cause mortality	6.54[5.23, 7.1]	<0.0001***	4.54[3.55, 5.11]	<0.0001***

AF: atrial fibrillation, HR: hazard ratio, CI: confidence interval.

[#] Adjusted for significant demographics, past comorbidities, and non- sulphonylurea/metformin medications.

Table 3. Risk of incident AF, stroke, cardiovascular mortality and all-cause mortality associated with treatment of sulphonylurea vs. metformin using different matching approaches.

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$

Outcome	HR after PS stratification [95% CI];P value	HR after HDPS matching [95% CI];P value	HR after PS IPTW [95% CI]; P value
New onset AF	3.85[3.45, 3.99]; <0.0001***	3.56[2.78, 4.02]; <0.0001***	2.45[1.45, 3.38]; <0.0001***
New onset stroke	3.45[3.11, 3.69]; <0.0001***	3.67[3.02, 3.99]; <0.0001***	3.45 [3.02, 3.79]; <0.0001***
Cardiovascular mortality	3.98[3.26, 4.77]; <0.0001***	4.01[3.34, 5.12]; <0.0001***	3.54[3.23, 4.09]; <0.0001***
All-cause mortality	5.57[4.76-6.62]; <0.0001***	6.01[5.56-6.88]; <0.0001***	5.45[4.43-5.69]; <0.0001***

AF: atrial fibrillation, HR: hazard ratio, CI: confidence interval, PS: propensity score, HDPS: high dimensional propensity score, IPTW: inverse probability of treatment weighting.

Figures

Figure 1

Procedures of data processing. HF: heart failure, MI: myocardial infarction, IR: incidence rate.

Figure 2

Kaplan Meier survival curves of new onset AF and new onset stroke stratified by sulphonylurea and metformin use before and after 1:2 propensity score matching.

Figure 3
Kaplan Meier survival curves of all-cause mortality and cardiovascular mortality stratified by sulphonylurea and metformin use before and after 1:2 propensity score matching.

Figure 4
Unbiased estimates of the cumulative incidence functions with competing risk analysis for cardiovascular mortality, all-cause mortality, new onset AF and new onset stroke stratified by sulphonylureas and metformin use before and after 1:2 propensity score matching.

Supplementary Files

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