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

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Abstract
Aims To gain insights on the cardiovascular effects of metformin and sulphonylurea, the present study compares the rates of incident atrial fibrillation, 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, 2000, and December 31, 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, 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 analyses using propensity score stratification, high-dimensional propensity score and inverse probability of treatment weighting were conducted. Subgroup analyses were conducted for age and gender in the matched cohort.

Results A total of 36,228 sulphonylurea users and 72,456 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]: 2.75–3.77; \(P < 0.0001\)), 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 techniques based on the propensity score also yielded similar results.

Conclusions Sulphonylurea use was associated with higher risks of incident AF, stroke, cardiovascular mortality and all-cause mortality compared to metformin. Males and patients older than 65 years with sulphonylurea use were exposed to the highest risks.

Keywords Sulphonylurea · Metformin · Diabetes · Atrial fibrillation · Stroke · Big data

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, sympathetic activity is also increased in T2DM patients [6]. Hence, it has been reported that T2DM patients have a 40% increase in AF risk.
Sulphonylurea.

Insights on the cardiovascular effects of metformin and sulphonylurea users amongst T2DM patients to provide outcomes of new-onset AF and stroke between metformin [16]. The present study aims to compare the all-cause mortality or cardiovascular mortality compared to metformin [15]. However, some studies indicated that sulphonylurea does not increase adverse cardiovascular events and mortality [15]. Yet, the risk of hypoglycaemic events, which raises the risk of cardiovascular caused mortality and all-cause mortality amongst T2DM patients [13]. On the other hand, sulphonylurea is another commonly prescribed anti-diabetic agent for patients who are refractory to metformin [14]. Sulphonylurea is 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 present study aims to compare the outcomes of new-onset AF and stroke between metformin and sulphonylurea users amongst T2DM patients to provide insights on the cardiovascular effects of metformin and sulphonylurea.

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 1, 2000, to December 31, 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 (including ischemic stroke, hemorrhagic stroke, transient ischemic attack) 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. The system has been previously used by both our team and other teams in Hong Kong [17].

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 anti-diabetic 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 amongst T2DM patients [13]. On the other hand, sulphonylurea is also another commonly prescribed anti-diabetic agent for patients who are refractory to metformin [14]. Sulphonylurea is 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 present study aims to compare the outcomes of new-onset AF and stroke between metformin and sulphonylurea users amongst T2DM patients to provide insights on the cardiovascular effects of metformin and sulphonylurea.

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 treatment. Patients were followed up to the endpoints of new-onset AF/stroke, mortality or the study end (December 31, 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 this study.

Descriptive statistics were used to summarize the characteristics of the patient cohort. Mean (SD) was utilized to depict the continuous variables and presented count (%) were applied to illustrate categorical variables. A standardized mean difference (SMD) of no more than 0.2 between the treatment groups post-weighting was deemed balanced. Propensity score matching with a 1:2 ratio between users of sulphonylureas and metformin based on demographics, CHA-DS-VASc score and Charlson comorbidity index were also calculated. The detailed standard International Classification of Disease, Ninth Edition (ICD-9) codes to identity 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 are provided in Supplementary Table 2. Lipid variability for low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol (TC) and triglyceride was calculated using SD.

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 are provided in Supplementary Table 2. Lipid variability for low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol (TC) and triglyceride was calculated using SD.

Univariable Cox regression was used to determine the significant risk factors and uncover the exposure effects of metformin and sulphonylurea on the adverse outcomes. Multivariable Cox 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 (PS) stratification [18], PS matching with inverse probability weighting (IPW) [19] and high-dimensional propensity score approach (HDPS) [20]. PS stratification splits the dataset into several strata based on the individual’s PS alone without reference to the treatment group. The treatment effect was then estimated within each stratum, and an overall estimated treatment effect was calculated by taking a weighted average across each stratum. IPW used the whole dataset, but reweighted individuals to increase the weights of those who received unexpected exposures. It effectively generated a pseudopopulation with a near-perfect covariate balance between treatment groups. IPW applied weights corresponding to 1/PS for patients in the treated cohort and [1/(1 − PS)] for those in the control cohort. The HDPS is an automated data-driven or empirical approach for deriving variables from administrative data for inclusion in propensity score models. Subgroup stratifications analyses were conducted for initial drug exposure age and gender in the matched cohort.

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 273,876 T2DM patients. Upon excluding patients that match the exclusion criteria (8809 patients with both medication use, 79,186 without either medication use and 10,946 patients with prior diagnosis of AF or stroke) yields a study cohort of 174,935 patients (Fig. 1). The cohort involved 46.61% males and had initial drug exposure at a mean age of 56.5 years. The two most common drug classes prescribed were sulphonylurea/metformin (59.1%) and DPP4 inhibitors/metformin (28.9%). The prescribed medication profile was strongly affected by age and gender, with sulphonylurea use higher in men and DPP4 inhibitors/metformin use higher in women.
64.5 years old [SD: 12.2]) after a mean follow-up duration of 3535.1 days (SD: 1250.4). Of these, 36,228 (20.7%) patients received sulphonylurea and 138,707 (79.3%) received metformin. Amongst this cohort, 10,925 patients developed new-onset AF (incidence ratio [IR] = 6.24%), 15,233 patients developed new-onset stroke (8.7%), 459 patients had cardiovascular mortality (IR = 0.26%), and 50,304 patients suffered from all-cause mortality (IR = 28.75%).

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 T2DM 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 PS 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) both before and after 1:2 PS matching. Cumulative incidence curves of new-onset AF, new-onset stroke, cardiovascular mortality and all-cause mortality, before and after 1:2 PS matching, stratified by sulphonylurea and metformin use, both show that metformin users were less likely to experience these adverse outcomes (Figs. 2 and 3).

Significant univariate predictors for all-cause mortality, cardiovascular mortality, new-onset AF and new onset stroke after 1:2 PS matching are shown in Table 2. Compared with metformin use, sulphonylurea use 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 remained after PS 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 was associated with higher risks of new-onset AF, new-onset stroke, cardiovascular mortality and all-cause mortality are consistent after matching via different propensity score matching approaches (Supplementary Table 5). The overall and annualized per-1000 incidence rates of new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality in the matched cohort are presented in Supplementary Table 5.

In addition, the HRs of lipid profiles and their variability measures are summarized in Supplementary Table 7. The patients with higher variability of HDL were associated with higher risks of AF, while higher variability of LDL and TC was associated with higher risks of stroke. Furthermore, patients with higher variability of LDL, HDL and TC were subjected to higher risks of cardiovascular mortality and all-cause mortality.

Competing risk analysis

Cause-specific and subdistribution hazard models demonstrate that sulphonylurea users have an increased risk for cardiovascular mortality, all-cause mortality, new-onset AF and new-onset stroke in comparison with metformin users (HR > 1, \( P \) value < 0.0001) (Table 2). 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 PS matching is presented in Fig. 4.

Subgroup and sensitivity analyses

The subgroup analysis for new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality stratified by initial drug exposure, age and gender is presented in Fig. 5A and B. Males and those older than 65 years old were exposed to higher adverse risks with sulphonylurea prescriptions.

Additional sensitivity analysis was conducted by calculating the number of prescriptions and cumulative exposure duration for metformin and sulphonylurea. The HRs of the number of prescriptions, as well as the drug exposure duration of sulphonylurea and metformin with the presentation of adverse events, were calculated (Supplementary Table 6). In addition, individual drugs in the class of sulphonylurea, including glimepiride, glibenclamide, gliclazide, glipizide, tolazamide, were associated with higher risks of adverse events, compared to metformin prescription (HR > 1, \( P < 0.05 \)) (Supplementary Table 8). Gliclazide, in particular, was associated with significantly higher risks of cardiovascular mortality (HR: 28.78 [23.51, 35.22], \( P \)
| Characteristics | Before matching | SMD | After 1:2 matching | SMD |
|-----------------|----------------|-----|--------------------|-----|
| **Outcomes**    | Sulphonylurea (N = 36,228) Mean(SD);Max;N or Count(%) | Metformin (N = 138,707) Mean(SD);Max;N or Count(%) | Sulphonylurea (N = 36,228) Mean(SD);Max;N or Count(%) | Metformin (N = 72,456) Mean(SD);Max;N or Count(%) |
| All-cause mortality | 26,065(71.94) 24,239(17.47) 1.31* | 26,065(71.94) 17,899(24.70) 1.07* |
| Cardiovascular mortality | 251(0.69) 208(0.14) 0.08 | 251(0.69) 126(0.17) 0.08 |
| New onset AF | 5633(15.54) 5292(3.81) 0.40* | 5633(15.54) 3947(5.44) 0.33* |
| New onset stroke | 7728(21.33) 7505(5.41) 0.48* | 7728(21.33) 4932(6.80) 0.43* |
| **Demographics** | | | | |
| Male gender | 17,522(48.36) 64,026(46.15) 0.04 | 17,522(48.36) 34,983(48.28) < 0.01 |
| Female gender | 18,706(51.63) 74,681(53.84) 0.04 | 18,706(51.63) 37,473(51.71) < 0.01 |
| Baseline age, years | 71.3(10.9);105.1;n = 36,228 | 63.0(11.9);104.1;n = 138,707 | 71.3(10.9);105.1;n = 36,228 | 71.1(10.7);99.5;n = 72,456 |
| < 50 | 1350(3.72) 19,379(13.97) 0.37* | 1350(3.72) 2699(3.72) < 0.01 |
| [50–60] | 4738(13.07) 38,069(27.44) 0.36* | 4738(13.07) 9462(13.05) < 0.01 |
| [60–70] | 8094(22.34) 37,957(27.36) | 8094(22.34) 16,212(22.37) < 0.01 |
| [70–80] | 13,724(37.88) 32,263(23.25) | 13,724(37.88) 27,557(38.03) < 0.01 |
| > 80 | 8325(22.97) 11,052(7.96) | 8325(22.97) 16,526(22.80) < 0.01 |
| Past comorbidities | | | | |
| CHA-DS-VASc score | 2.1(1.3);7.0;n = 36,228 | 1.6(1.3);7.0;n = 138,707 | 2.1(1.3);7.0;n = 36,228 | 2.1(1.3);7.0;n = 72,456 |
| Charlson score | 2.9(1.3);15.0;n = 36,228 | 2.2(1.6);16.0;n = 138,707 | 2.9(1.3);15.0;n = 36,228 | 2.9(1.4);15.0;n = 72,456 |
| Systemic embolism | 9(0.02) 46(0.03) 0 | 9(0.02) 18(0.02) < 0.01 |
| Hypertension | 9804(27.06) 25,562(18.42) | 9804(27.06) 19,429(26.81) 0.01 |
| Heart failure | 869(0.24) 2657(1.91) | 869(0.24) 1723(2.37) < 0.01 |
| New coronary heart disease | 60(0.17) 110(0.07) 0.03 | 60(0.17) 126(0.17) < 0.01 |
| Renal diseases | 148(0.40) 1798(1.29) | 148(0.40) 290(0.40) < 0.01 |
| Neurological diabetic complication | 62(0.18) 402(0.28) 0.02 | 62(0.18) 131(0.18) < 0.01 |
| Osteoporosis | 15(0.04) 53(0.03) < 0.01 | 15(0.04) 30(0.04) < 0.01 |
| Ophthalmic diabetic complication | 189(0.52) 1466(1.05) 0.06 | 189(0.52) 376(0.51) < 0.01 |
| Liver diseases | 56(0.15) | 56(0.15) 112(0.15) < 0.01 |
| Ventricular tachy/ fibrillation | 127(0.35) | 127(0.35) 250(0.34) < 0.01 |
| Dementia | 180(0.49) | 180(0.49) 357(0.49) < 0.01 |
| Anemia | 1534(4.23) | 1534(4.23) 2985(4.11) 0.01 |
| AMI | 499(1.37) | 499(1.37) 995(1.37) < 0.01 |
| COPD | 587(1.62) | 587(1.62) 1161(1.60) < 0.01 |
| IHD | 224(6.13) 7533(5.43) 0.03 | 224(6.13) 4428(6.11) < 0.01 |
| PVD | 156(0.43) 640(0.46) < 0.01 | 156(0.43) 310(0.42) < 0.01 |
| Gastrointestinal bleeding | 625(1.72) | 625(1.72) 1234(1.70) < 0.01 |
| Malignancy | 218(0.60) 755(0.54) 0.01 | 218(0.60) 436(0.60) < 0.01 |
| Obesity | 113(0.31) 1046(0.75) 0.06 | 113(0.31) 226(0.31) < 0.01 |
| Medications | | | | |
| Number of diabetes mellitus drugs | 1.8(0.6);6.0;n = 36,228 | 1.8(0.6);6.0;n = 138,707 | 1.8(0.5);5.0;n = 72,456 0.05 |
| Number of cardiovascular drugs | 1.9(1.2);5.0;n = 36,228 | 1.9(1.2);5.0;n = 138,707 | 1.9(1.2);5.0;n = 72,456 < 0.01 |
| ACEI/ARB | 18,529(51.14) | 18,529(51.14) 37,451(51.68) 0.01 |
| Beta blockers | 14,309(39.49) 45,613(32.88) | 14,309(39.49) 28,559(39.41) < 0.01 |
| Calcium channel blockers | 18,428(50.86) 53,427(38.51) | 18,428(50.86) 36,821(50.81) < 0.01 |
### Table 1 (continued)

| Characteristics | Before matching | SMD | After 1:2 matching | SMD |
|-----------------|----------------|-----|-------------------|-----|
| **Suflphonylurea (N = 36,228)** | | | | |
| Mean(SD);Max;N or Count(%) | Mean(SD);Max;N or Count(%) | | Mean(SD);Max;N or Count(%) | |
| **Metformin (N = 138,707)** | | | | |
| **SD** | 0.16 | 15.739(21.72) | 0.01 |
| **Mean, mmol/L** | 0.04 | 17.046(23.52) | 0.01 |
| **Normalized absolute successive variability score** | 0.02 | 0.00 | 0.00 |
| **Normalized percentage successive variability score** | 0.00 | 0.00 | 0.00 |
| **SD/Initial** | 0.01 | 22.4(19.9);378.8;n = 31,839 | 0.05 |

### Laboratory tests

#### Characteristics

- Lymphocyte, × 10⁹/L
- Neutrophil, × 10⁹/L
- Platelet, × 10⁹/L
- Urea, mmol/L
- Creatinine, umol/L
- Total protein, g/L
- Alkaline phosphatase, U/L
- Aspartate transaminase, U/L
- Alanine transaminase, U/L
- Bilirubin, μmol/L
- Triglycerides, mmol/L
- Total cholesterol, mmol/L
- HDL, mmol/L
- NLR
- Fasting blood glucose, mmol/L
- HbA1c, %

#### Variability measurements: Glucose

- Absolute successive variability score
- Percentage successive variability score
- SD
- Mean, mmol/L
- Normalized absolute successive variability score
- Normalized percentage successive variability score
- SD/Initial

### Notes

- Variability score
- Normalized
- Mean, mmol/L
- 24.0(4.4);21.2;n = 15,752
- 6.1(3.0);22.2;n = 58,148
- 6.1(3.0);22.2;n = 58,148
- 23.4(20.4);418.2;n = 15,751

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Discussion

The main finding for the present study is that in comparison with metformin users, sulphonylurea users have a higher risk of new-onset AF, new-onset stroke, cardiovascular mortality and all-cause mortality. Males and those older than 65 years receiving sulphonylurea were amongst those at the highest risks of these outcomes.

Metformin and sulphonylurea are two of the most prescribed drugs for initial diabetic control. One of the reasons is that clinicians would prescribe less metformin in patients with chronic kidney disease, which is prevalent in Hong Kong and Asia [21]. Other reasons included the socioeconomic factors that sulphonylurea is more affordable per year [22]. However, it was uncertain whether 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 [23]. This is partly explained by the fact that metformin enhances insulin sensitivity while sulphonylurea acts by increasing endogenous insulin levels. As such, metformin use has been associated with fewer hypoglycaemic events compared to sulphonylurea [24, 25]. 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 parts of the world [26–28]. It has been proposed that hyperinsulinaemia would raise the risk of cancers risks by increasing mitogenesis [29]. There are reports demonstrating an

value < 0.0001) and all-cause mortality (HR: 10.56 [9.45, 11.80], P value < 0.0001).

Table 1 (continued)

| Characteristics | Before matching | SMD | After 1:2 matching | SMD |
|-----------------|-----------------|-----|--------------------|-----|
|                 | Sulphonylurea (N = 36,228) | Metformin (N = 138,707) | Sulphonylurea (N = 36,228) | Metformin (N = 72,456) |
| Coefficient of variability | 20.2(12.2);110.9; n = 15,752 | 20.2(12.4);174.8; n = 58,148 | 0.01 | 20.2(12.2);110.9; n = 15,752 | 19.5(12.3);135.0; n = 31,839 | 0.06 |
| Variability independent of mean | 31.8(19.6);188.5; n = 15,752 | 31.8(19.9);323.1; n = 58,148 | < 0.01 | 31.8(19.6);188.5; n = 15,752 | 30.6(19.7);227.8; n = 31,839 | 0.06 |
| Variability measurements: HbA1c | 37.6(21.9);92.3; n = 16,935 | 37.0(21.5);93.3; n = 60,447 | 0.03 | 37.6(21.9);92.3; n = 16,935 | 36.1(21.9);90.9; n = 33,644 | 0.07 |
| Percentage successive variability score | 28.4(20.4);90.9; n = 16,935 | 27.5(19.9);90.9; n = 60,447 | 0.04 | 28.4(20.4);90.9; n = 16,935 | 26.8(20.0);90.0; n = 33,644 | 0.08 |
| SD | 0.9(0.7);8.0; n = 16,934 | 0.9(0.7);19.3; n = 60,440 | 0.02 | 0.9(0.7);8.0; n = 16,934 | 0.9(0.7);18.5; n = 33,637 | 0.06 |
| Mean, % | 7.7(1.1);19.0; n = 16,935 | 7.8(1.2);20.3; n = 60,447 | 0.08 | 7.7(1.1);19.0; n = 16,935 | 7.6(1.1);20.3; n = 33,644 | 0.04 |
| Normalized absolute successive variability score | 4.8(2.7);15.4; n = 16,935 | 4.7(2.7);14.6; n = 60,447 | 0.05 | 4.8(2.7);15.4; n = 16,935 | 4.6(2.7);14.3; n = 33,644 | 0.07 |
| Normalized percentage successive variability score | 3.6(2.6);15.4; n = 16,935 | 3.5(2.5);16.2; n = 60,447 | 0.06 | 3.6(2.6);15.4; n = 16,935 | 3.5(2.6);13.4; n = 33,644 | 0.07 |
| SD/Initial | 12.2(9.9);121.4; n = 16,686 | 12.4(10.6);296.4; n = 59,678 | 0.01 | 12.2(9.9);121.4; n = 16,686 | 11.7(9.9);253.2; n = 33,191 | 0.05 |
| Coefficient of variability | 11.3(7.7);74.5; n = 16,934 | 11.4(8.1);166.2; n = 60,440 | 0.01 | 11.3(7.7);74.5; n = 16,934 | 10.8(7.7);137.8; n = 33,637 | 0.06 |
| Variability independent of mean | 16.0(11.1);109.8; n = 16,934 | 16.2(11.6);252.1; n = 60,440 | 0.01 | 16.0(11.1);109.8; n = 16,934 | 15.3(11.1);214.2; n = 33,637 | 0.06 |
| Lipids | | | | |
| SD of LDL | 0.5(0.4);3.4; n = 6357 | 0.5(0.3);5.1; n = 23,852 | 0.04 | 0.5(0.4);3.4; n = 6357 | 0.5(0.3);3.0; n = 12,390 | 0.07 |
| SD of HDL | 0.1(0.1);1.2; n = 13,898 | 0.1(0.1);1.6; n = 54,920 | 0.07 | 0.1(0.1);1.2; n = 13,898 | 0.1(0.1);1.2; n = 28,779 | 0.06 |
| SD of TC | 0.6(0.4);8.3; n = 16,259 | 0.6(0.4);11.8; n = 62,537 | 0.02 | 0.6(0.4);8.3; n = 16,259 | 0.6(0.4);6.3; n = 32,886 | 0.06 |
| SD of TG | 0.6(0.9);28.0; n = 16,167 | 0.6(1.1);35.1; n = 62,344 | 0.06 | 0.6(0.9);28.0; n = 16,167 | 0.6(0.8);32.3; n = 32,815 | 0.02 |

*a for SMD ≥ 0.2, AF Atrial fibrillation, AMI Acute 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.*
increased risk of cancer in patients on sulphonylurea in comparison with metformin users [30]. Besides, sulphonylurea use was associated with higher risks of renal function decline and dementia [31–33] but similar pneumonia risk [34]. In particular, we identified that gliclazide increased the risks of cardiovascular mortality and increased the risks of causing all-cause mortality. A previous study suggested that gliclazide might increase the mortality risks compared to other sulphonylureas [35]. This raises the alarm bell regarding the safety concerns of gliclazide. Therefore, further research into the risks of gliclazide over other sulphonylureas on the other cardiovascular events is needed.

An abundance of evidence suggested strong associations between T2DM and AF occurrences [36]. 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 [37]. Reasonable glycaemic control would, therefore, reduce the AF onset as well as lessen the mortality rate amongst patients with AF. Our results are in accord with Ostropolets et al., which reported lower risks of AF in metformin compared to sulphonylurea [38]. These authors reported a 16% reduction in AF risk, compared to a 65% reduction in our study. A possible explanation for the differences is that our study included metformin or sulphonylurea users who were also on other anti-diabetic medications, whereas Ostropolets et al. only included patients on monotherapy. Metformin has antioxidant and anti-inflammatory effects that reduce atrial fibrosis and remodelling [39–41]. 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.

Fig. 2 Cumulative incidence curves of new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality stratified by sulphonylurea and metformin before 1:2 propensity score matching
Fig. 3 Cumulative incidence curves of new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality stratified by sulphonylurea and metformin use after 1:2 propensity score matching.

Table 2 HRs (and 95% CIs) of sulphonylurea vs. metformin from univariable Cox model, multivariable Cox model, cause-specific and subdistribution hazard models for cardiovascular mortality, all-cause mortality, new onset AF and stroke before and after 1:2 propensity score matching.

| Model                      | Outcome                  | Sulphonylurea vs. metformin (Before matching) HR [95% CI] | P value  | Sulphonylurea vs. metformin (After 1:2 matching) HR [95% CI] | P value |
|----------------------------|--------------------------|-----------------------------------------------------------|----------|------------------------------------------------------------|---------|
| Univariable 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***|
| Multivariable Cox model    | New onset AF             | 2.60[2.51, 2.79]                                          | <0.0001***| 2.89[2.75, 3.77]                                          | <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***|

*for p ≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001, AF: Atrial fibrillation, HR: Hazard ratio, CI: Confidence interval, *a*adjusted for significant demographics, past comorbidities and non-sulphonylurea/metformin medications.
duration and increase the cardiac excitability, resulting in AF [42].

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 glycaemic control [43]. Metformin activation of the glial cells 5’ adenosine monophosphate-activated protein kinase (AMPK) has neuroprotective effects [44]. 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 [45]. In contrast, sulphonylurea-induced hypoglycaemia contributes to stroke occurrence. Hypoglycaemic events have been reported to increase stroke risk via pathways such as increased platelet activation, thrombotic and atherosclerotic cytokine release, and inflammation [46, 47]. Furthermore, sulphonylurea stimulates the release of atherogenic C-peptide [48]. 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 are from a single locality; hence, external validation is needed to explore the applicability of these findings onto other populations. Secondly, important clinical factors, such as the body mass index, 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, given the retrospective nature, there is a lack of analysis of clinical outcomes during real-time follow-up. This study can only show the association between metformin and reducing AF and stroke outcomes but cannot demonstrate causality. 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. Males and patients older than 65 years with sulphonylurea use were at the highest risks of these adverse events.
Fig. 5  A Subgroup analysis for the cumulative incidence curves of new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality stratified by initial drug exposure age of sulphonylurea (Sul) and metformin (Met) prescription in the matched cohort. 

B Subgroup analysis for cumulative incidence curves of new onset AF, new onset stroke, cardiovascular mortality and all-cause mortality stratified by gender and sulphonylurea (Sul) and metformin (Met) prescription in the matched cohort.
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Authors' contributions JD, GZ, CC and OHIC carried out data analysis, data interpretation, statistical analysis, manuscript drafting and critical revision of manuscript. SL, KSKL, WTW, TL, AKCW and SHC were involved in project planning, data acquisition, data interpretation and critical revision of manuscript. QZ and GT took part in study conception, study supervision, project planning, data interpretation, statistical analysis, manuscript drafting and critical revision of manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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