Risk of New-Onset Prostate Cancer for Metformin Versus Sulfonylurea Use in Type 2 Diabetes Mellitus: A Propensity Score–Matched Study

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ABSTRACT

Background: The aim of this study was to compare the risks of new-onset prostate cancer between metformin and sulfonylurea users with type 2 diabetes mellitus (T2DM). **Methods:** This population-based retrospective cohort study included male patients with T2DM presenting to public hospitals/clinics in Hong Kong between January 1, 2000, and December 31, 2009. We only included patients prescribed either, but not both, metformin or sulfonylurea. All patients were followed up until December 31, 2019. The primary outcome was new-onset prostate cancer and the secondary outcome was all-cause mortality. One-to-one propensity score matching was performed between metformin and sulfonylurea users based on demographics, comorbidities, antidiabetic and cardiovascular medications, fasting blood glucose level, and hemoglobin A1c level. Subgroup analyses based on age and use of androgen deprivation therapy were performed. **Results:** The final study cohort consisted of 25,695 metformin users (mean [SD] age, 65.2 [11.8] years) and 25,695 matched sulfonylurea users (mean [SD] age, 65.3 [11.8] years) with a median follow-up duration of 119.6 months (interquartile range, 91.7–139.6 months) after 1:1 propensity score matching of 66,411 patients. Metformin users had lower risks of new-onset prostate cancer (hazard ratio, 0.80; 95% CI, 0.69–0.93; $P=.0031$) and all-cause mortality (hazard ratio, 0.89; 95% CI, 0.86–0.92; $P<.0001$) than sulfonylurea users. Metformin use was more protective against prostate cancer but less protective against all-cause mortality in patients aged <65 years (P for trend <.0001 for both) compared with patients aged ≥65 years. Metformin users had lower risk of all-cause mortality than sulfonylurea users, regardless of the use of androgen deprivation therapy (P for trend <.0001) among patients who developed prostate cancer. **Conclusions:** Metformin use was associated with significantly lower risks of new-onset prostate cancer and all-cause mortality than sulfonylurea use in male patients with T2DM.

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Background

Prostate cancer is the most common cancer diagnosis among male patients, and in 2019 was one of the main causes of death worldwide, with 487,000 deaths.[1] Known risk factors for prostate cancer include family history, ethnicity, and age.[2] Type 2 diabetes mellitus (T2DM) increases the risk of developing cancers such as colon, pancreatic, and bladder cancer.[3] However, the relationship between T2DM, glycemic control, and prostate cancer remains inconclusive.[4–6]

In addition, it has been suggested that the altered risk of new-onset prostate cancer in patients with T2DM is partly attributable to the use of antidiabetic drugs.[7] Metformin and sulfonylurea are the 2 most commonly prescribed oral antidiabetic drugs in the management of T2DM. Although most studies found that metformin was associated with lower incidence of new-onset cancers, there is limited discussion on prostate cancer in particular.[8] Among the few studies that focused on the association between the risk of prostate cancer and metformin, results have been inconclusive and, at times, contradictory.[9–11] Therefore, there is a need for further investigation into the effects of metformin or sulfonylurea on the risk of prostate

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cancer. This study aimed to compare the risks of new-onset prostate cancer between metformin and sulfonylurea users in a population-based cohort of patients with T2DM.

Methods

Study Design and Population

This study was 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. In this retrospective population-based cohort, we investigated the long-term effects of metformin versus sulfonylurea on the risk of new-onset prostate cancer using a propensity score matching approach. Patient data were collected from the Clinical Data Analysis and Reporting System, a comprehensive territory-wide database from individual public hospitals or outpatient facilities in Hong Kong. Data on mortality were accessed through the Hong Kong Death Registry, an official government registry with all of the registered death records in Hong Kong. No adjudication of the outcomes was performed in this study, because it depended on ICD-9 coding or death registry records. The coding was conducted by clinicians and other administrative staff who were not involved in the research process. This system has previously been used by our team and other teams to conduct population-based research on different diseases,[12,13] including diabetes mellitus.[14–17]

Inclusion criteria were patients with T2DM who were prescribed either metformin or sulfonylurea and who presented to local government hospitals or outpatient clinics between January 1, 2000, and December 31, 2009. Exclusion criteria were concomitant users of both metformin and sulfonylurea, <90 days of exposure of metformin/sulfonylurea in the first year after T2DM, baseline age <18 years, a cancer diagnosis before and within 90 days of T2DM or before initial metformin/sulfonylurea exposure, and patients who died within 90 days of T2DM, with prior renal failure diagnosis, new-onset prostate cancer within 1 year of drug exposure, and prior HIV infection.

Key comorbidities of patients before initial prescription of metformin/sulfonylurea drugs were extracted using the appropriate ICD-9 codes (supplemental eTable 1; available online, with this article, at JNCCN.org) to adjust and measure potential confounding variables. The number of prior comorbidities was also documented. In addition, prescription records of key medications, including insulin, acarbose, meglitinide, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, β-blockers, calcium channel blockers, diuretics, lipid-lowering agents, antiplatelets, and nonsteroidal anti-inflammatory drugs, were also recorded. Baseline laboratory test results obtained before the index prescription date of metformin/sulfonylurea were also extracted. The variability measures of fasting blood glucose and HbA1c were calculated; the underlying formulae are shown in supplemental eTable 2. The standard deviations (SDs) of high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride were calculated.

Outcomes and Follow-Up

The primary outcome was new-onset prostate cancer. The secondary outcome was all-cause mortality. All patients were followed up until December 31, 2019.

Statistical Analyses

Continuous variables were presented as mean (95% CI or SD) or median (interquartile range [IQR]), and categorical variables were presented as frequency (percent). One-to-one propensity score matching was performed between metformin and sulfonylurea users based on demographics, standard Charlson comorbidity score, past comorbidities, nonmetformin/nonsulfonylurea medications, fasting blood glucose level, and hemoglobin A1c (HbA1c) level to generate 2 matched cohorts of metformin and sulfonylurea users, respectively. Standardized mean differences (SMDs) were used to evaluate the balance in baseline covariates between treatment groups, and values <0.2 postweighting were considered negligible and indicative of good balance. Univariate Cox regression models were used to compare the risks of new-onset prostate cancer and all-cause mortality between treatment groups.

Sensitivity analyses were performed. First, a Cox proportional hazards model with a 1-year lag time was performed. Second, multiple propensity adjustment approaches were used, including propensity score stratification,[18] high-dimensional propensity score (HDPS) matching,[19] and inverse probability of treatment weighting (IPTW).[20] Third, cause-specific and subdistribution hazard models were used. Fourth, subgroup analysis by age was performed. Fifth, subgroup analysis was performed on patients who developed prostate cancer, with stratification for androgen deprivation therapy (ADT) use. A list of ADT agonist and antagonist drugs is available in supplemental eTable 3.

Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and P values were reported. All P values were 2-tailed, and values <.05 were considered statistically significant. Multiple imputations by chained equations were performed for missing values in fasting blood glucose and HbA1c. Each missing value was imputed 20 times using other variables. Propensity scores

of each patient in the cohort with the confounding variables were calculated with a logistic regression model. There was no blinding for the predictors, because the data were obtained automatically and directly from the electronic health records. RStudio software (version 1.1.456) and Python (version 3.6) were used for data analyses throughout the study.

Results

Study Cohort

A flow diagram of the cohort identification, inclusion, and exclusion is shown in Figure 1. In total, 131,160 male patients with T2DM were identified. After excluding patients without metformin or sulfonylurea use (n=22,797), those with both metformin or sulfonylurea use (n=40,311), with <90 days of exposure of metformin/sulfonylurea (n=1,015), with a baseline age <18 years (n=35), with a cancer diagnosis before and within 90 days of T2DM diagnosis or before initial metformin/sulfonylurea exposure (n=231), who died within 90 days of T2DM diagnosis (n=117), with prior renal failure diagnosis (n=135), and with new-onset prostate cancer within 1 year of drug exposure (n=89) or HIV infection (n=19), a total of 66,411 male patients were included (mean [SD] age at initial drug use, 65.3 [12.3] years) with a median follow-up duration of 119.6 months (IQR, 91.7–139.6). After 1:1 propensity score matching, the final matched study cohort consisted of 25,695 metformin users and 25,695 sulfonylurea users. HbA1c (expressed as a percentage) was similar in both metformin and sulfonylurea users (mean [SD], 7.45 [1.47] vs 7.45 [1.42], respectively; SMD, <0.01). Baseline and clinical characteristics of the study cohort before and after propensity score matching are shown in Table 1 and supplemental eTable 4. Distributions of propensity scores for metformin and sulfonylurea users before and after propensity score matching with the nearest-neighbor matching strategy and a caliper of 0.1 are presented in supplemental eFigure 1.

Outcomes

The results of Cox regression are shown in Table 2 and supplemental eTable 5. Metformin users had significantly lower risks of new-onset prostate cancer (HR, 0.80; 95% CI, 0.69–0.93; P=.0031) and all-cause mortality (HR, 0.89; 95% CI, 0.86–0.92; P<.0001) than sulfonylurea users, as visualized in the Kaplan-Meier curves in Figure 2 and cumulative incidence curves in supplemental eFigure 2. The annualized total and drug-specific incidence rate of all-cause mortality and new-onset prostate cancer per 1,000 patients per year in the matched cohort are reported in supplemental eTables 6 and 7, respectively.

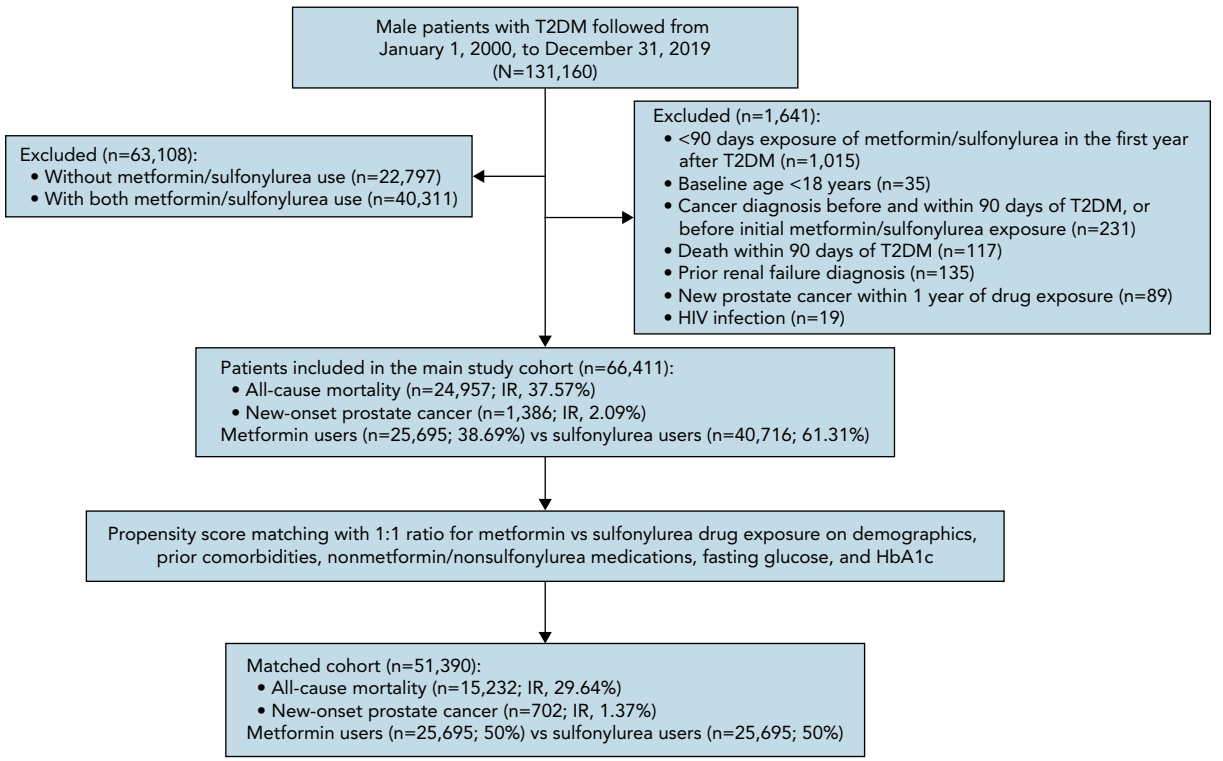

Figure 1. Procedures of data processing.
Abbreviations: HbA1c, hemoglobin A1c; IR, incidence rate; T2DM, type 2 diabetes mellitus.

Table 1. Baseline and Clinical Patient Characteristics

Characteristic	Before Matching				After Matching			
	All n (%)	Metformin Users n (%)	Sulfonylurea Users n (%)	SMD	All n (%)	Metformin Users n (%)	Sulfonylurea Users n (%)	SMD
Total, n	66,411	25,695	40,716		51,390	25,695	25,695	
Demographics								
Baseline age, mean [SD], y	65.3 [12.3]	65.2 [11.8]	65.3 [12.5]	0.01	65.3 [11.8]	65.2 [11.8]	65.3 [11.8]	<0.01
Past comorbidities								
CCS, mean 5[SD]	2.6 [1.8]	2.6 [1.8]	2.7 [1.9]	0.06	2.6 [1.7]	2.6 [1.8]	2.5 [1.7]	0.03
Hypertension	16,885 (25.42)	6,697 (26.06)	10,188 (25.02)	0.02	13,376 (26.02)	6,705 (26.09)	6,671 (25.96)	<0.01
Heart failure	2,966 (4.46)	1,233 (4.79)	1,733 (4.25)	0.03	2,433 (4.73)	1,232 (4.79)	1,201 (4.67)	0.01
Acute MI	1,684 (2.53)	654 (2.54)	1,030 (2.52)	<0.01	1,307 (2.54)	654 (2.54)	653 (2.54)	<0.01
PVD	494 (0.74)	161 (0.62)	333 (0.81)	0.02	322 (0.62)	160 (0.62)	162 (0.63)	<0.01
Stroke/TIA	3,527 (5.31)	1,351 (5.25)	2,176 (5.34)	<0.01	2,668 (5.19)	1,353 (5.26)	1,315 (5.11)	0.01
Hemiplegia or paraplegia	836 (1.25)	281 (1.09)	555 (1.36)	0.02	562 (1.09)	281 (1.09)	281 (1.09)	<0.01
VT/VF/SCD	2,273 (3.42)	1,004 (3.90)	1,269 (3.11)	0.04	1,995 (3.88)	1,004 (3.90)	991 (3.85)	<0.01
Atrial fibrillation	2,113 (3.18)	815 (3.17)	1,298 (3.18)	<0.01	1,618 (3.14)	816 (3.17)	802 (3.12)	<0.01
CHD	8,871 (13.35)	3,613 (14.06)	5,258 (12.91)	0.03	7,092 (13.80)	3,615 (14.06)	3,477 (13.53)	0.02
COPD	1,625 (2.44)	534 (2.07)	1,091 (2.67)	0.04	1,064 (2.07)	534 (2.07)	530 (2.06)	<0.01
Anemia	5,192 (7.81)	2,921 (11.36)	2,271 (5.57)	0.21[a]	5,480 (10.66)	2,915 (11.34)	2,565 (9.98)	0.04
Medications								
Insulin	7,147 (10.76)	2,060 (8.01)	5,087 (12.49)	0.15	4,068 (7.91)	2,060 (8.01)	2,008 (7.81)	0.01
Acarbose	1,087 (1.63)	375 (1.45)	712 (1.74)	0.02	745 (1.44)	374 (1.45)	371 (1.44)	<0.01
Meglitinide	1,021 (1.53)	643 (2.50)	378 (0.92)	0.12	1,275 (2.48)	642 (2.49)	633 (2.46)	<0.01
Laboratory examinations, mean [SD]								
Urea/Creatinine ratio	64.5 [18.8]; n=36,432	63.8 [18.2]; n=15,218	65.0 [19.2]; n=21,214	0.07	64.4 [18.2]; n=28,730	63.8 [18.2]; n=15,215	65.0 [18.3]; n=13,515	0.07
Creatinine, μmol/L	111.5 [85.9]; n=36,750	122.1 [108.3]; n=15,340	103.8 [64.3]; n=21,410	0.21[a]	115.7 [96.8]; n=28,965	122.1 [108.3]; n=15,337	108.6 [81.4]; n=13,628	0.14
HDL, mmol/L	1.1 [0.3]; n=42,394	1.13 [0.32]; n=16,019	1.13 [0.31]; n=26,375	<0.01	1.1 [0.3]; n=32,526	1.13 [0.32]; n=16,027	1.12 [0.3]; n=16,499	0.02
LDL, mmol/L	2.8 [0.9]; n=27,148	2.84 [0.87]; n=10,086	2.82 [0.85]; n=17,062	0.02	2.8 [0.9]; n=20,966	2.84 [0.87]; n=10,095	2.84 [0.85]; n=10,871	<0.01
TC, mmol/L	4.6 [1.0]; n=46,790	4.61 [1.0]; n=17,711	4.63 [0.99]; n=29,079	0.02	4.6 [1.0]; n=35,950	4.61 [1.0]; n=17,715	4.63 [0.99]; n=18,235	0.02
TG, mmol/L	1.7 [1.4]; n=46,712	1.6 [1.4]; n=17,679	1.7 [1.4]; n=29,033	0.04	1.6 [1.4]; n=35,895	1.6 [1.4]; n=17,683	1.7 [1.4]; n=18,212	0.04
FBG, mmol/L	7.8 [2.7]; n=31,823	7.77 [2.66]; n=12,587	7.77 [2.65]; n=19,236	<0.01	7.8 [2.7]; n=24,651	7.77 [2.65]; n=12,590	7.81 [2.69]; n=12,061	0.01
HbA1c, %	7.5 [1.5]; n=32,250	7.45 [1.47]; n=12,807	7.47 [1.46]; n=19,443	0.01	7.5 [1.4]; n=25,036	7.45 [1.47]; n=12,810	7.45 [1.42]; n=12,226	<0.01

Abbreviations: CCS, Charlson comorbidity score; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PVD, peripheral vascular disease; SCD, sudden cardiac death; SMD, standardized mean difference; TC, total cholesterol; TG, triglyceride; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]For SMD≥0.2.

Sensitivity analyses for the study outcomes in the matched cohort are presented in the following sections, which included analyses with a 1-year lag time, with different propensity score–matching approaches (supplemental eTable 8), and with cause-specific and subdistribution hazard competing risks models (supplemental

Table 2. Univariable Cox Regression to Identify Significant Risk Predictors of New-Onset Prostate Cancer and All-Cause Mortality

Characteristic	Before Matching		After Matching	
	All-Cause Mortality HR (95% CI); *P* Value	New-Onset Prostate Cancer HR (95% CI); *P* Value	All-Cause Mortality HR (95% CI); *P* Value	New-Onset Prostate Cancer HR (95% CI); *P* Value
Demographics				
Baseline age, y	1.089 (1.087–1.090); <.0001***	1.05 (1.05–1.06); <.0001***	1.10 (1.09–1.10); <.0001***	1.06 (1.05–1.06); <.0001***
Past comorbidities				
CCS	1.41 (1.40–1.42); <.0001***	1.19 (1.16–1.22); <.0001***	1.49 (1.48–1.50); <.0001***	1.22 (1.17–1.27); <.0001***
Hypertension	2.19 (2.14–2.25); <.0001***	1.20 (1.07–1.36); .0025**	2.48 (2.40–2.56); <.0001***	1.14 (0.97–1.36); .1197
Heart failure	3.95 (3.78–4.12); <.0001***	1.05 (0.78–1.42); .7486	5.00 (4.76–5.24); <.0001***	1.01 (0.66–1.55); .9511
Acute MI	1.73 (1.63–1.85); <.0001***	0.71 (0.47–1.07); .0969	1.82 (1.67–1.97); <.0001***	0.48 (0.24–0.97); .0413*
PVD	2.81 (2.54–3.12); <.0001***	0.61 (0.25–1.47); .2707	3.37 (2.95–3.85); <.0001***	0.60 (0.15–2.41); .4746
Stroke/TIA	2.53 (2.42–2.64); <.0001***	0.97 (0.75–1.27); .8450	2.92 (2.78–3.08); <.0001***	0.74 (0.48–1.13); .1588
Hemiplegia or paraplegia	2.65 (2.44–2.87); <.0001***	0.78 (0.43–1.41); .4083	3.27 (2.95–3.61); <.0001***	0.67 (0.25–1.79); .4227
VT/VF/SCD	1.76 (1.66–1.86); <.0001***	0.69 (0.48–0.99); .0452*	2.00 (1.88–2.14); <.0001***	0.63 (0.38–1.04); .0732
Atrial fibrillation	2.93 (2.78–3.08); <.0001***	1.14 (0.82–1.57); .4362	3.25 (3.05–3.46); <.0001***	1.30 (0.85–1.99); .2247
CHD	1.78 (1.72–1.83); <.0001***	1.19 (1.02–1.38); .0286*	1.82 (1.75–1.90); <.0001***	0.88 (0.70–1.12); .3003
COPD	2.72 (2.56–2.88); <.0001***	1.11 (0.77–1.59); .5881	2.99 (2.77–3.23); <.0001***	1.30 (0.78–2.18); .3088
Anemia	3.90 (3.77–4.03); <.0001***	0.91 (0.71–1.16); .4369	5.52 (5.32–5.72); <.0001***	0.97 (0.73–1.30); .8468
Medications				
Metformin vs sulfonylurea	0.59 (0.58–0.61); <.0001***	0.50 (0.44–0.57); <.0001***	0.89 (0.86–0.92); <.0001***	0.80 (0.69–0.93); .0031**
Metformin duration, d	1.000 (1.000–1.0001); <.0001***	1.000 (1.000–1.0001); .0002***	1.000 (1.000–1.0001); <.0001***	1.000 (1.000–1.0001); .0011**
Sulfonylurea duration, d	1.000 (1.000–1.0001); <.0001***	1.000 (1.000–1.000); .5488	1.000 (1.000–1.0001); <.0001***	1.000 (1.000–1.000); .1612
Insulin	1.55 (1.49–1.61); <.0001***	0.84 (0.69–1.01); .0630	1.70 (1.62–1.79); <.0001***	0.93 (0.69–1.25); .6260
Acarbose	1.57 (1.44–1.70); <.0001***	1.13 (0.75–1.71); .5606	1.60 (1.43–1.79); <.0001***	0.98 (0.51–1.89); .9508
Meglitinide	2.24 (2.07–2.42); <.0001***	0.69 (0.39–1.22); .2065	2.90 (2.70–3.12); <.0001***	0.66 (0.34–1.26); .2076
Laboratory examinations				
Urea/Creatinine ratio	0.999 (0.998–1.000); .0173*	1.01 (1.00–1.01); .0025**	0.997 (0.996–0.998); <.0001***	1.00 (1.00–1.01); .1886
Creatinine, μmol/L	1.002 (1.002–1.003); <.0001***	1.000 (0.998–1.001); .5294	1.003 (1.003–1.003); <.0001***	1.000 (0.998–1.001); .8595
HDL, mmol/L	0.96 (0.91–1.01); .1071	0.93 (0.74–1.16); .5077	0.92 (0.86–0.98); .0085**	0.78 (0.56–1.08); .1272
LDL, mmol/L	0.90 (0.88–0.93); <.0001***	1.07 (0.97–1.18); .1709	0.92 (0.89–0.94); <.0001***	0.96 (0.83–1.11); .5733
TC, mmol/L	0.84 (0.82–0.85); <.0001***	0.95 (0.89–1.02); .1319	0.83 (0.81–0.84); <.0001***	0.94 (0.85–1.03); .1806
TG, mmol/L	0.90 (0.89–0.92); <.0001***	0.96 (0.91–1.01); .1490	0.91 (0.89–0.92); <.0001***	1.01 (0.95–1.07); .8074
FBG, mmol/L	1.00 (0.99–1.01); .7192	0.99 (0.96–1.02); .6439	0.99 (0.99–1.00); .1816	0.99 (0.95–1.03); .6725
HbA1c, %	1.00 (0.99–1.01); .6516	0.99 (0.93–1.04); .5806	1.00 (0.99–1.02); .6525	0.96 (0.89–1.04); .3583

Abbreviations: CCS, Charlson comorbidity score; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MI, myocardial infarction; PVD, peripheral vascular disease; SCD, sudden cardiac death; TC, total cholesterol; TG, triglycerides; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 9). Subgroup analyses are reported in the following sections, which included analyses after age stratification (supplemental eTable 10), and by use of ADT (supplemental eTables 11–14).

Sensitivity Analysis With a 1-Year Lag Time

When analyzed with a 1-year lag time, metformin users had lower risks of new-onset prostate cancer (HR, 0.54; 95% CI, 0.53–0.62; $P<.0001$) and all-cause

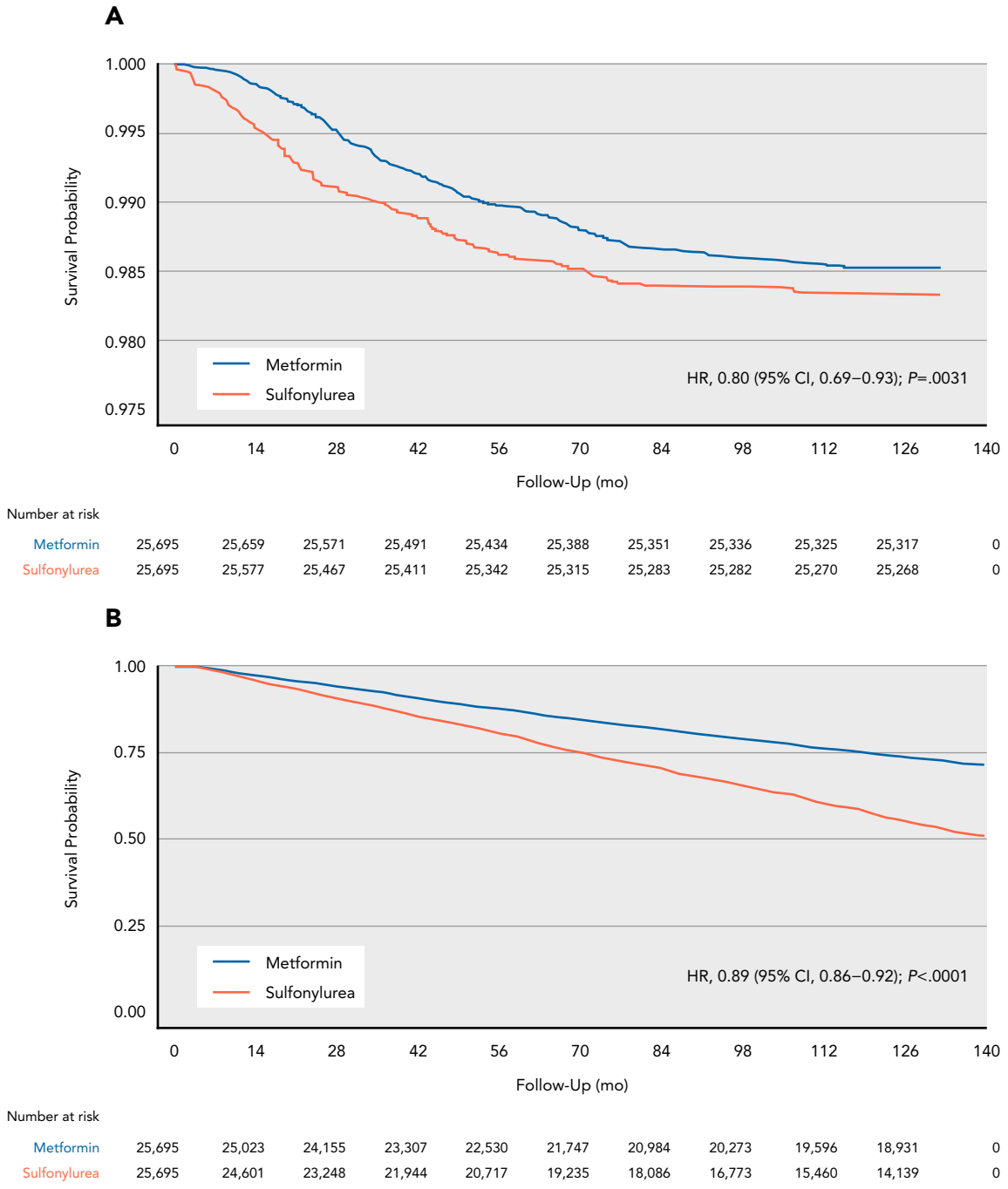

Figure 2. Kaplan-Meier survival curves of **(A)** new-onset prostate cancer and **(B)** all-cause mortality, stratified by prescription of metformin versus sulfonylurea in the matched cohort.
Abbreviations: CI, confidence interval; HR, hazard ratio.

mortality (HR, 0.88; 95% CI, 0.85–0.93; $P<.0001$) than sulfonylurea users.

Sensitivity Analysis Based on Different Propensity Score Matching Approaches

Metformin users had consistently lower risk of developing new-onset prostate cancer than sulfonylurea users when analyzed with propensity score stratification (HR, 0.63; 95% CI, 0.54–0.69; $P<.0001$), HDPS matching (HR, 0.67; 95% CI, 0.55–0.75; $P<.0001$), and IPTW (HR, 0.72; 95% CI, 0.67–0.81; $P<.0001$). Metformin users also had lower risk of all-cause mortality than sulfonylurea users when analyzed with propensity score stratification (HR, 0.89; 95% CI, 0.82–0.95; $P<.0001$), HDPS matching (HR, 0.86; 95% CI, 0.75–0.90; $P<.0001$), and IPTW (HR, 0.89; 95% CI,

0.85–0.97; $P<.0001$). These are summarized in supplemental eTable 8.

Sensitivity Analysis Based on Cause-Specific and Subdistribution Hazard Models

Metformin users had lower risk of developing new-onset prostate cancer than sulfonylurea users in both cause-specific (HR, 0.89; 95% CI, 0.75–0.95; $P<.0001$) and subdistribution hazard models (HR, 0.83; 95% CI, 0.72–0.89; $P<.0001$). Metformin users also had lower risk of all-cause mortality than sulfonylurea users in both cause-specific (HR, 0.61; 95% CI, 0.56–0.72; $P<.0001$) and subdistribution hazard models (HR, 0.59; 95% CI, 0.51–0.66; $P<.0001$). These are summarized in supplemental eTable 9.

Subgroup Analysis by Age Stratification

Risk of developing the study outcomes was assessed between patients aged ≥65 years and those aged <65 years (supplemental eTable 10), as visualized in the Kaplan-Meier curves and cumulative incidence curves in supplemental eFigures 3 and 4. Among patients aged ≥65 years, metformin users had a lower risk of developing prostate cancer (HR, 0.93; 95% CI, 0.79–0.98; $P=.0272$) and all-cause mortality (HR, 0.45; 95% CI, 0.44–0.47; $P<.0001$). Among patients aged <65 years, metformin users had consistently lower risk of developing prostate cancer (HR, 0.78; 95% CI, 0.60–0.95; $P=.0401$) and all-cause mortality (HR, 0.57; 95% CI, 0.53–0.61; $P<.0001$). There were significant interactions between age groups for the risks of both developing prostate cancer and all-cause mortality ($P<.0001$ for both), suggesting that metformin was more protective against prostate cancer but less protective against all-cause mortality in younger patients.

Subgroup Analysis by Use of ADT

We analyzed the effect of ADT, including gonadotropin-releasing hormone (GnRH) agonists and antagonists, on all-cause mortality among metformin and sulfonylurea users who developed prostate cancer (supplemental eTables 11–14). No significant differences were seen in the risk of all-cause mortality between ADT users and nonusers (HR, 0.80; 95% CI, 0.62–1.04; $P=.1015$), which remained insignificant on further analysis by the subgroup of ADT (GnRH antagonists vs non-ADT: HR, 0.71; 95% CI, 0.39–1.30; $P=.2670$; and GnRH agonists vs non-ADT: HR, 0.76; 95% CI, 0.58–1.00; $P=.0504$). Use of ADT was not associated with significantly different risk of all-cause mortality (metformin and ADT vs metformin alone: HR, 0.97; 95% CI, 0.45–2.10; $P=.9448$), which was also consistently observed for both users of GnRH antagonists and GnRH agonists. Importantly, sulfonylurea users consistently had higher risks of all-cause mortality than metformin users among ADT users, GnRH antagonist users, and GnRH agonist users (P for trend <.0001 for all).

Discussion

In this population-based cohort study, we showed that long-term metformin use in male patients with T2DM was associated with significantly lower risks of new-onset prostate cancer and all-cause mortality than sulfonylurea use. In addition, such differences seemed to be stronger in younger patients.

Metformin and sulfonylureas are 2 of the most prescribed drugs for T2DM. Metformin is recommended as first-line therapy for its high efficacy, low cost, weight neutrality, and good safety profile.[21] Sulfonylureas, compared with metformin, are associated with an increased risk of myocardial infarction and all-cause mortality.[22] These findings have led to relegation of sulfonylureas in recent guidelines.[23] This was accompanied by persistent increases in metformin prescriptions and decreases in sulfonylurea prescriptions both locally[24] and internationally.[25] Our findings suggest a further reason to discourage the use of sulfonylureas, particularly in the male population. We acknowledge that our findings contradict those of a recent study, which found that metformin use was not associated with any change in the risk of developing prostate cancer, although it has a selective protective effect against liver cancer.[4] Nonetheless, the study included patients who, on average, had relatively low HbA1c levels, which may explain the low incidence of new-onset prostate cancer due to better glycemic control.[5]

AMP-activated protein kinase (AMPK) activation is the main mechanism by which metformin inhibits prostate cancer growth.[26] AMPK arrests the cell cycle and cell growth by inhibiting the AKT/mTOR signaling pathway.[27] Metformin not only activates AMPK and inactivates AKT but also inactivates p70S6 kinase, which is downstream of mTOR.[28] Metformin's antiproliferative effect in prostate cancer cells can also be AMPK-independent through acting on REDD1,[29] an inhibitor of mTOR, and cyclin D1.[30] In addition, metformin represses the COX-2/PGE2/STAT3 axes to inhibit castration-induced epithelial–mesenchymal transition in prostate cancer, which is closely related to drug resistance, tumor relapse, and metastasis.[31] Inhibition of the GTPase Rac1 is a novel mechanism by which metformin reduces metastases in prostate cancer.[32] Furthermore, it was reported that metformin treatment decreases c-MYC oncogene expression and the incidence of prostate intraepithelial lesion formation, and its proapoptotic effects are limited to malignant cells.[33]

Our study also found that the protective effect of metformin was stronger in patients aged <65 years. This may again be related to AMPK activity. In animal models, it was found that the sensitivity of AMPK activation is

higher in young tissues.[34] Age-related changes in the function of protein phosphatases (PP2A, PP2Cα, and Ppm1E) may be involved in suppressing AMPK signaling with aging.[35–37] Furthermore, aging and aging-related disorders are associated with oxidative stress,[38] which is heavily implicated in the development of prostate cancer.[39] In prostate cancer, a supraphysiological concentration of reactive oxygen species is a hallmark of aggressive disease.[40] In older adults with T2DM, oxidative stress and hyperglycemia can increase the formation of advanced glycation end products.[41] When combined with elevated levels of reactive oxygen species, advanced glycation end products enhance the antiapoptotic nuclear factor-κB pathway.[42]

Research is underway to explore the role of metformin in the treatment of prostate cancer. ADT is the first-line treatment of prostate cancer, but many patients eventually do not respond well and develop castrate resistance.[43] Metformin, when combined with ADT, is associated with improved survival in advanced prostate cancer.[44] In addition, ADT can cause metabolic[45] and cardiovascular consequences,[46] and metformin is shown to ameliorate these adverse effects.[47] Metformin may also be used as an adjuvant to chemotherapy because it reduces the dose necessary to prolong remission.[48] As an adjuvant agent to radical radiotherapy, metformin may improve survival outcomes.[49]

Our study also highlights the importance of pharmacotherapeutic choice for patients with T2DM at high risk of prostate cancer. Although the antineoplastic effects of metformin have been widely studied, they are still not completely understood in different cancer types. More study is needed to determine the dose of metformin required to exert antitumor control in prostate cancer and whether it can be safely recommended in current practice.

The main strength of the present study was that a large and representative territory-wide database with long follow-up duration was used. Our findings are thus generalized and may broadly reflect the real-world practice in Hong Kong. In addition, sensitivity analyses based on different approaches were performed with consistent results, indicating that our findings were robust. However, some limitations are present. First, this study is an observational cohort study, and therefore residual confounding cannot be excluded. The possible presence of observational bias, coding error, and undercoding should be noted. Second, data about medication adherence are lacking due to the nature of these data.

Conclusions

Long-term metformin use was associated with significantly lower risk of new-onset prostate cancer and all-cause mortality in male patients with T2DM than sulfonylurea use. Metformin seemed to be more protective against prostate cancer but less protective against all-cause mortality in those aged <65 years.

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Supplemental online content for:

Risk of New-Onset Prostate Cancer for Metformin Versus Sulfonylurea Use in Type 2 Diabetes Mellitus: A Propensity Score–Matched Study

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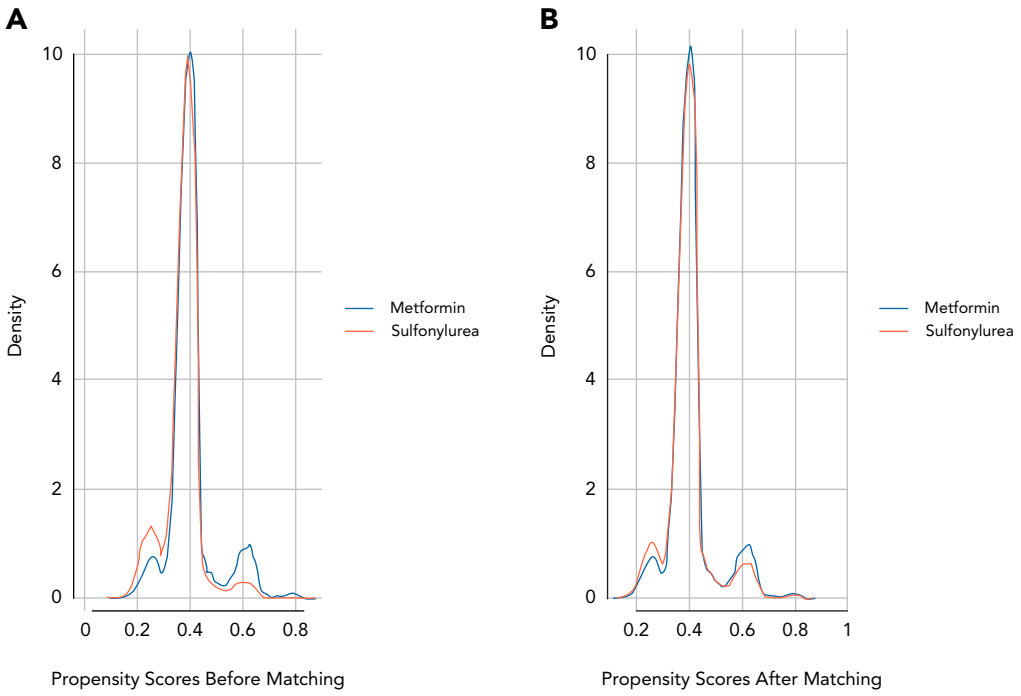
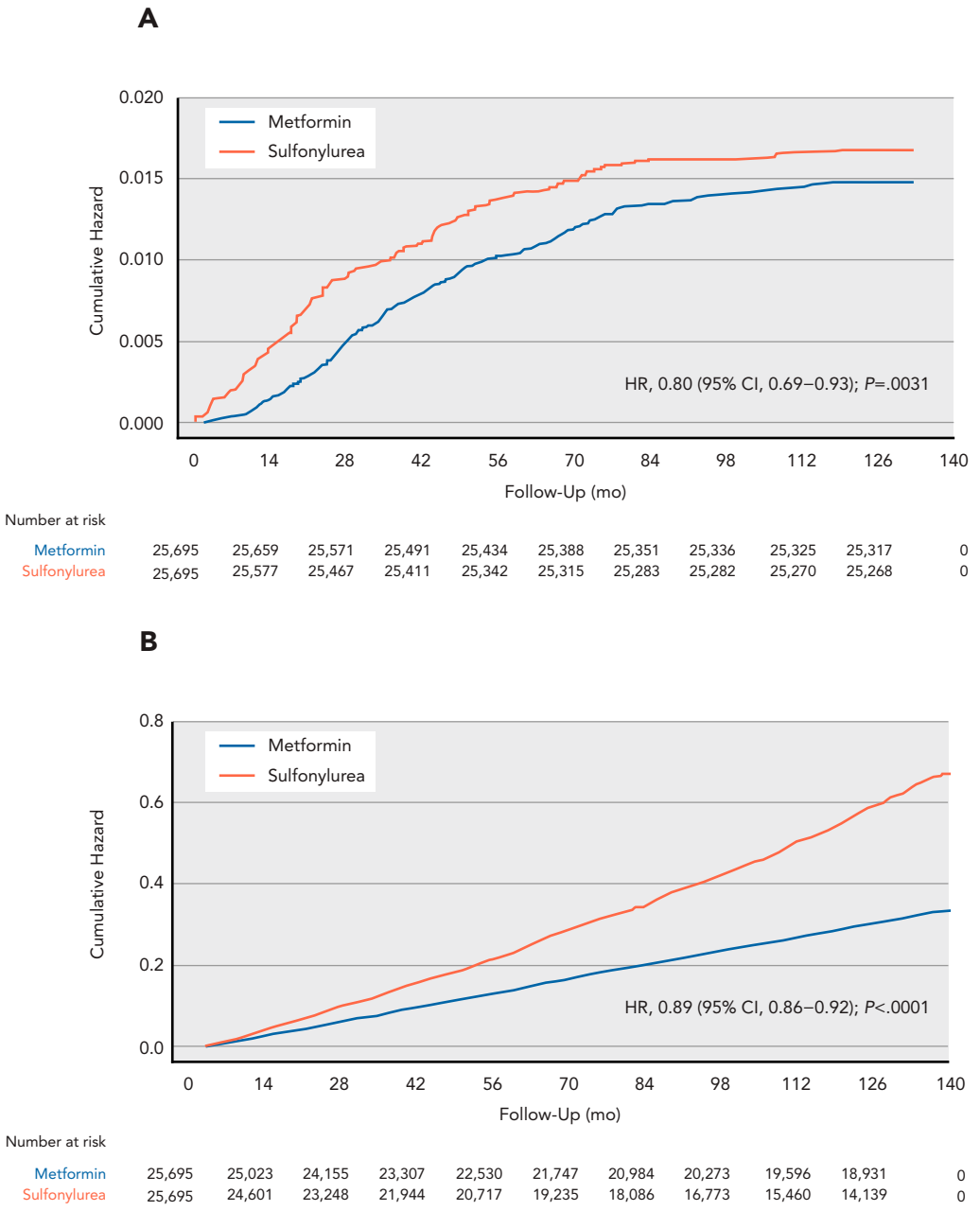
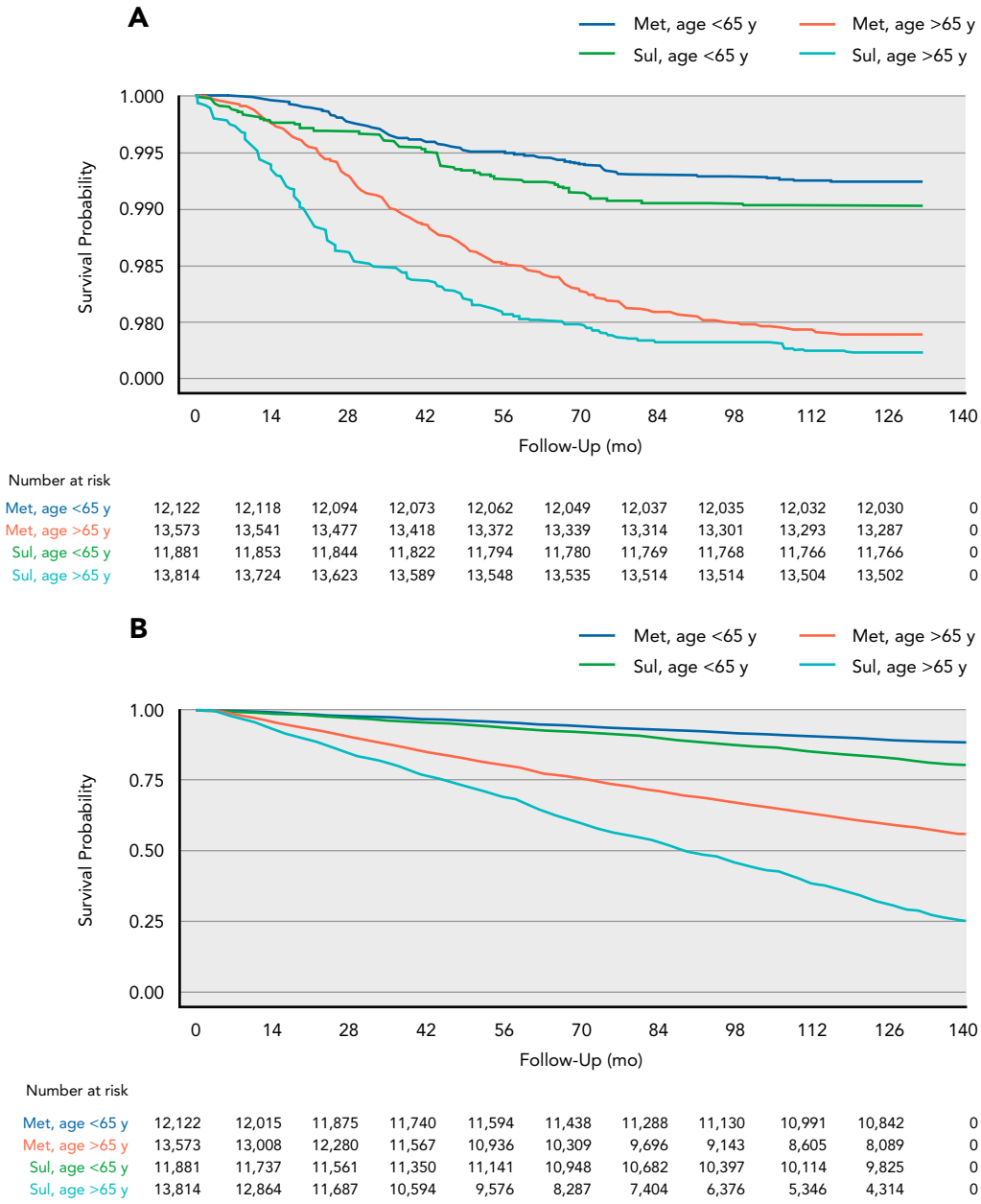


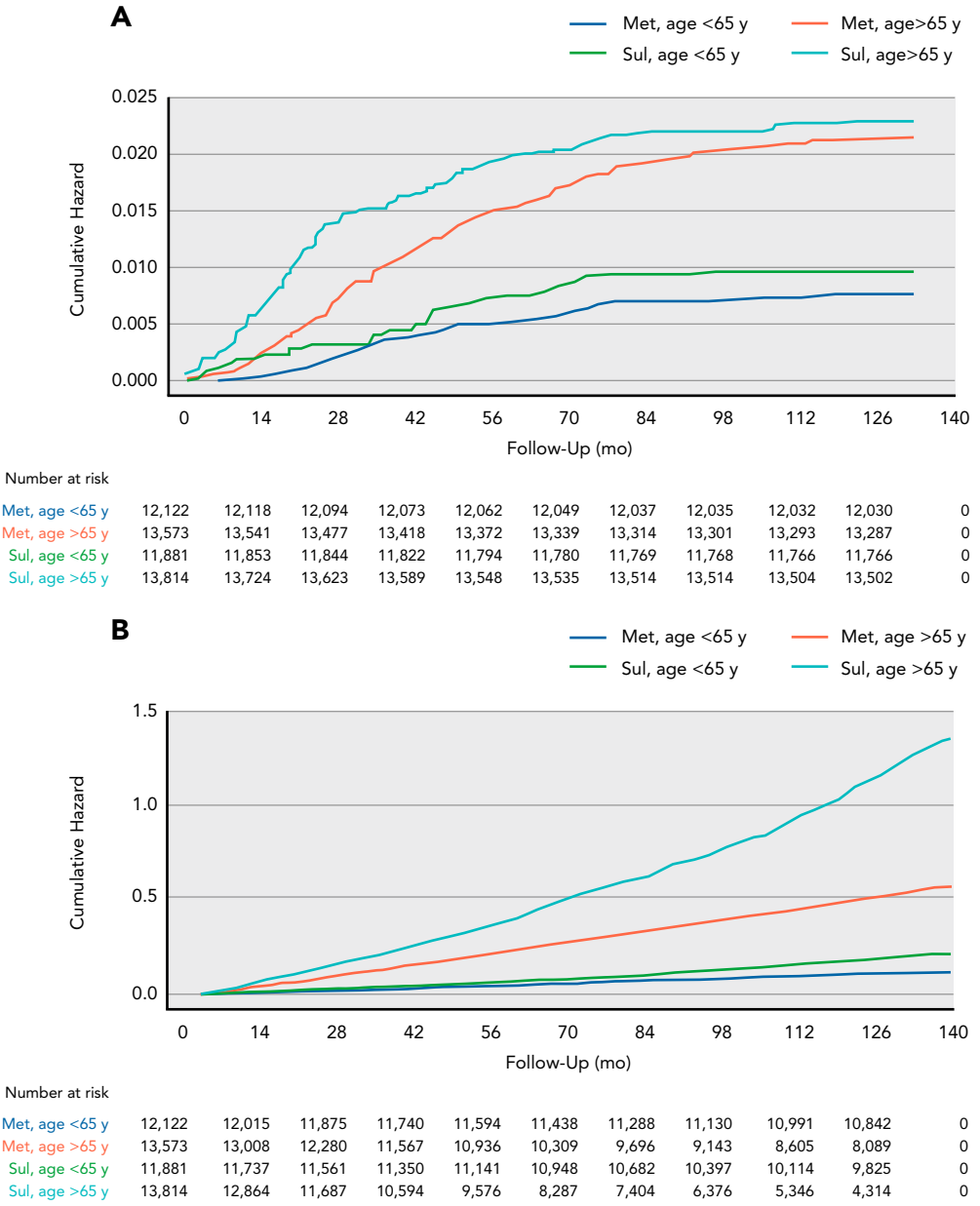
eFigure 1. Propensity score matching for metformin versus sulfonylurea **(A)** before and **(B)** after 1:1 matching with nearest neighbor search strategy (caliper = 0.1).



eFigure 2. Cumulative incidence curves of **(A)** new-onset prostate cancer and **(B)** all-cause mortality stratified by prescription of metformin versus sulfonylurea in the matched cohort.



eFigure 3. Subgroup stratification analysis: Kaplan-Meier survival curves of **(A)** new-onset prostate cancer and **(B)** all-cause mortality stratified by age at initial drug exposure and prescription of metformin versus sulfonylurea after 1:1 matching.
Abbreviations: met, metformin; sul, sulfonylurea.



eFigure 4. Subgroup stratification analysis: cumulative incidence curves of **(A)** new-onset prostate cancer and **(B)** all-cause mortality stratified by age at initial drug exposure and prescription of metformin versus sulfonylurea after 1:1 matching.
Abbreviations: met, metformin; sul, sulfonylurea.

eTable 1. ICD-9 Codes for Comorbidities

Diabetes mellitus	250; 250.01; 250.02; 250.03; 250.1; 250.11; 250.12; 250.13; 250.2; 250.21; 250.22; 250.23; 250.3; 250.31; 250.32; 250.33; 250.4; 250.41; 250.42; 250.43; 250.5; 250.51; 250.52; 250.53; 250.6; 250.61; 250.62; 250.63; 250.7; 250.71; 250.72; 250.73; 250.8; 250.81; 250.82; 250.83; 250.9; 250.91; 250.92; 250.93
Renal failure	582; 582.1; 582.2; 582.4; 582.8; 582.81; 582.89; 582.9; 583; 583.1; 583.2; 583.4; 583.6; 583.7; 585; 585.1; 585.2; 585.3; 585.4; 585.5; 585.6; 585.9; 586; 588; 588.1; 588.8; 588.81; 588.89; 588.9
Hypertension	401; 401.1; 401.9; 402; 402.01; 402.1; 402.11; 402.9; 402.91; 403; 403.01; 403.1; 403.11; 403.9; 403.91; 404; 404.01; 404.02; 404.03; 404.1; 404.11; 404.12; 404.13; 404.9; 404.91; 404.92; 404.93; 405; 405.01; 405.09; 405.1; 405.11; 405.19; 405.9; 405.91; 405.99; 437.2
Heart failure	428; 428.1; 428.2; 428.21; 428.22; 428.23; 428.3; 428.31; 428.32; 428.33; 428.4; 428.41; 428.42; 428.43; 428.9; 398.91; 402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93
Atrial fibrillation	427.31; 429.4
Hemiplegia or paraplegia	344.1; 342; 342.01; 342.02; 342.1; 342.11; 342.12; 342.8; 342.8; 342.81; 342.82; 342.9; 342.9; 342.91; 342.92
VT/VF/Sudden cardiac death	427.1; 427.4; 427.5; 427.1; 427.4; 427.5
Anemia	285.9
Chronic obstructive pulmonary disease	490; 491; 492; 493; 494; 495; 496; 491.1; 491.2; 491.21; 491.22; 491.8; 491.9; 492.8; 493.01; 493.02; 493.1; 493.11; 493.12; 493.2; 493.21; 493.22; 493.8; 493.81; 493.82; 493.9; 493.91; 493.92; 494.1; 495.1; 495.2; 495.3; 495.4; 495.5; 495.6; 495.7; 495.8; 495.9
Peripheral vascular disease	250.7; 443.9; 443; 443.1; 443.2; 443.21; 443.22; 443.23; 443.24; 443.29; 443.8; 443.81; 443.82; 443.89; 441; 443.9; 785.4; V43.4
Stroke/Transient ischemic attack	435; 435.1; 435.2; 435.3; 435.8; 435.9; 433.81; 433.91; 434; 436; 437; 437.1; 433.31; 433.01; 434.01; 434.1; 434.11; 434.9; 434.91; 437.2; 437.3; 437.4; 437.5; 437.6; 437.7; 437.8; 437.9; 430; 431; 432; 432.1; 432.9
Coronary heart disease	410.01; 410.02; 410.1; 410.11; 410.12; 410.2; 410.21; 410.22; 410.3; 410.31; 410.32; 410.4; 410.41; 410.42; 410.5; 410.51; 410.52; 410.6; 410.61; 410.62; 410.7; 410.71; 410.72; 410.8; 410.81; 410.82; 410.9; 410.91; 410.92; 411; 411.1; 411.8; 411.81; 411.89; 413; 413.1; 413.9; 414; 414.01; 414.02; 414.03; 414.04; 414.05; 414.06; 414.07; 414.1; 414.11; 414.12; 414.19; 414.2; 414.3; 414.4; 414.8; 414.9; 410; 412
Cancer	140–239
Acute myocardial infarction	410

Abbreviations: VF, ventricular fibrillation; VT, ventricular tachycardia.

eTable 2. Codes for Variability Measures Calculation

Variability Measure	Definition
Standard deviation	
Absolute successive variability score	$\frac{100 * \textit{number of measurements} > 0.5}{\textit{number of measurements}}$
Percentage successive variability score	$\frac{100 * \textit{number of measurements} > 10\% \textit{ of previous measurement}}{\textit{number of measurements}}$
Normalized score	
Normalized absolute successive variability score	$\frac{100 * \textit{number of measurements} > 0.5}{\textit{number of measurements} * \textit{individual mean}}$
Normalized percentage successive variability score	$\frac{100 * \textit{number of measurements} > 10\% \textit{ of previous measurement}}{\textit{number of measurements} * \textit{individual mean}}$
Coefficient of variation	$\frac{SD}{\textit{individual mean}}$
Standard deviation/initial	$\frac{SD}{\textit{individual initial value}}$
Variability independent of mean	$\frac{SD}{\textit{individual mean}^{\frac{\ln(\textit{population SD})}{\ln(\textit{population mean})}}}$

eTable 3. Items of GnRH Antagonist Drugs and GnRH Agonist Drugs in the Study

GnRH Agonists	GnRH Antagonists
ENANTONE (LEUPRORELIN) (INJECTION) (11.25MG) (LEUP03)	DEGARELIX (DEGARELIX) (SUBCUTANEOUS) (120MG) (DEGA02)
ENANTONE (LEUPRORELIN) (INJECTION) (11.25MG) (LEUP09)	DEGARELIX (DEGARELIX) (SUBCUTANEOUS) (120MG) (S00885)
ENANTONE (LEUPRORELIN) (INJECTION) (11.25MG) (S01099)	DEGARELIX (DEGARELIX) (SUBCUTANEOUS) (80MG) (DEGA01)
ENANTONE (LEUPRORELIN) (SUBCUTANEOUS) (3.75MG) (LEUP08)	DEGARELIX (DEGARELIX) (SUBCUTANEOUS) (80MG) (S00884)
ENANTONE (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (LEUP04)	DEGARELIX (FREE GOODS) (DEGARELIX (FREE GOODS)) (SUBCUTANEOUS) (120MG) (DEGA04)
ENANTONE (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (LEUP05)	DEGARELIX (FREE GOODS) (DEGARELIX (FREE GOODS)) (SUBCUTANEOUS) (80MG) (DEGA03)
ENANTONE (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (S01129)	DEGARELIX (YOTCSU DONATED DRUG) (DEGARELIX (YOTCSU DONATED DRUG)) (SUBCUTANEOUS) (120MG) (DEGA06)
TRIPTORELIN (TRIPTORELIN) (INJECTION) (0.1MG/ML) (S00116)	DEGARELIX (YOTCSU DONATED DRUG) (DEGARELIX (YOTCSU DONATED DRUG)) (SUBCUTANEOUS) (80MG) (DEGA05)
TRIPTORELIN (TRIPTORELIN) (INJECTION) (0.1MG/ML) (TRIP04)	
TRIPTORELIN (TRIPTORELIN) (INJECTION) (3.75MG) (TRIP02)	
TRIPTORELIN (TRIPTORELIN) (INJECTION) (3.75MG) (TRIP03)	
TRIPTORELIN (TRIPTORELIN) (INJECTION) (3.75MG) (TRIP09)	
TRIPTORELIN (TRIPTORELIN) (INTRAMUSCUL.) (11.25MG) (S00449)	
TRIPTORELIN (TRIPTORELIN) (INTRAMUSCUL.) (11.25MG) (TRIP05)	
TRIPTORELIN (TRIPTORELIN) (INTRAMUSCUL.) (22.5MG) (TRIP07)	
TRIPTORELIN (TRIPTORELIN) (INTRAMUSCUL.) (3.75MG) (TRIP06)	
TRIPTORELIN (TRIPTORELIN) (SUBCUTANEOUS) (0.1MG/ML) (TRIP08)	
TRIPTORELIN (CLINICAL TRIAL) (TRIPTORELIN (CLINICAL TRIAL)) (INJECTION) (3.75MG) (S01302)	
DIPHERELINE PR (TRIPTORELIN) (INTRAMUSCUL.) (11.25MG) (S00449)	
DIPHERELINE PR (TRIPTORELIN) (INTRAMUSCUL.) (11.25MG) (TRIP05)	
DIPHERELINE PR (TRIPTORELIN) (INTRAMUSCUL.) (22.5MG) (TRIP07)	
DIPHERELINE PR (TRIPTORELIN) (INTRAMUSCUL.) (3.75MG) (TRIP06)	
ENANTONE (LEUPRORELIN) (INJECTION) (3.75MG) (LEUP02)	
ENANTONE SR (LEUPRORELIN) (INJECTION) (3.75MG) (S00408)	
LEUPRORELIN (LEUPRORELIN) (INJECTION) (11.25MG) (LEUP03)	
LEUPRORELIN (LEUPRORELIN) (INJECTION) (11.25MG) (LEUP09)	
LEUPRORELIN (LEUPRORELIN) (INJECTION) (11.25MG) (S01099)	
LEUPRORELIN (LEUPRORELIN) (INJECTION) (3.75MG) (LEUP02)	
LEUPRORELIN (LEUPRORELIN) (INJECTION) (3.75MG) (S00408)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (3.75MG) (LEUP08)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (3.75MG) (LEUP10)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (LEUP04)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (LEUP05)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (30MG) (S01129)	
LEUPRORELIN (LEUPRORELIN) (SUBCUTANEOUS) (5MG/ML) (LEUP01)	
LEUPRORELIN (ELIGARD) (LEUPRORELIN (ELIGARD)) (SUBCUTANEOUS) (22.5MG) (LEUP06)	
LEUPRORELIN (ELIGARD) (LEUPRORELIN (ELIGARD)) (SUBCUTANEOUS) (45MG) (LEUP07)	
LEUPRORELIN (ELIGARD) (LEUPRORELIN (ELIGARD)) (SUBCUTANEOUS) (45MG) (S00988)	
GOSERELIN (GOSERELIN) (SUBCUTANEOUS) (10.8MG) (GOSE02)	
GOSERELIN (GOSERELIN) (SUBCUTANEOUS) (3.6MG) (GOSE01)	
GOSERELIN (CLINICAL TRIAL) (GOSERELIN (CLINICAL TRIAL)) (SUBCUTANEOUS) (3.6MG) (S01061)	

Abbreviation: GnRH, gonadotropin-releasing hormone.

eTable 4. Baseline and Clinical Patient Characteristics

Characteristic	Before Matching				After Matching			
	All	Metformin Users	Sulfonylurea Users	SMD	All	Metformin Users	Sulfonylurea Users	SMD
Total	66,411	25,695	40,716		51,390	25,695	25,695	
Medications, n (%)								
ACEI/ARB	34,267 (51.59%)	12,756 (49.64%)	21,511 (52.83%)	0.06	25,866 (50.33%)	12,759 (49.65%)	13,107 (51.00%)	0.03
β-blockers	23,257 (35.01%)	9,079 (35.33%)	14,178 (34.82%)	0.01	18,121 (35.26%)	9,083 (35.34%)	9,038 (35.17%)	<0.01
Calcium channel blockers	27,092 (40.79%)	10,071 (39.19%)	17,021 (41.80%)	0.05	20,168 (39.24%)	10,081 (39.23%)	10,087 (39.25%)	<0.01
Diuretics	11,916 (17.94%)	4,669 (18.17%)	7,247 (17.79%)	0.01	9,196 (17.89%)	4,671 (18.17%)	4,525 (17.61%)	0.01
Lipid-lowering agents	17,219 (25.92%)	6,526 (25.39%)	10,693 (26.26%)	0.02	13,027 (25.34%)	6,536 (25.43%)	6,491 (25.26%)	<0.01
Antiplatelets	274 (0.41%)	93 (0.36%)	181 (0.44%)	0.01	185 (0.35%)	93 (0.36%)	92 (0.35%)	<0.01
Nonsteroidal anti-inflammatory drugs	4,292 (6.46%)	1,484 (5.77%)	2,808 (6.89%)	0.05	2,922 (5.68%)	1,486 (5.78%)	1,436 (5.58%)	0.01
Laboratory examinations, mean [SD]								
ALP, U/L	77.9 [36.9]; n=32,783	80.9 [36.4]; n=12,696	76.1 [37.2]; n=20,087	0.13	78.5 [34.1]; n=25,318	80.9 [36.4]; n=12,694	76.2 [31.4]; n=12,624	0.14
ALT, U/L	28.0 [25.5]; n=27,329	28.6 [26.7]; n=10,662	27.7 [24.7]; n=16,667	0.04	28.3 [26.2]; n=21,214	28.6 [26.8]; n=10,658	27.9 [25.7]; n=10,556	0.03
Total protein, g/L	74.0 [6.8]; n=17,344	74.3 [6.8]; n=9,448	73.7 [6.7]; n=7,896	0.09	73.8 [7.0]; n=14,826	74.3 [6.8]; n=9,439	72.9 [7.2]; n=5,387	0.2
Albumin, g/L	39.2 [5.3]; n=17,406	39.7 [5.3]; n=9,483	38.7 [5.3]; n=7,923	0.19	39.1 [5.4]; n=14,875	39.7 [5.3]; n=9,474	38.0 [5.5]; n=5,401	0.31[a]
Hemoglobin, g/dL	13.1 [2.0]; n=12,494	13.2 [2.1]; n=7,419	13.0 [2.0]; n=5,075	0.08	12.9 [2.1]; n=11,171	13.2 [2.1]; n=7,412	12.2 [2.0]; n=3,759	0.49[a]
Lymphocyte, $x10^9$/L	1.7 [1.0]; n=10,657	1.8 [0.9]; n=6,137	1.7 [1.0]; n=4,520	0.02	1.7 [0.9]; n=9,545	1.8 [0.9]; n=6,131	1.6 [0.8]; n=3,414	0.17
Neutrophil, $x10^9$/L	5.4 [2.7]; n=10,657	5.3 [2.7]; n=6,137	5.6 [2.7]; n=4,520	0.11	5.4 [2.8]; n=9,545	5.3 [2.7]; n=6,131	5.5 [3.0]; n=3,414	0.09
Potassium, mmol/L	4.2 [0.5]; n=40,057	4.23 [0.47]; n=15,898	4.21 [0.46]; n=24,159	0.04	4.2 [0.5]; n=31,060	4.23 [0.47]; n=15,898	4.2 [0.45]; n=15,162	0.06
Sodium, mmol/L	139.5 [3.1]; n=40,076	139.6 [3.0]; n=15,900	139.4 [3.1]; n=24,176	0.09	139.5 [3.1]; n=31,073	139.6 [3.0]; n=15,900	139.4 [3.1]; n=15,173	0.07
Urea, mmol/L	6.9 [3.7]; n=36,432	7.3 [4.5]; n=15,218	6.5 [3.1]; n=21,214	0.21[a]	7.1 [4.1]; n=28,730	7.3 [4.5]; n=15,215	6.7 [3.5]; n=13,515	0.15
HDL, mmol/L	1.1 [0.3]; n=42,394	1.13 [0.32]; n=16,019	1.13 [0.31]; n=26,375	<0.01	1.1 [0.3]; n=32,526	1.13 [0.32]; n=16,027	1.12 [0.3]; n=16,499	0.02
SD of HDL	0.1 [0.1]; n=27,835	0.14 [0.09]; n=10,336	0.13 [0.09]; n=17,499	0.09	0.1 [0.1]; n=21,282	0.14 [0.09]; n=10,345	0.13 [0.08]; n=10,937	0.1
LDL, mmol/L	2.8 [0.9]; n=27,148	2.84 [0.87]; n=10,086	2.82 [0.85]; n=17,062	0.02	2.8 [0.9]; n=20,966	2.84 [0.87]; n=10,095	2.84 [0.85]; n=10,871	<0.01
SD of LDL	0.5 [0.3]; n=11,820	0.52 [0.36]; n=4,068	0.49 [0.34]; n=7,752	0.07	0.5 [0.3]; n=8,888	0.52 [0.36]; n=4,075	0.5 [0.34]; n=4,813	0.06
Total cholesterol, mmol/L	4.6 [1.0]; n=46,790	4.61 [1.0]; n=17,711	4.63 [0.99]; n=29,079	0.02	4.6 [1.0]; n=35,950	4.61 [1.0]; n=17,715	4.63 [0.99]; n=18,235	0.02
SD of total cholesterol	0.6 [0.4]; n=32,527	0.6 [0.41]; n=12,176	0.57 [0.4]; n=20,351	0.06	0.6 [0.4]; n=24,972	0.6 [0.41]; n=12,183	0.57 [0.38]; n=12,789	0.08
Triglyceride, mmol/L	1.7 [1.4]; n=46,712	1.6 [1.4]; n=17,679	1.7 [1.4]; n=29,033	0.04	1.6 [1.4]; n=35,895	1.6 [1.4]; n=17,683	1.7 [1.4]; n=18,212	0.04
SD of triglyceride	0.6 [1.1]; n=32,392	0.63 [1.07]; n=12,115	0.64 [1.08]; n=20,277	0.01	0.6 [1.0]; n=24,863	0.63 [1.07]; n=12,123	0.63 [0.94]; n=12,740	<0.01

(*continued on next page*)

eTable 4. Baseline and Clinical Patient Characteristics (cont.)

Characteristic	Before Matching				After Matching			
	All	Metformin Users	Sulfonylurea Users	SMD	All	Metformin Users	Sulfonylurea Users	SMD
Fasting glucose and variability measures, mean [SD]								
Fasting glucose, mmol/L	7.8 [2.7]; n=31,823	7.77 [2.66]; n=12,587	7.77 [2.65]; n=19,236	<0.01	7.8 [2.7]; n=24,651	7.77 [2.65]; n=12,590	7.81 [2.69]; n=12,061	0.01
Absolute successive variability score (fasting glucose)	55.4 [21.2]; n=31,823	55.6 [20.5]; n=12,587	55.3 [21.7]; n=19,236	0.01	54.9 [21.0]; n=24,651	55.6 [20.5]; n=12,590	54.3 [21.5]; n=12,061	0.06
Percentage successive variability score (fasting glucose)	48.5 [21.9]; n=31,823	48.9 [21.3]; n=12,587	48.2 [22.3]; n=19,236	0.03	48.1 [21.6]; n=24,651	48.9 [21.3]; n=12,590	47.3 [21.9]; n=12,061	0.08
SD of fasting glucose	1.7 [1.3]; n=31,823	1.65 [1.3]; n=12,587	1.7 [1.33]; n=19,236	0.04	1.6 [1.3]; n=24,651	1.7 [1.3]; n=12,590	1.6 [1.3]; n=12,061	0.02
Mean fasting glucose, mmol/L	7.9 [1.8]; n=31,823	7.7 [1.7]; n=12,587	8.0 [1.8]; n=19,236	0.16	7.8 [1.7]; n=24,651	7.7 [1.7]; n=12,590	7.8 [1.7]; n=12,061	0.09
Normalized absolute successive variability score (fasting glucose)	7.2 [2.9]; n=31,823	7.4 [2.9]; n=12,587	7.1 [2.9]; n=19,236	0.11	7.2 [2.9]; n=24,651	7.4 [2.9]; n=12,590	7.0 [2.9]; n=12,061	0.12
Normalized percentage successive variability score (fasting glucose)	6.4 [3.1]; n=31,823	6.6 [3.2]; n=12,587	6.2 [3.1]; n=19,236	0.12	6.4 [3.1]; n=24,651	6.6 [3.2]; n=12,590	6.2 [3.1]; n=12,061	0.13
SD/Initial (glucose)	23.8 [21.8]; n=31,822	23.75 [21.37]; n=12,586	23.77 [22.13]; n=19,236	<0.01	23.3 [21.5]; n=24,650	23.7 [21.4]; n=12,589	22.9 [21.6]; n=12,061	0.04
Coefficient of variation (glucose)	20.6 [13.4]; n=31,823	20.7 [13.4]; n=12,587	20.5 [13.3]; n=19,236	0.02	20.3 [13.3]; n=24,651	20.7 [13.4]; n=12,590	19.9 [13.1]; n=12,061	0.06
Variability independent of mean (fasting glucose)	32.2 [21.5]; n=31,823	32.2 [21.6]; n=12,587	32.1 [21.5]; n=19,236	<0.01	31.6 [21.3]; n=24,651	32.2 [21.6]; n=12,590	31.1 [21.0]; n=12,061	0.05
HbA1c and variability measures, mean [SD]								
HbA1c, %	7.5 [1.5]; n=32,250	7.45 [1.47]; n=12,807	7.47 [1.46]; n=19,443	0.01	7.5 [1.4]; n=25,036	7.45 [1.47]; n=12,810	7.45 [1.42]; n=12,226	<0.01
Absolute successive variability score (HbA1c)	35.3 [22.0]; n=32,723	34.3 [21.9]; n=12,985	35.9 [22.1]; n=19,738	0.08	34.8 [22.1]; n=25,415	34.3 [21.9]; n=12,987	35.3 [22.3]; n=12,428	0.05
Percentage successive variability score (HbA1c)	26.9 [20.3]; n=32,723	26.3 [20.2]; n=12,985	27.3 [20.3]; n=19,738	0.05	26.7 [20.3]; n=25,415	26.3 [20.2]; n=12,987	27.0 [20.4]; n=12,428	0.03
SD of HbA1c	0.9 [0.8]; n=32,721	0.91 [0.78]; n=12,985	0.92 [0.75]; n=19,736	0.01	0.9 [0.7]; n=25,409	0.91 [0.78]; n=12,987	0.87 [0.71]; n=12,422	0.04
Mean HbA1c, %	7.5 [1.2]; n=32,723	7.4 [1.1]; n=12,985	7.6 [1.2]; n=19,738	0.2a	7.5 [1.1]; n=25,415	7.4 [1.1]; n=12,987	7.5 [1.2]; n=12,428	0.1
Normalized absolute successive variability score (HbA1c)	4.6 [2.8]; n=32,723	4.5 [2.8]; n=12,985	4.6 [2.7]; n=19,738	0.03	4.6 [2.8]; n=25,415	4.5 [2.8]; n=12,987	4.6 [2.8]; n=12,428	0.02
Normalized percentage successive variability score (HbA1c)	3.5 [2.6]; n=32,723	3.5 [2.65]; n=12,985	3.52 [2.61]; n=19,738	0.01	3.5 [2.6]; n=25,415	3.5 [2.65]; n=12,987	3.53 [2.64]; n=12,428	0.01
SD/Initial (HbA1c)	12.7 [11.3]; n=32,270	12.7 [11.7]; n=12,817	12.6 [11.1]; n=19,453	0.01	12.5 [11.2]; n=25,078	12.7 [11.7]; n=12,819	12.2 [10.7]; n=12,259	0.04
Coefficient of variation (HbA1c)	11.6 [8.7]; n=32,721	11.7 [9.0]; n=12,985	11.6 [8.5]; n=19,736	0.02	11.5 [8.6]; n=25,409	11.7 [9.0]; n=12,987	11.2 [8.2]; n=12,422	0.06
Variability independent of mean (HbA1c)	16.5 [12.5]; n=32,721	16.6 [12.9]; n=12,985	16.4 [12.2]; n=19,736	0.01	16.2 [12.4]; n=25,409	16.6 [12.9]; n=12,987	15.9 [11.7]; n=12,422	0.06

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine transaminase; ARB, angiotensin-receptor blocker; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a]SMD≥0.2.

eTable 5. Univariable Cox Regression to Identify Significant Risk Predictors of New-Onset Prostate Cancer and All-Cause Mortality

Characteristic	Before Matching		After Matching	
	All-Cause Mortality HR (95% CI); *P* Value	New-Onset Prostate Cancer HR (95% CI); *P* Value	All-Cause Mortality HR (95% CI); *P* Value	New-Onset Prostate Cancer HR (95% CI); *P* Value
Medications				
ACEI/ARB	1.38 (1.35–1.42); <.0001***	1.07 (0.96–1.19); .2282	1.46 (1.41–1.50); <.0001***	0.95 (0.82–1.11); .5309
β-blockers	1.32 (1.29–1.35); <.0001***	1.07 (0.96–1.19); .2326	1.45 (1.40–1.49); <.0001***	0.96 (0.82–1.13); .6300
Calcium channel blockers	1.71 (1.66–1.75); <.0001***	1.33 (1.20–1.48); <.0001***	1.85 (1.79–1.91); <.0001***	1.22 (1.05–1.41); .0101*
Diuretics	2.16 (2.10–2.22); <.0001***	1.25 (1.09–1.43); .0012**	2.65 (2.56–2.74); <.0001***	1.15 (0.95–1.40); .1575
Lipid-lowering agents	1.18 (1.15–1.22); <.0001***	1.06 (0.94–1.20); .3284	1.28 (1.24–1.33); <.0001***	0.99 (0.84–1.18); .9257
Antiplatelets	2.85 (2.48–3.27); <.0001***	0.67 (0.22–2.09); .4959	2.98 (2.48–3.57); <.0001***	1.02 (0.25–4.07); .9822
Nonsteroidal anti-inflammatory drugs	1.16 (1.11–1.21); <.0001***	1.08 (0.89–1.33); .4260	1.10 (1.03–1.17); .0049**	1.24 (0.93–1.64); .1365
Laboratory examinations				
ALP, U/L	1.003 (1.003–1.003); <.0001***	1.001 (0.998–1.003); .6050	1.00 (1.00–1.01); <.0001***	1.001 (0.998–1.005); .4634
ALT, U/L	0.988 (0.987–0.989); <.0001***	0.99 (0.99–1.00); .0012**	0.99 (0.98–0.99); <.0001***	0.99 (0.99–1.00); .0404*
Total protein, g/L	0.97 (0.96–0.97); <.0001***	1.00 (0.98–1.02); .9418	0.960 (0.957–0.963); <.0001***	1.00 (0.98–1.02); .9651
Albumin, g/L	0.910 (0.907–0.913); <.0001***	1.00 (0.97–1.02); .8664	0.91 (0.90–0.91); <.0001***	1.01 (0.98–1.04); .4227
Hemoglobin, g/dL	0.77 (0.76–0.77); <.0001***	0.98 (0.91–1.06); .6469	0.75 (0.74–0.76); <.0001***	1.06 (0.97–1.16); .2028
Lymphocyte, $x10^9$/L	0.69 (0.67–0.72); <.0001***	0.91 (0.73–1.14); .4194	0.68 (0.65–0.71); <.0001***	0.99 (0.79–1.23); .8956
Neutrophil, $x10^9$/L	1.05 (1.04–1.06); <.0001***	0.96 (0.90–1.03); .2964	1.05 (1.04–1.06); <.0001***	0.98 (0.90–1.05); .5306
Potassium, mmol/L	1.07 (1.03–1.10); .0001***	1.00 (0.86–1.16); .9882	1.08 (1.03–1.12); .0004***	0.89 (0.72–1.10); .2744
Sodium, mmol/L	0.95 (0.95–0.96); <.0001***	1.03 (1.01–1.06); .0100*	0.95 (0.95–0.96); <.0001***	1.02 (0.99–1.05); .2367
Urea, mmol/L	1.092 (1.089–1.095); <.0001***	1.02 (1.00–1.04); .0435*	1.101 (1.098–1.104); <.0001***	1.02 (1.00–1.05); .1102
HDL, mmol/L	0.96 (0.91–1.01); .1071	0.93 (0.74–1.16); .5077	0.92 (0.86–0.98); .0085**	0.78 (0.56–1.08); .1272
SD of HDL	3.18 (2.94–3.44); <.0001***	0.31 (0.10–0.96); .0415*	19.86 (15.89–24.81); <.0001***	0.07 (0.01–0.44); .0041**
LDL, mmol/L	0.90 (0.88–0.93); <.0001***	1.07 (0.97–1.18); .1709	0.92 (0.89–0.94); <.0001***	0.96 (0.83–1.11); .5733
SD of LDL	1.38 (1.28–1.49); <.0001***	0.86 (0.57–1.28); .4495	1.73 (1.57–1.91); <.0001***	0.83 (0.47–1.49); .5373
Total cholesterol, mmol/L	0.84 (0.82–0.85); <.0001***	0.95 (0.89–1.02); .1319	0.83 (0.81–0.84); <.0001***	0.94 (0.85–1.03); .1806
SD of total cholesterol	1.26 (1.21–1.30); <.0001***	0.87 (0.71–1.07); .1785	1.42 (1.36–1.48); <.0001***	0.65 (0.47–0.90); .0098**
Triglyceride, mmol/L	0.90 (0.89–0.92); <.0001***	0.96 (0.91–1.01); .1490	0.91 (0.89–0.92); <.0001***	1.01 (0.95–1.07); .8074
SD of triglyceride	0.91 (0.89–0.93); <.0001***	0.93 (0.85–1.02); .1113	0.92 (0.90–0.95); <.0001***	0.93 (0.82–1.07); .3181
Fasting glucose and variability measures				
Fasting glucose, mmol/L	1.00 (0.99–1.01); .7192	0.99 (0.96–1.02); .6439	0.99 (0.99–1.00); .1816	0.99 (0.95–1.03); .6725
Absolute successive variability score (fasting glucose)	1.007 (1.006–1.008); <.0001***	1.00 (0.99–1.00); .0060**	1.009 (1.008–1.010); <.0001***	1.00 (0.99–1.00); .0531
Percentage successive variability score (fasting glucose)	1.008 (1.008–1.009); <.0001***	1.00 (0.99–1.00); .0054**	1.011 (1.010–1.012); <.0001***	1.00 (0.99–1.00); .0714
SD of fasting glucose	1.10 (1.09–1.11); <.0001***	0.86 (0.80–0.92); <.0001***	1.11 (1.09–1.12); <.0001***	0.92 (0.83–1.01); .0845
Mean fasting glucose, mmol/L	0.99 (0.98–1.00); .2466	0.94 (0.89–0.98); .0055**	0.95 (0.93–0.96); <.0001***	0.93 (0.87–1.00); .0472*
Normalized absolute successive variability score (fasting glucose)	1.06 (1.06–1.07); <.0001***	0.98 (0.95–1.00); .0782	1.09 (1.08–1.10); <.0001***	0.98 (0.94–1.02); .2505
Normalized percentage successive variability score (fasting glucose)	1.07 (1.06–1.07); <.0001***	0.97 (0.95–1.00); .0466*	1.10 (1.09–1.10); <.0001***	0.98 (0.94–1.01); .2245

(*continued on next page*)

eTable 5. Univariable Cox Regression to Identify Significant Risk Predictors of New-Onset Prostate Cancer and All-Cause Mortality (cont.)

	Before Matching		After Matching	
Characteristic	**All-Cause Mortality HR (95% CI); *P* Value**	**New-Onset Prostate Cancer HR (95% CI); *P* Value**	**All-Cause Mortality HR (95% CI); *P* Value**	**New-Onset Prostate Cancer HR (95% CI); *P* Value**
SD/Initial (glucose)	1.006 (1.005–1.006); <.0001***	0.99 (0.99–1.00); .0009***	1.007 (1.006–1.008); <.0001***	1.00 (0.99–1.00); .1333
Coefficient of variation (glucose)	1.013 (1.012–1.014); <.0001***	0.99 (0.98–0.99); .0001***	1.02 (1.01–1.02); <.0001***	0.99 (0.98–1.00); .1386
Variability independent of mean (fasting glucose)	1.007 (1.007–1.008); <.0001***	0.99 (0.99–1.00); <.0001***	1.009 (1.008–1.010); <.0001***	1.00 (0.99–1.00); .1218
HbA1c and variability measures				
HbA1c, %	1.00 (0.99–1.01); .6516	0.99 (0.93–1.04); .5806	1.00 (0.99–1.02); .6525	0.96 (0.89–1.04); .3583
Absolute successive variability score (HbA1c)	1.007 (1.006–1.007); <.0001***	1.00 (0.99–1.00); .0145*	1.006 (1.005–1.007); <.0001***	1.00 (0.99–1.00); .2113
Percentage successive variability score (HbA1c)	1.008 (1.007–1.008); <.0001***	1.00 (0.99–1.00); .0155*	1.008 (1.007–1.009); <.0001***	1.00 (0.99–1.00); .1583
SD of HbA1c	1.13 (1.11–1.15); <.0001***	0.84 (0.75–0.94); .0034**	1.15 (1.12–1.18); <.0001***	0.85 (0.72–1.00); .0473*
Mean HbA1c, %	1.08 (1.06–1.09); <.0001***	0.89 (0.83–0.95); .0005***	1.04 (1.02–1.05); .0001***	0.84 (0.76–0.93); .0011**
Normalized absolute successive variability score (HbA1c)	1.05 (1.04–1.06); <.0001***	0.98 (0.95–1.00); .1013	1.05 (1.04–1.06); <.0001***	0.99 (0.95–1.03); .6795
Normalized percentage successive variability score (HbA1c)	1.06 (1.05–1.06); <.0001***	0.97 (0.95–1.00); .0845	1.06 (1.05–1.07); <.0001***	0.99 (0.95–1.03); .4751
SD/Initial (HbA1c)	1.007 (1.005–1.008); <.0001***	0.99 (0.98–1.00); .0293*	1.008 (1.007–1.010); <.0001***	0.99 (0.98–1.00); .2132
Coefficient of variation (HbA1c)	1.010 (1.008–1.012); <.0001***	0.99 (0.98–1.00); .0094**	1.012 (1.010–1.014); <.0001***	0.99 (0.98–1.00); .1336
Variability independent of mean (HbA1c)	1.007 (1.006–1.008); <.0001***	0.99 (0.98–1.00); .0078**	1.008 (1.007–1.010); <.0001***	0.99 (0.98–1.00); .1108

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine transaminase; ARB, angiotensin-receptor blocker; CI, confidence interval; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; SD, standard deviation.
*$P \leq .05$; **$P \leq .001$; ***$P \leq .001$.

eTable 6. Annualized Incidence Rate of Adverse Events in the Matched Cohort

Year Cohort	Person-Years	Failures	Incidence Rate (95% CI)
All-cause mortality			
Year 1	51,001.3	1,094	21.5 (20.2–22.8)
Year 2	49,443.9	1,572	31.8 (30.3–33.4)
Year 3	47,917.4	1,515	31.6 (30.1–33.2)
Year 4	46,384.6	1,494	32.2 (30.6–33.9)
Year 5	44,955.1	1,501	33.4 (31.7–35.1)
Year 6	43,439.6	1,360	31.3 (29.7–33)
Year 7	42,138.3	1,270	30.1 (28.5–31.8)
Year 8	40,844.7	1,266	31 (29.3–32.8)
Year 9	39,702.8	1,094	27.6 (26–29.2)
Year 10	38,548.1	1,160	30.1 (28.4–31.9)
Year 11	37,373.8	1,210	32.4 (30.6–34.3)
≥Year 12	22,924.6	696	30.4 (28.2–32.7)
New-onset prostate cancer			
Year 1	51,002	0	–
Year 2	49,386.6	138	2.8 (2.4–3.3)
Year 3	47,757.2	120	2.5 (2.1–3)
Year 4	46,143.4	104	2.3 (1.9–2.7)
Year 5	44,641.2	86	1.9 (1.6–2.4)
Year 6	43,088.7	76	1.8 (1.4–2.2)
Year 7	41,746	69	1.7 (1.3–2.1)
Year 8	40,450.2	31	0.8 (0.5–1.1)
Year 9	39,313.1	32	0.8 (0.6–1.2)
Year 10	38,159.4	29	0.8 (0.5–1.1)
Year 11	37,007.4	14	0.4 (0.2–0.6)
≥Year 12	687.5	3	0.5 (0.3–1.1)

Abbreviation: CI, confidence interval.

eTable 7. Annualized Drug-Specific Incidence Rate of Per 1,000 Patients Per Year in the Matched Cohort

	Metformin Users			Sulfonylurea Users		
Year Cohort	Person-Time	Failures	Incidence Rate (95% CI)	Person-Time	Failures	Incidence Rate (95% CI)
All-cause mortality						
Year 1	25,507.8	533	20.9 (19.2–22.7)	25,396.3	862	33.9 (31.8–36.3)
Year 2	24,779.5	715	28.9 (26.8–31)	24,253.2	1,141	47 (44.4–49.9)
Year 3	24,060.2	715	29.7 (27.6–32)	23,112.9	1,091	47.2 (44.5–50.1)
Year 4	23,331.9	737	31.6 (29.4–34)	21,987.8	1,117	50.8 (47.9–53.9)
Year 5	22,636.2	688	30.4 (28.2–32.8)	20,916.9	1,149	54.9 (51.8–58.2)
Year 6	21,939	661	30.1 (27.9–32.5)	19,639.8	1,269	64.6 (61.2–68.3)
Year 7	21,279.3	646	30.4 (28.1–32.8)	18,551.1	951	51.3 (48.1–54.6)
Year 8	20,667.6	593	28.7 (26.5–31.1)	17,477.1	1,113	63.7 (60–67.5)
Year 9	20,086.1	570	28.4 (26.1–30.8)	16,447.6	1,029	62.6 (58.9–66.5)
Year 10	19,515.2	588	30.1 (27.8–32.7)	15,333.7	1,142	74.5 (70.3–78.9)
Year 11	18,939.9	547	28.9 (26.6–31.4)	14,164.6	1,167	82.4 (77.8–87.3)
≥Year 12	11,648.9	347	29.8 (26.8–33.1)	8,384.8	565	67.4 (62.1–73.2)
New-onset prostate cancer						
Year 1	25,685.9	29	1.1 (0.8–1.6)	25,648.2	101	3.9 (3.2–4.8)
Year 2	25,636.8	63	2.5 (1.9–3.1)	25,542.4	112	4.4 (3.6–5.3)
Year 3	25,557.7	87	3.4 (2.8–4.2)	25,456.8	43	1.7 (1.3–2.3)
Year 4	25,490	51	2 (1.5–2.6)	25,407.3	61	2.4 (1.9–3.1)
Year 5	25,440.3	39	1.5 (1.1–2.1)	25,351.7	45	1.8 (1.3–2.4)
Year 6	25,405	44	1.7 (1.3–2.3)	25,323.2	29	1.1 (0.8–1.6)
Year 7	25,362.3	31	1.2 (0.9–1.7)	25,291	21	0.8 (0.5–1.3)
Year 8	25,345.1	13	0.5 (0.3–0.9)	25,282.8	1	0 (0–0.3)
Year 9	25,332.6	11	0.4 (0.2–0.8)	25,280.2	10	0.4 (0.2–0.7)
Year 10	25,321.4	10	0.4 (0.2–0.7)	25,269.9	4	0.2 (0.1–0.4)
Year 11	25,317	0	–	25,268	0	–
≥Year 12	346.8	0	–	346.1	0	–

Abbreviation: CI, confidence interval.

eTable 8. Sensitivity Analysis: Incidence Rates of Per 1,000 Patients per Year and HRs of New-Onset Prostate Cancer and All-Cause Mortality in the Matched Cohort Associated With Metformin vs Sulfonylurea Treatment Using Different Propensity Matching Approaches (1:1)

Outcome	Person-Year	Event Number	IR (95% CI)	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 prostate cancer	479,000	702	1.5 (1.4–1.6)	0.63 (0.54–0.69); <.0001***	0.67 (0.55–0.75); <.0001***	0.72 (0.67–0.81); <.0001***
All-cause mortality	505,000	15,232	30.2 (29.7–30.7)	0.89 (0.82–0.95); <.0001***	0.86 (0.75–0.90); <.0001***	0.89 (0.85–0.97); <.0001***

Abbreviations: CI, confidence interval; HDPS, high dimensional propensity score; HR, hazard ratio; IPTW, inverse probability of treatment weight; IR, incidence rate; PS, propensity score.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 9. Sensitivity Analysis: HRs of Metformin vs Sulfonylurea With Competing Risks Consideration

Outcome	Cause-Specific Models HR (95% CI); *P* Value	Subdistribution Hazard Models HR (95% CI); *P* Value
New-onset prostate cancer	0.89 (0.75–0.95); <.0001***	0.83 (0.72–0.89); <.0001***
All-cause mortality	0.61 (0.56–0.72); <.0001***	0.59 (0.51–0.66); <.0001***

Abbreviations: CI, confidence interval; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 10. Age-Specific HRs of Metformin vs Sulfonylurea on All-Cause Mortality and New-Onset Prostate Cancer in the Matched Cohort

	All-Cause Mortality HR (95% CI); *P* Value	New-Onset Prostate Cancer HR (95% CI); *P* Value
Metformin vs sulfonylurea, age ≥65 y	0.45 (0.44–0.47); <.0001***	0.93 (0.79–0.98); .0272*
Metformin vs sulfonylurea, age <65 y	0.57 (0.53–0.61); <.0001***	0.78 (0.60–0.95); .0401*
P for trend	<.0001***	<.0001***

Abbreviations: CI, confidence interval; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 11. HRs of Mortality in Patients With New-Onset Prostate Cancer (N=702)

Medication Group vs Non-ADT Group	Patients n (%)	All-Cause Mortality HR (95% CI); *P* Value
ADT	146 (20.79%)	0.80 (0.62–1.04); .1015
GnRH antagonists	25 (3.56%)	0.71 (0.39–1.30); .2670
GnRH agonists	133 (18.94%)	0.76 (0.58–1.00); .0504

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 12. HRs of Prescribing Metformin + ADT, and Sulfonylurea + ADT for Mortality in Patients With New-Onset Prostate Cancer

Characteristic	Patients With New-Onset Prostate Cancer (N=702) n (%)	All-Cause Mortality HR (95% CI); *P* Value
Metformin monotherapy	152 (21.65%)	Ref
Metformin + ADT	51.0 (7.26%)	0.97 (0.45–2.10); .9448
Sulfonylurea + ADT	95.0 (13.53%)	4.76 (2.95–7.68); <.0001***
P for trend	–	<.0001***

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 13. HRs of Prescribing Metformin + GnRH Antagonists, and Sulfonylurea + GnRH Antagonists for Mortality in Patients With New-Onset Prostate Cancer

Characteristic	Patients With New-Onset Prostate Cancer (N=702) n (%)	All-Cause Mortality HR (95% CI); *P* Value
Metformin monotherapy	152 (21.65%)	Ref
Metformin + GnRH antagonists	7.0 (0.99%)	0.76 (0.10–5.64); .7894
Sulfonylurea + GnRH antagonists	18.0 (2.56%)	3.60 (1.71–7.59); .0007***
P for trend	–	<.0001***

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.

eTable 14. HRs of Prescribing Metformin + GnRH Agonists, and Sulfonylurea + GnRH Agonists for Mortality in Patients With New-Onset Prostate Cancer

Characteristic	Patients With New-Onset Prostate Cancer (N=702) n (%)	All-Cause Mortality HR (95% CI); *P* Value
Metformin monotherapy	152 (21.65%)	Ref
Metformin + GnRH agonists	47.0 (6.69%)	0.94 (0.42–2.11); .8837
Sulfonylurea + GnRH agonists	86.0 (12.25%)	4.46 (2.74–7.26); <.0001***
P for trend	–	<.0001***

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, hazard ratio.
*$P \leq .05$; **$P \leq .01$; ***$P \leq .001$.