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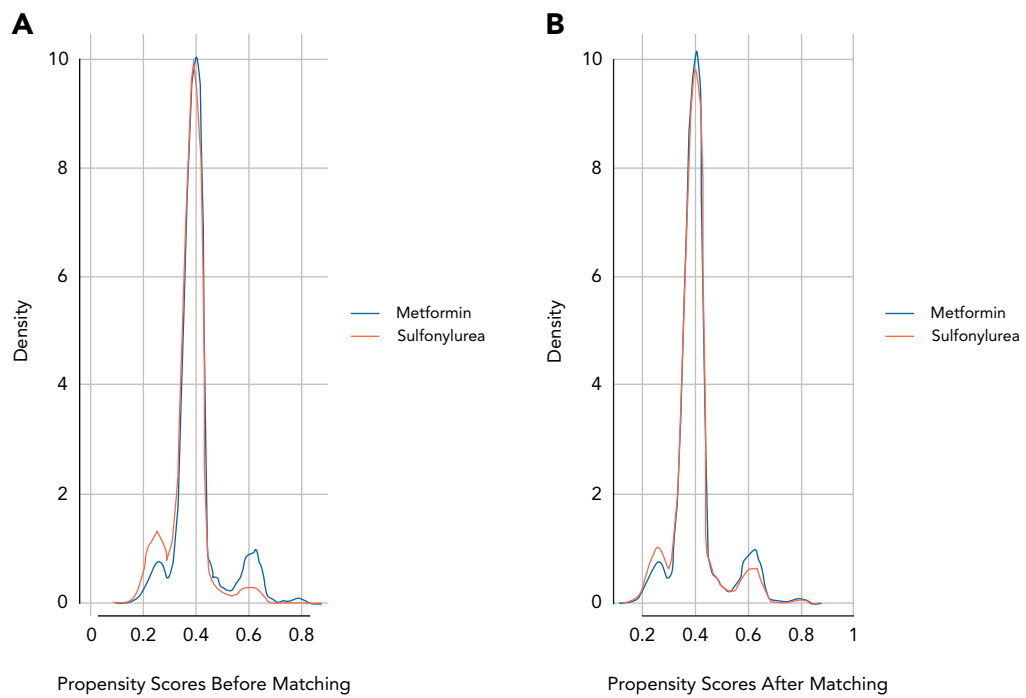
Risk of New-Onset Prostate Cancer for Metformin Versus Sulfonylurea Use in Type 2 Diabetes Mellitus: A Propensity Score–Matched Study

Yan Hiu Athena Lee, MBChB; Jiandong Zhou, PhD; Jeremy Man Ho Hui, MBBS; Xuejin Liu, MSc; Teddy Tai Loy Lee, BPharm; Kyle Hui, MBBS; Jeffrey Shi Kai Chan, MBChB; Abraham Ka Chung Wai, MBChB; Wing Tak Wong, PhD; Tong Liu, MD, PhD; Kenrick Ng, PhD, MA, MBBChir, MRCP; Sharen Lee, MBChB; Edward Christopher Dee, MD; Qingpeng Zhang, PhD; and Gary Tse, MD, PhD

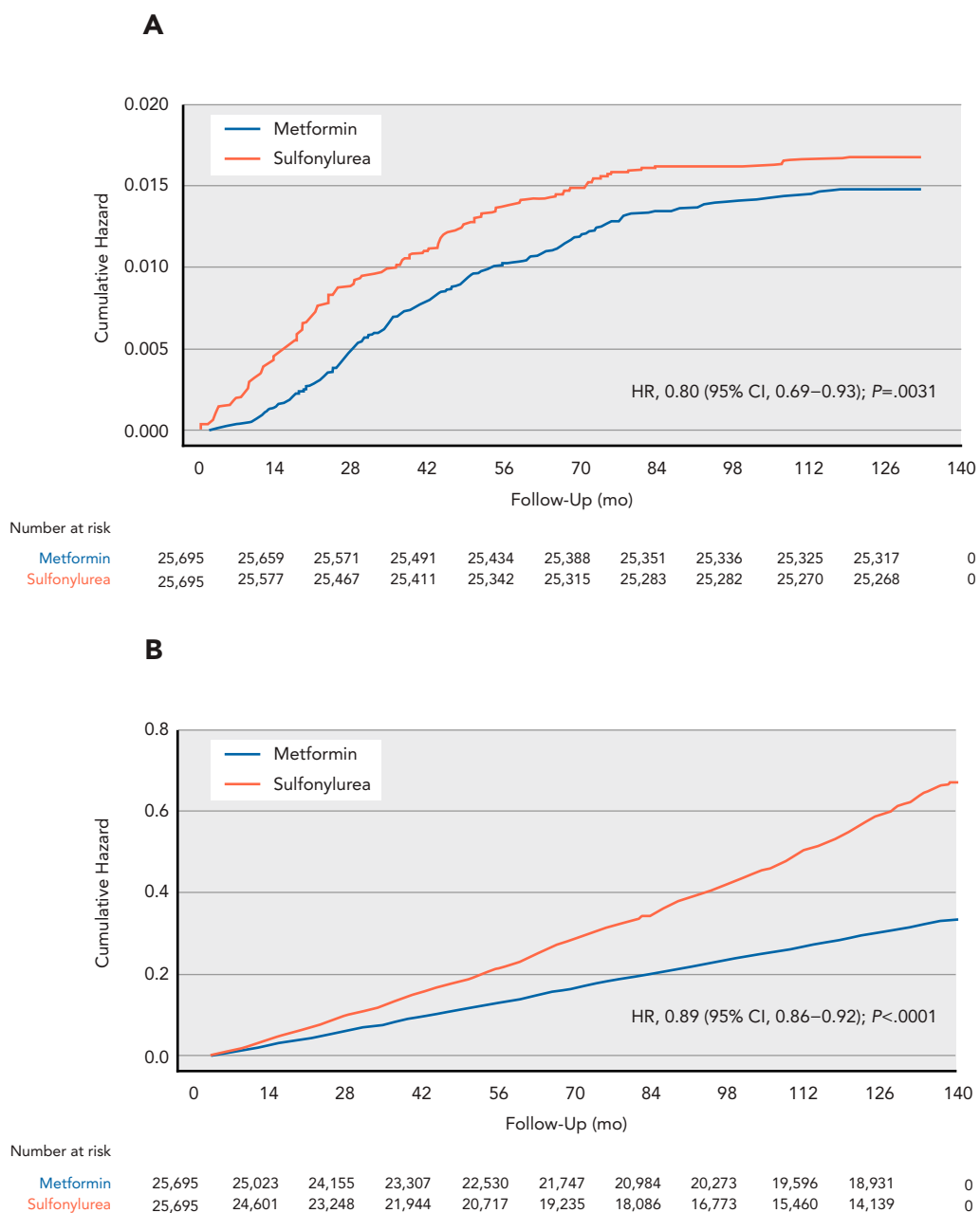
J Natl Compr Canc Netw 2022;20(6):674–682.e14

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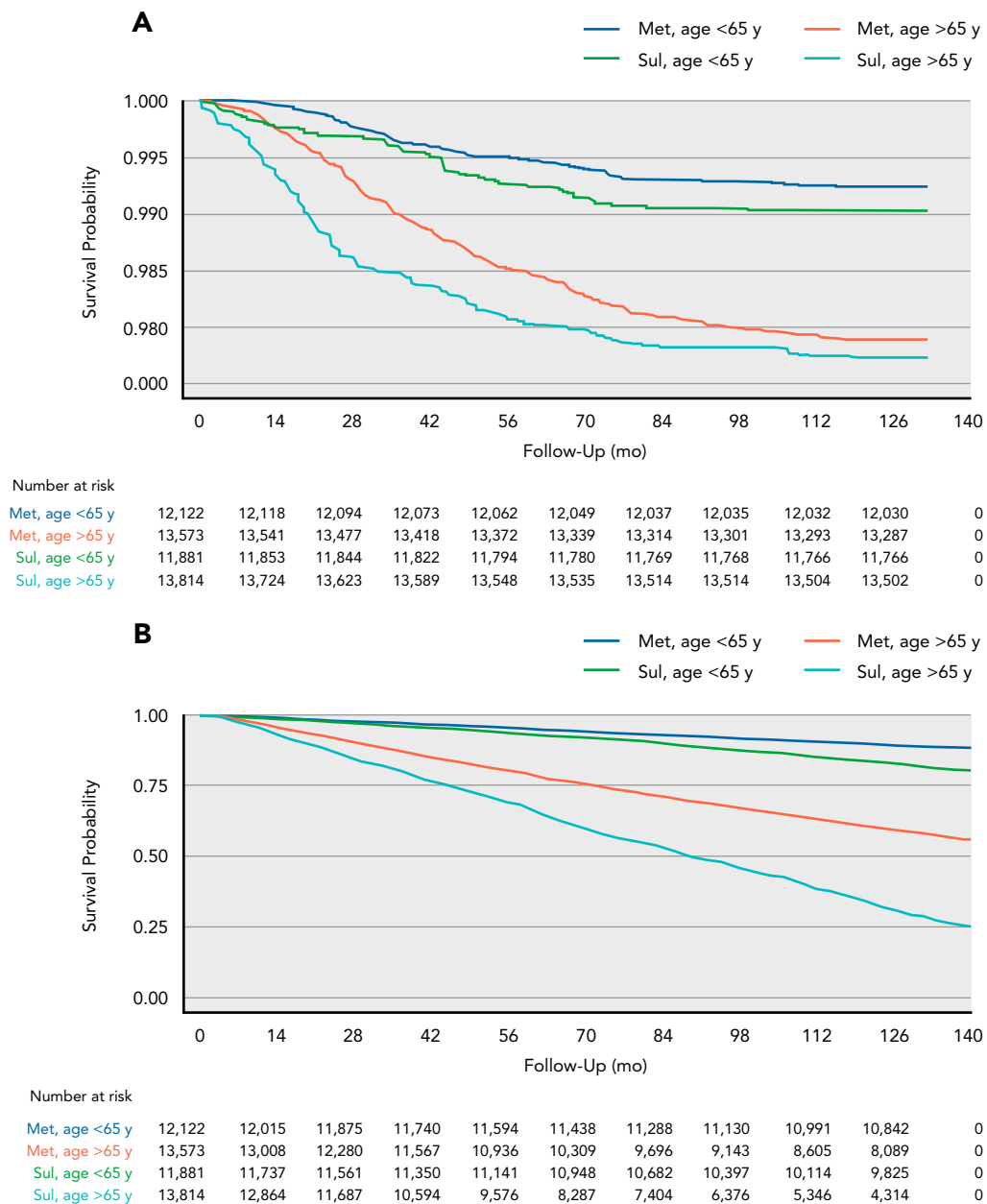
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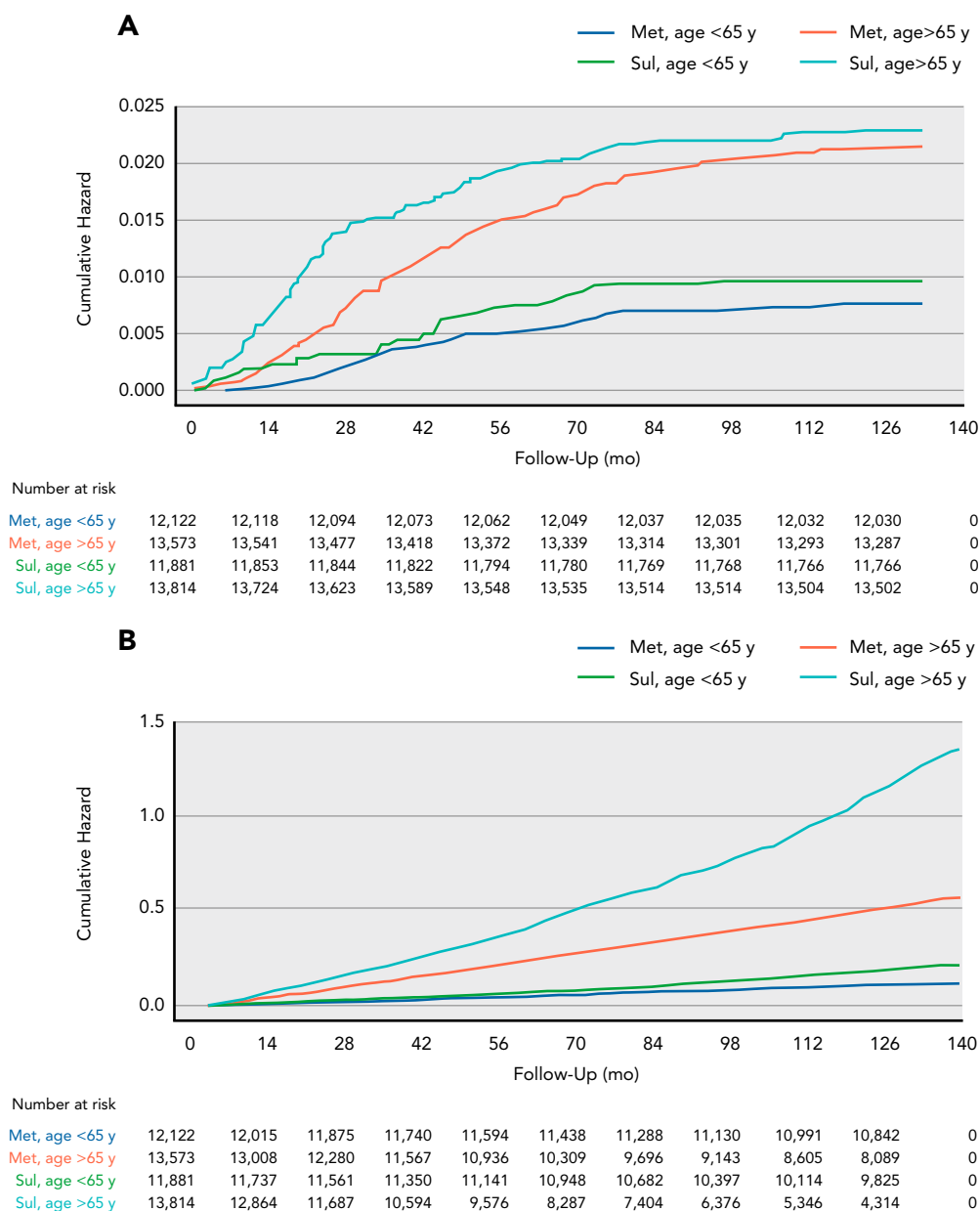
eFigure 1. Propensity score matching for metformin versus sulfonylurea **(A)** before and **(B)** after 1:1 matching with nearest neighbor search strategy (caliper = 0.1).



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

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

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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.

^aSMD \geq 0.2.

Table 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)

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

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
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

Year Cohort	Metformin Users			Sulfonylurea Users		
	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.
* $P \leq .05$; ** $P \leq .01$; *** $P \leq .001$.