

Supplemental Online Content

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eMethods. Diagnostic codes and medication codes

eFigure 1. The cumulative incidence of outcomes amongst different groups

eTable 1. Diagnostic codes and medication codes

eTable 2. Incidence and hazard ratios of all-cause mortality

eTable 3. Incidence and hazard ratios of major adverse cardiovascular events

eTable 4. Incidence and hazard ratios of cardiovascular mortality

eTable 5. Incidence and hazard ratios of myocardial infarction

eTable 6. Incidence and hazard ratios of cerebrovascular diseases

eTable 7. Incidence and hazard ratios of ischemic heart diseases

eTable 8. Incidence and hazard ratios of heart failure

eTable 9. Incidence and hazard ratios of peripheral artery diseases

eTable 10. Incidence and hazard ratios of hypoglycemia

eTable 11. Incidence and hazard ratios of non-cardiovascular mortality

eTable 12. Incidence and hazard ratios of outcomes and cumulative days of GLP-1RA and TZD usage

eTable 13. Hazard ratios of outcomes for comparisons amongst non-GLP-1RA/TZD, GLP-1RA, TZD, and GLP-1RA/TZD

eTable 14. Incidence and hazard ratios of outcomes in cumulative days of GLP-1RA and TZD usage by using Fine and Gray's competing risk model

eTable 15. Incidence and hazard ratios of outcomes after inverse probability of treatment weighting matching

eTable 16. A comparative review of diabetic practice guidelines in Taiwan, the United States and Europe

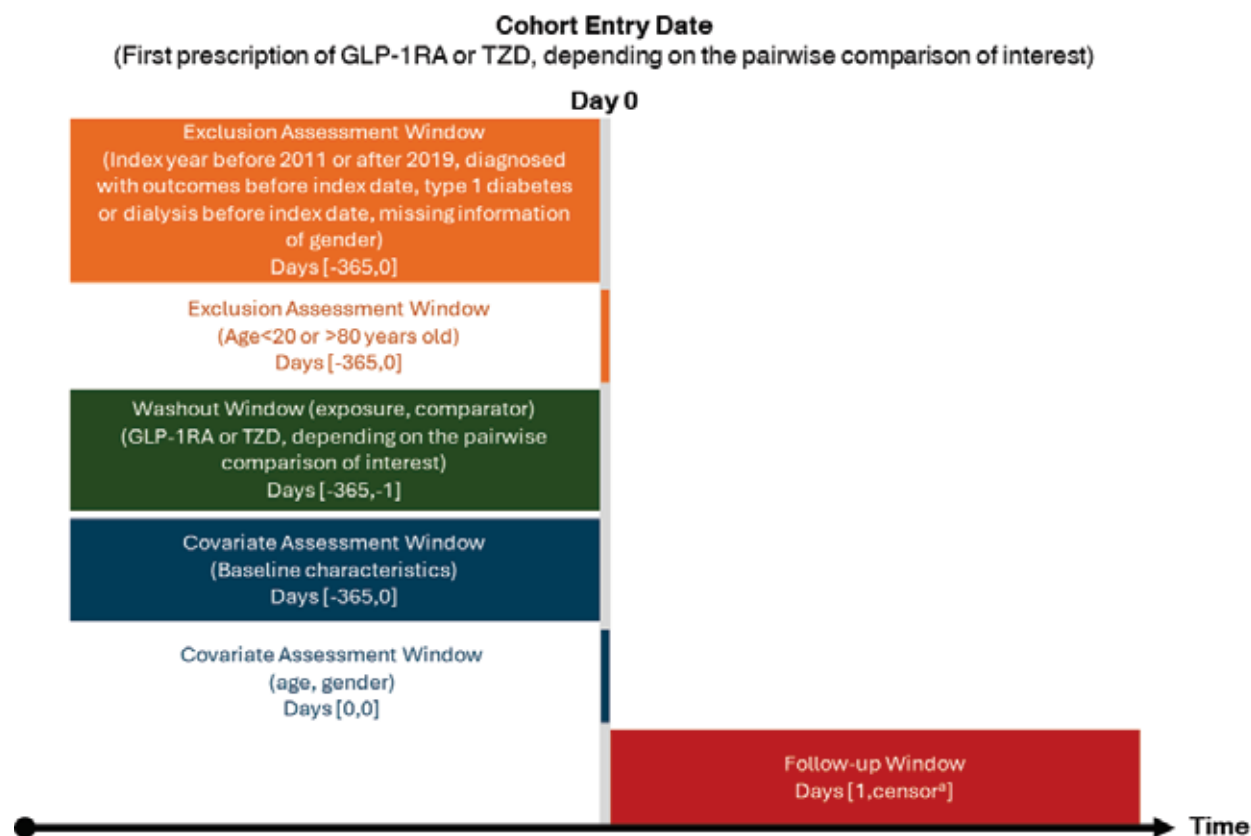
eTable 17. Landmark clinical trials on diabetes mellitus management and cardiovascular diseases before 2020

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods. Study design with timeframe.

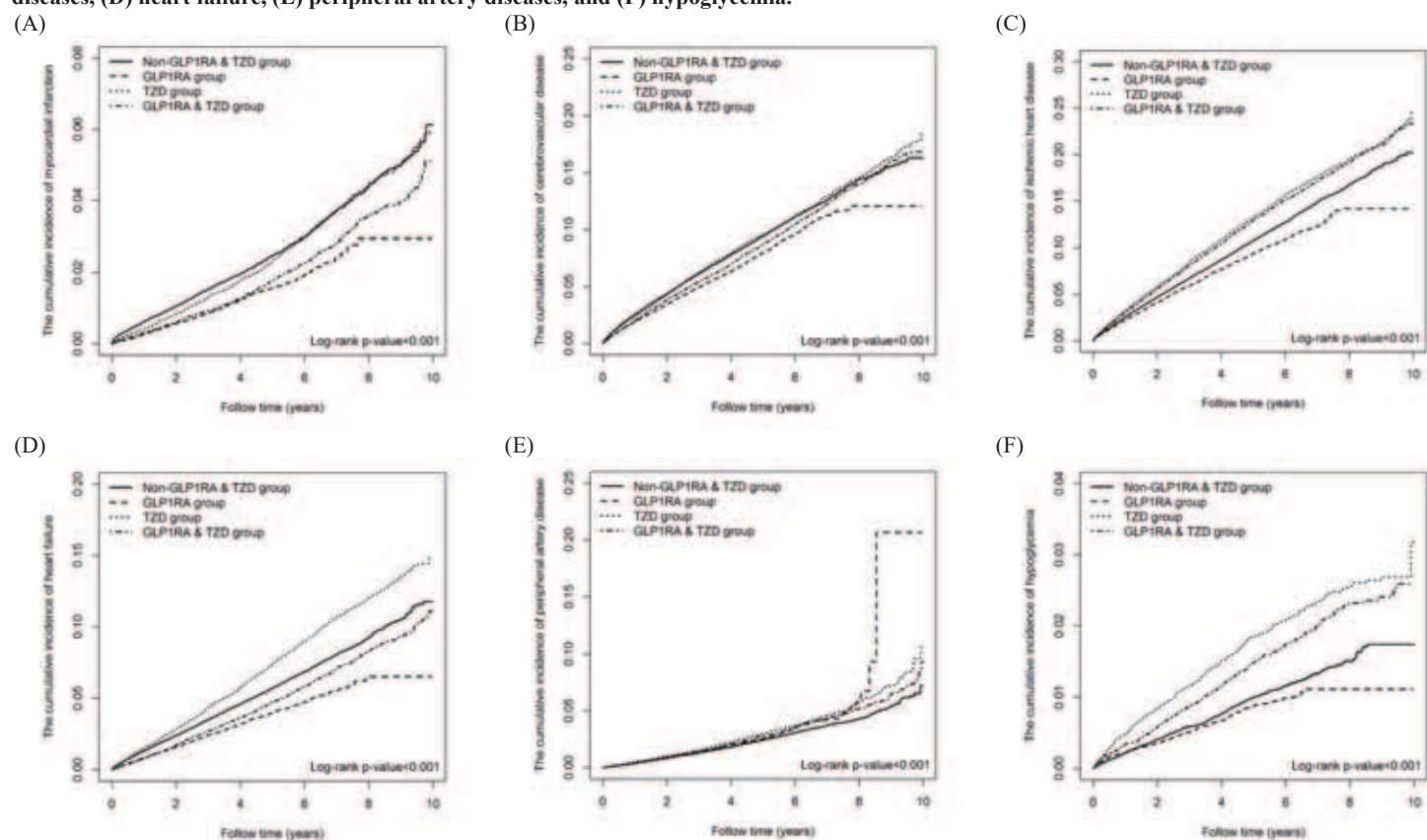
Study design: Retrospective cohort study

Study period: 2009–2019 (tracked to 2020)



^a Earliest of death, respective outcomes, or at the end of the study period. GLP-1RA, glucagon-like peptide-1 receptor agonists; TZD, thiazolidinedione.

eFigure 1. The cumulative incidence of outcomes amongst different groups. (A) myocardial infarction, (B) cerebrovascular diseases, (C) ischemic heart diseases, (D) heart failure, (E) peripheral artery diseases, and (F) hypoglycemia.



eTable 1. Diagnostic codes and medication codes.

Category	Coding
Population	Type 2 diabetes mellitus (ICD-9-CM code: 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92; ICD-10-CM code: E11)
Exposure	Control group: Non-GLP-1RA/TZD Case group: GLP-1RA (ATC code: A10BJ), TZD (ATC code: A10BG), GLP-1RA/TZD
Outcome	All-cause mortality Major adverse cardiovascular events Non-fatal myocardial infarction (ICD-9-CM code: 410; ICD-10-CM code: I21) Non-fatal cerebrovascular diseases (ICD-9-CM code: 430–438; ICD-10-CM code: I60–I69) Cardiovascular mortality Die of myocardial infarction (ICD-10-CM code: I21) Die of cerebrovascular diseases (ICD-10-CM code: I60–I69) Die of ischemic heart diseases (ICD-10-CM code: I20–I25) Die of heart failure (ICD-10-CM code: I11, I13, I50) Die of peripheral artery diseases (ICD-10-CM code: I70–I79) Myocardial infarction (ICD-9-CM code: 410; ICD-10-CM code: I21) Cerebrovascular diseases (ICD-9-CM code: 430–438; ICD-10-CM code: I60–I69) Ischemic heart diseases (ICD-9-CM code: 410–414; ICD-10-CM code: I20–I25) Heart failure (ICD-9-CM code: 428; ICD-10-CM code: I50) Peripheral artery diseases (ICD-9-CM code: 443.9; ICD-10-CM code: I73.9) Hypoglycemia (ICD-9-CM code: 251.2; ICD-10-CM code: E16.2)
Comorbidity	(Diagnosed diseases 12 months before and including the date of cohort entry) Hypertension (ICD-9-CM code: 401–405; ICD-10-CM code: I10–I13, I15, N26.2) Dyslipidemia (ICD-9-CM code: 272; ICD-10-CM code: E71.30, E75.21, E75.22, E75.24, E75.3, E75.5, E75.6, E77, E78.0–E78.6, E78.70, E78.79, E78.8, E78.9) Chronic liver disease (ICD-9-CM code: 571; ICD-10-CM code: K70, K73–K76) Chronic kidney disease (ICD-9-CM code: 580–589, 593.9; ICD-10-CM code: N00–N08, N14–N19, N25–N27, N28.9, N29) Chronic obstructive pulmonary disease (ICD-9-CM code: 491, 492, 496; ICD-10-CM code: J41–J44)
Medication	(Use within 6 months prior to baseline; cumulative drug day>30 days during follow-up) Metformin (ATC code: A10BA) Sulfonylurea (ATC code: A10BB), Meglitinide (ATC code: A10BX) Insulin (ATC code: A10A) Alpha-glucosidase inhibitors (ATC code: A10BF) Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ATC code: C09) Aspirin (ATC code: B01AC06, N02BA01) Antiplatelets (ATC code: B01AB, B01AC) Anticoagulants (ATC code: B01AA, B01AE, B01AF) Beta-blockers (ATC code: C07) Calcium-channel blockers (ATC code: C08) Corticosteroids (ATC code: C05AA), Diuretics (ATC code: C03) Non-steroidal anti-inflammatory drugs (ATC code: M01A) Statins (ATC code: C10AA, C10BA, C10BX)

*ATC, anatomical therapeutic chemical; ICD, International Classification of Diseases; CM, Clinical Modification.

eTable 2. Incidence and hazard ratios of all-cause mortality.

Variables	All-cause mortality			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	29214	348499	83.83	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	4757	159784	29.77	0.36 (0.35, 0.37)***	<.001	0.38 (0.37, 0.39)***	<.001
TZD	6163	142344	43.30	0.55 (0.54, 0.57)***	<.001	0.49 (0.48, 0.50)***	<.001
GLP-1RA/TZD	2205	152783	14.43	0.19 (0.18, 0.20)***	<.001	0.20 (0.19, 0.21)***	<.001
Gender							
Female	15306	375504	40.76	1.00 (reference)	-	1.00 (reference)	-
Male	27033	427906	63.18	1.52 (1.49, 1.55)***	<.001	1.52 (1.49, 1.55)***	<.001
Age, years							
20–35	484	34941	13.85	1.00 (reference)	-	1.00 (reference)	-
36–50	5763	171049	33.69	2.40 (2.19, 2.63)***	<.001	2.22 (2.02, 2.43)***	<.001
51–65	18083	379018	47.71	3.38 (3.09, 3.70)***	<.001	3.30 (3.01, 3.61)***	<.001
>65	18009	218402	82.46	5.70 (5.20, 6.23)***	<.001	5.50 (5.02, 6.03)***	<.001
Comorbidities							
Hypertension							
No	12838	279564	45.92	1.00 (reference)	-	1.00 (reference)	-
Yes	29501	523845	56.32	1.22 (1.20, 1.25)***	<.001	0.93 (0.90, 0.95)***	<.001
Dyslipidemia							
No	19108	255075	74.91	1.00 (reference)	-	1.00 (reference)	-
Yes	23231	548335	42.37	0.56 (0.55, 0.57)***	<.001	0.66 (0.64, 0.67)***	<.001
Chronic liver diseases							
No	31853	673834	47.27	1.00 (reference)	-	1.00 (reference)	-
Yes	10486	129576	80.93	1.61 (1.58, 1.65)***	<.001	1.57 (1.53, 1.60)***	<.001
Chronic kidney diseases							
No	32134	672321	47.80	1.00 (reference)	-	1.00 (reference)	-
Yes	10205	131089	77.85	1.59 (1.55, 1.63)***	<.001	1.08 (1.06, 1.11)***	<.001
COPD							
No	38382	757711	50.66	1.00 (reference)	-	1.00 (reference)	-
Yes	3957	45699	86.59	1.61 (1.56, 1.67)***	<.001	1.35 (1.31, 1.39)***	<.001
Medication							
Metformin							
No	5776	117503	49.16	1.00 (reference)	-	1.00 (reference)	-
Yes	36563	685907	53.31	1.09 (1.06, 1.12)***	<.001	1.03 (1.00, 1.06)	.089
Sulfonylureas							
No	7859	204966	38.34	1.00 (reference)	-	1.00 (reference)	-
Yes	34480	598443	57.62	1.55 (1.51, 1.59)***	<.001	1.52 (1.47, 1.56)***	<.001
Meglitinide							
No	35660	717254	49.72	1.00 (reference)	-	1.00 (reference)	-
Yes	6679	86155	77.52	1.55 (1.51, 1.59)***	<.001	1.23 (1.19, 1.26)***	<.001
Insulin							
No	19556	505488	38.69	1.00 (reference)	-	1.00 (reference)	-
Yes	22783	297922	76.47	1.95 (1.92, 1.99)***	<.001	1.68 (1.65, 1.71)***	<.001
SGLT2i							
No	41948	787494	53.27	1.00 (reference)	-	1.00 (reference)	-
Yes	391	15916	24.57	0.36 (0.32, 0.40)***	<.001	0.48 (0.43, 0.53)***	<.001
AGi							
No	31947	641091	49.83	1.00 (reference)	-	1.00 (reference)	-
Yes	10392	162318	64.02	1.29 (1.26, 1.32)***	<.001	1.08 (1.05, 1.10)***	<.001
ACEi/ARB							
No	19056	390895	48.75	1.00 (reference)	-	1.00 (reference)	-
Yes	23283	412515	56.44	1.15 (1.13, 1.17)***	<.001	0.90 (0.88, 0.93)***	<.001
Aspirin							
No	34158	667227	51.19	1.00 (reference)	-	1.00 (reference)	-
Yes	8181	136183	60.07	1.18 (1.15, 1.20)***	<.001	0.87 (0.84, 0.91)***	<.001
Antiplatelets							
No	30750	624221	49.26	1.00 (reference)	-	1.00 (reference)	-
Yes	11589	179188	64.68	1.31 (1.29, 1.34)***	<.001	1.14 (1.10, 1.18)***	<.001
Anticoagulants							
No	41715	796573	52.37	1.00 (reference)	-	1.00 (reference)	-
Yes	624	6836	91.28	1.67 (1.54, 1.81)***	<.001	1.19 (1.10, 1.29)***	<.001

β -blockers								
No	37186	725160	51.28	1.00 (reference)	-	1.00 (reference)	-	
Yes	5153	78250	65.85	1.26 (1.22, 1.29)***	<.001	1.14 (1.11, 1.18)***	<.001	
CCB								
No	20412	456868	44.68	1.00 (reference)	-	1.00 (reference)	-	
Yes	21927	346541	63.27	1.41 (1.38, 1.44)***	<.001	1.17 (1.14, 1.20)***	<.001	
Corticosteroids								
No	41090	785142	52.33	1.00 (reference)	-	1.00 (reference)	-	
Yes	1249	18267	68.37	1.26 (1.19, 1.34)***	<.001	1.21 (1.14, 1.28)***	<.001	
Diuretics								
No	28083	660336	42.53	1.00 (reference)	-	1.00 (reference)	-	
Yes	14256	143073	99.64	2.29 (2.25, 2.34)***	<.001	1.77 (1.73, 1.81)***	<.001	
NSAIDs								
No	11080	166178	66.68	1.00 (reference)	-	1.00 (reference)	-	
Yes	31259	637232	49.05	0.70 (0.69, 0.72)***	<.001	0.77 (0.76, 0.79)***	<.001	
Statins								
No	24139	387789	62.25	1.00 (reference)	-	1.00 (reference)	-	
Yes	18200	415620	43.79	0.69 (0.68, 0.71)***	<.001	0.84 (0.82, 0.86)***	<.001	
DCSI score								
0	11671	282660	41.29	1.00 (reference)	-	1.00 (reference)	-	
1	6258	150987	41.45	0.99 (0.96, 1.02)	.455	0.98 (0.95, 1.01)	.134	
2	9220	162666	56.68	1.36 (1.32, 1.40)***	<.001	1.11 (1.08, 1.14)***	<.001	
≥ 3	15190	207098	73.35	1.76 (1.72, 1.80)***	<.001	1.22 (1.19, 1.25)***	<.001	
DM duration	-	-	-	0.81 (0.80, 0.81)***	<.001	0.76 (0.76, 0.77)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium-glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

*** p <.001.

eTable 3. Incidence and hazard ratios of major adverse cardiovascular events.

Variables	MACE			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	8994	331913	27.10	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	3120	153510	20.32	0.75 (0.72, 0.79)***	<.001	0.82 (0.79, 0.86)***	<.001
TZD	3410	132798	25.68	0.96 (0.93, 1.00)	.063	0.84 (0.81, 0.88)***	<.001
GLP-1RA/TZD	3200	143269	22.34	0.85 (0.81, 0.88)***	<.001	0.85 (0.82, 0.89)***	<.001
Gender							
Female	7757	356809	21.74	1.00 (reference)	-	1.00 (reference)	-
Male	10967	404682	27.10	1.24 (1.21, 1.28)***	<.001	1.41 (1.37, 1.45)***	<.001
Age, years							
20–35	210	34423	6.10	1.00 (reference)	-	1.00 (reference)	-
36–50	2288	166011	13.78	2.25 (1.96, 2.59)***	<.001	1.68 (1.46, 1.93)***	<.001
51–65	8085	360322	22.44	3.66 (3.19, 4.20)***	<.001	2.14 (1.86, 2.45)***	<.001
>65	8141	200734	40.56	6.58 (5.73, 7.54)***	<.001	2.99 (2.61, 3.44)***	<.001
Comorbidities							
Hypertension							
No	4242	270256	15.70	1.00 (reference)	-	1.00 (reference)	-
Yes	14482	491234	29.48	1.88 (1.81, 1.94)***	<.001	1.20 (1.15, 1.26)***	<.001
Dyslipidemia							
No	6561	240699	27.26	1.00 (reference)	-	1.00 (reference)	-
Yes	12163	520791	23.35	0.86 (0.83, 0.88)***	<.001	0.86 (0.83, 0.89)***	<.001
Chronic liver diseases							
No	15857	637490	24.87	1.00 (reference)	-	1.00 (reference)	-
Yes	2867	124001	23.12	0.92 (0.88, 0.95)***	<.001	0.97 (0.93, 1.01)	.174
Chronic kidney diseases							
No	14260	639512	22.30	1.00 (reference)	-	1.00 (reference)	-
Yes	4464	121978	36.60	1.63 (1.58, 1.69)***	<.001	0.54 (0.53, 0.56)***	<.001
COPD							
No	17411	718388	24.24	1.00 (reference)	-	1.00 (reference)	-
Yes	1313	43102	30.46	1.24 (1.17, 1.31)***	<.001	1.01 (0.95, 1.06)	.854
Medication							
Metformin							
No	2513	111561	22.53	1.00 (reference)	-	1.00 (reference)	-
Yes	16211	649929	24.94	1.11 (1.06, 1.16)***	<.001	0.76 (0.72, 0.80)***	<.001
Sulfonylureas							
No	3594	196947	18.25	1.00 (reference)	-	1.00 (reference)	-
Yes	15130	564543	26.80	1.48 (1.42, 1.53)***	<.001	1.08 (1.04, 1.13)***	<.001
Meglitinide							
No	16029	681038	23.54	1.00 (reference)	-	1.00 (reference)	-
Yes	2695	80452	33.50	1.42 (1.36, 1.48)***	<.001	1.05 (1.00, 1.09)*	.028
Insulin							
No	10353	481486	21.50	1.00 (reference)	-	1.00 (reference)	-
Yes	8371	280005	29.90	1.38 (1.35, 1.43)***	<.001	0.94 (0.92, 0.97)***	<.001
SGLT2i							
No	18490	745804	24.79	1.00 (reference)	-	1.00 (reference)	-
Yes	234	15686	14.92	0.56 (0.49, 0.64)***	<.001	0.65 (0.57, 0.74)***	<.001
AGi							
No	14324	608670	23.53	1.00 (reference)	-	1.00 (reference)	-
Yes	4400	152820	28.79	1.22 (1.18, 1.27)***	<.001	0.93 (0.90, 0.96)***	<.001
ACEi/ARB							
No	7250	374388	19.36	1.00 (reference)	-	1.00 (reference)	-
Yes	11474	387103	29.64	1.53 (1.48, 1.57)***	<.001	0.86 (0.83, 0.90)***	<.001
Aspirin							
No	14478	634882	22.80	1.00 (reference)	-	1.00 (reference)	-
Yes	4246	126608	33.54	1.47 (1.42, 1.52)***	<.001	1.04 (0.98, 1.10)	.215
Antiplatelets							
No	12997	595021	21.84	1.00 (reference)	-	1.00 (reference)	-
Yes	5727	166469	34.40	1.57 (1.53, 1.62)***	<.001	0.89 (0.84, 0.94)***	<.001
Anticoagulants							
No	18493	755076	24.49	1.00 (reference)	-	1.00 (reference)	-
Yes	231	6414	36.01	1.46 (1.28, 1.66)***	<.001	0.73 (0.64, 0.84)***	<.001

β-blockers								
No	16816	687498	24.46	1.00 (reference)	-	1.00 (reference)	-	
Yes	1908	73992	25.79	1.05 (1.00, 1.10)*	.042	0.98 (0.93, 1.02)	.311	
CCB								
No	8221	438032	18.77	1.00 (reference)	-	1.00 (reference)	-	
Yes	10503	323458	32.47	1.73 (1.68, 1.78)***	<.001	1.19 (1.14, 1.23)***	<.001	
Corticosteroids								
No	18333	744027	24.64	1.00 (reference)	-	1.00 (reference)	-	
Yes	391	17463	22.39	0.90 (0.82, 1.00)*	.044	0.89 (0.80, 0.98)*	.023	
Diuretics								
No	13761	628887	21.88	1.00 (reference)	-	1.00 (reference)	-	
Yes	4963	132603	37.43	1.70 (1.64, 1.75)***	<.001	1.12 (1.09, 1.16)***	<.001	
NSAIDs								
No	4325	156711	27.60	1.00 (reference)	-	1.00 (reference)	-	
Yes	14399	604779	23.81	0.86 (0.83, 0.89)***	<.001	0.81 (0.78, 0.84)***	<.001	
Statins								
No	9072	367194	24.71	1.00 (reference)	-	1.00 (reference)	-	
Yes	9652	394297	24.48	0.99 (0.96, 1.02)	.458	0.90 (0.87, 0.93)***	<.001	
DCSI score								
0	255	282660	0.90	1.00 (reference)	-	1.00 (reference)	-	
1	105	150987	0.70	0.77 (0.62, 0.97)*	.027	0.84 (0.67, 1.06)	.135	
2	5411	150112	36.05	40.00 (35.28, 45.35)***	<.001	44.10 (38.94, 50.11)***	<.001	
≥ 3	12953	177732	72.88	80.90 (71.47, 91.57)***	<.001	99.50 (87.86, 112.86)***	<.001	
DM duration	-	-	-	0.95 (0.94, 0.96)***	<.001	0.91 (0.90, 0.91)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, *** $p < .001$.

eTable 4. Incidence and hazard ratios of cardiovascular mortality.

Variables	Cardiovascular mortality			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	2691	348499	7.72	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	416	159784	2.60	0.34 (0.31, 0.38)***	<.001	0.39 (0.35, 0.43)***	<.001
TZD	632	142344	4.44	0.59 (0.54, 0.64)***	<.001	0.49 (0.45, 0.54)***	<.001
GLP-1RA/TZD	223	152783	1.46	0.20 (0.17, 0.23)***	<.001	0.20 (0.18, 0.23)***	<.001
Gender							
Female	1463	375504	3.90	1.00 (reference)	-	1.00 (reference)	-
Male	2499	427906	5.84	1.49 (1.39, 1.58)***	<.001	1.57 (1.47, 1.68)***	<.001
Age, years							
20–35	32	34941	0.92	1.00 (reference)	-	1.00 (reference)	-
36–50	530	171049	3.10	3.36 (2.35, 4.80)***	<.001	2.59 (1.81, 3.70)***	<.001
51–65	1613	379018	4.26	4.60 (3.24, 6.53)***	<.001	2.96 (2.08, 4.21)***	<.001
>65	1787	218402	8.18	8.75 (6.17, 12.41)***	<.001	4.57 (3.21, 6.50)***	<.001
Comorbidities							
Hypertension							
No	741	279564	2.65	1.00 (reference)	-	1.00 (reference)	-
Yes	3221	523845	6.15	2.32 (2.14, 2.51)***	<.001	1.34 (1.21, 1.49)***	<.001
Dyslipidemia							
No	1635	255075	6.41	1.00 (reference)	-	1.00 (reference)	-
Yes	2327	548335	4.24	0.66 (0.62, 0.71)***	<.001	0.68 (0.63, 0.73)***	<.001
Chronic liver diseases							
No	3419	673834	5.07	1.00 (reference)	-	1.00 (reference)	-
Yes	543	129576	4.19	0.80 (0.73, 0.88)***	<.001	0.88 (0.80, 0.96)**	.007
Chronic kidney diseases							
No	2934	672321	4.36	1.00 (reference)	-	1.00 (reference)	-
Yes	1028	131089	7.84	1.78 (1.66, 1.91)***	<.001	0.75 (0.70, 0.81)***	<.001
COPD							
No	3637	757711	4.80	1.00 (reference)	-	1.00 (reference)	-
Yes	325	45699	7.11	1.45 (1.29, 1.62)***	<.001	1.23 (1.10, 1.38)***	<.001
Medication							
Metformin							
No	546	117503	4.65	1.00 (reference)	-	1.00 (reference)	-
Yes	3416	685907	4.98	1.07 (0.98, 1.17)	.126	0.87 (0.79, 0.97)*	.011
Sulfonylureas							
No	703	204966	3.43	1.00 (reference)	-	1.00 (reference)	-
Yes	3259	598443	5.45	1.60 (1.48, 1.74)***	<.001	1.34 (1.22, 1.47)***	<.001
Meglitinide							
No	3357	717254	4.68	1.00 (reference)	-	1.00 (reference)	-
Yes	605	86155	7.02	1.50 (1.37, 1.63)***	<.001	1.09 (1.00, 1.19)	.0611
Insulin							
No	2173	505488	4.30	1.00 (reference)	-	1.00 (reference)	-
Yes	1789	297922	6.00	1.39 (1.30, 1.48)***	<.001	1.07 (1.01, 1.15)*	.031
SGLT2i							
No	3921	787494	4.98	1.00 (reference)	-	1.00 (reference)	-
Yes	41	15916	2.58	0.46 (0.34, 0.63)***	<.001	0.60 (0.44, 0.82)**	.001
AGi							
No	2920	641091	4.55	1.00 (reference)	-	1.00 (reference)	-
Yes	1042	162318	6.42	1.41 (1.31, 1.51)***	<.001	1.10 (1.02, 1.18)*	.012
ACEi/ARB							
No	1340	390895	3.43	1.00 (reference)	-	1.00 (reference)	-
Yes	2622	412515	6.36	1.85 (1.73, 1.98)***	<.001	1.02 (0.93, 1.10)	.727
Aspirin							
No	3000	667227	4.50	1.00 (reference)	-	1.00 (reference)	-
Yes	962	136183	7.06	1.57 (1.46, 1.69)***	<.001	0.92 (0.82, 1.04)	.165
Antiplatelets							
No	2631	624221	4.21	1.00 (reference)	-	1.00 (reference)	-
Yes	1331	179188	7.43	1.76 (1.65, 1.88)***	<.001	1.16 (1.04, 1.29)**	.01
Anticoagulants							
No	3891	796573	4.88	1.00 (reference)	-	1.00 (reference)	-
Yes	71	6836	10.39	2.09 (1.65, 2.64)***	<.001	1.16 (0.92, 1.47)	.220

β-blockers							
No	3576	725160	4.93	1.00 (reference)	-	1.00 (reference)	-
Yes	386	78250	4.93	0.99 (0.89, 1.10)	.89	0.99 (0.89, 1.10)	.889
CCB							
No	1497	456868	3.28	1.00 (reference)	-	1.00 (reference)	-
Yes	2465	346541	7.11	2.16 (2.03, 2.31)***	<.001	1.40 (1.29, 1.51)***	<.001
Corticosteroids							
No	3894	785142	4.96	1.00 (reference)	-	1.00 (reference)	-
Yes	68	18267	3.72	0.74 (0.58, 0.94)*	.014	0.79 (0.62, 1.01)	.057
Diuretics							
No	2699	660336	4.09	1.00 (reference)	-	1.00 (reference)	-
Yes	1263	143073	8.83	2.13 (1.99, 2.28)***	<.001	1.37 (1.27, 1.47)***	<.001
NSAIDs							
No	1186	166178	7.14	1.00 (reference)	-	1.00 (reference)	-
Yes	2776	637232	4.36	0.60 (0.56, 0.65)***	<.001	0.62 (0.58, 0.67)***	<.001
Statins							
No	1997	387789	5.15	1.00 (reference)	-	1.00 (reference)	-
Yes	1965	415620	4.73	0.92 (0.86, 0.98)**	.007	0.96 (0.89, 1.03)	.231
DCSI score							
0	517	282660	1.83	1.00 (reference)	-	1.00 (reference)	-
1	254	150987	1.68	0.92 (0.79, 1.07)	.257	0.94 (0.81, 1.10)	.463
2	956	162666	5.88	3.20 (2.88, 3.56)***	<.001	2.94 (2.64, 3.28)***	<.001
≥ 3	2235	207098	10.79	5.88 (5.34, 6.47)***	<.001	5.10 (4.60, 5.66)***	<.001
DM duration	-	-	-	0.83 (0.81, 0.84)***	<.001	0.79 (0.77, 0.80)***	<.001

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 5. Incidence and hazard ratios of myocardial infarction.

Variables	Myocardial infarction			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	1851	346084	5.35	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	495	158966	3.11	0.60 (0.55, 0.67)***	<.001	0.70 (0.63, 0.77)***	<.001
TZD	719	140920	5.10	0.92 (0.85, 1.01)	.071	0.79 (0.73, 0.87)***	<.001
GLP-1RA/TZD	591	151403	3.90	0.71 (0.65, 0.78)***	<.001	0.73 (0.66, 0.80)***	<.001
Gender							
Female	1240	373537	3.32	1.00 (reference)	-	1.00 (reference)	-
Male	2416	423835	5.70	1.73 (1.61, 1.85)***	<.001	1.84 (1.71, 1.97)***	<.001
Age, years							
20–35	68	34793	1.95	1.00 (reference)	-	1.00 (reference)	-
36–50	582	169942	3.42	1.76 (1.37, 2.26)***	<.001	1.19 (0.92, 1.53)	.177
51–65	1670	376095	4.44	2.28 (1.79, 2.90)***	<.001	1.16 (0.91, 1.48)	.242
>65	1336	216543	6.17	3.19 (2.50, 4.07)***	<.001	1.24 (0.97, 1.59)	.087
Comorbidities							
Hypertension							
No	777	278350	2.79	1.00 (reference)	-	1.00 (reference)	-
Yes	2879	519022	5.55	1.99 (1.84, 2.16)***	<.001	1.23 (1.10, 1.36)***	<.001
Dyslipidemia							
No	1187	253211	4.69	1.00 (reference)	-	1.00 (reference)	-
Yes	2469	544161	4.54	0.98 (0.92, 1.05)	.634	0.90 (0.84, 0.98)*	.014
Chronic liver diseases							
No	3185	668447	4.76	1.00 (reference)	-	1.00 (reference)	-
Yes	471	128925	3.65	0.78 (0.71, 0.86)***	<.001	0.81 (0.73, 0.89)***	<.001
Chronic kidney diseases							
No	2494	668120	3.73	1.00 (reference)	-	1.00 (reference)	-
Yes	1162	129252	8.99	2.44 (2.28, 2.62)***	<.001	0.79 (0.74, 0.85)***	<.001
COPD							
No	3432	751966	4.56	1.00 (reference)	-	1.00 (reference)	-
Yes	224	45406	4.93	1.10 (0.96, 1.26)	.149	0.92 (0.80, 1.05)	.224
Medication							
Metformin							
No	491	116632	4.21	1.00 (reference)	-	1.00 (reference)	-
Yes	3165	680740	4.65	1.11 (1.01, 1.22)*	.036	0.77 (0.69, 0.86)***	<.001
Sulfonylureas							
No	637	203861	3.12	1.00 (reference)	-	1.00 (reference)	-
Yes	3019	593511	5.09	1.61 (1.47, 1.75)***	<.001	1.16 (1.05, 1.27)**	.003
Meglitinide							
No	3055	712132	4.29	1.00 (reference)	-	1.00 (reference)	-
Yes	601	85240	7.05	1.64 (1.51, 1.80)***	<.001	1.12 (1.02, 1.22)*	.017
Insulin							
No	1881	502235	3.75	1.00 (reference)	-	1.00 (reference)	-
Yes	1775	295137	6.01	1.61 (1.51, 1.71)***	<.001	1.04 (0.98, 1.12)	.206
SGLT2i							
No	3615	781488	4.63	1.00 (reference)	-	1.00 (reference)	-
Yes	41	15884	2.58	0.59 (0.43, 0.80)***	<.001	0.63 (0.47, 0.86)**	.004
AGi							
No	2743	636457	4.31	1.00 (reference)	-	1.00 (reference)	-
Yes	913	160915	5.67	1.31 (1.22, 1.42)***	<.001	0.95 (0.88, 1.03)	.185
ACEi/ARB							
No	1316	388726	3.39	1.00 (reference)	-	1.00 (reference)	-
Yes	2340	408646	5.73	1.70 (1.59, 1.82)***	<.001	0.90 (0.82, 0.98)*	.014
Aspirin							
No	2859	662497	4.32	1.00 (reference)	-	1.00 (reference)	-
Yes	797	134875	5.91	1.37 (1.27, 1.48)***	<.001	0.86 (0.76, 0.97)*	.017
Antiplatelets							
No	2507	620044	4.04	1.00 (reference)	-	1.00 (reference)	-
Yes	1149	177328	6.48	1.60 (1.50, 1.72)***	<.001	1.02 (0.91, 1.14)	.746
Anticoagulants							
No	3621	790586	4.58	1.00 (reference)	-	1.00 (reference)	-
Yes	35	6786	5.16	1.14 (0.82, 1.59)	.439	0.63 (0.45, 0.87)**	.006

β-blockers								
No	3386	719514	4.71	1.00 (reference)	-	1.00 (reference)	-	
Yes	270	77858	3.47	0.74 (0.66, 0.84)***	<.001	0.74 (0.65, 0.84)***	<.001	
CCB								
No	1533	454271	3.37	1.00 (reference)	-	1.00 (reference)	-	
Yes	2123	343101	6.19	1.84 (1.72, 1.96)***	<.001	1.23 (1.14, 1.34)***	<.001	
Corticosteroids								
No	3597	779203	4.62	1.00 (reference)	-	1.00 (reference)	-	
Yes	59	18169	3.25	0.71 (0.55, 0.92)*	.011	0.74 (0.57, 0.96)*	.024	
Diuretics								
No	2637	655957	4.02	1.00 (reference)	-	1.00 (reference)	-	
Yes	1019	141415	7.21	1.80 (1.67, 1.93)***	<.001	1.12 (1.03, 1.21)**	.006	
NSAIDs								
No	959	164668	5.82	1.00 (reference)	-	1.00 (reference)	-	
Yes	2697	632704	4.26	0.75 (0.70, 0.81)***	<.001	0.77 (0.72, 0.84)***	<.001	
Statins								
No	1598	385107	4.15	1.00 (reference)	-	1.00 (reference)	-	
Yes	2058	412265	4.99	1.22 (1.15, 1.31)***	<.001	1.12 (1.03, 1.21)**	.005	
DCSI score								
2	910	160984	5.65	1.00 (reference)	-	1.00 (reference)	-	
≥ 3	2746	202742	13.54	2.40 (2.23, 2.59)***	<.001	2.50 (2.31, 2.70)***	<.001	
DM duration	-	-	-	0.95 (0.93, 0.96)***	<.001	0.91 (0.89, 0.92)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 6. Incidence and hazard ratios of cerebrovascular diseases.

Variables	Cerebrovascular diseases			cHR (95% CI)	<i>p</i> -value	aHR ^a (95% CI)	<i>p</i> -value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	6894	333896	20.65	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	2615	154240	16.95	0.82 (0.79, 0.86)***	<.001	0.89 (0.85, 0.93)***	<.001
TZD	2739	133984	20.44	1.01 (0.96, 1.05)	.704	0.89 (0.85, 0.93)***	<.001
GLP-1RA/TZD	2690	144471	18.62	0.93 (0.89, 0.97)***	<.001	0.93 (0.89, 0.97)**	0.002
Gender							
Female	6512	358405	18.17	1.00 (reference)	-	1.00 (reference)	-
Male	8426	408188	20.64	1.13 (1.09, 1.17)***	<.001	1.29 (1.25, 1.33)***	<.001
Age, years							
20–35	143	34555	4.14	1.00 (reference)	-	1.00 (reference)	-
36–50	1668	167019	9.99	2.41 (2.03, 2.85)***	<.001	1.79 (1.51, 2.12)***	<.001
51–65	6355	362813	17.52	4.21 (3.57, 4.97)***	<.001	2.44 (2.07, 2.88)***	<.001
>65	6772	202205	33.49	8.01 (6.78, 9.45)***	<.001	3.60 (3.04, 4.25)***	<.001
Comorbidities							
Hypertension							
No	3421	271310	12.61	1.00 (reference)	-	1.00 (reference)	-
Yes	11517	495282	23.25	1.84 (1.77, 1.91)***	<.001	1.18 (1.12, 1.24)***	<.001
Dyslipidemia							
No	5301	242208	21.89	1.00 (reference)	-	1.00 (reference)	-
Yes	9637	524384	18.38	0.84 (0.81, 0.87)***	<.001	0.86 (0.83, 0.89)***	<.001
Chronic liver diseases							
No	12590	642022	19.61	1.00 (reference)	-	1.00 (reference)	-
Yes	2348	124570	18.85	0.95 (0.91, 0.99)*	.016	1.01 (0.97, 1.06)	.587
Chronic kidney diseases							
No	11620	643083	18.07	1.00 (reference)	-	1.00 (reference)	-
Yes	3318	123509	26.86	1.48 (1.42, 1.54)***	<.001	0.49 (0.47, 0.51)***	<.001
COPD							
No	13878	723243	19.19	1.00 (reference)	-	1.00 (reference)	-
Yes	1060	43349	24.45	1.26 (1.18, 1.34)***	<.001	1.01 (0.95, 1.08)	.727
Medication							
Metformin							
No	1996	112297	17.77	1.00 (reference)	-	1.00 (reference)	-
Yes	12942	654295	19.78	1.11 (1.06, 1.17)***	<.001	0.76 (0.72, 0.80)***	<.001
Sulfonylureas							
No	2922	197884	14.77	1.00 (reference)	-	1.00 (reference)	-
Yes	12016	568709	21.13	1.44 (1.38, 1.50)***	<.001	1.04 (0.99, 1.09)	.088
Meglitinide							
No	12844	685429	18.74	1.00 (reference)	-	1.00 (reference)	-
Yes	2094	81163	25.80	1.37 (1.31, 1.44)***	<.001	1.03 (0.98, 1.08)	.221
Insulin							
No	8295	484266	17.13	1.00 (reference)	-	1.00 (reference)	-
Yes	6643	282326	23.53	1.37 (1.33, 1.41)***	<.001	0.93 (0.90, 0.96)***	<.001
SGLT2i							
No	14750	750879	19.64	1.00 (reference)	-	1.00 (reference)	-
Yes	188	15713	11.96	0.57 (0.49, 0.66)***	<.001	0.66 (0.57, 0.77)***	<.001
AGi							
No	11504	612612	18.78	1.00 (reference)	-	1.00 (reference)	-
Yes	3434	153980	22.30	1.19 (1.14, 1.23)***	<.001	0.91 (0.87, 0.95)***	<.001
ACEi/ARB							
No	5879	376282	15.62	1.00 (reference)	-	1.00 (reference)	-
Yes	9059	390310	23.21	1.48 (1.43, 1.53)***	<.001	0.85 (0.82, 0.89)***	<.001
Aspirin							
No	11529	638946	18.04	1.00 (reference)	-	1.00 (reference)	-
Yes	3409	127646	26.71	1.48 (1.42, 1.54)***	<.001	1.10 (1.03, 1.18)**	.003
Antiplatelets							
No	10421	598608	17.41	1.00 (reference)	-	1.00 (reference)	-
Yes	4517	167984	26.89	1.54 (1.49, 1.60)***	<.001	0.83 (0.78, 0.88)***	<.001
Anticoagulants							
No	14749	760139	19.40	1.00 (reference)	-	1.00 (reference)	-
Yes	189	6453	29.29	1.49 (1.29, 1.72)***	<.001	0.75 (0.65, 0.86)***	<.001

β-blockers							
No	13332	692264	19.26	1.00 (reference)	-	1.00 (reference)	-
Yes	1606	74328	21.61	1.12 (1.06, 1.18)***	<.001	1.02 (0.97, 1.07)	.491
CCB							
No	6632	440299	15.06	1.00 (reference)	-	1.00 (reference)	-
Yes	8306	326293	25.46	1.69 (1.63, 1.74)***	<.001	1.16 (1.12, 1.21)***	<.001
Corticosteroids							
No	14606	749049	19.50	1.00 (reference)	-	1.00 (reference)	-
Yes	332	17543	18.92	0.96 (0.86, 1.07)	.503	0.94 (0.84, 1.05)	.284
Diuretics							
No	11028	632626	17.43	1.00 (reference)	-	1.00 (reference)	-
Yes	3910	133966	29.19	1.66 (1.60, 1.73)***	<.001	1.11 (1.07, 1.16)***	<.001
NSAIDs							
No	3332	157957	21.09	1.00 (reference)	-	1.00 (reference)	-
Yes	11606	608635	19.07	0.89 (0.86, 0.93)***	<.001	0.82 (0.79, 0.86)***	<.001
Statins							
No	7389	369424	20.00	1.00 (reference)	-	1.00 (reference)	-
Yes	7549	397168	19.01	0.95 (0.92, 0.98)***	<.001	0.85 (0.82, 0.89)***	<.001
DCSI score							
2	4329	160984	26.89	1.00 (reference)	-	1.00 (reference)	-
≥ 3	10609	202742	52.33	2.00 (1.93, 2.07)***	<.001	2.12 (2.04, 2.20)***	<.001
DM duration	-	-	-	0.96 (0.95, 0.97)***	<.001	0.92 (0.91, 0.92)***	<.001

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 7. Incidence and hazard ratios of ischemic heart diseases.

Variables	Ischemic heart diseases			cHR (95% CI)	<i>p</i> -value	aHR ^a (95% CI)	<i>p</i> -value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	7690	329931	23.31	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	3064	152690	20.07	0.86 (0.83, 0.90)***	<.001	0.90 (0.87, 0.94)***	<.001
TZD	3687	130237	28.31	1.23 (1.18, 1.28)***	<.001	1.14 (1.10, 1.19)***	<.001
GLP-1RA/TZD	3826	139793	27.37	1.19 (1.15, 1.24)***	<.001	1.22 (1.17, 1.27)***	<.001
Gender							
Female	7951	352058	22.58	1.00 (reference)	-	1.00 (reference)	-
Male	10316	400592	25.75	1.14 (1.10, 1.17)***	<.001	1.23 (1.20, 1.27)***	<.001
Age, years							
20–35	320	34058	9.40	1.00 (reference)	-	1.00 (reference)	-
36–50	2854	162908	17.52	1.86 (1.66, 2.09)***	<.001	1.56 (1.39, 1.76)***	<.001
51–65	8644	354205	24.40	2.59 (2.31, 2.89)***	<.001	1.84 (1.64, 2.06)***	<.001
>65	6449	201479	32.01	3.38 (3.03, 3.79)***	<.001	1.96 (1.75, 2.20)***	<.001
Comorbidities							
Hypertension							
No	4289	267622	16.03	1.00 (reference)	-	1.00 (reference)	-
Yes	13978	485028	28.82	1.80 (1.74, 1.86)***	<.001	1.27 (1.21, 1.33)***	<.001
Dyslipidemia							
No	5514	239741	23.00	1.00 (reference)	-	1.00 (reference)	-
Yes	12753	512909	24.86	1.08 (1.05, 1.12)***	<.001	1.02 (0.98, 1.05)	.371
Chronic liver diseases							
No	15606	629557	24.79	1.00 (reference)	-	1.00 (reference)	-
Yes	2661	123093	21.62	0.87 (0.83, 0.90)***	<.001	0.86 (0.83, 0.90)***	<.001
Chronic kidney diseases							
No	13680	633101	21.61	1.00 (reference)	-	1.00 (reference)	-
Yes	4587	119549	38.37	1.77 (1.71, 1.83)***	<.001	0.94 (0.90, 0.97)***	<.001
COPD							
No	17012	710124	23.96	1.00 (reference)	-	1.00 (reference)	-
Yes	1255	42526	29.51	1.22 (1.15, 1.30)***	<.001	1.05 (0.99, 1.12)	.08
Medication							
Metformin							
No	2538	110252	23.02	1.00 (reference)	-	1.00 (reference)	-
Yes	15729	642398	24.48	1.06 (1.02, 1.11)**	.004	0.81 (0.77, 0.85)***	<.001
Sulfonylureas							
No	3812	194669	19.58	1.00 (reference)	-	1.00 (reference)	-
Yes	14455	557981	25.91	1.33 (1.28, 1.38)***	<.001	1.11 (1.07, 1.16)***	<.001
Meglitinide							
No	15666	673348	23.27	1.00 (reference)	-	1.00 (reference)	-
Yes	2601	79302	32.80	1.41 (1.35, 1.47)***	<.001	1.09 (1.05, 1.14)***	<.001
Insulin							
No	10415	475527	21.90	1.00 (reference)	-	1.00 (reference)	-
Yes	7852	277123	28.33	1.29 (1.25, 1.33)***	<.001	1.07 (1.04, 1.10)***	<.001
SGLT2i							
No	18019	737010	24.45	1.00 (reference)	-	1.00 (reference)	-
Yes	248	15640	15.86	0.63 (0.55, 0.71)***	<.001	0.65 (0.57, 0.74)***	<.001
AGi							
No	13865	602420	23.02	1.00 (reference)	-	1.00 (reference)	-
Yes	4402	150230	29.30	1.27 (1.23, 1.32)***	<.001	1.04 (1.00, 1.07)*	.04
ACEi/ARB							
No	7058	370817	19.03	1.00 (reference)	-	1.00 (reference)	-
Yes	11209	381833	29.36	1.54 (1.50, 1.59)***	<.001	0.94 (0.91, 0.98)**	.003
Aspirin							
No	13891	628730	22.09	1.00 (reference)	-	1.00 (reference)	-
Yes	4376	123920	35.31	1.60 (1.54, 1.65)***	<.001	0.99 (0.94, 1.05)	.802
Antiplatelets							
No	12380	589857	20.99	1.00 (reference)	-	1.00 (reference)	-
Yes	5887	162793	36.16	1.72 (1.67, 1.78)***	<.001	1.21 (1.14, 1.27)***	<.001
Anticoagulants							
No	18051	746343	24.19	1.00 (reference)	-	1.00 (reference)	-
Yes	216	6307	34.25	1.41 (1.23, 1.61)***	<.001	0.90 (0.79, 1.03)	.142

β-blockers								
No	16342	679737	24.04	1.00 (reference)	-	1.00 (reference)	-	
Yes	1925	72913	26.40	1.10 (1.04, 1.15)***	<.001	1.02 (0.97, 1.07)	.457	
CCB								
No	8198	433603	18.91	1.00 (reference)	-	1.00 (reference)	-	
Yes	10069	319047	31.56	1.67 (1.62, 1.72)***	<.001	1.17 (1.13, 1.22)***	<.001	
Corticosteroids								
No	17867	735406	24.30	1.00 (reference)	-	1.00 (reference)	-	
Yes	400	17244	23.20	0.95 (0.86, 1.05)	.332	0.90 (0.81, 0.99)*	.037	
Diuretics								
No	13613	622037	21.88	1.00 (reference)	-	1.00 (reference)	-	
Yes	4654	130613	35.63	1.62 (1.57, 1.68)***	<.001	1.13 (1.09, 1.17)***	<.001	
NSAIDs								
No	3576	156098	22.91	1.00 (reference)	-	1.00 (reference)	-	
Yes	14691	596552	24.63	1.07 (1.03, 1.11)***	<.001	1.02 (0.98, 1.05)	.42	
Statins								
No	8165	364633	22.39	1.00 (reference)	-	1.00 (reference)	-	
Yes	10102	388017	26.03	1.16 (1.13, 1.20)***	<.001	0.98 (0.95, 1.02)	.285	
DCSI score								
0	3406	272118	12.52	1.00 (reference)	-	1.00 (reference)	-	
1	2127	144653	14.70	1.17 (1.11, 1.24)***	<.001	1.13 (1.07, 1.19)***	<.001	
2	4063	151472	26.82	2.14 (2.05, 2.24)***	<.001	1.96 (1.87, 2.06)***	<.001	
≥ 3	8671	184407	47.02	3.75 (3.60, 3.90)***	<.001	3.21 (3.07, 3.36)***	<.001	
DM duration	-	-	-	0.97 (0.97, 0.98)***	<.001	0.94 (0.94, 0.95)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

eTable 8. Incidence and hazard ratios of heart failure.

Variables	Heart failure			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	4128	340965	12.11	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	1280	157430	8.13	0.68 (0.64, 0.72)***	<.001	0.77 (0.72, 0.82)***	<.001
TZD	2121	136816	15.50	1.27 (1.20, 1.34)***	<.001	1.11 (1.05, 1.17)***	<.001
GLP-1RA/TZD	1495	148858	10.04	0.82 (0.78, 0.87)***	<.001	0.85 (0.80, 0.90)***	<.001
Gender							
Female	4354	365789	11.90	1.00 (reference)	-	1.00 (reference)	-
Male	4670	418280	11.16	0.94 (0.90, 0.98)**	.003	1.00 (0.96, 1.05)	.953
Age, years							
20–35	155	34556	4.49	1.00 (reference)	-	1.00 (reference)	-
36–50	1172	168370	6.96	1.55 (1.31, 1.84)***	<.001	1.10 (0.93, 1.30)	.285
51–65	3739	370631	10.09	2.25 (1.92, 2.65)***	<.001	1.16 (0.98, 1.36)	.081
>65	3958	210513	18.80	4.23 (3.60, 4.96)***	<.001	1.52 (1.29, 1.79)***	<.001
Comorbidities							
Hypertension							
No	1886	275731	6.84	1.00 (reference)	-	1.00 (reference)	-
Yes	7138	508338	14.04	2.06 (1.95, 2.16)***	<.001	1.07 (1.00, 1.15)*	.038
Dyslipidemia							
No	3372	248049	13.59	1.00 (reference)	-	1.00 (reference)	-
Yes	5652	536020	10.54	0.78 (0.75, 0.81)***	<.001	0.77 (0.74, 0.81)***	<.001
Chronic liver diseases							
No	7819	656681	11.91	1.00 (reference)	-	1.00 (reference)	-
Yes	1205	127388	9.46	0.80 (0.75, 0.85)***	<.001	0.83 (0.78, 0.88)***	<.001
Chronic kidney diseases							
No	6200	658793	9.41	1.00 (reference)	-	1.00 (reference)	-
Yes	2824	125276	22.54	2.41 (2.31, 2.52)***	<.001	0.74 (0.70, 0.77)***	<.001
COPD							
No	8393	739582	11.35	1.00 (reference)	-	1.00 (reference)	-
Yes	631	44487	14.18	1.26 (1.16, 1.37)***	<.001	1.04 (0.96, 1.13)	.356
Medication							
Metformin							
No	1242	114764	10.82	1.00 (reference)	-	1.00 (reference)	-
Yes	7782	669305	11.63	1.08 (1.01, 1.14)*	.017	0.75 (0.70, 0.81)***	<.001
Sulfonylureas							
No	1636	201588	8.12	1.00 (reference)	-	1.00 (reference)	-
Yes	7388	582481	12.68	1.55 (1.47, 1.64)***	<.001	1.09 (1.03, 1.16)**	.006
Meglitinide							
No	7499	700999	10.70	1.00 (reference)	-	1.00 (reference)	-
Yes	1525	83070	18.36	1.72 (1.63, 1.81)***	<.001	1.09 (1.03, 1.16)**	.002
Insulin							
No	4291	495848	8.65	1.00 (reference)	-	1.00 (reference)	-
Yes	4733	288221	16.42	1.90 (1.82, 1.98)***	<.001	1.19 (1.14, 1.24)***	<.001
SGLT2i							
No	8924	768260	11.62	1.00 (reference)	-	1.00 (reference)	-
Yes	100	15809	6.33	0.56 (0.46, 0.68)***	<.001	0.63 (0.52, 0.77)***	<.001
AGi							
No	6642	626816	10.60	1.00 (reference)	-	1.00 (reference)	-
Yes	2382	157253	15.15	1.43 (1.36, 1.50)***	<.001	1.00 (0.95, 1.05)	.995
ACEi/ARB							
No	3137	384357	8.16	1.00 (reference)	-	1.00 (reference)	-
Yes	5887	399712	14.73	1.81 (1.73, 1.89)***	<.001	0.93 (0.88, 0.99)*	.018
Aspirin							
No	6908	652344	10.59	1.00 (reference)	-	1.00 (reference)	-
Yes	2116	131725	16.06	1.52 (1.45, 1.59)***	<.001	0.96 (0.89, 1.04)	.329
Antiplatelets							
No	6082	611102	9.95	1.00 (reference)	-	1.00 (reference)	-
Yes	2942	172967	17.01	1.71 (1.64, 1.79)***	<.001	0.94 (0.87, 1.01)	.075
Anticoagulants							
No	8832	777624	11.36	1.00 (reference)	-	1.00 (reference)	-
Yes	192	6445	29.79	2.64 (2.29, 3.05)***	<.001	1.27 (1.10, 1.46)**	.001

β-blockers								
No	8144	707591	11.51	1.00 (reference)	-	1.00 (reference)	-	
Yes	880	76478	11.51	1.00 (0.94, 1.08)	.91	0.86 (0.80, 0.92)***	<.001	
CCB								
No	3591	449285	7.99	1.00 (reference)	-	1.00 (reference)	-	
Yes	5433	334784	16.23	2.03 (1.95, 2.12)***	<.001	1.24 (1.18, 1.31)***	<.001	
Corticosteroids								
No	8852	766182	11.55	1.00 (reference)	-	1.00 (reference)	-	
Yes	172	17887	9.62	0.84 (0.72, 0.97)*	.022	0.82 (0.71, 0.96)*	.011	
Diuretics								
No	5842	647788	9.02	1.00 (reference)	-	1.00 (reference)	-	
Yes	3182	136281	23.35	2.59 (2.48, 2.71)***	<.001	1.54 (1.47, 1.62)***	<.001	
NSAIDs								
No	2180	161436	13.50	1.00 (reference)	-	1.00 (reference)	-	
Yes	6844	622633	10.99	0.82 (0.79, 0.87)***	<.001	0.75 (0.72, 0.79)***	<.001	
Statins								
No	4366	378425	11.54	1.00 (reference)	-	1.00 (reference)	-	
Yes	4658	405644	11.48	1.00 (0.96, 1.05)	.897	0.87 (0.83, 0.91)***	<.001	
DCSI score								
2	2004	158325	12.66	1.00 (reference)	-	1.00 (reference)	-	
≥ 3	7020	192098	36.54	2.90 (2.76, 3.05)***	<.001	2.89 (2.74, 3.04)***	<.001	
DM duration	-	-	-	0.97 (0.96, 0.98)***	<.001	0.92 (0.91, 0.93)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 9. Incidence and hazard ratios of peripheral artery diseases.

Variables	Peripheral artery diseases			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	1705	345689	4.93	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	830	158505	5.24	1.11 (1.02, 1.21)*	.013	1.16 (1.07, 1.26)***	<.001
TZD	943	140392	6.72	1.26 (1.16, 1.37)***	<.001	1.17 (1.08, 1.26)***	<.001
GLP-1RA/TZD	911	150594	6.05	1.14 (1.05, 1.24)**	.002	1.17 (1.08, 1.27)***	<.001
Gender							
Female	2121	371372	5.71	1.00 (reference)	-	1.00 (reference)	-
Male	2268	423807	5.35	0.95 (0.89, 1.01)	.075	1.07 (1.00, 1.13)*	.043
Age, years							
20–35	71	34798	2.04	1.00 (reference)	-	1.00 (reference)	-
36–50	576	169959	3.39	1.67 (1.31, 2.14)***	<.001	1.41 (1.10, 1.81)**	.006
51–65	1995	375074	5.32	2.64 (2.08, 3.34)***	<.001	1.85 (1.46, 2.35)***	<.001
>65	1747	215349	8.11	4.11 (3.24, 5.21)***	<.001	2.27 (1.78, 2.89)***	<.001
Comorbidities							
Hypertension							
No	1145	277250	4.13	1.00 (reference)	-	1.00 (reference)	-
Yes	3244	517929	6.26	1.52 (1.42, 1.63)***	<.001	1.02 (0.93, 1.12)	.61
Dyslipidemia							
No	1289	252480	5.11	1.00 (reference)	-	1.00 (reference)	-
Yes	3100	542699	5.71	1.15 (1.08, 1.23)***	<.001	1.12 (1.04, 1.20)**	.003
Chronic liver diseases							
No	3774	666561	5.66	1.00 (reference)	-	1.00 (reference)	-
Yes	615	128619	4.78	0.89 (0.82, 0.97)**	.008	0.87 (0.79, 0.94)**	.001
Chronic kidney diseases							
No	3255	665928	4.89	1.00 (reference)	-	1.00 (reference)	-
Yes	1134	129251	8.77	1.85 (1.73, 1.98)***	<.001	0.90 (0.84, 0.97)**	.007
COPD							
No	4075	749975	5.43	1.00 (reference)	-	1.00 (reference)	-
Yes	314	45204	6.95	1.35 (1.21, 1.52)***	<.001	1.10 (0.98, 1.23)	.121
Medication							
Metformin							
No	600	116398	5.15	1.00 (reference)	-	1.00 (reference)	-
Yes	3789	678782	5.58	1.09 (1.00, 1.19)	.055	0.81 (0.73, 0.89)***	<.001
Sulfonylureas							
No	887	203404	4.36	1.00 (reference)	-	1.00 (reference)	-
Yes	3502	591776	5.92	1.32 (1.22, 1.42)***	<.001	1.04 (0.95, 1.13)	.409
Meglitinide							
No	3691	710260	5.2	1.00 (reference)	-	1.00 (reference)	-
Yes	698	84919	8.22	1.59 (1.47, 1.72)***	<.001	1.18 (1.08, 1.28)***	<.001
Insulin							
No	2434	500779	4.86	1.00 (reference)	-	1.00 (reference)	-
Yes	1955	294401	6.64	1.38 (1.30, 1.46)***	<.001	1.08 (1.01, 1.14)*	.021
SGLT2i							
No	4326	779315	5.55	1.00 (reference)	-	1.00 (reference)	-
Yes	63	15864	3.97	0.88 (0.68, 1.12)	.298	0.90 (0.70, 1.15)	.393
AGi							
No	3274	634879	5.16	1.00 (reference)	-	1.00 (reference)	-
Yes	1115	160301	6.96	1.35 (1.26, 1.44)***	<.001	1.05 (0.97, 1.12)	.211
ACEi/ARB							
No	1810	387257	4.67	1.00 (reference)	-	1.00 (reference)	-
Yes	2579	407923	6.32	1.37 (1.29, 1.45)***	<.001	0.84 (0.77, 0.90)***	<.001
Aspirin							
No	3288	660929	4.97	1.00 (reference)	-	1.00 (reference)	-
Yes	1101	134250	8.2	1.65 (1.54, 1.77)***	<.001	0.69 (0.62, 0.76)***	<.001
Antiplatelets							
No	2717	618973	4.39	1.00 (reference)	-	1.00 (reference)	-
Yes	1672	176206	9.49	2.17 (2.04, 2.30)***	<.001	1.93 (1.76, 2.12)***	<.001
Anticoagulants							
No	4306	788467	5.46	1.00 (reference)	-	1.00 (reference)	-
Yes	83	6713	12.36	2.35 (1.89, 2.92)***	<.001	1.37 (1.10, 1.70)**	.005

β-blockers							
No	3863	717871	5.38	1.00 (reference)	-	1.00 (reference)	-
Yes	526	77309	6.8	1.29 (1.18, 1.42)***	<.001	1.12 (1.02, 1.22)*	.02
CCB							
No	2035	452866	4.49	1.00 (reference)	-	1.00 (reference)	-
Yes	2354	342313	6.88	1.54 (1.45, 1.63)***	<.001	1.09 (1.01, 1.18)*	.02
Corticosteroids							
No	4273	777104	5.5	1.00 (reference)	-	1.00 (reference)	-
Yes	116	18075	6.42	1.21 (1.01, 1.45)*	.043	1.08 (0.89, 1.29)	.438
Diuretics							
No	3186	654163	4.87	1.00 (reference)	-	1.00 (reference)	-
Yes	1203	141017	8.53	1.77 (1.66, 1.90)***	<.001	1.21 (1.13, 1.30)***	<.001
NSAIDs							
No	743	164747	4.51	1.00 (reference)	-	1.00 (reference)	-
Yes	3646	630433	5.78	1.37 (1.27, 1.48)***	<.001	1.19 (1.10, 1.30)***	<.001
Statins							
No	2021	383829	5.27	1.00 (reference)	-	1.00 (reference)	-
Yes	2368	411351	5.76	1.13 (1.06, 1.19)***	<.001	0.86 (0.80, 0.92)***	<.001
DCSI score							
0	580	281491	2.06	1.00 (reference)	-	1.00 (reference)	-
1	633	149801	4.23	2.10 (1.88, 2.35)***	<.001	1.95 (1.74, 2.19)***	<.001
2	834	161024	5.18	2.53 (2.28, 2.82)***	<.001	2.25 (2.02, 2.51)***	<.001
≥ 3	2342	202865	11.54	5.68 (5.19, 6.22)***	<.001	4.56 (4.12, 5.03)***	<.001
DM duration	-	-	-	1.03 (1.02, 1.05)***	<.001	0.99 (0.98, 1.01)	.26

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium-glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 10. Incidence and hazard ratios of hypoglycemia.

Variables	Hypoglycemia			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP-1RA/TZD	685	346961	1.97	1.00 (reference)	-	1.00 (reference)	-
GLP-1RA	275	159200	1.73	0.87 (0.75, 1.00)*	.047	0.97 (0.84, 1.11)	.648
TZD	497	140708	3.53	1.84 (1.64, 2.07)***	<.001	1.69 (1.51, 1.90)***	<.001
GLP-1RA/TZD	437	151438	2.89	1.51 (1.34, 1.70)***	<.001	1.61 (1.43, 1.82)***	<.001
Gender							
Female	947	372763	2.54	1.00 (reference)	-	1.00 (reference)	-
Male	947	425543	2.23	0.87 (0.80, 0.95)**	.003	0.90 (0.82, 0.99)*	.028
Age, years							
20–35	42	34821	1.21	1.00 (reference)	-	1.00 (reference)	-
36–50	264	170242	1.55	1.28 (0.93, 1.78)	.134	1.17 (0.84, 1.62)	.356
51–65	762	377029	2.02	1.67 (1.22, 2.28)**	.001	1.37 (1.00, 1.87)	.051
>65	826	216215	3.82	3.14 (2.30, 4.28)***	<.001	2.15 (1.56, 2.95)***	<.001
Comorbidities							
Hypertension							
No	501	278231	1.80	1.00 (reference)	-	1.00 (reference)	-
Yes	1393	520076	2.68	1.49 (1.34, 1.65)***	<.001	0.98 (0.85, 1.13)	.82
Dyslipidemia							
No	751	253058	2.97	1.00 (reference)	-	1.00 (reference)	-
Yes	1143	545249	2.10	0.70 (0.64, 0.77)***	<.001	0.75 (0.67, 0.83)***	<.001
Chronic liver diseases							
No	1549	669534	2.31	1.00 (reference)	-	1.00 (reference)	-
Yes	345	128773	2.68	1.14 (1.02, 1.29)*	.024	1.12 (1.00, 1.27)	.057
Chronic kidney diseases							
No	1344	668739	2.01	1.00 (reference)	-	1.00 (reference)	-
Yes	550	129568	4.24	2.10 (1.90, 2.32)***	<.001	1.08 (0.97, 1.21)	.176
COPD							
No	1764	752944	2.34	1.00 (reference)	-	1.00 (reference)	-
Yes	130	45363	2.87	1.21 (1.01, 1.44)*	.038	1.02 (0.85, 1.23)	.801
Medication							
Metformin							
No	235	116819	2.01	1.00 (reference)	-	1.00 (reference)	-
Yes	1659	681488	2.43	1.21 (1.05, 1.39)**	.007	0.88 (0.76, 1.03)	.12
Sulfonylureas							
No	300	204112	1.47	1.00 (reference)	-	1.00 (reference)	-
Yes	1594	594195	2.68	1.84 (1.62, 2.08)***	<.001	1.51 (1.31, 1.74)***	<.001
Meglitinide							
No	1581	712951	2.22	1.00 (reference)	-	1.00 (reference)	-
Yes	313	85356	3.67	1.65 (1.46, 1.86)***	<.001	1.12 (0.99, 1.27)	.071
Insulin							
No	754	503392	1.50	1.00 (reference)	-	1.00 (reference)	-
Yes	1140	294915	3.87	2.57 (2.35, 2.82)***	<.001	2.01 (1.83, 2.22)***	<.001
SGLT2i							
No	1881	782408	2.40	1.00 (reference)	-	1.00 (reference)	-
Yes	13	15899	0.82	0.32 (0.19, 0.56)***	<.001	0.37 (0.21, 0.63)***	<.001
AGi							
No	1354	637438	2.12	1.00 (reference)	-	1.00 (reference)	-
Yes	540	160869	3.36	1.58 (1.43, 1.75)***	<.001	1.19 (1.07, 1.32)**	.001
ACEi/ARB							
No	762	388866	1.96	1.00 (reference)	-	1.00 (reference)	-
Yes	1132	409441	2.76	1.41 (1.29, 1.54)***	<.001	0.95 (0.84, 1.07)	.411
Aspirin							
No	1528	663132	2.30	1.00 (reference)	-	1.00 (reference)	-
Yes	366	135175	2.71	1.17 (1.05, 1.32)**	.006	0.74 (0.62, 0.88)***	<.001
Antiplatelets							
No	1343	620623	2.16	1.00 (reference)	-	1.00 (reference)	-
Yes	551	177684	3.10	1.43 (1.30, 1.58)***	<.001	1.19 (1.02, 1.39)*	.029
Anticoagulants							
No	1878	791517	2.37	1.00 (reference)	-	1.00 (reference)	-
Yes	16	6790	2.36	0.98 (0.60, 1.61)	.947	0.61 (0.37, 1.00)*	.05

β -blockers								
No	1670	720610	2.32	1.00 (reference)	-	1.00 (reference)	-	
Yes	224	77697	2.88	1.24 (1.08, 1.42)**	.003	1.08 (0.94, 1.24)	.291	
CCB								
No	856	454538	1.88	1.00 (reference)	-	1.00 (reference)	-	
Yes	1038	343769	3.02	1.60 (1.46, 1.75)***	<.001	1.16 (1.03, 1.30)*	.013	
Corticosteroids								
No	1854	780135	2.38	1.00 (reference)	-	1.00 (reference)	-	
Yes	40	18172	2.20	0.92 (0.67, 1.26)	.598	0.87 (0.64, 1.19)	.384	
Diuretics								
No	1298	656791	1.98	1.00 (reference)	-	1.00 (reference)	-	
Yes	596	141516	4.21	2.12 (1.92, 2.34)***	<.001	1.39 (1.25, 1.55)***	<.001	
NSAIDs								
No	435	165003	2.64	1.00 (reference)	-	1.00 (reference)	-	
Yes	1459	633304	2.30	0.86 (0.78, 0.96)**	.007	0.82 (0.74, 0.92)***	<.001	
Statins								
No	989	385132	2.57	1.00 (reference)	-	1.00 (reference)	-	
Yes	905	413175	2.19	0.85 (0.78, 0.93)***	<.001	0.81 (0.73, 0.90)***	<.001	
DCSI score								
0	331	281788	1.17	1.00 (reference)	-	1.00 (reference)	-	
1	206	150490	1.37	1.16 (0.98, 1.38)	.093	1.10 (0.92, 1.31)	.29	
2	409	161469	2.53	2.15 (1.86, 2.49)***	<.001	1.77 (1.52, 2.05)***	<.001	
≥ 3	948	204559	4.63	3.94 (3.47, 4.46)***	<.001	2.65 (2.30, 3.050)***	<.001	
DM duration	-	-	-	0.97 (0.95, 0.99)**	.007	0.93 (0.91, 0.95)***	<.001	

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium-glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

* $p < .05$, ** $p < .01$, *** $p < .001$.

eTable 11. Incidence and hazard ratios of non-cardiovascular mortality.

Variables	Non-cardiovascular mortality			cHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
	Event	PY	IR				
Exposure							
Non-GLP1RA&TZD	26523	348499	76.11	1 (reference)	-	1 (reference)	-
GLP1RA	4341	159784	27.17	0.36 (0.35, 0.37)***	<.001	0.38 (0.37, 0.39)***	<.001
TZD	5531	142344	38.86	0.55 (0.53, 0.57)***	<.001	0.49 (0.47, 0.50)***	<.001
GLP1RA&TZD	1982	152783	12.97	0.19 (0.18, 0.20)***	<.001	0.2 (0.19, 0.21)***	<.001
Gender							
Female	13843	375504	36.87	1 (reference)	-	1 (reference)	-
Male	24534	427906	57.34	1.53 (1.49, 1.56)***	<.001	1.49 (1.46, 1.52)***	<.001
Age, years							
20–35	452	34940.6	12.94	1 (reference)	-	1 (reference)	-
36–50	5233	171049	30.59	2.33 (2.12, 2.56)***	<.001	2.16 (1.96, 2.37)***	<.001
51–65	16470	379018	43.45	3.29 (3.00, 3.62)***	<.001	3.2 (2.91, 3.52)***	<.001
>65	16222	218402	74.28	5.48 (4.99, 6.02)***	<.001	5.3 (4.83, 5.83)***	<.001
Comorbidities							
Hypertension							
No	12097	279564	43.27	1 (reference)	-	1 (reference)	-
Yes	26280	523845	50.17	1.16 (1.13, 1.18)***	<.001	0.89 (0.87, 0.92)***	<.001
Dyslipidemia							
No	17473	255075	68.50	1 (reference)	-	1 (reference)	-
Yes	20904	548335	38.12	0.55 (0.54, 0.56)***	<.001	0.67 (0.66, 0.69)***	<.001
Chronic liver diseases							
No	28434	673834	42.20	1 (reference)	-	1 (reference)	-
Yes	9943	129576	76.73	1.71 (1.67, 1.75)***	<.001	1.64 (1.60, 1.68)***	<.001
Chronic kidney diseases							
No	29200	672321	43.43	1 (reference)	-	1 (reference)	-
Yes	9177	131089	70.01	1.57 (1.53, 1.61)***	<.001	1.11 (1.08, 1.15)***	<.001
COPD							
No	34745	757711	45.86	1 (reference)	-	1 (reference)	-
Yes	3632	45699	79.48	1.63 (1.57, 1.69)***	<.001	1.37 (1.32, 1.41)***	<.001
Medication							
Metformin							
No	5230	117503	44.51	1 (reference)	-	1 (reference)	-
Yes	33147	685907	48.33	1.09 (1.06, 1.12)***	<.001	0.98 (0.95, 1.02)	.272
Sulfonylureas							
No	7156	204966	34.91	1 (reference)	-	1 (reference)	-
Yes	31221	598443	52.17	1.54 (1.50, 1.58)***	<.001	1.5 (1.46, 1.55)***	<.001
Meglitinide							
No	32303	717254	45.04	1 (reference)	-	1 (reference)	-
Yes	6074	86155.2	70.50	1.56 (1.52, 1.60)***	<.001	1.22 (1.18, 1.25)***	<.001
Insulin							
No	17383	505488	34.39	1 (reference)	-	1 (reference)	-
Yes	20994	297922	70.47	2.02 (1.98, 2.06)***	<.001	1.7 (1.66, 1.73)***	<.001
SGLT2i							
No	38027	787494	48.29	1 (reference)	-	1 (reference)	-
Yes	350	15915.6	21.99	0.35 (0.31, 0.39)***	<.001	0.45 (0.41, 0.50)***	<.001
AGi							
No	29027	641092	45.28	1 (reference)	-	1 (reference)	-
Yes	9350	162318	57.60	1.28 (1.25, 1.31)***	<.001	1.07 (1.04, 1.10)***	<.001
ACEi/ARB							
No	17716	390895	45.32	1 (reference)	-	1 (reference)	-
Yes	20661	412515	50.09	1.1 (1.08, 1.12)***	<.001	0.89 (0.87, 0.91)***	<.001
Aspirin							
No	31158	667227	46.70	1 (reference)	-	1 (reference)	-
Yes	7219	136183	53.01	1.14 (1.11, 1.17)***	<.001	0.87 (0.83, 0.91)***	<.001
Antiplatelets							
No	28119	624221	45.05	1 (reference)	-	1 (reference)	-
Yes	10258	179188	57.25	1.27 (1.24, 1.30)***	<.001	1.14 (1.10, 1.18)***	<.001
Anticoagulants							
No	37824	796573	47.48	1 (reference)	-	1 (reference)	-

Yes	553	6836.36	80.89	1.63 (1.50, 1.77)***	<.001	1.2 (1.10, 1.31)***	<.001
β-blockers							
No	33610	725160	46.35	1 (reference)	-	1 (reference)	-
Yes	4767	78249.6	60.92	1.29 (1.25, 1.32)***	<.001	1.15 (1.12, 1.19)***	<.001
CCB							
No	18915	456868	41.40	1 (reference)	-	1 (reference)	-
Yes	19462	346541	56.16	1.35 (1.32, 1.38)***	<.001	1.14 (1.11, 1.17)***	<.001
Corticosteroids							
No	37196	785142	47.37	1 (reference)	-	1 (reference)	-
Yes	1181	18267.4	64.65	1.32 (1.24, 1.39)***	<.001	1.24 (1.17, 1.32)***	<.001
Diuretics							
No	25384	660336	38.44	1 (reference)	-	1 (reference)	-
Yes	12993	143073	90.81	2.31 (2.26, 2.36)***	<.001	1.8 (1.76, 1.84)***	<.001
NSAIDs							
No	9894	166178	59.54	1 (reference)	-	1 (reference)	-
Yes	28483	637232	44.70	0.72 (0.70, 0.73)***	<.001	0.8 (0.78, 0.82)***	<.001
Statin							
No	22142	387789	57.10	1 (reference)	-	1 (reference)	-
Yes	16235	415620	39.06	0.67 (0.66, 0.69)***	<.001	0.81 (0.79, 0.83)***	<.001
DCSI							
0	11154	282660	39.46	1 (reference)	-	1 (reference)	-
1	6004	150987	39.77	0.99 (0.96, 1.02)	.57	0.98 (0.95, 1.01)	.131
2	8264	162666	50.80	1.28 (1.24, 1.31)***	<.001	1.02 (0.99, 1.05)	.164
≥ 3	12955	207098	62.56	1.57 (1.53, 1.61)***	<.001	1.05 (1.01, 1.08)**	.003
DM duration	-	-	-	0.81 (0.80, 0.81)***	<.001	0.76 (0.76, 0.77)***	<.001

ACEi, angiotensin-converting enzyme inhibitor; AGi, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aHR, adjusted hazard ratio; CCB, calcium channel blocker; cHR, crude hazard ratio; COPD, chronic obstructive pulmonary disease; DCSI, diabetes complications severity index; DM, diabetes mellitus; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; NSAIDs, non-steroidal anti-inflammatory drugs; PY, person-year; SGLT2i, sodium–glucose cotransporter 2 inhibitor; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis, including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

** $p < .01$, *** $p < .001$.

eTable 12. Incidences and hazard ratios of outcomes and cumulative days of GLP-1RA and TZD usage.

Outcomes	Variables	Event	PY	IR	cHR	(95% CI)	p-value	aHR ^a	(95% CI)	p-value
All-cause mortality	Non-use	29214	348499	83.83	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	3359	53787.9	62.45	0.72	(0.70, 0.75)***	<.001	0.71	(0.69, 0.74)***	<.001
	GLP1RA, 360–900	871	39189.2	22.23	0.25	(0.23, 0.27)***	<.001	0.28	(0.26, 0.30)***	<.001
	GLP1RA, >900	527	66807.3	7.89	0.1	(0.09, 0.11)***	<.001	0.11	(0.10, 0.12)***	<.001
	TZD, <360	4136	54001.1	76.59	0.96	(0.93, 0.99)*	.018	0.75	(0.73, 0.78)***	<.001
	TZD, 360–900	1231	30705.8	40.09	0.48	(0.46, 0.51)***	<.001	0.46	(0.44, 0.49)***	<.001
	TZD, >900	796	57636.9	13.81	0.18	(0.17, 0.20)***	<.001	0.18	(0.17, 0.19)***	<.001
	GLP1RA/TZD, <360	979	27109.4	36.11	0.45	(0.43, 0.48)***	<.001	0.45	(0.42, 0.48)***	<.001
	GLP1RA/TZD, 360–900	688	41796.6	16.46	0.21	(0.19, 0.22)***	<.001	0.22	(0.20, 0.24)***	<.001
	GLP1RA/TZD, >900	538	83876.7	6.41	0.09	(0.08, 0.09)***	<.001	0.09	(0.08, 0.10)***	<.001
MACE	Non-use	8994	331913	27.10	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	1429	51277.9	27.87	1.02	(0.97, 1.08)	.412	1.14	(1.07, 1.20)***	<.001
	GLP1RA, 360–900	749	37842	19.79	0.72	(0.67, 0.78)***	<.001	0.77	(0.71, 0.83)***	<.001
	GLP1RA, >900	942	64389.9	14.63	0.55	(0.52, 0.59)***	<.001	0.61	(0.57, 0.65)***	<.001
	TZD, <360	1814	49225.5	36.85	1.37	(1.30, 1.44)***	<.001	1.09	(1.04, 1.15)**	.001
	TZD, 360–900	734	28724.9	25.55	0.94	(0.87, 1.02)	.122	0.82	(0.76, 0.88)***	<.001
	TZD, >900	862	54848	15.72	0.59	(0.55, 0.64)***	<.001	0.58	(0.54, 0.63)***	<.001
	GLP1RA/TZD, <360	878	24872.6	35.30	1.32	(1.23, 1.41)***	<.001	1.23	(1.14, 1.32)***	<.001
	GLP1RA/TZD, 360–900	987	39038.1	25.28	0.95	(0.89, 1.01)	.094	0.94	(0.88, 1.01)	.077
	GLP1RA/TZD, >900	1335	79358.5	16.82	0.64	(0.60, 0.68)***	<.001	0.67	(0.63, 0.71)***	<.001
Cardiovascular mortality	Non-use	2691	348499	7.72	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	289	53787.9	5.37	0.7	(0.62, 0.79)***	<.001	0.76	(0.67, 0.86)***	<.001
	GLP1RA, 360–900	74	39189.2	1.89	0.24	(0.19, 0.31)***	<.001	0.28	(0.22, 0.35)***	<.001
	GLP1RA, >900	53	66807.3	0.79	0.11	(0.08, 0.14)***	<.001	0.12	(0.09, 0.16)***	<.001
	TZD, <360	407	54001.1	7.54	0.98	(0.88, 1.09)	.726	0.73	(0.65, 0.81)***	<.001
	TZD, 360–900	133	30705.8	4.33	0.56	(0.47, 0.67)***	<.001	0.49	(0.41, 0.59)***	<.001
	TZD, >900	92	57636.9	1.60	0.21	(0.17, 0.26)***	<.001	0.21	(0.17, 0.25)***	<.001
	GLP1RA/TZD, <360	94	27109.4	3.47	0.46	(0.37, 0.56)***	<.001	0.44	(0.36, 0.55)***	<.001
	GLP1RA/TZD, 360–900	66	41796.6	1.58	0.21	(0.16, 0.27)***	<.001	0.22	(0.17, 0.28)***	<.001
	GLP1RA/TZD, >900	63	83876.7	0.75	0.1	(0.08, 0.13)***	<.001	0.11	(0.08, 0.14)***	<.001
Myocardial infarction	Non-use	1851	346084	5.35	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	256	53413.4	4.79	0.93	(0.82, 1.06)	.296	1.06	(0.93, 1.21)	.356
	GLP1RA, 360–900	116	39015.2	2.97	0.58	(0.48, 0.71)***	<.001	0.65	(0.54, 0.79)***	<.001
	GLP1RA, >900	123	66537	1.85	0.35	(0.29, 0.42)***	<.001	0.42	(0.35, 0.51)***	<.001
	TZD, <360	423	53212.2	7.95	1.42	(1.28, 1.58)***	<.001	1.1	(0.98, 1.22)	.092
	TZD, 360–900	167	30348.8	5.50	1.01	(0.87, 1.19)	.866	0.84	(0.72, 0.99)*	.037
	TZD, >900	129	57358.7	2.25	0.4	(0.34, 0.48)***	<.001	0.4	(0.34, 0.48)***	<.001
	GLP1RA/TZD, <360	172	26735.9	6.43	1.19	(1.01, 1.39)*	.032	1.08	(0.92, 1.27)	.33
	GLP1RA/TZD, 360–900	201	41356.6	4.86	0.9	(0.78, 1.04)	.144	0.87	(0.75, 1.01)	.07
	GLP1RA/TZD, >900	218	83310.6	2.62	0.47	(0.41, 0.54)***	<.001	0.51	(0.44, 0.58)***	<.001
Cerebrovascular diseases	Non-use	6894	333896	20.65	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	1144	51609.6	22.17	1.07	(1.00, 1.13)*	.048	1.17	(1.10, 1.25)***	<.001
	GLP1RA, 360–900	643	37996.6	16.92	0.81	(0.74, 0.88)***	<.001	0.85	(0.78, 0.92)***	<.001
	GLP1RA, >900	828	64634.1	12.81	0.63	(0.59, 0.68)***	<.001	0.69	(0.64, 0.74)***	<.001
	TZD, <360	1421	49883.5	28.49	1.39	(1.32, 1.48)***	<.001	1.11	(1.04, 1.17)***	<.001
	TZD, 360–900	582	29009.7	20.06	0.97	(0.89, 1.06)	.512	0.85	(0.78, 0.92)***	<.001
	TZD, >900	736	55091.3	13.36	0.66	(0.62, 0.72)***	<.001	0.66	(0.62, 0.72)***	<.001
	GLP1RA/TZD, <360	735	25176.1	29.19	1.43	(1.32, 1.54)***	<.001	1.31	(1.21, 1.41)***	<.001
	GLP1RA/TZD, 360–900	810	39423.7	20.55	1.01	(0.94, 1.08)	.821	1	(0.93, 1.07)	.971
	GLP1RA/TZD, >900	1145	79871.5	14.34	0.72	(0.67, 0.76)***	<.001	0.75	(0.70, 0.80)***	<.001
Ischemic heart diseases	Non-use	7690	329931	23.31	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	1227	51157.1	23.98	1.02	(0.96, 1.09)	.472	1.1	(1.03, 1.17)**	.002
	GLP1RA, 360–900	770	37649.2	20.45	0.87	(0.81, 0.93)***	<.001	0.9	(0.84, 0.97)**	.007
	GLP1RA, >900	1067	63883.4	16.70	0.73	(0.68, 0.77)***	<.001	0.75	(0.71, 0.81)***	<.001
	TZD, <360	1723	48544	35.49	1.53	(1.46, 1.62)***	<.001	1.37	(1.30, 1.45)***	<.001
	TZD, 360–900	799	28278.9	28.25	1.21	(1.13, 1.30)***	<.001	1.11	(1.04, 1.20)**	.004
	TZD, >900	1165	53413.7	21.81	0.95	(0.90, 1.01)	.135	0.92	(0.87, 0.98)*	.011
	GLP1RA/TZD, <360	869	24605.8	35.32	1.53	(1.42, 1.64)***	<.001	1.54	(1.43, 1.65)***	<.001
	GLP1RA/TZD, 360–900	1134	38258.2	29.64	1.28	(1.21, 1.37)***	<.001	1.29	(1.21, 1.38)***	<.001
	GLP1RA/TZD, >900	1823	76928.7	23.70	1.04	(0.99, 1.09)	.166	1.07	(1.01, 1.12)*	.014
Heart failure	Non-use	4128	340965	12.11	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	660	52658.6	12.53	1.05	(0.97, 1.14)	.227	1.2	(1.10, 1.30)***	<.001
	GLP1RA, 360–900	319	38625.1	8.26	0.7	(0.62, 0.78)***	<.001	0.76	(0.68, 0.86)***	<.001
	GLP1RA, >900	301	66146.5	4.55	0.38	(0.34, 0.42)***	<.001	0.43	(0.38, 0.48)***	<.001
	TZD, <360	1195	50934.5	23.46	1.91	(1.79, 2.03)***	<.001	1.46	(1.37, 1.56)***	<.001
	TZD, 360–900	473	29553.6	16.00	1.32	(1.20, 1.45)***	<.001	1.13	(1.02, 1.24)*	.014

	TZD, >900	453	56328	8.04	0.65	(0.59, 0.72)***	<.001	0.67	(0.61, 0.74)***	<.001
	GLP1RA/TZD, <360	450	26051.2	17.27	1.42	(1.29, 1.56)***	<.001	1.3	(1.18, 1.43)***	<.001
	GLP1RA/TZD, 360–900	457	40666.6	11.24	0.92	(0.84, 1.02)	.106	0.91	(0.83, 1.01)	.067
	GLP1RA/TZD, >900	588	82140	7.16	0.58	(0.53, 0.63)***	<.001	0.64	(0.58, 0.70)***	<.001
Peripheral artery diseases	Non-use	1705	345689	4.93	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	303	53330.8	5.68	1.23	(1.09, 1.40)***	<.001	1.33	(1.17, 1.50)***	<.001
	GLP1RA, 360–900	213	38891.5	5.48	1.22	(1.06, 1.41)**	.007	1.23	(1.06, 1.42)**	.005
	GLP1RA, >900	314	66283.1	4.74	0.96	(0.86, 1.09)	.561	1	(0.88, 1.13)	.987
	TZD, <360	413	53144.5	7.77	1.45	(1.30, 1.62)***	<.001	1.29	(1.16, 1.44)***	<.001
	TZD, 360–900	218	30311.3	7.19	1.42	(1.23, 1.63)***	<.001	1.26	(1.09, 1.45)**	.001
	TZD, >900	312	56935.9	5.48	1	(0.89, 1.13)	.971	0.99	(0.87, 1.11)	.817
	GLP1RA/TZD, <360	200	26675	7.50	1.46	(1.26, 1.69)***	<.001	1.45	(1.26, 1.69)***	<.001
	GLP1RA/TZD, 360–900	261	41217.5	6.33	1.23	(1.08, 1.41)**	.002	1.23	(1.08, 1.40)**	.002
	GLP1RA/TZD, >900	450	82701.4	5.44	0.99	(0.89, 1.10)	.899	1.05	(0.94, 1.16)	.404
Hypoglycemia	Non-use	685	346961	1.97	1	(reference)	-	1	(reference)	-
	GLP1RA, <360	142	53504.8	2.65	1.32	(1.10, 1.59)**	.002	1.47	(1.22, 1.76)***	<.001
	GLP1RA, 360–900	60	39070.4	1.54	0.76	(0.59, 0.99)*	.044	0.85	(0.65, 1.10)	.217
	GLP1RA, >900	73	66624.6	1.10	0.56	(0.44, 0.71)***	<.001	0.63	(0.49, 0.80)***	<.001
	TZD, <360	278	53150	5.23	2.71	(2.36, 3.12)***	<.001	2.27	(1.97, 2.62)***	<.001
	TZD, 360–900	111	30317.7	3.66	1.87	(1.53, 2.29)***	<.001	1.72	(1.41, 2.11)***	<.001
	TZD, >900	108	57240.5	1.89	0.99	(0.81, 1.21)	.92	1.02	(0.83, 1.25)	.883
	GLP1RA/TZD, <360	118	26784.8	4.41	2.26	(1.86, 2.75)***	<.001	2.26	(1.86, 2.75)***	<.001
	GLP1RA/TZD, 360–900	150	41353.4	3.63	1.87	(1.56, 2.23)***	<.001	1.93	(1.62, 2.30)***	<.001
	GLP1RA/TZD, >900	169	83299.6	2.03	1.06	(0.90, 1.26)	.482	1.17	(0.99, 1.39)	.066

aHR, adjusted hazard ratio; cHR, crude hazard ratio; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; PY, person-year; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

eTable 13. Hazard ratios of outcomes for comparisons amongst non-GLP-1RA/TZD, GLP-1RA, TZD, and GLP-1RA/TZD.

All-cause mortality		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	2.64	2.05	5.04
	(95% CI)	-	(2.56, 2.72)***	(1.99, 2.10)***	(4.82, 5.26)***
	p-value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.38	-	0.78	1.91
	(95% CI)	(0.37, 0.39)***	-	(0.75, 0.81)***	(1.82, 2.01)***
	p-value	<.001	-	<.001	<.001
TZD	aHR	0.49	1.29	-	2.46
	(95% CI)	(0.48, 0.50)***	(1.24, 1.34)***	-	(2.34, 2.59)***
	p-value	<.001	<.001	-	<.001
GLP-1RA/TZD	aHR	0.20	0.52	0.41	-
	(95% CI)	(0.19, 0.21)***	(0.50, 0.55)***	(0.39, 0.43)***	-
	p-value	<.001	<.001	<.001	-

*** p <.001.

MACE		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.21	1.19	1.17
	(95% CI)	-	(1.16, 1.26)***	(1.14, 1.23)***	(1.12, 1.22)***
	p-value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.82	-	0.98	0.96
	(95% CI)	(0.79, 0.86)***	-	(0.93, 1.03)	(0.92, 1.01)
	p-value	<.001	-	.364	.161
TZD	aHR	0.84	1.02	-	0.99
	(95% CI)	(0.81, 0.88)***	(0.97, 1.08)	-	(0.94, 1.04)
	p-value	<.001	.364	-	.605
GLP-1RA/TZD	aHR	0.85	1.04	1.01	-
	(95% CI)	(0.82, 0.89)***	(0.99, 1.09)	(0.96, 1.06)	-
	p-value	<.001	.161	.605	-

MACE, major adverse cardiovascular events.

*** p <.001.

Cardiovascular mortality		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	2.59	2.03	4.91
	(95% CI)	-	(2.33, 2.87)***	(1.86, 2.21)***	(4.28, 5.64)***
	p-value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.39	-	0.78	1.90
	(95% CI)	(0.35, 0.43)***	-	(0.69, 0.89)***	(1.61, 2.24)***
	p-value	<.001	-	<.001	<.001
TZD	aHR	0.49	1.28	-	2.43
	(95% CI)	(0.45, 0.54)***	(1.13, 1.45)***	-	(2.08, 2.83)***
	p-value	<.001	<.001	-	<.001
GLP-1RA/TZD	aHR	0.20	0.53	0.41	-
	(95% CI)	(0.18, 0.23)***	(0.45, 0.62)***	(0.35, 0.48)***	-
	p-value	<.001	<.001	<.001	-

* p <0.05, ** p <0.01, *** p <.001.

Myocardial infarction		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.43	1.26	1.38
	(95% CI)	-	(1.30, 1.58)***	(1.16, 1.38)***	(1.25, 1.51)***
	p-value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.70	-	0.88	0.96
	(95% CI)	(0.63, 0.77)***	-	(0.78, 0.99)*	(0.85, 1.09)
	p-value	<.001	-	.033	.526
TZD	aHR	0.79	1.14	-	1.09
	(95% CI)	(0.73, 0.87)***	(1.01, 1.28)*	-	(0.98, 1.22)
	p-value	<.001	.033	-	.116
GLP-1RA/TZD	aHR	0.73	1.04	0.92	-
	(95% CI)	(0.66, 0.80)***	(0.92, 1.17)	(0.82, 1.02)	-
	p-value	<.001	.526	.116	-

* $p < 0.05$, *** $p < .001$.

Cerebrovascular diseases		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.13	1.13	1.07
	(95% CI)	-	(1.08, 1.18)***	(1.08, 1.18)***	(1.03, 1.12)**
	p-value	-	<.001	<.001	.002
GLP-1RA	aHR	0.89	-	1.00	0.95
	(95% CI)	(0.85, 0.93)***	-	(0.95, 1.06)	(0.90, 1.01)
	p-value	<.001	-	.991	.090
TZD	aHR	0.89	1.00	-	0.95
	(95% CI)	(0.85, 0.93)***	(0.95, 1.06)	-	(0.90, 1.01)
	p-value	<.001	.991	-	.083
GLP-1RA/TZD	aHR	0.93	1.05	1.05	-
	(95% CI)	(0.89, 0.97)**	(0.99, 1.11)	(0.99, 1.11)	-
	p-value	.002	.090	.083	-

** $p < 0.01$, *** $p < .001$.

Ischemic heart diseases		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.11	0.88	0.82
	(95% CI)	-	(1.06, 1.15)***	(0.84, 0.91)***	(0.79, 0.85)***
	p-value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.90	-	0.79	0.74
	(95% CI)	(0.87, 0.94)***	-	(0.76, 0.83)***	(0.71, 0.78)***
	p-value	<.001	-	<.001	<.001
TZD	aHR	1.14	1.26	-	0.94
	(95% CI)	(1.10, 1.19)***	(1.20, 1.32)***	-	(0.89, 0.98)**
	p-value	<.001	<.001	-	.004
GLP-1RA/TZD	aHR	1.22	1.35	1.07	-
	(95% CI)	(1.17, 1.27)***	(1.28, 1.41)***	(1.02, 1.12)**	-
	p-value	<.001	<.001	.004	-

** $p < 0.01$, *** $p < .001$.

Heart failure		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.30	0.90	1.17
	(95% CI)	-	(1.22, 1.39)***	(0.86, 0.95)***	(1.11, 1.25)***
	<i>p</i> -value	-	<.001	<.001	<.001
GLP-1RA	aHR	0.77	-	0.69	0.90
	(95% CI)	(0.72, 0.82)***	-	(0.65, 0.74)***	(0.84, 0.97)**
	<i>p</i> -value	<.001	-	<.001	.007
TZD	aHR	1.11	1.44	-	1.30
	(95% CI)	(1.05, 1.17)***	(1.34, 1.55)***	-	(1.21, 1.39)***
	<i>p</i> -value	<.001	<.001	-	<.001
GLP-1RA/TZD	aHR	0.85	1.11	0.77	-
	(95% CI)	(0.80, 0.90)***	(1.03, 1.20)**	(0.72, 0.82)***	-
	<i>p</i> -value	<.001	.007	<.001	-

p*<0.01, *p*<.001.

Peripheral artery diseases		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	0.86	0.86	0.85
	(95% CI)	-	(0.79, 0.94)***	(0.79, 0.93)***	(0.79, 0.93)***
	<i>p</i> -value	-	<.001	<.001	<.001
GLP-1RA	aHR	1.16	-	0.99	0.99
	(95% CI)	(1.07, 1.26)***	-	(0.90, 1.09)	(0.90, 1.09)
	<i>p</i> -value	<.001	-	.879	.804
TZD	aHR	1.17	1.01	-	1.00
	(95% CI)	(1.08, 1.26)***	(0.92, 1.11)	-	(0.91, 1.09)
	<i>p</i> -value	<.001	.879	-	.919
GLP-1RA/TZD	aHR	1.17	1.01	1.00	-
	(95% CI)	(1.08, 1.27)***	(0.92, 1.11)	(0.92, 1.10)	-
	<i>p</i> -value	<.001	.804	.919	-

****p*<.001.

Hypoglycemia		Reference			
		Non-GLP-1RA/TZD	GLP-1RA	TZD	GLP-1RA/TZD
Non-GLP-1RA/TZD	aHR	-	1.03	0.59	0.62
	(95% CI)	-	(0.90, 1.19)	(0.53, 0.66)***	(0.55, 0.70)***
	<i>p</i> -value	-	.6484	<.001	<.001
GLP-1RA	aHR	0.97	-	0.57	.60
	(95% CI)	(0.84, 1.11)	-	(0.49, 0.66)***	(0.52, 0.70)***
	<i>p</i> -value	.648	-	<.001	<.001
TZD	aHR	1.69	1.75	-	1.05
	(95% CI)	(1.51, 1.90)***	(1.51, 2.03)***	-	(0.92, 1.20)
	<i>p</i> -value	<.001	<.001	-	.438
GLP-1RA/TZD	aHR	1.61	1.66	0.95	-
	(95% CI)	(1.43, 1.82)***	(1.43, 1.94)***	(0.83, 1.08)	-
	<i>p</i> -value	<.001	<.001	.438	-

****p*<.001.

eTable 14. Incidence and hazard ratios of outcomes in cumulative days of GLP-1RA and TZD usage by using Fine and Gray's competing risk model.

Outcomes	Variables	cSHR ^a (95% CI)	p-value	aSHR ^b (95% CI)	p-value
MACE	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.51 (0.48, 0.53)***	<.001	1.06 (1.00, 1.12)	.059
	GLP1RA, 360–900	0.36 (0.34, 0.39)***	<.001	0.76 (0.70, 0.82)***	<.001
	GLP1RA, >900	0.31 (0.29, 0.33)***	<.001	0.66 (0.61, 0.70)***	<.001
	TZD, <360	0.73 (0.69, 0.76)***	<.001	1.09 (1.04, 1.15)***	<.001
	TZD, 360–900	0.49 (0.45, 0.53)***	<.001	0.84 (0.78, 0.91)***	<.001
	TZD, >900	0.34 (0.32, 0.36)***	<.001	0.65 (0.61, 0.70)***	<.001
	GLP1RA/TZD, <360	0.71 (0.67, 0.76)***	<.001	1.23 (1.14, 1.31)***	<.001
	GLP1RA/TZD, 360–900	0.52 (0.49, 0.55)***	<.001	0.99 (0.92, 1.06)	.724
	GLP1RA/TZD, >900	0.37 (0.35, 0.39)***	<.001	0.75 (0.71, 0.79)***	<.001
Myocardial infarction	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.11 (0.09, 0.12)***	<.001	0.80 (0.70, 0.92)**	.001
	GLP1RA, 360–900	0.06 (0.05, 0.08)***	<.001	0.53 (0.44, 0.65)***	<.001
	GLP1RA, >900	0.05 (0.04, 0.06)***	<.001	0.40 (0.33, 0.48)***	<.001
	TZD, <360	0.19 (0.17, 0.21)***	<.001	0.94 (0.85, 1.05)	.275
	TZD, 360–900	0.13 (0.11, 0.15)***	<.001	0.80 (0.68, 0.93)**	.005
	TZD, >900	0.06 (0.05, 0.07)***	<.001	0.40 (0.33, 0.48)***	<.001
	GLP1RA/TZD, <360	0.15 (0.13, 0.18)***	<.001	0.90 (0.77, 1.05)	.172
	GLP1RA/TZD, 360–900	0.12 (0.10, 0.14)***	<.001	0.80 (0.70, 0.93)**	.003
	GLP1RA/TZD, >900	0.07 (0.06, 0.08)***	<.001	0.51 (0.45, 0.59)***	<.001
Cerebrovascular diseases	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.43 (0.41, 0.46)***	<.001	1.05 (0.99, 1.12)	.102
	GLP1RA, 360–900	0.32 (0.30, 0.35)***	<.001	0.79 (0.72, 0.85)***	<.001
	GLP1RA, >900	0.28 (0.26, 0.30)***	<.001	0.70 (0.65, 0.75)***	<.001
	TZD, <360	0.60 (0.57, 0.64)***	<.001	1.06 (1.00, 1.12)*	.045
	TZD, 360–900	0.41 (0.38, 0.44)***	<.001	0.83 (0.77, 0.91)***	<.001
	TZD, >900	0.30 (0.28, 0.32)***	<.001	0.69 (0.64, 0.75)***	<.001
	GLP1RA/TZD, <360	0.62 (0.57, 0.66)***	<.001	1.23 (1.14, 1.33)***	<.001
	GLP1RA/TZD, 360–900	0.44 (0.41, 0.47)***	<.001	0.98 (0.91, 1.05)	.562
	GLP1RA/TZD, >900	0.33 (0.31, 0.35)***	<.001	0.78 (0.74, 0.83)***	<.001
Ischemic heart diseases	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.44 (0.42, 0.47)***	<.001	1.04 (0.98, 1.10)	.211
	GLP1RA, 360–900	0.37 (0.35, 0.40)***	<.001	0.86 (0.80, 0.93)***	<.001
	GLP1RA, >900	0.34 (0.32, 0.36)***	<.001	0.78 (0.74, 0.84)***	<.001
	TZD, <360	0.70 (0.67, 0.74)***	<.001	1.37 (1.30, 1.44)***	<.001
	TZD, 360–900	0.54 (0.50, 0.58)***	<.001	1.11 (1.04, 1.20)**	.004
	TZD, >900	0.46 (0.43, 0.49)***	<.001	0.98 (0.92, 1.04)	.501
	GLP1RA/TZD, <360	0.70 (0.65, 0.75)***	<.001	1.53 (1.43, 1.64)***	<.001
	GLP1RA/TZD, 360–900	0.59 (0.56, 0.63)***	<.001	1.31 (1.24, 1.40)***	<.001
	GLP1RA/TZD, >900	0.50 (0.48, 0.53)***	<.001	1.13 (1.08, 1.19)***	<.001
Heart failure	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.26 (0.25, 0.29)***	<.001	1.03 (0.95, 1.12)	.445
	GLP1RA, 360–900	0.17 (0.15, 0.19)***	<.001	0.68 (0.60, 0.76)***	<.001
	GLP1RA, >900	0.11 (0.10, 0.12)***	<.001	0.43 (0.39, 0.49)***	<.001
	TZD, <360	0.53 (0.50, 0.57)***	<.001	1.38 (1.29, 1.47)***	<.001
	TZD, 360–900	0.35 (0.32, 0.38)***	<.001	1.10 (1.00, 1.21)*	.045
	TZD, >900	0.20 (0.18, 0.21)***	<.001	0.71 (0.64, 0.78)***	<.001
	GLP1RA/TZD, <360	0.39 (0.36, 0.43)***	<.001	1.20 (1.09, 1.33)***	<.001
	GLP1RA/TZD, 360–900	0.26 (0.24, 0.28)***	<.001	0.90 (0.81, 0.99)*	.026
	GLP1RA/TZD, >900	0.18 (0.16, 0.19)***	<.001	0.68 (0.62, 0.74)***	<.001
Peripheral artery diseases	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.13 (0.11, 0.14)***	<.001	1.01 (0.89, 1.14)	.874
	GLP1RA, 360–900	0.12 (0.10, 0.13)***	<.001	0.98 (0.85, 1.13)	.798
	GLP1RA, >900	0.12 (0.10, 0.13)***	<.001	0.97 (0.86, 1.10)	.666
	TZD, <360	0.18 (0.17, 0.20)***	<.001	1.20 (1.08, 1.33)***	<.001
	TZD, 360–900	0.16 (0.14, 0.19)***	<.001	1.21 (1.05, 1.39)**	.008
	TZD, >900	0.14 (0.12, 0.15)***	<.001	1.08 (0.95, 1.21)	.23
	GLP1RA/TZD, <360	0.18 (0.15, 0.20)***	<.001	1.30 (1.12, 1.50)***	<.001
	GLP1RA/TZD, 360–900	0.15 (0.13, 0.17)***	<.001	1.18 (1.04, 1.34)*	.013

	GLP1RA/TZD, >900	0.14 (0.12, 0.15)***	<.001	1.14 (1.02, 1.26)*	.015
Hypoglycemia	Non-use	1.00 (reference)	-	1.00 (reference)	-
	GLP1RA, <360	0.06 (0.05, 0.07)***	<.001	1.00 (0.84, 1.19)	.997
	GLP1RA, 360–900	0.03 (0.03, 0.04)***	<.001	0.65 (0.50, 0.85)**	.001
	GLP1RA, >900	0.03 (0.02, 0.04)***	<.001	0.54 (0.43, 0.69)***	<.001
	TZD, <360	0.13 (0.11, 0.15)***	<.001	1.66 (1.45, 1.90)***	<.001
	TZD, 360–900	0.09 (0.07, 0.10)***	<.001	1.41 (1.16, 1.72)***	<.001
	TZD, >900	0.05 (0.04, 0.06)***	<.001	0.88 (0.72, 1.07)	.194
	GLP1RA/TZD, <360	0.11 (0.09, 0.13)***	<.001	1.64 (1.35, 1.99)***	<.001
	GLP1RA/TZD, 360–900	0.09 (0.08, 0.11)***	<.001	1.54 (1.29, 1.83)***	<.001
	GLP1RA/TZD, >900	0.05 (0.05, 0.06)***	<.001	1.00 (0.85, 1.18)	.97

aSHR, adjusted subdistribution hazard ratio; cSHR, crude subdistribution hazard ratio; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; PY, person-year; 95% CI, 95% confidence interval.

^a Each outcome consider death as a competing risk.

^b Adjusted subdistribution hazard ratio estimated by multivariable analysis including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

eTable 15. Incidence and hazard ratios of outcomes after inverse probability of treatment weighting matching.

Variables	cHR (95% CI)	<i>p</i> -value	aHR ^a (95% CI)	<i>p</i> -value
All-cause mortality				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.42 (0.41, 0.43)***	<.001	0.34 (0.34, 0.35)***	<.001
TZD	0.65 (0.64, 0.66)***	<.001	0.55 (0.54, 0.55)***	<.001
GLP-1RA/TZD	0.22 (0.22, 0.23)***	<.001	0.19 (0.18, 0.19)***	<.001
MACE				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.63 (0.62, 0.64)***	<.001	0.61 (0.60, 0.63)***	<.001
TZD	0.86 (0.84, 0.88)***	<.001	0.84 (0.82, 0.86)***	<.001
GLP-1RA/TZD	0.73 (0.71, 0.75)***	<.001	0.72 (0.70, 0.73)***	<.001
Cardiovascular mortality				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.40 (0.38, 0.41)***	<.001	0.33 (0.32, 0.35)***	<.001
TZD	0.60 (0.57, 0.63)***	<.001	0.52 (0.49, 0.54)***	<.001
GLP-1RA/TZD	0.20 (0.19, 0.21)***	<.001	0.17 (0.16, 0.19)***	<.001
Myocardial infarction				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.47 (0.45, 0.50)***	<.001	0.46 (0.44, 0.49)***	<.001
TZD	0.81 (0.77, 0.85)***	<.001	0.80 (0.76, 0.84)***	<.001
GLP-1RA/TZD	0.59 (0.56, 0.62)***	<.001	0.58 (0.55, 0.61)***	<.001
Cerebrovascular diseases				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.69 (0.67, 0.70)***	<.001	0.68 (0.66, 0.69)***	<.001
TZD	0.89 (0.87, 0.92)***	<.001	0.88 (0.86, 0.90)***	<.001
GLP-1RA/TZD	0.81 (0.79, 0.83)***	<.001	0.80 (0.77, 0.82)***	<.001
Ischemic heart diseases				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.73 (0.71, 0.75)***	<.001	0.74 (0.72, 0.75)***	<.001
TZD	1.12 (1.10, 1.15)***	<.001	1.13 (1.11, 1.16)***	<.001
GLP-1RA/TZD	1.07 (1.04, 1.09)***	<.001	1.08 (1.05, 1.10)***	<.001
Heart failure				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.56 (0.54, 0.57)***	<.001	0.56 (0.54, 0.58)***	<.001
TZD	1.10 (1.07, 1.13)***	<.001	1.11 (1.08, 1.15)***	<.001
GLP-1RA/TZD	0.68 (0.66, 0.70)***	<.001	0.69 (0.66, 0.71)***	<.001
Peripheral artery diseases				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.98 (0.94, 1.03)	0.3909	1.05 (1.01, 1.10)*	0.0291
TZD	1.09 (1.04, 1.14)***	<.001	1.16 (1.11, 1.22)***	<.001
GLP-1RA/TZD	1.06 (1.01, 1.12)*	0.0109	1.13 (1.08, 1.19)***	<.001
Hypoglycemia				
Non-GLP-1RA/TZD	1.00 -	-	1.00 (reference)	-
GLP-1RA	0.65 (0.61, 0.71)***	<.001	0.66 (0.61, 0.72)***	<.001
TZD	1.48 (1.38, 1.58)***	<.001	1.50 (1.39, 1.61)***	<.001
GLP-1RA/TZD	1.48 (1.38, 1.59)***	<.001	1.50 (1.40, 1.61)***	<.001

aHR, adjusted hazard ratio; cHR, crude hazard ratio; IR, incidence rate, per 1000 person-year; MACE, major adverse cardiovascular events; PY, person-year; 95% CI, 95% confidence interval.

^a Adjusted hazard ratio estimated by multivariable analysis including gender, age, comorbidities, medications, DCSI score, and duration of type 2 diabetes mellitus.

eTable 16. A comparative review of diabetic practice guidelines in Taiwan, the United States and Europe.

Country	Taiwan	United States	Europe
Organization	Diabetes Association of Republic of China (DAROC)	American Diabetes Association (ADA)	European Association for the Study of Diabetes (EASD)
Glycemic target			
2007	HbA1c $\leq$ 6.5% FPG $\leq$ 6 mmol/L ($\leq$ 108 mg/dL) PPG $\leq$ 7.5 mmol/L ($\leq$ 135 mg/dL)	HbA1c $<$ 7.0% FPG $<$ 6.7 mmol/L ($<$ 120 mg/dL)	HbA1c $\leq$ 6.5% FPG $\leq$ 6 mmol/L ($\leq$ 108 mg/dL) PPG $\leq$ 7.5 mmol/L ($\leq$ 135 mg/dL)
2012	HbA1c $<$ 7.0%	HbA1c $<$ 7.0% FPG 3.9–7.2 mmol/L (70–130 mg/dL) PPG $<$ 10 mmol/L ($<$ 180 mg/dL)	HbA1c $<$ 7.0% FPG $<$ 7.2 mmol/L (120 mg/dL) PPG 9–10 mmol/L (160–180 mg/dL)
2018	HbA1c $<$ 7.0%	HbA1c $<$ 7.0% FPG $<$ 7.2 mmol/L (120 mg/dL) PPG 9–10 mmol/L (160–180 mg/dL)	
Pharmacotherapy^a			
2018	<u>DM with HTN</u> Monotherapy: Metformin Dual therapy: Metformin + SGLT2i Triple therapy: Metformin + SGLT2i + (GLP-1RA > TZD > DPP4i > SU or glinide or AGi) <u>DM with CAD</u> Monotherapy: Metformin Dual therapy: Metformin + (TZD > SGLT2i > GLP-1RA) Triple therapy: Metformin + TZD + SGLT2i > Metformin + TZD + GLP-1RA > Metformin + SGLT2i + GLP-1RA <u>DM with stage 3 CKD</u> Monotherapy: Metformin Dual therapy: Metformin + SGLT2i Triple therapy: Metformin + SGLT2i + GLP-1RA > Metformin + SGLT2i + TZD > Metformin + SGLT2i + DPP4i > Metformin + SGLT2i + SU or glinide or AGi <u>DM with history of CVD</u> Monotherapy: Metformin Dual therapy: Metformin + TZD > Metformin + GLP-1RA > Metformin + SGLT2i Triple therapy: Metformin + TZD + GLP-1RA > Metformin + TZD + SGLT2i > Metformin + GLP-1RA + SGLT2i	First-line: Metformin <u>ASCVD or HF or CKD</u> - ASCVD predominates Second line: GLP-1RA or SGLT2i Third line: DPP4i if not on GLP-1RA, basal insulin, TZD, SU - HF or CKD predominates Second-line: SGLT2i. GLP1-RA if eGFR less than adequate Third-line: DPP4i if not on GLP-1RA or HF. DPP4i or basal insulin or SU <u>Absent of ASCVD or CKD</u> - Minimize hypoglycemia (Second-line + Third-line) DPP4i + SGLT2i or TZD GLP1-RA + SGLT2i or TZD SGLT2i + GLP1-RA or DPP4i or TZD TZD + SGLT2i or DPP4i or GLP-1RA Fourth-line: SU or basal insulin - Minimize weight gain Second-line: GLP-1RA or SGLT2i Third-line: SGLT2i or GLP-1RA Fourth-line: DPP4i. SU or TZD or basal insulin if not tolerated DPP4i - Economical issue (Second-line + Third-line) SU + TZD TZD + SU Fourth-line: DPP4i or basal insulin	

AGi, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; HTN, hypertension; PPG, post-prandial glucose; SGLT2i, sodium-glucose cotransporter two inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^a No specific pharmacotherapy guidelines were available before 2018 around the world.

eTable 17. Landmark clinical trials on diabetes mellitus management and cardiovascular diseases before 2020.

Trial (Full Name)	Year	Participant	Objective	Key Findings
UKPDS (United Kingdom Prospective Diabetes Study)	1998	5,102	Long-term effects of glucose and blood pressure control on complications	Intensive control reduced microvascular complications
STENO-2 Study	2003	160	Impact of multifactorial intervention on diabetes outcomes	Reduced cardiovascular events and all-cause mortality
PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events)	2005	5,238	Effect of pioglitazone on macrovascular outcomes	Reduced recurrent cardiovascular events; increased heart failure
ACCORD (Action to Control Cardiovascular Risk in Diabetes)	2008	10,251	Intensive glucose control to reduce cardiovascular events	Increased mortality with intensive control
ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation)	2008	11,140	Effects of intensive glucose control on vascular outcomes	Reduced microvascular events; no significant effect on macrovascular events
VADT (Veterans Affairs Diabetes Trial)	2009	1,791	Impact of intensive glucose control on cardiovascular events	No significant reduction in major cardiovascular events
ORIGIN (Outcome Reduction with an Initial Glargine Intervention)	2012	12,537	Effects of insulin glargine on cardiovascular outcomes	Neutral cardiovascular impact; reduced progression to diabetes
SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus - Thrombolysis in Myocardial Infarction 53)	2013	16,492	Cardiovascular safety of saxagliptin	No increase in cardiovascular risk; higher risk of heart failure hospitalization
EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care)	2013	5,380	Cardiovascular safety of alogliptin in type 2 diabetes patients with recent acute coronary syndrome	Cardiovascular safety confirmed
TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin)	2015	14,671	Cardiovascular safety of sitagliptin	No increase in cardiovascular risk or heart failure
EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)	2015	7,020	Cardiovascular outcomes of empagliflozin	Reduced cardiovascular death and heart failure hospitalization
LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)	2016	9,340	Cardiovascular safety of liraglutide	Reduced major cardiovascular events and all-cause mortality
CANVAS (Canagliflozin Cardiovascular Assessment Study)	2017	10,142	Cardiovascular safety of canagliflozin	Reduced cardiovascular events; increased risk of amputations
DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events - Thrombolysis in Myocardial Infarction 58)	2018	17,160	Cardiovascular and renal outcomes of dapagliflozin	Reduced hospitalization for heart failure; renal benefits
REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes)	2019	9,901	Effect of dulaglutide on cardiovascular outcomes	Reduced cardiovascular events
CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)	2019	4,401	Renal and cardiovascular effects of canagliflozin in type 2 diabetes with chronic kidney disease	Reduced risk of renal failure and cardiovascular events