Supplemental Online Content

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

eTable 1. Demographic, Diagnostic, Procedural, Medication, Visit, and Laboratory Codes Used in the Definition of the Cohorts

| Category | Code | Description | | | | |
|---------------------------|---|---|--|--|--|--|
| Tirzepatide gro | Tirzepatide group | | | | | |
| #1: At least 18 years old | | | | | | |
| Demographics | Age | Age (at least 18 years) | | | | |
| | n type 2 diabetes mellitus treated with ulfilled within 6 months before or any | tirzepatide but not GLP-1 receptor agonists. time after #2.1) | | | | |
| | | ith tirzepatide (must have both of the following) I between Jun 1, 2022 and Jun 30, 2023 | | | | |
| Diagnosis | UMLS:ICD10CM:E11 | Type 2 diabetes mellitus | | | | |
| Medication | NLM:RXNORM:2601723 | Tirzepatide | | | | |
| #2.2 : Not receiv | ing GLP-1 receptor agonists (cannot l | have the following) | | | | |
| medication | NLM:ATC:A10BJ | Glucagon-like peptide-1 (GLP-1) analogues | | | | |
| | ent major adverse cardiovascular ever fulfilled within 60 days on or before # | its (cannot have any of the following) 2.1 | | | | |
| Diagnosis | UMLS:ICD10CM:I21 | Acute myocardial infarction | | | | |
| Diagnosis | UMLS:ICD10CM:I22 | Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction | | | | |
| Diagnosis | UMLS:ICD10CM:I61 | Nontraumatic intracerebral hemorrhage | | | | |
| Diagnosis | UMLS:ICD10CM:I62 | Other and unspecified nontraumatic intracranial hemorrhage | | | | |
| Diagnosis | UMLS:ICD10CM:I63 | Cerebral infarction | | | | |
| #4: Incident use | r (cannot have the following) #4 must | be fulfilled before #2.1 | | | | |
| Medication | NLM:RXNORM:2601723 | Tirzepatide | | | | |
| GLP-1 receptor | r agonist group | | | | | |
| #1: At least 18 y | vears old | | | | | |
| Demographics | Age | Age (at least 18 years) | | | | |
| | n type 2 diabetes mellitus treated with ulfilled within 6 months before or any | tirzepatide but not GLP-1 receptor agonists. time after #2.1) | | | | |
| | | ith tirzepatide (must have both of the following; between Jun 1, 2022 and Jun 30, 2023) | | | | |
| Diagnosis | UMLS:ICD10CM:E11 | Type 2 diabetes mellitus | | | | |
| Medication | NLM:ATC:A10BJ | Glucagon-like peptide-1 (GLP-1) analogues | | | | |
| #2.2 : Not receiv | ing GLP-1 receptor agonists (cannot l | nave the following) | | | | |
| Medication | NLM:RXNORM:2601723 | Tirzepatide | | | | |
| | ent major adverse cardiovascular ever fulfilled within 60 days on or before # | ats (cannot have any of the following) 2.1 | | | | |
| Diagnosis | UMLS:ICD10CM:I21 | Acute myocardial infarction | | | | |
| Diagnosis | UMLS:ICD10CM:I22 | Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction | | | | |
| Diagnosis | UMLS:ICD10CM:I61 | Nontraumatic intracerebral hemorrhage | | | | |
| Diagnosis | UMLS:ICD10CM:I62 | Other and unspecified nontraumatic intracranial hemorrhage | | | | |
| Diagnosis | UMLS:ICD10CM:I63 | Cerebral infarction | | | | |
| #4: Incident use | r (cannot have the following) #4 must | be fulfilled before #2.1 | | | | |
| Medication | NLM:ATC:A10BJ | Glucagon-like peptide-1 (GLP-1) analogues | | | | |

eTable 2. Demographic, Diagnostic, and Laboratory Codes Used in the Definition of Covariates

| Code | Description |
|---------|---|
| AI | Age at index |
| F | Female |
| 2106-3 | White |
| 2054-5 | Black or African American |
| 2028-9 | Asian |
| E08-E13 | Diabetes mellitus |
| I10-I16 | Hypertensive diseases |
| C00-D49 | Neoplasms |
| J40-J47 | Chronic lower respiratory diseases |
| I20-I25 | Ischemic heart diseases |
| N18 | Chronic kidney disease (CKD) |
| D60-D64 | Aplastic and other anemias |
| I50 | Heart failure |
| I48 | Atrial fibrillation and flutter |
| I60-I69 | Cerebrovascular diseases |
| I73.9 | Peripheral vascular disease, unspecified |
| K75 | Other inflammatory liver diseases |
| K74 | Fibrosis and cirrhosis of liver |
| M30-M36 | Systemic connective tissue disorders |
| M05 | Rheumatoid arthritis with rheumatoid factor |
| B20-B20 | Human immunodeficiency virus (HIV) disease |
| F03 | Unspecified dementia |
| E11.2 | Type 2 diabetes mellitus with kidney complications |
| E11.3 | Type 2 diabetes mellitus with ophthalmic complications |
| E11.4 | Type 2 diabetes mellitus with neurological complications |
| E11.5 | Type 2 diabetes mellitus with circulatory complications |
| Z55-Z65 | Health hazards related to socioeconomic and psychosocial circumstances |
| C10AA | HMG CoA reductase inhibitors |
| A10BA | Biguanides |
| C03 | Diuretics |
| A10A | Insulins and analogues |
| C07 | Beta blocking agents |
| C09C | Angiotensin II receptor blockers |
| C09A | Ace inhibitors |
| A10BK | Sodium-glucose co-transporter 2 (SGLT2) inhibitors |
| C08 | Calcium channel blockers |
| A10BB | Sulfonylureas |
| A10BH | Dipeptidyl peptidase 4 (DPP-4) inhibitors |
| C10AB | Fibrates |
| A10BG | Thiazolidinediones |
| 341248 | Ezetimibe |
| 8001 | Glomerular filtration rate by creatinine-based formula |
| 0001 | , |
| | AI F 2106-3 2054-5 2028-9 E08-E13 I10-I16 C00-D49 J40-J47 I20-I25 N18 D60-D64 I50 I48 I60-I69 I73.9 K75 K74 M30-M36 M05 B20-B20 F03 E11.2 E11.3 E11.4 E11.5 Z55-Z65 C10AA A10BA C03 A10A C07 C09C C09A A10BK C08 A10BB A10BB A10BB A10BG 341248 |

| Category | Code | Description |
|------------|------|---------------------------------------|
| Laboratory | 9014 | Hemoglobin in blood |
| Laboratory | 9085 | Blood pressure, systolic |
| Laboratory | 9002 | Cholesterol in LDL in serum or plasma |
| Laboratory | 9000 | Cholesterol in serum or plasma |
| Laboratory | 9083 | Body mass index (BMI) |

eTable 3. Diagnostic, Visit, and Procedural Codes Used in the Definition of Outcomes

| | • | | | | |
|--|---|---|--|--|--|
| Dama a au 1. 1 T | ortality (have any of the follow | ing) | | | |
| Demographics I | Deceased | Deceased | | | |
| Diagnosis U | UMLS:ICD10CM:R99 | Ill-defined and unknown cause of mortality | | | |
| #2: Major advers | se cardiovascular events (have | any of the following) | | | |
| Diagnosis U | UMLS:ICD10CM:I21 | Acute myocardial infarction | | | |
| Diagnosis U | UMLS:ICD10CM:I46.2 | Cardiac arrest due to underlying cardiac condition | | | |
| Diagnosis U | UMLS:ICD10CM:I46.9 | Cardiac arrest, cause unspecified | | | |
| Diagnosis U | UMLS:ICD10CM:I63 | Cerebral infarction | | | |
| Diagnosis U | UMLS:ICD10CM:I61 | Nontraumatic intracerebral hemorrhage | | | |
| Diagnosis | UMLS:ICD10CM:I22 | Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction | | | |
| Diagnosis U | UMLS:ICD10CM:I62 | Other and unspecified nontraumatic intracranial hemorrhage | | | |
| #3: Kidney event | ts (have any of the following) | | | | |
| Diagnosis U | UMLS:ICD10CM:N18.5 | Chronic kidney disease, stage 5 | | | |
| Diagnosis U | UMLS:ICD10CM:N18.6 | End stage renal disease | | | |
| Diagnosis U | UMLS:ICD10CM:Z99.2 | Dependence on renal dialysis | | | |
| Diagnosis U | UMLS:ICD10CM:N19 | Unspecified kidney failure | | | |
| Procedure U | UMLS:CPT:1012740 | Dialysis Services and Procedures | | | |
| Procedure U | UMLS:CPT:1029674 | Dialysis Circuit Procedures | | | |
| #4: Acute kidney | injury (have any of the follow | ving) | | | |
| Diagnosis U | UMLS:ICD10CM:N17 | Acute kidney failure | | | |
| #5: Major advers | se cardiovascular event or all-c | ause mortality (have #1 or #2) | | | |
| #6: Major advers | se kidney event (have #1 or #3) |) | | | |
| #7: Glycated hen | noglobin (HbA1c) level | | | | |
| Laboratory | ΓNX:9037 | Hemoglobin A1c/hemoglobin in blood | | | |
| #8: Body weight | | | | | |
| Laboratory | ΓNX:9081 | Body weight | | | |
| #9: Negative con | ntrol outcomes | | | | |
| #9.1 : Hernia, exc | cluding patients with outcome | prior to the follow-up time window | | | |
| Diagnosis U | UMLS:ICD10CM:K40-K46 | Hernia | | | |
| #9.2 : Traumatic l | brain injury, excluding patients | s with outcome prior to the follow-up time window | | | |
| Diagnosis U | UMLS:ICD10CM:S06.5 | Traumatic subdural hemorrhage | | | |
| Diagnosis U | UMLS:ICD10CM:S06.6 | Traumatic subarachnoid hemorrhage | | | |
| Diagnosis U | UMLS:ICD10CM:S06.2 | Diffuse traumatic brain injury | | | |
| Diagnosis U | UMLS:ICD10CM:S06.3 | Focal traumatic brain injury | | | |
| #9.3 : Lumbar rad | diculopathy, excluding patients | s with outcome prior to the follow-up time window | | | |
| Diagnosis U | UMLS:ICD10CM:M54.16 | Radiculopathy, lumbar region | | | |
| #9.4: Sensorineural hearing loss, excluding patients with outcome prior to the follow-up time window | | | | | |
| Diagnosis U | UMLS:ICD10CM:H90 | Conductive and sensorineural hearing loss | | | |
| #9.5 : Skin cancer | #9.5: Skin cancer, excluding patients with outcome prior to the follow-up time window | | | | |
| Diagnosis U | UMLS:ICD10CM:C44 | Other and unspecified malignant neoplasm of skin | | | |

eTable 4. Numbers and Characteristics of Individuals Excluded Because of a Lack of any Follow-Up

| No follow-up Included No follow-up Included No follow-up | | GLP-1 receptor agonist, No (%) | | Tirzepatide, No (%) | |
|---|--------------------------------------|--------------------------------|-----------------|---------------------|----------------------------------|
| Demographics Age, mean (SD), y 58.1 (13.3) 56 (13.7)*** 55.4 (11.8) 51.8 (13.0)**** Female 67.474 (53.8) 2,127 (51.4)*** 8.444 (56.9) 179 (51.3)*** African American/Black 25,212 (20.1) 992 (24.0)*** 2,517 (17.0) 73 (20.9)*** Asian 4,558 (3.6) 149 (3.6) 337 (2.3) ≤10 (≤ 2.9)** Hispanic/Latinx 11,676 (9.3) 320 (7.7)** 957 (6.5) 19 (5.4) White 75,762 (6.4) 2,251 (54.4)**** 9,978 (67.3) 206 (59.0)** Comorbidites 16.814 (13.4) 295 (7.1)*** 1,623 (10.9) ≤10 (≤ 2.9)** Ischemic heart diseases 16,814 (13.4) 295 (7.1)*** 1,623 (10.9) ≤10 (≤ 2.9)** Ischemic heart diseases 16,814 (13.4) 295 (7.1)*** 1,623 (10.9) ≤10 (≤ 2.9)** Ischemic heart diseases 15,814 (13.4) 295 (7.1)*** 1,623 (10.9) ≤10 (≤ 2.9)** Ischemic heart diseases 15,814 (13.4) 295 (7.1)*** 1,623 (10.9) ≤10 (≤ 2.9)** Cerebrovascular diseases 5,579 (4.4 | Variables | Included | No follow-up | Included | No follow-up |
| Age, mean (SD), y $58.1 (13.3)$ $56 (13.7)^{***}$ $55.4 (11.8)$ $51.8 (13.0)^{***}$ Female $67.474 (53.8)$ $21.27 (51.4)^{***}$ $8.444 (56.9)$ $179 (51.3)^{**}$ African American/Black $25.212 (20.1)$ $992 (24.0)^{***}$ $2.517 (17.0)$ $73 (20.9)^{***}$ Asian $4.558 (3.6)$ $149 (3.6)$ $337 (2.3)$ $510 (2.9)^{**}$ Hispanic/Latinx $11.676 (9.3)$ $320 (7.7)^{***}$ $957 (6.5)$ $19 (5.4)$ White $75,762 (60.4)$ $2.251 (54.4)^{****}$ $9.78 (67.3)$ $206 (59.0)^{***}$ Combridities Hypertensive diseases $16.814 (13.4)$ $295 (7.1)^{****}$ $1.623 (10.9)$ $210 (\leq 2.9)$ Hypertensive diseases $16.814 (13.4)$ $295 (7.1)^{****}$ $1.623 (10.9)$ $210 (\leq 2.9)$ Heart failure $9.447 (7.5)$ $161 (3.9)^{*****}$ $8.21 (5.5)$ $510 (\leq 2.9)$ Heart failure $9.447 (7.5)$ $161 (3.9)^{*****}$ $821 (5.5)$ $510 (\leq 2.9)$ Atrial fibrillation or flutter $7.334 (5.8)$ $120 (2.9)^{*************** 670 (4.5) 510 (\leq 2.9)$ | Number of patients | 125,474 | 4,141 | 14,834 | 348 |
| Female $67,474$ (53.8) $2,127$ (51.4)*** $8,444$ (56.9) 179 (51.3)* African American/Black $25,212$ (20.1) 992 (24.0)*** $2,517$ (17.0) 73 (20.9)** Asian $4,558$ (3.6) 149 (3.6) 337 (2.3) $\le 10 (\le 2.9)$! Hispanic/Latinx 11.676 (9.3) 320 (7.7)** 957 (6.5) 19 (54.) White $75,762$ (60.4) $2,251$ (54.4)**** $9,78$ (67.3) 206 (59.0)** Comorbidities Hypertensive diseases $16,814$ (13.4) 295 (7.1)*** $8,265$ (55.7) 87 (24.9)*** Ischemic heart diseases $16,814$ (13.4) 295 (7.1)*** $1,623$ (10.9) ≤ 10 (≤ 2.9)* Heart failure $9,447$ (7.5) 161 (3.9)**** 821 (5.5) ≤ 10 (≤ 2.9)* Cerebrovascular diseases $5,579$ (4.4) 86 (2.1)**** 437 (2.9) ≤ 10 (≤ 2.9)* Cerebrovascular diseases $1,673$ (14.1) 264 (6.4)**** $1,789$ (12.1) ≤ 10 (≤ 2.9)* Chronic kidney disease $17,673$ (14.1) 264 (6.4)**** $1,789$ (12.1) ≤ 10 (≤ 2.9)* | Demographics | | | | |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | Age, mean (SD), y | 58.1 (13.3) | 56 (13.7)*** | 55.4 (11.8) | 51.8 (13.0)*** |
| $ \begin{array}{c} \text{Asian} & 4,558 (3.6) & 149 (3.6) & 337 (2.3) & \le 10 (\le 2.9)^1 \\ \text{Hispanic/Latinx} & 11,676 (9.3) & 320 (7.7)^{++} & 957 (6.5) & 19 (5.4) \\ \text{White} & 75,762 (60.4) & 2,251 (54.4)^{****} & 9,978 (67.3) & 206 (59.0)^{***} \\ \textbf{Comorbidities} \\ \text{Hypertensive diseases} & 72,438 (57.7) & 1,383 (33.4)^{****} & 8,265 (55.7) & 87 (24.9)^{****} \\ \text{Ischemic heart diseases} & 16,814 (13.4) & 295 (7.1)^{****} & 1,623 (10.9) & \le 10 (\le 2.9)^4 \\ \text{Heart failure} & 9,447 (7.5) & 161 (3.9)^{****} & 821 (5.5) & \le 10 (\le 2.9)^4 \\ \text{Atrial fibrillation or flutter} & 7,334 (5.8) & 120 (2.9)^{****} & 670 (4.5) & \le 10 (\le 2.9)^4 \\ \text{Cerebrovascular diseases} & 5,579 (4.4) & 86 (2.1)^{****} & 320 (2.2) & \le 10 (\le 2.9)^4 \\ \text{Chronic lower respiratory diseases} & 17,673 (14.1) & 264 (6.4)^{****} & 1,789 (12.1) & \le 10 (\le 2.9)^4 \\ \text{Chronic kidney disease} & 14,841 (11.8) & 253 (6.1)^{****} & 320 (2.2) & \le 10 (\le 2.9)^4 \\ \text{Chronic kidney diseases} & 1,4841 (11.8) & 253 (6.1)^{****} & 320 (2.2) & \le 10 (\le 2.9)^4 \\ \text{Inflammatory liver diseases} & 2,064 (1.6) & 17 (0.4)^{****} & 320 (2.1) & \le 1.9 (\le 2.9)^4 \\ \text{Inflammatory liver diseases} & 2,244 (1.6) & 16 (4.6)^{****} & 329 (2.1) & \le 1.9 (\le 2.9)^4 \\ \text{Reumatoid arthritis} & 632 (0.5) & \le 10 (\le 0.2)^4 & 36 (0.2) & 0 (0.0) \\ \text{Disentic connective tissue disorders} & 2,124 (1.7) & 17 (0.4)^{****} & 248 (1.7) & \le 10 (\le 2.9)^4 \\ \text{Rheumatoid arthritis} & 632 (0.5) & \le 10 (\le 0.2)^4 & 30 (0.2) & 0 (0.0) \\ \text{Diabetic complications} & 13,700 (10.8) & 302 (7.3)^{****} & 1,281 (8.6) & 15 (4.3)^{****} \\ \text{Ophthalmic complications} & 13,700 (10.8) & 302 (7.3)^{****} & 30.4) & 0 (0.0) \\ \text{Dementia} & 14,143 (11.2) & 223 (5.4)^{****} & 302 (2.2) & \le 10 (\le 2.9)^4 \\ \text{SES and psychosocial-related hazards} & 4,019 (3.2) & 58 (1.4)^{****} & 322 (2.2) & \le 10 (\le 2.9)^4 \\ \text{SES and psychosocial-related hazards} & 4,019 (3.2) & 58 (1.1)^{****} $ | Female | 67,474 (53.8) | 2,127 (51.4)** | 8,444 (56.9) | 179 (51.3)* |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | African American/Black | 25,212 (20.1) | 992 (24.0)*** | 2,517 (17.0) | 73 (20.9)** |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Asian | 4,558 (3.6) | 149 (3.6) | 337 (2.3) | ≤10 (≤ 2.9)† |
| Comorbidities Hypertensive diseases 72,438 (57.7) 1,383 (33.4)*** 8,265 (55.7) 87 (24.9)*** Ischemic heart diseases 16,814 (13.4) 295 (7.1)*** 1,623 (10.9) $\leq 10 \leq 2.9$)* Heart failure 9,447 (7.5) 161 (3.9)*** 821 (5.5) $\leq 10 (\leq 2.9)$ * Atrial fibrillation or flutter 7,334 (5.8) 120 (2.9)*** 670 (4.5) $\leq 10 (\leq 2.9)$ * Cerebrovascular diseases 5,579 (4.4) 86 (2.1)*** 437 (2.9) $\leq 10 (\leq 2.9)$ * Chronic lower respiratory diseases 1,150 (3.3) 51 (1.2)*** 320 (2.2) $\leq 10 (\leq 2.9)$ * Chronic kidney diseases 17,673 (14.1) 264 (6.4)*** 1,789 (12.1) $\leq 10 (\leq 2.9)$ * Chronic kidney diseases 14,841 (11.8) 253 (6.1)*** 1,261 (8.5) 15 (4.3)*** Anemia 10,552 (8.4) 181 (4.4)*** 822 (5.5) $\leq 10 (\leq 2.9)$ * Inflammatory liver diseases 2,064 (1.6) 17 (0.4)**** 308 (2.1) $\leq 10 (\leq 2.9)$ * Liver cirrhosis 2,241 (1.8) 26 (0.6)**** 259 (1.7) 0 (0.0)* <td< td=""><td>Hispanic/Latinx</td><td>11,676 (9.3)</td><td>320 (7.7)**</td><td>957 (6.5)</td><td>19 (5.4)</td></td<> | Hispanic/Latinx | 11,676 (9.3) | 320 (7.7)** | 957 (6.5) | 19 (5.4) |
| Hypertensive diseases 72,438 (57.7) 1,383 (33.4)*** 8,265 (55.7) 87 (24.9)*** Ischemic heart diseases 16,814 (13.4) 295 (7.1)*** 1,623 (10.9) $\leq 10 (\leq 2.9)^{\dagger}$ Heart failure 9,447 (7.5) 161 (3.9)*** 821 (5.5) $\leq 10 (\leq 2.9)^{\dagger}$ Atrial fibrillation or flutter 7,334 (5.8) 120 (2.9)*** 670 (4.5) $\leq 10 (\leq 2.9)^{\dagger}$ Cerebrovascular diseases 5,579 (4.4) 86 (2.1)*** 437 (2.9) $\leq 10 (\leq 2.9)^{\dagger}$ Cerebrovascular diseases 4,150 (3.3) 51 (1.2)*** 320 (2.2) $\leq 10 (\leq 2.9)^{\dagger}$ Chronic lower respiratory diseases 17,673 (14.1) 264 (6.4)*** 1,789 (12.1) $\leq 10 (\leq 2.9)^{\dagger}$ Chronic kidney disease 14,841 (11.8) 253 (6.1)*** 822 (5.5) $\leq 10 (\leq 2.9)^{\dagger}$ Inflammatory liver diseases 2,064 (1.6) 17 (0.4)*** 308 (2.1) $\leq 10 (\leq 2.9)^{\dagger}$ Inflammatory liver diseases 2,241 (1.8) 26 (0.6)*** 259 (1.7) 0 (0.0)** Neoplasms 19,460 (15.5) 227 (5.5)*** 2,166 (14.6) 16 (4.6)*** Systemic connective tissue disorders 2,124 (1.7) 17 (0.4)*** 248 (1.7) $\leq 10 (\leq 2.9)^{\dagger}$ HIV disease 895 (0.7) $\leq 10 (\leq 0.2)^{\dagger}$ 74 (0.5) $\leq 10 (\leq 2.9)^{\dagger}$ HIV disease 895 (0.7) $\leq 10 (\leq 0.2)^{\dagger}$ 73 (0.4) 0 (0.0) Dementia 614 (0.5) 17 (0.4) 36 (0.2) 0 (0.0) Diabetic complications 13,700 (10.8) 302 (7.3)*** 1,281 (8.6) 15 (4.3)*** Neurological complications 14,143 (11.2) 223 (5.4)*** 1,610 (10.9) 11 (3.2)*** Neurological complications 14,143 (11.2) 223 (5.4)*** 1,610 (10.9) 11 (3.2)*** Neurological-related hazards 4,019 (3.2) 58 (1.4)*** 350 (3.7) $\leq 10 (\leq 2.9)^{\dagger}$ See and psychosocial-related hazards 4,019 (3.2) 58 (1.4)*** 5,530 (37.3) 79 (22.6)*** Fibrates 3,715 (3.0) 93 (2.2)** 461 (3.1) $\leq 10 (\leq 2.9)^{\dagger}$ See and psychosocial-related hazards 4,019 (3.2) 58 (1.5)** 427 (2.9) $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides 54,056 (43.1) 1,184 (28.6)** 5,530 (37.3) 79 (22.6)*** Fibrates 3,715 (3.0) 93 (2.2)** 461 (3.1) $\leq 10 (\leq 2.9)^{\dagger}$ Bigua | White | 75,762 (60.4) | 2,251 (54.4)*** | 9,978 (67.3) | 206 (59.0)** |
| Ischemic heart diseases | Comorbidities | | | | |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | Hypertensive diseases | 72,438 (57.7) | 1,383 (33.4)*** | 8,265 (55.7) | 87 (24.9)*** |
| Atrial fibrillation or flutter 7,334 (5.8) $120 (2.9)^{***}$ $670 (4.5)$ $\le 10 (\le 2.9)^*$ Cerebrovascular diseases 5,579 (4.4) $86 (2.1)^{***}$ $437 (2.9)$ $\le 10 (\le 2.9)^*$ Peripheral vascular diseases 4,150 (3.3) $51 (1.2)^{***}$ $320 (2.2)$ $\le 10 (\le 2.9)^*$ Chronic lower respiratory diseases 17,673 (14.1) $264 (6.4)^{***}$ $1,789 (12.1)$ $\le 10 (\le 2.9)^*$ Chronic kidney disease 14,841 (11.8) $253 (6.1)^{***}$ $1,261 (8.5)$ $15 (4.3)^{***}$ Anemia 10,552 (8.4) $181 (4.4)^{***}$ $822 (5.5)$ $\le 10 (\le 2.9)^*$ Inflammatory liver diseases $2,064 (1.6)$ $17 (0.4)^{***}$ $308 (2.1)$ $\le 10 (\le 2.9)^*$ Liver cirrhosis $2,241 (1.8)$ $26 (0.6)^{***}$ $259 (1.7)$ $0 (0.0)^*$ Neoplasms $19,460 (15.5)$ $227 (5.5)^{***}$ $248 (1.7)$ $200 (0.9)^*$ Systemic connective tissue disorders $2,124 (1.7)$ $17 (0.4)^{***}$ $248 (1.7)$ $210 (\le 2.9)^*$ HIV disease $895 (0.7)$ $\le 10 (\le 0.2)^*$ $53 (0.4)$ $0 (0.0)$ Dementia $614 (0.5)$ $17 (0.4)$ $36 (0.2)$ $0 (0.0)$ Diabetic complications $13,700 (10.8)$ $302 (7.3)^{***}$ $1,281 (8.6)$ $15 (4.3)^{***}$ Ophthalmic complications $13,700 (10.8)$ $302 (7.3)^{***}$ $1,281 (8.6)$ $15 (4.3)^{***}$ Ophthalmic complications $14,143 (11.2)$ $223 (5.4)^{***}$ $850 (5.7)$ $10 (\le 2.9)^*$ Neurological complications $14,143 (11.2)$ $223 (5.4)^{***}$ $850 (5.7)$ $10 (\le 2.9)^*$ SES and psychosocial-related hazards $4,019 (3.2)$ $58 (1.4)^{***}$ $322 (2.2)$ $10 (\le 2.9)^*$ Medication $10 (3.2) ($ | Ischemic heart diseases | 16,814 (13.4) | 295 (7.1)*** | 1,623 (10.9) | $\leq 10 \ (\leq 2.9)^{\dagger}$ |
| $ \begin{array}{c} \text{Cerebrovascular diseases} & 5,579(4.4) & 86(2.1)^{***} & 437(2.9) & \leq 10(\leq 2.9)^{**} \\ \text{Peripheral vascular diseases} & 4,150(3.3) & 51(1.2)^{***} & 320(2.2) & \leq 10(\leq 2.9)^{**} \\ \text{Chronic lower respiratory diseases} & 17,673(14.1) & 264(6.4)^{****} & 1,789(12.1) & \leq 10(\leq 2.9)^{**} \\ \text{Chronic kidney disease} & 14,841(11.8) & 253(6.1)^{****} & 1,261(8.5) & 15(4.3)^{***} \\ \text{Anemia} & 10,552(8.4) & 181(4.4)^{****} & 822(5.5) & \leq 10(\leq 2.9)^{**} \\ \text{Inflammatory liver diseases} & 2,064(1.6) & 17(0.4)^{****} & 308(2.1) & \leq 10(\leq 2.9)^{**} \\ \text{Liver cirrhosis} & 2,241(1.8) & 26(0.6)^{****} & 259(1.7) & 0(0.0)^{**} \\ \text{Neoplasms} & 19,460(15.5) & 227(5.5)^{****} & 2,166(14.6) & 16(4.6)^{****} \\ \text{Systemic connective tissue disorders} & 2,124(1.7) & 17(0.4)^{****} & 248(1.7) & \leq 10(\leq 2.9)^{**} \\ \text{HV disease} & 895(0.7) & \leq 10(\leq 0.2)^{**} & 74(0.5) & \leq 10(\leq 2.9)^{**} \\ \text{HV disease} & 895(0.7) & \leq 10(\leq 0.2)^{**} & 53(0.4) & 0(0.0) \\ \text{Diabetic complications} & 13,700(10.8) & 302(7.3)^{****} & 1,281(8.6) & 15(4.3)^{****} \\ \text{Ophthalmic complications} & 13,700(10.8) & 302(7.3)^{****} & 699(4.7) & \leq 10(\leq 2.9)^{**} \\ \text{Neurological complications} & 14,143(11.2) & 223(5.4)^{****} & 1,610(10.9) & 11(3.2)^{****} \\ \text{Circulatory complications} & 7,503(5.9) & 129(3.1)^{****} & 850(5.7) & \leq 10(\leq 2.9)^{**} \\ \text{Medication} & 3,715(3.0) & 93(2.2)^{***} & 461(3.1) & 210(\leq 2.9)^{**} \\ \text{Medication} & 3,715(3.0) & 93(2.2)^{***} & 461(3.1) & 210(\leq 2.9)^{**} \\ \text{Signanides} & 54,056(43.1) & 1,184(28.6)^{****} & 5,530(37.3) & 79(22.6)^{****} \\ \text{Sulfonylureas} & 17,517(14.0) & 426(10.3)^{****} & 427(2.9) & \leq 10(\leq 2.9)^{**} \\ \text{Sulfonylureas} & 17,517(14.0) & 426(10.3)^{****} & 393(2.7) & \leq 10(\leq 2.9)^{**} \\ \text{Sulfonylureas} & 17,517(14.0) & 426(10.3)^{****} & 393(2.7) & \leq 10(\leq 2.9)^{***} \\ \text{Sulfonylureas} & 17,517(14.0) & 426(10.3)^{****} & 393(2.7) & \leq 10(\leq 2.9)^{***} \\ \text{Sulfonylureas} & 17,517(14.0) & 426(10.3)^{****} & 393(2.7) & \leq 1$ | Heart failure | 9,447 (7.5) | 161 (3.9)*** | 821 (5.5) | ≤10 (≤ 2.9)† |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | Atrial fibrillation or flutter | 7,334 (5.8) | 120 (2.9)*** | 670 (4.5) | ≤10 (≤ 2.9)† |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | Cerebrovascular diseases | 5,579 (4.4) | 86 (2.1)*** | 437 (2.9) | $\leq 10 \ (\leq 2.9)^{\dagger}$ |
| $ \begin{array}{c} \text{Chronic kidney disease} & 14,841 (11.8) & 253 (6.1)^{***} & 1,261 (8.5) & 15 (4.3)^{**} \\ \text{Anemia} & 10,552 (8.4) & 181 (4.4)^{***} & 822 (5.5) & \leq 10 (\leq 2.9)^t \\ \text{Inflammatory liver diseases} & 2,064 (1.6) & 17 (0.4)^{***} & 308 (2.1) & \leq 10 (\leq 2.9)^t \\ \text{Liver cirrhosis} & 2,241 (1.8) & 26 (0.6)^{***} & 259 (1.7) & 0 (0.0)^* \\ \text{Neoplasms} & 19,460 (15.5) & 227 (5.5)^{***} & 2,166 (14.6) & 16 (4.6)^{***} \\ \text{Systemic connective tissue disorders} & 2,124 (1.7) & 17 (0.4)^{***} & 248 (1.7) & \leq 10 (\leq 2.9)^t \\ \text{Rheumatoid arthritis} & 632 (0.5) & \leq 10 (\leq 0.2)^t & 74 (0.5) & \leq 10 (\leq 2.9)^t \\ \text{HIV disease} & 895 (0.7) & \leq 10 (\leq 0.2)^t & 53 (0.4) & 0 (0.0) \\ \text{Dementia} & 614 (0.5) & 17 (0.4) & 36 (0.2) & 0 (0.0) \\ \text{Diabetic complications} & 13,700 (10.8) & 302 (7.3)^{***} & 1,281 (8.6) & 15 (4.3)^{***} \\ \text{Ophthalmic complications} & 13,700 (10.8) & 302 (7.3)^{***} & 1,281 (8.6) & 15 (4.3)^{***} \\ \text{Ophthalmic complications} & 14,143 (11.2) & 223 (5.4)^{***} & 1,610 (10.9) & 11 (3.2)^{***} \\ \text{Circulatory complications} & 14,143 (11.2) & 223 (5.4)^{***} & 1,610 (10.9) & 11 (3.2)^{***} \\ \text{SES and psychosocial-related hazards} & 4,019 (3.2) & 58 (1.4)^{***} & 322 (2.2) & \leq 10 (\leq 2.9)^t \\ \textbf{Medication} & & & & & & & & & & & & & & & & & & &$ | Peripheral vascular diseases | 4,150 (3.3) | 51 (1.2)*** | 320 (2.2) | ≤10 (≤ 2.9)† |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Chronic lower respiratory diseases | 17,673 (14.1) | 264 (6.4)*** | 1,789 (12.1) | ≤10 (≤ 2.9)† |
| $ \begin{array}{ l c c c c c }\hline Inflammatory liver diseases & 2,064 (1.6) & 17 (0.4)*** & 308 (2.1) & \leq 10 (\leq 2.9)*\\ \hline Liver cirrhosis & 2,241 (1.8) & 26 (0.6)*** & 259 (1.7) & 0 (0.0)*\\ \hline Neoplasms & 19,460 (15.5) & 227 (5.5)*** & 2,166 (14.6) & 16 (4.6)***\\ \hline Systemic connective tissue disorders & 2,124 (1.7) & 17 (0.4)*** & 248 (1.7) & \leq 10 (\leq 2.9)*\\ \hline Rheumatoid arthritis & 632 (0.5) & \leq 10 (\leq 0.2)* & 74 (0.5) & \leq 10 (\leq 2.9)*\\ \hline HIV disease & 895 (0.7) & \leq 10 (\leq 0.2)* & 53 (0.4) & 0 (0.0)\\ \hline Dementia & 614 (0.5) & 17 (0.4) & 36 (0.2) & 0 (0.0)\\ \hline Diabetic complications & 13,700 (10.8) & 302 (7.3)*** & 1,281 (8.6) & 15 (4.3)***\\ \hline Ophthalmic complications & 13,700 (10.8) & 302 (7.3)*** & 699 (4.7) & \leq 10 (\leq 2.9)*\\ \hline Neurological complications & 14,143 (11.2) & 223 (5.4)*** & 1,610 (10.9) & 11 (3.2)***\\ \hline Circulatory complications & 7,503 (5.9) & 129 (3.1)*** & 850 (5.7) & \leq 10 (\leq 2.9)*\\ \hline \textbf{Medication} & & & & & & & & & & & & & & & & & & &$ | Chronic kidney disease | 14,841 (11.8) | 253 (6.1)*** | 1,261 (8.5) | 15 (4.3)** |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Anemia | 10,552 (8.4) | 181 (4.4)*** | 822 (5.5) | ≤10 (≤ 2.9)† |
| Neoplasms 19,460 (15.5) 227 (5.5)*** 2,166 (14.6) 16 (4.6)*** Systemic connective tissue disorders 2,124 (1.7) 17 (0.4)*** 248 (1.7) $\leq 10 \leq 2.9$)† Rheumatoid arthritis 632 (0.5) $\leq 10 \leq 0.2$)† 74 (0.5) $\leq 10 \leq 2.9$)† HIV disease 895 (0.7) $\leq 10 \leq 0.2$)† 53 (0.4) 0 (0.0) Dementia 614 (0.5) 17 (0.4) 36 (0.2) 0 (0.0) Diabetic complications 13,700 (10.8) 302 (7.3)*** 1,281 (8.6) 15 (4.3)*** Ophthalmic complications 6,015 (4.8) 77 (1.9)*** 699 (4.7) $\leq 10 \leq 2.9$)† Neurological complications 14,143 (11.2) 223 (5.4)*** 1,610 (10.9) 11 (3.2)*** Circulatory complications 7,503 (5.9) 129 (3.1)*** 850 (5.7) $\leq 10 \leq 2.9$)† SES and psychosocial-related hazards 4,019 (3.2) 58 (1.4)*** 322 (2.2) $\leq 10 \leq 2.9$)† Medication HMG CoA reductase inhibitors 55,876 (44.5) 1,274 (30.8)*** 5,530 (37.3) 79 (22.6)*** Fibrates 3,715 (3.0) 93 (| Inflammatory liver diseases | 2,064 (1.6) | 17 (0.4)*** | 308 (2.1) | ≤10 (≤ 2.9)† |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | Liver cirrhosis | 2,241 (1.8) | 26 (0.6)*** | 259 (1.7) | 0 (0.0)* |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$ | Neoplasms | 19,460 (15.5) | 227 (5.5)*** | 2,166 (14.6) | 16 (4.6)*** |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Systemic connective tissue disorders | 2,124 (1.7) | 17 (0.4)*** | 248 (1.7) | ≤10 (≤ 2.9)† |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Rheumatoid arthritis | 632 (0.5) | ≤10 (≤ 0.2)† | 74 (0.5) | ≤10 (≤ 2.9)† |
| $\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$ | HIV disease | 895 (0.7) | ≤10 (≤ 0.2)† | 53 (0.4) | 0 (0.0) |
| Kidney complications $13,700 (10.8)$ $302 (7.3)^{***}$ $1,281 (8.6)$ $15 (4.3)^{***}$ Ophthalmic complications $6,015 (4.8)$ $77 (1.9)^{***}$ $699 (4.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ Neurological complications $14,143 (11.2)$ $223 (5.4)^{***}$ $1,610 (10.9)$ $11 (3.2)^{***}$ Circulatory complications $7,503 (5.9)$ $129 (3.1)^{***}$ $850 (5.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SES and psychosocial-related hazards $4,019 (3.2)$ $58 (1.4)^{***}$ $322 (2.2)$ $\leq 10 (\leq 2.9)^{\dagger}$ Medication HMG CoA reductase inhibitors $55,876 (44.5)$ $1,274 (30.8)^{***}$ $5,530 (37.3)$ $79 (22.6)^{***}$ Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ 84 | Dementia | 614 (0.5) | 17 (0.4) | 36 (0.2) | 0 (0.0) |
| $\begin{array}{ c c c c c c }\hline Ophthalmic complications & 6,015 (4.8) & 77 (1.9)^{***} & 699 (4.7) & \leq 10 (\leq 2.9)^{\dagger} \\\hline Neurological complications & 14,143 (11.2) & 223 (5.4)^{***} & 1,610 (10.9) & 11 (3.2)^{***} \\\hline Circulatory complications & 7,503 (5.9) & 129 (3.1)^{***} & 850 (5.7) & \leq 10 (\leq 2.9)^{\dagger} \\\hline SES and psychosocial-related hazards & 4,019 (3.2) & 58 (1.4)^{***} & 322 (2.2) & \leq 10 (\leq 2.9)^{\dagger} \\\hline \textbf{Medication} \\\hline HMG CoA reductase inhibitors & 55,876 (44.5) & 1,274 (30.8)^{***} & 5,530 (37.3) & 79 (22.6)^{***} \\\hline Fibrates & 3,715 (3.0) & 93 (2.2)^{**} & 461 (3.1) & \leq 10 (\leq 2.9)^{\dagger} \\\hline Ezetimibe & 3,536 (2.8) & 61 (1.5)^{***} & 427 (2.9) & \leq 10 (\leq 2.9)^{\dagger} \\\hline Biguanides & 54,056 (43.1) & 1,184 (28.6)^{***} & 5,449 (36.7) & 74 (21.2)^{***} \\\hline Sulfonylureas & 17,517 (14.0) & 426 (10.3)^{***} & 1,397 (9.4) & 23 (6.6) \\\hline DPP-4 inhibitors & 10,329 (8.2) & 228 (5.5)^{***} & 842 (5.7) & 14 (4.0) \\\hline Thiazolidinediones & 3,565 (2.8) & 87 (2.1)^{**} & 393 (2.7) & \leq 10 (\leq 2.9)^{\dagger} \\\hline SGLT2 inhibitors & 19,843 (15.8) & 477 (11.5)^{***} & 2,544 (17.2) & 31 (8.9)^{***} \\\hline \end{array}$ | Diabetic complications | | | | |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Kidney complications | 13,700 (10.8) | 302 (7.3)*** | 1,281 (8.6) | 15 (4.3)*** |
| Circulatory complications $7,503 (5.9)$ $129 (3.1)^{***}$ $850 (5.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SES and psychosocial-related hazards $4,019 (3.2)$ $58 (1.4)^{***}$ $322 (2.2)$ $\leq 10 (\leq 2.9)^{\dagger}$ Medication HMG CoA reductase inhibitors $55,876 (44.5)$ $1,274 (30.8)^{***}$ $5,530 (37.3)$ $79 (22.6)^{***}$ Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{***}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Ophthalmic complications | 6,015 (4.8) | 77 (1.9)*** | 699 (4.7) | ≤10 (≤ 2.9)† |
| SES and psychosocial-related hazards $4,019 (3.2)$ $58 (1.4)^{***}$ $322 (2.2)$ $\leq 10 (\leq 2.9)^{\dagger}$ Medication HMG CoA reductase inhibitors $55,876 (44.5)$ $1,274 (30.8)^{***}$ $5,530 (37.3)$ $79 (22.6)^{***}$ Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{**}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Neurological complications | 14,143 (11.2) | 223 (5.4)*** | 1,610 (10.9) | 11 (3.2)*** |
| Medication HMG CoA reductase inhibitors $55,876 (44.5)$ $1,274 (30.8)^{***}$ $5,530 (37.3)$ $79 (22.6)^{***}$ Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{**}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Circulatory complications | 7,503 (5.9) | 129 (3.1)*** | 850 (5.7) | $\leq 10 \ (\leq 2.9)^{\dagger}$ |
| HMG CoA reductase inhibitors $55,876 (44.5)$ $1,274 (30.8)^{***}$ $5,530 (37.3)$ $79 (22.6)^{***}$ Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{**}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | SES and psychosocial-related hazards | 4,019 (3.2) | 58 (1.4)*** | 322 (2.2) | ≤10 (≤ 2.9)† |
| Fibrates $3,715 (3.0)$ $93 (2.2)^{**}$ $461 (3.1)$ $\leq 10 (\leq 2.9)^{\dagger}$ Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{**}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Medication | | | | |
| Ezetimibe $3,536 (2.8)$ $61 (1.5)^{***}$ $427 (2.9)$ $\leq 10 (\leq 2.9)^{\dagger}$ Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{***}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{****}$ | HMG CoA reductase inhibitors | 55,876 (44.5) | 1,274 (30.8)*** | 5,530 (37.3) | 79 (22.6)*** |
| Biguanides $54,056 (43.1)$ $1,184 (28.6)^{***}$ $5,449 (36.7)$ $74 (21.2)^{***}$ Sulfonylureas $17,517 (14.0)$ $426 (10.3)^{***}$ $1,397 (9.4)$ $23 (6.6)$ DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{***}$ $393 (2.7)$ $\le 10 (\le 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Fibrates | 3,715 (3.0) | 93 (2.2)** | 461 (3.1) | $\leq 10 \ (\leq 2.9)^{\dagger}$ |
| Sulfonylureas 17,517 (14.0) 426 (10.3)*** 1,397 (9.4) 23 (6.6) DPP-4 inhibitors 10,329 (8.2) 228 (5.5)*** 842 (5.7) 14 (4.0) Thiazolidinediones 3,565 (2.8) 87 (2.1)** 393 (2.7) $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors 19,843 (15.8) 477 (11.5)*** 2,544 (17.2) 31 (8.9)*** | Ezetimibe | 3,536 (2.8) | 61 (1.5)*** | 427 (2.9) | $\leq 10 \ (\leq 2.9)^{\dagger}$ |
| DPP-4 inhibitors $10,329 (8.2)$ $228 (5.5)^{***}$ $842 (5.7)$ $14 (4.0)$ Thiazolidinediones $3,565 (2.8)$ $87 (2.1)^{**}$ $393 (2.7)$ $\leq 10 (\leq 2.9)^{\dagger}$ SGLT2 inhibitors $19,843 (15.8)$ $477 (11.5)^{***}$ $2,544 (17.2)$ $31 (8.9)^{***}$ | Biguanides | 54,056 (43.1) | 1,184 (28.6)*** | 5,449 (36.7) | 74 (21.2)*** |
| Thiazolidinediones 3,565 (2.8) 87 (2.1)** 393 (2.7) ≤10 (≤ 2.9)† SGLT2 inhibitors 19,843 (15.8) 477 (11.5)*** 2,544 (17.2) 31 (8.9)*** | Sulfonylureas | 17,517 (14.0) | 426 (10.3)*** | 1,397 (9.4) | 23 (6.6) |
| SGLT2 inhibitors 19,843 (15.8) 477 (11.5)*** 2,544 (17.2) 31 (8.9)*** | DPP-4 inhibitors | 10,329 (8.2) | 228 (5.5)*** | 842 (5.7) | 14 (4.0) |
| | Thiazolidinediones | 3,565 (2.8) | 87 (2.1)** | 393 (2.7) | ≤10 (≤ 2.9) [†] |
| 11 | SGLT2 inhibitors | 19,843 (15.8) | 477 (11.5)*** | 2,544 (17.2) | 31 (8.9)*** |
| insuins 34,311 (27.3) 956 (23.1)*** 3,870 (26.1) 39 (11.2)*** | Insulins | 34,311 (27.3) | 956 (23.1)*** | 3,870 (26.1) | 39 (11.2)*** |

| Beta blockers | 31,563 (25.2) | 676 (16.3)*** | 3,082 (20.8) | 32 (9.2)*** |
|----------------------------------|---------------|----------------|--------------|-----------------|
| ACE inhibitors | 25,812 (20.6) | 613 (14.8)*** | 2,871 (19.4) | 42 (12.0)*** |
| Angiotensin II receptor blockers | 27,153 (21.6) | 552 (13.3)*** | 2,628 (17.7) | 28 (8.0)*** |
| Diuretics | 35,796 (28.5) | 771 (18.6)*** | 3,775 (25.5) | 45 (12.9)*** |
| Calcium channel blockers | 24,569 (19.6) | 528 (12.8)*** | 2,298 (15.5) | 26 (7.4)*** |
| Laboratory tests, mean (SD) | | | | |
| Hemoglobin A1c, % | 8.01 (1.95) | 8.39 (2.18)*** | 7.66 (1.82) | 8.26 (2.26)*** |
| Hemoglobin, mg/dL | 13.4 (1.9) | 13.3 (2.1) | 13.7 (1.8) | 14.1 (1.6)* |
| eGFR, mL/min/1.73m ² | 80.3 (27.7) | 83.1 (30.3)*** | 81.4 (24.9) | 87.8 (25.6)*** |
| SBP, mmHg | 131.8 (17.9) | 132.0 (9.1) | 131.4 (17.1) | 130.0 (14.9) |
| LDL cholesterol, mg/dL | 92.3 (38.6) | 98.4 (38.9)*** | 92.9 (37.3) | 103.1 (38.4)*** |
| Total cholesterol, mg/dL | 169.3 (49.2) | 172.0 (50.3) | 169.0 (50.8) | 173.2 (48.4) |
| BMI, kg/m ² | 34.8 (6.7) | 35.0 (6.8) | 36.7 (6.2) | 36.7 (6.3) |

^{*:} p <0.05, **: p <0.01, ***: p <0.001 compared with the included group.

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; HMG CoA, hydroxymethylglutaryl-CoA; LDL, low-density lipoprotein; SD, standard deviation; SES, socioeconomic status; SGLT2, sodium-glucose cotransporter 2.

[†]Patient counts for rare circumstances or diseases are obfuscated up to 10 by the database platform to safeguard protected health information that could lead to identification of certain individuals.

eTable 5. Adjusted Hazard Ratios for the Components of Major Adverse Cardiovascular and Kidney Events

| | No. of patients | s with outcome | A directed begand | | |
|--------------------------------|--|----------------|-------------------------------------|-----------------|--|
| Outcomes | Tirzepatide GLP-1 RA (n=14,832) (n=14,832) | | - Adjusted hazard ratio (95% CI) | <i>p</i> -value | |
| Major adverse cardiovascular e | vents | | | | |
| Myocardial infarction | 230 | 286 | 0.81 (0.68–0.97) | 0.02 | |
| Ischemic/hemorrhagic stroke | 284 | 363 | 0.78 (0.67–0.91) | 0.002 | |
| Cardiac death | 33 | 36 | 0.91 (0.56–1.45) | 0.68 | |
| Major adverse kidney events | | | | | |
| Stage 5 chronic kidney disease | 16 | 35 | 0.45 (0.25–0.82) | 0.01 | |
| End-stage renal disease | 55 | 111 | 0.49 (0.35–0.67) | < 0.001 | |

Abbreviations: CI, confidence interval; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists.

eTable 6. Sensitivity Analysis Incorporating Individuals Without Follow-Up Into Propensity Score Matching and Survival Analysis of Primary and Secondary Outcomes

| Outcomes | Main analy | ysis | Sensitivity analysis | |
|---|------------------|-----------------|----------------------|-----------------|
| Outcomes | aHR (95%CI) | <i>p</i> -value | aHR (95%CI) | <i>p</i> -value |
| No. of patients in each group, post-PSM | 14,832 | | 15,181 | |
| Primary outcome | | | | |
| All-cause mortality | 0.58 (0.45–0.75) | < 0.001 | 0.52 (0.40–0.67) | < 0.001 |
| Secondary outcomes | | | | |
| MACE | 0.80 (0.71-0.91) | < 0.001 | 0.83 (0.73-0.93) | < 0.001 |
| MACE and all-cause mortality | 0.76 (0.68–0.84) | < 0.001 | 0.75 (0.67–0.84) | < 0.001 |
| Kidney events | 0.52 (0.37-0.73) | < 0.001 | 0.53 (0.38–0.74) | < 0.001 |
| AKI | 0.78 (0.70-0.88) | < 0.001 | 0.82 (0.73–0.92) | < 0.001 |
| MAKE | 0.54 (0.44–0.67) | < 0.001 | 0.51 (0.41–0.64) | < 0.001 |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events; PSM, propensity score matching.

eTable 7. Changes in Mean Glycated Hemoglobin Level and Body Weight (95% CI)

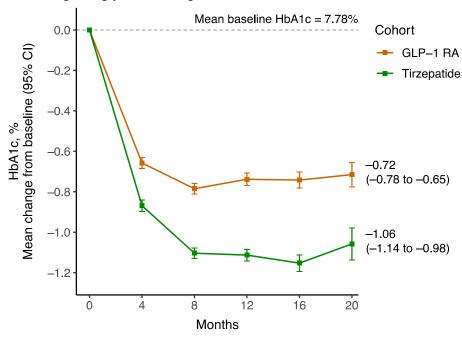
| Times | Glycated hemog | globin level, % | Body weight, kg | | |
|-----------|------------------------|-------------------------|--------------------------------------|---------------------|--|
| points | Tirzepatide | GLP-1 RA | Tirzepatide | GLP-1 RA | |
| 4 months | -0.87 (-0.90 to -0.84) | -0.66 (-0.69 to -0.63) | -2.8 (-3.1 to -2.5) | -1.5 (-1.8 to -1.2) | |
| 8 months | -1.10 (-1.13 to -1.08) | -0.78 (-0.81 to -0.76) | -5.6 (-6.0 to -5.3) | -3.2 (-3.5 to -2.8) | |
| 12 months | -1.11 (-1.14 to -1.08) | -0.74 (-0.77 to -0.71) | -7.3 (-7.9 to -6.8) | -4.5 (-5.0 to -4.0) | |
| 16 months | -1.15 (-1.20 to -1.11) | -0.74 (-0.78 to -0.70) | -9.1 (-10.0 to -8.2) | -6.5 (-7.4 to -5.7) | |
| 20 months | -1.06 (-1.14 to -0.98) | -0.72 (-0.78 to -0.65) | -9.8 (-11.1 to -8.4) | -6.8 (-8.1 to -5.5) | |
| TD* | -0.34 (-0.44 to | −0.24), <i>p</i> <0.001 | −2.9 (−4.8 to −1.1), <i>p</i> =0.002 | | |

^{*} Mean treatment difference at 20 months (95% CI).

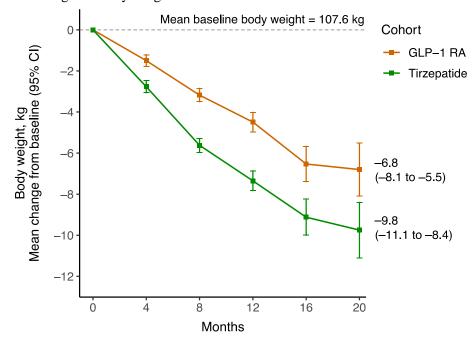
Abbreviations: CI, confidence interval; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists.

eFigure 1. Changes in Glycated Hemoglobin Level and Body Weight From Baseline

1A. Changes in glycated hemoglobin level



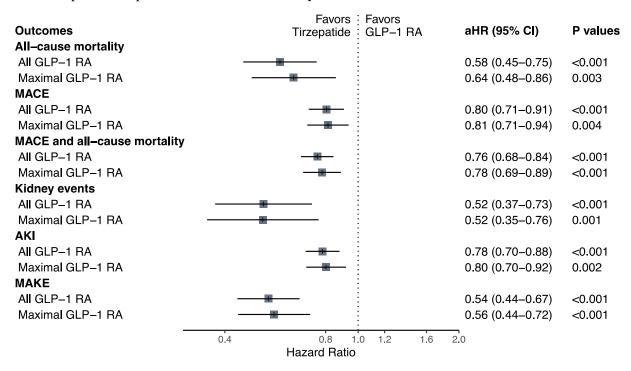
1B. Changes in body weight



Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

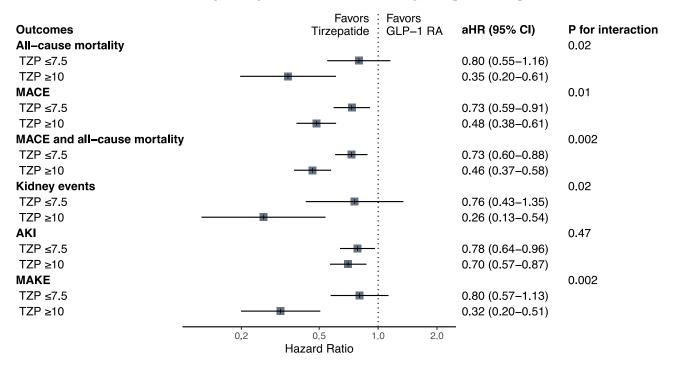
eFigure 2. Forest Plot of Primary and Secondary Outcomes Compared Between Different Doses of Tirzepatide and GLP-1 RA

2A. Tirzepatide compared to all GLP-1 RA or only those who received the maximal doses of GLP-1 RA



Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; 95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events.

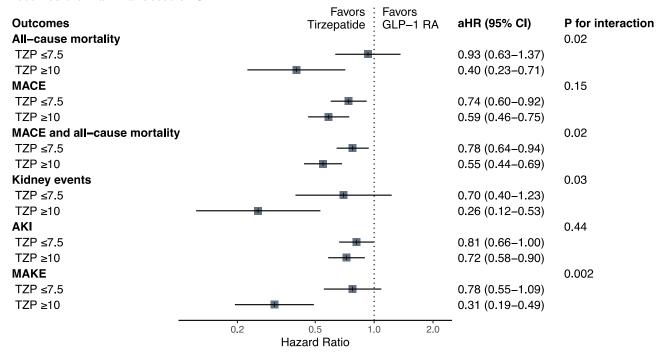
2B. Low-dose (maximum ≤7.5 mg) or high-dose (maximum ≥10 mg) tirzepatide compared to all GLP-RA



Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; 95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events; TZP, tirzepatide.

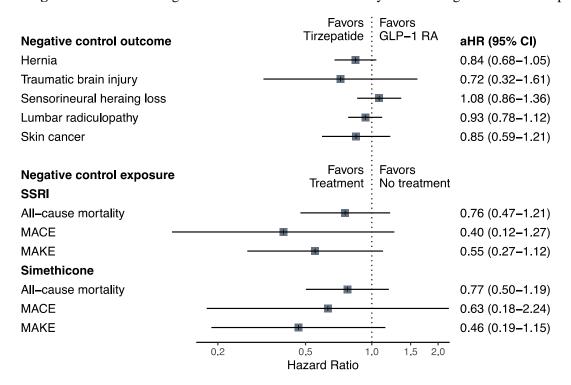
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2C. Low-dose (maximum \leq 7.5 mg) or high-dose (maximum \geq 10 mg) tirzepatide compared to those who received the maximal doses of GLP1-RA



Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; 95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events; TZP, tirzepatide.

eFigure 3. Results for Negative Control Outcomes and Analysis With Negative Control Exposure



Abbreviations: aHR, adjusted hazard ratio; 95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events; SSRI, selective serotonin reuptake inhibitors.

eFigure 4. Subgroup Analysis of All-Cause Mortality Between Tirzepatide and GLP-1 RA Groups

| | Favors Tirzepatide : Favors GLP-1 RA | LID (050(OI) | D |
|-------------------------|---|------------------|-------------------|
| Subgroups | i avois fiizepalide : Favois dei – Fria | (00/004) | P for interaction |
| Overall | | 0.58 (0.45–0.75) | 0.00 |
| eGFR, mL/min/1.73m² | _ : | 0.05 (0.40.000) | 0.80 |
| ≥45 | | 0.65 (0.48–0.89) | |
| <45 | | 0.70 (0.45–1.09) | |
| HbA1c, % | | | 0.09 |
| ≥7 | | 0.86 (0.58–1.29) | |
| <7 | | 0.54 (0.38–0.77) | |
| Hypertension | _ : | , , , | 0.10 |
| HTN (+) | | 0.67 (0.51–0.89) | |
| HTN (–) | : | 0.35 (0.17–0.72) | |
| Ischemic heart diseases | : | | 0.29 |
| IHD (+) | - : | 0.78 (0.52–1.19) | |
| IHD (–) | | 0.59 (0.43–0.82) | |
| Heart failure | <u>:</u> | | 0.67 |
| HF (+) | | 0.74 (0.47–1.16) | |
| HF (–) | | 0.66 (0.48–0.90) | |
| Proteinuria | <u>:</u> | | 0.39 |
| Poteinuria (+) | | 0.45 (0.20–0.98) | |
| Proteinuria (–) | | 0.64 (0.49-0.84) | |
| Metformin | <u>:</u> | | 0.09 |
| Metformin (+) | | 0.94 (0.41-2.19) | |
| Metformin (–) | | 0.43 (0.31-0.60) | |
| Insulin | : | | 0.49 |
| Insulin (+) | | 0.54 (0.39-0.76) | |
| Insulin (–) | | 0.37 (0.14-1.01) | |
| SGLT2i | : | | 0.10 |
| SGLT2i (+) | | 0.84 (0.52-1.34) | |
| SGLT2i (–) | : | 0.53 (0.39-0.71) | |
| ACEi/ARBs | : | , | 0.16 |
| ACEi/ARB (+) | | 0.74 (0.52-1.05) | |
| ACEi/ARB (-) | | 0.51 (0.35-0.75) | |
| Previous GLP-1 RA | : | | 0.36 |
| Ever user | | 0.69 (0.46-1.02) | |
| Never user | | 0.54 (0.39-0.76) | |
| LDL, mg/dL | <u>:</u> | | 0.39 |
| ≥160 | | 0.79 (0.21-2.94) | |
| 100–160 | | 0.47 (0.26-0.83) | |
| <100 | | 0.74 (0.53-1.02) | |
| DM complications | <u>:</u> | | 0.31 |
| Complicaitons (+) | ; | 0.65 (0.48-0.87) | |
| Complications (–) | | 0.48 (0.30-0.77) | |
| BMI, kg/m² | : | , | 0.36 |
| ≥30 | | 0.63 (0.47-0.85) | |
| <30 | : | 0.46 (0.25-0.85) | |
| Indication | : | , | 0.96 |
| For DM | | 0.62 (0.41-0.95) | |
| For OW/OB | | 0.57 (0.34–0.95) | |
| For both | - | 0.62 (0.39–0.98) | |
| | · · · · · · · · · · · · · · · · · · · | _ | |
| | 0.2 0.5 1.0 2.0 3.0 | | |
| | Hazard Ratio | | |

eFigure 5. Subgroup Analysis of Major Adverse Cardiovascular Events Between Tirzepatide and GLP-1 RA Groups

| Subgroups | Favors Tirzepatide : Favors G | LP–1 RA aHR (95% CI) | P for interaction |
|---------------------------------|-------------------------------|--------------------------------------|--------------------|
| Overall | | 0.80 (0.71–0.91) | r ioi iiiteraction |
| eGFR, mL/min/1.73m ² | | 0.80 (0.71-0.91) | 0.06 |
| ≥45 | | 0.75 (0.66–0.86) | 0.00 |
| <45 | <u> </u> | 1.02 (0.77–1.35) | |
| HbA1c, % | : | 1.02 (0.77=1.55) | 0.34 |
| nbarc, % ≥7 | | 0.91 (0.75–1.09) | 0.34 |
| <7 | | 0.80 (0.68–0.94) | |
| Hypertension | - | 0.80 (0.08–0.94) | 0.37 |
| | | 0.80 (0.70, 0.01) | 0.57 |
| HTN (+) HTN (–) | | 0.80 (0.70–0.91) 0.67 (0.47–0.95) | |
| Ischemic heart diseases | - | 0.67 (0.47=0.93) | 0.49 |
| IHD (+) | <u>-</u> : | 0.86 (0.73-1.02) | 0.49 |
| • • | | 0.79 (0.65–0.95) | |
| IHD (–) Heart failure | - : | 0.79 (0.05–0.95) | 0.11 |
| | | 0.89 (0.70–1.13) | 0.11 |
| HF (+) | | 0.89 (0.70-1.13) | |
| HF (–) Proteinuria | | 0.71 (0.62–0.62) | 0.70 |
| | | 0.90 (0.59, 1.11) | 0.72 |
| Poteinuria (+) | | 0.80 (0.58–1.11) | |
| Proteinuria (–) | | 0.75 (0.66–0.85) | 0.74 |
| Metformin | _ | 0.01 (0.07, 0.07) | 0.74 |
| Metformin (+) | | 0.81 (0.67–0.97) | |
| Metformin (–) | : | 0.77 (0.66–0.91) | 0.55 |
| Insulin | _ : | 0.05 (0.70, 0.00) | 0.55 |
| Insulin (+) | | 0.85 (0.73–0.99) | |
| Insulin (–) | : | 0.78 (0.64–0.96) | 0.00 |
| SGLT2i | _ : | 0.77 (0.00 0.00) | 0.82 |
| SGLT2i (+) | | 0.77 (0.62–0.96) | |
| SGLT2i (–) | | 0.79 (0.69–0.92) | 0.40 |
| ACEI/ARBs | _ : | 0 =0 (0 00 0 00) | 0.43 |
| ACEI/ARB (+) | | 0.73 (0.62–0.85) | |
| ACEi/ARB (–) | : | 0.80 (0.66–0.97) | |
| Previous GLP-1 RA | _ : | 0.00 (0.55, 0.00) | 0.16 |
| Ever user | - | 0.66 (0.55–0.80) | |
| Never user | : | 0.79 (0.67–0.92) | |
| LDL, mg/dL | _ | 0 74 (0 00 4 10) | 0.63 |
| ≥160 ← | | 0.71 (0.36–1.40) | |
| 100–160 | | 0.72 (0.54–0.96) | |
| <100 | : | 0.83 (0.72–0.96) | 0.40 |
| DM complications | _ : | 0.00 (0.70, 0.00) | 0.16 |
| Complications (+) | | 0.80 (0.70–0.92) | |
| Complications (–) | - | 0.66 (0.52–0.83) | 0.00 |
| BMI, kg/m² | _ : | 0.00 (0.70 0.00) | 0.69 |
| ≥30 | | 0.80 (0.70–0.92) | |
| <30 | | 0.76 (0.62–0.94) | 0.00 |
| Indication | _ | 0.70 (0.00 0.00) | 0.86 |
| For DM | | 0.79 (0.63–0.99) | |
| For OW/OB | | 0.73 (0.60–0.91) | |
| For both | | 0.79 (0.65–0.96) | |
| 0.4 | 0.8 1.0 1.2 | 1.6 2.0 | |
| | Hazard Ratio | | |

eFigure 6. Subgroup Analysis of the Composite of Major Adverse Cardiovascular Events and All-Cause Mortality Between Tirzepatide and GLP-1 RA Groups

| Subgroups | Favors Tirzepatide | Favors GLP-1 RA | aHR (95% CI) | P for interaction |
|---------------------------------|----------------------------|--|------------------|-------------------|
| Overall | | • | 0.76 (0.68–0.84) | |
| eGFR, mL/min/1.73m ² | | · · | , | 0.57 |
| ≥45 | | • • | 0.72 (0.64-0.82) | |
| <45 | | <u>: </u> | 0.82 (0.55-1.22) | |
| HbA1c, % | | | , | 0.12 |
| ≥7 | | <u>-</u> | 0.89 (0.75-1.06) | |
| <7 | | | 0.75 (0.64–0.87) | |
| Hypertension | | | , | 0.19 |
| HTN (+) | | • | 0.77 (0.68-0.87) | |
| HTN (–) — | - | • • | 0.61 (0.45–0.84) | |
| Ischemic heart diseases | | • • • | , | 0.21 |
| IHD (+) | | • • • | 0.83 (0.71-0.98) | |
| IHD (–) | | | 0.72 (0.61–0.85) | |
| Heart failure | | | , | 0.12 |
| HF (+) | | : | 0.85 (0.68-1.05) | |
| HF (–) | | | 0.69 (0.61–0.79) | |
| Proteinuria | | • | , | 0.80 |
| Poteinuria (+) | - | ! | 0.75 (0.55-1.02) | |
| Proteinuria (–) | | • • • | 0.72 (0.64–0.81) | |
| Metformin | | • | , | 0.30 |
| Metformin (+) | | | 0.79 (0.67-0.93) | |
| Metformin (–) | | | 0.70 (0.60-0.81) | |
| Insulin | | | , | 0.80 |
| Insulin (+) | | | 0.79 (0.69-0.91) | |
| Insulin (–) | - | • • | 0.82 (0.68-0.99) | |
| SGLT2i | | • | , | 0.81 |
| SGLT2i (+) | | | 0.77 (0.63-0.94) | |
| SGLT2i (–) | | • • | 0.75 (0.65–0.85) | |
| ACEi/ARBs | | | , | 0.74 |
| ACEi/ARB (+) | | | 0.71 (0.61-0.82) | |
| ACEi/ARB (–) | | | 0.74 (0.62-0.87) | |
| Previous GLP-1 RA | | • | , | 0.28 |
| Ever user | | | 0.65 (0.55-0.77) | |
| Never user | | • • • | 0.73 (0.63-0.84) | |
| LDL, mg/dL | | • • • | | 0.53 |
| ≥160 | 1 | <u>:</u> : | 0.79 (0.43-1.46) | |
| 100–160 | | | 0.68 (0.52-0.88) | |
| <100 | - | • • • | 0.81 (0.70-0.92) | |
| DM complications | | • | | 0.09 |
| Complicaitons (+) | - | • • • | 0.76 (0.67-0.86) | |
| Complications (-) | | • | 0.61 (0.49-0.76) | |
| BMI, kg/m² | | • | | 0.42 |
| ≥30 | - | | 0.77 (0.68-0.88) | |
| <30 | - | | 0.70 (0.58-0.86) | |
| Indication | | • • | | 0.87 |
| For DM | | • | 0.76 (0.62-0.92) | |
| For OW/OB | | • • • | 0.72 (0.59-0.88) | |
| For both | | • • • | 0.78 (0.65-0.93) | |
| 0.4 | 00 4 | .0 1.2 1.6 2 | 2.0 | |
| 0.4 | 0.8 1 Hazard R a | .0 1.2 1.6 2 | 2.0 | |
| | Hazaiu Ni | auo | | |

eFigure 7. Subgroup Analysis of Kidney Events Between Tirzepatide and GLP-1 RA Groups

| Subgroups | Favors Tirzepatide : | Favors GI P-1 BA | aHR (95% CI) | P for interaction |
|---------------------------------|----------------------|------------------|--|----------------------|
| Overall | | | 0.52 (0.37–0.73) | P IOI IIILEI ACLIOII |
| | | | 0.52 (0.57-0.73) | 0.50 |
| eGFR, mL/min/1.73m ² | _ | | 0.47 (0.00, 0.77) | 0.53 |
| ≥45 | | | 0.47 (0.29–0.77) | |
| <45 | | | 0.58 (0.38–0.89) | 0.00 |
| HbA1c, % | _ | | 0.44 (0.05.0.70) | 0.90 |
| ≥7 | | | 0.44 (0.25–0.76) | |
| <7 | | | 0.46 (0.31–0.68) | 0.07 |
| Hypertension | _ | | 0.04 (0.40, 0.07) | 0.67 |
| HTN (+) | | | 0.61 (0.43–0.87) | |
| HTN (-) - | • | | 0.46 (0.14–1.54) | 0.00 |
| Ischemic heart diseases | _ | | (- (- (- (- () | 0.28 |
| IHD (+) | _ | | 0.79 (0.47–1.31) | |
| IHD (–) | • | = | 0.47 (0.21–1.04) | |
| Heart failure | | | | 0.11 |
| HF (+) | | + | 1.05 (0.58–1.90) | |
| HF (–) | | | 0.58 (0.38–0.89) | |
| Proteinuria | | | | 0.92 |
| Poteinuria (+) | | | 0.52 (0.27-0.99) | |
| Proteinuria (–) | - | | 0.50 (0.34-0.73) | |
| Metformin | | | | 0.18 |
| Metformin (+) | | | 0.72 (0.42-1.22) | |
| Metformin (–) | | | 0.45 (0.29-0.69) | |
| Insulin | | | , | 0.44 |
| Insulin (+) | | | 0.54 (0.36-0.82) | |
| Insulin (–) | - | | 0.73 (0.40–1.34) | |
| SGLT2i É | : | | , | 0.16 |
| SGLT2i (+) | | | 0.89 (0.49-1.63) | |
| SGLT2i (–) | | | 0.53 (0.35-0.80) | |
| ACEi/ARBs | | | (1100 (1100 1100) | 0.90 |
| ACEi/ARB (+) | | | 0.57 (0.36-0.89) | |
| ACEi/ARB (–) | | | 0.54 (0.33–0.89) | |
| Previous GLP-1 RA | | | (, , , , , , , , , , , , , , , , , , , | 0.09 |
| Ever user | | | 0.33 (0.18-0.59) | |
| Never user | | | 0.61 (0.41–0.92) | |
| LDL, mg/dL | : | | (| 0.70 |
| ≥160 ← | | | 0.43 (0.08-2.19) | |
| 100–160 | | | 0.52 (0.22–1.22) | |
| <100 | | _ | 0.71 (0.46–1.11) | |
| DM complications | _ : | | | 0.07 |
| Complications (+) | | | 0.60 (0.42-0.84) | |
| Complications (–) | | | 0.15 (0.03–0.65) | |
| BMI, kg/m ² | | | 0.10 (0.00 0.00) | 0.08 |
| ≥30 | | | 0.59 (0.41–0.86) | 0.00 |
| <30 | | | 0.31 (0.17–0.58) | |
| Indication | - | | 3.31 (3.17 3.33) | 0.76 |
| For DM | | | 0.49 (0.26–0.93) | 0.70 |
| For OW/OB | | | 0.44 (0.26–0.73) | |
| For both | | | 0.58 (0.34–0.98) | |
| | • | | · · · · · · · · · · · · · · · · · · · | |
| | 0.2 0.5 1. | | | |
| | Hazard Ration | ס | | |

eFigure 8. Subgroup Analysis of Acute Kidney Injury Between Tirzepatide and GLP-1 RA Groups

| Subgroups | Favors Tirzepatide | : Favors GLP-1 RA | aHR (95% CI) | P for interaction |
|--------------------------------------|--------------------|--|-------------------|--------------------|
| Overall | | : | 0.78 (0.70–0.88) | r ioi iiiteraction |
| eGFR, mL/min/1.73m ² | _ | • • • | 0.70 (0.70 0.00) | 0.46 |
| ≥45 | | | 0.74 (0.65–0.85) | 0.40 |
| <45 | | | 0.81 (0.67–0.99) | |
| HbA1c, % | _ | · · | 0.01 (0.07 0.00) | 0.09 |
| ≥7 | | <u>:</u> | 0.89 (0.74-1.07) | 0.00 |
| <7 | | • • • | 0.72 (0.62–0.85) | |
| Hypertension | _ | • | 0112 (0102 0100) | 0.59 |
| HTN (+) | | | 0.76 (0.67-0.86) | 0.00 |
| HTN (–) | | <u>: </u> | 0.84 (0.58–1.23) | |
| Ischemic heart diseases | | · · | , | 0.46 |
| IHD (+) | | • • • | 0.77 (0.63-0.93) | |
| IHD (–) | | | 0.84 (0.72–0.97) | |
| Heart failure | | | , | 0.95 |
| HF (+) | | • • | 0.80 (0.64-0.98) | |
| HF (–) | | • • | 0.80 (0.70-0.93) | |
| Proteinuria | | • | | 0.23 |
| Poteinuria (+) | - | • | 0.71 (0.55-0.92) | |
| Proteinuria (–) | - | | 0.85 (0.74-0.97) | |
| Metformin | | | | 0.33 |
| Metformin (+) | | | 0.80 (0.67–0.97) | |
| Metformin (–) | | | 0.72 (0.62–0.83) | |
| Insulin | | • | | 0.58 |
| Insulin (+) | - | <u>:</u> : | 0.91 (0.74–1.12) | |
| Insulin (–) | | | 0.99 (0.80-1.23) | |
| SGLT2i | | · · | | 0.18 |
| SGLT2i (+) | | <u>. </u> | 0.91 (0.67–1.24) | |
| SGLT2i (–) | | | 0.72 (0.62–0.83) | |
| ACEI/ARBs | _ | | 0 (0 0- 0 0-) | 0.48 |
| ACEi/ARB (+) | | • | 0.75 (0.65–0.87) | |
| ACEi/ARB (–) | | | 0.82 (0.67–0.99) | 0.00 |
| Previous GLP-1 RA | | | 0.77 (0.04, 0.00) | 0.88 |
| Ever user | | | 0.77 (0.64–0.92) | |
| Never user | | | 0.75 (0.65–0.88) | 0.05 |
| LDL , mg/dL ≥160 —— | | • • • | 0.86 (0.44–1.69) | 0.95 |
| 100–160 | | <u>: </u> | 0.82 (0.63–1.07) | |
| <100 | | | 0.83 (0.72–0.95) | |
| DM complications | | | 0.63 (0.72-0.93) | 0.73 |
| Complications (+) | | | 0.74 (0.65–0.84) | 0.75 |
| Complications (+) | | | 0.74 (0.65–0.04) | |
| BMI, kg/m² | _ | • | 0.70 (0.00 1.01) | 0.60 |
| ≥30 | | | 0.73 (0.64-0.83) | 5.00 |
| <30 | | | 0.68 (0.56–0.83) | |
| Indication | _ | | 1.00 (0.00 0.00) | 0.25 |
| For DM | | · · · | 0.82 (0.68-0.99) | .— - |
| For OW/OB | | • • | 0.75 (0.62–0.92) | |
| For both | | | 0.95 (0.78–1.16) | |
| | | · | _ | |
| 0.4 | | | 2.0 | |
| | Hazard Ra | สแบ | | |

eFigure 9. Subgroup Analysis of Major Adverse Kidney Events Between Tirzepatide and GLP-1 RA Groups

| Subarauna | Favors Tirzenatide | : Favors GLP-1 RA | aHR (95% CI) | P for interaction |
|---------------------------------|---------------------|-------------------|---|----------------------|
| Subgroups Overall | | | 0.54 (0.44–0.67) | P IOI IIILEI ACLIOII |
| eGFR, mL/min/1.73m ² | | | 0.54 (0.44-0.07) | 0.74 |
| ≥45 | | | 0.58 (0.44–0.77) | 0.74 |
| <45 | | | 0.61 (0.44–0.86) | |
| HbA1c, % | _ | | 0.01 (0.11 0.00) | 0.11 |
| ≥7 | | • | 0.68 (0.48-0.95) | 0.11 |
| <7 | | | 0.47 (0.35–0.62) | |
| Hypertension | | | , (, , , , , , , , , , , , , , , , , , | 0.07 |
| HTN (+) | - | | 0.66 (0.52-0.84) | |
| HTN (–) — | - | : | 0.35 (0.18–0.68) | |
| Ischemic heart diseases | | | , | 0.09 |
| IHD (+) | | <u>-</u> | 0.78 (0.55-1.12) | |
| IHD (–) | | | 0.43 (0.24-0.77) | |
| Heart failure | | • | | 0.22 |
| HF (+) | | : | 0.84 (0.56-1.25) | |
| HF (–) | | | 0.62 (0.47-0.81) | |
| Proteinuria | | | | 0.74 |
| Poteinuria (+) | - | | 0.51 (0.31–0.86) | |
| Proteinuria (–) | | | 0.56 (0.45–0.72) | |
| Metformin | | | | 0.12 |
| Metformin (+) | - | ! | 0.73 (0.52–1.03) | |
| Metformin (–) | | | 0.44 (0.25–0.76) | |
| Insulin | | | | 0.87 |
| Insulin (+) | | • • | 0.51 (0.39–0.68) | |
| Insulin (–) | | | 0.55 (0.24–1.26) | |
| SGLT2i | _ | • | 0.00 (0.04 4.04) | 0.75 |
| SGLT2i (+) | | | 0.62 (0.24–1.61) | |
| SGLT2i (–) | | | 0.53 (0.40–0.68) | 0.00 |
| ACE:/ARBs | | : | 0.60 (0.51, 0.01) | 0.20 |
| ACE:/ARB (+) | | | 0.68 (0.51–0.91) | |
| ACEi/ARB (-) Previous GLP-1 RA | | | 0.51 (0.37–0.71) | 0.70 |
| Ever user | | | 0.50 (0.36–0.71) | 0.70 |
| Never user | | • • | 0.55 (0.42–0.72) | |
| LDL, mg/dL | _ | | 0.00 (0.42-0.72) | 0.34 |
| ≥160 | | | 0.73 (0.23–2.30) | 0.07 |
| 100–160 | | | 0.46 (0.28–0.76) | |
| <100 | | • | 0.70 (0.53–0.93) | |
| DM complications | _ | | 0170 (0100 0100) | 0.23 |
| Complications (+) | | | 0.59 (0.46-0.76) | 5.25 |
| Complications (–) | | | 0.43 (0.28–0.68) | |
| BMI, kg/m² | | • • • | , | 0.39 |
| ≥30 | - | | 0.62 (0.48-0.79) | |
| <30 | | | 0.49 (0.30-0.79) | |
| Indication | | | . , | 0.83 |
| For DM | | | 0.53 (0.36-0.78) | |
| For OW/OB | | • | 0.52 (0.36–0.77) | |
| For both | - | | 0.61 (0.42–0.88) | |
| 0.2 | 2 0.5 1 | .0 2.0 3.0 | _ | |
| 0.2 | 2 0.5 1 Hazard R | | | |
| | ΠαζαΙΟΤί | ano | | |