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Glucagon-Like Peptide 1 Receptor Agonists, Mortality, and Cardiovascular Outcomes in Serious Mental Illness

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IMPORTANCE Bipolar disorder, major depressive disorder, and schizophrenia are associated with substantial excess mortality, principally from cardiovascular disease. Identifying strategies to reduce this burden is a critical psychiatric priority.

OBJECTIVE To evaluate associations between initiation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) vs sodium-glucose cotransporter-2 (SGLT2) inhibitors and all-cause mortality and major adverse cardiovascular events (MACEs) among adults with and without serious mental illness (SMI).

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective target trial emulation within the TriNetX Analytics Network, a multinational federated electronic health record network. Adults initiating GLP-1 RAs or SGLT2 inhibitors were included using a new-user, active-comparator design with propensity score matching and separate psychiatric and nonpsychiatric cohorts. The study included all available data in the TriNetX network through the most recent database refresh. Data were queried and analyzed in March 2026, with prespecified follow-up intervals of 1, 4, and 10 years. Additional subgroup analyses were conducted following peer review in May 2026.

EXPOSURE First-recorded GLP-1 RA vs SGLT2 inhibitor prescription.

MAIN OUTCOMES AND MEASURES The primary outcome was 4-year all-cause mortality; the key secondary outcome, 1-year mortality. Additional outcomes included 3- and 5-point MACEs and individual cardiovascular end points. Sensitivity analyses included diabetes stratification, exclusion of baseline heart failure and chronic kidney disease, and censoring at crossover. Exploratory analyses examined SMI subgroups, agent-specific effects, and combination therapy.

RESULTS For the primary 4-year analysis, 1 528 230 adults were propensity score matched (764 115 pairs; 195 184 pairs with serious mental illness [SMI] and 568 931 pairs without SMI). The mean [SD] age in the GLP-1RA and SGLT2 inhibitor groups was 60.5 [12.0] and 60.2 [13.3] years, respectively, in the SMI cohort and 60.9 [12.2] and 60.6 [13.0] years, respectively, in the non-SMI cohort; 112 911 [57.8%], 113 488 [58.1%], 251 679 [44.2%], and 260 480 [45.8%] were female, respectively. Among participants with SMI, mortality was lower with GLP-1RA initiation than with SGLT2 inhibitor initiation (9585 of 195 184 [4.91%] vs 12 584 of 195 184 [6.45%]; hazard ratio [HR], 0.76; 95% CI, 0.74-0.78; absolute risk difference [ARD], −1.54 percentage points; 95% CI, −1.68 to −1.39; $P < .001$). Among participants with SMI and type 2 diabetes, semaglutide initiation, compared with SGLT2 inhibitor initiation, was associated with lower risks of 3-point MACE (HR, 0.77; 95% CI, 0.76-0.79), 5-point MACE, myocardial infarction, stroke, heart failure, and coronary artery bypass grafting. In a separately matched 1-year SMI cohort, mortality was lower with GLP-1RA initiation than with SGLT2 inhibitor initiation (2898 of 198 065; 1.46% vs 5624 of 198 065; 2.84%; RR, 0.52; 95% CI, 0.49-0.54; ARD, −1.38 percentage points; 95% CI, −1.47 to −1.29; $P < .001$). In 10-year exploratory analyses among participants with type 2 diabetes, semaglutide initiation, compared with SGLT2 inhibitor initiation, was associated with lower mortality in the major depressive disorder (RR, 0.55; 95% CI, 0.53-0.56), bipolar disorder (RR, 0.57; 95% CI, 0.51-0.63), and schizophrenia (RR, 0.67; 95% CI, 0.59-0.75) groups (all $P < .001$). The primary mortality association persisted across prespecified sensitivity analyses.

CONCLUSIONS AND RELEVANCE In this study, GLP-1 RA initiation was associated with lower mortality and cardiovascular events compared to SGLT2 inhibitor initiation, with greater absolute reductions in SMI. Benefits were evident within 1 year, consistent across SMI subgroups, and driven by semaglutide and tirzepatide. Prospective randomized trials are warranted.

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Multimedia

Supplemental content

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Persons with bipolar disorder, major depressive disorder, and schizophrenia are differentially affected by cardiovascular disease, which is the leading cause of death among individuals living with these serious mental illnesses (SMIs).[1,2] Life expectancy among individuals with SMI is 10 to 25 years shorter than that of the general population, and cardiovascular disease is the predominant contributor to this excess premature mortality.[3,4] The excess cardiovascular morbidity and mortality in SMI reflects the convergence of elevated cardiometabolic risk factor burden, psychopharmacotherapy-related metabolic effects, and systemic disparities in preventive care delivery, chronic disease screening, and guideline-concordant treatment.[5-10] Narrowing the mortality gap in SMI has emerged as a priority across public health and clinical domains, with growing emphasis on scalable interventions that address both metabolic risk and cardiovascular outcomes.[11,12]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are highly effective for weight reduction and glucose lowering and have multiple additional US Food and Drug Administration-approved indications related to metabolic disease.[13] For example, GLP-1 RAs have been reported to decrease all-cause and cardiovascular mortality in persons with type 2 diabetes.[14,15] In addition to lowering glucose, GLP-1 RAs have demonstrated weight-independent cardiometabolic benefits, including anti-inflammatory, anti-atherogenic, and endothelial-protective effects, that may be of particular relevance in populations with heightened cardiovascular risk.[4,16-18] GLP-1 RAs have also been reported to improve anthropometric and metabolic measures in persons with SMI with comorbid obesity and early-stage metabolic abnormalities and are recommended as strategies to mitigate psychotropic medication-associated weight gain.[19-22]

For example, 3 randomized clinical trials[21-23] provide converging evidence across the spectrum of antipsychotic-associated metabolic risk. In the Semaglutide and Early-Stage Metabolic Abnormalities in Individuals With Schizophrenia Spectrum Disorders (SemaPsychiatry) randomized clinical trial,[23] semaglutide reduced hemoglobin A_{1c} by 0.25 percentage points and body weight by 9.2 kg over 26 weeks during early metabolic dysregulation following clozapine or olanzapine initiation. In the Semaglutide Treatment of Antipsychotic-Treated Patients With Schizophrenia, Prediabetes, and Obesity (HISTORI) randomized clinical trial,[21] semaglutide reduced body weight by 9.21 kg and hemoglobin A_{1c} by 0.46 percentage points over 30 weeks in patients treated with antipsychotic medication who had schizophrenia, prediabetes, and obesity. In the Efficacy and Safety of Semaglutide Versus Placebo for People With Schizophrenia on Clozapine With Obesity (COaST) trial,[22] semaglutide resulted in 13.88% body weight reduction over 36 weeks in individuals treated with clozapine, with no effect on clozapine concentrations or psychotic symptom severity.

The mortality-lowering effects and reduction in cardiovascular morbidity observed with GLP-1 RAs in persons with type 2 diabetes raise the hypothesis that these agents may also reduce mortality and cardiovascular morbidity in persons living with SMI.[24] Given the disproportionate burden of cardiometabolic disease in SMI, therapies that simultaneously address metabolic risk and cardiovascular outcomes may represent an important opportunity to reduce excess medical morbidity and premature mortality in this population.[3,4,25-27] Herein, we sought to determine whether GLP-1 RAs are associated with reductions in all-cause mortality and cardiovascular morbidity among persons with SMI.

Key Points

Question Are glucagon-like peptide-1 receptor agonists (GLP-1 RAs) associated with lower all-cause mortality and major adverse cardiovascular events (MACEs) among adults with serious mental illness (SMI), including major depressive disorder, bipolar disorder, and schizophrenia?

Findings In this target trial emulation encompassing more than 1.5 million propensity score–matched participants, GLP-1 RA initiation was associated with lower 4-year mortality, 1-year mortality, 3-point MACEs, 5-point MACEs, myocardial infarction, stroke, heart failure, and coronary revascularization.

Meaning The findings of this study indicate that GLP-1 RAs, particularly semaglutide and tirzepatide, may represent a treatment option to narrow the cardiovascular mortality gap in persons living with SMI.

Methods

Ethical Considerations

The study used fully deidentified electronic health record data obtained from the TriNetX Research Network. The State University of New York Upstate Medical University institutional review board approved the study. Because the dataset contained only deidentified information, informed consent was not required.

Study Design and Data Source

A large-scale retrospective cohort study was conducted as a target trial emulation using deidentified longitudinal electronic health record data from the TriNetX Analytics Network.[28] The study included all available data in the TriNetX network through the most recent database refresh. Data were queried and analyzed in March 2026, with prespecified follow-up intervals of 1, 4, and 10 years. Additional subgroup analyses were conducted following peer review in May 2026.

Target Trial Specification

Eligibility criteria, treatment strategies, time zero, follow-up, outcome ascertainment, and estimands were defined as per established target trial emulation principles. The 2 strategies were GLP-1 RA or SGLT2 inhibitor initiation; the estimand was comparative mortality incidence under an intention-to-treat framework.

Time 0 was the first qualifying prescription. Participants were analyzed by initial treatment assignment regardless of subsequent modifications. Follow-up extended from cohort entry until the outcome, death, loss to follow-up, or end of available data.

Table 1. Baseline Demographic and Clinical Characteristics of Individuals Initiating Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in the Primary Analysis

	Before propensity score matching			After propensity score matching		
Characteristic	GLP-1 RA	SGLT2 inhibitor	SMD	GLP-1 RA	SGLT2 inhibitor	SMD
SMI cohort						
Total No.	565 758	254 751	NA	195 184	195 184	NA
Age at the index event, mean (SD), y	51.7 (14.5)	62.7 (13.5)	0.7848	60.5 (12)	60.2 (13.3)	0.0196
Sex, No. (%)						
Female	422 285 (74.663)	134 576 (52.836)	0.4662	112 911 (57.848)	113 488 (58.144)	0.0060
Male	142 959 (25.276)	119 959 (47.097)	0.4663	82 163 (42.095)	81 551 (41.782)	0.0064
Race, No. (%)[a]						
American Indian or Alaska Native	2864 (0.506)	1228 (0.482)	0.0035	1006 (0.515)	987 (0.506)	0.0014
Asian	8994 (1.59)	8942 (3.511)	0.1220	5086 (2.606)	5444 (2.789)	0.0113
Black or African American	83 522 (14.767)	38 478 (15.107)	0.0095	29 325 (15.024)	29 317 (15.02)	0.0001
Native Hawaiian or Other Pacific Islander	2666 (0.471)	1586 (0.623)	0.0205	1138 (0.583)	1163 (0.596)	0.0017
White	414 639 (73.311)	177 322 (69.619)	0.0818	138 270 (70.841)	137 491 (70.442)	0.0088
Other[b]	21 246 (3.756)	10 118 (3.972)	0.0112	7828 (4.011)	7950 (4.073)	0.0032
Unknown	31 660 (5.598)	17 031 (6.687)	0.0454	12 531 (6.42)	12 832 (6.574)	0.0063
Blood pressure, mean (SD), mm Hg						
Systolic	129 (16.5)	129 (19.7)	0.0061	131 (17.8)	130 (19.2)	0.0712
Diastolic	77.4 (10.8)	74.2 (12.4)	0.2752	75.7 (11.3)	75 (12.2)	0.0607
Glomerular filtration rate, mean (SD), mL/min/1.73 m^2	83 (26)	73.4 (28.9)	0.3500	75.5 (27.2)	76.2 (28.9)	0.0244
BMI, mean (SD)	37.7 (8.31)	32.8 (8.21)	0.5982	35.5 (8.14)	33.9 (8.24)	0.1870
BMI category, No. (%)						
<30	183 158 (32.383)	109 883 (43.141)	0.2233	68 239 (34.961)	73 907 (37.865)	0.0604
30-<35	246 018 (43.498)	100 113 (39.305)	0.0852	75 077 (38.465)	77 264 (39.585)	0.0230
35-<40	233 123 (41.218)	73 955 (29.036)	0.2573	60 943 (31.223)	61 227 (31.369)	0.0031
≥40	206 115 (36.442)	54 885 (21.548)	0.3328	47 806 (24.493)	47 330 (24.249)	0.0057
Total cholesterol, mean (SD), mg/dL	181 (45.1)	163 (50.2)	0.3635	170 (48.1)	168 (50.7)	0.0461
Hemoglobin A_{1c}, mean (SD), %	6.86 (2.02)	7.56 (2.04)	0.3461	7.66 (2.13)	7.7 (2.07)	0.0168
Triglycerides, mean (SD), mg/dL	162 (137)	173 (183)	0.0664	179 (154)	182 (197)	0.0157
Low-density lipoprotein cholesterol (calculated), mean (SD), mg/dL	102 (37.3)	86 (38.5)	0.4209	90.5 (38.4)	88.7 (38.9)	0.0465
Essential hypertension, No. (%)	326 810 (57.782%)	193 026 (75.784%)	0.3894	143 447 (73.493%)	141 138 (72.31%)	0.0266
Type 2 diabetes, No. (%)						
Overall	257 578 (45.541)	176 467 (69.283)	0.4946	142 166 (72.837)	132 436 (67.852)	0.1093
With circulatory complications	23 310 (4.121)	24 648 (9.677)	0.2205	16 683 (8.547)	15 218 (7.797)	0.0274
With neurological complications	64 745 (11.447)	52 535 (20.626)	0.2521	42 519 (21.784)	37 336 (19.129)	0.0659
With ophthalmologic complications	27 628 (4.885)	21 659 (8.504)	0.1452	18 663 (9.562)	15 204 (7.79)	0.0630
With kidney complications	44 851 (7.930)	48 308 (18.966)	0.3278	32 361 (16.58)	30 200 (15.473)	0.0302
With other specified complications	130 283 (23.035)	96 249 (37.788)	0.3249	76 114 (38.996)	71 827 (36.8)	0.0453

(continued)

Study Population

Adults aged 18 years and older with a first recorded prescription of either a GLP-1 RA or an SGLT2 inhibitor before the data query date were eligible. To approximate a new-user, active-comparator design and minimize confounding by indication, individuals with documented prior exposure to the comparator drug class were excluded. A 365-day washout period was applied before cohort entry to identify new initiators and exclude individuals with prescriptions for the comparator drug class within the preceding year. GLP-1 RAs included semaglutide, tirzepatide, dulaglutide, liraglutide, exenatide, lixisenatide, and albiglutide. SGLT2 inhibitors included empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin.

Separate cohorts were constructed according to the presence or absence of SMI. Baseline cardiometabolic comorbidities and cardiovascular outcomes were identified using standardized *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnostic groupings and structured procedural coding algorithms within the TriNetX platform, including predefined composite defi-

Table 1. Baseline Demographic and Clinical Characteristics of Individuals Initiating Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in the Primary Analysis (continued)

	Before propensity score matching			After propensity score matching		
Characteristic	GLP-1 RA	SGLT2 inhibitor	SMD	GLP-1 RA	SGLT2 inhibitor	SMD
Overweight and obesity, No. (%)	356 775 (63.08)	114 518 (44.961)	0.3697	102 328 (52.426)	90 503 (46.368)	0.1214
Morbid obesity due to excess calories, No. (%)	197 302 (34.884)	53 128 (20.859)	0.3167	45 739 (23.434)	45 408 (23.264)	0.0040
Atherosclerosis of native arteries of the extremities, No. (%)	9083 (1.606)	11 965 (4.698)	0.1777	6388 (3.273)	6868 (3.519)	0.0136
Disorders of lipoprotein metabolism and other lipidemias, No. (%)	323 362 (57.172)	184 709 (72.519)	0.3257	136 728 (70.051)	135 021 (69.176)	0.0190
Cerebral infarction, No. (%)	22 973 (4.062)	25 729 (10.101)	0.2371	14 468 (7.412)	15 221 (7.798)	0.0146
Ischemic heart diseases, No. (%)	90 768 (16.048)	107 292 (42.124)	0.5994	60 634 (31.065)	63 662 (32.616)	0.0333
Heart failure, No. (%)	43 911 (7.764)	92 207 (36.201)	0.7311	40 033 (20.51)	45 602 (23.364)	0.0690
Atrial fibrillation and flutter, No. (%)	31 972 (5.653)	52 645 (20.669)	0.4556	21 876 (11.208)	28 490 (14.596)	0.1012
Chronic kidney disease, No. (%)	56 938 (10.067)	67 021 (26.313)	0.4308	38 834 (19.896)	40 482 (20.74)	0.0210
Other chronic obstructive pulmonary disease, No. (%)	48 396 (8.557)	51 565 (20.245)	0.3376	29 352 (15.038)	31 645 (16.213)	0.0324
Neoplasms, No. (%)	205 858 (36.397)	96 133 (37.743)	0.0279	75 513 (38.688)	69 493 (35.604)	0.0639
Nicotine dependence, No. (%)	105 694 (18.687)	63 376 (24.882)	0.1505	43 053 (22.058)	44 159 (22.624)	0.0136
Alcohol-related disorders, No. (%)	33 169 (5.864)	23 330 (9.160)	0.1253	14 161 (7.255)	14 990 (7.68)	0.0162
Problems related to lifestyle, No. (%)	67 998 (12.022)	37 194 (14.603)	0.0760	24 307 (12.453)	26 338 (13.494)	0.0310
Mental and behavioral disorders due to psychoactive substance use, No. (%)	141 732 (25.059)	82 008 (32.197)	0.1584	56 127 (28.756)	57 560 (29.49)	0.0162
Persons with potential health hazards related to socioeconomic and psychosocial circumstances, No. (%)	55 200 (9.760)	28 865 (11.333)	0.0512	18 547 (9.502)	19 548 (10.015)	0.0173
Insulins and analogues, No. (%)	144 135 (25.484)	114 652 (45.014)	0.4176	83 727 (42.896)	80 602 (41.295)	0.0324
Antidepressants, No. (%)	399 637 (70.658)	164 698 (64.662)	0.1284	123 137 (63.088)	125 775 (64.439)	0.0281
Antipsychotics, No. (%)	165 738 (29.304)	83 040 (32.602)	0.0714	56 891 (29.147)	59 135 (30.297)	0.0252
Valproate, No. (%)	26 043 (4.605)	13 931 (5.469)	0.0396	10 179 (5.215)	10 405 (5.331)	0.0052
Carbamazepine, No. (%)	9511 (1.682)	3727 (1.463)	0.0176	2924 (1.498)	2991 (1.532)	0.0028
Lamotrigine, No. (%)	30 119 (5.325)	8976 (3.524)	0.0877	7191 (3.684)	7578 (3.882)	0.0104
Lithium, No. (%)	1661 (0.294)	794 (0.312)	0.0033	636 (0.326)	629 (0.322)	0.0006
Without SMI cohort						
Total No.	1 186 880	568 931	NA	936 083	568 931	NA
Age at the index event, mean (SD), y	53.7 (14.5)	64.5 (13.2)	0.7791	60.9 (12.2)	60.6 (13.0)	0.0237
Sex, No. (%)						
Female	721 225 (60.78)	358 200 (38.269)	0.4621	251 679 (44.237)	260 480 (45.784)	0.0311
Male	463 026 (39.021)	575 510 (61.485)	0.4611	315 440 (55.444)	306 926 (53.948)	0.0301

(continued)

nitions for 3-point and 5-point major adverse cardiovascular events. Propensity score matching was conducted independently within psychiatric and nonpsychiatric cohorts.

Exposure Definition

Exposure was defined as initiation of a GLP-1 RA or initiation of an SGLT2 inhibitor based on the first qualifying prescription record. Participants were analyzed under an intention-to-treat framework whereby treatment assignment was defined by the initial prescription and was not modified by subsequent discontinuation, switching, or addition of other therapies.

Outcome Definitions

The primary outcome was all-cause mortality at 4 years, identified using structured mortality indicators within the TriNetX platform. The key secondary outcome was all-cause mortality at 1 year. A 4-year follow-up interval was selected because it approximates the mean follow-up duration of major cardiovascular outcomes trials involving GLP-1 RAs and represents the longest interval during which all individual GLP-1 RA agents included in the analyses, notably tirzepatide following its 2022 US Food and Drug Administration approval, had contemporaneous regulatory availability and observable follow-up within the dataset.

Secondary cardiovascular outcomes included 3-point and 5-point MACEs (eMethods in Supplement 1). Secondary cardiovascular outcomes were analyzed among matched participants with SMI and type 2 diabetes, comparing semaglutide with SGLT2 inhibitor initiation using the primary time-to-event methods (eMethods in Supplement 1).

Covariates

Baseline covariates were obtained from records preceding the index date and included demographic characteristics, cardiometabolic comorbidities, psychiatric treatment variables, substance use indicators, diabetes severity markers, and laboratory measures associated with cardiovascular risk and treatment allocation (**Table 1**). Race and ethnicity were ob-

Table 1. Baseline Demographic and Clinical Characteristics of Individuals Initiating Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in the Primary Analysis (continued)

Characteristic	Before propensity score matching			After propensity score matching		
	GLP-1 RA	SGLT2 inhibitor	SMD	GLP-1 RA	SGLT2 inhibitor	SMD
Race, No. (%)[a]						
American Indian or Alaska Native	5628 (0.474)	3447 (0.368)	0.0164	2615 (0.46)	2543 (0.447)	0.0019
Asian	46 485 (3.917)	93 661 (10.006)	0.2410	34 961 (6.145)	36 403 (6.398)	0.0105
Black or African American	201 580 (16.988)	128 365 (13.714)	0.0909	89 016 (15.646)	87 909 (15.452)	0.0054
Native Hawaiian or Other Pacific Islander	8574 (0.723)	7408 (0.791)	0.0079	4543 (0.799)	4457 (0.783)	0.0017
White	734 283 (61.88)	463 572 (49.526)	0.2507	322 770 (56.733)	318 615 (56.002)	0.0147
Other[b]	47 400 (3.995)	40 711 (4.349)	0.0177	25 561 (4.493)	25 422 (4.468)	0.0012
Unknown	142 670 (12.023)	198 851 (21.244)	0.2495	89 465 (15.725)	93 582 (16.449)	0.0197
Blood pressure, mean (SD), mm Hg						
Systolic	130 (17)	130 (20.3)	0.0094	132 (17.9)	131 (19.5)	0.0381
Diastolic	77.8 (10.9)	74.6 (12.6)	0.2713	76.5 (11.1)	76 (12.2)	0.0445
Glomerular filtration rate, mean (SD), mL/min/1.73 m^2	83.7 (25.9)	73.8 (28.6)	0.3628	77.6 (26.9)	78 (28.7)	0.0149
BMI, mean (SD)	36.1 (7.81)	30.9 (7.22)	0.6887	33.9 (7.3)	32.7 (7.4)	0.1605
BMI category, No. (%)						
<30	284 366 (23.964)	317 299 (33.899)	0.2204	145 733 (25.615)	154 556 (27.166)	0.0352
30-<35	372 348 (31.379)	222 983 (23.823)	0.1696	148 776 (26.15)	149 833 (26.336)	0.0042
35-<40	319 530 (26.928)	133 263 (14.237)	0.3178	103 326 (18.161)	101 219 (17.791)	0.0096
≥40	264 089 (22.256)	86 671 (9.260)	0.3625	71 642 (12.592)	69 751 (12.260)	0.0101
Total cholesterol, mean (SD), mg/dL	178 (44.8)	160 (47.5)	0.3729	168 (47)	166 (48.8)	0.0404
Hemoglobin A_{1c}, mean (SD), %	7 (2.03)	7.57 (1.95)	0.2840	7.65 (2.08)	7.77 (2.01)	0.0597
Triglycerides, mean (SD), mg/dL	154 (135)	158 (162)	0.0254	166 (149)	170 (183)	0.0210
Low-density lipoprotein cholesterol (calculated), mean (SD), mg/dL	101 (37.2)	85.8 (37.5)	0.4069	90.8 (37.7)	89.5 (38.2)	0.0351
Essential hypertension, No. (%)	491 104 (41.387)	474 386 (50.681)	0.1873	267 653 (47.045)	262 496 (46.138)	0.0182
Type 2 diabetes, No. (%)						
Overall	409 992 (34.551)	463 858 (49.557)	0.3075	277 355 (48.75)	261 812 (46.018)	0.0547
With circulatory complications	28 316 (2.386)	39 899 (4.263)	0.1048	21 749 (3.823)	18 818 (3.308)	0.0278
With neurological complications	61 879 (5.215)	68 923 (7.363)	0.0886	46 303 (8.139)	38 443 (6.757)	0.0526
With ophthalmologic complications	34 678 (2.922)	40 484 (4.325)	0.0751	26 722 (4.697)	21 602 (3.797)	0.0446
With kidney complications	63 174 (5.324)	105 245 (11.244)	0.2160	50 528 (8.881)	46 387 (8.153)	0.0261
With other specified complications	185 368 (15.622)	192 970 (20.616)	0.1299	125 739 (22.101)	114 599 (20.143)	0.0480

(continued)

tained from structured TriNetX electronic health record fields recorded by participating health care organizations rather than assigned by the investigators and were included as baseline covariates in propensity score matching because of their associations with health care access, cardiometabolic risk, cardiovascular outcomes, and SMI.

Propensity Score Matching

Propensity scores for receiving a GLP-1 RA vs an SGLT2 inhibitor were estimated using prespecified baseline covariates measured before cohort entry. Nearest-neighbor 1:1 matching without replacement was performed within a caliper of 0.2 standard deviations of the logit of the propensity score. Covariate balance was assessed using standardized mean differences (SMDs), with values ≤0.1 considered adequate.

Statistical Analysis

Time-to-event outcomes were analyzed using Kaplan-Meier methods with comparisons assessed using log-rank tests. Associations were estimated using Cox proportional hazards models incorporating robust variance estimators to account for the propensity score-matched design and are presented as hazard ratios (HRs) with 95% confidence intervals. Cumulative risk differences and risk ratios with 95% confidence intervals were

Table 1. Baseline Demographic and Clinical Characteristics of Individuals Initiating Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors in the Primary Analysis (continued)

	Before propensity score matching			After propensity score matching		
Characteristic	GLP-1 RA	SGLT2 inhibitor	SMD	GLP-1 RA	SGLT2 inhibitor	SMD
Overweight and obesity, No. (%)	455 469 (38.384)	186 208 (19.894)	0.4156	160 533 (28.217)	126 608 (22.254)	0.1376
Morbid obesity due to excess calories, No. (%)	216 249 (18.224)	68 899 (7.361)	0.3296	55 509 (9.757)	54 302 (9.545)	0.0072
Atherosclerosis of native arteries of the extremities, No. (%)	9961 (0.839)	19 676 (2.102)	0.1050	7638 (1.343)	8169 (1.436)	0.0080
Disorders of lipoprotein metabolism and other lipidemias, No. (%)	482 369 (40.651)	451 955 (48.285)	0.1541	255 976 (44.992)	252 104 (44.312)	0.0137
Cerebral infarction, No. (%)	22 729 (1.915)	47 206 (5.043)	0.1713	16 848 (2.961)	17 841 (3.136)	0.0102
Ischemic heart diseases, No. (%)	122 589 (10.331)	259 010 (27.672)	0.4532	94 538 (16.617)	99 199 (17.436)	0.0218
Heart failure, No. (%)	49 248 (4.15)	204 599 (21.859)	0.5457	46 747 (8.217)	54 654 (9.606)	0.0488
Atrial fibrillation and flutter, No. (%)	49 147 (4.142)	126 775 (13.544)	0.3358	36 505 (6.416)	45 149 (7.936)	0.0589
Chronic kidney disease, No. (%)	78 178 (6.588)	154 996 (16.559)	0.3155	61 078 (10.736)	63 967 (11.243)	0.0162
Other chronic obstructive pulmonary disease, No. (%)	35 059 (2.955)	68 153 (7.281)	0.1973	24 324 (4.275)	26 976 (4.742)	0.0225
Neoplasms, No. (%)	268 818 (22.654)	207 143 (22.13)	0.0126	126 898 (22.305)	111 681 (19.63)	0.0657
Nicotine dependence, No. (%)	81 457 (6.865)	80 533 (8.604)	0.0651	41 295 (7.258)	41 853 (7.356)	0.0038
Alcohol-related disorders, No. (%)	17 497 (1.475)	23 498 (2.510)	0.0742	10 043 (1.765)	10 263 (1.804)	0.0029
Problems related to lifestyle, No. (%)	47 443 (3.998)	40 346 (4.31)	0.0156	21 052 (3.700)	21 588 (3.794)	0.0050
Mental and behavioral disorders due to psychoactive substance use, No. (%)	102 659 (8.651)	102 018 (10.899)	0.0757	51 982 (9.137)	52 529 (9.233)	0.0033
Persons with potential health hazards related to socioeconomic and psychosocial circumstances, No. (%)	27 460 (2.314)	22 529 (2.407)	0.0061	10 772 (1.893)	11 169 (1.963)	0.0051
Insulins and analogues, No. (%)	223 339 (18.821)	277 974 (29.698)	0.2558	152 525 (26.809)	148 260 (26.059)	0.0170
Antidepressants, No. (%)	275 511 (23.218)	150 232 (16.05)	0.1812	94 917 (16.683)	98 189 (17.259)	0.0153
Antipsychotics, No. (%)	110 245 (9.291)	102 829 (10.986)	0.0562	48 692 (8.559)	50 610 (8.896)	0.0119
Valproate, No. (%)	22 732 (1.916)	13 499 (1.442)	0.0369	8981 (1.579)	8934 (1.570)	0.0007
Carbamazepine, No. (%)	15 307 (1.29)	6705 (0.716)	0.0576	4838 (0.850)	4988 (0.877)	0.0028
Lamotrigine, No. (%)	7813 (0.658)	3922 (0.419)	0.0327	2644 (0.465)	2662 (0.468)	0.0005
Lithium, No. (%)	168 (0.014)	112 (0.012)	0.0019	82 (0.014)	74 (0.013)	0.0012

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; SMD, standardized mean difference; SMI, serious mental illness.

[a] Race was obtained from structured electronic health record demographic fields available in TriNetX, as recorded by participating health care organizations. The data available to the investigators did not specify whether individual entries were self-reported, entered by clinical or administrative personnel, or obtained through another institution-specific process. Race was included in propensity score matching because social and structural factors associated with race may influence health care access, treatment selection, cardiometabolic risk, cardiovascular outcomes, and serious mental illness care. Race was not interpreted as a biological determinant.

[b] Other was a standardized source-data category and was not created by the investigators. In the TriNetX Dataworks-USA Network, this category is used when more than 1 race is recorded or when the recorded race does not correspond to one of the available standardized categories. The deidentified data did not provide a more granular breakdown of the individual races or multiracial combinations included within this category.

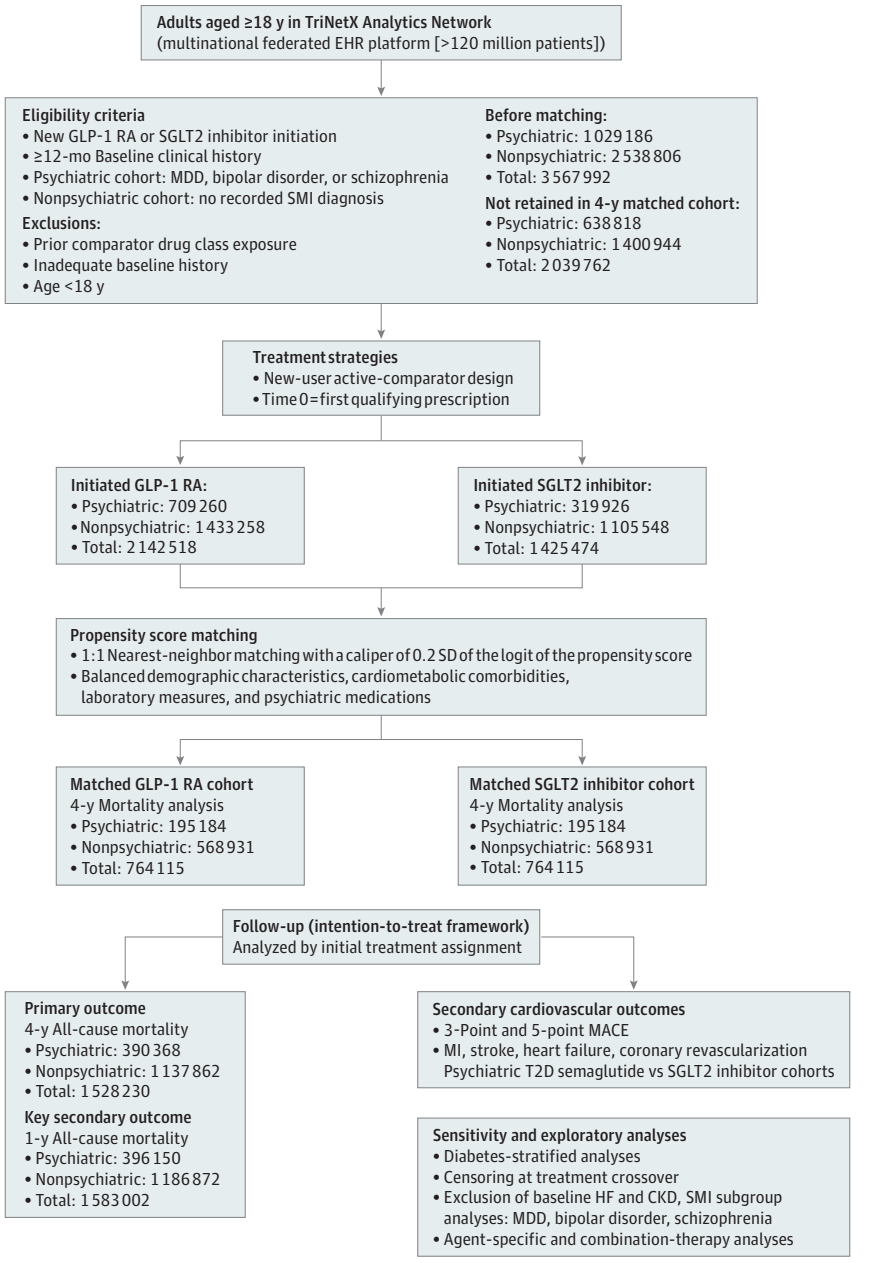
estimated at prespecified follow-up intervals. Follow-up was summarized using means with standard deviations and medians with interquartile ranges. Missing values were not imputed, and analyses were conducted using available electronic health record data. Participants were censored at their last recorded encounter or the end of available data. Since deidentified TriNetX data could not distinguish loss to follow-up from care received outside participating health care organizations, follow-up completeness was assessed using observed follow-up duration. All tests were 2-sided with $P < .05$ considered statistically significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Results

Study Population

The target trial emulation design and cohort derivation are illustrated in **Figure 1**. Application of prespecified eligibility cri-

Figure 1. Flow Diagram of the Target Trial Emulation Design and Primary Cohort Derivation for Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Initiation in Serious Mental Illness (SMI)



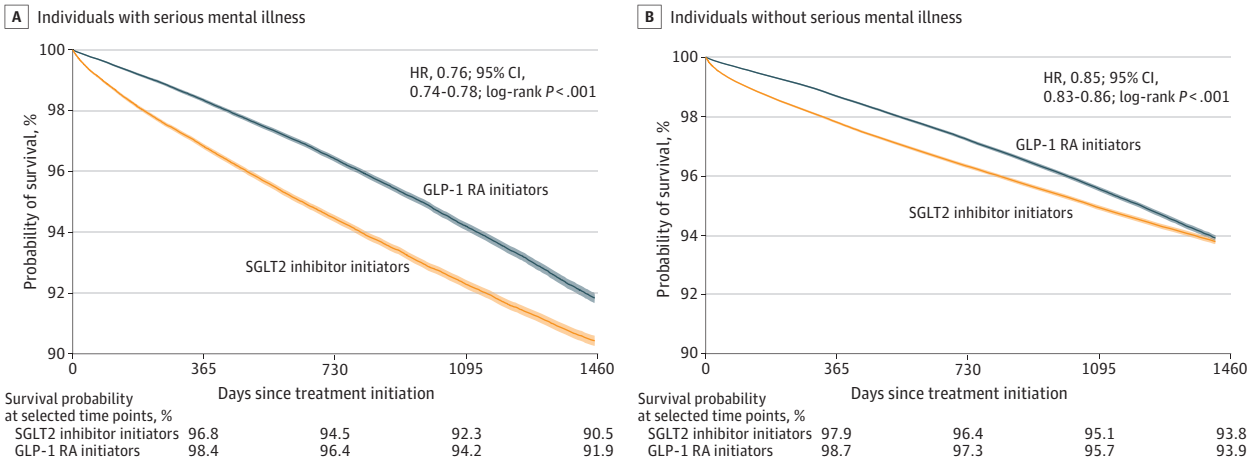
This figure shows the target trial emulation used to compare GLP-1 RA with SGLT2 inhibitor initiation. TriNetX includes more than 120 million patients; the query snapshot included 127 035 455 patients from 114 health care organizations. Adults with and without serious mental illness were analyzed using a new-user, active-comparator design and 1:1 propensity score matching. Time 0 was the first qualifying prescription, and participants were monitored until outcome, death, loss of observable follow-up, or end of available data. The primary outcome was 4-year all-cause mortality; secondary outcomes included 1-year mortality, major adverse cardiovascular events (MACEs), myocardial infarction, stroke, heart failure, and coronary revascularization. Analysis-specific sample sizes for secondary, sensitivity, and exploratory analyses are reported in Table 2 and the eResults in Supplement 1. CKD indicates chronic kidney disease; EHR, electronic health record; HF, heart failure; MDD, major depressive disorder; MI, myocardial infarction.

teria followed by propensity score matching yielded balanced cohorts for all primary, secondary, sensitivity, and exploratory analyses.

For the primary 4-year all-cause mortality analysis, the psychiatric cohort comprised 195 184 GLP-1 RA initiators matched 1:1 to 195 184 SGLT2 inhibitor initiators; the nonpsychiatric cohort comprised 568 931 matched pairs. Matched sample sizes varied across analyses according to outcome availability, follow-up window, and sensitivity-analysis eligibility criteria.

Baseline characteristics before and after propensity score matching are presented in Table 1. After matching, demographic characteristics, cardiometabolic comorbidities, psychiatric medication use, diabetes severity markers, alcohol use disorder, nicotine dependence, and laboratory values were well balanced between treatment groups. The propensity score model was refined to incorporate baseline antipsychotic, antidepressant, and mood stabilizer exposure, as well as alcohol use disorder, insulin use, morbid obesity, and categorical body mass index, to mitigate potential confounding re-

Figure 2. Kaplan-Meier Survival Curves for All-Cause Mortality by Treatment and Serious Mental Illness Status



Kaplan-Meier curves show all-cause mortality among propensity score–matched individuals initiating glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Time 0 was the first qualifying prescription. HR indicates hazard ratio.

lated to psychiatric pharmacotherapy, metabolic disease severity, and treatment selection.

Residual imbalance in continuous body mass index (BMI) and type 2 diabetes persisted in the SMI cohort after matching. Supplementary double-adjusted analyses incorporating BMI (calculated as weight in kilograms divided by height in meters squared) and type 2 diabetes improved balance (type 2 diabetes SMD: 0.1054-0.0371; BMI SMD: 0.5373-0.1431) without altering effect estimates (eResults in Supplement 1). Additional categorical BMI balancing demonstrated excellent balance across obesity strata, supporting robustness against residual metabolic confounding.

Primary Outcome: 4-Year All-Cause Mortality

Participants With SMI

Kaplan-Meier survival curves for the psychiatric and nonpsychiatric cohorts are shown in **Figure 2**. Among 390 368 propensity score-matched individuals with SMI (195 184 per group), death occurred in 9585 GLP-1 RA initiators (4.91%) vs 12 584 SGLT2 inhibitor initiators (6.45%), yielding an absolute risk difference (ARD) of −1.54 percentage points (95% CI, −1.68 to −1.39). Median follow-up was 949 days in the GLP-1 RA group and 945 days in the SGLT2 inhibitor group; the corresponding IQR widths were 1037 and 1053 days, respectively. GLP-1 RA initiation was associated with significantly lower all-cause mortality (risk ratio [RR], 0.76; 95% CI, 0.74-0.78; $P < .001$; HR, 0.76; 95% CI, 0.74-0.78; log-rank $P < .001$).

Participants Without SMI

Among 1 137 862 propensity score-matched individuals without SMI (568 931 per group), death occurred in 16 904 GLP-1 RA initiators (2.97%) vs 20 302 SGLT2 inhibitor initiators (3.57%), yielding an ARD of −0.60 percentage points (95% CI, −0.66 to −0.53). Median follow-up was 658 days vs 684 days. GLP-1 RA initiation was associated with lower all-cause mortality (RR, 0.83; 95% CI, 0.82-0.85; $P < .001$; HR, 0.85 95% CI, 0.83-0.86; log-rank $P < .001$).

Key Secondary Outcome: 1-Year All-Cause Mortality

Participants With SMI

At 1 year, death occurred in 2898 of 198 065 individuals initiating GLP-1 RAs (1.46%) vs 5624 of 198 065 initiating SGLT2 inhibitors (2.84%), yielding an ARD of −1.38 percentage points (95% CI, −1.47 to −1.29). Median (IQR) follow-up was 365 (365-365) days in both groups. GLP-1 RA initiation was associated with a 48% lower relative risk of 1-year mortality (RR, 0.52; 95% CI, 0.49-0.54; $P < .001$; HR, 0.51; 95% CI, 0.49-0.53; log-rank $P < .001$).

Participants Without SMI

At 1 year, death occurred in 6178 of 593 436 individuals initiating GLP-1 RAs (1.04%) vs 10 551 of 593 436 initiating SGLT2 inhibitors (1.78%), yielding an ARD of −0.74 percentage points (95% CI, −0.78 to −0.69). Median (IQR) follow-up was 365 days in both groups, with IQRs of 243 to 365 days in the GLP-1 RA group and 232 to 365 days in the SGLT2 inhibitor group. GLP-1 RA initiation was associated with lower 1-year mortality (RR, 0.59; 95% CI, 0.57-0.60; $P < .001$; HR, 0.58; 95% CI, 0.56-0.60; log-rank $P < .001$).

Secondary Cardiovascular Outcomes

Secondary cardiovascular outcomes were assessed among propensity score-matched individuals in the psychiatric cohort with type 2 diabetes, comparing semaglutide with SGLT2 inhibitor initiation. Results are summarized in **Table 2** and **Figure 3**; full details are provided in eResults in Supplement 1.

Semaglutide initiation was associated with lower risk of 3-point MACEs (RR, 0.72; 95% CI, 0.71-0.74; HR, 0.77; 95% CI, 0.76-0.79), 5-point MACEs (RR, 0.76; 95% CI, 0.75-0.77; HR, 0.76; 95% CI, 0.75-0.77), myocardial infarction (RR, 0.65; 95% CI, 0.63-0.68; HR, 0.71; 95% CI, 0.69-0.73), stroke (RR, 0.82; 95% CI, 0.80-0.85; HR, 0.89; 95% CI, 0.86-0.92), heart failure (RR, 0.73; 95% CI, 0.72-0.74; HR, 0.73; 95% CI, 0.72-0.74), and coronary artery bypass grafting (RR, 0.69; 95% CI, 0.62-0.76; HR, 0.77; 95% CI, 0.70-0.85) (all $P < .001$).

Table 2. Mortality and Cardiovascular Outcomes Associated With Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) vs Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Initiation

Population	Target drug	Comparator drug class	No./total No. (%)		Follow-up window; median follow-up[a]	ARD, percentage points (95% CI)	RR (95% CI)	*P* value[b]	HR (95% CI)	Log-rank *P* value[c]
			Target outcomes	Comparator outcomes						
Primary outcome: all-cause mortality										
Psychiatric cohort	GLP-1 RA class	SGLT2 inhibitor class	9585/195 184 (4.911)	12 584/195 184 (6.447)	4-y Window; 949 vs 945 d	−1.54 (−1.68 to −1.39)	0.76 (0.74 to 0.78)	<.001	0.76 (0.74 to 0.78)	<.001
Nonpsychiatric cohort	GLP-1 RA class	SGLT2 inhibitor class	16 904/568 931 (2.971)	20 302/568 931 (3.568)	4-y Window; 658 vs 684 d	−0.60 (−0.66 to −0.53)	0.83 (0.82 to 0.85)	<.001	0.85 (0.83 to 0.86)	<.001
Key secondary outcome: early all-cause mortality										
Psychiatric cohort	GLP-1 RA class	SGLT2 inhibitor class	2898/198 065 (1.463)	5624/198 065 (2.839)	1-y Window; 365 vs 365 d	−1.38 (−1.47 to −1.29)	0.52 (0.49 to 0.54)	<.001	0.51 (0.49 to 0.53)	<.001
Nonpsychiatric cohort	GLP-1 RA class	SGLT2 inhibitor class	6178/593 436 (1.041)	10 551/593 436 (1.778)	1-y Window; 365 vs 365 d	−0.74 (−0.78 to −0.69)	0.59 (0.57 to 0.60)	<.001	0.58 (0.56 to 0.60)	<.001
Diabetes-stratified sensitivity analyses: all-cause mortality										
Psychiatric + T2D	GLP-1 RA class	SGLT2 inhibitor class	9260/172 238 (5.376)	11 262/172 238 (6.539)	4-y Window; 1063 vs 1065 d	−1.16 (−1.32 to −1.00)	0.82 (0.80 to 0.84)	<.001	0.81 (0.79 to 0.84)	<.001
Nonpsychiatric + T2D	GLP-1 RA class	SGLT2 inhibitor class	13 850/403 120 (3.436)	15 251/403 120 (3.783)	4-y Window; 869 vs 890 d	−0.35 (−0.43 to −0.27)	0.91 (0.80 to 0.93)	<.001	0.91 (0.89 to 0.93)	<.001
Sensitivity analyses: all-cause mortality										
Psychiatric + T2D, no HF/CKD	GLP-1 RA class	SGLT2 inhibitor class	4901/133 732 (3.665)	5913/133 732 (4.422)	4-y Window; 1118 vs 1237 d	−0.76 (−0.91 to −0.61)	0.83 (0.80 to 0.86)	<.001	0.85 (0.82 to 0.89)	<.001
No treatment crossover	GLP-1 RA class	SGLT2 inhibitor class	9210/145 458 (6.332)	12 323/145 458 (8.472)	4-y Window; 757 vs 674 d	−2.14 (−2.33 to −1.95)	0.75 (0.73 to 0.77)	<.001	0.70 (0.68 to 0.72)	<.001
Secondary cardiovascular outcomes										
3-Point MACE										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	15 452/123 344 (12.528)	21 427/123 344 (17.372)	4-y Window; 827 vs 1078 d	−4.84 (−5.13 to −4.56)	0.72 (0.71 to 0.74)	<.001	0.77 (0.76 to 0.79)	<.001
5-Point MACE										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	29 619/123 344 (24.013)	39 169/123 344 (31.756)	4-y Window; 827 vs 1078 d	−7.74 (−8.10 to −7.39)	0.76 (0.75 to 0.77)	<.001	0.76 (0.75 to 0.77)	<.001
Myocardial infarction										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	5571/112 596 (4.948)	8524/112 596 (7.570)	4-y Window; 821 vs 1097 d	−2.62 (−2.82 to −2.42)	0.65 (0.63 to 0.68)	<.001	0.71 (0.69 to 0.73)	<.001
Stroke										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	6658/112 596 (5.913)	8100/112 596 (7.194)	4-y Window; 821 vs 1097 d	−1.28 (−1.49 to −1.08)	0.82 (0.80 to 0.85)	<.001	0.89 (0.86 to 0.92)	<.001

(continued)

Table 2. Mortality and Cardiovascular Outcomes Associated With Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) vs Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Initiation (continued)

Population	Target drug	Comparator drug class	No./total No. (%)		Follow-up window; median follow-up[a]	ARD, percentage points (95% CI)	RR (95% CI)	*P* value[b]	HR (95% CI)	Log-rank *P* value[c]
			Target outcomes	Comparator outcomes						
Heart failure										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	26 381/147 636 (17.869)	36 144/147 636 (24.482)	4-y Window; 815 vs 1084 d	−6.61 (−6.91 to −6.32)	0.73 (0.72 to 0.74)	<.001	0.73 (0.72 to 0.74)	<.001
Coronary artery bypass grafting										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	645/130 148 (0.496)	941/130 148 (0.723)	4-y Window; 822 vs 1091 d	−0.23 (−0.29 to −0.17)	0.69 (0.62 to 0.76)	<.001	0.77 (0.70 to 0.85)	<.001
Exploratory analyses: all-cause mortality										
SMI diagnostic subgroups										
MDD + T2D	Semaglutide	SGLT2 inhibitor class	5601/127 905 (4.38)	10 272/127 905 (8.03)	10-y Window; 830 vs 1103 d	−3.65 (−3.84 to −3.47)	0.55 (0.53 to 0.56)	<.001	0.75 (0.73 to 0.78)	<.001
Bipolar + T2D	Semaglutide	SGLT2 inhibitor class	483/13 905 (3.47)	851/13 905 (6.12)	10-y Window; 778 vs 1007 d	−2.65 (−3.15 to −2.15)	0.57 (0.51 to 0.63)	<.001	0.76 (0.68 to 0.85)	<.001
Schizophrenia + T2D	Semaglutide	SGLT2 inhibitor class	448/8045 (5.57)	674/8045 (8.38)	10-y Window; 761 vs 942 d	−2.81 (−3.60 to −2.02)	0.67 (0.59 to 0.75)	<.001	0.85 (0.75 to 0.95)	<.001
Agent-specific										
Psychiatric + T2D	Semaglutide	SGLT2 inhibitor class	6207/140 691 (4.41)	11 253/140 691 (8.00)	10-y Window; 815 vs 1084 d	−3.59 (−3.76 to −3.41)	0.55 (0.54 to 0.57)	<.001	0.76 (0.74 to 0.79)	<.001
Nonpsychiatric + T2D	Semaglutide	SGLT2 inhibitor class	7763/284 438 (2.73)	13 791/284 438 (4.85)	10-y Window; 707 vs 916 d	−2.12 (−2.22 to −2.02)	0.56 (0.55 to 0.58)	<.001	0.77 (0.74 to 0.79)	<.001
Psychiatric + T2D	Tirzepatide	SGLT2 inhibitor class	937/69 326 (1.352)	3515/69 326 (5.07)	4-y Window; 424 vs 1102 d	−3.72 (−3.90 to −3.53)	0.27 (0.25 to 0.29)	<.001	0.49 (0.45 to 0.52)	<.001
Nonpsychiatric + T2D	Tirzepatide	SGLT2 inhibitor class	1000/136 628 (0.732)	4231/136 628 (3.097)	4-y Window; 378 vs 953 d	−2.37 (−2.47 to −2.26)	0.24 (0.22 to 0.25)	<.001	0.43 (0.40 to 0.46)	<.001
Psychiatric + T2D	Dulaglutide	SGLT2 inhibitor class	6185/116 677 (5.301)	6137/116 677 (5.26)	4-y Window; 1275 vs 1133 d	0.04 (−0.14 to 0.22)	1.01 (0.97 to 1.04)	0.66	0.92 (0.89 to 0.95)	<.001
Psychiatric + T2D	Liraglutide	SGLT2 inhibitor class	2507/54 342 (4.613)	2371/54 342 (4.363)	4-y Window; 1460 vs 1259 d	0.25 (0.004 to 0.50)	1.06 (1.00 to 1.12)	0.046	0.86 (0.82 to 0.91)	<.001
Psychiatric + T2D	Exenatide	SGLT2 inhibitor class	1229/27 408 (4.484)	1119/27 408 (4.083)	4-y Window; 1460 vs 1340 d	0.40 (0.062 to 0.74)	1.10 (1.02 to 1.19)	0.02	0.86 (0.80 to 0.94)	<.001
Psychiatric + T2D	Lixisenatide	SGLT2 inhibitor class	197/2634 (7.479)	138/2634 (5.239)	4-y Window; 1460 vs 1119 d	2.24 (0.92 to 3.56)	1.43 (1.16 to 1.76)	<.001	1.26 (1.01 to 1.57)	0.04
Psychiatric + T2D	Albiglutide	SGLT2 inhibitor class	86/1509 (5.699)	57/1509 (3.777)	4-y Window; 1460 vs 1295 d	1.92 (0.41 to 3.44)	1.51 (1.09 to 2.09)	0.01	1.11 (0.80 to 1.56)	0.52

(continued)

Table 2. Mortality and Cardiovascular Outcomes Associated With Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) vs Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Initiation (continued)

Population	Target drug	Comparator drug class	No./total No. (%)		Follow-up window; median follow-up[a]	ARD, percentage points (95% CI)	RR (95% CI)	*P* value[b]	HR (95% CI)	Log-rank *P* value[c]
			Target outcomes	Comparator outcomes						
GLP-1 RA + SGLT2 inhibitor combination therapy										
Psychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	149/10 242 (1.455)	217/10 242 (2.119)	1-y Window; 365 vs 365 d	−0.66 (−1.03 to −0.30)	0.69 (0.56 to 0.84)	<.001	0.70 (0.57 to 0.86)	<.001
Nonpsychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	308/28 576 (1.078)	459/28 576 (1.606)	1-y Window; 365 vs 365 d	−0.53 (−0.72 to −0.34)	0.67 (0.58 to 0.78)	<.001	0.69 (0.59 to 0.79)	<.001
Psychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	427/10 242 (4.169)	601/10 242 (5.868)	4-y Window; 973 vs 1179 d	−1.70 (−2.30 to −1.10)	0.71 (0.63 to 0.80)	<.001	0.77 (0.68 to 0.87)	<.001
Nonpsychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	629/27 000 (2.33)	959/27 000 (3.552)	4-y Window; 712 vs 924 d	−1.22 (−1.51 to −0.94)	0.66 (0.59 to 0.72)	<.001	0.73 (0.66 to 0.81)	<.001
Psychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	438/9009 (4.862)	664/9009 (7.37)	10-y Window; 993 vs 1212 d	−2.51 (−3.21 to −1.81)	0.66 (0.59 to 0.74)	<.001	0.71 (0.63 to 0.80)	<.001
Nonpsychiatric + T2D	SGLT2 inhibitor + semaglutide ≤30 d	SGLT2 inhibitor alone	699/25 549 (2.736)	1216/25 549 (4.759)	10-y Window; 721 vs 930 d	−2.02 (−2.35 to −1.70)	0.58 (0.53 to 0.63)	<.001	0.66 (0.60 to 0.72)	<.001

Abbreviations: ARD, absolute risk difference; CKD, chronic kidney disease; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MDD, major depressive disorder; RR, risk ratio; SGLT2, sodium-glucose cotransporter-2; SMI, serious mental illness; T2D, type 2 diabetes.

[a] Follow-up windows indicate the maximum observation period, and median follow-up values are reported as target vs comparator cohort follow-up.

[b] *P* values are reported from risk-difference/risk-ratio analyses unless otherwise specified.

[c] Log-rank *P* values compare Kaplan-Meier survival curves between treatment groups.

Sensitivity Analyses

All primary findings persisted across prespecified sensitivity analyses, including diabetes stratification, exclusion of baseline heart failure and chronic kidney disease, and censoring at treatment crossover (eResults in Supplement 1). The crossover-censored analysis yielded a larger effect size (HR, 0.70; 95% CI, 0.68-0.72), suggesting that treatment switching attenuated the primary estimate.

Exploratory Analyses

In 10-year exploratory analyses among participants with type 2 diabetes, semaglutide initiation, compared with SGLT2 inhibitor initiation, was associated with lower mortality in the major depressive disorder subgroup (RR, 0.55; 95% CI, 0.53-0.56; HR, 0.75; 95% CI, 0.73-0.78), bipolar disorder subgroup (RR, 0.57; 95% CI, 0.51-0.63; HR, 0.76; 95% CI, 0.68-0.85), and schizophrenia subgroup (RR, 0.67; 95% CI, 0.59-0.75; HR, 0.85; 95% CI, 0.75-0.95) (eResults in Supplement 1). Agent-specific analyses demonstrated that semaglutide (RR, 0.55; 95% CI, 0.54 to 0.57) and tirzepatide (RR, 0.27; 95% CI, 0.25 to 0.29) were associated with the observed mortality reductions, whereas older GLP-1 RAs, including dulaglutide, liraglutide, exenatide, lixisenatide, and albiglutide, conferred no consistent survival advantage (eResults in Supplement 1). SGLT2 inhibitor–semaglutide combination therapy was associated with incremental mortality benefit compared with SGLT2 inhibitor monotherapy, with the largest relative risk reduction observed at the 10-year horizon in the psychiatric cohort (RR, 0.66; 95% CI, 0.59-0.74) (eResults in Supplement 1).

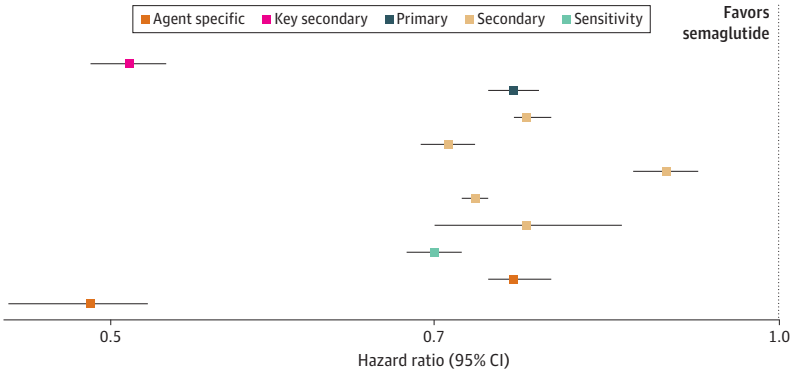
Discussion

To our knowledge, this cohort study represents one of the largest population-based investigations examining the association between GLP-1 RAs and cardiovascular outcomes and mortality among individuals with SMI. GLP-1 RA initiation was associated with reduced cardiovascular morbidity and all-cause mortality, as indexed by 3- and 5-point MACEs, relative to SGLT2 inhibitor initiation. Associations were consistent across psychiatric and nonpsychiatric cohorts and extended across myocardial infarction, stroke, heart failure, and coronary revascularization, supporting a broad cardiometabolic benefit rather than an isolated outcome-specific signal. The magnitude of the mortality reduction was greater in the SMI cohort (RR, 0.76; ARD, −1.5 percentage points) than in the nonpsychiatric cohort (RR, 0.83; ARD, −0.60 percentage points), suggesting that individuals with SMI may derive a proportionally larger absolute benefit from GLP-1 RA initiation. These results accord with prior evidence indicating that GLP-1 RAs reduce cardiometabolic morbidity and mortality.[16]

A notable finding was the early separation of mortality curves. At 1 year, GLP-1 RA initiation was associated with a 48% lower relative risk of death in the SMI cohort (RR, 0.52; ARD, −1.38 percentage points) and a 41% lower relative risk in the nonpsychiatric cohort (RR, 0.59; ARD, −0.74 percentage points). The rapidity of this divergence exceeds what would be expected from gradual metabolic improvements alone, rais-

Figure 3. Forest Plot Showing Cardiovascular Outcomes Associated With Semaglutide vs Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor Initiation in Serious Mental Illness

Outcome (group)	Time, y	Hazard ratio (95% CI)
All-cause mortality (SMI)	4	0.76 (0.74-0.78)
All-cause mortality (SMI)	1	0.51 (0.49-0.53)
3-Point MACE (SMI)	4	0.77 (0.76-0.79)
Myocardial infarction (SMI)	4	0.71 (0.69-0.73)
Stroke (SMI)	4	0.89 (0.86-0.92)
Heart failure (SMI)	4	0.73 (0.72-0.74)
Coronary revascularization (SMI)	4	0.77 (0.70-0.85)
Treatment crossover (SMI)	4	0.70 (0.68-0.72)
Semaglutide mortality (SMI + T2D)	4	0.76 (0.74-0.79)
Tirzepatide mortality (SMI + T2D)	4	0.49 (0.45-0.52)



The forest plot shows hazard ratios and 95% CIs for cardiovascular outcomes among propensity score–matched adults with serious mental illness (SMI) and type 2 diabetes (T2D) who initiated semaglutide or an SGLT2 inhibitor.

Outcomes included 3-point and 5-point major adverse cardiovascular events (MACEs), myocardial infarction, stroke, heart failure, and coronary artery bypass grafting. Hazard ratios below 1 favored semaglutide.

ing the possibility that GLP-1 RAs exert acute cardioprotective effects that manifest before the full realization of weight loss or glycemic optimization.

The mortality gap in persons living with SMI is well documented.[29-32] Cardiovascular disease accounts for the largest share of excess deaths, reflecting high baseline prevalence and cumulative cardiometabolic risk burden.[3,11,30-32] Despite therapeutic advances, the mortality differential has persisted or widened over recent decades.[33] Currently, only lithium, clozapine, and select second-generation long-acting injectable antipsychotics have demonstrated mortality reduction in SMI.[34,35] The present findings suggest that therapies developed for cardiometabolic disease may represent an underrecognized opportunity to reduce premature mortality by targeting the principal medical drivers of excess death. The consistency of the mortality benefit across major depressive disorder (RR, 0.55), bipolar disorder (RR, 0.57), and schizophrenia (RR, 0.67) demonstrates generalizability across the full SMI diagnostic spectrum. That the benefit extended to schizophrenia, a population burdened by severe cardiometabolic risk and substantial barriers to health care engagement, suggests the protective association does not depend on optimal adherence or health system access.

Agent-specific analyses revealed marked heterogeneity within the GLP-1 RA class. Semaglutide and tirzepatide demonstrated robust mortality reductions, with tirzepatide yielding the largest observed effect (RR, 0.27; HR, 0.49), while older agents showed no consistent survival benefit. These findings suggest the mortality association is driven by pharmacologic properties of newer incretin-based therapies, including higher receptor-binding affinity, prolonged duration of action, greater weight reduction, and dual GIP/GLP-1 receptor agonism with tirzepatide. The discordance between risk ratio and hazard ratio estimates observed with several older agents reflects differential follow-up duration and censoring patterns. These agent-level results have direct relevance for formulary prioritization in SMI populations.

The mechanisms underlying the observed mortality reduction likely include anti-inflammatory and anti-atherogenic effects, improvements in endothelial function, and metabolic benefits partially independent of weight loss and glycemic improvement.[36] Additional contributors may include GLP-1 RA effects on motivation, behavior, and cognitive organization, as well as potential mitigation of other cardiovascular risk factors such as alcohol use disorder.[37-41] The persistence of the mortality benefit after exclusion of individuals with baseline heart failure and chronic kidney disease (RR, 0.83; HR, 0.85) suggests that the observed associations are not driven by confounding from SGLT2 inhibitor-responsive comorbidities. SGLT2 inhibitors, but not GLP-1 RAs, are US Food and Drug Administration approved for heart failure, and patients with more advanced heart failure may have been preferentially prescribed SGLT2 inhibitors. Heart failure was balanced in the propensity score model, and sensitivity analyses excluding baseline heart failure and chronic kidney disease yielded consistent findings; however, binary diagnostic codes cannot fully capture differences in heart failure severity, and residual channeling bias cannot be entirely excluded.

The combination-therapy analyses demonstrated that SGLT2 inhibitor plus semaglutide initiation was associated with lower mortality compared with SGLT2 inhibitor monotherapy, with progressive relative risk reductions from 1 year (RR, 0.69) to 10 years (RR, 0.66). That additive benefit was observed against an active comparator with established cardiovascular advantages is consistent with partially distinct and synergistic cardioprotective pathways, extending the dual-mechanism paradigm to psychiatric populations.

Limitations

This study has several important limitations (eDiscussion in Supplement 1). First, although target trial emulation mimics a randomized clinical trial, it cannot fully control for unmeasured confounding, including medication adherence, lifestyle factors, socioeconomic determinants, and psychiatric ill-

ness severity. Second, generalizability warrants consideration, as cost barriers and structural inequities in access to incretin-based therapies disproportionately affect persons with SMI.[42] Third, GLP-1 RAs were prescribed predominantly for type 2 diabetes and obesity; however, diabetes-stratified sensitivity analyses yielded consistent findings. Fourth, tirzepatide's shorter median follow-up (424 days) necessitates cautious interpretation of its large effect estimates. Fifth, residual imbalance in continuous BMI and type 2 diabetes prevalence persisted after matching; supplementary double-adjusted analyses and categorical BMI balancing yielded concordant findings, reducing the likelihood that residual metabolic imbalance materially influenced the results.

Strengths include the target trial emulation design, large sample size, incorporation of baseline cardiometabolic and socioeconomic codes into the propensity model, and convergence of findings across time-to-event analyses, fixed-interval analyses, and multiple independent cardiovascular end points. The no-treatment-crossover analysis yielded a larger effect size (HR, 0.70) than the primary analysis (HR, 0.76), suggesting treatment crossover conservatively attenuated the primary estimate.

Conclusions

Identifying strategies to reduce the mortality gap in SMI is a critical public health priority.[12] The heterogeneity of effect across agents underscores the importance of agent-level rather than class-level evidence when informing clinical guidelines. The additive survival benefit with combination therapy provides rationale for prospective trials evaluating dual-mechanism strategies in this population. These findings highlight the potential for GLP-1 RAs to address the disproportionate burden of cardiovascular disease and premature mortality in SMI and support equitable integration of GLP-1 RAs within multidisciplinary care models aimed at preventing premature cardiovascular morbidity.

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Acquisition, analysis, or interpretation of data: Zhang-James, Kwan.
Drafting of the manuscript: McIntyre, Kwan.
Critical review of the manuscript for important intellectual content: All authors.
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