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Cardiovascular Outcomes of Tirzepatide vs Semaglutide in Obesity Without Type 2 Diabetes: A Matched Cohort Study

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Article

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Abstract

Background/Objectives: Tirzepatide, a dual GIP/GLP-1 receptor agonist, achieves greater weight loss than semaglutide in adults with obesity without type 2 diabetes (T2D), but no randomised trial has directly compared their cardiovascular outcomes in this population. We compared major adverse cardiovascular events (MACE) and other cardiorenal outcomes between the two agents.

Subjects/Methods: We conducted an active-comparator, propensity score–matched cohort study in the TriNetX Global Collaborative Network (178 healthcare organisations). Adults aged 18–80 years with obesity (BMI ≥30 kg/m²) initiating tirzepatide or subcutaneous semaglutide in 2024, with no prior T2D (ICD-10 E11.x or HbA1c ≥6.5%), were eligible. After 1:1 propensity score matching, outcomes were assessed under a 6-month landmark at 6–12 and 6–18 months after the index date. The primary outcome was 3-point MACE (acute myocardial infarction, ischaemic stroke, or all-cause mortality). Secondary outcomes included incident atrial fibrillation (AF) and a chronic kidney disease (CKD) progression composite. Two prespecified negative controls and E-values assessed residual confounding.

Results: After matching, 54,978 pairs were analysed (mean age 46.6 years; 74.0% female; mean BMI 39.5 kg/m²). Tirzepatide was associated with lower MACE at 12 months (hazard ratio [HR] 0.80; 95% CI 0.69–0.92) and 18 months (HR 0.84; 95% CI 0.75–0.94). Significant reductions were also observed for incident AF (HR 0.83–0.84) and CKD progression (HR 0.82–0.84) at both horizons. All-cause mortality and acute MI showed directionally concordant but non-significant reductions. Negative controls were null; the primary MACE E-value was 1.81 (point estimate) and 1.39 (upper confidence limit). BMI-stratified sensitivity analyses confirmed consistency across obesity classes I–III.

Conclusions: In adults with obesity without T2D, tirzepatide was associated with lower risks of MACE, incident AF, and CKD progression compared with semaglutide. These findings generate the hypothesis that dual GIP/GLP-1 receptor agonism may confer cardiovascular benefits beyond selective GLP-1 receptor agonism, warranting confirmation in randomised trials.

What is already known about this subject

- Semaglutide (2.4 mg/week) reduces major adverse cardiovascular events (MACE) by 20% versus placebo in adults with overweight or obesity and established cardiovascular disease without diabetes (SELECT trial).
- Tirzepatide achieves substantially greater weight loss than semaglutide in non-diabetic obese adults (−20.2% vs −13.7% at 72 weeks; SURMOUNT-5 trial).
- No randomised trial has directly compared cardiovascular outcomes of tirzepatide versus semaglutide in adults with obesity without type 2 diabetes; SURMOUNT-MMO will not report until 2027.

What this study adds

- In 109,956 propensity score–matched adults with obesity without type 2 diabetes, tirzepatide was associated with 20% lower MACE at 12 months (HR 0.80; 95% CI 0.69–0.92) and 16% lower MACE at 18 months (HR 0.84; 95% CI 0.75–0.94) compared with semaglutide.
- Consistent reductions were observed in incident atrial fibrillation (16–17%) and chronic kidney disease progression (16–18%) at both time horizons.
- Two prespecified null negative controls and E-value sensitivity analysis support robustness against residual confounding; effect consistency was confirmed across obesity classes I–III.

Introduction

Obesity affects more than 40% of adults in the United States and is an independent driver of cardiovascular disease, type 2 diabetes mellitus (T2D), and premature mortality (1, 2). Incretin-based pharmacotherapy has transformed obesity management, with semaglutide and tirzepatide emerging as the two most widely prescribed agents. Understanding whether the superior weight-loss efficacy of tirzepatide translates into incremental cardiovascular protection is thus a central question in obesity medicine, directly informing pharmacological treatment selection for the growing global population of patients with obesity without diabetes.

Semaglutide, a selective GLP-1 receptor agonist, was the first incretin therapy to demonstrate a cardiovascular benefit in adults with overweight or obesity without diabetes in the SELECT trial (HR for MACE 0.80; 95% CI 0.72–0.90) (3); the real-world SCORE study reported similarly lower MACE risk with semaglutide 2.4 mg (4). Tirzepatide, a dual GIP/GLP-1 receptor agonist, achieved greater weight reduction than semaglutide in the head-to-head SURMOUNT-5 trial (− 20.2% vs − 13.7% at 72 weeks) (5), has shown cardiac benefits in heart failure with preserved ejection fraction (SUMMIT) (6), and was associated with greater predicted 10-year cardiovascular risk reduction than semaglutide in a SURMOUNT-5 post hoc analysis (7). However, no randomised trial has directly compared the cardiovascular outcomes of tirzepatide and semaglutide in adults with obesity without T2D, and a recent systematic review confirmed a class MACE benefit for incretin therapies without resolving whether dual receptor agonism confers additional benefit (8).

Whether the dual GIP/GLP-1 agonism of tirzepatide—through enhanced glucose-dependent insulin secretion, lipid effects, and possible anti-inflammatory action (9, 10)—translates into incremental cardiovascular protection beyond selective GLP-1 receptor agonism is unknown. An individual participant data meta-analysis of phase 3 tirzepatide trials reported a 33% MACE reduction (11), but large-scale real-world head-to-head data remain limited.

Large-scale electronic health record (EHR) databases provide an opportunity to address this question. The TriNetX Global Collaborative Network aggregates de-identified EHR data from approximately 190 million patients across 178 healthcare organisations (12). We used a propensity score–matched

cohort design within TriNetX to compare MACE, all-cause mortality, and other cardiovascular and renal outcomes between tirzepatide and semaglutide in adults with obesity without T2D, with outcomes ascertained at 12 and 18 months under a 6-month landmark.

Methods

Study Design and Data Source

This retrospective, propensity score–matched cohort study used data from the TriNetX Global Collaborative Network (Cambridge, Massachusetts), a federated platform that aggregates de-identified EHR data from US and international healthcare organisations (12). All data remain at source institutions; only aggregate, de-identified results are returned for analysis. The protocol was approved by the Institutional Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital (IRB No. 2026028), with a waiver of informed consent because the analysis used only de-identified secondary data. The study followed the STROBE reporting guideline (13).

Study Population

We included adults aged 18–80 years with a diagnosis of obesity (ICD-10 E66.x) and a recorded body mass index (BMI; LOINC 39156-5) of ≥ 30 kg/m² within 12 months before the index date. New users of tirzepatide (RxNorm 2601723) with a first prescription between January 1 and December 31, 2024, formed the tirzepatide cohort (Cohort A); new users of subcutaneous semaglutide (RxNorm 1991302) over the same window formed the semaglutide cohort (Cohort B). The index date was the first qualifying prescription.

Patients were excluded for any of the following: T2D (ICD-10 E11.x at any time) or HbA1c ≥ 6.5% (LOINC 4548-4) within 12 months before index; type 1 diabetes (E10.x); CKD stage 5 or end-stage kidney disease (N18.5/N18.6); dialysis dependence (Z99.2); renal transplant (Z94.0); active malignancy (C00–C97) within 12 months; pregnancy within 12 months; or any prescription for a GLP-1 receptor agonist, GIP receptor agonist, or tirzepatide in the 12 months preceding index (new-user washout). Figure 1 presents the study flow diagram.

Propensity Score Matching

Propensity scores were estimated by logistic regression using the following 12-month lookback covariates: age, sex, race, ethnicity, BMI, HbA1c, estimated glomerular filtration rate (eGFR), comorbidities (hypertension, chronic ischaemic heart disease, prior MI, prior ischaemic stroke, peripheral vascular disease, dyslipidaemia, nicotine dependence), and concomitant medications (beta-blockers, calcium channel blockers, angiotensin II receptor blockers, ACE inhibitors, statins). One-to-one nearest-neighbour matching without replacement used a calliper of 0.1 SD of the logit of the propensity score.

Covariate balance was assessed with standardized mean differences (SMDs); SMD < 0.10 was considered adequate (14).

Outcomes

The primary outcome was a modified 3-point MACE composite of acute myocardial infarction (ICD-10 I21.x), ischaemic stroke (I63.x), or all-cause mortality. Cardiovascular death was not used as the third component because TriNetX lacks linkage to a national death registry, and ICD-10 I46.x denotes a clinical event rather than a certified cause-of-death classification. Algorithmic identification of cardiovascular death from administrative records achieves only 55–70% positive predictive value without registry linkage (15); substitution of all-cause mortality for cardiovascular death is the dominant approach in EHR- and claims-based MACE studies when adjudication is unavailable (16) and has been used in prior TriNetX analyses (17). Because non-cardiovascular deaths are unlikely to differ systematically between two weight-loss therapies with comparable safety, this substitution is expected to bias estimates conservatively toward the null.

Secondary outcomes were all-cause mortality; incident atrial fibrillation (AF; I48.x, excluding patients with any prior I48.x at baseline); acute MI; ischaemic stroke; and a CKD progression composite defined as new-onset CKD stage 3–5 or end-stage renal disease (N18.3–N18.6) or dialysis dependence (Z99.2) among patients without a prior renal diagnosis at baseline. CKD stage 3 was retained to preserve power, recognising that this threshold captures a more heterogeneous stage than the Major Adverse Kidney Events construct (18); KDIGO eGFR-trajectory progression was not feasible because TriNetX does not support longitudinal eGFR calculations (19). Heart failure hospitalisation, incident T2D, and all-cause hospitalisation were considered but excluded a priori because of platform constraints on primary-position coding, ascertainment validity over 12–18 months, and composite interpretability (20).

All outcomes were assessed at two prespecified horizons—12 and 18 months after index—to characterise the initial signal and its durability. Two prespecified negative control outcomes (21) probed for residual confounding: hernia (ICD-10 K40–K46) and age-related cataract (ICD-10 H25). Hernia was selected in concordance with its prespecified use in an ongoing federally registered head-to-head evaluation of tirzepatide versus semaglutide (NCT07096063) (22) because it shares a confounding structure with cardiovascular outcomes (age, obesity, physical activity, healthcare engagement) but is biologically unrelated to incretin pharmacology. Age-related cataract was chosen from a different organ system so that concordant null associations would provide stronger evidence against systematic bias.

Statistical Analysis

A 6-month landmark was applied to all analyses. Patients with an outcome event or death before month 6 were excluded; follow-up was measured from the landmark date. This approach allows time for pharmacological effects to manifest and minimises early-period outcome misclassification due to

incomplete adherence or baseline severity. Outcome ascertainment spanned months 6–12 and months 6–18 after index.

Kaplan-Meier curves were compared with the log-rank test. Cox proportional hazards regression estimated hazard ratios (HRs) with 95% CIs (semaglutide reference). The proportional hazards assumption was tested using Schoenfeld residuals ($P > 0.05$ indicating the assumption was met). Risk differences were calculated as absolute differences in event proportions. Two-sided $P < 0.05$ was considered statistically significant. No multiplicity adjustment was applied to secondary outcomes; these results are exploratory.

To quantify robustness of the primary MACE association, E-values were calculated for the point estimate and the confidence-interval bound closest to the null, following the VanderWeele-Ding method (29). The E-value represents the minimum risk-ratio strength of association an unmeasured confounder would need with both exposure and outcome—above and beyond measured covariates—to fully explain away the observed association. All analyses were performed within the TriNetX analytics platform.

Patients whose follow-up did not extend to 18 months—primarily those with later 2024 index dates—were administratively right-censored at the date of last recorded clinical encounter. Approximately 79% of matched patients reached the 18-month time point.

Results

Study Population and Baseline Characteristics

Of 1,716,771 adults aged 18–80 years with obesity and BMI ≥ 30 kg/m² in the TriNetX network, 821,942 remained eligible after exclusions; 54,990 initiated tirzepatide and 81,609 initiated semaglutide during 2024 (Fig. 1). After 1:1 propensity score matching, 54,978 matched pairs were analysed. Mean (SD) age was 46.6 (13.0) years for tirzepatide and 46.5 (13.6) years for semaglutide. Women constituted 74.0% and 74.5% of the cohorts, respectively. Mean (SD) BMI was 39.5 (7.4) in both groups; mean HbA1c was 5.58% (0.67%) and 5.58% (0.70%). Before matching, the proportion of Black or African American patients was higher in the semaglutide group (18.1% vs 14.0%; SMD 0.113), and the proportion of White patients was higher in the tirzepatide group (74.8% vs 70.3%; SMD 0.102); both imbalances were resolved after matching (SMDs < 0.01). All covariates achieved SMD < 0.10 after matching (Table 1).

Table 1
Patient Characteristics Before and After Propensity Score Matching

Characteristic	Before Matching			After Matching		
	Tirzepatide	Semaglutide	SMD	Tirzepatide	Semaglutide	SMD
No. of patients	54,990	81,609	—	54,978	54,978	—
Age at index, mean (SD), y	46.6 (13.0)	47.3 (13.7)	0.050	46.6 (13.0)	46.5 (13.6)	0.009
Female, No. (%)	40,692 (74.0)	60,896 (74.6)	0.014	40,691 (74.0)	40,969 (74.5)	0.012
Male, No. (%)	14,266 (25.9)	20,683 (25.3)	0.014	14,263 (25.9)	13,984 (25.4)	0.012
White, No. (%)	41,155 (74.8)	57,360 (70.3)	0.102	41,147 (74.8)	41,148 (74.8)	< 0.001
Black or African American, No. (%)	7,694 (14.0)	14,804 (18.1)	0.113	7,693 (14.0)	7,827 (14.2)	0.007
Asian, No. (%)	708 (1.3)	1,205 (1.5)	0.016	708 (1.3)	665 (1.2)	0.007
American Indian / Alaska Native, No. (%)	242 (0.4)	521 (0.6)	0.027	242 (0.4)	258 (0.5)	0.004
Native Hawaiian / Pacific Islander, No. (%)	145 (0.3)	247 (0.3)	0.007	145 (0.3)	147 (0.3)	< 0.001
Other / Unknown, No. (%)	5,046 (9.2)	7,472 (9.2)	0.003	5,043 (9.2)	4,933 (9.0)	0.008
Hispanic or Latino, No. (%)	3,439 (6.3)	6,153 (7.5)	0.051	3,438 (6.3)	3,483 (6.3)	0.003
BMI, mean (SD), kg/m²	39.5 (7.4)	39.5 (7.3)	0.007	39.5 (7.4)	39.5 (7.4)	0.005
HbA1c, mean (SD), %	5.58 (0.67)	5.62 (0.76)	0.055	5.58 (0.67)	5.58 (0.70)	0.002

The table presents demographic, clinical, comorbidity, and medication characteristics for the tirzepatide and semaglutide cohorts before and after 1:1 propensity score matching. Continuous variables are presented as mean ± SD; categorical variables as No. (%). Propensity score matching was performed 1:1 using nearest-neighbour matching (calliper 0.1 SD of the logit of the propensity score). All standardised mean differences (SMDs) were less than 0.10 after matching, indicating adequate covariate balance. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate (MDRD formula); HbA1c, glycated haemoglobin; ACE, angiotensin-converting enzyme; SMD, standardised mean difference.

Characteristic	Before Matching			After Matching		
	Tirzepatide	Semaglutide	SMD	Tirzepatide	Semaglutide	SMD
eGFR (MDRD), mean (SD), mL/min/1.73m²	87.2 (20.9)	87.8 (22.2)	0.030	87.2 (20.9)	87.8 (21.9)	0.030
Essential hypertension (I10), No. (%)	24,534 (44.6)	39,259 (48.1)	0.070	24,532 (44.6)	24,109 (43.9)	0.015
Dyslipidaemia (E78), No. (%)	24,588 (44.7)	37,716 (46.2)	0.030	24,582 (44.7)	24,231 (44.1)	0.013
Chronic ischaemic heart disease (I25), No. (%)	3,152 (5.7)	6,180 (7.6)	0.074	3,151 (5.7)	3,066 (5.6)	0.007
Prior acute MI (I21), No. (%)	665 (1.2)	1,601 (2.0)	0.060	664 (1.2)	662 (1.2)	< 0.001
Prior ischaemic stroke (I63), No. (%)	717 (1.3)	1,416 (1.7)	0.035	716 (1.3)	698 (1.3)	0.003
Peripheral vascular disease (I73.9), No. (%)	716 (1.3)	1,262 (1.5)	0.021	716 (1.3)	718 (1.3)	< 0.001
Nicotine dependence (F17), No. (%)	6,910 (12.6)	11,915 (14.6)	0.059	6,909 (12.6)	6,811 (12.4)	0.005
History of nicotine dependence (Z87.891), No. (%)	8,331 (15.2)	13,900 (17.0)	0.051	8,331 (15.2)	8,165 (14.9)	0.008
Beta-blockers, No. (%)	14,965 (27.2)	24,251 (29.7)	0.055	14,963 (27.2)	14,726 (26.8)	0.010
Calcium channel blockers, No. (%)	10,261 (18.7)	16,862 (20.7)	0.050	10,258 (18.7)	9,988 (18.2)	0.013
ACE inhibitors, No. (%)	8,565 (15.6)	14,069 (17.2)	0.045	8,563 (15.6)	8,383 (15.2)	0.009

The table presents demographic, clinical, comorbidity, and medication characteristics for the tirzepatide and semaglutide cohorts before and after 1:1 propensity score matching. Continuous variables are presented as mean ± SD; categorical variables as No. (%). Propensity score matching was performed 1:1 using nearest-neighbour matching (calliper 0.1 SD of the logit of the propensity score). All standardised mean differences (SMDs) were less than 0.10 after matching, indicating adequate covariate balance. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate (MDRD formula); HbA1c, glycated haemoglobin; ACE, angiotensin-converting enzyme; SMD, standardised mean difference.

Characteristic	Before Matching			After Matching		
	Tirzepatide	Semaglutide	SMD	Tirzepatide	Semaglutide	SMD
Angiotensin II receptor blockers, No. (%)	8,968 (16.3)	14,307 (17.5)	0.033	8,967 (16.3)	8,775 (16.0)	0.009
Atorvastatin, No. (%)	7,245 (13.2)	12,770 (15.6)	0.070	7,244 (13.2)	7,098 (12.9)	0.008
Rosuvastatin, No. (%)	4,300 (7.8)	6,490 (8.0)	0.005	4,297 (7.8)	4,108 (7.5)	0.013

The table presents demographic, clinical, comorbidity, and medication characteristics for the tirzepatide and semaglutide cohorts before and after 1:1 propensity score matching. Continuous variables are presented as mean ± SD; categorical variables as No. (%). Propensity score matching was performed 1:1 using nearest-neighbour matching (calliper 0.1 SD of the logit of the propensity score). All standardised mean differences (SMDs) were less than 0.10 after matching, indicating adequate covariate balance. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate (MDRD formula); HbA1c, glycated haemoglobin; ACE, angiotensin-converting enzyme; SMD, standardised mean difference.

Primary Outcome: MACE

At 6–12 months, MACE occurred in 343 patients (0.62%) in the tirzepatide group and 424 (0.77%) in the semaglutide group (HR 0.80; 95% CI 0.69–0.92; log-rank P = 0.002) (Table 2; Fig. 2A). At 6–18 months, MACE occurred in 526 (0.96%) and 631 (1.15%) patients, respectively (HR 0.84; 95% CI 0.75–0.94; P = 0.002). Schoenfeld residuals supported the proportional hazards assumption at both horizons.

Table 2
Clinical Outcomes After Propensity Score Matching at 6–12 Months and 6–18 Months After Index Date

Outcome	6–12 Months After Index Date				6–18 Months After Index Date			
	Tirz No. (%)	Sema No. (%)	HR (95% CI) P value	RD, pp (95% CI)	Tirz No. (%)	Sema No. (%)	HR (95% CI) P value	RD, pp (95% CI)
Matched cohort: 54,978 patients per group (n = 109,956 total). 6-month landmark design applied.								
MACE (AMI + ischaemic stroke + all-cause mortality) [Primary outcome]	343 (0.62)	424 (0.77)	0.80 (0.69–0.92) *P = .002*	−0.15 *(− 0.25 to − 0.05)*	526 (0.96)	631 (1.15)	0.84 (0.75–0.94) *P = .002*	−0.19 *(− 0.31 to − 0.07)*
All-cause mortality	37 (0.07)	46 (0.08)	0.80 (0.52–1.23) *P = .302*	−0.02 *(− 0.05 to 0.02)*	67 (0.12)	90 (0.16)	0.75 (0.55–1.03) *P = .077*	−0.04 *(− 0.09 to 0.01)*
Incident atrial fibrillation	327 (0.59)	388 (0.71)	0.83 (0.72–0.97) *P = .016*	−0.11 *(− 0.21 to − 0.01)*	478 (0.87)	571 (1.04)	0.84 (0.74–0.95) *P = .005*	−0.17 *(− 0.28 to − 0.06)*
Acute myocardial infarction	136 (0.25)	162 (0.29)	0.83 (0.66–1.04) *P = .112*	−0.05 *(− 0.11 to 0.01)*	205 (0.37)	247 (0.45)	0.83 (0.69–1.00) *P = .053*	−0.08 *(− 0.16 to 0.00)*
Ischaemic stroke	184 (0.33)	226 (0.41)	0.81 (0.66–0.98) *P = .030*	−0.08 *(− 0.15 to − 0.01)*	279 (0.51)	312 (0.57)	0.90 (0.76–1.05) *P = .187*	−0.06 *(− 0.14 to 0.02)*

A 6-month landmark design was applied; events occurring before month 6 were excluded, and follow-up was measured from month 6 after the index date. Event risk is expressed as the percentage of matched patients experiencing the outcome within each window. RD, risk difference in percentage points (tirzepatide minus semaglutide); positive RD favours semaglutide, negative RD favours tirzepatide. 95% CIs for RD were calculated using the standard formula for difference in proportions. An HR < 1 favours tirzepatide. Green shading indicates outcomes meeting the primary pre-specified significance threshold (P < .05) for both HR and RD in at least one time window. MACE was a modified 3-point composite of acute MI (ICD-10 I21), ischaemic stroke (I63), or all-cause mortality. CKD progression composite included new-onset CKD stage 3–5 (N18.3–N18.6) and dialysis dependence (Z99.2) among patients without prior renal diagnosis at baseline. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events; pp, percentage points; RD, risk difference; Sema, semaglutide; Tirz, tirzepatide.

Outcome	6–12 Months After Index Date				6–18 Months After Index Date			
	Tirz No. (%)	Sema No. (%)	HR (95% CI) P value	RD, pp (95% CI)	Tirz No. (%)	Sema No. (%)	HR (95% CI) P value	RD, pp (95% CI)
Matched cohort: 54,978 patients per group (n = 109,956 total). 6-month landmark design applied.								
CKD progression composite	380 (0.69)	448 (0.81)	0.84 (0.73–0.96) *P = .012*	−0.12 *(− 0.22 to − 0.02)*	532 (0.97)	648 (1.18)	0.82 (0.73–0.92) *P < .001*	−0.21 *(− 0.33 to − 0.09)*
Negative control: hernia (K40–K46)	1,150 (2.09)	1,155 (2.10)	0.99 (0.91–1.07) *P = .745*	−0.01 *(− 0.24 to 0.22)*	1,775 (3.23)	1,748 (3.18)	1.02 (0.96–1.09) *P = .539*	+ 0.05 *(− 0.26 to 0.36)*
Negative control: age-related cataract (H25)	407 (0.74)	419 (0.76)	0.96 (0.84–1.10) *P = .590*	−0.02 *(− 0.13 to 0.09)*	663 (1.21)	652 (1.19)	1.02 (0.92–1.14) *P = .673*	+ 0.02 *(− 0.14 to 0.18)*

A 6-month landmark design was applied; events occurring before month 6 were excluded, and follow-up was measured from month 6 after the index date. Event risk is expressed as the percentage of matched patients experiencing the outcome within each window. RD, risk difference in percentage points (tirzepatide minus semaglutide); positive RD favours semaglutide, negative RD favours tirzepatide. 95% CIs for RD were calculated using the standard formula for difference in proportions. An HR < 1 favours tirzepatide. Green shading indicates outcomes meeting the primary pre-specified significance threshold (P < .05) for both HR and RD in at least one time window. MACE was a modified 3-point composite of acute MI (ICD-10 I21), ischaemic stroke (I63), or all-cause mortality. CKD progression composite included new-onset CKD stage 3–5 (N18.3–N18.6) and dialysis dependence (Z99.2) among patients without prior renal diagnosis at baseline. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events; pp, percentage points; RD, risk difference; Sema, semaglutide; Tirz, tirzepatide.

Secondary Outcomes

All-cause mortality was rare. Between months 6 and 12, 37 deaths (0.07%) occurred in the tirzepatide group and 46 (0.08%) in the semaglutide group (HR 0.80; 95% CI 0.52–1.23; P = 0.30). Between months 6 and 18, 67 (0.12%) and 90 (0.16%) deaths occurred (HR 0.75; 95% CI 0.55–1.03; P = 0.08), a directional but statistically inconclusive reduction (Fig. 2B).

Tirzepatide was associated with a lower risk of incident AF at both intervals (6–12 months: 327 [0.59%] vs 388 [0.71%]; HR 0.83; 95% CI 0.72–0.97; P = 0.016; 6–18 months: 478 [0.87%] vs 571 [1.04%]; HR 0.84; 95% CI 0.74–0.95; P = 0.005) (Fig. 2C).

For individual MACE components, tirzepatide was associated with lower ischaemic stroke at 6–12 months (184 [0.33%] vs 226 [0.41%]; HR 0.81; 95% CI 0.66–0.98; P = 0.030), attenuating by 6–18 months

(HR 0.90; 95% CI 0.76–1.05; P = 0.19). Acute MI showed a directional reduction at 6–12 months (HR 0.83; 95% CI 0.66–1.04; P = 0.11) and a borderline reduction at 6–18 months (HR 0.83; 95% CI 0.69–1.00; P = 0.053).

The CKD progression composite was significantly lower with tirzepatide at both horizons: 6–12 months (380 [0.69%] vs 448 [0.81%]; HR 0.84; 95% CI 0.73–0.96; P = 0.012) and 6–18 months (532 [0.97%] vs 648 [1.18%]; HR 0.82; 95% CI 0.73–0.92; P < 0.001) (Fig. 2D).

Negative Control Outcomes

Neither prespecified negative control showed a differential association with tirzepatide. For hernia, HRs were 0.99 (0.91–1.07; P = 0.75) at 6–12 months and 1.02 (0.96–1.09; P = 0.54) at 6–18 months. For age-related cataract, HRs were 0.96 (0.85–1.10; P = 0.59) and 1.02 (0.92–1.14; P = 0.67). The concordant null findings provide reassurance against a systematic bias favouring tirzepatide.

E-Value Sensitivity Analysis

For the primary 12-month MACE outcome (HR 0.80; 95% CI 0.69–0.92), the E-value for the point estimate was 1.81 and for the upper confidence limit, 1.39. At 18 months (HR 0.84; 95% CI 0.75–0.94) the corresponding E-values were 1.67 and 1.32. For the three significant secondary outcomes, point-estimate E-values ranged from 1.67 (AF and CKD progression at 18 months) to 1.77 (ischaemic stroke at 12 months), with confidence-limit E-values from 1.16 to 1.39 (Table 3). Any unmeasured confounder fully explaining away the MACE benefit would need a risk-ratio association of at least 1.81 (point estimate) or 1.39 (upper 95% confidence limit) with both tirzepatide exposure and MACE—above and beyond measured covariates.

Table 3
E-Value Sensitivity Analysis for the Primary MACE Outcome and Significant Secondary Outcomes

Outcome	Time point	HR (95% CI)	E-value (Point estimate)	E-value (Upper CI bound)
MACE (primary)	12 months	0.80 (0.69–0.92)	**1.81**	1.39
MACE (primary)	18 months	0.84 (0.75–0.94)	**1.67**	1.32
Incident atrial fibrillation	12 months	0.83 (0.72–0.97)	**1.70**	1.21
Incident atrial fibrillation	18 months	0.84 (0.74–0.95)	**1.67**	1.29
Ischaemic stroke	12 months	0.81 (0.66–0.98)	**1.77**	1.16
CKD progression composite	12 months	0.84 (0.73–0.96)	**1.67**	1.25
CKD progression composite	18 months	0.82 (0.73–0.92)	**1.74**	1.39

E-values were calculated using the VanderWeele–Ding formula for HR < 1: E = (1/HR) + √[(1/HR) × ((1/HR) − 1)]. The E-value (point estimate) is the minimum risk-ratio association that an unmeasured confounder would need with both tirzepatide exposure and the outcome—above and beyond all measured covariates—to fully explain the observed HR. The E-value (upper CI bound) applies the same calculation to the upper 95% CI limit (the bound closest to the null). Only outcomes achieving statistical significance (P < .05) at one or both time horizons are included. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events.

BMI-Stratified Sensitivity Analysis

In prespecified sensitivity analyses stratifying by obesity class, HRs for MACE consistently favoured tirzepatide across all three subgroups at both horizons (HR range, 0.77–0.93; Supplementary Fig. 1). Point estimates were directionally concordant with the primary analysis with no qualitative interaction by BMI severity; individual subgroup analyses had limited power.

Proportional Hazards Assessment

The proportional hazards assumption was met for all primary and secondary outcomes at both 12- and 18-month analyses (Schoenfeld residuals, all P > 0.05).

Discussion

In this propensity score–matched cohort of 109,956 adults with obesity without T2D, tirzepatide was consistently associated with lower cardiovascular and renal event rates than semaglutide. The primary MACE composite was reduced by 20% at 12 months (HR 0.80; 95% CI 0.69–0.92) and 16% at 18 months

(HR 0.84; 95% CI 0.75–0.94), with statistically significant reductions in incident AF (16%–17%), 12-month ischaemic stroke (19%), and the CKD progression composite (16%–18%). Acute MI and all-cause mortality were directionally concordant (HR 0.83 for MI at both horizons; HR 0.75 for mortality at 18 months) but did not reach conventional statistical significance, with MI borderline at 18 months (P = 0.053). Across six prespecified outcomes, all point estimates favoured tirzepatide, four reaching significance, none reversing—a coherent pattern more consistent with a shared underlying effect than with isolated findings. Two prespecified negative controls were null and E-value analysis quantified robustness to unmeasured confounding. The consistency of effect estimates across obesity classes I–III (Supplementary Fig. 1) argues against a single-subgroup driver and supports generalisability across the obesity severity spectrum.

These findings extend prior evidence. SELECT showed that semaglutide 2.4 mg reduced MACE by 20% versus placebo in adults with overweight or obesity and established cardiovascular disease without diabetes (3); the SCORE study reported 37%–44% lower MACE with real-world semaglutide 2.4 mg (4); and a meta-analysis confirmed a class MACE benefit of incretin therapies in adults with obesity without diabetes (8). Our study suggests tirzepatide may offer additional cardiovascular protection beyond semaglutide, although absolute risk differences were small (12-month MACE RD, − 0.15 percentage points) and event rates were low, consistent with the younger, lower-risk profile of this real-world population versus SELECT.

The 16%–17% reduction in incident AF merits cautious interpretation against a heterogeneous prior literature. GLP-1 receptor agonists have reduced AF in patients with diabetes, heart failure, or HFpEF (23, 24), and a recent meta-analysis reported that GLP-1 receptor agonists and co-agonists reduced AF events in adults with overweight or obesity (25). However, a propensity-matched TriNetX analysis in adults with obesity without diabetes reported an increased risk of new-onset AF among GLP-1 receptor agonist users versus non-users (HR 1.09; P = 0.02) (26). Our results are not directly comparable because that study's comparator was non-use, whereas ours is an active incretin therapy. The 16%–17% lower AF risk with tirzepatide versus semaglutide may therefore reflect an additive effect of dual GIP/GLP-1 agonism—plausibly via greater weight loss (5), an established modifiable AF risk factor (27)—rather than a class effect; this hypothesis requires confirmation in randomised trials.

The numerically lower mortality (HR 0.75 at 18 months; P = 0.08) is directionally consistent but reflects limited power for a rare outcome over 18 months. A real-world comparison of semaglutide and tirzepatide in T2D found comparable cardiovascular benefits between the two agents (28), suggesting our findings may be population-specific.

Our findings should be considered alongside the STEER study, a propensity-matched analysis of 21,250 US adults with overweight or obesity and established cardiovascular disease but without T2D presented at ESC 2025 (Novo Nordisk–funded) (31). STEER reported that semaglutide 2.4 mg was associated with lower MACE than tirzepatide in a per-protocol analysis (HR 0.43; 95% CI 0.24–0.78). Three considerations inform interpretation: (i) STEER’s per-protocol mean follow-up was only 3.8 months—too

brief to capture true differences in hard cardiovascular endpoints—whereas our analyses span 6–12 and 6–18 months from a 6-month landmark; (ii) the gap between STEER's per-protocol (HR 0.43) and intent-to-treat (HR 0.71) estimates is consistent with healthy-user selection, potentially disadvantaging tirzepatide given its higher early gastrointestinal side-effect rate; (iii) STEER did not employ negative control endpoints, whereas ours were null. The Krüger et al trial-emulation analysis benchmarked against known trial results and found no significant difference between the agents in T2D (HR 1.06; 95% CI 0.95–1.18) (28). Taken together, current evidence does not establish definitive cardiovascular superiority of either agent, and our findings require randomised confirmation before drug-class distinctions guide clinical decisions.

Whether the cardiovascular advantage of tirzepatide observed in this study is mediated primarily through its greater magnitude of weight loss, through differential GIP/GLP-1 receptor signalling on cardiac and vascular tissue, or through synergistic mechanisms, cannot be determined from the present observational design. Tirzepatide produced 6.5 percentage points greater weight reduction than semaglutide in SURMOUNT-5 (5), and greater weight loss is associated with proportionally greater improvements in blood pressure, lipids, and inflammatory markers—all established cardiovascular risk mediators in obesity. Mediation analyses stratified by achieved weight loss at 6 months, or treatment-effect modification studies incorporating adiposity change as an intermediate variable, would be informative in future research to distinguish weight-dependent from weight-independent mechanisms of cardiovascular protection.

The durable reduction in CKD progression with tirzepatide (HR 0.82 at 18 months; $P < 0.001$) is consistent with emerging evidence that incretin-based therapies confer nephroprotection beyond glycaemic and cardiovascular effects, exemplified by the FLOW trial of semaglutide in diabetic kidney disease (≥ 50% eGFR decline threshold) (19). Our renal endpoint relied on ICD-10 coding of new-onset CKD stage 3–5 or dialysis rather than longitudinal eGFR trajectories, and CKD stage 3 may include patients with mild, non-progressive impairment. The renal findings should therefore be regarded as hypothesis-generating; whether the benefit reflects direct mechanisms or pathways mediated by weight loss, blood pressure, and insulin sensitivity cannot be determined here.

Limitations

First, despite rigorous propensity score matching, residual confounding cannot be excluded; however, two prespecified negative controls yielded HRs near 1.00 and E-value analysis indicates a confounder would need a risk-ratio of at least 1.81 with both exposure and MACE (1.39 for the upper confidence limit) to fully account for the primary finding (29). Second, cardiovascular death could not be reliably ascertained in TriNetX; all-cause mortality was therefore used in the MACE composite, a construction common in EHR/claims-based studies (16) and likely conservative because non-cardiovascular mortality is unlikely to differ between two incretin therapies with comparable safety profiles. Third, 12- and 18-month windows are insufficient to characterise long-term outcomes such as cardiovascular death and heart failure incidence; the latest-indexed patients were administratively right-censored at the data

extraction date (April 14, 2026), although ~ 79% reached 18 months. Fourth, TriNetX identifies subcutaneous semaglutide via a single RxNorm code (1991302) that does not distinguish 2.4 mg (Wegovy) from lower-dose diabetes formulations (Ozempic), a platform-level constraint shared by prior TriNetX analyses (30); because we excluded T2D by both ICD-10 and HbA1c, the majority of semaglutide use here would be Wegovy, and any residual sub-2.4 mg use would bias estimates toward the null. Fifth, the CKD composite incorporated CKD stage 3 (N18.3), which may include mild, non-progressive impairment, and KDIGO eGFR-trajectory metrics could not be computed in TriNetX; the renal findings should be considered exploratory. Sixth, several clinically relevant variables (patient-reported outcomes, adherence, achieved dose, cause-specific mortality) are unavailable in structured EHR data, and coding-based misclassification is possible though likely non-differential. Seventh, BMI-stratified subgroups were underpowered, and effect modification by age or sex was not formally evaluated. Finally, the cohort is predominantly US-based, limiting generalisability to other healthcare systems and populations.

Notwithstanding these limitations, strengths include a large and geographically diverse matched cohort drawn from a federated EHR platform spanning approximately 190 million patients (12); rigorous 1:1 propensity score matching across an extensive covariate set; two prespecified time horizons; two biologically distinct prespecified negative control endpoints; quantitative E-value sensitivity analysis; formal proportional hazards testing; and a prespecified BMI-stratified sensitivity analysis confirming consistency across obesity classes I–III.

Conclusion

In this propensity score–matched cohort study of adults with obesity without T2D, tirzepatide was associated with lower risks of MACE, incident AF, and CKD progression compared with semaglutide at 6–12 and 6–18 months of follow-up, with consistent directional reductions in acute MI, ischaemic stroke, and all-cause mortality. Supported by null negative-control analyses and E-value sensitivity, these findings generate the hypothesis that dual GIP/GLP-1 receptor agonism may confer cardiovascular benefits beyond those of selective GLP-1 receptor agonism. Modest absolute risk differences, short-to-intermediate follow-up, and the inherent limitations of observational data underscore the need for a dedicated randomised cardiovascular outcomes trial directly comparing tirzepatide and semaglutide in adults with obesity without T2D.

Abbreviations

AF – atrial fibrillation

BMI – body mass index

CI – confidence interval

CKD – chronic kidney disease

CV – cardiovascular

CVD – cardiovascular disease

EHR – electronic health record

eGFR – estimated glomerular filtration rate

GIP – glucose-dependent insulinotropic polypeptide

GLP-1 – glucagon-like peptide-1

GLP-1 RA – glucagon-like peptide-1 receptor agonist

HbA1c – glycated haemoglobin

HR – hazard ratio

ICD-10 – International Classification of Diseases, Tenth Revision

IRB – Institutional Review Board

LOINC – Logical Observation Identifiers Names and Codes

MACE – major adverse cardiovascular events

MI – myocardial infarction

PSM – propensity score matching

RCT – randomised controlled trial

SD – standard deviation

SMD – standardized mean difference

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

T2D – type 2 diabetes

Declarations

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Disclosure / Conflicts of Interest: The authors declared no conflict of interest.

Clinical trial registration: Not applicable. This is a retrospective observational study using de-identified electronic health record data and is not a clinical trial.

Data availability: De-identified data underlying this study were obtained from the TriNetX Global Collaborative Network under a third-party data-use agreement and cannot be redistributed by the authors. Researchers may apply for data access directly through TriNetX (www.trinetx.com).

Author contributions: Y.T.C. and S.C.C. conceived and designed the study. S.C.C. performed data acquisition, statistical analysis, and interpretation. Y.T.C. drafted the manuscript. S.C.C. critically revised the manuscript for important intellectual content, provided administrative and technical support, and supervised the work. Y.T.C. had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors approved the final version.

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Figures

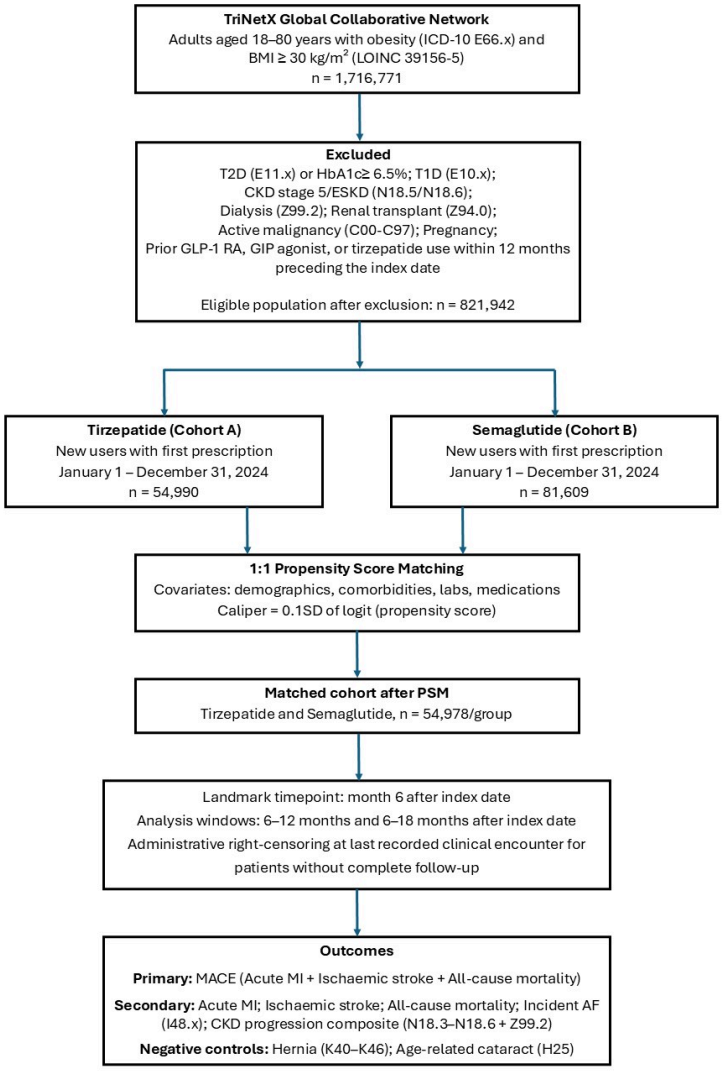


Figure 1

Study Flow Diagram. STROBE-style flow chart depicting patient identification, application of inclusion and exclusion criteria, cohort formation, propensity score matching, and the analytic framework. The tirzepatide cohort (Cohort A; n=54,990) and semaglutide cohort (Cohort B; n=81,609) were matched 1:1, yielding 54,978 matched pairs. GIP indicates glucose-dependent insulinotropic polypeptide; GLP-1 RA,

glucagon-like peptide-1 receptor agonist; PSM, propensity score matching; SMD, standardized mean difference.

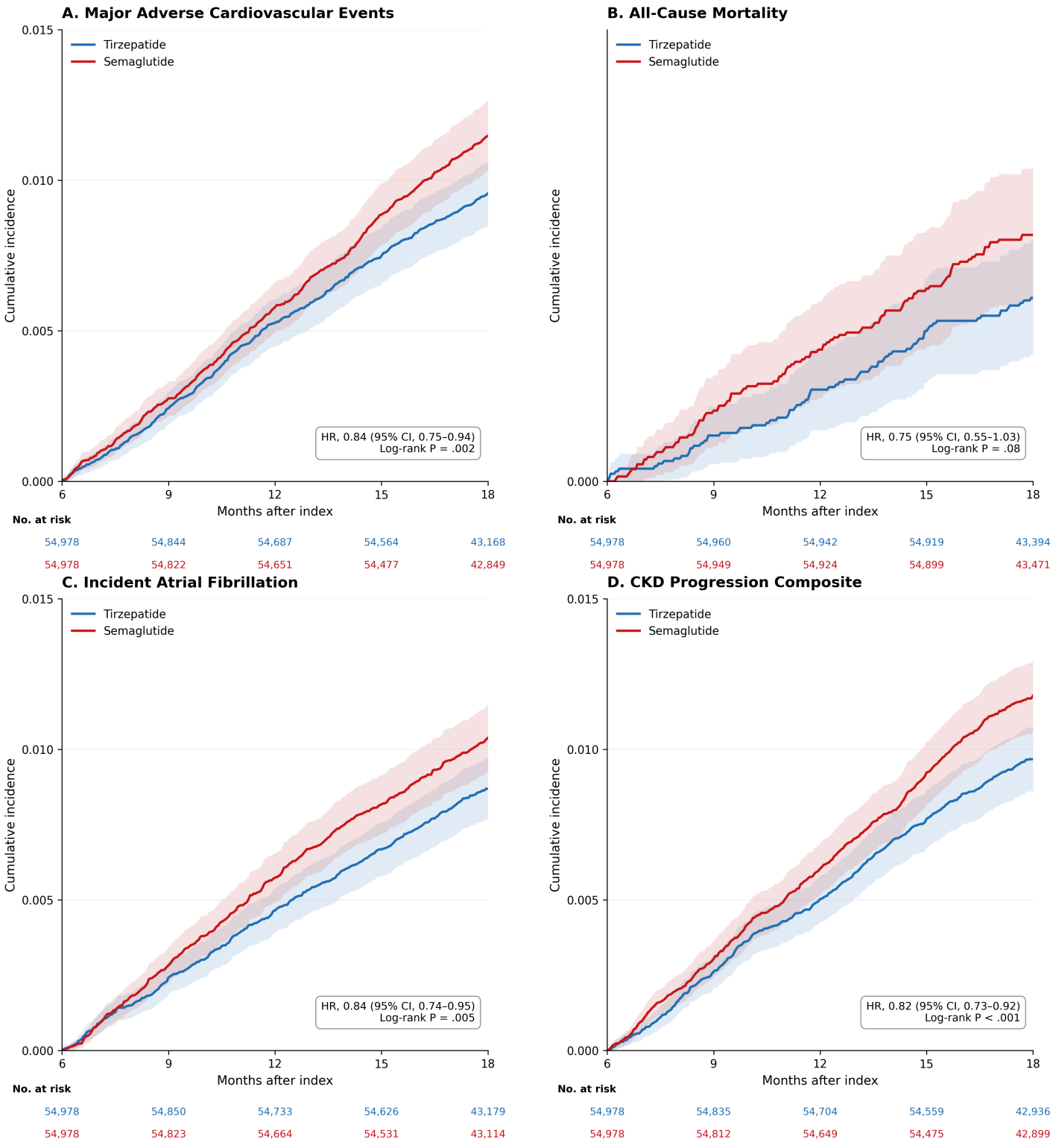


Figure 2

Kaplan-Meier Cumulative Incidence Curves for the Primary and Key Secondary Outcomes After Propensity Score Matching. Panel A shows MACE (composite of acute MI, ischaemic stroke, or all-

cause mortality). Panel B shows all-cause mortality. Panel C shows incident atrial fibrillation. Panel D shows the CKD progression composite. A 6-month landmark design was applied; outcome ascertainment began at month 6 after the index date, with follow-up extended to 12 and 18 months. The x-axis originates at month 6. The y-axis of Panel B is scaled to the lower event rate of all-cause mortality; the other three panels share a common y-axis (0–0.020). Shaded areas represent 95% CIs. HRs (95% CIs) and log-rank P values from the Cox model are annotated within each panel.