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Semaglutide and tirzepatide effects on cardiovascular outcomes in people with overweight or obesity in the real world (STEER)

Lauren Wilson MPH¹ | Zhenxiang Zhao PhD¹ | Victoria Divino BA¹ |
Matthew Bassan DO¹ | Bríain Ó. Hartaigh PhD¹ | Signe Stensen MD² |
Kerem Ozer MD¹

¹Novo Nordisk, Inc., Plainsboro, New Jersey, USA

²Novo Nordisk A/S, Søborg, Denmark

Correspondence

Lauren Wilson, Novo Nordisk, Inc., Plainsboro, NJ, USA.

Email: lywi@novonordisk.com

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Novo Nordisk, Inc.

Abstract

Aims: To assess the real-world effectiveness of semaglutide versus tirzepatide in reducing major adverse cardiovascular events (MACE) among patients with overweight/obesity and established atherosclerotic cardiovascular disease (ASCVD) without diabetes in an insured US population.

Materials and Methods: This retrospective, observational cohort study used Komodo Research Data and included patients ≥ 45 years of age with overweight/obesity and ≥ 1 claim for myocardial infarction (MI), ischemic stroke, or peripheral artery disease first treated with semaglutide or tirzepatide between 13/5/2022–31/1/2025. Propensity score matching was used to balance key baseline characteristics between cohorts. Primary outcomes included revised 3-point MACE (rMACE-3: MI, stroke, all-cause mortality) and revised 5-point MACE (rMACE-5: rMACE-3, coronary revascularization, hospitalisation for heart failure). Cox proportional hazard models were used to compare time to first event for study outcomes. A secondary per-protocol analysis was conducted where patients were censored at treatment discontinuation (gap in therapy >30 days).

Results: 10 625 patients were included in each matched cohort. Semaglutide was associated with statistically significant 29% (hazard ratio [HR] 0.71; $p = 0.046$) and 22% (HR 0.78; $p = 0.040$) reductions in the risk of rMACE-3 and rMACE-5, respectively, compared with tirzepatide. In the per-protocol analysis, semaglutide continued to be associated with a significantly lower risk of rMACE-3 (HR 0.43; $p = 0.005$) and rMACE-5 (HR 0.57; $p = 0.003$) compared with tirzepatide.

Conclusions: This real-world analysis of a large US claims database shows semaglutide was associated with early and significantly greater reductions in the risk of

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atherosclerotic cardiovascular disease, major cardiovascular events, obesity, real-world evidence, semaglutide, tirzepatide

Patients newly initiating semaglutide or tirzepatide on or after 13 May 2022 and after their eligibility date were identified. The first pharmacy claim was considered the index date. Given the recent approval for tirzepatide for weight management, this cohort included patients treated with Zepbound[®] as well as off-label use of Mounjaro[®] in those without any observed history of diabetes, given their equivalent dosing. The semaglutide cohort included patients treated with Wegovy[®] but off-label Ozempic[®] use was not included due to differences in semaglutide dosing for T2DM versus weight

management. Patients with any history of diabetes based on diagnosis, treatment, or HbA1c $\geq 6.5\%$ were excluded from both cohorts. There were no specific dosing requirements for either treatment. The maximum dose filled and last dose filled during the study period were reported for both cohorts.

All patients were required to have ≥ 12 months of continuous enrollment prior to the index date (baseline period), during which reconfirmation of overweight or obesity was required. Eligible patients were followed from index date to the earliest of end of continuous enrollment, end of study period, initiation of a non-index GLP-1 or GIP/GLP-1 RA, a bariatric surgical procedure, or death.

Patients were excluded if, during the 12-month baseline period, they had evidence of acute pancreatitis, end-stage kidney disease, pregnancy, prior use of a GLP-1 or GLP-1/GIP RA, or bariatric surgery. Patients with evidence of the following conditions at any point prior to index date were excluded: chronic pancreatitis, multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, or diabetes.

2.2 | Study outcomes

Primary outcomes included revised 3-point MACE (rMACE-3), defined as any occurrence of MI, stroke [ischemic or hemorrhagic], or all-cause mortality, and revised 5-point MACE (rMACE-5), defined as any occurrence of MI, stroke, hospitalisation for HF, coronary revascularization, or all-cause mortality.¹¹ Secondary outcomes included traditional MACE-3 and MACE-5, which include CV-related mortality instead of all-cause mortality, and individual components of all composite outcomes.

The occurrence of MI, stroke, and hospitalisation for HF were identified as a primary diagnosis during an inpatient visit. Coronary revascularization was identified using procedure codes in any claim. CV-related mortality was defined based on a previously published algorithm¹¹ as a death event with a primary diagnosis of MI, ischemic or haemorrhagic stroke, HF, CV haemorrhage, other CV conditions, or evidence of peripheral arterial revascularization, coronary revascularization, or carotid intervention within 30 days before death.^{14,15} Because of the difficulties identifying CV-related mortality in claims data, rMACE-3 and rMACE-5, which included all-cause mortality, were chosen as primary endpoints.

Baseline patient demographics, clinical characteristics (cardiometabolic markers, smoking status, type of ASCVD, procedure history, medication use, CV- and obesity-related comorbidities [ORCs]), and healthcare resource utilisation (HCRU) were described.

2.3 | Statistical methods

The main study analyses were conducted using an intention-to-treat (ITT) approach and followed patients through the end of follow-up, regardless of persistence on therapy. Baseline characteristics were compared between cohorts. To alleviate the effect of potential confounding or systematic differences in patient characteristics based on

treatment exposure, propensity score matching was used to balance key baseline characteristics across the two groups.

A propensity score matched analysis set was formed by matching each tirzepatide-treated patient to a semaglutide-treated patient using a 1:1 ratio. Standardised mean differences (SMDs) were utilised to evaluate the balance between the two cohorts both before and after matching with SMDs ≤ 0.10 constituting a successful balance. Patients were matched on baseline demographics and any imbalanced clinical characteristics. Covariates included age at index, gender, race/ethnicity, region, primary insurance, time from identification period start (13 May 2022) to index date, BMI category, number of ORCs, and number of outpatient visits during the baseline period. Matching was done using nearest neighbour matching with a calliper width threshold of 0.2 of the pooled standard deviation (SD) of the logit of the propensity score of semaglutide and tirzepatide users.

Time-to-event outcomes were described and compared between the two matched study cohorts. The number of events and corresponding proportions, as well as incidence per 1000 patient-years (95% CIs calculated using the Poisson distribution), were reported and cumulative incidence functions were visualised. A Cox proportional hazard model was fit with a binary covariate indicating semaglutide or tirzepatide use. Hazard ratios, 95% CI, and corresponding *p*-values were reported. For all statistical tests, *p*-values of < 0.05 were considered significant and no multiple comparison corrections were applied. All analyses were conducted in R (version 4.2.1).¹⁶

A secondary analysis was conducted using a per-protocol approach, in which patients were censored at index treatment discontinuation (defined as a gap in therapy of more than 30 days). Occurrence and time to rMACE-3 and rMACE-5, as well as their individual components, were described and compared between the two matched cohorts.

A sensitivity analysis was conducted evaluating the association between semaglutide versus tirzepatide and negative control outcomes including sensorineural hearing loss, dog bites, nail disorders, hearing tests without abnormal findings, and sebaceous cysts. These conditions were chosen as they are unlikely to be influenced by semaglutide or tirzepatide use but could be impacted by differences in unmeasured confounders. An exploratory analysis was done to evaluate the change in body weight over time among patients with available weight data (at index and ≥ 1 measurement post-index).

3 | RESULTS

A total of 22 691 922 patients ≥ 45 years of age with overweight or obesity and ASCVD were identified with 14 483 receiving semaglutide and 10 642 receiving tirzepatide and fulfilling the remaining inclusion criteria (Figure 1). Following propensity score matching, 10 625 patients were included in each study cohort.

Prior to propensity-score matching, more patients in the semaglutide cohort were over 65 (20.9% vs. 16.7%) and had Medicaid or Medicare (35.2% vs. 22.8%) compared with tirzepatide. After matching, study groups were well balanced on baseline demographics,

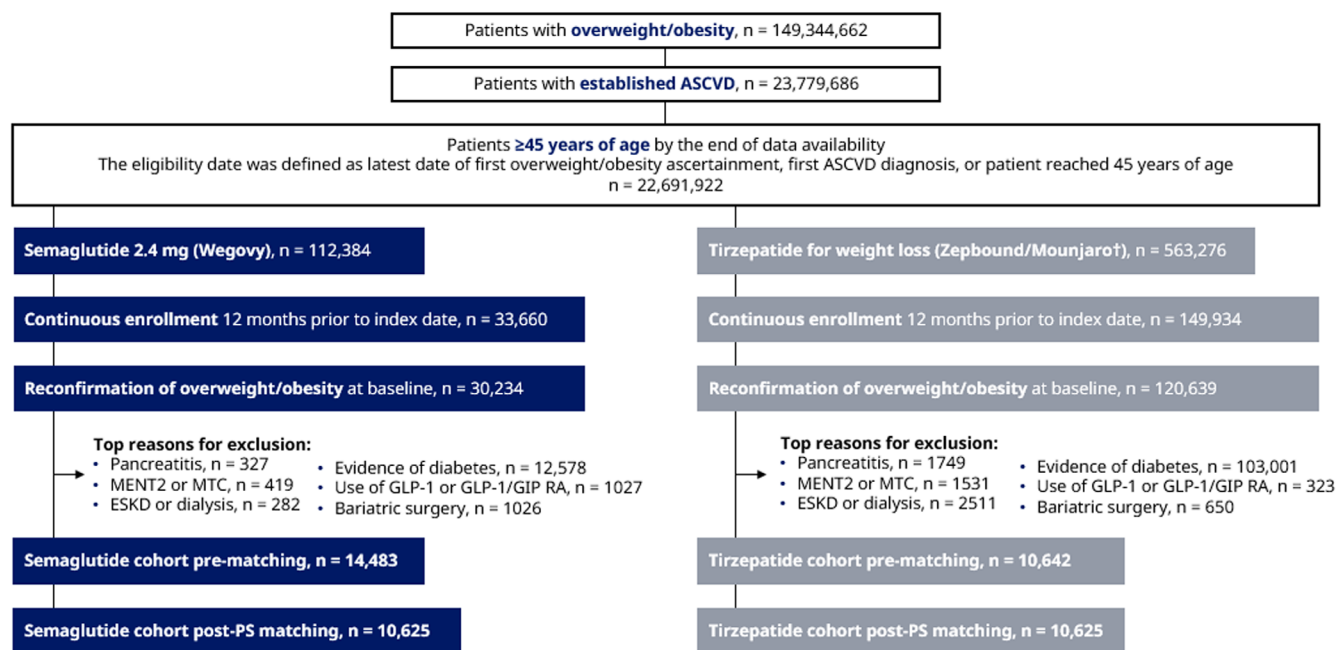


FIGURE 1 Study Cohort Attrition. ASCVD, atherosclerotic cardiovascular disease; ESKD, end-stage kidney disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated haemoglobin; MENT2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; PS, propensity score; RA, receptor agonist. †Given the recent approval of tirzepatide for weight loss (Zepbound), this study also included the off-label use of Mounjaro by including all patients with any fill for tirzepatide but no history of diabetes based on diagnosis, treatment, or elevated HbA1c.

clinical characteristics, and HCRU (Table 1). Some imbalance remained on the year of index date; however, patients were matched on time from identification period start to index date, which controls for timing of treatment initiation while avoiding discarding patients who did not initiate treatment within the same calendar year. Patients in both cohorts were most frequently 55–65 years of age, White, females, and from the South or Northeast. Most patients had hypertension (71%–73%) or dyslipidemia (70%–71%), and the majority used statins (56%–59%).

The mean follow-up duration for the semaglutide cohort was 8.3 (SD 6.4) months and patients had a mean of 5.1 (SD 4.8) prescription fills during this time. For the tirzepatide cohort, the mean follow-up duration was 8.6 (SD 7.1) months and included a mean of 5.6 (SD 5.0) prescription fills. At the end of follow-up, 21.7% of patients were taking the highest dose of semaglutide (2.4 mg) and 24.1% had ≥ 1 2.4 mg fill during the study period. For tirzepatide, 7.2% were taking the highest dose (15 mg) at the end of follow-up with 8.7% having ≥ 1 15 mg fill. Maintenance doses per label were reached by 38.0% of semaglutide users (1.7 or 2.4 mg) compared with 49.0% of tirzepatide users (5, 10, or 15 mg). At the end of follow-up, 35.8% of semaglutide users and 47.9% of tirzepatide users were taking a maintenance dose (Figure 2A).

3.1 | Revised MACE outcomes

In the ITT analysis, a lower risk of CV events was observed in patients who received semaglutide compared with those who received tirzepatide. The incidence per 1000 patient-years for rMACE-3 was 7.6 (95% CI

5.7–9.8) for the semaglutide cohort and 10.8 (95% CI 8.6–13.3) for the tirzepatide cohort (Figure 3A). The risk of rMACE-3 was significantly lower by 29% with semaglutide (HR 0.71; 95% CI 0.50–0.99; $p = 0.046$). Between-cohort differences in the incidence of CV events are observable at early timepoints with separation initiating less than 3 months post-index and continuing through the end of follow-up (Figure 4A).

The incidence per 1000 patient-years for rMACE-5 was 16.7 (95% CI 13.9–19.8) for the semaglutide cohort and 21.0 (95% CI 17.9–24.4) for the tirzepatide cohort (Figure 3A). The risk of rMACE-5 was significantly lower by 22% with semaglutide (HR 0.78; 95% CI 0.62–0.99; $p = 0.040$). Again, between-cohort differences in the incidence of CV events were visually observable early in treatment, occurring less than 2 months post-index and continuing through follow-up (Figure 4B).

There were no statistically significant differences between study cohorts for each of the individual components of rMACE-3 and rMACE-5 (Figure 3A). However, directionally consistent effects were observed for all individual component endpoints with semaglutide compared with tirzepatide in incidence per 1000 patient-years for MI (3.8 vs. 5.4), hospitalisation for HF (4.3 vs. 6.1), stroke (2.4 vs. 3.9), coronary revascularization (7.6 vs. 8.7), and all-cause mortality (1.5 vs. 1.7).

3.2 | MACE outcomes

The differences in MACE-3, which included CV-related mortality instead of all-cause mortality, did not reach statistical significance

TABLE 1 Pre- and post-propensity score matching baseline demographics, clinical characteristics, costs, and healthcare resource utilisation.

	Pre-matching			Post-matching		
Variable	Semaglutide (N = 14 483)	Tirzepatide (N = 10 642)	SMD	Semaglutide (N = 10 625)	Tirzepatide (N = 10 625)	SMD
Demographics						
Age at index, mean (SD)	59.1 (8.6)	58.3 (8.2)	0.093	58.5 (8.3)	58.3 (8.2)	0.020
Age group, n (%)			0.110			0.047
45–55 years	5471 (37.8)	4316 (40.6)		4233 (39.8)	4302 (40.5)	
56–65 years	5978 (41.3)	4549 (42.8)		4461 (42.0)	4546 (42.8)	
66–75 years	2354 (16.3)	1374 (12.9)		1545 (14.5)	1374 (12.9)	
≥ 76 years	680 (4.7)	403 (3.8)		386 (3.6)	403 (3.8)	
Gender, n (%)			0.042			0.006
Female	9216 (63.6)	6554 (61.6)		6566 (61.8)	6541 (61.6)	
Male	5067 (35.0)	3929 (36.9)		3906 (36.8)	3925 (36.9)	
Race/Ethnicity, n (%)			0.126			0.029
Asian/Pacific Islander	695 (4.8)	538 (5.1)		546 (5.1)	538 (5.1)	
Black/African American	1767 (12.2)	1060 (10.0)		1142 (10.8)	1060 (10.0)	
Hispanic/Latino	1389 (9.6)	945 (8.9)		923 (8.7)	945 (8.9)	
White	8123 (56.1)	5782 (54.3)		5784 (54.4)	5782 (54.4)	
Unknown	2509 (17.3)	2317 (21.8)		2230 (21.0)	2300 (21.7)	
Geographic region, n (%)			0.271			0.073
Midwest	3145 (21.7)	2088 (19.6)		2233 (21.0)	2088 (19.7)	
Northeast	5327 (36.8)	3066 (28.8)		3267 (30.8)	3066 (28.9)	
South	4210 (29.1)	4410 (41.4)		4033 (38.0)	4409 (41.5)	
West	1790 (12.4)	1053 (9.9)		1081 (10.2)	1053 (9.9)	
Unknown	11 (0.1)	25 (0.2)		11 (0.1)	9 (0.1)	
Medical insurance provider, n (%)			0.321			0.029
Commercial	9341 (64.5)	8191 (77.0)		8126 (76.5)	8174 (76.9)	
Medicaid	1960 (13.5)	585 (5.5)		547 (5.2)	585 (5.5)	
Medicare	2845 (19.6)	1700 (16.0)		1784 (16.8)	1700 (16.0)	
Dual eligible	293 (2.0)	142 (1.3)		137 (1.3)	142 (1.3)	
Unknown	44 (0.3)	24 (0.2)		31 (0.3)	24 (0.2)	
Clinical characteristics						
Follow-up time in months, mean (SD)	8.0 (6.3)	8.6 (7.1)	−0.098	8.30 (6.4)	8.64 (7.1)	−0.050
Index year, n (%)			0.173			0.125
2022	317 (2.2)	2142 (20.1)		254 (2.4)	2141 (20.2)	
2023	6659 (46.0)	2516 (23.6)		5179 (48.7)	2514 (23.7)	
2024	7150 (49.4)	5617 (52.8)		4976 (46.8)	5604 (52.7)	
2025	357 (2.5)	367 (3.5)		216 (2.0)	366 (3.4)	
Time from ID to index date in days, mean (SD) ^a	587.4 (240.9)	562.3 (270.0)	0.098	570.49 (238.7)	561.99 (269.9)	0.033
Time from eligibility date to index date in months, mean (SD)	36.76 (27.5)	35.28 (26.7)	0.055	36.14 (27.1)	35.30 (26.7)	0.031
BMI, mean (SD)	36.98 (5.1)	36.71 (5.3)	0.052	36.72 (5.1)	36.71 (5.3)	0.001
BMI category, n (%) ^b			0.083			0.030
Overweight	714 (4.9)	687 (6.5)		616 (5.8)	686 (6.5)	
Obesity class I	3201 (22.1)	2332 (21.9)		2392 (22.5)	2332 (22.0)	
Obesity class II	2968 (20.5)	2007 (18.9)		2031 (19.1)	2007 (18.9)	
Obesity class III	3243 (22.4)	2254 (21.2)		2246 (21.1)	2252 (21.2)	
Obesity BMI class unspecified	4357 (30.1)	3362 (31.6)		3340 (31.4)	3348 (31.5)	

(Continues)

TABLE 1 (Continued)

Variable	Pre-matching		SMD	Post-matching		SMD
	Semaglutide (N = 14 483)	Tirzepatide (N = 10 642)		Semaglutide (N = 10 625)	Tirzepatide (N = 10 625)	
Evidence of smoking history, n (%)	3302 (22.8)	2178 (20.5)	0.068	2256 (21.2)	2174 (20.5)	0.041
ASCVD before index date, n (%)						
MI	5558 (38.4)	3741 (35.2)	0.067	4111 (38.7)	3741 (35.2)	0.072
Stroke	4636 (32.0)	3212 (30.2)	0.039	3382 (31.8)	3212 (30.2)	0.035
PAD	6054 (41.8)	4669 (43.9)	−0.042	4311 (40.6)	4652 (43.8)	−0.065
Comorbidities during baseline, n (%)						
CV and renal						
Hypertension	10 656 (73.6)	7570 (71.1)	0.055	7726 (72.7)	7557 (71.1)	0.035
Dyslipidemia	10 385 (71.7)	7475 (70.2)	0.032	7560 (71.2)	7469 (70.3)	0.019
HF	1395 (9.6)	839 (7.9)	0.062	915 (8.6)	839 (7.9)	0.026
Unstable angina	1265 (8.7)	878 (8.3)	0.017	919 (8.7)	877 (8.3)	0.014
Atrial fibrillation	1529 (10.6)	1019 (9.6)	0.033	1055 (9.9)	1019 (9.6)	0.011
CKD	1002 (6.9)	651 (6.1)	0.032	631 (5.9)	651 (6.1)	−0.008
Other ORC						
Musculoskeletal pain	6952 (48.0)	4787 (45.0)	0.061	4857 (45.7)	4781 (45.0)	0.014
Pre-diabetes	5558 (38.4)	4324 (40.6)	−0.046	3971 (37.4)	4318 (40.6)	−0.067
OSA	5120 (35.4)	3663 (34.4)	0.020	3682 (34.7)	3660 (34.5)	0.004
GERD	4688 (32.4)	3189 (30.0)	0.052	3315 (31.2)	3187 (30.0)	0.026
Knee osteoarthritis	2677 (18.5)	1762 (16.6)	0.051	1764 (16.6)	1761 (16.6)	0.001
Asthma	2345 (16.2)	1567 (14.7)	0.041	1564 (14.7)	1567 (14.8)	−0.001
Number of ORCs, mean (SD)	3.47 (1.7)	3.34 (1.7)	0.079	3.35 (1.6)	3.34 (1.7)	0.008
MASH/MAFLD						
MASH	123 (0.9)	97 (0.9)	−0.007	83 (0.8)	97 (0.9)	−0.014
MAFLD	1286 (8.9)	943 (8.9)	0.001	872 (8.2)	943 (8.9)	−0.024
Procedures during baseline, n (%)						
Peripheral arterial revascularization	73 (0.5)	42 (0.4)	0.016	50 (0.5)	42 (0.4)	0.011
Carotid intervention	22 (0.2)	13 (0.1)	0.008	19 (0.2)	13 (0.1)	0.015
Coronary revascularization	364 (2.5)	257 (2.4)	0.006	259 (2.4)	257 (2.4)	0.001
Medication usage during baseline, n (%)						
Statin therapy	8648 (59.7)	5923 (55.7)	0.082	6246 (58.8)	5922 (55.7)	0.062
Beta-blocker	6009 (41.5)	4164 (39.1)	0.048	4335 (40.8)	4163 (39.2)	0.033
ARBs	4399 (30.4)	3263 (30.7)	−0.006	3232 (30.4)	3253 (30.6)	−0.004
Thiazides	3839 (26.5)	2818 (26.5)	0.001	2823 (26.6)	2811 (26.5)	0.003
Calcium channel blockers	3945 (27.2)	2679 (25.2)	0.047	2795 (26.3)	2674 (25.2)	0.026
ACE inhibitors	3067 (21.2)	2096 (19.7)	0.037	2219 (20.9)	2094 (19.7)	0.029
Loop diuretics	1972 (13.6)	1319 (12.4)	0.036	1324 (12.5)	1318 (12.4)	0.002
Anticoagulants	2000 (13.8)	1375 (12.9)	0.026	1399 (13.2)	1375 (12.9)	0.007
Antiplatelets ^c	1868 (12.9)	1249 (11.7)	0.035	1377 (13.0)	1249 (11.8)	0.037
Obesity medications ^d	167 (1.2)	108 (1.0)	0.013	134 (1.3)	108 (1.0)	0.023
Aldosterone antagonists	46 (0.32)	31 (0.3)	0.005	28 (0.3)	31 (0.3)	−0.005
Healthcare resource utilisation during 12-month baseline period						
Inpatient visits, mean (SD)	0.19 (1.3)	0.16 (0.8)	0.022	0.15 (0.8)	0.17 (0.8)	−0.017
ED visits, mean (SD)	0.76 (1.9)	0.62 (1.3)	0.086	0.67 (1.6)	0.62 (1.3)	0.032
Outpatient visits, mean (SD)	30.55 (38.0)	26.12 (26.9)	0.134	26.18 (24.7)	26.15 (26.9)	0.001

TABLE 1 (Continued)

Variable	Pre-matching		SMD	Post-matching		SMD
	Semaglutide (N = 14 483)	Tirzepatide (N = 10 642)		Semaglutide (N = 10 625)	Tirzepatide (N = 10 625)	
Receipt of weight management consultation and specialty care service, n (%)	2389 (16.5)	1632 (15.3)	0.032	1719 (16.2)	1629 (15.3)	0.023

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; ED, emergency department; GERD, gastroesophageal reflux disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ID, identification; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; ORC, obesity-related complication; OSA, obstructive sleep apnea; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCOS, polycystic ovary syndrome; PPPY, per patient per year; RX, prescription; SD, standard deviation; SMD, standardised mean difference; UI, urinary incontinence.

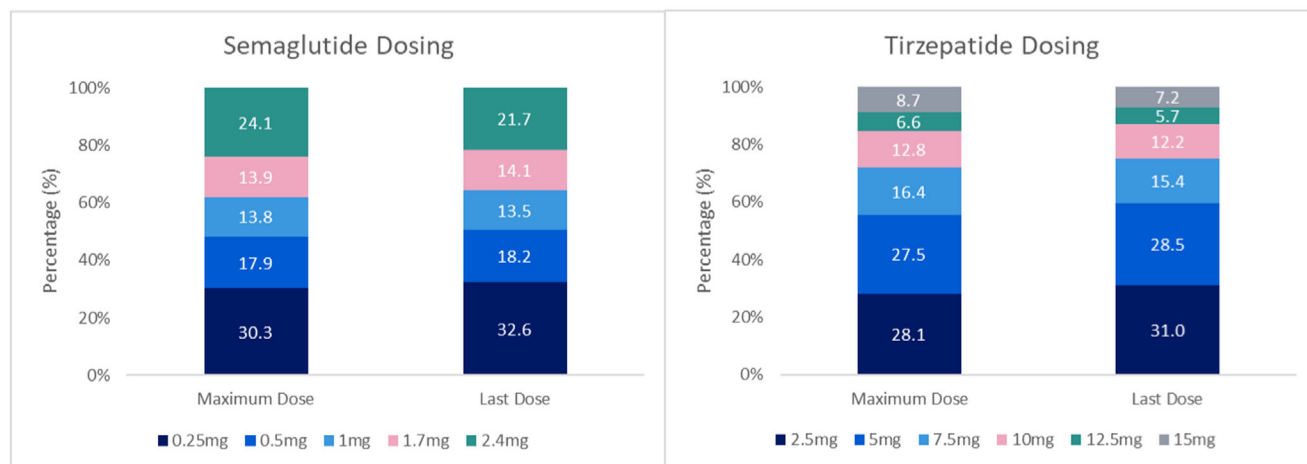
^aReflects time from the start of the identification period (1 January, 2016) to index date.

^bPatients with BMI category information refer to individuals without exact BMI values available; patients with detailed BMI value information refer to individuals with exact BMI values available.

^cIncluding warfarin, thrombin inhibitors, and direct factor Xa inhibitors.

^dIncluding orlistat, phentermine-topiramate, phentermine, and naltrexone-bupropion.

(A)



(B)

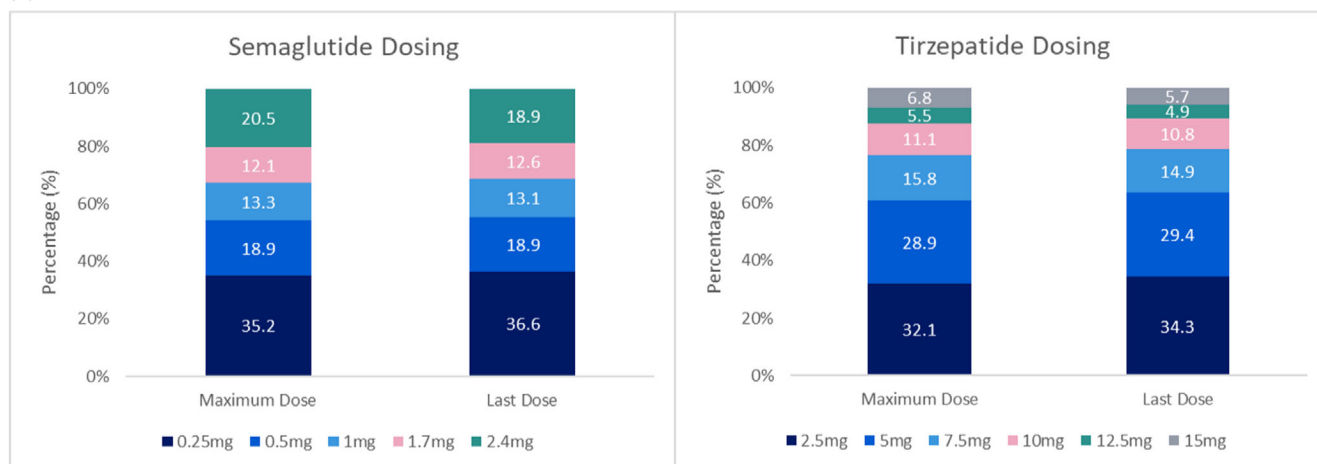
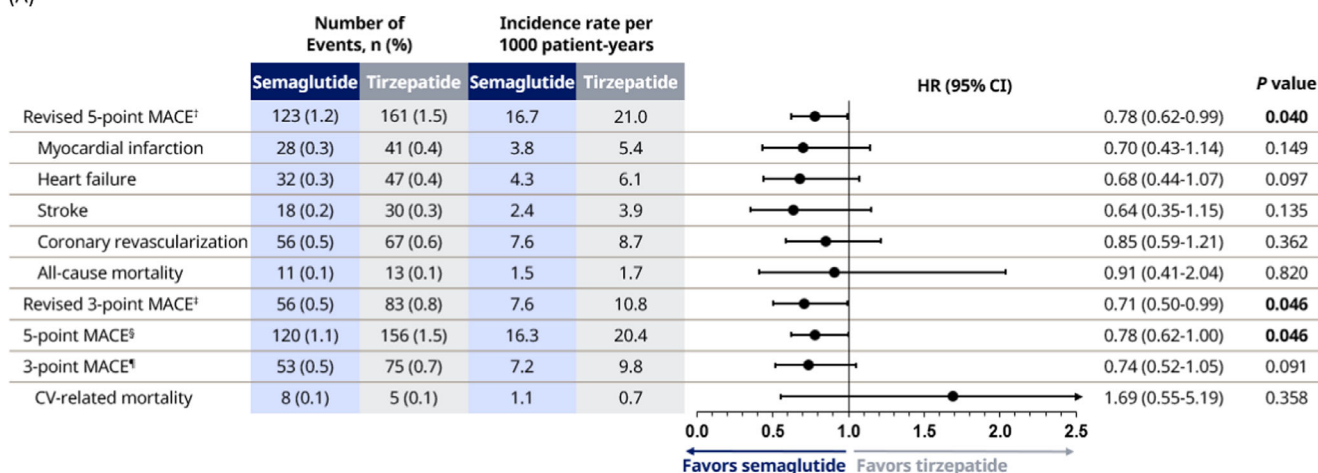


FIGURE 2 Maximum dose and Last dose reached by treatment cohort (ITT and per-protocol analysis; propensity score matched). (A) ITT analysis. (B) Per-protocol analysis. ITT, intention-to-treat.

(A)



(B)

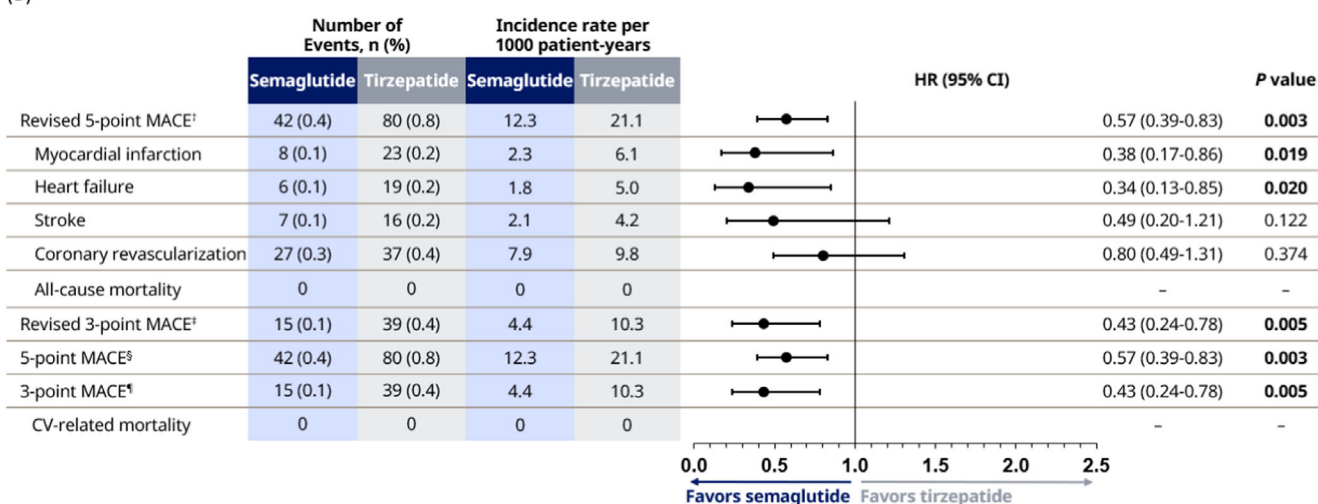


FIGURE 3 Incidence rates and hazard ratios for major adverse cardiovascular events with semaglutide versus tirzepatide for weight loss (ITT and per-protocol analysis; propensity score matched). (A) ITT analysis. (B) Per-protocol analysis. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; MACE, major adverse cardiovascular event. [†]Revised 5-point MACE includes myocardial infarction, stroke, hospitalisation for heart failure, coronary revascularization, and all-cause mortality. [‡]Revised 3-point MACE includes myocardial infarction, stroke, and all-cause mortality. [§]5-point MACE includes myocardial infarction, heart failure, stroke, coronary revascularization, and CV-related mortality. [¶]3-point MACE includes myocardial infarction, stroke, and CV-related mortality.

(HR 0.74; 95% CI 0.52–1.05; $p = 0.091$; Figure 3A). The risk of MACE-5 was significantly lower by 22% with semaglutide compared with tirzepatide (HR 0.78; 95% CI 0.62–1.00; $p = 0.046$). The difference in the risk of CV-related mortality was not statistically significant (HR 1.69; 95% CI 0.55–5.19; $p = 0.358$).

3.3 | Secondary per-protocol analysis

In the per-protocol analysis, the mean follow-up period for the semaglutide cohort was 3.8 (SD 4.1) months and patients had a mean of 4.4 (SD 4.4) prescription fills during this time. For the tirzepatide cohort, the mean follow-up period was 4.3 months and included a mean of 4.8 (SD 4.6) prescription fills. Dosing patterns were similar to the ITT analysis (Figure 2B).

Use of semaglutide was associated with significant reductions in the risk of rMACE-3 and rMACE-5 compared with use of tirzepatide (Figure 4C,D). The risk of rMACE-3 was reduced by 57% (HR 0.43; 95% CI 0.24–0.78; $p = 0.005$; Figure 3B) and the risk of rMACE-5 was lower by 43% with semaglutide (HR 0.57; 95% CI 0.39–0.83; $p = 0.003$) compared with tirzepatide. No mortality events were observed in the per-protocol analysis, resulting in equivalent MACE and rMACE outcomes.

The per-protocol analysis showed significantly decreased risk of some individual CV outcomes associated with use of semaglutide compared with tirzepatide (Figure 3B). The risk of MI was lower by 62% (HR 0.38; 95% CI 0.17–0.86; $p = 0.019$) with semaglutide compared with tirzepatide and the risk of hospitalisation for HF was 66% lower (HR 0.34; 95% CI 0.13–0.85; 0.02). Directionally consistent effects were observed for semaglutide compared with tirzepatide in

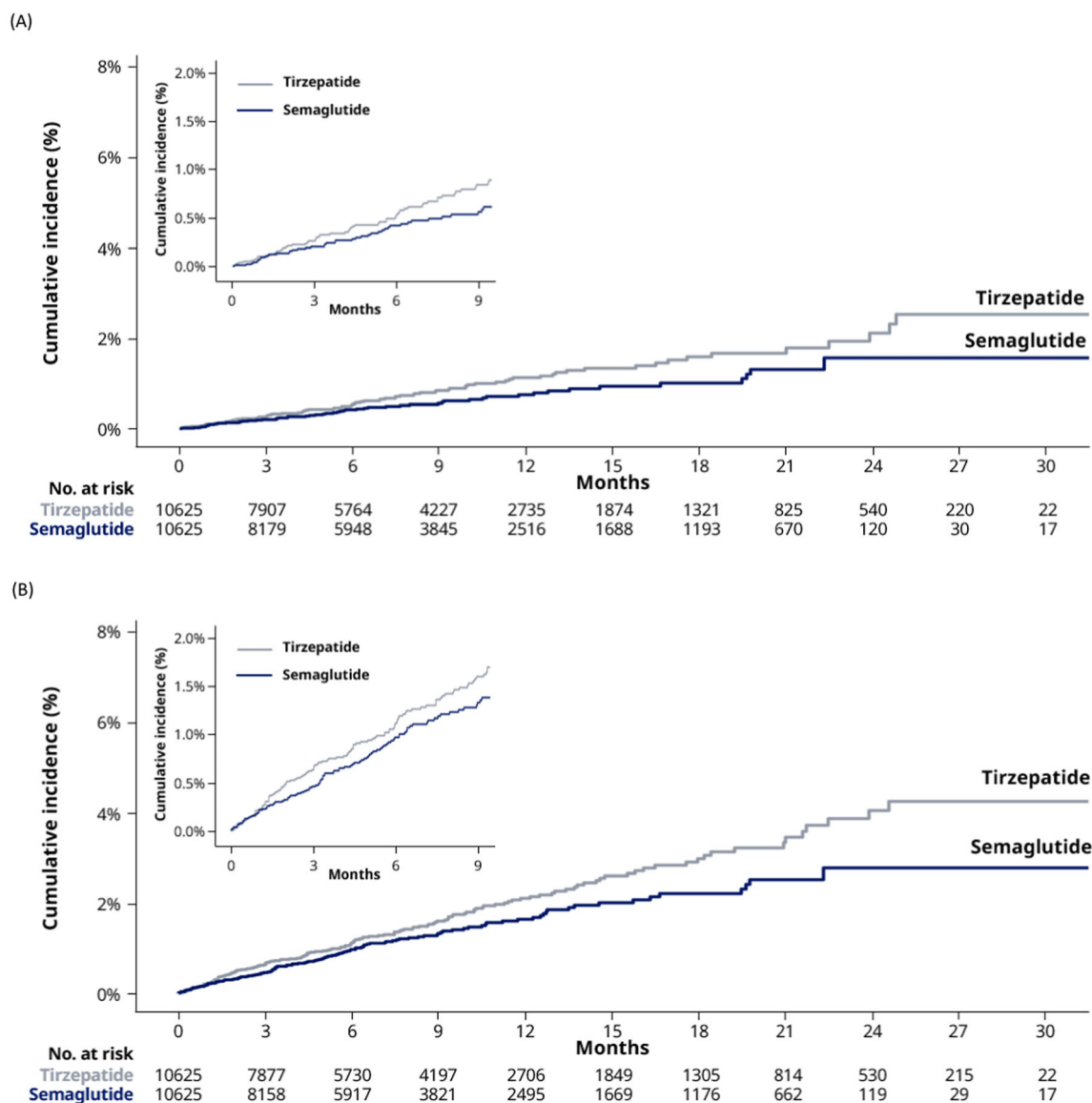


FIGURE 4 Cumulative incidence of major adverse cardiovascular events with semaglutide versus tirzepatide for weight loss (propensity score matched)[†]. (A) Revised 3-Point MACE[‡]—ITT Analysis[‡]. (B) Revised 5-Point MACE[§]—ITT Analysis[‡]. (C) Revised 3-Point MACE[‡]—Per-Protocol Secondary Analysis[¶]. (D) Revised 5-Point MACE[§]—Per-Protocol Secondary Analysis[¶]. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; ITT, intention-to-treat; MACE, major adverse cardiovascular event; No, number. Revised 3-point MACE includes myocardial infarction, stroke, and all-cause mortality. [‡]Analysis includes patients who were followed through the end of follow-up regardless of persistence on therapy. End of follow-up was defined as the earliest of the end of the study period (31 January 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death. [§] Revised 5-point MACE includes myocardial infarction, stroke, hospitalisation for heart failure, coronary revascularization, and all-cause mortality. Analysis includes patients who were censored at treatment discontinuation (i.e., a gap in therapy of >30 days).

incidence per 1000 patient-years for stroke (2.1 vs. 4.2) and coronary revascularization (7.9 vs. 9.8).

The exploratory analyses showed a greater average weight loss over 12 months with tirzepatide versus semaglutide among patients with available data (Supplemental Figure 2).

3.4 | Sensitivity and exploratory analyses

The sensitivity analysis showed no significant differences between semaglutide and tirzepatide users for the five negative control outcomes (Supplemental Table 1).

4 | DISCUSSION

The STEER study assessed the real-world incidence of MACE during treatment with semaglutide or tirzepatide among patients with

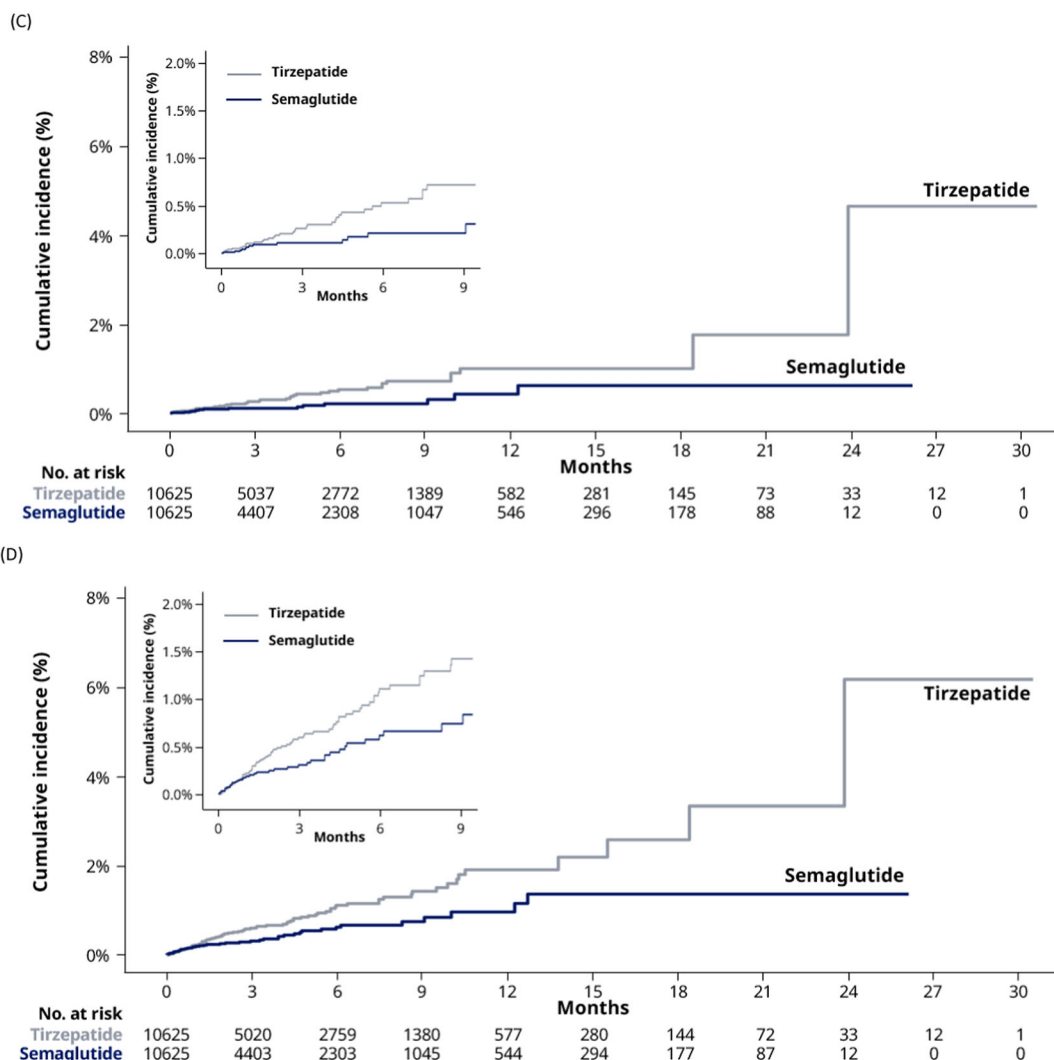


FIGURE 4 (Continued)

overweight or obesity and ASCVD, without diabetes, in routine clinical practice in the US. This comparative ITT analysis found semaglutide was associated with statistically significant 29% and 22% reductions in rMACE-3 and rMACE-5, respectively, compared with tirzepatide. Results were even more pronounced in the per-protocol analysis, including patients actively on treatment, where semaglutide was associated with statistically significant 57% and 43% reductions in rMACE-3 and rMACE-5, respectively.

This study adds to the existing body of evidence demonstrating the beneficial impact of semaglutide on CV outcomes from clinical trials^{7,17-19} and real-world populations.^{9,10} The landmark trial, SELECT, demonstrated the superiority of semaglutide over placebo with a 20% reduction in the risk of MACE.⁷ These beneficial CV effects of semaglutide were observed early after treatment initiation, with the first statistically significant differences observed at Day 20 and sustained from Day 86 through the end of follow-up.²⁰ Results of the current study are consistent with the findings of SELECT and also support early and sustained effectiveness with semaglutide versus tirzepatide, as the between group difference in the incidence of

rMACE-3 and rMACE-5 was observed as early as 2–3 months after semaglutide initiation and continued through the end of follow-up.

Semaglutide has demonstrated both direct and indirect benefits on CV outcomes.²⁰⁻²² GLP-1 RAs have been reported to directly influence the CV system through several independent mechanisms²³⁻³²; thus, recent data supports that the significant improvement in CV outcomes associated with semaglutide is not attributable to the magnitude of weight loss. Prespecified mediation analyses from SELECT show the cardioprotective effects of semaglutide are independent of baseline adiposity and weight loss, suggesting a benefit beyond weight reduction.²² Additionally, the benefit of semaglutide on MACE risk reduction preceded any clinically meaningful changes in body weight.²⁰ In the current study, patients treated with tirzepatide showed consistently greater weight loss compared with semaglutide (Supplemental Figure 2); however, the reduction in CV risk was significantly greater with semaglutide. Data from SELECT also showed changes in several other measured CV risk factors (e.g., high-sensitivity C-reactive protein, blood pressure) did not fully explain the effect of semaglutide on MACE risk reduction. Thus, the

CV benefits with semaglutide may also be independent of improvements in cardiometabolic risk factors. Further investigation into the mechanism of semaglutide's direct effect on CV outcomes is needed. The CV benefit with semaglutide may also be independent of dose. In SELECT, the benefit of semaglutide on MACE risk reduction occurred early, prior to full titration to the target maintenance dose of 2.4 mg for weight loss,²⁰ and only 77% of patients were taking this dose by study Year 2.⁷ In the current study, only 38% of semaglutide-treated patients reached maintenance doses; however, a significantly lower risk of CV events was still observed compared with tirzepatide.

To our knowledge, this is the first study to assess the real-world effectiveness of semaglutide compared with tirzepatide on CV outcomes among patients with overweight or obesity and ASCVD without diabetes. The significant benefit on MACE risk reduction with semaglutide over tirzepatide further supports the growing body of evidence suggesting the CV benefit of semaglutide is molecule-specific and not simply a class effect of GLP-1 or GIP/GLP-1 RAs. However, this study did not investigate factors driving the difference in CV risk reduction between semaglutide and tirzepatide. Given the exploratory finding that tirzepatide patients had consistently greater weight loss, the CV benefits observed in this study appear to be weight loss independent. It could be hypothesised that disparities in CV risk reduction may instead be due to differences in the mechanisms of action, including dissimilarities in signalling pathways.³³ There is evidence of potential CV risk reduction with therapies targeting the GIP receptor, like tirzepatide, partly attributable to weight loss and partly to improved glycemic control.³⁴ However, there may not be additional CV benefit from adding GIP agonism to a GLP-1 RA based on results of the SURPASS-CVOT study, which showed that in patients with established ASCVD and T2DM, tirzepatide was non-inferior to the GLP-1 RA, dulaglutide, in CV risk reduction despite having significantly greater weight loss and improvement in glycemic control.¹² Factors affecting the differences in CV risk reduction among this class of medications are not well understood and additional research is needed.

4.1 | Strengths and limitations

The STEER study has several strengths. It is the first to compare the effectiveness of semaglutide and tirzepatide on reducing CV outcomes using a large, diverse, nationally representative database reflecting current clinical practice in patients with overweight or obesity without diabetes. This study used rigorous propensity score matching methodology to achieve cohorts that were well-balanced across a comprehensive list of comorbidities and concomitant medications. To prevent confounding, a new user design excluding patients with use of GLP-1 or GIP/GLP-1 RAs during the baseline period was used. Additionally, the association between semaglutide versus tirzepatide and five negative control outcomes was assessed to address unmeasured bias.

Study limitations include those generally associated with any retrospective claims analysis including potential diagnostic or procedural

coding inaccuracies and incomplete or missing data, which may contribute to potential measurement errors or limit the generalizability of study results.³⁵ These limitations may have impacted the exclusion of T2DM patients; however, since patients were also excluded based on HbA1c levels and treatment use, any impact should be minimal. To ensure that T2DM was adequately excluded among off-label Mounjaro® users, further study restricted to Zepbound® users is needed to validate these findings. Additionally, although the study cohorts were balanced using propensity-score matching, the potential for biases or residual confounding from unmeasured variables, such as diet or physical activity, cannot be eliminated.

Because STEER was an observational study, it is not possible to establish causality. CV benefits with semaglutide have been demonstrated in this patient population via the SELECT trial⁷; however, clinical trial evidence on the potential CV benefit of tirzepatide is pending from the ongoing SURMOUNT-MMO trial.³⁶ Randomised controlled trials are needed to confirm the findings of this real-world analysis.

Another limitation included the limited follow-up duration, which could have led to a low number of observed CV events. Given the lag in prescribing uptake and availability of claims data that affect all retrospective claims analyses, the mean follow-up period was approximately 8 months for the ITT analysis and 4 months for the per-protocol analysis. Further research with extended follow-up is needed to examine whether these trends persist. However, clinical trial data from SELECT²⁰ show semaglutide's early benefit on CV risk reduction, which is supported by the current study despite the short follow-up duration.

In conclusion, results from this comparative real-world analysis of a large, US claims database show semaglutide is associated with early and significantly greater reductions in the risk of rMACE-3, rMACE-5, and MACE-5 compared with tirzepatide among patients with overweight or obesity and ASCVD without diabetes. This study adds to the growing body of evidence suggesting the established CV benefit of semaglutide is molecule specific and cannot be generalised to the broader GLP-1 or GIP/GLP-1 RA classes.

AUTHOR CONTRIBUTIONS

Lauren Wilson: Design, Conduct/Data Collection, Analysis, Manuscript Writing. **Zhenxiang Zhao:** Design, Analysis, Manuscript Writing. **Victoria Divino:** Design, Analysis, Manuscript Writing. **Matthew Basan:** Analysis, Manuscript Writing. **Briain Ó. Hartaigh:** Design, Analysis, Manuscript Writing. **Signe Stensen:** Analysis, Manuscript Writing. **Kerem Ozer:** Analysis, Manuscript Writing.

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CONFLICT OF INTEREST STATEMENT

Lauren Wilson, Zhenxiang Zhao, Victoria Divino, Matthew Bassan, Bráin Ó. Hartaigh, Signe Stensen, and Kerem Ozer were employees and shareholders of Novo Nordisk at the time of the study.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70436>.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during the study were derived from the privately held Komodo Research Data and are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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