Semaglutide is associated with a lower risk of cardiovascular events compared with tirzepatide in patients with overweight or obesity and ASCVD and without diabetes in routine clinical practice

Results from the **STEER study**
(**S**emaglutide and **T**irzepatide **E**ffects on Cardiovascular Outcomes in People With Overweight or Obesity in th**E** **R**eal World)

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Disclosures

- All authors are employees and shareholders of Novo Nordisk Inc.

Background

Semaglutide injection 2.4 mg GLP-1 receptor agonist (hereafter referred to as "semaglutide")	**Tirzepatide** GIP and GLP-1 receptor co-agonist

Semaglutide injection 2.4 mg
GLP-1 receptor agonist (hereafter referred to as "semaglutide")

- FDA approved in June 2021 for chronic weight management (Wegovy®)[1]
- The only weight management treatment indicated to reduce the risk of MACE in adults with overweight or obesity and established CVD[1] based on a **20% reduction in the risk of 3-point MACE** (myocardial infarction, stroke, CV-related) compared with placebo in the randomized SELECT trial[2]

Tirzepatide
GIP and GLP-1 receptor co-agonist

- FDA approved in May 2022 for type 2 diabetes (Mounjaro®)[3] and November 2023 for chronic weight management (Zepbound®)[4]
- Ongoing cardiovascular outcomes trial in patients with established ASCVD or those at high risk of ASCVD but without diabetes[5]

The **STEER study** aimed to assess the **real-world incidence of MACE** during treatment with semaglutide or tirzepatide for chronic weight management in routine clinical practice in the United States

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; FDA, US Food and Drug Administration; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event.

1. Wegovy (semaglutide) injection, for subcutaneous use [package insert]. Novo Nordisk Inc.; 2025; 2. Lincoff AM, et al. N Engl J Med. 2023;389(24):2221-2232; doi: 10.1056/NEJMoa2307563; 3. Mounjaro (tirzepatide) injection, solution [package insert]. Eli Lilly and Company; 2024; 4. Zepbound (tirzepatide) injection, solution [package insert]. Eli Lilly and Company; 2024; 5. Lam CSP, et al. Obesity (Silver Spring). 2025. [Online ahead of print]; doi: 10.1002/oby.24332.

STEER Study Design

US Komodo Research Database

Study population

- ≥45 years of age
- Overweight/obesity*
- Established ASCVD†
- Without diabetes
- Initiated semaglutide or tirzepatide on or after May 13, 2022

Jan 1, 2016 —— **Jan 31, 2025**

Index date = treatment initiation

End of follow-up‡

The propensity score model matched semaglutide and tirzepatide patients 1:1

Primary outcome measures:

- **Revised 3-point MACE:** Myocardial infarction, stroke, and all-cause mortality
- **Revised 5-point MACE:** Myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality

**Defined as body mass index ≥27 kg/m². †Defined as a diagnosis of myocardial infarction or ischemic stroke and/or evidence of peripheral artery disease. ‡End of follow-up for each patient was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*
ASCVD, atherosclerotic cardiovascular disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiovascular event.

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Eligibility Criteria and Cohort Attrition

Patients with **overweight/obesity**, n = 149,344,662

Patients with **established ASCVD**, n = 23,779,686

Patients **≥45 years of age** by the end of data availability
The eligibility date was defined as latest date of first overweight/obesity ascertainment, first ASCVD diagnosis, or patient reached 45 years of age
n = 22,691,922

Semaglutide (Wegovy), n = 112,384

Continuous enrolment 12 months prior to index date, n = 33,660

Reconfirmation of overweight/obesity at baseline, n = 30,234

Top reasons for exclusion:

- Pancreatitis, n = 327
- MENT2 or MTC, n = 419
- ESKD or dialysis, n = 282
- Evidence of diabetes, n = 12,578
- Use of GLP-1 or GLP-1/GIP RA, n = 1027
- Bariatric surgery, n = 1026

Semaglutide cohort pre-matching, n = 14,483

Tirzepatide (Mounjaro/Zepbound), n = 563,276

Continuous enrolment 12 months prior to index date, n = 149,934

Reconfirmation of overweight/obesity at baseline, n = 120,638

Top reasons for exclusion:

- Pancreatitis, n = 1749
- MENT2 or MTC, n = 1531
- ESKD or dialysis, n = 2511
- Evidence of diabetes, n = 103,001
- Use of GLP-1 or GLP-1/GIP RA, n = 323
- Bariatric surgery, n = 650

Tirzepatide cohort pre-matching, n = 10,642

ASCVD, atherosclerotic cardiovascular disease; ESKD, end-stage kidney disease; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MENT2, multiple endocrine neoplasia type 2; MTC, medullary thyroid cancer; RA, receptor agonist.

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Baseline Demographic Characteristics

(Post-Matching)

Characteristic	Semaglutide (n = 10,625)	Tirzepatide (n = 10,625)	Difference*
Mean (SD) follow-up time, months	8.3 (6.4)	8.6 (7.1)	−0.050
Mean (SD) age, years	58.5 (8.3)	58.3 (8.2)	0.020
Female, n (%)	6566 (61.8)	6541 (61.6)	0.006
Race, n (%)			0.029
White	5784 (54.4)	5782 (54.4)	
Black/African-American	1142 (10.7)	1060 (10.0)	
Hispanic/Latino	923 (8.7)	945 (8.9)	
Asian/Pacific Islander	546 (5.1)	538 (5.1)	
Unknown	2230 (21.0)	2300 (21.6)	

Characteristic	Semaglutide (n = 10,625)	Tirzepatide (n = 10,625)	Difference*
Region, n (%)			0.073
South	4033 (38.0)	4409 (41.5)	
Northeast	3267 (30.7)	3066 (28.9)	
Midwest	2233 (21.0)	2088 (19.7)	
West	1081 (10.2)	1053 (9.9)	
Unknown	11 (0.1)	9 (0.1)	
Primary insurance, n (%)			0.029
Commercial	8126 (76.5)	8174 (76.9)	
Medicare	1784 (16.8)	1700 (16.0)	
Medicaid	547 (5.1)	585 (5.5)	
Dual eligible	137 (1.3)	142 (1.3)	
Unknown	31 (0.3)	24 (0.2)	

**Standardized mean difference.*
SD, standard deviation.

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Baseline Disease Characteristics

(Post-Matching)

Characteristic	Semaglutide (n = 10,625)	Tirzepatide (n = 10,625)	Difference*
ASCVD eligibility criteria, n (%)			
Peripheral artery disease	4311 (40.6)	4652 (43.8)	−0.065
Myocardial infarction	4111 (38.7)	3741 (35.2)	0.072
Stroke	3382 (31.8)	3212 (30.2)	0.035
Additional CV and renal comorbidities, n (%)			
Hypertension	7726 (72.7)	7557 (71.1)	0.035
Dyslipidaemia	7560 (71.2)	7469 (70.3)	0.019
Atrial fibrillation	1055 (9.9)	1019 (9.6)	0.011
Angina	919 (8.6)	877 (8.3)	0.014
Heart failure	915 (8.6)	839 (7.9)	0.026
Chronic kidney disease	631 (5.9)	651 (6.1)	−0.008

Characteristic	Semaglutide (n = 10,625)	Tirzepatide (n = 10,625)	Difference*
Concomitant CV medication use, n (%)			
Statins	6245 (58.8)	5922 (55.7)	0.062
Beta-blockers	4335 (40.8)	4163 (39.2)	0.033
ARB	3232 (30.4)	3253 (30.6)	−0.004
Thiazide	2823 (26.6)	2811 (26.5)	0.003
Calcium channel blockers	2795 (26.3)	2674 (25.2)	0.026
ACE inhibitors	2219 (20.9)	2094 (19.7)	0.029
Mean (SD) BMI,† kg/m^2	36.7 (5.1)	36.7 (5.3)	0.001
BMI category, n (%)			0.030
Overweight	616 (5.8)	686 (6.5)	
Obesity class 1	2392 (22.5)	2332 (21.9)	
Obesity class 2	2031 (19.1)	2007 (18.9)	
Obesity class 3	2246 (21.1)	2252 (21.2)	
Obesity unspecified	3340 (31.4)	3348 (31.5)	

**Standardized mean difference. †Unspecified/not available for 3340 patients who were treated with semaglutide and 3348 patients who were treated with tirzepatide.*
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; BMI, body mass index; SD, standard deviation.

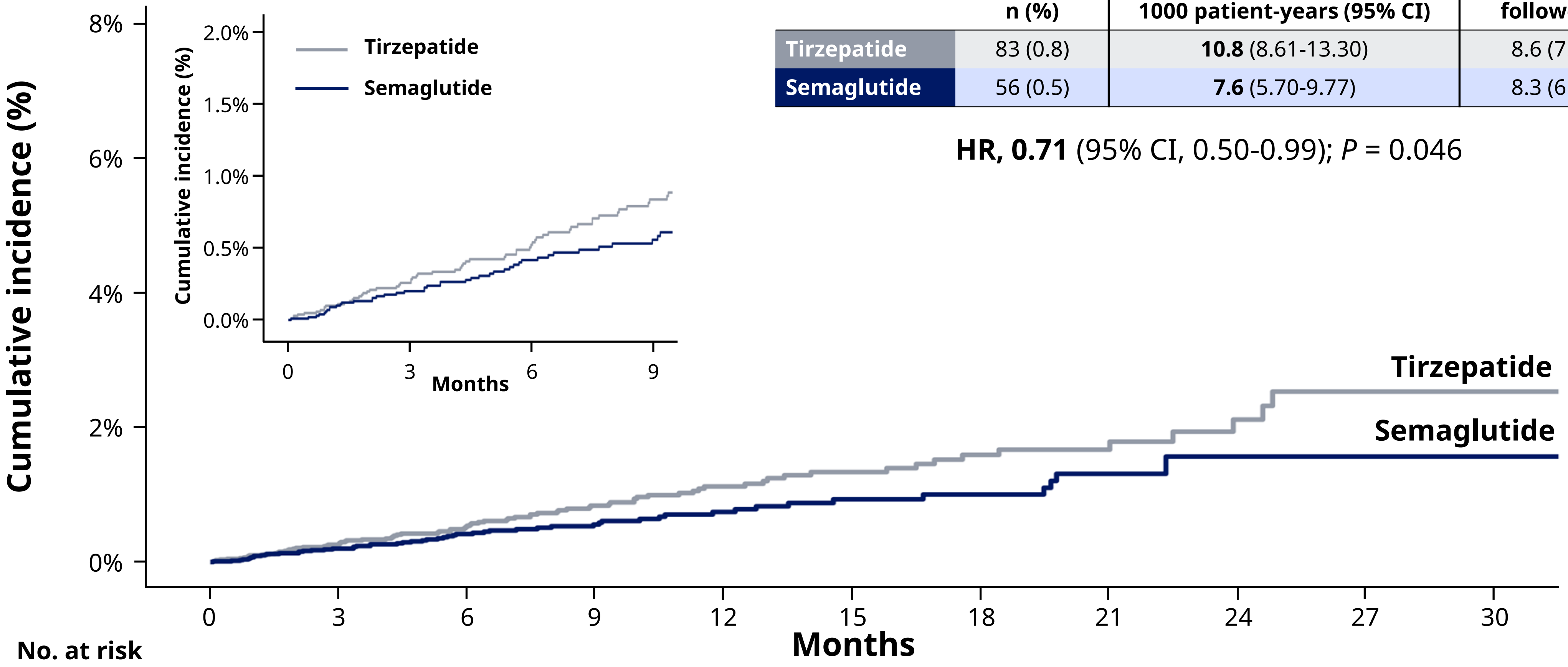
Revised 3-Point MACE*

(ITT Analysis)

The ITT analysis followed patients through the end of follow-up† regardless of persistence on therapy

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	83 (0.8)	**10.8** (8.61-13.30)	8.6 (7.1)
Semaglutide	56 (0.5)	**7.6** (5.70-9.77)	8.3 (6.4)

HR, 0.71 (95% CI, 0.50-0.99); *P* = 0.046



No. at risk	0	3	6	9	12	15	18	21	24	27	30
Tirzepatide	10625	7907	5764	4227	2735	1874	1321	825	540	220	22
Semaglutide	10625	8179	5948	3845	2516	1688	1193	670	120	30	17

**Revised 3-pont MACE includes myocardial infarction, stroke, and all-cause mortality. †End of follow-up was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*
CI, confidence interval; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event; SD, standard deviation.

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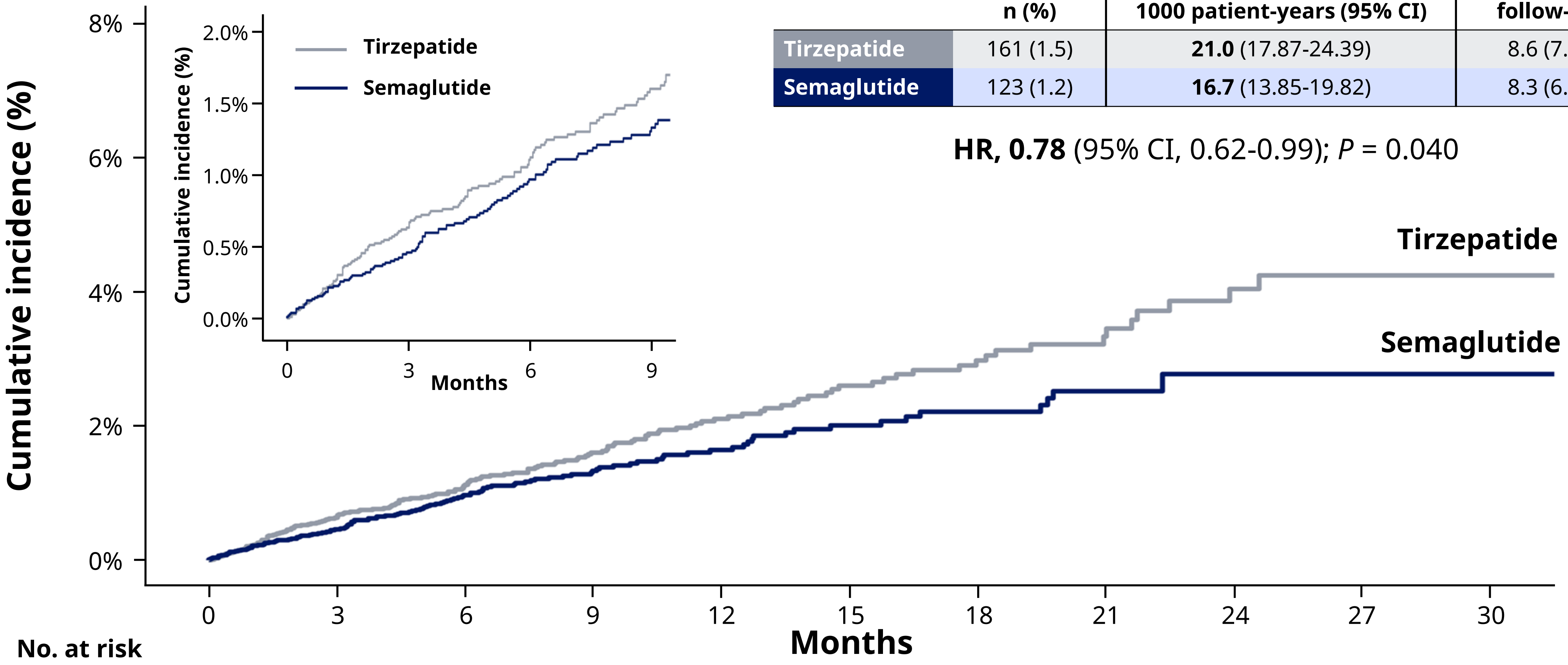
Revised 5-Point MACE*

(ITT Analysis)

The ITT analysis followed patients through the end of follow-up† regardless of persistence on therapy

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	161 (1.5)	**21.0** (17.87-24.39)	8.6 (7.1)
Semaglutide	123 (1.2)	**16.7** (13.85-19.82)	8.3 (6.4)

HR, 0.78 (95% CI, 0.62-0.99); *P* = 0.040



No. at risk	0	3	6	9	12	15	18	21	24	27	30
Tirzepatide	10625	7877	5730	4197	2706	1849	1305	814	530	215	22
Semaglutide	10625	8158	5917	3821	2495	1669	1176	662	119	29	17

**Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality. †End of follow-up was defined as the earliest of the end of the study period (Jan 31, 2025), end of continuous enrolment, initiation of a non-index GLP-1 or GLP-1/GIP receptor agonist, bariatric surgery, or death.*

CI, confidence interval; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event; SD, standard deviation.

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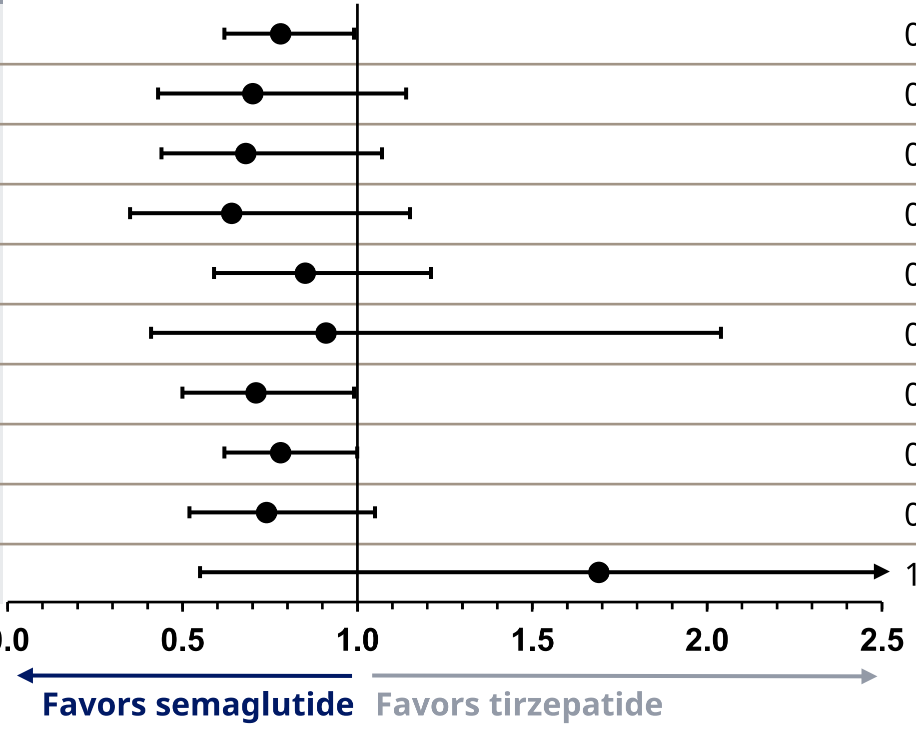
MACE Outcomes

(ITT Analysis)

	Incidence rate per 1000 patient-years				
	Semaglutide	**Tirzepatide**	**HR (95% CI)**		***P* value**
Revised 5-point MACE*	16.7	21.0		0.78 (0.62-0.99)	**0.040**
Myocardial infarction	3.8	5.4		0.70 (0.43-1.14)	0.149
Heart failure	4.3	6.1		0.68 (0.44-1.07)	0.097
Stroke	2.4	3.9		0.64 (0.35-1.15)	0.135
Coronary revascularization	7.6	8.7		0.85 (0.59-1.21)	0.362
All-cause mortality	1.5	1.7		0.91 (0.41-2.04)	0.820
Revised 3-point MACE[†]	7.6	10.8		0.71 (0.50-0.99)	**0.046**
5-point MACE[‡]	16.3	20.4		0.78 (0.62-1.00)	**0.046**
3-point MACE[§]	7.2	9.8		0.74 (0.52-1.05)	0.091
CV-related mortality	1.1	0.7		1.69 (0.55-5.19)	0.358



*Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization 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.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event.

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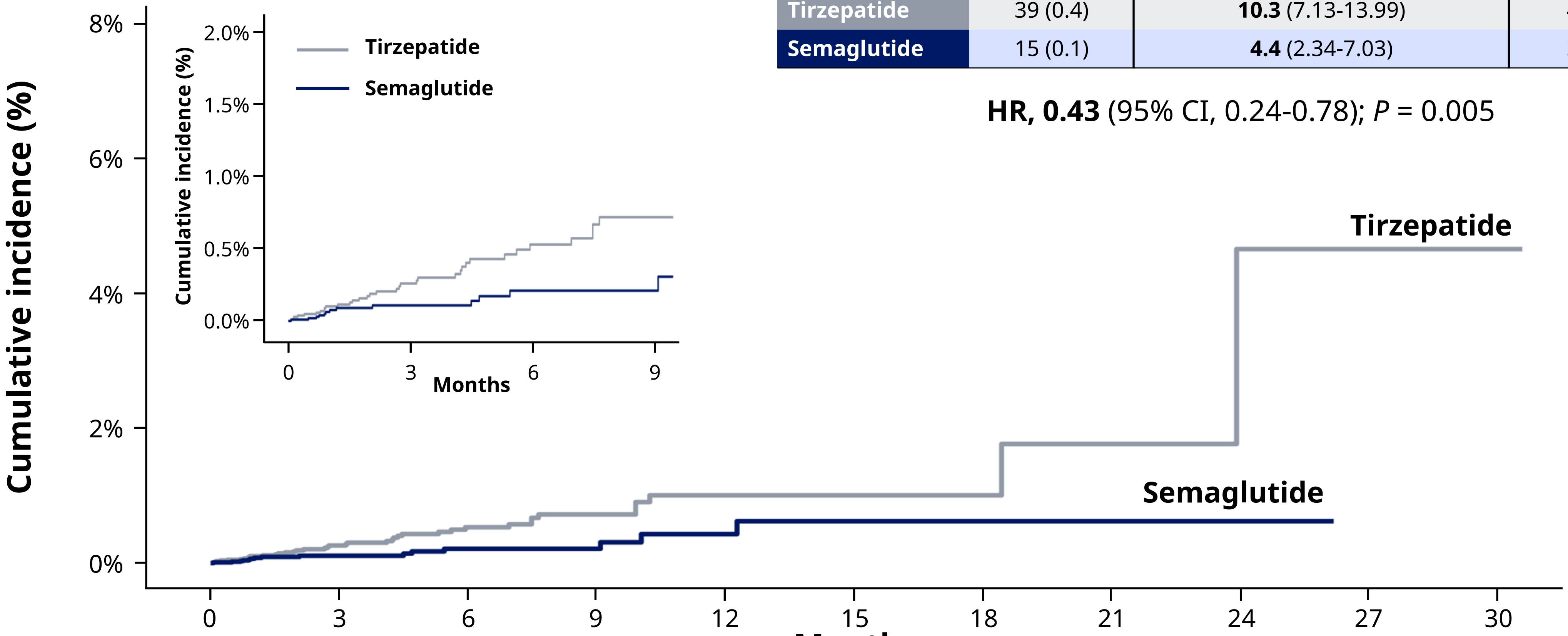
Revised 3-Point MACE*

(Per-Protocol Analysis)

Per-protocol sensitivity analysis censored patients at treatment discontinuation (gap in therapy >30 days)

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	39 (0.4)	**10.3** (7.13-13.99)	4.3 (4.2)
Semaglutide	15 (0.1)	**4.4** (2.34-7.03)	3.8 (4.1)

HR, 0.43 (95% CI, 0.24-0.78); *P* = 0.005



No. at risk	0	3	6	9	12	15	18	21	24	27	30
Tirzepatide	10625	5037	2772	1389	582	281	145	73	33	12	1
Semaglutide	10625	4407	2308	1047	546	296	178	88	12	0	0

**Revised 3-pont MACE includes myocardial infarction, stroke, and all-cause mortality.*
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation.

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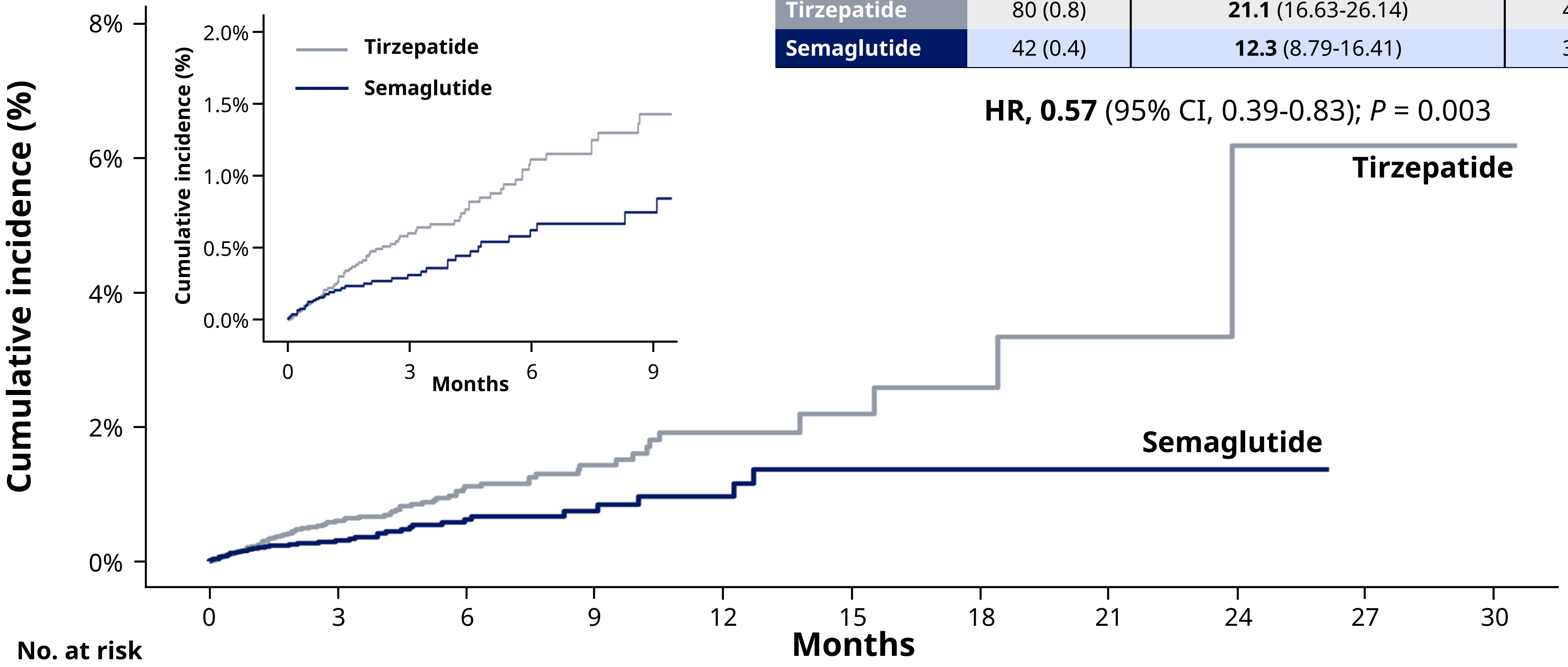
Revised 5-Point MACE*

(Per-Protocol Analysis)

Per-protocol sensitivity analysis censored patients at treatment discontinuation (gap in therapy >30 days)

	Events, n (%)	Incidence rate per 1000 patient-years (95% CI)	Mean (SD) follow-up
Tirzepatide	80 (0.8)	**21.1** (16.63-26.14)	4.3 (4.2)
Semaglutide	42 (0.4)	**12.3** (8.79-16.41)	3.8 (4.1)



No. at risk											
Tirzepatide	10625	5020	2759	1380	577	280	144	72	33	12	1
Semaglutide	10625	4403	2303	1045	544	294	177	87	12	0	0

**Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality.*
CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; SD, standard deviation.

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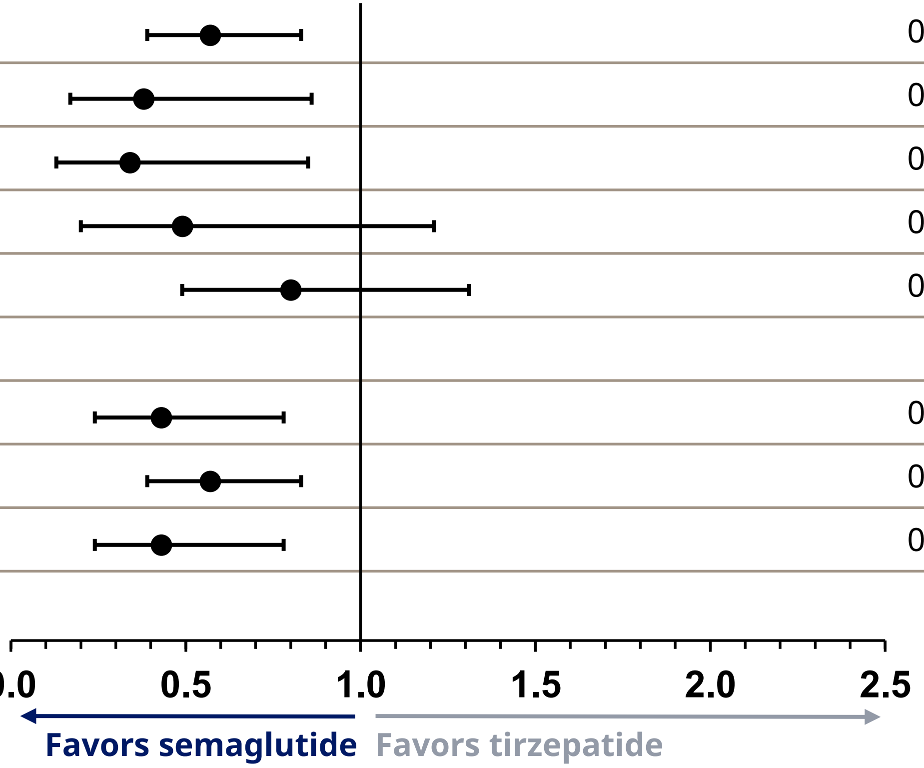
MACE Outcomes

(Per-Protocol Analysis)

0 mortality events were reported, resulting in equivalent traditional MACE (CV-related mortality) and revised MACE (all-cause mortality) outcomes

	Incidence rate per 1000 patient-years			
	Semaglutide	**Tirzepatide**	**HR (95% CI)**	***P* value**
Revised 5-point MACE*	12.3	21.1	0.57 (0.39-0.83)	**0.003**
Myocardial infarction	2.3	6.1	0.38 (0.17-0.86)	**0.019**
Heart failure	1.8	5.0	0.34 (0.13-0.85)	**0.020**
Stroke	2.1	4.2	0.49 (0.20-1.21)	0.122
Coronary revascularization	7.9	9.8	0.80 (0.49-1.31)	0.374
All-cause mortality[†]	0	0	–	–
Revised 3-point MACE[‡]	4.4	10.3	0.43 (0.24-0.78)	**0.005**
5-point MACE[§]	12.3	21.1	0.57 (0.39-0.83)	**0.003**
3-point MACE[‖]	4.4	10.3	0.43 (0.24-0.78)	**0.005**
CV-related mortality	0	0	–	–



*Revised 5-pont MACE includes myocardial infarction, stroke, hospitalization for heart failure, coronary revascularization, and all-cause mortality. [†]No mortality was reported in the per-protocol analysis. [‡]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.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

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Strengths and Limitations

Strengths

Cohorts were well balanced across a large number of comorbid conditions and concomitant medications

Large sample size, with ~10,000 patients per treatment group

Limitations

Administrative claims data may be subject to coding inaccuracies

Potential for unmeasured confounding

Limited follow-up duration

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Conclusions

From the STEER Real-World Study

In this real-world study of US patients with overweight or obesity and ASCVD but without diabetes, the primary endpoint demonstrated **a lower risk of CV events with semaglutide compared with tirzepatide**

Our findings support growing evidence that the established **CV benefit of semaglutide is molecule specific** and cannot be generalized to the GLP-1 or GIP/GLP-1 receptor agonist classes

Significantly lower risk of revised 3-point MACE with semaglutide vs tirzepatide

29%

ITT analysis

7.6 vs 10.8 incidence per 1000 patient-years

HR, 0.71; *P* = 0.046

57%

Per-protocol analysis

4.4 vs 10.3 incidence per 1000 patient-years

HR, 0.43; *P* = 0.005

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HR, hazard ratio; ITT, intention to treat; MACE, major adverse cardiovascular event.

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