Tirzepatide and the risk of atherosclerotic cardiovascular events: population based cohort study

Nils Krüger,[1,2,3,4] Sebastian Schneeweiss,[1,2] Shirley V Wang[1,2]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston 02120, MA, USA

[2]Harvard Medical School, Boston, MA, USA

[3]Department of Cardiology, TUM University Hospital German Heart Center, Technical University of Munich, Munich, Germany

[4]Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

Correspondence to: N Krüger nkruger1@bwh.harvard.edu; (ORCID 0009-0008-3190-0462)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;394:e100011 http://dx.doi.org/10.1136/bmj-2026-100011

Accepted: 17 June 2026

ABSTRACT

OBJECTIVE

To estimate the magnitude of reduction in major adverse cardiovascular events (MACE) that would be observed in clinical practice from adding tirzepatide to standard of care treatment.

DESIGN

Population based cohort study, using a design, data, and analytical approach previously benchmarked against randomised trials.

SETTING

Two national US claims databases, May 2022 to May 2025.

PARTICIPANTS

52 971 participants aged ≥40 years with type 2 diabetes and established atherosclerotic cardiovascular disease who initiated tirzepatide (n=35 353) or sitagliptin (n=17 618), a cardiovascular outcome neutral comparator serving as a placebo proxy. Baseline characteristics were well balanced between treatment groups after propensity score overlap weighting.

MAIN OUTCOME MEASURES

The main outcome, MACE, was a composite of myocardial infarction, stroke, and all cause mortality and its individual components. Follow-up started the day after treatment initiation and continued until occurrence of the outcome, disenrollment from the health plan, treatment discontinuation or switching, or one year. Safety outcomes included infections requiring hospital admission and infection related mortality. Two negative control outcomes, lumbar radiculopathy and abdominal hernia, were analysed to assess residual confounding.

RESULTS

At one year, the weighted one year risk of MACE was 2.9% (95% confidence interval (CI) 2.5% to 3.4%) in the tirzepatide group and 4.4% (3.8% to 4.9%) in the sitagliptin group (risk difference -1.4%, 95% CI -2.1% to -0.7%; number needed to treat (NNT)=70), corresponding to a hazard ratio of 0.68 (95% CI 0.58 to 0.80). For individual MACE components, tirzepatide was associated with a lower hazard for myocardial infarction (hazard ratio 0.67, 0.52 to 0.87; NNT=130), whereas ischaemic stroke showed no meaningful difference (0.91, 0.64 to 1.28; NNT 2500). Infections requiring hospital admission were lower with tirzepatide (0.64, 0.55 to 0.75; NNT=48), as was infection related mortality (0.40, 0.26 to 0.61; NNT=200) and all cause mortality (0.55, 0.42 to 0.72; NNT=122). Negative control outcomes showed no association.

CONCLUSIONS

In this cohort study using an approach benchmarked against randomised trials, initiating tirzepatide reduced the risk of MACE compared with a placebo proxy among people with type 2 diabetes and established atherosclerotic cardiovascular disease. Reductions in infection related events suggest broader non-atherosclerotic biological mechanisms may contribute to the observed benefit. This study shows how trial-anchored evidence from clinical practice can estimate the expected cardiovascular benefit of initiating tirzepatide beyond standard background treatment and inform shared decision making.

TRIAL REGISTRATION

ClinicalTrials.gov NCT07203677.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Randomised trials of glucagon-like peptide-1 based treatments are increasingly shifting towards head-to-head comparisons between active agents rather than placebo controlled designs

In the cardiovascular outcomes trial SURPASS-CVOT in patients with type 2 diabetes and established cardiovascular disease, tirzepatide was non-inferior to dulaglutide for major adverse cardiovascular events (MACE)

Although head-to-head trials provide evidence on the relative benefits of alternative agents, this focus leaves unclear the magnitude of benefit from adding tirzepatide on top of contemporary background therapy

WHAT THIS STUDY ADDS

This study estimates the magnitude of effect from adding tirzepatide to standard care for diabetes and expresses results in terms relevant to clinicians and patients to inform shared decision making

Adding tirzepatide to standard of care was associated with a lower risk of MACE than adding sitagliptin, a cardiovascular outcome neutral comparator, driven by lower risks of myocardial infarction

Infections requiring hospital admission were lower in the tirzepatide group, as were infection related mortality and all cause mortality

Introduction

Tirzepatide is an incretin based drug that activates both the glucagon-like peptide-1 receptor and the glucose dependent insulinotropic peptide receptor. Its dual action has led to reductions in blood glucose and body weight,[1 2] but cardiovascular effects remain debated.[3] Although randomised trials and observational studies have consistently shown protective effects of tirzepatide on all cause mortality and hospital admission for heart failure relative to placebo,[4-6] evidence for major cardiovascular events is more limited. To date, tirzepatide has shown only non-inferiority to dulaglutide in the SURPASS-CVOT (A Study of Tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes) trial, whereas dulaglutide has shown modest reductions in cardiovascular events

in the placebo controlled REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial.[4 7 8]

This lack of evidence has resulted in regulatory and clinical uncertainty, as the US Food and Drug Administration (FDA) traditionally requires drugs to show superiority to placebo in outcomes trials before granting a label expansion for cardiovascular risk reduction. Antidiabetic treatments have not received such an indication based on non-inferiority to an active comparator. However, randomised cardiovascular outcomes trials for glucagon-like peptide-1 based treatments are increasingly shifting towards head-to-head designs between active agents rather than placebo controlled trials, with SURPASS-CVOT among the first in this class.[9] While comparative trials are essential for informing the choice between active treatments, they do not directly answer the question clinicians and patients routinely ask: what is the incremental benefit of initiating tirzepatide beyond contemporary background treatment of diabetes—that is, compared with a placebo-like or standard care comparator? Without an anchor to standard care, comparative estimates from head-to-head trials are difficult to translate into decisions about whether to start treatment, particularly for patients at high cardiovascular risk. Recognising this decisional dilemma, SURPASS-CVOT investigators conducted an indirect comparison using historical placebo data from the REWIND trial.[4 10] Although suggestive of superiority, direct comparisons in clinical practice are needed to further resolve uncertainty over the magnitude of tirzepatide's effect on atherosclerotic events if added to standard of care treatment. A transparent and reproducible real world evidence approach that is prespecified and benchmarked against randomised trials is one way to generate such clinically interpretable estimates, and it is increasingly relevant as regulators, including the FDA and European Medicines Agency, are moving towards relying more on real world evidence to complement randomised trials in the approval process across therapeutic areas.[11 12]

For these reasons, we sought to directly compare tirzepatide with a validated placebo proxy in a cohort study that emulated the design and eligibility criteria of SURPASS-CVOT using healthcare claims data.[11 13 14] A validated placebo proxy is an active comparator the cardiovascular neutrality of which has been shown in a dedicated placebo controlled outcomes trial and further corroborated in empirical benchmarking studies against placebo arms from randomised trials.[15-17] Such proxies are used in observational settings to approximate the counterfactual comparison with placebo that would otherwise require a randomised trial.

Methods

Data sources

We analysed deidentified data from two national US administrative claims databases, Optum Clinformatics and Merative MarketScan, between May 2022 and May 2025. These databases include detailed longitudinal information on personal characteristics, medical diagnoses, procedures, and dispensed outpatient drugs

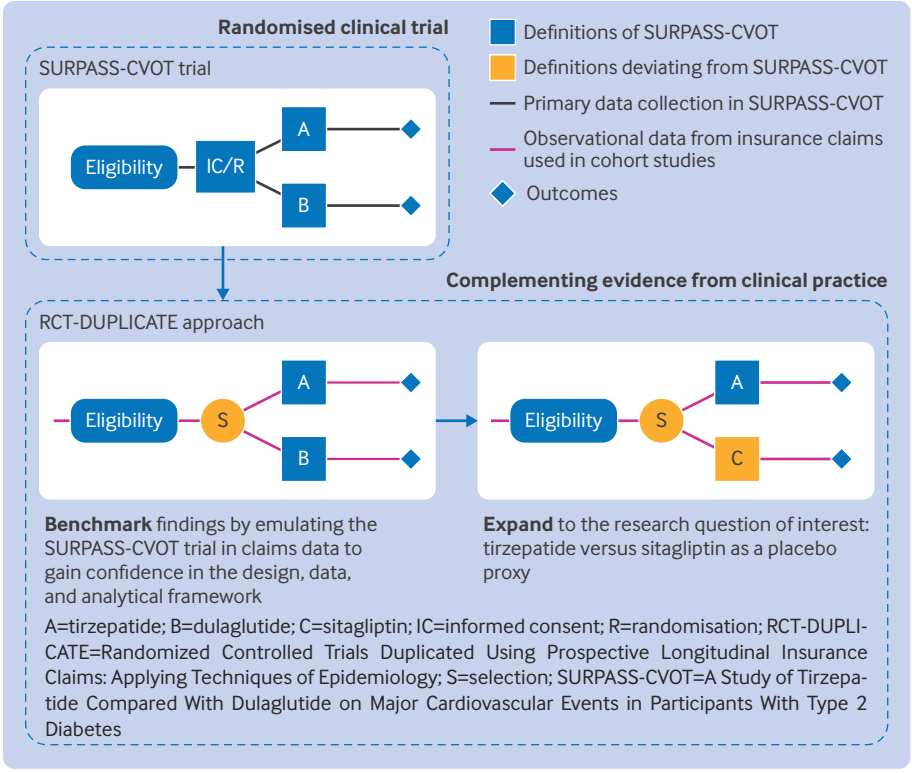

Fig 1 | Study design overview

doi: 10.1136/bmj-2026-100011 | *BMJ* 2026;394:e100011 | the bmj

for millions of commercially insured and Medicare Advantage beneficiaries across the US. Continuous enrolment for at least 12 months before cohort entry was required to allow complete assessment of baseline covariates.

Study design and conduct

In a previous study, we used the RCT-DUPLICATE (Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) approach to emulate the design of SURPASS-CVOT (comparing tirzepatide with dulaglutide) and the SUSTAIN-6 trial (comparing semaglutide with the placebo proxy sitagliptin) (see supplemental table S1).[16] This exercise allowed us to benchmark our results from the database studies against those of the reference trials to understand the fitness of our data, design, and analytical framework.[13 18] In these studies, we found close alignment with SURPASS-CVOT across all endpoints, whereas the results for all cause mortality in SUSTAIN-6 raised potential concerns about preferred prescribing of sitagliptin over glucagon-like peptide-1 drugs when a shortened life expectancy was prognosticated. In light of the trial benchmark, we viewed the outcome of death with caution. However, the indirect comparison from SURPASS-CVOT provided some support for the observed mortality signalled. Therefore, in the present study we focused on evaluating all components of major adverse cardiovascular events (MACE) for tirzepatide versus a placebo proxy using an active comparator, new user cohort design. (fig 1).

Transparency

We preregistered the fully specified study protocol using the HARmonized Protocol Template to Enhance Reproducibility (HARPER) in the Real-World Evidence Registry (osf.io/zmfke) before inferential analyses were conducted and deposited the protocols in ClinicalTrials.gov (NCT07203677).[19 20] Amendments were documented contemporaneously. The preregistered protocol provides details of how key study variables were operationally defined, including temporality of assessment windows relative to the index date and code lists. Specification and emulation of the target trial followed the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guidance[21] (see supplemental table S2).

In line with the eligibility criteria for SURPASS-CVOT,[10] our study included patients aged 40 years or older with type 2 diabetes and established atherosclerotic cardiovascular disease. All eligibility criteria were assessed relative to the index date (the date of first qualifying outpatient dispensing of the drug of interest). Supplemental figure S2A shows the study design in detail. Briefly, patients were required to have a body mass index (BMI) of 25 or higher and documented evidence of previous myocardial infarction, ischaemic stroke, or coronary, carotid, or peripheral arterial disease confirmed through diagnostic codes or revascularisation procedures. We excluded individuals if they had advanced heart failure, end stage kidney disease, active liver disease, cardiovascular events or revascularisation in the past 60 days, recent use of glucagon-like peptide-1 receptor agonists or pramlintide, or conditions predisposing to incretin related adverse effects, including a history of pancreatitis, severe gastric emptying disorders, or medullary thyroid carcinoma. We also excluded pregnant women at treatment initiation.

Study drug use and follow-up

The index date was defined as the date of a first outpatient dispensing of tirzepatide or sitagliptin (precluding a 183 day washout period) that met eligibility criteria. Both drugs are second line type 2 treatments for diabetes in US clinical practice. Sitagliptin was chosen as a neutral placebo proxy based on numerous randomised and observational studies showing no effect on cardiovascular outcomes.[15 17] Follow-up began the day after cohort entry and continued until the earliest occurrence of the outcome of interest, disenrollment from the health plan, treatment discontinuation or switching (defined as initiation of any other glucagon-like peptide-1 receptor agonist or, for the tirzepatide arm, initiation of sitagliptin, and vice versa) (with a 45 day grace period), or one year. The main analysis used an "on-treatment" (per protocol analogue) causal contrast to mimic the high adherence typically observed in SURPASS-CVOT.

Outcomes

Study endpoints included MACE, a composite of myocardial infarction, stroke, and all cause mortality, assessed as a composite with and without mortality as well as individually. In line with the emulation of SURPASS-CVOT,[16] we measured all cause mortality rather than cardiovascular mortality. Previous validation studies of all cause mortality in claims showed high sensitivity (>99%) compared with the National Death Index.[22] In an exploratory analysis we assessed infection related mortality (infections leading to mortality within 90 days of onset).[23-25] We used validated outcome algorithms that were based on inpatient diagnostic codes that showed a positive predictive value of 94% for myocardial infarction and 95% for ischaemic stroke.[26-29] An expanded composite included myocardial infraction, stroke, coronary revascularisation, and unstable angina. Safety outcomes leading to hospital admission included infections and gastrointestinal adverse events.[30-32] We also assessed infections in any care setting as well as urinary tract infections.[33] Additionally, we assessed two negative control outcomes: lumbar radiculopathy and abdominal hernia.[5 16]

Covariates

We assessed a comprehensive set of pretreatment covariates to control for potential confounding, following the same causal framework used in the successful emulation of SURPASS-CVOT. Within this framework, covariate selection targeted common

causes of treatment assignment and the study outcomes, including factors plausibly influencing a clinician's choice between an injectable incretin based treatment and an oral dipeptidyl peptidase-4 inhibitor (eg, age, frailty indicators, BMI, previous cardiovascular and renal disease, and concomitant glucose lowering regimens), as well as established risk factors for cardiovascular events and for the prespecified safety outcomes (see supplemental figure S3). Covariates included personal characteristics (age, sex, race) and detailed cardiovascular risk factors and comorbidities, encompassing smoking, obesity, hypertension, dyslipidaemia, and established cardiovascular disease such as previous myocardial infarction, angina, ischaemic stroke or transient ischaemic attack, peripheral artery disease, and previous coronary or peripheral revascularisation. To further capture metabolic and diabetes related burden, we included markers of cardiometabolic health and complications such as nephropathy, neuropathy, retinopathy, diabetic foot ulcers, and episodes of hypoglycaemia or hyperglycaemia. Broader systemic comorbidities were accounted for, including chronic kidney disease, chronic lung disease, depression, dementia, and recent serious infections. Absence of a code was interpreted as absence of the condition. Drug history covered glucose lowering, cardiovascular, and other chronic treatments, whereas healthcare utilisation summarised hospital admissions, emergency visits, and preventive care. Although socioeconomic status and access to healthcare could not be measured directly in claims data, we included several proxies, including geographical region, out-of-pocket drug costs, the brand-to-generic drug ratio, markers of care utilisation, and receipt of preventive services. The supplemental material provides the full set of covariates and associated coding algorithms.

Statistical analysis

Propensity scores were estimated using logistic regression models predicting treatment assignment based on all baseline covariates. We applied propensity score overlap weighting, which emphasises patients with the greatest clinical equipoise between treatment groups.[34] Balance was assessed using standardised mean differences, with values below 0.1 indicating acceptable balance. Event-free survival was estimated using weighted Kaplan-Meier methods, and hazard ratios with 95% confidence intervals (CIs) were derived from Cox proportional hazards models incorporating overlap weights. Absolute risks and risk differences at one year were computed from the weighted survival curves. Analyses were performed separately in the two databases and pooled via fixed effects meta-analysis weighted by effective sample size. For all analyses we used Python and R as well as the Aetion Evidence Platform, a validated system benchmarked against FDA Sentinel analytical workflows.[35 36] Analyses were conducted using Python version 3.13, R version 4.4, and the Aetion Evidence Platform. The causal estimand was the average treatment effect in the overlap population, corresponding to the one year risk and hazard of each outcome that would be observed if patients with clinical equipoise initiated tirzepatide versus sitagliptin. The proportional hazards assumption was examined by inspecting scaled Schoenfeld residuals and graphically using log-log survival plots; no violations were identified within the one year follow-up window. Numbers needed to treat (NNT) were derived as the reciprocal of the weighted one year absolute risk difference and assumed that the estimated risk difference was unconfounded, no informative censoring had occurred over the follow-up time, and the estimate was transportable to similar populations.

Sensitivity and subgroup analyses

Prespecified sensitivity analyses tested the robustness of results to key analytical assumptions. These included an as-started (intention-to-treat analogue) analysis carrying forward initial treatment assignment for up to one year; a competing risk analysis treating death as a competing event for non-fatal outcomes, modelled using Fine-Gray subdistribution hazard models; and the negative control outcomes of lumbar radiculopathy and abdominal hernia. Predefined subgroup analyses were stratified by age (<70 *v* ≥70 years) and sex.

Patient and public involvement

Data included in this study were deidentified, and data use agreements precluded contacting individuals. In addition, funding for this study did not support patient or public involvement.

Results

Study population

A total of 52 971individuals were included in the analysis, of whom 35 353 initiated tirzepatide and 17 618 initiated sitagliptin. Before propensity score weighting, individuals who initiated tirzepatide were younger, had higher body mass index, and had fewer comorbidities compared with individuals who initiated sitagliptin (see supplemental table S3). After weighting, all baseline characteristics included in the propensity score were perfectly balanced between treatment groups, as expected with overlap weighting (table 1). The overlap weighted population included about 7442 per group, corresponding to the region of clinical equipoise where both treatments were plausible choices. In the weighted cohort, the median age was 69.8 years and 3783/7442 (50.8%) were female patients. Of these 7444 patients, statin use was recorded in 6339 (85.2%), sodium-glucose co-transporter-2 inhibitor use in 1567 (21.1%), and insulin use in 1349 (18.1%) per group.

Endpoint of major adverse cardiovascular events

During a pooled mean on-treatment follow-up of 182 days (standard deviation (SD) 118 days) (median 150 (interquartile range (IQR) 71-291) for tirzepatide versus 173 (SD 111) days (median 133 (75-253)) for sitagliptin, the weighted risk of MACE was 2.9% (95%

Table 1 | Weighted baseline characteristics of patients with type 2 diabetes and atherosclerotic cardiovascular disease initiating tirzepatide versus sitagliptin. Values are number (percentage) unless stated otherwise

	Before overlap weighting			After overlap weighting		
Characteristicsv	Tirzepatide (n=35 353)	Sitagliptin (n=17 618)	SMD	Tirzepatide (n=7442)	Sitagliptin (n=7442)	SMD
Mean (SD) age (years)	65.5 (9.6)	72.7 (9.0)	0.78	69.8 (8.6)	69.8 (9.0)	0.00
Sex:						
Female	18 022 (51.0)	8809 (50.0)	0.02	3783 (50.8)	3783 (50.8)	0.00
Male	17 331 (49.0)	8809 (50.0)	0.02	3659 (49.2)	3659 (49.2)	0.00
Lifestyle risk factors						
BMI class:						
25.0-29.9	2336 (6.6)	4201 (23.8)	0.49	1014 (13.6)	1014 (13.6)	0.00
30.0-34.9	6407 (18.1)	4650 (26.4)	0.20	1814 (24.4)	1814 (24.4)	0.00
35.0-39.9	10 893 (30.8)	3913 (22.2)	0.20	2053 (27.6)	2053 (27.6)	0.00
≥40.0	8852 (25.0)	1990 (11.3)	0.36	1191 (16.0)	1191 (16.0)	0.00
Unspecified obesity	6865 (19.4)	2864 (16.3)	0.08	1367 (18.4)	1367 (18.4)	0.00
Smoking or tobacco use	9358 (26.5)	4376 (24.8)	0.04	1925 (25.9)	1925 (25.9)	0.00
Selected comorbidities						
Coronary atherosclerosis	16 005 (45.3)	7788 (44.2)	0.02	3344 (45.0)	3344 (45.0)	0.00
Myocardial infarction	2604 (7.4)	1329 (7.5)	0.01	553 (7.4)	553 (7.4)	0.00
Ischaemic stroke	347 (1.0)	332 (1.9)	0.08	97 (1.3)	97 (1.3)	0.00
Peripheral vascular disease	6173 (17.5)	4068 (23.1)	0.14	1519 (20.4)	1519 (20.4)	0.00
Atrial fibrillation	5709 (16.2)	3236 (18.34)	0.06	1278 (17.2)	1278 (17.2)	0.00
Heart failure	7469 (21.1)	4194 (23.8)	0.06	1668 (22.4)	1668 (22.4)	0.00
Hypertension	32 466 (91.8)	16562 (94.0)	0.08	6938 (93.3)	6938 (93.3)	0.00
Hyperlipidaemia	31 533 (89.2)	15879 (90.1)	0.03	6704 (90.1)	6704 (90.1)	0.00
Microalbuminuria or proteinuria	2468 (7.0)	1297 (7.4)	0.01	530 (7.1)	530 (7.1)	0.00
CKD stage 3-4	6896 (19.5)	4936 (28.0)	0.20	1808 (24.3)	1808 (24.3)	0.00
Drug treatments						
Metformin	15 544 (44.0)	9714 (55.1)	0.22	3852 (51.8)	3852 (51.8)	0.00
Insulins	7894 (22.3)	2573 (14.6)	0.20	1349 (18.1)	1349 (18.1)	0.00
SGLT-2 inhibitors	7282 (20.6)	3328 (18.9)	0.04	1567 (21.1)	1567 (21.1)	0.00
ACE/ARB inhibitors	25 627 (72.5)	13 167 (74.7)	0.05	5551 (74.6)	5551 (74.6)	0.00
Thiazides	11 989 (33.9)	5532 (31.4)	0.05	2441 (32.8)	2441 (32.8)	0.00
Beta blockers	19 843 (56.1)	10 373 (58.9)	0.06	4328 (58.2)	4328 (58.2)	0.00
Statins	28 887 (81.7)	15 101 (85.7)	0.11	6339 (85.2)	6339 (85.2)	0.00
Antiplatelets	6433 (18.2)	3439 (19.5)	0.03	1418 (19.1)	1418 (19.1)	0.00
Oral anticoagulants	5657 (16.0)	3163 (18.0)	0.05	1256 (16.9)	1256 (16.9)	0.00

Data are pooled from Optum and MarketScan databases. The full set of baseline characteristics are from pooled and individual databases (see supplemental tables S3-S5).
ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; BMI=body mass index; CKD=chronic kidney disease; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2; SMD=standardised mean difference.

CI 2.5% to 3.4%) with tirzepatide and 4.4% (3.8% to 4.9%) with sitagliptin, yielding a risk difference of -1.4% (95% CI -2.1% to -0.7%) and an NNT of 70 at one year (table 2). The corresponding hazard ratio for MACE was 0.68 (95% CI 0.58 to 0.80) (fig 2). Cumulative incidence curves diverged within the first three months and continued to separate throughout the observation period.

Components of the composite endpoint

When mortality was excluded from the composite endpoint, the effect estimates for myocardial infarction or stroke remained similar (hazard ratio 0.74, 0.61 to 0.91) with an NNT of 124. For individual MACE components, the hazard ratios (95% CIs) were 0.67 (0.52 to 0.87) for myocardial infarction, 0.91 (0.64 to 1.28) for ischaemic stroke, and 0.55 (0.42 to 0.72) for all cause mortality (fig 2), corresponding to NNTs of 130, 2500, and 122, respectively. Table 2 shows the weighted cumulative incidences and absolute risk differences for each outcome.

Infection related mortality was lower among individuals initiating tirzepatide than among individuals initiating sitagliptin (hazard ratio 0.40, 0.26 to 0.61), corresponding to an NNT of 200.

The expanded composite (myocardial infraction, stroke, coronary revascularisation, and unstable angina) also favoured tirzepatide, with a hazard ratio of 0.92 (0.85 to 0.99) and an NNT of 72.

Safety endpoints

Compared with sitagliptin, tirzepatide was associated with a markedly lower risk of infections leading to hospital admission (hazard ratio 0.64, 0.55 to 0.75), a slightly lower risk of infections in any care setting (0.83, 0.78 to 0.87) or urinary tract infections (0.83, 0.76 to 0.91), and no difference in gastrointestinal adverse events (1.00, 0.79 to 1.27). Table 2 shows the weighted cumulative incidences and absolute risks, risk differences, and NNT for each outcome.

Negative control, sensitivity, and subgroup analyses

The negative control outcomes of lumbar radiculopathy (hazard ratio 1.03, 0.93 to 1.15) and abdominal hernia (0.93, 0.83 to 1.06) were similar between the

Table 2 | Study endpoints in the weighted and pooled population of patients with type 2 diabetes and atherosclerotic cardiovascular disease initiating tirzepatide versus sitagliptin. Values are percentage (95% CI) unless stated otherwise

Endpoints	1 year risk			Hazard ratio (95% CI)	NNT
	Tirzepatide	Sitagliptin	Difference		
MACE*	2.9 (2.5 to 3.4)	4.4 (3.8 to 4.9)	-1.4 (-2.1 to -0.7)	0.68 (0.58 to 0.80)	70
Myocardial infarction or stroke	1.8 (1.5 to 2.1)	2.6 (2.2 to 3.0)	-0.8 (-1.4 to -0.3)	0.74 (0.61 to 0.91)	124
Myocardial infarction	1.1 (0.9 to 1.4)	1.9 (1.5 to 2.3)	-0.8 (-1.2 to -0.3)	0.67 (0.52 to 0.87)	130
Stroke	0.7 (0.5 to 0.9)	0.7 (0.5 to 1.0)	-0.0 (-0.4 to 0.3)	0.91 (0.64 to 1.28)	2500
All cause mortality*	1.3 (1.0 to 1.5)	2.1 (1.7 to 2.5)	-0.8 (-1.3 to -0.3)	0.55 (0.42 to 0.72)	122
Infection related mortality* †	0.5 (0.3 to 0.7)	1.0 (0.7 to 1.2)	-0.5 (-0.8 to 0.2)	0.40 (0.26 to 0.61)	200
Myocardial infarction, stroke, coronary revascularisation, unstable angina	13.1 (12.3 to 13.9)	14.5 (13.6 to 15.4)	-1.4 (-2.6 to -0.2)	0.92 (0.85 to 0.99)	72
Safety endpoints					
Infection related hospital admissions	3.3 (2.8 to 3.7)	5.4 (4.7 to 6.1)	-2.1 (-2.9 to -1.3)	0.64 (0.55 to 0.75)	48
Infections in any care setting†	26.5 (25.4 to 27.5)	31.8 (30.5 to 33.0)	-5.3 (-7.0 to -3.6)	0.83 (0.78 to 0.87)	19
Urinary tract infections	9.7 (9.0 to 10.4)	11.5 (10.7 to 12.4)	-1.8 (-2.9 to -0.7)	0.83 (0.76 to 0.91)	55
Gastrointestinal adverse events	1.7 (1.3 to 2.0)	1.5 (1.2 to 1.8)	0.2 (-0.3 to 0.6)	1.00 (0.79 to 1.27)	NE‡

Endpoints including all cause mortality should be viewed cautiously in light of a previously conducted benchmarking study. NNT is the reciprocal of the weighted one year absolute risk difference.
CI=confidence interval; MACE=major adverse cardiovascular events; NE=not estimable; NNT=number needed to treat.
*Composite of myocardial infarction, stroke, and all cause mortality.
†Post hoc analysis.
‡The observed risk difference was not statistically distinguishable from zero.

tirzepatide group and sitagliptin groups, providing support for the robustness of confounding adjustment (see supplemental table S9).

Results were consistent in the as-started (emulation of an intention-to-treat analysis) analysis, with similar effect estimates for MACE (hazard ratio 0.72, 0.63 to 0.82) and for non-fatal MACE (0.77, 0.65 to 0.92). Competing risk analyses treating death as a competing event also yielded similar results (see supplemental table S11). Exploratory subgroup analyses by age (<70 *v* ≥70 years), sex, BMI (<35 *v* ≥35), and the presence versus absence of concomitant treatment with sodium-glucose cotransporter-2 inhibitors or insulin showed similar patterns of association across groups (see supplemental table S10).

Discussion

In this study, adding tirzepatide to standard of care was associated with a lower risk of MACE compared with adding a cardiovascular neutral comparator, the placebo proxy sitagliptin, with an absolute one year risk difference of -1.4% (NNT=70) or a 32% reduction in hazard rates. The results were driven primarily by lower hazards of myocardial infarction and all cause mortality, which were in turn driven by infection related deaths. The hazard for stroke was not meaningfully different between groups. Prespecified safety endpoints showed lower rates of serious bacterial infections leading to hospital admission and of urinary tract infections in the tirzepatide group, with no meaningful difference in gastrointestinal adverse events.

Comparison with other studies

These findings complement those of SURPASS-CVOT, yet rather than drawing indirect inferences from a historical trial that showed superiority over placebo,[4 37] our approach provides a direct comparison with standard of care and quantifies absolute risk differences and NNT—measures that are directly interpretable for clinical decision making. Our analysis builds on closely benchmarking to the results of SURPASS-CVOT, building confidence in our design, data, and analytical framework.[13 16 18]

Although it is not surprising that tirzepatide, which showed non-inferiority to dulaglutide in SURPASS-CVOT, was associated with a reduction in cardiovascular risk compared with cardiovascular outcome neutral comparators such as sitagliptin or a placebo arm from a historical trial, the marked reduction in all cause mortality was observed in both the indirect trial comparison (hazard ratio for indirect comparison 0.61, 95% CI 0.45 to 0.82) and our database study (hazard ratio for direct comparison 0.55, 95% CI 0.42 to 0.72).[37] One plausible explanation that our study supports is the substantial reduction in serious bacterial infections observed among individuals who initiated tirzepatide, suggesting that part of the survival benefit may reflect effects beyond atherosclerotic mechanisms. Obesity is recognised as a strong risk factor for both infection related hospital admissions and mortality, and SURPASS-CVOT has shown a marked reduction in these endpoints with tirzepatide use compared with dulaglutide use,[8 38] as did semaglutide when compared with placebo.[39] Supporting this possibility was the strong benefit observed for infection related mortality, suggesting that infection related pathways may account for a substantial share of the observed survival benefit. These findings support a plausible hypothesis that will need to be substantiated. At the same time, mortality findings should be interpreted cautiously, as in previous benchmarking analyses we found evidence of possible residual confounding for mortality endpoints when glucagon-like peptide-1 receptor agonists were compared with dipeptidyl peptidase-4 inhibitors, which are often prescribed for frailer patients.[17] Future studies should disentangle atherosclerotic from non-atherosclerotic mechanisms underlying tirzepatide's survival benefit and clarify the

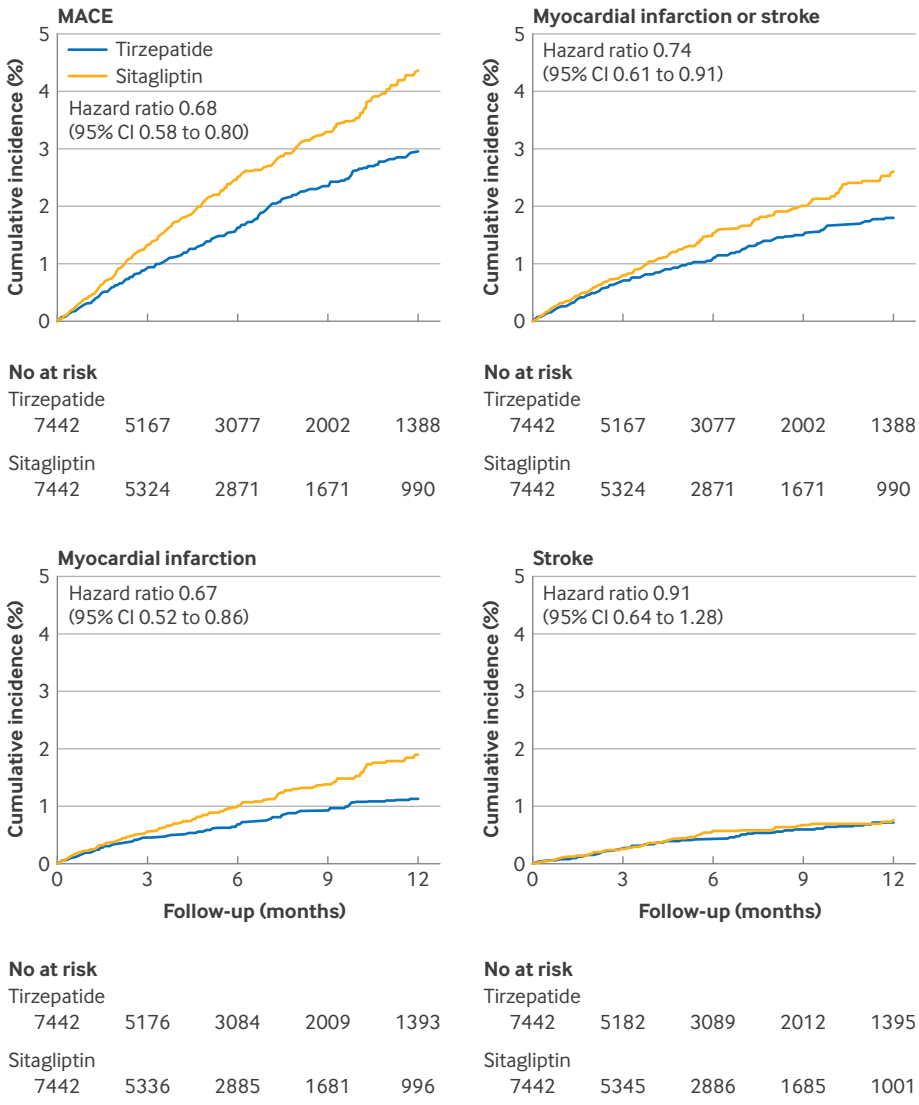

Fig 2 | Propensity score adjusted cumulative incidences for risk of atherosclerotic cardiovascular events in patients meeting eligibility criteria for SURPASS-CVOT and initiating tirzepatide or sitagliptin. MACE is defined as the composite of myocardial infarction, stroke, and all cause mortality. CI=confidence interval; MACE=major adverse cardiovascular events; SURPASS-CVOT=A Study of Tirzepatide Compared With Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes

degree to which the magnitude of mortality reduction observed in clinical practice is influenced by residual confounding or represents a true effect that can be reproduced in other trials of glucagon-like peptide-1 drugs.

Policy implications

Consistent with trials of glucagon-like peptide-1 based treatments, the early divergence of cardiovascular event curves starting before meaningful weight loss could have taken place suggests mediators beyond weight reduction. Such early effects may reflect improvements in systemic and vascular inflammation that act independently of metabolic benefits.[3 40] Clinically, this observation may prompt prescribers to reconceptualise incretin drugs as cardiometabolic treatments capable of conferring early vascular protection rather than solely as agents for glucose or weight control. However, early separation within short time frames could also arise from non-atherosclerotic mechanisms or channeling of treatment to healthier individuals in non-randomised research. While non-definitive, these findings add to the growing and consistent evidence base from both randomised and trial benchmarked observational studies that the cardiovascular effects of incretin based treatments may emerge earlier than expected and independently of weight loss.[5 16 41 42] From a patient perspective, framing the protective effects in absolute terms such as the difference in event risk if tirzepatide is added to treatment versus maintaining standard background treatment may help communicate the tangible magnitude of benefit and support shared decision making.[43 44]

Limitations of this study

Limitations of this study include the relatively short follow-up period of one year, with a median on-treatment follow-up short of half a year in the US, which may underestimate long term cardiovascular and safety effects, and the reliance on sitagliptin as a proxy for placebo, which differs from tirzepatide in how it is administered (oral versus subcutaneous). Although comprehensive propensity score weighting achieved well balanced groups for comparison, residual confounding from unmeasured factors which could partially explain the reduced risk of all cause mortality and rapid onset cardiovascular benefits cannot be ruled out. Minor misclassification of treatment duration or outcomes is possible given the use of imperfect algorithms in administrative claims data, including dosing and timing of treatment escalation, which were not observed in this study. The more modest effect size for the expanded composite endpoint including revascularisation and unstable angina may be more sensitive to clinical decision making and intensity of surveillance and may therefore dilute treatment effects observed for hard endpoints that are clinically overt and less discretionary. Finally, these findings may not generalise to uninsured patients, non-US healthcare systems, or populations without established atherosclerotic cardiovascular disease.

Conclusions

In this study, tirzepatide was associated with cardio-protective effects in clinical practice settings. While awaiting accrual of further trial evidence for tirzepatide in cardiovascular indications, this study shows how randomised controlled trial evidence anchored in the real world complements randomised clinical trials for timely regulatory and clinical decision making.

Contributors: NK, SS, and SVW conceptualised and designed the study. NK drafted the protocol, conducted the analyses, and drafted the manuscript. SS and SVW supervised the research, reviewed the analyses, and critically revised the manuscript for important intellectual content. NK had full access to the data and takes responsibility for the integrity of the data and the accuracy of the analysis. NK is the guarantor of this work. All authors approved the final version submitted for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This work was funded by the National Institutes of Health (R01-HL141505, R01-AR080194) and the German Heart Foundation (S/02/24, SRF-HF/24, NK-HF/25). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Institutes of Health (NIH) and the German Heart Foundation for the submitted work. NK reports support from the German Heart Foundation for the submitted work. SVW reports grants or contracts to Brigham and Women's Hospital from the Food and Drug Administration and NIH; personal consulting fees from Cytel, Exponent, and MITRE, a Federally Funded Research and Development Center for the Centers for Medicare and Medicaid Services, for unrelated work; SS reports grants or contracts to the Brigham and Women's Hospital institution from the Food and Drug Administration and NIH, Boehringer Ingelheim, Takeda, and UCB, and consulting fees from Aetion for unrelated work.

Ethical approval: This study was approved by the Mass General Brigham institutional review board (IRB approval 2018P002966), and the use of deidentified secondary data qualified for a waiver of informed consent under US federal regulations.

Data sharing: Data use agreements prohibit public sharing of patient level claims data; however, access to source data can be requested directly from data vendors (Optum Clinformatics: connected@optum.com; Merative MarketScan: marketscan.support@merative.com). All analytical code used to generate tables, figures, and statistical results is publicly available (github.com/nilskruger/Tirzepatide-and-the-Risk-of-Atherosclerotic-Cardiovascular-Events).

Transparency: The lead author (NK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Results of the study will be disseminated in scientific meetings and across scientific communities. Lay material summarising the results of this study will be disseminated to patient facing organisations.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Aronne LJ, Horn DB, le Roux CW, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. *N Engl J Med* 2025;393:26-36. doi:10.1056/NEJMoa2416394
2 Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021;385:503-15. doi:10.1056/NEJMoa2107519
3 Hammoud R, Drucker DJ. Beyond the pancreas: contrasting cardiometabolic actions of GIP and GLP1. *Nat Rev Endocrinol* 2023;19:201-16. doi:10.1038/s41574-022-00783-3
4 Zoungas S. *SURPASS-CVOT* . Presented at the 61st conference of the European Association for the Study of Diabetes. Vienna, 18 Sep 2025
5 Krüger N, Schneeweiss S, Fuse K, et al. Semaglutide and Tirzepatide in Patients With Heart Failure With Preserved Ejection Fraction. *JAMA* . 2025;334:1255-66. doi:10.1001/jama.2025.14092
6 Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med* . 2025;392:427-37. doi:10.1056/NEJMoa2410027
7 Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *The Lancet* 2019;394:121-30. doi:10.1016/S0140-6736(19)31149-3
8 Nicholls SJ, Pavo I, Bhatt DL, et al. Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes. *N Engl J Med* 2025;393:2409-20. doi:10.1056/NEJMoa2505928
9 Neuen BL, Ostrominski JW, Vaduganathan M. Is Placebo Still Ethical in Trials of Incretin Therapies? *Circulation* 2026;153:1005-8. doi:10.1161/CIRCULATIONAHA.125.077277
10 Nicholls SJ, Bhatt DL, Buse JB, et al. Comparison of tirzepatide and dulaglutide on major adverse cardiovascular events in participants with type 2 diabetes and atherosclerotic cardiovascular disease: SURPASS-CVOT design and baseline characteristics. *Am Heart J* 2024;267:1-11. doi:10.1016/j.ahj.2023.09.007
11 Prasad V, Makary MA. One Pivotal Trial, the New Default Option for FDA Approval - Ending the Two-Trial Dogma. *N Engl J Med* 2026;394:815-7. doi:10.1056/NEJMsb2517623
12 Bachinger M, Jankowski MA, Kesselheim AS, et al. Real-World Evidence in Drug Approvals at the European Medicines Agency. *JAMA Netw Open* 2025;8:e2542041. doi:10.1001/jamanetworkopen.2025.42041
13 Schneeweiss S, Krüger N. Non-Randomized Database Analyses to Complement Randomized Clinical Trials: Promising Approaches for Cardiovascular Medicine. *Circulation* 2025;151:1495-7. doi:10.1161/CIRCULATIONAHA.125.073235
14 Makary MA, Prasad V. Priorities for a New FDA. *JAMA* 2025;334:565-66. doi:10.1001/jama.2025.10116
15 Wang SV, Schneeweiss S, RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA* 2023;329:1376-85. doi:10.1001/jama.2023.4221
16 Krüger N, Schneeweiss S, Desai RJ, et al. Cardiovascular outcomes of semaglutide and tirzepatide for patients with type 2 diabetes in clinical practice. *Nat Med* 2025:32:342-52. doi:10.1038/s41591-025-04102-x

17 Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015;373:232-42. doi:10.1056/NEJMoa1501352
18 Wang SV, Russo M, Glynn RJ, et al. A Benchmark, Expand, and Calibration (BenchExCal) Trial Emulation Approach for Using Real-World Evidence to Support Indication Expansions: Design and Process for a Planned Empirical Evaluation. *Clin Pharmacol Ther* 2025;117:1820-8. doi:10.1002/cpt.3621
19 Wang SV, Schneeweiss S. Data Checks Before Registering Study Protocols for Health Care Database Analyses. *JAMA* 2024;331:1445-6. doi:10.1001/jama.2024.2988
20 Wang SV, Pottegård A, Crown W, et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. *Pharmacoepidemiol Drug Saf* 2023;32:44-55. doi:10.1002/pds.5507
21 Cashin AG, Hansford HJ, Hernán MA, et al. Transparent reporting of observational studies emulating a target trial: the TARGET Statement. *BMJ* 2025;390:e087179. doi:10.1136/bmj-2025-087179
22 Desai RJ, Levin R, Lin KJ, et al. Bias Implications of Outcome Misclassification in Observational Studies Evaluating Association Between Treatments and All-Cause or Cardiovascular Mortality Using Administrative Claims. *J Am Heart Assoc* 2020;9:e016906. doi:10.1161/JAHA.120.016906
23 Dulhunty JM, Brett SJ, De Waele JJ, et al. Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial. *JAMA* 2024;332:629-37. doi:10.1001/jama.2024.9779
24 Ramírez-Soto MC. Long-term, all-cause mortality risk after infection episodes in older adults. *Lancet Healthy Longev* 2023;4:e452-4. doi:10.1016/S2666-7568(23)00166-6
25 Reitz KM, Kennedy J, Li SR, et al. Association Between Time to Source Control in Sepsis and 90-Day Mortality. *JAMA Surg* 2022;157:817-26. doi:10.1001/jamasurg.2022.2761
26 Kiyota Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J* 2004;148:99-104. doi:10.1016/j.ahj.2004.02.013
27 Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf* 2012;21:100-28. doi:10.1002/pds.2312
28 Roumie CL, Mitchel E, Gideon PS, et al. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. *Pharmacoepidemiol Drug Saf* 2008;17:20-6. doi:10.1002/pds.1518
29 Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. *Pharmacoepidemiol Drug Saf* 2010;19:596-603. doi:10.1002/pds.1924
30 Sodhi M, Rezaeianzadeh R, Kezouh A, et al. Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. *JAMA* 2023;330:1795-7. doi:10.1001/jama.2023.19574
31 Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol* 2007;60:397-409. doi:10.1016/j.jclinepi.2006.07.011
32 Barber C, Lacaille D, Fortin PR. Systematic Review of Validation Studies of the Use of Administrative Data to Identify Serious Infections. *Arthritis Care Res* 2013;65:1343-57. doi:10.1002/acr.21959
33 Fortin SP, Swerdel J, Sarnecki M, et al. Performance characteristics of code-based algorithms to identify urinary tract infections in large United States administrative claims databases. *Pharmacoepidemiol Drug Saf* 2022;31:953-62. doi:10.1002/pds.5492
34 Thomas LE, Li F, Pencina MJ. Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial. *JAMA* 2020;323:2417-8. doi:10.1001/jama.2020.7819
35 Wang SV, Verpillat P, Rassen JA, et al. Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther* 2016;99:325-32. doi:10.1002/cpt.329
36 Wang SV, Sreedhara SK, Schneeweiss S, et al. Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. *Nat Commun* 2022;13:5126. doi:10.1038/s41467-022-32310-3
37 Sattar N, Gerstein HC, D'Alessio D, et al. Estimating the True MACE Benefits From Tirzepatide in SURPASS-CVOT Using an Imputed Placebo Analysis of REWIND. *Diabetes Care* . Published online 6 Apr 2026:dc260298. doi:10.2337/dc26-0298
38 Nyberg ST, Frank P, Ahmadi-Abhari S, et al. Adult obesity and risk of severe infections: a multicohort study with global burden estimates. *Lancet* 2026;407:951-62. doi:10.1016/S0140-6736(25)02474-2
39 Scirica BM, Lincoff AM, Lingvay I, et al. The Effect of Semaglutide on Mortality and COVID-19-Related Deaths. *J Am Coll Cardiol* . 2024;84:1632-42. doi:10.1016/j.jacc.2024.08.007
40 Kahles F, Birkenfeld AL, Marx N. GLP-1 and the cardiovascular system. *J Clin Invest* 2026;136:e194748. doi:10.1172/JCI194748
41 Deanfield J, Lincoff AM, Kahn SE, et al. Semaglutide and cardiovascular outcomes by baseline and changes in adiposity measurements: a prespecified analysis of the SELECT trial. *The Lancet* . 2025;406:2257-68. doi:10.1016/S0140-6736(25)01375-3
42 Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Engl J Med* 2023;389:2221-32. doi:10.1056/NEJMoa2307563
43 Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;375:1834-44. doi:10.1056/NEJMoa1607141
44 Zikmund-Fisher BJ, Thorpe A, Fagerlin A. How to Communicate Medical Numbers. *JAMA* 2025;334:1474-75. doi:10.1001/jama.2025.13655