Diabetes Care
American Diabetes Association

Estimating the True MACE Benefits From Tirzepatide in SURPASS-CVOT Using an Imputed Placebo Analysis of REWIND

Naveed Sattar, Hertzel C. Gerstein, David D'Alessio, Deepak L. Bhatt, John B. Buse, Stefano Del Prato, Steven E. Kahn, A. Michael Lincoff, Darren K. McGuire, Michael A. Nauck, Steven E. Nissen, Bernard Zinman, Sophia Zoungas, Amy Bartee, Debra Miller, Hiroshi Nishiyama, Yongming Qu, Govinda Weerakkody, Russell J. Wiese, Imre Pavo, and Stephen J. Nicholls

Diabetes Care 2026;49(00):1–8 | https://doi.org/10.2337/dc26-0298

Tirzepatide Versus an Imputed Placebo: Indirect Comparison Using Different Methods

Tirzepatide, When Compared With Imputed Placebo (PBO), was Associated With Reduced CV Outcomes in Participants With T2D and Established ASCVD, Irrespective of Method Used

Context

Dulaglutide reduced CV risk compared with PBO in the REWIND trial. Tirzepatide demonstrated noninferiority for CV death, myocardial infarction, or stroke (MACE-3) compared with dulaglutide in SURPASS-CVOT.

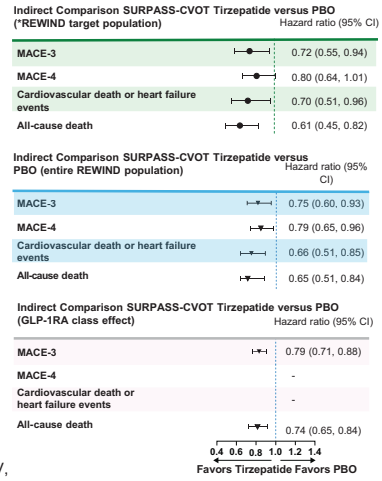
Aim

Indirectly estimate the treatment effect of tirzepatide compared with imputed PBO in participants from SURPASS-CVOT and REWIND with clinical characteristics predictive of high CV risk.

Design

The indirect comparison to PBO was conducted for primary (MACE-3) and key secondary outcomes of SURPASS-CVOT.

The analysis included data from SURPASS-CVOT, REWIND participants who would have been eligible for SURPASS-CVOT (prespecified), all REWIND participants, and data from a meta-analysis of GLP-1RA CVOTs.



CVOT, cardiovascular outcomes trial; MACE, major adverse cardiovascular event; PBO, placebo; CV, cardiovascular; T2D, type 2 diabetes; ASCVD, atherosclerotic cardiovascular disease. *REWIND population meeting SURPASS-CVOT criteria.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The SURPASS–Cardiovascular Outcomes Trial (SURPASS-CVOT) compared tirzepatide with dulaglutide for effects on major adverse cardiovascular events (MACE), but it is also useful to estimate tirzepatide's impact versus placebo.

- **What is the specific question we wanted to answer?**
  Using a prespecified indirect comparison referencing the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial plus a recent meta-analysis, we estimated tirzepatide's effect versus an imputed placebo.

- **What did we find?**
  Tirzepatide was estimated to reduce three-component MACE versus placebo, with a hazard ratio of 0.72 (95% CI 0.55, 0.94). Results were broadly consistent across other cardiovascular outcomes, all-cause mortality, and in a post hoc analysis using a glucagon-like peptide 1 receptor agonist meta-analysis as the reference.

- **What are the implications of our findings?**
  These findings support cardiovascular outcome benefits for tirzepatide versus placebo in type 2 diabetes with established atherosclerotic cardiovascular disease.

Estimating the True MACE Benefits From Tirzepatide in SURPASS-CVOT Using an Imputed Placebo Analysis of REWIND

https://doi.org/10.2337/dc26-0298

Naveed Sattar,[1] Hertzel C. Gerstein,[2] David D'Alessio,[3] Deepak L. Bhatt,[4] John B. Buse,[5] Stefano Del Prato,[6] Steven E. Kahn,[7] A. Michael Lincoff,[8] Darren K. McGuire,[9] Michael A. Nauck,[10] Steven E. Nissen,[11] Bernard Zinman,[12] Sophia Zoungas,[13] Amy Bartee,[14] Debra Miller,[14] Hiroshi Nishiyama,[14] Yongming Qu,[14] Govinda Weerakkody,[14] Russell J. Wiese,[14] Imre Pavo,[14] and Stephen J. Nicholls[15]

ORIGINAL ARTICLE

OBJECTIVE

In prespecified analyses, the treatment effect for MACE of tirzepatide compared with imputed placebo was estimated using SURPASS-CVOT and REWIND data.

RESEARCH DESIGN AND METHODS

The indirect comparison with placebo was conducted for primary (MACE-3) and secondary outcomes of SURPASS-CVOT. The analysis included data from REWIND participants who would have been eligible for SURPASS-CVOT and all participants from SURPASS-CVOT. Propensity score estimation was used to adjust for differences in participant characteristics between studies. The indirect analysis of the treatment effect was derived by multiplying the hazard ratio (HR) for MACE-3 between tirzepatide and dulaglutide in SURPASS-CVOT by the HR for dulaglutide versus placebo in REWIND. Sensitivity analyses were performed using unadjusted analyses, including both the selected REWIND and the entire REWIND populations, and adjusted analysis in the entire REWIND population. Post hoc sensitivity analyses used data from a recent GLP-1RA meta-analysis that included REWIND.

RESULTS

Analyses included 2,055 of 9,901 participants from REWIND and all 13,165 participants from SURPASS-CVOT. In indirect treatment effect comparisons, tirzepatide versus placebo was associated with lower MACE-3 (HR 0.72; 95% CI 0.55, 0.94), death from CV cause or heart failure events (HR 0.70; 95% CI 0.51, 0.96), and all-cause death (HR 0.61; 95% CI 0.45, 0.82). Sensitivity analyses, including nonadjusted or the entire REWIND cohort data or meta-analysis data for GLP-1RAs, were generally consistent.

CONCLUSIONS

In this indirect prespecified exploratory comparison, tirzepatide compared with imputed placebo was associated with reduced CV outcomes and all-cause mortality in participants with type 2 diabetes and established atherosclerotic CV disease.

Tirzepatide is a dual agonist of both the glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1) receptors (1). Clinical trials conducted in participants with type 2 diabetes have shown that tirzepatide reduces glucose, HbA_{1c}, body

[1]School of Cardiovascular Medicine and Metabolic Health, University of Glasgow, Glasgow, U.K.
[2]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
[3]Duke University Medical Center, Durham, NC
[4]Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY
[5]University of North Carolina at Chapel Hill, Chapel Hill, NC
[6]Interdisciplinary Research Center "Health Science", Sant'Anna School of Advanced Studies, Pisa, Italy
[7]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA
[8]Department of Cardiovascular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH
[9]University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas, TX
[10]Diabetes, Endocrinology and Metabolism Section, Department of Medicine, St. Josef-Hospital, Katholisches Klinikum Bochum gGmbH, Ruhr University of Bochum, Bochum, Germany
[11]Cleveland Clinic Coordinating Center for Clinical Research and Department of Medicine, Cleveland Clinic, Cleveland, OH
[12]University of Toronto, Lunenfeld-Tanenbaum Research Institute and Mount Sinai Hospital, Toronto, Ontario, Canada

weight, atherogenic lipoproteins, inflammatory markers, and blood pressure and preserves kidney function compared with placebo, various insulins, or selective GLP-1 receptor agonists (GLP-1RAs) (2–7). The cardiovascular (CV) safety of tirzepatide was confirmed in a meta-analysis of phase 2 and 3 tirzepatide trials (8).

The recently completed SURPASS–Cardiovascular Outcomes Trial (SURPASS-CVOT) (9) evaluated the CV efficacy and safety of tirzepatide compared with dulaglutide in participants with type 2 diabetes and established CV disease. SURPASS-CVOT was a randomized, double-blind, active comparator trial in which time to the first three-component major adverse cardiovascular event (MACE-3) (CV death, myocardial infarction, or stroke) was the primary end point (10). During a median follow-up of 4 years, tirzepatide was noninferior to dulaglutide (hazard ratio [HR] 0.92; 95.3% CI 0.83, 1.01) and met a prespecified criterion for CV benefit compared with imputed placebo (11,12).

The noninferiority of tirzepatide to dulaglutide in the SURPASS-CVOT trial for MACE-3, plus prior evidence that dulaglutide is superior to placebo for MACE-3 in the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial (13) (which was conducted in participants with type 2 diabetes at lower risk for MACE-3), is consistent with the hypothesis that tirzepatide would be superior to placebo for this outcome. Multiplying the HRs for MACE-3 of 0.92 from SURPASS-CVOT and 0.88 from REWIND yields an unadjusted HR of 0.81 for the effect of tirzepatide versus an imputed placebo on MACE-3. However, this approach does not account for the overall difference in risk of CV events in the populations of the two trials because inclusion in SURPASS-CVOT required evidence of prior atherosclerotic CV disease while REWIND included participants with and without evident disease. To gain insight into the effect of tirzepatide on MACE-3, prespecified analyses were designed to compare participants in SURPASS-CVOT with a group from REWIND who had a similar high risk for new CV events. This REWIND subset was then used to model the effect of tirzepatide versus an imputed placebo on MACE-3 and related outcomes, with further unadjusted and adjusted analyses in this subset, as well as in all REWIND participants.

As a post hoc analysis, we also used prior GLP-1RA meta-analysis data for GLP-1RAs type 2 diabetes CVOTs (except for the Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA] trial) (14), given that there was no heterogeneity seen, as a measure of the CV benefit of dulaglutide. This then gave us a range of estimates of imputed CV benefit of tirzepatide, each with differing merits.

RESEARCH DESIGN AND METHODS

SURPASS-CVOT and REWIND Trial Designs

Both SURPASS-CVOT and REWIND were randomized, double-blind, event-driven trials in which the primary outcome was the time to the first occurrence of MACE-3. SURPASS-CVOT compared tirzepatide 15 mg or maximum tolerated dose with dulaglutide 1.5 mg weekly, whereas REWIND compared the same dose of dulaglutide with placebo. The inclusion criteria for both trials are shown in Supplementary Table 1.

Selection of Target Population for Indirect Comparison

The indirect treatment comparison target group included intention-to-treat (ITT) participants from REWIND who would have been eligible to enroll in SURPASS-CVOT and all modified ITT (mITT) participants from SURPASS-CVOT (all randomized participants except for those randomized in error). REWIND participants who would have been enrolled in SURPASS-CVOT were identified if they had a baseline HbA_{1c} $\geq$7.0% and a history of at least one of the following: myocardial infarction, >50% stenosis, coronary revascularization, ischemic stroke, carotid artery revascularization, ankle-brachial index <0.9, peripheral revascularization (iliac or femoral artery), or amputation (Supplementary Table 1).

End Points Analyzed

Primary and key secondary CV end points of SURPASS-CVOT were composite MACE-3, CV death, all-cause death, composite CV death or heart failure events, and composite MACE-4 (MACE-3 components or coronary revascularization). The number needed to treat to composite MACE-3 at a median follow-up of SURPASS-CVOT at 4.0 years was calculated.

Statistical Approach

In the indirect treatment comparison target population, the propensity score (15), defined as the probability of belonging to SURPASS-CVOT, was estimated using a logistic regression model adjusted for the dependent variable (1 for SURPASS-CVOT, 0 for REWIND) and baseline covariates, including age, sex, baseline BMI, history of coronary revascularization, history of heart failure, history of myocardial infarction, history of stroke, type 2 diabetes duration, baseline HbA_{1c}, baseline systolic blood pressure, baseline estimated glomerular filtration rate (by the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation), logarithm of baseline urine albumin-to-creatinine ratio, baseline non-HDL cholesterol, smoking habit (current or noncurrent), and the missingness pattern of missing values. The propensity score estimation accounted for missing covariates guided by the multiple imputation missingness pattern approach (16), generating 100 imputed complete data sets. It was anticipated that only a small number of missing baseline covariate values from a limited number of patients would require imputation.

HR estimates from Cox proportional hazard models, repeated for each complete data set, were weighted based on the stabilized inverse probability weight (17), calculated based on the estimated propensity score where weights >10 were replaced by 10 (18), and the robust sandwich approach was used to obtain variance of weighted estimates of HR (19). In the SURPASS-CVOT mITT population, the HR of tirzepatide versus dulaglutide was estimated based on a

[13]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[14]Eli Lilly and Company, Indianapolis, IN
[15]Victorian Heart Institute, Monash University, Melbourne, Australia

Corresponding author: Naveed Sattar, naveed.sattar@glasgow.ac.uk

Received 6 February 2026 and accepted 6 March 2026

This article contains supplementary material online at https://doi.org/10.2337/figshare.31629613.

Cox proportional hazard model stratified by sodium–glucose cotransporter 2 inhibitor (SGLT-2i) use at baseline with treatment as a fixed effect. In the REWIND target population, the HR of dulaglutide versus placebo was estimated based on a Cox proportional hazard model with treatment as a fixed effect.

The indirect treatment effect of tirzepatide versus placebo was derived by multiplying the HR for SURPASS-CVOT tirzepatide versus dulaglutide by the HR for REWIND dulaglutide versus placebo. The SEs of the weighted estimates of the logarithm of HRs were obtained using the Rubin formula and back transformed to the HR, 95% CI, and *P* value.

Number needed to treat in terms of MACE-3 was derived as the inverse of the estimated absolute risk reduction (placebo minus tirzepatide) at the median follow-up of SURPASS-CVOT (4.0 years). For each complete data set, the survival functions for participants treated with dulaglutide and tirzepatide were estimated in the SURPASS-CVOT using the weighted Kaplan-Meier method. The survival function estimates were pooled across complete data sets using the Rubin rule under the log-log transform. The survival function for placebo was estimated to use the survival function for dulaglutide in SURPASS-CVOT and the weighted HR of dulaglutide versus placebo in REWIND, under the proportional hazard assumption. The absolute risk reduction at a time point is calculated by the difference in survivals between placebo and tirzepatide.

Sensitivity Analyses

An indirect treatment comparison was also performed for the entire participant population from REWIND and SURPASS-CVOT. In addition, a post hoc indirect treatment comparison was undertaken using the estimate for tirzepatide versus dulaglutide from the entire SURPASS-CVOT population combined with an estimate of GLP-1RAs versus placebo from an external meta-analysis (14), where GLP-1RAs are considered to represent the treatment outcome of dulaglutide given no formal heterogeneity.

Data and Resource Availability

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available upon request 6 months after the indication studied has been approved in the U.S. and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

RESULTS

The baseline characteristics differed between the overall REWIND and SURPASS-CVOT populations due to differences in inclusion criteria (Table 1). Participants in SURPASS-CVOT had a longer duration of type 2 diabetes, higher HbA_{1c}, and higher proportion with established atherosclerotic CV disease. There was a smaller proportion of female participants in SURPASS-CVOT.

The indirect comparison target population included REWIND participants who met the inclusion criteria for SURPASS-CVOT. When the analysis was limited to the target population, baseline sex, use of tobacco, history of stroke, history of myocardial infarction, urinary albumin-to-creatinine ratio, and estimated glomerular filtration rate were similar between the studies. All other baseline characteristics were significantly different between the studies, notably SGLT-2i use, which was 30.6% in SURPASS-CVOT vs. 0% in REWIND. Of the 9,901 participants in REWIND, 2,055 (21%) were eligible to be enrolled in SURPASS-CVOT (Table 1).

When baseline characteristics were adjusted using propensity score–based weighting, the standardized mean differences in baseline characteristics between studies were generally smaller in the adjusted compared with the unadjusted analysis (Supplementary Table 2). In this analysis, SURPASS-CVOT had 503 (3.8%) fewer participants than the mITT population, and there were 121 (5.9%) fewer participants in the REWIND indirect comparison target population (Table 2 and Supplementary Table 3). In these participants, at least one covariate was missing, requiring individuals' propensity score estimate. In indirect comparison analysis, missing values were accounted for by the multiple imputation missingness pattern approach.

In the 2,055 REWIND participants included in the indirect treatment comparison, MACE-3 occurred in 165 (16.3%; 3.52 events per 100 person-years) in the dulaglutide group and 210 (20.1%; 4.47 events per 100 person-years) in the placebo group (HR 0.78; 95% CI 0.61, 1.01; *P* = 0.056). In the SURPASS-CVOT population, the primary composite outcome occurred in 801 participants (12.2%; 3.19 events per 100 person-years) in the tirzepatide group and 862 (13.1%; 3.47 events per 100 person-years) in the dulaglutide group (HR 0.92; 95% CI 0.83, 1.01; *P* = 0.085). The estimated indirect treatment effect of tirzepatide versus placebo in MACE-3 was an HR of 0.72 (95% CI 0.55, 0.94; *P* = 0.016) (Fig. 1 and Supplementary Table 4).

The estimated indirect treatment effect did not differ between the unadjusted (HR 0.72; 95% CI 0.58, 0.91; *P* = 0.005) and adjusted (HR 0.72; 95% CI 0.55, 0.94; *P* = 0.016) analyses in the indirect comparison target population (Supplementary Tables 4 and 5). The indirect treatment effect for tirzepatide versus imputed placebo was consistent for all-cause death (HR 0.61; 95% CI 0.45, 0.82; *P* = 0.001) and composite CV death or heart failure events (HR 0.70; 95% CI 0.51, 0.96; *P* = 0.025). The estimated indirect treatment effect did not meet statistical significance for MACE-4 (HR 0.80; 95% CI 0.64, 1.01; *P* = 0.057) or CV death (HR 0.75; 95% CI 0.52, 1.09; *P* = 0.131) with tirzepatide compared with imputed placebo (Fig. 1 and Supplementary Table 4). The estimated indirect treatment effects for key secondary CV outcomes were similar between the unadjusted and adjusted analyses in the indirect comparison target population (Supplementary Table 5).

The estimated indirect treatment effect for primary and key secondary outcomes was slightly different between the unadjusted and adjusted analyses in the entire REWIND population (Supplementary Table 6). However, adjusted estimates for MACE-3 were similar between the indirect comparison target population (Supplementary Table 4) and the entire participant population from REWIND (Supplementary Table 6). In addition, the

Table 1—Baseline characteristics for the SURPASS-CVOT mITT population, REWIND target population, and REWIND full ITT population

Characteristic	SURPASS-CVOT mITT population (*n* = 13,165)	REWIND target population (*n* = 2,055)	REWIND full ITT population (*n* = 9,901)
Age, years	64.1 (8.8)	64.8 (7.3)	66.2 (6.5)
Female, *n* (%)	3,817 (29.0)	632 (30.8)	4,589 (46.3)
Duration of T2D, years	14.74 (8.77)	11.77 (7.65)	10.54 (7.22)
HbA_{1c}, %	8.39 (0.93)	8.03 (0.74)	7.34 (1.05)
Systolic blood pressure, mmHg	135.30 (15.66)	136.59 (17.42)	137.16 (16.81)
Height, cm	168.27 (9.89)	167.49 (9.84)	165.44 (10.09)
Weight, kg	92.57 (18.82)	89.89 (18.68)	88.67 (18.51)
BMI, kg/m^2	32.59 (5.49)	31.96 (5.67)	32.31 (5.74)
Lipids, mg/dL			
Cholesterol	159.24 (47.65)	168.88 (45.19)	174.88 (44.91)
HDL cholesterol	41.19 (10.88)	42.65 (11.01)	45.69 (13.23)
LDL cholesterol	80.60 (37.40)	95.07 (37.81)	98.82 (37.84)
Non-HDL cholesterol	117.95 (45.63)	126.19 (43.68)	129.10 (43.15)
Triglycerides, median (IQR)	159.43 (116.03, 224.98)	146.15 (108.00, 203.72)	141.72 (104.00, 196.63)
CV history, *n* (%)			
Prior heart failure	2,678 (20.3)	283 (13.9)	853 (8.6)
Prior stroke	2,525 (19.2)	357 (17.4)	687 (7.0)
Prior myocardial infarction	6,216 (47.2)	942 (46.1)	1,602 (16.3)
Prior coronary revascularization	7,529 (57.2)	958 (46.6)	1,657 (16.7)
Current tobacco use, *n* (%)	1,959 (14.9)	299 (14.5)	1,407 (14.2)
Current alcohol use, *n* (%)	4,774 (36.3)	746 (36.3)	3,502 (35.4)
eGFR, mL/min/1.73 m^2	80.30 (21.54)	80.31 (20.49)	80.65 (19.42)
UACR, median (IQR), g/kg	22.00 (9.00, 83.00)	18.59 (6.20, 78.77)	15.05 (5.55, 58.41)
SGLT-2i use, *n* (%)	4,027 (30.6)	0	3 (0.0)

Data are mean (SD) unless otherwise indicated. eGFR, estimated glomerular filtration rate; IQR, interquartile range; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

estimates replacing the treatment outcome of dulaglutide versus placebo (Fig. 2) with that of GLP-1RAs versus placebo were consistent, as shown in Table 2, which collates all estimates for all methods. The estimated indirect absolute risk difference of imputed placebo versus tirzepatide in cumulative incidence of MACE-3 was 4.2%, so the estimated number needed to treat was 23.6 for 4 years.

CONCLUSIONS

In SURPASS-CVOT, tirzepatide met a primary prespecified criterion for noninferiority to dulaglutide, and superiority to imputed placebo, in rates of MACE-3 events. The prespecified analysis presented here sought to support the conclusions reached in SURPASS-CVOT by using an alternative approach. The findings of this indirect comparison are compatible with the results inferred from the tirzepatide-dulaglutide comparison, that

Table 2—Comparison of the magnitude of indirect placebo treatment outcomes of tirzepatide in SURPASS-CVOT by various analyses

	Considering REWIND target population		Considering full REWIND population		
Outcome	PS-based adjustment	Without PS-based adjustment	PS-based adjustment	Without PS-based adjustment	Considering GLP-1RA class effect
MACE-3	0.72 (0.55, 0.94)	0.72 (0.58, 0.91)	0.75 (0.60, 0.93)	0.81 (0.70, 0.94)	0.79 (0.71, 0.88)
MACE-4	0.80 (0.64, 1.01)	0.78 (0.64, 0.94)	0.79 (0.65, 0.96)	0.80 (0.71, 0.91)	
CV death or HF events	0.70 (0.51, 0.96)	0.74 (0.57, 0.96)	0.66 (0.51, 0.85)	0.80 (0.67, 0.95)	
All-cause death	0.61 (0.45, 0.82)	0.70 (0.55, 0.90)	0.65 (0.51, 0.84)	0.75 (0.64, 0.88)	0.74 (0.65, 0.84)
CV death	0.75 (0.52, 1.09)	0.79 (0.58, 1.08)	0.72 (0.53, 0.98)	0.81 (0.66, 0.99)	0.77 (0.65, 0.90)

Data are HR (95% CI). Estimated indirect placebo treatment effects of tirzepatide in SURPASS-CVOT for primary and key secondary CV end points comparing analyses in the indirect comparison target REWIND population using PS-based adjustment (primary analysis) and without adjustment, in the full REWIND population with and without adjustment, and with substitution of dulaglutide-placebo effects by GLP-1RA class–placebo effects (sensitivity analyses). HF, heart failure; PS, propensity score.

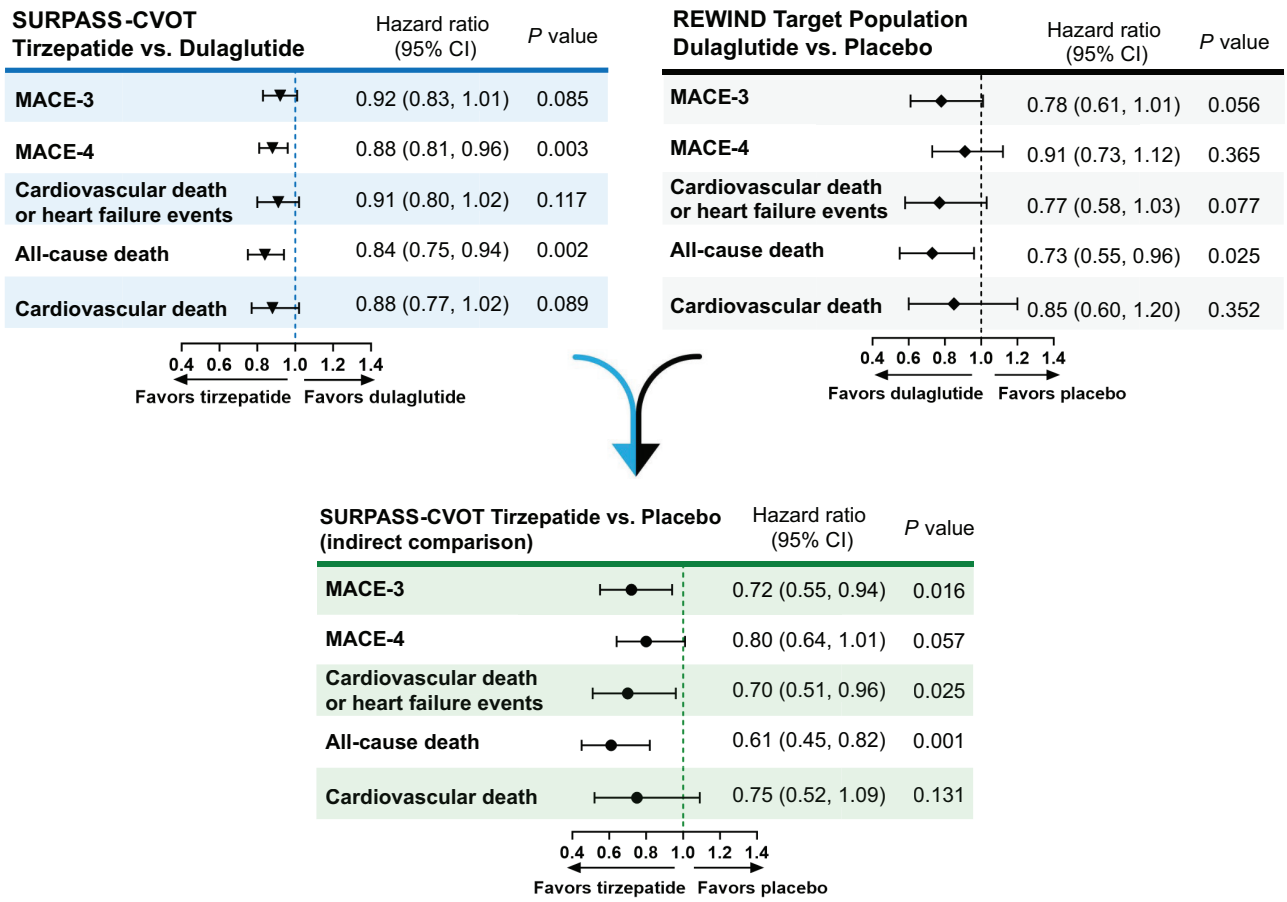


Figure 1—Primary and key secondary CV end points for indirect treatment effect of tirzepatide (SURPASS-CVOT mITT) vs. placebo (REWIND target), tirzepatide vs. dulaglutide in SURPASS-CVOT, and dulaglutide vs. placebo in REWIND target; all were adjusted using inverse probability weighting from propensity scores with multiple imputation for missing covariates. In SURPASS-CVOT, *n* = 6,579 for dulaglutide and *n* = 6,586 for tirzepatide. In REWIND, *n* = 1,044 for placebo and *n* = 1,011 for dulaglutide.

is, that tirzepatide has benefits to reduce MACE-3 events and provides an estimate of the magnitude of the difference that would occur in a tirzepatide versus placebo trial. While cross-trial comparisons are fraught with confounders, access to participant-level data presented an opportunity to propensity score match participants from SURPASS-CVOT and REWIND. Broadly consistent results were observed in both the unadjusted analysis in the indirect comparison target population and analyses involving the entire REWIND cohort, findings that support the superiority of tirzepatide over placebo in CV outcomes and in all-cause mortality. In addition, in post hoc analyses, the estimated benefits were further determined using a recent meta-analysis of incretin-based drugs in participants with type 2 diabetes, which reported a MACE risk reduction of 14% (14). Using these data to reflect the MACE-3 treatment outcome of dulaglutide, the MACE-3 benefit of tirzepatide was estimated at HR 0.79 (95% CI 0.71, 0.88) (Fig. 2 and Table 2), a more conservative estimate but, nevertheless, still strongly in keeping with a robust CV benefit of tirzepatide relative to placebo. Finally, these analyses also consistently suggested that tirzepatide has benefits relative to placebo in various MACE outcomes and all-cause death.

Returning to the prespecified analyses, the fact that MACE rates are generally higher in participants with established CV disease (20–25) likely contributes to the lower MACE-3 rates in the dulaglutide arm of REWIND (2.35 per 100 person-years) relative to the dulaglutide arm of SURPASS-CVOT (3.54 per 100 person-years) and provided a rationale for the selection of high-risk patients for comparisons across the two trials used here. A comparison for a lower-risk population like the one in REWIND remains to be established. The REWIND and SURPASS-CVOT cohorts had many relevant differences, including time and place of enrollment, background clinical care, and availability of potentially confounding medications, such as SGLT-2is. However, the ability to match participant characteristics and enrollment criteria, along with further propensity scoring, provides a reasonable approximation of CV risk status at the onset of the studies, a major determinant of incident MACE.

Methodologies to estimate an indirect treatment effect of tirzepatide compared with imputed placebo may vary, including a network meta-analysis using published aggregate summary data of previous randomized controlled CVOTs with GLP-1RA versus placebo and an emulation approach using a public database. Advantages in the present approach include *1*) inclusion of prospective, randomized, double-blind studies with independently adjudicated CV events; *2*) demographics, baseline characteristics, and medical histories at the individual participant level to allow for selection of similar populations and

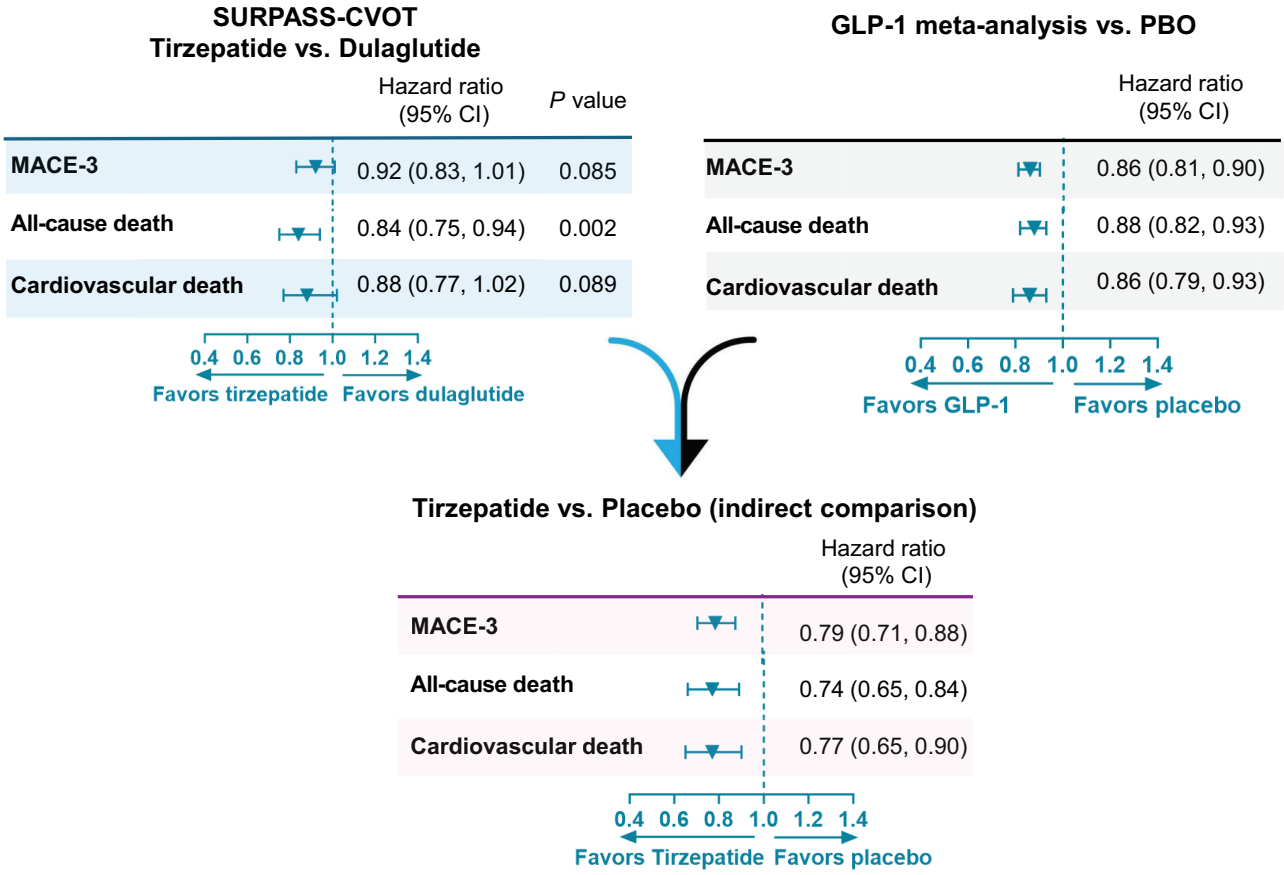


Figure 2—Sensitivity analyses replacing the outcome of dulaglutide treatment vs. placebo with that of GLP-1RAs vs. placebo. The HR was obtained by multiplying the two individual HRs. The CI was calculated using the reported lower and upper bounds from each estimate.

further adjustment; *3*) long-term and similar follow-up duration (median of 4.0 years in SURPASS-CVOT and 5.4 years in REWIND); and *4*) unbiased data reports.

Limitations of this study included that the indirect treatment effect estimates, calculated by multiplying the HR for SURPASS-CVOT tirzepatide versus dulaglutide by the HR for REWIND dulaglutide versus placebo, relied on the assumption of no interaction between background standard of care, including SGLT-2i use, and treatment effect. This assumption is based on findings from the subgroup analysis by SGLT-2i use at baseline in SURPASS-CVOT, where 30.6% of participants used an SGLT-2i, as well as results from a recent meta-analysis of GLP-1RA trials in individuals with type 2 diabetes confirming no interaction (12,14,26). Additionally, the different inclusion criteria for REWIND and SURPASS-CVOT resulted in exclusion of ∼80% of the REWIND population who did not meet the inclusion criteria for SURPASS-CVOT. Due to the different inclusion criteria, there were no REWIND participants with HbA_{1c} >9.5% and <10.5%. Moreover, the two trials were performed at different times, so the use of SGLT-2is was much lower, the use of other drugs was higher, secular rates of CV events were different, and the sites and countries that participated were different in REWIND. Some of these are obvious but are not explicitly measured and cannot be adjusted for. These are all caveats in the interpretation. For all these caveats, the addition of a post hoc analyses that estimated the dulaglutide MACE treatment outcome to be reflective of all prior GLP-1RA CVOT data generated in trials of patients with type 2 diabetes (14) suggested broadly similar MACE and other outcome benefits for tirzepatide relative to placebo. While some indirect adjusted estimates had wider CIs, this is expected due to wider variability introduced from inverse probability weighting and multiple imputation techniques. Finally, we acknowledge that we did not compare the MACE impact of tirzepatide against the highest (5 mg) dose of dulaglutide, which may have resulted in different findings.

In summary, by using data from the REWIND trial, this predefined, indirect comparison of results from SURPASS CVOT and REWIND reported in several ways, along with additional post hoc sensitivity analysis—suggests that tirzepatide would meaningfully lower MACE, the combined end point of heart failure events and CV death. It also suggests that tirzepatide would reduce all-cause mortality relative to placebo in participants with type 2 diabetes and cardiovascular disease.

Acknowledgments. The authors thank Jonathan Broder and Alan Herschtal (Monash University, Melbourne, Australia) for data validation and review and Dr. Gary Grant and Dr. Emer Farrell (Eli Lilly and Company, Indianapolis, IN) for editorial assistance.

N.S., J.B.B., and S.E.K. are editors of *Diabetes Care* but were not involved in any of the decisions regarding review of the manuscript or its acceptance.

Funding. Funding of these analyses and of both SURPASS-CVOT and REWIND were by Eli Lilly and Company.

Duality of Interest. N.S. has consulted for and/or received speaker honoraria from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly and Company, Gan & Lee, GlaxoSmithKline, Hanmi Pharmaceuticals, Kailera, Mass Medicines, Menarini-Ricerche, Metsera, Novo Nordisk, Pfizer, Regeneron, Roche, UCB Pharma, and Verdiva Bio and received grant support paid to his University from AstraZeneca, Boehringer

Ingelheim, Novartis, and Roche outside the submitted work. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly and Company, Novo Nordisk, and Hanmi; continuing education grants from Eli Lilly and Company, Abbott, Sanofi, Novo Nordisk, and Boehringer Ingelheim; honoraria for speaking from AstraZeneca, Eli Lilly and Company, Novo Nordisk, Zuellig, Sanofi, and Jiangsu Hanson; and consulting fees from Abbott, Bayer, Eli Lilly and Company, Novo Nordisk, and Sanofi. He holds a patent for the use of GDF15 as a biomarker for metformin intake. D.D. has consulted for Eli Lilly and Company, Sun Pharmaceuticals, Structure Therapeutics, MBX, Fractyl, Proteostasis, Arrowhead, and Vertex. D.L.B. discloses the following relationships: advisory board participation for Angiowave, Antlia Bioscience, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, E-Star Biotech, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, NirvaMed, Novo Nordisk, Repair Biotechnologies, Stasys, and Tourmaline Bio; board of directors participation for the American Heart Association New York City, Angiowave (stock options), Bristol-Myers Squibb (stock), DRS.LINQ (stock options), and High Enroll (stock); consultation with Alnylam, Altimmune, Broadview Ventures, Corcept Therapeutics, Corsera, GlaxoSmithKline, Hims, SERB, SFJ, Summa Therapeutics, and Worldwide Clinical Trials; data monitoring committee participation for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research, Boston Scientific (chair, Pulmonary Embolish International Thrombolysis High Risk [PEITHO] trial), Cleveland Clinic, Contego Medical (chair, Protection Against Emboli During Carotid Artery Stenting [PERFORMANCE 2] trial), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ABILITY–Diabetes Mellitus [ABILITY-DM] trial, funded by Concept Medical, and for the Safety and Efficacy of the Alleviant System for No-Implant Interatrial Shunt Creation in Patients With Chronic Heart Failure [ALLAY-HF], funded by Alleviant Medical), Novartis, Population Health Research Institute, and Rutgers University (for the National Institutes of Health–funded Myocardial Ischemia and Transfusion [MINT] Trial); honoraria from the American College of Cardiology (ACC) (senior associate editor, *Clinical Trials and News*, ACC.org; chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (ApoA-I Event Reducing in Ischemic Syndromes II [AEGIS-II] executive committee funded by CSL Behring), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (American Heart Association lecture), Duke Clinical Research Institute, Engage Health Media, HMP Global (editor in chief, *Journal of Invasive Cardiology*), Medtelligence/ReachMD (continuing medical education [CME] steering committees), MJH Life Sciences, Oakstone CME (course director, Comprehensive Review of Interventional Cardiology), Philips (Becker's Webinar on artificial intelligence), Population Health Research Institute, WebMD (CME steering committees), and Wiley (steering committee); other for *Clinical Cardiology* (deputy editor) and *Progress in Cardiovascular Diseases* (deputy editor); named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon, for which neither he nor Brigham and Women's Hospital receive any income); research funding from Abbott, Acesion Pharma, Afimmune, Alnylam, Amarin, Amgen, AstraZeneca, Atricure, Bayer, Boehringer Ingelheim, Boston Scientific, CellProthera, Cereno Scientific, Chiesi, Cleerly, CSL Behring, Faraday Pharmaceuticals, Fractyl, Idorsia, Janssen, Javelin, Lexicon, Eli Lilly and Company, Medtronic, Merck, MiRUS, Moderna, Novartis, Novo Nordisk, Pfizer, PhaseBio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, 89Bio; royalties from Elsevier (editor, *Braunwald's Heart Disease*); and site coinvestigator for Cleerly. J.B.B. has received salary support from clinical trial contracts to his employer by Corcept, Dexcom, GentiBio, and Novo Nordisk; is a consultant with personal compensation from Aardvark Therapeutics, Altimmune, Alveus Therapeutics, Amgen, Antag, Aqua Medical, AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Dexcom, Eli Lilly and Company, Embecta, GentiBio, Insulet, Metsera, MiniMed, Novo Nordisk, Tandem, Recordati, Sparrow Pharmaceuticals, Vertex, vTv Therapeutics, and Zealand; and has stock/stock options in Glyscend, Mellitus Health, Metsera, Pendulum Therapeutics, Praetego, and Stability Health. S.D.P. has served as an advisor for Abbott, Applied Therapeutics, Biomea Fusion, Eli Lilly and Company, Menarini International, Novo Nordisk, Roche, and Sun Pharmaceuticals; has received fees for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Laboratori Guidotti, Menarini International, and Novo Nordisk; has served as past-president of the European Association for the Study of Diabetes; and is currently president of the European Diabetes Forum and of the Menarini Foundation. S.E.K., during the course of the study, has received grant support from Corcept Therapeutics and consulted or served on advisory boards for Amgen, AltPep, Anji Pharmaceuticals, Biomea Fusion, Boehringer Ingelheim, Casma Therapeutics, Congruence Therapeutics, Intarcia, Eli Lilly and Company, Merck, Neurochem, Novo Nordisk, Oramed, Pfizer, and Third Rock Ventures. A.M.L. has received honoraria for consultancy from Novo Nordisk, Eli Lilly and Company, Alnylam, Amgen, Ardelyx, Brainstorm Cell, Capricor, Cadrenal, Johnson & Johnson, Medtronic, Neovasc, ReCor, TD Cowen, and V-Wave and has received research funding paid to his institution from AbbVie, AstraZeneca, CSL Behring, Eli Lilly and Company, Esperion, and Novartis. D.K.M. has received honoraria for clinical trial leadership from Novo Nordisk, Eli Lilly and Company USA, Pfizer, Boehringer Ingelheim, NewAmsterdam, Amgen, and Lexicon and for consultancy from Eli Lilly and Company USA, Boehringer Ingelheim, Novo Nordisk, Lexicon, Amgen, Neurotronic, Kailera, Metsera, Alveus, Zealand, CSL Behring and has stock option equity interest in Kailera. M.A.N. has been a member on advisory boards or has consulted with Boehringer Ingelheim, Eli Lilly and Company, Medtronic, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Regor, Sun Pharmaceuticals, and Structure Therapeutics (ShouTi, Gasherbrum); has received grant support from Merck Sharp & Dohme; served on the speakers' bureaus of Eli Lilly and Company, Merck Sharp & Dohme, Medscape, Medical Learning Institute, and Novo Nordisk; and is on a data monitoring and safety board for Inventiva. S.E.N. reports that the Cleveland Clinic Center for Clinical Research has received funding to perform clinical trials from AbbVie, AstraZeneca, Amgen, Arrowhead, Bristol-Myers Squibb, Kardigan, CRISPR Therapeutics, Eli Lilly and Company, Esperion, Medtronic, MyoKardia, NewAmsterdam, Novartis, Pfizer, and Silence Therapeutics. He is involved in conducting these clinical trials but receives no personal remuneration for his participation, and he consults for these pharmaceutical companies but does not accept compensation. B.Z. reports being a consultant for Eli Lilly and Company. S.Z. reports previous payments to her institution (Monash University) from AstraZeneca, Boehringer Ingelheim, CSL Seqirus, Eli Lilly and Company Australia, GlaxoSmithKline, Moderna, Sanofi, and Novo Nordisk for her participation on advisory boards, on steering committees, and in educational meetings. S.J.N. received grant/research support from AstraZeneca, NewAmsterdam, Amgen, Anthera, Cyclarity, Eli Lilly and Company, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience and was a consultant for Abcentra, AstraZeneca, Amarin, Akcea, Eli Lilly and Company, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim, Daiichi Sankyo, Scribe, Silence Therapeutics, CSL Seqirus, and Vaxxinity. A.B., D.M., H.N., Y.Q., G.W., R.J.W., and I.P. are current employees and shareholders of Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. N.S. and H.C.G. wrote the first draft. H.N. and G.W. were responsible for the data analysis. All authors contributed to the interpretation of the results, participated in the drafting and critical review of the manuscript, and gave approval for the final version to be published. I.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editor responsible for overseeing the review of the manuscript was M. Sue Kirkman.

References

1. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovasc Diabetol 2022;21:169

2. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet 2018; 392:2180–2193

3. Del Prato S, Kahn SE, Pavo I, et al.; SURPASS-4 Investigators. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet 2021; 398:1811–1824

4. Frías JP, Davies MJ, Rosenstock J, et al.; SURPASS-2 Investigators. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021;385:503–515

5. Heerspink HJL, Sattar N, Pavo I, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 2022;10: 774–785
6. Várkonyi TT, Pósa A, Pávó N, Pavo I. Perspectives on weight control in diabetes - tirzepatide. Diabetes Res Clin Pract 2023;202:110770
7. Bhatt DL, Wilson JM, Wiese RJ, Yang Z, Duffin KL, Pavo I. Tirzepatide reduces high-sensitivity C-reactive protein in patients with type 2 diabetes and high cardiovascular risk: a post hoc analysis of the SURPASS-4 Trial. Circulation 2023;148:A16779
8. Sattar N, McGuire DK, Pavo I, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nat Med 2022;28:591–598
9. Eli Lilly and Company. A study of tirzepatide (LY3298176) compared with dulaglutide on major cardiovascular events in participants with type 2 diabetes (SURPASS-CVOT). In: ClinicalTrials.gov. Bethesda, MD, National Library of Medicine, 2025. NLM Identifier: NCT04255433. Accessed 23 March 2026. Available from https://clinicaltrials.gov/show/NCT04255433
10. Nicholls SJ, Bhatt DL, Buse JB, et al.; SURPASS-CVOT Investigators. 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
11. McGuire DK, D'Alessio D, Nicholls SJ, et al. Transitioning to active-controlled trials to evaluate cardiovascular safety and efficacy of medications for type 2 diabetes. Cardiovasc Diabetol 2022; 21:163
12. Nicholls SJ, Pavo I, Bhatt DL, et al.; SURPASS-CVOT Investigators. Cardiovascular outcomes with tirzepatide versus dulaglutide in type 2 diabetes. N Engl J Med 2025;393:2409–2420
13. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130
14. Lee MMY, Sattar N, Pop-Busui R, et al.; SOUL Trial Investigators. Cardiovascular and kidney outcomes and mortality with long-acting injectable and oral glucagon-like peptide 1 receptor agonists in individuals with type 2 diabetes: a systematic review and meta-analysis of randomized trials. Diabetes Care 2025;48:846–859
15. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424
16. Qu Y, Lipkovich I. Propensity score estimation with missing values using a multiple imputation missingness pattern (MIMP) approach. Stat Med 2009;28:1402–1414
17. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–560
18. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med 2014; 275:570–580
19. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Amer Stat Assoc 1989;84:1074–1078
20. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239
21. Husain M, Birkenfeld AL, Donsmark M, et al.; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–851
22. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
23. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
24. Hernandez AF, Green JB, Janmohamed S, et al.; Harmony Outcomes Committees and Investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–1529
25. Gerstein HC, Sattar N, Rosenstock J, et al.; AMPLITUDE-O Trial Investigators. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med 2021;385:896–907
26. Marx N, Deanfield JE, Mann JFE, et al.; SOUL Study Group. Oral semaglutide and cardiovascular outcomes in people with type 2 diabetes, according to SGLT2i use: prespecified analyses of the SOUL randomized trial. Circulation 2025;151: 1639–1650