Cardiovascular Outcome Profile of Tirzepatide in Adults with Type 2 Diabetes: A Clinical Trial and Real-World Evidence Synthesis

The management of type 2 diabetes mellitus has evolved from a glucose-centric paradigm to a comprehensive risk-reduction model that prioritizes cardioprotection and renal preservation. Within this therapeutic landscape, incretin-based therapies have emerged as central agents. Tirzepatide, a unimolecular dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, represents a major innovation in this drug class.[1] By co-activating GIP and GLP-1 pathways, tirzepatide achieves substantial glycemic control and weight reduction.[4] However, defining its precise impact on major adverse cardiovascular events (MACE) has required extensive clinical trial investigation.[6]

To address whether tirzepatide demonstrates a statistically significant reduction in MACE compared to placebo in dedicated cardiovascular outcome trials (CVOTs), or if current data are limited to exploratory endpoints, this report synthesizes findings from randomized clinical trials, post hoc cardiorenal analyses, imputed placebo models, and real-world cohort studies.

The clinical trial evidence confirms that tirzepatide has not yet been evaluated against a placebo in a completed, dedicated CVOT of patients with type 2 diabetes.[8] Because placebo-controlled trials in high-risk patients with diabetes are increasingly considered unethical due to the proven benefits of selective GLP-1RAs, investigators designed the landmark dedicated CVOT for tirzepatide, **SURPASS-CVOT**, using an active comparator (dulaglutide) rather than a placebo.[9] In this dedicated trial, tirzepatide demonstrated robust cardiovascular safety by meeting noninferiority criteria against dulaglutide, but it did not achieve statistically significant superiority for the primary 3-point MACE endpoint.[12] Direct placebo-controlled evidence of MACE reduction in patients with type 2 diabetes is therefore estimated through matched-patient imputed placebo analyses [8], while direct placebo-controlled outcomes are available in overlapping populations, such as patients with obesity and heart failure.[15]

Active-Comparator Dedicated Trial Evidence: SURPASS-CVOT

The definitive cardiovascular safety and efficacy data for tirzepatide in adults with type 2 diabetes and established cardiovascular disease derive from the SURPASS-CVOT trial (NCT04255433).[11] Published in the *New England Journal of Medicine*, SURPASS-CVOT is the first large-scale cardiovascular outcomes trial to use an active comparator—the established GLP-1RA dulaglutide—rather than a placebo.[18] Because dulaglutide had already demonstrated a significant 12% reduction in MACE compared to placebo in the REWIND trial, it provided a rigorous active control for validating the cardiovascular safety of dual GIP/GLP-1 receptor

agonism.[9]

The double-blind, noninferiority trial screened 16,979 patients and randomized 13,299 adults aged 40 years and older with type 2 diabetes and confirmed atherosclerotic cardiovascular disease (ASCVD) in a 1:1 ratio.[12] Following the exclusion of 134 participants who did not meet baseline inclusion criteria, the modified intention-to-treat population consisted of 6,586 patients in the tirzepatide group and 6,579 in the dulaglutide group.[12]

The study population represented a high-risk cohort with long-standing diabetes and a substantial burden of macrovascular disease: 65% of participants had coronary artery disease (with 47.3% reporting a history of myocardial infarction and 57.4% a prior coronary revascularization), 19.1% had a history of stroke, and 25.3% had peripheral artery disease.[20] Concomitant antidiabetic therapies at enrollment included metformin (81.4%), insulin (48.8%), sodium-glucose cotransporter-2 (SGLT2) inhibitors (30.2%), and sulfonylureas (21.6%).[13]

Participants received once-weekly subcutaneous injections of either tirzepatide (dose-escalated from 2.5 mg up to a maximum tolerated dose of 5 mg, 10 mg, or 15 mg) or dulaglutide (fixed dose of 1.5 mg) over a median follow-up period of 4.0 years.[12] The primary composite endpoint was 3-point MACE, defined as the time to the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.[10] Noninferiority was defined as an upper limit of less than 1.05 for the 95.3% confidence interval (CI) of the hazard ratio (HR).[12] If noninferiority was met, superiority was tested, requiring an upper limit of less than 1.00.[10]

Efficacy and Safety Outcomes

A primary 3-point MACE endpoint occurred in 12.2% (n = 801) of the tirzepatide group compared to 13.1% (n = 862) of the dulaglutide group.[13] This translated to a hazard ratio of 0.92, with a 95.3% confidence interval of 0.83 to 1.01.[10] These findings met the prespecified statistical threshold for noninferiority ($P = 0.003$), confirming that tirzepatide does not increase cardiovascular risk compared to dulaglutide.[12] However, the difference did not achieve statistical superiority ($P = 0.09$).[12]

The rates of individual MACE components numerically favored tirzepatide but did not reach statistical significance:

- **Cardiovascular death** occurred in 5.6% of the tirzepatide group versus 6.2% of the dulaglutide group ($HR =$).[10]
- **Non-fatal myocardial infarction** occurred in 4.7% versus 5.4% ($HR =$).[10]
- **Non-fatal stroke** occurred in 3.5% versus 3.8% ($HR =$).[10]

In contrast, an expanded 4-point MACE endpoint that added coronary revascularization to the primary composite demonstrated a statistically significant 12% risk reduction with tirzepatide (16.5% versus 18.5%; $HR =$; 95% CI, 0.81–0.96).[13] Additionally, all-cause mortality, a prespecified secondary endpoint, was reduced by 16% in the tirzepatide group compared to

dulaglutide (8.6% versus 10.2%; $HR = 0.84$; 95% CI, 0.75–0.94).[10] This survival benefit was primarily driven by a significant reduction in non-cardiovascular deaths (3.0% versus 4.0%; $HR =$; 95% CI, 0.63–0.91), which investigators classified as exploratory and hypothesis-generating.[10]

Tirzepatide demonstrated superior metabolic efficacy, achieving an additional 0.78% reduction in glycated hemoglobin (HbA1c) and an additional 6.8% reduction in body weight compared to dulaglutide.[13] The safety profiles of both therapies were consistent with the incretin class.[9] Gastrointestinal adverse events, primarily nausea, diarrhea, and vomiting, were more frequent with tirzepatide (42.5% versus 35.9%).[18] Discontinuation of the study drug due to adverse events was also higher in the tirzepatide group (13.2% versus 10.1%).[13] However, the incidence of serious adverse events remained virtually identical between the cohorts (31.8% versus 31.9%).[18]

Clinical Characteristic or Event	Tirzepatide (N = 6,586)	Dulaglutide (N = 6,579)	Hazard Ratio (HR) / Treatment Difference (95% or 95.3% CI)	Statistical Significance (P-value)
Primary 3-Component MACE [10]	12.2% (n = 801)	13.1% (n = 862)	$HR = 0.92$ (0.83–1.01)	$P = 0.003$ (Noninferiority) $P = 0.09$ (Superiority)
All-Cause Mortality [10]	8.6% (n = 566)	10.2% (n = 669)	$HR = 0.84$ (0.75–0.94)	Nominally Significant (Secondary)
Non-Cardiovascular Death [10]	3.0% (n = 198)	4.0% (n = 263)	$HR =$ (0.63–0.91)	Exploratory / Hypothesis-Generating
Cardiovascular Death [10]	5.6%	6.2%	$HR =$ (not specified)	Not Statistically Significant

Non-fatal Myocardial Infarction [10]	4.7%	5.4%	$HR =$ (not specified)	Not Statistically Significant
Non-fatal Stroke [10]	3.5%	3.8%	$HR =$ (not specified)	Not Statistically Significant
Expanded 4-Component MACE [13]	16.5%	18.5%	$HR =$ (0.81–0.96)	Statistically Significant
Mean HbA1c Reduction [13]	-1.66%	-0.88%	Difference: -0.78%	$P < 0.001$
Mean Body Weight Reduction [13]	-11.6%	-4.8%	Difference: -6.8%	$P < 0.001$
Discontinuation due to Adverse Events [13]	13.2%	10.1%	Risk Difference: 3.1%	Higher with Tirzepatide

Expanded Post Hoc Outcomes: JAMA Cardiology Cardiorenal Synthesis

To establish a comprehensive comparison of cardiorenal outcomes between the two drugs, Nissen et al. conducted a major post hoc analysis of the SURPASS-CVOT trial, published in *JAMA Cardiology*.[18] This analysis evaluated a broad 6-component cardiorenal composite endpoint over a median treatment duration of 46.9 months.[18] The composite included all-cause mortality, myocardial infarction, stroke, coronary revascularization, hospitalization for heart failure, and serious adverse kidney outcomes.[18] The kidney composite captured severe outcomes, specifically a persistent doubling of serum creatinine, the initiation of kidney replacement therapy, or death due to kidney disease.[18]

The cardiorenal composite endpoint occurred in 23.7% (n = 1,559) of the tirzepatide group compared to 27.4% (n = 1,803) of the dulaglutide group.[18] This represents a statistically significant 16% risk reduction ($HR = 0.84$; 95% CI, 0.79–0.90; $P < 0.001$) and an absolute risk reduction of 3.7%.[18] Under this composite, the number needed to treat (NNT) to prevent one cardiorenal event over approximately four years was 27 patients.[18]

A key finding of this analysis was the robust renal protection demonstrated by tirzepatide, which

showed a 21% reduction in serious adverse renal events compared to dulaglutide (4.9% versus 6.1%).[18] Sensitivity analyses confirmed that this cardiorenal benefit was consistent across multiple endpoint configurations:

- A **5-component composite** (which excluded the renal composite) maintained a significant 14% risk reduction ($HR =$; 95% CI, 0.80–0.93).[26]
- A **4-component composite** (which excluded both the renal composite and heart failure hospitalization) demonstrated an identical 14% risk reduction ($HR =$; 95% CI, 0.80–0.93).[26]

These findings indicate that the cardiorenal benefits of tirzepatide are robust and not driven by any single outcome component.[26]

The divergence between the lack of statistically significant superiority in macrovascular atherothrombotic events (MI and stroke) and the clear improvements in mortality, coronary revascularization, and renal function is a major focus of clinical discussion.[23] Cardiologists note that GIP receptors are highly expressed in human epicardial adipose tissue and the ventricular myocardium.[25] Co-activation of GIP pathways may suppress local vascular inflammation, promote metabolic flexibility, and reduce volume overload.[25] These physiological mechanisms would have a more direct impact on heart failure, kidney function, and overall mortality than on atherothrombotic events like myocardial infarction or stroke, which are heavily mediated by established arterial plaque.[25]

Evaluated Cardiorenal Endpoint	Tirzepatide (N = 6,586)	Dulaglutide (N = 6,579)	Hazard Ratio (HR) (95% CI)	Statistical Significance (P-value)
Primary 6-Component Cardiorenal Composite [18]	23.7% (n = 1,559)	27.4% (n = 1,803)	$HR = 0.84$ (0.79–0.90)	$P < 0.001$
5-Component Composite (No Kidney Outcomes) [26]	Not specified	Not specified	$HR =$ (0.80–0.93)	Statistically Significant
4-Component Composite (No Kidney/Heart Failure) [26]	Not specified	Not specified	$HR =$ (0.80–0.93)	Statistically Significant

All-Cause Mortality [18]	8.6% (n = 566)	10.2% (n = 669)	$HR = 0.84$ (0.75–0.94)	Nominally Significant
Coronary Revascularization [18]	8.0% (n = 527)	9.4% (n = 617)	$HR = 0.84$ (0.75–0.95)	Nominally Significant
Serious Adverse Kidney Composite [18]	4.9% (n = 326)	6.1% (n = 404)	$HR =$ (not specified)	21% Relative Risk Reduction
Myocardial Infarction [18]	4.7% (n = 311)	5.4% (n = 357)	$HR =$ (0.74–1.00)	Nominally Significant
Stroke [27]	3.5% (n = 231)	3.8% (n = 250)	$HR =$ (0.76–1.09)	Not Statistically Significant
Hospitalization for Heart Failure [27]	3.0% (n = 198)	3.1% (n = 204)	$HR =$ (0.79–1.17)	Not Statistically Significant

Estimating Placebo-Controlled Efficacy: Matched-Patient Imputed Placebo Analyses

To address the lack of direct placebo-controlled CVOT data for tirzepatide in type 2 diabetes, Sattar et al. conducted a prespecified indirect treatment comparison (ITC) published in *Diabetes Care*.[8] This analysis estimated the treatment effect of tirzepatide compared to an imputed placebo by combining patient-level data from the SURPASS-CVOT and REWIND trials.[8]

The analysis matched all 13,165 participants from SURPASS-CVOT with 2,055 of the 9,901 participants from REWIND who met the same high-risk eligibility criteria.[8] The investigators used propensity score matching to adjust for baseline differences in age, gender, renal function, body weight, HbA1c, and cardiovascular risk factors across the two study populations.[8] The placebo-controlled effect of tirzepatide was estimated mathematically by multiplying the hazard ratio of tirzepatide versus dulaglutide from SURPASS-CVOT by the hazard ratio of dulaglutide versus placebo from the matched REWIND cohort.[8]

In this matched-patient analysis, tirzepatide was associated with a statistically significant 28% reduction in the risk of 3-point MACE compared to an imputed placebo ($HR = 0.72$; 95% CI, 0.55–0.94).[8] The analysis also estimated a 30% reduction in the risk of cardiovascular death

or heart failure events ($HR =$; 95% CI, 0.51–0.96) and a 39% reduction in all-cause mortality ($HR = 0.61$; 95% CI, 0.45–0.82).[8]
These findings remained directionally consistent across sensitivity analyses, including unadjusted models and analyses utilizing the entire REWIND trial population or meta-analyzed selective GLP-1RA data.[8] These indirect results support the hypothesis that tirzepatide provides cardioprotection comparable to or exceeding that of selective GLP-1RAs when evaluated against a placebo.[8]

Estimated Clinical Endpoint vs. Imputed Placebo	Matched-Patient Matched Population (HR [95% CI])	Entire REWIND Cohort Reference (HR [95% CI])	Clinical Interpretation & Implications
3-Point MACE Composite	$HR = 0.72$ (0.55–0.94)	$HR =$ (0.60–0.93)	Estimated 25% to 28% risk reduction vs. placebo, matching established GLP-1RA outcomes.[8]
All-Cause Mortality	$HR = 0.61$ (0.45–0.82)	$HR =$ (0.51–0.84)	Estimated 35% to 39% reduction in overall mortality risk, driven by cardiorenal protection.[8]
Cardiovascular Death or Heart Failure Composite	$HR =$ (0.51–0.96)	$HR =$ (0.51–0.85)	Significant reduction in congestive heart failure and vascular death composite.[8]
4-Point MACE Composite	$HR =$ (0.64–1.01)	$HR =$ (0.65–0.96)	Trend toward risk reduction including coronary revascularization.[14]

Historical Context: Prior Exploratory Safety Data

Before the publication of the SURPASS-CVOT trial, clinical data regarding the cardiovascular

profile of tirzepatide in type 2 diabetes were limited to exploratory endpoints from glycemic efficacy trials.[2] A major prespecified meta-analysis by Sattar et al., published in *The Lancet Diabetes & Endocrinology* in 2022, pooled safety data from seven randomized controlled trials in the SURPASS clinical development program.[7] The analysis included 4,887 participants treated with tirzepatide and 2,328 control participants receiving a placebo, insulin glargine, or selective GLP-1RAs.[7]

The primary safety endpoint was the time to the first occurrence of a confirmed 4-component major adverse cardiovascular event (MACE-4), which added hospitalized unstable angina to the standard 3-component MACE composite.[7] Because the individual glycemic trials enrolled populations with low cardiovascular risk and had short follow-up periods, the baseline event rate was low.[2] Across all seven trials, only 142 participants experienced a MACE-4 event, with 109 of those events occurring in the high-risk SURPASS-4 trial.[7]

The pooled hazard ratio comparing tirzepatide to controls was 0.80 (95% CI, 0.57–1.11) for MACE-4, 0.90 (95% CI, 0.50–1.61) for cardiovascular death, and 0.80 (95% CI, 0.51–1.25) for all-cause death.[7] While these hazard ratios numerically favored tirzepatide, the wide confidence intervals crossing 1.00 meant the meta-analysis could only confirm cardiovascular safety, rather than prove efficacy.[2]

The largest single study in this pooled safety cohort was SURPASS-4, which compared tirzepatide to titrated insulin glargine in 1,995 patients with inadequately controlled type 2 diabetes and high cardiovascular risk.[36] Over a median treatment period of 85 weeks, once-weekly tirzepatide led to substantial reductions in body weight (-11.7 kg for the 15 mg dose versus a 1.9 kg weight gain with glargine) and SBP.[36] In the safety analysis, the hazard ratio for MACE-4 was 0.74 (95% CI, 0.51–1.08), confirming that tirzepatide did not increase cardiovascular risk compared to insulin glargine, but lacking the statistical power to show a significant reduction in events.[36]

Placebo-Controlled Trial Outcomes in Heart Failure and Obesity

Although direct placebo-controlled MACE trials in type 2 diabetes are absent, clinical trialists have obtained high-quality, placebo-controlled cardiovascular outcomes evidence for tirzepatide in overlapping patient populations, particularly in patients with obesity and heart failure.[15]

The SUMMIT Trial: Heart Failure with Preserved Ejection Fraction and Obesity

The SUMMIT trial (NCT04847557) is the first clinical trial to evaluate a dual GIP/GLP-1 receptor agonist in patients with heart failure with preserved ejection fraction (HFpEF) and obesity.[38] The trial randomized 731 adults with class II to IV heart failure, an ejection fraction of 50% or higher, and a BMI of 30 kg/m² or higher in a 1:1 ratio to receive weekly subcutaneous tirzepatide (titrated up to 15 mg) or a placebo.[16] The median follow-up period was 104 weeks.[16] Approximately 60% of the participants also had chronic kidney disease, and the trial was stratified by baseline diabetes status, history of HF decompensation, and BMI.[15]

At the conclusion of the study, the primary composite endpoint—defined as the time to the first occurrence of cardiovascular death or a worsening heart failure event requiring hospitalization, urgent care, or intensification of oral diuretics—occurred in 9.9% of the tirzepatide group compared to 15.3% of the placebo group.[16] This represented a statistically significant 38% reduction in risk ($HR = 0.62$; 95% CI, 0.41–0.95; $P = 0.026$).[39]

The primary driver of this benefit was a 46% reduction in worsening heart failure events (8.0% versus 14.2%; $HR = 0.54$; 95% CI, 0.34–0.85).[16] No statistically significant difference was observed in cardiovascular death (2.2% versus 1.4%; $HR = 1.58$; 95% CI, 0.52–4.83, based on 15 total deaths).[16]

Additionally, tirzepatide met its co-primary endpoint by significantly improving the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) at 52 weeks, showing a mean increase of 19.5 points in the tirzepatide group versus 12.7 points in the placebo group ($P < 0.001$).[38]

Tirzepatide also produced improvements in other clinical metrics, including a mean body weight reduction of 13.9% (versus 2.2% with placebo), an 18.3-meter increase in the 6-minute walk distance, and a 38.8% reduction in high-sensitivity C-reactive protein (hs-CRP).[38] These cardiorenal benefits were consistent across participants with and without chronic kidney disease, as well as those with and without type 2 diabetes.[15]

The SURMOUNT Program: Upstream Cardiometabolic Trials

To evaluate the cardiorenal benefits of tirzepatide across its clinical development, investigators have examined glycemic, hemodynamic, and weight-loss outcomes in the broader SURMOUNT clinical trial program.[43] These trials have established the metabolic foundation that underlies the drug's cardiorenal effects:

- **SURMOUNT-1 (Prediabetes and Obesity)**: A 3-year extension of the trial in adults with obesity and prediabetes showed that once-weekly tirzepatide achieved up to a 22.9% mean weight loss (versus 2.1% with placebo).[45] More importantly, tirzepatide achieved a 94% reduction in the risk of developing type 2 diabetes ($HR = 0.06$; 95% CI, 0.03–0.13).[45]
- **SURMOUNT-2 (Obesity and Type 2 Diabetes)**: Evaluated the 10 mg and 15 mg doses of tirzepatide over 72 weeks in adults with obesity and type 2 diabetes.[43] Tirzepatide achieved a mean weight reduction of 15.7% (versus 3.3% with placebo).[43] It also improved cardiovascular risk factors, reducing systolic blood pressure by a mean of 7.2 mmHg (versus 1.0 mmHg with placebo) and significantly improving triglycerides and cholesterol.[43]
- **SURMOUNT-5 (Head-to-Head Weight Loss)**: Directly compared tirzepatide to semaglutide (2.4 mg) in adults with obesity or overweight and at least one weight-related condition.[3] At week 72, tirzepatide achieved a statistically superior mean weight loss of

20.2% (22.8 kg) compared to 13.7% (15.0 kg) for semaglutide ($P < 0.001$).[44] It also led to greater reductions in systolic blood pressure (-10.2 mmHg versus -7.7 mmHg).[44] Women showed a more pronounced weight-loss response than men on both medications.[44]

- **SURMOUNT-MMO (Dedicated Cardiovascular Outcomes in Obesity)**: To confirm whether these cardiometabolic benefits translate into direct cardiovascular protection in individuals without diabetes, the SURMOUNT-MMO trial (NCT05556512) is currently ongoing.[1] This event-driven, placebo-controlled trial has enrolled approximately 15,000 participants aged 40 and older with a BMI of 27 kg/m² or higher and established cardiovascular disease or multiple risk factors.[46] The primary composite endpoint is the time to the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or heart failure events.[29]

Real-World Evidence and Comparative Effectiveness

Observational analyses and database studies have provided complementary evidence comparing tirzepatide to other treatments in clinical practice.[2]

Post-PCI Outcomes in High-Risk Patients

Using the TriNetX database, researchers identified 1,281 propensity-score-matched adults with type 2 diabetes undergoing percutaneous coronary intervention (PCI) who initiated either tirzepatide or dulaglutide.[48] At one month post-procedure, the tirzepatide cohort experienced significantly lower rates of MACE ($RR = 0.46$), acute myocardial infarction ($RR = 0.47$), and heart failure exacerbation ($RR = 0.54$).[48]

At one year, these benefits remained consistent, showing reductions in MACE, AMI, and heart failure hospitalization, as well as a 62% reduction in all-cause mortality ($RR =$; $P < 0.001$), stroke ($RR = 0.56$; $P = 0.01$), and cardiac arrest ($RR = 0.32$; $P < 0.001$).[48] While encouraging, these observational findings require confirmation in prospective, randomized trials.[48]

Post-TAVR Outcomes in Patients with Obesity

Another database study utilized TriNetX to compare clinical outcomes over one year in adults with obesity undergoing transcatheter aortic valve replacement (TAVR) based on tirzepatide use.[49] At one year post-TAVR, patients who did not receive tirzepatide experienced significantly worse event-free survival (77.7% versus 84.1%).[49]

Non-users also faced a 54% higher risk of hospitalization for acute heart failure ($HR =$; 95% CI, 1.11–2.13) and experienced MACE—defined as a composite of death, MI, stroke, heart

failure, arrhythmia, or intracerebral hemorrhage—44% more frequently ($HR = 1.44$; 95% CI, 1.22–1.70).[49] No significant differences were observed in individual rates of ischemic stroke or acute kidney injury.[50]

Clinical Profile in Thyroid Dysfunction and Obesity

A retrospective cohort study presented at the AACE 2026 Scientific Sessions matched 42,940 obese patients with hypothyroidism who initiated either semaglutide or tirzepatide, tracking outcomes for up to 5 years.[25] Tirzepatide use was associated with lower all-cause mortality, chronic kidney disease (2.6% versus 2.9%), and cerebrovascular disease (1.5% versus 1.9%) compared to semaglutide.[25] However, the rates of acute myocardial infarction were comparable between the groups.[25]

These findings align with the post hoc cardiorenal composite data from SURPASS-CVOT, suggesting that the GIP component of tirzepatide may suppress epicardial adipose tissue inflammation and reduce volume overload, leading to cardiorenal benefits rather than a direct reduction in plaque-mediated ischemic events.[25]

Insurance Cohort Trial Emulations

A major cohort study emulated the SUSTAIN-6 trial (comparing semaglutide to a sitagliptin/placebo proxy) and the SURPASS-CVOT trial (comparing tirzepatide to dulaglutide) using real-world data from US insurance programs between 2018 and 2025.[52] Comparing tirzepatide to dulaglutide for a composite cardiovascular outcome yielded a hazard ratio of 0.86.[52]

In a head-to-head comparison of tirzepatide versus semaglutide, the hazard ratio for a composite of MI, stroke, or all-cause mortality was 1.06 (95% CI, 0.95–1.18), indicating comparable real-world cardiovascular benefit for both agents.[52]

Dispensing Trends Following Cardiovascular Label Expansion

An interrupted time series analysis of over 2 million adults with established cardiovascular disease and obesity between January 2021 and May 2025 examined how regulatory approvals translate into clinical practice.[53] Following the FDA's March 2024 approval of semaglutide for cardiovascular risk reduction based on the SELECT trial, first-time semaglutide dispensing showed an immediate 23% increase ($IRR = 1.23$; 95% CI, 1.14–1.32).[53]

No corresponding immediate change was observed for tirzepatide, which instead maintained a steady, gradual rise in first-time dispensing over time.[53] Despite these increases, the overall proportion of eligible adults receiving either drug remained low, representing a missed therapeutic opportunity among high-risk patients.[53]

Real-World	Comparative	Primary Evaluated	Key Statistical	Clinical

Study Cohort	Groups	Endpoint	Result	Implications
TriNetX T2D Post-PCI [48]	Tirzepatide vs. Dulaglutide (N = 1,281)	MACE and Mortality at 1 Year	$RR =$ for 1-Year Mortality ($P < 0.001$)	Suggests immediate, significant post-procedure protection in high-risk patients.[48]
TriNetX Obesity Post-TAVR [49]	Tirzepatide vs. Untreated (Obese TAVR Patients)	Composite MACE and HF Hospitalization	$HR =$ for HF Hospitalization in Non-Users	Highlights potential cardioprotective benefits of metabolic therapy post-valve replacement.[49]
TriNetX Hypothyroidism & Obesity [25]	Tirzepatide vs. Semaglutide (N = 42,940 per group)	All-Cause Mortality & Cardiorenal Events	CKD: 2.6% vs. 2.9% Cerebrovascular: 1.5% vs. 1.9%	Suggests potential advantages in renal and volume-mediated heart failure outcomes.[25]
US Claims Cohort Emulation [52]	Tirzepatide vs. Semaglutide (Head-to-Head)	Composite of MI, Stroke, or All-Cause Mortality	$HR =$ (95% CI, 0.95–1.18)	Suggests comparable real-world cardiovascular protection in clinical practice.[52]

Conclusions

A critical synthesis of the clinical trial evidence and real-world data provides a clear answer to the primary question regarding tirzepatide's cardiovascular outcomes.

In adults with type 2 diabetes, tirzepatide has not demonstrated a statistically significant reduction in major adverse cardiovascular events (MACE) compared to placebo in a completed, dedicated cardiovascular outcome trial.[8] Because placebo-controlled trials in high-risk populations with diabetes are increasingly considered unethical due to the proven benefits of

selective GLP-1RAs, investigators designed the landmark dedicated CVOT, **SURPASS-CVOT**, using an active comparator (dulaglutide) rather than a placebo.[9]

In this trial, tirzepatide met its primary safety objective by demonstrating robust noninferiority to dulaglutide for the primary 3-point MACE endpoint ($HR = 0.92$; 95.3% CI, 0.83–1.01; $P = 0.003$), but it did not achieve statistically significant superiority ($P = 0.09$).[12]

However, the available evidence is no longer limited to exploratory endpoints from early glycemic trials:

1. **Robust Safety Validation**: SURPASS-CVOT established that tirzepatide maintains the cardiovascular protection of a proven active comparator (dulaglutide) while delivering superior glycemic control and weight reduction.[9]
2. **Imputed Placebo Efficacy**: Prespecified matched-patient analyses combining data from SURPASS-CVOT and REWIND estimate a statistically significant 28% reduction in 3-point MACE ($HR = 0.72$; 95% CI, 0.55–0.94) and a 39% reduction in all-cause mortality ($HR = 0.61$; 95% CI, 0.45–0.82) compared to an imputed placebo.[8]
3. **Superior Cardiorenal Outcomes**: A post hoc analysis of SURPASS-CVOT published in *JAMA Cardiology* showed that tirzepatide achieved a statistically significant 16% reduction in a broad 6-component cardiorenal composite endpoint compared to dulaglutide ($HR = 0.84$; 95% CI, 0.79–0.90; $P < 0.001$).[18]
4. **Heart Failure and Obesity Protection**: The placebo-controlled SUMMIT trial demonstrated that tirzepatide achieved a significant 38% reduction in cardiovascular death or worsening heart failure ($HR = 0.62$; 95% CI, 0.41–0.95; $P = 0.026$) in patients with HFpEF and obesity.[38]
5. **Ongoing Placebo-Controlled CVOT**: The event-driven SURMOUNT-MMO trial is currently evaluating the placebo-controlled cardiovascular efficacy of tirzepatide in approximately 15,000 adults with obesity but without diabetes.[46]

From a regulatory perspective, tirzepatide remains approved under the trade names Mounjaro (for glycemic control in type 2 diabetes) and Zepbound (for chronic weight management and sleep apnea).[21] Unlike semaglutide, tirzepatide does not currently hold an FDA indication for cardiovascular risk reduction.[53]

Nevertheless, the cumulative clinical and real-world evidence confirms the cardiovascular safety and cardiorenal benefits of tirzepatide, supporting its role as a front-line therapy for patients with type 2 diabetes, obesity, and established cardiovascular risk.[9]

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