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# Cardiovascular Outcomes of Tirzepatide Compared with Glucagon-Like Peptide-1 Receptor Agonist (GLP-1) and Insulin in Patients with Type-2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Keywords**
Cardiovascular; Meta-Analysis; Systematic Review; Tirzepatide; Type 2 Diabetes Mellitus.

**ABSTRACT**
Cardiovascular disease remains a major cause of morbidity and mortality among patients with type 2 diabetes mellitus, highlighting the need for antidiabetic therapies that provide metabolic benefits without increasing cardiovascular risk. This study aimed to evaluate the cardiovascular outcomes of tirzepatide compared with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), insulin therapy, and placebo in adults with type 2 diabetes mellitus. A systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines. PubMed, Scopus, CENTRAL, and ScienceDirect databases were searched from inception to April 2026. Seven randomized controlled trials involving 21,108 participants met the eligibility criteria. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel method, and subgroup analyses were performed according to comparator class. Tirzepatide did not significantly alter the risk of myocardial infarction compared with pooled comparators (RR 1.97; 95% CI 0.52–7.43; p = 0.31) or stroke (RR 2.47; 95% CI 0.45–13.52; p = 0.30). The risk of all-cause mortality was also comparable between groups (RR 1.05; 95% CI 0.38–2.89; p = 0.92). Comparator-based subgroup analyses yielded similarly nonsignificant results. In conclusion, tirzepatide demonstrated a cardiovascular safety profile comparable to GLP-1 receptor agonists, insulin therapy, and placebo; however, additional long-term studies are required to determine whether it provides superior cardiovascular benefits.

## INTRODUCTION

The therapeutic landscape for type 2 diabetes mellitus (T2DM) has undergone a paradigm shift over the past decade, transitioning from a strictly glucocentric approach to a comprehensive strategy focused on cardiovascular and renal risk reduction. This evolution was primarily driven by mandated cardiovascular outcomes trials (CVOTs), which demonstrated that specific classes of antihyperglycemic agents, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, provide significant protection against major adverse cardiovascular events (MACE) and mortality,

independent of their glucose-lowering effects (Kristensen et al., 2019; Zelniker et al., 2019). Consequently, current international guidelines recommend prioritizing these agents in patients with established atherosclerotic cardiovascular disease (ASCVD) or those at high cardiovascular risk (Davies et al., 2022).

Despite the widespread use of these cardioprotective therapies, patients with T2DM continue to experience substantial residual cardiovascular risk, driven by concurrent increases in severe obesity, treatment-resistant hypertension, and atherogenic dyslipidemia (Sattar et al., 2021). To address these overlapping metabolic abnormalities, pharmacological research has progressed toward unimolecular multi-receptor agonists (Huang et al., 2024; Patil et al., 2026). Tirzepatide is a first-in-class dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. Across the SURPASS clinical trial program, tirzepatide has demonstrated substantial efficacy, achieving marked reductions in glycated hemoglobin (HbA1c) and body weight, with weight reductions of up to 20% reported in clinical studies, exceeding those observed with some high-dose selective GLP-1 receptor agonists and basal insulin therapies (Frías et al., 2021; Ludwig et al., 2022).

Mechanistically, the synergistic effects of GIP and GLP-1 receptor agonism are hypothesized to produce beneficial pleiotropic effects on the cardiovascular system. While GLP-1 receptor agonists are known to improve endothelial function and reduce systemic inflammation, additional GIP receptor agonism may further influence lipid metabolism through reductions in postprandial triglycerides and apolipoprotein B, as well as through the modulation of ectopic fat accumulation (Samms et al., 2020). However, the definitive effects of this metabolic improvement on clinically relevant cardiovascular outcomes remain uncertain.

Currently available Phase 2 and Phase 3 trials within the SURPASS program were primarily designed to evaluate surrogate outcomes, such as HbA1c reduction and weight loss, rather than adjudicated cardiovascular events (Sattar et al., 2022). The relatively low incidence of major adverse cardiovascular events (MACE) in individual, short-duration trials limits their statistical power to conclusively exclude cardiovascular harm or demonstrate superiority. Therefore, pooling data from multiple high-quality randomized controlled trials (RCTs) is methodologically important to address these limitations. This systematic review and meta-analysis aimed to rigorously evaluate the cardiovascular safety profile of tirzepatide by analyzing the risks of myocardial infarction, stroke, and all-cause mortality compared with established antidiabetic therapies in adults with T2DM.

The urgency of this analysis arises from the increasing clinical use of tirzepatide and the need to select treatments that simultaneously improve glycemic control, reduce body weight, and minimize cardiovascular complications. Clinicians frequently need to determine whether tirzepatide should replace or be used before established GLP-1 receptor agonists or insulin therapy. Such decisions require considerations beyond HbA1c reduction because cardiovascular safety, mortality outcomes, tolerability, hypoglycemia risk, and patient characteristics influence treatment selection. Although current evidence suggests that tirzepatide is not associated with increased cardiovascular risk, the relatively small number of cardiovascular events in several trials and the wide confidence intervals surrounding effect estimates require cautious interpretation. Synthesizing available randomized evidence can improve statistical precision and clarify the consistency of findings across different comparator classes.

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The novelty of this systematic review and meta-analysis lies in its focused evaluation of individual hard cardiovascular outcomes and stratification according to comparator classes. Rather than considering GLP-1 receptor agonists, insulin therapies, and placebo as equivalent comparators, this study evaluated them separately to reduce clinical heterogeneity and potential comparator-related confounding. The analysis was also restricted to adults with T2DM, excluding trials conducted exclusively among individuals with obesity without diabetes. By integrating randomized evidence from the SURPASS clinical program and relevant cardiovascular analyses, this study provided a clinically interpretable assessment of myocardial infarction, stroke, and all-cause mortality associated with tirzepatide use.

Accordingly, this study aimed to systematically evaluate and quantitatively synthesize the cardiovascular outcomes of tirzepatide compared with GLP-1 receptor agonists, insulin therapy, and placebo in adults with T2DM. Specifically, it examined the risks of myocardial infarction, stroke, and all-cause mortality while assessing whether the direction and magnitude of effects varied across comparator classes. This study contributes updated and methodologically focused evidence regarding the cardiovascular safety of dual GIP/GLP-1 receptor agonism. The findings may support evidence-based treatment decisions, identify remaining uncertainties for future research, and strengthen the integration of glycemic management, weight reduction, and cardiovascular risk reduction in the care of patients with T2DM.

## METHOD

### Information Sources and Search Strategies

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). A systematic search was performed in PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and ScienceDirect from inception to April 2026. The search strategy used Medical Subject Headings (MeSH) and relevant keywords, including "tirzepatide," "LY3298176," "type 2 diabetes," "cardiovascular outcomes," "myocardial infarction," and "mortality."

### Data Selection, Collection, and Extraction

Two independent investigators screened the retrieved literature. Disagreements were resolved by a third reviewer. The population, intervention, comparator, and outcomes (PICO) framework was predefined. Population: Adults (≥18 years) with confirmed type 2 diabetes mellitus (T2DM), spanning the spectrum of cardiovascular risk. Strict Exclusion: Studies involving non-diabetic individuals solely for weight management/obesity were entirely excluded to prevent demographic confounding. Intervention: Tirzepatide at any approved therapeutic dose (5 mg, 10 mg, or 15 mg once weekly) administered subcutaneously. Comparator: Active antidiabetic comparators or placebo. Outcomes: The primary cardiovascular outcomes were nonfatal/fatal myocardial infarction (MI) and nonfatal/fatal stroke. The secondary cardiovascular outcome was all-cause mortality.

To prevent confounding from class-specific cardiovascular protection, the meta-analysis was stratified strictly by active comparator classes rather than pooled blindly. The subgroups were defined as GLP-1 receptor agonists (e.g., semaglutide, dulaglutide), basal/prandial insulin (e.g., glargine, lispro), and placebo. Data extraction captured study characteristics, baseline

demographics (age, HbA1c, body mass index), intervention doses, comparator classes, and the number of clinical events.

**Quality Assessment**

The risk of bias for included randomized controlled trials (RCTs) was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) tool. Assessment domains included the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

**Data Analysis and Synthesis**

Statistical analyses were performed using the meta package in R software. The Mantel-Haenszel method was applied to calculate Risk Ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes. Heterogeneity among studies was quantified using the I2 statistic, with values greater than 50% indicating substantial heterogeneity. Both common and random-effect models were evaluated. Subgroup analyses were driven by the assigned comparator class.

## RESULTS AND DISCUSSION

**Study Selection and Characteristics**

Seven RCTs involving 21,108 participants met inclusion criteria. The PRISMA flow diagram is summarized in Figure 1.

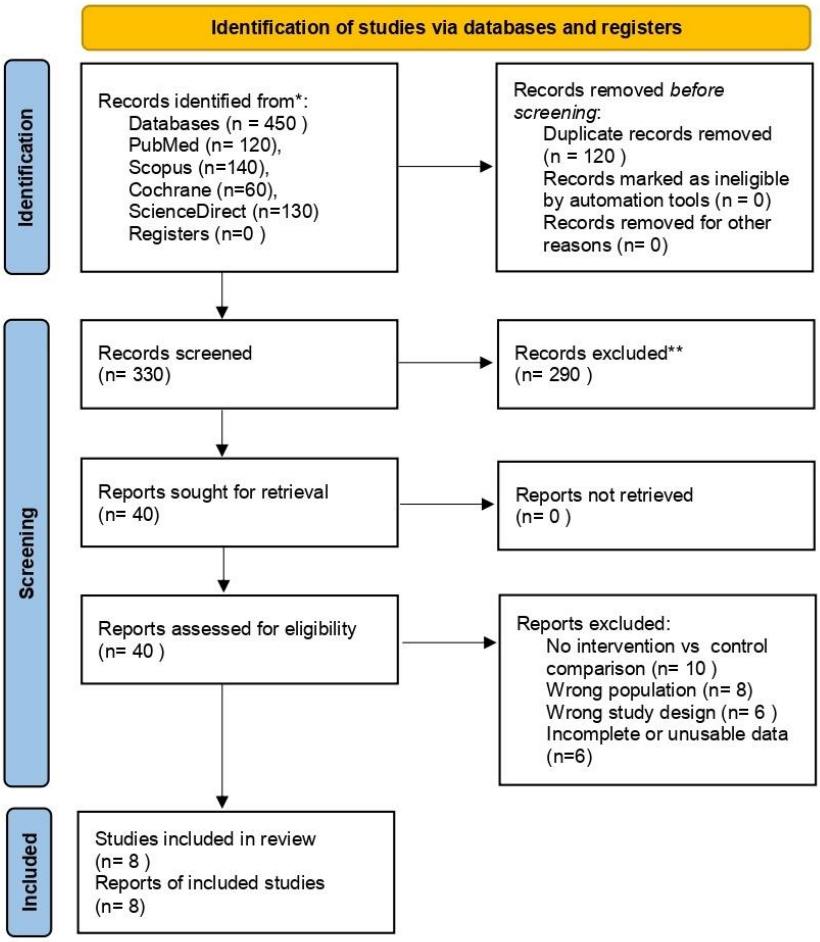


**Figure 1.** PRISMA Flow Diagram of Study Selection

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Study-level characteristics are detailed below.

**Table 1.** Characteristics of Included Randomized Controlled Trials

| Study | Phase | N (Total) | Intervention | Comparator | Mean Age | Baseline HbA1c (%) |
|---|---|---|---|---|---|---|
| Nissen et al. (2026) | Post-hoc/CVOT | 13165 | Tirzepatide (≤15 mg) | Dulaglutide 1.5 mg | NR | NR |
| Frías et al. (2021; SURPASS-2) | Phase 3 | 1879 | Tirzepatide (5/10/15 mg) | Semaglutide 1 mg | 56.6 | 8.28 |
| Prato et al. (2021; SURPASS-3) | Phase 3 | 1444 | Tirzepatide (5/10/15 mg) | Insulin Degludec | 57.4 | 8.17 |
| Frías et al. (2018) | Phase 2 | 316 | Tirzepatide | Dulaglutide/Placebo | 57 | 8.1 |
| Inagaki et al. (2022; J-mono) | Phase 3 | 636 | Tirzepatide (5/10/15 mg) | Dulaglutide 0.75 mg | 56.6 | NR |
| Rosenstock et al. (2023; SURPASS-6) | Phase 3 | 1425 | Tirzepatide (5/10/15 mg) | Insulin Lispro | 58.8 | 8.8 |
| Gao et al. (2023; AP-Combo) | Phase 3 | 889 | Tirzepatide (5/10/15 mg) | Insulin Glargine | 57.4 | 8.6 |

**Risk of Bias Assessment**

Risk of Bias (RoB 2.0) assessment showed generally Low Risk across all 7 studies. Objective hard outcomes like mortality and MI are not biased by the open-label design of some SURPASS trials. The independent clinical adjudication committees utilized in these trials ensured that the measurement of outcomes remained robust against potential performance bias.

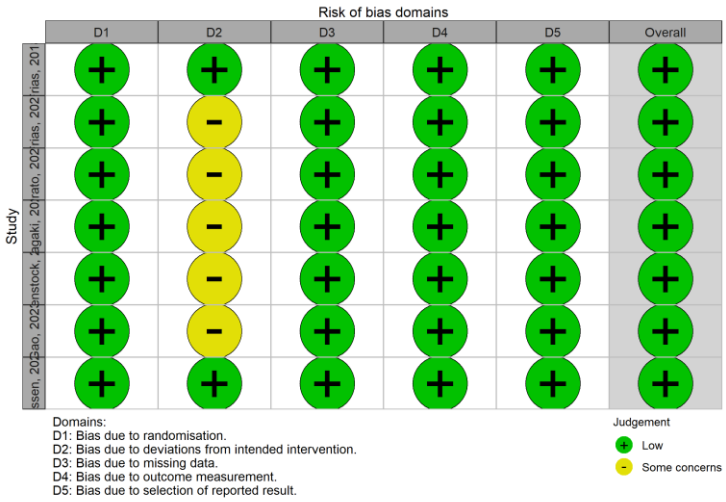


**Figure 2.** Risk of Bias Summary Traffic Light Plot

**Primary Outcomes**

**Myocardial Infarction (MI)**

Data on nonfatal and fatal MI were analyzed across trials reporting the event (Frías et al., 2021; Gao et al., 2023; Rosenstock et al., 2023). Overall, tirzepatide demonstrated no statistically significant difference in the incidence of MI compared to pooled active comparators (RR 1.97, 95% CI [0.52, 7.43], p = 0.31). Heterogeneity was absent ($I^2$ = 0.0%). When stratified by comparator class, the RR against GLP-1 RAs was 3.00 (95% CI [0.16, 55.54]), and against insulin, it was 1.70 (95% CI [0.39, 7.47]).

**Stroke**

Stroke event rates were uniformly low across the short-term reporting trials (Frías et al., 2021; Gao et al., 2023). Tirzepatide did not significantly alter the risk of stroke compared to active comparators (RR 2.47, 95% CI [0.45, 13.52], p = 0.30). Subgroup analysis revealed no significant variance whether compared against GLP-1 RAs (RR 1.67, 95% CI [0.08, 34.60]) or insulin glargine (RR 2.87, 95% CI [0.37, 22.53]). Statistical heterogeneity was 0.0%.

Figure 4. (A) Forest Plot of Stroke. (B) Forest Plot of Stroke Stratified by Comparator.

**Secondary Outcomes**

**All-Cause Mortality**

Analysis of all-cause mortality (Frías et al., 2021; Gao et al., 2023; Rosenstock et al., 2023) yielded a total of 22 events. Tirzepatide showed a comparable risk of all-cause mortality to the active control arms (RR 1.05, 95% CI [0.38, 2.89], p = 0.92). Moderate heterogeneity was observed ($I^2$ = 43.3%). Stratification indicated an RR of 3.99 (95% CI [0.52, 30.61]) when compared directly to semaglutide 1 mg, and an RR of 0.38 (95% CI [0.09, 1.55]) when compared to insulin therapy, though neither comparison reached statistical significance.

This systematic review and meta-analysis synthesized adjudicated cardiovascular data from seven randomized controlled trials to evaluate the safety profile of tirzepatide in patients with T2DM. Our comprehensive analysis demonstrates that tirzepatide does not significantly increase the risk of myocardial infarction (MI), stroke, or all-cause mortality when compared to a pooled cohort of active antidiabetic therapies and placebo. These findings provide critical near-term reassurance that the unprecedented metabolic potency of dual GIP/GLP-1 receptor agonism does not incur a cardiovascular penalty.

The absence of a statistically significant reduction in cardiovascular events in our analysis—despite tirzepatide's profound improvements in body weight, blood pressure, and lipid profiles—requires careful contextualization. The translation of modified surrogate risk factors into the prevention of hard atherothrombotic events typically exhibits a prolonged latency period. Historical CVOTs of GLP-1 RAs, such as the LEADER trial (liraglutide) and SUSTAIN-6 (semaglutide), demonstrated that Kaplan-Meier survival curves for MACE only begin to separate after 12 to 18 months of continuous therapy (Marso, Bain, et al., 2016; Marso, Daniels, et al., 2016). Given that the majority of the SURPASS trials included in this meta-analysis had follow-up durations ranging from 40 to 52 weeks, the temporal window was likely insufficient to capture the anticipated downstream cardioprotective benefits of tirzepatide.

A central strength of our meta-analysis is the rigorous subgroup stratification based on comparator classes, which mitigates the confounding effect of varying background cardioprotection. When compared directly against GLP-1 RAs (such as semaglutide and dulaglutide), the relative risk (RR) estimates for MI, stroke, and mortality exhibited wide confidence intervals but crossed the line of no effect. This effectively suggests that tirzepatide is clinically non-inferior to GLP-1 RAs concerning short-term cardiovascular safety, satisfying a high comparative benchmark given the established cardioprotective status of the GLP-1 class (Kristensen et al., 2019).

Conversely, in comparisons against insulin therapy (glargine, degludec, and lispro), tirzepatide demonstrated a numerical trend toward reduced all-cause mortality (RR 0.38, 95% CI [0.09, 1.55]). Although this did not achieve statistical significance due to the low absolute

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number of fatal events (e = 22), it aligns with recognized pathophysiological paradigms. Insulin therapy in T2DM is frequently associated with dose-dependent weight gain and iatrogenic hypoglycemia, both of which are potent triggers for sympathetic nervous system activation, fatal arrhythmias, and atherothrombotic events (Zoungas et al., 2010). By eliminating hyperinsulinemia and promoting weight loss, tirzepatide inherently curtails these pro-arrhythmogenic and pro-inflammatory pathways.

Mechanistically, there were initial theoretical concerns regarding the GIP component of tirzepatide. Early physiological studies suggested that GIP might promote adipogenesis and potentially exert divergent cardiovascular effects compared to GLP-1 (Samms et al., 2020). However, our aggregated clinical data dispel these concerns, supporting recent preclinical models showing that unimolecular co-agonism downregulates systemic inflammation, improves endothelial nitric oxide bioavailability, and stabilizes atherosclerotic plaques (Finan et al., 2013). The synergistic reduction in visceral adiposity achieved by tirzepatide likely overrides any isolated, tissue-specific lipogenic effects of GIP.

This meta-analysis is subject to several methodological limitations. Foremost is the exceptionally low incidence of total cardiovascular events across the included studies, which resulted in wide confidence intervals and constrained the precision of our risk estimates. Furthermore, the baseline cardiovascular risk of the populations varied significantly across the SURPASS program; while some cohorts included high proportions of patients with established ASCVD, others were predominantly primary prevention populations. Finally, while trial-level data were thoroughly aggregated, the absence of patient-level data prevents a deeper time-to-event analysis.

In conclusion, our meta-analysis confirms that tirzepatide exhibits a benign cardiovascular safety profile comparable to existing active therapies, including GLP-1 RAs and basal insulins, over short-to-medium-term follow-up. While current data confirm safety, the definitive establishment of cardiovascular superiority or MACE reduction awaits the completion of the dedicated SURPASS-CVOT (Nicholls et al., 2024). Until those long-term results are available, clinicians can confidently utilize tirzepatide to achieve aggressive metabolic targets without compounding cardiovascular risk.

## CONCLUSION

This systematic review and meta-analysis concluded that tirzepatide demonstrated a cardiovascular safety profile comparable to GLP-1 receptor agonists, insulin therapy, and placebo in adults with type 2 diabetes mellitus. The pooled analyses showed no significant differences in the risks of myocardial infarction, stroke, or all-cause mortality between tirzepatide and the evaluated comparators. These findings suggest that tirzepatide may be considered a cardiovascularly acceptable therapeutic option for glycemic management and weight reduction in patients with type 2 diabetes. However, the limited number of cardiovascular events, relatively short follow-up periods of available trials, and wide confidence intervals indicate the need for longer-term cardiovascular outcome trials to further clarify its potential benefits and establish whether tirzepatide provides superior cardiovascular protection compared with existing glucose-lowering therapies. Future studies should also investigate diverse patient populations, including individuals with established cardiovascular

disease and higher baseline cardiovascular risk, to strengthen the clinical applicability of the findings.

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