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TIRZEPATIDE FOR CARDIOVASCULAR RISK REDUCTION: A LITERATURE REVIEW

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ABSTRACT

Background: Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, shows promise beyond glycemic control for managing cardiovascular risk factors. Recent studies suggest that tirzepatide may also offer cardiovascular benefits by improving weight, glycemic control, blood pressure, systemic inflammation, and cardiometabolic risk factors.
Aim: Our review summarizes the current evidence on tirzepatide's cardiovascular effects, mechanisms of action, clinical outcomes, and safety profile in populations at increased cardiovascular risk.
Methodology: We conducted a narrative literature review of tirzepatide and cardiovascular outcomes using PubMed and Google Scholar.
Conclusion: Tirzepatide appears to be a promising therapeutic option for reducing cardiovascular risk, particularly in patients with type 2 diabetes, obesity, and heart failure. Current data support its positive effects on multiple cardiovascular risk factors. However, further confirmation from large clinical trials is needed to fully establish its long-term benefits and safety.

KEYWORDS

Tirzepatide, Cardiovascular Risk, Type 2 Diabetes Mellitus, Obesity, Heart Failure, GLP-1, GIP, Clinical Outcomes, Safety

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Introduction

Tirzepatide is a long-acting dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. It was initially developed for type 2 diabetes mellitus (T2DM), where it has demonstrated superior glycemic control, substantial weight loss, and improved cardiometabolic risk factors (Taktaz et al., 2024). Given the strong association between T2DM, obesity, and cardiovascular disease (CVD), therapies that address these metabolic dysfunctions hold promise for reducing cardiovascular risk. In fact, GLP-1 receptor agonists (GLP-1 RAs) have already been proven to reduce the incidence of major adverse cardiovascular events in high-risk patients and are now recommended to reduce atherosclerotic risk (Hegedűs et al., 2025). Tirzepatide activates both GIP and GLP-1 receptors, which may enhance its benefits compared to traditional GLP-1 therapies (Taktaz et al., 2024). Early studies suggest that tirzepatide not only improves glucose and weight but may also directly benefit cardiovascular health [3]. Potential advantages include improved endothelial function, reduced systemic inflammation, better blood pressure control, and effects on myocardial health (Yang et al., 2024). This has raised the possibility that tirzepatide could play a broader role in cardiovascular prevention, extending its use beyond glucose-lowering indications.

This review aims to explore the current evidence on tirzepatide's cardiovascular effects, its proposed mechanisms of action, and summarise its potential role in managing patients at increased cardiovascular risk.

Methodology

We searched PubMed and Google Scholar to August 2025 using terms related to tirzepatide and cardiovascular outcomes.

Tirzepatide's Cardiovascular Effects

Tirzepatide activates both GLP-1 and GIP receptors, producing combined metabolic and cardiovascular effects. In the vascular endothelium, it increases nitric oxide production and reduces oxidative stress and inflammation, which may improve vascular function and slow atherosclerosis. In the myocardium, tirzepatide has been linked to reduced cardiac fibrosis, less hypertrophy, lower inflammatory activity, enhanced autophagy, and decreased cardiomyocyte apoptosis (Hegedűs et al., 2025; Taktaz et al., 2024). These changes may help preserve cardiac structure and its function. Additionally, tirzepatide promotes significant weight loss and lowers blood pressure, further reducing cardiovascular strain (Krumholz et al., 2024; Yang et al., 2024).

Tirzepatide lowers cardiovascular risk by inducing substantial weight loss- up to 15% in participants with T2DM and 21% in those without, despite similar baseline body weight (Jensen et al., 2024). These metabolic effects, along with reductions in blood pressure and improvements in lipid profiles help reduce cardiovascular strain. Beyond metabolic control, tirzepatide reduces systemic inflammation. In patients with heart failure, high-sensitivity C-reactive protein levels decreased by approximately 37% after 52 weeks of treatment compared to placebo. This anti-inflammatory effect may contribute to vascular stability (Borlaug et al., 2025). Levels of troponin T (around 10% decrease), and N-terminal pro-BNP, both indicators of myocardial strain, were reduced in patients receiving tirzepatide. Preclinical studies support these findings, showing that tirzepatide suppresses the expression of genes involved in cardiac fibrosis and hypertrophy (Borlaug et al., 2025; Hegedűs et al., 2025). Laboratory models also suggest that tirzepatide protects heart muscle cells by decreasing programmed cell death and enhancing autophagy. These effects may support myocardial efficiency under stress(Luna-Marco et al., 2024; Taktaz et al., 2024). Tirzepatide positively influences the vascular system by improving endothelial function and reducing vascular inflammation. Its activation of GLP-1/GIP receptors increases nitric oxide production, which enhances vascular health. At the same time, tirzepatide limits foam cell formation and atherogenic activity, processes that drive plaque buildup. By targeting these pathways, tirzepatide may help slow the progression of atherosclerosis and reduce the risk of plaque rupture, myocardial infarction, and stroke (Sztanek et al., 2024; Taktaz et al., 2024)

Tirzepatide addresses multiple cardiovascular risk factors simultaneously, including weight, glycemic control, blood pressure, lipid profiles, and systemic inflammation. These combined effects may contribute to the overall reduction of cardiovascular strain, as summarized in Figure 1.

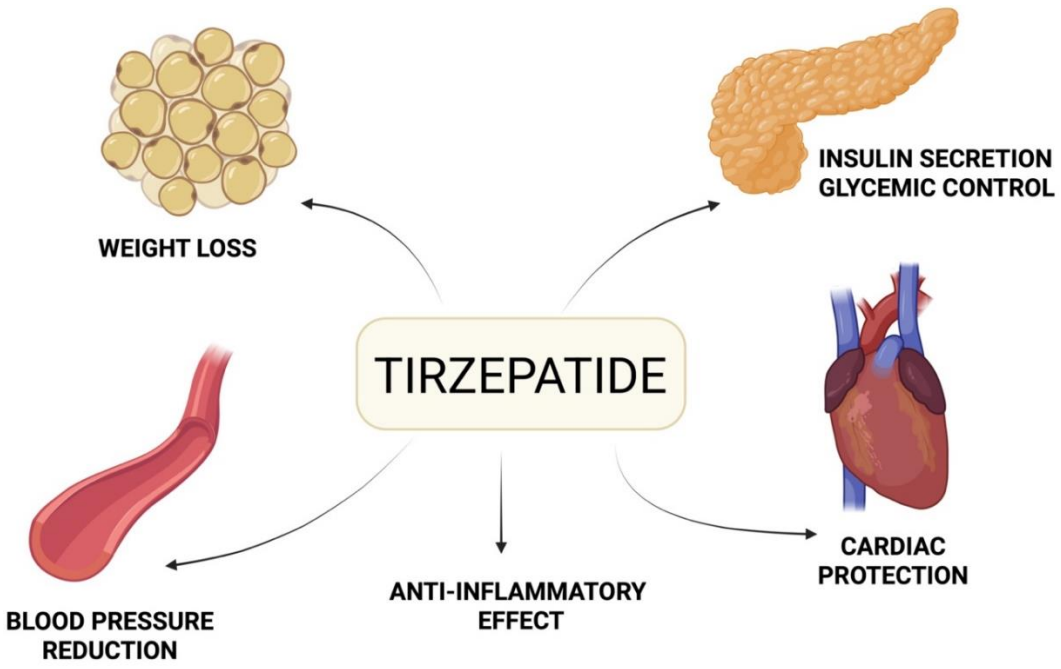

Fig. 1. *Tirzepatide's main therapeutic benefits (Created in BioRender. Layla, L. (2025) Https://BioRender.Com/V0bumom, n.d.).*

Clinical Evidence of Cardiovascular Outcomes with Tirzepatide

Clinical and real-world studies have begun to reveal tirzepatide's potential for reducing cardiovascular risk, particularly in populations with diabetes, obesity, and heart failure.

SUMMIT Trial- Heart Failure with Preserved Ejection Fraction (HFpEF)

The SUMMIT randomized controlled trial evaluated tirzepatide in 731 obese patients (BMI ≥30 kg/m²) with HFpEF (LVEF ≥50%) over a median follow-up of 104 weeks. Tirzepatide significantly reduced the risk of a composite endpoint (cardiovascular death or worsening heart failure) by 38% compared to placebo (HR 0.62; 95% CI 0.41–0.95; p=0.026). Moreover, patients reported improvements in quality of life (mean increase in KCCQ-CSS of 6.9 points) and exercise capacity (mean increase of 19m in the 6-minute walk test) while experiencing around 11-12% weight loss and reduced inflammation (hs-CRP)(Packer et al., 2025). Secondary analysis of the SUMMIT trial further revealed that tirzepatide decreased blood pressure, circulating volume overload, albuminuria, troponin T, and BNP, showing combined benefits for cardiovascular and renal function (Borlaug et al., 2025).

Real-World Evidence of Tirzepatide's Effects in HFpEF

A large retrospective analysis using TriNetX data evaluated tirzepatide in 14,154 patients with HFpEF, including both diabetic and non-diabetic individuals. Over one year, tirzepatide treatment significantly lowered the combined risk of heart failure exacerbation and all cause mortality compared to matched controls (HR 0.52; 95% CI 0.42–0.63; p<0.001). The study also found significant reductions in secondary endpoints, including major adverse cardiovascular events (MACE; HR 0.64) and major adverse kidney events (MAKE; HR 0.44). These benefits were consistent across patient subgroups stratified by age, sex, comorbidities, and baseline kidney function (Lin et al., 2025).

Observational Study in T2DM with Ischemic Heart Disease

A retrospective multicenter cohort study evaluated 47,719 adults over the age of 40 with T2DM and established ischemic heart disease. The study compared outcomes between 753 patients treated with tirzepatide and 46,966 patients with GLP-1 receptor agonists. After matching for baseline characteristics, patients treated with tirzepatide had a 40% lower risk of the composite outcome of myocardial infarction, stroke, or all-cause death (HR 0.60; 95% CI 0.43–0.84; p<0.001). Notably, the risks of myocardial infarction (HR 0.59) and all cause mortality (HR 0.35) were individually and significantly reduced over one year (Dani et al., 2025).

Meta-Analysis of SURPASS Trials

A meta-analysis of seven SURPASS trials, including 4,887 patients treated with tirzepatide and 2,328 control participants, assessed the drug's effect on cardiovascular outcomes. The analysis showed a 20% relative reduction in the 4-component major adverse cardiovascular events (MACE) endpoint. However, this reduction did not reach statistical significance (HR 0.80; 95% CI 0.57- 1.11). Despite the lack of statistical significance, the results suggest cardiovascular safety and a possible benefit in high-risk patients with T2DM (Sattar et al., 2022).

Safety and Tolerability of Tirzepatide

Tirzepatide has shown an acceptable safety profile across clinical studies. The most common side effects are gastrointestinal, nausea, vomiting, and diarrhea (Bettge et al., 2017; Filippatos et al., 2014). These events are typically mild to moderate and decrease over time, especially when drug is introduced with gradual dose escalation. Data from a 12-week randomized trial demonstrated that nausea occurred in approximately 24% of participants in the 12mg group and up to 39% in the 15mg group when dose increases were introduced more quickly. However, these gastrointestinal side effects rarely led to treatment discontinuation, and most cases resolved without intervention (Frias et al., 2020). Importantly, no episodes of severe hypoglycemia were reported in participants not using insulin or sulfonylureas. Additionally, no cases of pancreatitis or gallbladder-related complications were observed during the study period. Mild increases in heart rate were noted but are consistent with effects commonly seen in other GLP-1 receptor agonists (Frias et al., 2020). Across available studies, including the SUMMIT trial and real-world analyses, tirzepatide has not been linked to an increased risk of arrhythmias, heart failure exacerbations, or other serious cardiovascular events. This supports its cardiovascular safety profile when used in patients at high cardiometabolic risk (Augusto et al., 2025; Borlaug et al., 2025; Dani et al., 2025; Packer et al., 2025).

Overall, tirzepatide is well-tolerated, especially when dose escalation is carefully managed. Its safety profile aligns with that of other incretin-based therapies, with gastrointestinal symptoms being the most frequent but manageable adverse events.

Table 1. Summary of Cardiovascular Studies Evaluating Tirzepatide.

Study	Population and Design	Main Findings
SUMMIT Trial	731 obese patients (BMI ≥30 kg/m²) with HFpEF; randomized controlled trial; median follow-up 104 weeks	38% reduction in CV death or HF events; improved quality of life and exercise capacity; reduced hs-CRP
SUMMIT Sub-analysis	Subset of SUMMIT trial participants with HFpEF; mechanistic analysis	Decreases in systolic blood pressure, blood volume, hs-CRP, troponin T; improved renal parameters
TriNetX Real-World Study	14,154 patients with HFpEF; retrospective cohort study	48% lower risk of HF exacerbation and all-cause mortality; reduced MACE and kidney events
JACC Observational Study	47,719 adults with T2DM and ischemic heart disease; 753 treated with tirzepatide, 46,966 with GLP-1 RAs; retrospective cohort study	40% lower risk of MI, stroke, or all-cause mortality; individual risk reductions in MI and mortality
SURPASS Meta-Analysis	4,887 patients treated with tirzepatide vs. 2,328 controls; meta-analysis	20% reduction in MACE; not statistically significant but supports cardiovascular safety

BMI – Body Mass Index; CV – Cardiovascular; HF – Heart Failure; HFpEF – Heart Failure with Preserved Ejection Fraction; hs-CRP – High-sensitivity C-reactive Protein; MACE – Major Adverse Cardiovascular Events; MI – Myocardial Infarction; T2DM – Type 2 Diabetes Mellitus; GLP-1 RAs – Glucagon-like Peptide-1 Receptor Agonists.

Conclusions

Current studies suggest tirzepatide significantly benefits cardiovascular health through both metabolic and direct cardiovascular mechanisms. Clinical studies show reductions in heart failure events, myocardial infarction, stroke, and mortality among patients treated with tirzepatide, particularly those with heart failure with preserved ejection fraction, obesity, and T2DM. While large cardiovascular outcome trials are underway to confirm these findings, the current data strongly support tirzepatide as a promising therapeutic option for managing patients with elevated cardiovascular risk.

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Authors' contribution statement:

Conceptualization, E.S, and K.M.; methodology, E.S, and K.M.; check, L.S., J.B., D.G., and M.A.; formal analysis, E.S., J.B., D.G., and M.A.; investigation, E.S.; resources, E.S., and K.M.; writing - rough preparation, E.S., K.M., and L.S.; writing - review and editing, J.B., D.G., and M.A.; visualization, L.S.; supervision, J.B., D.G., and M.A.; project administration, L.S., K.M., and E.S.

All authors have read and agreed with the published version of the manuscript.

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