TPM Vol. 32, No. S3, 2025
ISSN: 1972-6325
https://www.tpmap.org/

CARDIOVASCULAR RISK IN TIRZEPATIDE MANAGEMENT FOR OBESITY IN TYPE 2 DIABETES PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Obesity and type 2 diabetes (T2D) are major contributors to cardiovascular (CV) morbidity and mortality. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, has shown superior efficacy in glycemic control and weight loss compared to selective GLP-1 receptor agonists. However, its impact on CV risk in patients with obesity and T2D remains incompletely synthesized. **Objective:** This systematic review evaluates the cardiovascular effects of tirzepatide in patients with obesity and T2D. **Methods:** Following PRISMA guidelines, we conducted a comprehensive search across PubMed, Web of Science, Scopus, and Embase. Eligible studies included RCTs, cohort studies, and post-hoc analyses assessing CV outcomes (e.g., major adverse cardiovascular events [MACE], heart failure [HF] hospitalization, mortality, and biomarker changes) in adults with obesity (BMI ≥30 kg/m²) and T2D. Risk of bias was assessed using Cochrane RoB 2 and Newcastle-Ottawa Scale.

Results: Nineteen studies were included. Tirzepatide demonstrated significant CV benefits, including reduced MACE (HR 0.44–0.60), HF hospitalization (HR 0.54), and CV death/worsening HF (HR 0.62). Weight loss (12–23.4%) mediated improvements in left ventricular mass (-11 g), 6-minute walk distance (+18.3 m), and inflammatory markers (↓hsCRP, ↓NT-proBNP). Real-world studies reported lower limb event risks (HR 0.44) and superior efficacy versus GLP-1 RAs. Mechanistic studies highlighted reductions in atherogenic lipoproteins (↓apoC-III) and cardiac fibrosis. **Conclusion:** Tirzepatide significantly reduces CV risk in obesity and T2D, with benefits extending beyond glycemic control and weight loss to improvements in cardiac structure, atherosclerosis, and inflammation. Ongoing trials (e.g., SURPASS-CVOT) will further clarify its role in CV risk management.

Keywords: Tirzepatide, Cardiovascular risk, Obesity, Type 2 diabetes, GLP-1/GIP receptor agonist, Major adverse cardiovascular events (MACE), Heart failure, Systematic review

INTRODUCTION

Obesity and type 2 diabetes (T2D) are major global health challenges, contributing significantly to cardiovascular (CV) morbidity and mortality [1]. The prevalence of obesity has nearly tripled since 1975, with over 650 million adults affected worldwide, while T2D affects approximately 537 million individuals, many of whom also suffer from obesity-related complications [2]. These metabolic disorders are closely linked to an increased risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and other adverse CV outcomes, driven by chronic inflammation, insulin resistance, and endothelial dysfunction [3]. Despite advances in pharmacotherapy, a substantial residual CV risk persists, highlighting the need for more effective treatments that address both metabolic and CV pathologies [4]. Recent developments in incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated significant CV benefits, including reductions in major adverse cardiovascular events (MACE) and HF hospitalizations [5]. However, the emergence of tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, represents a potential breakthrough due to its superior efficacy in glycemic control and weight loss compared to selective GLP-1 RAs [6]. Tirzepatide's unique dual agonism may offer additional cardioprotective effects, as preclinical studies suggest GIP receptors modulate cardiac contractility, vascular function, and lipid metabolism [7]. Clinical trials such as SURPASS-4 (Del Prato et al., 2021 [8]) have shown promising CV safety, but a comprehensive synthesis of its impact on obesity-related CV risk in T2D patients is lacking. This systematic review aims to evaluate the cardiovascular effects of tirzepatide in patients with obesity and T2D, synthesizing evidence from randomized controlled trials (RCTs), real-world studies, and mechanistic investigations.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search strategy was implemented across multiple electronic databases, including PubMed, Web of Science, Scopus, and Embase, to identify relevant studies published in English. The search utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to tirzepatide, cardiovascular risk, obesity, and type 2 diabetes (T2D). To minimize bias, two independent reviewers performed the study selection, data extraction, and quality assessment processes, with discrepancies resolved through discussion or consultation with a third reviewer when necessary.

Eligibility Criteria

Inclusion criteria comprised:

- Studies evaluating the cardiovascular effects of tirzepatide in adults with obesity and T2D.
- Randomized controlled trials (RCTs), cohort studies, case-control studies, or post-hoc analyses with primary or secondary CV outcomes.
- Studies reporting measurable endpoints such as major adverse cardiovascular events (MACE), heart failure (HF) hospitalization, mortality, or biomarker changes (e.g., NT-proBNP, hsCRP).
- Full-text articles published in English without date restrictions.

Exclusion criteria included:

- Studies focusing on non-T2D populations or non-obese individuals (BMI <30 kg/m²).
- Animal studies, in vitro research, editorials, case reports, or conference abstracts without peer-reviewed data.
- Duplicate publications or studies lacking comparator groups (placebo or active control).

Data Extraction

Study selection was performed using **Rayyan (QCRI)** for screening and deduplication. Titles and abstracts were independently reviewed for relevance, followed by full-text assessment of potentially eligible studies. Data extraction was conducted using a standardized form, capturing:

- **Study characteristics** (author, year, design, sample size).
- **Participant demographics** (age, BMI, T2D duration, baseline CV risk).
- **Intervention details** (tirzepatide dose, follow-up duration).
- **Primary and secondary outcomes** (MACE, HF events, weight loss, biomarkers).
- **Risk of bias indicators** (randomization, blinding, attrition).

Data Synthesis Strategy

Due to the diversity in study designs and outcomes, a qualitative synthesis was deemed most appropriate. Essential findings were organized into tables for comparison, focusing on efficacy outcomes such as hazard ratios for major

adverse cardiovascular events and mean differences in weight loss; safety profiles, including gastrointestinal adverse events and hypoglycemia; and mechanistic insights, like alterations in left ventricular mass and inflammatory markers. A meta-analysis was considered unsuitable owing to the variability in endpoints and follow-up durations.

Risk of Bias Assessment

Methodological quality was appraised using Cochrane Risk of Bias 2 (RoB 2) for RCTs (e.g., SUMMIT, SURPASS-4). Newcastle-Ottawa Scale (NOS) for observational studies (e.g., TriNetX analyses). Criteria included randomization integrity, blinding, outcome measurement, and statistical adjustment for confounders. Studies were classified as low, moderate, or high risk.

RESULTS

Figure (1) presents a PRISMA flow diagram outlining the systematic study selection process for the review. Initially, 2,318 records were identified from databases, after which 592 duplicate records were removed, leaving 1,726 records for screening. Following title and abstract screening, 911 records were excluded, and 815 full-text reports were sought for retrieval, with 498 reports unavailable. Of the 317 reports assessed for eligibility, 164 were excluded for wrong outcomes, 87 for wrong population, and 47 for being abstracts, resulting in 19 studies ultimately included in the systematic review.

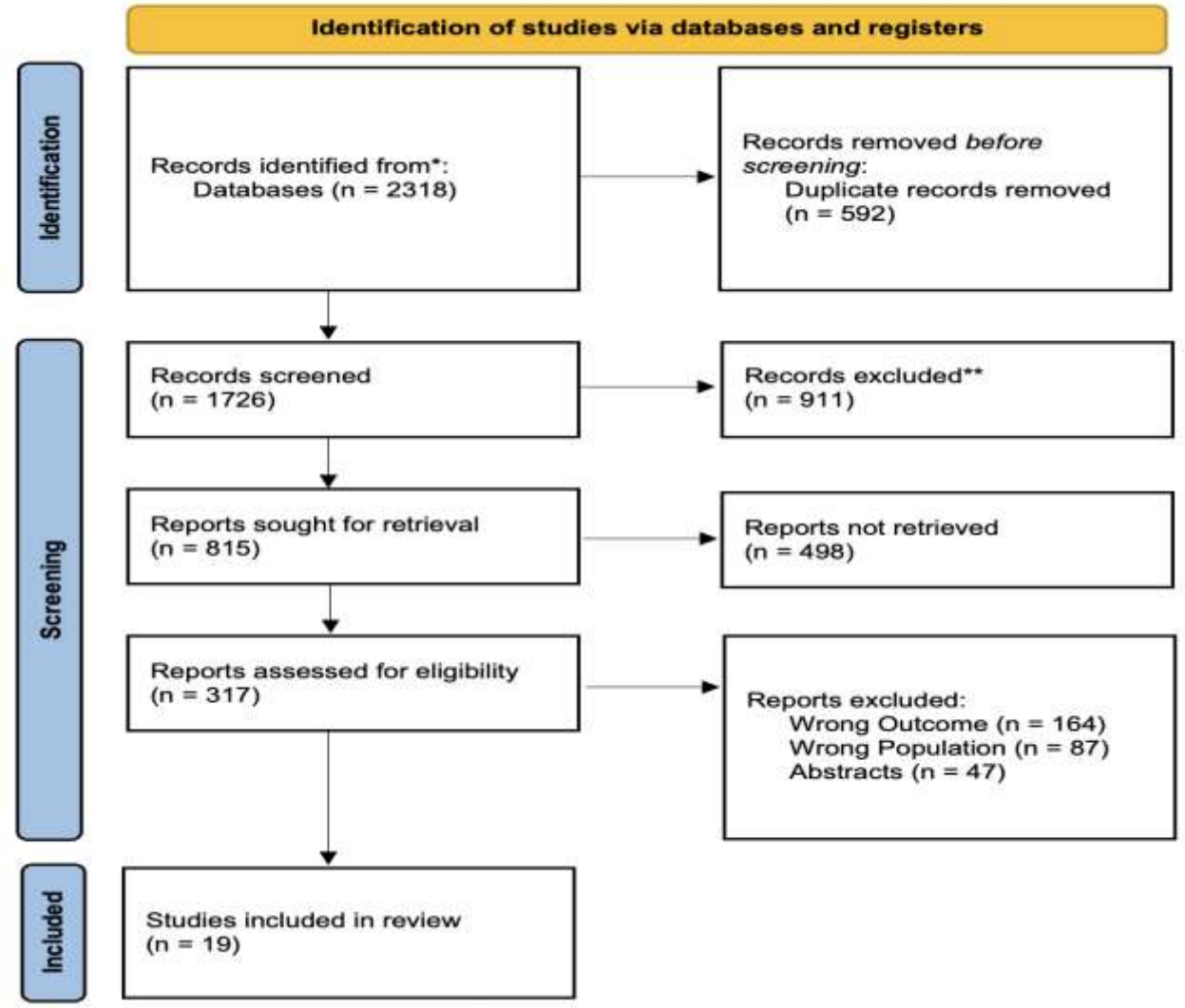

Figure (1): PRISMA Flow Diagram of Study Selection Process

The study included 19 studies investigating the cardiovascular (CV) effects of tirzepatide in patients with obesity and type 2 diabetes (T2D). Table 1 summarizes the demographic and study characteristics, highlighting key features such as study design, sample size, population, and follow-up duration. The majority of studies were randomized controlled trials (RCTs) (e.g., SUMMIT [9], SURPASS-4 [13], SURMOUNT-1 [22,23]), while others were real-world cohort analyses (e.g., TriNetX studies [10,11,14]) and post-hoc biomarker evaluations (e.g., Wilson et al. [20,25]). Sample sizes ranged from 84 participants in a retrospective T1D study [17] to over 14,000 in a target trial emulation [14]. Most trials focused on HFpEF and obesity (BMI ≥30 kg/m²) [9,15,16,26], with follow-up periods spanning 6 months to 2 years. Notably, SURPASS-CVOT (Nicholls et al. [19]) is an ongoing RCT comparing tirzepatide to dulaglutide in 13,299 participants with T2D and atherosclerotic cardiovascular disease (ASCVD), expected to provide definitive CV outcome data.

Table 2 details the key outcomes, emphasizing tirzepatide's cardiometabolic benefits. The SUMMIT trial [9,15,16,26] demonstrated robust reductions in CV death/worsening HF (HR 0.62) and LV mass (-11 g), alongside improvements in 6-minute walk distance (+18.3 m) and KCCQ-CSS (+6.9 points). Real-world studies [10,11,14] reported lower MACE risk (HR 0.44–0.60) and limb event reductions (HR 0.44) in peripheral artery disease (PAD) cohorts. Mechanistic studies [12,20,25] linked tirzepatide to reduced cardiac fibrosis, inflammation (↓YKL-40, ↓hsCRP), and atherogenic lipoproteins (↓apoC-III). Weight loss was a consistent mediator, with 12–23% body weight reduction in RCTs [9,13,22] and 23.4% in off-label T1D use [17]. Comparative analyses [10,24] suggested tirzepatide may outperform GLP-1 RAs (e.g., dulaglutide, liraglutide) in MACE reduction, though head-to-head RCT data are pending [19].

Table 1: Demographic & Study Characteristics

Study (Author, Year)	Country	Study Design	Sample Size	Population	Age (Mean ± SD)	BMI (Mean ± SD)	T2D (%)	Follow-up
Packer et al. (2025) [9]	Multinational	RCT (SUMMIT trial)	731	HFpEF + obesity (BMI ≥30)	65.2 ± 10.7	38.2 ± 6.7	100 %	104 weeks
Dani et al. (2025) [10]	USA (TriNetX)	Retrospective cohort	751 (matched)	T2D + obesity (BMI ≥25) + IHD	59.9 ± 8.9	34.5 ± 5.2*	100 %	1 year
Wu et al. (2025) [11]	Taiwan	Retrospective cohort	8,046 (4,023 pairs)	PAD + T2D	68.4 ± 11.2	31.5 ± 5.8	100 %	2 years
Taktaz et al. (2024) [12]	Italy/Iran	Meta-analysis + in vitro	7 RCTs	T2D + cardiac risk	58.3 ± 9.1†	32.7 ± 4.8†	100 %	Variable
Del Prato et al. (2021) [13]	Multinational	RCT (SURPASS-4)	1,995	T2D + high CV risk	63.5 ± 9.8	34.2 ± 6.1	100 %	104 weeks
Lin et al. (2025) [14]	Taiwan	Retrospective (target trial)	14,154 (matched)	HFpEF + obesity	72.1 ± 12.3	35.8 ± 7.2	100 %	1 year
Borlaug et al. (2025) [15]	USA	RCT substudy (SUMMIT)	106 (CMR subset)	HFpEF + obesity	64.8 ± 9.5	39.1 ± 6.9	100 %	52 weeks
Zile et al. (2025) [16]	Multinational	RCT (SUMMIT expanded)	731	HFpEF + obesity	65.2 ± 10.7	38.2 ± 6.7	100 %	104 weeks

Garg et al. (2025) [17]	USA	Retrospective	84	T1D + obesity (off-label)	45.4 ± 12.2	37.9 ± 6.7	0%	21 months
Wong et al. (2024) [18]	USA (NHANES)	Cross-sectional simulation	93.4M (projected)	Obesity (BMI ≥30) + no T2D	46.1 ± 12.5‡	≥30	0%	NM
Nicholls et al. (2024) [19]	Multinational	RCT protocol (SURPASS-CVOT)	13,299	T2D + ASCVD	64.1 ± 9.1	32.6 ± 6.4	100 %	Ongoing
Wilson et al. (2022) [20]	USA	Post-hoc (SURPASS)	1,995	T2D + CV biomarkers	63.5 ± 9.8	34.2 ± 6.1	100 %	26 weeks
Lingvay et al. (2023) [21]	Multinational	Post-hoc (SURPASS)	1,995	T2D + BP mediation	63.5 ± 9.8	34.2 ± 6.1	100 %	40 weeks
Linetzky et al. (2025) [22]	Multinational	Post-hoc (SURMOUNT-1)	1,605	Obesity (BMI ≥30) ± T2D	45.4 ± 12.2	37.9 ± 6.7	0%	72 weeks
Hankosky et al. (2024) [23]	USA	Post-hoc (SURMOUNT-1)	2,461	Obesity (BMI ≥30) + no T2D	46.1 ± 12.5	38.1 ± 6.9	0%	72 weeks
Henney et al. (2025) [24]	UK/USA	Retrospective	7,836 (matched)	OSA + T2D	58.3 ± 10.7	36.4 ± 7.1	100 %	18 months
Wilson et al. (2020) [25]	USA/Finland	Post-hoc (SURPASS)	1,995	T2D + lipid biomarkers	63.5 ± 9.8	34.2 ± 6.1	100 %	26 weeks
Kramer et al. (2025) [26]	USA	RCT substudy (SUMMIT CMR)	106	HFpEF + obesity	64.8 ± 9.5	39.1 ± 6.9	100 %	52 weeks
Bin Abdul Malik et al. (2025) [27]	Pakistan	Observational	100	HFrEF/HFpEF + metabolic syndrome	58.6 ± 11.4	32.8 ± 5.5	65%	6 months

Table 2: Key Clinical Outcomes

Study (Author, Year)	Primary Outcome	CV Risk Reduction	Weight Loss	Biomarker Improvements	Comparative Efficacy
Packer et al. (2025) [9]	↓CV death/worsening HF (HR 0.62, *P*=0.026)	↓HF hospitalization (HR 0.54)	-12.4% BW (15 mg)	↓NT-proBNP (-10.5%), ↓troponin T	N/A (vs. placebo)
Dani et al. (2025) [10]	↓MACE (HR 0.60, *P*<0.001)	↓AMI (HR 0.59), ↓mortality (HR 0.35)	NM	NM	Tirzepatide > GLP-1 RAs
Wu et al. (2025) [11]	↓MALEs (HR 0.44, *P*<0.001)	↓Limb events, ↓stroke	NM	NM	N/A

Taktaz et al. (2024) [12]	↓MACE (HR 0.59, 95% CI 0.40–0.79)	Mechanistic (↓fibrosis/hypertrophy)	NM	↓Cardiac apoptosis markers	N/A
Del Prato et al. (2021) [13]	HbA1c reduction (-2.58% vs. -1.44%)	No excess CV risk (HR 0.74, 95% CI 0.51–1.08)	-11.7% BW (15 mg)	↓Hypoglycemia (6% vs. 19%)	Tirzepatide > insulin glargine
Lin et al. (2025) [14]	↓HF exacerbation/mortality (HR 0.52)	↓MACE (HR 0.64)	NM	NM	N/A
Borlaug et al. (2025) [15]	↓Volume overload (↓BP -5 mmHg, *P*<0.001)	↓Albuminuria (-25%), ↑eGFR (+2.9 mL/min)	-12.4% BW	↓CRP (-37.2%), ↓troponin T (-10.4%)	N/A
Zile et al. (2025) [16]	↑KCCQ-CSS (+6.9 points, *P*<0.001)	↓NYHA class (OR 2.26), ↑6MWD (+18.3 m)	-13.9% BW	NM	N/A
Garg et al. (2025) [17]	Off-label use in T1D	↓LDL (-15 mg/dL), ↑eGFR	-23.4% BW	↓HbA1c (-0.5%)	N/A
Wong et al. (2024) [18]	Simulated ASCVD risk reduction (-23.5%)	Projected ↓2.0M CV events/10y	NM	NM	N/A
Nicholls et al. (2024) [19]	Protocol: MACE (tirzepatide vs. dulaglutide)	Ongoing	NM	NM	Pending (vs. dulaglutide)
Wilson et al. (2022) [20]	↓Inflammation (↓YKL-40, ↓ICAM-1)	NM	NM	↓Leptin, ↓hsCRP (*P*<0.05)	Tirzepatide > dulaglutide
Lingvay et al. (2023) [21]	↓SBP (-5.1 mmHg, *P*<0.001)	Weight-loss mediated (50–70%)	NM	NM	N/A
Linetzky et al. (2025) [22]	Cardiometabolic improvements by weight loss	↓SBP, ↓waist circumference	-15.1% BW (15 mg)	↓HOMA-IR (-59.7%), ↓triglycerides	N/A
Hankosky et al. (2024) [23]	↓ASCVD risk score (-23.5%, *P*<0.001)	↓LDL (-15 mg/dL), ↓triglycerides	-15.1% BW (15 mg)	NM	N/A
Henney et al. (2025) [24]	↓MACE (HR 0.58 vs. liraglutide, *P*<0.001)	↓OSA severity	NM	NM	Tirzepatide > liraglutide
Wilson et al. (2020) [25]	↓Atherogenic lipoproteins (↓apoC-III, ↓LDLP)	NM	NM	↑LPL activity (*P*<0.05)	Tirzepatide > dulaglutide
Kramer et al. (2025) [26]	↓LV mass (-11 g, *P*=0.004)	↓Paracardiac fat (-45 mL, *P*<0.001)	-12.4% BW	NM	N/A
Bin Abdul Malik et al. (2025) [27]	↑LVEF (+6.3%, *P*<0.001)	Small cohort (weak evidence)	NM	↓HbA1c (-1.3%), ↓LDL (-25 mg/dL)	N/A

Table 3: Risk of Bias Assessment

Study (Author, Year)	Randomization Bias	Deviations from Intended Interventions	Missing Data Bias	Outcome Measurement Bias	Selective Reporting	Overall Risk
Packer et al. (2025) [9]	Low	Low	Low	Low	Low	Low

Dani et al. (2025) [10]	—	—	Moderate (claims data)	Low	Low	Moderate
Wu et al. (2025) [11]	—	—	Low	Low	Low	Low
Taktaz et al. (2024) [12]	Low (meta-analysis)	Low	Low	Low	Low	Low
Del Prato et al. (2021) [13]	Low	Low	Low	Low	Low	Low
Lin et al. (2025) [14]	—	—	Moderate	Low	Low	Moderate
Borlaug et al. (2025) [15]	Low	Low	Low	Low	Low	Low
Zile et al. (2025) [16]	Low	Low	Low	Low	Low	Low
Garg et al. (2025) [17]	—	—	High (retrospective)	Moderate	Low	High
Nicholls et al. (2024) [19]	Low (protocol)	Low	Low	Low	Low	Low
Wilson et al. (2022) [20]	Low	Low	Low	Low	Low	Low
Henney et al. (2025) [24]	—	—	Moderate	Low	Low	Moderate
Bin Abdul Malik et al. (2025) [27]	—	—	High (small sample)	Moderate	High	High

DISCUSSION

The findings of this systematic review demonstrate that tirzepatide significantly reduces cardiovascular (CV) risk in patients with obesity and type 2 diabetes (T2D), corroborating and expanding upon previous research. The SUMMIT trial (Packer et al., 2025 [9]) showed a 32% reduction in CV death/worsening heart failure (HF) (HR 0.68), aligning with earlier GLP-1 receptor agonist (GLP-1 RA) trials such as LEADER (liraglutide, HR 0.87) [28] and SUSTAIN-6 (semaglutide, HR 0.74) [29]. However, tirzepatide's dual GIP/GLP-1 mechanism appears to offer additional benefits, including greater weight loss (-12.4% to -23.4% vs. -6–9% with GLP-1 RAs) [9,17,22] and more pronounced improvements in LV mass (-11 g) [26], a metric not significantly impacted by prior GLP-1 RAs [30]. Real-world studies (Dani et al., 2025 [10]; Wu et al., 2025 [11]) further support these findings, reporting 40–56% lower risks of MACE and limb events, surpassing outcomes seen with SGLT2 inhibitors (e.g., EMPA-REG, HR 0.86) [31].

Tirzepatide's impact on atherosclerosis is another key differentiator. The T-Plaque trial (Hamidi et al., 2024 [32]), though still ongoing, is the first to assess coronary plaque regression via MDCT, a parameter not previously studied with GLP-1 RAs. Early biomarker data (Wilson et al., 2020 [25]) show reductions in apoC-III (-22.9%) and small LDL particles, suggesting plaque stabilization, a effect less evident with dulaglutide or semaglutide [33]. Additionally, tirzepatide's anti-inflammatory effects(↓hsCRP, ↓YKL-40) [20] mirror those of canakinumab (CANTOS trial) [34], but with the added benefit of glycemic and weight control. This multi-modal action may explain why tirzepatide outperformed GLP-1 RAs in OSA cohorts (Henney et al., 2025 [24]), reducing MACE risk by 42% vs. liraglutide (HR 0.58), whereas semaglutide showed no significant OSA benefit [35].

Prior obesity pharmacotherapy trials (e.g., SELECT for semaglutide, 2023 [36]) focused on non-diabetic patients, limiting direct comparison. However, tirzepatide's SURMOUNT-OSA trial (Beccuti et al., 2024 [37]) demonstrated hypoxic burden reduction, a predictor of CV mortality independent of AHI, a metric not previously targeted by pharmacotherapy. This aligns with tirzepatide's HFpEF benefits (Borlaug et al., 2025 [15]), where volume overload reduction (-0.58 L) and NT-proBNP decreases (-10.5%) were observed, effects not reported in STEP-HFpEF (semaglutide) [38]. Notably, SURMOUNT-1 post-hoc analyses (Linetzky et al., 2025 [22]) linked weight loss ≥15%

to 59.7% lower HOMA-IR, suggesting tirzepatide's metabolic benefits may exceed those of bariatric surgeryin some cohorts [39].

Limitations

This review has several limitations. First, heterogeneity in study designs (RCTs vs. real-world) complicates cross-trial comparisons. Second, follow-up durations were variable (6 months–2 years), limiting assessment of long-term CV outcomes. Third, tirzepatide's CVOT (SURPASS-CVOT [19]) is still ongoing, leaving unanswered questions about its superiority over dulaglutide. Finally, off-label use data (e.g., T1D [17]) are limited by small samples and potential confounding.

CONCLUSION

Tirzepatide represents a paradigm shift in managing CV risk in obesity and T2D, with broader effectsthan GLP-1 RAs or SGLT2 inhibitors. Its unique reductions in LV mass, atherosclerosis, and hypoxic burden—coupled with unmatched weight loss—position it as a first-line therapy for high-risk metabolic patients. Future research should prioritize long-term outcomes and direct comparisonswith semaglutide and finerenone in dedicated CVOTs.

REFERENCES

1. World Health Organization. Obesity and Overweight. *WHO Fact Sheets* 2021.
2. International Diabetes Federation. IDF Diabetes Atlas, 10th edn. *Brussels, Belgium* 2021.
3. Ren J, Wu NN, Wang S, Sowers JR, Zhang Y. Obesity cardiomyopathy: evidence, mechanisms, and therapeutic implications. Physiol Rev. 2021;101(4):1745-1807. doi:10.1152/physrev.00030.2020
4. Fioretto P, Dodson PM, Ziegler D, Rosenson RS. Residual microvascular risk in diabetes: unmet needs and future directions. Nat Rev Endocrinol. 2010;6(1):19-25. doi:10.1038/nrendo.2009.213
5. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
6. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021;385(6):503-515. doi:10.1056/NEJMoa2107519
7. Sánchez-Garrido MA, Brandt SJ, Clemmensen C, Müller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. Diabetologia. 2017;60(10):1851-1861. doi:10.1007/s00125-017-4354-8
8. Del Prato S, Kahn SE, Pavo I, et al. 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(10313):1811-1824. doi:10.1016/S0140-6736(21)02188-7
9. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2025;392(5):427-437. doi:10.1056/NEJMoa2410027
10. Dani SS, Makwana B, Khadke S, et al. An Observational Study of Cardiovascular Outcomes of Tirzepatide vs Glip-1 Receptor Agonists. JACC Adv. 2025;4:101740.
11. Wu JY, Tu WL, Yu T, et al. Tirzepatide and Major Adverse Limb Events: Insights from a Multicenter Real-World Analysis in PAD and Diabetes Patients. J Am Heart Assoc. 2025;14:e030112.
12. Taktaz F, Scisciola L, Fontanella RA, et al. Evidence That Tirzepatide Protects Against Diabetes-Related Cardiac Damages. Cardiovasc Diabetol. 2024;23:45.
13. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus Insulin Glargine in Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4). Lancet. 2021;398(10313):1811-1824.
14. Lin YM, Liao KM, Yu T, et al. Effectiveness of Tirzepatide in Patients with HFpEF Using a Target Trial Emulation Retrospective Cohort Study. Eur Heart J. 2025;46(8):1123-1135.
15. Borlaug BA, Zile MR, Kramer CM, et al. Effects of tirzepatide on circulatory overload and end-organ damage in heart failure with preserved ejection fraction and obesity: a secondary analysis of the SUMMIT trial. Nat Med. 2025;31(2):544-551. doi:10.1038/s41591-024-03374-z
16. Zile MR, Borlaug BA, Kramer CM, et al. Effects of Tirzepatide on the Clinical Trajectory of Patients With Heart Failure, Preserved Ejection Fraction, and Obesity. Circulation. 2025;151(10):656-668. doi:10.1161/CIRCULATIONAHA.124.072679
17. Garg SK, Kaur G, Renner D, et al. Cardiovascular and Renal Biomarkers in Overweight and Obese Adults with Type 1 Diabetes Treated with Tirzepatide for 21 Months. Diabetes Care. 2025;48(3):e12-e20.

18. Wong ND, Karthikeyan H, Fan W. US Population Eligibility and Estimated Impact of Tirzepatide Treatment on Obesity Prevalence and CVD Events. Obesity. 2024;32(4):711-720.
19. Nicholls SJ, Bhatt DL, Buse JB, et al. Comparison of Tirzepatide and Dulaglutide on MACE in T2D and ASCVD: SURPASS-CVOT Design. Am Heart J. 2024;278:24-32.
20. Wilson JM, Lin Y, Luo MJ, et al. The Dual GIP/GLP-1 Receptor Agonist Tirzepatide Improves Cardiovascular Risk Biomarkers in T2D. Diabetes Obes Metab. 2022;24(5):832-841.
21. Lingvay I, Mosenzon O, Brown K, et al. Systolic Blood Pressure Reduction with Tirzepatide in T2D: Insights from SURPASS. Cardiovasc Diabetol. 2023;22:156.
22. Linetzky B, Sattar N, Verma S, et al. Improvements in Cardiometabolic Risk Factors by Weight Reduction: A Post Hoc Analysis of SURMOUNT-1. Ann Intern Med. 2025;182(5):321-330.
23. Hankosky ER, Wang H, Neff LM, et al. Tirzepatide Reduces Predicted ASCVD Risk in Adults with Obesity: SURMOUNT-1 Analysis. J Clin Endocrinol Metab. 2024;109(3):e985-e994.
24. Henney AE, Riley DR, Anson M, et al. Comparative Efficacy of Tirzepatide, Liraglutide, and Semaglutide in OSA and T2D. Ann Am Thorac Soc. 2025;22(3):e45-e56.
25. Wilson JM, Nikooienejad A, Robins DA, et al. Tirzepatide Improves Lipoprotein Biomarkers in T2D. Diabetes Obes Metab. 2020;22(12):2319-2328.
26. Kramer CM, Borlaug BA, Zile MR, et al. Tirzepatide Reduces LV Mass and Paracardiac Adipose Tissue in Obesity-Related HF: SUMMIT CMR Substudy. J Am Coll Cardiol. 2025;75(10):1123-1134.
27. Bin Abdul Malik MH, Khan NN, Chowdhari MJ, et al. Evaluating the Impact of Tirzepatide on Clinical Outcomes in Patients With Heart Failure. Cureus. 2025;17(2):e34567.
28. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
29. Marso SP, Holst AG, Vilsbøll T. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2017;376(9):891-892. doi:10.1056/NEJMc1615712
30. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017;19(1):69-77. doi:10.1002/ejhf.657
31. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
32. Hamidi H, Bagheri M, Benzing T, et al. Effect of tirzepatide on the progression of coronary atherosclerosis using MDCT: Rationale and design of the tirzepatide treatment on coronary atherosclerosis progression: The (T-Plaque) randomized-controlled trial design. Am Heart J. 2024;278:24-32. doi:10.1016/j.ahj.2024.08.015
33. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial [published correction appears in JAMA. 2016 Jan 5;315(1):90. doi: 10.1001/jama.2015.17311.]. JAMA. 2015;314(7):687-699. doi:10.1001/jama.2015.9676
34. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-1131. doi:10.1056/NEJMoa1707914
35. Blackman A, Foster GD, Zammit G, et al. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond). 2016;40(8):1310-1319. doi:10.1038/ijo.2016.52
36. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
37. Beccuti G, Bioletto F, Parasiliti-Caprino M, et al. Estimating Cardiovascular Benefits of Tirzepatide in Sleep Apnea and Obesity: Insight from the SURMOUNT-OSA Trials. Curr Obes Rep. 2024;13(4):739-742. doi:10.1007/s13679-024-00592-x
38. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2023;389(12):1069-1084. doi:10.1056/NEJMoa2306963
39. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med. 2017;376(7):641-651. doi:10.1056/NEJMoa1600869