

EDITORIAL



Cardiovascular efficacy of tirzepatide: what real-world evidence promises

Athina Nasoufidou^a, Panagiotis Stachteas^a, Paschalis Karakasis^a, Nikolaos Fragakis^a and Dimitrios Patoulas^b

^aSecond Department of Cardiology, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital of Thessaloniki, Thessaloniki, Greece; ^bSecond Propedeutic Department of Internal Medicine, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital of Thessaloniki, Thessaloniki, Greece

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1. Introduction

Tirzepatide, a new dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), has emerged as a notable therapy for managing type 2 diabetes mellitus (T2DM) and obesity. Large randomized controlled trials (RCTs) have demonstrated its robust efficacy, offering not only substantial improvements in glycemic control and weight reduction but also promising cardiovascular benefits, especially in GLP-1 RA naïve individuals [1]. A former meta-analysis confirmed that tirzepatide significantly lowered HbA1c and body weight compared with placebo, other GLP-1 RAs, and basal insulin, with a comparable risk of hypoglycemia and no increase in serious adverse events or mortality [2]. While RCTs provide high-quality evidence, real-world studies are essential to validate these findings in broader, more heterogeneous patient populations under routine clinical conditions.

2. Cardiovascular outcomes

Cardiovascular disease remains the leading contributor to mortality worldwide, making major adverse cardiovascular events (MACEs) a critical focus in evaluating therapies for metabolic diseases. Following the important findings of tirzepatide's efficacy in improving T2DM management and promoting substantial weight loss, attention has shifted toward understanding its cardiovascular impact. Multiple studies have reported MACE outcomes – either as primary endpoints, secondary endpoints, or within dedicated safety meta-analyses – reflecting the central importance of cardiovascular protection in assessing tirzepatide's overall clinical value. A study by Dani et al. compared tirzepatide with other GLP-1 RAs. In this study, enrolling 751 patients in each group, after adjusting for differences in baseline characteristics, tirzepatide resulted in a 40% reduction in the risk of the cumulative endpoint of acute myocardial infarction (AMI), ischemic stroke, and all-cause mortality [hazard ratio (HR): 0.60, 95% CI: 0.43–0.84, $p < 0.001$]. Subgroup analyses also revealed a significant decrease in the risk of acute myocardial infarction (HR: 0.59, 95% CI: 0.38–0.91, $p = 0.001$) and all-cause mortality (HR: 0.35, 95% CI: 0.14–0.88, $p = 0.001$) [3]. Another study

assessing the comparative effectiveness of tirzepatide vs other GLP-1 RAs also showed lower adjusted hazard ratios on all-cause mortality (HR, 0.58; 95% CI, 0.45–0.75; $p < .001$), MACEs (HR, 0.80; 95% CI, 0.71–0.91; $p < .001$), adverse kidney events, and acute kidney injury (AKI) (HR, 0.78; 95% CI, 0.70–0.88; $p < .001$), in patients with T2DM [4]. A pre-specified pooled analysis of seven randomized controlled trials from the SURPASS program evaluated the cardiovascular safety of tirzepatide in patients with T2DM across varying baseline cardiovascular risks and with multiple comparators, including placebo and active glucose-lowering agents. The analysis found no increased risk of MACEs with tirzepatide. Subgroup analyses – by sex, age, baseline HbA1c, race, geographic region, and concomitant sodium-glucose co-transporter-2 (SGLT-2) inhibitor use – revealed no significant treatment effect modification. These findings underscore the consistency of tirzepatide's cardiovascular safety profile, even though cardiovascular superiority was not demonstrated [5]. These findings provide critical information that tirzepatide offers additional benefits in weight loss, and these benefits are extensive and robust, especially in established cardiovascular disease. All these as the dedicated cardiovascular outcome trial, namely the SURPASS-CVOT, is eagerly awaited [6].

3. Outcomes in heart failure

Another critical comorbidity contributing to mortality and hospitalizations in patients with obesity is heart failure (HF). In the SUMMIT trial enrolling individuals with obesity and concomitant HF with preserved ejection fraction (HFpEF), treatment with tirzepatide over 52 weeks significantly reduced the composite risk of cardiovascular death or worsening HF compared with placebo [7]. Additionally, patients receiving tirzepatide reported meaningful improvements in health status, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), highlighting potential benefits for both clinical outcomes and quality of life in this challenging subgroup [7]. Although categorized as an obesity trial, SUMMIT's inclusion criteria allowed patients with HbA1c levels below 9.5%, thereby including individuals with diabetes. This complicates the interpretation of the outcomes and highlights

the necessity for dedicated trials to distinguish effects attributable to obesity from those related to diabetes, as diabetic patients carry a higher cardiovascular risk. In the aforementioned observational study by Dani et al., tirzepatide was also associated with a reduced risk of new-onset systolic HF (HR 0.74, 95% CI 0.55–0.99, $p = 0.045$) and a significantly lower risk of HF exacerbations (HR 0.61, 95% CI 0.38–0.98, $p = 0.04$) among patients with diabetes and obesity. These were secondary outcomes, yet clinically meaningful, given that approximately 30% of the study population had preexisting HF, and 6% of them had a left ventricular ejection fraction (LVEF) lower than 45% [3].

4. Data on arrhythmias and peripheral arterial disease

Beyond its effects on myocardial infarction and MACE, tirzepatide has also been evaluated for its impact on atrial fibrillation (AF) burden. In a retrospective study utilizing a large health database of 11,194 patients with diabetes, investigators found that the primary composite outcome – including cardioversion, intravenous antiarrhythmic drug use, and AF ablation – was significantly reduced with tirzepatide treatment (HR 0.65, 95% CI 0.55–0.76, $p < 0.001$) [8]. New-onset AF or atrial flutter was also assessed in the study by Dani et al., with tirzepatide demonstrating a significant reduction in relevant risk compared with the control group (HR 0.23, 95% CI 0.08–0.69, $p = 0.004$) [3]. These findings suggest a potential antiarrhythmic benefit, highlighting another dimension of cardiovascular protection that warrants further prospective investigation, since underlying mechanisms are not fully elucidated.

In the field of peripheral arterial disease (PAD), a retrospective study that included 8,046 patients with diabetes and PAD from a large database demonstrated that treatment with tirzepatide was associated with a statistically significant reduction in major adverse limb events, suggesting a potential protective effect against diabetic limb amputation – a devastating complication of diabetes. In the same study, secondary outcome analyses revealed that tirzepatide was associated with lower rates of all-cause mortality, stroke, and MACEs compared with placebo. However, the hazard ratio for AMI remained similar between groups [9].

5. Bariatric metabolic surgery and renal outcomes

An important real-world study from China used a large database to compare tirzepatide with bariatric metabolic surgery (BMS) in adults with obesity. Using propensity score matching, researchers analyzed 84,884 matched pairs, focusing on all-cause mortality as the primary outcome and MACEs and major adverse kidney events (MAKEs) as secondary endpoints. Over the follow-up period, tirzepatide demonstrated a markedly lower risk of all-cause mortality compared with BMS (HR 0.31, 95% CI 0.26–0.38, $p < 0.0001$), with benefits consistent across age, sex, and BMI subgroups. Additionally, tirzepatide significantly reduced the risk of MACEs (HR 0.74) and MAKEs (HR 0.38) relative to surgery [10]. These findings position tirzepatide as a compelling non-surgical alternative to bariatric metabolic surgery in managing obesity, which could potentially offer greater cardio-renal benefits.

Surrogate renal outcomes have also been evaluated in relevant real-world studies, mostly as secondary outcomes. In the study by Dani et al., tirzepatide showed a potential reno-protective effect, reducing the risk for AKI by almost

Table 1. Summary of tirzepatide studies mentioned in the manuscript.

Study	Population	Key Findings
Karagiannis et al. [2] Meta-analysis	T2DM & obesity	Tirzepatide lowers HbA1c & weight more than placebo, other GLP-1 RA and insulin; no increase in adverse events or mortality
Dani et al. [3] CV outcomes HF Renal outcomes	T2DM	↓ 40% risk AMI, stroke, all-cause mortality; ↓ AMI & mortality risk in subgroups ↓ risk new HF (HR 0.74) & HF exacerbations (HR 0.61) ↓ AKI risk by 32%
Chuang et al. [4] Comparative effectiveness study	T2DM	↓ all-cause mortality, MACEs, adverse kidney events, AKI
SURPASS pooled Analysis [5]	T2DM	No increase in MACEs; consistent safety across subgroups
SUMMIT trial [7] (HFpEF & obesity)	Obesity + HFpEF	↓ CV death/worsening HF; improved KCCQ health status
Wu et al. [8] Retrospective AF study	T2DM	↓ composite AF outcome; ↓ new-onset AF/flutter
Wu et al. [9] PAD retrospective study	T2DM + PAD	↓ major adverse limb events, all-cause mortality, stroke, MACEs; no change in AMI risk
Wu et al. [10] BMS vs Tirzepatide	Obesity	Tirzepatide ↓ all-cause mortality (HR 0.31), MACEs, MAKEs vs BMS
Karakasis et al. [11] (renal outcomes)	Obesity + T2DM	↓ albuminuria; neutral effect on creatinine clearance
SURPASS-CVOT [12] (pending publication)	T2DM	Non-inferior to dulaglutide; superiority not shown
SURMOUNT-MMO [14] (ongoing)	Obesity with/without T2DM	No pre-specified outcome reduction yet

This table summarizes key characteristics and main findings from real-world and randomized controlled studies evaluating tirzepatide in patients with type 2 diabetes, obesity, cardiovascular disease, and kidney disease.

Abbreviations: T2DM, Type 2 Diabetes Mellitus; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HbA1c, Glycated Hemoglobin; MACE, Major Adverse Cardiovascular Event; AMI, Acute Myocardial Infarction; HF, Heart Failure; HFpEF, Heart Failure with Preserved Ejection Fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; AF, Atrial Fibrillation; PAD, Peripheral Arterial Disease; AKI, Acute Kidney Injury; MAKE, Major Adverse Kidney Event; BMS, Bariatric Metabolic Surgery.

32% (HR: 0.676, 95% CI: 0.476–0.960, $p = 0.028$) [3]. In another cohort study enrolling individuals with diabetes, renal effects of tirzepatide were also explored, demonstrating a significant reduction in the risk for AKI (HR, 0.78; 95% CI, 0.70–0.88), and MAKEs (HR, 0.54; 95% CI, 0.44–0.67) [4]. A recent meta-analysis of 8 RCTs reported that tirzepatide leads to a significant reduction in albuminuria across all administered doses, while its use is associated with a neutral effect on creatinine clearance as a measure of renal function [11].

A summary table of the tirzepatide studies referenced in this manuscript is provided below (Table 1).

6. Expert opinion

In summary, tirzepatide evolves from a new metabolic therapy to an agent with broad cardio-renal benefits, based on its multiple, pleiotropic effects. Evidence emerging from real-world studies consistently demonstrates improvements not only in glycemic control and body weight but also significant cardio-renal benefits across a number of surrogate endpoints. GLP-1 RAs could mostly benefit patients with multiple comorbidities, as these patients may derive advantages both from improved glycemic control and from the broader pleiotropic effects observed with this drug class. Cost-effectiveness studies have not yet been conducted, and it will be important to assess whether these clinical benefits can also translate into meaningful advantages in terms of health-care resource utilization and economic outcomes.

Nevertheless, certain considerations should temper expectations. Real-world populations are heterogeneous, with variable adherence and comorbidities that may influence outcomes. Gastrointestinal adverse events remain the most frequently reported side effects, consistent with the known profile of incretin-based therapies.

While tirzepatide demonstrates cardiovascular safety, dedicated trials such as SURPASS-CVOT have shown non-inferiority to dulaglutide rather than superiority [12]. Although the publication of the paper reporting the results is still pending. GLP-1 receptor agonists, such as semaglutide, have already demonstrated clear cardiovascular benefits in large outcome trials, providing a strong foundation for ongoing studies with incretin-based therapies. Long-term effectiveness also remains uncertain; whereas the SELECT trial of semaglutide was stopped early after demonstrating a significant cardiovascular benefit [13], the SURMOUNT-MMO trial with tirzepatide continues beyond three years without a pre-specified outcome reduction being reported [14]. This contrast highlights both the promise of tirzepatide and the need for further definitive evidence before its long-term cardiovascular impact can be fully established.

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ORCID

Paschalis Karakasis  <http://orcid.org/0000-0002-3561-5713>

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