

EFFECT OF TIRZEPATIDE ON THE REDUCTION OF CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

EFEITO DA TIRZEPATIDA NA REDUÇÃO DE DESFECHOS CARDIOVASCULARES EM PACIENTES COM DIABETES TIPO 2

EFFECTO DE LA TIRZEPATIDA EN LA REDUCCIÓN DE EVENTOS CARDIOVASCULARES EN PACIENTES CON DIABETES TIPO 2



<https://doi.org/10.56238/sevenced2026.020-037>

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) represents a major global public health challenge due to its close association with cardiovascular morbidity and mortality. In this context, tirzepatide, a dual GIP and GLP-1 receptor agonist, has emerged as an innovative therapeutic approach in the cardiometabolic management of T2DM, demonstrating significant effects on glycemic control, weight reduction, and cardiovascular risk factors. This study aimed to critically analyze the available scientific evidence regarding the effects of tirzepatide on cardiovascular outcomes in individuals with T2DM. This integrative literature review was based on the methodological framework proposed by Whitemore and Knafl and conducted using PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect databases between March and April 2026. Studies published between 2016 and 2026 involving randomized clinical trials, meta-analyses, systematic reviews, observational studies, and narrative reviews related to the cardiovascular effects of tirzepatide were included. After applying the eligibility criteria, 13 studies composed the final sample. The findings demonstrated that tirzepatide promotes significant reductions in glycated hemoglobin (HbA1c), substantial weight loss, and consistent improvement in cardiometabolic parameters, including blood pressure, lipid profile, insulin resistance, and visceral adiposity. Furthermore, observational studies and meta-analyses suggested a favorable trend toward reduction of major adverse cardiovascular events and all-cause mortality, without evidence of increased cardiovascular risk. However, most currently available evidence derives from post-hoc analyses and studies with relatively short follow-up periods, limiting definitive conclusions regarding the magnitude of cardiovascular protection associated with tirzepatide. It is concluded that tirzepatide presents a promising cardiometabolic profile in the treatment of T2DM, although dedicated cardiovascular outcome trials are still required.

Keywords: Tirzepatide. Type 2 Diabetes Mellitus. Cardioprotection. Cardiovascular Risk. Cardiovascular Outcomes.

RESUMO

O Diabetes Mellitus tipo 2 (DM2) constitui importante problema de saúde pública global devido à sua estreita associação com morbimortalidade cardiovascular. Nesse contexto, a tirzepatida, agonista dual dos receptores de GIP e GLP-1, emergiu como abordagem terapêutica inovadora no manejo cardiometabólico do DM2, apresentando efeitos relevantes sobre controle glicêmico, perda ponderal e fatores de risco cardiovascular. O presente estudo teve como objetivo analisar criticamente as evidências científicas disponíveis acerca dos efeitos da tirzepatida na redução de desfechos cardiovasculares em indivíduos com DM2. Trata-se de revisão integrativa da literatura fundamentada no referencial metodológico de Whitemore e Knafl, realizada nas bases PubMed/MEDLINE, Scopus, Web of Science e ScienceDirect, entre março e abril de 2026. Foram incluídos estudos publicados entre 2016 e 2026 envolvendo ensaios clínicos randomizados, meta-análises, revisões sistemáticas, estudos observacionais e revisões narrativas relacionados aos efeitos cardiovasculares da tirzepatida. Após aplicação dos critérios de elegibilidade, 13 estudos compuseram a amostra final. Os achados demonstraram que a tirzepatida promove reduções significativas da

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hemoglobina glicada (HbA1c), perda ponderal expressiva e melhora consistente de parâmetros cardiometabólicos, incluindo pressão arterial, perfil lipídico, resistência insulínica e adiposidade visceral. Além disso, estudos observacionais e meta-análises sugeriram tendência favorável à redução de eventos cardiovasculares maiores e mortalidade geral, sem evidência de aumento do risco cardiovascular. Entretanto, a maior parte das evidências disponíveis deriva de análises pós-hoc e estudos com seguimento relativamente curto, limitando conclusões definitivas acerca da magnitude da cardioproteção associada à tirzepatida. Conclui-se que a tirzepatida apresenta perfil cardiometabólico promissor no tratamento do DM2, embora estudos cardiovasculares dedicados ainda sejam necessários.

Palavras-chave: Tirzepatida. Diabetes Mellitus Tipo 2. Cardioproteção. Risco Cardiovascular. Desfechos Cardiovasculares.

RESUMEN

La diabetes mellitus tipo 2 (DM2) constituye un importante problema de salud pública mundial debido a su estrecha relación con la morbilidad y mortalidad cardiovascular. En este contexto, la tirzepatida, un agonista dual de los receptores GIP y GLP-1, ha surgido como una estrategia terapéutica innovadora en el manejo cardiometabólico de la DM2, mostrando efectos relevantes en el control glucémico, la pérdida de peso y los factores de riesgo cardiovascular. Este estudio tuvo como objetivo analizar críticamente la evidencia científica disponible sobre los efectos de la tirzepatida en la reducción de eventos cardiovasculares en personas con DM2. Se trata de una revisión bibliográfica integradora basada en el marco metodológico de Whitemore y Knafl, realizada en las bases de datos PubMed/MEDLINE, Scopus, Web of Science y ScienceDirect entre marzo y abril de 2026. Se incluyeron estudios publicados entre 2016 y 2026 que comprendían ensayos clínicos aleatorizados, metaanálisis, revisiones sistemáticas, estudios observacionales y revisiones narrativas relacionados con los efectos cardiovasculares de la tirzepatida. Tras aplicar los criterios de elegibilidad, la muestra final se conformó con 13 estudios. Los resultados demostraron que la tirzepatida promueve reducciones significativas de la hemoglobina glicosilada (HbA1c), una pérdida de peso sustancial y una mejora constante de los parámetros cardiometabólicos, incluyendo la presión arterial, el perfil lipídico, la resistencia a la insulina y la adiposidad visceral. Además, estudios observacionales y metaanálisis sugirieron una tendencia favorable hacia la reducción de eventos cardiovasculares mayores y la mortalidad general, sin evidencia de un aumento del riesgo cardiovascular. Sin embargo, la mayor parte de la evidencia disponible proviene de análisis post-hoc y estudios con un seguimiento relativamente corto, lo que limita las conclusiones definitivas sobre la magnitud de la cardioprotección asociada a la tirzepatida. Se concluye que la tirzepatida presenta un perfil cardiometabólico prometedor en el tratamiento de la diabetes mellitus tipo 2 (DM2), aunque aún se necesitan estudios cardiovasculares específicos.

Palabras clave: Tirzepatida. Diabetes Mellitus Tipo 2. Cardioprotección. Riesgo Cardiovascular. Resultados Cardiovasculares.

1 INTRODUCTION

Type 2 Diabetes Mellitus (DM2) is one of the main chronic non-communicable diseases of contemporary times, assuming epidemic proportions and representing an important challenge for health systems on a global scale, especially due to its high cardiovascular morbidity and mortality and significant socioeconomic impact (DE BLOCK et al., 2022; SATTAR et al., 2025). Characterized by a complex metabolic disorder involving insulin resistance, progressive impairment of pancreatic β cell function, and systemic alterations of glycemic homeostasis, T2DM is closely associated with the development of atherosclerotic disease, heart failure, stroke, and early cardiovascular mortality, with cardiovascular diseases being the leading cause of death in this population (SATTAR et al., 2022; TAKTAZ et al., 2024). In addition to persistent hyperglycemia, the frequent coexistence of obesity, systemic arterial hypertension, atherogenic dyslipidemia, and chronic low-grade inflammation contributes to the maintenance of a highly pro-inflammatory and prothrombotic cardiometabolic state, responsible for the substantial amplification of global cardiovascular risk (NAUCK; D'ALESSIO, 2022; SATTAR et al., 2025).

Historically, the treatment of DM2 has been predominantly directed to glycemic control, with the main objective of preventing microvascular complications. However, the recognition of the close relationship between diabetes, obesity, and cardiovascular disease promoted an important paradigmatic change in the therapeutic approach to the disease, shifting the focus to strategies capable of simultaneously promoting metabolic control and cardiovascular risk reduction (DE BLOCK et al., 2022). In this context, incretinal therapies have come to occupy a central position in the modern management of T2DM, particularly glucagon-like peptide receptor agonists type 1 (GLP-1RA), whose efficacy goes beyond the reduction of glycemia and includes relevant cardiovascular benefits, such as reduction of major adverse cardiovascular events (MACE), improvement of cardiometabolic function, and reduction of mortality in individuals at high cardiovascular risk (SATTAR et al., 2022; SATTAR et al., 2025).

Based on the advances provided by GLP-1 agonists, the development of tirzepatide introduced a new pharmacological perspective in the treatment of T2DM. Tirzepatide is the first dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors approved for the treatment of type 2 diabetes mellitus, simultaneously combining the metabolic and incretin effects of both hormonal systems (NAUCK; D'ALESSIO, 2022). This dual activation seems to potentiate physiological mechanisms related to glucose-dependent insulin secretion, reduced glucagon secretion, appetite control, and improved insulin

sensitivity, resulting in metabolic benefits superior to those observed with GLP-1 agonists alone (DE BLOCK et al., 2022; YU et al., 2022).

Clinical studies in the SURPASS program have shown that tirzepatide promotes significant reductions in glycated hemoglobin (HbA1c) and body weight, often higher than those seen with semaglutide, basal insulin, and other active comparators (NAUCK; D'ALESSIO, 2022; DE BLOCK et al., 2022). At the same time, different investigations have shown substantial improvement in multiple cardiometabolic parameters associated with cardiovascular risk, including reduction in visceral adiposity, improvement in lipid profile, decrease in systemic blood pressure, reduction in insulin resistance, and favorable modulation of inflammatory and metabolic markers (KAORE et al., 2024; SATTAR et al., 2025). These findings reinforce the hypothesis that the clinical effects of tirzepatide transcend glycemic control alone, suggesting a potential impact on pathophysiological mechanisms directly involved in the progression of atherosclerotic cardiovascular disease.

From a pathophysiological perspective, the potential cardiovascular benefit of tirzepatide seems to result from multifactorial and integrated mechanisms. Recent evidence suggests that GIP/GLP-1 dual agonism may contribute to reduced vascular inflammation, improved endothelial function, reduced oxidative stress, modulated lipotoxicity, and improved myocardial energy metabolism (TAKTAZ et al., 2024). In addition, mechanisms related to the reduction of cell apoptosis, stimulation of autophagy, and attenuation of cardiovascular remodeling have been proposed as possible mediators of the cardioprotection observed in experimental and clinical studies (TAKTAZ et al., 2024). The concomitant improvement of obesity, insulin resistance, and other cardiometabolic risk factors potentially contributes to the reduction of residual cardiovascular risk often present in individuals with T2DM.

In this context, recent meta-analyses have reinforced the cardiovascular safety of tirzepatide by demonstrating no significant increase in major cardiovascular events, acute myocardial infarction, stroke, or heart failure compared with placebo or active therapies (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025). In addition, real-world observational studies have shown promising results in cardiovascular clinical outcomes. Chuang et al. (2024), when comparing tirzepatide with conventional GLP-1 receptor agonists in patients with T2DM, observed a significant reduction in overall mortality, MACE, renal events, and acute kidney injury among individuals treated with tirzepatide, suggesting possible clinical superiority in complex cardiometabolic scenarios (CHUANG et al., 2024). Similarly, integrated analyses of the SURPASS program demonstrated a favorable trend towards the reduction of MACE-4 without evidence of increased overall cardiovascular risk, reinforcing

the hypothesis of safety and potential cardiovascular benefit associated with the drug (SATTAR et al., 2022).

However, despite the growing body of favorable evidence, important methodological limitations persist that make it difficult to definitively consolidate the magnitude of the cardiovascular benefit of tirzepatide. Most of the available studies show significant heterogeneity in terms of the populations evaluated, therapeutic comparators, cardiovascular outcome criteria, and clinical follow-up time (KAORE et al., 2024; WARDEH et al., 2024). In addition, many cardiovascular outcomes still derive from secondary, post-hoc analyses or extrapolations based predominantly on the improvement of cardiometabolic factors, without necessarily reflecting a definitive reduction in cardiovascular events in the long term (SATTAR et al., 2022; TAKTAZ et al., 2024). In addition, there is a lack of robust consensus on the cardiovascular superiority of tirzepatide compared to traditional GLP-1 receptor agonists already consolidated in dedicated cardiovascular outcome studies.

In view of this scenario, it is relevant to conduct an integrative review of the literature capable of gathering, critically analyzing, and synthesizing the scientific evidence currently available on the impact of tirzepatide on cardiovascular outcomes in patients with DM2. Thus, the present study aims to critically analyze the scientific evidence related to the effects of tirzepatide on the reduction of cardiovascular outcomes in individuals with type 2 Diabetes Mellitus, addressing clinical efficacy, cardiometabolic mechanisms involved, cardiovascular safety and methodological limitations present in the contemporary literature.

2 METHODOLOGY

The present study is characterized as an integrative literature review, with a descriptive, exploratory nature and a qualitative approach, developed with the purpose of gathering, critically analyzing and synthesizing the available scientific evidence on the effects of tirzepatide on cardiovascular outcomes in patients with type 2 diabetes mellitus (DM2).

The integrative review was adopted as a methodological design because it enables the inclusion and integration of different research designs, allowing a comprehensive and in-depth analysis of complex and multifactorial clinical phenomena. This approach is particularly pertinent in view of the emerging and still consolidating nature of the evidence related to the cardiovascular and cardiometabolic effects of tirzepatide in individuals with DM2, enabling critical articulation between experimental and observational studies and reviews of a mechanistic nature.

The methodological path of this investigation was based on the classic framework proposed by Whittemore and Knafl (2005), widely used in integrative reviews in the health

area. According to this theoretical-methodological model, the development of the review occurred in six interdependent stages: identification of the problem and definition of the guiding question; establishment of inclusion and exclusion criteria; definition of search and selection strategies for studies; categorization and standardized extraction of data; critical evaluation and interpretation of findings; and integrative synthesis of the knowledge produced.

The guiding question of the present review was structured as follows: "What is the available scientific evidence on the effects of tirzepatide on cardiovascular outcomes in patients with type 2 diabetes mellitus?"

The bibliographic search was carried out between March and April 2026 in the electronic databases PubMed/MEDLINE, Scopus, Web of Science and ScienceDirect, selected due to their recognized relevance in the indexing of biomedical literature of high methodological rigor and international scientific impact.

To construct the search strategy, controlled and uncontrolled descriptors obtained from the vocabularies DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) were used, combined using Boolean operators AND and OR. The main terms used included "tirzepatide", "type 2 diabetes mellitus", "cardiovascular outcomes", "major adverse cardiovascular events", "MACE", "heart failure", "cardiovascular risk", "cardiometabolic risk", "GLP-1 receptor agonist" and "GIP/GLP-1 agonist".

Studies published between 2016 and 2026, available entirely in English, indexed in the selected databases, and directly related to the cardiovascular effects of tirzepatide in individuals with DM2 were considered eligible. Investigations addressing cardiovascular and cardiometabolic outcomes, such as major cardiovascular events (MACE), heart failure, cardiovascular mortality, cardiometabolic factors, lipid profile, blood pressure, obesity, and cardiovascular protection, were included. Regarding the methodological design, randomized clinical trials, observational studies, meta-analyses, systematic reviews, and narrative reviews considered methodologically relevant for the clinical and pathophysiological understanding of the investigated topic were included.

The inclusion of narrative reviews in the corpus of this integrative review was based on the need to broaden the mechanistic and pathophysiological understanding of the potential cardiovascular effects of tirzepatide. Considering that a substantial part of the available evidence still derives from consolidation studies and exploratory analyses, narrative reviews were considered relevant for critical integration between pharmacological mechanisms, pathophysiological pathways, and cardiometabolic repercussions observed in clinical and observational studies.

Duplicate studies, publications without access to full text, conference abstracts without complete data, letters to the editor, expert opinions without defined methodology, investigations without a direct relationship with tirzepatide or without a relevant cardiovascular approach, as well as articles involving exclusively obesity without association with T2DM or cardiovascular risk were excluded.

The process of selecting studies occurred in a systematic manner and in multiple stages. Initially, the identification of potentially relevant publications was carried out through the application of previously defined search strategies. Then, the titles and abstracts were read for a preliminary evaluation of eligibility. Subsequently, potentially eligible articles were submitted to full reading to confirm adherence to the established methodological criteria.

The screening, eligibility and final selection of studies were conducted independently by two reviewers, with the aim of reducing selection biases and increasing the methodological reliability of the review. Any disagreements related to the inclusion of the articles were resolved by consensus after joint critical reevaluation of the selected studies.

After methodological evaluation and analysis of scientific relevance, 13 studies were selected to compose the final sample of this integrative review. The sample set included different methodological designs, including multicenter randomized clinical trials, meta-analyses, systematic reviews, real-world observational studies, post-hoc analyses, and narrative reviews of a mechanistic and cardiometabolic nature.

Data extraction was carried out in a standardized manner using a previously structured instrument, including information regarding the authors, year of publication, methodological design, population/sample, study objectives, main cardiovascular outcomes analyzed, cardiometabolic effects observed, main results, and conclusions relevant to clinical practice.

Subsequently, the data were organized and analyzed in a descriptive, comparative, and critical manner, seeking to identify convergences, divergences, methodological limitations, and gaps in the scientific literature on the cardiovascular effects of tirzepatide in individuals with DM2. The integrative synthesis was conducted in a thematic manner, prioritizing the critical interpretation of the findings and the articulation between pathophysiological mechanisms, cardiometabolic effects, and clinical cardiovascular outcomes.

As this is an integrative review based exclusively on secondary data available in the scientific literature, without direct involvement of human beings, the present study was not submitted to the Research Ethics Committee, in accordance with the current ethical guidelines for literature searches.

3 RESULTS

The literature search strategy carried out in the PubMed/MEDLINE, Scopus, Web of Science and ScienceDirect databases made it possible to identify potentially relevant studies on the cardiovascular effects of tirzepatide in individuals with type 2 diabetes mellitus (DM2). After applying the eligibility criteria, removing duplicates, and critical methodological evaluation, 13 studies made up the final sample of this integrative review.

The included studies showed significant methodological heterogeneity, including multicenter randomized clinical trials, meta-analyses, systematic reviews, real-world observational studies, post-hoc analyses, and mechanistic narrative reviews.

Overall, the evidence analyzed demonstrated consistency regarding the high metabolic efficacy of tirzepatide in individuals with type 2 diabetes mellitus (DM2), especially with regard to the reduction of glycated hemoglobin (HbA1c) and body adiposity. The included trials showed superiority of tirzepatide compared to traditional GLP-1 receptor agonists and basal insulins, promoting significant glycemic reductions associated with clinically significant and sustained weight loss (NAUCK; D'ALESSIO, 2022; DE BLOCK et al., 2022). Recent meta-analyses have corroborated these findings by demonstrating a dose-dependent relationship between tirzepatide, glycemic improvement, and weight reduction, maintaining a favorable overall cardiovascular safety profile (YU et al., 2022; KHAN et al., 2023).

In addition to intensive glycemic control, the studies analyzed demonstrated consistent improvement of multiple cardiometabolic parameters in individuals with type 2 diabetes mellitus (DM2). A reduction in systolic blood pressure, an improvement in the lipid profile, a decrease in triglyceride levels, a reduction in visceral adiposity, and an improvement in insulin resistance were observed (SATTAR et al., 2025; KAORE et al., 2024). Mechanistic reviews included in this review pointed to favorable modulation of inflammatory biomarkers, reduction of oxidative stress, and improvement of endothelial function associated with the use of tirzepatide (TAKTAZ et al., 2024).

The evidence related to clinical cardiovascular outcomes showed less methodological robustness when compared to metabolic and cardiometabolic findings. Most of the available investigations were originally designed to assess metabolic efficacy and glycemic safety, with cardiovascular outcomes predominantly being analysed as secondary endpoints, exploratory or derived from post-hoc analyses.

The pre-specified meta-analysis based on the SURPASS program demonstrated no increase in cardiovascular risk associated with tirzepatide and a trend in favor of reducing major cardiovascular events (MACE-4) (SATTAR et al., 2022). Real-world observational

studies have suggested an association between tirzepatide use and significant reduction in overall mortality, major cardiovascular events, and adverse renal outcomes compared to conventional GLP-1 receptor agonists (CHUANG et al., 2024). Recent meta-analyses have also demonstrated no significant increase in acute myocardial infarction, stroke, or heart failure in individuals treated with tirzepatide (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025).

The included studies showed heterogeneity related to the populations evaluated, therapeutic comparators, follow-up time, definition of cardiovascular outcomes, and clinical eligibility criteria. Overall, the included studies demonstrated a favorable cardiometabolic profile associated with the use of tirzepatide in individuals with type 2 diabetes mellitus (DM2), including glycemic improvement, weight reduction, and favorable effects on metabolic and cardiovascular parameters.

4 DISCUSSION

The findings of this integrative review demonstrate that tirzepatide has significant cardiometabolic potential in individuals with type 2 diabetes mellitus (DM2), mainly due to its ability to promote intensive glycemic control associated with significant weight loss and comprehensive improvement of multiple cardiovascular risk factors. The body of evidence analyzed suggests that the observed benefits transcend the hypoglycemic effect alone, involving metabolic and vascular changes potentially related to the reduction of residual cardiovascular risk that is often persistent in this population (DE BLOCK et al., 2022; SATTAR et al., 2025).

The high metabolic efficacy observed in the included studies may be partially explained by the dual agonism of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide type 1 (GLP-1) receptors. Unlike traditional GLP-1 receptor agonists, the simultaneous activation of these incretin axes seems to potentiate mechanisms related to glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, appetite control, and improved insulin sensitivity (NAUCK; D'ALESSIO, 2022). This integrated action possibly justifies the superior results of glycated hemoglobin (HbA1c) reduction and weight loss observed in the SURPASS and SURMOUNT programs compared to GLP-1 agonists alone and basal insulin (DE BLOCK et al., 2022; YU et al., 2022).

From a cardiovascular perspective, the simultaneous improvement of visceral obesity, insulin resistance, systemic arterial hypertension, and atherogenic dyslipidemia represents a particularly relevant aspect. Central obesity and chronic metabolic inflammation play a determining role in the progression of atherosclerosis, endothelial dysfunction, and heart

failure in individuals with DM2. In this context, the significant weight reduction promoted by tirzepatide can directly contribute to reducing the systemic inflammatory burden and improving vascular function, favoring a reduction in overall cardiometabolic risk (SATTAR et al., 2025).

In addition to the effects related to weight loss and glycemic control, the included studies suggest the participation of additional biological mechanisms potentially involved in the favorable cardiovascular effects of tirzepatide. Recent mechanistic reviews indicate that dual GIP/GLP-1 agonism can modulate pathways related to oxidative stress, vascular inflammation, lipotoxicity, and myocardial energy metabolism (TAKTAZ et al., 2024). Additionally, effects on cell apoptosis, autophagy, and cardiovascular remodeling have been proposed as possible mediators of the cardioprotection observed in experimental and clinical studies (TAKTAZ et al., 2024).

At the same time, the included studies demonstrated consistent improvement in metabolic parameters known to be associated with long-term cardiovascular risk reduction. A significant reduction in systolic blood pressure, improved lipid profile, decreased triglyceride levels, and reduced visceral adiposity were observed (KAORE et al., 2024; SATTAR et al., 2025). Although these parameters are considered surrogate outcomes, their integrated improvement has significant clinical relevance in view of the close relationship between residual cardiometabolic risk and progression of cardiovascular complications in DM2.

However, despite the strong biological plausibility and consistency of the metabolic effects observed, the robustness of the evidence related to the direct reduction of major cardiovascular events still remains limited. Much of the available research was originally designed to assess metabolic efficacy and glycemic safety, with cardiovascular outcomes predominantly being analyzed as secondary endpoints, exploratory or derived from post-hoc analyses. In this scenario, although the pre-specified meta-analysis based on the SURPASS program has shown no increase in cardiovascular risk and a favorable trend towards the reduction of MACE-4, there is still no definitive confirmation of statistically consolidated cardiovascular superiority (SATTAR et al., 2022).

In addition, real-world observational studies have demonstrated an association between tirzepatide use and significant reduction in overall mortality, major cardiovascular events, and adverse renal outcomes compared to conventional GLP-1 receptor agonists (CHUANG et al., 2024). Recent meta-analyses have also reinforced the absence of a significant increase in acute myocardial infarction, stroke, or heart failure in individuals treated with tirzepatide (YU et al., 2022; KHAN et al., 2023; LIU et al., 2025). Even so, such

evidence derives predominantly from indirect analyses, heterogeneous populations, and studies with relatively short follow-up, limiting robust causal inferences about the real magnitude of cardioprotection promoted by tirzepatide.

Another relevant aspect identified in this review refers to the predominance of surrogate outcomes to the detriment of hard clinical cardiovascular outcomes. Although body weight reduction, glycemic improvement, blood pressure decrease, and lipid profile improvement are recognized as associated with lower cardiovascular risk in the long term, the extrapolation of these benefits to effective reduction of major cardiovascular events, heart failure, and cardiovascular mortality still requires confirmation by randomized cardiovascular studies specifically designed for this purpose (SATTAR et al., 2022; LIU et al., 2025).

In addition, important methodological heterogeneity was observed among the included studies, involving differences related to the profile of the populations evaluated, therapeutic comparators, duration of clinical follow-up, and definition of the outcomes analyzed. The predominant presence of narrative reviews, indirect meta-analyses, and post-hoc analyses reinforces the need for critical interpretation of the evidence currently available (WARDEH et al., 2024; KAORE et al., 2024). Added to this is the absence, to date, of a definitive consensus on the magnitude of the cardiovascular benefit of tirzepatide compared to traditional GLP-1 receptor agonists already consolidated in dedicated cardiovascular outcome studies.

Despite these limitations, the data analyzed in this integrative review indicate that tirzepatide represents one of the most promising therapeutic approaches in the contemporary context of cardiometabolic management of DM2. Its ability to act simultaneously on obesity, insulin resistance, metabolic inflammation, and multiple vascular risk factors suggests important translational potential in the context of modern cardiovascular prevention. Although the definitive confirmation of a reduction in major cardiovascular events still depends on dedicated randomized cardiovascular studies, the currently available evidence indicates that tirzepatide may occupy a strategic position in the integrated treatment of T2DM and its future cardiometabolic complications.

In this context, it is essential to carry out specific randomized cardiovascular studies, with longer follow-up time and primary evaluation of major cardiovascular events, heart failure, and cardiovascular mortality. The consolidation of this evidence may establish more definitively the real role of tirzepatide in cardiovascular prevention in individuals with type 2 diabetes mellitus.

5 CONCLUSION

The present integrative review demonstrated that tirzepatide has a highly promising therapeutic profile in the management of type 2 diabetes mellitus (DM2), especially due to its high metabolic efficacy associated with comprehensive improvement of multiple cardiovascular risk factors. The evidence analyzed indicated that the dual agonism of GIP and GLP-1 receptors promotes significant reductions in glycated hemoglobin (HbA1c), significant weight loss, and consistent improvement in cardiometabolic parameters, including blood pressure, lipid profile, insulin resistance, and visceral adiposity. In addition, the studies suggested a potential favorable impact on global cardiovascular risk, possibly related to the modulation of pathophysiological mechanisms involved in the progression of atherosclerosis, vascular inflammation, endothelial dysfunction, and cardiovascular remodeling.

However, despite the largely favorable results, the robustness of the evidence related to the direct reduction of major cardiovascular events, heart failure, and cardiovascular mortality still remains limited. Most of the available studies were originally designed to assess metabolic efficacy and glycemic safety, and cardiovascular outcomes were predominantly analyzed as secondary endpoints, exploratory or derived from post-hoc analyses. In addition, the methodological heterogeneity observed among the included studies, involving differences related to the populations evaluated, clinical follow-up time, and definition of the cardiovascular outcomes analyzed, reinforces the need for careful interpretation of the findings currently available.

Despite these limitations, the data analyzed position tirzepatide as one of the most innovative and potentially relevant therapeutic approaches in the contemporary context of cardiometabolic management of DM2. Its ability to act simultaneously on multiple metabolic and cardiovascular mechanisms suggests an important translational potential for future reduction of cardiovascular morbidity and mortality in this population. In this context, the performance of dedicated randomized cardiovascular studies, with prolonged follow-up and primary evaluation of robust clinical outcomes, will be fundamental for the definitive consolidation of the role of tirzepatide in cardiovascular prevention in individuals with type 2 diabetes mellitus.

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