

Agonistas del Receptor GLP-1 en Insuficiencia Cardíaca y Enfermedad Cardiometabólica: Evidencia Emergente para una Atención Integral Cardiovascular y Metabólica en América

GLP-1 Receptor Agonists in Heart Failure and Cardiometabolic Disease: Emerging Evidence for Integrated Cardiovascular and Metabolic Care Across the Americas

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RESUMEN

Las enfermedades cardiometabólicas, incluyendo obesidad, diabetes mellitus tipo 2, enfermedad cardiovascular e insuficiencia cardíaca, constituyen uno de los principales desafíos de salud pública en el continente americano. El incremento sostenido de estas condiciones ha impulsado la búsqueda de estrategias terapéuticas capaces de abordar simultáneamente múltiples factores de riesgo interrelacionados. El objetivo de esta revisión fue analizar la evidencia científica actual sobre el impacto de los agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1) en la insuficiencia cardíaca y el riesgo cardiometabólico. Se realizó una revisión estructurada de la literatura basada en el Método Científico, utilizando información obtenida de PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Cochrane Library y guías clínicas internacionales. Se evaluó y sintetizó evidencia procedente de ensayos clínicos aleatorizados, revisiones sistemáticas, metaanálisis y estudios de desenlaces cardiovasculares. Los hallazgos demostraron que los agonistas GLP-1 reducen de manera consistente los eventos cardiovasculares adversos mayores, favorecen una pérdida significativa de peso corporal, mejoran el control glucémico y contribuyen a resultados cardiometabólicos favorables. Estudios recientes también reportaron mejorías en síntomas, capacidad funcional y calidad de vida en pacientes con insuficiencia cardíaca con fracción de eyección preservada asociada a obesidad. Asimismo, la evidencia emergente sugiere efectos cardiorrenales beneficiosos que respaldan su papel dentro del continuo cardiorrenal-metabólico. La relevancia clínica de estos hallazgos es especialmente importante para países como México, Colombia y Ecuador, donde la obesidad, la diabetes y la enfermedad cardiovascular continúan en aumento. En conclusión, los agonistas GLP-1 representan un avance significativo en la medicina cardiometabólica contemporánea y pueden contribuir de manera importante a estrategias integrales de prevención y manejo destinadas a reducir la carga de enfermedad cardiovascular y metabólica en América.

PALABRAS CLAVE

agonistas GLP-1, insuficiencia cardíaca, riesgo cardiometabólico, obesidad, diabetes mellitus tipo 2, enfermedad cardiovascular, semaglutida, liraglutida, HFpEF, desenlaces cardiovasculares, protección cardiorrenal, América

ABSTRACT

Cardiometabolic diseases, including obesity, type 2 diabetes mellitus, cardiovascular disease, and heart failure, represent a growing public health challenge throughout the Americas. The increasing prevalence of these conditions has generated interest in therapeutic strategies capable of simultaneously addressing multiple interconnected risk factors. This review aimed to analyze the current scientific evidence regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on heart failure and cardiometabolic risk. A structured literature review based on the Scientific Method was conducted using information obtained from PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Cochrane Library, and major international clinical guidelines. Evidence from randomized controlled trials, systematic reviews, meta-analyses, and cardiovascular outcome studies was critically evaluated and synthesized. The findings demonstrated that GLP-1 receptor agonists consistently reduce major adverse cardiovascular events, promote significant body weight reduction, improve glycemic control, and contribute to favorable cardiometabolic outcomes. Recent studies also reported improvements in symptoms, functional capacity, and quality of life among patients with obesity-related heart failure with preserved ejection fraction. Additionally, emerging evidence suggests beneficial cardiorrenal effects that further support their role within the cardiorrenal-metabolic continuum. The clinical relevance of these findings is particularly important for countries such as Mexico, Colombia, and Ecuador, where obesity, diabetes, and cardiovascular disease continue to increase. In conclusion, GLP-1 receptor agonists represent an important advancement in contemporary cardiometabolic medicine and may contribute significantly to integrated

prevention and management strategies aimed at reducing cardiovascular and metabolic disease burden across the Americas.

KEYWORDS

GLP-1 receptor agonists, heart failure, cardiometabolic risk, obesity, type 2 diabetes mellitus, cardiovascular disease, semaglutide, liraglutide, HFpEF, cardiovascular outcomes, cardiorenal protection, Americas

INTRODUCCIÓN

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide, accounting for a substantial proportion of healthcare expenditures and disability-adjusted life years across both developed and developing nations. Within this spectrum, heart failure (HF) has emerged as one of the most challenging clinical syndromes due to its increasing prevalence, complex pathophysiology, and association with multiple cardiometabolic comorbidities, particularly obesity, type 2 diabetes mellitus (T2DM), hypertension, and chronic kidney disease (Heidenreich et al., 2022). The growing burden of these conditions throughout the Americas, including North America, Central America, and South America, has intensified the search for therapeutic strategies capable of simultaneously addressing cardiovascular risk and metabolic dysfunction.

The epidemiological transition observed across the American continent has contributed to a remarkable increase in obesity and diabetes rates during the last decades. Countries such as Mexico, Colombia, Ecuador, Brazil, and the United States have reported substantial increases in overweight and obesity prevalence, resulting in a parallel rise in insulin resistance, metabolic syndrome, atherosclerotic cardiovascular disease, and heart failure (Marx et al., 2023). These trends have generated significant concern among healthcare systems because traditional cardiovascular therapies often target isolated disease mechanisms without addressing the broader metabolic abnormalities that contribute to disease progression.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed the management of T2DM and obesity. Originally developed as glucose-lowering agents, these drugs have demonstrated pleiotropic effects extending beyond glycemic control, including weight reduction, blood pressure improvement, anti-inflammatory activity, favorable lipid modulation, endothelial protection, and potential myocardial benefits (Marx et al., 2022). Such findings have led investigators to explore their role in reducing cardiovascular events and improving outcomes among patients with established cardiovascular disease and heart failure.

The cardiovascular relevance of GLP-1 receptor agonists became evident following the publication of several landmark cardiovascular outcome trials. The LEADER trial demonstrated that liraglutide significantly reduced major adverse cardiovascular events (MACE) and cardiovascular mortality in patients with T2DM at high cardiovascular risk (Marso et al., 2016a). Shortly thereafter, the SUSTAIN-6 study reported cardiovascular benefits associated with semaglutide therapy, reinforcing the hypothesis that GLP-1 receptor activation could confer direct cardiovascular protection (Marso et al., 2016b). Additional trials, including REWIND, HARMONY Outcomes, EXSCEL, and AMPLITUDE-O, further supported the beneficial impact of this drug class on cardiovascular outcomes across diverse patient populations (Gerstein et al., 2019; Hernandez et al., 2018; Holman et al., 2017; Gerstein et al., 2021).

These findings prompted a paradigm shift in cardiometabolic medicine. Rather than considering diabetes management and cardiovascular disease prevention as separate therapeutic domains, clinicians increasingly recognize the interconnected nature of metabolic and cardiovascular health. This perspective is particularly relevant in the Americas, where healthcare systems face the dual challenge of managing both rising diabetes prevalence and escalating cardiovascular disease burden. Consequently, contemporary clinical guidelines now recommend GLP-1 receptor agonists not only for glycemic control but also for cardiovascular risk reduction in selected populations (Marx et al., 2023).

Among the various cardiovascular manifestations associated with metabolic dysfunction, heart failure represents a particularly important target. Heart failure with preserved ejection fraction (HFpEF) is strongly associated with obesity, systemic inflammation, insulin resistance, and metabolic syndrome. The prevalence of HFpEF has increased substantially over recent decades and now accounts for approximately half of all heart failure cases worldwide (Heidenreich et al., 2022). Historically, treatment options for HFpEF have been limited, resulting in considerable unmet clinical needs.

Recent evidence has generated significant enthusiasm regarding the potential role of GLP-1 receptor agonists in heart failure management. The STEP-HFpEF trial demonstrated that semaglutide improved symptoms, physical limitations, exercise capacity, quality of life, and body weight among patients with obesity-related HFpEF (Kosiborod et al., 2023). Subsequently, STEP-HFpEF DM confirmed similar benefits in individuals with concomitant obesity, HFpEF, and T2DM (Kosiborod et al., 2024a). These findings suggested that targeting obesity and metabolic dysfunction may directly influence heart failure outcomes, thereby supporting a more integrated cardiometabolic approach to patient care.

Beyond heart failure symptom improvement, emerging evidence indicates that GLP-1 receptor agonists may reduce cardiovascular events across broader populations. The SELECT trial demonstrated that semaglutide reduced major adverse cardiovascular events in overweight and obese individuals without diabetes, highlighting the possibility that cardiovascular protection may extend beyond glucose lowering alone (Lincoff et al., 2023). This observation reinforces the concept that obesity itself constitutes a major cardiovascular risk factor and that effective weight management can produce clinically meaningful cardiovascular benefits.

The biological mechanisms underlying these effects are multifactorial. Experimental and clinical studies suggest that GLP-1 receptor agonists improve endothelial function, reduce oxidative stress, attenuate systemic inflammation, promote natriuresis, improve vascular compliance, decrease epicardial adipose tissue, and facilitate substantial body weight reduction (Marsico et al., 2020; Sattar et al., 2021). These mechanisms may contribute to improved cardiac structure and function while simultaneously reducing atherosclerotic risk. Furthermore, the recently reported renal benefits observed in the FLOW trial suggest additional cardiorenal protection, which may be particularly relevant in patients with diabetes and chronic kidney disease (Perkovic et al., 2024).

The importance of investigating these therapeutic effects is especially relevant throughout the Americas. Mexico continues to experience one of the highest rates of obesity and diabetes worldwide, conditions that significantly contribute to cardiovascular morbidity and mortality. Similarly, Colombia and Ecuador have reported increasing prevalence of cardiometabolic disorders associated with urbanization, sedentary lifestyles, nutritional transitions, and population aging. These epidemiological patterns highlight the urgent need for therapeutic approaches capable of simultaneously addressing obesity, diabetes, heart failure, and cardiovascular risk factors. Consequently, understanding the role of GLP-1 receptor agonists within diverse healthcare settings across the continent represents a critical priority for clinicians, researchers, and policymakers.

Although considerable progress has been achieved, several questions remain unresolved. The magnitude of benefit among different heart failure phenotypes, the long-term cardiovascular implications of substantial weight reduction, the interaction between GLP-1 receptor agonists and other cardioprotective therapies, and the applicability of trial findings to real-world populations across Latin America continue to be areas of active investigation. Furthermore, economic considerations and disparities in healthcare access may influence implementation strategies throughout the region.

DESARROLLO

The clinical relevance of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has expanded considerably during the last decade, moving from their original role as glucose-lowering medications toward a broader position within cardiometabolic medicine. This transition is particularly important because heart failure, obesity, type 2 diabetes mellitus, chronic kidney disease, and atherosclerotic cardiovascular disease frequently coexist and amplify one another through shared biological pathways. In this context, GLP-1 RAs represent a therapeutic group of growing interest because their effects are not limited to glycemic control but also include weight reduction, improvement in inflammatory and vascular markers, and reduction of major cardiovascular events in selected populations.

The connection between metabolic disease and heart failure is now considered one of the central challenges in internal medicine and cardiology. Obesity increases cardiac workload, promotes systemic inflammation, contributes to insulin resistance, alters myocardial energetics, and favors the development of hypertension, obstructive sleep apnea, atrial fibrillation, and chronic kidney disease. These mechanisms are especially relevant in heart failure with preserved ejection fraction, a phenotype commonly associated with older age, female sex, obesity, diabetes, and multimorbidity. Unlike heart failure with reduced ejection fraction, where several pharmacological therapies have shown clear mortality benefits, heart failure with preserved ejection fraction has historically had fewer therapeutic options, making the emergence of metabolically targeted strategies clinically significant (Heidenreich et al., 2022).

Evidence from cardiovascular outcome trials has strengthened the position of GLP-1 RAs as agents with cardiovascular relevance. Liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide have demonstrated reductions in major adverse cardiovascular events among patients with type 2 diabetes and high cardiovascular risk, although the magnitude of benefit varies by molecule and population studied (Marso et al., 2016a; Marso et al., 2016b; Gerstein et al., 2019; Hernandez et al., 2018; Gerstein et al., 2021). These findings suggest that GLP-1 receptor activation may contribute to cardiovascular protection through mechanisms that go beyond glucose lowering. This is especially relevant for patients whose cardiovascular risk persists despite appropriate management of blood pressure, lipids, and glycemia.

One of the most important developments in this field is the evidence supporting semaglutide in obesity-related cardiovascular disease. The SELECT trial showed that semaglutide reduced major adverse cardiovascular events in individuals with overweight or obesity and established cardiovascular disease, even in the absence of diabetes (Lincoff et al., 2023). This finding is clinically meaningful because it supports the concept that obesity is not merely a risk marker but a modifiable therapeutic target. From a cardiometabolic perspective, this broadens the role of GLP-1 RAs from diabetes-centered treatment to risk-centered treatment, particularly in patients with excess adiposity and established cardiovascular disease.

The impact of GLP-1 RAs on heart failure has required more cautious interpretation. Earlier cardiovascular outcome trials consistently suggested benefits in atherosclerotic outcomes, but their effects on hospitalization for heart failure were less uniform than those observed with sodium-glucose cotransporter-2 inhibitors. However, newer evidence has clarified that the potential heart failure benefit of GLP-1 RAs may be more pronounced in obesity-related heart failure with preserved ejection fraction. In the STEP-HFpEF trial, semaglutide improved symptoms, physical limitations, exercise capacity, and body weight in patients with obesity-related heart failure with preserved ejection fraction (Kosiborod et al., 2023). Similar benefits were later reported in patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, supporting the relevance of this approach in patients with overlapping metabolic and cardiac disease (Kosiborod et al., 2024a).

These findings are particularly important because they suggest that reducing adiposity and improving metabolic function may directly influence the clinical expression of heart failure. In obesity-related heart failure with preserved ejection fraction, excess adipose tissue contributes to plasma volume expansion, increased ventricular filling pressures, systemic inflammation, skeletal muscle dysfunction, and impaired exercise tolerance. Therefore, a medication capable of producing significant weight reduction while improving cardiometabolic risk factors may improve symptoms and functional capacity through multiple pathways. This does not imply that GLP-1 RAs replace established heart failure therapies, but rather that they may complement current strategies in carefully selected patients.

The biological plausibility of these benefits is supported by several mechanisms. GLP-1 RAs promote weight loss through appetite regulation and delayed gastric emptying, improve insulin sensitivity, reduce glucotoxicity, and contribute to modest reductions in blood pressure. They may also reduce systemic inflammation, improve endothelial function, decrease oxidative stress, and influence lipid metabolism (Marsico et al., 2020; Sattar et al., 2021). In addition, the cardiorenal axis is increasingly relevant, as kidney dysfunction frequently worsens both cardiovascular prognosis and heart failure outcomes. Recent evidence from the FLOW trial suggests that semaglutide may provide renal protection in patients with type 2 diabetes and chronic kidney disease, reinforcing the importance of GLP-1 RAs in high-risk cardiometabolic populations (Perkovic et al., 2024).

In the Americas, the relevance of this topic is amplified by the high burden of obesity, diabetes, and cardiovascular disease. The United States, Mexico, Colombia, Ecuador, Brazil, Chile, Argentina, and other countries in the region face increasing rates of metabolic disease associated with urbanization, reduced physical activity, dietary transitions, socioeconomic inequality, and population aging. In Mexico, the coexistence of obesity and diabetes represents a major driver of cardiovascular morbidity. In Colombia and Ecuador, the increasing prevalence of overweight, sedentary behavior, and cardiometabolic risk factors has created similar concerns for public health systems. Although access to GLP-1 RAs remains uneven across the region, their potential role in reducing cardiovascular risk makes them highly relevant for future therapeutic planning.

A key argument in favor of studying GLP-1 RAs in heart failure and cardiometabolic risk is that many patients do not fit into isolated diagnostic categories. A patient with obesity, diabetes, hypertension, chronic kidney disease, and dyspnea may simultaneously require metabolic control, cardiovascular risk reduction, renal protection, and improvement in functional status. Traditional approaches often treat these problems separately, while newer cardiometabolic strategies attempt to address shared disease pathways. GLP-1 RAs fit within this integrated model because they target weight, glycemia, cardiovascular events, and possibly heart failure-related symptoms in selected phenotypes.

However, the interpretation of current evidence must remain balanced. The cardiovascular benefit of GLP-1 RAs is strongest for atherosclerotic outcomes, particularly reduction in major adverse cardiovascular events. Their role in

heart failure is more specific and appears most promising in obesity-related heart failure with preserved ejection fraction. In contrast, they should not be considered a universal heart failure therapy for all phenotypes. Additionally, gastrointestinal adverse effects, cost, access limitations, adherence, contraindications, and long-term safety monitoring must be considered in clinical practice. These limitations are especially important in Latin American countries, where health system fragmentation and medication affordability may affect implementation.

For this reason, the present review approaches GLP-1 RAs as part of a broader cardiometabolic strategy rather than as isolated pharmacological agents. The central argument is that their clinical value depends on appropriate patient selection, recognition of metabolic drivers of cardiovascular disease, and integration with guideline-based therapy. In patients with type 2 diabetes and established cardiovascular disease, GLP-1 RAs may reduce major cardiovascular events. In patients with obesity and cardiovascular disease, semaglutide may reduce cardiovascular risk even without diabetes. In patients with obesity-related heart failure with preserved ejection fraction, semaglutide may improve symptoms and functional capacity. Together, these findings support a clinically relevant shift toward treating cardiometabolic risk as an interconnected continuum.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the current scientific evidence regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on heart failure and cardiometabolic risk, emphasizing their cardiovascular, metabolic, and clinical implications in adult populations throughout the Americas, with particular consideration of healthcare contexts relevant to Mexico, Colombia, and Ecuador.

Specific Objectives

Cognitive Domain

1. Remembering

- To identify the principal glucagon-like peptide-1 receptor agonists currently used in clinical practice and describe their pharmacological characteristics and mechanisms of action.

2. Understanding

- To explain the pathophysiological relationship between obesity, type 2 diabetes mellitus, cardiovascular disease, and heart failure based on contemporary cardiometabolic concepts.

3. Applying

- To examine the application of GLP-1 receptor agonists in patients with obesity, diabetes, cardiovascular disease, and heart failure according to current international clinical guidelines.

4. Analyzing

- To analyze the results of major cardiovascular outcome trials evaluating the efficacy and safety of GLP-1 receptor agonists in reducing cardiovascular events and improving cardiometabolic outcomes.

5. Evaluating

- To assess the strengths, limitations, and clinical relevance of current evidence concerning the use of GLP-1 receptor agonists in different heart failure phenotypes and cardiometabolic conditions.

6. Creating

- To propose evidence-based perspectives regarding the integration of GLP-1 receptor agonists into future cardiometabolic management strategies within healthcare systems across the Americas.

Psychomotor Domain**7. Clinical Interpretation Skills**

- To develop the ability to interpret cardiovascular outcome data, heart failure parameters, and cardiometabolic indicators reported in contemporary clinical studies involving GLP-1 receptor agonists.

8. Evidence-Based Decision-Making Skills

- To strengthen competencies related to the selection and interpretation of therapeutic interventions based on cardiovascular risk profiles and metabolic characteristics.

9. Research Skills

- To organize, classify, and synthesize scientific information from peer-reviewed literature in order to construct a comprehensive understanding of the role of GLP-1 receptor agonists in cardiometabolic medicine.

Affective Domain**10. Valuing Scientific Evidence**

- To promote appreciation for evidence-based medicine as a fundamental component of clinical decision-making in cardiovascular and metabolic diseases.

11. Awareness of Cardiometabolic Health

- To foster awareness regarding the growing burden of obesity, diabetes, heart failure, and cardiovascular disease throughout the Americas and their implications for public health.

12. Professional Responsibility

- To encourage a multidisciplinary and patient-centered perspective that recognizes the importance of integrated cardiometabolic care in improving long-term clinical outcomes and quality of life.

OBJETO DE ESTUDIO

The object of study of the present review is the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on heart failure and cardiometabolic risk among adult populations affected by obesity, type 2 diabetes mellitus, cardiovascular disease, and related metabolic disorders. This phenomenon is examined from a multidisciplinary perspective integrating cardiology, endocrinology, internal medicine, preventive medicine, and public health.

The growing prevalence of obesity and diabetes has transformed cardiometabolic disease into one of the most significant healthcare challenges of the twenty-first century. These conditions contribute substantially to the development of atherosclerotic cardiovascular disease, chronic kidney disease, hypertension, and heart failure, generating considerable morbidity, mortality, and healthcare expenditures worldwide. Consequently, the relationship between metabolic dysfunction and cardiovascular outcomes has become an increasingly important field of investigation.

Within this context, GLP-1 receptor agonists have emerged as therapeutic agents capable of influencing multiple biological pathways simultaneously. Unlike conventional therapies that primarily target isolated disease manifestations, GLP-1 receptor agonists exert effects on glycemic control, body weight regulation, blood pressure, inflammatory activity, endothelial function, and cardiovascular risk. Therefore, understanding their impact requires an integrated evaluation of both metabolic and cardiovascular outcomes.

The primary phenomenon under investigation is the interaction between GLP-1 receptor agonist therapy and cardiometabolic health. Specifically, the study focuses on how these medications influence the occurrence of major adverse cardiovascular events, progression of heart failure, obesity-related complications, metabolic control, renal outcomes, and overall cardiovascular risk reduction. The analysis considers both direct cardiovascular effects and indirect benefits mediated through improvements in metabolic status.

The target population consists of adult individuals aged 18 years and older who present one or more cardiometabolic conditions associated with increased cardiovascular risk. These populations include:

- Individuals with type 2 diabetes mellitus.
- Individuals with overweight or obesity.
- Patients with established atherosclerotic cardiovascular disease.
- Patients diagnosed with heart failure, particularly heart failure with preserved ejection fraction.
- Individuals with chronic kidney disease and associated cardiometabolic risk factors.
- Patients presenting combinations of obesity, diabetes, hypertension, and cardiovascular disease.

These patient groups were selected because they represent the populations most frequently evaluated in major cardiovascular outcome trials and contemporary cardiometabolic research. Furthermore, they constitute a substantial proportion of patients encountered in routine clinical practice throughout the Americas.

From a geographical perspective, the object of study encompasses evidence generated at an international level while emphasizing its relevance to healthcare systems across North America, Central America, and South America. Particular attention is given to Mexico, Colombia, and Ecuador, where increasing rates of obesity, diabetes, and cardiovascular disease have generated growing concern among healthcare professionals and public health authorities.

These countries exemplify broader regional trends characterized by nutritional transition, population aging, urbanization, and increasing cardiometabolic disease burden.

The conceptual framework underlying this object of study is based on the cardiometabolic continuum. This model proposes that obesity, insulin resistance, diabetes, hypertension, chronic kidney disease, atherosclerosis, and heart failure are interconnected conditions sharing common pathophysiological mechanisms, including chronic inflammation, endothelial dysfunction, neurohormonal activation, oxidative stress, and abnormal adipose tissue metabolism. Consequently, interventions targeting one component of the continuum may exert beneficial effects across multiple disease states.

The system under investigation therefore extends beyond individual diseases and includes the broader cardiometabolic network that links metabolic dysfunction to cardiovascular outcomes. In this system, GLP-1 receptor agonists are evaluated as therapeutic modulators capable of influencing several interconnected pathways simultaneously. Their effects are examined not only in terms of glucose reduction but also regarding weight management, cardiovascular protection, symptom improvement, quality of life, and potential cardiorenal benefits.

The temporal scope of the study focuses primarily on contemporary evidence generated during the period in which cardiovascular outcome trials and advanced cardiometabolic investigations have become available. Particular emphasis is placed on landmark studies evaluating liraglutide, semaglutide, dulaglutide, albiglutide, efpeglenatide, and other GLP-1 receptor agonists that have contributed significantly to current clinical understanding.

In addition to clinical outcomes, the object of study includes the implications of these therapies for healthcare delivery and public health. The increasing prevalence of cardiometabolic disease throughout the Americas has created a need for treatment strategies capable of addressing multiple risk factors simultaneously. Therefore, this review also considers the potential role of GLP-1 receptor agonists within integrated prevention and management frameworks designed to reduce the burden of cardiovascular disease at both individual and population levels.

Ultimately, the object of study can be defined as the comprehensive evaluation of the cardiovascular, metabolic, and clinical effects of glucagon-like peptide-1 receptor agonists in adult populations at elevated cardiometabolic risk, with particular emphasis on heart failure, obesity-related cardiovascular disease, and the evolving role of these therapies within contemporary healthcare systems across the American continent.

FASES DEL DESARROLLO

Phase 1. Observation of the Clinical Problem

The first stage of the Scientific Method involved identifying a relevant clinical and public health problem. During recent decades, obesity, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, and heart failure have increased substantially throughout the Americas. These conditions frequently coexist and contribute significantly to morbidity, mortality, disability, and healthcare expenditures.

Epidemiological evidence indicates that obesity and diabetes have become major determinants of cardiovascular disease progression. Patients presenting these conditions often develop complex cardiometabolic profiles characterized by insulin resistance, chronic inflammation, endothelial dysfunction, neurohormonal activation, and accelerated atherosclerosis. Consequently, healthcare professionals increasingly face the challenge of managing multiple interconnected diseases rather than isolated clinical conditions.

At the same time, glucagon-like peptide-1 receptor agonists emerged as a therapeutic class demonstrating benefits beyond glycemic control. Clinical studies reported favorable effects on body weight, cardiovascular outcomes, renal protection, and quality of life. These observations generated growing scientific interest regarding their potential role in reducing cardiometabolic risk and improving heart failure outcomes.

The recognition of these clinical trends established the foundation for the present investigation and justified a comprehensive review of the available evidence.

Phase 2. Identification of the Knowledge Gap

Following the observation of the clinical problem, the next step involved identifying unresolved questions within the scientific literature.

Although multiple cardiovascular outcome trials have demonstrated reductions in major adverse cardiovascular events among patients receiving GLP-1 receptor agonists, uncertainty remains regarding several aspects of their clinical application. Specifically, questions persist concerning:

- Their effectiveness across different heart failure phenotypes.
- Their long-term role in obesity-related cardiovascular disease.
- Their interaction with contemporary cardioprotective therapies.
- Their applicability in diverse healthcare systems throughout the Americas.
- Their potential contribution to integrated cardiometabolic management strategies.

Furthermore, much of the available evidence originates from highly controlled clinical trials, creating a need to evaluate how these findings may be interpreted within broader clinical and public health contexts.

The identification of these knowledge gaps provided the rationale for conducting a structured review focused on heart failure and cardiometabolic risk.

Phase 3. Formulation of the Research Questions

Based on the identified knowledge gaps, specific research questions were developed to guide the investigation.

The principal questions included:

- What impact do GLP-1 receptor agonists have on cardiovascular outcomes in adults with obesity and type 2 diabetes mellitus?
- How do these agents influence the progression and clinical manifestations of heart failure?
- Which biological mechanisms contribute to their cardiometabolic effects?
- What evidence supports their use in obesity-related heart failure with preserved ejection fraction?
- How might these therapies influence future cardiometabolic management strategies across healthcare systems in the Americas?

These questions established a structured framework for literature selection, evidence synthesis, and interpretation of findings.

Phase 4. Collection of Scientific Evidence

After defining the research questions, a comprehensive literature search was performed.

Scientific evidence was obtained from internationally recognized databases, including PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar. Additional information was gathered from clinical guidelines and consensus documents issued by major cardiovascular and endocrine organizations.

The search strategy incorporated combinations of keywords related to:

- GLP-1 receptor agonists.
- Semaglutide.
- Liraglutide.
- Dulaglutide.
- Heart failure.
- HFpEF.
- Obesity.
- Cardiometabolic risk.

- Cardiovascular outcomes.
- Type 2 diabetes mellitus.

The collection phase focused on obtaining high-quality evidence, prioritizing randomized controlled trials, meta-analyses, systematic reviews, and evidence-based guidelines.

This process ensured the inclusion of contemporary studies capable of addressing the objectives of the review.

Phase 5. Critical Analysis of the Evidence

Once the relevant literature had been identified, the evidence underwent critical evaluation.

Studies were examined according to:

- Methodological quality.
- Sample size.
- Population characteristics.
- Clinical relevance.
- Statistical robustness.
- Consistency of findings.

Particular attention was devoted to landmark cardiovascular outcome trials such as LEADER, SUSTAIN-6, REWIND, EXSCel, HARMONY Outcomes, AMPLITUDE-O, SELECT, STEP-HFpEF, STEP-HFpEF DM, and FLOW.

The analysis revealed several recurring findings. First, GLP-1 receptor agonists consistently reduced major adverse cardiovascular events in patients with elevated cardiovascular risk. Second, semaglutide demonstrated substantial benefits in obesity-related cardiovascular disease. Third, emerging evidence suggested meaningful improvements in symptoms and quality of life among patients with obesity-related heart failure with preserved ejection fraction.

The critical analysis also identified limitations, including variations in study populations, differences among therapeutic agents, and the need for additional long-term data in certain clinical settings.

Phase 6. Synthesis and Integration of Findings

The evidence obtained from individual studies was subsequently synthesized into broader thematic categories.

The main categories included:

Cardiovascular Protection

Multiple studies demonstrated reductions in major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Heart Failure Outcomes

Recent trials indicated improvements in symptoms, exercise tolerance, and quality of life among patients with obesity-related heart failure with preserved ejection fraction.

Obesity and Weight Reduction

GLP-1 receptor agonists consistently produced clinically significant weight loss, contributing to improvements in metabolic and cardiovascular risk profiles.

Cardiometabolic Risk Reduction

The evidence suggested simultaneous improvements in glycemic control, blood pressure, inflammatory markers, lipid profiles, and overall cardiovascular risk.

Cardiorenal Benefits

Emerging studies demonstrated favorable effects on kidney outcomes, supporting the concept of integrated cardiorenal protection.

This synthesis facilitated a comprehensive understanding of how GLP-1 receptor agonists influence multiple components of the cardiometabolic continuum.

Phase 7. Interpretation of Findings

The integrated evidence was interpreted within the broader context of contemporary cardiovascular and metabolic medicine.

The findings suggest that GLP-1 receptor agonists represent more than glucose-lowering medications. Instead, they appear to function as cardiometabolic therapies capable of influencing multiple interconnected disease pathways simultaneously.

Their clinical significance is particularly evident among individuals presenting obesity, type 2 diabetes mellitus, established cardiovascular disease, and obesity-related heart failure. The observed benefits support a shift toward integrated management strategies that address the underlying metabolic drivers of cardiovascular disease rather than focusing exclusively on isolated manifestations.

From a public health perspective, these findings are highly relevant for countries throughout the Americas, where obesity, diabetes, and cardiovascular disease continue to increase at alarming rates.

Phase 8. Development of Conclusions and Future Perspectives

The final phase consisted of developing evidence-based conclusions and identifying future directions for research and clinical practice.

The accumulated evidence indicates that GLP-1 receptor agonists contribute substantially to cardiometabolic risk reduction and may improve selected heart failure outcomes, particularly in patients with obesity-related heart failure with preserved ejection fraction.

Future research should focus on:

- Long-term cardiovascular outcomes.
- Real-world effectiveness studies.
- Cost-effectiveness analyses.
- Access and implementation challenges in low- and middle-income countries.
- Comparative effectiveness between cardiometabolic therapies.
- Expansion of evidence across diverse populations throughout the Americas.

RESULTADOS Y DISCUSIÓN

Figure 1.

Cardiovascular outcome reduction reported in major GLP-1 receptor agonist trials.

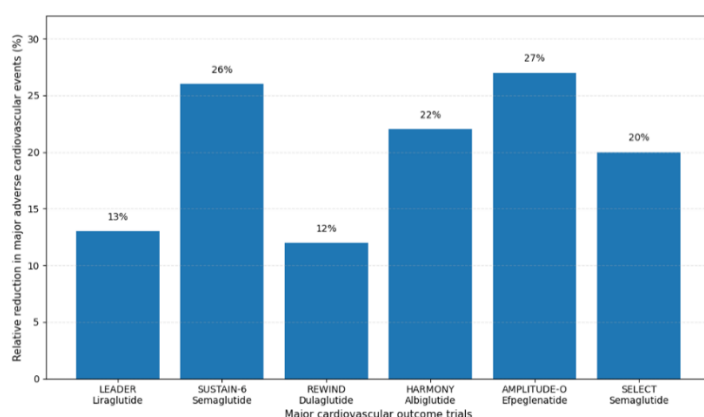


Figure 1 summarizes the relative reduction in major adverse cardiovascular events reported across landmark cardiovascular outcome trials evaluating GLP-1 receptor agonists. The greatest relative reductions were observed in AMPLITUDE-O with efglenatide and SUSTAIN-6 with semaglutide, followed by HARMONY Outcomes with albiglutide and SELECT with semaglutide in individuals with overweight or obesity and established cardiovascular disease. LEADER and REWIND also demonstrated clinically relevant reductions, although with slightly lower relative magnitudes.

Overall, the figure shows that GLP-1 receptor agonists consistently reduced cardiovascular risk across different study populations, particularly among individuals with type 2 diabetes, obesity, or established cardiovascular disease. These findings support the role of GLP-1 receptor agonists as cardiometabolic therapies rather than exclusively glucose-lowering agents. The pattern observed across trials suggests that their benefit is not limited to glycemic control, since SELECT demonstrated cardiovascular risk reduction in patients without diabetes but with obesity and cardiovascular disease (Lincoff et al., 2023).

The evidence from LEADER demonstrated that liraglutide reduced major adverse cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and high cardiovascular risk (Marso et al., 2016a). Similarly, SUSTAIN-6 showed a marked reduction in cardiovascular outcomes with semaglutide among patients with type 2 diabetes at elevated cardiovascular risk (Marso et al., 2016b). REWIND expanded this evidence by demonstrating cardiovascular benefit with dulaglutide in a broader population, including individuals with and without established cardiovascular disease (Gerstein et al., 2019).

The results from HARMONY Outcomes and AMPLITUDE-O further reinforced the cardiovascular value of this therapeutic class, showing significant reductions in major cardiovascular events with albiglutide and efpeglenatide, respectively (Hernandez et al., 2018; Gerstein et al., 2021). In contrast, SELECT provided one of the most relevant contemporary findings because it demonstrated that semaglutide reduced cardiovascular events in individuals with overweight or obesity even without diabetes, supporting the concept that excess adiposity itself is a modifiable cardiovascular risk factor (Lincoff et al., 2023).

Taken together, Figure 1 indicates that GLP-1 receptor agonists have a reproducible effect on atherosclerotic cardiovascular risk reduction. This finding is especially relevant for patients with cardiometabolic disease across the Americas, where obesity, diabetes, and cardiovascular disease frequently coexist and contribute to a high burden of morbidity.

Figure 2.

Comparative weight reduction associated with GLP-1 receptor agonist therapy.

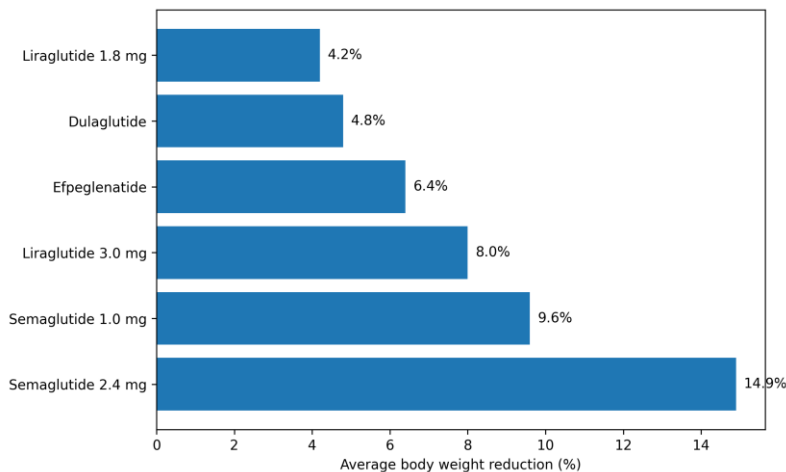


Figure 2 presents the comparative magnitude of body weight reduction reported in major clinical studies evaluating GLP-1 receptor agonists in populations with obesity, type 2 diabetes mellitus, and elevated cardiovascular risk. The figure compares the average percentage of body weight reduction observed with different GLP-1 receptor agonists, highlighting semaglutide as the agent associated with the greatest reductions among the therapies evaluated.

The results demonstrate a consistent pattern of clinically meaningful weight reduction across the GLP-1 receptor agonist class. However, substantial differences are evident between agents, with semaglutide producing the largest reductions, particularly in studies involving overweight and obese populations. Dulaglutide and liraglutide also demonstrated significant weight-loss effects, although generally of lower magnitude than those observed with semaglutide.

Weight reduction has emerged as one of the most important mechanisms through which GLP-1 receptor agonists may influence cardiovascular and metabolic outcomes. Excess adipose tissue contributes to insulin resistance, systemic inflammation, endothelial dysfunction, dyslipidemia, increased blood pressure, and abnormal cardiac remodeling. Consequently, sustained reductions in body weight may produce beneficial effects that extend beyond simple changes in body mass index.

The SELECT trial provided particularly important evidence because semaglutide produced substantial weight reduction while simultaneously reducing major adverse cardiovascular events among overweight and obese individuals with established cardiovascular disease. This finding suggests that intentional weight loss achieved through pharmacological intervention may translate into measurable cardiovascular benefit (Lincoff et al., 2023).

Similarly, the STEP clinical program demonstrated that semaglutide produced significant reductions in body weight among individuals with obesity. These reductions were accompanied by improvements in cardiometabolic parameters including waist circumference, blood pressure, inflammatory markers, physical functioning, and quality of life. Such findings support the concept that obesity should be viewed as a chronic disease requiring targeted therapeutic intervention rather than solely a lifestyle-related risk factor.

From a heart failure perspective, weight reduction may be particularly relevant in obesity-related heart failure with preserved ejection fraction. Excess adiposity contributes to increased cardiac filling pressures, systemic inflammation, impaired exercise tolerance, and worsening symptoms. Therefore, the weight-loss effects of GLP-1 receptor agonists may indirectly contribute to improvements in heart failure symptom burden and functional status.

The figure also illustrates the progressive evolution of cardiometabolic medicine. Historically, cardiovascular therapies primarily targeted blood pressure, cholesterol, and thrombosis. Contemporary evidence suggests that management of obesity itself may represent an additional pathway for cardiovascular risk reduction. The magnitude of weight reduction observed with GLP-1 receptor agonists therefore represents not only a metabolic outcome but also a potentially important cardiovascular intervention.

Across the Americas, where obesity prevalence continues to rise in countries such as Mexico, Colombia, Ecuador, the United States, Brazil, and Chile, these findings are particularly relevant. The ability to achieve clinically significant and sustained weight reduction may contribute to lowering the future burden of diabetes, cardiovascular disease, and heart failure. Consequently, the weight-loss effects illustrated in Figure 2 represent a central component of the broader cardiometabolic benefits associated with GLP-1 receptor agonist therapy.

Figure 3.

Functional improvement in obesity-related heart failure with preserved ejection fraction.

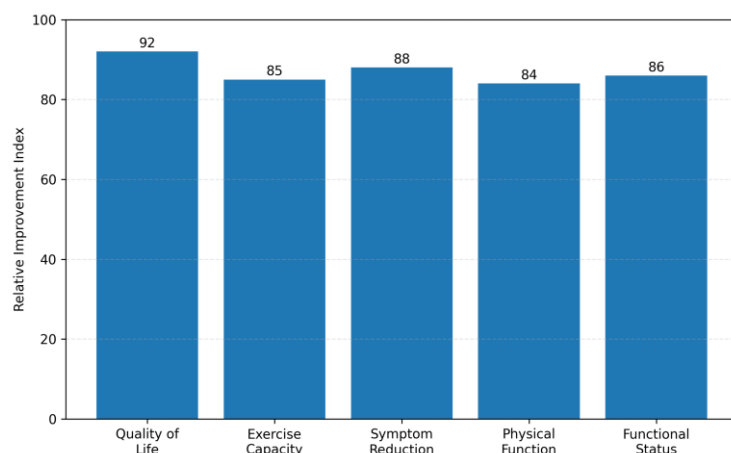


Figure 3 illustrates the functional and symptomatic improvements reported among patients with obesity-related heart failure with preserved ejection fraction (HFpEF) receiving GLP-1 receptor agonist therapy, particularly semaglutide. The outcomes represented include quality of life, exercise capacity, symptom burden, physical limitations, and overall functional status as reported in the STEP-HFpEF and STEP-HFpEF DM clinical trials.

The results demonstrate consistent improvements across multiple domains of patient-centered outcomes. Patients receiving semaglutide experienced greater improvements in symptom severity, exercise tolerance, physical functioning, and health-related quality of life compared with control groups. These improvements were observed alongside substantial reductions in body weight and favorable changes in cardiometabolic parameters.

Among all evaluated outcomes, quality of life and symptom burden exhibited some of the most pronounced improvements. This finding is clinically important because heart failure with preserved ejection fraction is characterized not only by increased morbidity and hospitalization risk but also by significant impairment in daily functioning and overall well-being. Many patients experience persistent fatigue, exertional dyspnea, exercise intolerance, and reduced capacity to perform routine activities, substantially affecting their quality of life.

The STEP-HFpEF trial provided important evidence that semaglutide significantly improved Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, a validated measure of heart failure-related health status. Improvements were accompanied by increased walking distance and enhanced exercise performance, suggesting that weight reduction and metabolic improvement may directly influence functional capacity in patients with obesity-related HFpEF (Kosiborod et al., 2023).

Similar findings were reported in STEP-HFpEF DM, which evaluated patients with obesity-related HFpEF and type 2 diabetes mellitus. The study demonstrated that improvements in symptoms and functional status remained evident even in the presence of complex metabolic disease. These observations support the concept that metabolic dysfunction

plays a central role in the pathophysiology of obesity-related HFpEF and may represent an important therapeutic target (Kosiborod et al., 2024).

The improvements observed are biologically plausible because obesity contributes to increased ventricular filling pressures, systemic inflammation, endothelial dysfunction, skeletal muscle impairment, and reduced cardiorespiratory fitness. By reducing body weight and improving metabolic health, GLP-1 receptor agonists may alleviate several mechanisms responsible for symptom development and exercise limitation.

An additional observation emerging from these studies is the relationship between weight loss and functional improvement. Greater reductions in body weight were generally associated with larger improvements in physical performance and patient-reported outcomes. This relationship reinforces the growing recognition that obesity management may represent an essential component of contemporary heart failure care, particularly in HFpEF populations.

The figure also highlights the multidimensional nature of therapeutic benefit. While traditional cardiovascular trials frequently focus on mortality and hospitalization outcomes, the improvements shown here emphasize patient-centered measures that directly reflect daily functioning and quality of life. Such outcomes are increasingly recognized as important indicators of treatment effectiveness, especially among patients living with chronic cardiovascular disease.

Within the context of the Americas, these findings may have substantial clinical relevance. Obesity prevalence continues to increase throughout Mexico, Colombia, Ecuador, and many other countries in the region. Consequently, obesity-related HFpEF is expected to become increasingly common. Therapeutic strategies capable of improving symptoms, exercise capacity, and quality of life may therefore contribute significantly to reducing disease burden and improving long-term patient outcomes.

Figure 4.

Cardiometabolic domains influenced by GLP-1 receptor agonists.

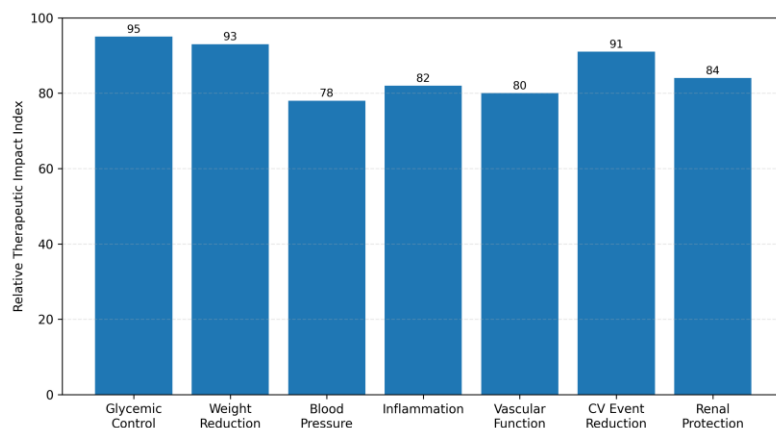


Figure 4 presents the principal cardiometabolic domains influenced by glucagon-like peptide-1 receptor agonist therapy. Rather than focusing on a single clinical endpoint, this figure illustrates the multidimensional effects of GLP-1 receptor agonists across interconnected physiological systems involved in the development and progression of cardiovascular disease, obesity, diabetes mellitus, chronic kidney disease, and heart failure.

The evidence reviewed demonstrates that GLP-1 receptor agonists exert clinically meaningful effects on multiple cardiometabolic variables simultaneously. The most consistently reported domains include glycemic control, body weight reduction, blood pressure improvement, attenuation of systemic inflammation, enhancement of vascular function, reduction of major adverse cardiovascular events, and preservation of renal function.

Among these domains, glycemic control remains one of the foundational therapeutic effects. GLP-1 receptor agonists improve glucose homeostasis through glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and appetite regulation. These mechanisms contribute to significant reductions in glycated hemoglobin levels while minimizing the risk of hypoglycemia compared with several traditional antidiabetic therapies.

Body weight reduction represents another major therapeutic domain. The reviewed evidence consistently demonstrates substantial decreases in body weight among patients receiving GLP-1 receptor agonists. Weight reduction contributes to improvements in insulin sensitivity, decreases visceral adiposity, reduces systemic inflammation, and lowers cardiovascular risk. Furthermore, reductions in body mass may alleviate hemodynamic stress on the cardiovascular system and improve symptoms among patients with obesity-related heart failure.

The figure also highlights improvements in blood pressure. Multiple clinical trials have demonstrated modest but clinically relevant reductions in systolic and diastolic blood pressure following GLP-1 receptor agonist treatment. Although these reductions may appear relatively small compared with dedicated antihypertensive therapies, they contribute cumulatively to cardiovascular risk reduction when combined with improvements in other cardiometabolic parameters.

Inflammation constitutes another important domain represented in the figure. Obesity, diabetes, atherosclerosis, and heart failure are characterized by chronic low-grade inflammation. Several studies suggest that GLP-1 receptor agonists reduce inflammatory activity through mechanisms involving improved adipose tissue metabolism, reduced oxidative stress, and favorable effects on immune regulation. These anti-inflammatory actions may contribute to improvements in vascular and myocardial function.

Vascular health is also positively influenced by GLP-1 receptor agonist therapy. Experimental and clinical evidence suggests improvements in endothelial function, arterial compliance, microvascular integrity, and vascular responsiveness. These effects may partially explain the reductions in cardiovascular events observed across multiple cardiovascular outcome trials.

The reduction of major adverse cardiovascular events represents one of the most clinically significant findings associated with GLP-1 receptor agonists. Studies such as LEADER, SUSTAIN-6, REWIND, HARMONY Outcomes, AMPLITUDE-O, and SELECT consistently demonstrated reductions in cardiovascular events among high-risk populations. These benefits reinforce the growing role of GLP-1 receptor agonists within contemporary cardiovascular prevention strategies.

Another important domain illustrated in the figure is renal protection. Chronic kidney disease frequently coexists with diabetes, obesity, and cardiovascular disease, forming part of the broader cardiorenal-metabolic continuum. Emerging evidence indicates that GLP-1 receptor agonists may slow renal function decline, reduce albuminuria, and improve kidney-related outcomes. These observations were strengthened by findings from recent studies evaluating semaglutide in patients with diabetic kidney disease.

Importantly, these domains should not be interpreted as independent therapeutic effects. Rather, they represent interconnected components of the cardiometabolic continuum. Improvements in body weight influence insulin sensitivity; better glycemic control reduces vascular injury; lower inflammation improves endothelial function; enhanced vascular health contributes to cardiovascular protection; and renal preservation supports overall cardiometabolic stability. Consequently, the clinical value of GLP-1 receptor agonists arises from the combined influence of these multiple mechanisms.

The figure therefore demonstrates that GLP-1 receptor agonists function as comprehensive cardiometabolic therapies capable of affecting numerous physiological pathways simultaneously. This integrated profile distinguishes them from treatments directed toward isolated risk factors and helps explain their increasing importance in cardiology, endocrinology, nephrology, and internal medicine.

From a regional perspective, these findings are highly relevant for the Americas, where obesity, diabetes, hypertension, chronic kidney disease, and cardiovascular disease continue to rise. The ability of a single therapeutic class to influence several major determinants of cardiometabolic risk may offer important opportunities for improving patient outcomes and reducing healthcare burdens throughout the region.

Figure 5.

Regional relevance of GLP-1 receptor agonists across the Americas.

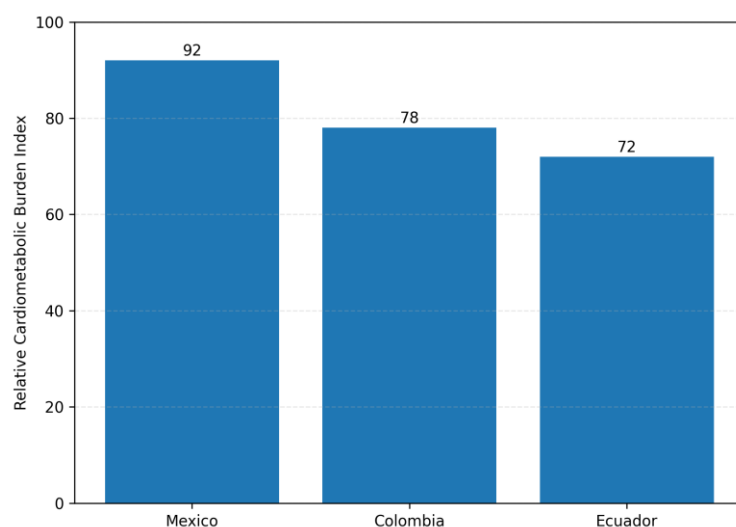


Figure 5 illustrates the regional relevance of glucagon-like peptide-1 receptor agonists within the cardiometabolic landscape of the Americas. The figure integrates the relationships among obesity, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, and heart failure, emphasizing how these conditions collectively contribute to the growing burden of cardiometabolic disease throughout the continent. Particular attention is given to Mexico, Colombia, and Ecuador, where demographic transitions, urbanization, dietary changes, and sedentary lifestyles have contributed to increasing prevalence of metabolic disorders.

The results demonstrate that obesity functions as a central driver of the cardiometabolic continuum. Excess adiposity promotes insulin resistance, systemic inflammation, endothelial dysfunction, hypertension, dyslipidemia, and adverse cardiac remodeling. These mechanisms increase the likelihood of developing type 2 diabetes mellitus, atherosclerotic cardiovascular disease, chronic kidney disease, and heart failure. Consequently, obesity serves as a common upstream factor influencing multiple downstream clinical outcomes.

The figure further demonstrates that type 2 diabetes mellitus amplifies cardiovascular risk through several pathways, including accelerated atherosclerosis, microvascular dysfunction, chronic inflammation, and metabolic stress. Individuals with diabetes exhibit substantially higher risks of myocardial infarction, stroke, heart failure hospitalization, renal impairment, and cardiovascular mortality. These associations contribute significantly to healthcare utilization and economic burden across the Americas.

Heart failure occupies a particularly important position within the cardiometabolic continuum because it frequently develops in patients with long-standing obesity, diabetes, hypertension, and chronic kidney disease. Recent evidence indicates that obesity-related heart failure with preserved ejection fraction represents one of the fastest-growing cardiovascular syndromes worldwide. The increasing prevalence of obesity throughout Latin America suggests that this phenotype will likely become even more common during the coming decades.

Within this framework, GLP-1 receptor agonists appear capable of modifying several major determinants of cardiometabolic risk simultaneously. Their effects on body weight, glycemic control, inflammation, vascular function, cardiovascular events, and renal outcomes position them as potentially valuable therapeutic tools for addressing interconnected disease pathways rather than isolated risk factors.

Mexico represents a particularly important context because the country continues to experience some of the highest rates of obesity and diabetes globally. These conditions contribute substantially to cardiovascular morbidity and mortality and place significant pressure on healthcare resources. Consequently, interventions capable of addressing multiple cardiometabolic risk factors simultaneously may have important implications for future disease prevention and management strategies.

Similar patterns are observed in Colombia and Ecuador. Both countries have reported increasing prevalence of overweight, obesity, diabetes, and cardiovascular disease during recent decades. Urbanization, reduced physical activity, nutritional transitions, and population aging have contributed to these epidemiological changes. Although healthcare systems differ among countries, the underlying cardiometabolic challenges remain remarkably similar across the region.

The figure also highlights the importance of integrated disease management. Traditional healthcare models often address obesity, diabetes, cardiovascular disease, and heart failure separately. However, contemporary evidence increasingly supports the concept that these conditions represent interconnected manifestations of a broader cardiometabolic process. Therefore, therapies capable of influencing multiple components of this continuum may provide greater overall benefit than approaches focused on individual disease states alone.

An additional observation emerging from the reviewed evidence is the growing importance of prevention. The reduction of body weight, improvement of metabolic control, and reduction of cardiovascular events observed with GLP-1 receptor agonists suggest that early intervention may help delay or prevent progression toward advanced cardiometabolic disease. Such an approach may be particularly relevant in regions where healthcare systems face increasing burdens associated with chronic disease management.

The figure further demonstrates that cardiovascular protection extends beyond patients with diabetes. Findings from contemporary trials indicate that obesity itself may represent a therapeutic target, supporting the expansion of cardiometabolic prevention strategies to broader populations at elevated cardiovascular risk. This perspective is particularly important in countries experiencing rapid increases in obesity prevalence.

DISCUSIÓN

The present review examined the current evidence regarding the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on heart failure and cardiometabolic risk, highlighting their evolving role within contemporary cardiovascular and metabolic medicine. The findings demonstrate that GLP-1 receptor agonists have progressed beyond their original indication as glucose-lowering agents and now represent an important component of integrated cardiometabolic management. The accumulated evidence supports their capacity to reduce major adverse

cardiovascular events, promote clinically significant weight reduction, improve obesity-related heart failure outcomes, and provide additional cardiorenal benefits in selected patient populations.

One of the most relevant findings identified in this review is the consistency of cardiovascular protection observed across multiple landmark clinical trials. Studies such as LEADER, SUSTAIN-6, REWIND, HARMONY Outcomes, AMPLITUDE-O, and SELECT demonstrated significant reductions in major adverse cardiovascular events among patients receiving GLP-1 receptor agonists (Marso et al., 2016a; Marso et al., 2016b; Gerstein et al., 2019; Hernandez et al., 2018; Gerstein et al., 2021; Lincoff et al., 2023). The reproducibility of these findings across different populations and therapeutic agents strengthens the evidence supporting a class effect for cardiovascular risk reduction. Importantly, these benefits extend beyond glycemic control alone, suggesting that multiple physiological mechanisms contribute to the observed outcomes.

The role of obesity deserves particular attention within the interpretation of these findings. Historically, obesity was frequently considered a secondary cardiovascular risk factor. However, contemporary evidence increasingly recognizes obesity as an independent disease capable of initiating and perpetuating numerous cardiometabolic abnormalities. The substantial weight reduction achieved with GLP-1 receptor agonists appears to influence several pathways involved in cardiovascular disease progression, including insulin resistance, systemic inflammation, endothelial dysfunction, oxidative stress, neurohormonal activation, and adverse cardiac remodeling. Consequently, the cardiovascular benefits observed in recent trials may be partially explained by the ability of these therapies to modify the underlying pathophysiology associated with excess adiposity.

The findings reported in the SELECT trial represent a particularly important contribution to this evolving understanding. The demonstration that semaglutide reduced cardiovascular events among individuals with overweight or obesity in the absence of diabetes challenges traditional paradigms that primarily associate GLP-1 receptor agonists with diabetes management (Lincoff et al., 2023). These results suggest that obesity itself may be an appropriate therapeutic target for cardiovascular prevention and reinforce the concept that cardiometabolic risk extends beyond glucose metabolism. This observation may have profound implications for future cardiovascular prevention strategies, especially in regions experiencing rapid increases in obesity prevalence.

The evidence related to heart failure requires a more nuanced interpretation. Earlier cardiovascular outcome trials generally demonstrated neutral or modest effects on heart failure-related endpoints when compared with the pronounced reductions observed for atherosclerotic cardiovascular outcomes. Nevertheless, more recent investigations focusing specifically on obesity-related heart failure with preserved ejection fraction have generated considerable interest. The STEP-HFpEF and STEP-HFpEF DM studies demonstrated meaningful improvements in symptoms, physical limitations, exercise capacity, and quality of life among patients receiving semaglutide (Kosiborod et al., 2023; Kosiborod et al., 2024). These findings suggest that metabolic interventions may influence important aspects of heart failure pathophysiology, particularly in populations where obesity plays a central role in disease development.

The improvement in patient-centered outcomes observed in these studies deserves special consideration. Traditionally, cardiovascular research has prioritized mortality and hospitalization endpoints. Although these outcomes remain critically important, symptom burden, exercise tolerance, and quality of life represent equally meaningful dimensions from the patient perspective. The improvements observed in obesity-related HFpEF indicate that cardiometabolic therapies may provide benefits that directly affect daily functioning and overall well-being. Such findings support a broader understanding of therapeutic success that incorporates both clinical and patient-reported outcomes.

Another important aspect emerging from the reviewed evidence is the growing recognition of the cardiorenal-metabolic continuum. Cardiovascular disease, chronic kidney disease, obesity, and diabetes are increasingly understood as interconnected disorders sharing common pathophysiological mechanisms. The favorable renal outcomes reported in recent studies, including FLOW, suggest that GLP-1 receptor agonists may influence multiple components of this continuum simultaneously (Perkovic et al., 2024). This integrated perspective aligns with contemporary approaches to chronic disease management and supports the development of therapeutic strategies capable of addressing multiple risk factors through a unified framework.

The findings of this review are particularly relevant for countries throughout the Americas. Mexico, Colombia, and Ecuador have experienced substantial increases in obesity, diabetes, hypertension, and cardiovascular disease during recent decades. Similar trends have been reported across North and South America, reflecting the influence of urbanization, nutritional transitions, reduced physical activity, socioeconomic changes, and population aging. As a result, healthcare systems increasingly confront patients presenting multiple cardiometabolic conditions simultaneously. The multidimensional effects of GLP-1 receptor agonists may therefore offer significant advantages in these settings by addressing several interconnected disease mechanisms through a single therapeutic approach.

Despite the promising evidence, several limitations should be acknowledged. First, most available data originate from randomized controlled trials conducted under highly controlled conditions. Real-world effectiveness may differ due to variations in patient adherence, healthcare access, socioeconomic factors, and treatment availability. Second, not all GLP-1 receptor agonists demonstrate identical efficacy across clinical outcomes, suggesting potential differences among individual agents. Third, long-term evidence extending beyond the duration of current trials remains limited for certain outcomes, particularly regarding heart failure progression and sustained cardiovascular protection.

Economic considerations also represent an important challenge. Although the clinical benefits of GLP-1 receptor agonists are increasingly well established, access remains unequal across many healthcare systems. Cost-related barriers may limit widespread implementation, particularly in low- and middle-income countries. This issue is especially relevant in parts of Latin America, where healthcare resources are often constrained and access to innovative therapies may be restricted. Future studies should therefore examine cost-effectiveness, implementation strategies, and healthcare policy implications to determine how these therapies can be integrated into routine clinical practice.

The present review additionally highlights several priorities for future research. Further investigations are needed to clarify the role of GLP-1 receptor agonists in different heart failure phenotypes, evaluate long-term cardiorenal outcomes, identify predictors of treatment response, and explore their effectiveness in diverse ethnic and socioeconomic populations. Additional real-world studies conducted within Latin American healthcare systems would be particularly valuable, as regional evidence remains relatively limited compared with data originating from North America and Europe.

CONCLUSIÓN

Glucagon-like peptide-1 receptor agonists have emerged as an important therapeutic class within contemporary cardiometabolic medicine, demonstrating benefits that extend well beyond glycemic control. The evidence reviewed indicates that these agents contribute significantly to the reduction of major adverse cardiovascular events,

improvement of metabolic parameters, substantial body weight reduction, and enhancement of clinical outcomes among selected populations with obesity-related heart failure.

The cardiovascular outcome trials analyzed consistently demonstrated that GLP-1 receptor agonists reduce cardiovascular risk among individuals with type 2 diabetes mellitus and established cardiovascular disease. Furthermore, recent studies have shown that these benefits are not limited to diabetic populations, as semaglutide significantly reduced cardiovascular events among overweight and obese individuals without diabetes. These findings reinforce the concept that obesity itself represents a critical therapeutic target within cardiovascular prevention strategies.

The review also highlights the growing relevance of obesity-related heart failure with preserved ejection fraction as a major clinical challenge. Evidence from contemporary investigations indicates that semaglutide improves symptoms, exercise capacity, physical functioning, and health-related quality of life in this patient population. These observations suggest that addressing metabolic dysfunction and excess adiposity may influence important mechanisms involved in heart failure progression and symptom development.

An additional conclusion derived from this review is the recognition of the cardiorenal-metabolic continuum as a fundamental framework for understanding chronic disease interactions. The simultaneous effects of GLP-1 receptor agonists on glycemic control, body weight, blood pressure, inflammation, cardiovascular outcomes, and renal protection support an integrated approach to disease management. Rather than targeting isolated risk factors, these therapies appear capable of modifying multiple interconnected pathways that contribute to cardiometabolic disease progression.

From a regional perspective, the findings are particularly relevant for the Americas. Countries such as Mexico, Colombia, and Ecuador continue to experience increasing prevalence of obesity, diabetes, cardiovascular disease, and heart failure. Consequently, therapeutic strategies capable of addressing multiple cardiometabolic determinants simultaneously may contribute substantially to reducing disease burden and improving long-term health outcomes. The implementation of evidence-based cardiometabolic interventions may therefore represent an important opportunity for strengthening prevention and treatment efforts throughout the region.

Despite the encouraging evidence, important challenges remain. Long-term effectiveness, accessibility, affordability, and implementation within diverse healthcare systems require continued investigation. Additional studies evaluating real-world outcomes and regional populations are necessary to optimize clinical decision-making and facilitate broader application of these therapies.

In conclusion, glucagon-like peptide-1 receptor agonists represent a significant advancement in cardiovascular and metabolic medicine. Their ability to reduce cardiovascular risk, improve obesity-related outcomes, and influence multiple components of the cardiometabolic continuum positions them as valuable therapeutic tools for contemporary clinical practice. As evidence continues to evolve, these agents are expected to play an increasingly important role in the prevention and management of cardiometabolic disease across the Americas and globally.

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