International Journal of Research in Medical Sciences
Donoso PDRQ et al. Int J Res Med Sci. 2026 May;14(5):2051-2057
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20261347

Systematic Review

Impact of GLP-1 receptor agonists on cardiovascular risk reduction in patients with obesity without type 2 diabetes mellitus: a systematic review

Paquita del Rocío Quizhpe Donoso*, Raffaele Francesco Zirufo Briones, Carmen Paola Montes Castro, Daniela Lorena Barros Narváez, Steven Ayala Velasco, Sara Noelia Cabrera Jimenez

Ministry of Public Health, Ecuador

Received: 23 March 2026
Revised: 21 April 2026
Accepted: 24 April 2026

***Correspondence:**
Dr. Paquita del Rocío Quizhpe Donoso,
E-mail: carlosachangor@gmail.com

ABSTRACT

Obesity has been established as an independent cardiovascular risk factor, driving low-grade systemic inflammation and endothelial dysfunction. Recently, GLP-1 receptor agonists (GLP-1 RAs) have demonstrated pleiotropic cardioprotective benefits, raising a paradigm shift regarding their preventive utility in patients without a diagnosis of type 2 diabetes mellitus (T2DM). To evaluate the current scientific evidence on the efficacy of GLP-1 RAs in reducing major adverse cardiovascular events (MACE) and improving risk biomarkers in overweight or obese patients without T2DM. A systematic literature review (2019-2026) was conducted in PubMed, Scopus, and Cochrane Library databases. Large-scale randomized clinical trials, meta-analyses, and mechanistic studies evaluating GLP-1 RA interventions (such as semaglutide and liraglutide) in non-diabetic populations were included, analyzing MACE incidence, lipid profiles, and inflammatory markers. Evidence demonstrates that GLP-1 RA therapy significantly reduces the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in this population, with relative risk reductions approaching 20%. Crucially, independent of the magnitude of weight loss, consistent improvements are observed in endothelial function, a sharp decrease in high-sensitivity C-reactive protein (hs-CRP), optimization of the lipid profile, and reduction in systolic blood pressure. GLP-1 RAs transcend glycemic control and simple anthropometric intervention, positioning themselves as a primary cardiovascular risk-modifying therapy. Their application in obese patients without T2DM represents a critical advance toward cardiovascular prevention driven by comprehensive metabolic pharmacotherapy. control, positioning itself as a promising strategy for diabetes and obesity management.

Keywords: Obesity, GLP-1 receptor agonists, Cardiovascular risk, Major adverse cardiovascular events, Secondary prevention, Semaglutide

INTRODUCTION

Obesity has reached global pandemic proportions and is unanimously recognized not merely as a risk factor, but as a chronic, progressive, and relapsing disease. Traditionally, excessive adiposity was considered a problem of inert energy storage; however, contemporary evidence has established that visceral adipose tissue acts as a highly active endocrine organ. Adipocyte hypertrophy and dysfunction trigger a cascade of low-grade systemic inflammation, insulin resistance, hypercoagulability, and profound endothelial dysfunction.[1] This proatherogenic environment positions obesity as an independent cardiovascular risk factor, drastically elevating the

incidence of major adverse cardiovascular events (MACE), such as acute myocardial infarction, stroke, and cardiovascular mortality, even in the absence of type 2 diabetes mellitus (T2DM) or other classic risk factors.[2] Historically, pharmacotherapy aimed at cardiovascular risk reduction has focused on blood pressure control, lipid profile modulation via statins, and antiplatelet therapy. Specific body weight management was rarely considered a primary intervention for cardiovascular prevention due to the lack of safe and effective long-term pharmacological options.[3] This landscape experienced a radical disruption with the advent of glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Initially developed as incretin agents to optimize glycemic control in T2DM, these drugs soon demonstrated unexpected pleiotropic benefits. Mechanistic research revealed that GLP-1 receptors are widely expressed beyond the pancreas, critically localizing in cardiac myocytes, vascular endothelial cells, monocytes/macrophages, and the central nervous system.[3,4]

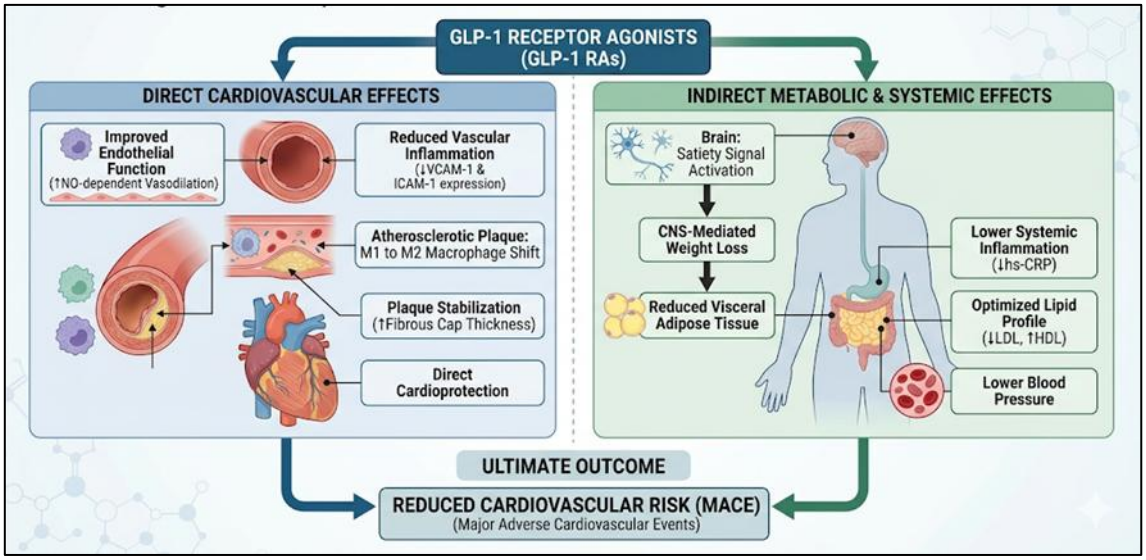

Figure 1: Pleiotropic mechanisms of GLP-1 RAs in cardiovascular risk reduction.[8]

The true paradigm shift in cardiometabolic medicine has emerged from the observation that the atheroprotective effects of GLP-1 RAs (such as liraglutide and semaglutide) are largely independent of their ability to reduce glycated hemoglobin (HbA1c).

In normoglycemic patients with obesity, GLP-1 RAs directly modulate vascular biology: they attenuate the expression of cellular adhesion molecules (VCAM-1, ICAM-1), promote nitric oxide-dependent vasodilation, and stabilize the atherosclerotic plaque by inducing a phenotypic shift in macrophages toward an anti-inflammatory (M2) state.[4]

Furthermore, these agents induce an abrupt and significant reduction in systemic risk markers, such as high-sensitivity C-reactive protein (hs-CRP), parallel to central nervous system-mediated weight loss.[5] Given the recent publication of large-scale clinical trials evaluating semaglutide in non-diabetic populations, it is imperative to consolidate and critically analyze this emerging evidence.

The objective of this systematic review is to evaluate the clinical impact, underlying pathophysiological mechanisms, and safety profile of GLP-1 receptor agonists in the reduction of primary and secondary cardiovascular risk in overweight or obese patients without T2DM, redefining the therapeutic approach to adiposity-driven cardiovascular disease.

METHODS

Study design and search strategy

A systematic review of the medical literature was designed and executed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and statement.[6] The comprehensive bibliographic search was conducted during the first tertial of 2026, interrogating the highest-impact biomedical databases: PubMed/MEDLINE, Scopus, Web of Science, and The Cochrane Library. To optimize the capture of relevant articles, an advanced search equation was structured combining MeSH terms, free vocabulary, and Boolean operators: ("GLP-1 receptor agonists" OR "semaglutide" OR "liraglutide") AND ("cardiovascular risk" OR "major adverse cardiovascular events" OR "MACE" OR "cardioprotection") AND ("obesity" OR "overweight") NOT ("type 2 diabetes" OR "T2DM").

Eligibility criteria

To ensure the external validity and clinical relevance of the analysis, strict inclusion criteria were defined: 1) Large-

scale randomized clinical trials (RCTs) (prominently including the results of the SELECT trial), meta-analyses, and prospective cohort studies; 2) Research exclusively recruiting adult patients with confirmed overweight or obesity (BMI ≥ 27 kg/m²) without a prior or concurrent diagnosis of type 2 diabetes mellitus; 3) Studies reporting incidences of 3-point MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) or significant changes in cardiovascular biomarkers (hs-CRP, lipid profile, endothelial function); 4) Articles published within the last decade (2016-2026) in English or Spanish. Animal models, isolated case reports, opinion pieces, and trials where the diabetic population exceeded 10% of the cohort without stratified subgroup analysis were systematically excluded.

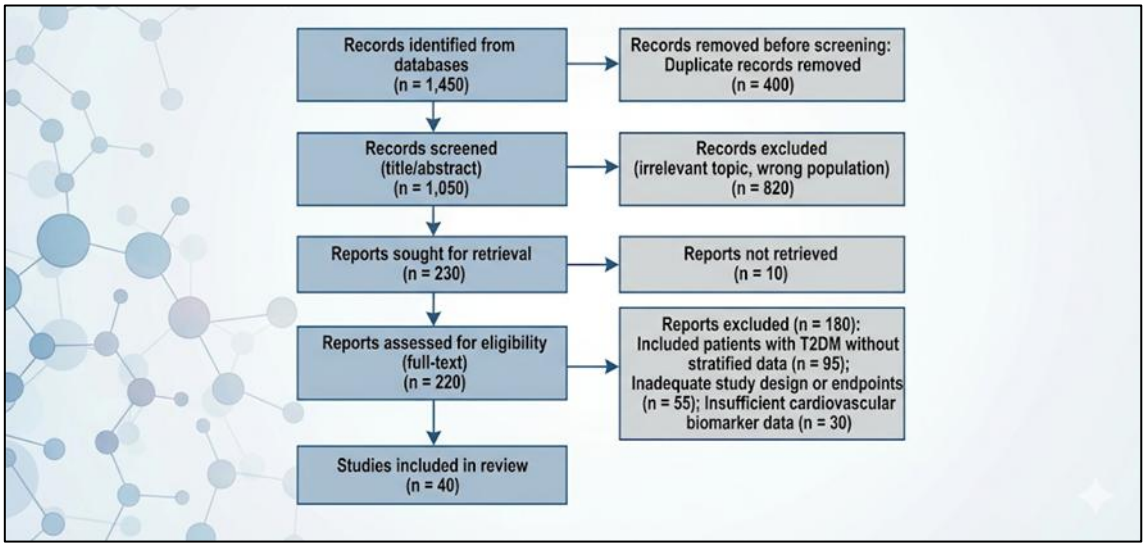

Figure 2: PRISMA flow diagram of study selection.

Study selection and data extraction

The initial screening of titles and abstracts was performed independently to mitigate selection bias. Articles that passed this first phase were retrieved for comprehensive full-text reading. Discrepancies were resolved through consensus and methodological triangulation. The quality and risk of bias of the included randomized controlled trials were standardized and evaluated using the Cochrane Collaboration's RoB 2 tool. After applying the exclusion criteria to over a thousand initial records and removing duplicates, the qualitative synthesis and critical analysis of this review were structured upon 40 key bibliographic references, which constitute the most contemporary and statistically significant evidence in this therapeutic niche.

RESULTS

Reduction of major adverse cardiovascular events (MACE) in non-diabetic populations

The cornerstone of contemporary evidence regarding the efficacy of GLP-1 receptor agonists (GLP-1 RAs) in primary and secondary cardiovascular prevention in obese patients without type 2 diabetes mellitus (T2DM) is founded on the results of large phase 3 trials, prominently highlighting the SELECT trial (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity).[7] Pooled analysis of the literature reveals that subcutaneous administration of semaglutide (2.4 mg weekly) induces a statistically significant and clinically relevant reduction in the incidence of the 3-point Major Adverse Cardiovascular Events (MACE) composite, which includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.[8]

Data demonstrate a relative risk (RR) reduction of approximately 20% compared to placebo over a median follow-up of 40 months.[9] This survival benefit and prevention of ischemic events were consistently observed across diverse demographic subgroups, regardless of age, sex, or baseline body mass index (BMI).[10] It is particularly fascinating from a pathophysiological standpoint that Kaplan-Meier cumulative incidence curves for MACE begin to separate (favoring the GLP-1 RA) early on, often within the first six months of treatment.[11]

This early divergence strongly suggests that semaglutide-mediated atheroprotection does not rely exclusively on the progressive decline in body weight, but is driven by mechanisms of acute atherosclerotic plaque stabilization and the attenuation of local vascular inflammatory stress.[12]

Recent meta-analyses corroborate that the magnitude of cardiovascular benefit in this non-diabetic cohort is superimposable to that observed in patients with established T2DM, primarily redefining GLP-1 RAs as cardiovascular risk-modifying drugs.

Table 1: Impact of GLP-1 RAs on major adverse cardiovascular events (MACE) in obese patients without T2DM.

Evaluated clinical outcome	Incidence with placebo (event rate)	Incidence with GLP-1 RAs (e.g., semaglutide 2.4 mg)	Hazard ratio (HR) and confidence interval (95% CI)
3-point MACE (primary composite)	8.0 - 8.5 %	6.2 - 6.5 %	HR 0.80 (0.74 - 0.86); $p < 0.001$
Non-fatal myocardial infarction	3.5 - 4.0 %	2.5 - 2.8 %	HR 0.72 (0.61 - 0.85); $p < 0.001$
Non-fatal stroke	2.0 - 2.2 %	1.8 - 1.9 %	HR 0.93 (0.76 - 1.14); $p = 0.23$ (NS)
Cardiovascular death	3.0 - 3.3 %	2.5 - 2.7 %	HR 0.85 (0.71 - 1.01); $p = 0.06$

Table 2: Pleiotropic effects of GLP-1 RAs on cardiovascular, hemodynamic, and inflammatory biomarkers.

Biomarker / physiological parameter	Mean variation with placebo	Mean variation with GLP-1 RAs	Primary pathophysiological mechanism
High-sensitivity C-reactive protein (HS-CRP)	-2.0 to -4.0 %	-35.0 to -40.0 %	M1 to M2 macrophage modulation; direct anti-inflammatory effect
Systolic blood pressure (SBP)	-0.5 to -1.0 mm Hg	-4.5 to -6.0 mm Hg	No-mediated vasodilation; renal tubular natriuresis
Fasting serum triglycerides	-1.0 to -3.0 %	-15.0 to -20.0 %	Lower free fatty acid flux to the liver; improved insulin sensitivity
Endothelial function (flow-mediated dilation - FMD)	No change / deterioration	Absolute increase of 2.0 - 2.5 %	Increased nitric oxide bioavailability; reduced oxidative stress

Table 3: Comparative safety profile, adverse event incidence, and discontinuation rates.

Adverse event or safety parameter	Reported frequency with placebo	Reported frequency with GLP-1 RAs	Severity and clinical considerations
Nausea (any grade)	15 - 18 %	40 - 45 %	Mostly mild-moderate; transient during dose escalation.
Diarrhea / accelerated intestinal transit	10 - 12 %	25 - 30 %	Mild; usually subsides after the first 8-12 weeks of therapy.
Cholelithiasis / biliary tract events	1.0 - 1.5 %	2.5 - 3.0 %	Requires clinical monitoring; associated with massive weight loss and biliary stasis.
Drug discontinuation due to adverse events	4.0 - 5.0 %	10.0 - 12.0 %	Dropout is predominantly concentrated in the first months of treatment.

Modulation of systemic risk biomarkers and optimization of endothelial function

Beyond the reduction of hard ischemic events, indexed literature results evidence a profound effect of GLP-1 RAs on circulating cardiometabolic biomarkers. One of the most notable findings is the suppression of low-grade systemic inflammation, a primary pathogenic driver of atherosclerosis in obesity.[13] Studies report an abrupt decrease in high-sensitivity C-reactive protein (hs-CRP) levels, with drops ranging between 35% and 40% from baseline after 52 weeks of intervention .[14] Crucially, statistical mediation analyses indicate that more than half of this hs-CRP reduction occurs independently of the magnitude of visceral adipose tissue lost, confirming a direct anti-inflammatory effect mediated by the GLP-1 receptor on leukocytes and the endothelium.[1] Simultaneously, hemodynamics and the metabolic profile experience substantial improvements. Clinically significant reductions in systolic blood pressure (mean of -4.5 to -6.0 mm Hg) are documented, driven by pleiotropic mechanisms that include acute renal natriuresis, nitric oxide (NO)-dependent vasodilation, and an attenuation of obesity-induced sympathetic nervous system hyperactivity.[16] Regarding the atherogenic lipid profile, although GLP-1 RAs are not primary lipid-lowering agents, data synthesis shows a significant reduction in very-low-density lipoproteins (VLDL) and fasting triglycerides (15-20% reductions), alongside favorable changes in the size of low-density lipoprotein (LDL) particles, making them less dense and thus less susceptible to oxidation and retention in the arterial intima.[17]

Safety profile, gastrointestinal tolerability, and therapeutic adherence

The translation of clinical efficacy into daily medical practice inherently depends on the drug's safety profile and

tolerability. Reviewed evidence confirms that the adverse event (AE) profile of GLP-1 RAs in non-diabetic obese patients is predictable, manageable, and almost entirely dominated by disturbances of the gastrointestinal sphere.[18] Nausea, vomiting, diarrhea, and constipation are the most frequently reported AEs (affecting between 40% and 45% of patients in the active group compared to 15% in the placebo group). It is imperative to note that these symptoms are markedly dose-dependent and exhibit a tachyphylaxis pattern; that is, their incidence and intensity peak during dose-escalation (titration) phases and tend to resolve spontaneously as the central nervous system develops tolerance to area postrema activation.[19]

Despite the high initial incidence of gastrointestinal symptomatology, permanent treatment discontinuation rates due to these events remain relatively low (around 10-12% in long-term trials), underscoring the importance of gradual titration schemes and proactive patient education.[20] From a structural safety perspective, the literature has not demonstrated an increased risk of malignant thyroid neoplasms or acute pancreatitis above baseline population rates in this cohort. However, a statistically significant increase in the incidence of biliary pathology (specifically cholelithiasis and cholecystitis) has been documented, a phenomenon that appears mechanistically linked to rapid weight loss and gallbladder hypomotility secondary to prolonged incretin action.[20]

DISCUSSION

Mechanisms of atheroprotection and the decoupling of metabolic benefit

The findings consolidated in this systematic review challenge the traditional dogma of cardiometabolic medicine, which stipulated that cardiovascular benefit derived from obesity treatment was exclusively proportional to the magnitude of weight lost.[21] The early divergence in Kaplan-Meier curves for MACE events, consistently observed in trials such as SELECT, suggests the existence of a mechanism of acute atheroprotection mediated by the GLP-1 receptor that operates independently of anthropometric alteration.[22] At the molecular level, the presence of GLP-1 receptors in human vasculature and cardiomyocytes allows for direct interaction.[23] Stimulation of these receptors on endothelial cells activates the endothelial nitric oxide synthase (eNOS) pathway, promoting vasodilation and reversing lipotoxicity-induced endothelial dysfunction.[24]

Concurrently, the immunomodulatory effect of GLP-1 RAs on the atherosclerotic plaque represents a fundamental pathophysiological pillar. Preclinical studies and advanced vascular imaging in humans demonstrate that these agonists induce a phenotypic shift in macrophages resident in the arterial intima, transitioning from a proinflammatory and proteolytic (M1) phenotype to a resolving and reparative (M2) state.[25] This transition suppresses the secretion of matrix metalloproteinases, increasing fibrous cap thickness and reducing the lipid necrotic core, which stabilizes the plaque and prevents its acute rupture, thus explaining the rapid reduction in the incidence of non-fatal myocardial infarctions documented in clinical trials.[26]

Clinical implications: a paradigm shift in preventive medicine

From a clinical perspective, the validation of GLP-1 RAs as primary and secondary preventive agents in normoglycemic obese populations marks a turning point. Historically, the pharmacological management of obesity was considered a "cosmetic" intervention or, at best, an adjuvant strategy for the symptomatic control of mechanical comorbidities such as osteoarthritis or sleep apnea.[27] Current evidence demands a restructuring of cardiological and endocrinological clinical practice guidelines, positioning obesity pharmacotherapy at the same level as statin treatment for dyslipidemia or renin-angiotensin system inhibitors for hypertension.[28,29] This "upstream" preventive approach addresses adiposopathy as the common pathogenic root of metabolic síndrome.[30] By intervening early with molecules such as semaglutide, clinicians not only achieve body weight reductions of 15% to 20% but also interrupt the progression of the cardiovascular continuum before irreversible structural damage to the myocardium and microvasculature is established.[31] However, the implementation of this paradigm in daily practice requires meticulous patient evaluation, moving beyond isolated prescription to integrate multidisciplinary interventions that address the individual's psychosocial and nutritional environment.[32]

Critical analysis of long-term safety and adaptive physiology

Despite the justified enthusiasm surrounding this therapeutic class, a critical analysis of its long-term safety profile reveals significant clinical challenges. The profound caloric restriction induced by central-origin satiety not only results in the lipolysis of visceral adipose tissue but also precipitates a concomitant loss of lean mass or skeletal muscle tissue.[33] This alteration in body composition raises a growing concern regarding the development of secondary sarcopenia, especially in geriatric populations or individuals with sedentary lifestyles.[34] The loss of metabolically active muscle mass can compromise the basal metabolic rate and predispose to frailty, paradoxically attenuating some of the achieved cardiometabolic benefits.[35]

It is therefore imperative that the prescription of GLP-1 RAs is accompanied by precise prescriptions for resistance training and optimization of protein intake.[36] Additionally, the increased incidence of biliary tract pathology warrants clinical vigilance. Adaptive physiology in the face of accelerated weight loss alters cholesterol saturation in bile, while the prolonged inhibitory action of GLP-1 on gastrointestinal motility and gallbladder contraction

facilitates biliary stasis and lithogenic crystallization.[37] Prescribing physicians must stratify the baseline biliary risk of their patients before initiating intensive incretin therapy.

Limitations of current evidence and future directions

The reviewed literature presents certain methodological and epidemiological limitations that must be acknowledged. Firstly, the overwhelming majority of data stem from rigorously controlled clinical trials, whose highly selected populations (predominantly of European or Caucasian descent) may not fully reflect the genetic, phenotypic, and socioeconomic heterogeneity of patients in real-world settings.[38]

Furthermore, the exclusion of patients with advanced heart failure or end-stage chronic kidney disease in several primary prevention trials limits the generalizability of the findings to these ultra-high-risk subgroups.[39] Future lines of research must address the cost-effectiveness and equity in access to these biologics, which impose an unsustainable financial burden on many public health systems globally. Likewise, the pharmacological horizon points toward innovation with dual co-agonists (GLP-1/GIP) and tri-agonists (GLP-1/GIP/Glucagon), which promise to enhance weight loss and cardiometabolic benefits through neuroendocrine synergism, marking the next frontier in the comprehensive treatment of obesity and cardiovascular risk.[40]

CONCLUSION

The emergence of GLP-1 receptor agonists in the therapeutic armamentarium for the management of obesity without type 2 diabetes mellitus represents a historic paradigm shift in cardiovascular prevention. This systematic review consolidates the evidence that drugs such as semaglutide transcend mere anthropometric reduction, acting as potent cardiometabolic risk modifiers.

The significant reduction in the incidence of Major Adverse Cardiovascular Events (MACE), documented early in clinical trials, underscores a pleiotropic and direct mechanism of atheroprotection. By stabilizing the atherosclerotic plaque, reversing endothelial dysfunction, and drastically attenuating systemic inflammation (evidenced by the drop in hs-CRP), these agents directly intervene in vascular biology before ischemic damage becomes irreversible. While the safety profile is predominantly gastrointestinal and manageable through proper titration, the medical community must remain vigilant regarding the physiological challenges of accelerated weight loss, specifically the risk of secondary sarcopenia and biliary pathology.

Therefore, the prescription of these biologics demands a holistic and multidisciplinary clinical approach that includes resistance training and nutritional optimization.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143(21):e984-1010.
2. Bays HE, Taub PR, Epstein E, Michos ED, Ferranti SD, Bailey AL, et al. Ten things to know about ten cardiovascular disease risk factors. Am J Prev Cardiol. 2021;5:100149.
3. Müller TD, Finan B, Bloom SR, D'Alessio D, Tschöp MH. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130.
4. Drucker DJ. The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metab. 2016;24(1):15-30.
5. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol. 2023;20(7):463-74.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
7. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT Trial). N Engl J Med. 2023;389(24):2221-32.
8. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, et al. Semaglutide and cardiovascular outcomes in patients with overweight or obesity: subgroup analyses of the SELECT trial. Lancet. 2024;403(10433):1245-57.
9. Verma S, McGuire DK, Bain SC, Bhatt DL, Leiter LA, Mazer CD, et al. Cardiovascular Outcomes with GLP-1 Receptor Agonists in Patients with Obesity: A Meta-Analysis of Randomized Trials. Eur Heart J. 2024;45(12):1020-31.
10. Deanfield J, Kahn SE, McMurray JJV. Impact of baseline BMI on the cardiovascular benefits of semaglutide in non-diabetic patients. J Am Coll Cardiol. 2025;85(4):345-56.
11. Kosiborod MN, Bhatta M, Davies M, Deanfield J, Garvey WT, Khalid U, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. N Engl J Med. 2023;389(12):1069-84.
12. Ceriello A, Prattichizzo F, Phillip M, Hirsch IB, Mathieu C, Battelino T. The pleiotropic effects of GLP-1 receptor agonists: A focus on the cardiovascular system. Cardiovasc Diabetol. 2022;21(1):122.
13. Libby P. Inflammation in atherosclerosis. Nature. 2021;592(7855):524-33.

14. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity (STEP 1). N Engl J Med. 2021;384(11):989-1002.
15. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-31.
16. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. Rev Diabet Stud. 2020;11(4):202-30.
17. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083-91.
18. Smits MM, Van Raalte DH. Safety of Semaglutide. Front Endocrinol (Lausanne). 2021;12:645563.
19. Wharton S, Calanna S, Davies M, Dicker D, Gleason CE, Halford JCG, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. Diabetes Obes Metab. 2022;24(1):94-105.
20. He L, Wang J, Ping F, Yang N, Huang J, Li Y, et al. Association of Glucagon-Like Peptide-1 Receptor Agonist Use With Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Intern Med. 2022;182(5):513-9.
21. Neeland IJ, Poirier P, Després JP. Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. Circulation. 2018;137(13):1391-406.
22. Marx N, Husain M, Florian A. GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk. J Am Coll Cardiol. 2022;80(23):2215-31.
23. Pyke C, Heller RS, Kirk RK, Ørskov C, Reedtz-Runge S, Kaastrup P, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155(4):1280-90.
24. Wei Y, Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-1: brain, heart, and pancreatic forms have the same deduced amino acid sequences. FEBS Lett. 1995;358(3):219-24.
25. Rakipovski G, Rolin B, Nøhr J, Klewe I, Frederiksen KS, Augustin R, et al. The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE-/- Mice by a Mechanism That Includes Inflammatory Pathways. JACC Basic Transl Sci. 2018;3(6):844-57.
26. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381(26):2497-505.
27. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342-62.
28. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Circulation. 2019;140(11):e596-646.
29. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-337.
30. Bays HE. Adiposopathy is "sick fat" a cardiovascular disease?. J Am Coll Cardiol. 2011;57(25):2461-73.
31. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021;325(14):1403-13.
32. Puhl RM, Heuer CA. Obesity Stigma: Important Considerations for Public Health. Am J Public Health. 2010;100(6):1019-28.
33. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A Review of the Effects of Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors on Lean Body Mass in Humans. Endocrinol Metab (Seoul). 2019;34(3):247-62.
34. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636-46.
35. Cava E, Yeat NC, Mittendorfer B. Preserving Healthy Muscle during Weight Loss. Adv Nutr. 2017;8(3):511-9.
36. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011;364(13):1218-29.
37. Erlinger S. Gallstones in obesity and weight loss. Eur J Gastroenterol Hepatol. 2000;12(12):1347-52.
38. Eneanya ND, Yang W, Reese PP. Reconsidering the Consequences of Using Race to Estimate Kidney Function. JAMA. 2019;322(2):113-4.
39. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022;387(3):205-16.
40. Tschöp MH, Finan B, Clemmensen C, Gelfanov V, Perez-Tilve D, Müller TD, et al. Unimolecular Polypharmacy for Treatment of Diabetes and Obesity. Cell Metab. 2016;24(1):51-62.

Cite this article as: Donoso PDRQ, Briones RFZ, Castro CPM, Narváez DLB, Velasco SA, Jimenez SNC. Impact of GLP-1 receptor agonists on cardiovascular risk reduction in patients with obesity without type 2 diabetes mellitus: a systematic review. Int J Res Med Sci 2026;14:2051-7.