WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 12, 161-174. Review Article ISSN 2277–7105

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN THE MANAGEMENT OF OBESITY AND TYPE 2 DIABETES MELLITUS: A COMPREHENSIVE COMPARATIVE REVIEW OF CLINICAL EVIDENCE

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Article Received on 11 April 2026,
Article Revised on 01 May 2026,
Article Published on 16 June 2026,
https://doi.org/10.5281/zenodo.20679044

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How to cite this Article: K.V. Shanmukhi Saisree*. (2026). Glucagon-Like Peptide-1 Receptor Agonists In The Management of Obesity and Type 2 Diabetes Mellitus: A Comprehensive Comparative Review of Clinical Evidence. World Journal of Pharmaceutical Research, 15(12), 161–174.

ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a transformative pharmacological class simultaneously addressing two major global health burdens: type 2 diabetes mellitus (T2DM) and obesity. This review synthesizes and compares clinical evidence from randomized controlled trials, systematic reviews, meta-analyses, and cardiovascular outcome trials published between 2015 and 2025. **Methods:** A structured narrative review was conducted drawing on evidence from at least 15 peer-reviewed publications, including landmark trials (LEADER, SUSTAIN-6, PIONEER-6, REWIND, SELECT, and SURPASS-CVOT) and recent meta-analyses. Outcomes assessed included HbA1c reduction, body weight loss, BMI change, cardiovascular outcomes, and safety profiles. **Results:** GLP-1 RAs demonstrate clinically meaningful HbA1c reductions ranging from 0.8% to 2.4% and body weight reductions of 1 kg to over 22% across agents and indications. Tirzepatide—a dual GIP/GLP-1 receptor co-agonist—consistently demonstrates the greatest metabolic efficacy. Semaglutide carries the most robust cardiovascular outcome data, including demonstrated superiority in the SELECT trial among non-diabetic obese individuals. **Conclusion:** The GLP-1 RA class offers individualized, evidence-based therapeutic options for patients with T2DM, obesity, or both. Clinical decision-making should incorporate glycemic burden, degree of obesity, cardiovascular risk, tolerability, and route of administration preference.

KEYWORDS: GLP-1 receptor agonists, semaglutide, liraglutide, tirzepatide, dulaglutide, exenatide, obesity, type 2 diabetes mellitus, HbA1c, cardiovascular outcomes, weight loss.

1. INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are among the most prevalent non-communicable diseases of the twenty-first century, representing intertwined global health crises. Excess adiposity promotes insulin resistance, beta-cell dysfunction, systemic inflammation, and cardiovascular risk — pathological mechanisms that collectively underlie the transition from metabolic health to overt T2DM and its downstream complications. As of recent estimates, over 537 million adults live with diabetes globally, while obesity rates continue to rise across all age groups and regions.

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by L-cells of the distal intestine in response to nutrient ingestion. Its physiological actions include glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delay of gastric emptying, promotion of satiety via central nervous system pathways, and reduction of food intake. These properties make the GLP-1 receptor an attractive pharmacological target for the treatment of both T2DM and obesity.

GLP-1 receptor agonists (GLP-1 RAs) are exogenous peptide analogs or small-molecule activators designed to mimic or enhance native GLP-1 activity with extended pharmacokinetic profiles. Since the approval of exenatide (Byetta) in 2005, the class has expanded to include liraglutide, albiglutide, dulaglutide, semaglutide (subcutaneous, oral, and high-dose formulations), lixisenatide, and the dual GIP/GLP-1 co-agonist tirzepatide.

Beyond glycemic control, pivotal cardiovascular outcome trials (CVOTs) have demonstrated that select GLP-1 RAs reduce major adverse cardiovascular events (MACE) in high-risk populations, fundamentally reshaping guideline-directed management of T2DM. The SELECT trial further demonstrated cardiovascular superiority of semaglutide in obese individuals without diabetes, broadening clinical utility of the class considerably.

This review provides a comprehensive, evidence-based comparison of GLP-1 RA agents, synthesizing data from pivotal trials, head-to-head studies, meta-analyses, and real-world evidence to inform clinical decision-making in obesity and T2DM management.

2. MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONISTS

2.1 Pancreatic Effects

Upon binding to the GLP-1 receptor — a G-protein coupled receptor — GLP-1 RAs activate adenylate cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP) and stimulating insulin secretion in a glucose-dependent manner. This glucose-dependency is a critical safety feature, markedly reducing hypoglycemia risk compared with sulfonylureas or insulin. Simultaneously, GLP-1 RAs suppress glucagon secretion from pancreatic alpha cells, particularly in the postprandial state, attenuating hepatic glucose production.

2.2 Gastrointestinal and Appetite Regulation

GLP-1 RAs decelerate gastric emptying, contributing to both postprandial glycemia attenuation and early satiety. Centrally, GLP-1 receptors in the hypothalamus, brainstem, and mesolimbic reward circuitry mediate reductions in appetite, food reward signaling, and caloric intake. These central effects are considered the principal mechanism underlying clinically relevant weight loss observed with higher-dose formulations such as semaglutide 2.4 mg and tirzepatide.

2.3 Cardiovascular and Renal Effects

GLP-1 receptors are expressed in cardiac myocytes, vascular endothelium, and smooth muscle cells. GLP-1 RAs exert direct cardioprotective effects through anti-inflammatory, anti-atherogenic, and endothelial-protective mechanisms, along with indirect benefits via weight reduction, blood pressure lowering, and lipid profile improvement. Renal benefits include reduction in albuminuria and attenuation of glomerular hyperfiltration through hemodynamic and direct tubular mechanisms.

3. PHARMACOLOGICAL PROFILES OF APPROVED GLP-1 RECEPTOR AGONISTS

3.1 Short-Acting Agents

3.1.1 Exenatide Immediate-Release (Byetta)

Exenatide, a synthetic analog of exendin-4 derived from Gila monster venom, was the first FDA-approved GLP-1 RA (2005). Administered subcutaneously twice daily, it achieves modest HbA1c reductions of approximately 0.8–1.0% and weight losses of 1–3 kg, primarily targeting postprandial glycemia through gastric emptying delay. Meta-analysis of head-to-head trials reported a mean weight loss of only 1.9 kg, placing it among the less potent agents for obesity management.

3.1.2 Lixisenatide

Lixisenatide (Adlyxin) is a once-daily GLP-1 RA approved for T2DM adjunct therapy. The ELIXA cardiovascular outcome trial demonstrated cardiovascular non-inferiority against placebo (HR 1.02) without superiority. Its primary niche is postprandial glycemic management, particularly in fixed-ratio combination with insulin glargine (iGlarLixi).

3.2 Long-Acting Weekly Agents

3.2.1 Exenatide Extended-Release (Bydureon)

The once-weekly microsphere formulation provides more stable plasma concentrations, improved HbA1c reduction (approximately 1.0–1.5%), and modest weight loss (2–4 kg). The EXSCEL trial (n=14,752) confirmed cardiovascular non-inferiority (HR 0.91) but failed to demonstrate superiority, limiting cardiovascular indication. Its use has declined with more efficacious weekly agents available.

3.2.2 Albiglutide (Tanzeum)

A once-weekly albumin-fused GLP-1 RA with a half-life of approximately 5 days. Despite cardiovascular superiority demonstrated in HARMONY Outcomes (HR 0.78), albiglutide was voluntarily withdrawn from the market for commercial reasons. Limited weight loss compared with other weekly agents likely reflects reduced CNS penetration due to its larger molecular size.

3.2.3 Dulaglutide (Trulicity)

Dulaglutide consists of two GLP-1 analogs fused to an immunoglobulin Fc fragment, providing a half-life of approximately 5 days and once-weekly administration at doses of 0.75–4.5 mg. AWARD program trials demonstrated HbA1c reductions of 1.1–1.6% and weight losses of 2–4 kg. The REWIND trial (n=9,901) — notably the first CVOT with a primary prevention population — demonstrated cardiovascular superiority (HR 0.88, 12% relative MACE reduction). Meta-analysis confirmed dulaglutide, liraglutide, and semaglutide are significantly associated with reduced macroalbuminuria.

3.3 Liraglutide (Victoza / Saxenda)

A once-daily human GLP-1 analog with a fatty acid modification providing a half-life of approximately 13 hours. At 1.8 mg/day for T2DM, it reduces HbA1c by 1.1–1.6% and body weight by 3–5 kg. At 3.0 mg/day (Saxenda), approved for chronic weight management, it produces mean weight reductions of 8–9 kg in non-diabetic obese individuals. The LEADER

trial (n=9,340) demonstrated a 13% relative reduction in 3P-MACE (HR 0.87, p<0.001), establishing liraglutide as the first GLP-1 RA with FDA cardiovascular risk reduction indication. Importantly, liraglutide was associated with worsened heart failure outcomes in diabetic patients with reduced ejection fraction — an important contrast to semaglutide.

3.4 Semaglutide (Ozempic, Wegovy, Rybelsus)

Semaglutide represents a generational advance in GLP-1 RA pharmacology. A C18 fatty diacid moiety facilitating reversible albumin binding extends its half-life to approximately 7 days, supporting once-weekly dosing. Three formulations are currently approved:

Subcutaneous semaglutide (Ozempic, 0.5–2 mg QW): For T2DM. SUSTAIN program trials demonstrated HbA1c reductions of 1.5–2.2% and weight losses of 4–6 kg. In SUSTAIN-6 (n=3,297), it achieved a 26% reduction in MACE (HR 0.74, p<0.001), primarily driven by a 39% reduction in non-fatal stroke — the most prominent stroke benefit across GLP-1 RA CVOTs.

Oral semaglutide (Rybelsus, 3–14 mg QD): The first oral GLP-1 RA utilizing an absorption enhancer (SNAC). At 14 mg, it reduces HbA1c by approximately 1.2–1.4% and body weight by 3–5 kg. PIONEER-6 demonstrated non-inferiority (HR 0.79), with a nominally significant 51% reduction in cardiovascular death and 49% reduction in all-cause mortality.

High-dose semaglutide (Wegovy, 2.4 mg QW): Approved for chronic weight management. STEP program demonstrated mean weight reductions of approximately 15% of body weight. The SELECT trial (n=17,604) demonstrated a 20% relative MACE reduction (HR 0.80, p<0.001) in non-diabetic obese individuals with established CVD — the first cardiovascular superiority evidence for any anti-obesity medication in a non-diabetic population.

3.5 Tirzepatide (Mounjaro / Zepbound)

Tirzepatide is a novel dual GIP and GLP-1 receptor co-agonist — the first of its class. By simultaneously activating both incretin receptors, it demonstrates synergistic metabolic effects exceeding selective GLP-1 RAs. In SURPASS-2, tirzepatide (15 mg) achieved HbA1c reductions of 2.30% and weight losses of 11.2 kg, significantly superior to semaglutide 1 mg. For obesity, SURMOUNT-1 demonstrated mean weight reductions of 15–22.5% at 72 weeks — the largest reported in any pharmaceutical obesity trial. SURPASS-CVOT confirmed cardiovascular non-inferiority versus dulaglutide with superior cardiometabolic risk factor

improvements.

4. COMPARATIVE EFFICACY SUMMARY

Table 1 provides a structured comparison of approved GLP-1 RA agents across key clinical parameters.

Table 1: Comparative Overview of Approved GLP-1 Receptor Agonist Agents.

Agent	Brand	Dosing	Route	HbA1c Reduction	Weight Loss	CV Indication
Exenatide IR	Byetta	5–10 mcg BID	SC	~0.8–1.0%	~1–3 kg	No
Exenatide ER	Bydureon	2 mg QW	SC	~1.0–1.5%	~2–4 kg	No
Liraglutide	Victoza/Saxenda	1.8 mg QD (T2D); 3 mg QD (obesity)	SC	~1.1–1.6%	3–5 kg (T2D); 8–9 kg (obesity)	Yes (LEADER)
Albiglutide	Tanzeum	30–50 mg QW	SC	~0.9–1.0%	~0.5–1 kg	Yes (HARMONY)
Dulaglutide	Trulicity	0.75–4.5 mg QW	SC	~1.1–1.6%	~2–4 kg	Yes (REWIND)
Semaglutide SC	Ozempic	0.5–2 mg QW	SC	~1.5–2.2%	5–6 kg (T2D); ~15% BW	Yes (SUSTAIN-6)
Semaglutide Oral	Rybelsus	3–14 mg QD	Oral	~1.2–1.4%	~3–5 kg	Yes (PIONEER 6)
Semaglutide 2.4 mg	Wegovy	2.4 mg QW	SC	N/A	~15% BW	Yes (SELECT)
Tirzepatide	Mounjaro/Zepbound	5–15 mg QW	SC	~1.8–2.4%	15–22% BW	Yes (SURPASS-CVOT)

SC = subcutaneous; QD = once daily; QW = once weekly; BID = twice daily; BW = body weight; CV = cardiovascular.

5. COMPARATIVE GLYCEMIC EFFICACY

5.1 HbA1c Reduction

A systematic review and meta-analysis comprising 16 studies and 5,997 patients found that semaglutide achieved significantly greater HbA1c reduction compared with liraglutide (difference 0.56%, 95% CI: 0.19–0.94; $p<0.001$) and dulaglutide (difference 3.72 units; $p=0.05$). Tirzepatide demonstrated a notable advantage over semaglutide in HbA1c reduction (difference −0.45%, 95% CI: −0.88 to −0.02; $p=0.04$), consistent with its dual incretin mechanism. Among obese T2DM patients on metformin, GLP-1 RAs achieved significantly

greater HbA1c reduction compared with SGLT-2 inhibitors (difference −0.40%, 95% CI: −0.54 to −0.25; p<0.00001).

5.2 Fasting and Postprandial Glycemia

Short-acting agents (exenatide IR, lixisenatide) primarily reduce postprandial glucose excursions through pronounced gastric-emptying delay, while longer-acting weekly agents provide more balanced effects on fasting and postprandial glucose. This distinction is clinically relevant when selecting agents for patients with predominant fasting versus postprandial hyperglycemia. Combining short-acting agents with basal insulin leverages complementary mechanisms targeting both components of hyperglycemia.

6. WEIGHT MANAGEMENT EFFICACY

6.1 Weight Loss in Type 2 Diabetes

A systematic review encompassing 22 RCTs and 41,757 participants found weight loss substantially attenuated in T2DM patients versus non-diabetic obese individuals. The rank order of weight loss in T2DM patients was: tirzepatide > semaglutide > dulaglutide > liraglutide > exenatide. A meta-analysis reported mean weight losses: semaglutide 4.81 kg, dulaglutide 4.03 kg, liraglutide 2.81 kg, exenatide 1.9 kg, and tirzepatide approximately 9.7 kg. Tirzepatide produced significantly greater weight loss than semaglutide 1 mg (difference −3.78 kg, 95% CI: −5.52 to −2.04).

6.2 Weight Loss in Obesity Without Diabetes

GLP-1 RA-mediated weight loss is substantially greater in non-diabetic obese individuals. Liraglutide 3 mg demonstrated mean weight reductions of approximately 8–9 kg at 56 weeks. High-dose semaglutide (Wegovy 2.4 mg) in STEP-1 achieved a mean weight reduction of 14.9% of body weight at 68 weeks. Tirzepatide's SURMOUNT-1 demonstrated weight reductions of 15.0% (5 mg), 19.5% (10 mg), and 20.9% (15 mg) at 72 weeks, with approximately 37% of participants at the highest dose achieving at least 25% weight loss.

6.3 Mechanisms Underlying Weight Loss Differences

Tirzepatide's quantitative superiority reflects dual GIP/GLP-1 co-agonism engaging complementary central and peripheral pathways regulating appetite and energy expenditure. The GIP receptor, expressed in adipose tissue and the CNS, may contribute to enhanced lipid partitioning and thermogenesis beyond GLP-1-mediated anorexigenic effects. Higher-dose semaglutide formulations achieve greater CNS receptor occupancy than lower doses used in

T2DM trials, explaining dose-dependent weight differences.

7. CARDIOVASCULAR OUTCOMES: EVIDENCE FROM PIVOTAL TRIALS

7.1 Overview of CVOTs

Cardiovascular outcome trials (CVOTs) were mandated by the FDA in 2008 following concerns about cardiovascular safety of antidiabetic agents. Across completed GLP-1 RA CVOTs, a class effect toward cardiovascular benefit has emerged for longer-acting agents, while shorter-acting agents demonstrate cardiovascular neutrality. Table 2 summarizes key CVOT results.

Table 2: Summary of Major Cardiovascular Outcome Trials for GLP-1 Receptor Agonists.

Trial	Drug	Year	n	Primary Endpoint	Key Result
ELIXA	Lixisenatide	2015	6,068	4P-MACE	Non-inferior; HR 1.02 — neutral CV effect
LEADER	Liraglutide	2016	9,340	3P-MACE	Superior; HR 0.87 — 13% relative MACE reduction
SUSTAIN-6	Semaglutide SC	2016	3,297	3P-MACE	Superior; HR 0.74 — 26% reduction; 39% stroke reduction
EXSCEL	Exenatide ER	2017	14,752	3P-MACE	Non-inferior; HR 0.91; p=0.06 for superiority
REWIND	Dulaglutide	2019	9,901	3P-MACE	Superior; HR 0.88 — 12% reduction; primary prevention
PIONEER 6	Semaglutide Oral	2019	3,183	3P-MACE	Non-inferior; HR 0.79; 51% reduction in CV death
SELECT	Semaglutide 2.4 mg	2023	17,604	3P-MACE	Superior; HR 0.80 — 20% reduction in non-diabetic obese population
SURPASS-CVOT	Tirzepatide	2024	13,000+	3P-MACE	Non-inferior vs. dulaglutide; superior cardiometabolic risk factor improvements

3P-MACE = CV death, non-fatal MI, non-fatal stroke; 4P-MACE = 3P-MACE + hospitalization for unstable angina; HR = hazard ratio.

7.2 Liraglutide: LEADER Trial

The LEADER trial (n=9,340) randomized patients with T2DM at high cardiovascular risk to liraglutide or placebo. After a median follow-up of 3.8 years, liraglutide significantly reduced MACE by 13% (HR 0.87, 95% CI: 0.78–0.97; p=0.01), driven primarily by reductions in cardiovascular mortality. Post-hoc analyses confirmed cardiovascular and renal outcome benefits were consistent across all BMI subgroups, establishing liraglutide as the first GLP-1

RA with FDA cardiovascular risk reduction indication.

7.3 Semaglutide: SUSTAIN-6, PIONEER 6, and SELECT

In SUSTAIN-6 (n=3,297), subcutaneous semaglutide achieved a 26% reduction in 3P-MACE (HR 0.74, 95% CI: 0.58–0.95), most prominently via a 39% reduction in non-fatal stroke. PIONEER-6 (n=3,183) confirmed non-inferiority of oral semaglutide (HR 0.79) with nominally significant 51% reduction in cardiovascular death and 49% reduction in all-cause mortality. The SELECT trial (n=17,604) enrolled non-diabetic obese individuals with established CVD and demonstrated a 20% relative reduction in 3P-MACE with semaglutide 2.4 mg (HR 0.80, $p<0.001$) — the first cardiovascular superiority evidence for any anti-obesity medication in a non-diabetic population.

7.4 Tirzepatide: SURPASS-CVOT

SURPASS-CVOT enrolled over 13,000 adults with T2DM and established atherosclerotic cardiovascular disease, comparing tirzepatide with dulaglutide. Results confirmed non-inferiority for 3P-MACE while producing superior improvements in cardiometabolic risk factors. Across completed head-to-head trials, tirzepatide consistently achieved greater reductions in body weight and HbA1c than semaglutide. However, semaglutide retains the most mature and comprehensive cardiovascular outcome evidence, particularly for stroke prevention and benefit in non-diabetic obesity.

8. RENAL AND METABOLIC BENEFITS BEYOND GLYCEMIA

Semaglutide 1 mg once weekly produced a 24% reduction in the rate of eGFR decline in patients with T2DM. A meta-analysis confirmed that semaglutide, dulaglutide, and liraglutide were each significantly associated with reductions in new or persistent macroalbuminuria, though effects on eGFR deterioration and renal replacement therapy were less consistent. Exenatide should be avoided in patients with severe renal impairment (CrCl <30 mL/min), whereas dulaglutide, liraglutide, and semaglutide do not require dose adjustments.

Additional metabolic benefits include systolic blood pressure reductions of approximately 2–5 mmHg, modest LDL-cholesterol and triglyceride lowering, and favorable effects on non-alcoholic fatty liver disease (NAFLD/NASH). Emerging trials are evaluating GLP-1 RA potential in peripheral artery disease, Alzheimer disease, and Parkinson disease, reflecting broad receptor distribution beyond metabolic tissues.

9. SAFETY PROFILE AND TOLERABILITY

9.1 Gastrointestinal Adverse Events

Gastrointestinal adverse events — primarily nausea, vomiting, diarrhea, and constipation — are the most common class effect, occurring in 10–40% of patients depending on agent and dose. These are largely dose-dependent, most pronounced during escalation, and typically attenuate over 4–8 weeks with gradual titration. Systematic reviews confirm gastrointestinal adverse events cause treatment discontinuation in approximately 5–10% of patients.

9.2 Pancreatitis, Thyroid Effects, and Oncological Safety

Prior concerns regarding GLP-1 RA-associated acute pancreatitis and pancreatic cancer have been dispelled by long-term CVOTs and post-marketing surveillance. GLP-1 RAs carry an FDA black box warning regarding medullary thyroid carcinoma (MTC) based on rodent data, and remain contraindicated in patients with personal or family history of MTC or MEN2. Sight-threatening diabetic retinopathy worsening associated with rapid glycemic improvement has been observed with semaglutide, and retinal screening before initiation is recommended for high-risk patients.

9.3 Special Populations

GLP-1 RAs demonstrate favorable safety profiles in elderly populations. Semaglutide has demonstrated positive outcomes in heart failure with preserved ejection fraction (HFpEF) in STEP-HFpEF, while liraglutide data in reduced ejection fraction HF have been less favorable. GLP-1 RAs are not recommended during pregnancy or lactation due to limited safety data. Real-world evidence from over 140,000 matched pairs confirmed favorable cardiovascular and kidney outcomes with GLP-1 RAs compared with other anti-obesity medications in non-diabetic obese individuals.

10. INDIVIDUALIZED THERAPY SELECTION: A FRAMEWORK FOR CLINICAL PRACTICE

The expanding GLP-1 RA landscape necessitates a structured, patient-centered approach to agent selection:

Primary glycemic control: Tirzepatide or high-dose semaglutide are preferred when maximal HbA1c reduction is the primary goal. Semaglutide demonstrates superiority over liraglutide and dulaglutide in comparative meta-analyses.

Combined glycemic and weight management in T2DM: Tirzepatide (Mounjaro) or higher-dose semaglutide (Ozempic 2 mg, Wegovy) offer superior combined benefits. Transitioning from liraglutide or dulaglutide to semaglutide yields significant additional weight loss (2.48 kg, p=0.02).

Obesity without diabetes: Semaglutide 2.4 mg (Wegovy) and tirzepatide 15 mg (Zepbound) represent the most efficacious pharmacological options. Liraglutide 3 mg (Saxenda) is an alternative for cost-sensitive situations.

Cardiovascular risk reduction: Semaglutide carries the broadest cardiovascular outcome evidence including superiority in non-diabetic obesity (SELECT) and the most compelling stroke reduction data (SUSTAIN-6). Liraglutide and dulaglutide also have cardiovascular superiority indications in T2DM.

Chronic kidney disease: Semaglutide, dulaglutide, and liraglutide are preferred; exenatide must be avoided in severe renal impairment.

Route of administration: Oral semaglutide (Rybelsus) is the only approved oral GLP-1 RA for injection-averse patients, though adherence to specific fasting requirements is critical for efficacy.

Cost and access: Older agents may offer cost advantages. Tirzepatide and high-dose semaglutide carry premium pricing; insurance coverage varies significantly by indication and jurisdiction.

11. EMERGING AGENTS AND FUTURE DIRECTIONS

Novel molecular entities continue to advance. Retatrutide — a triple GLP-1/GIP/glucagon receptor co-agonist — demonstrated up to 24% weight reduction in phase 2 trials. Survodutide, a dual GLP-1/glucagon agonist, and maritide — which blocks GIP while activating GLP-1 receptors — provide mechanistic insights into dual incretin pharmacology. Oral small-molecule GLP-1 agonists (orforglipron, danuglipron) circumvent peptide absorption challenges with promising phase 3 glycemic and weight data.

Beyond cardiometabolic indications, ongoing trials evaluate GLP-1 RA efficacy in metabolic liver disease (MASH), peripheral artery disease, chronic kidney disease without diabetes, Alzheimer disease, and Parkinson disease — reflecting broad GLP-1 receptor distribution and

pleiotropic physiological actions.

12. CONCLUSION

GLP-1 receptor agonists represent a pharmacological class of exceptional therapeutic breadth, addressing glycemic control, obesity, and cardiovascular risk within a single mechanism-driven framework. Evidence from over 15 high-quality publications confirms a clear hierarchy of metabolic efficacy: tirzepatide > semaglutide > dulaglutide/liraglutide > exenatide/lixisenatide. For cardiovascular outcomes, semaglutide demonstrates the most comprehensive evidence base.

Clinical decision-making must remain individualized, incorporating the patient's primary therapeutic target, renal and hepatic status, cardiovascular history, injection tolerance, and economic constraints. As long-term safety and cardiovascular data mature for tirzepatide and novel agents enter clinical practice, the GLP-1 RA class is poised to remain at the forefront of evidence-based cardiometabolic pharmacotherapy.

ACKNOWLEDGEMENT

The author sincerely acknowledges Vision College of Pharmacy, Boduppal, Hyderabad, for providing the academic environment, library resources, and institutional support that made this review possible.

Gratitude is extended to the faculty members of the Department of Pharmacology and Clinical Pharmacy at Vision College of Pharmacy for their guidance and encouragement throughout this work.

The author also acknowledges the researchers, clinicians, and participants of the landmark cardiovascular outcome trials — LEADER, SUSTAIN-6, PIONEER-6, REWIND, SELECT, and SURPASS-CVOT — whose contributions form the evidence base of this review.

No funding was received for the preparation of this review. The author declares no conflict of interest.

REFERENCES

1. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med., 2016; 375(4): 311–322. [LEADER Trial]
2. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med., 2016; 375(19): 1834–1844. [SUSTAIN-6]

3. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med., 2019; 381(9): 841–851. [PIONEER 6]
4. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND). Lancet, 2019; 394(10193): 121–130.
5. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med., 2023; 389(24): 2221–2232. [SELECT]
6. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med., 2022; 387(3): 205–216. [SURMOUNT-1]
7. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec in T2D (SURPASS-3). Lancet, 2021; 398(10300): 583–598.
8. Drucker DJ. Efficacy and safety of GLP-1 medicines for type 2 diabetes and obesity. Diabetes Care., 2024; 47(11): 1873–1888.
9. Tan H, Hashim NH, et al. Comparative effectiveness of semaglutide versus liraglutide, dulaglutide or tirzepatide: a systematic review and meta-analysis. Front Pharmacol, 2025. [PMC12120964]
10. Nuffer W, Brunner K, Vo T, et al. Semaglutide versus other GLP-1 agonists for weight loss in T2DM: a systematic review and meta-analysis. Cureus, 2024. [PMC11463578]
11. Ding L, Sun B, Xiao X. Comparing GLP-1 RAs with SGLT-2 inhibitors for obese T2DM on metformin: a meta-analysis. J Diabetes Res., 2020; 2020: 1626484.
12. Doughty EN, Janssen IS, Patel S, et al. Efficacy and safety of GLP-1 RAs for obesity management with and without T2DM: a systematic review. Obes Rev., 2025. [PMC12591819]
13. Canas C, Mendez B, Gonzalez D. Tirzepatide vs. semaglutide for obesity, glycemic control, and cardiovascular outcomes: a narrative review. Front Med., 2026; 13: 1764664.
14. Vasconcelos TF, da Silva MP, et al. GLP-1 receptor agonists for the treatment of obesity. Front Endocrinol, 2023; 13: 1085799.
15. Habib ZF, Ahmed A, Al-Qattan M. GLP-1 receptor agonism: a transformative approach for managing T2DM and obesity. Mol Cell Biochem, 2025. [PMC12460220]
16. Ahmed T, Rahman MR. GLP-1 agonists in cardiovascular diseases: mechanisms, clinical evidence, and emerging therapies. J Clin Med., 2025; 14(19): 6758.
17. Bhat VK, Gibbons CH, O'Brien T. A review and meta-analysis of the safety and efficacy of GLP-1 receptor agonists. Front Endocrinol, 2024. [PMC10972401]

18. Mellbin LG, Bhatt DL, et al. Semaglutide and cardiovascular outcomes by baseline HbA1c: SUSTAIN 6 and PIONEER 6. Eur Heart J., 2024; 45(15): 1371–1380.
19. Drucker DJ, Nauck MA. After LEADER and SUSTAIN-6: cardiovascular benefits of GLP-1 receptor agonists. Lancet Diabetes Endocrinol, 2017; 5(6): 404–405.
20. Li C, Zhao Y, Zhang W, et al. Real world study of GLP-1 receptor agonists in overweight or obese T2DM. Medicine (Baltimore), 2024; 103: e38612.