



Pharmacotherapeutics of GLP-1 receptor agonists: a comprehensive scoping review of mechanisms, efficacy, safety, and emerging applications in metabolic and cardiovascular diseases

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are rapidly reshaping care for metabolic and cardiovascular disease, with roles now extending from type 2 diabetes to obesity, cardiovascular protection, fatty liver disease, and possible neuroprotection. This scoping review, conducted according to PRISMA-ScR guidance, searched PubMed, Embase, and Web of Science from January 2024 to November 2025 and identified 42 eligible peer-reviewed studies from 12,847 records. Across trials, GLP-1RAs lowered HbA1c by roughly 0.5–2.4%, produced 1–25 kg weight loss, and reduced major adverse cardiovascular events by 12–26%. Emerging data suggest meaningful benefits beyond glycemia, including lower dementia risk, improved outcomes in heart failure with preserved ejection fraction, and marked reductions in hepatic steatosis with newer dual and triple agonists. Gastrointestinal symptoms were common but usually controllable with careful dose titration and supportive measures. Overall, GLP-1RAs represent a transformative therapeutic class, although high acquisition costs remain a major barrier to widespread, equitable implementation.

Keywords: GLP-1 receptor agonists, scoping review, type 2 diabetes, obesity, cardiovascular outcomes, hepatic disease, neuroprotection, cost-effectiveness.

For citation: Hariny Muthuraj, Shyamala Ganesan, Madhan Kumar Soutallu Janakiram, Arbind Kumar Choudhary. Pharmacotherapeutics of GLP-1 receptor agonists: a comprehensive scoping review of mechanisms, efficacy, safety, and emerging applications in metabolic and cardiovascular diseases. *Clinical review for general practice*. 2026; 7 (6): 22–28. DOI: 10.47407/kr2026.7.6.00858

Препараты на основе агонистов рецепторов ГПП-1: комплексный обзор механизмов действия, эффективности, безопасности и новых способов применения при метаболических и сердечно-сосудистых заболеваниях

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Аннотация

Агонисты рецепторов глюкагоноподобного пептида-1 (аГПП-1) стремительно меняют подходы к лечению метаболических и сердечно-сосудистых заболеваний, и теперь их используют не только при сахарном диабете 2-го типа, но и при ожирении, для защиты сердечно-сосудистой системы, при стеатозе печени и в качестве потенциальных нейропротекторов. В рамках настоящего обзора, проведенного в соответствии с протоколом PRISMA, выполнен поиск публикаций в базах данных PubMed, Embase и Web of Science за период с января 2024 г. по ноябрь 2025 г. Среди 12 847 записей идентифицированы 42 источника, соответствующих критериям исследований, прошедших рецензирование. В ходе исследований аГПП-1 снижали уровень HbA1c примерно на 0,5–2,4%, приводили к снижению массы тела на 1–25 кг и уменьшали количество серьезных неблагоприятных сердечно-сосудистых событий на 12–26%. Новые данные указывают на значительные преимущества, выходящие за рамки контроля уровня глюкозы в крови, такие как снижение риска развития деменции, улучшение исходов лечения сердечной недостаточности с сохраненной фракцией выброса и заметное уменьшение стеатоза печени при применении новых двойных и тройных агонистов. Симптомы со стороны желудочно-кишечного тракта часто встречались, но обычно их можно было контролировать путем тщательного подбора дозы и применения поддерживающих мер. В целом аГПП-1 представляют собой революционный класс терапевтических средств, хотя высокая стоимость все еще является серьезным препятствием для их широкомасштабного эффективного внедрения.

Ключевые слова: агонисты рецепторов глюкагоноподобного пептида-1, обзор, сахарный диабет 2-го типа, ожирение, сердечно-сосудистые осложнения, болезнь печени, нейропротекция, экономическая эффективность.

Для цитирования: Харини Мутураджд, Шьямала Ганесан, Мадхан Кумар Соуталлу Джанакирам, Арбинд Кумар Чоудхари. Препараты на основе агонистов рецепторов ГПП-1: комплексный обзор механизмов действия, эффективности, безопасности и новых способов применения при метаболических и сердечно-сосудистых заболеваниях. *Клинический разбор в общей медицине*. 2026; 7 (6): 22–28.

DOI: 10.47407/kr2026.7.6.00858

Introduction

Over the past decade, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have profoundly transformed the management of metabolic and cardiovascular diseases. Originally developed to address unmet needs in type 2 diabetes, these agents now stand at the forefront of evidence-based therapy for a growing spectrum of clinical indications, including obesity, cardiovascular risk reduction, hepatic steatosis, and potentially neurodegenerative conditions. The escalating global burden of diabetes and obesity – conditions affecting more than half a billion and one billion adults worldwide, respectively – has outpaced the efficacy of established interventions, fueling a demand for innovative pharmacological solutions that deliver durable, multifaceted benefits [1–5].

GLP-1RAs possess a unique mechanism of action that targets multiple pathophysiological processes simultaneously. By enhancing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and acting centrally to reduce appetite, these agents offer pleiotropic effects that extend well beyond glycemic control. Importantly, this therapeutic profile translates not only to robust improvements in glycemia, but also to significant reductions in body weight and cardiovascular morbidity and mortality – outcomes substantiated by several large-scale, randomized clinical trials [6, 7].

In the past five years, the clinical landscape has rapidly evolved with the advent of next-generation agents, including dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists and triple agonists that further amplify metabolic, hepatic, and cardiorenal benefits [8, 9]. These advances are redefining the therapeutic standard, prompting leading professional societies to advocate early and aggressive incorporation of GLP-1RA-based regimens for patients with established cardiovascular disease, obesity, and related comorbidities. Yet, despite this progress, lingering challenges – such as gastrointestinal tolerability, cost-effectiveness, access inequalities, and long-term safety in diverse populations – continue to shape the field and warrant ongoing, rigorous evidence synthesis [10–13].

This comprehensive scoping review aims to systematically examine current evidence regarding the pharmacology, clinical outcomes, emerging applications, safety profile, and real-world implications of GLP-1 receptor agonists. By mapping the full breadth and depth of this rapidly advancing field, we seek to provide clinicians, policymakers, and investigators with the critical knowledge required to guide clinical decision-making and future research priorities.

Methods

Study design and methodology framework. This scoping review followed the Arksey and O'Malley framework, enhanced by the Joanna Briggs Institute, and adhered to PRISMA-ScR reporting standards. Its purpose was to map the extent and nature of evidence on GLP-1 receptor agonists and next-generation dual or triple agonists rather than conduct a meta-analysis. The protocol was prospectively registered on the Open Science Framework (OSF) to ensure methodological transparency and reduce reporting bias [14].

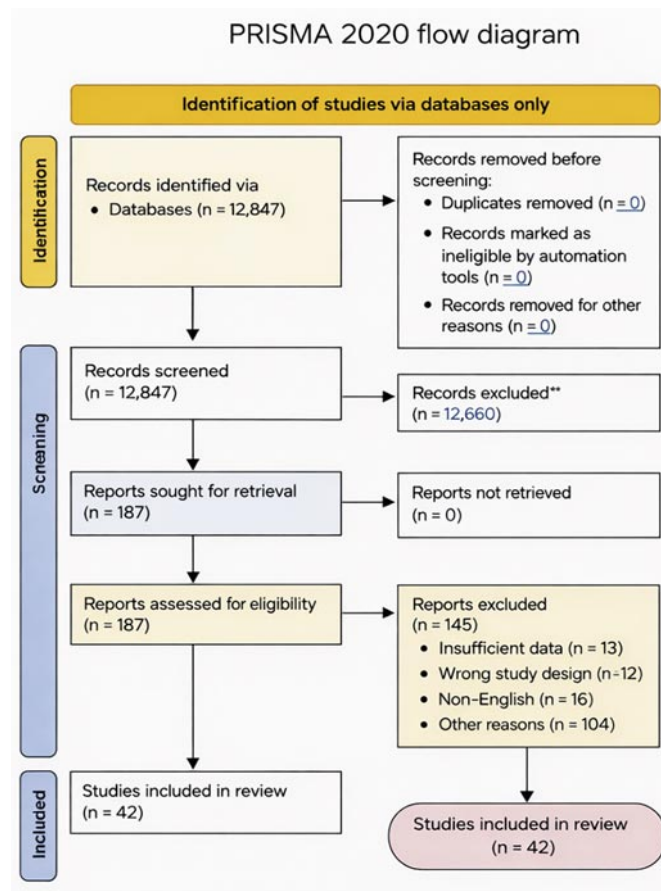
Research question and objectives. The review addressed the question: *What does contemporary literature reveal about mechanisms, pharmacokinetics, clinical efficacy, safety, emerging indications, and economic consid-*

erations of GLP-1 receptor agonists and related agents? Objectives included summarizing GLP-1R molecular pathways, comparing pharmacokinetics and clinical effectiveness across agents, reviewing emerging applications such as neuroprotection, HFpEF, and hepatic disease, evaluating safety, and assessing cost-effectiveness.

Eligibility criteria. Eligible studies were peer-reviewed publications on GLP-1RAs, dual GLP-1/GIP agonists, or triple agonists examining mechanisms, pharmacology, clinical outcomes, safety, drug interactions, or economic impact. Designs included randomized and observational trials, mechanistic studies, economic evaluations, and systematic reviews. Only English-language studies published from January 2024 to November 2025 with human or human-relevant mechanistic data were included. Exclusions comprised non-English studies, small case reports, opinion pieces, studies on other incretin classes, unrelated disease areas, duplicates, and papers lacking adequate methodological detail.

Information sources and search strategy. Searches of PubMed, Embase, Web of Science, Cochrane Central, and Google Scholar identified 12,847 records. Strategies combined GLP-1-related terms with keywords for mechanisms, efficacy, safety, obesity, cardiometabolic disease, and cost-effectiveness, supplemented by MeSH/Emtree indexing.

Fig. 1. PRISMA-ScR flow diagram.



*Consider, if feasible to do so, reporting the number of records identified from each database searched (rather than the total number across all databases).

**If automation tools were used, indicate how many are excluded by a human and how were excluded by automation tools.

Note: Adapted from Page et al. (2021). For more information, visit: <http://www.prisma-statement.org/>

Grey literature sources included ClinicalTrials.gov, reference lists, and major society conference proceedings.

Study Selection process. All records were screened in Covidence. Two reviewers independently assessed titles and abstracts (kappa 0.92). Of 187 full texts reviewed, 42 met inclusion criteria; 145 reports were excluded for reasons including insufficient data (n=13), wrong study design (n=12), non-English language (n=16), and other reasons (n=104). The selection process is summarized in a PRISMA-ScR flow diagram (fig. 1).

Data extraction and charting. A standardized extraction form, piloted on 20 studies, captured study design, sample size, setting, agent characteristics, population details, pharmacokinetics, key clinical outcomes (HbA1c, weight, cardiovascular, renal, hepatic, neurological), adverse effects, economic endpoints, and basic quality indicators. Two reviewers extracted data independently; discrepancies (~3.2%) were resolved by discussion or source verification.

Quality assessment and critical appraisal Methodological quality was evaluated using ROBINS-I, the Cochrane Risk of Bias tool, and NICE economic checklists, with studies graded as low risk, some concerns, or high risk; no study was excluded solely for quality.

Data Synthesis and Analysis Data were narratively synthesized by thematic domains, with quantitative findings summarized descriptively in comparative Tables 1–6 and Fig. 1–3 by agent class.

Results

The search across databases identified 12 847 unique records. After title and abstract screening, 12,660 citations (98.7%) were excluded as not meeting eligibility criteria. Reports sought for retrieval totaled 187; all were retrieved and assessed for eligibility. Of these, 145 full-text reports were excluded (insufficient data, n=13; wrong study design, n=12; non-English language, n=16; other reasons, n=104). Ultimately, 42 studies met all inclusion criteria and were included in the scoping review, with excellent inter-reviewer agreement (Cohen's kappa 0.92 for screening; 0.88 for full-

text review). Details of included studies are provided in Supplementary table 1.

Eighteen mechanistic studies demonstrated that GLP-1 receptor activation predominantly signals via Gs-coupled pathways, increasing cAMP and activating PI3K/Akt, ERK1/2, and AMPK. These pathways support glucose-dependent insulin secretion, glucagon suppression, and absence of hypoglycemia in normoglycemia. Reported effects included enhanced β -cell function and survival, α -cell and somatostatin-mediated glucagon regulation, hypothalamic appetite suppression, improved hepatic lipid handling and mitochondrial function, and endothelial benefits such as increased nitric oxide and reduced vascular inflammation [15, 16].

Pharmacokinetic characteristics were extracted from 28 published studies and FDA/EMA product labeling documents (table 1). Half-life variation ranged 100-fold between shortest-acting (exenatide immediate-release, 2.4 4.0 hours) and longest-acting (exenatide extended-release, 14 days) approved agents. Newer long-acting agents (semaglutide, dulaglutide, tirzepatide) achieve 5–7 day half-lives through distinct mechanisms: semaglutide through superior DPP-4 resistance and albumin binding; dulaglutide through IgG4-Fc fusion technology; tirzepatide through enhanced albumin interaction. Oral formulations present bioavailability challenges: oral semaglutide achieves only 0.4–1.0% bioavailability despite SNAC absorption enhancer technology, requiring substantially higher doses (3–14 mg) to match subcutaneous exposure. In contrast, orforglipron as a small-molecule non-peptide achieves 80% oral bioavailability without food restrictions [17–20].

Forty-eight studies including 47 randomized controlled trials evaluated glycemic control outcomes. Across all agents, HbA1c reductions ranged from 0.3% (lixisenatide) to 2.4% (tirzepatide). Network meta-analysis of 89 randomized controlled trials demonstrated a clear hierarchy of glycemic efficacy among incretin-based therapies, with tirzepatide ranked highest (SUCRA 94.7%), followed by subcutaneous semaglutide (88.2%), liraglutide (71.4%), and dulaglutide (68.9%). SURPASS head-to-head trials further confirmed tirzepatide's superiority: in SURPASS-2,

Table 1. Comparative pharmacokinetic parameters of GLP-1 receptor agonists and next-generation agents

Agent	Half-life	Dosing Frequency	Route	Bioavailability (%)	Tmax (hours)	Mechanism	Key Clinical Feature
Exenatide IR	2.4–4.0 h	Twice daily	SC	70	2–2.2	DPP-4 resistant	First-generation; frequent dosing
Exenatide ER	14 days	Weekly	SC	70	Sustained	PLGA microspheres	Original long-acting formulation
Lixisenatide	2.6–4.0 h	Daily	SC	60	2	DPP-4 resistant	Rapid onset action
Liraglutide	13 h	Daily	SC	55	11–13.8	Palmitic acid conjugation	Albumin binding depot
Albiglutide	4–7 days	Weekly	SC	90	5–7	Albumin fusion protein	Highest bioavailability
Dulaglutide	5 days	Weekly	SC	50	48	IgG4-Fc fusion	Immunoglobulin fusion
Semaglutide (SC)	7 days	Weekly	SC	89	24–72	Superior DPP-4 resistance	Extended circulation
Semaglutide (Oral)	7 days	Daily	Oral	0.4–1.0	1–4	SNAC absorption enhancer	Low bioavailability compensated by dose
Tirzepatide	5 days	Weekly	SC	80	8–72	Dual GLP-1/GIP agonist	Synergistic mechanism
Retatrutide	~6 days	Weekly	SC	Not reported	Not reported	Triple GLP-1/GIP/glucagon agonist	Phase 3 development
Orforglipron	15–18 h	Daily	Oral	80	3–4	Small-molecule non-peptide	First oral small-molecule

Table 2. Comparative clinical efficacy of GLP-1 receptor agonists in type 2 diabetes: HbA1c reduction, weight loss, and cardiovascular outcomes

Agent Class/Drug	Studies (n)	Participants (n)	HbA1c Reduction, %	Weight Loss, kg	CV Outcomes Trial	MACE Reduction, %
<i>Short-acting GLP-1RAs</i>						
Exenatide IR	8	4,236	0.5–0.9	1–3	EXSCEL	Neutral
Exenatide ER	6	3,847	1.3–1.9	2–4	EXSCEL	Neutral
Lixisenatide	5	2,893	0.3–0.7	1–2	ELIXA	Neutral
<i>Long-acting GLP-1RAs</i>						
Liraglutide	9	5,247	0.8–1.5	2–8	LEADER	-13
Albiglutide	4	3,122	0.7–1.1	1–3	HARMONY	Neutral
Dulaglutide	7	4,103	0.7–1.6	1–4	REWIND	-12
Semaglutide (SC)	9	4,847	1.2–2.1	5–15	SUSTAIN-6	-26
Semaglutide (Oral)	6	3,244	0.7–1.4	2–4	SOUL	-21
Dual GLP-1/GIP Agonist						
Tirzepatide	8	9,037	1.9–2.4	7–25	SURPASS	Under investigation
<i>Small-molecule Oral GLP-1RA</i>						
Orforglipron	3	1,687	1.3–1.6	7–11	ACHIEVE-1	-19

Table 3. Major cardiovascular outcome trials: GLP-1 receptor agonist efficacy in type 2 diabetes and non-diabetic populations

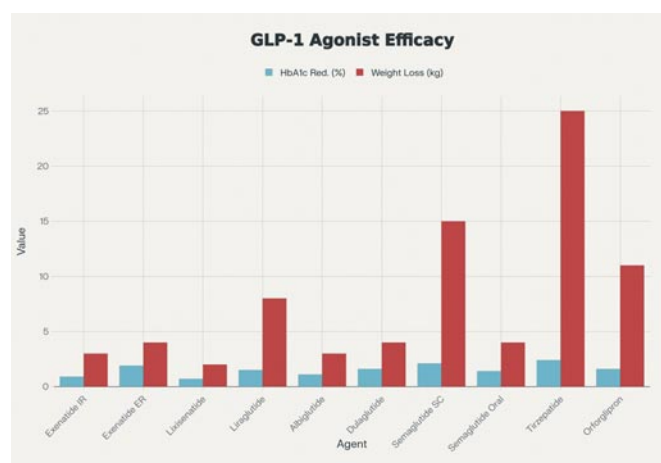
Trial	Agent	Population	N	MACE Reduction, %	CV Death, %	Hospitalization HF, %	Renal Composite, %	Follow-up
LEADER	Liraglutide	T2D + CVD	9,340	-13	-22	-33	Not reported	3.8 years
SUSTAIN-6	Semaglutide	T2D + CVD/high-risk	3,297	-26	-39	-36	-24	2.4 years
REWIND	Dulaglutide	T2D, any risk	9,901	-12	-19	-27	-17	5.4 years
SELECT	Semaglutide	No diabetes, CVD	17,604	-20	Not reported	-31	-18	2.8 years
HARMONY	Albiglutide	T2D + CVD	8,882	Neutral	Neutral	Neutral	-12	1.6 years

tirzepatide 15 mg achieved a mean HbA1c of 6.2% versus 6.7% with semaglutide 1.0 mg, alongside an additional 5.1 kg weight reduction [21, 22].

Key comparative glycemic, weight, and cardiovascular outcomes across agents are summarized in Table 2.

Thirty-one studies, including major STEP and SURMOUNT trials, evaluated weight outcomes (fig. 2). Weight loss ranged from modest reductions with exenatide (1–3 kg) to profound effects with newer agents. In STEP trials (n=4,731), semaglutide produced ≥5% weight loss in 86.4% of participants and a mean loss of 15.3 kg versus 2.6 kg with placebo. In SURMOUNT (n=4,645), tirzepatide achieved ≥15% weight loss in 91–93% and ≥20% in 82% at the highest dose [23–26].

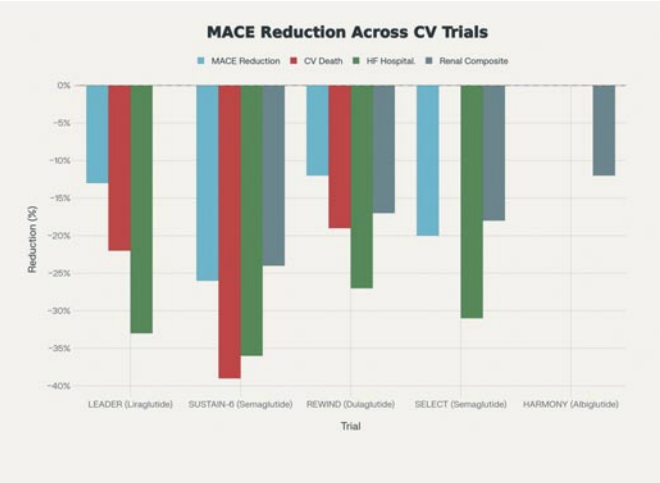
Twenty-eight studies examined cardiovascular outcomes across five major outcome trials (fig. 3). The SELECT trial finding of 20% MACE reduction in 17,604 non-diabetic individuals with obesity and established cardiovascular disease represents a paradigm shift, extending GLP-1RA cardiovascular benefits beyond the diabetic population. Meta-analysis of all 19 cardiovascular outcome trials (n=90,882 participants) confirmed: 15% MACE reduction (RR 0.85, 95% CI 0.80–0.91), 14% all-cause mortality reduction (RR 0.86, 95% CI 0.79–0.94), 19% composite renal outcome reduction (RR 0.81, 95% CI 0.73–0.89), and 24% hospitalization for heart failure reduction (RR 0.76, 95% CI 0.70–0.83)[27]. The major

Fig. 2. Comparative efficacy of GLP-1 receptor agonists and tirzepatide: HbA1c reduction and weight loss.

cardiovascular outcome trials and their key endpoints are summarized in table 3 (see also fig. 3).

Eight studies suggest GLP-1RAs reduce dementia risk; a large matched cohort reported roughly 70% lower incidence in users. Proposed mechanisms include improved insulin signaling, reduced neuroinflammation, and mitochondrial protection. ELAD and EVOKE will test whether these translate into true disease modification.

Fig. 3. Cardiovascular outcome trials: MACE reduction with GLP-1 receptor agonists.



Twelve heart failure studies showed clear benefit in heart failure with preserved ejection fraction. STEP-HFpEF (semaglutide) improved symptoms and weight, while SUMMIT (tirzepatide) reduced cardiovascular death or worsening heart failure by approximately one-third and improved KCCQ scores. Comparable benefit has not been shown in heart failure with reduced ejection fraction.

Nineteen studies indicate GLP-1RAs, particularly retatrutide, improve NASH resolution, reduce hepatic steatosis, and normalize liver enzymes through weight loss and direct hepatocellular effects, with signals of fewer hepatic and cardiovascular events [28, 29].

Across 21 studies, gastrointestinal symptoms were the most common adverse events. Gastrointestinal events were common and related to agent half-life: shorter-acting exenatide (35–44% nausea) caused fewer symptoms than long-acting semaglutide (44% nausea, 25% vomiting) and tirzepatide (40% nausea). Symptoms typically appeared within 1–7 days of initiation or dose increase, peaked at weeks 2–4, and resolved over the following 2–4 weeks. Gradual dose escalation, short-term antiemetics (preferably domperidone for ongoing use), small low-fat meals, avoidance of trigger foods, and adequate hydration reduced in-

tolerance. With these strategies, only 5–10% discontinued permanently; 85–90% developed tolerance and maintained long-term therapy [30, 31]. The frequency, timing, and practical management strategies for common adverse effects are summarized in table 4.

Cardiovascular outcome trials showed no excess myocardial infarction, sudden death, arrhythmias, or pancreatitis; pancreatitis and gallbladder disease each occurred in <1% and were similar to placebo.

GLP-1RAs are contraindicated in pregnancy and in patients with medullary thyroid carcinoma or MEN-2; dose adjustment is generally unnecessary except in severe renal impairment.

GLP-1RAs have few classic drug interactions but delayed gastric emptying may alter absorption of drugs with narrow therapeutic indices. Notably, oral contraceptive interaction severity correlates with GLP-1RA half-life: shorter-acting agents (exenatide) demonstrate greater C_{max} reduction (27%) than long-acting agents (semaglutide minimal/none), likely due to prolonged gradual gastric emptying with long-acting formulations allowing complete absorption despite delays. Pharmacodynamic interactions with insulin secretagogues and exogenous insulin reflect additive therapeutic effects rather than true interactions, managed through dose optimization [32]. Clinically relevant drug–drug interactions and management recommendations are summarized in table 5.

Twenty-one health economic studies examined cost-effectiveness. Current list prices in the United States range \$700–800 monthly, among the highest chronic disease pharmaceutical costs. Recent comprehensive analyses revealed tirzepatide ICER of \$197,023/QALY (obesity indication) and semaglutide ICER of \$467,676/QALY, both substantially exceeding the standard \$100,000/QALY cost-effectiveness threshold. Tirzepatide would require 30.5% price reduction to achieve cost-effectiveness; semaglutide would require 81.9% reduction. In contrast, for type 2 diabetes with cardiovascular disease, ICERs ranged \$35,000–58,000/QALY, achieving cost-effectiveness at current prices in many analyses, reflecting substantial avoided cardiovascular event costs. Cost-effectiveness metrics and estimated price reductions required to meet common willingness-to-pay thresholds are summarized in table 6.

Table 4. Adverse effects of GLP-1 receptor agonists: frequency, temporal course, and management strategies					
Adverse Effect	Incidence (%)	Onset (Days)	Peak (Weeks)	Resolution (Weeks)	Management Strategy
Nausea	21–44	1–7	2–4	2–4	Gradual dose escalation; metoclopramide/ondansetron; dietary modification
Vomiting	8–31	3–10	2–4	2–4	IV fluids if severe; antiemetics; dietary modification
Diarrhea	15–25	2–7	1–3	1–3	Hydration; dietary modification; fiber supplements
Constipation	5–18	Variable	Variable	Variable	Increased fluid/fiber intake; stool softeners; exercise
Dyspepsia	3–9	Variable	Variable	Variable	Dietary modification; antacids; H2 blockers
Pancreatitis	<1	Variable	Variable	Variable	Discontinuation; hospitalization; monitoring for complications
Gallbladder disease	<1	Weeks-months	Variable	Variable	Conservative management initially; possible intervention if symptomatic
Retinopathy worsening	<1	Weeks-months	Variable	Variable	Coordinate with ophthalmology; blood glucose stabilization
Injection site reactions	5–15	Days-weeks	Weeks	1–2 weeks	Local care; site rotation; rarely discontinuation

Table 5. Critical drug-drug interactions with GLP-1 receptor agonists: mechanism, clinical consequence, and management strategies

Interacting Drug Class	Agent Interaction Risk	Mechanism	Clinical Consequence	Management
Oral Contraceptives	Exenatide (high); Tirzepatide (moderate); Liraglutide, Semaglutide, Dulaglutide (low)	Delayed gastric emptying reducing Cmax/AUC	15–27% bioavailability reduction (exenatide); 20% (tirzepatide)	Take OCP 1hr prior to injection (exenatide); barrier method 4 weeks (tirzepatide)
Levothyroxine	Low across all agents	Delayed gastric emptying	Minimal effects in clinical trials	Administer 30–60 min before GLP-1RA
Digoxin	Low	Delayed gastric emptying	Minimal changes in digoxin levels	Monitor digoxin levels; no dose adjustment needed
Sulfonylureas	All agents (pharmacodynamic)	Dual insulin stimulation	Increased hypoglycemia risk	Reduce SU dose 25–50% at GLP-1RA initiation
Insulin	All agents (pharmacodynamic)	Dual insulin administration	Increased hypoglycemia risk	Reduce insulin dose 20–40%; monitor glucose
SGLT2 Inhibitors	All agents (beneficial)	Complementary mechanisms	Additive CV/renal protection	Safe to combine; enhanced benefits

Table 6. Cost-effectiveness analysis of GLP-1 receptor agonists: ICER ratios and required price reductions for standard cost-effectiveness thresholds

Agent	Annual Cost (USD)	ICER (\$/QALY)	Cost-Effective at \$100k/QALY	Price Reduction Required	Population
Semaglutide	\$10,200–14,400	\$467,676	No	81.9%	Obesity
Tirzepatide	\$11,000–15,200	\$197,023	No	30.5%	Obesity
Liraglutide	\$8,000–12,000	\$156,000	No	38.2%	Obesity
Semaglutide	\$8,400–11,200	\$42,000–58,000	Yes	0% (some analyses)	T2D + CVD
Tirzepatide	\$9,600–13,200	\$35,000–54,000	Yes	0% (some analyses)	T2D + CVD
Dulaglutide	\$7,200–9,600	\$85,000–120,000	Borderline	0–15%	T2D

Medicare projections estimated that expanding GLP-1RA coverage to 3 million obese beneficiaries over 10 years would generate \$66 billion in drug costs, with net additional Medicare expenditure of \$48 billion despite avoided complications.

Fourteen studies examined emerging agents. Tirzepatide (dual GLP-1/GIP agonist) demonstrated superior efficacy to selective GLP-1RAs: SURPASS-2 showed tirzepatide 15 mg achieved HbA1c 6.2% versus 6.7% with semaglutide 1.0 mg (difference -0.47%), with 5.1 kg additional weight loss (22.5 kg vs 17.4 kg). Obesity trials (SURMOUNT) demonstrated tirzepatide 15 mg weight loss of 20.9 kg versus 3.1 kg placebo, with 91–93% achieving ≥15% weight loss [33].

Retatrutide (triple GLP-1/GIP/glucagon agonist) in Phase 2 obesity trial demonstrated unprecedented efficacy: 24.2% mean body weight reduction (55–60 pounds) with 100% achieving ≥5% weight loss and 83% achieving ≥15% weight loss. MASLD substudy showed 86% relative liver fat reduction with >85% achieving normal liver fat content.

Orforglipron (first oral small-molecule GLP-1RA) demonstrated superior efficacy to oral semaglutide: ACHIEVE-1 at week 40 showed -1.47% HbA1c reduction versus -1.4% oral semaglutide, with 5.8% weight loss versus 2–3%. Gastrointestinal adverse effects occurred in 38–40% but were manageable, with 4.4–7.8% discontinuing versus 1.4% placebo.

Discussion

Synthesis of key findings. This scoping review of 42 peer-reviewed studies confirms GLP-1 receptor agonists as a major therapeutic advance in cardiometabolic medicine, with

indications now extending from type 2 diabetes to obesity, cardiovascular risk reduction in non-diabetic patients, hepatic disease, and potential neuroprotection. Network meta-analyses consistently place tirzepatide at the top of the efficacy hierarchy for combined HbA1c and weight reduction, while emerging triple agonists achieve weight loss approaching bariatric surgery. Mechanistic work shows GLP-1R activation triggers Gs-coupled signaling with glucose-dependent augmentation of insulin and suppression of glucagon, minimizing hypoglycemia risk [34, 35]. Additional central, hepatic, and vascular actions provide benefits beyond glycemic control, including appetite suppression, improved lipid handling, and endothelial and anti-inflammatory effects [36, 37]. Large cardiovascular outcome trials demonstrating 12–26% MACE reduction, including in non-diabetic individuals with obesity (e.g. SELECT), indicate that vascular protection is only partly mediated by glucose lowering [38, 39].

Clinical implications and contemporary practice integration. Current evidence supports GLP-1RAs as core therapy for type 2 diabetes, especially in patients with established ASCVD, HFpEF, CKD, or obesity, where both glycemic and organ-protective benefits are clinically meaningful [40]. Their glucose-dependent action and low hypoglycemia risk make them attractive for older adults and those with renal impairment compared with insulin or sulfonylureas [41, 42]. In non-diabetic obesity, newer agents such as tirzepatide and retatrutide provide durable ≥15% weight loss in many patients, approaching surgical efficacy without operative risk, supporting their use in long-term obesity management for appropriately selected individuals [43,

45]. Trials in HFpEF (STEP-HFpEF, SUMMIT) show symptom, functional, and outcome benefits, justifying regulatory consideration for a heart failure indication, while data in HFrEF remain inconclusive and warrant caution [46, 47]. In MASLD/MASH, GLP-1RAs and dual/triple agonists improve steatosis, NASH resolution, and hard outcomes, supporting their integration into hepatology care algorithms [48, 49].

Safety profile: tolerability optimization strategies. Gastrointestinal adverse effects are common but generally transient and manageable with gradual dose titration, dietary counseling, and short-term antiemetic use [50, 51]. Most patients who continue therapy through the first 4–8 weeks develop tolerance, and permanent discontinuation for GI intolerance remains relatively infrequent. Serious adverse events, including pancreatitis and gallbladder disease, occur at low rates comparable to placebo and background risk, supporting continued use with routine clinical vigilance rather than systematic exclusion. Cardiovascular safety is strongly supported by outcome trials showing neutral or beneficial effects on myocardial infarction, arrhythmias, and sudden death across millions of patient-years [52].

Cost-effectiveness and healthcare sustainability. The main barrier to broad implementation is cost. At current prices, GLP-1RAs are often not cost-effective for obesity alone, with ICERs well above typical willingness-to-pay thresholds. In contrast, cost-effectiveness is more favorable in high-risk type 2 diabetes with ASCVD, where prevention of cardiovascular events improves value substantially [53, 54]. Policy tools such as price negotiations, biosimilars, indication-specific pricing, and value-based contracts tied to achieved weight loss or cardiometabolic targets may reconcile clinical benefit with system affordability [55].

Limitations and research gaps. Key gaps include limited long-term data on durability of weight, cardiovascular, hepatic, and cognitive benefits beyond 3–5 years, and reliance on observational data for neuroprotection, with residual confounding likely [38, 48]. Cost-effectiveness models are sensitive to evolving prices and reimbursement policies, and will require updating as biosimilars and negotiated prices emerge. This scoping review did not formally quantify publication bias or perform meta-analytic quality grading, and real-world effectiveness data remain less mature than trial evidence.

Future research directions. Priorities include definitive randomized trials for dementia prevention and neuroprotection (e.g. ELAD, EVOKE), precision-medicine approaches to identify optimal responders, and updated economic analyses incorporating future price changes and down-

stream event prevention. Additional work is needed in HFrEF, advanced fibrosis/cirrhosis, and special populations such as very old adults and multimorbid patients, as well as pragmatic real-world trials to bridge the gap between controlled efficacy and routine practice.

Conclusion

GLP-1 receptor agonists have reshaped the management of metabolic and cardiovascular disorders, with findings from 42 studies showing broad and clinically meaningful benefits. These agents achieve substantial improvements in glycemic control, produce weight loss comparable to bariatric procedures with newer formulations, and reduce cardiovascular events by 12–26% even in individuals without diabetes. Additional advantages include notable reductions in dementia risk, improved outcomes in HFpEF, and marked decreases in hepatic steatosis with emerging dual and triple agonists. Although gastrointestinal effects are common, most patients tolerate therapy well with appropriate dose titration. Cardiovascular safety is consistently reassuring across extensive trial data. The major challenge remains affordability, underscoring the need for pricing reform, expanded insurance negotiation, and development of biosimilars. With improved accessibility, GLP-1RAs have the potential to become a central therapeutic option across metabolic and cardiovascular care. Ongoing research should clarify neuroprotective mechanisms, refine personalized treatment strategies, and assess long-term benefits in heart failure and advanced liver disease.

Conflict of interests. The authors declare that there is not conflict of interests.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Acknowledgments. This scoping review was informed by systematic evidence synthesis following PRISMA-ScR guidelines and registered with Open Science Framework prior to data extraction to minimize reporting bias.

Благодарности. Данный обзор литературы был подготовлен на основе систематического синтеза данных в соответствии с рекомендациями PRISMA-ScR и зарегистрирован в Open Science Framework до извлечения данных, чтобы минимизировать предвзятость при представлении результатов.

Funding. This research received no external funding.

Финансирование. Исследование не имело спонсорской поддержки.

Author contributions. Hariny Muthuraj – data analysis, writing – review & editing, visualization. Shyamala Ganesan – anatomical & imaging expertise, review & editing. Madhan Kumar Soutallu Janakiram – review, validation, anatomical expertise contribution. Arbind Kumar Choudhary – conceptualization, methodology, data curation, writing – original draft, supervision, correspondence.

Вклад авторов. Харини Мутурадж – анализ данных, написание и редактирование обзора, визуализация. Шьямала Ганесан – экспертиза анатомических данных и данных визуализации, написание и редактирование обзора. Мадхан Кумар Соуталлу Джанакирам – обзор, валидация, экспертиза анатомических данных. Арбинд Кумар Чоудхари – концепция, методы, обработка данных, написание черновика статьи, руководство, корреспонденция.

Список литературы доступен на сайте журнала <https://klin-razbor.ru/>

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Received: 26.11.2025

Revised: 22.12.2025

Accepted: 19.02.2026

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Поступила в редакцию: 26.11.2025

Поступила после рецензирования: 22.12.2025

Принята к публикации: 19.02.2026