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How do Dual GLP-1/GIP Receptor Agonists Differ from GLP-1 Agonists for Diabetes Management: A Systematic Review

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Abstract

Introduction: Type 2 diabetes is a chronic metabolic disorder driven by insulin resistance and impaired β-cell function. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become central to diabetes management by improving insulin secretion, reducing glucagon, promoting weight loss, and lowering cardiovascular risk. Dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, such as tirzepatide, represent an emerging therapeutic class designed to enhance metabolic outcomes by activating complementary incretin pathways. This review evaluates how dual GLP-1/GIP agonists differ from GLP-1 RAs in mechanism, efficacy, safety, and therapeutic potential.

Methods: A systematic review was conducted using PubMed, Scopus, and the Cochrane Library to identify randomized trials, meta-analyses, and observational studies published from 2010 to 2025. Studies included adults with type 2 diabetes and directly compared dual GLP-1/GIP agonists with GLP-1 RAs. Primary outcomes were hemoglobin A1c reduction and weight change; secondary outcomes included safety, cardiovascular measures, and β-cell function.

Results: Across phase 3 trials, dual agonists achieved greater reductions in hemoglobin A1c (up to 2.4%) and body weight (up to 22%) compared to GLP-1 RAs. These effects reflect synergistic actions on insulin secretion, glucagon suppression, appetite regulation, and adipocyte metabolism. Dual agonists also demonstrated higher rates of normoglycemia and durable glycemic control, with gastrointestinal side effects similar to GLP-1 RAs. Preliminary data suggest improvements in blood pressure, lipid levels, and inflammatory markers, although dedicated cardiovascular outcome trials remain ongoing. Beyond diabetes, dual agonists show therapeutic potential in obesity, obstructive sleep apnea, and steatohepatitis

Discussion: Dual GLP-1/GIP agonists differ from GLP-1 RAs by activating two incretin pathways, resulting in superior glucose lowering, more pronounced weight reduction, and broader metabolic benefits. These advantages appear without added safety concerns. Distinct GIP-mediated effects on adipose tissue and central appetite pathways contribute to their enhanced efficacy.

Conclusion: Dual GLP-1/GIP receptor agonists represent a major advancement over GLP-1 RAs by delivering deeper glycemic improvement and greater weight loss through combined hormonal activation. Pending results from cardiovascular outcome trials, these agents may reshape diabetes management, particularly for individuals requiring substantial metabolic improvement beyond what GLP-1 RAs alone can provide.

Keywords: dual GLP-1/GIP receptor agonists; incretin-based therapy; type 2 diabetes management

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive pancreatic β-cell dysfunction, and persistent hyperglycemia [1]. Closely linked to obesity and cardiometabolic disease, T2DM represents a major global health burden requiring therapies that address both glycemic control and underlying metabolic dysfunction [1]. Current treatment guidelines from the American Diabetes Association and the European Association for the Study of Diabetes emphasize incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), due to their demonstrated efficacy in lowering hemoglobin A1c (HbA1c), promoting weight loss, and reducing cardiovascular risk [1–3].

The incretin effect refers to the enhanced insulin secretion observed following oral glucose ingestion compared with intravenous administration, mediated primarily by two gut-derived hormones: GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) (Figure 1) [2, 6]. In T2DM, this effect is diminished. GLP-1 secretion is modestly reduced, while β-cell responsiveness to GIP is markedly impaired, contributing to inadequate postprandial insulin secretion and progressive glycemic dysregulation [2, 6].

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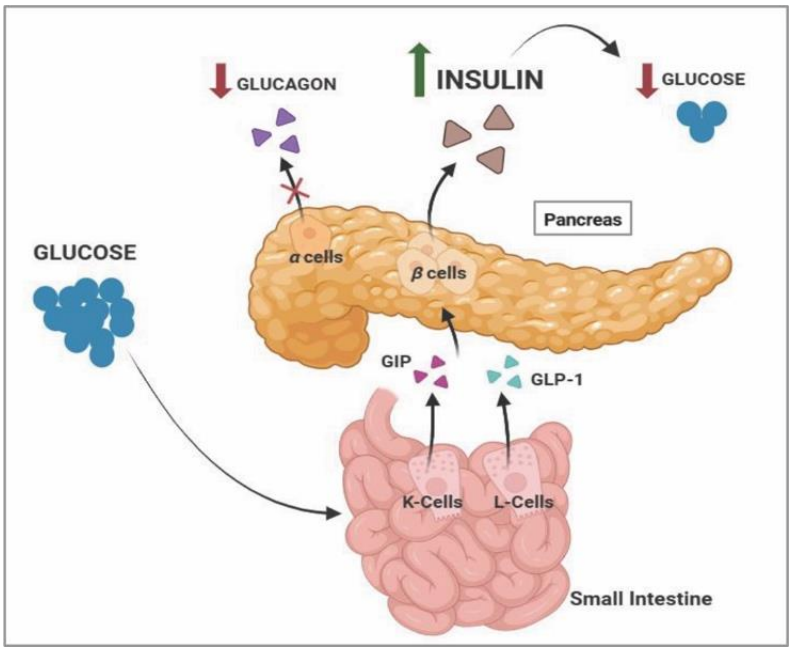

Figure 1. The Incretin Effect: After oral glucose intake, rising glucose levels stimulate K-cells and L-cells in the small intestine to release the incretin hormones GLP-1 and GIP. These hormones enhance glucose-dependent insulin secretion from pancreatic β-cells and suppress glucagon release from α-cells. Together, this results in a stronger post-meal insulin response and a more effective reduction in blood glucose levels (created using biorender.com).

GLP-1 RAs mimic endogenous GLP-1 activity by enhancing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety through central and vagal pathways (Figure 2) [4–6, 9]. Large cardiovascular outcome trials, including LEADER, SUSTAIN-6, and REWIND, have demonstrated cardioprotective benefits in high-risk populations, solidifying GLP-1 RAs as foundational therapy in T2DM management [11–12, 17]. However, some patients experience suboptimal glycemic response or insufficient weight reduction, suggesting that activation of GLP-1 signaling alone may not fully address the multifactorial pathophysiology of metabolic disease.

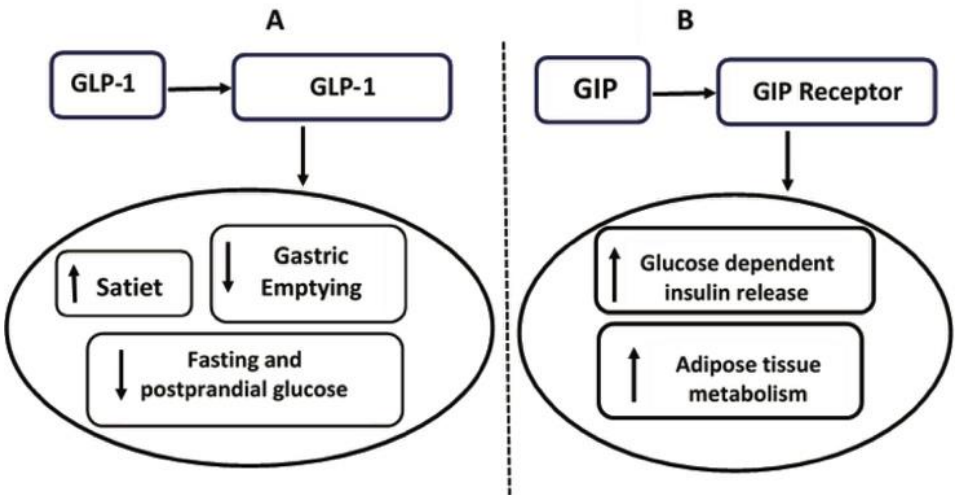

Figure 2. Schematic representation of GLP-1 and GIP receptor signaling. (A) Binding of GLP-1 to its receptor promotes satiety, delays gastric emptying, and lowers fasting and postprandial glucose levels. (B) Binding of GIP to its receptor enhances glucose-dependent insulin release and stimulates adipose tissue metabolism, contributing to integrated regulation of glucose and lipid homeostasis (created using Microsoft Word).

GIP, the second principal incretin hormone, binds to receptors on pancreatic β-cells to potentiate insulin secretion and acts on adipocytes to influence lipid metabolism and energy storage [6–8]. Although GIP responsiveness is diminished when stimulated alone in T2DM, emerging evidence indicates that simultaneous activation of GLP-1 and GIP receptors restores insulinotropic activity and produces complementary metabolic effects (Figure 3) [5, 8, 14]. Dual receptor activation enhances insulin secretion, modulates adipocyte metabolism, augments appetite suppression, and may attenuate GLP-1 associated gastrointestinal intolerance [5, 9, 14].

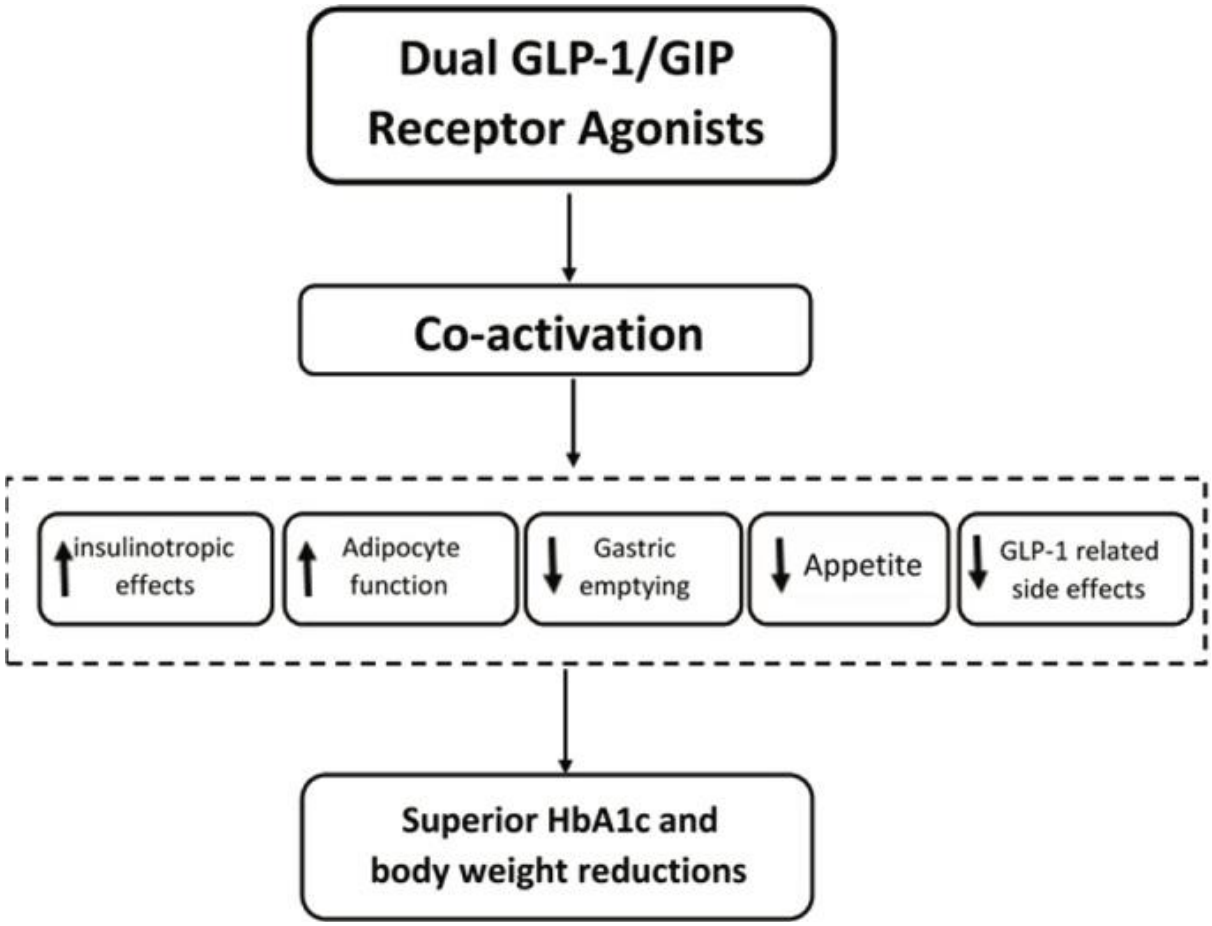

Figure 3. Schematic representation of dual GLP-1/GIP receptor agonist mechanisms. Co-activation of GLP-1 and GIP receptors amplifies insulinotropic effects, enhances adipocyte function, and mitigates GLP-1 related gastrointestinal side effects, resulting in superior HbA1c reduction and weight loss (created using Microsoft Word).

This mechanistic rationale has led to the development of dual GLP-1/GIP RAs, most notably tirzepatide. Phase 3 clinical trials, including the SURPASS and SURMOUNT programs, have demonstrated greater reductions in HbA1c and body weight compared with GLP-1 receptor agonists alone [5, 7, 13]. These findings suggest that dual incretin therapy may represent a significant advancement in the pharmacologic management of T2DM and related metabolic conditions. Accordingly, this review systematically evaluates how dual GLP-1/GIP RAs differ from GLP-1 RAs in pharmacologic rationale, clinical efficacy, safety profile, cardiovascular implications, and broader therapeutic potential.

Methods

This structured literature review was conducted in academic research setting to compare the mechanisms, clinical efficacy, safety, and therapeutic applications of dual GLP-1/GIP receptor agonists and GLP-1 receptor agonists in adults with type 2 diabetes. Searches were performed in PubMed, EMBASE, and Web of Science for studies published between January 2005 and January 2025 using terms related to incretin-based therapies, including "GLP-1 receptor agonist," "glucagon-like peptide-1," semaglutide (Ozempic, Wegovy), liraglutide (Victoza, Saxenda), "GIP receptor agonist," "dual agonist," tirzepatide (Mounjaro, Zepbound), "incretin therapy," "dual incretin," and "type 2 diabetes mellitus."

Reference lists of key articles were screened manually. Eligible studies were peer-reviewed randomized controlled trials, meta-analyses, or large observational studies involving adults aged 18 years or older that evaluated GLP-1 receptor agonists or dual GLP-1/GIP receptor agonists compared with placebo, standard therapy, or other incretin-based agents, and reported outcomes related to hemoglobin A1c, body weight, cardiovascular measures, or safety. Exclusion criteria included non-English publications, preclinical studies unless mechanistically essential, case reports, commentaries, conference abstracts, and studies restricted to pediatric or type 1 diabetes populations. Screening involved title and abstract review followed by full-text evaluation. Extracted data included study design, sample size, participant characteristics, interventions and comparators, drug doses, follow-up duration, and reported clinical outcomes, with particular attention to major trials such as SURPASS and SURMOUNT-1. Because of heterogeneity across study designs and outcome definitions, findings were synthesized narratively rather than through meta-analysis, and a power calculation was not applicable due to the absence of participant-level data.

Results

This review synthesizes comparative clinical outcomes between dual GLP-1/GIP RAs and GLP-1 RAs. Primary outcomes included glycemic control and body weight reduction, followed by cardiovascular outcomes and safety profiles.

Glycemic Control

GLP-1 RAs reduce HbA1c by approximately 1.0–1.5% in major trials, including SUSTAIN-6 (semaglutide) and REWIND (dulaglutide) [1, 9–12]. In the SURPASS trials, tirzepatide achieved HbA1c reductions up to 2.4%, exceeding those observed with semaglutide at the highest studied doses [5, 13]. A greater proportion of participants receiving tirzepatide achieved HbA1c levels below 5.7% across baseline HbA1c categories [2]. Long-term extension studies have reported sustained glycemic control with tirzepatide compared with GLP-1 receptor agonists [14].

Weight Loss Effects

GLP-1 RAs, particularly semaglutide, have shown significant weight loss benefits, with patients in the 68-week STEP trials losing 10-15% of baseline weight [16].

In comparison, the 72-week SURMOUNT-1 trial demonstrated that tirzepatide achieved even greater weight loss, with obese, non-diabetic participants losing up to 22% of baseline body weight [7]. Among patients with T2DM, tirzepatide also resulted in significantly greater weight reduction compared with semaglutide [5]. A larger proportion of participants receiving tirzepatide achieved weight reductions of 15% or more compared to GLP-1 RAs [7, 13].

Cardiovascular Outcomes

GLP-1 RAs have demonstrated significant reductions in major adverse cardiovascular events (MACE) across several large trials, including LEADER (liraglutide), SUSTAIN-6 (semaglutide), and REWIND (dulaglutide) [11–12, 17].

Cardiovascular outcome data for dual agonists are not yet available. Preliminary analyses have reported improvements in surrogate measures such as blood pressure, lipid levels, and inflammatory biomarkers [2]. The ongoing SURPASS-CVOT trial (tirzepatide vs. dulaglutide) will determine the long-term cardiovascular impact of dual receptor agonists [13].

Safety and Tolerability

Both GLP-1 RAs and dual agonists are generally well tolerated. Gastrointestinal (GI) adverse effects, including nausea, vomiting, and diarrhea occur in 20-30% of patients and are dose-dependent [3, 9]. These side effects typically diminish with continued therapy [3]. The risk of hypoglycemia remains low unless combined with insulin and sulfonylureas [9].

Dual agonists share a similar safety profile, with slightly higher rates of GI intolerance at higher doses of tirzepatide [2, 5]. Discontinuation rates due to side effects are comparable to GLP-1 RAs [5]. Rare adverse events include pancreatitis and gallbladder disease [9, 14]. Long-term safety outcomes, including pancreatitis and cardiovascular effects, remain under investigation [9, 14].

Expanded Indications Beyond T2DM

GLP-1 RAs are FDA-approved for obesity management and have demonstrated efficacy in individuals without diabetes [16]. In obesity-focused trials, tirzepatide achieved up to 22% body weight reduction and was associated with reductions in blood pressure (6–8 mmHg), triglycerides (20–25%), and inflammatory markers [7]. Improvements in obesity-related obstructive sleep apnea have also been reported, reflected by reductions in apnea-hypopnea index and body weight [4, 8]. Ongoing studies are evaluating dual agonists in metabolic dysfunction-associated steatohepatitis and metabolic syndrome [14–15].

Summary of Findings

Across major phase 3 clinical trials, dual GLP-1/GIP RAs consistently demonstrated superior glycemic and weight outcomes compared with GLP-1 RAs, with similar tolerability profiles (Table 1) [5, 7, 13]. Cardiovascular outcome data remain pending, although improvements in cardiometabolic risk markers have been observed [2, 9].

Table 1. Summary of pharmacologic mechanisms, clinical efficacy, and safety profiles of GLP-1 RAs and dual GLP-1/GIP RAs, illustrating their distinct and overlapping effects on glycemic control, weight reduction, and cardiovascular outcomes.

Category	GLP-1 Receptor Agonists (e.g., Semaglutide)	Dual GLP-1/GIP Receptor Agonists (e.g., tirzepatide)	Key References
Pharmacologic Rationale	Mimic GLP-1 to enhance glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying, and promote satiety	Activate both GLP-1 and GIP receptors to achieve synergistic enhancement of insulin secretion, adipocyte metabolism, and appetite suppression	Holst, 2007; Nauck & Meier, 2019; Drucker, 2022
Mechanistic Insight	Acts mainly via GLP-1 receptor-mediated satiety and delayed gastric emptying	Dual activation augments satiety and lipid metabolism beyond GLP-1 alone; mechanisms under ongoing study	Drucker, 2022; Min & Bain, 2021; De Block et al., 2022
Glycemic Control	HbA1c reduction: ~1.0–1.5% (SUSTAIN-6, REWIND). Proven durability	HbA1c reduction: up to 2.4% (SURPASS trials). More patients achieve normoglycemia (HbA1c <5.7%) and sustained control over time	Marso et al., 2016; Gerstein et al., 2019; Frias et al., 2021; Del Prato et al., 2021
Weight Loss	10–15% mean reduction in baseline weight (STEP program with semaglutide)	Up to 22% weight reduction in obesity trials (SURMOUNT-1). Greater proportion achieve ≥15% loss; significant benefit in T2DM and obesity	Wilding et al., 2021; Jastreboff et al., 2022
Cardiovascular Outcomes	Significant reduction in MACE (LEADER, SUSTAIN-6, REWIND). FDA/ADA guideline–endorsed, proven CV safety	Early data show BP, lipid, and inflammatory improvement; definitive outcomes pending SURPASS-CVOT results	Marso et al., 2016; Gerstein et al., 2019; Davies et al., 2022; Drucker, 2022
Safety Profile	GI side effects (nausea, vomiting, diarrhea in 20–30% of patients), mild and dose-dependent. Low hypoglycemia risk unless combined with insulin or sulfonylureas	Similar safety; slightly more GI intolerance at high doses. Comparable discontinuation rates. Pancreatitis and gallbladder risks remain low but monitored	Min & Bain, 2021; De Block et al., 2022; Drucker, 2022
Expanded Indications	Approved for T2DM and obesity (semaglutide)	Under investigation for obesity, OSA, MASH, and metabolic syndrome with strong early efficacy	El-Solh et al., 2025; Malhotra et al., 2024
Overall Efficacy Trend	Proven efficacy and safety, particularly for glycemic control and CV protection	Superior weight and HbA1c reduction, comparable safety, with pending long-term CV validation	Drucker, 2022; Frias et al., 2021; De Block et al., 2022

Discussion

The emergence of dual GLP-1/GIP RAs represents a major advancement in the pharmacologic management of type 2 diabetes. While GLP-1 RAs have transformed care through robust glycemic and cardiovascular benefits, the addition of GIP receptor activation offers an opportunity to further enhance metabolic control. Clinical evidence from phase 3 trials demonstrates that dual agonists, particularly tirzepatide, achieve greater reductions in HBA1c and body weight than GLP-1 RAs without compromising safety [5, 7, 13].

Therapeutic Significance

Findings from the SURPASS phase 3 trials (glycemic efficacy) and SURMOUNT-1 (obesity) trials demonstrate the enhanced metabolic effects achieved through dual GLP-1/GIP receptor activation [5, 7, 13]. These outcomes are supported by the complementary actions of GLP-1 and GIP. GLP-1 primarily enhances glucose-dependent insulin secretion, suppresses glucagon, delays gastric emptying, and suppresses appetite through central and vagal pathways [6, 9, 10], while GIP augments β-cell insulinotropic activity and modulates adipocyte metabolism [7, 9, 14]. Together, these mechanisms produce an integrated metabolic response that addresses both insulin resistance and excess adiposity, the two central drivers of T2DM progression [2, 14–15].

Cardiovascular Implications

Cardiovascular outcomes represent a critical distinction between established GLP-1 receptor agonists and emerging dual agonists. GLP-1 RAs have demonstrated consistent reductions in major adverse cardiovascular events (MACE) across multiple large trials, including LEADER,

SUSTAIN-6, and REWIND [11–12, 17]. These findings have informed ADA and EASD guidelines, which recommend GLP-1 receptor agonists as first-line injectable therapy in patients with established cardiovascular disease [1]. In contrast, definitive cardiovascular outcome data for dual GLP-1/GIP RAs are not yet available. Preliminary analyses report improvements in surrogate markers such as blood pressure, lipid levels, and inflammatory biomarkers [2, 9], and the ongoing SURPASS-CVOT trial will determine whether these agents confer cardiovascular protection comparable to GLP-1 receptor agonists [13]. Until outcome data mature, GLP-1 RAs remain the preferred option for patients with established atherosclerotic cardiovascular disease.

Safety Considerations

Safety and tolerability profiles are generally comparable between GLP-1 RAs and dual agonists, with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea, being most frequently reported [2–3, 5, 9]. Tirzepatide demonstrates slightly higher rates of gastrointestinal intolerance at higher doses, though these effects are typically transient and dose-dependent [5, 13]. Hypoglycemia risk remains low unless therapy is combined with insulin or insulin secretagogues [9]. However, long-term data regarding pancreatic safety, gallbladder disease, and β-cell preservation remain limited, underscoring the importance of ongoing surveillance and extended follow-up studies [9, 14].

Expanded Indications

Beyond T2DM, dual agonists demonstrate substantial promise in obesity and related metabolic conditions. The SURMOUNT-1 trial demonstrated that tirzepatide achieves weight loss of up to 22%, a magnitude approaching that historically observed with bariatric surgery, while also improving cardiometabolic risk factors including insulin sensitivity, lipid profiles, and systemic inflammation [7]. These findings position dual agonists as promising agents for obesity management, MASH, and obesity-related OSA [4, 8, 14]. Their broad metabolic activity also suggests potential utility in conditions such as metabolic syndrome and heart failure with preserved ejection fraction, where improvements in insulin resistance and weight are clinically advantageous [2, 14–15].

Limitations of Current Evidence

Despite compelling efficacy, interpretation of the current evidence is limited by the absence of definitive cardiovascular outcome data for dual GLP-1/GIP RAs, as dedicated trials such as SURPASS-CVOT remain ongoing [2, 5, 13]. In addition, long-term safety data, including risks of pancreatitis, gallbladder disease, and effects on β-cell preservation, remain limited and require extended follow-up and post-marketing surveillance [9, 14]. Furthermore, most available data derive from randomized clinical trial populations, which may not fully reflect real-world adherence patterns, cost-related barriers, or access disparities encountered in routine practice [1, 9].

Future Directions

Future research should prioritize completion of cardiovascular outcome trials, including SURPASS-CVOT, to determine whether dual GLP-1/GIP RAs confer cardioprotection comparable to GLP-1 RAs [2, 5, 13]. Long-term safety studies and mechanistic investigations into GIP-mediated effects on adipose tissue metabolism and appetite regulation are also needed to clarify durability of benefit and optimize patient selection [9, 14–15]. Expanded evaluation in obesity-related comorbidities such as metabolic dysfunction-associated steatohepatitis and obstructive sleep apnea will further define the therapeutic scope of dual agonists [4, 7–8].

Conclusions

Dual GLP-1/GIP RAs represent a significant advancement in incretin-based therapy, demonstrating greater reductions in HbA1c and body weight than GLP-1 RAs while maintaining comparable safety profiles [5, 7, 13]. Although definitive cardiovascular outcome data are pending, current evidence suggests potential benefit in patients with obesity or suboptimal metabolic control despite GLP-1 receptor agonist therapy [1–2]. These findings highlight the expanding therapeutic landscape in metabolic disease and underscore the importance of individualized treatment selection based on glycemic needs, cardiovascular risk, and weight-related comorbidities. As ongoing outcome trials clarify long-term cardiovascular and safety effects, dual agonists may assume an increasingly prominent role in the management of metabolic disease.

List of Abbreviations

A1c / HbA1c: hemoglobin A1c
ADA: american diabetes association
CVD: cardiovascular disease
EASD: European association for the study of diabetes
FDA: United States food and drug administration
GI: gastrointestinal
GIP: glucose-dependent insulinotropic polypeptide
GLP-1 RA: glucagon-like peptide-1 receptor agonist
GLP-1: glucagon-like peptide-1
HFpEF: heart failure with preserved ejection fraction
IV: intravenous
K-cells: intestinal K enteroendocrine cells
L-cells: intestinal L enteroendocrine cells
MACE: major adverse cardiovascular events
MASH: metabolic dysfunction-associated steatohepatitis
OSA: obstructive sleep apnea
RCT: randomized controlled trial
SURMOUNT-1: tirzepatide obesity trial
SURPASS: tirzepatide phase 3 clinical trial program
SURPASS-CVOT: tirzepatide cardiovascular outcomes trial
T2DM: type 2 diabetes mellitus

Conflicts of Interest
The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent
No ethics/participant consent was required to conduct this study.

Authors' Contributions
PB: made substantial contributions to the conception and design of the study, conducted the literature search, collected and analyzed the data, drafted the manuscript, revised the final version critically for intellectual content, approved it for publication, and agrees to be accountable for all aspects of the work.

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