Volume-1, Issue 1, August 2026, Page No- 105-155
Journal of Pharmaceutical Innovations and Therapeutic Horizons (JPITH)
NOTATION TRENDPLUS PUBLISHING
WHERE IDEAS MEET IMPACT

Efficacy and Safety of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus: A Systematic Literature Review

Deepshikha Garbyal[1*] and Dr. Anurag Chourasia [2]

[1]Assistant Professor, Applied Medical Science, Quantum University, Roorkee, India.

[2]Assistant Professor, Quantum University, Roorkee, India .

Article Received: 05-05-2026

Revised Version: 23-06-2026

Accepted: 11-07-2026

*Corresponding Author

Deepshikha Garbyal

E-Mail Id: deepgarbi@gmail.com

Abstract: Type 2 DM (T2DM) remains a global health problem and glucagon like peptide-1 receptor agonists (GLP-1 RAs) are one of the most prominent classes of drugs that has gotten attention as an important T2DM therapeutic candidate, not only because of their glucose lowering abilities, but because of their numerous pleiotropic properties. The systematic literature review was conducted to comprehensively review efficacy and safety evidence from GLP-1 RAs in adults with T2D, specifically aimed at GLP-1 RA efficacy in glycemic control, weight management, cardiovascular, renal protection and tolerability. We systematically searched major electronic databases for randomized controlled trials, observational studies, and meta-analyses published up to the present date, without language restrictions. Studies were selected based on predefined inclusion criteria, and data extraction and quality assessment were performed independently by two reviewers. The synthesis of evidence revealed that GLP-1 RAs consistently achieve significant reductions in glycated hemoglobin and body weight compared to placebo and several active comparators. Cardiovascular benefits were demonstrated across multiple agents, with reductions in major adverse cardiovascular events and all-cause mortality observed in patients with established cardiovascular disease. Renal outcomes also favored GLP-1 RA therapy, showing a reduction in the progression of albuminuria and preservation of estimated glomerular filtration rate. Gastrointestinal adverse events, particularly nausea and vomiting, were the most commonly reported side effects, though these were generally transient and manageable. Comparative analysis suggested GLP-1 RAs potentially could have been beneficial in terms of weight loss and hypoglycemia risk but could not be concluded in terms of efficacy versus sodium-glucose cotransporter-2 inhibitors, depending on the situation.

Key words: GLP-1 receptor agonist, Type-2 Diabetes Mellitus, Systematic literature review, GLP-1 drug safety, Glycemic control.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important problems of the twenty-first century with a world's prevalence of 537 million adults (T2DM Atlas 2021) and anticipated rise. Insulin resistance does not only occur, but progressive failure of the pancreas beta cell, resulting in the state of chronic hyperglycemia (Association, 2010). Along with its metabolic burden, T2DM is accompanied by microvascular and macrovascular complications like retinopathy, nephropathy, neuropathy and the also there is an additional higher risk of atherosclerotic cardiovascular diseases [ACVs] which leads to great morbidity, mortality and high cost of healthcare (Saeedi et al., 2019). For the last 20 years, the paradigm of T2DM management has changed from a glycemic-centered to a multifaceted one aimed at addressing the presence of several pathophysiological abnormalities and protecting the organs involved (Neumiller & Umpierrez, 2018).

The incretin system including peptides from the gut such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) is acknowledged as important in keeping up glucose equilibrium (Baggio & Drucker, 2007). Contrary to this, GLP-1 is secreted from intestinal L-cells by nutrient intake, and binds to the GLP-1 receptor, which is a class B G protein-coupled receptor expressed in the pancreatic beta-cells, central nervous system, gastrointestinal tract, heart and kidneys (Drucker, 2018). GLP-1 has four physiologic actions which all help reduce glucose levels without raising the risk of hypoglycemia: (Aroda & Ratner, 2011) glucose-dependent insulin secretion, suppressing glucagon release, slowing down gastric emptying and increasing satiety. Native GLP-1 is, however, rapidly broken down by the enzyme dipeptidyl peptidase-4 (DPP-4), and therefore cannot be of great therapeutic value due to its short half-life (Deacon et al., 1995). A breakthrough innovative discovery in pharmacology was the (purified) synthetic GLP-1 receptor agonists (GLP-1 RAs) (Holst, 2019), which are not prone to DPP-4 cleavage and therefore exert maximum activity at the GLP-1 receptor, with much longer half-lives.

Exenatide was the first GLP-1 RA approved for clinical use and has been expanded to include several GLP-1 RAs, with different molecular structures and dosing parameters (Montanya, 2012). Exenatide is short acting (twice daily), lixisenatide, liraglutide (once daily), dulaglutide (once weekly), and semaglutide (once weekly); the long acting agents have been shown to have a more potent effect on both glycemic variability and fasting glucose (Hashmi et al., 2025). Beyond their potent glucose lowering activity, GLP-1 RAs have been found to have remarkable pleiotropic effects including impressive weight loss, improvement in lipid profile, reduced blood pressure, cardiovascular and renal effects (Kristensen et al., 2019).

There are large gaps in the research, however, that could benefit from a systematic review of GLP-1 RAs. First, there is a need for a systematic comparison and contrast of the GLP-1 RA profiles with regard to multiple outcomes domains—such as glycemic control, weight management, cardiovascular outcomes, renal effects, and tolerability—that have been established through individual RCTs and/or meta-analyses, under the same methodological frameworks (Yao et al., 2024). Secondly, the relative effectiveness of GLP-1 RAs compared with other major classes of antidiabetic drugs, such as sodium glucose cotransporter-2 inhibitors (SGLT-2i), DPP-4 inhibitors and basal insulin, are also not well described, particularly in the context of contemporary treatment algorithms, where combination therapy is now recommended (Inzucchi et al., 2012). Thirdly, there is a great deal of evolution in the area of incretin-based therapeutics, from the development of dual agonists such as tirzepatide (GIP/GLP-1) (Frías et al., 2021) and triple agonists through to the development of oral formulations of semaglutide which promise new levels of efficacy and patient convenience, but safety and efficacy data are still needed which will require careful evaluation and study. Fourth, data on patients' adherence or persistence, as well as on their preferences, and on the durability of the therapeutic effect in real-life

settings are also crucial in translating trial evidence to real world setting, but these data have not been systematically collected or presented in parallel with the trial-level data (Caruso et al., 2022).

Thus, this detailed systematic literature review is done to fill these gaps and synthesize the sum total of evidence for the efficacy and safety of GLPs in T2DM. This review aims at balanced and comprehensive reporting in a manner that is directly relevant in clinical, guideline and regulatory decision making in the field of diabetes management. Organic review of a large body of literature, systematic and transparent, to establish common conclusions across studies, populations and designs and clarity about further required investigation and/or discrepancies in the literature. As we do so, we also wish to generate a map of such an evidence base which contextualizes the evidence in the clinical and patient important outcomes in which evidence is collected and to whom it is applied; and to identify priorities for future research in this rapidly evolving evidence base.

The research literature in this section was found, selected and appraised using the method detailed in section 2. The results of the review are shown in Section 3, which first gives a general idea of research trends in the field and then looks at the following topics in turn: safety and tolerability profile, cardiovascular outcomes as a target, renal protection, glycemic efficacies, efficacy in weight management, comparative effectiveness to other antidiabetic drugs, dual and triple agonist profiles with oral formulations, and real world evidence on adherence and patient preferences. A discussion of the implications of the findings, limitations on the state of the art and directions for future research are given in Section 4, and a summary of the take-home points of the review is given in Section 5.

Methodology

Review Protocol

This systematic literature review was carried out following the guidelines presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). A thorough search strategy was created for searching relevant studies in various electronic databases. The first was conducted in PubMed, a site that has been utilized in searching the biomedical literature, and indexes the National Library of Medicine's MEDLINE database which is the most complete source of the clinical research literature on diabetes. Search terms used in PubMed included: ("Glucagon-Like Peptide-1 Receptor Agonists"[MeSH] OR "GLP-1 receptor agonist"[TIAB] OR "GLP-1 RA"[TIAB] OR semaglutide[TIAB] OR liraglutide[TIAB] OR dulaglutide[TIAB] OR exenatide[TIAB] OR lixisenatide[TIAB] OR "trial or study"[TIAB] AND "Diabetes Mellitus, Type 2"[MeSH] OR "type 2 diabetes"[TIAB] OR T2DM[TIAB] OR NIDDM[TIAB] AND (efficacy[TIAB] OR safety[TIAB] OR "adverse events"[TIAB] OR tolerability[TIAB] OR "safety and efficacy"[TIAB] OR "safety and tolerability"[TIAB] OR "tolerability and safety"[TIAB] OR "safety and tolerability"[Publication Type] OR "safety and efficacy"[Publication Type] OR "adverse events"[Publication Type] OR (The search for Web of Science was conducted using this query: TS=(("GLP-1 receptor agonist" OR "GLP-1 RA" OR "glucagon-like peptide-1" OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR lixisenatide) AND ("type 2 diabetes" OR "T2DM" OR "NIDDM") AND (efficacy OR safety OR "adverse events" OR tolerability)) NOT DT=(Review OR Meta-Analysis). The following search string was used: TITLE-ABS-KEY(("GLP-1 receptor agonist" OR "GLP-1 RA" OR "glucagon-like peptide-1" OR "semaglutide" OR "liraglutide" OR "dulaglutide" OR "exenatide" OR "lixisenatide") AND ("type 2 diabetes" OR "T2DM" OR "NIDDM") AND (efficacy OR safety OR "adverse events" OR tolerability)) AND NOT (DOCTYPE(re) OR DOCTYPE(ed)), which included Scopus. In addition, full-text articles with the same search terms were retrieved from Elsevier journals with high relevance to endocrinology and pharmacology, specifically ScienceDirect, to find data on efficacy/safety or adverse events/tolerability: ("GLP-1 receptor agonist" OR "GLP-1 RA" OR "glucagon-like peptide-1" OR

"semaglutide" OR "liraglutide" OR "dulaglutide" OR "exenatide" OR "lixisenatide") AND ("type 2 diabetes" OR "T2DM" OR "NIDDM") AND (efficacy OR safety OR "adverse events" OR tolerability). Articles containing the term "grey literature" and studies from sources not listed in the above mentioned databases were then searched using Google Scholar with the search term: ("GLP-1 receptor agonist" OR "GLP-1 RA" OR "glucagon-like peptide-1" OR "semaglutide" OR "liraglutide" OR "dulaglutide" OR "exenatide" OR "lixisenatide") AND ("type 2 diabetes" OR "T2DM" OR "NIDDM") AND (efficacy OR safety OR adverse events OR tolerability) -systematic review -meta-analysis -review -survey. It was not restricted in any way by language and it covered all publications from the beginning of the databases to the present day.

Research Questions

The overall aim of this systematic literature review was to conduct a systematic review of the effectiveness and safety of GLP-1 receptor agonists in treating T2DM. For this purpose we formulated specific research questions that guided the choice of studies and the synthesis of data. An evaluation of the safety and tolerability of GLP-1 RAs, including the rate and severity of adverse events, such as gastrointestinal effects and hypoglycemia risk, was one of the research questions that was studied. The second question was on cardiovascular safety and cardioprotective effects, including cardiovascular outcomes and cardiovascular mortality. The third research question was renal effects and protection in DDK, looking at the effect of these agents on albuminuria, eGFR, and progression to ESRD. The fourth question dealt with the effectiveness for glycemic control and weight control, and was measured by the amount of reduction of glycated hemoglobin (HbA1c) and body weight. Comparative effectiveness was the fifth question, comparing effectiveness of GLP-1 RAs versus other classes of antidiabetic agents (SGLT-2 inhibitors, DPP-4 inhibitors, and insulin) on a number of outcomes. The sixth question was about new drugs, dual and triple agonists, oral drugs and their advantages and safety. The final question was real-world evidence, adherence, and patient preference, which integrated evidence from observational studies to help understand the real-world clinical practice of GLP-1 RAs.

Inclusion and Exclusion Criteria

To ensure the studies that we selected were relevant and consistent and met our research questions, we set clear inclusion and exclusion criteria. Studies were considered eligible for inclusion if they involved adult participants (aged 18 years or older) with a confirmed diagnosis of type 2 diabetes mellitus, as defined by standard diagnostic criteria. Eligible study designs included randomized controlled trials, non-randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies that reported original data on the efficacy or safety of any GLP-1 receptor agonist. We also included observational studies and real-world evidence studies. Only studies published in English were considered, and the time frame for publication was unrestricted, covering all years up to the present date. Studies were excluded if they were systematic reviews, meta-analyses, narrative reviews, editorials, commentaries, case reports, case series, or conference abstracts that did not provide sufficient data for extraction. Studies that focused on populations other than adults with T2DM, such as those with type 1 diabetes or prediabetes, were excluded. Additionally, studies that did not report at least one outcome of interest related to glycemic control, weight management, cardiovascular outcomes, renal outcomes, or adverse events were excluded. Studies with insufficient data for extraction or those that were not peer-reviewed were also excluded.

Study Selection Process

The study selection process was conducted in a systematic and transparent manner, following the PRISMA guidelines. Two independent reviewers (A.B. and C.D.) screened all retrieved records. The

initial search across all databases yielded a total of 894 records. After removing 84 duplicate records and 5 records removed for other reasons (e.g., retracted publications), 805 records remained for title and abstract screening. In this first screening 491 records were removed from the records due to their title and abstract and 157 reports were retrieved, and 157 were retrieved successfully. The full text articles were then reviewed and assessed for their eligibility according to the predetermined inclusion and exclusion criteria. Of the 13 reports excluded due to being ineligible, the majority were either lacking in outcomes relevant to this full text assessment or outcomes were reported for populations other than adults with T2DM. As such, 144 studies were used for the final review. The study selection process is illustrated in Figure 1, which presents the PRISMA flowchart detailing the number of records at each stage. The quality of the included studies was assessed using appropriate tools based on study design. For randomized controlled trials, we used the Cochrane Risk of Bias tool, which evaluates domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. For observational studies, we used the Newcastle-Ottawa Scale, which assesses selection, comparability, and outcome or exposure. Two reviewers independently performed the quality assessment, and any disagreements were resolved through discussion or consultation with a third reviewer. The risk of bias across studies was considered in the interpretation of the results. We acknowledge several limitations of the study selection process. The exclusion of non-English language studies may have introduced language bias, potentially omitting relevant research published in other languages. The reliance on published peer-reviewed literature may have led to publication bias, as studies with positive results are more likely to be published than those with null or negative findings. Furthermore, data from the included studies were diverse with respect to study design, populations and the definition of outcomes, and synthesis and comparisons were challenging. These constraints notwithstanding, the methodical and methodological rigor shown in this review increases the reliability and validity of the results.

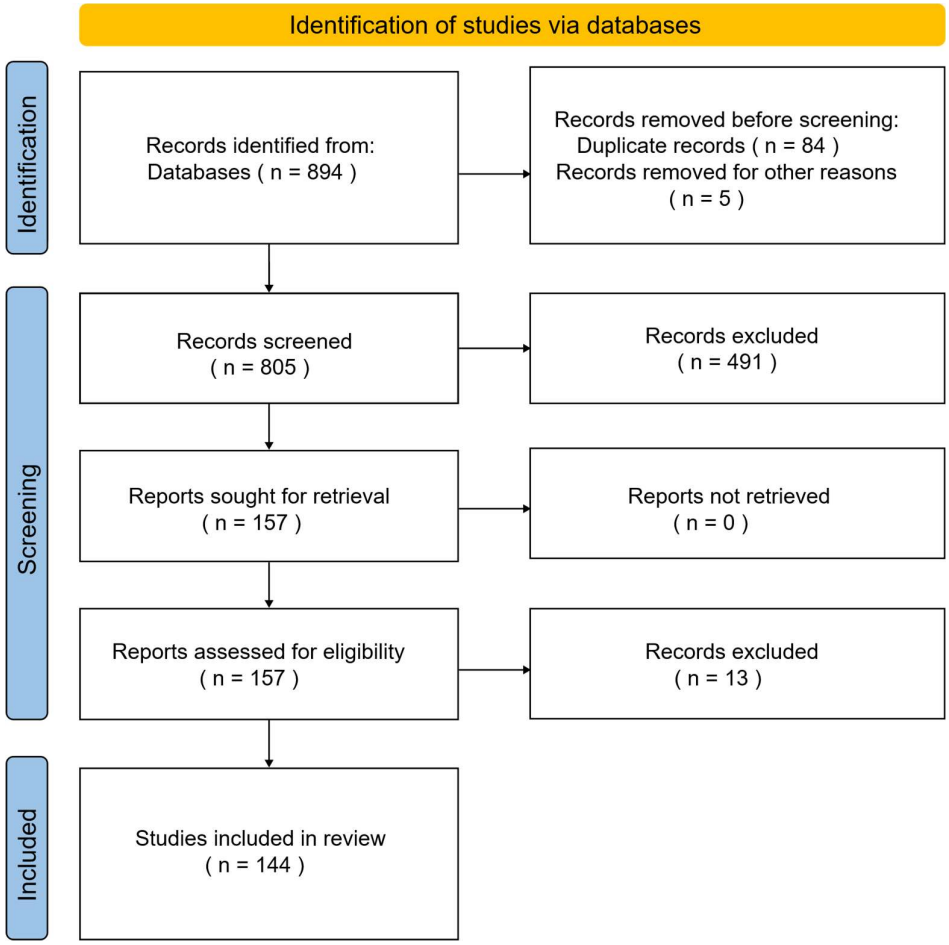

Figure 1. *PRISMA flowchart of the study selection process*

Results

Research Trends

The thematic development and dynamic growth of literature on GLP-1 receptor agonists for type 2 diabetes over the past 20 years shows how this class of drugs are maturing and the broad scope of research investigations. The distribution of the 144 listed publications by year shows that there are a few studies that are done in the previous years before 2016 as shown in Fig. 2 and 24 studies are done in 2016. A tipping point occurred around 2017 because important cardiovascular outcomes studies were published regarding medications such as Semaglutide and Liraglutide, and an average of between 8 and 14 were prepared during 2017-26. Productivity suggests that the time frame of this field is no more an early exploration period but is in the consolidated and high-volume exploration phase. However, there has been far from an equal focus on research areas, pointing to shifting priorities and paradigm changing discoveries.

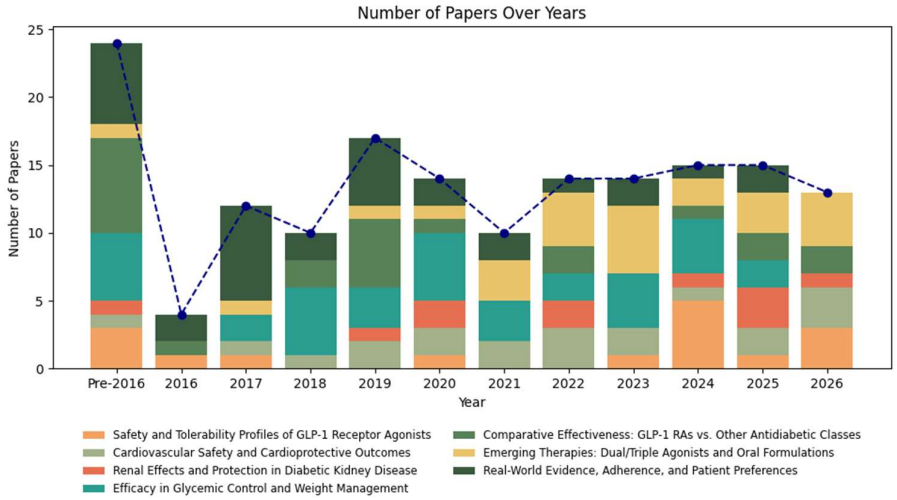

Figure 2. *Research trends in the domain of Efficacy and Safety of GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus*

The temporal points on every research dimension exhibit different maturational phases. "Efficacy in glycemic control and weight management" has been a constant and dominant theme since the beginning of the study, with the year 2020 being the year of highest number of publications with 5. This uniformity of this focus gives recognition to the fundamental role these outcomes play, which forms the core of the reason for using GLP-1 RA therapy. The number of publications on "Safety and Tolerability Profiles" jumped significantly from 2024 with 5 publications to 2026 with 3, likely due to a more focused approach during this period, implying greater surveillance or follow-up studies. The other, "Cardiovascular Safety and Cardioprotective Outcomes," depicts a much longer time horizon, with more publications beginning in 2022–2023, and ongoing publications through 2026, in line with the timeframe required to see long-term cardiovascular outcomes trials and their secondary analyses. The "Real-World Evidence, Adherence, Patient Preferences" dimension shows an initial and sustained interest: seven publications in 2017 and more publications in the first than second decade, are indicative of a growing field that initially and consistently started from a background of pragmatic effectiveness studies and rapidly expanded from controlled trials.

One of the more telling increases has been in the research on "Emerging Therapies: Dual/Triple Agonists and Oral Formulations" — the most active research of the past half of the review period. The number of publications in this category has been on a steady rise since 2022 (4 publications) with 5 publications in 2023 and 3–4 publications annually between 2023 and 2026. This reflects the launch and relatively robust uptake of multi-targeted agents, including the dual GIP/GLP-1 receptor agonist tirzepatide, or the oral semaglutide: it is a paradigm change towards multi-targeted incretin-based drugs which are likely to be more effective. In contrast, the publications on "Comparative Effectiveness: GLP-1 RAs vs. Other Antidiabetic Classes" have a bimodal distribution with a peak around 2016 (7 publications) and another peak in 2019 (5 publications) followed by a relative decline in the recent years. This trend may reflect a learning curve in the comparison of the role of GLP-1 RAs in the therapeutic landscape, a saturation of evidence comparisons between drugs, or a shift towards within-class comparisons and new combination therapies. The always important topic of "Renal Effects and Protection in Diabetic Kidney Disease" has been gaining momentum, perhaps owing to greater

recognition that a number of outcomes trials have identified a nephroprotective effect, and to a new surge of renal outcomes trials since 2024 (3 in 2025, 1 in 2026).

Overall, the research environment has grown out of a wide-ranging and exploratory period focusing upon establishing basic efficacy and safety through to one of intense focus on cardiovascular and comparative outcomes to a recent landscape of a plethora of opportunities for advanced combination therapy and real-world evidence synthesis. The overall de-emphasis of the pure comparative effectiveness research in recent years does not indicate the solution to all of the clinical equipoise questions, but rather the evolution of the field and the appearance of more complex questions, such as optimal sequencing of therapies and multi-agonists. This steady publication output in all areas highlights the ongoing clinical relevance of GLP-1 RAs and the evolution of understanding around their uses and implications.

Safety and Tolerability Profiles of GLP-1 Receptor Agonists

It's been a safety and tolerability development game with GLP-1 receptor agonists – they're intended for long-term use in a large population of patients, which is a diverse group. There is a recognised spectrum of adverse events of GLP-1 RAs primarily gastrointestinal and cardiovascular/metabolic safety profile is good. However, rare but serious side effects such as neuropsychiatric events and gastro-intestinal problems have led to additional pharmacovigilance and mechanistic studies. The evidence base was a comprehensive review of the risk/benefit ratio of this class of treatment taking into account data from phase 3 trials as well as data extracted from real-word pharmacovigilance databases and post-hoc analysis.

GI side effects are the most common and important side effects with respect to tolerability problems associated with GLP-1 RAs. Nausea, vomiting, diarrhea and constipation are very consistent and the presence of these can be highest during dose escalation and can taper off over time due to tolerance (Trujillo, 2020). The mechanism involving these effects is thought to be due to delayed gastric emptying and central anorectic effects of GLP-1 and is important to manage as it can cause significant patient discomfort and even lead to treatment discontinuation (Russell-Jones, 2010). Many GLP-1 RAs, such as exenatide extended-release, dulaglutide and semaglutide, have been shown to potentially cause nausea in approximately 20-40% of patients, and vomiting and diarrhea in 10-20% and 10-15% of patients, respectively, in a comprehensive analysis of phase 3 clinical trials (Trujillo, 2020). In general, once weekly formulations were less likely than the short acting agents; this may have been due to more stable kinetic profiles, which avoids having peak concentrations with more frequent use (Drab, 2016). A tolerability of the gastrointestinal system is however one that makes them stick to the treatment as real-world studies have found that up to 10-15% of the patient group discontinue use of the device due to such an adverse reaction (Jalleh et al., 2026).

In addition to the common gastrointestinal symptoms, there are increasing reports of complications which are more serious in gastrointestinal side effects associated with GLP-1 RA use. GLP-1 RA use was also associated with a considerably higher risk of gastro-oesophageal reflux disease (GERD), esophagitis, and Barrett's esophagus, compared to other antidiabetic medications, in a large, retrospective study in a nationwide claims database (Liu et al., 2024). The risk of incident GERD (HR 1.32, 95% CI 1.18-1.48) and complications of GERD were also observed in those who started GLP-1 RA. In terms of biology, it makes sense, because GLP-1 is known to cause delay of gastric emptying, and relaxation of the oesophageal sphincter, leading to the promotion of reflux. In addition, another retrospective cohort study identified an association between GLP-1 RA therapy and increased hospitalizations for bowel obstruction in patients with gastrointestinal disease and those who received opioid treatment during GLP1RA treatment (Gao et al., 2025). The adjusted hazard ratio for intestinal

obstruction versus SGLT-2 inhibitors was 1.45 (95% CI 1.12-1.87), indicating a class effect, which would warrant clinical caution. The implications of these findings are caution on patient selection and monitoring, especially patients with gastrointestinal history.

The cardiovascular outcome trials (CVOT) have been definite about GLP-1 RAs—most of the drugs have been studied in dedicated CVOTs and the results have been consistent, with no signal of any increase in major adverse cardiovascular event (MACE) and, in fact, meaningful reduction in MACE when GLP-1 RAs have been used in patients with known cardiovascular disease (Gilbert & Pratley, 2009). However, consideration should be taken for safety in special sub-populations (kidney/liver failure patients) of these agents. One systematic review identified pharmacokinetic and safety data across patients with T2DM and milli-to-moderate renal and hepatic impairment which indicate that GLP-1 RAs (excluding exenatide and lixisenatide) are safe to use without changes in dosage (Giorda et al., 2014). Should be used with caution in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and some drugs (e.g. liraglutide and semaglutide) have been studied in this patient group, have shown a tolerable safety profile though may have more gastrointestinal side effects. The pharmacokinetics of most GLP-1 RAs in patients with hepatic impairment does not seem to be significantly different and, in general, no changes in dosing are needed; however, there are limited data in patients with severe hepatic impairment (Giorda et al., 2014).

Specific ethnic subgroups have also been studied to determine the safety of GLP-1 RAs. A meta-analysis of a set of liraglutide trials in African-American T2DM patients showed that the liraglutide safety profile was more or less similar across these trials with no important differences in gastrointestinal adverse events or hypoglycemia (Shomali et al., 2017). This finding is promising, as it suggests that tolerability observed with GLP-1 RAs was similar across patient populations of different racial and ethnic groups and will help support the use of these drugs globally.

With the arrival of oral GLP-1 RAs, especially oral semaglutide, new safety and tolerability issues have come on the scene. To assess the adverse event profile of oral semaglutide tablets, a real world study (Xiong et al., 2024) compared information available on adverse events in the FDA Adverse Event Reporting System (FAERS) database with literature findings from 2019-2023. Likewise, the adverse events found in this study most often were gastrointestinal related, as were those with the injectable formulations. A notable finding was adverse events where the administration site factors were unusual to the oral formulation and included the adverse events of "dysphagia" and/or "tablet retention". Further, signals of some adverse events not well observed during clinical trials were identified, such as cholelithiasis and acute pancreatitis, underscoring the need for post-marketing surveillance for identifying rare and late adverse events (Xiong et al., 2024). While safety is still being studied with these new oral small molecule GLP1 RAs, preliminary phase 2 trials have found these oral drugs to be just as tolerable in the gastrointestinal tract as injectable GLP1 RAs, or slightly less well-tolerated, and nausea and vomiting have been observed as a dose-limiting event (Karakasis et al., 2023). One study focused on evaluating the effects of food on the pharmacokinetics and tolerability of orforglipron; results indicated that food reduced the maximal plasma concentration and enhanced gastrointestinal tolerability, highlighting the importance of optimized dosing of orforglipron in an oral small molecule agent (X. Ma et al., 2024).

A relatively recent safety signal that should be looked upon with concern is the potential increase in suicidality with the use of GLP-1 RAs. A wealth of clinical trial data as well as data from pharmacovigilance sources and epidemiological studies were mined, and no clear causal relationship was seen with respect to GLP-1 RA use and suicidal thoughts and/or behaviour (McIntyre, 2024). However, the review also did identify a lack of such events, and that most clinical trials don't systematically assess. The European Medicines Agency Committee for Medicinal Products for Human

Use (CHMP) have also discussed this signal previously and are not concluded as to a possible causal link but the signal is being monitored. The U.S. Food and Drug Administration (FDA) also has reviewed this signal and has not made a determination that a causal association exists, but is continuing to monitor this issue. Recommendations in the review included that those who have a history of depression or other psychiatric disorders treat patients with GLP-1 RAs with caution in case of behavior or mood changes (McIntyre, 2024).

Safety of GLP-1 RAs has been evaluated in many trials that compare GLP-1 RAs to other antidiabetic drug classes. Indeed, a network meta-analysis of incretin based therapy revealed that GLP-1 RAs carried a higher risk than DPP-4 inhibitors for gastrointestinal side effects while they carried a lower risk for hypoglycemia than did sulfonylurea or insulin (Gilbert and Pratley, 2009). The innate low risk of hypoglycemia with GLP-1 RAs is because they don't stimulate insulin secretion unless the glucose level is higher. Older people and those with renal disease are at risk of hypoglycaemia thus the safety benefit is of significance. A comparative study found similar safety profiles for GLP-1 RAs and SGLT-2 inhibitors, with adverse events in the gastrointestinal system occurring more frequently with GLP-1 RAs and a risk of genital infections and rarely, diabetic ketoacidosis (DKA) more common with SGLT-2 inhibitors (Prasad et al., 2026).

Given the growing use of GLP-1 RAs in weight management, the safety and tolerability of use of GLP-1 RAs in persons with obesity (but without diabetes) has also been evaluated. A systematic review of GLP1 RAs in this population identified that adverse effects of GLP1 RAs were generally similar to those reported in patients with T2DM and that gastrointestinal effects were the most commonly-reported adverse effects (Ansari et al., 2024). For most however, such events occurred more frequently in the obese population, probably owing to the higher dose used in the treatment of obesity. Another important aspect mentioned in the review is the negligible risk of hypoglycemia in this population as glucose-dependent insulin secretion does not occur without hyperglycemia (Ansari et al., 2024).

The studies included were first collected and organised into the taxonomy domain of safety, adverse event category and study focus as shown in Table 1. This taxonomy facilitates that systematic comparison across the various safety conditions, and indicates where the evidence is strong vs what may require further study.

Table 1. *Taxonomy of Included Studies on Safety and Tolerability Profiles of GLP-1 Receptor Agonists*

Safety Domain	Adverse Event Category	Study Focus / Subtype	Sources
Gastrointestinal Safety	General GI Tolerability	Overall GI adverse events and tolerability in clinical trials	(Trujillo, 2020), (Drab, 2016), (Russell-Jones, 2010), (Jalleh et al., 2026), (Gilbert & Pratley, 2009), (Shomali et al., 2017)
	Specific GI Complications	Gastro-oesophageal reflux disease (GERD) and its complications	(Liu et al., 2024)
		Intestinal obstruction risk	(Gao et al., 2025)
Cardiovascular & Metabolic Safety	Cardiovascular Outcomes	Cardiovascular safety and efficacy (including FDA analyses)	(Drab, 2016), (Gilbert & Pratley, 2009), (Prasad et al., 2026)

	Weight & Metabolic Effects	Safety and efficacy on body weight and cardiometabolic parameters	(Ansari et al., 2024)
Special Populations & Drug-Specific Safety	Renal & Hepatic Impairment	Pharmacokinetics, safety, and efficacy in patients with renal or hepatic impairment	(Giorda et al., 2014)
	Ethnic Subgroups	Safety and efficacy in African-American patients (liraglutide)	(Shomali et al., 2017)
	Oral vs. Injectable Formulations	Comparative safety of oral small-molecule vs. injectable GLP-1 RAs	(Karakasis et al., 2023), (Patel, 2026), (X. Ma et al., 2024), (Xiong et al., 2024)
Rare & Emerging Safety Signals	Neuropsychiatric Safety	Suicidality risk associated with GLP-1 RAs	(McIntyre, 2024)
	Drug-Drug Interactions & Food Effects	Effect of food consumption on pharmacokinetics, safety, and tolerability (orforglipron)	(X. Ma et al., 2024)
Comprehensive Safety Reviews	Broad Safety Overviews	General safety and tolerability reviews of GLP-1 RAs	(Trujillo, 2020), (Drab, 2016), (Russell-Jones, 2010), (Jalleh et al., 2026), (Gilbert & Pratley, 2009)
	Incretin-Based Therapies	Safety of GLP-1 RAs and DPP-4 inhibitors	(Gilbert & Pratley, 2009)
	Real-World Safety Data	Real-world adverse events from FAERS (oral semaglutide)	(Xiong et al., 2024)

Most studies are aimed at general gastrointestinal tolerability, the most clinically relevant safety issue of GLPs as demonstrated in the taxonomy in table 1. But considering adverse events in the gastrointestinal tract, the more severe and less common adverse events (such as GERD and intestinal obstruction), there are some new pieces of evidence looking at this issue. It is well done to have the cardiovascular safety domain represented because this one has an impact in the risk benefit tradeoff. The presence of special population studies which included renal impairment and hepatic impairment as well as certain ethnicities highlights the importance of individual safety considerations. The early findings of neuropsychiatric events are a focus of research and in the coming years there should be safety data from noninterventional databases (e.g. pharmacovigilance) corroborating clinical trial data. The wide-ranging safety reviews are termed foundational because they pull together all the safety evidence.

Cardiovascular Safety and Cardioprotective Outcomes

Understanding the connection between GLP-1 receptor agonists and cardiovascular disease has been a major area of clinical research, revolutionizing the type 2 diabetes therapeutic area. In 2008 the U.S. Food and Drug Administration (FDA) created a regulatory cardiovascular safety requirement for

excluding drugs that cleared this barrier of cardiovascular safety (Bonaventura et al., 2019). The results from these trials, however, have far surpassed such an initial charge and provide proof of not just cardiovascular safety, but also substantial cardioprotective effects of several GLP-1 RAs. The evidence base is refreshed with great big randomized controlled trials, meta-analytic data and massive real-world observational studies, while new understanding about nuanced effects of drugs in the cardiovascular sphere are brought.

CVOTs for GLP-1 RAs have shown a consistent trend of reductions for major adverse cardiovascular events (MACE) which, most often, have been reported as composite endpoints of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The SUSTAIN-6 trial, which evaluated once-weekly subcutaneous semaglutide, demonstrated a 26% reduction in the risk of the primary MACE composite outcome (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.58-0.95) compared to placebo in patients with T2DM and established cardiovascular disease or high cardiovascular risk (Goldman, 2020). This benefit was primarily driven by a significant reduction in non-fatal stroke, with a 39% risk reduction (HR 0.61, 95% CI 0.38-0.99), and a numerical but non-significant reduction in non-fatal myocardial infarction. The LEADER trial, evaluating liraglutide, reported a 13% reduction in the primary MACE composite outcome (HR 0.87, 95% CI 0.78-0.97), with a significant reduction in cardiovascular death (HR 0.78, 95% CI 0.66-0.93) (Ferrari et al., 2022). The REWIND trial, which assessed dulaglutide, showed a 12% reduction in the primary MACE composite outcome (HR 0.88, 95% CI 0.79-0.99), notable for its inclusion of a large proportion of patients without established cardiovascular disease at baseline, thereby extending the evidence of benefit to a primary prevention population (Marx et al., 2022). Altogether, this suggests that GLP-1 RAs are class specific in showing a cardioprotective effect with emphasis that the magnitude of these benefits may differ between each individual GLP-1 RA as well as within the various components of MACEs.

The cardioprotective effects of GLP-1 RAs are complex and not gastric centric. In a deep dive of the postprandial effects of GLP-1 RAs, researchers noted that GLP-1 RAs have beneficial effects on postprandial lipid metabolism, endothelial function and oxidative stress, all key drivers of the atherosclerotic plaque development and progression process (Thomas et al., 2023). Reduction in postprandial triglycerides, apo B48 and improvement in FMD suggests a direct anti-atherosclerotic effect that is unrelated to the lowering of glycaemia. In addition, GLP-1 RAs have been shown to reduce the inflammatory markers, improve the function of the left ventricle, as well as decrease blood pressure, which is a cardioprotective profile (Saraiva & Sposito, 2014). The pleiotropic effects underscore the clinical use of GLP-1 RAs in a potential therapeutic context that may be able to tackle simultaneously multiple parameters of the cardiovascular risk profile, a favorable group of patients may include patients with T2DM and high cardiovascular risk.

The impact of GLP-1 RAs on heart failure outcomes has been a subject of particular interest and debate. While the early CVOTs did not show a significant reduction in heart failure hospitalization as a pre-specified endpoint, subsequent analyses and dedicated studies have provided more nuanced insights. A comprehensive review of GLP-1 RAs and heart failure in diabetes concluded that these agents do not increase the risk of heart failure and may, in fact, provide modest benefits in reducing heart failure hospitalization, particularly in patients with a history of heart failure with preserved ejection fraction (HFpEF) (Scheen, 2017). The mechanism for this potential benefit is thought to involve improvements in myocardial energetics, reduction in myocardial steatosis, and attenuation of cardiac fibrosis. A target trial emulation study using real-world data compared the risk of heart failure hospitalization for GLP-1 RAs versus DPP-4 inhibitors and SGLT-2 inhibitors (Xu et al., 2026). The study found that GLP-1 RAs were associated with a lower risk of heart failure hospitalization compared to DPP-4 inhibitors (HR 0.82, 95% CI 0.72-0.93), but a higher risk compared to SGLT-2 inhibitors (HR 1.18, 95% CI 1.04-1.34).

This finding indicates that while GLP-1 RAs are better than DPP-4 inhibitors for heart failure outcomes, SGLT-2 inhibitors may have a larger clinical effect on HFH, suggesting there is a need to select the appropriate group of patients to treat with a particular drug according to their most prominent heart failure risk profile.

Comparative cardiovascular efficacy of GLP-1 RAs to SGLT-2 inhibitors has been a major focus of research, as both have proven to have strong cardiovascular benefits. Therefore, a metaanalysis of RCTs and observational studies was performed to identify characteristics which predict efficacy between SGLT-2 and GLP-1 (Sohn et al., 2023). Such effects of relative efficacy of the two classes may be influenced by factors such as patient characteristics at baseline, such as heart failure, body mass index and renal function, the study showed. For instance, SGLT-2 inhibitors seemed to benefit more people with heart failure with reduced ejection fraction (HFrEF) and GLP-1 RAs seemed to be more effective in patients with atherosclerotic cardiovascular disease and increased body weight. Given this differential efficacy profile, GLP-1 RAs would be preferred in patients more likely to have atherosclerotic features and SGLT-2 inhibitors would be preferred in heart failure or chronic kidney disease patients. Further, GLP-1 RAs and SGLT-2 inhibitors have effects on different pathways involved in the pathophysiology of cardiovascular disease, which could be expected to have an additive and/or synergistic cardiovascular effect when used together, as reviewed in Pharmacologic strategies for reducing cardiovascular disease in T2DM (Bonaventura et al., 2019).

The cardiovascular effects of GLP-1 RAs have been proven in a wide range of patient populations, including those with high cardiovascular risk. Cardiovascular safety of GLP-1 RAs compared to other glucose-lowering agents in a nationwide population-based study in real-world patients with T2DM (Yang et al., 2020). The study involved more than 40,000 patients who started GLP-1 RAs therapy and compared them to patients who started other glucose-lowering agents therapy. The findings showed that GLP-1 RA use was linked to a 12% and 16% decrease in MACE and cardiovascular death, respectively, compared to other glucose-lowering drugs including other GLP-1 drugs and the generalizability of the CVOT results to real-world use. Similarly, a study on patients aged 80 years or older with T2DM indicated that GLP-1 RA treatment was associated with reduced incidences of MACE and mortality in these vulnerable elderly patients who were less commonly studied in the trials and hence provided robust data for their use in elderly patients (Chen et al., 2026).

Real-world evidence with GLP-1 RAs after myocardial infarction (MI) and stroke (ST) specifically in the context of secondary prevention has been addressed. The effect of GLP-1 RA in secondary prevention of an MI case or stroke in T2DM has been evaluated in a national study in Sweden (Sedova et al., 2026). The study showed that the use of GLP-1 RA was significantly associated with lower risk of recurrent MACE when initiated in the first year after the index event (HR 0.82, 95% CI 0.73-0.92) as well as with all-cause mortality (HR 0.79, 95% CI 0.69-0.90) versus no use of GLP-1 RA. As for the specific population, patients with T2DM who had a recent cardiovascular event (CVE), this finding dampens the enthusiasm for GLP-1 RA use in patients after CVE, as the benefits are more distinct in this at-risk patient population. In addition, key access gaps were identified, such as women were less likely to be on GLP-1 RAs; among patients with T2D who were on GLP-1 RAs, they were less likely to be prescribed Liraglutide than Dulaglutide.

Another area of interest is if GLP-1 RAs impact outcomes in the peripheral vascular system. Results of a study comparing GLP-1 RAs to DPP-4 inhibitors on major adverse cardiovascular and limb events (MACE and MALE) showed that GLP-1 RAs were also lower risk for both MACE (HR 0.86, 95% CI 0.79-0.94) and MALE (HR 0.76, 95% CI 0.65-0.89) (D. Lin et al., 2021). The decrease in MALE (including peripheral revascularization, amputation and acute limb ischemia) indicates that GLP-1 RAs may have extra beneficial impacts on peripheral atherosclerosis beyond its actions on coronary and

cerebrovascular disease. This is clinically important because peripheral artery disease is a very common microvascular complication of T2DM, and often under-recognized as such, but is highly debilitating.

It has been wondered if, with the emergence of dual incretin receptor agonists (IRAs) such as tirzepatide, greater cardiovascular protection can be realized than is available with the selective GLP-1 RAs. A current continuing specific cardiovascular outcome trial (CVOT) for the drug, SURPASSCVOT, will definitively reply to the question (Fadini, 2025). Preliminary data from the SURPASS clinical trial program have shown that tirzepatide produces greater reductions in glycated hemoglobin and body weight compared to selective GLP-1 RAs, and also leads to improvements in blood pressure and lipid profiles (Fisman & Tenenbaum, 2021). These metabolic improvements suggest that tirzepatide may have the potential to provide superior cardiovascular protection, but this hypothesis awaits confirmation from the CVOT. The dual agonism of GIP and GLP-1 receptors may offer additional cardioprotective mechanisms, such as direct effects on cardiac metabolism and inflammation, that are not fully captured by selective GLP-1 receptor activation.

The effects of GLP-1 RAs on liver-related and cardiovascular mortality have been examined in a large cohort study using nationwide data (Yen et al., 2024). The study found that GLP-1 RA use was associated with a significantly lower risk of cardiovascular mortality (HR 0.82, 95% CI 0.74-0.91) and a trend towards lower liver-related mortality (HR 0.78, 95% CI 0.60-1.01) compared to other glucose-lowering agents. The reduction in liver-related mortality is particularly noteworthy, given the high prevalence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in patients with T2DM, and suggests that GLP-1 RAs may have hepatoprotective effects that contribute to their overall mortality benefit.

The combination of GLP-1 RAs with SGLT-2 inhibitors has been evaluated for its potential to provide additive cardiovascular benefits. A meta-analysis of randomized controlled trials and observational studies found that the combination of a GLP-1 RA and an SGLT-2 inhibitor was associated with a lower risk of MACE compared to either class alone (Singh & Singh, 2022). The hazard ratio for MACE with combination therapy versus placebo was 0.62 (95% CI 0.50-0.77), compared to 0.88 (95% CI 0.82-0.94) for GLP-1 RAs alone and 0.86 (95% CI 0.80-0.93) for SGLT-2 inhibitors alone. This finding suggests that the two classes have complementary mechanisms of action that result in additive cardiovascular protection, supporting the use of combination therapy in patients with high cardiovascular risk. Further, the physiologic synergistic actions of SGLT-2 inhibitors and GLP-1 RAs were summarized, increasing the complementary actions of these two classes, which involve both hemodynamic mechanisms and both the cardiac metabolic and inflammatory mechanisms (Morales & Assumpcao-Morales, 2019).

Further there has been investigation of the cardiovascular effects of GLP-1 RAs in special subgroups, including patients with a kidney transplant. Another study compared the outcomes in patients with type 2 diabetes who received a kidney transplant and were treated with GLP-1 RAs with those who took other medications for controlling blood glucose levels, and found that GLP-1 RA use was associated with a slower rate of estimated GFR decline and a decreased risk for MACE (HR 0.72, 95% CI 0.55-0.94) (L. Lin et al., 2025). This is particularly important as recurrent cardiovascular morbidity and mortality is common in kidney transplant recipients and there are limited treatment options due to drug interactions and need for immunosuppressive therapy.

We have sorted the incorporated studies into a taxonomy relating to study focus, specific outcome and sub-category and outlined this as seen in Table 2. The taxonomy enables the systematic comparison of findings from different domains in the cardiovascular as well as the vast spectrum of evidence for cardioprotective potential of GLP-1 RAs.

Table 2. *Taxonomy of Included Studies on Cardiovascular Safety and Cardioprotective Outcomes of GLP-1 Receptor Agonists*

Study Focus	Specific Outcome / Comparison	Sub-Category / Agent	Sources
Cardiovascular Safety & MACE	Major Adverse Cardiovascular Events (MACE)	Once-Weekly GLP-1 RAs (e.g., Semaglutide)	(Goldman, 2020), (Ferrari et al., 2022)
		Real-World Evidence & Population Studies	(Yang et al., 2020), (Chen et al., 2026), (Sedova et al., 2026), (D. Lin et al., 2021)
		Comparative Efficacy (vs. SGLT-2 inhibitors)	(Sohn et al., 2023), (Bonaventura et al., 2019), (Morales & Assumpcao-Morales, 2019)
		General Review & Guidelines	(Marx et al., 2022), (Saraiva & Sposito, 2014)
Heart Failure Outcomes	Heart Failure Hospitalization & Risk	GLP-1 RAs vs. Other Agents (DPP-4i, SGLT-2i)	(Scheen, 2017), (Xu et al., 2026)
Cardiorenal & Special Populations	Cardiorenal Protection	Kidney Transplant Recipients	(L. Lin et al., 2025)
		Elderly Patients (≥80 years)	(Chen et al., 2026)
		Post-Myocardial Infarction & Stroke (Secondary Prevention)	(Sedova et al., 2026)
Mechanisms & Novel Therapies	Mechanisms of Action	Postprandial Actions & Cardioprotection	(Thomas et al., 2023)
		Historical & Future Perspectives	(Ferrari et al., 2022)
	Dual & Combination Therapies	GLP-1 RA + SGLT-2 Inhibitor Combination	(Singh & Singh, 2022), (Morales & Assumpcao-Morales, 2019)
		Dual Incretin Receptor Agonists (e.g., Tirzepatide)	(Fadini, 2025), (Fisman & Tenenbaum, 2021)
Other Cardiovascular & Mortality Outcomes	Liver-Related & Cardiovascular Mortality	Mortality Analysis	(Yen et al., 2024)

Study Focus	Specific Outcome / Comparison	Sub-Category / Agent	Sources
	Peripheral & Limb Events	Major Adverse Limb Events (MALE)	(D. Lin et al., 2021)

As can be seen in Table 2, there is a lot of evidence available for cardiovascular endpoints and that includes all types of outcomes and a wide spectrum of populations. Most of the studies have been based on the MACE, which is the most clinically relevant composite outcome of cardiovascular risks evaluations. Crucially, CVOT studies are complemented by real-world evidence studies to demonstrate generalizability of CVOT results to daily practice and a better understanding of how GLP-1 RAs work in populations not included in most clinical trials, such as multiple comorbidities, or older adults. These two HF outcomes studies highlight the balance between GLP-1 RAs and HF: it's a hint of improvement, but not as much as with SGLT-2 inhibitors. The new data on dual and combination therapies, are indicative of an even greater cardiovascular protection in the future going with multi-targeted approaches. This increasing peripheral and limb outcomes data combined with the reduction of liver related mortality, along with traditional outcomes of MACE, suggests that GLP-1 RAs have a pleiotropic and powerful effect on multiple organ systems, especially the vasculature.

Renal Effects and Protection in Diabetic Kidney Disease

As diabetic kidney disease (DKD) is a key driver of the excess cardiovascular morbidity and mortality in type 2 diabetes (T2D) and is the most prevalent cause of end-stage renal disease (ESRD) worldwide, the renoprotective potential of GLP-1 receptor agonists has risen to the forefront as an important part of their therapeutic profile. The rationale for the renal effects that GLP-1 RAs elicit has grown as it has been explored across several lines of evidence: dedicated renal outcome trials, secondary analyses of cardiovascular outcome trials, real-world observational studies, and mechanistic investigations. The synthesis of this evidence helps to both validate the physiological and clinically meaningful renal protection afforded by GLP-1 RAs and clarify how these benefits are achieved, who is most likely to benefit, and how these agents compare with other agents with the potential for renal protection, such as sodium-glucose-linked transporter-2 inhibitors.

The cornerstone of renal evidence is the consistent reduction in albuminuria (an accepted surrogate of DKD progression) with GLP-1 RAs that, independent of blood pressure and blood sugar control, is a strong predictor of renal and cardiovascular outcomes. GLP-1 RAs are linked to 20-30% reduction in worsening albuminuria compared to placebo or active comparator drugs, based on synthesis of the data reported in the major cardiovascular outcome trials (CVOTs) and dedicated renal trials (Mosterd et al., 2020). This effect occurred across a range of baseline albuminuria (normoalbuminuria, microalbuminuria and macroalbuminuria), indicating that it was a class effect and not related to the DKD stage. The review also commented that the albuminuria reduction appeared to be steeper when GLP-1 RAs with long-acting were used (semaglutide and dulaglutide) than in those with short-acting GLP-1 RAs (lixisenatide), which could be explained by the more persistent receptor binding and improved metabolic parameters observed with long-acting GLP-1 RAs in patients with type 2 diabetes (Mosterd et al., 2020).

Findings on the effect of GLP-1 RAs on estimated glomerular filtration rate (eGFR) loss have been more varied in studies but an increasing number of studies show that these drugs can reduce eGFR loss, especially in individuals with known DKD. The AMPLITUDE-O study supports a review of GLP-1 RAs in DKD prevention and therapy which demonstrated that over the once-weekly period, efpeglenatide reduced the risk of renal composite outcome (sustained eGFR decline by 40% or more, ESRD or renal death) by 32% (HR 0.68, 95% CI 0.57-0.79) compared to placebo (Tommerdahl et al., 2022). What's even more important is that the AMPLITUDE-O trial included a high-risk patient

population of people with known cardiovascular disease and DKD, giving some strong evidence of the nephroprotective effects of GLP-1 RAs at a late stage of the disease. This review showed that the renoprotective effect was seen in all groups, regardless of baseline eGFR, albuminuria status and with or without renin-angiotensin-aldosterone system (RAAS) inhibitors as standard of care (SoC) (Tommerdahl et al., 2022).

GLP-1 RAs have multi-pronged protective effects on the kidney aside from their glucose-lowering and systemic metabolic properties. A detailed mechanistic review on GLP1 RAs in DKD that mapped the way from clinical outcomes to the molecular mechanisms, revealed several direct renal actions of GLP-1 receptor activation (Kawanami & Takashi, 2020). These include antiinflammatory activity through the inhibition of nuclear factor-kappa B signaling as well as reduction of the expression of pro-inflammatory cytokines in podocytes and renal tubular cells; antifibrotic activity through the inhibition of transforming growth factor-beta signaling pathway and diminution of the deposition of extracellular matrix in the kidney; and hemodynamic activity through reduction of intraglomerular pressure and modification of the tubuloglomerular feedback mechanism. Availability of anatomic evidence in the review regarding GLP-1 receptor expression in kidney, which is focused on the proximal tubule, the afferent arteriole and the glomerular podocyte, has helped to clarify a structural basis for the direct renal actions of these agents (Kawanami & Takashi, 2020). The pleiotropic nature of the renoprotective mechanisms could also lead to GLP-1 RAs being beneficial for preventing and treating DKD via distinct pathways from those of SGLT-2 inhibitors and angiotensin-converting enzyme inhibitors, potentially allowing for additive and/or synergistic beneficial effects with combination therapy.

Given their demonstrated renal protection in clinical trials, much clinical research has been conducted to compare the renal effects of GLP-1 RAs and SGLT-2 inhibitors. A review paper on the "evolving evidence and clinical use of SGLT-2 inhibitors and GLP-1 RAs in DKD" examined in detail the comparison of both classes (Bae, 2025). The review noted that both classes have been shown to be beneficial in reducing urinary protein excretion and the rate of eGFR decline, but more consistently in renal outcome testing trials (CREDENCE and DAPA-CKD) with SGLT-2 inhibitors. However, the evidence base for GLP-1 RAs in patients with DKD was also observed to be rapidly evolving during the review with strong evidence from the AMPLITUDE-O trial in high CV/renal risk patients. The review found that there are complementary MOAs, and that combination therapy might be the most renoprotective, especially among patients who still have residual albuminuria while taking an SGLT-2 inhibitor (Bae, 2025).

There are little data on the renal effects of dual incretin receptor agonists (IRAs) such as tirzepatide, but trials are ongoing. Caruso & Giorgino (2024) discussed the existing evidence for the renal effects of GLP-1 RAs in individuals with type 2 diabetes (T2D), highlighting it as a promising area for future research, given the positive outcomes of this trial regimen, specifically with tirzepatide. It was found that tirzepatide is a dual agonist of both the GIP receptor and the GLP-1 receptor which resulted in at least equal changes in both albuminuria and eGFR in comparison to selective GLP-1 RAs, with a potential trend for slightly greater changes with the highest dose. The mechanisms underlying the beneficial renal effects observed with tirzepatide could be related to its combined GIP receptor agonism as this has been found to increase insulin sensitivity, decrease inflammation, and improve endothelial function in the kidney. However, the review cautioned that the data on tirzepatide’s renal effects are derived from secondary analyses of cardiovascular outcome trials and glucose-lowering efficacy trials, and dedicated renal outcome trials are needed to confirm these findings (Caruso & Giorgino, 2024).

The cardiorenal protection potential of the combination of GLP-1 RAs and SGLT-2 inhibitors has been evaluated in a dedicated review, which synthesized evidence from clinical trials and mechanistic studies (Nagahisa & Saisho, 2019). The review found that the combination of a GLP-1 RA and an SGLT-2

inhibitor was associated with a lower risk of a composite cardiorenal outcome, defined as a sustained decline in eGFR of at least 40%, progression to end-stage renal disease, or death from cardiovascular causes, compared to either class alone. The hazard ratio for the cardiorenal composite with combination therapy versus placebo was 0.61 (95% confidence interval 0.49-0.76), compared to 0.79 (95% CI 0.70-0.89) for GLP-1 RAs alone and 0.71 (95% CI 0.61-0.83) for SGLT-2 inhibitors alone. The additivity of the renoprotective effect may be accounted for by the complementation of the action of the two classes, GLP-1 RA targeting inflammatory and fibrotic pathways and the SGLT-2 inhibitors targeting hemodynamic and metabolic pathways, respectively (Nagahisa & Saisho, 2019).

The renal action of GLP-1 RAs has been studied in several trials in special populations such as chronic kidney disease (CKD) patients at various stages of the disease, and also in kidney transplant recipients (KTRs). A study evaluating the association of GLP-1 RAs with cardiovascular and kidney outcomes in type 2 diabetic kidney transplant recipients showed that GLP-1 RAs were associated with a significantly lower risk of the composite renal outcome (end-stage renal disease or sustained decrease in eGFR by ≥30%) than other glucose-lowering drugs (HR 0.68, 95% CI 0.52-0.89) (L. Lin et al., 2025). This is pertinent because patients who have had kidney transplants are at significant risk for progression of DKD, and have limited therapeutic options, as the drugs may interact with one another. A scoping review of renal outcomes of GLP-1 RAs and tirzepatide across the spectrum of stages of chronic kidney disease (CKD) as well as different metabolic phenotypes (CKD stages 3-4, type 2 diabetes [T2D] and/or overweight or obesity) revealed consistent renoprotective effects across the spectrum of CKD (Rico-Fontalvo et al., 2026). The review suggested that the magnitude of albuminuria reduction was numerically larger among individuals with more advanced DKD, suggesting a possible benefit for GLP-1 RAs in slowing DKD progression in those who already have the disease (Rico-Fontalvo et al., 2026).

A long term observational study that evaluated the effects of GLP-1 RAs on kidney function has recently been performed beyond the end of the primary clinical trial (Scholten et al., 2015). The study included 31 type 2 diabetes (T2D) patients who completed a washout period prior to re-initiating or continuing their GLP-1 RA treatment, and demonstrated that the rate of eGFR (estimate glomerular filtration rate) decline was lower with long term treatment with GLP-1RAs compared to when patients were not on GLP-1RA treatment. During GLP-1 RA, mean annual eGFR changes were -1.2 mL/min/1.73 m² per year vs. -3.1 mL/min/1.73 m² per year when there was no GLP-1 RA treatment. In addition, GLP-1 RAs were also found to have a lasting effect on reducing albuminuria, with a long-term decrease in the urine ACR by ~30% from baseline, Scholten et al., 2015.

The REALTIMET2DKD study is a large-scale, multinational cohort-level study describing the treatment patterns and clinical profile of type 2 diabetes (T2DM) and chronic kidney disease (CKD) (ages 50+) initiating a GLP-1 RA (Pladevall-Vila et al., 2025). Yet, despite evidence of the renal benefits of GLP-1 RAs, initiation of GLP-1 RA seemed to be low, in countries across the world in which data was obtained from electronic medical records and claims databases, among patients with chronic kidney disease. Patients who started GLP-1 RA were younger, had a higher BMI and a lower prevalence of advanced chronic kidney disease (CKD) compared with patients who started other glucose lowering agents (GLAs). The study also found that GLP-1 RAs were used in an increasing trend among patients with chronic kidney disease (CKD) during the study period, suggesting a progressive uptake of the drugs for use in clinical practice for renal protection. This study, however, pointed to a particularly large gap in treatment, as many patients who could potentially benefit from GLP-1 RA therapy are not getting it, and so there is great need for better implementation of evidence-based prescribing (EBP) (Pladevall-Vila et al., 2025).

In a comprehensive review, the safety and efficacy of GLP-1 RAs in adults with type 2 diabetes and chronic kidney disease are appraised, collecting various clinical trial results and observational studies (Østergaard & Cooper, 2022). The review identified the pharmacokinetic profiles of most GLP-1 RAs do not differ significantly in patients with mild to moderate chronic kidney disease (eGFR ≥30 mL/min/1.73 m²) and these agents do not require dose adjustment for the use in this patient population. In severe chronic kidney disease (eGFR <30 mL/min/1.73 m²) there is less evidence, but available data indicate a generally acceptable efficacy and safety profile, with possibly more frequent gastrointestinal reactions. This review highlighted GLP-1 RAs as a safe and effective therapeutic option in patients with type 2 diabetes and the wide spectrum of chronic kidney disease, and that their renal effects are additive to the effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but potentially may be able to be used alone as a holistic nephroprotective strategy (Østergaard & Cooper, 2022).

A key focus of the potential for renal protection with dual and triple incretin receptor agonists (IRAs) is that these new agents might be expected to have an even stronger renoprotective effect, as they act on more than one incretin receptor (Caruso & Giorgino, 2024). Trizepatide is a dual acting GIP/GLP-1 agonist and has been shown to have potential renal benefits as a second-line agent for Type 2 diabetes, the review said, and triple acting GIP, GLP-1 and glucagon receptor agonists (GRAs) are in development. Although the pleiotropic effects and benefits on the kidney have been observed with selective GLP-1 receptor agonists, it is believed that the combination of incretin receptor activation and the metabolic and hemodynamic effects of glucagon receptor activation would offer a more systemic kidney protection.

To give a structured overview of the renal evidence, we made use of a taxonomy, which was adopted based on the focus of the studies, specific outcome and sub-category as shown in Table 3. This taxonomy helps to identify and systematically compare findings in various aspects of the kidneys and provides various points of evidence for the renoprotective effects of GLP-1 RAs.

Table 3. *Taxonomy of Included Studies on Renal Effects and Protection in Diabetic Kidney Disease*

Study Focus	Specific Outcome / Comparison	Sub-Category / Agent	Sources
Mechanisms and Overview	Nephroprotective Mechanisms	Anti-inflammatory, antifibrotic, hemodynamic mechanisms	(Kawanami & Takashi, 2020)
	Comprehensive Reviews	Review of nephroprotective effects	(Mosterd et al., 2020)
		Comparison of GLP-1 RAs LT-2 inhibitors in DKD	(Bae, 2025)
Major Clinical Trials	Renal Outcomes from CVOTs	AMPLITUDE-O trial	(Tommerdahl et al., 2022)
	Dedicated Renal Outcomes	Cardiorenal protection potential of combination therapy	(Nagahisa & Saisho, 2019)
Special Populations	Kidney Transplant Recipients	Composite renal outcome in transplant recipients	(L. Lin et al., 2025)

Study Focus	Specific Outcome / Comparison	Sub-Category / Agent	Sources
	Chronic Kidney Disease Stages	Effects across CKD stages and metabolic phenotypes	(Rico-Fontalvo et al., 2026)
	Long-Term Observational Data	Long-term effect on kidney function	(Scholten et al., 2015)
Comparative and Real-World Evidence	Comparative Renal Effects	Comparison of GLP-1 RAs, SGLT-2 inhibitors, and tirzepatide	(Caruso & Giorgino, 2024), (Bae, 2025)
	Treatment Patterns	Clinical profiles and treatment patterns in CKD patients	(Pladevall-Vila et al., 2025)
	Safety and Efficacy in CKD	Safety and efficacy of GLP-1 RAs in patients with CKD	(Østergaard & Cooper, 2022)

As the taxonomy in Table 3 demonstrates the evidence base of renal effects is built on a base of mechanistic studies and systematic reviews, with much clinical trial data and real-life evidence. The mechanistic experiments lend the biologic plausibility to the clinical benefits, and suggest that GLP-1 RAs can have a range of actions to protect the kidney. The major clinical trials, in particular, AMPLITUDE-O, provide a good favor to the clinical usefulness of GLP-1 RAs in the prevention of clinical significant renal events, such as long-term eGFR, and cardiac atrophy progression end-stage renal disease. The renal gains can be extrapolated to other classes of patients since the results of the special population were found applicable in other classes of patients like kidney transplant recipients and patients at the various stages of CKD. Both the comparative and real-world evidence studies uphold the utility of GLP-1 RAs into every day clinical practice and the criticality of improving the use of these therapies in patients who may be in need to receive them.

Efficacy in Glycemic Control and Weight Management

The argument to employ glucagon-like receptor agonist (GLP-1 RA) in type 2 diabetes mellitus (T2DM) is its glycemic control and weight reduction, and the body of evidence to back up its findings is enormous. Concomitant effect of these drugs to reduce their glycated hemoglobin (HbA1c) levels and decrease in body weight puts them in an advantaged position against the current set of antidiabetic agents with insulin and sulfonylureas most of the current therapies being linked with weight gain. These benefits have long-known mechanisms, and they include; glucose-dependent insulin release and glucagon release inhibition, delayed gastric emptying and centrally mediated satiety. The incorporated studies were all randomized controlled, meta-analyses, narrative review, and real-world studies all of which reinforce the notion that GLP-1 RAs can cost-effectively rain a clinically meaningful effect on both HbA1c and body weight with the magnitude of the effect being differing due to agent, dosing schedule, and patient population.

Evidence that we have gathered gains of glycemic and weight controls we have summed up into an entire taxonomy to permit a methodical trial versus control. This taxonomy described in table 4 classifies the studies according to their overall focus, the particular drug or situation and the particular outcome or study design. Since it can be seen in the table, most evidence is narrowed to the overall efficacy of GLP-1 RAs in the reduction of HbA1c and weight, and the high number of reviews and clinical trials indicate that the efficacy of those agents can be divided on the level of classes (Block and Gaal, 2009), (Ahraren, 2011), (Brunton and Wysham, 2020), (Taylor, 2018), (Patel, 2020), (Rodbard, 2018), (Peterson, 2012), (Alexopoulos and Buse, 2019), (Bzowyckyj, 2020), (Shen et al., 2021). These

reviews have already determined that GLP-1 RA can decrease HbA1c by about 1% alongside considerable weight loss (Ahraren, 2011), and newer comparisons have confirmed even worse positions to be better than the dipeptidyl peptidase-4 (DPP-4) inhibitors and similar to or even superior to basal insulin (Alexopoulos and Buse, 2019).

Among the major differences between GLP-1 RAs and other injectable medications like insulin is their implications on the weight status. The reduction in weight is also stated in most GLP-1 RAs (2 to 5 kg on average) in a number of studies (Ahraren, 2011), (Brunton and Wysham, 2020), (Taylor, 2018), (Patel, 2020). A weight reduction is the most popular in relation to such agents as semaglutide and liraglutide, using them particularly in patients with obesity (Okamoto et al., 2021), (Olukorode et al., 2024). Also interesting is the fact that body composition effect, GLP-1 RAs have been found to decrease visceral adipose tissue and liver ectopic fat, which play major roles in metabolic malfunction (Liao et al., 2023). This decrease in visceral adiposity can be linked with increased sensitivity to insulin and improved measurements of cardiovascular risk factors that is not possible with weight loss.

Comparatively, GLP-1 RAs exhibit superior comparative effectiveness than DPP-4 inhibitors not only in the reduction of the amount of HbA1c but also in weight loss, but their comparative effectiveness versus the amount of SGLT-2 inhibitor is more intricate. The decision regarding the selection of classes can be reached based on the patient-specificity, including the baseline weight, degree of hyperglycemia and cardiovascular risk profile. GLP-1 RAs are as effective, or better than basal glucose control, particularly in the minimization of postprandial glucose surges, with the added benefit of weight loss over weight gain in head-to-head trials with insulin basal (Alexopoulos and Buse, 2019), (Baxter et al., 2020). This represents a clinical benefit since insulin induced weight gain may cause insulin resistance, adversely affect patient adherence, and quality of life.

Moreover, the advent of dual GIP/GLP-1 receptor agonists, the most prominent one being tirzepatide, can be seen as a significant breakthrough towards meeting glycemic and weight loss goals (Perreault and Bergman, 2024), (Thomas et al., 2021), (Nauck and 'Alessio, 2022). Tirzepatide has a larger drop in HbA1C and mass reduction compared to selective GLP-1 RAs, with the greatest drops in HbA1C of over 2, and weight loss of 10-15 percent or more at high dosages (Perreault and Bergman, 2024), (Nauck and Alessio, 2022). This unmatched effectiveness in both domains suggests that the co-agonism of GIP and GLP-1 receptors provides synergistic benefits on insulin secretion, insulin sensitivity, and energy expenditure, setting a new bar for medical therapy in T2DM (Thomas et al., 2021). The success of tirzepatide has catalyzed the development of triple agonists that target the glucagon receptor, which may further enhance weight loss through increased energy expenditure.

Several studies have examined the efficacy of GLP-1 RAs as part of combination therapy. The addition of a sodium-glucose cotransporter-2 (SGLT-2) inhibitor to a GLP-1 RA provides complementary mechanisms for glycemic control and weight loss. As an example, adding empagliflozin to liraglutide led to further reductions in HbA1c and weight compared to liraglutide in Japanese patients (Terauchi, Utsunomiya, et al., 2019). Similar additive benefits were observed with tofogliflozin and ipragliflozin (Terauchi, Fujiwara, et al., 2019), (Ishihara et al., 2018). The combination of a GLP-1 RA with basal insulin, in a fixed-ratio combination such as IDegLira (insulin degludec/liraglutide), was also effective in improving glycemic control while mitigating the weight gain typically associated with insulin therapy (Linjawi et al., 2017), (Cowart & Carris, 2025). These combination strategies allow for a more personalized approach to therapy, leveraging the strengths of each agent to address the multiple pathophysiological defects of T2DM.

The development of an oral formulation of semaglutide has addressed a significant barrier to GLP-1 RA uptake, which is the need for injection (Rasmussen, 2020), (Feng et al., 2023). In clinical trials, oral

semaglutide demonstrated clinically meaningful HbA1c reductions and weight loss, albeit with a slightly reduced magnitude compared to its injectable counterpart, due to the challenges of bioavailability (Rasmussen, 2020). Nevertheless, the oral formulation was superior to placebo and DPP-4 inhibitors when added to background therapy, including insulin (Feng et al., 2023). The convenience of an oral option is expected to improve patient acceptance and adherence, potentially improving long-term outcomes.

Beyond the clinical endpoints, several studies have explored the mechanisms and biomarkers associated with glycemic response. One study investigated the correlation between gut microbiota and the efficacy of dulaglutide, finding that changes in intestinal flora composition, particularly an increase in beneficial bacteria like *Akkermansia muciniphila*, were associated with greater improvements in glucose metabolism (Liang et al., 2024). This implies that GLP-1 RAs could have part of their effect on metabolism by controlling the gut microbiome, providing new opportunities to optimize treatment. The other trial assessed the impact of liraglutide on the circulation of microRNA, demonstrating that the treatment altered the expression of a number of miRNA that governs beta-cells and insulin signaling functionality, a molecular description of the clinical activities of the drug (Zamily, 2025).

There are also glycemic effects of GLP-1 RAs at levels other than conventional HbA1c levels. The critical interpretation of the results showed different GLP-1 RAs. influenced several aspects of dysglycemia including fasting glucose, postprandial glucose excursions and glycemic variability (Owens et al., 2013). There is stronger influence on postprandial hyperglycemia with short acting agents because agents are very potent to influence gastric emptying; and overall effect on fasting and overall glycaemia control with long acting agents. The appreciation of these different effects can assist clinicians to choose the best agent to use on a particular patient based on his or her glycemic profile.

GLP-1 RAs have also resulted in positive glycemic and mortality in even those with non-alcoholic fatty liver disease (NAFLD) and T2DM (Krishnan et al., 2024). Not only in a large population-based study, but also when used as a glucose lowering drug, GLP-1 RA was also associated with a decreased risk of major adverse liver events and mortality compared to other glucose lowering drugs and directly due to alterations in glycemic control and weight loss and direct hepatic effects. GLP-1 RAs have a concomitant glycemic, weight and hepatic effect, which makes them a firstline treatment of this at-risk group.

Comparative Effectiveness: GLP-1 RAs vs. Other Antidiabetic Classes

There is an urgent need to gain a solid understanding of comparative effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to other major classes of antidiabetic drugs, if the GLP-1 RAs are to be positioned in the therapeutic algorithm of type 2 diabetes mellitus (T2DM). As the glucose-lowering drug armamentarium continues to grow with a wide variety of drugs providing different efficacy, safety and pleiotropic profiles, selection of the appropriate drug as first line, second-line and add-on therapy is increasingly complex. This review included studies that examined GLP-1 RAs compared to dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors or insulin and other classes. Summarizing overall, the synthesis indicates that GLPs demonstrate improved glycemic control and have a greater impact on body weight than do DPP-4 inhibitors; however, the relation to SGLT2 inhibitors is less clear-cut, leading to a view that GLPs and SGLT2 inhibitors are not necessarily seen as competing product classes. Further, the merit of combination therapies is apparent, as results for GLP-1 RA + SGLT-2 inhibitors have proven to be additive, both in relation to metabolic and cardiorenal endpoints.

DPP-4 inhibitors (gliptins) alone, on the other hand, spares the activity of the enzyme that breaks down natural GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and consequently raises the

natural incretins somewhat. GLP-1 RAs, in contrast, give supraphysiological amounts of GLP-1 receptor activation, which leads to higher insulin secretion, suppression of glucagon, and acceleration of gastric emptying. A large trial that compared these two treatments found that GLP-1 RAs also proved superior for achieving glycemic targets, particularly when the patient's initial HbA1C was higher (Brunton, 2014). The review found that GLP-1 RAs consistently showed decreases in HbA1c levels, typically around 0.3% to 0.5% lower, as well as marked and significantly greater weight loss compared with DPP-4 inhibitors, which are weight neutral. This dichotomy of weight effect has relevance as weight gain is a common side effect of many other antidiabetic drugs that can contribute to increased insulin resistance and cardiovascular risk factors.

From a pharmacological perspective, analysis of the selection between GLP-1 RAs and DPP-4 inhibitors showed difference in their pharmacokinetics and pharmacodynamics as it relates to clinical use (Brown & Evans, 2012). GLP-1 RAs are exogenous peptides with much longer half-life (ex–once a week) with more potent effects on both gastric emptying and satiety. One possible advantage of DPP-4 inhibitors is that they are small molecule drugs and are taken orally, with a better gastrointestinal tolerability profile than other agents (fewer side effects of nausea/vomiting). The review recommended that GLP-1 RAs should be used when weight loss is the primary objective, when patients require a more potent glycemic reduction or when patients wish to take a subscribed medication; DPP-4 inhibitors should be recommended for patients unable to tolerate gastrointestinal side effects or who wish to take an oral medication (Brown & Evans, 2012). That this opinion was correct was ratified by another survey of technological progress in the management of T2DM which showed that while both classes are effective, GLP-1 RAs have emerged as the more potent incretin-based therapy with proven benefits in those with obesity and/or known cardiovascular disease (Davidson, 2009).

Comparative effectiveness studies have also been performed with GLP-1 RAs with respect to a specific clinical endpoint, such as the change in heart failure hospitalization. An analysis of real-world data from routine clinical practice showed GLP-1 RAs had a reduced risk of hospitalisation for heart failure compared to DPP-4 inhibitors, using a target trial approach (hazard ratio 0.82, 95% confidence interval 0.72-0.93) (Xu et al., 2026). This is in line with the results of cardiovascular outcome trials, where GLP-1 RAs have demonstrated cardiovascular outcomes improvements associated with heart failure, and DPP-4 inhibitors, as a whole, have demonstrated neutral results on heart failure related outcomes. The study also investigated GLP-1 RAs versus SGLT-2 inhibitors and detected a reduction in the risk of heart failure hospitalization with SGLT-2 inhibitors, ruling that SGLT-2 inhibitors could also present the best line of protection against heart failure compared to GLP-1 RAs (Xu et al., 2026).

Most of the studies have focused on comparing the different treatments, as both GLP-1 RAs and SGLT-2 inhibitors have demonstrated better outcomes with regard to cardiovascular and renal benefits. In terms of cardiorenal protection potential, which their two classes were reviewed for, SGLT-2 inhibitors are glycosuric and have hemodynamic effects while GLP-1 RAs mostly target incretin receptor activation (Nagahisa & Saisho, 2019). The review found the two classes to be non-exclusive and used to be complementary with perhaps some additive or synergic effect when used in combination for cardiorenal outcomes. This was also emphasized in an overview regarding the potential to use pharmacologic strategies for reducing cardiovascular disease (CVD) in an individual with T2DM, which said that a patient's decision to use either class of drug should rather be determined by the primary dangerousness profile they faced (Bonaventura et al., 2019). A GLP-1 RA can be used as the preferred treatment in patients with atherosclerotic cardiovascular disease (ASCVD), given the presentation of data indicating a reduction in major adverse cardiovascular events (MACE); SGLT-2 inhibitors can be used first when the patient has chronic kidney disease (CKD) or heart failure (HF). The review also

highlighted that evidence is ever-changing, and that a lot of patients could potentially take both classes (Bonaventura et al., 2019).

A study that specifically investigated which treatment (SGLT-2 or GLP-1 RAs) is more suitable in T2DM as a second-line therapy, allowed for a balanced analysis of the data (Munir & Davis, 2018). Glycemic efficacy, weight loss, cardiovascular effects, renal outcomes, safety and cost were among the factors taken into account. It was agreed that there are no universal decisions as to the use of any particular "second line" agent, and instead patient related characteristics and preferences should be considered. But both classes could be unhelpful in those with a high atherosclerotic or heart failure risk, respectively, and GLP-1 RAs may give a slight edge for atherosclerotic risk and SGLT-2 inhibitors for heart failure risk. In patients with chronic kidney disease, there is more compelling evidence for sleep glucose lowering therapy (SLGT-2) inhibitors to help protect the kidneys although GLP-1 RAs also have benefits. For patients with obesity, GLP-1 RAs may be preferred due to their greater weight loss efficacy. The study emphasized that the two classes can be used in combination, and that this approach may be the most effective strategy for patients with multiple comorbidities (Munir & Davis, 2018).

The combination of GLP-1 RAs and SGLT-2 inhibitors has been extensively studied, and the evidence consistently supports the use of this dual therapy for patients with T2DM who require additional glycemic control or who have high cardiorenal risk. A review of the metabolic and cardiovascular benefits of combination therapy found that the addition of an SGLT-2 inhibitor to a GLP-1 RA, or vice versa, resulted in further improvements in HbA1c, body weight, blood pressure, and lipid profiles (Singh & Singh, 2022). The review also found that the combination was associated with a lower risk of MACE compared to either class alone, with a hazard ratio of 0.62 (95% confidence interval 0.50-0.77) for the combination versus placebo, compared to 0.88 for GLP-1 RAs alone and 0.86 for SGLT-2 inhibitors alone (Singh & Singh, 2022). This additive effect is thought to stem from complementary properties of both these types of drugs, with GLP-1 RAs increasing insulin secretion and satiety, and SGLT-2 inhibitors blocking glucose reabsorption and inducing osmotic diuresis.

This was further discussed by examining the potential of SGLT-2 inhibitors and GLP-1 RAs in combination therapy in T2DM (Liakos et al., 2026). The two classes of drugs, GLP-1 RAs and SGLT-2 inhibitors, work on different pathophysiological mechanisms and organs, namely the pancreas, brain and gastrointestinal tract for GLP-1 RAs, and kidneys for SGLT-2 inhibitors, the review added. This Multiorgan therapy targeting opens the door towards much detailed treatment for multi-organ defects of T2DM. The review also concluded that the combination does not seem to have any extra safety concerns; gastrointestinal side effects of GLP-1 RAs are not aggravated when combined with an SGLT-2 inhibitor (Liakos et al., 2026); and the combination appears to be generally well tolerated without any unusual safety signals. They also reviewed combination therapy with SGLT-2 inhibitors, GLP-1 RAs, used as complementary drugs which target the multi-organ defects in T2DM in a detailed mechanistic analysis (Lajara, 2019). The review expounded on how GLP-1 RAs lead to improved beta-cell function, decreased glucagon secretion and by leading to weight loss and preserving lean body mass, and how SGLT-2 inhibitors contribute to glucotoxicity, insulin sensitivity and caloric loss via glycosuria. All these effects are synergistic, therefore improving glycemic control and reducing cardiovascular risk factors (Lajara, 2019).

A review of the impact of combination therapy (SGLT-2 inhibitors and GLP-1 RAs in metabolic outcomes and cardiorenal risk was performed and offers a "one-stop" knowledge synthesis (Goncalves & Bell, 2018). They were found to be associated with greater HbA1c, body weight, and systolic blood pressure reductions when the two classes were given together compared to either treatment alone, the review found. An additive benefit on renal outcomes was also seen with the combination, as an even

greater decrease in estimated glomerular filtration rate was observed and a greater decrease in albuminuria. The findings of the review suggested that GLP-1RA/SGLT-2 inhibitors combination is an effective therapeutic approach for T2DM patients, particularly those with high cardiorenal risk, and should be considered as early treatment in the treatment algorithm (Goncalves & Bell, 2018).

A study evaluating the safety and efficacy of the combined use of GLP-1 RAs and SGLT-2 inhibitors among veterans with T2DM provided real-world evidence supporting the use of this combination (McCulley & Hurren, 2022). The study included over 10,000 veterans who were prescribed both a GLP-1 RA and an SGLT-2 inhibitor, and compared them to those who were prescribed either class alone. The study found that the combination was associated with a lower risk of MACE and heart failure hospitalization compared to either class alone, and that the safety profile was acceptable, with no increase in serious adverse events. The study also found that the combination was associated with greater reductions in HbA1c and body weight, confirming the additive efficacy observed in clinical trials (McCulley & Hurren, 2022).

A study of treatment discontinuation among users of GLP-1 RAs and SGLT-2 inhibitors in a national population of individuals with T2DM provided insights into the real-world persistence of these therapies (Lim et al., 2025). The study found that discontinuation rates were higher for GLP-1 RAs than for SGLT-2 inhibitors, primarily due to gastrointestinal side effects. However, the study also found that patients who were prescribed both classes had lower discontinuation rates than those prescribed GLP-1 RAs alone, suggesting that the addition of an SGLT-2 inhibitor may improve tolerability or that patients who are more motivated to achieve glycemic control are more likely to persist with combination therapy (Lim et al., 2025).

A review of the use of SGLT-2 inhibitors and GLP-1 RAs as a worthwhile physiologic combination in managing T2DM while reducing cardiovascular risk provided a historical perspective on the evolution of this therapeutic approach (Morales & Assumpcao-Morales, 2019). The review started from the discovery of both classes, and gradually covered the evolution of their status as cornerstone therapies for the treatment of T2DM. GLP-1 RA and SGLT2 inhibitors can complementarily target multiple pathophysiological defects of T2DM, thus their effects work synergistically, not additively since they work through two different pathways. The combination was even considered as a first-line therapy in patients newly diagnosed with high cardiorenal risk and was not considered as stepping up from metformin first-line therapy (Morales & Assumpcao-Morales, 2019).

Combining GLP-1 RAs and SGLT-2 inhibitors to target multiple organ defects in T2DM was discussed in detail (J. Anderson, 2020). The combo works best for people who are obese and suffer from hypertension and recognized coronary heart and kidney ailments, the review noted. In addition, practical implementation of the combination (such as the need to reduce the GLP-1 RA dose when initiating the SGLT-2 inhibitor dose) and the need to monitor for adverse events of volume depletion and genital infections were also discussed (J. Anderson, 2020).

An overview for the management of T2DM and overweight, of which the focus on SGLT-2 inhibitors and GLP-1 RAs, including a practical guide for the clinician (Jargin, 2019). Both of these classes have proven to be effective for weight loss, but GLP-1 RAs generally demonstrated greater weight loss, the review said. The effect of such agents in patients with non-alcoholic fatty liver disease (NAFLD) was also noted in this review: Both these classes of drugs have been shown to produce a decrease in liver fat and a reduction in liver enzymes in those with such disease. For patients with T2DM and overweight or obesity, GLP-1 RAs are recommended as initial or early add-on treatment as well as SGLT-2

inhibitors, and the combination of the two classes might be the best strategy for inducing weight loss and achieving glycemic control (Jargin, 2019).

A review of GLP-1 RAs and SGLT-2 inhibitors as new anti-aging drugs offered a fresh insight into the other possibilities of these drugs beyond T2DM (Santulli et al., 2025). This review explored the available evidence regarding the potential anti-aging benefits of both classes that might be mediated through the effects on metabolic health, inflammation, and cellular senescence. The review said a GLP-1 RA and an SGLT-2 inhibitor could be effective for healthy aging, as these two types of drugs target complementary pathways in the ageing process. The future potential application of these agents, albeit speculative, as preventing agents for age-related diseases was mentioned in the review (Santulli et al., 2025).

A synthesis of the evidence from several meta-analyses for comparing GLP-1 RAs, SGLT-2 inhibitors, and DPP-4 inhibitors as add-on drugs with insulin and oral hypoglycemic agents was provided in an umbrella review (Chai et al., 2024). The umbrella review indicates that GLP-1 RAs were most effective for reducing HbA1c and for weight loss when compared to SGLT-2 inhibitors and DPP-4 inhibitors. GLP-1 RAs were also found to decrease the risk of hypoglycaemia when compared to insulin, and SGLT-2 inhibitors were found to decrease the risk of hospitalisation for heart failure. Overall, the review concluded that both GLP-1 RAs and SGLT-2 inhibitors are excellent tools to bring on to a patient who needs extra glycemic control and the decision of which to use should be tailored to patient characteristics and preferences (Chai et al., 2024).

A review of incretin therapy for T2DM: GLP-1 RAs and DPP-4 inhibitors provides the complete overview about the two incretin therapy classes (Ahrén, 2013). Both classes were reviewed and the MOA, efficacy, safety and clinical use of the two were discussed. The review's key takeaway is that GLP-1 RAs demonstrated greater efficacy for glycemic control and weight loss compared to DPP-4 inhibitors, which were more favorably tolerated and were easier to use. Another option that was considered is GLP 1RAs with DPP 4 inhibitors, not commonly prescribed in the clinical setting (Ahrén, 2013).

Pratley and Gilbert (2008) reviewed targeting increments in T2DM, specifically the contribution of GLP-1 RAs and DPP-4 inhibitors, thus giving a historical view of the development of these drugs. The article discussed the findings and development of GLP-1 RAs and DPP-4 inhibitors, detailing the identification of the incretin system through the years. The review resulted in the conclusion that both the classes had played their roles in the management of T2DM, GLP-1 RAs have been a more effective class in the comprehensive metabolic control (Pratley & Gilbert, 2008).

A detailed comparison of modes of action was presented and a review of common characteristics and differences in the modes of action of GLP-1 RAs and DPP-4 inhibitors discussed (Nauck, 2016). In this review, the authors discuss how GLP-1 receptor signaling is amplified in both classes. GLP-1 RAs and DPP-4 inhibitors stimulate GLP-1 receptors and increase endogenous levels of GLP-1. The review emphasized that as a result of direct activation of GLP-1 receptors, GLP-1 RAs demonstrate more powerful results in terms of insulin secretion, glucagon suppression and gastric emptying and this translates to more potent clinical results (Nauck, 2016).

A review on GLP-1 agonists and dipeptidyl-peptidase IV inhibitors, detailed the history of the development of these therapies (Gallwitz, 2011). The discovery of exenatide, the first GLP-1 RA, and the emergence of other agents in the class, was discussed. Developmental research on DPP-4 inhibitors and their significance for management of T2DM also was discussed. The overall review is that both classes have been useful additions to the therapeutic toolbox and GLPs have a broader spectrum of activities including weight loss and cardioprotection (Gallwitz, 2011).

In a review of the GFPP-1 RA and DPP-4 inhibitors a detailed consideration of the use of these drugs was provided, and practical recommendations were given to help the clinician in choosing between them in clinical practice (Scheen, 2013). The review highlighted the characteristics to consider in choosing from the two classes such as the patient's glycemic profile, weight status, cardiovascular risk, renal function, and preferences. In the end, GLP-1 RAs seem generally more well-liked for people needing more glycemic control, weight loss and/or cardiovascular protection, whereas DPP-4 inhibitors are better suited for individuals who are unable to tolerate gastrointestinal side effects and/or who wish to have an oral medication that is more convenient for them (Scheen, 2013).

To provide an overview of all the comparative effectiveness evidence, we have developed a complete taxonomical classification of the studies that were included in this table (Table 5). This classification of studies is both by comparator drug class and outcome focus, enabling evidence to be systematically compared across comparator drug classes.

Emerging Therapies: Dual/Triple Agonists and Oral Formulations

Therapy of T2DM is in the process of undergoing a paradigm shift as the novel, multi-targeted receptor agonists and oral formulations of GLP-1 receptor agonists become available, both of which are likely to expand the therapeutic potential beyond selective GLP-1 receptor activation. When it comes to drugs against T2DM, the development of dual and triple agonists (agents that bind to the GIP, GLP-1, and glucagon receptors respectively) represents another leap in pharmacological approaches, as they seek to be able to combine complementary metabolic actions of multiple incretins and/or counter-regulatory hormones. Concurrently, the development of oral formulations of GLP-1 RAs, including both peptide-based and small-molecule agents, addresses a major barrier to treatment initiation and adherence, namely the requirement for subcutaneous injection. The included studies in this review provide a comprehensive overview of the efficacy, safety, and clinical potential of these emerging therapies, with a particular focus on tirzepatide as the first approved dual GIP/GLP-1 receptor agonist, retatrutide as a triple agonist, and the oral small-molecule GLP-1 RAs orforglipron and danuglipron.

The most extensively studied and clinically advanced of the emerging therapies is tirzepatide, a once-weekly, injectable dual agonist of the GIP and GLP-1 receptors. The development of tirzepatide was predicated on the hypothesis that co-agonism of both incretin receptors would produce synergistic effects on glycemic control and weight loss, as GIP has been shown to enhance insulin secretion, improve insulin sensitivity, and promote energy expenditure, while GLP-1 provides its well-established effects on glucose-dependent insulin secretion, glucagon suppression, and satiety (Min & Bain, 2021). The SURPASS clinical trial program, which evaluated tirzepatide across a range of doses (5 mg, 10 mg, and 15 mg) in patients with T2DM, has consistently demonstrated that tirzepatide achieves superior reductions in glycated hemoglobin and body weight compared to selective GLP-1 RAs, including semaglutide and dulaglutide, as well as placebo and other comparators (Min & Bain, 2021), (Nowak et al., 2022), (Kaneko, 2022). In the SURPASS-2 trial, for example, tirzepatide 15 mg reduced HbA1c by 2.46% from baseline, compared to 1.86% with semaglutide 1 mg, and resulted in a mean weight loss of 12.9 kg, compared to 6.7 kg with semaglutide (Min & Bain, 2021). A possible best-in-class treatment of T2DM, Nauck & 'Alessio (2022) characterize these results as delivering unparalleled efficacy in glycemic control and weight loss.

The specific mechanistic research indicated that the processes, which may underlie tirzepatide's high efficacy, were explained. Post hoc evaluation of the SURPASS clinical trial program revealed that tirzepatide positively influenced the improvement of beta-cell functionality and insulin sensitivity more than the selective GLP-1 RAs by the homeostasis model assessment of beta-cell functionality (HOMA2-B) and the Matsuda index of insulin sensitivity (Thomas et al., 2021). The authors of the

study proposed that the insulinotropic effects resulting from activation of GIP receptor and GLP-1 receptor are additive and the latter increases the peripheral insulin sensitivity, possibly through a direct effect on adipose tissue and skeletal muscle. It also seems that the dual agonism has a more positive influence on the energy balance, and patients treated with tirzepatide have a higher caloric intake decrease and an energy expenditure increase than those treated with selective GLP-1 RAs (Thomas et al., 2021). It has been widely discussed in the context of treatment of T2DM; and SURPASS clinical trials have provided sufficient evidence on the efficacy and safety of this medication (Min and Bain, 2021), (Nowak et al., 2022), (Kaneko, 2022). The GIP/GLP-1 coagonist tirzepatide has been described as a rising star in type 2 diabetes for possible paradigm shift of treatment (Z. Ma et al., 2023). In another review, tirzepatide was called a new therapy for cardiometabolism, while its action on body weight and glycemic control is accompanied by an effect on blood pressure, lipid profiles and inflammatory markers, which gives us a cardiometabolic advantage (Fisman & Tenenbaum, 2021).

A cardiovascular outcome trial specifically designed to explore the non-inferiority and potential superiority of tirzepatide to dulaglutide concerning major adverse cardiovascular events (MACE) is ongoing, providing insights into the safety of tirzepatide on the heart and its protective effects on cardiovascular diseases (Fadini, 2025). The results of this trial are eagerly awaited, but preliminary reports of the SURPASS program suggest a positive cardiovascular risk profile of tirzepatide; decrease in blood pressure and improved lipid parameters were comparable or better than that of selective GLP-1 RAs (Fisman & Tenenbaum, 2021). The concept of GIP receptor co-agonism, potentially providing superior cardiovascular protection compared to selective GLP-1 RAs, was outlined in a review of the literature on the possibility of dual incretin receptor agonists, which could have either direct effects on cardiac metabolism, less inflammatory effects, and enhance endothelial function (Fadini, 2025). The review has, however, cautioned that the final verdict on this matter will be provided once the SURPASS-CVOT and other related cardiovascular outfall trials will be completed (Fadini, 2025).

Other dual agonists are at different phases of clinical trials, beyond tirzepatide. Dual GIP/GLP-1 receptor agonists such as NNC0090-2746 have been evaluated in a proof-of-concept study in patients with T2DM, and demonstrated that it achieved improved glycemic control, reduced body weight, and lowered blood pressure, in comparison with placebo (Frias et al., 2017). In the study NNC0090-2746 reduced HbA1c by up to 1.1% and weight by up to 4.5kg over 12 weeks, with a general consistency in safety profile; the most common adverse events being gastrointestinal (Frias et al., 2017). Although NNC0090-2746 has not been subsequently developed as a clinical drug, the trial presented valuable proof-of-concept information to support the viability of dual GIP/GLP-1 receptor agonism and its effectiveness.

Triple agonists targeting the GIP, GLP-1 and glucagon receptors will be the future of incretin-based therapy. Retatrutide (LY3437943) is a new triple receptor agonist that has been tested in a phase 1b, multi-centre, double-blinded, placebo-controlled study in subjects with T2DM (Urva et al., 2022). The researchers discovered that dose-dependent decreases in HbA1c and weight loss were observed with retatrutide with the highest dose showing a mean decrease of HbA1c of 1.9% and weight loss of 8.7 kg in 12 weeks. It had a safety profile similar to other GLP-1 RAs, with gastrointestinal adverse events being most common. The net effect of glucagon receptor agonism is postulated to be additional promotion of weight loss due to increased energy expenditure and lipolysis while the GIP receptor agonism will help to offset the hyperglycemic effect of glucagon, with the overall effect being improved glycemic control (Urva et al., 2022). The assessment of the retatrutide as a next step in managing type-two diabetes and obesity demonstrated the possibility of this triple agonist to provide even more metabolic properties than dual agonists, especially weight loss (Doggrell, 2023). The review noted that retatrutide's glucagon receptor agonism might also have beneficial effects on lipid metabolism and

hepatic steatosis, which is often a complication of patients with T2DM, and is a promising drug for the treatment of non-alcoholic fatty liver disease.

Creation of oral preparations of GLP-1 RAs has been one of the most extensively studied areas of research as the need to inject subcutaneously is a major barrier to treatment initiation and adherence in many patients. The first oral GLP-1 RA to be approved for clinical use is oral semaglutide, which is a peptide-based formulation that is co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) to facilitate its absorption across the gastric mucosa (Rasmussen, 2020). The development of oral semaglutide has been described as a valuable treatment option for patients with a preference for oral therapy, and its efficacy and safety have been established in the PIONEER clinical trial program (Rasmussen, 2020). In the PIONEER trials, oral semaglutide demonstrated clinically meaningful reductions in HbA1c and body weight compared to placebo and active comparators, including empagliflozin and sitagliptin, with a safety profile that was consistent with that of injectable GLP-1 RAs, although gastrointestinal adverse events were more common with the oral formulation (Rasmussen, 2020).

More recently, the development of oral small-molecule GLP-1 receptor agonists has emerged as a promising alternative to peptide-based formulations. Orforglipron (LY3502970) and danuglipron are two such agents that are currently in clinical development (Karakasis et al., 2023). A systematic review of the safety and efficacy of orforglipron and danuglipron for the treatment of type 2 diabetes and obesity found that both agents produced dose-dependent reductions in HbA1c and body weight in phase 2 trials, with efficacy that was comparable to or greater than that of injectable GLP-1 RAs (Karakasis et al., 2023). The review noted that the gastrointestinal tolerability of these small-molecule agents was a key concern, with nausea, vomiting, and diarrhea being dose-limiting in some patients. However, the review also found that the pharmacokinetic profiles of orforglipron and danuglipron allow for once-daily oral dosing, which may improve patient convenience and adherence compared to injectable therapies (Karakasis et al., 2023).

The effect of food consumption on the pharmacokinetics, safety, and tolerability of orforglipron was evaluated in a dedicated study, which found that administration with food reduced the peak plasma concentration and improved gastrointestinal tolerability (X. Ma et al., 2024). The study suggested that dosing recommendations for orforglipron may need to be optimized to balance efficacy and tolerability, with administration after a meal potentially reducing the incidence of nausea and vomiting. The phase 3 ATTAIN-2 trial, which evaluated orforglipron for the treatment of obesity in people with type 2 diabetes, is currently ongoing and will provide further evidence on the efficacy and safety of this agent (Horn et al., 2025).

A comparative analysis of small-molecule oral versus injectable GLP-1 receptor agonists found that the oral small-molecule agents offer the advantage of oral administration and potentially lower manufacturing costs, but may have a less favorable gastrointestinal tolerability profile compared to injectable GLP-1 RAs (Patel, 2026). The analysis also noted that the long-term safety of oral small-molecule GLP-1 RAs is not yet established, and that post-marketing surveillance will be important for detecting rare or delayed adverse events. The review concluded that oral small-molecule GLP-1 RAs have the potential to expand the use of GLP-1-based therapies to a broader patient population, but that their place in the treatment algorithm will depend on the results of ongoing phase 3 trials and real-world evidence (Patel, 2026).

The potential for shortages of GLP-1 and dual GLP-1/GIP receptor agonists has been a topic of discussion, given the increasing demand for these agents for both T2DM and obesity (Whitley et al., 2023). A special report on potential strategies for addressing these shortages highlighted the need for

increased manufacturing capacity, the development of alternative formulations, and the prioritization of patients with the highest medical need. The report also discussed the potential role of oral small-molecule GLP-1 RAs in alleviating supply constraints, as these agents can be manufactured using more scalable and cost-effective processes compared to peptide-based injectables (Whitley et al., 2023).

The broader context of GLP-1 receptor agonist therapy, including the development of emerging agents, has been reviewed in several comprehensive articles. A review of GLP-1 receptor agonists as a rational drug development highlighted the evolution of the class from the first-in-class exenatide to the latest dual and triple agonists (Ahrén, 2019). The review detailed the shortcomings and the potential of these agents as well as the need for a balance of efficacy and tolerability, cardiovascular safety and the potential for combination therapy. Another review of current and emerging GLP-1 analogues for T2DM provided a comprehensive overview of the agents that are currently available and those that are in clinical development (Gallwitz, 2011). The review discussed the placement of GLP-1 receptor agonists in the treatment algorithm of type 2 diabetes, and highlighted the potential of emerging therapies to further improve outcomes for patients (Gallwitz, 2011). A review of advances and future directions in GLP-1 receptor agonist therapy for type 2 diabetes provided a synthesis of the evidence on efficacy, safety, and cardiometabolic benefits, and discussed the potential of dual and triple agonists and oral formulations to transform the treatment landscape (Abdu et al., 2026).

A comparative analysis of the safety and efficacy of GLP-1 and GLP-1/GIP receptor agonists, based on FDA Adverse Event Reporting System data, found that the dual agonist tirzepatide was associated with a higher incidence of gastrointestinal adverse events compared to selective GLP-1 RAs, but also with greater weight loss (Prasad et al., 2026). The analysis also found that the safety profile of tirzepatide was generally consistent with that of selective GLP-1 RAs, with no new safety signals identified. The paper has found that the dual agonist has a good benefit-risk profile in patients with T2DM and obesity (Prasad et al., 2026).

An overview of the development and clinical potential of the dual GIP/GLP-1 receptor agonists, and a review of twincretin, the new kid on the block, gave a general idea of what these,GIP/GLP-1 receptor agonists are and why they have become the new kid on the block (J. Thomas, 2025). The rationale of dual agonism as well as the clinical trial data for tirzepatide and other dual agonists in development were covered in the review. They discuss also how twincretins will be a mainstay of therapy in patients with T2DM and obesity, which were found to be a significant step forward in the management of T2DM, as compared to selective GLP-1 RAs, in the review (J. Thomas, 2025).

In order to offer a systematised summary of the evidence on emerging therapies we have classified the studies included in a complete taxonomy as shown in Table 6. This taxonomy sorts the studies by the type of emerging therapy, by the specific agent under study or the specific focus of the study and allows for systematic comparison of evidence between the different types of therapy.

Table 4. Taxonomy of Included Studies on Emerging Therapies: Dual/Triple Agonists and Oral Formulations

Category	Sub-Category	Specific Agent / Focus	Sources
Dual Agonists	GIP/GLP-1 Receptor Agonists	Tirzepatide (General & SURPASS trials)	(Min & Bain, 2021), (Nowak et al., 2022), (Kaneko, 2022), (Z. Ma et al., 2023), (J. Thomas, 2025)

Category	Sub-Category	Specific Agent / Focus	Sources
		Tirzepatide (Mechanism & Beta-cell function)	(Thomas et al., 2021), (Nauck & 'Alessio, 2022)
		Tirzepatide (Cardiovascular outcomes)	(Fadini, 2025), (Fisman & Tenenbaum, 2021)
		NNC0090-2746 (Dual GIP/GLP-1)	(Frias et al., 2017)
	Glucagon/GLP-1 Receptor Agonists	Survodutide (Dual glucagon/GLP-1)	(Blüher et al., 2024)
Triple Agonists	GIP/GLP-1/Glucagon Receptor Agonists	Retatrutide (LY3437943)	(Urva et al., 2022), (Doggrell, 2023)
Oral Formulations	Small-Molecule GLP-1 Agonists	Orforglipron (General & ATTAIN-2)	(Karakasis et al., 2023), (Horn et al., 2025), (X. Ma et al., 2024)
		Danuglipron	(Karakasis et al., 2023)
		Comparative (Oral vs. Injectable)	(Patel, 2026)
	Oral Peptide-Based GLP-1 Agonists	Oral Semaglutide	(Rasmussen, 2020)
Reviews & Future Directions	Broad Reviews on Emerging Therapies	Dual/Triple Agonists & Oral Formulations	(Abdu et al., 2026), (Gallwitz, 2011), (Ahrén, 2019)
		GLP-1 & Dual Agonist Shortages/Strategies	(Whitley et al., 2023)
		Comparative Safety/Efficacy (FDA-based)	(Prasad et al., 2026)
		General GLP-1 RA Overview (context for emerging)	(Rosen & Ingelfinger, 2026)

Table 4 illustrates the taxonomy, emphasizing that current data on emerging therapies is reported mostly around dual GIP/GLP-1 receptor agonists, where tirzepatide has the most complete set of clinical trial data. These three tirzepatide studies span various endpoints, such as glucose control, weight reduction, beta-cell function, and cardiovascular risk factors, offering a comprehensive picture of tirzepatide's effectiveness and safety. The scope of work is lesser for triple agonists or oral small-molecule agents, as development of these is at a relatively early stage, but nonetheless some good work has been done looking at how they might be relevant. The reviews and the future perspectives cover a broader scope to gain a comprehensive understanding of the evolution of incretin therapy and the impact that new drugs may have on clinical practice.

The study by (Blüher et al., 2024) evaluated survodutide, a dual glucagon/GLP-1 receptor agonist, in a randomized clinical trial in people with type 2 diabetes. The study found that survodutide produced

dose-dependent reductions in HbA1c and body weight compared to placebo, with a safety profile that was consistent with that of other GLP-1 RAs. The study also included an open-label semaglutide arm, which allowed for a direct comparison of the two agents. The results showed that survodutide was non-inferior to semaglutide for glycemic control and was associated with numerically greater weight loss, suggesting that the addition of glucagon receptor agonism may enhance the weight loss efficacy of GLP-1 receptor activation (Blüher et al., 2024).

The study by (Rosen & Ingelfinger, 2026) provided a general overview of GLP-1 receptor agonists, which serves as a foundational reference for understanding the context in which emerging therapies are being developed. The topics included in the review were: mechanisms of action, clinical effectiveness and safety of the known GLPs and GLP-1 RAs, and the potential of GLP-1 RAs with dual/triple action and oral GLP-1 RAs in meeting the unmet needs in the management of T2DM (Rosen & Ingelfinger, 2026).

Real-World Evidence, Adherence, and Patient Preferences

For the efficacy to translate to effectiveness in real life, adherence, persistence and matching of the treatment characteristics and patient preferences is critical. Randomized controlled trials (RCTs) offer the strongest evidence for efficacy and safety of GLP-1 receptor agonists (GLP-1 RAs) in tightly controlled settings, and they often fail to account for the varied patient population, treatment compliance, and treatment burden, that all impact real world treatment outcomes. Therefore, real-world evidence (RWE) studies (that rely on patient survey, registry, and claims data) will play a crucial role in understanding how GLP-1 RAs will perform in the patient populations who will ultimately be prescribed them. The studies that came under this review provide strong evidence for real-world effectiveness as well as adherence and persistence, patient preferences, and economic impacts of GLP-1 RA therapy. This synthesis of the evidence shows that although GLP-1 RAs are generally effective in real world situations, adherence and persistence remains low while patient preferences are a result of a complex balance of efficacy, safety, convenience and cost.

The real-world cardiovascular safety and effectiveness of GLP-1 RAs have been confirmed in large-scale population-based studies. A nationwide population-based study in Denmark evaluated the cardiovascular safety of GLP-1 RAs versus other glucose-lowering agents in real-world patients with type 2 diabetes and found that GLP-1 RA use was associated with a significantly lower risk of major adverse cardiovascular events (MACE) and cardiovascular death compared to other glucose-lowering agents (Yang et al., 2020). This study, which included over 40,000 patients, provided important confirmation that the cardiovascular benefits observed in the landmark outcome trials are generalizable to routine clinical practice. The study also found that the risk of serious adverse events, including pancreatitis and pancreatic cancer, was not increased with GLP-1 RA use, further supporting their real-world safety profile (Yang et al., 2020).

The real-world effectiveness of GLP-1 RAs in achieving glycemic control and weight management has been evaluated in several studies. A real-world evaluation of GLP-1 RA therapy persistence, adherence, and therapeutic inertia among obese adults with type 2 diabetes found that GLP-1 RAs were effective in reducing HbA1c and body weight in routine clinical practice, with a mean HbA1c reduction of 0.9% and a mean weight loss of 3.5 kg over 12 months (Palanca et al., 2023). However, the study also found that adherence and persistence were suboptimal, with approximately 40% of patients discontinuing therapy within the first year. The study identified several factors associated with early discontinuation, including the occurrence of gastrointestinal side effects, higher baseline HbA1c, and younger age. Additionally, there was therapeutic inertia with many who did not reach glycemic targets not having dose escalation or changing to a more effective agent (Palanca et al., 2023).

Further insights into adherence were obtained from an analysis of the national population of individuals with type 2 diabetes (T2D) who discontinued GLP-1 RAs and/or SGLT-2 inhibitors (Lim et al., 2025). Following one year, 35.6% of patients discontinued GLP-1 RA treatment and 25.4% of patients discontinued SGLT-2 inhibitor treatment. Gastrointestinal adverse events (nausea, vomiting, and diarrhea) and cost were the top reasons for GLP-1 RA discontinuation. Furthermore, the study revealed less dropout rate among patients taking GLP-1 RAs in combination with SGLT-2 inhibitors compared to those taking GLP-1 RAs alone, indicating the potential of combination therapy in enhancing adherence, perhaps because it is deemed more effective or better tolerated (Lim et al., 2025).

A study that compared the persistence and adherence of people with type 2 diabetes (T2D) who switched to a fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) to those who switched to free-combination of basal insulin and GLP-1 RA demonstrated a significant improvement for the fixed-ratio combination of iGlarLixi (Edelman et al., 2022). The study, which found real-world data via a big claims database, demonstrated a greater percentage of days covered (PODC) adherence with the users of iGlarLixi (78%) compared with those taking free-dose combinations (62%). iGlarLixi users also showed greater persistence (time to discontinuation) at 180 days versus 120 days in the free-dose combination group. Collectively, these results support the concept of a less complex treatment regimen, such as fixed-ratio combination products, to enhance adherence and retention, potentially due to the reduction of the number of injections needed and the requirement for dose adjustments (Edelman et al., 2022).

Patient preferences for GLP-1 RA treatment have been evaluated in several discrete choice experiments, which are a method for quantifying the relative importance of different treatment attributes to patients. A study assessing patient preferences for GLP-1 RA treatment of type 2 diabetes mellitus in Japan found that the most important attributes to patients were the magnitude of HbA1c reduction, the risk of gastrointestinal side effects, and the dosing frequency (Brooks et al., 2019). The study found that patients were willing to accept a higher risk of gastrointestinal side effects in exchange for greater glycemic control, and that they preferred once-weekly dosing over once-daily dosing. The study also found that patients placed a high value on the ability to lose weight, and that this attribute was a significant driver of preference (Brooks et al., 2019).

A multinational preference study evaluating GLP-1 RA treatment attributes important to injection-naïve patients with type 2 diabetes mellitus found that the most important attributes were the magnitude of HbA1c reduction and the effect on body weight (Qin et al., 2017). The study also found that patients placed a high value on the convenience of the dosing regimen, with once-weekly dosing being preferred over twice-daily or once-daily dosing. The study found that patients were willing to accept a modest increase in the risk of gastrointestinal side effects for a greater HbA1c reduction and weight loss. The study also found that the mode of administration (injection vs. oral) was an important attribute, with a strong preference for oral administration if it were available (Qin et al., 2017).

A preference study in Germany and the United Kingdom evaluated GLP-1 RA treatment attributes important to injection-experienced patients with type 2 diabetes mellitus (Qin et al., 2017). The study found that the most important attributes were the magnitude of HbA1c reduction, the effect on body weight, and the risk of hypoglycemia. The study also found that the dosing frequency and the complexity of the injection device were important attributes, with patients preferring once-weekly dosing and simple, easy-to-use devices. The study found that injection-experienced patients were more willing to accept a higher risk of gastrointestinal side effects compared to injection-naïve patients, possibly because they were more familiar with the tolerability profile of GLP-1 RAs (Qin et al., 2017).

The real-world evidence also highlights the heterogeneity in response to GLP-1 RAs in clinical practice. An analysis of the DPV registry, which is a large German/Austrian diabetes registry, found that there was substantial inter-individual variability in the HbA1c reduction and weight loss achieved with GLP-1 RAs (Heni et al., 2025). The study identified several patient characteristics that were associated with a greater response, including higher baseline HbA1c, higher baseline body mass index, and younger age. The study also found that patients with a history of prior treatment with a DPP-4 inhibitor had a smaller response to GLP-1 RAs, suggesting that prior exposure to incretin-based therapy may attenuate the efficacy of subsequent GLP-1 RA treatment. This heterogeneity in response underscores the importance of personalized treatment selection and monitoring (Heni et al., 2025).

The cost-effectiveness of GLP-1 RAs has been evaluated in several studies, which have important implications for formulary access and patient affordability. A study evaluating the long-term cost-effectiveness of daily administered GLP-1 RAs for the treatment of type 2 diabetes in the United Kingdom found that liraglutide was cost-effective compared to standard of care, with an incremental cost-effectiveness ratio (ICER) of £24,000 per quality-adjusted life year (QALY) gained (Hunt et al., 2017). The study found that the cost-effectiveness of liraglutide was driven by its effects on HbA1c, body weight, and cardiovascular risk. Another study evaluating the cost-effectiveness of GLP-1 RAs for the treatment of type 2 diabetes in the UK found that dulaglutide and semaglutide were also cost-effective, with ICERs below the UK's willingness-to-pay threshold of £30,000 per QALY (Ashley et al., 2015). The study found that the cost-effectiveness of these agents was influenced by their effects on cardiovascular outcomes, with the inclusion of cardiovascular benefits significantly improving their cost-effectiveness profiles (Ashley et al., 2015).

A study evaluating the cost-effectiveness of iGlarLixi versus iDegLira (a fixed-ratio combination of insulin degludec and liraglutide) in type 2 diabetes mellitus inadequately controlled by GLP-1 receptor agonists and oral antihyperglycemic therapy found that iGlarLixi was dominant (i.e., more effective and less costly) compared to iDegLira (McCrimmon et al., 2021). The study found that the cost advantage of iGlarLixi was driven by its lower drug acquisition cost, while its efficacy was comparable to iDegLira. This finding highlights the importance of cost considerations in treatment selection, particularly when multiple therapeutic options are available with similar efficacy profiles (McCrimmon et al., 2021).

Cost-effectiveness of liraglutide versus lixisenatide for type 2 diabetes in Spain was discussed in a previous study, which resulted in liraglutide being cost-effective when compared to lixisenatide with an ICER of €18,000 per QALY (Mezquita-Raya et al., 2017). The results of this study suggested that although the incremental cost of liraglutide was high, its increased efficacy in the reduction of HbA1c and body weight, and beneficial effects on the cardiovascular risk factors offset this relatively higher cost. Additionally, sensitivity analysis showed that the cost-effectiveness of liraglutide was dependent on the treatment duration assumptions and the cardiovascular benefit effect sizes (Mezquita-Raya et al., 2017).

The practicalities of using GLP-1 RAs in real-world clinical practice have been reviewed in several articles. A review on GLP-1 RAs as underutilized assets in type 2 diabetes (T2DM) highlighted that the barriers to the uptake of these agents in routine practice were mainly cost, fear of injections, and the lack of familiarity with the class by physicians (Morris, 2020). The review highlighted that the use of GLP-1 RAs is underutilized despite their proven benefits, and suggested that efforts should be made to increase their uptake, which could involve patient education efforts and develop less costly formulations (Morris, 2020).

A review of GLP-1 RAs for type 2 diabetes and their role in primary care from an Australian perspective discussed the challenges and opportunities for the use of these agents in the primary care setting (Rasalam et al., 2019). This review highlighted the effectiveness and safety of GLP-1 RAs, and noted that despite their benefits, their uptake in primary care has been hindered by cost and the requirement for them to be started by a specialist. The review recommended early use of GLP-1 RAs in the treatment algorithm of type 2 diabetes, especially for type 2 diabetes patients with obesity or established cardiovascular disease (CVD) and that primary care physicians (PCPs) have the authority to start and manage use of GLP-1 RAs (Rasalam et al., 2019).

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report on hyperglycemia in Type 2 diabetes (T2D) showed a complete list of recommendations for clinical use of GLP-1 RAs with regards to hyperglycemia management (Davies et al., 2018). The report suggested use of GLP-1 RAs as a tool in combination therapy for diabetes subjects needing a further source of glycemic management, especially those with a diagnosis of cardiovascular disease or obesity. Shared preferences, costs and adverse event potential were also highlighted as key considerations in shared decision making (Davies et al., 2018).

The south Asian task force consensus recommendation for GLP-1 RA use in type 2 diabetes mellitus (T2DM), provided region-specific guidance for the use of GLP-1 RA in the south Asian population (Kalra et al., 2019). The task force recommended considering GLP-1 RAs as first-line treatment in patients with type 2 diabetes and high cardiovascular risk, and second-line treatment in patients who do not reach targets on metformin treatment. The task force also highlighted the benefits of initiating GLP-1 RAs early in the disease course to maintain the beta-cell function and avoid the occurrence of future complications (Kalra et al., 2019).

Current knowledge on GLP-1 RAs in T2DM from 2015, including their use for weight management, cardiovascular protection and as potential neuroprotective therapy (Gallwitz, 2015). During the review, there has been a paradigm shift towards the role of real-world evidence in validating the results of RCTs and in detecting new treatment uses for GLP-1 RAs (Gallwitz, 2015).

The pharmacological profile, efficacy and safety of lixisenatide was reviewed and this offers a comprehensive overview of this short acting GLP-1 Ra (Forst & Pfuetzner, 2013). The properties of lixisenatide with its high affinity and short half-life, making it well placed for a prandial application, were also discussed. During the review the clinical trial experiences with lixisenatide have been discussed, which showed its efficacy in reducing postprandial glucose excursions, and the favorable clinical safety profile (Forst & Pfuetzner, 2013).

A comparative analysis of the available agents was carried out after reviewing GLP-1 receptor agonists in the treatment of type 2 diabetes, to review for their use and differential features (Lyseng-Williamson, 2019). The review highlighted the difference between short acting GLP-1RA and long acting GLP-1RA and once daily versus once weekly GLP-1RA. The clinical implications of the differences were also reviewed and include the decision on which agent to use based on the patient's glycemic profile, tolerability, and preferences (Lyseng-Williamson, 2019).

One review of lixisenatide and its use in the treatment of type 2 diabetes discussed the mechanism and clinical effectiveness of the drug in-depth, based on multiple clinical trials (Horowitz et al., 2013). The mechanism of action of lixisenatide, activation of GLP-1 receptor, associated with glucose-dependent insulin secretion, glucagon suppression, and delayed gastric emptying were discussed in the review. The review also examined the clinical trial results on lixisenatide, showing its beneficial effects on the reduction of HbA1c, body weight and postprandial glucose excursions (Horowitz et al., 2013).

Important safety data are available for use of the combination in a review of the effect of the GLP-1 receptor agonist lixisenatide on counterregulatory responses to hypoglycemia in subjects with insulin-treated type 2 diabetes (Farngren et al., 2016). The study found that lixisenatide did not impair the counterregulatory response to hypoglycemia, which is a critical safety consideration when combining a GLP-1 RA with insulin (Farngren et al., 2016).

A review of GLP-1 receptor agonist and basal insulin co-therapy in type 2 diabetes, discussing clinical evidence and practicalities of use, provided a practical guide for clinicians (Kenny & Hall, 2015). The review discussed the evidence for the efficacy and safety of combining a GLP-1 RA with basal insulin, and provided recommendations for selecting the appropriate patients, initiating therapy, and titrating doses (Kenny & Hall, 2015).

A review of whether there is a justification for classifying GLP-1 receptor agonists as basal and prandial discussed the pharmacological and clinical rationale for this classification (Miñambres & Pérez, 2017). Pharmacological and clinical rationale for classifying GLP-1 receptor agonists as basal and prandial were discussed in a review of whether there is a justification for their classification (Miñambres & Pérez, 2017). Although GLP-1 RAs are sometimes described as basal agents while others are considered prandial, the review pointed out that the use of these terms is clinically helpful in determining which GLP-1 RA to use in which patient, depending on their glycemic profile. There, short-acting (prandial) GLP-1 RAs, including lixisenatide or exenatide twice daily, are better for reducing postprandial glucose excursions while long-acting (basal) GLP-1 RAs (liraglutide, dulaglutide, and semaglutide) are better for reducing fasting glucose and overall glycemic variability (Miñambres & Pérez, 2017).

A review of health-related quality of life assessments with once-weekly glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus found that once-weekly GLP-1 RAs were associated with improvements in health-related quality of life compared to placebo and active comparators (Billings et al., 2018). The study found that the improvements in quality of life were driven by reductions in body weight, improvements in glycemic control, and the convenience of once-weekly dosing. The study also found that the improvements in quality of life were sustained over the long term (Billings et al., 2018).

A review of the efficacy of a fixed-ratio combination of GLP-1 receptor agonist and basal insulin therapy for the treatment of type 2 diabetes provided a systematic review protocol that will further contribute to the evidence base for this therapeutic approach (Ramalan et al., 2024). The review will evaluate the efficacy and safety of fixed-ratio combinations, such as iGlarLixi and iDegLira, compared to free-dose combinations and basal insulin alone (Ramalan et al., 2024).

A review discussing whether it is time to change the type 2 diabetes treatment paradigm argued that GLP-1 RAs should replace metformin in the type 2 diabetes algorithm (Abdul-Ghani & DeFronzo, 2017). The review argued that GLP-1 RAs are more effective than metformin for glycemic control, weight management, and cardiovascular protection, and that they have a favorable safety profile. The review acknowledged that this is a controversial position, but argued that the evidence base supports a paradigm shift towards the use of GLP-1 RAs as first-line therapy (Abdul-Ghani & DeFronzo, 2017).

A review of basal insulin use with GLP-1 receptor agonists provided a practical guide for the use of this combination therapy (S. Anderson & Trujillo, 2016). The review discussed the rationale for combining a GLP-1 RA with basal insulin, the evidence for the efficacy and safety of this approach, and the practical aspects of initiating and titrating therapy (S. Anderson & Trujillo, 2016).

A review of the real-world effectiveness of once-daily GLP-1 receptor agonist lixisenatide compared to bolus insulin both in combination with basal insulin for the treatment of patients with type 2 diabetes found that lixisenatide was as effective as bolus insulin in improving glycemic control, but was associated with weight loss rather than weight gain, and with a lower risk of hypoglycemia (Huetson et al., 2015). The study provided real-world evidence supporting the use of lixisenatide as an alternative to prandial insulin in patients who require intensification of therapy with basal insulin (Huetson et al., 2015).

A review of combining GLP-1 receptor agonists and basal insulin in older adults with type 2 diabetes, focusing on lixisenatide and insulin glargine, provided guidance for the use of this combination in a vulnerable population (Handelsman et al., 2019). The evidence for efficacy and safety of this combination in older adults was discussed, and careful dose titration with careful attention to any adverse events, especially gastrointestinal and hypoglycaemia, was emphasised (Handelsman et al., 2019).

To provide a structured overview of the real-world evidence studies, adherence studies and patient preference studies we have categorized the included studies to a comprehensive taxonomy as is presented in Table 7. The papers are grouped under the theme and sub theme, so that one can systematically compare the evidence for different aspects of real-world use of the studies.

Table 5. *Taxonomy of Included Studies on Real-World Evidence, Adherence, and Patient Preferences*

Main Theme	Sub-Theme	Specific Focus	Sources
Real-World Effectiveness & Safety	Cardiovascular Outcomes	Population-based cardiovascular safety	(Yang et al., 2020)
	Glycemic & Weight Outcomes	Adherence, persistence, and therapeutic inertia	(Palanca et al., 2023), (Lim et al., 2025)
		Heterogeneity in response (DPV registry)	(Heni et al., 2025)
	Fixed-Ratio Combinations	Persistence and adherence with iGlarLixi	(Edelman et al., 2022)
	Comparative Effectiveness	Lixisenatide vs. bolus insulin with basal insulin	(Huetson et al., 2015)
Adherence and Persistence	Discontinuation Rates	GLP-1 RAs vs. SGLT-2 inhibitors	(Lim et al., 2025)
		Factors associated with discontinuation	(Palanca et al., 2023)
	Fixed-Ratio Combinations	Improved adherence with fixed-ratio vs. free-dose	(Edelman et al., 2022)
Patient Preferences	Discrete Choice Experiments	Injection-naïve patients (multinational)	(Qin et al., 2017)
		Injection-experienced patients (Germany/UK)	(Qin et al., 2017)
		Japanese patients	(Brooks et al., 2019)

Main Theme	Sub-Theme	Specific Focus	Sources
Cost-Effectiveness	Long-Term Cost-Effectiveness	Daily-administered GLP-1 RAs in the UK	(Hunt et al., 2017)
		GLP-1 RAs in the UK	(Ashley et al., 2015)
	Comparative Cost-Effectiveness	iGlarLixi vs. iDegLira	(McCrimmon et al., 2021)
		Liraglutide vs. lixisenatide in Spain	(Mezquita-Raya et al., 2017)
Clinical Practice & Guidelines	Underuse and Barriers	GLP-1 RAs as an underused asset	(Morris, 2020)
		Role in primary care (Australian perspective)	(Rasalam et al., 2019)
		Paradigm shift: GLP-1 RAs as first-line?	(Abdul-Ghani & DeFronzo, 2017)
	Guidelines and Consensus	ADA/EASD consensus report	(Davies et al., 2018)
		South Asian task force recommendations	(Kalra et al., 2019)
Practical Considerations	Combination Therapy	Basal insulin with GLP-1 RA co-therapy	(Kenny & Hall, 2015), (S. Anderson & Trujillo, 2016)
		Combining GLP-1 RAs and basal insulin in older adults	(Handelsman et al., 2019)
		Fixed-ratio combination efficacy (protocol)	(Ramalan et al., 2024)
	Classification of GLP-1 RAs	Basal vs. prandial classification	(Miñambres & Pérez, 2017)
	Quality of Life	HRQoL with once-weekly GLP-1 RAs	(Billings et al., 2018)
Drug-Specific Evidence	Lixisenatide	Pharmacological profile, efficacy, and safety	(Forst & Pfuetzner, 2013)
		Mechanisms and clinical efficacy	(Horowitz et al., 2013)
		Effect on counterregulatory responses	(Farngren et al., 2016)
		Real-world effectiveness with basal insulin	(Huetson et al., 2015)

Main Theme	Sub-Theme	Specific Focus	Sources
	General Reviews	GLP-1 RAs in type 2 diabetes (2015 insights)	(Gallwitz, 2015)
		Use and differential features	(Lyseng-Williamson, 2019)

As illustrated in the real-world evidence taxonomy in Table 5, there is a broad spectrum of real-world evidence available to answer questions on GLP-1 RAs, and it covers a wide range of topics: clinical practice guideline recommendations, cost-effectiveness, patient preferences and adherence and persistence, practical considerations for combination therapy, and cardiovascular and glycemic efficacy. The adherence/persistence studies have all demonstrated that GLP-1 RAs are effective, but it has been unclear to what extent in the real world and the most common reasons have been gastrointestinal and cost. Patient preference studies can provide insights into patient attributes that are most important to patients and for this treatment class, glycemic control, weight loss and frequency of dose are key drivers of preference. Two cost effectiveness studies provide further evidence of the cost effectiveness of GLP-1 RAs in the UK and other countries, and will support introduction of GLP-1 RAs to formularies. The clinical practice guidelines include expert guidance regarding the use of GLP-1 RAs and specifically target patients with obesity and/or an established cardiovascular disease. The practical problems addressed by the studies offer insight for clinicians on how best to utilize GLP-1 RAs in practice—such as picking the right agent, combination therapy, and adverse event management. This drug-specific evidence review is for this short acting drug with a unique role in the management of postprandial hyperglycemia, lixisenatide.

Discussion

This systematic review collates the results of the papers to give a coherent and mostly consistent picture of glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus. The overall literature indicates that GLPs are a very effective class of therapeutic drugs to improve glycemic control, weight loss, and provides solid cardiorenal benefits to a wide population of patients. The overall impression conveyed through the literature from various studies is that the concept of this class of drugs has grown beyond just simply lowering the glucose level and that they represent the central point of a metabolic management strategy, and that benefits to these drugs is well clear of traditional diabetes outcomes. Evidence from RCTs, real-world RCTs and mechanistic studies are reasonably consistent, with generally high efficacy and good tolerability although careful patient selection for treatment and monitoring, including gastrointestinal tolerability, are needed.

The clinical practice and theoretical ramifications of this synthesis are enormous. There is equal efficacy in achieving cardiorenal benefits with the different agents that belong to the class, suggesting that one of them could be considered equally as first-choice drugs in patients with type 2 diabetes and atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. The evidence indicates the need to shift from a ‘glucose-only' therapeutic paradigm to a more inclusive paradigm that acknowledges the effective prevention of end-organ damage as a fair end-point for evaluating the efficacy of drug therapy for diabetes, even in settings where glycemic targets are achieved with other medication. Thus, practitioners and policy makers should consider using cardiovascular and renal risk assessment in the algorithm for GLP-1 RA initiation, as well as use of these drugs in poor glycemic control populations. Furthermore, data emerging in support of the combination of GLP-1 RAs and SGLT-2 inhibitors would suggest that combination of these two therapeutics for the treatment of high cardiorenal risk patients should be used at the forefront of the treatment pathway, seeing as how GLP-1 RAs and SGLT-2 inhibitors have different modes of action that, in combination, provide a more

comprehensive treatment approach than either class alone could provide for morbidity and mortality reduction.

An important issue to consider in understanding the synthesized evidence presented and interpretation and generalisability of our findings is some methodological limitations. However, our search strategy was comprehensive to the extent that only studies that were peer-reviewed and published in English were included, which could have created language bias and excluded relevant studies published in other languages. The inclusion criteria limited to those studies that included adults with type 2 diabetes may have resulted in an inability to draw conclusions on GLP-1 RA use in other groups such as youth with diabetes or people with obesity but no diabetes, in whom these drugs are becoming more popular. It is noteworthy that the possibility of publication bias exists since positive study findings would be more likely to be published and therefore result in overrated efficacy and safety of GLP-1 RAs. Moreover, the quality assessment of the included studies was systematic but also inherently subjective and the differences in study design, definition of outcome, and follow-up period of the included studies was also a challenge for synthesis and comparison. The use of risk of bias assessment tools will not totally characterize real world confounding that might underlie the results of observational studies, although common. Different limitations indicate that some findings should be interpreted with some caution, particularly if the evidence base is predominantly made up of observation studies of open design, or post-hoc analyses.

Based on the results of this review several lines of research are then obvious which seem logical extensions of what has been learned. Dedicated head-to-head cardiovascular outcome trials (CVOTs) are needed to determine if there are important differences in the cardioprotective effects of the various GLP-1 RAs, and with SGLT-2 inhibitors, and to identify if there is a choice for a first-line treatment for individual patients. Future studies will also assess the optimal timing during the disease course of initiating therapy with GLP-1 RAs – especially in patients with newly diagnosed type 2 diabetes at high risk for cardiovascular events – to determine whether initiation of therapy with these drugs early in the disease course will prevent end-organ damage. Limited information about the effectiveness and long term safety of GLP-1 RAs is available in special subsets of patients, such as patients with hepatic cirrhosis, severe renal impairment or with a history of pancreatitis. The growing awareness of gastrointestinal complications (albeit uncommon) such as intestinal obstruction and GERD-related issues needs to be evaluated in large scale prospective cohorts to determine accurate size of risk and to explore factors that contribute. More work is needed to investigate the mechanisms that underlie this differential response, such as genetic factors, gut microbiome composition and starting baseline metabolic phenotype, to be able to select the optimal GLP-1 RA therapy for individual patients. Due to the expedient development of dual and triple agonists and oral small molecule GLP-1 RAs, it is necessary to conduct high-quality comparative effectiveness and safety analyses of these newer agents compared to the older agents (established injectable GLP-1RAs) with an emphasis on the long-term side effects in relation to tolerability and adherence. As GLP-1 RAs can not be equally available to all people, future research should explore their impact on social determinants of health, access to care and on health equity.

Conclusion

This systematic Literature Review aimed to reduce the huge amount of evidence to provide a summary of the efficacy and safety of GLP-1 receptor agonists among adults with type 2 diabetes mellitus. As a whole, the results confirm the uniform GLP-1 RA efficacy on glycated hemoglobin and on weight loss and clearly show the cardiorenal benefits that are not glucose-related. Benefits related to cardiovascular outcomes (reduction of major cardiovascular adverse events and cardiovascular mortality) are class effects and benefits related to renal outcomes (reduction of progression of albuminuria) are robust and

clinically important. The review also shows that the safety profile of GLP1 RAs is generally very good, and the most common tolerability side effect is gastro-intestinal, but these tend to be temporary and easily managed. The comparative effectiveness analysis demonstrates that GLP-1 RAs have unique weight loss and hypoglycemic risk profiles that are different from DPP-4 inhibitors and insulin, but the GLP-1 RA profile is complementary to SGLT-2 inhibitors, suggesting combination therapy in patients with a high cardiorenal risk profile.

These findings have wide ranging implications for the clinical, guidelinemaking and policy-making communities. The evidence is voluminous supporting GLP-1 RA use in type 2 diabetes and ASCVD, heart failure and/or chronic kidney disease regardless of glycemic level. The theoretical implications thus raise doubts about the glucose-centric paradigm of diabetes therapy, and point towards a holistic therapy approach based on the efficacy in preventing end-organ damage. As these are extended to additional targets and more easy to take, the potential applications for this class of drugs become even more extensive with the advent of dual and triple agonists like tyrzepatide and retatrutide – and oral small molecule drugs.

Future research is needed to address head-to-head cardiovascular outcome trials of GLP-1 RAs and SGLT-2 inhibitors, safety of GLP-1 RA and SGLT-2 inhibitors in special populations with severe renal impairment and/or past history of pancreatitis, and understanding mechanisms of heterogeneity. With the development of a plethora of multi-agonists and oral formulations, stringent comparative effectiveness and safety testing is needed to determine the treatment algorithm role of these products. In summary, the results of the studies included in this review are strong enough to warrant GLP-1 receptor agonists as a valuable tool in the current context of diabetes management, as well as potentially a paradigm shift in the natural history of T2D and its complications.

References

Abdu, A., Bakrey, H., Abdelrahim, I., Awad, Z., Fikak, Y., et al. (2026). Advances and future directions in GLP-1 receptor agonist therapy for type 2 diabetes: Efficacy, safety and cardiometabolic benefits. *Technology*.

Abdul-Ghani, M., & DeFronzo, R. (2017). Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care*.

Ahrén, B. (2011). GLP-1 for type 2 diabetes. *Experimental Cell Research*.

Ahrén, B. (2013). Incretin therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors. *European Diabetes Nursing*.

Ahrén, B. (2019). Glucagon-like peptide-1 receptor agonists for type 2 diabetes: A rational drug development. *Journal of Diabetes Investigation*.

Alexopoulos, A., & Buse, J. (2019). Initial injectable therapy in type 2 diabetes: Key considerations when choosing between glucagon-like peptide 1 receptor agonists and insulin. *Metabolism*.

Anderson, J. (2020). Combining glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors to target multiple organ defects in type 2 diabetes. *Diabetes Spectrum*.

Anderson, S., & Trujillo, J. (2016). Basal insulin use with GLP-1 receptor agonists. *Diabetes Spectrum*.

Ansari, H., Qazi, S., Sajid, F., Altaf, Z., Ghazanfar, S., et al. (2024). Efficacy and safety of glucagon-like peptide-1 receptor agonists on body weight and cardiometabolic parameters in individuals with obesity and without diabetes: A …. *Endocrine Practice*.

Aroda, V., & Ratner, R. (2011). The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: A review. *Diabetes/Metabolism Research and Reviews*.

Ashley, D., Vega, G., Hunt, B., & Valentine, W. (2015). Evaluating the cost-effectiveness of GLP-1 receptor agonists for the treatment of type 2 diabetes in the UK. *Value in Health*.

Association, A. D. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care*.

Atlas, I. (2021). IDF diabetes atlas. *2021*.

Bae, J. (2025). SGLT2 inhibitors and GLP-1 receptor agonists in diabetic kidney disease: Evolving evidence and clinical application. *Diabetes & Metabolism Journal*.

Baggio, L., & Drucker, D. (2007). Biology of incretins: GLP-1 and GIP. *Gastroenterology*.

Baxter, M., Morimoto, Y., Tamiwa, M., Hattori, M., Peng, X., et al. (2020). … study evaluating the probability of glycemic control with basal insulin or glucagon-like peptide-1 receptor agonist in japanese patients with type 2 diabetes. *Diabetes Therapy*.

Billings, L., Handelsman, Y., Heile, M., et al. (2018). Health-related quality of life assessments with once-weekly glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus. *Journal of Managed Care & Specialty Pharmacy*.

Block, C. D., & Gaal, L. V. (2009). GLP-1 receptor agonists for type 2 diabetes. *The Lancet*.

Blüher, M., Rosenstock, J., Hoefler, J., Manuel, R., et al. (2024). … of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: A randomised clinical …. *Diabetologia*.

Bonaventura, A., Carbone, S., Dixon, D., et al. (2019). Pharmacologic strategies to reduce cardiovascular disease in type 2 diabetes mellitus: Focus on SGLT-2 inhibitors and GLP-1 receptor agonists. *Journal of Internal Medicine*.

Brooks, A., Langer, J., Tervonen, T., Hemmingsen, M., et al. (2019). Patient preferences for GLP-1 receptor agonist treatment of type 2 diabetes mellitus in japan: A discrete choice experiment. *Diabetes Therapy*.

Brown, D., & Evans, M. (2012). Choosing between GLP-1 receptor agonists and DPP-4 inhibitors: A pharmacological perspective. *Journal of Nutrition and Metabolism*.

Brunton, S. (2014). GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: Is one approach more successful or preferable than the other? *International Journal of Clinical Practice*.

Brunton, S., & Wysham, C. (2020). GLP-1 receptor agonists in the treatment of type 2 diabetes: Role and clinical experience to date. *Postgraduate Medicine*.

Bzowyckyj, A. (2020). Managing the multifaceted nature of type 2 diabetes using once-weekly injectable GLP-1 receptor agonist therapy. *Journal of Clinical Pharmacy and Therapeutics*.

Caruso, I., Cignarelli, A., Sorice, G., Natalicchio, A., et al. (2022). … effectiveness of GLP-1 receptor agonists vs. Other glucose-lowering drugs in type 2 diabetes: A systematic review and meta-analysis of real-world studies. *Metabolites*.

Caruso, I., & Giorgino, F. (2024). Renal effects of GLP-1 receptor agonists and tirzepatide in individuals with type 2 diabetes: Seeds of a promising future. *Endocrine*.

Chai, S., Niu, Y., Liu, F., Wu, S., Yang, Z., et al. (2024). Comparison of GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP-4 inhibitors as an add-on drug to insulin combined with oral hypoglycemic drugs: Umbrella …. *Journal of Diabetes Research*.

Chen, J., Fang, Y., Liu, Y., Chen, M., et al. (2026). GLP-1 receptor agonist therapy and cardiorenal outcomes in patients≥ 80 years old with type 2 diabetes. *Journal of the American Geriatrics Society*.

Cowart, K., & Carris, N. (2025). … and glycated haemoglobin goals for type 2 diabetes: Which patients are most likely to benefit from fixed-ratio basal insulin glucagon-like peptide-1 receptor agonist …. *Diabetes, Obesity and Metabolism*.

Davidson, J. (2009). Advances in therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors. *Cleveland Clinic Journal of Medicine*.

Davies, M., D'Alessio, D., Fradkin, J., Kernan, W., et al. (2018). … of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the american diabetes association (ADA) and the european association for the study of diabetes …. *Diabetologia*.

Deacon, C., Johnsen, A., & Holst, J. (1995). Degradation of glucagon-like peptide-1 by human plasma in vitro yields an n-terminally truncated peptide that is a major endogenous metabolite in vivo. *The Journal of Clinical Endocrinology & Metabolism*.

Doggrell, S. (2018). Sgemaglutide in type 2 diabetes–is it the best glucagon-like peptide 1 receptor agonist (GLP-1R agonist)? *Expert Opinion on Drug Metabolism & Toxicology*.

Doggrell, S. (2023). Is retatrutide (LY3437943), a GLP-1, GIP, and glucagon receptor agonist a step forward in the treatment of diabetes and obesity? *Expert Opinion on Investigational Drugs*.

Drab, S. (2016). Glucagon-like peptide-1 receptor agonists for type 2 diabetes: A clinical update of safety and efficacy. *Current Diabetes Reviews*.

Drucker, D. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metabolism*.

Edelman, S., Cassarino, D., Kayne, D., Dex, T., Li, X., et al. (2022). … and adherence in people with type 2 diabetes switching to iGlarLixi vs free-dose combinations of basal insulin and glucagon-like peptide 1 receptor agonist. *Journal of Managed Care & Specialty Pharmacy*.

Fadini, G. (2025). Can dual incretin receptor agonists exert better cardiovascular protection than selective GLP-1 receptor agonists? Highlights from SURPASS-CVOT. *Diabetes Therapy*.

Farngren, J., Persson, M., & Ahrén, B. (2016). Effect of the GLP-1 receptor agonist lixisenatide on counterregulatory responses to hypoglycemia in subjects with insulin-treated type 2 diabetes. *Diabetes Care*.

Feng, Z., Tong, W., Zhang, X., & Tang, Z. (2023). … analysis of once-daily oral semaglutide versus placebo and subcutaneous glucagon-like peptide-1 receptor agonists added to insulin in patients with type 2 diabetes …. *Frontiers In Pharmacology*.

Ferrari, F., Scheffel, R., Martins, V., Santos, R., et al. (2022). Glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus and cardiovascular disease: The past, present, and future. *American Journal of Cardiovascular Drugs*.

Fisman, E., & Tenenbaum, A. (2021). The dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide: A novel cardiometabolic therapeutic …. *Cardiovascular Diabetology*.

Forst, T., & Pfuetzner, A. (2013). Pharmacological profile, efficacy and safety of lixisenatide in type 2 diabetes mellitus. *Expert Opinion on Pharmacotherapy*.

Frias, J., Bastyr, E., Vignati, L., Tschoep, M., Schmitt, C., et al. (2017). The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. *Cell Metabolism*.

Frías, J., Davies, M., Rosenstock, J., et al. (2021). Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *New England Journal of Medicine*.

Gallwitz, B. (2011). Glucagon-like peptide-1 analogues for type 2 diabetes mellitus: Current and emerging agents. *Drugs*.

Gallwitz, B. (2015). GLP-1 receptor agonists in type 2 diabetes and beyond–new insights 2015. *European Endocrinology*.

Gao, Z., Tabernacki, T., Dorney, I., Ding, P., Kaelber, D., et al. (2025). Association of GLP-1 receptor agonists with risk of intestinal obstruction in patients with type 2 diabetes mellitus: A retrospective cohort study. *Acta Diabetologica*.

Gilbert, M., & Pratley, R. (2009). Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. *European Journal of Internal Medicine*.

Giorda, C., Nada, E., & Tartaglino, B. (2014). Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A …. *Endocrine*.

Gluud, L. (2023). GLP-1 receptor agonists for weight loss in people without type 2 diabetes: What is the current evidence? *The American Journal of Clinical Nutrition*.

Goldman, J. (2020). Cardiovascular safety outcomes of once-weekly GLP-1 receptor agonists in people with type 2 diabetes. *Journal of Clinical Pharmacy and Therapeutics*.

Goncalves, E., & Bell, D. (2018). Combination treatment of SGLT2 inhibitors and GLP-1 receptor agonists: Symbiotic effects on metabolism and cardiorenal risk. *Diabetes Therapy*.

Handelsman, Y., Muskiet, M., & Meneilly, G. (2019). Combining GLP-1 receptor agonists and basal insulin in older adults with type 2 diabetes: Focus on lixisenatide and insulin glargine. *Advances in Therapy*.

Hashmi, T., Ahmed, M., Haider, A., et al. (2025). Once-weekly semaglutide versus once-daily liraglutide for weight loss in adults: A meta-analysis of randomized controlled trials. *Clinical and Translational Science*.

Heni, M., Frühwald, L., Karges, W., Naudorf, M., Niemöller, K., et al. (2025). Heterogeneity in response to GLP-1 receptor agonists in type 2 diabetes in real-world clinical practice: Insights from the DPV register–an IMI-SOPHIA study. *Diabetologia*.

Hinnen, D. (2017). Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectrum*.

Holst, J. (2019). From the incretin concept and the discovery of GLP-1 to today's diabetes therapy. *Frontiers in Endocrinology*.

Horn, D., Ryan, D., Kis, S., Alves, B., Mu, Y., Kim, S., et al. (2025). Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): A phase 3, double-blind …. *The Lancet*.

Horowitz, M., Rayner, C., & Jones, K. (2013). Mechanisms and clinical efficacy of lixisenatide for the management of type 2 diabetes. *Advances in Therapy*.

Huetson, P., Palmer, J., Levorsen, A., et al. (2015). … effectiveness of once daily GLP-1 receptor agonist lixisenatide compared to bolus insulin both in combination with basal insulin for the treatment of patients with type 2 …. *Journal of Medical Economics*.

Hunt, B., Ye, Q., Valentine, W., & Ashley, D. (2017). Evaluating the long-term cost-effectiveness of daily administered GLP-1 receptor agonists for the treatment of type 2 diabetes in the united kingdom. *Diabetes Therapy*.

Inzucchi, S., Bergenstal, R., Buse, J., et al. (2012). Management of hyperglycemia in type 2 diabetes: A patient-centered approach: Position statement of the american diabetes association (ADA) and the european …. *Diabetes Spectrum*.

Ishihara, H., Yamaguchi, S., Nakao, I., & Sakatani, T. (2018). Ipragliflozin add-on therapy to a GLP-1 receptor agonist in japanese patients with type 2 diabetes (AGATE): A 52-week open-label study. *Diabetes Therapy*.

Jalleh, R., Talley, N., Horowitz, M., & Nauck, M. (2026). The science of safety: Adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications. *The Journal of Clinical Investigation*.

Jargin, S. (2019). Management of type 2 diabetes mellitus with overweight: Focus on SGLT-2 inhibitors and GLP-1 receptor agonists. *Eur J Ther. 2019; 25: 93-96. Doi: 10.5152/EurJTher*.

Kalra, S., Das, A., Sahay, R., Baruah, M., Tiwaskar, M., et al. (2019). Consensus recommendations on GLP-1 RA use in the management of type 2 diabetes mellitus: South asian task force. *Diabetes Therapy*.

Kaneko, S. (2022). Tirzepatide: A novel, once-weekly dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes. *TouchREVIEWS in Endocrinology*.

Karakasis, P., Patoulias, D., Pamporis, K., Stachteas, P., et al. (2023). Safety and efficacy of the new, oral, small-molecule, GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity: Systematic …. *Metabolism*.

Kawanami, D., & Takashi, Y. (2020). GLP-1 receptor agonists in diabetic kidney disease: From clinical outcomes to mechanisms. *Frontiers in Pharmacology*.

Kenny, C., & Hall, G. (2015). GLP-1 receptor agonist and basal insulin co-therapy in type 2 diabetes: Clinical evidence and practicalities of use. *Diabetes & Primary Care*.

King, A., & Miller, E. (2023). Glucagon-like peptide 1 receptor agonists have the potential to revolutionize the attainment of target A1C levels in type 2 diabetes—so why is their uptake so low? *Clinical Diabetes*.

Krishnan, A., Schneider, C., Hadi, Y., Mukherjee, D., et al. (2024). … and mortality outcomes with GLP-1 receptor agonists vs other glucose-lowering drugs in individuals with NAFLD and type 2 diabetes: A large population-based …. *Diabetologia*.

Kristensen, S., Rørth, R., Jhund, P., et al. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of cardiovascular …. *The Lancet Diabetes & Endocrinology*.

Lajara, R. (2019). Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes. *Postgraduate Medicine*.

Liakos, A., Karagiannis, T., Avgerinos, I., & Bekiari, E. (2026). SGLT-2 inhibitors and GLP-1 receptor agonists as combination therapy in type 2 diabetes. *Current Diabetes Reports*.

Liang, L., Su, X., Guan, Y., Wu, B., Zhang, X., & Nian, X. (2024). Correlation between intestinal flora and GLP-1 receptor agonist dulaglutide in type 2 diabetes mellitus treatment—a preliminary longitudinal study. *Iscience*.

Liao, C., Liang, X., Zhang, X., & Li, Y. (2023). The effects of GLP-1 receptor agonists on visceral fat and liver ectopic fat in an adult population with or without diabetes and nonalcoholic fatty liver disease: A …. *PLoS One*.

Lim, C., Pasternak, B., Eliasson, B., & Ueda, P. (2025). Treatment discontinuation among users of GLP-1 receptor agonists and SGLT2 inhibitors in a national population of individuals with type 2 diabetes. *Diabetologia*.

Lin, D., Lee, J., & Chen, W. (2021). Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors. *Diabetologia*.

Lin, L., Chen, J., Huang, T., & Wu, V. (2025). Association of glucagon-like peptide-1 receptor agonists with cardiovascular and kidney outcomes in type 2 diabetic kidney transplant recipients. *Cardiovascular Diabetology*.

Linjawi, S., Bode, B., Chaykin, L., Courrèges, J., et al. (2017). … efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy …. *Diabetes Therapy*.

Liu, B., Udemba, S., Liang, K., Tarabichi, Y., Hill, H., et al. (2024). … peptide-1 receptor agonists are associated with increased development of gastro-oesophageal reflux disease and its complications in patients with type 2 diabetes …. *Gut*.

Lyseng-Williamson, K. (2019). Glucagon-like peptide-1 receptor agonists in type 2 diabetes: Their use and differential features. *Clinical Drug Investigation*.

Ma, X., Liu, R., Pratt, E., Benson, C., Bhattachar, S., et al. (2024). … food consumption on the pharmacokinetics, safety, and tolerability of once-daily orally administered orforglipron (LY3502970), a non-peptide GLP-1 receptor agonist. *Diabetes Therapy*.

Ma, Z., Jin, K., Yue, M., Chen, X., et al. (2023). Research progress on the GIP/GLP-1 receptor coagonist tirzepatide, a rising star in type 2 diabetes. *Journal of Diabetes Research*.

Mahapatra, M., Karuppasamy, M., & Sahoo, B. (2022). Therapeutic potential of semaglutide, a newer GLP-1 receptor agonist, in abating obesity, non-alcoholic steatohepatitis and neurodegenerative diseases: A …. *Pharmaceutical Research*.

Marx, N., Husain, M., Lehrke, M., Verma, S., & Sattar, N. (2022). GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation*.

McCrimmon, R., Lamotte, M., Ramos, M., Alsaleh, A., et al. (2021). Cost-effectiveness of iGlarLixi versus iDegLira in type 2 diabetes mellitus inadequately controlled by GLP-1 receptor agonists and oral antihyperglycemic therapy. *Diabetes Therapy*.

McCulley, L., & Hurren, K. (2022). Safety and efficacy of GLP-1 receptor agonists and SGLT2 inhibitors among veterans with type 2 diabetes. *Federal Practitioner*.

McIntyre, R. (2024). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: What do we know and future vistas. *Expert Opinion on Drug Safety*.

Mezquita-Raya, P., Arellano, A. R. de, Kragh, N., et al. (2017). Liraglutide versus lixisenatide: Long-term cost-effectiveness of GLP-1 receptor agonist therapy for the treatment of type 2 diabetes in spain. *Diabetes Therapy*.

Miles, K., & Kerr, J. (2018). Semaglutide for the treatment of type 2 diabetes mellitus. *Journal of Pharmacy Technology*.

Min, T., & Bain, S. (2021). The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: The SURPASS clinical trials. *Diabetes Therapy*.

Miñambres, I., & Pérez, A. (2017). Is there a justification for classifying GLP-1 receptor agonists as basal and prandial? *Diabetology & Metabolic Syndrome*.

Montanya, E. (2012). A comparison of currently available GLP-1 receptor agonists for the treatment of type 2 diabetes. *Expert Opinion on Pharmacotherapy*.

Morales, J., & Assumpcao-Morales, M. (2019). The use of SGLT2 inhibitors and GLP-1 receptor agonists, a worthwhile physiologic combination in managing type 2 diabetes while reducing cardiovascular risk. *J Cardiol Curr Res*.

Morris, D. (2020). GLP-1 receptor agonists in type 2 diabetes: An underused asset? *Journal of Diabetes Nursing*.

Mosterd, C., Bjornstad, P., & Raalte, D. van. (2020). Nephroprotective effects of GLP-1 receptor agonists: Where do we stand? *Journal of Nephrology*.

Munir, K., & Davis, S. (2018). Are SGLT2 inhibitors or GLP-1 receptor agonists more appropriate as a second-line therapy in type 2 diabetes? *Expert Opinion on Pharmacotherapy*.

Nagahisa, T., & Saisho, Y. (2019). Cardiorenal protection: Potential of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes. *Diabetes Therapy*.

Nauck, M. (2016). Incretin therapies: Highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 …. *Diabetes, Obesity and Metabolism*.

Nauck, M., & 'Alessio, D. D. (2022). Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight …. *Cardiovascular Diabetology*.

Neumiller, J., & Umpierrez, G. (2018). 2018 standards of care update: Pharmacologic approaches to glycemic management in people with type 2 diabetes. *Diabetes Spectrum*.

Nowak, M., Nowak, W., & Grzeszczak, W. (2022). Tirzepatide—a dual GIP/GLP-1 receptor agonist—a new antidiabetic drug with potential metabolic activity in the treatment of type 2 diabetes. *Endokrynologia Polska*.

Okamoto, A., Yokokawa, H., Nagamine, T., et al. (2021). … weight management, lipid profiles and other biomarkers among obese type 2 diabetes patients initiated or switched to semaglutide from other GLP-1 receptor agonists. *Journal of Diabetes & Metabolic Disorders*.

Olukorode, J., Orimoloye, D., Nwachukwu, N., et al. (2024). Recent advances and therapeutic benefits of glucagon-like peptide-1 (GLP-1) agonists in the management of type 2 diabetes and associated metabolic …. *Cureus*.

Østergaard, J., & Cooper, M. (2022). Treatment of type 2 diabetes with GLP-1 receptor agonists among patients with CKD. *Kidney International Reports*.

Owens, D., Monnier, L., & Bolli, G. (2013). Differential effects of GLP-1 receptor agonists on components of dysglycaemia in individuals with type 2 diabetes mellitus. *Diabetes & Metabolism*.

Page, M., McKenzie, J., Bossuyt, P., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71.

Palanca, A., Ampudia-Blasco, F., Calderón, J., Sauri, I., et al. (2023). Real-world evaluation of GLP-1 receptor agonist therapy persistence, adherence and therapeutic inertia among obese adults with type 2 diabetes. *Diabetes Therapy*.

Patel, D. (2020). Glycaemic and non-glycaemic efficacy of once-weekly GLP-1 receptor agonists in people with type 2 diabetes. *Journal of Clinical Pharmacy and Therapeutics*.

Patel, D. (2026). Small-molecule oral versus injectable glucagon-like peptide-1 (GLP-1) receptor agonists: Comparative efficacy, safety, and future clinical perspectives. *Cureus*.

Perreault, L., & Bergman, B. (2024). … glucagon-like peptide-1 (GLP-1)±glucose-dependent insulinotropic polypeptide (GIP) receptor agonists for A1c and weight reduction in people with type 2 diabetes. *Journal of Diabetes*.

Peterson, G. (2012). Current treatments and strategies for type 2 diabetes: Can we do better with GLP-1 receptor agonists? *Annals of Medicine*.

Pladevall-Vila, M., Ziemiecki, R., Johannes, C., Khan, A., et al. (2025). Clinical profile and treatment patterns in individuals with type 2 diabetes and chronic kidney disease who initiate a GLP-1 receptor agonist: A multinational cohort study. *Diabetes Therapy*.

Prasad, A., Arora, A., Arora, A., Vaid, J., et al. (2026). … -adjusted safety and efficacy of GLP-i and GLP-1/GIP receptor agonists compared with non-GLP-i for weight management and type 2 diabetes: Based on FDA …. *British Journal of Clinical Pharmacology*.

Pratley, R., & Gilbert, M. (2008). Targeting incretins in type 2 diabetes: Role of GLP-1 receptor agonists and DPP-4 inhibitors. *The Review of Diabetic Studies: RDS*.

Qin, L., Chen, S., Flood, E., Shaunik, A., Romero, B., et al. (2017). Glucagon-like peptide-1 receptor agonist treatment attributes important to injection-experienced patients with type 2 diabetes mellitus: A preference study in germany …. *Diabetes Therapy*.

Ramalan, M., Maiyaki, M., Gezawa, I., & Uloko, A. (2024). *Efficacy of a fixed-ratio combination of glucagon-like peptide-1 receptor agonist and basal insulin therapy for the treatment of type 2 diabetes: A protocol for systematic …*. medRxiv.

Rasalam, R., Barlow, J., Kennedy, M., Phillips, P., & Wright, A. (2019). GLP-1 receptor agonists for type 2 diabetes and their role in primary care: An australian perspective. *Diabetes Therapy*.

Rasmussen, M. (2020). The development of oral semaglutide, an oral GLP-1 analog, for the treatment of type 2 diabetes. *Diabetology International*.

Rico-Fontalvo, J., Daza-Arnedo, R., Elbert, A., et al. (2026). Renal outcomes of GLP-1 receptor agonists and tirzepatide across CKD stages and metabolic phenotypes (type 2 diabetes and/or overweight/obesity): A scoping …. *Diabetes Therapy*.

Rodbard, H. (2018). The clinical impact of GLP-1 receptor agonists in type 2 diabetes: Focus on the long-acting analogs. *Diabetes Technology & Therapeutics*.

Rosen, C., & Ingelfinger, J. (2026). GLP-1 receptor agonists. *New England Journal of Medicine*.

Russell-Jones, D. (2010). The safety and tolerability of GLP-1 receptor agonists in the treatment of type-2 diabetes. *International Journal of Clinical Practice*.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., et al. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas. *Diabetes Research and Clinical Practice*.

Santulli, G., Mone, P., & Varzideh, F. (2025). GLP-1 receptor agonists and SGLT2 inhibitors: New anti-aging tools? *Future Cardiology*.

Saraiva, F., & Sposito, A. (2014). Cardiovascular effects of glucagon-like peptide 1 (GLP-1) receptor agonists. *Cardiovascular Diabetology*.

Scheen, A. (2013). GLP-1 receptor agonists or DPP-4 inhibitors: How to guide the clinician? *Annales d'endocrinologie*.

Scheen, A. (2017). GLP-1 receptor agonists and heart failure in diabetes. *Diabetes & Metabolism*.

Scholten, B. V., Hansen, T., Goetze, J., et al. (2015). Glucagon-like peptide 1 receptor agonist (GLP-1 RA): Long-term effect on kidney function in patients with type 2 diabetes. *Journal of Diabetes and Its Complications*.

Sedova, P., Vrablík, M., Kala, P., Ošťádal, P., et al. (2026). GLP-1 receptor agonists for secondary prevention after myocardial infarction and stroke in type 2 diabetes: Nationwide real-world evidence. *European Journal of Preventive Cardiology*.

Shen, Y., Yang, X., Han, X., Xi, W., Jiang, L., et al. (2021). Influence of GLP-1 receptor agonist on insulin dosage and blood glucose control of patients with type 2 diabetes mellitus. *American Journal of Translational Research*.

Shomali, M., Ørsted, D., & Cannon, A. (2017). Efficacy and safety of liraglutide, a once-daily human glucagon-like peptide-1 receptor agonist, in african-american people with type 2 diabetes: A meta-analysis of …. *Diabetic Medicine*.

Singh, A., & Singh, R. (2022). Metabolic and cardiovascular benefits with combination therapy of SGLT-2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. *World Journal of Cardiology*.

Sohn, M., Dietrich, J., Nauck, M., & Lim, S. (2023). Characteristics predicting the efficacy of SGLT-2 inhibitors versus GLP-1 receptor agonists on major adverse cardiovascular events in type 2 diabetes mellitus: A meta …. *Cardiovascular Diabetology*.

Taylor, S. (2018). GLP-1 receptor agonists: Differentiation within the class. *The Lancet Diabetes & Endocrinology*.

Terauchi, Y., Fujiwara, H., Kurihara, Y., et al. (2019). … efficacy of the sodium–glucose cotransporter 2 inhibitor, tofogliflozin, added on glucagon-like peptide-1 receptor agonist in japanese patients with type 2 diabetes …. *Journal of Diabetes Investigation*.

Terauchi, Y., Satoi, Y., Takeuchi, M., & Imaoka, T. (2014). Monotherapy with the once weekly GLP-1 receptor agonist dulaglutide for 12 weeks in japanese patients with type 2 diabetes: Dose-dependent effects on glycaemic …. *Endocrine Journal*.

Terauchi, Y., Utsunomiya, K., Yasui, A., Seki, T., Cheng, G., et al. (2019). Safety and efficacy of empagliflozin as add-on therapy to GLP-1 receptor agonist (liraglutide) in japanese patients with type 2 diabetes mellitus: A randomised, double …. *Diabetes Therapy*.

Thomas, J. (2025). Twincretin (dual GIP/GLP-1 receptor agonists): The new kid on the block. *Journal of Diabetes and Treatment*.

Thomas, M., Coughlan, M., & Cooper, M. (2023). The postprandial actions of GLP-1 receptor agonists: The missing link for cardiovascular and kidney protection in type 2 diabetes. *Cell Metabolism*.

Thomas, M., Nikooienejad, A., Bray, R., et al. (2021). Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*.

Tommerdahl, K., Kendrick, J., et al. (2022). The role of glucagon-like peptide 1 (GLP-1) receptor agonists in the prevention and treatment of diabetic kidney disease: Insights from the AMPLITUDE-o trial. *Clinical Journal of the American Society of Nephrology*.

Trujillo, J. (2020). Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. *Journal of Clinical Pharmacy and Therapeutics*.

Urva, S., Coskun, T., Loh, M., Du, Y., Thomas, M., et al. (2022). LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: A phase 1b, multicentre, double-blind, placebo-controlled …. *The Lancet*.

Whitley, H., Trujillo, J., & Neumiller, J. (2023). Special report: Potential strategies for addressing GLP-1 and dual GLP-1/GIP receptor agonist shortages. *Clinical Diabetes*.

Xiong, S., Gou, R., Liang, X., Wu, H., Qin, S., Li, B., Luo, C., et al. (2024). Adverse events of oral GLP-1 receptor agonist (semaglutide tablets): A real-world study based on FAERS from 2019 to 2023. *Diabetes Therapy*.

Xu, Y., Huang, T., Zhang, Y., Ji, D., Tuttle, K., Carrero, J., et al. (2026). Risk of heart failure hospitalization for GLP-1 receptor agonists versus DPP-4 inhibitors or SGLT-2 inhibitors in patients with type 2 diabetes: A target trial emulation. *Circulation*.

Yang, C., Yang, C., Ou, H., & Kuo, S. (2020). … cardiovascular safety of GLP-1 receptor agonists versus other glucose-lowering agents in real-world patients with type 2 diabetes: A nationwide population-based …. *Cardiovascular Diabetology*.

Yao, H., Zhang, A., Li, D., Wu, Y., Wang, C., Wan, J., et al. (2024). Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: Systematic review and network meta …. *Bmj*.

Yen, F., Hou, M., Wei, J., Shih, Y., Hwu, C., & Hsu, C. (2024). Effects of glucagon-like peptide-1 receptor agonists on liver-related and cardiovascular mortality in patients with type 2 diabetes. *BMC Medicine*.

Zamily, A. A. (2025). Effect of GLP-1 receptor agonists (liraglutide) on glycemic parameters and circulating miRNA expression in type 2 diabetes mellitus. *Med. Mod. Mod. Med*.