Section: Miscellaneous

Review Article

THE EVOLVING PLACE OF GLP-1 THERAPY IN THE TREATMENT ALGORITHM: FROM SECOND LINE TO FIRST LINE AND COMBINATION STRATEGIES – A REVIEW

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic, progressive cardiometabolic disorder associated with substantial cardiovascular and renal morbidity and mortality worldwide. Traditional glucose-centric treatment paradigms, focused on stepwise glycaemic control, have proven insufficient to address the broader cardiometabolic risk profile of individuals with T2DM. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as transformative therapies, demonstrating benefits that extend beyond glucose lowering to include weight reduction and significant cardiovascular and renal risk mitigation.

Materials and Methods: This narrative review examines the evolving role of GLP-1 receptor agonists in contemporary T2DM management, with particular emphasis on their transition from second-line therapies to first line and early combination treatment strategies. A comprehensive literature search of PubMed/MEDLINE, Embase, and the Cochrane Library was conducted to identify randomized controlled trials, cardiovascular and renal outcome trials, real-world evidence, and international clinical practice guidelines published between 2019 and 2025. Evidence was synthesized descriptively to contextualize emerging trends in global diabetes care.

Results: Findings from large cardiovascular outcome trials demonstrate that several GLP-1 receptor agonists significantly reduce major adverse cardiovascular events, with benefits observed across diverse patient populations, including those without established cardiovascular disease. Additional evidence supports favorable effects on renal outcomes, particularly reductions in albuminuria and slowing of kidney function decline. GLP-1 RAs also provide durable glycaemic control, clinically meaningful weight loss, and a low intrinsic risk of hypoglycaemia, supporting their suitability for early initiation. Combination strategies involving metformin, sodium–glucose cotransporter-2 inhibitors, and basal insulin further enhance metabolic durability and treatment flexibility.

Conclusion: In conclusion, GLP-1 receptor agonists have evolved into cornerstone therapies within modern, outcomes-driven T2DM treatment algorithms. Their integration into representized, patient-centered care pathways represent a paradigm shift toward proactive cardiometabolic risk reduction. Continued research improved global access, and long-term outcome data will be essential to fully realize their potential in improving population-level diabetes outcomes.

Keywords: Type 2 diabetes mellitus, Glucagon-like peptide-1 receptor agonists, Cardiometabolic risk reduction, Cardiovascular outcomes, Renal outcomes, First-line therapy, Combination therapy, Treatment algorithms, Obesity management, Global diabetes care.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic, progressive cardiometabolic disorder that has reached epidemic proportions worldwide. Its rising prevalence is driven by population ageing, urbanization, sedentary lifestyles, and increasing rates of overweight and obesity across both high-income and low- and middle-income countries.[1] Beyond hyperglycaemia, individuals with T2DM face a substantial burden of cardiovascular (CV) disease, chronic kidney disease (CKD), and premature mortality, emphasizing the need for treatment strategies that extend beyond glucose lowering alone.[2]

For decades, pharmacological management of T2DM followed a glucose-centric, stepwise paradigm, typically initiating with metformin and sequentially adding agents as glycated hemoglobin (HbA1c) targets were not achieved. While this approach effectively reduced blood glucose levels, it often failed to address key drivers of long-term risk, including weight gain, hypoglycaemia, and progression of cardiovascular and renal complications. As a result, contemporary diabetes care has shifted toward individualized, patient-centered algorithms that prioritize cardiometabolic risk reduction alongside glycaemic control.[3]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have played a pivotal role in this paradigm shift. Initially introduced as injectable second-line therapies for patients inadequately controlled on oral agents, GLP-1 RAs demonstrated effective glucose lowering with a low intrinsic risk of hypoglycaemia and the added benefit of clinically meaningful weight loss. Over time, accumulating evidence from large cardiovascular outcome trials (CVOTs) has shown that several GLP-1 RAs significantly reduce major adverse cardiovascular events, prompting reconsideration of their position within treatment algorithms.[4]

Importantly, the cardiovascular benefits of GLP-1 RAs are not restricted to patients with advanced cardiovascular disease. In the REWIND trial, dulaglutide reduced cardiovascular events in a broad T2DM population, including a large proportion of individuals without established atherosclerotic cardiovascular disease, supporting the concept of earlier intervention in appropriate patients.[5] In parallel, the development of oral formulations, such as oral semaglutide, has expanded therapeutic options and addressed barriers related to injectable therapy, with cardiovascular safety confirmed in dedicated outcome trials.[6]

Reflecting these advances, international clinical practice guidelines have undergone substantial revision. The joint consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasizes selection of glucose-lowering therapies based on comorbidities such as cardiovascular disease, heart failure, chronic kidney disease, and obesity, rather than reliance on a rigid stepwise escalation model.[3] Similarly, recent ADA Standards of Care highlight GLP-1 RAs as preferred agents in patients with established or high risk of cardiovascular disease, independent of baseline HbA1c levels.[1]

Chronic kidney disease further amplifies cardiovascular risk in T2DM and represents a major determinant of morbidity and mortality worldwide. Contemporary guidelines from kidney disease: Improving Global Outcomes (KDIGO) and joint ADA–KDIGO consensus statements advocate an integrated approach to diabetes and CKD management, recognizing GLP-1 RAs as important components of cardio-renal risk reduction strategies when glycaemic control and weight management are required.[7] These recommendations underscore the expanding role of GLP-1 RAs within holistic, outcomes-driven care pathways.

Against this evolving global backdrop, GLP-1 receptor agonists are increasingly viewed not merely as glucose-lowering agents, but as cornerstone therapies addressing multiple pathophysiological pathways in T2DM. The present review examines the evidence underpinning the transition of GLP-1 RAs from second-line therapies to first line and early combination strategies within contemporary treatment algorithms. By synthesizing data from randomized controlled trials, cardiovascular and renal outcome studies, and international guidelines, this review aims to provide a comprehensive, globally relevant perspective on the optimal positioning of GLP-1 therapy in modern T2DM management.

MATERIALS AND METHODS

Study Design: This article was conducted as a narrative review to comprehensively examine the evolving role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the treatment algorithm of type 2 diabetes mellitus (T2DM), with particular emphasis on their transition from second-line therapy to first line and combination treatment strategies. A narrative review methodology was chosen to allow integration of diverse forms of evidence, including randomized controlled trials, cardiovascular outcome trials, real-world studies, and international clinical practice guidelines, and to enable contextual interpretation of emerging trends in global diabetes care.[8]

Literature Search Strategy

A systematic literature search was undertaken across major biomedical databases, including PubMed/MEDLINE, Embase, and the Cochrane Library, to identify relevant publications evaluating GLP-1 receptor agonists in T2DM. Searches were conducted for studies published between January 2019 and March 2025 to ensure contemporary relevance. The search strategy employed a

combination of Medical Subject Headings (MeSH) and free-text terms, including "GLP-1 receptor agonist," "type 2 diabetes," "treatment algorithm," "first-line therapy," "early initiation," "combination therapy," "cardiovascular outcomes," and "renal outcomes." Boolean operators were used to refine the search and maximize sensitivity. In addition, reference lists of key reviews and landmark trials were manually screened to identify additional relevant studies not captured in the initial search.[9]

Eligibility Criteria

Studies were included in this review if they met the following criteria:

1. involved adult patients (≥18 years) with T2DM.
2. evaluated any approved GLP-1 receptor agonist.
3. reported outcomes related to glycaemic control, body weight, cardiovascular outcomes, renal outcomes, or treatment durability; and
4. were published as randomized controlled trials, cardiovascular outcome trials, meta-analyses, systematic reviews, real-world observational studies, or international guideline documents.

Studies were excluded if they focused on type 1 diabetes mellitus, gestational diabetes, pediatric populations, or preclinical animal models. Editorials, narrative commentaries without primary data synthesis, conference abstracts without full-text availability, and non-peer-reviewed publications were also excluded to maintain methodological rigor.[10]

Study Selection Process: Following database searches, titles and abstracts were independently screened to assess relevance to the objectives of the review. Full-text articles were retrieved when abstracts suggested potential relevance. Selection was guided by clinical importance, methodological quality, and contribution to understanding the evolving positioning of GLP-1 receptor agonists within treatment algorithms. Emphasis was placed on large-scale cardiovascular outcome trials, long-term real-world evidence, and publications that influenced international guideline recommendations.[11]

Data Extraction: Data extraction focused on key study characteristics, including study design, patient population, duration of follow-up, specific GLP-1 receptor agonist evaluated, comparator therapies, and reported outcomes. Outcomes of interest included changes in glycated hemoglobin (HbA1c), body weight, incidence of hypoglycaemia, cardiovascular events, renal endpoints, and safety or tolerability signals. Information regarding treatment sequencing, early initiation, and combination therapy strategies was also extracted where available to inform discussion of evolving treatment algorithms.[12]

Data Synthesis and Analysis: Given the narrative design of this review, data were synthesized descriptively rather than quantitatively. Findings from randomized controlled trials, cardiovascular outcome trials, and real-world studies were integrated to identify consistent patterns and areas of consensus regarding the benefits and limitations of GLP-1 receptor agonist therapy. Evidence was interpreted in the context of contemporary clinical practice and international guideline recommendations, with attention to heterogeneity among patient populations and between individual GLP-1 RA agents. No formal meta-analysis or statistical pooling was performed, consistent with the objectives of a narrative review.[13]

Methodological Considerations: This narrative approach allows flexibility in synthesizing complex and evolving evidence across multiple therapeutic domains; however, it is subject to inherent limitations, including potential selection bias and the absence of formal quality scoring. To mitigate these limitations, priority was given to high-quality trials, large meta-analyses, and authoritative guideline documents. The methodological framework adopted in this review aligns with established guidance for conducting narrative reviews in clinical medicine and supports a balanced, evidence-based interpretation of the literature.[14]

Evolution of GLP-1 Receptor Agonists in Diabetes Treatment Algorithms

The therapeutic positioning of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) within type 2 diabetes mellitus (T2DM) management has undergone a marked transformation over the past two decades. Early diabetes treatment algorithms were predominantly glucose-centric, prioritizing stepwise intensification based on glycated hemoglobin (HbA1c) thresholds rather than broader cardiometabolic risk profiles. Within this framework, GLP-1 RAs were initially reserved as injectable second- or third-line therapies for patients inadequately controlled on oral glucose-lowering agents, largely due to concerns regarding cost, route of administration, and limited long-term outcome data.[15]

As clinical experience with GLP-1 RAs expanded, evidence began to emerge demonstrating advantages beyond glycaemic control, including weight reduction and a low intrinsic risk of hypoglycaemia. These properties challenged the traditional reliance on insulin secretagogues and basal insulin as preferred escalation therapies, particularly in individuals with obesity or high hypoglycaemia risk. Comparative studies showed that GLP-1 RAs could achieve comparable or superior glycaemic efficacy with improved tolerability profiles, prompting reconsideration of their placement earlier in the treatment pathway.[16]

A major inflection points in the evolution of GLP-1 RA positioning occurred with the publication of large cardiovascular outcome trials (CVOTs). These trials, mandated to establish cardiovascular safety, unexpectedly demonstrated significant reductions in major adverse cardiovascular events with several GLP-1 receptor agonists. The demonstration of cardiovascular benefit fundamentally altered perceptions of GLP-1 RAs, shifting them from glucose-lowering adjuncts to therapies capable of modifying long-term cardiovascular risk in patients with T2DM.[17] Importantly, these benefits were

observed across diverse populations, supporting broader applicability beyond narrowly defined high-risk subgroups.

In parallel, treatment algorithms began to incorporate patient-specific factors—such as cardiovascular disease, chronic kidney disease, obesity, and hypoglycaemia vulnerability—into therapeutic decision-making. This shift toward individualized, outcomes-driven care reduced emphasis on rigid sequencing of therapies and instead prioritized early use of agents with proven cardiometabolic benefits. GLP-1 receptor agonists emerged as preferred options in patients where weight reduction and cardiovascular risk mitigation were central treatment goals, accelerating their transition toward first-line or early combination therapy in contemporary algorithms.[18]

Further reinforcing this evolution has been the expansion of available GLP-1 RA formulations, including once-weekly injectables and oral agents. These innovations addressed practical barriers related to treatment adherence and patient acceptance, facilitating earlier initiation and broader uptake in routine clinical practice. As a result, modern treatment algorithms increasingly depict GLP-1 receptor agonists not as late-stage interventions, but as integral components of early, comprehensive T2DM management strategies aimed at long-term cardiometabolic risk reduction.[19]

Glycaemic Efficacy and Durability of GLP-1 Receptor Agonists

Achieving and maintaining durable glycaemic control remains a central objective in the management of type 2 diabetes mellitus (T2DM), given the progressive nature of β-cell dysfunction and insulin resistance. Traditional glucose-lowering therapies, particularly sulfonylureas and basal insulin, are often associated with diminishing efficacy over time, weight gain, and increased risk of hypoglycaemia. In contrast, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exert glucose-dependent effects on insulin secretion and glucagon suppression, offering a mechanistic basis for sustained glycaemic control with a lower risk of treatment-related complications.[20]

Across randomized controlled trials, GLP-1 receptor agonists have consistently demonstrated robust reductions in glycated hemoglobin (HbA1c), typically ranging from 0.8% to 1.8%, depending on the specific agent, dose, and baseline glycaemic status. Comparative trials and pooled analyses indicate that GLP-1 RAs achieve glycaemic efficacy comparable to, or exceeding, that of basal insulin in many patient populations, while avoiding insulin-associated weight gain and hypoglycaemia. These findings have supported the use of GLP-1 RAs as effective alternatives to insulin during early treatment intensification.[21]

Beyond short-term glucose lowering, durability of glycaemic response is a critical determinant of long-term treatment success. Evidence from long-duration trials and real-world observational studies suggests that GLP-1 RAs provide more sustained HbA1c control compared with insulin secretagogues, which are prone to secondary failure. This durability is thought to reflect preservation of β-cell function, improvements in insulin sensitivity mediated by weight loss, and favorable effects on postprandial glucose excursions.[22] As a result, GLP-1 receptor agonists may delay the need for further treatment escalation in routine clinical practice.

Real-world evidence has further reinforced the durability observed in randomized trials. Large observational cohorts from Europe and North America have demonstrated sustained HbA1c reductions over follow-up periods extending beyond two years in patients initiated on GLP-1 RAs, including those with long-standing diabetes and multiple comorbidities. Importantly, treatment persistence and adherence have been higher with once-weekly GLP-1 RA formulations, suggesting that dosing convenience contributes meaningfully to long-term glycaemic stability.[23]

When evaluated in combination regimens, GLP-1 receptor agonists also appear to enhance glycaemic durability through complementary mechanisms of action. In particular, combination therapy with metformin or sodium–glucose cotransporter-2 (SGLT2) inhibitors has been associated with additive HbA1c reductions and reduced rates of treatment intensification compared with monotherapy. These findings support the integration of GLP-1 RAs into early combination strategies aimed at maintaining long-term glycaemic control while minimizing therapeutic burden and adverse effects.[24]

Collectively, the available evidence demonstrates that GLP-1 receptor agonists provide effective and durable glycaemic control across diverse patient populations and treatment settings. Their favorable efficacy profile, combined with low hypoglycaemia risk and sustained long-term effectiveness, underpins their evolving role as early-line and foundational components of contemporary T2DM treatment algorithms.[25]

Table 1: Clinical Characteristics of Approved Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 receptor agonist	Route of administration	Dosing frequency	Mean HbA1c reduction	Body-weight effect	Hypoglycaemia risk
Exenatide	Subcutaneous	Twice daily / once weekly	Moderate	Weight loss	Low
Liraglutide	Subcutaneous	Once daily	Moderate–high	Weight loss	Low
Dulaglutide	Subcutaneous	Once weekly	Moderate–high	Weight loss	Low
Semaglutide (SC)	Subcutaneous	Once weekly	High	Significant weight loss	Low
Semaglutide (oral)	Oral	Once daily	Moderate–high	Weight loss	Low
Lixisenatide	Subcutaneous	Once daily	Moderate	Weight loss	Low

Effects on Body Weight and Hypoglycaemia Risk

Excess body weight and hypoglycaemia represent two major barriers to achieving optimal long-term outcomes in type 2 diabetes mellitus (T2DM). Weight gain contributes to worsening insulin resistance, β-cell stress, and cardiovascular risk, while hypoglycaemia is associated with reduced quality of life, treatment nonadherence, and increased morbidity and mortality. Traditional glucose-lowering therapies such as insulin and sulfonylureas frequently exacerbate both issues, highlighting the need for therapeutic strategies that address glycaemic control without compromising weight or safety.[26]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exert their weight-reducing effects through multiple complementary mechanisms, including appetite suppression, delayed gastric emptying, and central regulation of satiety. Clinical trials have consistently demonstrated clinically meaningful and sustained weight loss with GLP-1 RA therapy across diverse patient populations. In the STEP-1 trial, once-weekly semaglutide produced substantial reductions in body weight in individuals with overweight or obesity, many of whom had T2DM or cardiometabolic risk factors, reinforcing the role of GLP-1–based therapies in addressing obesity as a core component of diabetes management.[27]

Comparative studies further illustrate the advantages of GLP-1 RAs over other glucose-lowering agents with respect to weight outcomes. Head-to-head trials have shown that GLP-1 RAs induce significantly greater weight loss than basal insulin and dipeptidyl peptidase-4 inhibitors, while providing comparable or superior glycaemic control. Notably, dual incretin receptor agonists have demonstrated even greater weight reductions compared with selective GLP-1 RAs, underscoring the central role of incretin-based mechanisms in modulating energy balance and metabolic health.[28]

In addition to favorable effects on body weight, GLP-1 receptor agonists are associated with a low intrinsic risk of hypoglycaemia due to their glucose-dependent stimulation of insulin secretion. This pharmacological property distinguishes GLP-1 RAs from insulin secretagogues and exogenous insulin, particularly in older adults and individuals with long-standing diabetes who are more vulnerable to hypoglycaemic events. Meta-analyses of randomized controlled trials confirm that rates of severe hypoglycaemia with GLP-1 RAs are consistently low, except when used in combination with agents that independently increase hypoglycaemia risk.[29]

The combined benefits of weight reduction and hypoglycaemia avoidance have important clinical implications for treatment sequencing and patient adherence. Improved weight outcomes are associated with better cardiometabolic profiles, while reduced hypoglycaemia risk enhances treatment confidence and persistence. Real-world studies indicate that these attributes contribute to higher long-term adherence with GLP-1 RA therapy compared with regimens that promote weight gain or frequent hypoglycaemic episodes. Consequently, the favorable weight and safety profile of GLP-1 receptor agonists supports their increasing use as early-line and foundational therapies within contemporary T2DM treatment algorithms.[30]

Cardiovascular Outcomes: Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among individuals with type 2 diabetes mellitus (T2DM), accounting for a substantial proportion of premature deaths worldwide. Despite improvements in glycaemic management, traditional glucose-lowering strategies alone have proven insufficient to mitigate excess cardiovascular risk, prompting a shift toward therapies capable of modifying cardiovascular outcomes directly. This evolving understanding has placed cardiovascular benefit at the forefront of contemporary diabetes treatment algorithms.[31]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as one of the first classes of glucose-lowering agents to demonstrate consistent cardiovascular benefit in large, randomized cardiovascular outcome trials (CVOTs). Landmark trials evaluating liraglutide, semaglutide, dulaglutide, albiglutide, and efpeglenatide have shown statistically significant reductions in major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. These benefits extend beyond glycaemic control and appear to be mediated through multiple mechanisms, including improvements in body weight, blood pressure, lipid profiles, endothelial function, and systemic inflammation.[32]

Notably, cardiovascular benefits with GLP-1 receptor agonists have been observed across a broad spectrum of patient populations. While early CVOTs primarily enrolled individuals with established atherosclerotic cardiovascular disease, subsequent trials included participants with multiple cardiovascular risk factors but without prior events. This broader inclusion has demonstrated that GLP-1 RAs can confer cardiovascular protection in both secondary and selected primary prevention settings, supporting their earlier use in patients with elevated cardiometabolic risk.[33]

Beyond composite cardiovascular endpoints, emerging evidence suggests that GLP-1 receptor agonists may favorably influence specific cardiovascular outcomes. Reductions in stroke incidence appear particularly robust across trials, while modest but consistent benefits on myocardial infarction have also been reported. In contrast, effects on hospitalization for heart failure have been neutral overall, highlighting important distinctions between GLP-1 RAs and other cardioprotective drug classes such as sodium–glucose cotransporter-2 inhibitors. These differential effects underscore the importance of individualized therapy selection based on predominant cardiovascular phenotypes.[34]

The demonstration of cardiovascular benefit has directly influenced international clinical practice guidelines, which now prioritize GLP-1 receptor

agonists in patients with T2DM and established atherosclerotic cardiovascular disease or high cardiovascular risk, independent of baseline glycated hemoglobin levels. From a global perspective, these recommendations represent a paradigm shift from glucose-centric care to outcome-driven management. As cardiovascular risk reduction increasingly guides treatment selection, GLP-1 receptor agonists have become integral components of comprehensive cardiometabolic strategies aimed at improving long-term survival and quality of life in people with T2DM.[35]

Table 2: Major Cardiovascular Outcome Trials of Glucagon-Like Peptide-1 Receptor Agonists

Trial name	GLP-1 RA evaluated	Study population	Primary CV endpoint	Key cardiovascular findings
LEADER	Liraglutide	T2DM with high CV risk	3-point MACE	Significant MACE reduction
SUSTAIN-6	Semaglutide	T2DM with CV risk	3-point MACE	Reduced MACE, stroke benefit
REWIND	Dulaglutide	Broad T2DM population	3-point MACE	Reduced MACE including primary prevention
HARMONY Outcomes	Albiglutide	T2DM with ASCVD	3-point MACE	Significant CV risk reduction
AMPLITUDE-O	Efpeglenatide	T2DM with CV/renal disease	CV and renal composite	Reduced CV and renal events

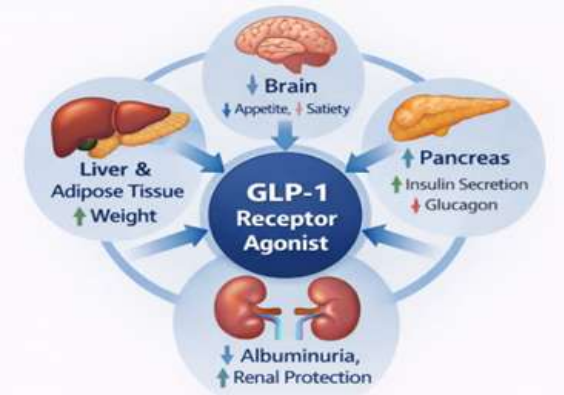

Figure 1: Cardiometabolic Mechanisms of Action of GLP-1 Receptor Agonists

Renal Outcomes: Chronic kidney disease (CKD) is a common and serious complication of type 2 diabetes mellitus (T2DM) and represents a major contributor to cardiovascular morbidity, progression to end-stage kidney disease, and premature mortality worldwide. Despite advances in glycaemic control, many individuals with T2DM experience progressive renal function decline, underscoring the need for therapeutic strategies that provide renal protection in addition to glucose lowering. Contemporary diabetes management therefore increasingly emphasizes therapies that address the interconnected cardio–renal–metabolic axis.[36]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated consistent renal benefits across randomized controlled trials and cardiovascular outcome trials, primarily through reductions in albuminuria and slowing of estimated glomerular filtration rate (eGFR) decline. Although most renal outcomes were evaluated as secondary or exploratory endpoints, pooled analyses have shown that GLP-1 RA therapy is associated with significant reductions in composite renal outcomes, driven largely by decreased progression of albuminuria. These effects appear to be partially independent of glycaemic control and are thought to reflect improvements in blood pressure, weight, endothelial function, and inflammation.[37]

Evidence from major outcome trials has reinforced the renal protective potential of GLP-1 receptor agonists. In trials evaluating liraglutide, semaglutide, dulaglutide, and efpeglenatide, treatment was associated with a lower incidence of new-onset macroalbuminuria and a reduced risk of sustained decline in renal function compared with placebo. Importantly, these benefits were observed across a wide range of baseline kidney function, including in patients with moderate chronic kidney disease, supporting the applicability of GLP-1 RAs in diverse clinical settings.[38]

Mechanistic studies suggest that the renal benefits of GLP-1 receptor agonists extend beyond indirect metabolic effects. Experimental and clinical data indicate that GLP-1 signaling may exert direct actions on renal hemodynamics, tubular sodium handling, and oxidative stress pathways. By reducing intraglomerular pressure and mitigating inflammatory and fibrotic processes, GLP-1 RAs may slow structural kidney damage and delay progression of diabetic kidney disease, although further dedicated renal outcome trials are warranted to fully elucidate these mechanisms.[39]

The recognition of renal benefits has influenced international guideline recommendations, which increasingly endorse GLP-1 receptor agonists as part of comprehensive risk-reduction strategies for patients with T2DM and CKD, particularly when weight management and cardiovascular protection are also desired. While sodium–glucose cotransporter-2 inhibitors remain foundational therapies for kidney protection, GLP-1 RAs are now viewed as important complementary agents, especially in patients who are unable to tolerate other renoprotective treatments or who require additional metabolic control. Collectively, the available evidence supports the integration of GLP-1 receptor agonists into modern, holistic approaches to diabetic kidney disease management.[40]

Table 3: Renal Outcomes Associated with Glucagon-Like Peptide-1 Receptor Agonist Therapy

Outcome domain	Observed effects with GLP-1 RAs	Clinical relevance
Albuminuria	Reduction in progression to macroalbuminuria	Slows diabetic kidney disease progression
eGFR decline	Slower rate of decline	Preserves renal function
Composite renal endpoints	Reduced risk in CVOT analyses	Supports cardio-renal protection
Use in CKD	Safe across mild–moderate CKD	Broad clinical applicability

First-Line and Early Use of GLP-1 Receptor Agonists: The concept of initiating glucose-lowering therapy based primarily on glycated hemoglobin (HbA1c) thresholds has evolved substantially in recent years. Accumulating evidence indicates that early therapeutic choices can meaningfully influence long-term cardiometabolic outcomes in type 2 diabetes mellitus (T2DM). As a result, contemporary treatment algorithms increasingly emphasize early use of agents that address multiple disease drivers, including obesity, cardiovascular risk, and renal dysfunction, rather than reserving such therapies for later stages of disease progression.[41]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as strong candidates for early-line therapy due to their combined effects on glycaemic control, body weight reduction, and cardiometabolic risk factors. Clinical trials have demonstrated that GLP-1 RAs provide substantial HbA1c lowering when used as initial injectable or early add-on therapy, with efficacy comparable to or exceeding that of basal insulin in many settings. Importantly, these benefits are achieved without the weight gain and hypoglycaemia risk commonly associated with insulin-based regimens, supporting consideration of GLP-1 RAs earlier in the treatment course.[42]

Obesity is a key determinant of insulin resistance and disease progression in T2DM and is increasingly recognized as a primary therapeutic target. Early initiation of GLP-1 receptor agonists in individuals with overweight or obesity has been associated with greater and more sustained weight reduction compared with delayed introduction. These effects may translate into improved insulin sensitivity, reduced cardiometabolic risk, and slower progression of β-cell dysfunction, reinforcing the rationale for early intervention rather than reactive escalation after treatment failure.[43]

International clinical practice guidelines now reflect this shift toward early, outcomes-focused therapy selection. Recent updates from major professional organizations recommend GLP-1 receptor agonists as preferred first-line or early combination options in patients with established atherosclerotic cardiovascular disease, high cardiovascular risk, or a compelling need for weight reduction, regardless of baseline HbA1c or prior metformin use. This represents a fundamental departure from traditional stepwise models and underscores the growing acceptance of GLP-1 RAs as foundational therapies in selected patient populations.[44]

Real-world data further support the feasibility and effectiveness of early GLP-1 RA use in routine clinical practice. Observational studies from diverse health-care systems demonstrate that patients initiated on GLP-1 receptor agonists earlier in the disease course experience better long-term glycaemic durability, greater weight loss, and lower rates of treatment intensification compared with those receiving GLP-1 RAs later. Collectively, these findings suggest that early incorporation of GLP-1 receptor agonists into treatment algorithms may optimize long-term outcomes and align diabetes management with a proactive, prevention-oriented care model.[45]

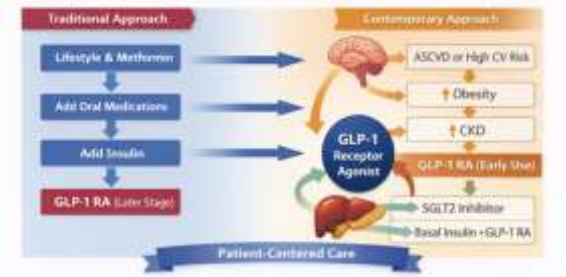

Figure 2: Evolution of the Treatment Algorithm for Type 2 Diabetes Incorporating GLP-1 Receptor Agonists

Combination Therapy Strategies Involving GLP-1 Receptor Agonists: As type 2 diabetes mellitus (T2DM) progresses, monotherapy often becomes insufficient to maintain long-term glycaemic control due to progressive β-cell dysfunction and increasing insulin resistance. Combination therapy therefore represents a cornerstone of durable diabetes management, particularly when therapies with complementary mechanisms of action are used. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are uniquely suited for combination strategies because of their glucose-dependent insulinotropic effects, favorable weight profile, and low intrinsic risk of hypoglycaemia.[46]

Combination with Metformin: Metformin remains widely used as foundational therapy in T2DM due to its efficacy, safety, and cost-effectiveness. When combined with GLP-1 receptor agonists, metformin provides complementary mechanisms—reducing hepatic glucose production while GLP-1 RAs enhance glucose-dependent insulin secretion and suppress glucagon. Clinical studies demonstrate additive reductions in glycated hemoglobin (HbA1c) and body weight with this combination compared with either agent alone. Importantly, early combination therapy with metformin and GLP-1 RAs has been associated with improved glycaemic durability and delayed need for further treatment intensification.[47]

Combination with Sodium–Glucose Cotransporter-2 Inhibitors: The combination of GLP-1 receptor agonists with sodium–glucose cotransporter-2 (SGLT2) inhibitors has gained considerable attention due to their complementary metabolic and cardioprotective effects. While SGLT2 inhibitors primarily reduce glucose through increased urinary glucose excretion and provide robust heart failure and renal benefits, GLP-1 RAs exert stronger effects on weight reduction and atherosclerotic cardiovascular risk. Randomized trials and real-world analyses indicate that this combination yields additive improvements in glycaemic control, weight loss, blood pressure, and cardiometabolic risk factors without a proportional increase in adverse events.[48]

Combination with Basal Insulin: For patients requiring injectable therapy intensification, combining GLP-1 receptor agonists with basal insulin offers a compelling alternative to traditional basal–bolus insulin regimens. GLP-1 RAs target postprandial hyperglycaemia and reduce insulin requirements, while basal insulin addresses fasting glucose levels. Fixed-ratio combinations of GLP-1 RAs with basal insulin have demonstrated superior glycaemic control compared with basal insulin alone, alongside reductions in weight gain and hypoglycaemia risk. These benefits support the use of GLP-1 RA–insulin combinations as effective and patient-friendly intensification strategies.[49]

Metabolic Durability and Treatment Simplification: Beyond glycaemic efficacy, combination regimens involving GLP-1 receptor agonists may enhance long-term treatment persistence and adherence. Once-weekly formulations and fixed-ratio combinations simplify treatment regimens, reduce injection burden, and improve patient satisfaction. Real-world evidence suggests that patients receiving GLP-1 RA–based combination therapy experience lower rates of treatment discontinuation and slower progression to complex insulin regimens, highlighting the role of these strategies in sustaining long-term metabolic control.[50]

Collectively, combination therapy strategies incorporating GLP-1 receptor agonists represent a flexible and effective approach to individualized diabetes management. By leveraging complementary mechanisms of action, these combinations address multiple pathophysiological pathways in T2DM and align with contemporary goals of durable glycaemic control, weight management, and cardiometabolic risk reduction.

Table 4: Combination Therapy Strategies Involving Glucagon-Like Peptide-1 Receptor Agonists

Combination strategy	Mechanistic rationale	Clinical benefits	Key considerations
GLP-1 RA + Metformin	Complementary glucose-lowering pathways	Improved HbA1c, weight loss	First-line or early combination
GLP-1 RA + SGLT2 inhibitor	Additive metabolic and cardio-renal effects	Weight loss, CV and renal benefit	Preferred in high CV/renal risk
GLP-1 RA + Basal insulin	Targets fasting and postprandial glucose	Improved glycaemia with less weight gain	Useful for treatment intensification
Fixed-ratio combinations	Simplifies regimen	Better adherence, fewer injections	Dose flexibility considerations

Figure 3: Complementary Effects of GLP-1 Receptor Agonists and Sodium–Glucose Cotransporter-2 Inhibitor

Safety and Tolerability: Safety and tolerability are critical determinants of long-term treatment success in type 2 diabetes mellitus (T2DM), particularly for therapies intended for early and sustained use. As treatment algorithms increasingly favor early initiation of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), careful consideration of their adverse event profile, patient acceptability, and real-world safety is essential. Overall, GLP-1 receptor agonists have demonstrated a favorable safety profile across randomized trials and observational studies, supporting their expanding role in contemporary diabetes management.[51]

Gastrointestinal Adverse Events: Gastrointestinal (GI) symptoms, including nausea, vomiting, and diarrhoea, are the most reported adverse events associated with GLP-1 receptor agonist therapy. These effects are generally dose-dependent and occur most frequently during the initiation and titration phases of treatment. Clinical trial data indicate that GI symptoms are typically mild to moderate in severity and tend to diminish over time with continued therapy. Gradual dose escalation and patient education regarding expected transient symptoms have been shown to significantly improve tolerability and treatment persistence.[52]

Hypoglycaemia and Glycaemic Safety: Due to their glucose-dependent mechanism of action, GLP-1 receptor agonists are associated with a low intrinsic risk of hypoglycaemia when used as monotherapy or in combination with agents that do not independently increase hypoglycaemia risk. Rates of severe

hypoglycaemia in clinical trials are consistently low and are primarily observed when GLP-1 RAs are combined with sulfonylureas or insulin. This safety profile is particularly advantageous in older adults and individuals with long-standing diabetes, in whom hypoglycaemia poses substantial clinical risk.[53]

Pancreatic and Gallbladder Safety: Concerns regarding pancreatitis and pancreatic cancer have been extensively evaluated in large outcome trials and post-marketing surveillance studies. Current evidence does not support a causal association between GLP-1 receptor agonist use and increased risk of pancreatic malignancy. However, a small increase in gallbladder-related events, including cholelithiasis and cholecystitis, has been reported, likely related to rapid weight loss. Clinicians should remain vigilant for symptoms of gallbladder disease, particularly in patients experiencing substantial weight reduction.[54]

Cardiovascular and Renal Safety: Beyond demonstrating cardiovascular benefit, GLP-1 receptor agonists have shown cardiovascular safety across a wide range of patient populations, including those with established cardiovascular disease and chronic kidney disease. No excess risk of arrhythmias, heart failure hospitalization, or acute kidney injury has been observed in large cardiovascular outcome trials. Moreover, GLP-1 RAs can be safely used across a broad spectrum of renal function, with dose adjustments required only for specific agents at advanced stages of kidney disease.[55]

Real-World Tolerability and Treatment Persistence: Real-world studies confirm that the tolerability profile observed in randomized trials translates into routine clinical practice. Persistence with GLP-1 receptor agonist therapy is influenced by dosing frequency, route of administration, and patient expectations regarding weight loss and glycaemic improvement. Once-weekly injectable formulations and oral GLP-1 receptor agonists have been associated with improved adherence and lower discontinuation rates, reinforcing their suitability for long-term use within individualized treatment algorithms.[56]

In summary, GLP-1 receptor agonists demonstrate a well-characterized and manageable safety profile that supports their early and sustained use in T2DM. Appropriate patient selection, gradual dose titration, and proactive management of adverse events are key to optimizing tolerability and maximizing long-term therapeutic benefit.

Table 5: Safety and Tolerability Profile of Glucagon-Like Peptide-1 Receptor Agonists

Adverse event category	Frequency	Clinical management
Gastrointestinal symptoms	Common (early phase)	Gradual dose titration
Hypoglycaemia	Rare (monotherapy)	Monitor when combined with insulin/SU
Gallbladder events	Uncommon	Monitor during rapid weight loss
Injection-site reactions	Mild	Rotate injection sites

Global Perspectives on GLP-1 Receptor Agonist Use: The global burden of type 2 diabetes mellitus (T2DM) continues to rise across regions with diverse health-care infrastructures, socioeconomic contexts, and disease phenotypes. While therapeutic advances have expanded the armamentarium for diabetes management, substantial disparities persist in access to evidence-based treatments. The uptake and integration of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) into routine clinical practice therefore vary widely across countries, reflecting differences in health-system capacity, reimbursement policies, and clinical priorities.[57]

In high-income countries, the adoption of GLP-1 receptor agonists has increased steadily over the past decade, driven by strong clinical trial evidence, guideline endorsement, and growing emphasis on cardiometabolic risk reduction. Real-world data from North America and Western Europe indicate that GLP-1 RAs are increasingly prescribed early in the disease course, particularly for patients with obesity and cardiovascular disease. However, even within these settings, marked variation exists in prescribing patterns, influenced by insurance coverage, out-of-pocket costs, and clinician familiarity with newer agents.[58]

In contrast, access to GLP-1 receptor agonists remains limited in many low- and middle-income countries (LMICs), where health systems often prioritize affordability and availability of essential medicines. High acquisition costs, lack of inclusion in national essential medicines lists, and limited reimbursement represent major barriers to widespread GLP-1 RA use. As a result, insulin and older oral agents continue to dominate diabetes care in these regions, despite their less favorable cardiometabolic profiles. These disparities raise concerns regarding global equity in access to therapies with proven long-term outcome benefits.[59]

Health-system factors further shape global utilization patterns. Countries with integrated care models and value-based reimbursement frameworks have been more successful in adopting GLP-1 receptor agonists within comprehensive cardiometabolic care pathways. Conversely, fragmented systems with siloed budgets may struggle to accommodate higher upfront drug costs, even when long-term cardiovascular and renal benefits could offset downstream expenditures. Economic modeling studies suggest that, in selected high-risk populations, GLP-1 RAs may be cost-effective when evaluated from a lifetime health-system perspective, although affordability remains a key constraint.[60]

From a global public health standpoint, the expanding role of GLP-1 receptor agonists also intersects with the rising prevalence of obesity and cardiometabolic

disease beyond diabetes alone. International experts increasingly view GLP-1–based therapies as part of a broader strategy to address the global syndemic of obesity, diabetes, and cardiovascular disease. Moving forward, improving global access will likely require a multipronged approach, including price negotiations, biosimilar development, context-specific guideline adaptation, and integration of GLP-1 RAs into universal health coverage frameworks. Such efforts are essential to ensure that the benefits of GLP-1 receptor agonist therapy are realized equitably across diverse global populations.[61]

Clinical Implications for Contemporary Practice: The evolving evidence base supporting glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has important implications for routine clinical management of type 2 diabetes mellitus (T2DM). Contemporary practice is increasingly shaped by the recognition that glycaemic control alone is insufficient to reduce long-term morbidity and mortality, and that treatment strategies should prioritize cardiometabolic risk reduction, weight management, and patient-centered outcomes.[62]

GLP-1 receptor agonists offer a therapeutic profile that aligns well with these goals, combining effective glucose lowering with weight reduction and proven cardiovascular and renal benefits. In clinical practice, this supports earlier consideration of GLP-1 RAs in individuals with obesity, established atherosclerotic cardiovascular disease, high cardiovascular risk, or chronic kidney disease, rather than reserving these agents for later stages after treatment failure. Such an approach represents a shift from reactive escalation to proactive risk modification.[63]

Individualization of therapy remains central to optimal diabetes care. Selection of GLP-1 receptor agonists should take into account patient preferences, comorbidities, risk of hypoglycaemia, route of administration, and treatment burden. Once-weekly injectable formulations and oral GLP-1 RAs may enhance adherence and persistence, particularly in patients reluctant to initiate injectable therapy. Shared decision-making is therefore critical to maximizing the long-term effectiveness of GLP-1 RA–based regimens.[64]

Integration of GLP-1 receptor agonists into modern treatment algorithms also requires consideration of health-system factors, including access, affordability, and reimbursement. While guideline recommendations increasingly support early use, real-world implementation may be constrained by cost and availability, underscoring the need for pragmatic, context-specific application of evidence-based guidance.[65]

Overall, the clinical implications of the expanding role of GLP-1 receptor agonists extend beyond glucose lowering to encompass comprehensive cardiometabolic care. Their thoughtful integration into individualized treatment strategies has the potential to improve long-term outcomes and align clinical practice with contemporary, outcome-driven models of T2DM management.[66]

Limitations and Knowledge Gaps

Despite substantial advances in the evidence base supporting glucagon-like peptide-1 receptor agonists (GLP-1 RAs), several limitations and unresolved questions remain. Many pivotal cardiovascular and renal outcome trials were designed primarily to assess safety and major adverse events rather than to directly compare optimal sequencing or timing of GLP-1 RA initiation. As a result, evidence guiding precise positioning of GLP-1 RAs relative to other glucose-lowering therapies—particularly in early disease stages—remains indirect and largely extrapolated from subgroup analyses.[67]

Long-term durability data beyond five to seven years are limited, especially with respect to sustained cardiovascular and renal benefits, treatment persistence, and potential late-emerging adverse effects. While real-world studies provide important insights, these analyses are subject to confounding and variability in adherence, dosing, and patient selection. Dedicated long-term prospective studies are needed to better define lifetime benefits and risks of early and prolonged GLP-1 RA therapy.[68]

Another important gap relates to heterogeneity of treatment response. Most randomized trials underrepresent older adults, individuals with advanced frailty, and populations from low- and middle-income countries. Genetic, ethnic, and socioeconomic factors that may influence efficacy, tolerability, and access are therefore insufficiently characterized, limiting generalizability of findings across diverse global populations.[69]

Economic considerations also represent a major knowledge gap. While modeling studies suggest cost-effectiveness of GLP-1 receptor agonists in high-risk populations, real-world affordability and budget impact remain substantial barriers in many health-care systems. More region-specific health economic analyses are required to inform sustainable implementation strategies, particularly in resource-limited settings.[70]

Finally, the rapidly evolving therapeutic landscape introduces uncertainty regarding the future role of GLP-1 RAs relative to emerging dual and multi-receptor agonists. Head-to-head comparative effectiveness studies assessing long-term outcomes, safety, and patient-reported measures are needed to clarify optimal treatment selection as incretin-based therapies continue to advance.[71]

Future Directions: The therapeutic landscape of type 2 diabetes mellitus (T2DM) is evolving rapidly, with incretin-based therapies at the forefront of innovation. While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have already reshaped treatment algorithms, ongoing developments are likely to further expand and refine their role in cardiometabolic disease management. Future research will be critical in defining optimal sequencing, combination strategies, and long-term

outcomes in increasingly heterogeneous patient populations.[72]

One major area of advancement is the emergence of dual and multi-receptor agonists, including glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 and triple agonists targeting GLP-1, GIP, and glucagon receptors. Early clinical trials demonstrate superior glycaemic control and greater weight reduction compared with selective GLP-1 receptor agonists, raising important questions regarding comparative effectiveness, safety, and long-term cardiovascular and renal outcomes. Head-to-head trials and outcome-focused studies will be essential to determine whether these agents should supersede or complement existing GLP-1 RA therapies.[73]

Another important direction involves novel delivery systems, including oral formulations and longer-acting injectable agents. Oral GLP-1 receptor agonists may improve accessibility and patient acceptance, particularly among individuals hesitant to initiate injectable therapy. Advances in formulation technology could further enhance adherence and persistence, potentially amplifying real-world effectiveness. Ongoing studies evaluating long-term outcomes with oral and ultra–long-acting GLP-1–based therapies will help clarify their place within future treatment algorithms.[74]

Expanding indications beyond diabetes also represent a key frontier. Increasing evidence supports the role of GLP-1–based therapies in obesity management, cardiovascular risk reduction, and metabolic dysfunction–associated steatotic liver disease. Integration of these agents into broader cardiometabolic prevention frameworks may shift clinical paradigms toward earlier intervention in high-risk individuals, blurring traditional distinctions between diabetes and obesity treatment pathways.[75]

Finally, future research must address implementation and equity. Improving global access, evaluating cost-effectiveness in diverse health-care systems, and understanding patient-reported outcomes will be essential to translating therapeutic advances into population-level benefit. Pragmatic trials and real-world studies conducted across varied socioeconomic and geographic contexts will be critical to ensuring that innovations in GLP-1–based therapy led to equitable and sustainable improvements in cardiometabolic health worldwide.[76]

CONCLUSION

The management of type 2 diabetes mellitus has undergone a fundamental shift over the past decade, moving from a glucose-centric paradigm toward a comprehensive, outcomes-driven approach that prioritizes cardiovascular, renal, and metabolic risk reduction. Within this evolving framework, glucagon-like peptide-1 receptor agonists have transitioned from adjunctive second-line therapies to cornerstone agents in contemporary diabetes care.

Robust evidence from randomized controlled trials, cardiovascular and renal outcome studies, real-world analyses, and international clinical practice guidelines consistently demonstrates that GLP-1 receptor agonists provide effective and durable glycaemic control, promote clinically meaningful weight loss, and reduce cardiovascular and renal risk in diverse patient populations. Their favourable safety and tolerability profile, coupled with low intrinsic hypoglycaemia risk, supports their suitability for early and sustained use across the spectrum of type 2 diabetes.

The expanding role of GLP-1 receptor agonists as first-line and early combination therapies reflects a broader paradigm shift toward individualized, patient-centred treatment algorithms. Rather than being reserved for later stages of disease progression, these agents are increasingly positioned based on comorbidities such as obesity, atherosclerotic cardiovascular disease, and chronic kidney disease, as well as patient preferences and treatment goals. Combination strategies with metformin, sodium–glucose cotransporter-2 inhibitors, and basal insulin further enhance metabolic durability and flexibility in treatment intensification.

Despite these advances, important challenges remain, including long-term outcome uncertainties, cost and access barriers, and underrepresentation of certain populations in clinical trials. Addressing these gaps, alongside continued innovation in incretin-based therapies and delivery systems, will be critical to optimizing global implementation and maximizing population-level benefit.

In conclusion, glucagon-like peptide-1 receptor agonists represent a major advancement in the holistic management of type 2 diabetes mellitus. Their integration into modern treatment algorithms underscores a shift toward proactive, cardiometabolic risk-focused care, positioning GLP-1 receptor agonists as central components of evidence-based, globally relevant diabetes management strategies.

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