

Pathophysiology, Clinical Impact, and Evidence-Based Management of Type 2 Diabetes Mellitus with GLP-1 Receptor Agonists: A Narrative Review

Dr. Fathima Ibrahim Abdulla¹, Dr. Abdulmueen Ali Alqahtani², Ms. Neelufur Sulaiman Sait^{3*}

¹Consultant Family Medicine Primary Health Care Corporation

²Senior Consultant, Orthodontics, Hamad Medical Corporation

³Dietitian, Primary Health care corporation, Doha, Qatar

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*Corresponding author: Ms. Neelufur Sulaiman Sait
Dietitian, Primary Health care corporation, Doha, Qatar

Abstract

Review Article

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with substantial cardiovascular and renal complications. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as important therapeutic agents because of their glucose-lowering effects, weight reduction, and potential cardiorenal benefits. **Objective:** This narrative review examines the pathophysiological rationale, clinical impact, efficacy, safety, and evidence-based management of GLP-1 RAs in adults with T2DM. **Methods:** Relevant literature published between 2015 and 2026 was reviewed using focused searches of biomedical literature and relevant clinical guidelines. Randomized controlled trials, meta-analyses, and contemporary recommendations were considered to evaluate glycemic outcomes, weight management, cardiovascular and kidney protection, and treatment-related safety concerns. **Results:** GLP-1 RAs enhance glucose-dependent insulin secretion, suppress inappropriate glucagon release, delay gastric emptying to varying degrees, and promote satiety. Clinical trials have demonstrated improvements in glycated hemoglobin and body weight, while several agents have reduced major adverse cardiovascular events in populations with T2DM and elevated cardiovascular risk. Emerging evidence also supports kidney-protective effects for selected agents. However, gastrointestinal adverse effects, treatment cost, accessibility, contraindications, and differences between individual drugs may influence treatment selection and long-term adherence. GLP-1 RAs should be selected according to individual clinical characteristics, comorbidities, treatment goals, and patient preferences. **Conclusion:** GLP-1 RAs represent a valuable component of contemporary T2DM management, offering benefits beyond glycemic control for appropriately selected patients. Individualized prescribing, careful safety assessment, and integration with lifestyle interventions and other evidence-based therapies are essential to optimize outcomes. **Keywords:** Type 2 diabetes mellitus; GLP-1 receptor agonists; glycemic control; weight management; cardiovascular outcomes; kidney protection.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease in which insulin resistance and progressive β -cell dysfunction produce persistent hyperglycaemia. Its clinical burden includes microvascular complications—retinopathy, nephropathy, and neuropathy—and macrovascular disease, particularly atherosclerotic cardiovascular disease. Management therefore extends beyond lowering glycated haemoglobin (HbA1c) to reducing cardiovascular and kidney risk, managing body weight, preventing hypoglycaemia, and supporting quality of life. Current guidance recommends person-centred

selection of glucose-lowering treatment based on comorbidities, efficacy, safety, treatment burden, access, and preferences. [1]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have changed the treatment landscape because their actions address several connected features of T2DM. They enhance glucosedependent insulin secretion, suppress inappropriate glucagon release, slow gastric emptying to varying degrees, and reduce appetite and energy intake. Their clinical effects can include meaningful reductions in HbA1c and body weight, and cardiovascular benefit has been demonstrated for

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selected agents. More recently, the FLOW trial provided dedicated evidence of kidney and cardiovascular benefit with semaglutide in people with T2DM and chronic kidney disease (CKD). [2,5]

This narrative review synthesizes mechanistic evidence, landmark randomized trials, and contemporary clinical guidance published between 2015 and October 2026. It emphasizes critical interpretation rather than assuming a uniform class effect: individual molecules differ in pharmacology, evidence base, formulations, indications, tolerability, and availability.

2. Literature Search and Review Approach

This article was developed as a narrative review of published medical literature on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the management of type 2 diabetes mellitus (T2DM). Focused searches were conducted in PubMed and relevant journal-publisher records using combinations of keywords and related terms covering T2DM, GLP-1 RAs, incretin physiology, glycaemic control, obesity and weight management, cardiovascular outcomes, kidney outcomes, adverse effects, and clinical treatment recommendations. The review prioritized publications published between January 2015 and October 2026, including landmark randomized controlled trials, cardiovascular and kidney outcome trials, meta-analyses, relevant clinical reviews, and current professional guidelines. Reference lists of key publications were also examined to identify additional clinically relevant studies.

Publications were considered for their relevance to the review objectives, methodological quality, clinical significance, and contribution to understanding the mechanisms of action, therapeutic efficacy, safety profile, and practical application of GLP-1 RAs in adults with T2DM. Particular emphasis was placed on randomized controlled trials evaluating glycaemic outcomes, body-weight changes, cardiovascular events, and kidney-related outcomes, together with evidence syntheses and professional recommendations informing contemporary clinical practice.

The literature was synthesized narratively, with findings compared across studies and interpreted in the context of their clinical applicability and limitations. Accordingly, this article represents a critical narrative synthesis of selected medical literature rather than a systematic review or original clinical investigation.

3. Pathophysiology of T2DM and the incretin rationale

3.1 Insulin resistance and β -cell dysfunction

Insulin resistance in skeletal muscle reduces insulin-stimulated glucose uptake, while hepatic insulin resistance impairs suppression of gluconeogenesis and glycogenolysis. In adipose tissue, impaired insulin action promotes lipolysis and increases circulating free fatty acids, which can further disrupt insulin signalling. Visceral adiposity, physical inactivity, genetic susceptibility, ageing, sleep and environmental factors contribute, but T2DM is heterogeneous and can occur in people without obesity.

Pancreatic β -cells initially compensate for insulin resistance by increasing insulin secretion. Over time, β -cell function becomes inadequate relative to metabolic demand. Glucotoxicity, lipotoxicity, oxidative stress, islet inflammation, and genetic factors may contribute to this decline. GLP-1 RAs enhance glucose-dependent insulin secretion but should not be represented as permanently reversing the underlying pathology or curing diabetes.

3.2 Glucagon and incretin physiology

Glucagon promotes hepatic glucose production. In T2DM, glucagon secretion may remain inappropriately high during hyperglycaemia, worsening fasting and postprandial glucose levels. GLP-1 signalling helps suppress glucagon when glucose is elevated, complementing its insulinotropic action.

The incretin effect describes the greater insulin response to oral glucose than to an equivalent intravenous glucose exposure. Endogenous GLP-1 is secreted by intestinal enteroendocrine cells after nutrient intake and is rapidly degraded by dipeptidyl peptidase-4. Although the incretin effect is reduced in T2DM, responsiveness to pharmacological GLP-1 receptor stimulation is sufficiently preserved to support treatment. GLP-1 receptor activation increases intracellular cyclic adenosine monophosphate signalling and potentiates insulin secretion in a glucosedependent manner.[6]

3.3 Appetite, gastric emptying, and body weight

GLP-1 receptor agonism influences central and peripheral pathways involved in satiety, hunger, and food intake. Delayed gastric emptying can reduce the rate of postprandial glucose appearance, although the magnitude of this effect differs by agent and may attenuate during ongoing exposure to some long-acting agents. Reduced energy intake is a major driver of weight loss. Weight reduction can improve insulin sensitivity, blood pressure, lipid levels, mobility, and obesity-related disease, but individual response varies and weight regain is common after treatment cessation.

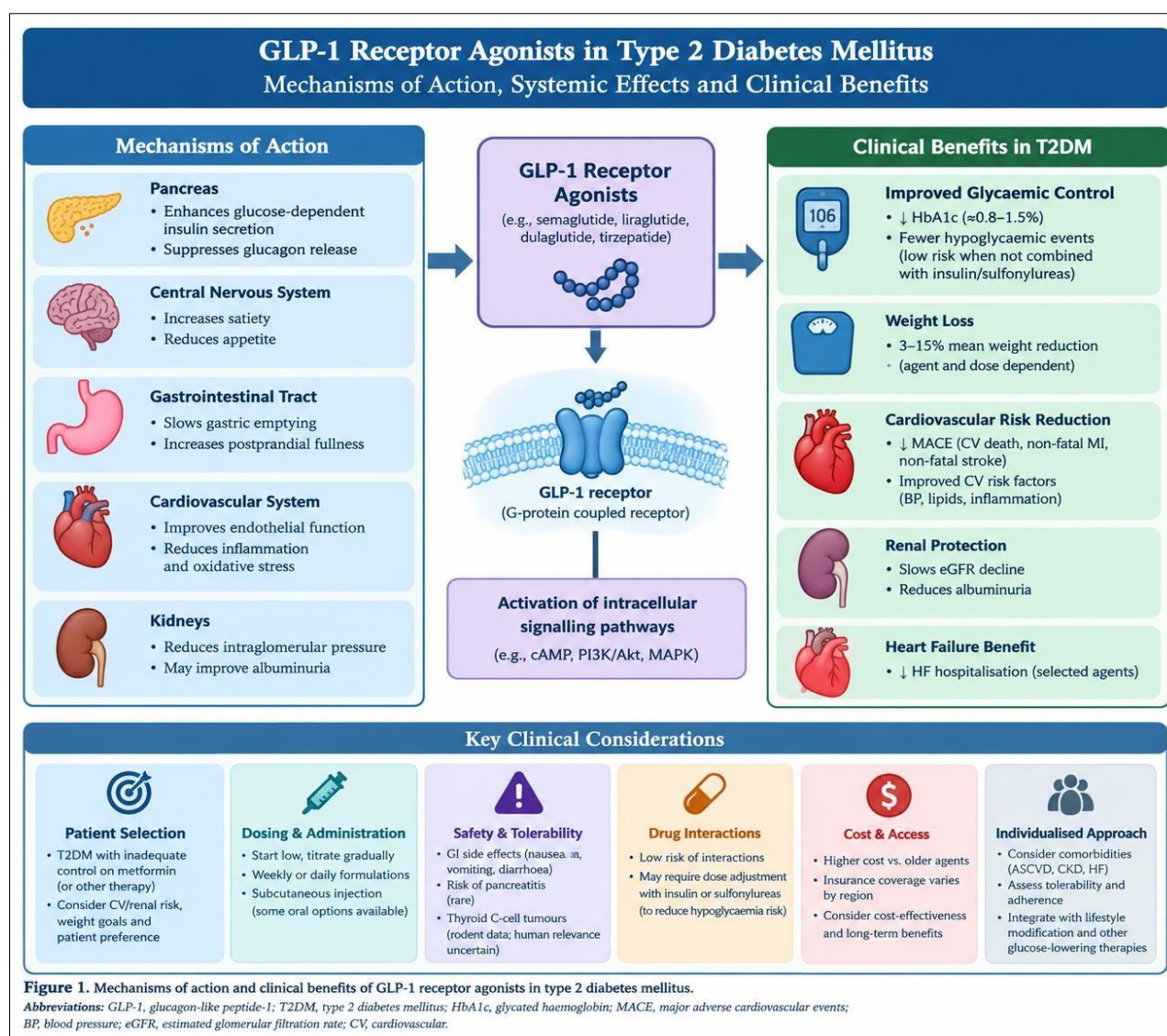


Figure 1: Mechanisms of Action and Clinical Benefits of GLP-1 Receptor Agonists

Figure 1. Mechanisms of action and clinical benefits of GLP-1 receptor agonists in type 2 diabetes mellitus. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular events.

4. Pharmacology and differences between agents

GLP-1 RAs differ in molecular structure, receptor exposure, half-life, dose, route, and trial evidence. Liraglutide is administered daily; dulaglutide and common injectable semaglutide formulations are administered weekly; oral semaglutide is available in some jurisdictions. Exenatide and lixisenatide have distinct pharmacokinetic profiles, with relatively prominent effects on postprandial glucose through gastric-emptying effects. Albiglutide demonstrated cardiovascular benefit in HARMONY Outcomes but is no longer commercially available in many markets.

Product availability, licensed indications, and prescribing restrictions vary by country.

These differences matter when comparing efficacy and safety. A head-to-head randomized trial can directly compare two agents under defined conditions; cross-trial comparisons are less reliable because baseline HbA1c, diabetes duration, body weight, background medication, endpoint definitions, and follow-up can differ. Tirzepatide is relevant to incretin-based diabetes treatment but activates both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. It should not be classified as a selective GLP-1 RA, and its effects cannot be attributed to GLP-1 agonism alone.

5. Clinical effectiveness

5.1 Glycaemic control

GLP-1 RAs lower HbA1c, with the magnitude of response determined by the molecule, dose, baseline HbA1c, adherence, duration, and concomitant treatment. Semaglutide, liraglutide, and dulaglutide have

demonstrated clinically meaningful glucose lowering. HbA1c remains important, but it is not the only determinant of treatment choice: cardiovascular disease, CKD, obesity, hypoglycaemia risk, cost, and patient priorities may justify a particular agent even when HbA1c is near an individualized target. Current American Diabetes Association guidance recommends GLP-1-based treatment with demonstrated benefit for people with T2DM and established or high-risk atherosclerotic cardiovascular disease when indicated, irrespective of the need for further HbA1c reduction.[1]

5.2 Body-weight outcomes

Weight loss is a central therapeutic advantage of GLP-1 RAs, especially for people with T2DM and overweight or obesity. The magnitude differs among molecules and doses. STEP 2 evaluated semaglutide 2.4 mg in adults with overweight or obesity and T2DM, whereas diabetes outcome trials generally use different doses and populations; effect sizes should not be transferred between these settings without qualification.⁷ Treatment-related weight reduction should be accompanied by attention to dietary quality, adequate nutrition, physical activity, and resistance exercise where appropriate, particularly in older adults or those at risk of muscle loss.

Discontinuation can lead to recurrence of appetite and weight gain, so the long-term plan should be discussed before treatment begins.

5.3 Cardiovascular outcome trials

Cardiovascular outcome trials were initially designed primarily to establish cardiovascular safety, but several have demonstrated superiority for major adverse cardiovascular events (MACE). In LEADER, 9,340 participants with T2DM and high cardiovascular risk were randomized to liraglutide or placebo; liraglutide reduced the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.[2] The trial also reported lower all-cause mortality, although interpretation should remain within the population and follow-up studied. SUSTAIN-6 evaluated semaglutide in a high-risk T2DM population. The primary MACE outcome was less frequent with semaglutide, establishing non-inferiority and suggesting benefit, but the trial was relatively short and was designed primarily to assess cardiovascular safety.[3] Retinopathy complications were more frequent in the semaglutide group, an important safety signal discussed below.

REWIND tested dulaglutide in a broader cardiovascular-risk population, including many participants without established cardiovascular disease, and demonstrated a reduction in MACE. [4] Its inclusion of a substantial primary-prevention subgroup increased the relevance of the findings beyond secondary prevention, although absolute benefit still depends on baseline risk. By contrast, ELIXA found lixisenatide to be cardiovascularly safe but did not demonstrate

superiority for MACE after acute coronary syndrome. [8] HARMONY Outcomes showed cardiovascular benefit with albiglutide in patients with T2DM and established cardiovascular disease. [9]

These trials support cardiovascular benefit for selected agents, not an automatic assumption that every GLP-1 RA has the same magnitude of effect. Trials differed in design, follow-up, population, background therapy, and statistical power. Relative risk reductions also need to be distinguished from absolute risk reductions: patients at higher baseline risk can experience greater absolute benefit even when relative effects are similar.

5.4 Kidney outcomes

Early kidney findings with GLP-1 RAs were often secondary outcomes in cardiovascular trials, including changes in albuminuria. FLOW provided dedicated kidney-outcome evidence. It enrolled people with T2DM and CKD and compared weekly semaglutide 1.0 mg with placebo. Semaglutide reduced the risk of the primary composite outcome involving kidney failure, substantial decline in estimated glomerular filtration rate, kidney death, or cardiovascular death.[5] This trial strengthens the role of semaglutide in selected patients with diabetic CKD, but it does not establish identical kidney benefits for every molecule or every CKD phenotype. Sodium–glucose cotransporter-2 (SGLT2) inhibitors remain central to kidney protection and prevention of heart-failure hospitalization for many patients with T2DM. GLP-1 RAs and SGLT2 inhibitors have complementary rather than interchangeable evidence profiles. Combination therapy may be appropriate when indicated and tolerated, but clinical decisions should account for kidney function, adverse effects, cost, treatment burden, and the evidence for the individual drug.

5.5 Other clinically relevant outcomes

GLP-1 RAs can produce modest improvements in blood pressure and lipid measures, partly related to weight loss and metabolic change. Their effects in metabolic dysfunction-associated steatotic liver disease and steatohepatitis are an active research area. Clinical interpretation should distinguish changes in weight or liver enzymes from histological improvement, prevention of cirrhosis, or other patient-important liver outcomes. SELECT demonstrated cardiovascular benefit with semaglutide in people with overweight or obesity and established cardiovascular disease without diabetes. [10] This is important adjacent evidence but is not direct evidence of glycaemic efficacy in T2DM because diabetes was excluded from that trial.

6. Critical appraisal of the evidence

The evidence base is strongest where large randomized trials used prespecified clinical outcomes and adequate follow-up. LEADER and REWIND provide superiority evidence for their tested agents,

while SUSTAIN-6 was principally a cardiovascular safety trial with a favorable MACE result. FLOW adds an important dedicated kidney trial. These distinctions matter: statistical noninferiority, superiority for a composite outcome, and improvement in a surrogate endpoint are different evidentiary claims.

Several limitations recur. Many cardiovascular trials enrolled participants with established disease or high baseline risk, limiting direct extrapolation to younger, low-risk people with recently diagnosed T2DM. Composite endpoints combine events of differing severity, and results can be driven by one component more than another. Background use of statins, antihypertensives, renin–angiotensin system blockers, and SGLT2 inhibitors has changed over time, affecting how older trials translate to contemporary practice. Trial adherence and follow-up may also exceed what is achievable in routine care.

Class-level meta-analyses increase precision for some outcomes but cannot eliminate heterogeneity in molecule, trial design, or population. Mechanistic hypotheses—such as direct vascular, anti-inflammatory, or renal effects—are biologically plausible, but clinical outcome trials establish whether a treatment improves outcomes, not necessarily the relative contribution of each mechanism. A balanced interpretation therefore combines pharmacological plausibility with agent-specific clinical evidence and recognizes uncertainty where direct comparative data are absent.

7. Safety, contraindications, and practical limitations

7.1 Gastrointestinal adverse effects

Nausea, vomiting, diarrhoea, constipation, and abdominal discomfort are the most common adverse effects, particularly during dose escalation. Product-specific titration, follow-up, and advice about meal size and hydration may improve tolerability. Persistent vomiting or reduced oral intake can cause dehydration, electrolyte disturbances, and acute kidney injury, particularly in people with CKD or concurrent diuretic use.

7.2 Hypoglycaemia

GLP-1 RAs have a relatively low intrinsic risk of hypoglycaemia because insulin secretion is glucose-dependent. Risk rises when they are combined with insulin or sulfonylureas. When initiating or escalating a GLP-1 RA, clinicians should review glucose patterns and consider reducing insulin-secretagogue doses when appropriate. Insulin should not be stopped abruptly when it is needed to prevent severe hyperglycaemia or metabolic decompensation.

7.3 Pancreatitis and gallbladder disease

Acute pancreatitis has been reported during treatment. Randomized evidence has not established a consistent large increase in risk, but rare events and uncertainty in susceptible patients warrant vigilance.

Persistent severe abdominal pain, especially with vomiting or radiation to the back, requires urgent assessment; treatment should be stopped while pancreatitis is evaluated when clinically suspected. Gallstones and gallbladder disease are also recognized concerns and may be influenced by rapid weight loss and altered gallbladder motility.

7.4 Diabetic retinopathy

The increased retinopathy complications observed in SUSTAIN-6 are clinically important. [3] Subsequent analyses suggested that rapid improvement in HbA1c, particularly in participants with pre-existing retinopathy and insulin use, may explain part of the association. This does not establish direct retinal toxicity. Clinicians should assess retinopathy status, coordinate ophthalmic follow-up, and plan glycaemic improvement carefully in patients at high risk. The finding should inform monitoring rather than be interpreted as a universal contraindication to semaglutide.

7.5 Product-specific warnings and special populations

Prescribing information must be checked for the selected product and jurisdiction. Some products in the United States carry boxed warnings concerning thyroid C-cell tumours observed in rodents and are contraindicated in people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Severe gastroparesis or other significant gastric motility disorders, serious hypersensitivity, pregnancy, and breastfeeding require particular consideration. GLP-1 RAs are generally not recommended during pregnancy because of insufficient safety evidence and the need for pregnancy-specific diabetes management.

7.6 Anaesthesia, treatment burden, and access

Delayed gastric emptying is relevant to patients undergoing anaesthesia or deep sedation because of the potential for retained gastric contents and aspiration. Periprocedural decisions should follow current local guidance and be individualized according to the drug, symptoms, procedure, and aspiration risk rather than applying a universal withholding rule. Cost, supply interruptions, insurance coverage, injection burden, and local licensing can restrict access. As long-term treatment may be necessary, affordability and likely persistence should be discussed early. Discontinuation can be followed by weight regain and deterioration in metabolic control.

8. Evidence-based clinical management

Treatment selection should integrate HbA1c, body weight, atherosclerotic cardiovascular disease, CKD, heart failure, hypoglycaemia risk, comorbidities, patient preference, and cost. Current ADA guidance recommends a GLP-1 RA and/or SGLT2 inhibitor with demonstrated cardiovascular benefit for people with T2DM and established or high-risk atherosclerotic

cardiovascular disease when indicated, irrespective of baseline HbA1c.[1] For heart failure, SGLT2 inhibitors have a particularly established role in preventing hospitalization; treatment should follow the heart-failure phenotype and current evidence.

For a patient with T2DM and CKD, semaglutide may be considered in light of FLOW, while SGLT2 inhibitors and other kidney-protective measures should be used where indicated. The drugs should not be framed as mutually exclusive. A patient with obesity may prioritize weight efficacy, while frailty, malnutrition, severe gastrointestinal disease, cost, or preference may change the balance. Treatment should also reflect local regulatory approval and product-specific instructions.

Before starting treatment, review medication history, contraindications, relevant kidney function, gastrointestinal history, pregnancy considerations, and

diabetic complications. Begin at the product-specific starting dose and escalate according to the approved schedule, slowing escalation when symptoms require it. Explain administration, missed doses, expected adverse effects, hydration, and warning symptoms. Oral semaglutide has administration requirements that differ from injectable formulations.

Follow-up should assess HbA1c and glucose where appropriate, body weight and nutritional status, blood pressure, lipid management, kidney function and albuminuria when indicated, gastrointestinal tolerability, hydration, retinopathy risk, adherence, and affordability. GLP-1 RAs complement rather than replace nutrition, physical activity, smoking cessation, blood-pressure control, lipid-lowering therapy, and routine screening for diabetes complications. Shared decision-making is essential for sustained, safe use.

Table 1: Evidence-to-practice summary for GLP-1 receptor agonist use in adults with type 2 diabetes mellitus

Clinical context	Evidence-based role of GLP-1 receptor agonists	Practical considerations
Glycaemic control and weight	Effective glucose lowering with low intrinsic hypoglycaemia risk; many agents also produce clinically meaningful weight loss.	Select agent and dose according to treatment goals, tolerability, access, and product-specific indication.
Established or high-risk ASCVD	An agent with demonstrated cardiovascular benefit may be appropriate; benefits are not solely explained by HbA1c reduction.	Consider absolute risk, preferences, cost, and evidence for the specific molecule.
Chronic kidney disease	Selected GLP-1 RAs have cardiovascular and kidney-outcome evidence; FLOW demonstrated kidney-outcome benefit with semaglutide in T2DM and CKD.	Do not assume all agents are interchangeable; continue indicated kidney-protective care and monitor kidney status.
Heart failure	GLP-1 RAs are not substitutes for SGLT2 inhibitors when the priority is reducing heart-failure events in eligible patients.	Prioritise therapies with established heartfailure outcome benefit; individualise GLP-1 RA use for coexisting obesity, glycaemia, or ASCVD.
Insufficient control on current therapy	For many adults without severe hyperglycaemia or catabolic symptoms, a GLP-1-based therapy may be considered before insulin.	Insulin may be needed with marked hyperglycaemia, catabolism, suspected insulin deficiency, or urgent clinical circumstances.
Safety and implementation	Gastrointestinal effects can limit persistence; rare but important risks and contraindications require review.	Titrate according to product instructions; counsel on nausea/vomiting, dehydration, gallbladder symptoms, pancreatitis warning symptoms, and peri-procedural aspiration considerations.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus. Treatment should follow current local guidance and product specific labelling.

9. Research gaps and future directions

Future research should compare individual agents and treatment strategies using clinically meaningful outcomes, particularly in contemporary populations receiving SGLT2 inhibitors and other cardiorenal therapies. Additional work is needed to understand the durability of weight and glycaemic effects, outcomes after discontinuation, muscle and nutritional effects in older adults, and the mechanisms through which cardiovascular and kidney benefits arise. Evidence in people with advanced CKD, frailty, and

diverse geographical and ethnic backgrounds remains important. Implementation research should address cost-effectiveness, equitable access, supply reliability, and strategies to improve persistence without compromising safety.

10. CONCLUSION

GLP-1 receptor agonists are important treatments for T2DM because they improve glycaemic control, support weight reduction, and, for selected agents, reduce cardiovascular events. The FLOW trial

provides additional evidence for kidney and cardiovascular benefit with semaglutide in a defined population with T2DM and CKD. Benefits are not uniform across all agents or outcomes and should be interpreted in the context of trial design, baseline risk, and absolute benefit.

Effective use requires individualized treatment selection, gradual dose escalation, monitoring for gastrointestinal adverse effects and other risks, attention to retinopathy in susceptible patients, and consideration of cost and long-term access. GLP-1 RAs should be integrated into comprehensive diabetes care rather than viewed as isolated glucose-lowering drugs. Continued research and transparent interpretation of agent-specific evidence will help refine their role in long-term metabolic and cardiorenal risk management.

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