GLP-1-Based Therapies in Type 2 Diabetes and Obesity: Current Evidence, Cardiorenal Benefits, Safety and Future Directions

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Abstract. *Type 2 diabetes mellitus (T2DM) and obesity are closely interrelated chronic metabolic diseases that substantially increase cardiovascular and kidney risk. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and newer incretin-based agents have expanded the therapeutic goals of endocrinology beyond glucose lowering and weight reduction toward cardiovascular risk modification and, for selected agents and populations, kidney protection. The aim of this narrative review was to synthesise the physiological rationale, glycaemic and weight efficacy, cardiovascular and kidney outcome evidence and safety of GLP-1-based therapies, and to formulate practical principles for their use in individualised care. Major randomised outcome trials, systematic reviews, consensus reports and professional guidance published predominantly between 2016 and 2025 were examined. In people with T2DM and high cardiovascular risk, liraglutide, subcutaneous semaglutide and dulaglutide reduced major adverse cardiovascular events (MACE) by 12–26 % relative to placebo. In people with overweight or obesity and established cardiovascular disease without diabetes, semaglutide 2.4 mg reduced MACE by 20 %, and in T2DM with chronic kidney disease (CKD) semaglutide reduced a composite of major kidney outcomes by 24 %. Weekly semaglutide 2.4 mg and tirzepatide produced mean weight reductions of approximately 15 % and up to 21 %, respectively, in obesity trials. Gastrointestinal adverse effects are the most common limitation and are largely dose-related. GLP-1-based therapies should be selected through shared decision-making on the basis of agent-specific evidence and integrated with SGLT2 inhibitors, lifestyle intervention and comprehensive risk-factor management rather than used as substitutes for them.*

Keywords: *type 2 diabetes mellitus; obesity; GLP-1 receptor agonists; incretin-based therapy; semaglutide; tirzepatide; cardiovascular outcomes; chronic kidney disease*

1. Introduction

Type 2 diabetes mellitus (T2DM) and obesity represent major and mutually reinforcing challenges for contemporary endocrinology. Excess adiposity contributes to insulin resistance, dyslipidaemia, hypertension, fatty liver disease and chronic low-grade inflammation, while progressive beta-cell dysfunction sustains hyperglycaemia. Their coexistence increases the probability of atherosclerotic cardiovascular disease (CVD), heart failure, chronic kidney disease (CKD) and other complications that determine long-term morbidity and mortality.

For decades, the management of T2DM was predominantly glucose-centred, and treatment success was judged largely by glycated haemoglobin (HbA1c). Since 2008, cardiovascular outcome trials have shown that several glucose-lowering drug classes also reduce cardiovascular and kidney events. As a result, the therapeutic paradigm has shifted

toward comprehensive cardiometabolic risk reduction, in which the choice of agent depends on comorbidities and organ-protective evidence as well as on glycaemic potency (Davies et al., 2022; American Diabetes Association Professional Practice Committee [ADA], 2025a).

Incretin-based medicines, particularly GLP-1 RAs, now occupy a central place in this paradigm because they improve glycaemic control, promote clinically meaningful weight loss and provide cardiovascular benefit in defined high-risk populations. Evidence for kidney outcomes has also strengthened, and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide has extended the magnitude of achievable weight reduction (Jastreboff et al., 2022).

The objectives of this review were (i) to summarise the biological rationale and mechanisms of GLP-1-based therapies; (ii) to evaluate their glycaemic and weight-management efficacy; (iii) to synthesise evidence from cardiovascular and kidney outcome trials; (iv) to describe safety considerations and precautions; and (v) to propose a practical framework for their integration into individualised care of T2DM and obesity.

2. Materials and Methods

This manuscript is a narrative review. Sources were identified in PubMed/MEDLINE, Scopus and Google Scholar using combinations of the terms "GLP-1 receptor agonist", "semaglutide", "liraglutide", "dulaglutide", "tirzepatide", "type 2 diabetes", "obesity", "cardiovascular outcome trial", "chronic kidney disease" and "SGLT2 inhibitor", supplemented by manual screening of the reference lists of key publications.

Priority was given to randomised cardiovascular and kidney outcome trials, pivotal weight-management trials, consensus reports of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), the ADA Standards of Care in Diabetes—2025 and the Kidney Disease: Improving Global Outcomes (KDIGO) guideline. Publications in English appearing predominantly between 2016 and 2025 were considered.

Information on trial population, intervention, follow-up, primary endpoint and principal results was extracted narratively and synthesised thematically. The review is not a registered systematic review or meta-analysis; no PRISMA selection process, risk-of-bias assessment, pooled effect estimate or original patient dataset is presented, and the conclusions should be interpreted accordingly.

3. Results

3.1. Biological rationale and mechanisms of action

GLP-1 is an incretin hormone secreted by intestinal L-cells after nutrient ingestion. Activation of the GLP-1 receptor enhances glucose-dependent insulin secretion, suppresses inappropriate glucagon secretion, slows gastric emptying and acts on hypothalamic and brainstem pathways that regulate appetite and satiety. Because insulin secretion is glucose-dependent, GLP-1 RAs carry a low intrinsic risk of hypoglycaemia when not combined with insulin or sulfonylureas. Therapeutic agents are modified to resist dipeptidyl peptidase-4 degradation, allowing daily or weekly dosing; oral semaglutide is also available.

Weight reduction improves insulin sensitivity, blood pressure, lipid parameters and hepatic steatosis. Potential cardiovascular effects may additionally involve reduced inflammation, improved endothelial function, natriuresis and modification of atherosclerotic pathways; however, these mechanistic hypotheses should not be interpreted as proof that each pathway independently mediates clinical outcomes. Dual GIP/GLP-1 receptor agonism, exemplified by tirzepatide, extends

incretin pharmacology, but its drug-specific indications and outcome evidence must be considered separately rather than assuming a uniform class effect.

3.2. Glycaemic and weight-management efficacy

GLP-1 RAs reduce HbA1c and body weight, with the magnitude depending on molecule, dose, treatment duration, baseline characteristics, adherence and concomitant therapy. In adults with overweight or obesity without diabetes, once-weekly semaglutide 2.4 mg in the STEP 1 trial reduced body weight by 14.9 % at 68 weeks compared with 2.4 % with placebo (Wilding et al., 2021). In SURMOUNT-1, tirzepatide reduced body weight by 15.0 %, 19.5 % and 20.9 % at doses of 5, 10 and 15 mg, respectively, versus 3.1 % with placebo at 72 weeks (Jastreboff et al., 2022).

These medicines are most effective when integrated with individualised nutrition therapy, physical activity and behavioural support (ADA, 2025b). Treatment goals should not be limited to HbA1c: body weight, waist circumference, blood pressure, lipid profile, kidney function, hypoglycaemia risk, quality of life and patient preferences should also inform follow-up.

3.3. Cardiovascular outcome evidence

Several GLP-1 RAs have reduced MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in people with T2DM and elevated cardiovascular risk (Table 1). The LEADER trial demonstrated benefit with liraglutide (Marso, Daniels et al., 2016), while SUSTAIN-6 and REWIND provided evidence for subcutaneous semaglutide and dulaglutide, respectively (Marso, Bain et al., 2016; Gerstein et al., 2019). REWIND is notable because only about one-third of participants had established CVD, suggesting benefit also in primary-prevention populations. Primary endpoints, populations and follow-up differed among trials, so direct comparisons between agents should be cautious.

The SELECT trial extended the evidence to 17 604 people with overweight or obesity and established CVD but without diabetes: semaglutide 2.4 mg reduced MACE by 20 % compared with placebo (Lincoff et al., 2023). This supports the concept that obesity pharmacotherapy can modify cardiovascular risk beyond glucose lowering, although the eligibility criteria must be considered when applying results to individual patients.

Table 1. Selected outcome and weight-management trials of GLP-1-based therapies.

Trial	Population (N)	Intervention vs placebo	Follow-up	Primary result
LEADER (Marso, Daniels et al., 2016)	T2DM, high CV risk (9 340)	Liraglutide 1.8 mg daily	Median 3.8 years	MACE HR 0.87 (95 % CI 0.78–0.97)
SUSTAIN-6 (Marso, Bain et al., 2016)	T2DM, high CV risk (3 297)	Semaglutide 0.5/1.0 mg weekly	Median 2.1 years	MACE HR 0.74 (95 % CI 0.58–0.95)
REWIND (Gerstein et al., 2019)	T2DM, CVD or risk factors (9 901)	Dulaglutide 1.5 mg weekly	Median 5.4 years	MACE HR 0.88 (95 % CI 0.79–0.99)
SELECT (Lincoff et al., 2023)	Overweight/obesity with CVD, no diabetes (17 604)	Semaglutide 2.4 mg weekly	Mean 39.8 months	MACE HR 0.80 (95 % CI 0.72–0.90)
FLOW (Perkovic et al., 2024)	T2DM and CKD (3 533)	Semaglutide 1.0 mg weekly	Median 3.4 years	Major kidney events HR 0.76 (95 % CI 0.66–0.88)
STEP 1 (Wilding et al., 2021)	Overweight/obesity, no diabetes (1 961)	Semaglutide 2.4 mg weekly	68 weeks	Weight change −14.9 % vs −2.4 %
SURMOUNT-1 (Jastreboff et al., 2022)	Obesity, no diabetes (2 539)	Tirzepatide 5/10/15 mg weekly	72 weeks	Weight change −15.0/−19.5/−20.9 % vs −3.1 %

3.4. Kidney outcomes and cardiorenal integration

The FLOW trial, which was stopped early for efficacy, showed that semaglutide reduced the risk of a composite of kidney failure, a sustained ≥ 50 % decline in estimated glomerular filtration rate (eGFR), and kidney or cardiovascular death by 24 % in people with T2DM and CKD (Perkovic et al., 2024). This has strengthened the role of GLP-1-based therapy in the cardiorenal-metabolic approach.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have a well-established role in reducing heart failure and progression of kidney disease; in DAPA-CKD, dapagliflozin reduced the primary kidney composite in patients with CKD with or without diabetes (Heerspink et al., 2020). Current guidance therefore views GLP-1 RAs and SGLT2 inhibitors as complementary rather than competing therapies: an SGLT2 inhibitor is recommended for most people with T2DM and CKD, and a GLP-1 RA with proven benefit is added when residual cardiovascular, glycaemic or weight-related risk remains (Kidney Disease: Improving Global Outcomes [KDIGO] Diabetes Work Group, 2022; ADA, 2025c).

3.5. Safety, contraindications and special populations

The most common adverse effects are gastrointestinal: nausea, vomiting, diarrhoea, constipation and abdominal discomfort. They are usually dose-related and transient and can be reduced by gradual dose escalation, smaller meals and adequate hydration. Persistent vomiting or severe abdominal pain requires clinical evaluation rather than automatic attribution to expected treatment effects, because dehydration may precipitate acute kidney injury and gallbladder disease and pancreatitis must be considered. Principal safety issues are summarised in Table 2.

Table 2. Key safety considerations and practical precautions for GLP-1-based therapies.

Issue	Clinical relevance	Practical measure
Gastrointestinal effects	Most frequent reason for discontinuation	Start low, titrate slowly; advise small meals and hydration
Volume depletion and acute kidney injury	Risk with severe vomiting or diarrhoea	Review hydration, diuretics and renal function
Gallbladder disease	Associated with rapid weight loss	Evaluate biliary symptoms promptly
Pancreatitis	Rare; causality uncertain	Stop treatment if suspected; avoid re-challenge if confirmed
Hypoglycaemia	Mainly with insulin or sulfonylureas	Reduce doses of these agents when starting therapy
Thyroid C-cell warnings	Labelling contraindications for medullary thyroid carcinoma or MEN2 history	Check product-specific prescribing information
Pregnancy	Not used for weight loss or glycaemic control in pregnancy	Review therapy when pregnancy is planned or confirmed
Anaesthesia and endoscopy	Delayed gastric emptying may increase aspiration risk	Follow current anaesthesia and institutional guidance

GLP-1-based medicines are not used during pregnancy for weight reduction or routine glycaemic management. Women planning pregnancy require timely medication review and transition to therapies with established safety under specialist supervision. In patients receiving insulin or sulfonylureas, doses of these agents may need reduction to limit hypoglycaemia. Periprocedural management should follow current anaesthesia, gastroenterology and institutional recommendations rather than a single universal withholding rule.

4. Discussion

The evidence reviewed here supports a shift from a glucose-centred to a risk-centred use of incretin-based therapy. In people with T2DM and established CVD or high cardiovascular risk, a GLP-1 RA with proven benefit should be considered independently of HbA1c, and in people with T2DM and CKD both SGLT2 inhibitors and GLP-1 RAs have outcome evidence that justifies their combined use when tolerated (Davies et al., 2022; KDIGO, 2022; ADA, 2025a). The SELECT trial further suggests that obesity itself, when combined with established CVD, may be an indication for pharmacotherapy with cardiovascular intent (Lincoff et al., 2023).

These benefits, however, are not interchangeable across molecules. Trials differed in agent, dose, population, endpoint definitions and duration, and not every GLP-1 RA has demonstrated cardiovascular or kidney benefit. Clinical decisions should therefore be based on the evidence available for the specific medicine and indication.

A practical framework begins with defining the principal treatment goals: glycaemic control, weight reduction, cardiovascular risk reduction, kidney protection or a combination. Baseline assessment should include body mass index and waist circumference, HbA1c, eGFR and urine albumin-to-creatinine ratio, blood pressure, lipid profile, current medications, pregnancy potential and contraindications. Shared decision-making should address expected benefits, adverse effects, cost and access, route of administration, titration and the likelihood of weight regain after discontinuation. Multidisciplinary care improves continuity.

GLP-1-based therapy does not replace established prevention. Blood-pressure control, lipid lowering, antiplatelet therapy when indicated, smoking cessation, physical activity and treatment of heart failure remain essential.

This review has limitations. It is a narrative synthesis, and study selection may be subject to bias. Trial populations may not represent people with frailty, advanced multimorbidity or limited access to long-term treatment. Head-to-head outcome data, durability of benefit after discontinuation, optimal sequencing with SGLT2 inhibitors, effects on microvascular outcomes and cost-effectiveness across health systems require further study, ideally in diverse populations and with patient-centred outcomes such as physical function and quality of life.

5. Conclusion

GLP-1-based therapies have reshaped the management of T2DM and obesity by combining glucose lowering and substantial weight reduction with cardiovascular benefit for selected agents and populations and with growing evidence of kidney protection. Their use should be individualised, grounded in agent-specific evidence and current guidelines, and integrated with SGLT2 inhibitors where indicated, lifestyle intervention and comprehensive cardiovascular and renal risk management. Continued research and multidisciplinary implementation are needed to translate trial efficacy into sustainable and equitable improvements in cardiometabolic health.

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