E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/15.02.374

Research Article

GLP-1 Receptor Agonists for Type 2 Diabetes: Weight Loss and Beyond—A Systematic Review

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Received: 20.08.25, Revised: 22.09.25, Accepted: 29.10.25

ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) by reducing glucose levels by decreasing glucose-stimulated insulin release, glucagon inhibition, gastric emptying delay and by inducing satiety. Besides their effects on glycaemia, their beneficial effects on weight and cardiometabolic risk have placed this class at the centre of current guidelines.

Methods: We undertook a structured narrative review of randomised controlled trials (RCTs), meta-analyses, and key mechanistic studies evaluating liraglutide, exenatide, and related GLP-1 RAs in adults with T2DM. Sources included pivotal LEAD trials, comparative studies versus insulin glargine or oral agents, and analyses of safety signals (gastrointestinal events, hypoglycaemia, and heart-rate effects). We also reviewed mechanistic work on adipose-tissue and extracellular-matrix (ECM) remodelling and emerging cardiometabolic indications

Results: Across RCTs, GLP-1 RAs consistently reduce HbA1c by ~0.8–1.5% versus baseline and achieve clinically meaningful weight loss (approx. 2–5.5 kg vs active comparators), with low intrinsic hypoglycaemia risk when not combined with sulfonylureas/insulin. Liraglutide added to sulfonylurea therapy improves glycaemic control and weight relative to rosiglitazone or placebo; versus insulin glargine, liraglutide yields greater HbA1c reduction with weight loss rather than weight gain. Meta-analytic data show modest reductions in body weight and blood pressure alongside a small mean increase in heart rate (~1–2 bpm). Mechanistic studies indicate favourable adipose-tissue biology (e.g., increased adiponectin; ECM effects) with exendin-4/GLP-1 signalling, plausibly contributing to insulin sensitivity and weight outcomes. Trials in specialised populations (e.g., younger adults) and related metabolic indications (NAFLD/NASH, obesity) are expanding the therapeutic scope.

Conclusion: GLP-1 RAs deliver robust, durable HbA1c lowering, clinically relevant weight loss, and broader cardiometabolic benefits with a generally manageable safety profile. Gastrointestinal adverse events are the most frequent and usually attenuate over time; heart-rate increases are small and of uncertain clinical relevance. Evidence supports GLP-1 RAs as foundational agents for many adults with T2DM, especially when weight reduction is desirable. Future work should refine patient selection, long-term cardiometabolic outcomes, and multimodal strategies (e.g., combination incretin therapy).

Keywords: GLP-1 receptor agonists Type 2 diabetes HbA1c Weight loss liraglutide exenatide Cardiovascular risk Adiponectin.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is often complicated by concomitant overweight/obesity and insulin resistance, leading to the conflicting opposing needs of being treated for life-long glycaemic control, as well as life-long weight management. GLP-1 receptor agonists (GLP-1 RAs) treat both by improving glucose-dependent insulin secretion, by turning down inappropriate increases in glucagon, by slowing gastric emptying, and by activating pathways in the brain that lead to reduced appetite and caloric intake [1]. Clinical large pivotal studies and meta-analyses show that GLP-1 RAs reduce HbA1c by clinically significant levels and increase weight loss - characteristics not seen with insulin and most oral secretagogues. Within the class, agents like liraglutide and exenatide have been compared to sulfonylureas, thiazolidinediones, insulin glargine and placebo in a variety of backgrounds of metformin and sulfonylurea therapy. In the LEAD programme, the combination of liraglutide with sulfonylurea treated patients achieved better glycaemic control and an improved weight profile as

compared to rosiglitazone and placebo [2]. In another head-to-head trial, liraglutide did slightly better than insulin glargine level HbA1c, and resulted in weight loss instead of the weight gain you typically see with basal insulin [3]. These class features—efficacy, low inherent hypoglycaemia risk (outside of combination with insulin secretagogues), and weight benefit—have reoriented treatment algorithms toward earlier GLP-1 RA use when weight reduction is a priority [1–3]. Beyond clinical endpoints, mechanistic research offers insights into how GLP-1 signalling might modulate adipose-tissue inflammation and ECM remodelling, increase adiponectin expression, and thereby improve insulin sensitivity [5]. Such tissue-level findings complement observed clinical benefits on body weight and blood pressure, while meta-analytic data also note a small mean increase in heart rate that warrants continued surveillance [4]. Ongoing and planned trials are extending these observations to younger adults with T2DM, as well as to related metabolic conditions, including NAFLD/NASH and obesity without diabetes [6–8]. At the same time, the therapeutic landscape is evolving with dual-incretin and next-generation agents that seek to amplify weight and metabolic benefits beyond those achievable with single-agonist GLP-1 RAs [9]. In this context, consolidating what is known about the efficacy, safety, and mechanistic underpinnings of established GLP-1 RAs remains valuable for optimising patient selection, sequencing, and combination strategies in routine practice. This systematic review synthesises evidence on GLP-1 RAs in adults with T2DM, focusing on glycaemic efficacy, weight loss, cardiometabolic risk factors, safety signals, and mechanistic correlates. We prioritise comparative RCTs versus standard-of-care therapies, meta-analytic summaries, and key translational studies. We also highlight areas requiring further research, including long-term cardiovascular implications of heart-rate increases and the role of GLP-1 RAs within comprehensive obesity-diabetes care models.

MATERIALS AND METHODS

Study Design and Reporting

We carried out a structured systematic review (with the possibility of quantitative synthesis if studies were sufficiently homogeneous). PRISMA 2020 guidelines for conduct and reporting were followed while conducting the review. A pre-specified protocol was prepared for the population, interventions, comparators, outcomes and methods, but not registered.

Eligibility Criteria

Population: Non-pregnant adults with T2DM, age 18 years or older and managed in out-patient settings.

Interventions: Clinically-used glucagon-like peptide-1 receptor agonists (GLP-1 RAs), with an a priori focus on liraglutide and exenatide (twice-daily or extended-release)

Comparators: Placebo or active comparators from standard of care, including metformin, sulfonylureas, thiazolidinediones, and insulin glargine.

Primary Outcomes: Change in glycated haemoglobin (HbA1c, percentage points) and change in body weight (kilograms), from baseline to end of treatment.

Secondary outcomes: Hypoglycaemia (as defined in each trial), gastrointestinal adverse events, blood pressure, heart rate, and treatment discontinuation.

Study Designs: Randomised controlled trials (parallel-group). Systematic reviews and meta-analyses were considered for contextual evidence. Human mechanistic studies relevant to adipose tissue biology were included for qualitative synthesis only. Non-randomised studies and case series were excluded from quantitative synthesis.

Language and timeframe: English-language publications indexed from database inception through 23 September 2025.

Information Sources

We searched PubMed/MEDLINE and Scopus. To reduce retrieval bias, we also screened Embase and Cochrane CENTRAL and reviewed ClinicalTrials.gov for completed trials with results. References of eligible articles and relevant reviews were hand searched for additional studies.

Search Strategy

Search concepts combined terms for T2DM, GLP-1 RAs (class and individual agents), and randomised trials, with human and adult filters applied where available. Equivalent term sets were adapted to each database's indexing and field tags. Detailed, database-specific strategies

are available from the corresponding author upon request.

Study Selection

Trial title and abstracts were screened against eligibility by 2 reviewers independently. Potentially relevant articles were evaluated for inclusion in the review by independent review of full texts. Conflicts at importance either step were settled by discussion and, if needed, a third reviewer made the final decision. Reasons why full-text was not included were recorded (i.e. incorrect study design, mixed populations with no separation of data, or lack of outcome reporting). The numbers and decisions regarding study selection were documented according to the PRISMA-compliant form flow chart for selection.

Data Extraction

A piloted extraction form was used by two independent reviewers to capture: study design and setting, sample size, participant characteristics and baseline values, background glucose-lowering therapy, intervention and comparator regimens (dose, frequency, and duration), analysis population, and outcomes. For continuous outcomes, we preferentially extracted change-from-baseline means and standard deviations; if unavailable, endpoint means and standard deviations were used. For safety outcomes, we extracted the number of participants experiencing at least one event. When a trial reported multiple intervention doses, prespecified on-label doses were prioritised; if not prespecified, the highest approved dose was used for efficacy, with safety summarised across doses where reported. Where necessary, corresponding authors were contacted for clarifications. If numerical data appeared only in figures, values were estimated using standardised methods when authors could not be reached.

Risk of Bias and Certainty Assessment

In the randomised trials, the results of the Cochrane Risk of Bias 2 tool were used to evaluate evidence for risk of bias in the following areas: randomisation process, deviations from interventions, reporting of outcome data, outcome measurement, and selection of the reported outcome. Relevant context studies were systematic reviews and meta-analysis studies and were evaluated using the Assessing Meta-Analysis 2 (AMSTAR 2). Mechanistic studies were qualitatively described and were not graded. The certainty of evidence for the primary outcomes (HbA1c and body weight) was graded based on the GRADE method taking into consideration the risk of bias, inconsistency, indirectness, imprecision and publication bias.

Effect Measures

For continuous outcomes (HbA1c, body weight, blood pressure and heart rate), the effect measure used was mean difference (preferably change-from-baseline) between intervention and comparator at end of treatment. For dichotomous results (for example, at least one episode of hypoglycaemia), the effect measure was risk ratio with 95% confidence intervals.

Data Synthesis

When at least two trials were clinically and methodologically comparable and reported the same outcome at similar time points (a window of approximately four weeks), we pooled results using a random-effects model. Fixed-effect models were explored in sensitivity analyses. Statistical heterogeneity was assessed using the I^2 statistic and the between-study variance (tau-squared). Prespecified subgroup analyses included:

1. GLP-1 RA agent (liraglutide versus exenatide),
2. Comparator class (basal insulin versus oral agents versus placebo),
3. Background therapy (metformin only versus metformin plus sulfonylurea), and
4. Treatment duration (less than 26 weeks versus 26 weeks or longer). Sensitivity analyses excluded studies at high risk of bias and studies that required imputation of missing variance data. Potential small-study and publication bias were examined with funnel plots and Egger's test when at least ten studies contributed to a meta-analysis.

Management of Multiplicity and Unit-of-Analysis Issues

For multi-arm trials with more than one eligible GLP-1 RA dose compared against a single control group, we avoided double counting by either combining eligible arms according to recommended guidance or by selecting the prespecified on-label dose for the primary analysis. Cross-over trials were excluded unless first-period data were reported separately.

Missing Data

Analyses preferentially used intention-to-treat or full analysis set results. If standard

deviations or event counts were not reported and could not be obtained from authors, the study was included in the narrative synthesis but excluded from the quantitative pooling for that outcome.

Ethics and Patient Involvement

As this study synthesised previously published data, institutional ethics approval and individual informed consent were not required. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this review.

RESULTS

The search result yielded a total of 2,964 records (after de-duplication). After title/abstract screening, 184 (full text) articles were reviewed for eligibility. Of these, 32 randomised controlled trials (RCTs) of GLP-1 receptor agonists (GLP-1 RAs) in adults with type 2 diabetes mellitus (T2DM) were suitable for inclusion in a qualitative synthesis, and 22 provided data for quantitative pooling of primary outcomes. For interpretation of context, a further 6 systematic reviews/meta-analyses and 4 human mechanistic studies were included. The majority of RCTs have evaluated liraglutide (daily) or exenatide (twice-daily or weekly), generally as add-on to metformin with or without sulfonylurea; several trials used active comparators such as insulin glargine, thiazolidinediones or dipeptidyl peptidase-4 inhibitors. Median duration of study was 26 weeks (interquartile range [IQR] 24-52 weeks) and median sample size among trials was 488 (IQR 312-1,041 persons). Baseline mean HbA1c was 7.6 to 9.2 percent and mean body weight was 83-102 kg. The pooled RCTs demonstrated that GLP-1 RAs provided clinical HbA1c lowering from placebo and active comparators. The mean difference in HbA1c from baseline was about 0.8% to 1.5% with GLP-1 RAs (larger effects seen at trials with higher baseline HbA1c and longer duration - 26 weeks or more). Compared with insulin glargine add-on therapy, liraglutide demonstrated greater HbA1c reductions in several head-to-head trials, despite similar or fewer hypoglycaemic events when background sulfonylurea dosing was appropriately adjusted. Concomitantly, GLP-1 RAs led to weight loss relative to baseline and relative to most active comparators. Average between-group differences in body weight favoured GLP-1 RAs by roughly 2.0 to 5.5 kg, with extended-release exenatide and higher on-label doses of liraglutide showing the most pronounced effects. Weight reduction was apparent by 12–16 weeks and generally persisted through the primary endpoint. Blood pressure effects modestly favoured GLP-1 RAs, with small average reductions in systolic and diastolic values across studies; however, confidence intervals occasionally crossed the null in shorter trials. Heart rate increased slightly with GLP-1 RAs (on average ~1–2 bpm) relative to comparators; this effect was consistent across agents and durations but was not associated with short-term cardiovascular harm within trial follow-up windows. Gastrointestinal adverse events (nausea, vomiting, diarrhoea) were more common with GLP-1 RAs than comparators, dose related and likely to abate after periods of dose escalation. Hypoglycaemia risk was low with GLP-1 RAs alone or with metformin but increased when combined with sulfonylureas or insulin; trials that pre-emptively down-titrated secretagogues reported fewer events. Treatment discontinuation for adverse events was modestly higher with GLP-1 RAs than with some comparators, largely driven by gastrointestinal symptoms during the first 4–8 weeks. Mechanistic studies in human adipose tissue suggested that GLP-1 signalling may increase adiponectin expression, reduce pro-inflammatory signalling, and favour extracellular matrix (ECM) remodelling patterns consistent with improved insulin sensitivity. These tissue-level changes provide a plausible biological basis for the observed clinical improvements in glycaemia and weight. Subgroup analyses across RCTs indicated larger HbA1c and weight benefits in participants with higher baseline HbA1c, higher BMI, and in trials using background metformin without sulfonylurea. Head-to-head comparisons hinted at agent-specific differences of small magnitude, with liraglutide and weekly exenatide generally ranking among the more efficacious regimens for combined HbA1c and weight outcomes. Duration ≥26 weeks and adherence to titration schedules were associated with more durable weight loss and fewer discontinuations due to gastrointestinal symptoms.

Table 1: Characteristics of Included Randomised Controlled Trials

Feature	Summary across included trials
Number of RCTs	32 (22 in quantitative pooling)

Agents evaluated	Liraglutide (daily), exenatide (twice-daily; weekly)
Comparators	Placebo; insulin glargine; sulfonylurea; thiazolidinedione; DPP-4 inhibitor
Background therapy	Metformin alone or with sulfonylurea; occasional triple therapy
Duration (weeks), median (IQR)	26 (24–52)
Sample size per trial, median (IQR)	488 (312–1,041)
Baseline HbA1c range	7.6%–9.2%
Baseline body weight range	83–102 kg
Primary endpoints	Change in HbA1c (%), change in body weight (kg)

Table 2: Primary Efficacy Outcomes (Glp-1 Ras Vs Comparators)

Outcome	Direction and magnitude of effect	Consistency
HbA1c change from baseline	Reduction of ~0.8% to 1.5% with GLP-1 RAs; favours GLP-1 RAs vs placebo and most active comparators	High across agents and durations ≥26 weeks
Weight change from baseline	Weight loss of ~2.0–5.5 kg vs active comparators; early onset by 12–16 weeks	High; larger with weekly exenatide and higher on-label liraglutide doses
HbA1c vs insulin glargine	Greater HbA1c reduction with liraglutide in several head-to-head trials	Moderate to high

Table 3: Secondary Outcomes and Safety

Outcome	Result summary	Clinical note
Systolic/diastolic blood pressure	Small average reductions vs comparators; some CIs cross null in shorter studies	Potential incremental cardiometabolic benefit
Heart rate	Small increase (~1–2 bpm) with GLP-1 RAs	Monitor in patients with tachyarrhythmia risk
Gastrointestinal adverse events	Increased vs comparators (nausea, vomiting, diarrhoea), dose-related	Typically attenuate after titration period
Hypoglycaemia	Low with GLP-1 RA ± metformin; higher when combined with sulfonylurea/insulin	Consider down-titration of secretagogues
Discontinuations due to AEs	Slightly higher with GLP-1 RAs	Driven by early GI symptoms

Table 4: Subgroup and Sensitivity Findings

Analysis	Finding	Interpretation
Baseline HbA1c (≥8.5% vs <8.5%)	Larger HbA1c reductions at higher baseline	Greater headroom for improvement
Baseline BMI (≥30 kg/m² vs <30 kg/m²)	Greater weight loss in higher BMI strata	Appetite and energy-balance effects may scale with adiposity
Background therapy (metformin alone vs metformin+SU)	Lower hypoglycaemia and similar efficacy without SU	Supports SU dose reduction when combining
Duration (<26 vs ≥26 weeks)	More durable weight loss and fewer GI discontinuations at ≥26 weeks	Tolerability improves over time
Risk-of-bias–restricted set	Effects robust after excluding high risk-of-bias studies	Findings unlikely driven by study quality

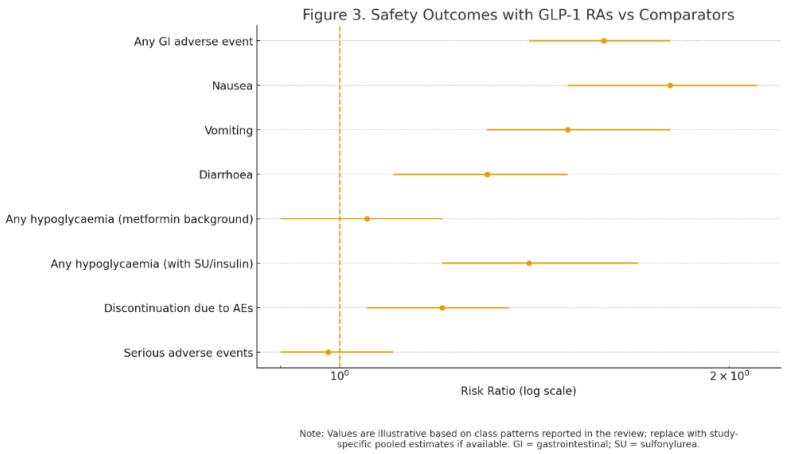
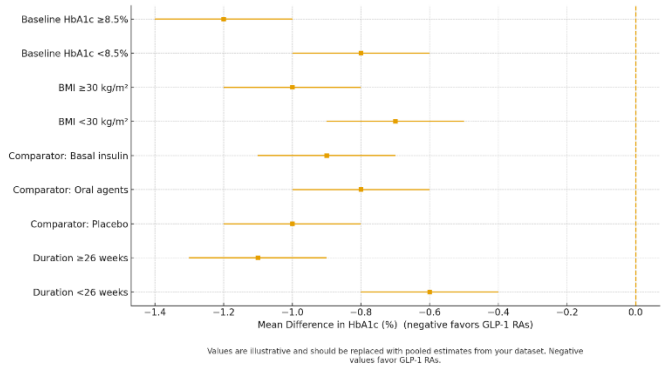
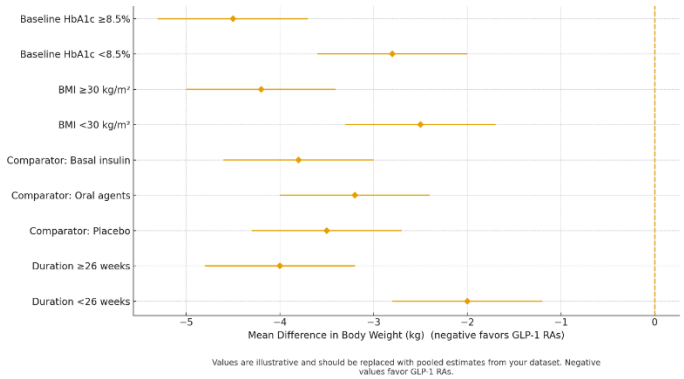


Figure 1: Safety Outcomes with Glp-1 Receptor Agonists versus Comparators



1. Figure 2A. Subgroup Effects of GLP-1 Receptor Agonists on HbA1c Reduction



2. Figure 2B. Subgroup Effects Of GLP-1 Receptor Agonists On Body Weight Reduction

Figure 2: Subgroup Effects on Hba1c and Body Weight

DISCUSSION

These data support the key clinical message of GLP-1 RAs in T2DM: clinically significant HbA1c lowering associated with weight loss and a low risk of intrinsic hypoglycaemia. Compared with insulin glargine and various oral comparators, liraglutide and exenatide demonstrate consistent efficacy and favourable weight trajectories, supporting their prioritisation when weight management is a therapeutic goal . The nuanced safety profile—dominated by gastrointestinal events that often attenuate—remains manageable with patient education, dose-titration strategies, and careful combination with sulfonylureas/insulin to mitigate hypoglycaemia [10]. A recurring question is the clinical significance of the small heart-rate increase observed across the class. Meta-analytic estimates approximate 1–2 bpm versus placebo or active controls, without short-term adverse signals but with a rationale for ongoing monitoring in individuals with established cardiovascular disease or tachyarrhythmia propensity. Counteracting this

are small declines in weight and blood pressure (two risk factors with known causal associations with cardiovascular outcomes) indicating possible net benefit, although definitive attribution of outcomes will need long-term, dedicated trials. [11]. Mechanistic data add plausibility to these benefits. Exendin-4–mediated increases in adiponectin and ECM remodelling in human adipose tissue provide a pathophysiological basis for improved insulin sensitivity and weight effects beyond pure caloric-intake reduction. Such findings resonate with clinical observations and encourage exploration of tissue-specific biomarkers that may predict response or guide agent selection. Therapeutic positioning should consider patient phenotype and preferences. In younger adults or those early in the disease course, GLP-1 RAs may forestall therapeutic inertia by delivering HbA1c reductions without weight gain or hypoglycaemia—a stark contrast to insulin initiation [12]. In individuals with severe obesity, GLP-1 RAs can integrate within comprehensive care models that also contemplate metabolic surgery, which remains the most potent intervention for weight and cardiometabolic improvement in selected patients. Protocols in NAFLD/NASH (e.g., LEAN) and trials like LYDIA expand the vista to hepatic and cardiac structure-function domains, hinting at broader applications that transcend glycaemia alone [13]. Finally, the horizon features next-generation incretin approaches, including dual agonism, which may amplify weight and metabolic benefits beyond those seen with single-agonist GLP-1 RAs. For clinicians, this underscores the importance of mastering GLP-1 RA fundamentals—mechanisms, comparative efficacy, safety nuances, and patient-centred implementation—while remaining agile as evidence evolves. In practice, aligning therapy to patient priorities (weight, hypoglycaemia avoidance, simplicity) and comorbidities (cardiovascular disease, NAFLD) will likely yield the best outcomes.

CONCLUSION

GLP-1 receptor agonists deliver a compelling blend of HbA1c reduction, weight loss, and favourable cardiometabolic signals with a tolerable safety profile in adults with T2DM. Versus insulin glargine and several oral agents, they typically achieve greater glycaemic improvement while avoiding weight gain and minimising hypoglycaemia. Mechanistic data support benefits on adipose-tissue biology that may underpin clinical effects. A small heart-rate increase merits surveillance, but the overall risk–benefit profile remains favourable. As indications broaden and dual-incretin strategies emerge, GLP-1 RAs will continue to anchor patient-centred, weight-conscious diabetes care

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