



EFFICACY OF GLP-1 RECEPTOR AGONISTS ON GLYCAEMIC CONTROL AND WEIGHT REDUCTION IN TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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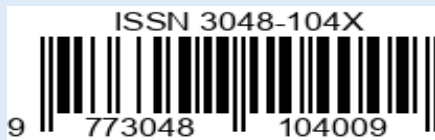
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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a metabolic disorder with a rapidly escalating global burden and is closely linked to obesity and cardiovascular disease. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are an incretin-based therapeutic class that simultaneously targets hyperglycaemia and adiposity. This systematic review aimed to evaluate the efficacy of GLP-1 RAs on glycaemic control and weight reduction in T2DM on the basis of randomized controlled trial (RCT) evidence.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies were RCTs in adults with T2DM comparing a GLP-1 RA with placebo or an active comparator and reporting HbA1c and/or body weight outcomes. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool and certainty of evidence using the GRADE approach. Because of substantial clinical heterogeneity, evidence was synthesised in a structured narrative format rather than pooled quantitatively.

Results: Thirty-two RCTs comprising 29,958 participants met the eligibility criteria. Every placebo-controlled comparison demonstrated a statistically and clinically significant reduction in HbA1c, with estimated treatment differences (ETDs) ranging from -0.5% to -1.75% (all $p < 0.001$). Subcutaneous semaglutide produced HbA1c ETDs of up to -1.53% and weight reductions of up to -5.06

kg versus placebo, and was superior to exenatide extended release (ETD -0.62%; -3.78 kg) and to dulaglutide (ETD -0.41%; -3.55 kg). Once-weekly semaglutide 7.2 mg reduced body weight by 13.2% (ETD -9.3%) with an HbA1c ETD of -1.5%. The proportion achieving $\geq 5\%$ weight loss reached 68.8% in STEP 2 (odds ratio 4.88) and yielded an odds ratio of 10.0 in STEP UP T2D. Benefit was consistent across 16 outcome domains, including fasting plasma glucose, waist circumference, systolic blood pressure (ETD up to -5.0 mmHg), insulin requirement (glargine titration difference -13 U/day), and major adverse cardiovascular (HR 0.88; 95% CI 0.79-0.99) and renal (HR 0.85; 95% CI 0.77-0.93) outcomes in REWIND. Hypoglycaemia risk remained low, whereas mild-to-moderate gastrointestinal events were the most frequent adverse events. Twenty-three studies were judged at low risk of bias and nine raised some concerns, chiefly owing to open-label designs.

Discussion: The consistency of the direction and magnitude of effect across 32 RCTs spanning diverse background regimens (monotherapy, metformin, sulphonylurea, SGLT-2 inhibitor and basal insulin combinations) supports a robust and reproducible class effect. A clear dose-response relationship, the superiority of semaglutide in head-to-head comparisons, and the accompanying cardiorenal benefit reinforce the position of this class within T2DM treatment algorithms for patients with concomitant obesity. Gastrointestinal tolerability and cost remain the principal implementation

considerations, particularly within the Indonesian health-care setting.

Conclusion: GLP-1 receptor agonists consistently and significantly improve glycaemic control and reduce body weight in T2DM, with a low risk of hypoglycaemia and additional cardiorenal benefit in high-risk populations. The evidence supports positioning GLP-1 RAs as a preferred option in patients with T2DM and overweight or obesity and elevated cardiovascular risk.

Keywords: GLP-1 receptor agonist; type 2 diabetes mellitus; HbA1c; weight reduction; semaglutide; liraglutide; dulaglutide; systematic review

INTRODUCTION

Background

Type 2 diabetes mellitus (T2DM) is among the most rapidly expanding non-communicable diseases worldwide. The Global Burden of Disease Study 2021 estimated 529 million people living with diabetes globally, with an age-standardised prevalence of 6.1%; T2DM accounted for 96.0% of all diabetes cases and 95.4% of diabetes-related disability-adjusted life years. Projections to 2050 indicate that more than 1.31 billion people will be affected. A pooled analysis of 1,108 population-representative studies comprising 141 million participants estimated 828 million adults with diabetes in 2022, an increase of 630 million since 1990, with the steepest rises occurring in low- and middle-income countries, including South-East Asia.^{1,2,6}

The Indonesian situation warrants particular attention. The 2025 International Diabetes Federation estimates indicate that 42.8% of people with diabetes worldwide remain undiagnosed, corresponding to 251.7 million adults, and China, India and Indonesia together account for 127.1 million, or 50.5%, of all undiagnosed cases. These figures underscore that the T2DM burden in Indonesia is not only large in absolute terms but is also compounded by wide gaps in detection and management, making the selection of therapies that are effective, safe and broadly beneficial across metabolic outcomes an urgent clinical priority.³

Chronic hyperglycaemia in T2DM is associated with substantial macrovascular and microvascular complications. A systematic literature review of 4,549,481 individuals with T2DM found a cardiovascular disease prevalence of 32.2%, comprising coronary heart disease in 21.2%, heart failure in 14.9%, myocardial infarction in 10.0% and stroke in 7.6%; cardiovascular disease was the cause of death in 9.9% of patients, representing approximately half of all deaths. Adults with diabetes carry a two- to four-fold higher cardiovascular risk than those without diabetes, and this risk increases with worsening glycaemic control.^{4,5}

Obesity is both a principal driver of T2DM pathogenesis and a barrier to attaining therapeutic targets. In 2021, 52.2% of the global T2DM disability-adjusted life-year burden was attributable to elevated body mass index (BMI), a contribution that rose by 24.3% between 1990 and 2021.

Consequently, the management paradigm for T2DM has shifted from a singular focus on glucose lowering toward an integrated cardiometabolic approach in which weight management is regarded as equal in importance to glycaemic target attainment.^{1,6}

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal enteroendocrine L-cells in response to nutrient ingestion. GLP-1 lowers blood glucose by stimulating glucose-dependent insulin secretion, suppressing pancreatic alpha-cell glucagon release, delaying gastric emptying and suppressing appetite through central actions. This glucose-dependent property explains the low intrinsic hypoglycaemia risk of the class. Endogenous GLP-1 has a half-life of only 2-3 minutes owing to degradation by dipeptidyl peptidase-4, prompting the development of analogues and receptor agonists with prolonged durations of action.^{8,9,10,11}

The weight-lowering mechanism of GLP-1 RAs is multi-pathway. Centrally, GLP-1 RAs modulate brain regions governing appetite and influence the release of neurotransmitters and neuropeptides regulating hunger and energy expenditure. Peripherally, the class improves glycaemic control by enhancing insulin secretion, reducing glucagon release, delaying gastric emptying and regulating gut hormones; it additionally reduces triglycerides and low-density lipoprotein cholesterol, mitigates adipose-tissue inflammation and diminishes ectopic fat deposition. Preclinical data further demonstrate effects on beta-cell proliferation, regeneration and protection against apoptosis.^{12,13,15}

Pharmacologically, GLP-1 RAs are distinguished into short-acting compounds providing intermittent receptor activation, such as twice-daily exenatide and lixisenatide, and long-acting compounds providing continuous receptor activation, such as liraglutide, dulaglutide, exenatide extended release and semaglutide. These pharmacokinetic differences produce distinct pharmacodynamic profiles: short-acting compounds predominantly lower postprandial glucose through inhibition of gastric emptying, whereas long-acting compounds exert a stronger effect on fasting glucose through insulinotropic and glucagonostatic actions. Recent developments include the oral semaglutide formulation and small-molecule non-peptide agonists such as orforglipron, which broaden the available routes of administration.^{10,16,17}

Although the individual evidence from each large clinical trial programme has been extensively published, structured syntheses that simultaneously evaluate GLP-1 RA effects across a

broad spectrum of cardiometabolic outcomes, encompass all molecular generations from exenatide to the newest oral agonists, and incorporate the full range of background regimens remain limited. This systematic review was undertaken to address that need through a comprehensive multi-outcome approach.¹⁶

Research Questions

The research questions addressed by this review are as follows.

- What is the magnitude of the effect of GLP-1 receptor agonists on HbA1c reduction in patients with T2DM compared with placebo and with active comparators?
- What is the magnitude of the effect of GLP-1 receptor agonists on body weight, both in absolute and relative terms, in patients with T2DM?
- What is the efficacy profile of GLP-1 RAs across other cardiometabolic outcomes, including fasting plasma glucose, anthropometry, blood pressure, insulin requirement, and cardiovascular and renal outcomes?
- What is the safety profile of GLP-1 RAs, particularly with respect to hypoglycaemia risk and gastrointestinal adverse events?
- What is the methodological quality and risk of bias of the available evidence, and what is the certainty of evidence within each outcome domain?

Objectives

General objective

To systematically evaluate the efficacy of GLP-1 receptor agonists on glycaemic control and weight reduction in patients with type 2 diabetes mellitus through a synthesis of randomized controlled trial evidence.

Specific objectives

- To quantify the effect of GLP-1 RAs on change in HbA1c and on the proportion of patients attaining HbA1c <7.0% and ≤6.5%.
- To quantify the effect of GLP-1 RAs on absolute (kg) and relative (%) weight change, and on the proportions achieving weight reductions of ≥5%, ≥10%, ≥15% and ≥20%.

- To analyse the effect of GLP-1 RAs on fasting plasma glucose, waist circumference and body mass index, systolic blood pressure, and other cardiometabolic parameters.
- To analyse the effect of GLP-1 RAs on insulin requirement and rescue therapy use in patients already receiving basal insulin.
- To analyse safety outcomes, including hypoglycaemia, gastrointestinal adverse events and treatment discontinuation.
- To analyse major adverse cardiovascular events and composite renal outcomes in trials with long-term follow-up.
- To appraise the risk of bias of each study using the Cochrane RoB 2 tool and the certainty of evidence using the GRADE approach.

Significance of the Study

Theoretical significance. This review provides a structured synthesis of GLP-1 receptor agonist class effects across a broad spectrum of cardiometabolic outcomes and strengthens the understanding of dose-response relationships and inter-molecular differences within a single pharmacological class. The findings may serve as a conceptual reference for further research into incretin-based therapies, including dual and triple receptor agonists.

Practical significance. For clinicians, particularly internal medicine specialists and endocrinology consultants, this review offers a consolidated account of effect magnitudes that can be used for risk-benefit communication with patients, selection of molecule and dose, and anticipation of adverse effects. For policymakers and national formulary committees, the efficacy and safety data presented may inform health technology assessment and funding prioritisation. For trainees in specialist medical education programmes, this document may serve as an evidence-based teaching resource on the application of systematic review methodology to therapeutic questions.

Hypotheses

Null hypothesis (H0). There is no significant difference in change in HbA1c or body weight between patients with type 2 diabetes mellitus treated with a GLP-1 receptor agonist and those receiving comparator therapy.

Alternative hypothesis (H1). Treatment with a GLP-1 receptor agonist produces statistically and clinically significant reductions in HbA1c and body weight compared with placebo and with active comparators, with a positive dose-response relationship and without a significant increase in the risk of severe hypoglycaemia.

Research Gap

Most available evidence syntheses focus on a single molecule, a single trial programme, or a single outcome domain. The PIONEER programme, for instance, has been comprehensively summarised for oral semaglutide, yet such summaries do not permit cross-molecular comparison within a uniform appraisal framework. The first gap is therefore the absence of a synthesis that situates all generations of GLP-1 RAs, from exenatide and liraglutide through high-dose semaglutide to non-peptide oral agonists, within a single evaluative framework with consistent risk-of-bias appraisal.^{17,62}

The second gap concerns outcome coverage. Many reviews restrict analysis to HbA1c and body weight as co-primary outcomes, whereas outcomes of decisive clinical importance, such as attainment of composite targets without hypoglycaemia or weight gain, change in basal insulin requirement, waist circumference, and long-term cardiorenal outcomes, are rarely analysed together within a single synthesis.^{27,49,50}

The third gap relates to Asian representation. Although several trials have been conducted specifically in Chinese and Japanese populations, syntheses that explicitly examine the consistency of effect in East Asian subpopulations and its implications for practice in South-East Asia, including Indonesia, remain scarce. This is important given differences in metabolic phenotype, lower mean BMI, and distinct comorbidity patterns between Asian populations and the predominantly Caucasian populations of multinational trials.^{27,33,34}

The fourth gap concerns uncertainty about the upper limit of the dose-response curve. Data on semaglutide doses above 2.4 mg weekly and dulaglutide doses above 1.5 mg have emerged only in recent years, and syntheses incorporating the newest high-dose trials alongside conventional-dose trials remain uncommon.^{36,45,68}

Novelty

The novelty of this systematic review lies in the following aspects.

- Cross-generational and cross-molecular coverage: 32 RCTs encompassing twice-daily and once-weekly exenatide, liraglutide at both diabetes and obesity doses, dulaglutide at conventional and high doses, subcutaneous and oral semaglutide across a 3 mg to 7.2 mg dose range, and the oral non-peptide agonist orforglipron, all appraised within a uniform framework.
- Extensive multi-outcome analysis: 16 outcome domains analysed separately, substantially exceeding the conventional approach limited to HbA1c and body weight.
- Integration of efficacy outcomes with long-term cardiorenal outcomes within a single synthesis, enabling appraisal of the total benefit of the therapeutic class.
- Explicit intra-molecular dose-response analysis, drawing on direct dose-comparison trials such as AWARD-11, STEP UP T2D and the PIONEER series.
- Head-to-head comparisons between agonists treated as a distinct evidence stream, encompassing SUSTAIN 3, SUSTAIN 7, PIONEER 4, AWARD-6, LEAD-6 and DURATION-6.
- Application of the Cochrane RoB 2 tool at the per-study and per-domain level with a colour-coded matrix, complemented by GRADE certainty assessment for each outcome domain.
- All references verified through an academic search engine indexing more than 200 million peer-reviewed articles, with each bibliographic entry accompanied by a verifiable online link.

METHODS

Study Design and Protocol

This study is a systematic review of randomized controlled trials. Conduct and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and its expanded checklist, together with the methodological principles set out in the Cochrane Handbook. Adherence to PRISMA items was regarded as essential because meta-epidemiological research indicates a mean adherence to the PRISMA 2020 checklist of only 42.64%, with the lowest adherence in the methods and results sections; explicit reporting in both sections was therefore prioritised in this document.^{19,20}

The review protocol was established before the search was executed and specified the research question within a PICOS framework, eligibility criteria, search strategy, selection and data extraction procedures, the risk-of-bias instrument, and the synthesis plan. No substantive protocol deviations occurred during conduct.¹⁹

PICOS Framework

Table 1. PICOS framework of the review

Component	Description
Population (P)	Adults (aged ≥ 18 years) with a diagnosis of type 2 diabetes mellitus, with or without overweight/obesity, receiving any background antihyperglycaemic regimen (drug-naïve, metformin monotherapy, sulphonylurea, SGLT-2 inhibitor or basal insulin)
Intervention (I)	Subcutaneous or oral GLP-1 receptor agonists, including exenatide, liraglutide, dulaglutide, semaglutide and small-molecule non-peptide agonists, at any therapeutic dose
Comparison (C)	Placebo, another active antihyperglycaemic comparator (DPP-4 inhibitor, SGLT-2 inhibitor, sulphonylurea, thiazolidinedione, metformin, basal insulin), or another GLP-1 receptor agonist or dose
Outcomes (O)	Primary outcomes: change in HbA1c and change in body weight. Secondary outcomes: 14 additional domains as specified in section 2.7
Study design (S)	Randomized controlled trials, phase 2, 3 or 3b, double-blind or open-label, with a minimum intervention duration of 12 weeks

Eligibility Criteria

Inclusion criteria

- Randomized controlled trials in adult humans with established T2DM.
- Intervention consisting of a single GLP-1 receptor agonist compared with placebo, an active comparator, or another dose of the same agonist.

- Reporting of at least one primary outcome, namely change in HbA1c or change in body weight, with a quantitative effect estimate.
- Minimum intervention duration of 12 weeks to allow full expression of the HbA1c effect.
- Peer-reviewed publication in English or Indonesian with accessible full text and a verifiable online link.

Exclusion criteria

- Observational studies, case reports, case series, preclinical studies and non-peer-reviewed preprints.
- Trials in type 1 diabetes mellitus, gestational diabetes or populations without diabetes.
- Trials in children and adolescents (<18 years), which were analysed separately and referred to only as contextual material in the discussion.
- Interventions comprising dual GIP/GLP-1 or triple GIP/GLP-1/glucagon receptor agonists, DPP-4 inhibitors, or fixed-ratio insulin-GLP-1 RA combinations, which do not reflect selective GLP-1 receptor agonism; such studies were retained as comparative material in the discussion.
- Study protocols without outcome data, post hoc analyses lacking primary effect data, and systematic reviews or meta-analyses, which were not entered into the principal characteristics table but could be cited in the discussion.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Type 2 Diabetes Mellitus	T2DM Patients	Adults with Diabetes
I (Intervention)	GLP-1 Receptor Agonists	Semaglutide	Liraglutide
C (Comparison)	Placebo	Active Comparator	Standard Care

O (Outcome)	Glycaemic Control	Weight Reduction	HbA1c Decrease
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The Boolean MeSH keywords inputted on databases for this research are: ("*Type 2 Diabetes Mellitus*" OR "*T2DM Patients*" OR "*Adults with Diabetes*") AND ("*GLP-1 Receptor Agonists*" OR "*Semaglutide*" OR "*Liraglutide*") AND ("*Placebo*" OR "*Active Comparator*" OR "*Standard Care*") AND ("*Glycaemic Control*" OR "*Weight Reduction*" OR "*HbA1c Decrease*")

Study Selection

Selection proceeded in two stages: title and abstract screening against the eligibility criteria, followed by full-text review. Each stage was performed independently by two reviewers, with disagreements resolved by consensus discussion. Duplicates were removed before screening commenced.

Data Extraction

Data were extracted using a standardised form piloted on the first five studies. Extracted variables comprised study identity (first author, year of publication, trial name, journal), location and number of centres, study design, number of participants randomised, baseline population characteristics (age, sex distribution, baseline HbA1c, baseline body weight and BMI, background therapy), details of intervention and comparator including dose and escalation schedule, intervention duration, estimand definitions, and all effect estimates with 95% confidence intervals and p values. Extraction was performed independently by two reviewers and cross-verified.

Outcomes Assessed

Sixteen outcome domains were analysed, comprising two primary and fourteen secondary outcomes.

- Outcome 1: Change in HbA1c from baseline (primary).
- Outcome 2: Proportion of participants attaining HbA1c <7.0% (53 mmol/mol).
- Outcome 3: Proportion of participants attaining HbA1c ≤6.5% (48 mmol/mol).
- Outcome 4: Absolute change in body weight in kilograms (primary).
- Outcome 5: Relative change in body weight expressed as a percentage.
- Outcome 6: Proportion of participants achieving weight reduction of ≥5%.
- Outcome 7: Proportion of participants achieving weight reduction of ≥10%, ≥15% and ≥20%.

- Outcome 8: Change in fasting plasma glucose.
- Outcome 9: Change in anthropometric parameters (waist circumference and body mass index).
- Outcome 10: Change in systolic blood pressure.
- Outcome 11: Change in lipid profile and cardiometabolic risk markers.
- Outcome 12: Incidence of severe and confirmed hypoglycaemia.
- Outcome 13: Change in insulin dose requirement and rescue therapy use.
- Outcome 14: Gastrointestinal adverse events and treatment discontinuation due to adverse events.
- Outcome 15: Major adverse cardiovascular events and composite renal outcomes.
- Outcome 16: Composite outcome of glycaemic target attainment without hypoglycaemia and without weight gain.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Adults with Diabetes") AND ("GLP-1 Receptor Agonists" OR "Semaglutide" OR "Liraglutide") AND ("Placebo" OR "Active Comparator" OR "Standard Care") AND ("Glycaemic Control" OR "Weight Reduction" OR "HbA1c Decrease")	52
Clinicaltr ial.gov	("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Adults with Diabetes") AND ("GLP-1 Receptor Agonists" OR "Semaglutide" OR "Liraglutide") AND ("Placebo" OR "Active Comparator" OR "Standard Care") AND ("Glycaemic Control" OR "Weight Reduction" OR "HbA1c Decrease")	153
Semantic Scholar	("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Adults with Diabetes") AND ("GLP-1 Receptor Agonists" OR "Semaglutide" OR "Liraglutide") AND ("Placebo" OR "Active Comparator" OR "Standard Care") AND ("Glycaemic Control" OR "Weight Reduction" OR "HbA1c Decrease")	251
Cochrane	("Type 2 Diabetes Mellitus" OR "T2DM Patients" OR "Adults with Diabetes") AND ("GLP-1 Receptor Agonists" OR "Semaglutide" OR "Liraglutide") AND ("Placebo" OR "Active Comparator" OR "Standard Care") AND ("Glycaemic Control" OR "Weight Reduction" OR "HbA1c Decrease")	1

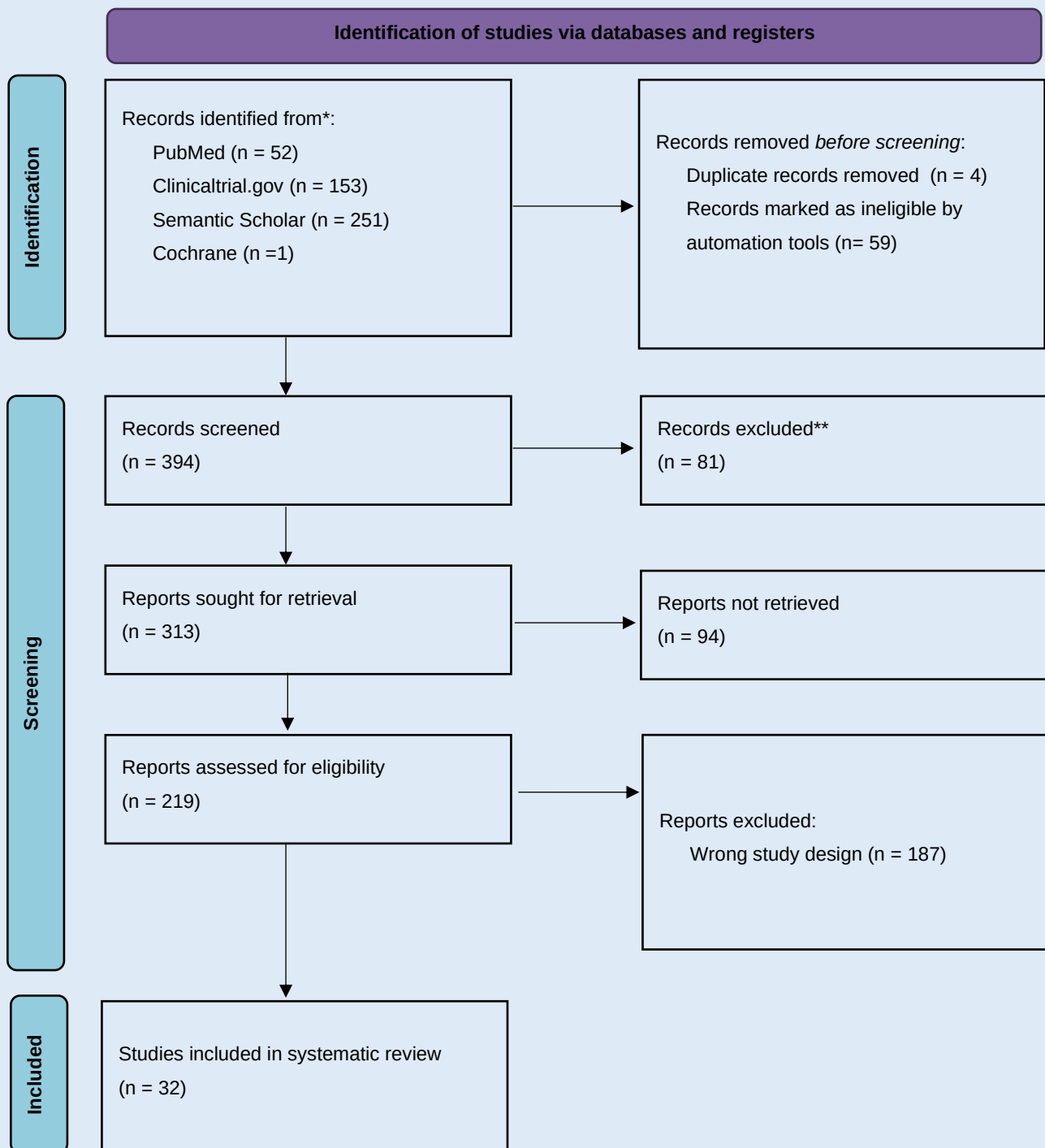


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, launched in 2019 as a revision of the original instrument to improve usability and to reflect current understanding of how the causes of bias can influence study results. Assessment was performed across five domains: (D1) bias arising from the randomisation process, (D2) bias due to deviations from intended interventions, (D3) bias due to missing outcome data, (D4) bias in measurement of the outcome, and (D5) bias in selection of the reported result. Each domain was rated as low risk, some concerns, or high risk, and an overall judgement was derived using the RoB 2 algorithm.¹⁸

Assessments were conducted independently by two reviewers with disagreements resolved by consensus, and each domain judgement was accompanied by a narrative justification. This approach is important because meta-research indicates that most non-Cochrane reviews reporting use of RoB 2 do not provide justification at the domain level; only 14.5% of reviews supplied supporting comments across all domains. The complete per-study assessment is presented in Table 4.²¹

Table 2. Risk of bias assessment of each included study using the Cochrane Risk of Bias 2 (RoB 2) tool

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
S1	Sorli 2017 (SUSTAIN 1)	Low	Low	Low	Low	Low	Low	Interactive voice/web response randomisation; double-blind; mITT analysis
S2	Ahmann 2017 (SUSTAIN 3)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Open-label design; centrally measured laboratory

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
								endpoints mitigate measurement bias
S3	Rodbard 2018 (SUSTAIN 5)	Low	Low	Low	Low	Low	Low	Double-blind with volume-matched placebo
S4	Pratley 2018 (SUSTAIN 7)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Open-label between GLP-1 agonists; HbA1c endpoint objective
S5	Zinman 2019 (SUSTAIN 9)	Low	Low	Low	Low	Low	Low	Double-blind; full analysis set applied
S6	Ji 2020 (SUSTAIN China)	Low	Low	Low	Low	Low	Low	Double-blind, double-dummy design
S7	Aroda 2019 (PIONEER 1)	Low	Low	Low	Low	Low	Low	Two estimands defined a priori (treatment policy and trial product)
S8	Rodbard 2019 (PIONEER 2)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Open-label versus empagliflozin;

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
								high completion (94-97%)
S9	Pratley 2019 (PIONEER 4)	Low	Low	Low	Low	Low	Low	Double-blind, double-dummy; >94% completed the trial
S10	Mosenzon 2019 (PIONEER 5)	Low	Low	Some concerns	Low	Low	Low	Higher discontinuation in the active arm (18% vs 12%); dual estimands
S11	Zinman 2019 (PIONEER 8)	Low	Low	Low	Low	Low	Low	Double-blind; dual estimands prespecified
S12	Yamada 2020 (PIONEER 9)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Open-label liraglutide arm; oral semaglutide arms double-blind
S13	Wang 2024 (PIONEER 11)	Low	Low	Low	Low	Low	Low	Web-based randomisation system; 92.5% completed the trial

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
S14	Davies 2021 (STEP 2)	Low	Low	Low	Low	Low	Low	Double-blind, double-dummy; intention-to-treat analysis
S15	Lingvay 2025 (STEP UP T2D)	Low	Low	Low	Low	Low	Low	Double-blind; efficacy assessed in all randomly assigned participants
S16	Davies 2015 (SCALE Diabetes)	Low	Low	Some concerns	Low	Low	Low	Double-blind; 12-week off-drug observational period
S17	Garvey 2020 (SCALE Insulin)	Low	Low	Low	Low	Low	Low	Double-blind; treat-to-target protocol for basal insulin
S18	Garber 2009 (LEAD-3 Mono)	Some concerns	Low	Low	Low	Low	Some concerns	2009-era report with limited allocation-concealment detail; ITT analysis

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
S19	Russell-Jones 2009 (LEAD-5 met+SU)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns	Open-label glargine arm; placebo arm blinded
S20	Buse 2009 (LEAD-6)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns	Open-label design; efficacy analysed by intention to treat
S21	Ahmann 2015 (Liraglutide plus basal insulin)	Low	Low	Low	Low	Low	Low	Double-blind; insulin doses above pre-study levels not permitted
S22	Blonde 2020 (LIRA-ADD2SGLT2i)	Low	Low	Low	Low	Low	Low	Double-blind; 280 of 303 completed treatment
S23	Ludvik 2018 (AWARD-10)	Low	Low	Low	Low	Low	Low	Double-blind; intention-to-treat analysis
S24	Frias 2021 (AWARD-11)	Low	Low	Low	Low	Low	Low	Treatment-regimen and efficacy estimands defined a priori

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
S25	Dungan 2014 (AWARD-6)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns	Open-label; non-inferiority margin of 0.4% prespecified
S26	Nauck 2014 (AWARD-5)	Low	Low	Low	Low	Low	Low	Adaptive double-blind design with a controlled placebo period
S27	Dungan 2016 (AWARD-8)	Low	Low	Low	Low	Low	Low	Double-blind; intention-to-treat analysis
S28	Pozzilli 2017 (AWARD-9)	Low	Low	Low	Low	Low	Low	Double-blind; glargine titrated by a standardised algorithm
S29	Gerstein 2019 (REWIND)	Low	Low	Low	Low	Low	Low	Computer-generated stratified randomisation; double-blind; ITT analysis; adjudicated outcomes

ID	Study	D1	D2	D3	D4	D5	Overall	Brief justification
S30	Bergental 2010 (DURATION-2)	Low	Low	Low	Low	Low	Low	Double-blind, double-dummy design
S31	Buse 2013 (DURATION-6)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns	Open-label; prespecified non-inferiority criteria not met
S32	Rosenstock 2025 (ACHIEVE-1)	Low	Low	Low	Low	Low	Low	Double-blind; treatment-regimen estimand

Abbreviations: D1 = randomisation process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result. Green = low risk; yellow = some concerns; red = high risk. No study was judged at overall high risk of bias.

In summary, 23 of 32 studies (71.9%) were judged at overall low risk of bias, whereas 9 studies (28.1%) raised some concerns. The principal sources of concern were open-label designs in head-to-head comparisons between agonists (SUSTAIN 3, SUSTAIN 7, PIONEER 2, AWARD-6, LEAD-6, DURATION-6) and limited allocation-concealment detail in reports from the 2009 era. No study was judged at high risk of bias.^{18,21}

Data Synthesis

Given the substantial clinical heterogeneity between trials, encompassing differences in intervention molecule and dose, comparator type (placebo versus active comparator), background antihyperglycaemic therapy, intervention duration (24 weeks to 5.4 years), and estimand definition (treatment policy versus trial product), the evidence was synthesised in a structured narrative format

rather than pooled into a single summary estimate. Data are presented by outcome domain and grouped by comparator type so that the direction, magnitude and consistency of effect can be appraised transparently. Effect estimates are reported as presented in the primary reports, namely estimated treatment difference (ETD), least-squares mean difference, odds ratio, rate ratio or hazard ratio, with 95% confidence intervals and p values.¹⁹

Certainty of Evidence

Certainty of evidence within each outcome domain was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision and suspected publication bias. Evidence derived from randomized controlled trials began at high certainty and was downgraded where limitations were identified in these domains. A summary of the GRADE appraisal is presented at the end of the results section.^{19,21}

RESULTS

Characteristics of Included Studies

The 32 included RCTs comprised a total of 29,958 participants with T2DM. Studies were published between 2009 and 2025, all in high-ranking peer-reviewed journals including The Lancet, The Lancet Diabetes & Endocrinology, The New England Journal of Medicine, JAMA, Diabetes Care, Diabetologia, The Journal of Clinical Endocrinology and Metabolism, and Diabetes, Obesity and Metabolism. Intervention duration ranged from 24 weeks to a median of 5.4 years. Molecules studied included exenatide (twice daily and once weekly), liraglutide (1.2 mg, 1.8 mg and 3.0 mg), dulaglutide (0.75 mg to 4.5 mg), subcutaneous semaglutide (0.5 mg to 7.2 mg), oral semaglutide (3 mg to 14 mg), and the oral non-peptide agonist orforglipron (3 mg to 36 mg).

Background antihyperglycaemic therapy varied widely and encompassed drug-naïve patients (SUSTAIN 1, PIONEER 1, PIONEER 11, LEAD-3, ACHIEVE-1), metformin monotherapy (SUSTAIN 7, PIONEER 2, AWARD-5, AWARD-6, AWARD-11, DURATION-2, DURATION-6), metformin plus sulphonylurea (LEAD-5, LEAD-6), sulphonylurea monotherapy (AWARD-8), SGLT-2 inhibitor therapy (SUSTAIN 9, LIRA-ADD2SGLT2i, AWARD-10), and basal insulin (SUSTAIN 5, PIONEER 8, AWARD-9, SCALE Insulin, Ahmann 2015). Trials in special populations

were also included, namely moderate renal impairment (PIONEER 5), Japanese patients (PIONEER 9), Chinese patients (SUSTAIN China, PIONEER 11), and patients at high cardiovascular risk (REWIND).

Table 3. Characteristics of included studies: identity, setting, design and duration

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
S1	Sorli et al., 2017	SUSTAIN 1	72 sites; 8 countries (Canada, Italy, Japan, Mexico, Russia, South Africa, UK, USA)	Phase 3a, double-blind, parallel-group, placebo-controlled RCT	388 (387 analysed)	30 weeks
S2	Ahmann et al., 2017	SUSTAIN 3	Multinational	Phase 3a, open-label, parallel-group RCT	813	56 weeks
S3	Rodbard et al., 2018	SUSTAIN 5	90 sites; 5 countries	Phase 3a, double-blind, placebo-controlled RCT	397	30 weeks
S4	Pratley et al., 2018	SUSTAIN 7	194 sites; 16 countries	Phase 3b, open-label, parallel-group RCT	1,201	40 weeks
S5	Zinman et al., 2019	SUSTAIN 9	61 centres; 6 countries	Double-blind, parallel-group,	302	30 weeks

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
				placebo-controlled RCT		
S6	Ji et al., 2020	SUSTAIN China	China plus 4 other countries (~70% of participants from China)	Phase 3a, double- blind, double- dummy, active- comparator RCT	868	30 weeks
S7	Aroda et al., 2019	PIONEER 1	93 sites; 9 countries	Phase 3a, double- blind, parallel- group, placebo- controlled RCT	703	26 weeks
S8	Rodbard et al., 2019	PIONEER 2	Multinational	Open-label, active-comparator RCT	822	52 weeks
S9	Pratley et al., 2019	PIONEER 4	100 sites; 12 countries	Phase 3a, double- blind, double- dummy RCT	711	52 weeks
S10	Mosenzon et al., 2019	PIONEER 5	88 sites; 8 countries	Phase 3a, double- blind, placebo- controlled RCT	324	26 weeks
S11	Zinman et al., 2019	PIONEER 8	Multinational	Double-blind, placebo-controlled RCT	731	52 weeks (primary

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
						endpoint at week 26)
S12	Yamada et al., 2020	PIONEER 9	16 sites; Japan	Phase 2/3a, double-blind RCT with an open-label active arm	243	52 weeks (primary endpoint at week 26)
S13	Wang et al., 2024	PIONEER 11	52 sites; China region, Hungary, Serbia, Ukraine	Phase 3a, double-blind, placebo-controlled RCT	521	26 weeks
S14	Davies et al., 2021	STEP 2	149 outpatient clinics; 12 countries	Phase 3, double-blind, double-dummy, superiority RCT	1,210	68 weeks
S15	Lingvay et al., 2025	STEP UP T2D	68 hospitals and specialist clinics; 8 countries	Phase 3b, double-blind, three-arm parallel-group RCT	512	72 weeks
S16	Davies et al., 2015	SCALE Diabetes	126 sites; 9 countries	Double-blind, parallel-group, placebo-controlled RCT (2:1:1)	846	56 weeks (plus 12-week off-drug observation)

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
S17	Garvey et al., 2020	SCALE Insulin	Multinational, multicentre	Double-blind, placebo-controlled RCT	396	56 weeks
S18	Garber et al., 2009	LEAD-3 Mono	Multinational	Phase III, double-blind, double-dummy, active-controlled RCT	746	52 weeks
S19	Russell-Jones et al., 2009	LEAD-5 met+SU	107 centres; 17 countries	Parallel-group RCT; blinded for placebo, open-label for glargine	581	26 weeks
S20	Buse et al., 2009	LEAD-6	15 countries	Open-label, parallel-group, multinational RCT	464	26 weeks
S21	Ahmann et al., 2015	Liraglutide plus basal insulin	Multinational	26-week, double-blind, parallel-group RCT	451	26 weeks
S22	Blonde et al., 2020	LIRA-ADD2SGLT2i	Multinational	Double-blind, parallel-group, placebo-controlled RCT (2:1)	303	26 weeks
S23	Ludvik et al., 2018	AWARD-10	40 clinical sites; 8 countries	Phase 3b, double-blind, parallel-	424	24 weeks

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
				arm, placebo- controlled RCT		
S24	Frias et al., 2021	AWARD-11	Multinational	Phase 3, blinded, parallel-group RCT	1,842	52 weeks (primary endpoint at week 36)
S25	Dungan et al., 2014	AWARD-6	62 sites; 9 countries	Phase 3, open- label, non- inferiority RCT	599	26 weeks (plus 4 weeks safety follow-up)
S26	Nauck et al., 2014	AWARD-5	Multicentre	Adaptive, double- blind, parallel-arm RCT	1,098	104 weeks (primary endpoint at week 52)
S27	Dungan et al., 2016	AWARD-8	Multicentre	Phase III, double- blind, placebo- controlled RCT (4:1)	300	24 weeks
S28	Pozzilli et al., 2017	AWARD-9	Multicentre	Phase III, double- blind, parallel- arm, placebo- controlled RCT	300	28 weeks

ID	Author, year	Trial	Setting and number of centres	Design	n	Duration
S29	Gerstein et al., 2019	REWIND	371 sites; 24 countries	Double-blind, placebo-controlled cardiovascular outcomes RCT	9,901	Median 5.4 years (IQR 5.1-5.9)
S30	Bergenstal et al., 2010	DURATION-2	72 sites; USA, India, Mexico	Double-blind, double-dummy, superiority RCT	491 (ITT)	26 weeks
S31	Buse et al., 2013	DURATION-6	105 sites; 19 countries	Open-label, parallel-group RCT	911 (ITT)	26 weeks
S32	Rosenstock et al., 2025	ACHIEVE-1	Multicentre	Phase 3, double-blind, placebo-controlled RCT	559	40 weeks

Abbreviations: n = number of participants randomised; RCT = randomized controlled trial; QW = once weekly. All studies are peer-reviewed publications verified as retrievable online.

Table 6. Population, intervention and comparator characteristics of included studies

ID	Trial	Intervention	Comparator	Baseline population characteristics
S1	SUSTAIN 1	Semaglutide SC 0.5 mg and 1.0 mg once weekly	Volume-matched placebo	Treatment-naïve T2DM; baseline HbA1c 8.05% (SD 0.85); body weight 91.93 kg (SD 23.83); diet and exercise only

ID	Trial	Intervention	Comparator	Baseline population characteristics
S2	SUSTAIN 3	Semaglutide SC 1.0 mg once weekly	Exenatide extended release 2.0 mg once weekly	T2DM on oral antidiabetic drugs; baseline HbA1c 8.3% (67.7 mmol/mol); body weight 95.8 kg
S3	SUSTAIN 5	Semaglutide SC 0.5 mg and 1.0 mg added to basal insulin	Placebo added to basal insulin	T2DM uncontrolled on basal insulin +/- metformin; baseline HbA1c 8.4% (67.9 mmol/mol)
S4	SUSTAIN 7	Semaglutide SC 0.5 mg and 1.0 mg once weekly	Dulaglutide 0.75 mg and 1.5 mg once weekly	T2DM on metformin monotherapy; inclusion HbA1c 7.0-10.5%
S5	SUSTAIN 9	Semaglutide SC 1.0 mg added to an SGLT-2 inhibitor	Placebo added to an SGLT-2 inhibitor	T2DM inadequately controlled on SGLT-2i for ≥ 90 days; HbA1c 7.0-10.0%; 71.5% on metformin
S6	SUSTAIN China	Semaglutide SC 0.5 mg and 1.0 mg once weekly plus metformin	Sitagliptin 100 mg daily plus metformin	T2DM inadequately controlled on metformin; HbA1c 7.0-10.5%
S7	PIONEER 1	Oral semaglutide 3 mg, 7 mg, 14 mg once daily	Placebo	T2DM managed by diet and exercise alone; mean age 55 years; 50.8% male; HbA1c 8.0% (64 mmol/mol)

ID	Trial	Intervention	Comparator	Baseline population characteristics
S8	PIONEER 2	Oral semaglutide 14 mg once daily	Empagliflozin 25 mg once daily	T2DM uncontrolled on metformin
S9	PIONEER 4	Oral semaglutide 14 mg once daily	Subcutaneous liraglutide 1.8 mg daily and placebo	T2DM on metformin +/- SGLT-2i; HbA1c 7.0-9.5%; mean age 56 years (SD 10); 48% female
S10	PIONEER 5	Oral semaglutide (escalated to 14 mg once daily)	Placebo	T2DM with moderate renal impairment (eGFR 30-59 mL/min/1.73 m ²); mean age 70 years (SD 8); 52% female
S11	PIONEER 8	Oral semaglutide 3 mg, 7 mg, 14 mg added to insulin	Placebo added to insulin	T2DM uncontrolled on insulin +/- metformin
S12	PIONEER 9	Oral semaglutide 3 mg, 7 mg, 14 mg once daily	Placebo and subcutaneous liraglutide 0.9 mg (open label)	Japanese patients aged ≥20 years; baseline HbA1c 8.2%; diet/exercise or OAD monotherapy (washed out)
S13	PIONEER 11	Oral semaglutide 3 mg, 7 mg, 14 mg once daily	Placebo	T2DM not receiving glucose-lowering drugs; 63.7% male; mean age 52 years; HbA1c 8.0% (63 mmol/mol); body weight 79.6 kg
S14	STEP 2	Semaglutide SC 2.4 mg once weekly plus lifestyle intervention	Semaglutide 1.0 mg and placebo	T2DM with BMI ≥27 kg/m ² ; HbA1c 7-10% (53-86

ID	Trial	Intervention	Comparator	Baseline population characteristics
				mmol/mol); T2DM diagnosed ≥ 180 days before screening
S15	STEP UP T2D	Semaglutide SC 7.2 mg once weekly plus lifestyle intervention	Semaglutide 2.4 mg and placebo	Obesity (BMI ≥ 30) with T2DM; 51.8% female; age 56 (SD 10) years; weight 110.1 (22.9) kg; BMI 38.6 (7.1); HbA1c 8.1% (0.9)
S16	SCALE Diabetes	Liraglutide SC 3.0 mg and 1.8 mg once daily	Placebo; all arms received a 500 kcal/day deficit and ≥ 150 min/week physical activity	T2DM with BMI ≥ 27 kg/m ² ; HbA1c 7.0-10.0%; 0-3 oral hypoglycaemic agents; baseline weight 105.7-106.5 kg
S17	SCALE Insulin	Liraglutide SC 3.0 mg plus intensive behavioural therapy	Placebo plus intensive behavioural therapy	Overweight/obesity with T2DM treated with basal insulin and ≤ 2 oral antidiabetic drugs
S18	LEAD-3 Mono	Liraglutide SC 1.2 mg and 1.8 mg once daily (monotherapy)	Glimepiride 8 mg daily	Early T2DM without prior advanced pharmacological therapy
S19	LEAD-5 met+SU	Liraglutide SC 1.8 mg plus metformin and glimepiride	Placebo and insulin glargine, both plus metformin and glimepiride	T2DM with HbA1c 7.0-10.0% (combination therapy) or 7.5-10% (prior monotherapy)

ID	Trial	Intervention	Comparator	Baseline population characteristics
S20	LEAD-6	Liraglutide SC 1.8 mg once daily	Exenatide 10 mcg twice daily	T2DM inadequately controlled on metformin, sulphonylurea, or both; baseline HbA1c 8.2%
S21	Liraglutide plus basal insulin	Liraglutide SC 1.8 mg plus basal insulin analogue +/- metformin	Placebo plus basal insulin analogue +/- metformin	T2DM inadequately controlled (HbA1c 7.0-10.0%) on basal insulin ≥ 20 U/day
S22	LIRA-ADD2SGLT2i	Liraglutide SC 1.8 mg/day plus SGLT-2i +/- metformin	Placebo plus SGLT-2i +/- metformin	T2DM with HbA1c 7.0-9.5% and BMI ≥ 20 kg/m ² on a stable SGLT-2i dose
S23	AWARD-10	Dulaglutide 1.5 mg and 0.75 mg once weekly added to SGLT-2i	Placebo added to SGLT-2i	Inadequately controlled T2DM (HbA1c 7.0-9.5%), BMI ≤ 45 kg/m ² , stable SGLT-2i > 3 months +/- metformin
S24	AWARD-11	Dulaglutide 3.0 mg and 4.5 mg once weekly	Dulaglutide 1.5 mg once weekly	T2DM inadequately controlled on metformin; age 57.1 years; HbA1c 8.6% (70 mmol/mol); weight 95.7 kg; BMI 34.2 kg/m ²
S25	AWARD-6	Dulaglutide 1.5 mg once weekly	Liraglutide 1.8 mg once daily	T2DM inadequately controlled on metformin $\geq 1,500$ mg/day; HbA1c 7.0-10.0%; BMI ≤ 45 kg/m ²

ID	Trial	Intervention	Comparator	Baseline population characteristics
S26	AWARD-5	Dulaglutide 1.5 mg and 0.75 mg once weekly plus metformin	Sitagliptin 100 mg daily and placebo (placebo-controlled period up to week 26)	T2DM uncontrolled on metformin; age 54 years; HbA1c 8.1%; weight 86.4 kg; diabetes duration 7 years
S27	AWARD-8	Dulaglutide 1.5 mg once weekly added to glimepiride	Placebo added to glimepiride	T2DM on sulphonylurea monotherapy; HbA1c 7.5-9.5%; age 58 years; weight 85.5 kg
S28	AWARD-9	Dulaglutide 1.5 mg once weekly plus titrated insulin glargine +/- metformin	Placebo plus titrated insulin glargine +/- metformin	T2DM with suboptimal control; baseline glargine dose 39 +/- 22 U/day
S29	REWIND	Dulaglutide 1.5 mg once weekly	Placebo	T2DM aged ≥ 50 years with previous cardiovascular event or risk factors; age 66.2 years (SD 6.5); median HbA1c 7.2% (IQR 6.6-8.1); 46.3% female
S30	DURATION-2	Exenatide 2 mg once weekly plus metformin	Sitagliptin 100 mg daily or pioglitazone 45 mg daily plus metformin	T2DM on metformin; HbA1c 8.5% (SD 1.1); fasting plasma glucose 9.1 mmol/L (2.6); weight 88.0 kg (20.1)

ID	Trial	Intervention	Comparator	Baseline population characteristics
S31	DURATION-6	Exenatide 2 mg once weekly	Liraglutide 1.8 mg once daily	T2DM treated with lifestyle modification and oral antihyperglycaemic drugs
S32	ACHIEVE-1	Oral orforglipron 3 mg, 12 mg, 36 mg once daily	Placebo	Early T2DM treated with diet and exercise only; HbA1c 7.0-9.5% (mean 8.0%); BMI $\geq$ 23 kg/m ²

Abbreviations: SC = subcutaneous; ER = extended release; OAD = oral antidiabetic drug; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; BMI = body mass index; eGFR = estimated glomerular filtration rate.

Outcome Synthesis

Change in HbA1c

Change in HbA1c was reported as a primary outcome in 30 of the 32 studies. Against placebo, every trial without exception demonstrated superiority of the GLP-1 receptor agonist, with p values consistently below 0.001. The magnitude of the estimated treatment difference (ETD) versus placebo ranged from -0.5% for the lowest dose of oral semaglutide 3 mg added to insulin, to -1.75% for subcutaneous semaglutide 1.0 mg added to basal insulin. This range exceeds the threshold generally regarded as the minimal clinically important difference in T2DM management.^{22,24,26,28,32}

The largest placebo-controlled effect was observed in SUSTAIN 5, with an ETD of -1.75% (95% CI -2.01 to -1.50) for semaglutide 1.0 mg, followed by SUSTAIN 1 with an ETD of -1.53% (95% CI -1.81 to -1.25) and SUSTAIN 9 with an ETD of -1.42% (95% CI -1.61 to -1.24). Among oral semaglutide trials, PIONEER 9 in a Japanese population recorded an ETD of up to -1.7 percentage points and PIONEER 11 in a predominantly Chinese population recorded an ETD of up to -1.5 percentage points (95% CI -1.8 to -1.3), indicating that the magnitude of effect in Asian populations is comparable to, or even greater than, that in multinational populations.^{24,26,33,34}

Against active comparators, GLP-1 receptor agonists also demonstrated consistent superiority. Oral semaglutide 14 mg was superior to empagliflozin 25 mg (ETD -0.4%; 95% CI -0.6 to -0.3) and non-inferior to subcutaneous liraglutide 1.8 mg. Dulaglutide was superior to sitagliptin (-1.10% versus -0.39%), and once-weekly exenatide was superior to sitagliptin (difference -0.6%) and to pioglitazone (difference -0.3%). Liraglutide was superior to glimepiride (ETD -0.62% at the 1.8 mg dose) and to insulin glargine (difference -0.24%).^{29,30,39,40,47,51}

Head-to-head comparisons revealed an intra-class efficacy hierarchy. Semaglutide 1.0 mg weekly was superior to exenatide extended release 2.0 mg (ETD -0.62%; 95% CI -0.80 to -0.44) and to dulaglutide 1.5 mg (ETD -0.41%; 95% CI -0.57 to -0.25). Liraglutide 1.8 mg was superior to exenatide 10 micrograms twice daily (ETD -0.33%; 95% CI -0.47 to -0.18) and to once-weekly exenatide in DURATION-6 (difference 0.21%; 95% CI 0.08 to 0.33 favouring liraglutide). Dulaglutide 1.5 mg was non-inferior to liraglutide 1.8 mg (difference -0.06%; 95% CI -0.19 to 0.07).^{23,25,41,46,52}

A dose-response relationship was consistently demonstrated for every molecule evaluated across multiple dose levels. In PIONEER 1, the ETD increased progressively from -0.6% (3 mg) to -0.9% (7 mg) and -1.1% (14 mg). In AWARD-11, escalation of dulaglutide from 1.5 mg to 4.5 mg conferred an additional ETD of -0.24% (treatment-regimen estimand). In ACHIEVE-1, orforglipron produced ETDs of -0.83 to -1.07 percentage points with a relative plateau between the 12 mg and 36 mg doses, and end-of-trial HbA1c values of 6.5-6.7%.^{28,45,53}

Table 4. Change in HbA1c from baseline across all included studies

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S1	Sorli 2017 (SUSTAIN 1)	Semaglutide 0.5 mg vs placebo	ETD -1.43% (-1.71 to -1.15)	<0.0001
S1	Sorli 2017 (SUSTAIN 1)	Semaglutide 1.0 mg vs placebo	ETD -1.53% (-1.81 to -1.25)	<0.0001
S2	Ahmann 2017 (SUSTAIN 3)	Semaglutide 1.0 mg vs exenatide ER	ETD -0.62% (-0.80 to -0.44)	<0.0001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S3	Rodbard 2018 (SUSTAIN 5)	Semaglutide 0.5 mg vs placebo	ETD -1.35% (-1.61 to -1.10)	<0.0001
S3	Rodbard 2018 (SUSTAIN 5)	Semaglutide 1.0 mg vs placebo	ETD -1.75% (-2.01 to -1.50)	<0.0001
S4	Pratley 2018 (SUSTAIN 7)	Semaglutide 0.5 mg vs dulaglutide 0.75 mg	ETD -0.40% (-0.55 to -0.25)	<0.0001
S4	Pratley 2018 (SUSTAIN 7)	Semaglutide 1.0 mg vs dulaglutide 1.5 mg	ETD -0.41% (-0.57 to -0.25)	<0.0001
S5	Zinman 2019 (SUSTAIN 9)	Semaglutide 1.0 mg + SGLT-2i vs placebo	ETD -1.42% (-1.61 to -1.24)	<0.0001
S6	Ji 2020 (SUSTAIN China)	Semaglutide 0.5 and 1.0 mg vs sitagliptin	Superior at both doses (ETD magnitude not detailed)	<0.001
S7	Aroda 2019 (PIONEER 1)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -0.6% / -0.9% / -1.1%	<0.001
S8	Rodbard 2019 (PIONEER 2)	Oral semaglutide 14 mg vs empagliflozin 25 mg	ETD -0.4% (-0.6 to -0.3)	<0.0001
S9	Pratley 2019 (PIONEER 4)	Oral semaglutide 14 mg vs placebo	ETD -1.1% (-1.2 to -0.9)	<0.0001
S9	Pratley 2019 (PIONEER 4)	Oral semaglutide 14 mg vs liraglutide 1.8 mg	ETD -0.1% (-0.3 to 0.0); non-inferior	<0.0001
S10	Mosenzon 2019 (PIONEER 5)	Oral semaglutide 14 mg vs placebo	ETD -0.8 percentage points (-1.0 to -0.6)	<0.0001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S11	Zinman 2019 (PIONEER 8)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -0.5% (-0.7 to -0.3) / -0.9% (-1.1 to -0.7) / -1.2% (-1.4 to -1.0)	<0.001
S12	Yamada 2020 (PIONEER 9)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -1.1 / -1.5 / -1.7 percentage points	<0.0001
S13	Wang 2024 (PIONEER 11)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -1.0 (-1.2 to -0.8) / -1.4 (-1.6 to -1.2) / -1.5 (-1.8 to -1.3) percentage points	<0.001
S14	Davies 2021 (STEP 2)	Semaglutide 2.4 mg vs placebo	HbA1c not a co-primary endpoint; improvement reported	NR
S15	Lingvay 2025 (STEP UP T2D)	Semaglutide 7.2 mg vs placebo	ETD -1.5% (-1.8 to -1.2)	<0.0001
S17	Garvey 2020 (SCALE Insulin)	Liraglutide 3.0 mg vs placebo	Significantly greater HbA1c reduction (magnitude not detailed)	<0.05
S18	Garber 2009 (LEAD-3)	Liraglutide 1.2 mg vs glimepiride	ETD -0.33% (-0.53 to -0.13)	0.0014
S18	Garber 2009 (LEAD-3)	Liraglutide 1.8 mg vs glimepiride	ETD -0.62% (-0.83 to -0.42)	<0.0001
S19	Russell-Jones 2009 (LEAD-5)	Liraglutide 1.8 mg vs placebo	Difference -1.09% (0.90 to 1.28)	<0.0001
S19	Russell-Jones 2009 (LEAD-5)	Liraglutide 1.8 mg vs insulin glargine	Difference -0.24% (0.08 to 0.39)	0.0015

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S20	Buse 2009 (LEAD-6)	Liraglutide 1.8 mg vs exenatide 10 mcg twice daily	ETD -0.33% (-0.47 to -0.18)	<0.0001
S21	Ahmann 2015	Liraglutide 1.8 mg + basal insulin vs placebo	-1.3% vs -0.1%	<0.0001
S22	Blonde 2020 (LIRA- ADD2SGLT2i)	Liraglutide 1.8 mg + SGLT-2i vs placebo	ETD -0.68% (-0.89 to -0.48)	<0.001
S23	Ludvik 2018 (AWARD-10)	Dulaglutide 1.5 mg + SGLT-2i vs placebo	ETD -0.79% (-0.97 to -0.61)	<0.0001
S23	Ludvik 2018 (AWARD-10)	Dulaglutide 0.75 mg + SGLT-2i vs placebo	ETD -0.66% (-0.84 to -0.49)	<0.0001
S24	Frias 2021 (AWARD-11)	Dulaglutide 4.5 mg vs 1.5 mg	ETD -0.24% (treatment-regimen estimand)	<0.001
S24	Frias 2021 (AWARD-11)	Dulaglutide 3.0 mg vs 1.5 mg	ETD -0.17% (efficacy estimand)	0.003
S25	Dungan 2014 (AWARD-6)	Dulaglutide 1.5 mg vs liraglutide 1.8 mg	Difference -0.06% (-0.19 to 0.07); non-inferior	<0.0001
S26	Nauck 2014 (AWARD-5)	Dulaglutide 1.5 and 0.75 mg vs sitagliptin	-1.10% and -0.87% vs -0.39%; superior	<0.001
S27	Dungan 2016 (AWARD-8)	Dulaglutide 1.5 mg + glimepiride vs placebo	Difference -1.3% (-1.6 to -1.0)	<0.001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S28	Pozzilli 2017 (AWARD-9)	Dulaglutide 1.5 mg + glargine vs placebo + glargine	Difference -0.77% (-0.97 to - 0.56)	<0.001
S30	Bergenstal 2010 (DURATION-2)	Exenatide QW vs sitagliptin	Difference -0.6% (-0.9 to -0.4)	<0.0001
S30	Bergenstal 2010 (DURATION-2)	Exenatide QW vs pioglitazone	Difference -0.3% (-0.6 to -0.1)	0.0165
S31	Buse 2013 (DURATION-6)	Exenatide QW vs liraglutide 1.8 mg	Difference 0.21% (0.08 to 0.33) favouring liraglutide	NR
S32	Rosenstock 2025 (ACHIEVE-1)	Orforglipron 3 / 12 / 36 mg vs placebo	ETD -0.83 (-1.10 to -0.56) / -1.06 (-1.33 to -0.79) / -1.07 (-1.33 to - 0.81) percentage points	<0.001

Abbreviations: ETD = estimated treatment difference; NR = not reported in the extracted report.

Negative values indicate an advantage for the GLP-1 receptor agonist.

Attainment of HbA1c Targets <7.0% and ≤6.5%

Eleven studies reported the proportion of participants attaining categorical glycaemic targets. The advantage of GLP-1 receptor agonists was most striking in placebo-controlled comparisons. In the trial of liraglutide added to basal insulin, 59% of participants attained HbA1c <7.0% compared with 14% on placebo, and 43% attained HbA1c ≤6.5% compared with only 4% on placebo (both $p<0.0001$). In LIRA-ADD2SGLT2i, 51.8% of liraglutide-treated participants attained HbA1c <7.0% versus 23.2% on placebo, with an odds ratio of 5.1 (95% CI 2.67 to 9.87).^{42,43}

Against active comparators the advantage persisted, albeit of more moderate magnitude. Semaglutide 1.0 mg enabled 67% of participants to attain HbA1c <7.0% compared with 40% on exenatide extended release. Liraglutide enabled 54% to attain the target compared with 43% on twice-daily exenatide, with an odds ratio of 2.02 (95% CI 1.31 to 3.11; $p=0.0015$). In AWARD-8,

dulaglutide added to glimepiride achieved target attainment in 55.3% of participants versus 18.9% on placebo.^{23,41,48}

Table 5. Proportion attaining HbA1c targets

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S2	Ahmann 2017 (SUSTAIN 3)	HbA1c <7.0%	Semaglutide 1.0 mg 67% vs exenatide ER 40%	<0.05
S6	Ji 2020 (SUSTAIN China)	HbA1c <7.0% (53 mmol/mol)	Significantly higher odds with both semaglutide doses vs sitagliptin	<0.05
S20	Buse 2009 (LEAD-6)	HbA1c <7.0%	Liraglutide 54% vs exenatide 43%; OR 2.02 (1.31 to 3.11)	0.0015
S21	Ahmann 2015	HbA1c <7.0%	Liraglutide 59% vs placebo 14%	<0.0001
S21	Ahmann 2015	HbA1c ≤6.5%	Liraglutide 43% vs placebo 4%	<0.0001
S22	Blonde 2020 (LIRA- ADD2SGLT2i)	HbA1c <7.0%	Liraglutide 51.8% vs placebo 23.2%; OR 5.1 (2.67 to 9.87)	<0.001
S26	Nauck 2014 (AWARD-5)	HbA1c <7.0% and ≤6.5%	Greater proportions with dulaglutide 1.5 and 0.75 mg vs sitagliptin	<0.05
S27	Dungan 2016 (AWARD-8)	HbA1c <7.0%	Dulaglutide 55.3% vs placebo 18.9%	<0.001
S32	Rosenstock 2025 (ACHIEVE-1)	End-of-trial HbA1c	6.5-6.7% across all orforglipron doses	NR

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S30	Bergental 2010 (DURATION-2)	Attainment of glycaemic targets	More frequent with exenatide QW than sitagliptin or pioglitazone	<0.05

Absolute Change in Body Weight

Twenty-six comparisons from 20 studies reported absolute weight change. Against placebo, additional weight reduction ranged from -0.9 kg to -5.06 kg. The greatest effect was achieved with subcutaneous semaglutide 1.0 mg added to basal insulin (ETD -5.06 kg; 95% CI -6.08 to -4.04) and semaglutide 1.0 mg added to an SGLT-2 inhibitor (ETD -3.81 kg; 95% CI -4.70 to -2.93). Oral semaglutide 14 mg produced an ETD of -3.8 kg versus placebo in PIONEER 4 and -3.3 kg in PIONEER 8.^{24,26,30,32}

The dose-response relationship for weight was even more pronounced than for HbA1c. In PIONEER 1, additional weight reduction increased from -0.1 kg (3 mg) to -0.9 kg (7 mg) and -2.3 kg (14 mg). In PIONEER 11, the 3 mg dose produced no significant weight reduction (ETD -0.0 kg; 95% CI -0.9 to 0.8), whereas the 7 mg and 14 mg doses produced ETDs of -1.2 kg and -2.0 kg respectively. These findings indicate that the dose threshold for the weight effect is higher than that for the glycaemic effect, an observation with direct implications for titration strategy.^{28,34}

In head-to-head comparisons, semaglutide 1.0 mg produced a weight reduction of 5.6 kg versus 1.9 kg with exenatide extended release (ETD -3.78 kg; 95% CI -4.58 to -2.98) and 6.5 kg versus 3.0 kg with dulaglutide 1.5 mg (ETD -3.55 kg; 95% CI -4.32 to -2.78). Oral semaglutide 14 mg was superior to subcutaneous liraglutide 1.8 mg with an ETD of -1.2 kg (95% CI -1.9 to -0.6; p=0.0003). Once-weekly exenatide produced a 2.3 kg reduction versus weight gain with pioglitazone, a difference of -5.1 kg (95% CI -5.9 to -4.3).^{23,25,30,51}

Against insulin, the weight advantage is twofold because insulin itself promotes weight gain. In LEAD-5, liraglutide was superior by -3.43 kg compared with insulin glargine (p<0.0001), and in AWARD-9 dulaglutide added to glargine produced a difference of -2.41 kg versus placebo with glargine, with weight falling in the dulaglutide arm and rising in the placebo arm.^{40,49}

Table 6. Absolute change in body weight (kilograms)

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S1	Sorli 2017 (SUSTAIN 1)	Semaglutide 0.5 / 1.0 mg vs placebo	ETD -2.75 kg (-3.92 to -1.58) / -3.56 kg (-4.74 to -2.38)	<0.0001
S2	Ahmann 2017 (SUSTAIN 3)	Semaglutide 1.0 mg vs exenatide ER	-5.6 vs -1.9 kg; ETD -3.78 kg (-4.58 to -2.98)	<0.0001
S3	Rodbard 2018 (SUSTAIN 5)	Semaglutide 0.5 / 1.0 mg vs placebo	ETD -2.31 kg (-3.33 to -1.29) / -5.06 kg (-6.08 to -4.04)	<0.0001
S4	Pratley 2018 (SUSTAIN 7)	Semaglutide 0.5 vs dulaglutide 0.75 mg	-4.6 vs -2.3 kg; ETD -2.26 kg (-3.02 to -1.51)	<0.0001
S4	Pratley 2018 (SUSTAIN 7)	Semaglutide 1.0 vs dulaglutide 1.5 mg	-6.5 vs -3.0 kg; ETD -3.55 kg (-4.32 to -2.78)	<0.0001
S5	Zinman 2019 (SUSTAIN 9)	Semaglutide 1.0 mg + SGLT-2i vs placebo	ETD -3.81 kg (-4.70 to -2.93)	<0.0001
S7	Aroda 2019 (PIONEER 1)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -0.1 / -0.9 / -2.3 kg	<0.001 (14 mg)
S8	Rodbard 2019 (PIONEER 2)	Oral semaglutide 14 mg vs empagliflozin (week 52)	-4.7 vs -3.8 kg	0.0114
S9	Pratley 2019 (PIONEER 4)	Oral semaglutide 14 mg vs placebo	-4.4 vs -0.5 kg; ETD -3.8 kg (-4.7 to -3.0)	<0.0001
S9	Pratley 2019 (PIONEER 4)	Oral semaglutide 14 mg vs liraglutide 1.8 mg	-4.4 vs -3.1 kg; ETD -1.2 kg (-1.9 to -0.6)	0.0003
S10	Mosenzon 2019 (PIONEER 5)	Oral semaglutide 14 mg vs placebo	-3.4 vs -0.9 kg; ETD -2.5 kg (-3.2 to -1.8)	<0.0001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S11	Zinman 2019 (PIONEER 8)	Oral semaglutide 3 / 7 / 14 mg vs placebo	ETD -0.9 kg (-1.8 to 0.0) / -2.0 kg (-3.0 to -1.0) / -3.3 kg (-4.2 to - 2.3)	0.039 / <=0.0001
S13	Wang 2024 (PIONEER 11)	Oral semaglutide 7 / 14 mg vs placebo	ETD -1.2 kg (-2.0 to -0.4) / -2.0 kg (-2.8 to -1.2)	<0.01 / <0.001
S13	Wang 2024 (PIONEER 11)	Oral semaglutide 3 mg vs placebo	ETD -0.0 kg (-0.9 to 0.8)	Not significant
S16	Davies 2015 (SCALE Diabetes)	Liraglutide 3.0 / 1.8 mg vs placebo	-6.4 kg / -5.0 kg vs -2.2 kg	<0.001
S19	Russell-Jones 2009 (LEAD-5)	Liraglutide 1.8 mg vs placebo	Difference -1.39 kg (2.10 to 0.69)	0.0001
S19	Russell-Jones 2009 (LEAD-5)	Liraglutide 1.8 mg vs insulin glargine	Difference -3.43 kg (4.00 to 2.86)	<0.0001
S20	Buse 2009 (LEAD-6)	Liraglutide vs exenatide	-3.24 vs -2.87 kg (similar)	Not significant
S21	Ahmann 2015	Liraglutide + basal insulin vs placebo	ETD -3.1 kg	<0.0001
S22	Blonde 2020 (LIRA- ADD2SGLT2i)	Liraglutide + SGLT-2i vs placebo	-2.81 vs -1.99 kg; ETD -0.82 kg (-1.73 to 0.09)	0.077
S24	Frias 2021 (AWARD-11)	Dulaglutide 4.5 mg vs 1.5 mg (week 36)	-4.6 vs -3.0 kg; ETD -1.6 kg	<0.001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S26	Nauck 2014 (AWARD-5)	Dulaglutide 1.5 / 0.75 mg vs sitagliptin	-3.03 / -2.60 kg vs -1.53 kg	<0.001
S27	Dungan 2016 (AWARD-8)	Dulaglutide + glimepiride vs placebo	Significant within-group reduction with dulaglutide; between-group difference not significant	<0.001 (within group)
S28	Pozzilli 2017 (AWARD-9)	Dulaglutide + glargine vs placebo + glargine	ETD -2.41 kg (SE 0.39)	<0.001
S30	Bergenstal 2010 (DURATION-2)	Exenatide QW vs sitagliptin	-2.3 kg; difference -1.5 kg (-2.4 to -0.7)	0.0002
S30	Bergenstal 2010 (DURATION-2)	Exenatide QW vs pioglitazone	Difference -5.1 kg (-5.9 to -4.3)	<0.0001

Relative Change in Body Weight

Six trials specifically designed for weight management reported relative change as a co-primary outcome. The effect sizes in these studies far exceeded those observed with conventional glycaemic doses, reflecting a strong dose-response relationship. Once-weekly semaglutide 2.4 mg reduced body weight by 9.6% versus 3.4% with placebo, with an ETD of -6.2 percentage points (95% CI -7.3 to -5.2; $p<0.0001$) in participants with T2DM and BMI ≥ 27 kg/m².³⁵

Further dose escalation conferred a substantial additional effect. In STEP UP T2D, once-weekly semaglutide 7.2 mg reduced body weight by 13.2% versus 3.9% with placebo, with an ETD of -9.3% (95% CI -11.0 to -7.7; $p<0.0001$), accompanied by an HbA1c ETD of -1.5% (95% CI -1.8 to -1.2). This is the largest magnitude among all included selective GLP-1 agonist trials and approaches effects historically achievable only through metabolic surgery.³⁶

Liraglutide at the obesity dose of 3.0 mg reduced body weight by 6.0% versus 2.0% with placebo (ETD -4.00%; 95% CI -5.10 to -2.90), while the 1.8 mg dose produced a 4.7% reduction

(ETD -2.71%; 95% CI -4.00 to -1.42). In insulin-treated participants, liraglutide 3.0 mg remained effective with a 5.8% reduction versus 1.5% on placebo (ETD -4.3%; 95% CI -5.5 to -3.2), an important finding because insulin pharmacologically promotes weight gain. Oral orforglipron produced dose-dependent reductions of up to 7.6% at the 36 mg dose.^{37,38,53}

Table 7. Relative change in body weight (percentage)

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S14	Davies 2021 (STEP 2)	Semaglutide 2.4 mg vs placebo	-9.6% vs -3.4%; ETD -6.2 percentage points (-7.3 to -5.2)	<0.0001
S15	Lingvay 2025 (STEP UP T2D)	Semaglutide 7.2 mg vs placebo	-13.2% vs -3.9%; ETD -9.3% (-11.0 to -7.7)	<0.0001
S16	Davies 2015 (SCALE Diabetes)	Liraglutide 3.0 mg vs placebo	-6.0% vs -2.0%; ETD -4.00% (-5.10 to -2.90)	<0.001
S16	Davies 2015 (SCALE Diabetes)	Liraglutide 1.8 mg vs placebo	-4.7% vs -2.0%; ETD -2.71% (-4.00 to -1.42)	<0.001
S17	Garvey 2020 (SCALE Insulin)	Liraglutide 3.0 mg vs placebo	-5.8% vs -1.5%; ETD -4.3% (-5.5 to -3.2)	<0.0001
S32	Rosenstock 2025 (ACHIEVE-1)	Orforglipron 3 / 12 / 36 mg vs placebo	-4.5% / -5.8% / -7.6% vs -1.7%	<0.001

Attainment of Weight Reduction Thresholds

Categorical analysis provides a more clinically meaningful picture than group means, since weight reduction of $\geq 5\%$ is the minimum threshold associated with meaningful improvement in metabolic comorbidities. In STEP 2, 68.8% of participants in the semaglutide 2.4 mg arm achieved a

$\geq 5\%$ reduction versus 28.5% on placebo, with an odds ratio of 4.88 (95% CI 3.58 to 6.64; $p < 0.0001$).³⁵

STEP UP T2D demonstrated a striking gradient of odds ratios across all thresholds: 10.0 (95% CI 6.0 to 16.9) for $\geq 5\%$, 11.3 (95% CI 5.9 to 21.4) for $\geq 10\%$, 8.1 (95% CI 3.7 to 17.7) for $\geq 15\%$, and 12.3 (95% CI 3.0 to 51.0) for $\geq 20\%$ (all $p \leq 0.0006$). Attainment of $\geq 20\%$ weight reduction in a T2DM population is a finding that has historically not been reported with pharmacological glucose-lowering therapy.³⁶

In SCALE Diabetes, liraglutide 3.0 mg enabled 54.3% of participants to achieve a $\geq 5\%$ reduction and 25.2% to achieve a $\geq 10\%$ reduction, versus 21.4% and 6.7% respectively on placebo. In SCALE Insulin, 51.8% of liraglutide-treated participants achieved a $\geq 5\%$ reduction versus 24.0% on placebo, with an odds ratio of 3.41 (95% CI 2.19 to 5.31).^{37,38}

Table 8. Attainment of weight reduction thresholds

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S14	Davies 2021 (STEP 2)	Weight reduction $\geq 5\%$	Semaglutide 2.4 mg 68.8% vs placebo 28.5%; OR 4.88 (3.58 to 6.64)	<0.0001
S15	Lingvay 2025 (STEP UP T2D)	Weight reduction $\geq 5\%$	OR 10.0 (6.0 to 16.9)	<0.0001
S15	Lingvay 2025 (STEP UP T2D)	Weight reduction $\geq 10\%$	OR 11.3 (5.9 to 21.4)	<0.0001
S15	Lingvay 2025 (STEP UP T2D)	Weight reduction $\geq 15\%$	OR 8.1 (3.7 to 17.7)	<0.0001
S15	Lingvay 2025 (STEP UP T2D)	Weight reduction $\geq 20\%$	OR 12.3 (3.0 to 51.0)	0.0006

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S16	Davies 2015 (SCALE Diabetes)	Weight reduction $\geq 5\%$	Liraglutide 3.0 mg 54.3%; 1.8 mg 40.4% vs placebo 21.4%	<0.001
S16	Davies 2015 (SCALE Diabetes)	Weight reduction $>10\%$	Liraglutide 3.0 mg 25.2%; 1.8 mg 15.9% vs placebo 6.7%	<0.001 / 0.006
S17	Garvey 2020 (SCALE Insulin)	Weight reduction $\geq 5\%$	Liraglutide 3.0 mg 51.8% vs placebo 24.0%; OR 3.41 (2.19 to 5.31)	<0.0001
S6	Ji 2020 (SUSTAIN China)	Weight reduction $\geq 5\%$ and $\geq 10\%$	Significantly higher odds with both semaglutide doses vs sitagliptin	<0.05

Fasting Plasma Glucose

Improvement in fasting plasma glucose (FPG) paralleled the HbA1c response and reflects the glucagonostatic and insulinotropic actions of long-acting agonists. In LEAD-6, liraglutide reduced FPG by 1.61 mmol/L versus 0.60 mmol/L with twice-daily exenatide, an ETD of -1.01 mmol/L (95% CI -1.37 to -0.65; $p<0.0001$); this pattern is consistent with the concept that long-acting agonists exert a dominant effect on fasting glucose whereas short-acting agonists act preferentially on postprandial glucose.^{10,41}

On a sulphonylurea background, dulaglutide significantly reduced FPG with a between-group difference of -1.86 mmol/L, or -33.54 mg/dL, versus placebo (95% CI -2.58 to -1.14; $p<0.001$). On a basal insulin background, liraglutide produced an FPG ETD of -1.3 mmol/L versus placebo ($p<0.0001$), accompanied by a reduction of -1.6 mmol/L in the seven-point glucose profile.^{42,48}

Table 9. Change in fasting plasma glucose

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S20	Buse 2009 (LEAD-6)	Liraglutide vs exenatide	-1.61 vs -0.60 mmol/L; ETD -1.01 mmol/L (-1.37 to -0.65)	<0.0001
S21	Ahmann 2015	Liraglutide + basal insulin vs placebo	ETD -1.3 mmol/L	<0.0001
S27	Dungan 2016 (AWARD-8)	Dulaglutide + glimepiride vs placebo	Difference -1.86 mmol/L (-2.58 to -1.14), i.e. -33.54 mg/dL	<0.001
S30	Bergental 2010 (DURATION-2)	Exenatide QW (baseline FPG 9.1 mmol/L)	Greater FPG reduction than oral comparators	<0.05
S32	Rosenstock 2025 (ACHIEVE-1)	Orforglipron vs placebo	Fasting glycaemic improvement consistent with HbA1c reduction	NR
S12	Yamada 2020 (PIONEER 9)	Oral semaglutide vs placebo	Fasting glucose reduction paralleled the dose-dependent HbA1c effect	NR

Anthropometric Parameters

Waist circumference, a marker of visceral adiposity, was reported as a confirmatory secondary endpoint in STEP UP T2D, with an ETD of -6.5 cm (95% CI -9.0 to -4.1; $p < 0.0001$) for semaglutide 7.2 mg versus placebo. This magnitude is clinically important because visceral adiposity correlates more strongly with insulin resistance and cardiovascular risk than total body weight.³⁶

Subgroup analysis in AWARD-11 showed that absolute weight reduction increased with higher baseline BMI category, whereas the percentage weight reduction was similar across BMI subgroups. This indicates that the proportional effect of GLP-1 receptor agonists is consistent irrespective of baseline degree of obesity, an important consideration for Asian populations, which typically exhibit lower mean BMI yet relatively high visceral adiposity.⁴⁵

Table 10. Anthropometric parameters

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S15	Lingvay 2025 (STEP UP T2D)	Waist circumference	ETD -6.5 cm (-9.0 to -4.1)	<0.0001
S24	Frias 2021 (AWARD-11)	Baseline BMI 34.2 kg/m ²	Dose-dependent weight reduction across all BMI subgroups	<0.001
S14	Davies 2021 (STEP 2)	BMI ≥27 kg/m ²	9.6% relative weight reduction with semaglutide 2.4 mg	<0.0001
S16	Davies 2015 (SCALE Diabetes)	Baseline weight 105.7- 106.5 kg	Absolute reduction up to 6.4 kg with liraglutide 3.0 mg	<0.001

Systolic Blood Pressure

Reduction in systolic blood pressure is a consistent accompanying effect of GLP-1 receptor agonist therapy. In LEAD-5, liraglutide reduced systolic blood pressure by 4.0 mmHg whereas insulin glargine increased it by 0.5 mmHg, producing a difference of -4.5 mmHg (95% CI -6.8 to -2.2; p=0.0001); however, the difference versus placebo in the same trial did not reach statistical significance (p=0.0791).⁴⁰

On a basal insulin background, liraglutide produced a systolic blood pressure ETD of -5.0 mmHg versus placebo (p<0.0001), accompanied by a pulse increase of 4.5 beats per minute, a recognised class effect. In LEAD-3, liraglutide likewise produced greater blood pressure reduction than glimepiride. A systolic blood pressure reduction of approximately 4-5 mmHg is epidemiologically equivalent to a meaningful reduction in cardiovascular risk in diabetic populations.^{39,42}

Table 11. Change in systolic blood pressure

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S19	Russell-Jones 2009 (LEAD-5)	SBP: liraglutide vs insulin glargine	-4.0 mmHg vs +0.5 mmHg; difference -4.5 mmHg (-6.8 to -2.2)	0.0001
S19	Russell-Jones 2009 (LEAD-5)	SBP: liraglutide vs placebo	Difference not statistically significant	0.0791
S21	Ahmann 2015	SBP: liraglutide + basal insulin vs placebo	ETD -5.0 mmHg	<0.0001
S18	Garber 2009 (LEAD-3)	SBP: liraglutide vs glimepiride	Greater blood pressure reduction with liraglutide	<0.05

Lipid Profile and Cardiometabolic Risk Markers

Lipid profile data were reported inconsistently across the included studies, precluding quantitative synthesis. Supporting evidence from related trials indicates that GLP-1 receptor agonist therapy is accompanied by improvement in cardiovascular risk markers. In a randomized trial of dulaglutide versus conventional therapy, the dulaglutide group demonstrated lower total cholesterol, LDL cholesterol, diastolic blood pressure, BMI and pulse wave velocity, and a higher reactive hyperaemia index, at the nine-month assessment.⁶⁵

Biomarker analyses within the orforglipron programme found significant placebo-adjusted reductions in blood pressure, LDL cholesterol, triglycerides, apolipoprotein B, apolipoprotein C3 and high-sensitivity C-reactive protein in participants with T2DM and/or overweight. These improvements were already apparent at the 12 mg dose and of similar magnitude at higher doses, indicating that cardiometabolic benefit does not track entirely in parallel with the magnitude of weight reduction.⁶⁹

Table 12. Lipid profile and cardiometabolic risk markers

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S18	Garber 2009 (LEAD-3)	Metabolic profile	Improvement in HbA1c, weight and blood pressure without excess hypoglycaemia	<0.05
S29	Gerstein 2019 (REWIND)	Cardiometabolic risk profile	Cardiovascular benefit consistent across a wide spectrum of glycaemic control	0.026
S31	Buse 2013 (DURATION-6)	Cardiometabolic improvement	Both agonists improved glycaemic control; liraglutide superior for HbA1c	NR

Hypoglycaemia

Fourteen studies reported hypoglycaemia outcomes explicitly. In monotherapy and in combination with metformin or SGLT-2 inhibitors, the incidence of severe hypoglycaemia was very low to nil. AWARD-5 and ACHIEVE-1 reported no episodes of severe hypoglycaemia, and DURATION-2 reported no major hypoglycaemic episodes. These findings are consistent with the glucose-dependent mechanism of the class, which does not stimulate insulin secretion at normal glucose concentrations.^{8,47,51,53}

On a basal insulin background, addition of a GLP-1 receptor agonist did not significantly increase hypoglycaemia risk. In SUSTAIN 5, the rate ratio for severe or blood-glucose-confirmed hypoglycaemia versus placebo was 2.08 (95% CI 0.67 to 6.51) and 2.41 (95% CI 0.84 to 6.96) for the 0.5 mg and 1.0 mg doses, neither statistically significant. In AWARD-9, hypoglycaemia rates were similar between dulaglutide and placebo, both combined with titrated glargine (7.69 versus 8.56 events per patient-year; $p=0.488$). In SCALE Insulin, hypoglycaemic events were in fact more frequent in the placebo arm.^{24,38,49}

An important exception arises on a sulphonylurea background. In AWARD-8, total hypoglycaemia was higher with dulaglutide than placebo (2.37 versus 0.07 events per patient-year; $p=0.025$), although no severe hypoglycaemia was reported. This underscores the need to reduce the

sulphonylurea dose when initiating a GLP-1 receptor agonist. Conversely, in head-to-head comparison, liraglutide produced less frequent minor hypoglycaemia than twice-daily exenatide (rate ratio 0.55; 95% CI 0.34 to 0.88; $p=0.0131$).^{41,48}

Table 13. Incidence of hypoglycaemia

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S3	Rodbard 2018 (SUSTAIN 5)	Severe or blood-glucose-confirmed hypoglycaemia	Rate ratio 2.08 (0.67 to 6.51) and 2.41 (0.84 to 6.96) vs placebo	Not significant
S5	Zinman 2019 (SUSTAIN 9)	Severe or confirmed hypoglycaemia	4 patients (2.7%) in the semaglutide arm	NR
S15	Lingvay 2025 (STEP UP T2D)	Level 2-3 hypoglycaemia	Low risk and comparable between arms	NR
S17	Garvey 2020 (SCALE Insulin)	Hypoglycaemic events	More frequent with placebo than liraglutide 3.0 mg	<0.05
S19	Russell-Jones 2009 (LEAD-5)	Major/minor/symptomatic hypoglycaemia	0.06 / 1.2 / 1.0 events per patient-year with liraglutide	NR
S20	Buse 2009 (LEAD-6)	Minor hypoglycaemia	1.93 vs 2.60 events per patient-year; RR 0.55 (0.34 to 0.88)	0.0131
S21	Ahmann 2015	Minor hypoglycaemia	18.2% (liraglutide) vs 12.4% (placebo); no severe hypoglycaemia	NR
S23	Ludvik 2018 (AWARD-10)	Severe hypoglycaemia	1 episode with dulaglutide 0.75 mg	NR

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S25	Dungan 2014 (AWARD-6)	Hypoglycaemia rate	0.34 (dulaglutide) vs 0.52 (liraglutide) events per patient-year; no severe events	NR
S26	Nauck 2014 (AWARD-5)	Severe hypoglycaemia	No events reported	NR
S27	Dungan 2016 (AWARD-8)	Total hypoglycaemia (sulphonylurea background)	2.37 vs 0.07 events per patient-year; no severe hypoglycaemia	0.025
S28	Pozzilli 2017 (AWARD-9)	Hypoglycaemia (≤ 3.9 mmol/L)	7.69 vs 8.56 events per patient-year	0.488
S30	Bergental 2010 (DURATION-2)	Major hypoglycaemia	No episodes occurred	NR
S32	Rosenstock 2025 (ACHIEVE-1)	Severe hypoglycaemia	No episodes reported	NR

Insulin Requirement and Rescue Therapy

In patients already receiving basal insulin, addition of a GLP-1 receptor agonist permitted attainment of glycaemic targets at lower insulin doses. In AWARD-9, the increase in glargine dose from baseline was markedly smaller with dulaglutide than with placebo (13 versus 26 units per day; $p < 0.001$), with final doses of 51 versus 65 units. In the trial of liraglutide added to a basal insulin analogue, the final insulin dose was 35.8 IU in the liraglutide arm versus 40.1 IU on placebo, despite substantially better target attainment in the liraglutide arm.^{42,49}

In SCALE Insulin, liraglutide 3.0 mg produced greater improvements in HbA1c and daytime glucose with a lower insulin requirement, despite the use of a treat-to-target protocol. This insulin-

sparing effect has dual clinical relevance: it mitigates insulin-induced weight gain and reduces the titration burden for patients.³⁸

Table 14. Insulin requirement and rescue therapy

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S28	Pozzilli 2017 (AWARD-9)	Increase in glargine dose	+13 U/day vs +26 U/day; final dose 51 vs 65 U	<0.001
S21	Ahmann 2015	Final insulin dose	35.8 IU (liraglutide) vs 40.1 IU (placebo)	NR
S17	Garvey 2020 (SCALE Insulin)	Basal insulin requirement	Lower with liraglutide 3.0 mg despite a treat-to-target protocol	<0.05
S11	Zinman 2019 (PIONEER 8)	Background insulin therapy	Efficacy maintained as add-on to insulin +/- metformin	<0.001
S29	Gerstein 2019 (REWIND)	Background antihyperglycaemic regimen	Dulaglutide added to existing regimens without excess serious adverse events	NR

Gastrointestinal Adverse Events and Treatment Discontinuation

Gastrointestinal adverse events were the most frequent and consistent adverse effects across all studies. The incidence of nausea ranged from 10.5% to 24% in GLP-1 receptor agonist arms versus 3.1% to 10% in comparator arms. In trials using high doses for weight indications, total gastrointestinal event incidence reached 63.5% with semaglutide 2.4 mg (STEP 2) and 53.1% with semaglutide 7.2 mg (STEP UP T2D), versus 34.3% and 25.5% respectively on placebo. Most events were mild to moderate, transient, and concentrated during the dose-escalation phase.^{35,36}

Nevertheless, discontinuation rates attributable to adverse events remained relatively low. In PIONEER 1, discontinuation ranged from 2.3% to 7.4% in oral semaglutide arms versus 2.2% on placebo. In ACHIEVE-1, permanent discontinuation occurred in 4.4-7.8% of orforglipron

participants versus 1.4% on placebo. The highest discontinuation rate was recorded in PIONEER 5, which enrolled older patients with moderate renal impairment (15% versus 5%), signalling the need for cautious titration in vulnerable populations.^{28,31,53}

Several molecule-specific safety findings merit note. Injection-site reactions were far less frequent with semaglutide than with exenatide extended release (1.2% versus 22.0%). In STEP UP T2D, dysaesthesia was reported more often with semaglutide 7.2 mg (18.9%) than with 2.4 mg (4.9%) or placebo (0%), an imbalance requiring further monitoring. In SCALE Diabetes, no cases of pancreatitis were reported. In REWIND, with a median follow-up of 5.4 years, gastrointestinal events were reported by 47.4% of dulaglutide participants versus 34.1% on placebo ($p < 0.0001$), without new safety signals.^{23,36,37,50}

Table 15. Gastrointestinal adverse events and treatment discontinuation

ID	Study (trial)	Gastrointestinal adverse events	Safety notes
S1	Sorli 2017 (SUSTAIN 1)	Nausea 20% / 24% vs 8%; diarrhoea 13% / 11% vs 2%	Mostly mild to moderate; no deaths reported
S2	Ahmann 2017 (SUSTAIN 3)	Gastrointestinal events 41.8% vs 33.3%	Injection-site reactions 1.2% (semaglutide) vs 22.0% (exenatide ER)
S3	Rodbard 2018 (SUSTAIN 5)	Discontinuation due to adverse events 4.5% / 6.1% vs 0.8%	Mainly gastrointestinal disorders
S4	Pratley 2018 (SUSTAIN 7)	Gastrointestinal disorders 43% / 44% (semaglutide) vs 33% / 48% (dulaglutide)	Most common reason for treatment discontinuation
S5	Zinman 2019 (SUSTAIN 9)	Gastrointestinal events 37.3% vs 13.2%	13 of 16 early discontinuations occurred with semaglutide
S7	Aroda 2019 (PIONEER 1)	Mild-to-moderate transient gastrointestinal events	Discontinuation 2.3-7.4% vs 2.2% (placebo)

ID	Study (trial)	Gastrointestinal adverse events	Safety notes
S10	Mosenzon 2019 (PIONEER 5)	Adverse events 74% vs 65%	Discontinuation 15% vs 5%; renal safety consistent with the class
S11	Zinman 2019 (PIONEER 8)	Nausea 11.4-23.2% vs 7.1%	Mostly mild to moderate
S14	Davies 2021 (STEP 2)	Gastrointestinal events 63.5% / 57.5% vs 34.3%	Mostly mild to moderate
S15	Lingvay 2025 (STEP UP T2D)	Gastrointestinal events 53.1% / 51.5% vs 25.5%	Serious adverse events 9.1% / 8.7% / 8.8%; dysaesthesia 18.9% at 7.2 mg
S16	Davies 2015 (SCALE Diabetes)	More gastrointestinal disorders with liraglutide 3.0 mg	No pancreatitis reported
S20	Buse 2009 (LEAD-6)	Nausea less persistent with liraglutide	Estimated treatment rate ratio 0.448 vs exenatide
S21	Ahmann 2015	Nausea 22.2% vs 3.1%	Pulse increase of 4.5 beats/min versus placebo
S22	Blonde 2020 (LIRA-ADD2SGLT2i)	Treatment-emergent adverse events 66.3% vs 47.0%	No unexpected safety findings
S23	Ludvik 2018 (AWARD-10)	Nausea 15% / 5% vs 4%; diarrhoea 6% / 10% vs 3%; vomiting 4% / 3% vs 1%	Serious adverse events 4% / 2% / 4%
S24	Frias 2021 (AWARD-11)	Nausea 13.4% / 15.6% / 16.4%; vomiting 5.6% / 8.3% / 9.3%	Comparable safety profile across doses

ID	Study (trial)	Gastrointestinal adverse events	Safety notes
S25	Dungan 2014 (AWARD-6)	Nausea 20% vs 18%; diarrhoea 12% vs 12%	Discontinuation due to adverse events 6% in both arms
S26	Nauck 2014 (AWARD-5)	Nausea, diarrhoea and vomiting most frequent with dulaglutide	Mostly mild to moderate and transient
S27	Dungan 2016 (AWARD-8)	Nausea 10.5%; diarrhoea 8.4%; eructation 5.9%	Favourable benefit-risk profile
S28	Pozzilli 2017 (AWARD-9)	Nausea 12.0%; diarrhoea 11.3%; vomiting 6.0%	Well tolerated overall
S29	Gerstein 2019 (REWIND)	Gastrointestinal events 47.4% vs 34.1% (p<0.0001)	Median follow-up 5.4 years
S30	Bergental 2010 (DURATION-2)	Nausea 24% (exenatide) vs 10% (sitagliptin)	Diarrhoea 18% vs 10%
S31	Buse 2013 (DURATION-6)	Nausea 21% vs 9%; diarrhoea 13% vs 6%; vomiting 11% vs 4%	Incidence decreased over time in both arms
S32	Rosenstock 2025 (ACHIEVE-1)	Mild-to-moderate gastrointestinal events during dose escalation	Permanent discontinuation 4.4-7.8% vs 1.4% (placebo)

Cardiovascular and Renal Outcomes

REWIND was the only study in this review specifically designed to assess cardiovascular outcomes. Among 9,901 participants with a median follow-up of 5.4 years, the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death occurred in 594 participants (12.0%) in the dulaglutide arm at an incidence rate of 2.4 per 100 person-years, versus 663 participants (13.4%) in the placebo arm at 2.7 per 100 person-years (hazard ratio 0.88; 95% CI 0.79 to 0.99; p=0.026). All-cause mortality did not differ significantly (HR 0.90; 95% CI 0.80 to 1.01; p=0.067).⁵⁰

Exploratory analysis of renal outcomes in the same population demonstrated a significant risk reduction. The composite renal outcome of new macroalbuminuria, sustained eGFR decline of $\geq 30\%$, or chronic renal replacement therapy occurred in 848 participants (17.1%) in the dulaglutide arm versus 970 participants (19.6%) on placebo (HR 0.85; 95% CI 0.77 to 0.93; $p=0.0004$). The clearest effect was on new macroalbuminuria (HR 0.77; 95% CI 0.68 to 0.87; $p<0.0001$).⁵⁴

It should be emphasised that this cardiovascular benefit was observed in a population with a median HbA1c of only 7.2% (IQR 6.6-8.1), encompassing both participants with established cardiovascular disease and those with risk factors alone. This indicates that the cardiorenal benefit is not mediated solely by glucose lowering.^{50,54}

Table 16. Major adverse cardiovascular events and renal outcomes

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S29	Gerstein 2019 (REWIND)	Three-point MACE (non-fatal MI, non-fatal stroke, cardiovascular death)	HR 0.88 (0.79 to 0.99)	0.026
S29	Gerstein 2019 (REWIND)	All-cause mortality	HR 0.90 (0.80 to 1.01)	0.067
S29b	Gerstein 2019 (REWIND renal)	Composite renal outcome	HR 0.85 (0.77 to 0.93)	0.0004
S29b	Gerstein 2019 (REWIND renal)	New macroalbuminuria	HR 0.77 (0.68 to 0.87)	<0.0001
S10	Mosenzon 2019 (PIONEER 5)	Renal safety at eGFR 30-59	Consistent with the GLP-1 receptor agonist class	NR

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S9	Pratley 2019 (PIONEER 4)	Overall safety	Comparable to subcutaneous liraglutide	NR

Composite Target Attainment Without Hypoglycaemia or Weight Gain

This composite outcome most closely reflects the goals of contemporary T2DM management, namely attainment of glycaemic targets without compromising safety or body weight. In SUSTAIN China, the odds of attaining the composite of HbA1c <7.0% without severe or blood-glucose-confirmed hypoglycaemia and without weight gain were significantly higher with both semaglutide doses than with sitagliptin. In DURATION-2, the combination of optimal glycaemic control, weight loss and minimal hypoglycaemia was achieved more frequently with once-weekly exenatide than with either sitagliptin or pioglitazone.^{27,51}

Table 17. Composite outcome

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S6	Ji 2020 (SUSTAIN China)	HbA1c <7.0% without severe/confirmed hypoglycaemia and without weight gain	Significantly higher odds with both semaglutide doses vs sitagliptin	<0.05
S30	Bergental 2010 (DURATION-2)	Optimal glycaemic control plus weight loss plus minimal hypoglycaemia	Achieved more often with exenatide QW than sitagliptin or pioglitazone	<0.05
S26	Nauck 2014 (AWARD-5)	Superior glycaemic control without severe hypoglycaemia	Achieved with dulaglutide 1.5 and 0.75 mg vs sitagliptin	<0.001

ID	Study (trial)	Comparison	Effect estimate (95% CI)	p value
S22	Blonde 2020 (LIRA- ADD2SGLT2i)	HbA1c <7.0% on triple- class combination therapy	51.8% vs 23.2%; OR 5.1 (2.67 to 9.87)	<0.001

Certainty of Evidence (GRADE)

GRADE appraisal indicated high certainty of evidence for the HbA1c and body weight outcomes, supported by a large number of studies, perfect consistency in the direction of effect, high precision of confidence intervals, and low risk of bias in the majority of studies. Certainty was downgraded to moderate for lipid profile and fasting plasma glucose owing to inconsistent reporting, and for cardiovascular and renal outcomes because these derived from a single trial within the included set.^{19,21}

Table 18. Summary of certainty of evidence using the GRADE approach

Outcome domain	Number of studies	Risk of bias	Inconsistency	Imprecision	Certainty
Outcome 1: Change in HbA1c	30	Not serious	Not serious	Not serious	High
Outcomes 2-3: HbA1c target attainment	10	Not serious	Not serious	Not serious	High
Outcome 4: Absolute weight change	20	Not serious	Not serious	Not serious	High
Outcome 5: Relative weight change	6	Not serious	Not serious	Not serious	High
Outcomes 6-7: Weight reduction thresholds	5	Not serious	Not serious	Not serious	High

Outcome domain	Number of studies	Risk of bias	Inconsistency	Imprecision	Certainty
Outcome 8: Fasting plasma glucose	6	Not serious	Not serious	Serious	Moderate
Outcome 9: Anthropometry	4	Not serious	Not serious	Serious	Moderate
Outcome 10: Systolic blood pressure	4	Not serious	Not serious	Serious	Moderate
Outcome 11: Lipid profile	3	Not serious	Serious	Serious	Low
Outcome 12: Hypoglycaemia	14	Not serious	Not serious	Not serious	High
Outcome 13: Insulin requirement	5	Not serious	Not serious	Serious	Moderate
Outcome 14: Gastrointestinal adverse events	24	Not serious	Not serious	Not serious	High
Outcome 15: Cardiovascular and renal outcomes	1	Not serious	Not assessable	Not serious	Moderate
Outcome 16: Composite outcome	4	Not serious	Not serious	Serious	Moderate

DISCUSSION

Summary of Principal Findings

This systematic review of 32 randomized controlled trials involving 29,958 participants yielded three principal findings. First, GLP-1 receptor agonists consistently reduce HbA1c by a clinically meaningful magnitude across all background regimens and all molecules, with ETDs versus placebo ranging from -0.5% to -1.75%. Not a single placebo-controlled trial failed to demonstrate superiority, a degree of consistency rarely encountered in other therapeutic classes. Second, the accompanying weight reduction is dose-dependent and reaches 13.2% at the highest dose studied. Third, these benefits are achieved without an increase in severe hypoglycaemia risk and, in trials with long-term follow-up, are accompanied by reductions in major adverse cardiovascular events and composite renal outcomes.^{22,26,36,50,54}

The alternative hypothesis of this review was supported by the data. The null hypothesis was rejected for both primary outcomes, with statistical significance consistently at $p < 0.001$ in nearly all placebo-controlled comparisons, and a positive dose-response relationship was confirmed for the four molecules studied at multiple dose levels, namely subcutaneous semaglutide, oral semaglutide, dulaglutide and orforglipron.^{28,34,45,53}

Mechanistic Interpretation of the Findings

The consistency of the glycaemic effect across background regimens is explicable by the mechanism of GLP-1 action, which operates through pathways that largely do not overlap with those of other antihyperglycaemic agents. GLP-1 controls meal-related glycaemic excursions through augmentation of insulin secretion and inhibition of glucagon secretion, while also inhibiting gastric emptying and food intake. Because insulin secretion is stimulated in a glucose-dependent manner, this effect ceases automatically as glucose approaches normal concentrations, which explains the low incidence of severe hypoglycaemia in all studies not employing sulphonylurea or insulin as background therapy.^{8,9,10}

Differences in effect magnitude between molecules are explicable by pharmacokinetic differences. Short-acting compounds provide intermittent receptor activation and primarily lower postprandial glucose through inhibition of gastric emptying, whereas long-acting compounds activate the receptor continuously at recommended doses and exert a stronger effect on fasting glucose through insulinotropic and glucagonostatic actions. This framework explains why liraglutide

produced a substantially greater FPG reduction than twice-daily exenatide (ETD -1.01 mmol/L) despite comparable weight reduction.^{10,41}

The weight-lowering effect operates through pathways distinct from those mediating glucose lowering. Centrally, GLP-1 receptor agonists modulate appetite-regulating brain regions and influence release of neurotransmitters and neuropeptides governing hunger and energy expenditure. Peripherally, there are reductions in triglycerides and LDL cholesterol, mitigation of adipose-tissue inflammation, and reduction of ectopic fat deposition. The existence of these separate pathways explains why the dose threshold for the weight effect exceeds that for the glycaemic effect, as clearly demonstrated in PIONEER 11, where oral semaglutide 3 mg effectively reduced HbA1c but did not significantly reduce body weight.^{12,13,34}

Intra-Class Efficacy Hierarchy and Implications for Molecule Selection

Head-to-head trials provide the highest level of evidence for establishing an efficacy hierarchy. The synthesised data indicate the following order of glycaemic and weight efficacy: subcutaneous semaglutide occupies the highest position, followed by oral semaglutide 14 mg and liraglutide 1.8 mg at comparable levels, then dulaglutide 1.5 mg, and finally exenatide extended release and twice-daily exenatide. Semaglutide 1.0 mg was superior to exenatide extended release with an HbA1c ETD of -0.62% and a weight ETD of -3.78 kg, and superior to dulaglutide 1.5 mg with corresponding values of -0.41% and -3.55 kg.^{23,25}

This hierarchy must nonetheless be interpreted in the light of dose effects. AWARD-11 demonstrated that escalating dulaglutide from 1.5 mg to 4.5 mg conferred an additional HbA1c reduction of 0.24% and an additional weight reduction of 1.6 kg, so that part of the gap relative to semaglutide can be narrowed by higher dosing. In other words, comparisons between molecules at conventional doses do not necessarily reflect the maximal potential of each molecule.⁴⁵

Practical considerations beyond efficacy also inform molecule selection. The markedly lower frequency of injection-site reactions with semaglutide compared with exenatide extended release (1.2% versus 22.0%) is an important determinant of long-term adherence. The availability of oral semaglutide and orforglipron opens the possibility of earlier initiation of incretin-based therapy in

patients who decline injectable treatment, a consideration of direct relevance to Indonesian clinical practice.^{23,30,53}

Efficacy Across Background Regimens

A principal strength of this synthesis is the breadth of background regimens covered. In drug-naive patients, GLP-1 receptor agonist monotherapy produced HbA1c reductions of up to 1.53% versus placebo and was superior to glimepiride and to metformin in several comparisons. In patients failing to reach target on metformin, addition of a GLP-1 receptor agonist was superior to addition of a DPP-4 inhibitor, an SGLT-2 inhibitor or a thiazolidinedione.^{22,29,39,47,51}

Combination with SGLT-2 inhibitors warrants particular attention because the two classes have complementary mechanisms and both confer cardiorenal benefit. SUSTAIN 9 demonstrated that adding semaglutide to SGLT-2 inhibitor therapy produced an HbA1c ETD of -1.42% and a weight ETD of -3.81 kg, while AWARD-10 produced an HbA1c ETD of -0.79% for dulaglutide 1.5 mg. In LIRA-ADD2SGLT2i, liraglutide produced an HbA1c ETD of -0.68%, although the weight difference did not reach statistical significance ($p=0.077$), plausibly because the SGLT-2 inhibitor had already produced weight reduction in the comparator arm.^{26,43,44}

In patients receiving basal insulin, addition of a GLP-1 receptor agonist confers the most clinically compelling benefit because it simultaneously addresses the three principal limitations of insulin intensification, namely weight gain, hypoglycaemia risk and titration complexity. The data demonstrate HbA1c reductions of up to 1.75% with weight reductions of up to 5.06 kg, accompanied by lower insulin requirements and without a significant increase in hypoglycaemia. This strategy represents a rational alternative to intensification toward a basal-bolus regimen.^{24,38,42,49}

Efficacy in Special Populations

PIONEER 5 provides evidence in a population with moderate renal impairment (eGFR 30-59 mL/min/1.73 m²) and a mean age of 70 years. Oral semaglutide 14 mg remained superior to placebo with an HbA1c ETD of -0.8 percentage points and a weight ETD of -2.5 kg, with a safety profile, including renal safety, consistent with the class. This is important because many antihyperglycaemic drugs are predominantly renally eliminated, restricting therapeutic options in this population.³¹

For Asian populations, PIONEER 9 in Japanese patients and PIONEER 11 and SUSTAIN China in Chinese patients provide direct evidence. The HbA1c ETD reached -1.7 percentage points in PIONEER 9 and -1.5 percentage points in PIONEER 11, comparable to or greater than in multinational trials. However, baseline body weight in these populations was lower (79.6 kg in PIONEER 11 versus 91.93 kg in SUSTAIN 1), so that the absolute weight reduction achieved was correspondingly smaller (maximum ETD -2.0 kg). This observation has direct implications for practice in Indonesia, where expectations of absolute weight reduction should be calibrated to local baseline body weight.^{22,33,34}

REWIND provides evidence in an older population at high cardiovascular risk with relatively good baseline glycaemic control (median HbA1c 7.2%). The observation of cardiovascular benefit in a population with HbA1c close to target indicates that the indication for GLP-1 receptor agonists is determined not solely by the degree of hyperglycaemia but also by the overall cardiovascular risk profile.⁵⁰

Cardiorenal Benefit in the Broader Evidence Context

The cardiovascular benefit of dulaglutide in REWIND (HR 0.88; 95% CI 0.79-0.99) aligns with evidence from cardiovascular outcome trials of other GLP-1 receptor agonists that fell outside the inclusion criteria of this review. AMPLITUDE-O demonstrated that efpeglenatide, an exendin-based agonist, reduced MACE risk with an HR of 0.73 (95% CI 0.58 to 0.92; $p=0.007$) and composite renal outcomes with an HR of 0.68 (95% CI 0.57 to 0.79; $p<0.001$) among 4,076 participants. Prespecified analyses of SOUL demonstrated that oral semaglutide reduced MACE risk by 14% (HR 0.86; 95% CI 0.77 to 0.96) among 9,650 participants, with effects independent of concomitant SGLT-2 inhibitor use.^{55,56}

The convergence of results across different molecules, routes of administration and populations strengthens the interpretation that cardiorenal benefit constitutes a class effect rather than a molecule-specific phenomenon. The consistency of benefit with concomitant SGLT-2 inhibitor use also supports combination of the two classes in high-risk patients, with a comparable adverse event profile.⁵⁶

The mechanism of cardiorenal benefit appears to extend beyond glucose and weight reduction. Supporting evidence demonstrates improvement in vascular markers such as pulse wave velocity, endothelial glycocalyx and reactive hyperaemia index after 12 months of GLP-1 receptor agonist therapy, of greater magnitude than with insulin therapy despite comparable HbA1c reduction. Biomarker data also demonstrate reductions in high-sensitivity C-reactive protein, apolipoprotein B and apolipoprotein C3, indicating anti-inflammatory effects and improvement in lipoprotein atherogenicity.^{69,75}

Safety Profile and Mitigation Strategies

Gastrointestinal adverse events represent the principal barrier to tolerability. This synthesis demonstrates that incidence correlates with dose and is concentrated during the escalation phase. Evidence-supported mitigation strategies include slower dose escalation, anticipatory patient education regarding the transient nature of symptoms, and dietary modification with smaller portions and reduced fat intake. Data from high-dose trials indicate that although gastrointestinal event incidence rises, treatment discontinuation rates remain within an acceptable range (4.4-9.9%).^{36,53}

The delay in gastric emptying that forms part of the drug's mechanism of action carries perioperative implications. Case reports describe retained solid gastric contents in patients undergoing elective gastroscopy despite 10-13 hours of fasting. Consideration of temporary withholding before elective anaesthetic procedures, and possible use of gastric ultrasonography to assess residual gastric content, are safety aspects of practical clinical relevance, although definitive evidence remains limited.⁶⁷

Hypoglycaemia risk requires a context-dependent approach. On regimens without secretagogues, severe hypoglycaemia risk is effectively nil. On a sulphonylurea background, AWARD-8 demonstrated a significant increase in total hypoglycaemia, so that sulphonylurea dose reduction at initiation is mandatory. On a basal insulin background, the data indicate that risk is not significantly increased even when glycaemic control is substantially better, provided that insulin doses are not escalated above pre-study levels, as in the protocol of Ahmann and colleagues.^{42,48}

The finding of more frequent dysaesthesia with semaglutide 7.2 mg (18.9%) than with 2.4 mg (4.9%) or placebo (0%) constitutes a novel safety signal that is not yet fully explained and warrants monitoring in subsequent studies and in post-marketing practice.³⁶

Comparison with Dual and Triple Receptor Agonists

Although dual and triple receptor agonists were excluded from the principal synthesis, comparative context is important for situating these results. Tirzepatide, a dual GIP and GLP-1 receptor agonist, produced HbA1c reductions of up to 1.94% and weight reductions of up to 11.3 kg at the 15 mg dose in a phase 2 study, significantly exceeding dulaglutide 1.5 mg. In SURPASS-4, tirzepatide 15 mg produced an HbA1c reduction of 2.58% versus 1.44% with insulin glargine, without excess cardiovascular risk.^{57,59}

Retatrutide, a triple GIP, GLP-1 and glucagon receptor agonist, produced HbA1c reductions of up to 2.02% and weight reductions of up to 16.94% at week 36 in a phase 2 study, far exceeding dulaglutide 1.5 mg. Survodutide, a dual glucagon and GLP-1 receptor agonist, produced weight reductions of up to 8.7% over 16 weeks, greater than semaglutide 1.0 mg (5.3%) within the same trial.^{58,60}

However, the STEP UP T2D result of 13.2% weight reduction with semaglutide 7.2 mg suggests that part of the apparent advantage of multi-receptor agonists may reflect differences in total agonist exposure rather than an intrinsic superiority of dual receptor mechanisms. Head-to-head comparison at pharmacodynamically equivalent doses is required before definitive conclusions can be drawn.³⁶

Clinical Implications for Practice in Indonesia

Several practical implications can be drawn for the Indonesian health-care context. First, in patients with T2DM and BMI ≥ 25 kg/m² by Asia-Pacific criteria whose HbA1c remains above target despite optimal metformin dosing, a GLP-1 receptor agonist represents an intensification option with a more favourable benefit-risk ratio than a sulphonylurea, providing comparable or greater HbA1c reduction together with weight reduction and a substantially lower hypoglycaemia risk.^{39,47}

Second, in patients already receiving basal insulin but not at target, addition of a GLP-1 receptor agonist is preferable to intensification toward a basal-bolus regimen, given the reduction in

injection burden, insulin sparing and prevention of weight gain. Third, in patients with atherosclerotic cardiovascular disease or chronic kidney disease, the indication for a GLP-1 receptor agonist may be established on cardiorenal grounds irrespective of the degree of hyperglycaemia.^{38,49,50,54}

Fourth, expectations regarding weight reduction should be calibrated to the characteristics of the Indonesian population, whose baseline body weight is lower than that of multinational trial populations. Fifth, limited availability and cost remain the principal barriers; oral formulations and small-molecule non-peptide agonists that do not require cold-chain storage may improve accessibility in future, particularly in primary care and in regions with limited infrastructure.^{34,53,62}

Strengths of the Review

This systematic review has several methodological strengths.

- Broad evidence coverage with 32 randomized controlled trials and 29,958 participants, encompassing all generations of selective GLP-1 receptor agonist molecules published in high-ranking peer-reviewed journals.
- Analysis of 16 outcome domains spanning efficacy, safety, anthropometric, cardiometabolic and cardiorenal endpoints, substantially exceeding the scope of conventional reviews.
- Application of the Cochrane RoB 2 tool at the domain level for every study with explicit justification, in accordance with current recommendations emphasising the importance of documented domain-level judgements.
- Inclusion of head-to-head comparisons between agonists as a distinct evidence stream, enabling construction of an intra-class efficacy hierarchy based on the highest level of evidence.
- Verification of the existence of every reference through an academic search engine with the medical-journal filter and preprint exclusion applied, with a verifiable link supplied for each bibliographic entry.

Directions for Future Research

On the basis of the gaps identified, the following directions for future research are recommended.

- Multicentre randomized controlled trials in Indonesia or South-East Asia to confirm effect magnitudes in local populations with differing metabolic phenotypes.

- Network meta-analysis to compare all molecules and doses simultaneously with probabilistic ranking estimates.
- Head-to-head comparison between high-dose selective GLP-1 agonists and dual or triple receptor agonists at pharmacodynamically equivalent levels of agonism.
- Cost-effectiveness studies within the Indonesian national health insurance system to inform formulary decision-making.
- Research on strategies to mitigate gastrointestinal adverse effects, including optimised dose-escalation schedules and structured dietary interventions.
- Long-term studies of the durability of weight reduction, patterns of weight regain after treatment cessation, and effects on body composition and muscle mass.
- Research on perioperative safety in relation to delayed gastric emptying and development of protocols for temporary withholding before anaesthetic procedures.

CONCLUSION AND RECOMMENDATIONS

Conclusion

On the basis of a synthesis of 32 randomized controlled trials involving 29,958 participants with type 2 diabetes mellitus, GLP-1 receptor agonists confer statistically and clinically significant improvements in glycaemic control and reductions in body weight. Versus placebo, estimated treatment differences in HbA1c ranged from -0.5% to -1.75%, with all p values below 0.001, and additional weight reduction ranged from -0.9 kg to -5.06 kg. Not a single placebo-controlled trial failed to demonstrate superiority on glycaemic outcomes.^{22,24,26,28,32}

At doses optimised for weight management, relative weight reduction reached 9.6% with semaglutide 2.4 mg and 13.2% with semaglutide 7.2 mg, with odds ratios for attaining $\geq 5\%$ weight loss of 4.88 and 10.0 respectively. A dose-response relationship was confirmed for four molecules, and the dose threshold for the weight effect was shown to exceed that for the glycaemic effect.^{35,36}

Head-to-head comparisons place subcutaneous semaglutide at the top of the efficacy hierarchy, followed by oral semaglutide and liraglutide, then dulaglutide, and finally exenatide. However, dose escalation of dulaglutide to 4.5 mg significantly narrows this gap.^{23,25,45}

The safety profile demonstrates an effectively nil risk of severe hypoglycaemia on regimens without secretagogues, with mild-to-moderate gastrointestinal adverse events as the most frequent adverse effect, concentrated during the dose-escalation phase. In the trial with a median follow-up of 5.4 years, dulaglutide reduced the risk of major adverse cardiovascular events by 12% (HR 0.88; 95% CI 0.79-0.99) and composite renal outcomes by 15% (HR 0.85; 95% CI 0.77-0.93).^{50,54}

The methodological quality of the evidence base is good, with 23 of 32 studies (71.9%) judged at low risk of bias and no study judged at high risk. GRADE certainty of evidence was rated high for HbA1c, body weight, hypoglycaemia and gastrointestinal adverse events.^{18,21}

Recommendations

For clinicians

- Consider a GLP-1 receptor agonist as second-line intensification in patients with T2DM and overweight or obesity who have not attained target on metformin, particularly where weight reduction is a co-equal therapeutic goal.
- In patients with atherosclerotic cardiovascular disease or chronic kidney disease, consider a GLP-1 receptor agonist on cardiorenal grounds irrespective of the degree of hyperglycaemia.
- In patients already receiving basal insulin but not at target, prioritise addition of a GLP-1 receptor agonist over intensification toward a basal-bolus regimen.
- Reduce the sulphonylurea dose when initiating a GLP-1 receptor agonist to prevent an increase in hypoglycaemia risk.
- Apply gradual dose escalation with anticipatory education about the transient nature of gastrointestinal symptoms to maximise tolerability and adherence.
- Calibrate expectations of absolute weight reduction to the patient's baseline body weight, since absolute magnitudes are smaller in patients with lower baseline weight.
- Consider temporary withholding before elective anaesthetic procedures and assess residual gastric content where clinically indicated.

For researchers

- Design randomized controlled trials in Indonesian populations to validate effect magnitudes in the local metabolic phenotype.

- Conduct network meta-analyses to compare all molecules and doses simultaneously with probabilistic ranking estimates.
- Standardise reporting of secondary outcomes, particularly lipid profile, body composition and patient-oriented outcomes, so that evidence synthesis in these domains can be more complete.
- Investigate durability of effect and patterns of weight regain after cessation of long-term therapy.

For policymakers

- Undertake health technology assessment that accounts for total benefit, encompassing HbA1c reduction, weight reduction, insulin sparing, and prevention of cardiovascular events and renal disease progression.
- Consider funding prioritisation for subgroups with the greatest absolute benefit, namely patients with atherosclerotic cardiovascular disease, chronic kidney disease or severe obesity.
- Support availability of oral formulations and non-peptide agonists that do not require cold-chain storage in order to broaden access in primary care and in regions with limited infrastructure.

DECLARATIONS

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Data availability. All data underpinning this review derive from publicly available peer-reviewed publications accessible through the links provided in the reference list.

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