INPLASY

Subcutaneous Tirzepatide Versus Semaglutide and Emerging Incretin Agents in Type 2 Diabetes: A Comprehensive Frequentist Network Meta-Analysis of 42 Trials Through May 2026

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ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202660011

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 June 2026 and was last updated on 2 June 2026.

INTRODUCTION

Review question / Objective What is the comparative efficacy hierarchy of incretin agents in T2DM for HbA1c and weight reduction, and does SURMOUNT-5 validate the prior indirect network estimates for tirzepatide versus semaglutide?

Rationale This systematic review addresses a critical evidence gap. No comprehensive synthesis with pre-specified interaction analyses currently exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Type 2 diabetes mellitus with overweight or obesity.

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Scopus from January 2013 to May 31, 2026. ClinicalTrials.gov on May 31, 2026. Search terms: tirzepatide, semaglutide, dulaglutide, liraglutide, exenatide, albiglutide, retatrutide, CagriSema, cagrilintide, oral semaglutide, GIP receptor agonist, GLP-1 receptor agonist, type 2 diabetes, HbA1c, body weight, SURPASS, SUSTAIN, SURMOUNT, REDEFINE.

Participant or population Adults aged 18 or above with confirmed T2DM and BMI 25 kg/m2 or above.

Intervention Any approved or investigational incretin-based agent: tirzepatide, SC semaglutide, oral semaglutide, dulaglutide, liraglutide, exenatide

ER, albiglutide, retatrutide, CagriSema — all at any evaluated dose.

Comparator Any other eligible agent-dose combination or placebo; all eligible agents form a connected treatment network.

Study designs to be included RCTs of minimum 12 weeks comparing any eligible incretin agent versus any other eligible agent or placebo in adults with T2DM and BMI 25 kg/m2 or above, reporting HbA1c or body weight change. Single-arm studies and real-world evidence excluded.

Eligibility criteria Inclusion: Adults with T2DM; BMI 25 kg/m2 or above; any eligible incretin agent at any approved or phase 3 dose; HbA1c or body weight change reported.Exclusion: Non-RCT designs; duration below 12 weeks; T1DM or gestational diabetes; studies without extractable efficacy data.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov.

Main outcome(s) HbA1c WMD versus placebo; percentage body weight WMD versus placebo; SUCRA rankings.

Additional outcome(s) Proportion achieving HbA1c below 7.0%; GI adverse events per unit weight lost; treatment discontinuation; network consistency P-values.

Data management Data will be managed using Covidence for screening and Rayyan for deduplication. Extracted data stored in pre-piloted Excel forms. Two reviewers screen and extract independently; disagreements resolved by consensus.

Quality assessment / Risk of bias analysis Cochrane RoB 2.0 for all included RCTs. GRADE network meta-analysis extension for overall certainty.

Strategy of data synthesis Frequentist random-effects NMA using netmeta package (R 4.3.2). Global consistency: design-by-treatment interaction model. Local consistency: node-splitting across all closed loops. SUCRA from cumulative ranking curves. P-consistency for SURMOUNT-5 direct edge as pre-specified primary validation test.

Subgroup analysis Baseline HbA1c below 8% versus 8% or above; BMI below 35 versus 35 or above kg/m2; diabetes duration below 10 versus 10 or above years; Asian versus non-Asian populations; background metformin use.

Sensitivity analysis Restriction to trials with minimum 24 weeks follow-up; exclusion of oral semaglutide; exclusion of active-comparator only trials without placebo arm.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Endocrinology; Comparative Effectiveness; Clinical Pharmacology; Diabetes Pharmacotherapy

Keywords tirzepatide; semaglutide; network meta-analysis; incretin; GLP-1; GIP; type 2 diabetes; HbA1c; body weight; SUCRA; SURMOUNT-5.

Dissemination plans Submission to high-impact endocrinology or pharmacotherapy journal; open-access.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceptualization and design of the systematic review and meta-analysis. Literature search strategy and execution (PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov through May 31, 2026). Study selection, data extraction, and risk-of-bias assessment. Statistical analysis (pooled HR/RR estimates, subgroup analyses, heterogeneity testing). Interpretation of clinical and pharmacological findings. Drafting and revising the.
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Author 2 - Basmah Alanazi - independent literature screening/data verification, clinical input from the health system perspective, and/or manuscript review and approval.
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