INPLASY

Dual Cardiorenal Coverage in Type 2 Diabetes: A Comprehensive Systematic Review and Meta-Analysis of GLP-1 Receptor Agonist and SGLT-2 Inhibitor Combination Therapy Versus Monotherapy Across Cardiovascular, Renal, and Metabolic Endpoints

INPLASY202660007
doi: 10.37766/inplasy2026.6.0007
Received: 2 June 2026
Published: 2 June 2026

Alanazi, AS; Alanazi, BA.

Corresponding author:
Abdulrahman S. Alanazi

aas2@hotmail.com

Author Affiliation:
Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail 81411, Saudi Arabia.

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: INPLASY202660007

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 Does GLP-1 RA plus SGLT-2 inhibitor combination therapy deliver additive cardiorenal and metabolic benefits over each class alone in type 2 diabetes, with formally verified class independence?

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.

METHODS

Search strategy PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, and Web of Science from January 1, 2000 to May 31, 2026. ClinicalTrials.gov and WHO-ICTRP on May 31, 2026. Search terms: GLP-1 receptor agonist, semaglutide, liraglutide, dulaglutide, tirzepatide, exenatide, SGLT-2 inhibitor, empagliflozin, dapagliflozin, canagliflozin, combination therapy, dual therapy, cardiorenal outcomes, MACE, heart failure, CKD, type 2 diabetes.

Participant or population Adults aged 18 years or above with confirmed type 2 diabetes, enrolled in phase 2-3 RCTs, CVOT subgroup analyses, or propensity-adjusted prospective cohort studies of at least 12 months duration.

Intervention Concurrent prescription of any GLP-1 receptor agonist (including tirzepatide) plus any SGLT-2 inhibitor at any approved dose.

Comparator GLP-1 receptor agonist monotherapy, SGLT-2 inhibitor monotherapy, or placebo/usual care.

Study designs to be included Phase 2-3 RCTs (minimum 12 weeks follow-up); pre-specified CVOT subgroup analyses stratified by background comparator class use; propensity-score-adjusted prospective cohort studies (minimum 12-month follow-up). All required at least one cardiorenal primary outcome.

Eligibility criteria Inclusion: Adults with confirmed T2DM; GLP-1 RA plus SGLT-2i dual therapy versus either class alone or placebo; minimum 12 weeks (RCTs) or 12 months (cohorts); at least one cardiorenal outcome reported.Exclusion: Type 1 diabetes; cross-sectional or retrospective studies without propensity adjustment; case reports or series; studies without extractable outcome data.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, Web of Science, ClinicalTrials.gov, WHO-ICTRP.

Main outcome(s) 3-point MACE, hospitalisation for heart failure, composite kidney endpoint (sustained 40% eGFR decline, ESKD, renal death), all-cause mortality.

Additional outcome(s) HbA1c, body weight, SBP, genital mycotic infections, DKA, severe hypoglycaemia, eGFR slope.

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 RCTs: Cochrane Risk of Bias 2.0 (RoB 2). Cohort studies: Newcastle-Ottawa Scale. CVOT subgroup analyses: GRADE for subgroup evidence. Overall certainty of evidence rated by GRADE.

Strategy of data synthesis Random-effects meta-analysis using DerSimonian-Laird method. Heterogeneity by I2 and tau2. Pre-specified interaction tests for cardiovascular risk category and background drug class. Sensitivity analyses excluding cohort studies and excluding propensity-matched data.

Subgroup analysis Established ASCVD versus risk-factor-only; eGFR below 60 versus 60 mL/min/1.73m2 or above; GCC/Arabian Peninsula region; HbA1c below 8% versus 8% or above; diabetes duration below 10 versus 10 or above years.

Sensitivity analysis Sensitivity analyses excluding cohort studies; excluding propensity-matched data; restricting to trials with at least 12-month follow-up.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Cardiovascular and Renal Pharmacotherapy; Endocrinology and Metabolism; Clinical Pharmacy.

Keywords GLP-1 receptor agonist; SGLT-2 inhibitor; combination therapy; type 2 diabetes; cardiorenal outcomes; meta-analysis.

Dissemination plans Peer-reviewed publication in a high-impact cardiology, nephrology, or diabetes journal; open-access preferred; national guideline committee submission.

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.
Email: aas2@hotmail.com
Author 2 - Basmah Alanazi - independent literature screening/data verification, clinical input from the health system perspective, and/or manuscript review and approval.
Email: drbasmah7@gmail.com