INPLASY

SGLT2 Inhibitors in Cardiorenal Protection: Protocol for a Systematic Review and Meta-Analysis of Efficacy, Safety, and Early Intervention Evidence

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ADMINISTRATIVE INFORMATION

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

Conflicts of interest - The authors declare no conflicts of interest. Neither author has received honoraria, consultancy fees, or research funding from any manufacturer of SGLT2 inhibitors or any pharmaceutical company with a financial interest in the outcomes of this review. This review is conducted as an independent academic work affiliated with the University of Hail.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2026 and was last updated on 29 May 2026.

INTRODUCTION

Review question / Objective This systematic review aims to synthesize evidence from randomized controlled trials and observational studies on the cardiorenal protective effects of SGLT2 inhibitors.

Primary question (PICOS framework):
In adults with type 2 diabetes mellitus (T2DM) and/or chronic kidney disease (CKD), do SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) compared with placebo or active comparators reduce cardiorenal composite outcomes — including eGFR decline, progression to ESRD, cardiovascular death, and hospitalisation for heart failure — over a follow-up of ≥12 months?

Secondary questions:
1. Do SGLT2 inhibitors reduce renal-specific outcomes (eGFR slope, albuminuria, ESRD) independently of glycemic control?
2. Does early initiation (eGFR ≥60 mL/min/1.73m^2) confer greater cardiorenal protection than later initiation?
3. Is there a differential benefit between individual SGLT2 inhibitors using network meta-analysis?
4. What is the safety profile of SGLT2 inhibitors across high-risk subgroups, including elderly patients and those with advanced CKD (eGFR 20–30)?

Rationale Chronic kidney disease (CKD) and cardiovascular disease (CVD) represent the most prevalent and prognostically significant comorbidities in type 2 diabetes. SGLT2 inhibitors, initially developed as glucose-lowering agents,

have demonstrated unexpectedly profound cardiorenal protective effects across multiple landmark outcome trials.

Three pivotal trials — CREDENCE (canagliflozin, 2019), DAPA-CKD (dapagliflozin, 2020), and EMPA-KIDNEY (empagliflozin, 2023) — have each demonstrated statistically significant reductions in renal composite outcomes. Additional cardiovascular benefit was established in EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58. Despite this evidence base, no comprehensive systematic review has synthesized all major trials to provide a unified evidence framework for practitioners.

Critical evidence gaps remain: no synthesis has stratified benefit by baseline eGFR or UACR; comparative efficacy between individual SGLT2 inhibitors has not been formally meta-analyzed via network meta-analysis; and evidence supporting early intervention — before significant eGFR decline — has not been systematically evaluated. This review directly addresses these gaps, offering clinically actionable guidance for nephrology and cardiology practitioners.

Condition being studied This review examines cardiorenal syndrome in the context of type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

CKD is defined as persistent abnormalities in kidney structure or function (eGFR <60 mL/min/1.73m² or markers of kidney damage such as albuminuria) for more than 3 months, classified by the KDIGO staging system (G1–G5 by eGFR; A1–A3 by albuminuria). Diabetic kidney disease (DKD) is the most common cause of CKD globally, affecting 30–40% of T2DM patients and substantially increasing risk of cardiovascular events, end-stage renal disease (ESRD), and mortality.

Cardiovascular disease in this population includes heart failure (both preserved and reduced ejection fraction), coronary artery disease, stroke, and cardiovascular death. The bidirectional relationship between cardiac and renal dysfunction — the cardiorenal syndrome — means that decline in either organ accelerates failure in the other, creating a high-risk clinical phenotype that requires dual-targeted intervention.

METHODS

Search strategy A comprehensive search will be conducted across MEDLINE/PubMed, Embase, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, CINAHL, Web of Science, Scopus, and International Pharmaceutical Abstracts.

The PubMed strategy uses four thematic blocks combined with Boolean logic:

Block A (SGLT2 inhibitors): "Sodium-Glucose Transporter 2 Inhibitors"[MeSH] OR "SGLT2 inhibitor*"[tiab] OR canagliflozin[tiab] OR dapagliflozin[tiab] OR empagliflozin[tiab] OR ertugliflozin[tiab] OR sotagliflozin[tiab] OR gliflozin*[tiab] OR flozin*[tiab]

Block B (Cardiovascular outcomes): "Heart Failure"[MeSH] OR "heart failure"[tiab] OR "MACE"[tiab] OR "major adverse cardiovascular event*"[tiab] OR "cardiovascular death"[tiab] OR "hospitalisation for heart failure"[tiab] OR "HHF"[tiab] OR "myocardial infarction"[MeSH]

Block C (Renal outcomes): "Renal Insufficiency, Chronic"[MeSH] OR "chronic kidney disease"[tiab] OR "CKD"[tiab] OR "glomerular filtration rate"[tiab] OR "eGFR"[tiab] OR "albuminuria"[tiab] OR "UACR"[tiab] OR "end stage renal disease"[tiab] OR "ESRD"[tiab] OR "nephropathy"[tiab]

Block D (Population): "Diabetes Mellitus, Type 2"[MeSH] OR "type 2 diabetes"[tiab] OR "T2DM"[tiab] OR "diabetic kidney disease"[tiab] OR "cardiorenal"[tiab]

Final query: Block A AND (Block B OR Block C) AND Block D
No date or language restrictions will be applied. Clinical trial registries (ClinicalTrials.gov, WHO ICTRP, EU CTR) and grey literature sources will also be searched.

Participant or population Inclusion: Adults aged ≥18 years with type 2 diabetes mellitus (T2DM) and/or chronic kidney disease (CKD; eGFR <90 mL/min/1.73m² or UACR ≥30 mg/g) and/or established cardiovascular disease or high cardiovascular risk. Both diabetic and non-diabetic CKD populations are included, as demonstrated in DAPA-CKD and EMPA-KIDNEY.Exclusion: Children and adolescents (<18 years); type 1 diabetes mellitus; organ transplant recipients (unless reported as a subgroup); patients with acute kidney injury as the primary diagnosis.

Intervention Any approved SGLT2 inhibitor at any licensed dose administered orally, including: canagliflozin (100 mg or 300 mg daily), dapagliflozin (10 mg daily), empagliflozin (10 mg or

25 mg daily), ertugliflozin (5 mg or 15 mg daily), and sotagliflozin. Both monotherapy and combination therapy with other glucose-lowering or cardiovascular agents are eligible, provided the SGLT2 inhibitor is the study intervention of interest.

Comparator Placebo (with or without background standard of care), active comparators including GLP-1 receptor agonists, DPP-4 inhibitors, sulfonylureas, or insulin. Studies with no comparator arm (single-arm observational studies) will be excluded unless they contribute to subgroup or safety data within a larger eligible cohort.

Study designs to be included Randomized controlled trials (RCTs); prospective cohort studies; retrospective cohort studies with propensity score matching; pre-specified subgroup analyses of major outcome trials. Case reports, case series, editorials, and narrative reviews will be excluded.

Eligibility criteria Inclusion criteria:1. Adults (≥18 years) with T2DM and/or CKD (eGFR <90 mL/min/1.73m²) and/or established CVD or high CV risk2. Intervention with any SGLT2 inhibitor at any approved dose3. Comparator: placebo or active comparator4. Reporting at least one cardiorenal outcome (eGFR change, ESRD, CV death, HHF, MACE, or renal composite)5. Follow-up ≥12 months for RCTs; ≥6 months for observational studies6. RCTs, prospective/retrospective cohort studies with propensity matchingExclusion criteria:1. Type 1 diabetes mellitus exclusively2. Patients <18 years3. Studies reporting only surrogate metabolic outcomes (HbA1c, weight) without cardiorenal endpoints4. Follow-up <6 months5. Case reports, case series, conference abstracts without full data, narrative reviews, editorials6. Non-human studies7. Duplicate publications (primary trial publication takes precedence).

Information sources Electronic databases: MEDLINE/PubMed, Embase, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, CINAHL, Web of Science (Core Collection), Scopus, International Pharmaceutical Abstracts, ProQuest Dissertations and Theses Global.

Clinical trial registries: ClinicalTrials.gov, WHO ICTRP, EU Clinical Trials Register, ISRCTN, Chinese Clinical Trial Registry (ChiCTR), Iranian Registry of Clinical Trials (IRCT).

Grey literature: FDA Drug Approval Documents, EMA European Public Assessment Reports, NICE Technology Appraisals, conference proceedings of ESC, ACC, ASN Kidney Week, ERA-EDTA, ADA Scientific Sessions (2015–2026).

Preprint servers: medRxiv, SSRN.

Additional methods: Forward and backward citation searching of included studies; manual screening of reference lists of relevant guidelines (KDIGO 2022, ESC/EASD 2023); contact with corresponding authors of trials with unpublished subgroup data; Google Scholar for grey literature.

Main outcome(s) 1. Renal composite outcome: ≥40% sustained decline in eGFR from baseline, progression to ESRD (dialysis, transplantation, or eGFR <15 mL/min/1.73m²), or renal death.

2. Cardiovascular composite (MACE-3): cardiovascular death, non-fatal myocardial infarction, non-fatal stroke.

3. Cardiorenal composite: cardiovascular death, hospitalisation for heart failure (HHF), or renal composite endpoint.

Effect measure: hazard ratios (HR) with 95% confidence intervals for time-to-event outcomes; weighted mean difference (WMD) for continuous outcomes (eGFR slope, UACR change).

Additional outcome(s) Secondary efficacy: all-cause mortality; CV death; HHF; non-fatal MI; non-fatal stroke; annual eGFR slope (mL/min/1.73m²/year); relative and absolute reduction in UACR; time to ESRD.

Safety outcomes: diabetic ketoacidosis (including euglycemic DKA); volume depletion/hypotension; genital mycotic infections; serious urinary tract infections; lower-limb amputations; bone fractures; acute kidney injury; severe hypoglycemia; serious adverse events and discontinuations.

Data management All search results will be exported to Rayyan QCRI (https://rayyan.qcri.org) for blinded duplicate screening. After deduplication, records will progress through two-stage screening: title/abstract then full-text, each conducted independently by two reviewers. Disagreements will be resolved by consensus or arbitration by a third reviewer.

Data will be extracted into a standardized form developed in Microsoft Excel and REDCap, piloted on five included studies before full deployment. Two reviewers will independently extract data; discrepancies will be resolved by discussion. Author contact will be attempted for missing data.

Inter-rater agreement will be measured using Cohen's kappa coefficient.

Quality assessment / Risk of bias analysis Risk of bias in randomized controlled trials will be assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each study will receive an overall rating of Low, Some Concerns, or High risk of bias.

Observational studies will be assessed using the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions) across seven domains.

All assessments will be performed independently by two reviewers; disagreements resolved by consensus or arbitration. Certainty of evidence for each outcome will be rated using the GRADE framework, presented in Summary of Findings tables generated with GRADEpro GDT.

Strategy of data synthesis Quantitative meta-analysis will be performed using R (packages: meta, metafor, netmeta) where ≥2 studies report comparable outcomes. A random-effects model (DerSimonian-Laird estimator) will be the primary pooling method to account for between-study heterogeneity. Fixed-effects model will be used in sensitivity analysis.

Dichotomous outcomes (composite endpoints, event rates) will be pooled as hazard ratios (HR) or relative risks (RR) with 95% CIs. Continuous outcomes (eGFR slope, UACR change) will be pooled as weighted mean differences (WMD) or standardized mean differences (SMD).

Heterogeneity will be assessed using Cochran's Q (p75%: considerable).

A frequentist network meta-analysis (NMA) using the netmeta package will compare individual SGLT2 inhibitors. Treatment rankings will be expressed as P-scores. Consistency between direct and indirect evidence will be evaluated by node-splitting.

Publication bias will be assessed for outcomes with ≥10 studies using Egger's test and contour-enhanced funnel plots, with trim-and-fill adjustment if asymmetry is detected.

Subgroup analysis Pre-specified subgroup analyses will be conducted where sufficient data are available:

1. Baseline eGFR strata: ≥60; 45–59; 30–44; <30 mL/min/1.73m²
2. Baseline UACR category: 300 mg/g (macroalbuminuria)
3. Diabetes status: T2DM vs. non-diabetic CKD
4. Individual SGLT2 inhibitor (canagliflozin vs. dapagliflozin vs. empagliflozin vs. ertugliflozin)
5. Presence of established CVD vs. CV risk factors only
6. Heart failure status (preserved vs. reduced ejection fraction)
7. Age group: <65 vs. ≥65 years
8. Sex: male vs. female
9. Background RAS blockade use: yes vs. no

Statistical interaction between subgroups will be assessed using chi-squared tests for interaction.

Sensitivity analysis Pre-specified sensitivity analyses will include:

1. Exclusion of studies with high risk of bias (RoB 2: High; ROBINS-I: Serious or Critical)
2. Fixed-effects vs. random-effects model comparison
3. Exclusion of industry-funded studies
4. Restriction to RCTs only (excluding observational studies)
5. Exclusion of open-label trials
6. Leave-one-out (influence) analysis to identify studies with disproportionate impact on pooled estimates
7. Analysis restricted to studies with follow-up ≥24 months
8. Exclusion of studies where UACR or eGFR data were imputed.

Language restriction No language restrictions will be imposed. Non-English articles will be translated as needed.

Country(ies) involved Saudi Arabia (University of Hail; Health Holding Company, Hail).

Other relevant information This protocol was developed in accordance with PRISMA-P 2015 guidelines. The completed review will be reported using PRISMA 2020, with the PRISMA-NMA extension for the network meta-analysis component and MOOSE guidelines for the observational study component. A full 26-week project timeline has been prospectively planned: database searches (weeks 3–4), title/abstract screening (weeks 5–7), full-text screening (weeks 8–10), data extraction and risk of bias assessment (weeks 11–15), statistical analysis and network meta-analysis (weeks 16–20), and manuscript preparation and submission (weeks 21–26). The

search strategy was developed with reference to the PRESS (Peer Review of Electronic Search Strategies) checklist. Statistical analyses will be performed using R software with the metafor and netmeta packages. GRADE Summary of Findings tables will be generated using GRADEpro GDT software. No ethics committee approval is required as this is a secondary analysis of previously published data. Patient-level data will not be accessed unless provided by trial investigators through established data-sharing platforms.

Keywords SGLT2 inhibitors; cardiorenal protection; chronic kidney disease; heart failure; cardiovascular outcomes; dapagliflozin; empagliflozin; canagliflozin; meta-analysis; systematic review.

Dissemination plans Findings will be submitted for publication in a peer-reviewed journal with scope in nephrology, cardiology, or clinical pharmacotherapy. Target journals include the Journal of the American Society of Nephrology, Kidney International, European Heart Journal, or Pharmacotherapy. The INPLASY registration number will be cited in the published article. A summary of findings will be shared through academic and clinical networks at the University of Hail. Relevant conference submissions to ASN Kidney Week and ESC Congress will be considered upon completion.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Contributions: Conceived and designed the protocol, developed the search strategy, will lead data extraction, risk of bias assessment, statistical analysis, and manuscript preparation.
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Author 2 - Basmah Alanazi - Contributions: Co-developed the protocol, will perform independent screening, data extraction, and risk of bias assessment; contributed to clinical content and manuscript revision.
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