INPLASY PROTOCOL

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None declared.

Effects of SGLT2 inhibitors on cardiovascular and renal outcomes in patients with CKD stage3/4: A meta-analysis

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Review question / Objective: **The magnitude of cardiovascular and renal benefits for CKD stage3/4 patients and with different baseline kidney function or underlying diseases remains unclear.**
Main outcome(s) **The primary cardiovascular outcomes of this study included: cardiovascular death or hospitalization for heart failure. The primary renal outcomes of this study included: worsening kidney function (defined as doubling of serum creatinine or sustained 40% decline in eGFR), end-stage kidney disease (ESKD) (defined as requirement for chronic dialysis or kidney transplantation, or sustained eGFR below 15 mL/min/1.73 m²) or renal death. If the study reported both doubling of serum creatinine and sustained 40% decline in eGFR, we prioritized sustained 40% decline in eGFR as the definition of worsening kidney function.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 August 2021 and was last updated on 06 August 2021 (registration number INPLASY202180022).

INTRODUCTION

Review question / Objective: **The magnitude of cardiovascular and renal benefits for CKD stage3/4 patients and with different baseline kidney function or underlying diseases remains unclear.**

Condition being studied: **Chronic kidney disease.**

METHODS

Participant or population: **The included population was patients >18 years old with**

CKD stage3/4, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2. There were no race or sex restrictions.

Intervention: The included trials required the intervention group to take an SGLT2 inhibitor, and there were no limits on specific doses. Trials of SGLT2 inhibitors in combination with other basic therapeutic agents (such as those for controlling blood pressure or blood sugar) were also permitted.

Comparator: Control groups without treatment or treated only with placebos were included. Control groups provided basic treatment were also included.

Study designs to be included: Trials were restricted to parallel-group multicenter randomized controlled trials. There were no regional or language restrictions. Repetitive studies, case reports, animal experiments, cohort studies, and retrospective studies were excluded.

Eligibility criteria: Patients with CKD stage3/4.

Information sources: Two authors searched for relevant randomized controlled trials that investigated the efficacy of SGLT2 inhibitors. The following electronic databases were searched: PubMed, Web of Science, Sciencedirect, Embase, and Clinical trials (http://www.clinicaltrials.gov) from their inception to April 15, 2021. Meanwhile, we performed several exhaustive searches of major international conference proceedings, grey literature (the noncommercial bibliography of doctors' and masters', technical documents (including government reports)) and clinical trials that may be ongoing or not yet published to minimize loss or omission of suitable articles that met our inclusion criterion. Additionally, the references in each study and meta-analysis of SGLT2 inhibitors were searched for potentially eligible studies. Details on the databases and search strategies are presented in the search strategies supplement. A check was indispensable for the integrity and veracity of studies. All records from the initial search were imported into NoteExpress v3.2.0.7535 to manage and confirm the above information, and was performed concurrently by four independent authors (NL, DL, YWZ, GWZ). Discrepancies during this process were resolved through discussion or mediated by a third author (LZ).

Main outcome(s): The primary cardiovascular outcomes of this study included: cardiovascular death or hospitalization for heart failure. The primary renal outcomes of this study included: worsening kidney function (defined as doubling of serum creatinine or sustained 40% decline in eGFR), end-stage kidney disease (ESKD) (defined as requirement for chronic dialysis or kidney transplantation, or sustained eGFR below 15 mL/min/1.73 m²) or renal death. If the study reported both doubling of serum creatinine and sustained 40% decline in eGFR, we prioritized sustained 40% decline in eGFR as the definition of worsening kidney function.

Quality assessment / Risk of bias analysis: The Cochrane quality assessment tool provided by RevMan was used to evaluate the risk of bias in each trial. Three authors (NL, DL, SJL) independently assessed the risk of bias. The assessment items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome assessment, incomplete outcome data, selective reporting, and other biases. Each item was rated as unknown risk, low risk, or high risk. Analysis of total bias for included studies was also measured. Any discrepancies were adjudicated by a third author (LZ or DZ).

Strategy of data synthesis: For cardiovascular and renal outcomes, we pooled HRs with 95% confidence intervals (CIs) to evaluate the effect of each trial. For safety outcome, we used the risk ratio (RR) for the calculation . For continuous variables, weighted mean differences

(WMD) were used for analysis. Additionally, we used a random-effects models with application of the DerSimonian–Laird estimator. We assessed heterogeneity between studies using the I^2 statistics. Values of 25%, 50%, and 75% represented mild, moderate, and high heterogeneity, respectively. If the number of included studies was over 10, we conducted a publication bias analysis using the Egger test Data were analyzed using STATA version 16.0.

Subgroup analysis: We performed subgroup analyses on primary outcomes to verify if there were any differences between different eGFR subgroups (CKD stage3a defined as eGFR 45-60 mL/min/1.73 m^2, CKD stage3b defined as eGFR 30-44 mL/min/1.73 m^2, CKD stage4 defined as eGFR $<$30 mL/min/1.73 m^2) and whether benefits changed in patients with different underlying diseases (such as type 2 diabetes, heart failure, atherosclerotic cardiovascular disease).

Sensitivity analysis: For sensitivity analysis, we excluded literature one by one for analysis.

Country(ies) involved: China.

Keywords: SGLT2 inhibitors, chronic kidney disease, cardiovascular outcome, renal outcome, meta-analysis.

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