INPLASY PROTOCOL

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All authors disclose that they have no conflicts of interest.

SGLT2 inhibitors for prevention of cardiorenal events in people with heart failure: a protocol for systematic review and meta-analysis

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Review question / Objective: **The efficacy of sodium glucose cotransporter 2 (SGLT2) inhibitors for heart failure (HF) is unestablished. The relative efficacy of different SGLT2 inhibitors for HF is unclear.**
Condition being studied: **We intend to conduct a series of meta-analysis studies to confirm the efficacy of SGLT2 inhibitors on cardiorenal endpoints in various HF subgroups, and to assess the relative efficacy of different SGLT2 inhibitors on HF.**
Information sources: **PubMed and Embase will be searched for relevant randomized trials using the above search strategy.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 June 2020 and was last updated on 24 June 2020 (registration number INPLASY202060092).

INTRODUCTION

Review question / Objective: **The efficacy of sodium glucose cotransporter 2 (SGLT2) inhibitors for heart failure (HF) is unestablished. The relative efficacy of different SGLT2 inhibitors for HF is unclear.**

Condition being studied: **We intend to conduct a series of meta-analysis studies**

to confirm the efficacy of SGLT2 inhibitors on cardiorenal endpoints in various HF subgroups, and to assess the relative efficacy of different SGLT2 inhibitors on HF.

METHODS

Search strategy: PubMed search strategy ("Heart Failure"[mesh] OR "Heart Failure"[tiab] OR "Cardiac Failure"[tiab] OR "Heart Decompensation"[tiab] OR "Myocardial Failure"[tiab]) AND (Sodium-Glucose Transporter 2 Inhibitors[MH] OR "Sodium glucose co-transporter 2*"[TIAB] OR SGLT2*[TIAB] OR "Empagliflozin"[tiab] OR "Dapagliflozin"[tiab] OR "Canagliflozin"[tiab] OR "ertugliflozin"[tiab] OR sotagliflozin[TIAB]) AND ("hospitalization for heart failure" OR "hospitalization due to heart failure" OR "heart failure hospitalization" OR HHF[TIAB] OR "cardiovascular death" OR "cardiac death") AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])). Embase search strategy ('Heart Failure'/exp OR 'Heart Failure':ab,ti) AND ('sodium glucose cotransporter 2 inhibitor'/exp OR 'Sodium glucose co-transporter 2*':ab,ti OR 'SGLT2*':ab,ti OR empagliflozin:ab,ti OR Canagliflozin:ab,ti OR dapagliflozin:ab,ti OR ertugliflozin:ab,ti OR sotagliflozin:ab,ti) AND ('hospitalization for heart failure' OR 'hospitalization due to heart failure' OR 'heart failure hospitalization' OR HHF:ab,ti OR 'cardiovascular death' OR 'cardiac death') AND (('randomized controlled trial'/exp OR 'controlled clinical study'/exp OR random$:ab,ti OR placebo:ab,ti OR 'drug therapy':lnk OR ((double OR single OR doubly OR singly) AND (blind OR blinded OR blindly):ti,ab OR 'double blind procedure'/exp) OR trial:ab,ti OR groups:ab,ti) NOT ('animal experiment'/exp NOT 'human experiment'/exp)).

Participant or population: Adults with HF.

Intervention: Interventions of interest are SGLT2 inhibitors (including but not limited to empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin).

Comparator: Comparison treatments are non-gliflozin active drugs or placebo.

Study designs to be included: Randomized, controlled, event-driven, cardiovascular outcome trials.

Eligibility criteria: As is shown in the above PICOS criteria.

Information sources: PubMed and Embase will be searched for relevant randomized trials using the above search strategy.

Main outcome(s): Main outcomes to be assessed in each of the three meta-analyses (i.e., CRD42020159567, CRD42020159584 and CRD42020159596) are the following three ones: 1. cardiovascular death (CVD) or hospitalization for heart failure (HHF). If this composite outcome is not available, we will use the composite outcome of CVD, HHF, or an urgent visit resulting in intravenous therapy for HF instead. 2. CVD. 3. HHF.

Additional outcome(s): Secondary outcomes to be assessed in the CRD42020159567 meta-analysis are the following three ones: 1. Major adverse cardiovascular events (MACE), defined as a composite of CVD, nonfatal myocardial infarction, or nonfatal stroke. 2. Death from any cause. 3. Worsening nephropathy, defined as sustained (measured ≥30 days apart) 40% reduction in the estimated glomerular filtration rate (eGFR), end-stage kidney disease (ESKD), or renal death. In this composite outcome, it is acceptable for 40% reduction in eGFR to be replaced by 50% reduction in eGFR or doubling of serum creatinine, as well as ESKD to be replaced by initiation of renal-replacement therapy. If this composite outcome is not available, we will use the composite outcome of worsening nephropathy or incident nephropathy [defined as progression to macroalbuminuria, i.e., urine albumin-creatinine ratio >300 mg/g], or worsening nephropathy or CVD instead. Secondary outcomes to be assessed in the CRD42020159596 meta-analysis are the

second and third secondary outcomes in the CRD42020159567 meta-analysis. No secondary outcome will be assessed in the CRD42020159584 meta-analysis.

Data management: Two authors will independently collect pre-specified data from included studies using standardized Excel data extraction sheets. The pre-specified data items to be extracted consist of study type, key patient characteristics, type of intervention, type of comparator, study outcomes based on overall participants and main subgroups. The inconsistencies on data extraction will be addressed by discussion between them or by the involvement of a third author.

Quality assessment / Risk of bias analysis: Two authors will independently perform risk of bias assessment for included RCTs according to the Cochrane risk of bias tool. According to this tool included trails will be assessed in the following seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The inconsistencies on quality assessment will be addressed by discussion between them or by the involvement of a third author.

Strategy of data synthesis: In order to complete the CRD42020159567 and CRD42020159584 meta-analyses, we will perform random-effects meta-analysis using trial-level survival data (i.e., HRs and 95% CIs from primary studies) to estimate pooled HRs and 95% CIs. Heterogeneity will be evaluated by I^2 statistic, and this value greater than 50% represents substantial heterogeneity. Random-effects meta-regression will be conducted to compute the p value for subgroup differences, and this p value less than 0.05 indicates statistical significance. Statistical analyses will be completed using Stata (version 15.1). In order to complete the CRD42020159596 meta-analysis, we will perform fixed-effects conventional meta-analysis and network meta-analysis within the Bayesian framework to synthesize HRs and 95% CIs based on trial-level survival data. Heterogeneity will be evaluated by I^2 statistic, and this value greater than 50% represents substantial heterogeneity. The node-splitting model will be created to assess the inconsistency between direct and indirect evidences when there is at least one closed loop in the evidence network. Surface under the cumulative ranking curve (SUCRA) will be calculated to rank drug treatments, and the rankings of treatments will be presented in radar plots. Radar plots and comparison-adjusted funnel plots will be made using Stata (version 15.1). Network meta-analyses will be done using R (version 3.6.0) and JAGS (version 4.3.0).

Subgroup analysis: For the CRD42020159567 and CRD42020159596 meta-analyses, subgroup analyses will be conducted according to the following three factors related to patient characteristics: 1. NYHA class: Class II, Class III or IV; 2. History of type 2 diabetes: Yes, No; 3. History of kidney disease (defined as eGFR 65 years; 2. Sex: Male, Female; 3. Race: Caucasian, Non-Caucasian; 4. Region: North America, Central/South America, Europe, Asia; 5. BMI: 40%; 7. Main cause of heart failure: Ischemic, Nonischemic; 8. Mineralocorticoid receptor antagonist: Yes, No; 9. NT-proBNP, AF/F, and HHF.

Sensibility analysis: For the CRD42020159567 and CRD42020159584 meta-analyses, included studies in which grouping criteria are slightly different will be omitted to perform sensitivity analysis. For the CRD42020159596 meta-analysis, we will perform sensitivity analysis using the random-effects model instead of the fixed-effects model when substantial heterogeneity (i.e., I^2 statistic greater than 50%) is observed.

Country(ies) involved: China.

Keywords: heart failure; SGLT2 inhibitors; cardiovascular death; hospitalization for heart failure.

Dissemination plans: **The findings from the studies will be disseminated through peer-reviewed publications and at scientific conferences.**

Contributions of each author:
Author 1 - Mei Qiu.
Author 2 - Xiaoling Cai.
Author 3 - Xubin Wei.
Author 4 - Xian Zhou.
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