

# INPLASY PROTOCOL

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**Review Stage at time of this submission:** Preliminary searches.

**Conflicts of interest:**  
None.

## SGLT2 inhibitors for prevention of cardiorenal events in patients 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.

**Condition being studied:** We intend to conduct a meta-analysis to evaluate the efficacy of SGLT2 inhibitors on cardiorenal endpoints in various HF subgroups, and to assess the relative efficacy of different SGLT2 inhibitors in patients with HF.

**Information sources:** We will search PubMed and Embase using the above search strategies, to obtain relevant studies potentially eligible to be included.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 June 2020 and was last updated on 29 June 2020 (registration number INPLASY202060109).

### INTRODUCTION

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

**Condition being studied:** We intend to conduct a meta-analysis to evaluate the

efficacy of SGLT2 inhibitors on cardiorenal endpoints in various HF subgroups, and to assess the relative efficacy of different SGLT2 inhibitors in patients with 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:** They are detailed in the above PICOS sections.

**Information sources:** We will search PubMed and Embase using the above search strategies, to obtain relevant studies potentially eligible to be included.

**Main outcome(s):** Main outcomes to be assessed in the meta-analysis are the following three ones: 1. CVD or 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 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  $\geq 30$  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.

**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.

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### 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 trials 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 evaluate the efficacy of SGLT2 inhibitors on cardiorenal endpoints in various HF subgroups defined by key factors related to patient characteristics, we will perform random-effects meta-analysis using trial-level survival data (i.e., HRs and 95% CIs from original 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 assess the comparative efficacy of different SGLT2 inhibitors for treatment of HF, 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:** Subgroup analyses will be conducted according to the following key 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; 5. Sex: Male, Female; 6. Race: Caucasian, Non-Caucasian; 7. Region: North America, Central/South America, Europe, Asia; 8. BMI: 40%; 10. Main cause of heart failure: Ischemic, Nonischemic; 11. Mineralocorticoid receptor antagonist: Yes, No; 12. NT-proBNP, AF/F, and HHF.

**Sensitivity analysis:** Included studies in which grouping criteria are slightly different will be omitted to perform sensitivity analysis. Meanwhile, 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 found.

**Country(ies) involved:** China.

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

**Dissemination plans:** Ethical approval is not required as the meta-analysis will analyze the data collected from published articles. The findings deriving from the study 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.

Author 5 - Yingxi Tang.