INPLASY PROTOCOL

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Conflicts of interest:
None.

Meta-analyzing the factors affecting the efficacy of SGLT2is on heart failure events based on cardiovascular outcome trials

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Review question / Objective: **The efficacy of sodium-glucose transporter 2 inhibitors (SGLT2is) in reducing heart failure (HF) events is unestablished in relevant subgroups defined by any of the six factors: type of underlying diseases, type of SGLT2is, left ventricular ejection fraction (LVEF) level, New York Heart Association (NYHA) functional class, region, and race.**
Condition being studied: **This meta-analysis will assess the efficacy of SGLT2is in reducing heart failure events in relevant subgroups defined by preplanned six factors.**
Information sources: **We will systematically search PubMed and Embase, for identifying relevant cardiovascular outcome trials (CVOTs), using the above retrieval strategies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 November 2020 and was last updated on 21 November 2020 (registration number INPLASY2020110094).

INTRODUCTION

Review question / Objective: **The efficacy of sodium-glucose transporter 2 inhibitors (SGLT2is) in reducing heart failure (HF) events is unestablished in relevant subgroups defined by any of the six factors: type of underlying diseases, type of SGLT2is, left ventricular ejection fraction (LVEF) level, New York Heart Association (NYHA) functional class, region, and race.**

Condition being studied: **This meta-analysis will assess the efficacy of SGLT2is in reducing heart failure events in relevant**

subgroups defined by preplanned six factors.

METHODS

Search strategy: ("sodium-glucose transporter-2 inhibitors"[MeSH Terms] OR "sodium-glucose cotransporter-2 inhibitors"[Title/Abstract] OR "sodium-glucose cotransporter-2 inhibitor"[Title/Abstract] OR "sodium-glucose transporter-2 inhibitors"[Title/Abstract] OR "sodium-glucose transporter-2 inhibitor"[Title/Abstract] OR "SGLT-2 Inhibitors"[Title/Abstract] OR "SGLT2 Inhibitors"[Title/Abstract] OR "SGLT-2 Inhibitor"[Title/Abstract] OR "SGLT2 Inhibitor"[Title/Abstract] OR "SGLT2i"[Title/Abstract] OR "SGLT2is"[Title/Abstract] OR "SGLT-2i"[Title/Abstract] OR "SGLT2-is"[Title/Abstract] OR "canagliflozin"[MeSH Terms] OR "canagliflozin"[Title/Abstract] OR "Invokana"[Title/Abstract] OR "empagliflozin"[Supplementary Concept] OR "empagliflozin"[Title/Abstract] OR "Jardiance"[Title/Abstract] OR "2 3 4 ethoxybenzyl 4 chlorophenyl 6 hydroxymethyltetrahydro 2h pyran 3 4 5 triol"[Supplementary Concept] OR "dapagliflozin"[Title/Abstract] OR "forxiga"[Title/Abstract] OR "ertugliflozin"[Supplementary Concept] OR "ertugliflozin"[Title/Abstract] OR "Steglatro"[Title/Abstract] OR "2s 3r 4r 5s 6r 2 4 chloro 3 4 ethoxybenzyl phenyl 6 methylthio tetrahydro 2h pyran 3 4 5 triol"[Supplementary Concept] OR "sotagliflozin"[Title/Abstract] OR "LX4211"[Title/Abstract] OR "ipragliflozin"[Supplementary Concept] OR "ipragliflozin"[Title/Abstract] OR "Suglat"[Title/Abstract]) AND (“cardiovascular death” [tiab] OR “CVD” [tiab] OR “heart failure hospitalization”[tiab] OR “heart failure hospitalisation”[tiab] OR “hospitalized heart failure”[tiab] OR “HHF”[tiab] OR "death"[tiab] OR "heart failure"[tiab] OR "HF"[tiab]) 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])).

Participant or population: Adults with congestive heart failure (CHF) or with chronic kidney disease (CKD) or with type 2 diabetes (T2D).

Intervention: Any SGLT2i. We will not consider the dosage of drugs as an effect modifier.

Comparator: Placebo or active control.

Study designs to be included: Cardiovascular outcome trials (CVOTs) of SGLT2is.

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

Information sources: We will systematically search PubMed and Embase, for identifying relevant cardiovascular outcome trials (CVOTs), using the above retrieval strategies.

Main outcome(s): The heart failure composite outcome, defined as a composite of cardiovascular death (CVD) or hospitalization for heart failure (HHF). If this composite outcome is not available, we will use a composite of CVD or HHF or an urgent visit for heart failure instead.

Data management: The articles identified by the retrieval of two online databases will be assessed for relevance according to their titles and abstracts, and then those potentially eligible studies will be assessed for the final eligibility according to the inclusion and exclusion criteria. Two authors will then independently extract pre-specified data from the included studies using a standardized Excel data extraction sheet. The pre-specified data to be extracted contain study design, type of underlying diseases, type of interventions, type of control, study outcomes from related subgroups defined by the factors of interest: type of underlying diseases, type of SGLT2is, LVEF level, NYHA functional class, region, and race. Any disagreements relevant with study selection and data extraction will be resolved through discussion with a third author. At the end of follow-up, using hazard ratios (HRs) and

95% confidence intervals (CIs) which are reported in original publications.

Quality assessment / Risk of bias analysis: Two authors will independently use the Cochrane risk of bias assessment tool to assess the risk of bias for included CVOTs. Any disagreements related to risk of bias assessment will be resolved through discussion with a third author.

Strategy of data synthesis: We will use the trial-level survival data (i.e., HRs and 95% CIs extracted from original publications) to perform fixed-effects meta-analysis. I2 statistic will be calculated to measure statistical heterogeneity. I2 > 50% will be considered as substantial heterogeneity. Cochran's Q test will be used to test for treatment-by-subgroup interactions. Funnel plots and Egger tests will be done to assess the publication bias. All statistical analyses will be conducted in the Stata software (version 15.1).

Subgroup analysis: Subgroup meta-analysis will be conducted according to each of the following factors of interest: 1. Type of underlying diseases: CHF, CKD, T2D; 2. Type of SGLT2is; 3. LVEF level (%): <40, 40 to <50, ≥50; 4. NYHA class: NYHA class II, NYHA class III or IV; 5. Region: North America, Latin America, Europe, Asia; 6. Race: White, Black, Asian.

Sensibility analysis: If substantial heterogeneity is observed, random-effects meta-analysis will be performed to assess the robustness of pooled results.

Country(ies) involved: China.

Keywords: SGLT2is, cardiovascular death, hospitalization for heart failure, heart failure, chronic kidney disease, type 2 diabetes.

Contributions of each author:
Author 1 - Mei Qiu.
Author 2 - Liang-Liang Ding.
Author 3 - Hai-Rong Zhou.