INPLASY PROTOCOL

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Conflicts of interest:
None.

Comparative efficacy of different SGLT2is on cardiorenal events: a network meta-analysis based on CVOTs

Qiu, M[1]; Ding, LL[2]; Zhou, HR[3].

Review question / Objective: **The relative efficacy of different SGLT2is on cardiorenal outcomes is unclear. It is unclear whether SGLT2is have the different efficacy on cardiorenal outcomes in different underlying diseases.**
Condition being studied: **This meta-analysis will assess the relative efficacy of different SGLT2is on cardiorenal outcomes, and assess the impact of type of underlying disorders on the efficacy of SGLT2is on cardiorenal outcomes.**
Information sources: **We will systematically search Embase and PubMed using pre-planned search strategies, for identifying relevant cardiovascular outcome trials (CVOTs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 December 2020 and was last updated on 21 December 2020 (registration number INPLASY2020120105).

INTRODUCTION

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Condition being studied: **This meta-analysis will assess the relative efficacy of different SGLT2is on cardiorenal outcomes, and assess the impact of type of underlying**

disorders on the efficacy of SGLT2is on cardiorenal outcomes.

METHODS

Search strategy: ("Diabetes Mellitus, Type 2"[Mesh] OR "type 2 diabetes mellitus"[tiab] OR "type 2 diabetes"[tiab] OR "T2DM"[tiab] OR "T2D"[tiab] OR "MODY"[tiab] OR "NIDDM"[tiab] OR "Noninsulin Dependent Diabetes Mellitus"[tiab] OR "Maturity Onset Diabetes"[tiab] OR "Heart Failure"[Mesh] OR "Heart Failure"[tiab] OR "Cardiac Failure"[tiab] OR "Congestive Heart Failure"[tiab] OR "Heart Decompensation"[tiab] OR "Myocardial Failure"[tiab] OR "Renal Insufficiency, Chronic"[Mesh] OR "Chronic Renal Insufficiencies"[tiab] OR "Chronic Renal Insufficiency"[tiab] OR "Chronic Kidney Insufficiency"[tiab] OR "Chronic Kidney Diseases"[tiab] OR "Chronic Kidney Disease"[tiab] OR "CKD"[tiab] OR "Chronic Renal Diseases"[tiab] OR "Chronic Renal Disease"[tiab]) AND ("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 "myocardial infarction"[TIAB] OR stroke[tiab] OR "Cardiovascular Events"[TIAB] OR "cardiac Events"[TIAB] OR "MACE"[tiab] OR "major adverse cardiovascular event*"[tiab] OR "major adverse cardiac event*"[tiab] OR "heart failure hospitalization"[tiab] OR "Kidney function progression"[tiab] OR "renal function progression"[tiab] OR "chronic renal disease progression"[tiab] OR "progression of CKD"[tiab] OR "CKD progression"[tiab] OR "renal events"[tiab] OR "cardiorenal events"[tiab] OR "All-cause death"[tiab] OR "All-cause mortality"[tiab] OR "death"[tiab] OR "heart failure"[tiab] OR GFR[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 type 2 diabetes (T2D), adults with heart failure (HF), and adults with chronic kidney disease (CKD).

Intervention: Any SGLT2 inhibitor. We will not consider the dosage of drugs as an effect modifier.

Comparator: Placebo or active control.

Study designs to be included: Randomized controlled trials (RCTs) aiming to assess cardiovascular or renal outcomes.
Eligibility criteria: They are detailed in the above PICOS sections.

Information sources: We will systematically search Embase and PubMed using pre-planned search strategies, for identifying relevant cardiovascular outcome trials (CVOTs).

Main outcome(s): 1. Major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death (CVD), nonfatal myocardial infarction (MI), or nonfatal stroke. 2. Fatal and nonfatal MI. 3. Fatal and nonfatal stroke. 4. CVD. 5. Cardiovascular death or hospitalization for heart failure (CVD or HHF). 6. Hospitalization for heart failure (HHF). 7. Kidney function progression (KFP), i.e., a renal composite outcome, defined as a composite of sustained 40% reduction in estimated glomerular filtration rate (eGFR) or doubling of serum creatinine, end-stage kidney disease (ESKD) or initiation of renal-replacement therapy, or renal death. If this composite outcome is not available, we will use other one which is similar with this one instead. 8. All-cause death (ACD).

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 disease, type of intervention, type of control, study outcomes. Any disagreements relevant with study selection and data extraction will be resolved through discussion with a third author.

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 RCTs. Any disagreements related to risk of bias assessment will be resolved through discussion with a third author.

Strategy of data synthesis: We will use hazard ratios (HRs) and 95% confidence intervals (CIs) as reported in included original studies to perform traditional meta-analysis and network meta-analysis with the fixed-effects model. Traditional meta-analysis within the frequentist framework will be conducted stratified by type of underlying disorders, to assess the effects of underlying disorders on the efficacy of SGLT2is. We will measure statistical heterogeneity by calculating I2 statistic, and examine subgroup effects by doing Cochran's Q test. Network meta-analysis within the Bayesian framework will be conducted, to produce the estimators of the relative efficacy of different SGLT2is. We will draw the network plots of direct comparisons, and will evaluate the inconsistency between direct and indirect evidence by performing inconsistency test if there is at least one closed loop existing in the network plots of direct evidence. $P \leq 0.05$ or the low limit of 95% CIs of HRs ≥ 1.0 or the upper limit of those ≤ 1.0 represents for statistical significance. We will do network meta-analyses and network plots using the R (version 3.6.0) and JAGS (version 4.3.0) software, and do other statistical analyses and forest plots using the Stata software (version 15.1).

Subgroup analysis: Subgroup analysis on all the endpoints of interest will be conducted according to type of underlying diseases.

Sensibility analysis: Not pre-planned.

Country(ies) involved: China.

Keywords: SGLT2is, type 2 diabetes, heart failure, chronic kidney disease, cardiovascular outcomes, renal outcomes.

Contributions of each author:
Author 1 - Mei Qiu.
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