# INPLASY PROTOCOL

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**Support:** **None.**

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

**Conflicts of interest:**
**None.**

# Comparison of the cardiorenal benefits from SGLT2 inhibitors for patients with different underlying disease: a meta-analysis of cardiovascular and renal outcome trials

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**Review question / Objective:** **Whether the cardiorenal benefits from sodium-glucose transporter 2 (SGLT2) inhibitors for patients with different underlying disease are similar or not remains unclear.**
**Condition being studied:** **This meta-analysis will assess the similarity and difference in the cardiorenal benefits from SGLT2 inhibitors for patients with different underlying disease.**
**Information sources:** **We will systematically search Embase and PubMed using appropriate search strategies, for identifying relevant large randomized trials. The search strategies are detailed in the above Search Strategy section.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 September 2020 and was last updated on 26 September 2020 (registration number INPLASY202090091).

## INTRODUCTION

**Review question / Objective:** **Whether the cardiorenal benefits from sodium-glucose transporter 2 (SGLT2) inhibitors for patients with different underlying disease are similar or not remains unclear.**

**Condition being studied:** **This meta-analysis will assess the similarity and difference in the cardiorenal benefits from SGLT2 inhibitors for patients with different underlying disease.**

## 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, adults with chronic heart failure and reduced ejection fraction, and adults with chronic kidney disease.

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

**Comparator:** Placebo.

**Study designs to be included:** Randomized, controlled, and cardiovascular or renal outcome trials.

**Eligibility criteria:** They are detailed in the above PICOS sections.

**Information sources:** We will systematically search Embase and PubMed using appropriate search strategies, for identifying relevant large randomized trials. The search strategies are detailed in the above Search Strategy section.

**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. CVD or

hospitalization for heart failure (HHF). 6. 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).

**Additional outcome(s):** None.

**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 (i.e., HRs and 95% CIs as reported at the end of follow-up in original studies). 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 the study-level survival data (i.e., HRs and 95% CIs extracted from original studies) to perform random-effects meta-analysis stratified by type of underlying disease. I2 statistic will be calculated to measure statistical 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 analysis on all the endpoints of interest will be conducted according to type of underlying disease.

**Sensibility analysis:** Not pre-planned.

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

**Keywords:** SGLT2 inhibitors, type 2 diabetes, chronic heart failure, chronic kidney disease, cardiovascular death, kidney function progression.

**Contributions of each author:**
Author 1 - Mei Qiu.
Author 2 - Liang-Liang Ding.
Author 3 - Miao Zhang.
Author 4 - Hai-Rong Zhou.