INPLASY PROTOCOL

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None.

Use of SGLT2 inhibitors and occurrence of respiratory disorders: a meta-analysis of large randomized trials of SGLT2 inhibitors

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Review question / Objective: **No studies are designed to assess the risk of respiratory disorders with sodium-glucose transporter 2 (SGLT2) inhibitors.**
Condition being studied: **This meta-analysis will evaluate the relationship between use of SGLT2 inhibitors and occurrence of respiratory disorders.**
Information sources: **We will systematically search Embase and PubMed using the above search strategies, for identifying relevant randomized controlled trials (RCTs).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 October 2020 and was last updated on 01 October 2020 (registration number INPLASY2020100002).

INTRODUCTION

Review question / Objective: **No studies are designed to assess the risk of respiratory disorders with sodium-glucose transporter 2 (SGLT2) inhibitors.**

Condition being studied: **This meta-analysis will evaluate the relationship between use of SGLT2 inhibitors and occurrence of respiratory disorders.**

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.

Study designs to be included: Cardiovascular or renal outcome RCTs in which each study arm includes more than 1000 participants.

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

Information sources: We will systematically search Embase and PubMed using the above search strategies, for identifying relevant randomized controlled trials (RCTs).

Main outcome(s): 1. Respiratory disorders. 2. Acute pulmonary oedema. 3. Acute respiratory distress syndrome. 4. Asthma. 5. Chronic obstructive pulmonary disease (COPD). 6. Interstitial lung disease. 7. Pulmonary hypertension (PH). 8.

Respiratory failure. 9. Sleep apnoea syndrome.

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 the 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, the number of the occurrence of the respiratory disorders of interest. Any disagreements relevant with study selection and data extraction will be resolved through discussion with a third author. Treatment effects will be measured by pooled risk ratios (RRs) and 95% confidence intervals (CIs) derived from meta-analysis of the dichotomous data in included studies.

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

Strategy of data synthesis: We will use the study-level binary data (i.e., the number of events in the intervention group, the number of patients in the intervention group, the number of events in the control group, and the number of patients in the control group) to perform random-effects meta-analysis. Effect size will be presented as risk ratio (RR) and 95% confidence interval (CI). 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 and type of SGLT2 inhibitors.

Sensibility analysis: Not pre-planned.

Country(ies) involved: China.

Keywords: SGLT2 inhibitors, respiratory disorders, chronic obstructive pulmonary disease, respiratory failure, acute pulmonary oedema.

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