INPLASY PROTOCOL

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Support: **None.**

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

Conflicts of interest:
None.

Comprehensive analysis of the safety of three new drug classes for type 2 diabetes: a meta-analysis of cardiovascular outcome trials

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Review question / Objective: **Sodium-glucose cotransporter-2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP1RAs), and dipeptidyl peptidase-4 inhibitors (DPP4is) are three new drug classes for type 2 diabetes (T2D). A series of large randomized trials have assessed the efficacy of these drugs on cardiovascular and renal endpoints. However, no studies are powered to fully assess the safety of these drugs in patients with T2D.**
Condition being studied: **This meta-analysis will evaluate the risk of three new antihyperglycemic agents (i.e., SGLT2is, GLP1RAs, and DPP4is) in leading to various serious adverse events (SAEs) related to various systems of the human body.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 November 2020 and was last updated on 09 November 2020 (registration number INPLASY2020110036).

INTRODUCTION

Review question / Objective: **Sodium-glucose cotransporter-2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP1RAs), and dipeptidyl peptidase-4 inhibitors (DPP4is) are three new drug classes for type 2 diabetes (T2D). A series of large randomized trials have assessed the efficacy of these drugs on cardiovascular and renal endpoints. However, no studies are powered to fully assess the safety of these drugs in patients with T2D.**

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Condition being studied: This meta-analysis will evaluate the risk of three new antihyperglycemic agents (i.e., SGLT2is, GLP1RAs, and DPP4is) in leading to various serious adverse events (SAEs) related to various systems of the human body.

METHODS

Participant or population: Adults with T2D.

Intervention: Any of SGLT2is, GLP1RAs, or DPP4is. We will not consider doses of drugs as effect modifiers.

Comparator: Placebo or active control.

Study designs to be included: Large randomized trials aiming at assessing cardiovascular or renal endpoints.

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

Information sources: We will search ClinicalTrials.gov, Embase, and PubMed for relevant cardiovascular outcome trials.

Main outcome(s): Various SAEs which were assessed in at least three of the included trials of SGLT2is, GLP1RAs, or DPP4is.

Data management: The articles identified by the retrieval of online databases will be assessed for relevance according to their titles and abstracts, and then those studies potentially eligible 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, patient characteristics, type of intervention, type of control, the number of the occurrence of various SAEs of interest and that of participants. 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 trials. Any disagreements related to quality assessment will be resolved through discussion with a third author.

Strategy of data synthesis: We will perform meta-analysis using the trial-level binary data (i.e., the number of patients with events and patients in the intervention group and in the control group) based on SGLT2i trials, GLP1RA trials, and DPP4i trials, respectively. Drug effects will be presented as risk ratios (RRs) and 95% confidence intervals (CIs). I2 statistic will be calculated to measure statistical heterogeneity. 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: Not preplanned.

Sensibility analysis: Both random-effects meta-analysis and fixed-effects meta-analysis will be conducted to assess the robustness of pooled results.

Country(ies) involved: China.

Keywords: SGLT2is, GLP1RAs, DPP4is, safety, type 2 diabetes.

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

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