INPLASY PROTOCOL

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Corresponding author:
Liang-Liang Ding

15887847798m0@sina.cn

Author Affiliation:
Longhua District Central Hospital

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Comparative efficacy of GLP-1 RAs and SGLT2is for prevention of major adverse cardiovascular events in type 2 diabetes: a network meta-analysis

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

Review question / Objective: **It has been proven that two new antidiabetic drug classes, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), significantly reduce the risk of major adverse cardiovascular events (MACE) in people with type 2 diabetes. However, the relative efficacy of different members of the two drug classes for prevention of MACE is unclear.**
Condition being studied: **This meta-analysis will evaluate the comparative efficacy of different GLP-1 RAs and SGLT2is for prevention of MACE in adults with type 2 diabetes.**
Information sources: **We will systematically search PubMed and Embase using pre-defined search strategies, for English articles reporting relevant randomized trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 April 2020 and was last updated on 26 April 2020 (registration number INPLASY202040177).

INTRODUCTION

Review question / Objective: **It has been proven that two new antidiabetic drug classes, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is), significantly reduce the risk of major adverse cardiovascular events (MACE) in people with type 2 diabetes. However, the relative efficacy of different members of the two drug classes for prevention of MACE is unclear.**

Condition being studied: **This meta-analysis will evaluate the comparative efficacy of different GLP-1 RAs and**

SGLT2is for prevention of MACE in adults with type 2 diabetes.

METHODS

Search strategy: We will systematically search PubMed and Embase using pre-defined search strategies, for English articles reporting relevant randomized trials.

Participant or population: Adults with type 2 diabetes.

Intervention: SGLT2is (including but not limited to empagliflozin, canagliflozin, and dapagliflozin) or GLP-1 RAs (including but not limited to lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, and dulaglutide). We will not consider doses of drugs as effect modifiers.

Comparator: Active or placebo control.

Study designs to be included: Randomized, controlled, event-driven, cardiovascular outcome trials.

Eligibility criteria: We will include randomized, controlled, event-driven, cardiovascular outcome trials assessing the efficacy of GLP-1 RAs or SGLT2is on MACE in adults with type 2 diabetes.

Information sources: We will systematically search PubMed and Embase using pre-defined search strategies, for English articles reporting relevant randomized trials.

Main outcome(s): Major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Additional outcome(s): None.

Data management: The studies retrieved via two electronic databases will be assessed for relevance according to the titles and abstracts, and then those potentially eligible studies will be assessed for final eligibility according to the inclusion and exclusion criteria. Two authors will then independently extract pre-specified data from the studies selected for inclusion using a standardized Excel data extraction sheet. The pre-specified data to be extracted contain study design, intervention characteristics, baseline characteristics of interest, study outcomes deriving from different subgroups. Any disagreements relevant with data extraction will be resolved through discussion with a third author.

Quality assessment / Risk of bias analysis: Two authors will independently assess risk of bias using the Cochrane risk of bias assessment tool. Any disagreements relevant with risk of bias assessment will be resolved through discussion with a third author.

Strategy of data synthesis: We will perform fixed-effects conventional meta-analysis and network meta-analysis within a Bayesian framework using R (version 3.6.0) and JAGS (version 4.3.0) softwares to estimate pooled hazard ratios (HRs) and 95% confidence intervals (CIs) based on trial-level survival data (i.e., HRs and 95% CIs from individual studies). I^2 statistic will be used to measure statistical heterogeneity. The node-splitting model will be built to assess the inconsistency between direct and indirect evidences when one or more closed loops exist in the evidence network. Comparison-adjusted funnel plots will be plotted to assess dominant publication bias.

Subgroup analysis: Subgroup analyses will be conducted according to the following different baseline characteristics: 1. History of cardiovascular disease: Yes, No 2. History of heart failure: Yes, No 3. Prevalent kidney disease (defined as eGFR <60 mL·min−1·1.73 m−2): Yes, No.

Sensibility analysis: When substantial heterogeneity (i.e., I2 statistic >50%) is observed in meta-analysis, we will use random-effects model instead of fixed-effects model to conduct sensitivity analysis.

Country(ies) involved: China.

Keywords: Type 2 diabetes; MACE; GLP-1 RAs; SGLT2is.

Contributions of each author:
Author 1 - Liang-Liang Ding
Author 2 - Mei Qiu
Author 3 - Xian Zhou