

INPLASY PROTOCOL

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Conflicts of interest:
None.

Comparative efficacy of GLP-1 RAs and SGLT2 inhibitors for prevention of cardiorenal events in type 2 diabetes: a network meta-analysis of cardiovascular outcome trials

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Review question / Objective: It has been proven that most members of two new antidiabetic drug classes, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, are able to significantly reduce the risk of cardiorenal events in people with type 2 diabetes. However, the relative efficacy of different members of the two drug classes for prevention of cardiorenal endpoints is unestablished.

Condition being studied: This network meta-analysis will evaluate the comparative efficacy of different GLP-1 RAs and SGLT2 inhibitors for prevention of cardiorenal events in adults with type 2 diabetes.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 May 2020 and was last updated on 22 May 2020 (registration number INPLASY202050081).

INTRODUCTION

Review question / Objective: It has been proven that most members of two new antidiabetic drug classes, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, are able to significantly reduce the risk of cardiorenal events in people with type 2 diabetes. However, the relative efficacy of different members of the two drug classes for prevention of cardiorenal endpoints is unestablished.

Condition being studied: This network meta-analysis will evaluate the comparative efficacy of different GLP-1 RAs and SGLT2 inhibitors for prevention of cardiorenal events in adults with type 2 diabetes.

METHODS

Participant or population: Adults with type 2 diabetes.

Intervention: SGLT2 inhibitors (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 or kidney outcome trials.

Eligibility criteria: They are detailed in the PICOS sections.

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

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. Hospitalization for heart failure (HHF). 3. Kidney function progression (KFP), defined as a composite of development of macroalbuminuria, doubling of serum creatinine or 40% or greater decline in estimated glomerular filtration rate (eGFR), development of end-stage kidney disease, or death due to kidney disease.

Additional outcome(s): 1. CVD. 2. MI, including fatal and nonfatal MI. 3. Stroke, including fatal and nonfatal stroke 4. All-cause death (ACD).

Data management: The studies retrieved via two electronic databases will be assessed for relevance according to the titles and abstracts, and then those studies potentially eligible to be included 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 to be included using a standardized Excel data extraction sheet. The pre-specified data

items to be extracted contain study design, intervention characteristics, baseline characteristics of interest, study outcomes. Any disagreements in the process of 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 for included trials using the Cochrane risk of bias tool. Any disagreements in the process of 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 the R (version 3.6.0) and JAGS (version 4.3.0) software to synthesize hazard ratios (HRs) and 95% confidence intervals (CIs) based on trial-level survival data (i.e., HRs and 95% CIs from individual studies). I² 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 there are one or more closed loops in the evidence network. Comparison-adjusted funnel plots will be drawn to assess publication bias.

Subgroup analysis: Not planned.

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; cardiorenal events; GLP-1 RAs; SGLT2 inhibitors; network meta-analysis.

Contributions of each author:

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Author 2 - Mei Qiu.

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