INPLASY PROTOCOL

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Corresponding author:
Chuanjun Zhuo

chuanjunzhuotjmh@163.com

Author Affiliation:
Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital

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The authors declare no conflict of interest.

Comparative safety of glucagon like peptide-1 receptor agonists in patients with type 2 diabetes: a network meta-analysis of cardiovascular outcome trials

Zhuo, CJ[1]; Tian, HJ[2]; Wang, LN[3]; Gao, XY[4]; Ding, L[5]; Liu, M[6].

Review question / Objective: **To provide the complete hierarchies of safety profile for different GLP1-RAs in cardiovascular outcome trials (COVTs).**
Condition being studied: **Patients with type 2 diabetes.**
Information sources: **A systematic review was conducted to identify published cardiovascular outcome trials for GLP-1 RA on the following databases since inception until August 1, 2020 Medline (via PubMed), Embase and Web of Knowledge.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 August 2020 and was last updated on 30 August 2020 (registration number INPLASY202080122).

INTRODUCTION

Review question / Objective: **To provide the complete hierarchies of safety profile for different GLP1-RAs in cardiovascular outcome trials (COVTs).**

Rationale: **There is no clear evidence of which GLP1-RA is optimal in terms of renal safety, hypoglycaemia, pancreatitis, thyroid carcinoma, pancreatic cancer, etc. We therefore performed a systematic review and network meta-analysis mapping all GLP1-RAs aiming to 1) compare them in terms of cardiovascular, renal and other key outcomes, 2) rank the ingetravie effect of them on key outcomes in patients with T2DM.**

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Condition being studied: Patients with type 2 diabetes.

METHODS

Search strategy: The following keywords and MeSH terms were used: "glucagon like peptide-1", "GLP-1 receptor agonist", "lixisenatide", "liraglutide", "semaglutide", "exenatide", "albiglutide", "dulaglutide", "myocardial infarction", "heart failure", "death", "mortality", "stroke", "angina" . We also reviewed references on identified articles and scrutinized the reference lists of relevant systematic reviews and meta-analyses to identify additional articles missed by the computerized database search. There was no limitation on language and publication year.

Participant or population: Patients with type 2 diabetes.

Intervention: Glucagon-like peptide 1 receptor agonist (GLP-1RAs) or Placebo.

Comparator: Glucagon-like peptide 1 receptor agonist (GLP-1RAs) or Placebo.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: Trials were included into the network meta-analysis if they met the following criteria: (i) randomized controlled trial that have addressed the cardiovascular safety of GLP-1 RA between a glucagon-like peptide 1 receptor agonist and another glucagon-like peptide 1 receptor agonist (or placebo) for patients with type 2 diabetes, (ii) both injectable and oral GLP-1 RA were included; iii) studies that have addressed the cardiovascular safety of GLP-1 RA as their primary outcomes.

Information sources: A systematic review was conducted to identify published cardiovascular outcome trials for GLP-1 RA on the following databases since inception until August 1, 2020 Medline (via PubMed), Embase and Web of Knowledge.

Main outcome(s): Primary outcomes were major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, stroke, all-cause mortality, hospital admission for heart failure, severe hypoglycaemia, pancreatitis, thyroid carcinoma.

Additional outcome(s): Secondary outcomes were composite kidney outcome, worsening of kidney function, macroalbuminuria, retinopathy, pancreatic cancer.

Data management: Data were independently extracted from the published studies by two authors, with conflicts over study inclusion resolved by consensus. Study design, characteristics of participants, treatment of pharmaceuticals, follow-up time, primary and secondary outcomes, existence of cardiovascular disease, history of heart failure, systolic blood pressure, estimated glomerular filtration rate (eGFR), other drugs used were documented. Any disagreement regarding to data extraction was determined by a third investigator.

Quality assessment / Risk of bias analysis: Risk of bias at the individual study level was assessed by two independent reviewers using the Cochrane risk of bias tool in randomised trials. Studies will be classified to be at high, low or unclear risk of bias based on adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, method of addressing incomplete data, selective reporting and other biases. Graphic representations of potential bias within and across studies will be generated using RevMan V.5.1. Disagreements will be resolved first by discussion and then by consulting a third arbitrator.

Strategy of data synthesis: A frequentist network meta-analysis was conducted to compare different GLP-1 RA using the network command in STATA[20-23]. The safety between one of GLP-1 RA and another GLP-1 RA or placebo was reported as odds ratios (ORs) and corresponding

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95% confidence interval (CI). Heterogeneity was examined using the Cochran's Q-statistic and a P-value of less than 0.01 was considered significant. The I2 test was also used to quantify heterogeneity (ranging from 0 to 100%). P < 0.01 for Q-test or I2 > 50% indicated the existence of heterogeneity across the studies. Random-effect model (DerSimonian-Laird method) was used to minimize the effect of heterogeneity if marked heterogeneity. The surface under the cumulative ranking curve (SUCRA), a simple transformation of the mean rank, is used to provide a hierarchy of the treatments and accounts both for the location and the variance of all relative treatment effects[24, 25]. An intervention with a SUCRA value of 100 is certain to be the best, whereas an intervention with 0 is certain to be the worst. Inconsistency was evaluated in each loop by contrasting direct and indirect estimates and by employing an omnibus test of consistency for the entire network based upon the assumption of a common heterogeneity parameter across all loops in the network as derived from the network meta-analysis model. Publication bias was evaluated visually using funnel plots. Forest plots were used to summarize pooled treatment comparison and comparison-adjusted funnel plots for small study effects. All statistical analysis in these meta-analyses was conducted using STATA version 14.0 (Stata Corp College Station, TX, USA).

Subgroup analysis: N/A.

Sensibility analysis: N/A.

Language: English.

Country(ies) involved: Mainland China.

Keywords: T2DM, GLP1-RAs, safety.

Contributions of each author:
Author 1 - Chuanjun Zhuo.
Author 2 - Hongjun Tian.
Author 3 - Lina Wang.
Author 4 - Xiangyang Gao.
Author 5 - Li Ding.
Author 6 - Ming Liu.

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