INPLASY PROTOCOL

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Support: **None.**

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

Conflicts of interest:
None declared.

The time-varying cardiovascular benefits of glucagon like peptide-1 agonist (GLP-RA)therapy in patients with type 2 diabetes mellitus: A meta-analysis of multinational randomized trials

Deo, SV[1]; McAllister, DA[2]; Sattar, N[3]; Pell, JP[4].

Review question / Objective: **P - patients with type 2 diabetes melllitus already receiving routine medical therapy; I - patients receiving glucagon like peptide 1 receptor agonist (GLP1 receptor agonist) therapy (semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide, efpeglenatide, abiglutide); C - patients receiving standard therapy for diabetes mellitus but not receiving GLP1 agonist therapy; O - composite end point as per invididual trial, cardiovascular mortality, all-cause mortality, myocardial infarction, stoke.**
Condition being studied: **Type 2 diabetes mellitus.**
Study designs to be included: **Randomised controlled trials which enroll a large number of patients (defined as > 500) and are multinational in origin. Studies included will need to have published Kaplan and Meier curves for the end-points presented in the manuscript.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 July 2021 and was last updated on 30 July 2021 (registration number INPLASY202170097).

INTRODUCTION

Review question / Objective: **P - patients with type 2 diabetes melllitus already receiving routine medical therapy; I - patients receiving glucagon like peptide 1 receptor agonist (GLP1 receptor agonist) therapy (semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide, efpeglenatide, abiglutide); C - patients receiving standard therapy for diabetes mellitus but not receiving GLP1 agonist therapy; O - composite end point as per invididual trial, cardiovascular mortality, all-**

cause mortality, myocardial infarction, stoke.

Rationale: The study will apply the restricted mean survival time (RMST) method to randomised trials. Using published Kaplan Meier curves for each trial and for each end-point, data will be abstracted. Difference in RMST will be obtained and pooled using a random effects model. The study will provide an easy to understand estimate of the possible benefit of using GLP1 RA on cardiovascular outcomes.

Condition being studied: Type 2 diabetes mellitus.

METHODS

Search strategy: ("glucagon-like peptide-1 receptor agonist", OR "albiglutide",OR "dulaglutide",OR "efpeglenatide",OR "exenatide",OR "liraglutide",OR "lixisenatide",OR "semaglutide")AND ("randomized clinical trial") AND ("death",OR "myocardial infarction",OR "stroke",OR "heart failure" OR "kidney").

Participant or population: Patients being treated for type 2 diabetes mellitus.

Intervention: Patients receiving glucagon like peptide 1 receptor agonist (GLP1 agonist) therapy (semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide, efpeglenatide, abiglutide).

Comparator: Patients receiving routine care for type 2 diabetes mellitus and any other medical conditions that they may have.

Study designs to be included: Randomised controlled trials which enroll a large number of patients (defined as > 500) and are multinational in origin. Studies included will need to have published Kaplan and Meier curves for the end-points presented in the manuscript.

Eligibility criteria: (1) Randomised control trials using GLP1 agonist agents to present clinical results of adult human subjects. (2) Trials should be multi-national and contain > 500 participants (3) Trials that contain a cardiovascular end-point (major adverse cardiovascular events, stroke, myocardial infarction, cardiovascular mortality, all-cause mortality) specified above will be included.

Information sources: Medline (Pubmed) from inception till July 30th 2021.

Main outcome(s): composite cardiovascular adverse events as per trial; all cause mortality; cardiovascular mortality; myocardial infarction; stroke.

Additional outcome(s): None.

Data management: Data will be stored in a central repository accessed by all authors. Data will be abstracted using a prespecified form. All Kaplan and Meier plots will be selected from included trials. Disagreement with data collection results will be resolved by discussion with senior authors (NS,JP).

Quality assessment / Risk of bias analysis: Heterogeniety will be evaluated for each end-point using I2 method. Cochran risk of bias tool will be utilised to evaluate risk of bias for included studies.

Strategy of data synthesis: Kaplan Meier plots from included trials will be collected. Data will be extracted using Scan IT software and the Guyot method. From the extracted data, a flexible parametric model will be fit for each trial curve. The RMST will be calculated for each trial included in that particular end-point. Data will be pooled using the random effects models and the DerSimonian and Laird method. Heterogeneity will be evaluated by calculating the I2. Results will be presented at 12, 24, 36 and 48 months for the endpoint of MACE. For mortality, CV mortality and myocardial infarction, results will be presented at 24 and 48 months.

Subgroup analysis: None planned.

Sensitivity analysis: Sensitivity analysis will be performed by using univariate direct

method rather than the parametric method. Effect estimates obtained from both models will be compare graphically to evaluate for overlap.

Language: English.

Country(ies) involved: United States.

Other relevant information: None.

Keywords: diabetes mellitus; glucagon like peptide 1 receptor agonist; cardiovascular outcomes.

Dissemination plans: Study will be published in a peer reviewed journal and also submitted as an abstract for conference presentation.

Contributions of each author:

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