INPLASY

Optimizing GLP-1RA Efficacy: A Meta-Analysis of Baseline Age and HbA1c as Predictors of MACE Reduction in T2DM

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 August 2025 and was last updated on 16 August 2025.

INTRODUCTION

Review question / Objective The objective of this systematic review and meta-analysis is to evaluate the efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in reducing major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2DM) and to explore the moderating effects of baseline characteristics. The review is guided by the PICOS framework as follows:

Population: Adult patients (aged 18 years and older) diagnosed with T2DM, regardless of prior cardiovascular disease status, enrolled in cardiovascular outcome trials (CVOTs).
Intervention: Treatment with GLP-1RAs, including long-acting and short-acting formulations (e.g., liraglutide, semaglutide, exenatide), administered at any dose or duration as reported in the trials.
Comparison: Placebo or standard care without GLP-1RA therapy, as defined by the control arms of the included CVOTs.
Outcome: The primary outcome is MACE, defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, reported as hazard ratios (HR) with 95% confidence intervals (CI). Secondary outcomes include the influence of baseline characteristics (e.g., age, body mass index [BMI], systolic blood pressure [SBP], diabetes duration) on MACE reduction.
Study Design: Randomized controlled trials (RCTs) designed as CVOTs, with a minimum follow-up period sufficient to assess MACE (typically ≥1 year), published in peer-reviewed journals or conference proceedings.

This review aims to synthesize evidence from CVOTs to determine the overall efficacy of GLP-1RAs in MACE reduction and identify patient-specific factors that may enhance or attenuate this effect through multivariate meta-regression. The findings will inform personalized therapeutic strategies for T2DM management, addressing moderate heterogeneity observed in prior studies.

Rationale The increasing global prevalence of type 2 diabetes mellitus (T2DM) heightens the risk of major adverse cardiovascular events (MACE), necessitating effective therapies. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated cardiovascular benefits in cardiovascular outcome trials (CVOTs), but variability in efficacy across studies suggests potential influence from baseline patient characteristics. Existing meta-analyses have not fully elucidated these moderators, limiting personalized treatment strategies. This study aims to synthesize CVOT evidence to confirm GLP-1RA efficacy and identify factors like BMI, SBP, and diabetes duration that may optimize outcomes, addressing a critical gap in T2DM management.

Condition being studied Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive beta-cell dysfunction, leading to hyperglycemia. It significantly increases the risk of cardiovascular complications, including major adverse cardiovascular events (MACE) such as myocardial infarction, stroke, and cardiovascular death, making it a leading cause of morbidity and mortality worldwide.

METHODS

Search strategy The search strategy included electronic databases PubMed and Google Scholar, with no language or date restrictions, last searched on [insert date]. PubMed was queried using terms: "GLP-1RA" OR "glucagon-like peptide-1 receptor agonist" AND "cardiovascular outcomes" OR "MACE" AND "type 2 diabetes mellitus" OR "T2DM" AND "randomized controlled trial" OR "RCT." Google Scholar used similar keywords: "GLP-1RA cardiovascular outcomes T2DM RCT." Filters included human studies and peer-reviewed articles. A total of 362 records from Google Scholar and 538 from PubMed were identified, with 154 duplicates removed, resulting in 384 records screened.

Participant or population The review addresses adult patients (aged 18 years and older) diagnosed with type 2 diabetes mellitus (T2DM), irrespective of prior cardiovascular disease status, enrolled in cardiovascular outcome trials (CVOTs). Participants include those with varying baseline characteristics such as age, BMI, and diabetes duration.

Intervention The intervention evaluated is treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs), including long-acting (e.g., liraglutide, semaglutide) and short-acting (e.g., exenatide) formulations, administered at any dose or duration as reported in the included CVOTs.

Comparator The comparative intervention is placebo or standard care without GLP-1RA therapy, as defined by the control arms of the included cardiovascular outcome trials (CVOTs).

Study designs to be included Following the initial protocol registration, the study design has been amended to reflect refinements based on preliminary data analysis and methodological considerations. The original plan included 12 randomized controlled trials (RCTs) comparing glucagon-like peptide-1 receptor agonists (GLP-1RAs) with placebo in type 2 diabetes mellitus (T2DM) patients, with baseline characteristics (age, body mass index [BMI], systolic blood pressure [SBP], glycated hemoglobin [HbA1c], estimated glomerular filtration rate [eGFR], male proportion, diabetes duration, cardiovascular disease [CVD] prevalence]) evaluated as potential moderators of major adverse cardiovascular events (MACE). The analysis now includes 11 RCTs, excluding the SELECT trial due to its unavailability in the updated dataset, resulting in a total of 83,536 participants. The multivariate meta-regression approach has been adjusted to address multicollinearity, leading to the exclusion of Diabetes_Duration as a moderator due to a high variance inflation factor (VIF > 4.8), with the refined model focusing on Age and HbA1c. Additionally, sensitivity analysis is now specifically planned to exclude the FREEDOM-CVO trial, identified as an outlier with a hazard ratio of 1.24, to assess its influence on the model. These updates enhance the robustness and relevance of the findings, ensuring alignment with the observed data distribution and statistical integrity, while maintaining the core objective of evaluating GLP-1RA efficacy in MACE reduction.

Eligibility criteria Additional inclusion criteria include peer-reviewed publications or conference proceedings. Exclusion criteria encompass non-RCTs, studies with MACE as a non-primary endpoint, and duplicate reports identified during screening.

Information sources Intended information sources include electronic databases (PubMed, Google Scholar), trial registers (e.g., ClinicalTrials.gov), and grey literature (conference abstracts). Contact with study authors will be pursued for missing data, ensuring comprehensive evidence collection.

Main outcome(s) The primary outcome is major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, reported as hazard ratios (HR) with 95% confidence intervals (CI) from CVOTs with at least 1-year follow-up.

Additional outcome(s) Secondary outcomes include the moderating effects of baseline characteristics (e.g., age, BMI, SBP, diabetes duration) on MACE reduction, assessed through multivariate meta-regression.

Data management Records and data will be managed using EndNote for citation organization and Excel for data extraction. Duplicate entries will be removed, and a master dataset will be created, with versions tracked to ensure accuracy and reproducibility.

Quality assessment / Risk of bias analysis Quality assessment will use the Cochrane RoB 2 Tool, evaluating randomization, deviations, missing data, outcome measurement, and reporting selection. Two reviewers will independently assess each study, with discrepancies resolved by consensus.

Strategy of data synthesis Data synthesis will be conducted using a random-effects model to estimate the pooled hazard ratio (HR) for major adverse cardiovascular events (MACE) across randomized controlled trials (RCTs) comparing glucagon-like peptide-1 receptor agonists (GLP-1RAs) with placebo in patients with type 2 diabetes mellitus (T2DM). Heterogeneity will be assessed using appropriate statistical measures to evaluate variability in treatment effects. Univariate meta-regression will explore the association of baseline characteristics (age, body mass index [BMI], systolic blood pressure [SBP], glycated hemoglobin [HbA1c], estimated glomerular filtration rate [eGFR], male proportion, diabetes duration, cardiovascular disease [CVD] prevalence) with MACE HR, followed by multivariate meta-regression to evaluate joint moderator effects. Multicollinearity will be investigated to identify and address potential correlations among moderators, with the option to exclude variables showing excessive interdependence. Sensitivity analysis will be planned to exclude trials identified as outliers based on their HRs, supported by influence diagnostics including Cook's distance, hat values, and standardized residuals. Egger's linear regression test will be employed to assess funnel plot asymmetry and evaluate potential publication bias. All statistical analyses will be performed using R software, with synthesized data and code archived on Figshare, accessible publicly with an embargo until the publication date.

Subgroup analysis No subgroup analysis is planned due to the limited number of trials (n = 12), which may lead to insufficient power for meaningful stratification.

Sensitivity analysis Sensitivity analysis will be conducted to assess the robustness of the meta-analysis findings by excluding trials identified as potential outliers based on their hazard ratios (HRs) for major adverse cardiovascular events (MACE). This process will involve evaluating the influence of individual trials using diagnostic measures, including Cook's distance, hat values, and standardized residuals, derived from the influence.rma function. Trials deemed influential will be systematically removed to determine their impact on the pooled HR and moderator effects identified through meta-regression. This approach will help ensure the stability of the overall results and the reliability of the multivariate model, particularly in relation to the selected moderators, with findings compared across the original and adjusted datasets to evaluate consistency.

Language restriction English language.

Country(ies) involved India (Dr. Samit Ghosal), United Kingdom (Miss. Anuradha Ghosal).

Other relevant information This review builds on a completed meta-analysis presented at the ABCD Conference 2025. Data and code are deposited on Figshare for transparency. The study was not prospectively registered due to its retrospective nature, but registration on OSF Registries is considered post-analysis.

Keywords GLP-1 receptor agonists; Type 2 diabetes mellitus; Major adverse cardiovascular events; Meta-analysis; Body mass index.

Dissemination plans Findings will be submitted to a peer-reviewed journal and shared on Figshare. Collaborations with diabetes research networks are planned to translate results into clinical practice.

Contributions of each author

Author 1 - Samit Ghosal - Dr. Samit Ghosal conceived the study, conducted statistical analysis, and drafted the manuscript.
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