

Unveiling the Power of GLP-1RAs: Optimizing MACE Reduction in T2DM Through BMI and Blood Pressure Insights

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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 14 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 Randomized controlled trials (RCTs) designed as cardiovascular outcome trials (CVOTs) with a minimum follow-up of 1 year to assess MACE.

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 will be synthesized using a random-effects model meta-analysis with the metafor package in R to estimate pooled HR for MACE. Multivariate meta-regression will assess baseline characteristic effects, with heterogeneity evaluated via prediction intervals and I^2 statistics. Results will be visualized with bubble plots.

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 analyses will exclude FREEDOM-CVO (neutral outcome, imputed data), ELIXA, and PIONEER 6 (neutral/borderline outcomes) to test robustness. FREEDOM-CVO SBP will be adjusted to 147.0 mmHg (upper IQR) to explore its impact.

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

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