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[Intervention Protocol]

Glucagon-like peptide-1 receptor agonist-based regimens compared with metformin-based regimens for preventing cardiovascular disease in adults with type 2 diabetes mellitus

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ABSTRACT

Objectives

This is a protocol for a Cochrane review (intervention). The objectives are as follows:

To assess the clinical benefits and adverse effects of glucagon-like peptide-1 receptor agonist-based regimens, compared with metformin-based glucose-lowering regimens, for preventing cardiovascular events including all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and metabolic adverse events (including transient hypoglycemia) in adults with type 2 diabetes mellitus across primary and secondary prevention settings.

BACKGROUND

Key terms and their definitions are provided in [Table 1](#).

Description of the condition

Type 2 diabetes is a complex metabolic disorder characterized by insulin resistance and an initial state of compensatory hyperinsulinemia, followed by progressive pancreatic β -cell dysfunction and insufficient insulin production [1]. Reduced postprandial secretion of the incretin hormone glucagon-like peptide-1 (GLP-1) [2, 3] disrupts glycemic control by reducing glucose-dependent insulin secretion, failing to suppress glucagon, increasing hepatic glucose output, and accelerating gastric emptying [4, 5, 6, 7], thereby intensifying postprandial hyperglycemia [8]. These glycemic abnormalities, alongside dyslipidemia, hypertension, weight gain, and ectopic fat accumulation in organs like the liver, heart, and pancreas elevate the risk of major adverse cardiovascular events (MACE), a composite cardiovascular outcome that includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality [9], by two to four times relative to individuals without type 2 diabetes [10, 11]. Cardiovascular disease is a primary contributor to morbidity and mortality in individuals with type 2 diabetes [12, 13, 14, 15] and given the strong association between type 2 diabetes and cardiovascular outcomes [16, 17], there is growing emphasis on therapies that not only optimize glycemic control but also confer cardiovascular protection [18].

Diabetes affects approximately 11% of the world's population, with over 90% of these individuals diagnosed with type 2 diabetes as of 2025 [15]. The prevalence of diabetes is projected to rise by 46% by 2050 [15], underscoring the urgent need for effective intervention to reduce its cardiovascular burden [19].

Description of the intervention and how it might work

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), commonly termed incretin mimetics, support glycemic control by augmenting the physiological incretin response to food ingestion, thereby enhancing insulin secretion and suppressing postprandial glucose excursions [15, 20, 21, 22]. GLP-1 RAs also offer low hypoglycemia risk, promote weight loss through appetite suppression and reduced energy intake, and delay gastric emptying. Evidence from randomized, head-to-head trials and meta-analyses consistently supports their glucose-normalizing efficacy [20, 21, 22, 23].

GLP-1 RAs are classified by pharmacological duration [24, 25, 26, 27, 28, 29]. Short-acting agents exenatide (twice daily) and lixisenatide (once daily) primarily lower postprandial glucose by slowing gastric emptying and intestinal glucose absorption. Long-acting agents liraglutide (once daily), extended-release exenatide, dulaglutide, semaglutide, and the dual agonist tirzepatide (once weekly) lower fasting glucose through sustained receptor activation, increased insulin secretion, and glucagon suppression [23, 30, 31, 32].

Clinical data show that GLP-1 RAs reduce MACE risk in type 2 diabetes through metabolic and direct cardioprotective effects (e.g. reduced inflammation, oxidative stress, fibrosis etc.) [18]. Large cardiovascular trials show that liraglutide, semaglutide, and dulaglutide reduce MACE in patients with type 2 diabetes with established cardiovascular disease or elevated risk [33, 34, 35]. Randomized controlled trials (RCTs) and meta-analyses show that

GLP-1 RAs reduce systolic and diastolic blood pressure compared with insulin and oral therapies [36, 37].

Metformin is an established first-line treatment for type 2 diabetes, lowering glucose primarily by suppressing hepatic gluconeogenesis and improving insulin sensitivity [38, 39, 40, 41]. Metformin also inhibits glucagon-mediated hepatic glucose production [42], enhances GLP-1 secretion [43, 44], modulates the gut microbiota [45, 46], and may contribute to weight loss [47, 48]. Beyond glycemic control, metformin has potential cardiovascular protective effects by improving endothelial function, thrombolysis, and lipid profiles, and reducing inflammation and oxidative stress [49, 50, 51, 52, 53]. Early and sustained glycemic control with metformin is associated with improved long-term cardiovascular outcomes [54].

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are glucose-lowering drugs with established cardiovascular benefit in type 2 diabetes [55] and are often co-prescribed alongside GLP-1 RA or metformin [56]. As concurrent SGLT-2i use may influence cardiovascular outcomes and confound the comparison, we will evaluate this as a predefined subgroup rather than part of the intervention or comparator in this review.

Why it is important to do this review

Metformin and early-generation therapies have long been the first-line treatments for type 2 diabetes. However, cardiovascular outcome trials indicate that GLP-1 RAs offer superior benefits, not only in glycemic control and weight reduction, but also in reducing MACE risk [57]. As GLP-1 RAs gain prominence in clinical guidelines, evaluating their comparative effectiveness is important to inform treatment strategies and resource allocation [58]. This review is relevant to multiple stakeholders. For healthcare professionals using evidence-based care, clarifying the relative efficacy of medications in reducing MACE in diabetes is essential. For policymakers, it may support optimized resource allocation and inform cost-effectiveness assessments guiding formularies and tiered care.

Studies comparing GLP-1 RAs with metformin for cardiovascular risk reduction have focused on metformin monotherapy rather than combination regimens. Recent systematic reviews have found no significant reduction in MACE with metformin [18, 59]. These findings were largely based on the LEADER and SUSTAIN 6 cardiovascular outcome trials, which enrolled high-risk patients with longstanding type 2 diabetes, limiting generalizability. Evidence on myocardial infarction remains limited [18]. This Cochrane review will include contemporary metformin-based combination regimens across the spectrum of type 2 diabetes to better reflect real-world clinical practice and inform treatment decisions for diverse patient populations. Despite strong clinical outcomes, GLP-1 RAs remain limited by cost, insurance coverage, supply, and access, particularly in low- and middle-income countries with most diabetes cases [60, 61, 62]. They are also contraindicated in some patients (e.g. those with medullary thyroid cancer, or irritable bowel syndrome) [63].

This review evaluates the relative benefits and adverse effects of GLP-1 RA-based versus metformin-based regimens. The key questions are: How does the effectiveness of GLP-1 RA-based regimens in preventing cardiovascular events compare to metformin-based regimens, and to what extent? The findings

will guide treatment decisions for patients with limited access or contraindications to GLP-1 RAs and support clinical and policy decisions regarding access, outcomes, and healthcare costs. As baseline cardiovascular risk differs between individuals with and without established cardiovascular disease, potentially altering the absolute and relative benefits of therapy across prevention settings, we will conduct analyses separately for primary and secondary prevention populations to ensure clinically interpretable findings.

OBJECTIVES

To assess the clinical benefits and adverse effects of glucagon-like peptide-1 receptor agonist-based regimens, compared with metformin-based glucose-lowering regimens, for preventing cardiovascular events including all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and metabolic adverse events (including transient hypoglycemia) in adults with type 2 diabetes mellitus across primary and secondary prevention settings.

METHODS

This review will follow the methodological guidance outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [64] and comply with the Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards [65]. The findings will be reported according to the PRISMA 2020 statement [66]. The protocol follows the PRISMA-P recommendations for reporting systematic review protocols [67].

Criteria for considering studies for this review

The eligibility criteria for this review have been documented in accordance with the InSynQ checklist [68].

Types of studies

We will include head-to-head RCTs directly comparing GLP-1 RA-based with metformin-based regimens for preventing cardiovascular events in adults with type 2 diabetes. Trials comparing either intervention with placebo, standard care, or other comparators will be excluded. We will analyze results separately for primary and secondary prevention populations; this stratification applies to the analysis, not study eligibility. We will include both parallel-group and cluster-randomized designs, provided appropriate statistical methods are used to account for clustering. Cross-over trials will be excluded, as the critical outcomes (all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, metabolic adverse events (including transient hypoglycemia)) are not reversible and carry a high risk of carry-over effects. We will also exclude quasi-RCTs because allocation to study groups is based on methods that are not truly random (e.g. date of birth or hospital record number).

We will impose no restrictions on setting, geographical location, language, year of dissemination, or publication status; unpublished trials and conference abstracts will be eligible. We will consider trial registry results if sufficient outcome data are available. Trials that have been withdrawn or retracted from trial registries will not be included. We will manage potentially problematic studies in accordance with Cochrane editorial policy [69].

Types of participants

We will include studies involving adults aged 18 years and older with type 2 diabetes mellitus. The diagnosis of type 2 diabetes will be based on the study authors' definition or diagnostic criteria, with no additional restrictions imposed by the review.

Definition of prevention settings

For this Cochrane review, established cardiovascular disease (secondary prevention) will include (but is not limited to) any of the following, as defined by study authors using validated diagnostic criteria:

- prior myocardial infarction;
- prior ischemic or hemorrhagic stroke or transient ischemic attack;
- documented coronary artery disease (angiographic, procedural, or physician-diagnosed);
- prior coronary or peripheral revascularization;
- peripheral arterial disease;
- heart failure.

We will classify participants without these conditions as primary prevention. Where possible, we will distinguish individuals at high cardiovascular risk (e.g. multiple risk factors, chronic kidney disease, longstanding diabetes) from lower-risk groups based on definitions provided in the included studies.

Subgroup analysis

Because SGLT-2i have cardiovascular benefits of their own, their concurrent use may confound the comparison between GLP-1 RA-based and metformin-based strategies. To address this, we will analyze the evidence in two predefined subgroups:

- participants not receiving SGLT-2i; and
- participants receiving SGLT-2i.

Within each subgroup, we will compare GLP-1 RA regimens with metformin regimens. We will treat SGLT-2i as background therapy, not a separate intervention. Only studies with similar SGLT-2i exposure across arms will be included. We will summarize studies with imbalance or poor reporting narratively or exclude them from meta-analysis. We will undertake sensitivity analyses to assess whether conclusions change under different assumptions about concomitant SGLT-2i use.

Standard care for type 2 diabetes includes managing comorbidities (e.g. hypertension, hypercholesterolemia) and promoting beneficial lifestyle changes. We will include patients on other cardiovascular treatments (e.g. statins, antihypertensives) and account for them in the analysis.

We will include studies including both eligible and non-eligible participants only if outcome data for eligible participants can be extracted separately. Where separate data are unavailable, we will assess whether the mixed population is sufficiently representative of the review population and exclude studies where non-eligible participants are likely to meaningfully influence the findings.

Types of interventions

Intervention

The interventions selected for this review are regimens containing GLP-1 RAs, with or without concomitant metformin. We will include only commercially available, subcutaneously administered GLP-1 RAs approved by the United States Food and Drug Administration (USFDA) [70, 71, 72, 73, 74], at any approved dose and for any treatment duration or intensity, provided the regimen meets the GLP-1 RA definition. Eligible agents include the following:

- mono-agonists: liraglutide, semaglutide, exenatide, and dulaglutide;
- dual-agonist: tirzepatide, which targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors.

We will exclude oral GLP-1 RAs formulations, compounded versions and albiglutide (withdrawn from clinical use). We will focus on studies examining these interventions as monotherapy or in combination with other anti-diabetic medications.

Comparator

The only eligible comparator will be metformin-based regimens that do not include a GLP-1 RA; placebo, standard care, and other active comparators are not eligible. We will compare GLP-1 RA-based and metformin-based regimens as two clinically relevant treatment strategies, rather than individual drugs. Although metformin remains the first-line therapy for type 2 diabetes because of its efficacy, safety, and affordability [75], its ability to reduce cardiovascular risk, particularly compared with newer agents, remains uncertain [76, 77]. This review will investigate this comparative effectiveness to inform clinical decision-making.

Metformin-based regimens are defined as those in which metformin is the primary glucose-lowering therapy, used alone or in combination with other agents (e.g. sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, meglitinides, or insulin). We will distinguish metformin monotherapy and combination therapy during data extraction and analysis, and we will only pool trials with clearly defined metformin-based comparators.

Concomitant SGLT-2i use will be permitted as background therapy in both arms and analyzed as a predefined subgroup.

Outcome measures

We will assess critical outcomes at short-term (two to five years) and long-term (beyond five years) follow-up, consistent with landmark cardiovascular outcome trials (LEADER [78], SUSTAIN-6 [34], and REWIND [33]). The primary endpoint will be the time to the first cardiovascular event. If an outcome is reported more than once within a time category, we will use the most recent time point within that category (e.g. if reported at both two and five years, we will use the two-year result for the short-term category) or the time point that best aligns with other studies in the comparison. We will include studies meeting the eligibility criteria for participants, interventions, comparators, and study design, regardless of the outcomes reported.

Critical outcomes

We will evaluate outcomes across the following domains, with specific measures detailed in Table 2:

1. Mortality (all-cause mortality; cardiovascular mortality).
2. Non-fatal myocardial infarction, non-fatal stroke.
3. Metabolic adverse events (transient hypoglycemia).

Important outcomes

1. Treatment discontinuation: the total number of participants who discontinued the allocated intervention due to adverse events.
2. Change in HbA1c level from baseline.
3. Other adverse events: the total number of participants with adverse events, as reported by the study authors, including common side effects of GLP-1 RAs such as gastrointestinal disorders and cardiovascular disorders. We will extract each adverse event type separately when reported, to avoid composite outcome double-counting [79].

Search methods for identification of studies

We will identify relevant studies in accordance with Cochrane methodological standards [80].

Electronic searches

We will conduct comprehensive searches across the following databases to identify RCTs, spanning from each database's inception up to the search date, with no restrictions on language, publication date, or status.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (via PubMed; 1946 to present)
- Embase (via Elsevier; 1974 to present)
- CINAHL with Full Text (via EBSCOhost; 1981 to present)
- Web of Science (via Clarivate Analytics; SCI-EXPANDED, SSCI, AHCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI; 1900 to present)

The search strategy will combine controlled vocabulary terms (e.g. MeSH in MEDLINE and Emtree in Embase) and free-text terms related to the following.

1. GLP-1 receptor agonists, including individual agents (liraglutide, semaglutide, exenatide, dulaglutide, tirzepatide, lixisenatide) and relevant brand names.
2. Metformin, including drug class, chemical names, and brand names (biguanides, dimethylbiguanidine, dimethylguanylguanidine, Glucophage, Fortamet, Glumetza, Riomet).
3. Major adverse cardiovascular events (MACE), myocardial infarction, stroke, cardiovascular mortality, heart failure, and related cardiovascular endpoints.

The preliminary MEDLINE search strategy will be adapted for other databases using appropriate syntax and indexing terms. The full search strategy is provided in the appendix as an example (Supplementary material 1).

We will export to EndNote and deduplicate the search results. Grey literature and unpublished datasets with sufficient data will be included. We will update the searches within 12 months of publication.

During full-text screening and data extraction, we will differentiate between trials in which metformin is the primary comparator and those in which it is used as background therapy in both arms. Only RCTs that directly compare GLP-1 RA-based regimens against metformin-based regimens as the two randomized arms will be eligible; we will exclude trials comparing either class against placebo, standard care, or any other active comparator at this stage.

Searching other resources

In addition to database searches, we will search trial registers, including ClinicalTrials.gov (<https://clinicaltrials.gov/>) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; <https://trialsearch.who.int/>), to identify ongoing or unpublished studies. We will examine the reference lists of all included studies and pertinent systematic reviews to identify any additional trials that meet the eligibility criteria. Following full-text screening, we will check the included studies for post-publication amendments (e.g. expressions of concern, errata, corrigenda, and retractions) and consider these during study selection, risk of bias assessment, and interpretation of the findings.

We will contact the study authors and field experts to clarify study details or identify unpublished and ongoing trials. In addition, we will contact manufacturers of GLP-1 RAs and metformin for information on completed or ongoing trials relevant to this review. Finally, we will screen abstracts from central diabetes and cardiology conference proceedings, such as those from the American Diabetes Association, the European Association for the Study of Diabetes, the American Heart Association, and the European Society of Cardiology, for potentially eligible studies.

Data collection and analysis

To reduce potential bias in the search process, we will follow the recommendations provided in Chapter 4 of the *Cochrane Handbook* [80]. We will also consult Chapter III of the *Cochrane Handbook* to ensure compliance with Cochrane methodological standards for study selection and overall review conduct [81]. Data collection procedures will be guided by the methods described in Chapter 5 of the *Cochrane Handbook* [82].

Selection of studies

We will conduct the study selection process in two distinct phases using Covidence, a web-based review management tool [83]. In the initial phase, two independent review authors (Kangning Peng (KP) and Saifuddin Nasir (SN)) will screen the titles and abstracts of all retrieved records, classifying each as 'include' (eligible or potentially eligible) or 'exclude' according to the predefined eligibility criteria.

In the second phase, two review authors (KP and SN) will independently assess the full texts of potentially eligible studies. Disagreements will be resolved through discussion or consultation with a third review author (Sana Ahmed (SA)). Studies that remain unclear will be classified as 'awaiting classification' and study authors may be contacted for clarification.

We will document the reasons for excluding studies at the full-text stage and present them in a 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study, rather than each publication, is the unit of analysis. To enhance transparency, we will illustrate the entire selection process using a PRISMA flow diagram [66]. If studies authored by review team members are identified, eligibility decisions will be made by review authors not involved in those studies to minimize potential conflicts of interest.

Data extraction and management

We will develop a standardized data extraction form ([Supplementary material 2](#)) in line with the *Cochrane Handbook* [64]. The form will be piloted on 5 to 10 included studies before full data extraction. Two review authors (SA and Arturo Martí-Carvajal (AMC)) will independently extract data from each included study. Any discrepancies will be resolved through discussion or, if necessary, with the involvement of a third review author (Sandra McCollin (SM)). One review author will enter the agreed data into Review Manager (RevMan) software [84], and a second review author will verify the accuracy of the entered data. Where information is unclear or incomplete, we will contact study authors for clarification. For reports published in languages not covered by the author team, translation support will be sought from colleagues or the Cochrane Engage community.

Risk of bias assessment in included studies

Two review authors (SM and Sara Abdul Razzaq (SAR)) will conduct independently and in duplicate the risk of bias assessments for each study, with the help of the Cochrane risk of bias tool (RoB 2), as described in the *Cochrane Handbook* [85, 86, 87].

We will resolve any disagreements through discussion or, if necessary, by consulting another author (Shayesteh Jahanfar (SJ)). We will evaluate the risk of bias for all review outcomes. As we want to estimate the effect of assignment to interventions at baseline, we will apply the intention-to-treat principle irrespective of whether participants received the interventions as planned.

We will evaluate risk of bias in individually randomized trials across the following domains ([Supplementary material 3](#)):

1. Bias arising from the randomization process.
2. Bias due to deviations from intended interventions (effect of intervention assignment).
3. Bias due to missing outcome data.
4. Bias in measurement of the outcome.
5. Bias in the selection of the reported result. We will focus on trials published after 2005 to improve transparency in outcome reporting [88, 89].

RoB 2 signaling questions will classify each domain as low risk, some concerns, or high risk of bias [86, 87].

We will assess cluster-randomized trials using the RoB 2 variant for cluster-randomized trials, with particular attention to bias arising from the timing of identification and recruitment of participants [90].

The signaling questions will have the following response options:

1. yes;

2. probably yes;
3. probably no;
4. no;
5. no information.

Where appropriate, we will use INSPECT-SR to assess the trustworthiness of included randomized trials before risk of bias assessment [91].

We will use the latest version of the RoB 2 Excel tool [87], which applies an algorithm to responses to the signaling questions for each outcome and generates risk of bias judgments for each domain. When we assign a specific level of risk of bias to an individual domain, it indicates that the overall result carries at least that level of bias. Accordingly, a judgment of high risk of bias in any domain implies that the trial results as a whole are at high risk of bias, regardless of the domain assessed. Concerns in several domains may prompt the review authors to rate the overall risk of bias as high for that particular outcome or group of outcomes [86]. We will base our assessment on the overall risk of bias for each study result rather than individual domains. The overall risk of bias of the result will reflect the least favorable judgment across all bias domains.

Overall risk of bias:

1. A low risk of bias judgment will indicate that the study is assessed as low risk of bias across all domains for that result.
2. Some concerns will indicate that the study has at least one domain with concerns, without any domain being rated as high risk of bias.
3. High risk of bias will indicate that the study has at least one domain rated as high risk, or multiple domains with some concerns that considerable lower confidence in the result.

We will ensure that this information is available online, with detailed information to be provided during the review stage.

Measures of treatment effect

We will perform all statistical analyses using RevMan [84]. We will select effect measures based on the nature of the outcomes and whether they are reported consistently across studies to facilitate interpretability and synthesis.

For dichotomous outcomes (e.g. all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, transient hypoglycemia, and treatment discontinuation), we will express treatment effects as risk ratios (RRs) with corresponding 95% confidence intervals (CIs). Where studies report time-to-event data (e.g. incidence of cardiovascular events over follow-up), we will extract and use hazard ratios (HRs) with 95% CIs when available. When HRs are not provided, we will estimate effect measures using alternative statistics or transformations following the recommendations in Section 6.4 of the *Cochrane Handbook* [92].

For continuous outcomes, we will calculate mean differences (MDs) and 95% CIs when the same scale is used, or standardized mean differences (SMDs) with 95% CIs when different scales measure the same construct. Where necessary, scales will be reversed so that higher values consistently represent the same direction of effect.

Where an established minimal important difference is available from the literature, we will use it to aid interpretation of the results.

Where available, we will prioritize change-from-baseline over end-of-treatment values because they account for baseline differences between groups. If unavailable, we will use end-of-treatment values. For outcomes measured at multiple time points, we will use data from the time points closest to our predefined short-term (two to five years) and long-term (beyond five years) windows.

We will summarize results in forest plots, with effect estimates and their 95% CIs. For continuous outcomes expressed as SMDs, we will interpret effect sizes according to Cohen's conventional thresholds: minor (0.2), moderate (0.5), and large (0.8). If reported data cannot be directly entered into meta-analyses, we will convert them into an appropriate format using established methods outlined in the *Cochrane Handbook*. If conversion is not possible, we will synthesize results narratively and summarize them in the 'Characteristics of included studies' table.

Unit of analysis issues

The individual participant will be the primary unit of analysis. Eligible studies will include both individually randomized controlled trials and cluster-randomized trials that directly compare GLP-1 RA-based regimens against metformin-based regimens (head-to-head); concomitant SGLT-2i use, where present in both arms, is treated as background therapy and examined as a predefined subgroup, not as part of the intervention or comparator definition.

For cluster-randomized trials, in which randomization occurs at the clinic, practice, or other group level rather than at the individual level, we will assess whether the original analyses appropriately accounted for intra-cluster correlation. If this adjustment is missing, we will recalculate the effective sample size using an intraclass correlation coefficient (ICC), following the recommendations outlined in Chapter 23 of the *Cochrane Handbook* [90]. When ICC values are not reported, we will derive estimates from comparable published studies or use a conservative assumed range (e.g. 0.01 to 0.10). We will conduct sensitivity analyses to evaluate the robustness of pooled estimates under these assumptions.

For trials with more than two intervention arms, only those directly relevant to the review question will be included in the analysis. When multiple eligible comparisons from a single study contribute to the same meta-analysis, we will avoid double-counting participants by either combining relevant arms into a single comparison or by splitting the shared control group evenly, in line with Section 6.2.9 of the *Cochrane Handbook* [92].

When outcomes are reported at multiple follow-up intervals, we will extract data according to predefined timeframes: short term (two to five years) and long term (beyond five years). If several time points fall within a single category, the most recent measurement will be selected to maintain consistency across studies.

Should both individually and cluster-randomized trials be included, we will pool their results in meta-analyses only if there is no significant methodological heterogeneity and if the intervention effects are unlikely to differ by randomization type. We will use sensitivity analyses to explore the potential impact of study design on treatment effect estimates.

Dealing with missing data

We will obtain missing data from the authors of the included studies if possible. We will carefully evaluate important numerical data, such as screening, random assignment of participants, and the intention-to-treat, as-treated, and per-protocol populations, in our risk of bias assessments. To address this, we will investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals) and critically appraise issues related to missing data and the use of imputation methods. For each included RCT, we will extract the number randomized, number analyzed, number lost to follow-up or withdrawn, and reasons for missing data per arm. When standard deviations (SDs) are missing for continuous outcomes, we will calculate them according to the *Cochrane Handbook* [64] if possible, and assess the impact of alternative SDs in sensitivity analyses.

For trials with missing outcome data, we will use an available-case (complete-case) analysis as the primary analysis, assuming data are missing at random (MAR). Sensitivity analyses will assess the robustness of the findings under alternative missing data assumptions, including missing not at random (MNAR), using appropriate imputation methods or best-case/worst-case scenarios.

In the Discussion, we will explicitly address how missingness and use of imputation may influence the certainty and validity of the meta-analysis findings, acknowledging that imputed values are not equivalent to first-hand observed data, and results should be interpreted with caution.

Reporting bias assessment

To minimize bias due to missing evidence, we will consult clinical trial registries, particularly ClinicalTrials.gov, clinical study reports, and relevant regulatory documents such as FDA drug packets [93]. We will also contact study authors for missing data. We will conduct an assessment of non-reporting bias for 10 or more studies selected for the meta-analysis. To examine potential non-reporting bias, we will generate a funnel plot that illustrates effect estimates relative to their standard errors, summarizing other factors in addition to sample size that affect statistical power [94]. Additionally, we will employ the ROB-ME tool, along with its template and matrix, to thoroughly assess the risk of bias attributed to missing evidence [95].

Synthesis methods

We will conduct the synthesis in accordance with Chapters 10 and 12 of the *Cochrane Handbook* [96, 97]. Quantitative or narrative synthesis will depend on the clinical, methodological, and statistical comparability of the included studies. We will conduct meta-analysis only when the populations, interventions, comparators, and outcomes (PICO) are sufficiently aligned to support meaningful aggregation and interpretation of effect estimates.

Prior to any meta-analytic procedures, we will summarize key study characteristics, including participant demographics, intervention dose and duration, comparator type, and outcome definitions, to evaluate their suitability for synthesis. We will only group trials that share consistent definitions of type 2 diabetes, comparable intervention strategies, and harmonized cardiovascular outcomes (e.g. all-cause mortality, cardiovascular mortality, non-fatal

myocardial infarction, non-fatal stroke, metabolic adverse events (including transient hypoglycemia)) for pooled analysis.

We will perform primary analyses separately for primary and secondary prevention populations. Where mixed populations are reported, we will analyze stratified data within the appropriate prevention group where available; otherwise, we will synthesize studies narratively or include them only in sensitivity analyses.

Quantitative synthesis (meta-analysis)

Where at least two studies demonstrate comparable design and outcome reporting, we will conduct pairwise meta-analyses using RevMan [84]. For binary outcomes (e.g. all-cause or cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, hypoglycemia, treatment discontinuation), we will estimate risk ratios (RRs) with 95% confidence intervals (CIs) using the Mantel-Haenszel method. For continuous outcomes (e.g. change in HbA1c level), we will calculate mean differences with 95% CIs when measurement scales are uniform, or standardized mean differences when scales differ. For time-to-event outcomes (e.g. time to first cardiovascular event), we will use hazard ratios (HRs) and their 95% CIs.

We will use a random-effects model as the primary meta-analysis model for binary, continuous, and time-to-event outcomes because clinical and methodological diversity is anticipated across studies. We will estimate between-study variance using the Restricted Maximum Likelihood (REML) estimator to quantify between-study variance, as implemented in STATA [98]. We will use the Hartung-Knapp-Sidik-Jonkman (HKSJ) method to calculate confidence intervals for pooled effect estimates when at least three studies are included and the estimate of heterogeneity is greater than zero. In pooled analyses of two studies, or when heterogeneity is estimated as zero, we will use the Wald-type method. We will explore fixed-effect models in sensitivity analyses when heterogeneity is minimal.

We will use forest plots to visualize pooled estimates, with treatment effects interpreted such that RRs or HRs below 1.0 favor GLP-1 RA-based therapies over metformin-based comparators.

Synthesis without meta-analysis (SWiM)

If meta-analysis is not feasible because of substantial heterogeneity or insufficient data, we will follow the Synthesis Without Meta-analysis (SWiM) framework described in Chapter 12 of the *Cochrane Handbook* [97]. We will provide a structured narrative summary of the direction and magnitude of effects and the certainty of the evidence, grouping studies by treatment comparison, outcome, follow-up duration (short term: two to five years; long term: beyond five years), and prevention setting (primary versus secondary), where appropriate. We will summarize study characteristics and results in tables and present findings using forest plots (where meta-analysis is conducted) and summary of findings tables with absolute and relative effects, participant numbers, and GRADE certainty ratings.

Software

We will conduct all statistical analyses using RevMan [84] and STATA [98], and share datasets and analysis scripts in supplementary materials, where feasible.

Investigation of heterogeneity and subgroup analysis

We anticipate clinical, methodological, and statistical heterogeneity across studies. We will assess heterogeneity and significance using forest plots, the Chi^2 statistic ($P < 0.10$), and the I^2 statistic, interpreted according to the *Cochrane Handbook* [64]:

- 0% to 40%: might not be important;
- 30% to 60%: moderate heterogeneity;
- 50% to 90%: substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

When the meta-analysis shows substantial heterogeneity (e.g. $I^2 > 50\%$), we will further explore potential sources of variability across studies through subgroup analyses by prevention type, concurrent SGLT-2i use, chronic kidney disease status, and geographic region. We will report prediction intervals (PrIs) for random-effects models to reflect the expected range of effects in future studies, accounting for between-study variability. Prevention setting (primary versus secondary) is a pre-specified stratification variable and not an exploratory subgroup. We will assess whether treatment effects differ meaningfully across prevention strata and report interaction where feasible.

SGLT-2i, frequently used as an add-on therapy, has been shown to have cardiovascular protective effects, and therefore we will analyze this as a subgroup to mitigate confounding. The analysis will incorporate a combination of study-level variables and within-study contrasts, as data permit, to assess the effects of the subgroup comprehensively.

The subgroup effects may vary in terms of combination therapies utilized as well as participant demographics, such as age or gender. We will report and further analyze significant heterogeneity in meta-regression.

Sensitivity analysis

We will conduct sensitivity analyses, in line with guidance from Chapter 10 of the *Cochrane Handbook* [96], to evaluate the reliability of the primary findings for key outcomes. To test the influence of methodological assumptions, we will re-run analyses under varying conditions, such as the following.

- Removing studies judged to have an overall high risk of bias (RoB 2).
- Excluding trials with substantial attrition ($\geq 20\%$) or those relying on imputed outcome data.
- Comparing results obtained using random-effects versus fixed-effect models.
- Adjusting intraclass correlation coefficients (ICCs) in cluster-randomized trials, where relevant.
- Omitting unpublished studies or those available only in trial registries.

We will interpret sensitivity analyses qualitatively, focusing on meaningful changes in effect direction or size, and present the findings in tables or figures to demonstrate the consistency of pooled estimates.

Certainty of the evidence assessment

We will prepare one summary of findings table for the comparison of GLP-1 RA-based regimens versus metformin-based regimens. The table will include the critical outcomes (mortality: all-cause mortality, cardiovascular mortality; non-fatal myocardial infarction, non-fatal stroke; and metabolic adverse events (transient hypoglycemia)) and important outcomes (treatment discontinuation, change in HbA1c level, and other adverse events). For each outcome, we will provide the primary time point for measuring the outcome (i.e. follow-up time, with mean/median and range).

For each outcome included in the summary of findings table, we will use the predefined short-term follow-up (two to five years), as this best reflects the objectives of the review. If these data are unavailable, we will use the longest available follow-up within our predefined time periods and report the corresponding time point. The assessment of risk of bias using RoB 2 will focus on the same time point selected for the summary of findings table to ensure alignment with the GRADE evaluation.

Two review authors (from SA, SM, or SJ), working independently, will make judgments about the certainty of the evidence. We will resolve disagreements by discussion, or we will involve two other review authors (SAR and AMC). We will justify, document, and incorporate all judgments into the reporting of results for each outcome [99].

We will use the five GRADE factors (risk of bias, heterogeneity (consistency of effect), imprecision (calculating also the optimal information size), indirectness, and publication bias) to assess the certainty of the body of evidence as it relates to the trials that contribute data to the meta-analyses for the prespecified outcomes [100].

We will determine the control group risk through one of two methods. We will use the median risk when we derive our data from a meta-analysis. If we lack meta-analytic data, we will calculate the risk directly from the control group proportion.

We will use the methods and recommendations described in Chapters 13, 14, and 15 of the *Cochrane Handbook* [93, 99, 100] and PRISMA 2020 [66]. We will use GRADEpro GDT [101]. As listed in [Types of interventions](#), we will only compare GLP-1 RA-based regimens (experimental intervention) with metformin-based regimens.

We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

We will communicate the findings for interventions following the GRADE Working Group's recommendations [102].

Equity considerations

We will adhere to the principles outlined in Chapter 16 of the *Cochrane Handbook* [103]. We will not undertake specific equity-related assessments in this review. However, we will collect contextual variables and participant characteristics that may affect the findings, including ethnicity, cultural background, residential setting (urban or rural; low-, middle-, or high-income countries), sex, and socio-economic status. We will summarize these factors

in a table describing the participant characteristics of the included trials to support assessment of the applicability of the findings across diverse settings.

Consumer involvement

We will not involve consumers in this review due to limited resources.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: [10.1002/14651858.CD016380](https://doi.org/10.1002/14651858.CD016380).

Supplementary material 1 Search strategies

Supplementary material 2 Data extraction and management

Supplementary material 3 Risk of bias assessment

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Cochrane supported the authors in the development of this protocol.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): William E Cayley Jr MD MDiv, Eau Claire Medical Clinic, Eau Claire, Wisconsin;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Luisa Fernandez Mauleffinch, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Joshua Guinoo, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Dr Denny Mathew John, Department of Community Medicine, Kerala Medical College Hospital Palakkad, Kerala, India (patient and public review); Clare Miles, Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review).

Contributions of authors

- Conceptualization: SA, SM, MA, DB, SAR, EH
- Methodology: SA, SM, AMC, MA, DB, PS, SAR, EH, SJ

- Project administration: SA, SM
- Supervision: AMC, MA, DB, EH, SJ
- Writing – original draft: SA, SM, AMC, SAR
- Writing – review and editing: SA, SM, AMC, MA, DB, SAR, PS, EH, SN, KP, SJ

Declarations of interest

Sana Ahmed: none declared.

Sandra McCollin: none declared.

Arturo Martí-Carvajal: none declared.

Monica Akus: Pfizer (1998 to 2001): pharmacy supply coordinator; this corporation may have an interest in the review given collaborations with companies in the diabetes space. Cambridge Health Alliance: Associate Chief Pharmacy Officer and clinical pharmacist provider.

David Baron: work as a medical doctor providing direct care for Cambridge Health Alliance.

Sara Abdul Razzaq: none declared.

Elizabeth Honigsberg: none declared.

Paige Scudder: none declared.

Saifuddin Nasir: currently working as a resident physician at UPMC Mercy.

Kangning Peng: work as a medical doctor providing direct care for Cambridge Health Alliance.

Shayesteh Jahanfar: none declared.

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Registration and protocol

The proposal for this review was approved by Cochrane in July 2025.

Data, code and other materials

Data sharing is not relevant for this article, as it is a protocol and no datasets were generated or analyzed.

Disclosure of artificial intelligence use

Artificial intelligence was used to improve the clarity and readability of the text. No content or scientific decisions were generated by artificial intelligence. The tool used was ChatGPT (GPT-5.5 model), in February and March 2026.

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ADDITIONAL TABLES

Table 1. Overview of key terms and definitions

Term	Definition	Source (MeSH/NLM)	Link to eligibility/outcomes
Major adverse cardiovascular events (MACE)	A composite cardiovascular outcome, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality.	Not a MeSH term; composite cardiovascular endpoint	Critical outcome

Glucagon-like peptide-1 receptor agonist-based regimens compared with metformin-based regimens for preventing cardiovascular disease in adults with type 2 diabetes mellitus (Protocol)

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Table 1. Overview of key terms and definitions (Continued)

		commonly used in cardio-vascular outcome trials	
Adverse effects	Undesired or harmful effects resulting from a medical intervention or pharmacological treatment.	MeSH: Drug-Related Side Effects and Adverse Reactions C25.100	Critical outcome: harms and safety
Cardiovascular diseases	Disorders affecting the heart and blood vessels.	MeSH: Cardiovascular Diseases C14.280	Population and outcomes (cardio-vascular endpoints)
Drug combinations	Therapeutic use of two or more active pharmacological agents administered together.	MeSH: Drug Combinations D26.255	Intervention structure (real-world regimens)
Glucagon-like peptide 1 receptor agonists	Pharmacological agents that activate the glucagon-like peptide 1 receptor to improve glycemic control and support weight reduction.	MeSH: Glucagon-Like Peptide 1 Receptor Agonists D27.505.696.422.125	Intervention group
Hypoglycemic agents	Drugs used to reduce blood glucose levels in diabetes mellitus.	MeSH: Hypoglycemic Agents D27.505.696	Intervention context (background therapy)
Metformin	A biguanide hypoglycemic agent that reduces hepatic glucose production and improves insulin sensitivity.	MeSH: Metformin D02.394.692	Comparator group
Obesity	A condition characterized by excessive accumulation of body fat that presents a risk to health.	MeSH: Obesity C23.888.144.699.500	Population (sub-group/ effect modifier)
Primary prevention	Interventions aimed at preventing the initial occurrence of disease.	NLM conceptual (Prevention framework)	Subgroup analysis (no established disease)
Secondary prevention	Interventions aimed at preventing recurrence or progression of established disease.	NLM conceptual (Prevention framework)	Subgroup analysis (established disease)
Type 2 diabetes mellitus	A metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and relative insulin deficiency.	MeSH: Diabetes Mellitus, Type 2 C18.452.394.750.149 C19.246.300	Core population

MeSH: Medical Subject Headings; NLM: National Library of Medicine

Table 2. Overview of types of outcomes (critical or important)

Outcome grouping	Outcome domain	Outcome measures
Critical		
Mortality	All-cause mortality	Death from any cause
	Cardiovascular mortality	Death due to myocardial infarction, heart failure, stroke, sudden cardiac death

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Table 2. Overview of types of outcomes (critical or important) *(Continued)*

Cardiovascular events	Myocardial infarction	Non-fatal myocardial infarction diagnosed according to WHO criteria, or study-specific validated criteria
	Stroke	Non-fatal stroke, diagnosed according to WHO criteria; clinical diagnosis with imaging confirmation; or study-specific validated criteria
Metabolic adverse events	Transient hypoglycemia	Symptomatic hypoglycemia as defined by the study authors
Important		
Safety outcomes	Treatment discontinuation	Discontinuation of study medication due to adverse events
	HbA1c	Change in HbA1c level
	Other adverse events	Gastrointestinal and cardiovascular adverse events

WHO: World Health Organization