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Effect of glucagon-like-peptide-1 receptor agonists on major cardiovascular outcomes: a systematic review and meta-analysis

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Abstract

Glucagon-like-peptide-1 (GLP-1) receptor agonists are an antihyperglycemic group of drugs that have emerged as potentially preventing the risk of cardiovascular events. This meta-analysis assesses the effect of GLP-1 receptor agonists on cardiovascular outcomes. A detailed search of existing literature was based on MEDLINE, the Cochrane Library, Embase, and [ClinicalTrials.gov](https://www.clinicaltrials.gov). The search included all the studies from inception to February 2026. Statistical analyses were performed using the RevMan software, and a random-effects model was used to conduct the meta-analysis. Data were represented via forest plots, and dichotomous outcomes were evaluated using the Mantel-Haenszel method. This meta-analysis includes 12 randomized control trials (RCTs) with 82,669 patients. The analysis showed that GLP-1 receptor agonists reduce risk of cardiac death [relative risk (RR): 0.89, 95% confidence interval (CI): 0.82-0.96, $p=0.003$, $I^2=0\%$], all-cause mortality (RR: 0.88, 95% CI: 0.84-0.93, $p<0.00001$, $I^2=0\%$), stroke (RR: 0.85, 95% CI: 0.77-0.94, $p=0.001$, $I^2=0\%$), non-fatal stroke (RR: 0.87, 95% CI: 0.79-0.96, $p=0.005$, $I^2=0\%$) and revascularization (RR: 0.82, 95% CI: 0.72-0.95, $p=0.007$, $I^2=59\%$). There was no statistically significant reduction in myocardial infarction (MI) (RR: 0.92, 95% CI: 0.84-1.01, $p=0.09$, $I^2=42\%$), fatal MI (RR: 1.15, 95% CI: 0.80-1.66, $p=0.44$, $I^2=0\%$), non-fatal MI (RR: 0.91, 95% CI: 0.82-1.01, $p=0.09$, $I^2=51\%$), fatal stroke (RR: 0.75, 95% CI: 0.55-1.00, $p=0.05$, $I^2=0\%$), heart failure hospitalization (RR: 0.94, 95% CI: 0.85-1.03, $p=0.20$, $I^2=17\%$), or hospitalization for unstable angina (RR: 0.97, 95% CI: 0.85-1.12, $p=0.71$, $I^2=0\%$). This meta-analysis demonstrates that GLP-1 receptor agonists have a significant impact on cardiovascular death. More thorough RCTs with longer follow-up periods are required to completely understand the possible cardiovascular advantages of GLP-1 receptor agonists.

Key words: glucagon-like receptor, major adverse cardiovascular events, myocardial infarction.

Introduction

Cardiovascular disease (CVD), along with diabetes, is considered among the top health conditions globally [1]. For patients who have type 2 diabetes mellitus (T2DM), the occurrence of atherosclerotic CVD is high. CVD remains one of the most common causes of death, even though progress has been made in glycemic and lipid-lowering therapies. One of the leading causes of CKD and kidney failure is T2DM. CKD affects one-tenth of the whole adult population worldwide, and if it progresses to end stage renal disease (ESRD), it is associated with a high risk of CV and all-cause mortality [2]. Diabetes was the eight most prevalent cause of death worldwide in 2019 [3]. Cardiorenal syndrome encompasses a spectrum of disorders involving both the heart and the kidneys: impaired kidney function leads to myocardial infarction, stroke, heart failure, hospitalization, and death, to which cardiovascular damage intensifies kidney injury by hemodynamic, inflammatory, and metabolic pathways [4]. Since these diseases are very common, their interaction is one of the main reasons for the increase of morbidity, mortality, and healthcare costs. Thus, a key goal in the treatment of individuals with type 2 diabetes or obesity is the prevention of cardiovascular events.

T2DM treatment approaches have gone beyond glycemic safety to interventions with evidence of cardiovascular benefits. Glucagon-like-peptide-1 (GLP-1) receptor agonists were first introduced for the purpose of improving glycemic control and promoting weight loss. Recent trials, such as cardiovascular outcome trials, have been conducted, which show the effectiveness of GLP-1 receptor agonists in the treatment of cardiovascular outcomes. These trials have shown the benefit of certain GLP-1 receptor agonists in the reduction of the first occurrences of major adverse cardiovascular outcomes (MACE), cardiovascular death, and all-cause mortality in patients with T2DM who have a high risk of cardiovascular issues [5]. Recent data points to the potential of having a positive effect on renal outcomes, such as progression of albuminuria, and estimated glomerular filtration rate (eGFR) [6]. Since GLP-1 receptor agonists are approved to treat obesity in individuals with and without diabetes, it is unclear if GLP-1 receptor agonists are beneficial for improvement in cardiovascular outcomes in individuals without diabetes.

GLP-1 receptor agonists bind to the GLP-1 receptor on pancreatic β -cells, leading to the secretion of insulin that is glucose dependent. The glucagon secretion is inhibited, which improves the glycemic control and limits the postprandial glucose secretions. Activation of the

GLP-1 receptor slows down gastric emptying, induces weight reduction, and decreases appetite. These metabolic effects are beneficial for cardiac and renal function, along with reducing hyperglycemia and obesity. GLP-1 receptor activation in cardiovascular tissues has been shown to improve endothelial function and reduce oxidative stress. It also lowers blood pressure, promotes natriuresis and reduces inflammation, with all these mechanisms contributing to slowing the rate of atherosclerotic progression, cardiac stress and renal damage [7].

Hence, this meta-analysis focuses on the GLP-1 receptor agonists' effects on cardiac outcomes based on the randomized evidence. Our objective is to measure the impact of these drugs on MACE, cardiac death, myocardial infarction (MI), heart failure (HF) hospitalization, stroke, and revascularization.

Materials and Methods

For this meta-analysis, we adhered to the guidelines, which are detailed in the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8,9]. PROSPERO, the International Prospective Register of Systematic Reviews, has our protocol listed in their database (CRD420261276892).

Data sources and searches

An exhaustive search was conducted in the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and ClinicalTrials.gov to identify our meta-analysis relevant articles from the beginning of the database until November 2025. Already published systematic reviews on GLP-1 receptor agonists with reported cardiovascular outcomes were assessed, and the reference lists of the included studies from our research were analyzed to find more relevant articles. Search terms were based on the combination of Medical Subject Headings (MeSH) and pertinent keywords related to “GLP-1 receptor agonist” and “Cardiovascular diseases.” Detailed search strategy is reported in *Supplementary Table 1*.

Eligibility criteria

The inclusion criteria during the research for our article were as follows: (1) study design: randomized controlled trials (RCTs); (2) intervention: GLP-1 receptor agonist; (3) comparison: placebo or standard treatment; and (4) outcome: cardiovascular.

Non-randomized studies, quasi-experimental trials, observational, or animal studies were excluded. No language or data restrictions were introduced.

Study selection and data abstraction

Each study that was searched from the data sources was imported into Rayyan, and duplicate records were excluded from the list. Two authors independently reviewed titles and abstracts, and a third reviewer resolved disagreements.

The data from the eligible trials were collected and organized in an Excel sheet. Data was comprised of the author's last name, year of publication, country, sample size, type of study, demographic data (age, sex), comorbidities (hypertension, coronary artery disease, heart failure, smoking), intervention details (type, dose, duration, frequency), and clinical outcomes.

Outcome measures

The primary outcome measure was cardiac death. Secondary outcomes were all-cause mortality, MI, fatal MI, non-fatal MI, stroke, fatal stroke, non-fatal stroke, heart failure (HF) hospitalization, unstable angina hospitalization, and revascularization.

Risk of bias assessment

The evaluation of risk of bias was performed through the implementation of the updated Cochrane Risk of Bias Tool for RCTs (RoB 2.0) which is oriented towards the following five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome and (5) bias in the selection of the reported result. Two reviewers independently rated each study as “low,” “high,” or “some concerns” for bias. In cases of disagreement, the reviewers sought resolution by discussion, or, if necessary, a decision from a third reviewer via arbitration.

Data synthesis

All statistical analyses were performed using Review Manager (RevMan, Version 5.4). The Mantel–Haenszel method was used to analyze dichotomous outcomes to obtain risk ratios (RRs) with 95% confidence intervals (CIs). The model of random effects was used. The pooled results were presented using forest plots, and heterogeneity was quantified with the Higgins I^2 statistic. In the event of multi-arm trials, active arms were combined or the shared control arm was partitioned to avoid double-counting. For trials with zero events in both arms, a continuity correction was applied.

Results

Search strategy

The initial database search retrieved 4,182 results. After removal of 1,218 duplicates and 1,141 other records, 1,823 articles were included in screening. Finally, after careful selection, 12 RCTs were included in our meta-analysis [10-21]. The process for study selection is visually summarized in Figure 1.

Study characteristics

Our meta-analysis comprises a total of 12 RCTs. One study included data from 13 countries across Asia, Europe, and North and South America [20], one included 49 countries [16], one included 20 countries ¹⁰, one included 28 countries in North and South America, Europe, Africa, and Asia [10], one included 24 countries [12], one included 41 countries ⁹, one included 26 countries [21], one included 28 countries [11], one included 410 sites from multiple countries [13], one included 21 countries [17], one included 35 countries [15] and one was based on data from the United States [14]. The detailed study characteristics are shown in Table 1.

Risk of bias assessment

The risk of bias in our 12 chosen RCTs was assessed via the revised Cochrane Risk of Bias (ROB 2.0) tool. Ten studies exhibited a low risk of bias. Two studies had some concerns, one because of bias arising from the randomization process and the other because of bias in the

measurement of the outcome. *Supplementary Figure 1* displays the quality assessment of selected studies.

Meta-analysis of primary outcome

Cardiac death

Eleven out of twelve studies reported data on cardiac death [10,12-21]. 39,272 people were included in the GLP-1 receptor agonists group and 39,321 in the control group. Our statistical analysis showed a reduction in cardiac death in people treated with GLP-1 receptor agonists compared to the control group (RR = 0.89, 95% CI = 0.82-0.96, P-value = 0.003). The level of heterogeneity recorded was zero ($I^2 = 0\%$) (Figure 2).

Meta-analysis of secondary outcomes

All-cause mortality

All twelve studies reported all-cause mortality [10-21]. 41,989 people were included in the GLP-1 receptor agonists group and 40,680 in the control group. Patients treated with GLP-1 receptor agonists were at a reduced risk of all-cause mortality (RR = 0.88, 95% CI = 0.84-0.93, P-value < 0.00001). No heterogeneity was observed ($I^2 = 0\%$) (*Supplementary Figure 2*).

Myocardial infarction

Out of twelve RCTs, seven provided data on MI [10-13,15-17]. 29,046 people were included in the GLP-1 receptor agonists group and 27,737 in the control group. There was no statistically significant difference in MI rates between GLP-1 receptor agonists and control groups, according to our statistical analysis (RR = 0.92, 95% CI = 0.84-1.01, P-value = 0.09). The level of heterogeneity recorded was moderate ($I^2 = 42\%$) (*Supplementary Figure 3*).

Fatal myocardial infarction

Four out of twelve studies reported data on fatal MI [11,12,15,16]. 18,056 people were included in the GLP-1 receptor agonists group and 16,741 in the control group. There was no statistically significant difference in GLP-1 receptor agonists and control groups (RR = 1.15, 95% CI = 0.80-1.66, P-value = 0.44). The level of heterogeneity recorded was zero ($I^2 = 0\%$) (*Supplementary Figure 4*).

Non-fatal myocardial infarction

Non-fatal MI data were reported in nine out of twelve trials [11-13,15-19,21]. 36,841 people were included in the GLP-1 receptor agonists group and 35,536 in the control group. Statistically, there was no significant difference in GLP-1 receptor agonists and control groups (RR = 0.91, 95% CI = 0.82-1.01, P-value = 0.09). The level of heterogeneity recorded was moderate ($I^2 = 51\%$) (*Supplementary Figure 5*).

Stroke

Seven studies reported data on stroke with 29,046 people in the GLP-1 receptor agonists group and 27,737 in the control group [10-13,15-17]. Pooled analysis shows that GLP-1 receptor agonists significantly reduced the risk of stroke as compared to the control (RR = 0.85, 95% CI = 0.77-0.94, P-value = 0.001). The level of heterogeneity recorded was zero ($I^2 = 0\%$) (*Supplementary Figure 6*).

Fatal stroke

Five studies have documented fatal stroke data [11,12,15,13,16]. The GLP-1 receptor agonists group comprised 22,724 people, with 21,413 in the control group. Comparison between GLP-1 receptor agonists and control groups showed borderline differences between both groups, but statistically insignificant (RR = 0.75, 95% CI = 0.55-1.00, P-value = 0.05). Heterogeneity was zero ($I^2 = 0\%$) (*Supplementary Figure 7*).

Non-fatal stroke

Nine different studies, with a total of 72,377 participants, reported data on non-fatal stroke [11-13,15-19,21]. GLP-1 receptor agonists lowered the incidence of non-fatal stroke (RR = 0.87, 95% CI = 0.79-0.96, P-value = 0.005). There was no heterogeneity noted ($I^2 = 0\%$) (*Supplementary Figure 8*).

Heart failure hospitalization

Ten studies reported data on heart failure hospitalization [12-21]. Analysis of the data showed that the GLP-1 receptor agonists and control groups were comparable. There was no significant

statistical difference between the groups (RR = 0.94, 95% CI = 0.85-1.03, P-value = 0.20). Low level of heterogeneity was recorded ($I^2 = 17\%$) (*Supplementary Figure 9*).

Unstable angina hospitalization

Hospitalization for unstable angina was reported in eight out of twelve studies, with 29,485 people in the GLP-1 receptor agonists group and 28140 people in the control group [11-13,16-19,21]. Data showed that there was no statistical difference between the GLP-1 receptor agonists group and the control group (RR = 0.97, 95% CI = 0.85-1.12, P-value = 0.71). There was no heterogeneity recorded ($I^2 = 0\%$) (*Supplementary Figure 10*).

Revascularization

Four trials showed data on revascularization with a total of 34,317 participants [11,13,18,19]. There was a significant decrease in revascularization events in participants who were on GLP-1 receptor agonists (RR = 0.82, 95% CI = 0.72-0.95, P-value = 0.007) with moderate heterogeneity recorded ($I^2 = 59\%$) (*Supplementary Figure 11*).

Discussion

Our meta-analysis of 12 randomized controlled trials including 82,669 patients found that GLP-1 receptor agonists were associated with reduced rates of all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, stroke, and coronary revascularization compared with placebo.

Outcomes for hospitalization for unstable angina, heart failure, and fatal myocardial infarction trended in favor of GLP-1 receptor agonists but did not reach statistical significance.

These findings corroborate prior meta-analyses that linked GLP-1 receptor agonist use to lower risk of major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [22-24]. Stefanou et al. reported similar results for all-cause mortality and MACE in obese and overweight populations without diabetes when GLP-1 receptor agonists or combined GIP/GLP-1 therapies were used, although some composite endpoints failed to reach statistical significance in their pooled estimates [25]. That analysis also observed reductions in myocardial infarction and non-fatal MI (OR: 0.72; 95% CI: 0.61–0.86

and OR: 0.72; 95% CI: 0.61–0.85, respectively) [25]. Our results align with these trends and with other large meta-analyses showing roughly a 10% relative risk reduction in the three-component MACE outcome with GLP-1 receptor agonist therapy.

The cardiovascular benefits seen with GLP-1 receptor agonists are likely multifactorial. They include glucose lowering and weight reduction [26], but also direct and indirect cardiovascular effects such as modest blood pressure reduction, improvements in lipid metabolism and endothelial function, natriuresis, and anti-inflammatory actions that together may slow atherosclerosis and reduce plaque instability and nephropathy [25,27-32].

GLP-1 is produced in multiple tissues and its receptors are expressed in cardiomyocytes, vascular endothelium, kidneys, the gastrointestinal tract, and the central nervous system, which provides a biological rationale for widespread cardiometabolic effects. The incretin-mediated insulinotropic and glucagon-suppressing effects further contribute to improved metabolic control [7, 33-36].

Two large RCTs included in our meta-analysis merit brief discussion because of their size and population differences. The SELECT trial enrolled 17,604 overweight and obese patients with established cardiovascular disease but without diabetes, and it contributed substantial weight to the pooled estimates [18]. SELECT reported fewer primary cardiovascular events with semaglutide than with placebo and showed large effects on body weight (mean change –9.3% with semaglutide versus 0.88% with placebo), which may mediate part of the cardiovascular benefit [28,36,37]. Limitations of SELECT include its focus on secondary prevention, older age of participants, and underrepresentation of women and some racial groups, which restricts generalizability to primary prevention and to younger or more diverse populations [18,25]. By contrast, the REWIND trial enrolled 9,901 people with type 2 diabetes regardless of prior cardiovascular events and showed a cardiovascular benefit with dulaglutide, notably a stronger effect on stroke than on myocardial infarction [12,38]. These two trials together illustrate that effects may differ by baseline risk and by outcome type.

Other included trials, such as the efpeglenatide study, support the class effect across different GLP-1 receptor agonists. That trial, conducted in patients with cardiovascular and renal comorbidities who were receiving contemporary cardioprotective therapies, found a lower incidence of MACE (3.9 vs 5.3 events per 100 person-years; HR 0.73; 95% CI 0.58–0.92) and suggested benefits on several secondary outcomes [11,37,39]. These data, together with prior

meta-analyses on revascularization, reinforce that GLP-1 receptor agonists may reduce the need for coronary procedures in selected populations [40].

Despite overall consistency, heterogeneity remains a concern. Clinical heterogeneity arises from differences in included agents, trial populations (primary versus secondary prevention), background therapies, and follow-up duration. These factors may explain why benefits are more robust and consistent for some outcomes (for example, stroke and all-cause mortality) than for others (for example, myocardial infarction and heart failure hospitalization). Trial duration and adherence also vary, and longer follow-up may be required to fully capture effects on some cardiovascular endpoints. Treatment adherence in real-world settings can differ from RCTs and may influence effectiveness outside trials [41].

The present analysis has several notable strengths. Restriction to RCTs minimizes the confounding and selection bias inherent to observational designs, supporting stronger causal inference than mixed-design pooled analyses. With 12 RCTs and 82,669 patients, this represents one of the largest randomized-only meta-analyses of GLP-1 receptor agonist cardiovascular outcomes to date, affording greater statistical precision across individual endpoints. Unlike prior pooled analyses that focused predominantly on composite three-point MACE, we provide separate effect estimates for all-cause mortality, cardiovascular mortality, non-fatal and fatal myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina, and hospitalization for heart failure, a granularity that more directly informs clinical and guideline decision-making. The inclusion of both diabetic and non-diabetic populations across a broad range of GLP-1 receptor agonist agents, and the incorporation of more recently completed large trials such as SELECT and REWIND, further extends the scope of prior meta-analyses.

Conclusions

In summary, pooled randomized evidence suggests that GLP-1 receptor agonists confer modest but clinically meaningful reductions in all-cause and cardiovascular mortality, stroke, and coronary revascularization. Benefits appear to be influenced by agent choice, patient baseline risk, and trial characteristics. These findings support the expanding role of GLP-1 receptor agonists in cardiometabolic care, but further studies with longer follow-up, more diverse populations, and head-to-head comparisons are needed to refine which patients and which agents derive the greatest cardiovascular benefit. Finally, evaluation of cost-effectiveness will be

important to guide implementation of GLP-1 receptor agonists for cardiovascular risk reduction, both in people with and without diabetes.

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Online supplementary material

Supplementary Table 1. Detailed search strategy.

Supplementary Figure 1. Risk of bias in randomized controlled trials.

Supplementary Figure 2. Forest plot of all-cause mortality.

Supplementary Figure 3. Forest plot of myocardial infarction.

Supplementary Figure 4. Forest plot of fatal myocardial infarction.

Supplementary Figure 5. Forest plot of non-fatal myocardial infarction.

Supplementary Figure 6. Forest plot of stroke.

Supplementary Figure 7. Forest plot of fatal stroke.

Supplementary Figure 8. Forest plot of non-fatal stroke.

Supplementary Figure 9. Forest plot of heart failure hospitalization.

Supplementary Figure 10. Forest plot of unstable angina hospitalization.

Supplementary Figure 11. Forest plot of revascularization.

Table 1. Characteristics of the included studies.

Study ID	Country	Sample size	Mean age, in years (SD)	Male (%)	HTN (%)	CAD (%)	HF (%)	Smoking (%)	GLP-1 agonist regimen
Kosiborod 2023	13 countries in Asia, Europe, and North and South America	529 (263 vs 266)	69 (62-75)	43.9	81.9	18.5	100	NR	Semaglutide 2.4 mg subcutaneously once a week for 52 weeks
Pfeffer 2015	49 countries	6068 (3034 vs 3034)	60.25 ± 9.6 (59.9 ± 9.7 vs 60.6 ± 9.6)	69.6% vs 69.1%	75.6% vs 77.1%	67.6% vs 66.8%	22.5% vs 22.3%	11.7% vs 11.7	Lixisenatide 10-20 µg subcutaneously once daily
Marso 2016	230 sites in 20 countries.	3297 (1648 vs 1649)	64.6±7.4	60.70%	92.8	NR	23.6	NR	Semaglutide 0.5mg or 1.0mg subcutaneously once a week for 104 weeks
Hernandez 2018	28 countries in North and South America, Europe, Africa, and Asia	9463 (4731 vs 4732)	64.1	69.41	86.48	71	20	NR	Albiglutide 30-50 mg subcutaneously once weekly
Gerstein 2019	371 sites in 24 countries	9901 (4949 vs 4952)	66.2 (59.7-72.7)	53.7	93.1	NR	8.6	14.2	Dulaglutide 1.5mg subcutaneously once a week
Lincoff 2023	804 clinical sites in 41 countries including Argentina, Australia, Austria, Belgium, Bulgaria, Brazil, Canada, Colombia, Czech Republic	17604(8803 vs 8801)	61.6±8.9	72.3	NR	67.6	NR	NR	Semaglutide 2.4mg subcutaneously once a week for 34.2±13.7 months
Ruff et al 2022	402 sites in 26 countries	4156 (2075 vs 2081)	63±7.4years	63.3	NR	49	16.1	48.6	ITCA 650 20 mcg per day 3 months followed by 60 mcg per day 6 months
Gerstein et al 2021	344 sites in 28 countries	4076 (2717 vs 1359)	64.5±8.2 years	67	91.3	NR	18.1	15.5	Épeglenatide 2-6 mg subcutaneously once weekly
Marso 2020	Multinational 410 sites	9340 (4668 vs 4672)	NR	64.27	NR	NR	17.84	NR	Liraglutide 1.8mg subcutaneously once daily for 3.5-5 yrs
Husain 2019	21 countries	3183 (1591 vs 1592)	66±7 years	68.4	NR	NR	NR	NR	Semaglutide 14mg orally once daily for 15.9 months
Holman 2022	687 sites in 35 countries	14752 (7356 vs 7396)	NR	62.01	NR	NR	16.1	NR	Extended-release Exenatide 2mg subcutaneously once weekly for 3.2 years
Margulies 2016	US	300 (154 vs 146)	62 (52-68)	79	78.3	82	87%	NR	Liraglutide 1.8mg subcutaneously once daily for 180 days

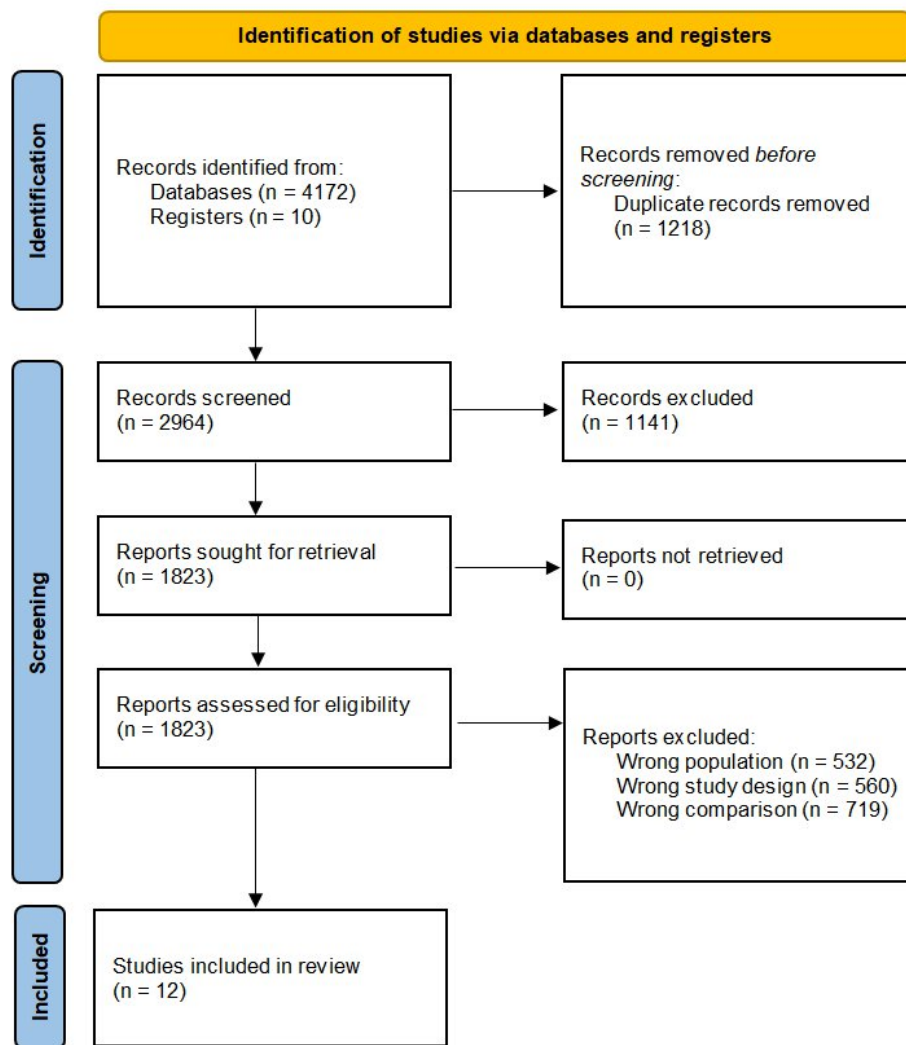


Figure 1. PRISMA flowchart.

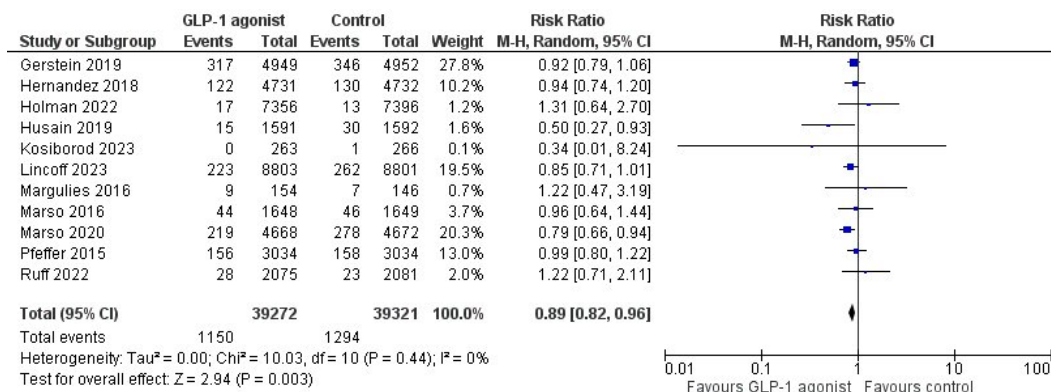


Figure 2. Forest plot of cardiac death.