American Journal of Preventive Cardiology 18 (2024) 100679

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Original Research

Cardiovascular and renal outcomes of glucagon-like peptide 1 receptor agonists among patients with and without type 2 diabetes mellitus: A meta-analysis of randomized placebo-controlled trials

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HIGHLIGHTS

- This is the largest meta-analysis of placebo-controlled GLP-1RA randomized controlled trials to report cardiovascular and renal outcomes among patients with and without diabetes mellitus.
- GLP-1RAs significantly reduced MACE, all-cause mortality, CV mortality fatal and non-fatal stroke, coronary revascularization, and composite kidney outcome among patients with and without diabetes mellitus.
- GLP-1RA reduced MACE in both sexes. Furthermore, GLP-1RA reduced MACE in patients with and without CVD history, in BMI above or below 30 kg/m^2, and in patients with an eGFR level of below or above 60 ml/min/1.73m^2.
- The cardiovascular benefits from GLP-1RAs beyond weight loss is clear.
- Health care professionals should consider prescribing GLP-1RAs to all eligible patients to improve cardiovascular and renal outcomes.

ARTICLE INFO

Keywords:
Glucagon-like peptide 1 receptor agonists
GLP-1RA
Cardiovascular outcomes
Renal outcomes
MACE

ABSTRACT

Background: Multiple cardiovascular outcomes trials (CVOTs) have shown the efficacy of GLP-1RAs in reducing major adverse cardiovascular events (MACEs) for high-risk patients. However, some CVOTs failed to demonstrate cardiovascular benefits.
Objectives: We analyzed the impact of GLP-1RA on cardiovascular and renal outcomes in patients with or without T2DM, with subgroup analysis based on sex, estimated glomerular filtration rate (eGFR), body mass index (BMI), and history of cardiovascular disease (CVD).
Methods: A comprehensive database search for placebo-controlled RCTs on GLP-1RA treatment was conducted until April 2024. Data extraction and quality assessment were carried out, employing a robust statistical analysis using a random effects model to determine outcomes with log odds ratios and 95 % confidence intervals (CIs).
Results: A total of 13 CVOTs comprising 83,258 patients were included. GLP-1RAs significantly reduced MACE (OR 0.86, 95 % CI: 0.80 to 0.94, $p < 0.01$) all-cause mortality OR 0.87, 95 % CI: 0.82 to 0.93, $p < 0.001$, CV mortality (OR 0.87, 95 % CI: 0.81 to 0.94, $p < 0.001$), stroke (fatal: OR 0.74, 95 % CI: 0.56 to 0.96, $p = 0.03$; non-fatal: OR 0.87, 95 % CI: 0.79 to 0.96, $p = 0.005$), coronary revascularization (OR 0.86, 95 % CI: 0.74 to 0.99, $p = 0.023$), and composite kidney outcome (OR 0.76, 95 % CI: 0.67 to 0.85, $p < 0.001$. GLP-1RA significantly

Funding: None.**Disclosures**: *MG: Consultant Fees/Honoraria:* Esperion, Novartis, and Boehringer Ingelheim *Research/Research Grants:* Congressionally Directed Medical Research Program-Department of Defense *(WARRIOR study)*.

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https://doi.org/10.1016/j.ajpc.2024.100679
Received 17 March 2024; Received in revised form 11 April 2024; Accepted 27 April 2024
Available online 7 May 2024

reduced MACE in both sexes. Furthermore, GLP-1RA reduced MACE regardless of CVD history, BMI, and eGFR level.

Conclusion: Significant reductions in MACE, overall and CV mortality, stroke, coronary revascularization, and composite kidney outcome with GLP-1RA treatment were noted across all subgroups.

Abbreviations

CVOT	Cardiovascular outcome trials
GLP-1RA	Glucagon-like peptide 1 receptor agonists
MACE	major adverse cardiovascular events
RCTs	randomized controlled trials
MI	myocardial infarction
CVD	cardiovascular disease
ASCVD	atherosclerotic cardiovascular disease

1. Introduction

In recent years, there has been a paradigm shift in the management of diabetes mellitus (DM), with the introduction of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2is). These antihyperglycemic agents have now been proven to reduce cardiovascular (CV) events among patients with and without DM [1]. The success of several sizable cardiovascular outcome trials (CVOT) utilizing GLP-1RAs has influenced this shift in DM management. The first CVOT was the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial in 2015; however, this trial failed to show significant CV benefits among patients with DM and recent acute coronary syndrome [2]. However, the subsequent LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, which aimed to determine the CV effect of liraglutide marked a turning point and was the first to show a reduction in major adverse cardiovascular events (MACE) [3]. Several CVOTs have followed since, such as the SUSTAIN-6 [4] (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), HARMONY [5] (Albiglutide and Cardiovascular Outcomes in Patients with Type 2 diabetes and Cardiovascular Disease) and REWIND trial [6] (Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes), demonstrating that semaglutide, albiglutide, and dulaglutide respectively, reduced MACE among patients with DM and high CV risk. The SELECT (Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes) trial evaluated semaglutide among patients with preexisting CVD who were overweight or obese and demonstrated to reduce MACE [7]. The STEP-HFpEF and STEP-HFpEF DM (Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity and Obesity and Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes) trial demonstrated that among patients with heart failure with preserved ejection fraction, obesity treatment with semaglutide led to reduced symptoms, limitations, and greater exercise function and weight loss [8,9].

GLP-1RAs have evolved from promising antihyperglycemic agents to becoming crucial cardiometabolic therapies with significant CV benefit. However, further research is still needed to elucidate cardiovascular and renal outcomes based on different subgroups. In this meta-analysis, we aimed to determine the cardiovascular and renal outcomes among patients with and without DM on GLP-1RA versus placebo. We also analyzed MACE outcomes based on sex, estimated glomerular filtration rate (eGFR), body mass index (BMI), and history of CVD.

2. Methods

This study was reported under the Preferred Reporting Items for a Review and Meta-Analysis (PRISMA) [10,11] and the checklist [11] was followed **(Figure S1 and Table S1)**. Certainty of evidence was rated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework [12]. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) [13], with the identification number CRD42022360886.

2.1. Data sources and searches

The literature search was performed using PubMed/MEDLINE, Ovid/Embase, google scholar, and clinicaltrials.gov from database inception until April 2024. Search terms included "glucagon-like peptide-1 receptor agonists", "GLP-1 agonist", "GLP-1RA", "semaglutide", "dulaglutide", "albiglutide", "exenatide", "liraglutide", "lixisenatide", "efpeglenatide", "placebo", "cardiovascular disease", "cardiovascular risk factors", "renal outcomes" "nephropathy" "randomization", "clinical trials", "intervention studies" and synonyms. Citations of selected articles and any relevant studies that evaluated GLP-1RA and cardiovascular outcomes were reviewed. After removing duplicates, records were reviewed at the title and abstract level, followed by the screening of full text based on our study criteria.

2.2. Study selection

Eligible phase III, double-blind placebo-controlled randomized controlled trials (RCTs) comparing treatment with GLP-1RA with placebo in adult patients aged 18 years and above were included. Moreover, the studies must have reported the primary efficacy endpoint which is MACE or any of the secondary efficacy endpoints namely, all-cause mortality, cardiovascular mortality, hospitalization due to HF, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, revascularization, hospitalization due to unstable angina, and renal endpoints. Studies were excluded if (1) they did not report a control arm, (2) the control arm was not placebo, (3) participants were younger than 18 years, and (4) studies reporting interim or post hoc analysis. Crossover trials were also excluded due to the nature of the outcomes considered. Review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other non-relevant studies were also excluded.

2.3. Data extraction

Key participant and intervention characteristics and reported data on efficacy outcomes were extracted independently by two investigators (JPA and LLC) using standard data extraction templates. Any disagreements were resolved by discussion or, if required, by a third author (FBR). Data on the following variables were extracted: first author's name, year of publication, journal, study phase, interventional and control treatments, randomization method, analysis tool, number of randomized patients, and demographic and clinical data. In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information. Quality assessment was performed independently by two review authors using the Revised Cochrane risk-of-bias tool for randomized trials.

2.4. Outcome measures

The primary endpoint of this meta-analysis was major adverse cardiac events (MACE). MACE was defined as death from cardiovascular causes, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina. Additionally, subgroup analyses were performed for applicable studies on the differences in MACE based on (1) sex, (2) eGFR and (3) BMI, and (4) presence of CVD.

Secondary endpoints included all-cause mortality, cardiovascular mortality, hospitalization due to HF, fatal and non-fatal MI, fatal and non-fatal stroke, revascularization, hospitalization due to unstable angina, and renal endpoints.

2.5. Bias assessment

All included studies reported a central randomization process, and outcomes were objectively determined. The included studies reported all primary and secondary outcomes as pre-specified in their protocols, so the risk of bias for selective reporting was judged as low. Three authors (JVM, LLC and JPA) independently assessed the risk of bias based on the Cochrane Risk of Bias Tool **(Figures S2)** for studies that fulfilled the inclusion criteria.

2.6. Statistical analysis

We pooled all estimates using a random effects model based on the restricted maximum likelihood (REML) model. Effect sizes were expressed using log odds ratio with 95 % confidence intervals (CIs). For all outcomes, the significance level was set at a p-value of <0.05 or 95 % CI not including 1. Funnel plot and Egger test were used for estimation of publication bias. Both Cochran's Q and Higgins and Thompson's I2 statistics were generated to describe the heterogeneities among the studies. We calculated the I^2 statistics (0–100 %) to explain the between-study heterogeneity, with $I^2 \leq 25$ % suggesting acceptable homogeneity, 25 % < $I^2 \leq 75$ % suggesting moderate heterogeneity, and $I^2 > 75$ % suggesting high heterogeneity. Forest plots were used to plot the effect size, either for each study or overall. Publication bias was evaluated by graphical inspection of funnel plot; estimation of publication bias was quantified by means of Egger linear regression and nonparametric rank correlation (Begg) tests. **(Table S2)** Prespecified subgroup analyses for MACE were performed according to (1) Sex, (2) eGFR, and (3) BMI, and (4) presence of CVD. Stata version 14 (*StataCorp, College Station, TX*) was used to conduct the included studies' meta-analyses.

3. Results

A literature search through April 2024, yielded 4178 potentially relevant references on GLP-1RA. (**Figure S1**). Of these, 1156 duplicates were removed. A total of 1.221 studies with unrelated interventions, outcomes, populations, non-original data (e.g., meta-analysis or review), descriptive or observational study design, and study protocols were excluded. A total of 679 studies were left, and 667 articles were removed for not meeting the eligibility criteria. One article was obtained from google scholar after it was simultaneously published during trial presentation in the American College of Cardiology conference. The remaining 13 related studies were retrieved as full-text publications for detailed evaluation. Overall, 13 studies were included in the final meta-analysis. From the 13 studies, 83,258 eligible individuals were included for analysis. There were 29,967 (36 %) females overall. The study characteristics are shown in Table 1. Majority of the RCTs were multinational and sponsored by drug companies.

Ten RCTs [2,4-7,14-18] reported MACE as the primary outcome, with eight [3-7,15,17,18] of them using a three-point MACE, which comprises death from cardiovascular causes, nonfatal MI, and nonfatal stroke, with some studies including death from undetermined cause. The other two (2) [2,14] RCTs that reported MACE as the primary outcome used a four-point MACE, which included the three-point MACE plus hospitalization for unstable angina. Two studies [8,9] used two primary outcomes: change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and change in body weight. Notable secondary outcomes shared by the RCTs include the individual MACE components, death from any cause, hospitalization for heart failure, hospitalization for unstable angina, coronary revascularization, microvascular complications of diabetes, composite renal outcome and its individual components (sustained worsening kidney function, macroalbuminuria, increase in urinary albumin to creatinine ratio, persistent need for continuous renal replacement therapy, death from renal causes), HbA1c, body weight, and lipids. Studies that recruited patients with HF also assessed functional status based on changes in the 6-minute walk test, changes in cardiac structure and function.

Nine RCTs [2,4-6,9,14-18] were done exclusively on patients with T2DM, and two [7,8] studies excluded patients with T2DM. Among the 13 RCTs in this study, four of them had a population exclusively of patients with baseline or established atherosclerotic cardiovascular disease (ASCVD). The nine remaining RCTs included patients with baseline ASCVD but included those with CV risk factors but without baseline ASCVD. No study excluded patients with ASCVD. According to the tool of Cochrane Collaboration for assessing risk of bias, there was no major risk of bias all the studies included.

3.1. Outcomes

As for the primary efficacy endpoint, 10 RCTs explored MACE as primary or secondary outcome. GLP-1RA significantly reduced MACE, (OR 0.86, 95 % CI: 0.80 to 0.94, $p < 0.01$), I^2=53.6 %, compared to placebo. (Fig. 1) Subgroup analyses showed that GLP-1RA significantly reduced MACE in both sexes (females OR 0.83, 95 % CI: 0.76 to 0.91, $p < 0.001$), males OR 0.85, 95 % CI: 0.80 to 0.90, $p < 0.001$) and the treatment effect was not significantly different (p interaction NS) (Fig. 2). Furthermore, GLP-1RA reduced MACE regardless of CVD history (with history of CVD OR 0.84, 95 % CI: 0.77 to 0.92, $p < 0.001$), no history of CVD OR 0.89, 95 % CI: 0.81 to 0.97, $p = 0.011$), (p interaction NS), (Fig. 3) BMI (BMI <30 OR 0.76, 95 % CI: 0.63 to 0.92, $p = 0.004$), BMI of 30 and above (OR 0.86, 95 % CI: 0.79 to 0.93, $p < 0.001$) (p interaction NS), (Fig. 4) and eGFR level (eGFR <60 OR 0.80, 95 % CI: 0.68 to 0.94, $p = 0.008$), eGFR greater than or equal to 60 (OR 0.86, 95 % CI: 0.80 to 0.93), $p < 0.001$) (p interaction NS) (Fig. 5).

As for secondary endpoints, GLP-1RA significantly reduced all-cause mortality compared to placebo (OR 0.87, 95 % CI: 0.82 to 0.93, $p < 0.001$). I^2=12.4 %. (Fig. 6) Furthermore, GLP-1RA reduced CV mortality (OR 0.87, 95 % CI: 0.81 to 0.94, $p < 0.001$) (I^2=0.0 %) (Fig. 7) and fatal (OR 0.74, 95 % CI: 0.56 to 0.96, $p = 0.03$) and non-fatal (OR 0.87, 95 % CI: 0.79 to 0.96, $p = 0.005$) stroke. (I^2=0.0 %) (Fig. 8) Our meta-analysis shows statistically insignificant reduction in HF hospitalization among patients who received GLP-1 RA compared to placebo (OR 0.90, 95 % CI: 0.80 to 1.01, $p = 0.092$). (I^2=33.8 %) (Fig. 9) Moreover, GLP-1RA reduced coronary revascularization (OR 0.86, 95 % CI: 0.74 to 0.99, $p = 0.023$). (I^2=71.6 %) (Fig. 10) Finally, GLP-1RA reduced the odds of the broad composite kidney outcome (OR 0.76, 95 % CI: 0.67 to 0.85, $p < 0.001$). (I^2=51.5 %) (Fig. 11) On the contrary, GLP-1RA did not reduce fatal (OR 0.88, 95 % CI: 0.61 to 1.27, $p = 0.50$), and non-fatal (OR 0.91, 95 % CI, 0.82 to 1.02, $p = 0.07$) MI (I^2=43.6 %) (Fig. 12), and hospitalization due to UA (OR 0.97, 95 % CI: 0.84 to 1.12, $p = 0.69$). (I^2=0.0 %) (Fig. 13).

4. Discussion

Our study comprehensively assessed the impact of GLP-1RAs on cardiovascular and renal outcomes across a spectrum of parameters. ***(See Fig. 14 for Central Illustration)*** While previous meta-analyses done by Kristensen et al. (2019) [19] and Giugliano et al. (2021) [20]

Table 1
Characteristics of included studies.

Author (year) / Name of Trial	Population	No. of patients	Follow-up	Age, years (mean)	Female, n (%)	Drug	Participants with established ASCVD, n (%)	Participants with established or history of HF, n (%)	Participants with eGFR < 60 ml/min per 1.73 m2 (n,%)	Primary endpoint
Kosiborod et al. (2024)/ STEP-HFpEF DM Trial	Patients with HFpEF, BMI of 30 or higher and T2DM	616 529	52 weeks 52 weeks	69 69	274 (44.3) 296 (56.1)	Semaglutide Semaglutide	148 (24) 98 (18)	616 (100) 529 (100)	- -	Change from baseline in the KCCQ-CSS scores Change from baseline in the KCCQ-CSS scores
Kosiborod et al. (2023)/ STEP-HFpEF Trial	Patients with HFpEF and a BMI of 30 or higher									
Lincoff et al. (2023)/ SELECT Trial	Patients who had preexisting CVD and a BMI of 27 or greater but no history of diabetes	17,604	39.8 months	61.6	4872 (27.7)	Semaglutide	14,452 (82)	4286 (24)	–	MACE
Ruff et al. (2022)	Patients with T2DM with, or at risk for ASCVD	4156	1.3 years	63	1525 (36.7 %)	Exenatide (ITCA 650)	3389 (82)	668 (16)	–	MACE
Gerstein et al. (2021)/ AMPLITUDE-O Trial	Persons with T2DM and a had a history of CVD and had kidney disease and at least one additional CV risk factor	4076	1.81 years	64.5	1344 (33.0)	Efpeglenatide	3650 (89.6)	737 (18.1)	–	MACE
Marso et al. (2020) / LEADER trial	Patients with T2DM age >/=50 years with either established CVD or CKD, or age >/=60 years with >/=1 CV risk factor.	9, 340	3.8 years	64.3	3337 (35.7)	Liraglutide	6764 (72.4)	1667 (17.8)	2158 (23.1)	MACE
Gerstein et al. (2019)/ REWIND Trial	Patients with T2DM who had either a previous CV event or CV risk factors	9901	5·4 years	66·2 years	4589 (46.3)	Dulaglutide	3109 (31.4)	853 (8.6)	2199 (22.2)	MACE
Husain et al. (2019)/ PIONEER 6 Trial	Patients with T2DM and had established CVD or CKD, or if they were 60 years of age or older and had CV risk factors only	3183	15.9 months	66	1007 (31.6)	Semaglutide	2695 (84.7)	388 (12.2)	856 (26.9)	MACE
Hernandez et al. (2018) / HARMONY Outcomes Trial	Patients with T2DM and established ASCVD	9463	1.6 years	64.1	2894 (30.6)	Albiglutide	9463 (100)	1922 (20.3)	2222 (23.5)	MACE
Margulies et al. (2016)/ FIGHT Trial	Patients with established diagnosis of HF and a LVEF of 40 % or lower during the preceding 3 months	300		61	64 (21.3)	Liraglutide	246 (82)	300 (100)	–	Global rank score
Holman et al. (2017)/ EXCEL trial	Adults with T2DM	14,752	3.2 years	62.0	5603 (38.0)	Exenatide	10,782 (73.1)	2389	3191 (21.7)	MACE
Marso et al. (2016)/ SUSTAIN-6 Trial)	Adults with T2DM	3297	3.1 years	64.6	1295 (39.3)	Semaglutide	2735 (83)	777 (23.6)	939 (28.5)	MACE
Pfeffer et al. (2015)/ ELIXA trial	Patients with T2DM who had a MI or who had been hospitalized for UA within the previous 180 days	6068	25 months	60.3	2894 (30.7)	Lixisenatide	6068 (100)	1922 (20.3)	1407 (23.2)	MACE

Abbreviations: ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; CKD=chronic kidney disease; CMR=cardiac magnetic resonance; CV=cardiovascular; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF=left ventricular ejection fraction; MACE=major adverse cardiovascular events; MI=myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; T2DM=Type 2 diabetes mellitus; UA=unstable angina.

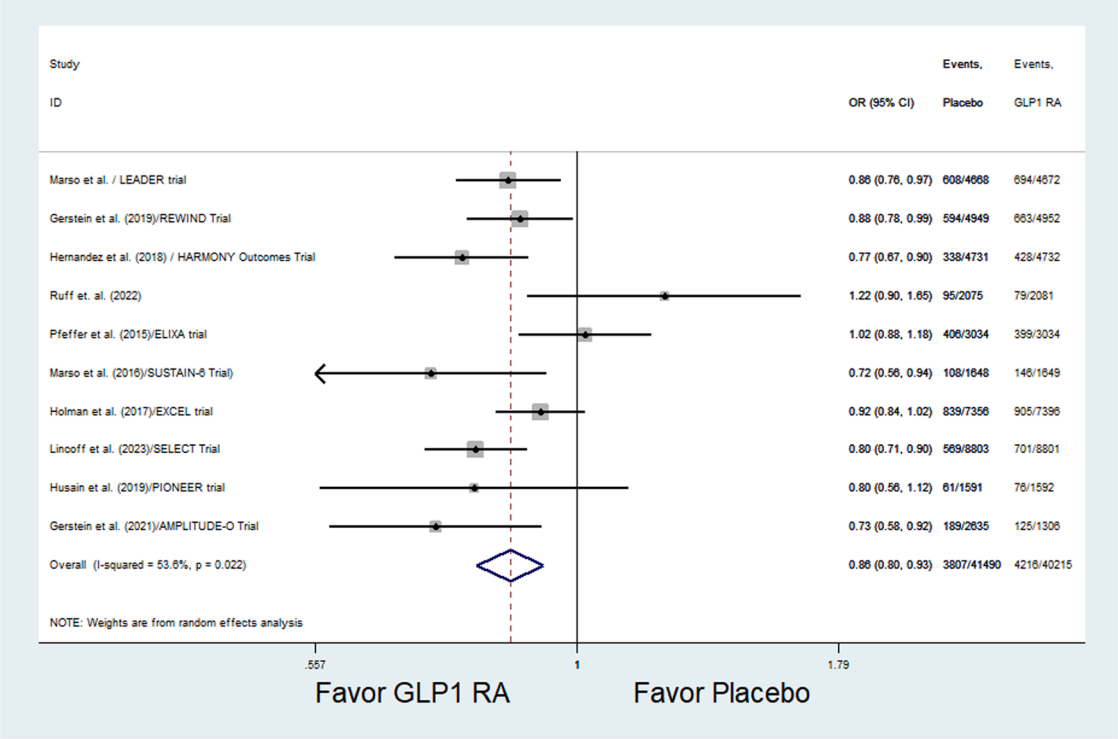

Fig. 1. Random effects meta-analysis on the effects of GLP-1RA on MACE. GLP-1RA=glucagon-like peptide 1receptor agonist; MACE=Major adverse cardiovascular events.

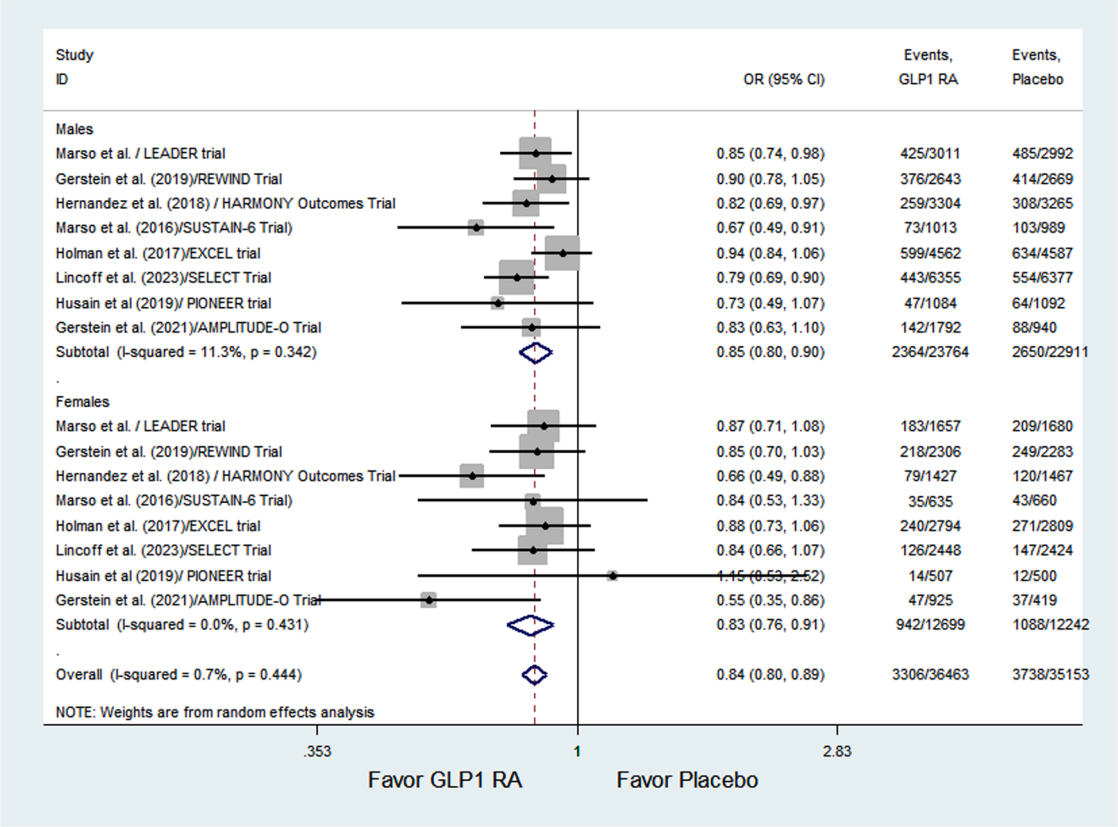

Fig. 2. Random effects meta-analysis on the effects of GLP-1RA on MACE, subgroup analysis based on sex. GLP-1RA=glucagon-like peptide 1 receptor agonist, MACE=Major adverse cardiovascular events.

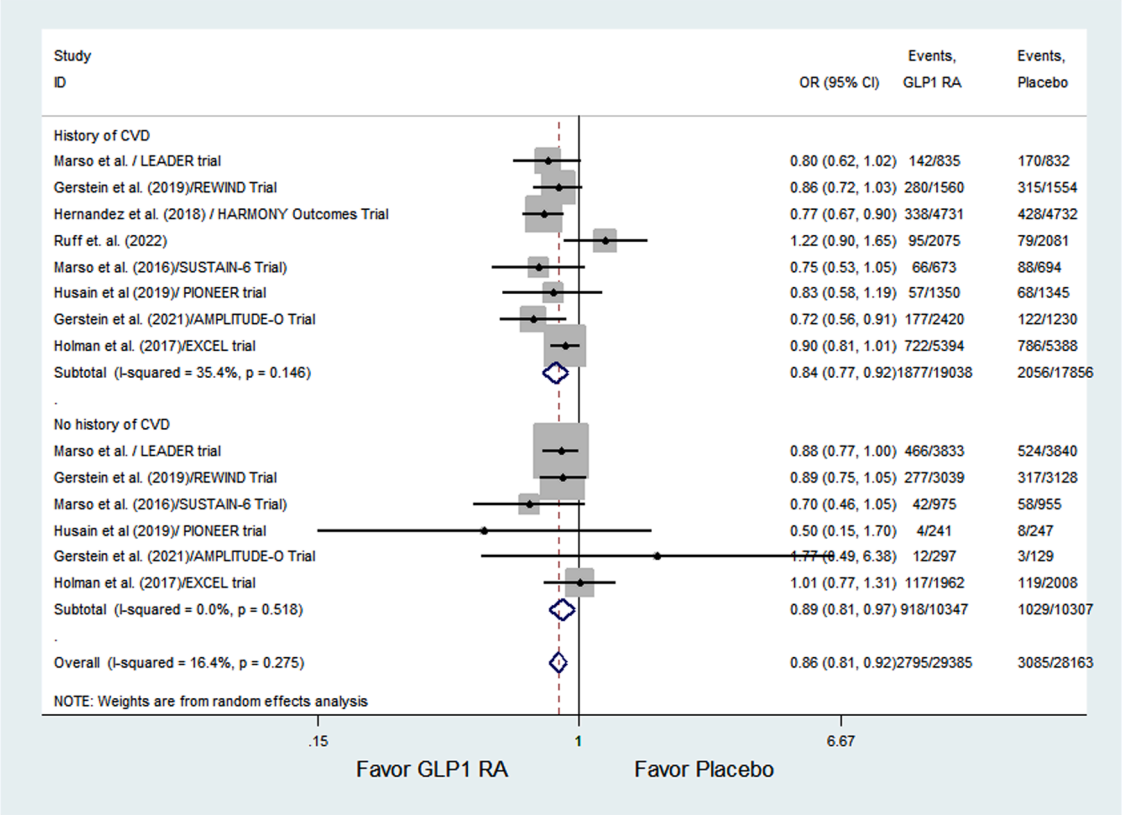

Fig. 3. Random effects meta-analysis on the effects of GLP-1RA on MACE, subgroup analysis based on CVD history. CVD=cardiovascular disease; GLP-1RA=glucagon-like peptide 1 receptor agonist, MACE=Major adverse cardiovascular events.

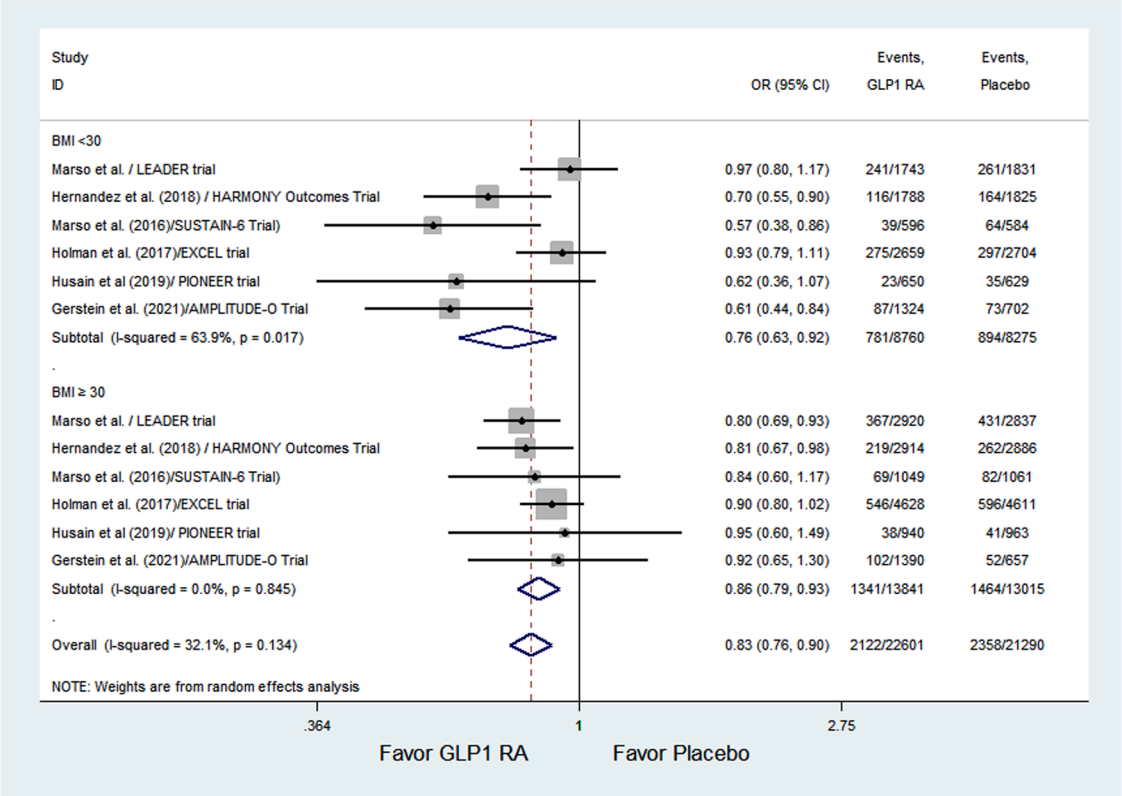

Fig. 4. Random effects meta-analysis on the effects of GLP-1RA on MACE, subgroup analysis based on BMI. BMI=body mass index; GLP-1RA=glucagon-like peptide 1 receptor agonist, MACE=Major adverse cardiovascular events.

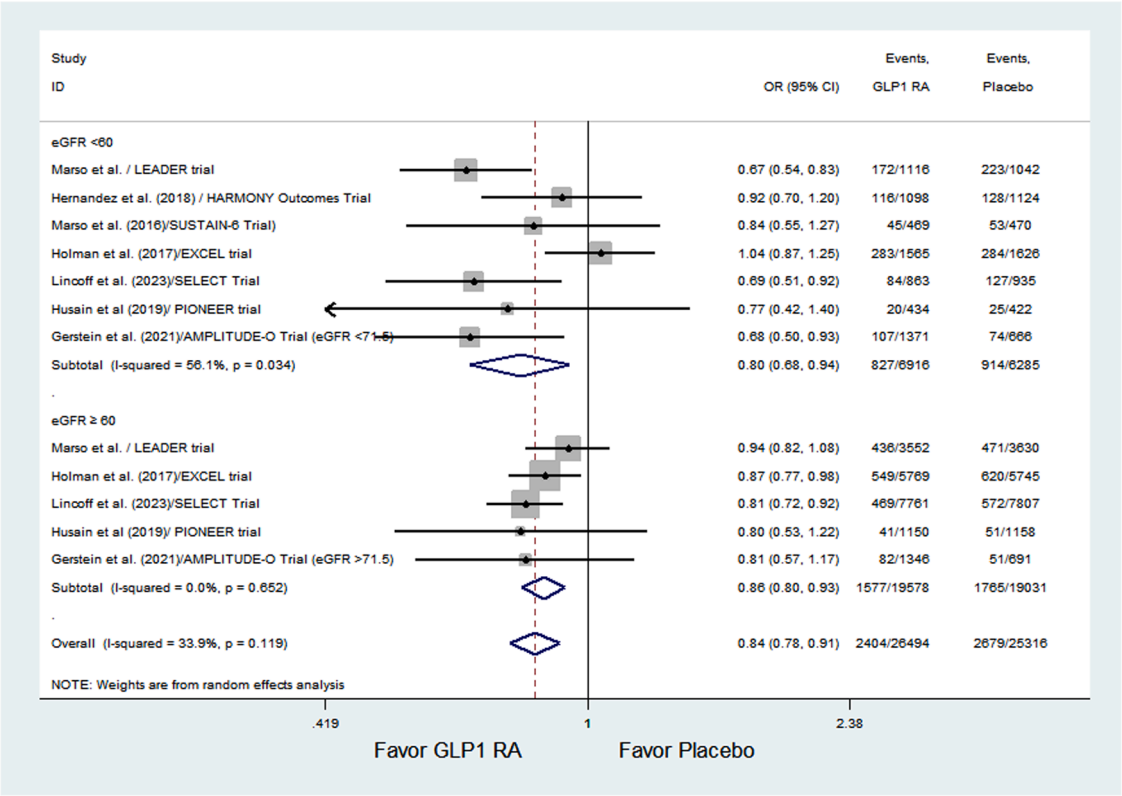

Fig. 5. Random effects meta-analysis on the effects of GLP-1RA on MACE, subgroup analysis based on eGFR. eGFR=estimated glomerular filtration rate; GLP-1RA=glucagon-like peptide 1 receptor agonist, MACE=Major adverse cardiovascular events.

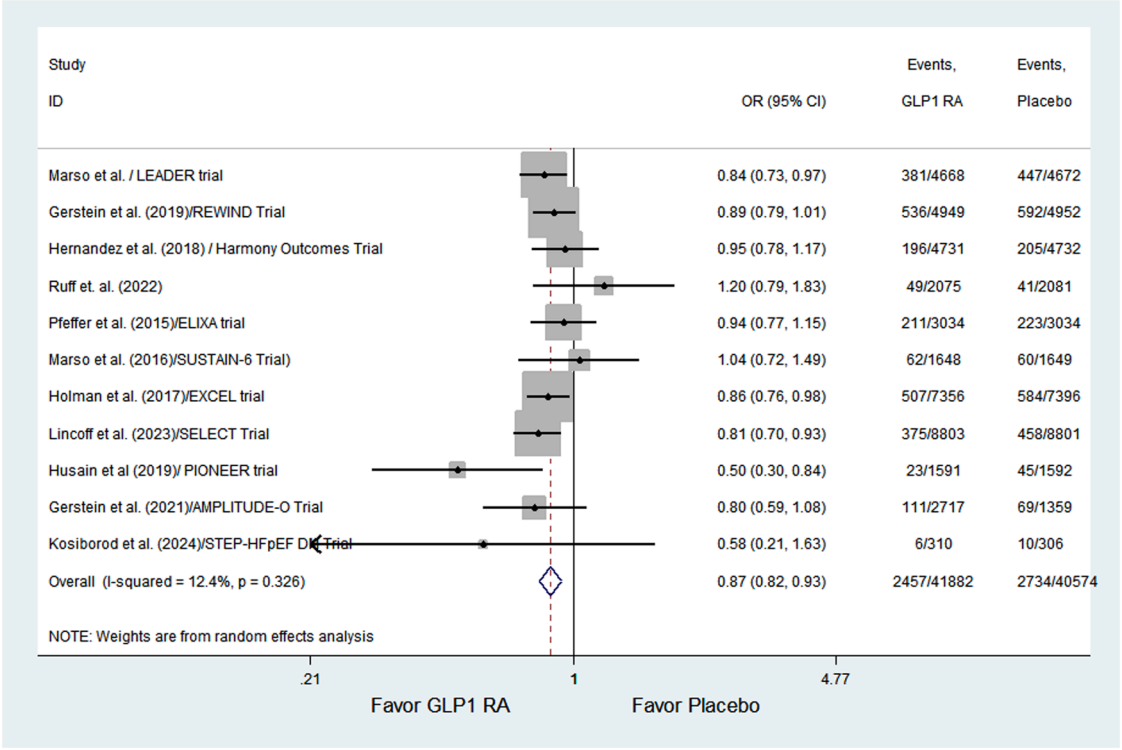

Fig. 6. Random effects meta-analysis on the effects of GLP-1RA on all-cause mortality. GLP-1RA=glucagon-like peptide 1 receptor agonist.

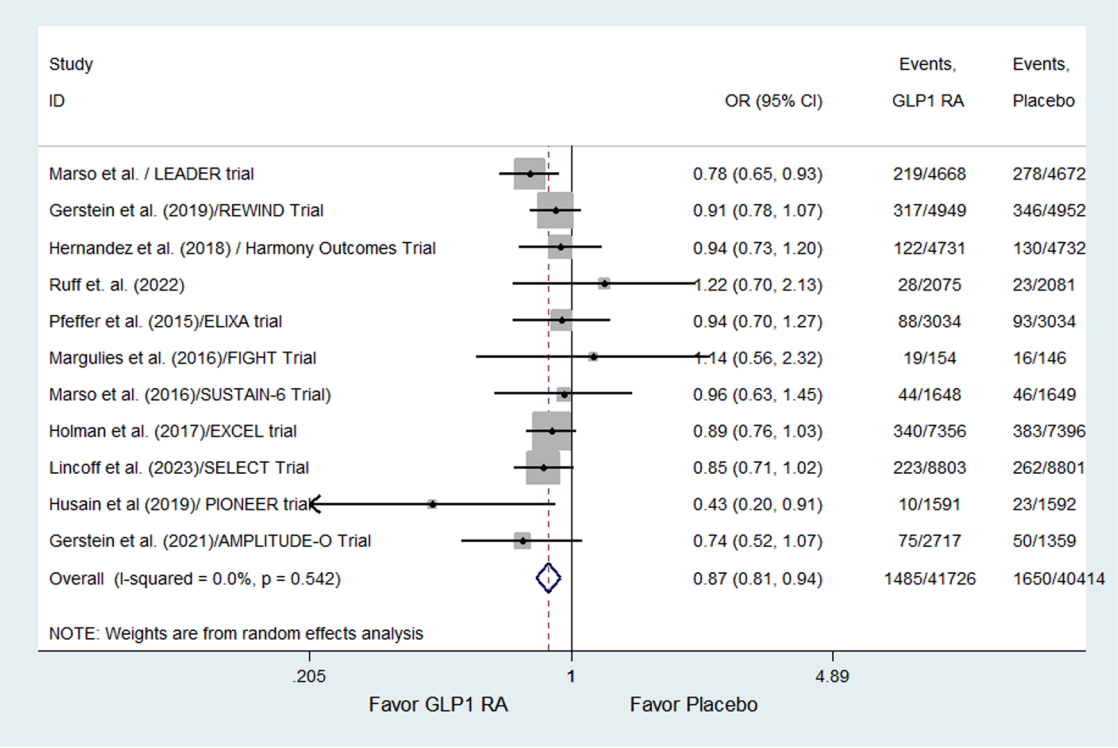

Fig. 7. Random effects meta-analysis on the effects of GLP-1RA on CV mortality. CV=cardiovascular; GLP-1RA=glucagon-like peptide 1 receptor agonist.

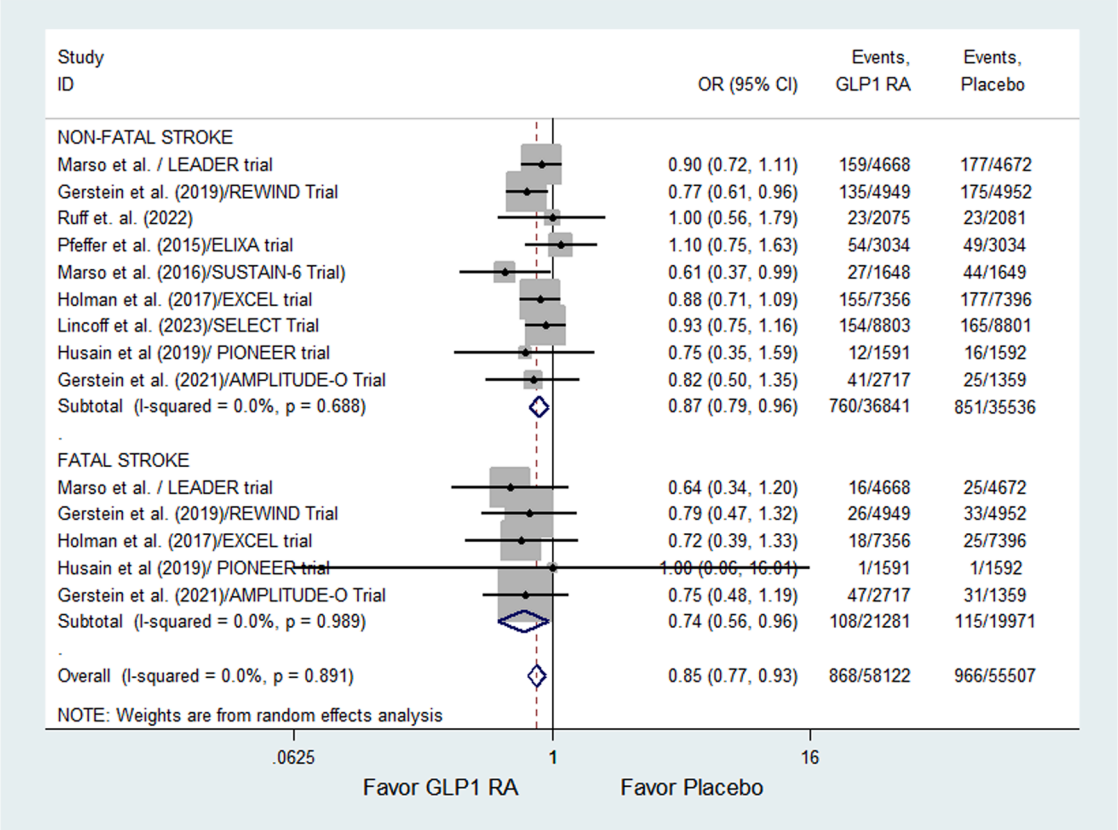

Fig. 8. Random effects meta-analysis on the effects of GLP-1RA on fatal and non-fatal stroke. GLP-1RA=glucagon-like peptide 1 receptor agonist.

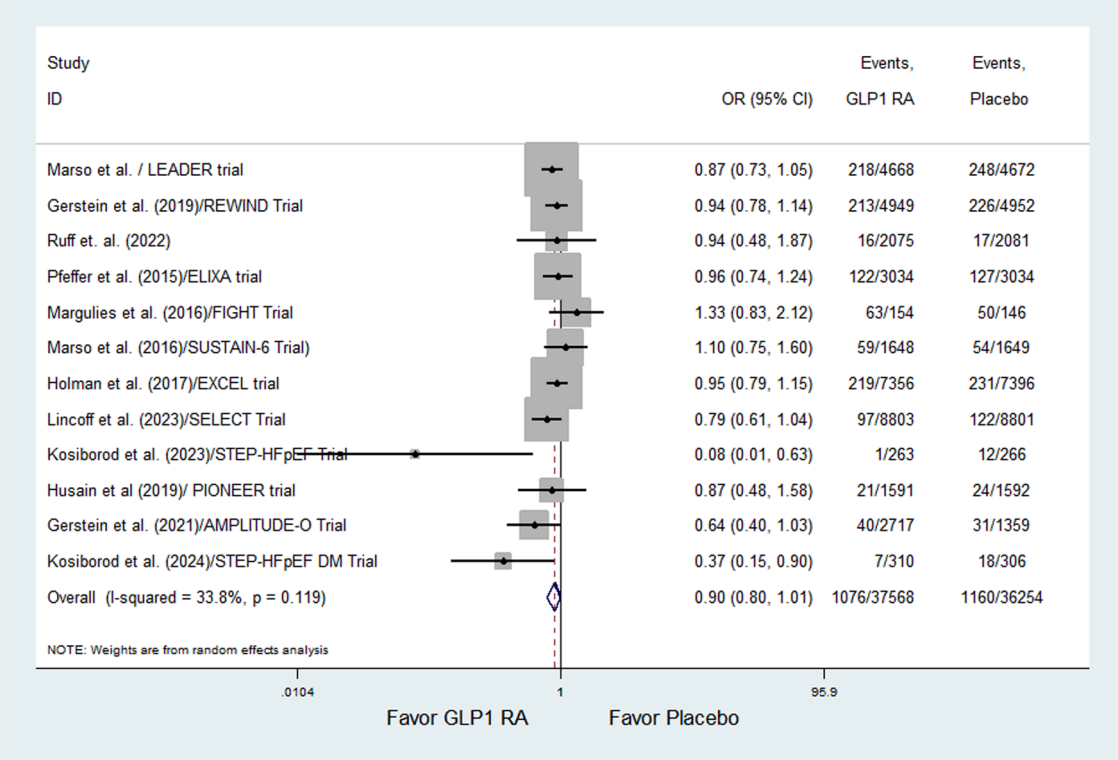

Fig. 9. Random effects meta-analysis on the effects of GLP-1RA on heart failure hospitalization. GLP-1RA=glucagon-like peptide 1 receptor agonist.

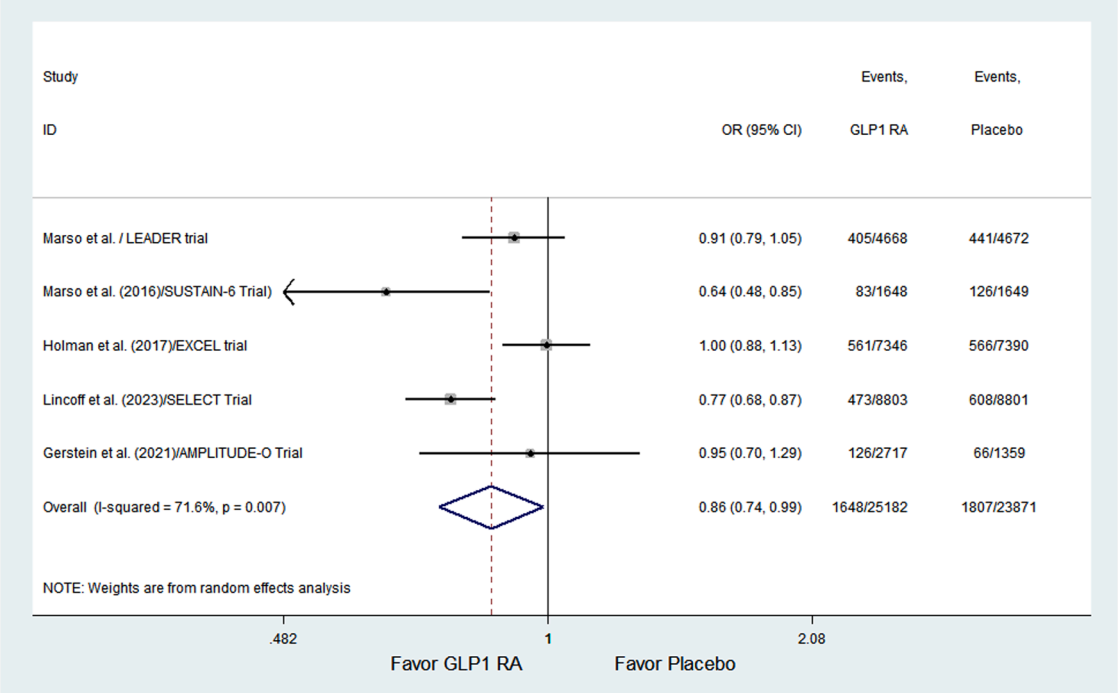

Fig. 10. Random effects meta-analysis on the effects of GLP-1RA on coronary revascularization. GLP-1RA=glucagon-like peptide 1 receptor agonist.

evaluated such outcomes of GLP-1RAs, the study population of the RCTs included consisted entirely of adult patients with T2DM, with subgroups consisting merely of the presence and absence of preexisting cardiovascular disease. Similarly, a network meta-analysis that evaluated RCTs of patients on SGLT2i or GLP-1RAs, and a meta-analysis of real-world studies of patients on GLP-1RA, only included patients with T2DM [21,22]. Meanwhile, our meta-analysis included placebo-controlled trials consisting of adult patients without T2DM (STEP-HFpEF and SELECT), as well as trials done on patients with HF. Our study evaluated the efficacy of patients across different subgroups of previous ASCVD, BMI, sex, and eGFR level, thereby highlighting the consistency of GLP-1RA efficacy across diverse patient characteristics.

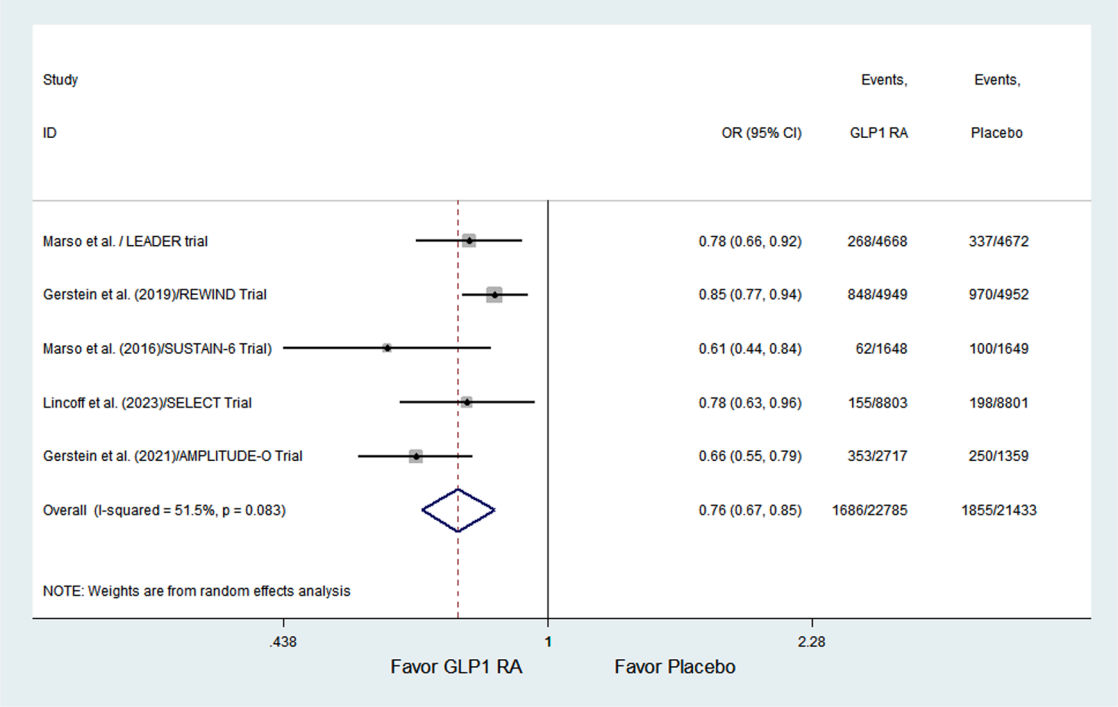

Fig. 11. Random effects meta-analysis on the effects of GLP-1RA on composite renal outcome. GLP-1RA=glucagon-like peptide 1 receptor agonist.

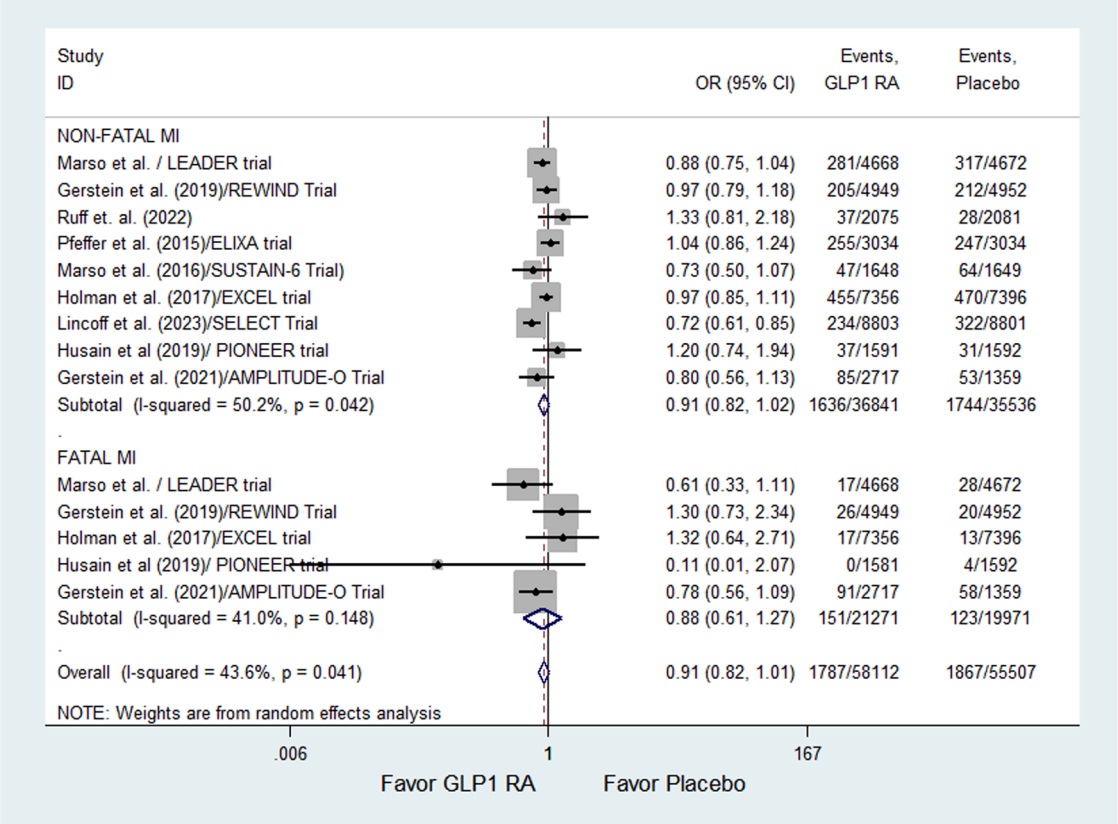

Fig. 12. Random effects meta-analysis on the effects of GLP-1RA on fatal and non-fatal MI. GLP-1RA=glucagon-like peptide 1 receptor agonist; MI=myocardial infarction.

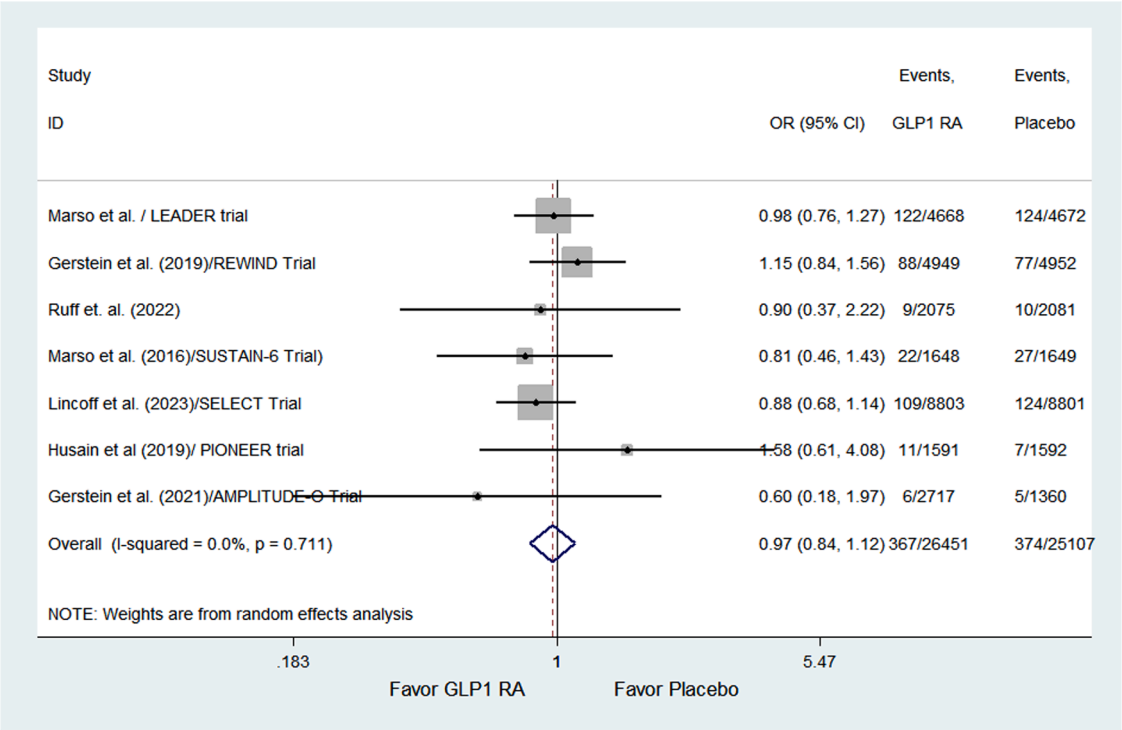

Fig. 13. Random effects meta-analysis on the effects of GLP-1RA on hospitalization due to unstable angina. GLP-1RA=glucagon-like peptide 1 receptor agonist.

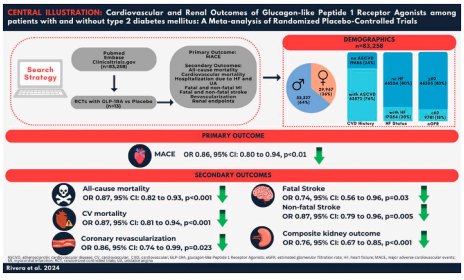

Fig. 14. Central illustration.

The results of our meta-analysis demonstrate that patients who received GLP-1RA have statistically significant reduction in overall mortality by 13 % compared to controls. Importantly, 63,572 of the 83,258 (76 %) patients included in our study had established ASCVD at baseline, which could potentially explain the concordance of these results. In order to explain the observed benefit of GLP-1RA use in mortality reduction, it is important to note the major contributors of mortality for these patients. Of major concern is the occurrence of MACE. Ten studies reported this outcome: eight RCTs used three-point MACE, which comprises death from cardiovascular causes, nonfatal MI, and nonfatal stroke. The other two RCTs used a four-point MACE, which included the three-point MACE plus hospitalization for unstable angina.

Overall, patients who received GLP-1 RA had experienced 14 % reduction in MACE compared to patients who received placebo. The heterogeneity can be explained by the differences in the comorbidities of the patients, including the presence of T2DM. Giugliano, et al. (2021) [20] cited in a meta-analysis that patients with diabetes experienced greater reduction in MACE compared to non-diabetics, which is similar to our findings. It is also important to note that Pfeffer, et al. (2015) [2] reported a trend toward, however minimal, increased odds of MACE among those who received GLP-1 RA; however, this study involved patients with history of recent MI or unstable angina within the last 180 days, which could independently increase their baseline risk of MACE. Most studies that reported nonsignificant MACE reduction tended to have shorter follow-up time, suggesting greater effect on MACE reduction over time. Bethel et al. (2017) [23], in a previous meta-analysis, reported similar findings, and postulated that GLP-1 RAs decrease cardiovascular risk over time through anti-atherogenic mechanisms, including its impact on usual cardiovascular risk factors such as blood pressure lowering, anti-inflammatory pathways, effects on cardiac output, and effects in endothelium including ischemic conditioning.

Compared to previous meta-analyses, our meta-analysis captured more females, comprising 29,967 out of the 83,258 patients included (36 %). Our study found that GLP-1RAs significantly reduce the risk of MACE in both males and females with no significant difference in effect between the two subgroups ($Q_b(1) = 0.14$, $p = 0.71$). These results are consistent with previous meta-analyses, which also found similar reduction in MACE in both sexes [24,25]. Although it is well-known that the risk of developing CVD is higher in women with type 2 DM than in men, GLP-1RAs remain effective in improving CV outcomes regardless of sex [26]. Regardless, women remain underrepresented in CVOTs [27-29] and those with T2DM present with worse metabolic control, hence the need for guidelines and policies to optimize DM therapy specific to both male and female sex [30].

There is no significant difference in odds reduction for MACE among those with ASCVD history compared to those without history of CVD. It is important to note that at baseline, 63,572 of the 83,258 (76 %) patients included in our study had established ASCVD. Significant heterogeneity may be brought about by various factors in this large, pooled population. Among these, differences in age, length of follow-up periods, comorbidity profile, intake of medications and number of years of diabetes could have ultimately resulted in this nonsignificant finding.

The odds reduction in MACE brought about by the use of GLP-1 RA do not significantly differ between patients with eGFR <60 ml/min and those with eGFR ≥ 60 ml/min. Our findings are consistent with Sattar et al. (2019) [31], in their meta-analysis that reported similar cardiovascular benefit among those who were given GLP-1 RA who had reduced eGFR (<60 ml/min) (HR 0.88, 95 % CI: 0.77 to 1.01) and

preserved eGFR (HR 0.83, 95 % CI: 0.74 to 0.93) as compared to placebo, with nonsignificant interaction ($p = 0.52$). Combination therapy with GLP-1 and SGLT2 inhibitor for improvement of MACE and microalbuminuria has been explored but is yet to be formally studied.

The odds reduction in MACE with GLP-1 RAs do not significantly differ between those with BMI<30 or BMI>30. The protective effect of GLP-1 can be due to its direct effect in GLP-1 receptors in the heart, independent of its ability to decrease body weight [32] and improve lipid metabolism which are acted upon by GLP-1 receptors in the brain and adipose tissues [33].

We were able to establish that patients who received GLP-1 RA had insignificant, but with a trend toward, reduction of odds of myocardial infarction for both fatal and non-fatal MI. The odds of getting hospitalized for unstable angina, among patients taking GLP-1 RA was also not statistically different from those who were taking placebo. These results illustrate the multifactorial nature of MI and UA, where various factors contribute to the development and progression of these conditions. While GLP-1RAs exhibit positive effects on broader cardiovascular outcomes, they may not be the primary driver for reducing the odds of having and/or dying from myocardial infarctions and incurring hospitalizations due to UA.

The use of GLP-1 RA in our meta-analysis has shown to avoid the need for coronary revascularization. However, on closer inspection, the significant heterogeneity of our result may be because only Lincoff, et al. (2023) and Marso (2016) had significant results. These two studies had longer follow-up periods compared to the others, presumably due to greater protective effect of GLP-1 RA with longer therapy [23].

Interestingly, reduction in the odds of stroke with GLP-1RAs appears to be more significant compared to myocardial infarction, both fatal stroke and nonfatal stroke. Lin et al. (2021) [34] in their meta-analyses concluded that only GLP-1 RAs reduce the risk of stroke as compared to novel antidiabetic agents like Dipeptidylpeptidase 4 inhibitor (DPP-4i) and Sodium Glucose Transporter 2 inhibitor therapy (SGLT2i). In another meta-analysis by Wei et al. (2022) [35], they specified that this effect is only significant for ischemic stroke in T2DM patients (RR 0.83, 95 % CI: 0.73 to 0.95, $p = 0.008$) and is not significant for risk reduction for hemorrhagic stroke (RR 1.54, 95 % CI: 0.74 to 3.23, $p = 0.25$). Among the potential mechanisms cited include potential antiatherosclerotic and vasculoprotective properties of GLP-1 RAs like inhibition of oxidative stress and inflammation in endothelial cells that enhances clot stability; reduction in cytokine production; and an independent neuroprotective effect.

Of the 83,258 patients included in studies that have included HF cohorts, a total of 17,054 patients (20 %) were identified. Two studies, Kosiborod, et al. (2023) [8,9] and Margulies et al. (2016) [36], had all participants (100 %) with established HF; but their results were noted to be conflicting. Our meta-analysis shows statistically insignificant, with trend toward reduction in HF hospitalization among patients who received GLP-1 RA compared to placebo. Other than Kosiborod et al. (2023) [8] (2024) [9], none of the studies were able to demonstrate statistically significant benefit. Zelnicker, et al. (2019) [1] demonstrated that GLP-1 RA paled in comparison to SGLT2-inhibitors in demonstrating benefit in reducing hospitalizations in heart failure, which is currently one of the standards of care in HF management (HR GLP-1 RA= 0.93, 95 % CI: 0.83 to 1.04) vs HR SGLT2i = 0.69, 95 % CI: 0.61 to 0.79). However, Sattar et al. (2021) [31] argues that by using a different mechanism of action like preventing coronary occlusion or salutary effect on myocardial small vessels, combined use of GLP-1 RA and SGLT2 inhibitor may be beneficial in reducing hospitalization for diabetic patients with HF.

Composite renal outcome, being a surrogate marker for renal disease progression we used for our meta-analysis, compasses a range of outcomes related to kidney health, especially highlighting kidney disease progression and complications with parameters such as increased urinary albumin:creatinine ratio, new-onset macroalbuminuria, sustained decline in eGFR, sustained increase in serum creatinine, need of continuous renal replacement therapy, and death due to renal disease. This finding is particularly significant considering the increasing recognition of the interplay between diabetes, cardiovascular disease, and renal complications. Our meta-analysis was able to identify 9781 patients (17.5 %) with eGFR of <60 ml/min, out of the 56,006 patients included in 7 component studies that measured this parameter. Pooled analysis of 5 studies revealed a protective effect of GLP-1 RA use compared to placebo versus occurrence of adverse composite renal outcomes. There was moderate heterogeneity observed (I2 = 50.3 %) however, all component studies demonstrated statistically significant benefit in favor of GLP-1 RA use compared to placebo. Our result is similar to the study of Zelniker, et al. (2019) [1], reporting a net benefit in composite renal outcomes among T2DM patients who were given GLP-1RA compared to placebo. However, this effect pales in comparison to SGLT2i which achieved superior results in renal outcomes vs GLP-1 RA and is currently the standard of care for reduction of adverse composite renal outcomes in this population. Mann, et al. (2017) [37], in his study on GLP-1 RA (Liraglutide) among those who have established type 2 DM, dissected the composite renal outcomes to identify which among new onset persistent macroalbuminuria, increase (doubling) of serum creatinine, need for renal replacement therapy and deaths due to renal disease do GLP-1 RA significantly exert its beneficial effect. GLP-1 RA was able to achieve a significant reduction in composite renal outcome (HR 0.78, 95 % CI: 0.67 to 0.92, $p = 0.03$), and this effect was significantly achieved mainly through reduction new-onset persistent macroalbuminuria (HR 0.74, 95 % CI: 0.60 to 0.91, $p = 0.004$). This effect is significant, even in terms of reduction of renal risk among those who have baseline microalbuminuria or macroalbuminuria (HR 0.81 95 % CI: 0.68 to 0.96). Among those with eGFR between 30 and 60 ml/min, significant reduction in eGFR decline compared to placebo was observed after 12 months in patients randomized to GLP1-RA.

The result of our study illustrates the substantial cardiovascular and renal effects of GLP-1RAs. Unlike earlier meta-analyses, our meta-analysis covered studies with diverse populations, not only patients with type 2 diabetes, but also those with HF and analyzed various subgroups. The reduction in critical cardiovascular outcomes including MACE, CV death, coronary revascularization, renal disease progression and overall mortality across diverse populations indicates that GLP-1RAs can be used as cornerstones in therapy to prevent ASCVD.

Both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) recommend (class I, level of evidence A) the use of GLP-1RAs for patients with T2DM and chronic coronary syndrome/disease (CCS/CCD) in order to reduce MACE [38,39]. While there were no recommendations from the ACC regarding the usage of GLP-1RAs for patients with STEMI and NSTE-ACS, the newly published 2023 ESC guidelines for the management of ACS mentioned that SGLT2 inhibitors (SGLT2i) and GLP-1RAs reduce the risk of new ACS events, HF, and renal impairment, and the reduction is independent of baseline HbA1c levels [40].

Furthermore, several key recommendations were made in the recent 2023 ESC Guidelines on Diabetes and Cardiovascular Diseases: GLP-1RAs such as liraglutide, semaglutide, or dulaglutide were recommended (class I, level of evidence A) among patients with T2DM and ASCVD to reduce CV risk, independent of baseline or target HbA1c [41]. These three medications may be considered (class IIb, level of evidence C) among patients with T2DM without ASCVD or severe target organ damage but with a calculated 10-year CVD risk >/= 10 % to reduce ASCVD risk. Liraglutide and semaglutide should be considered (class IIa, level of evidence B) among patients with DM and eGFR > 30 mL/min/1.73 m^2 for reduction of renal endpoints. Along with the three aforementioned GLP-1RAs, lixisenatide, exenatide ER, and efpeglenatide should be considered (class IIa, level of evidence A) for patients with T2DM at risk of, or with HF, for glucose-lowering treatment since they have a neutral effect on HF hospitalization [41]. This is in contrast with the earlier ESC heart failure guidelines in 2021, as it did not recommend GLP-1RAs for the prevention of HF events, basing the recommendation

on two trials that used liraglutide on patients with heart failure with reduced left ventricular ejection fraction [42]. Conversely, the 2022 ACC HF guidelines did not mention the use of GLP-1RAs for patients with HF. An earlier 2021 ESC guideline on CVD prevention recommended both SGLT2i and GLP-1RAs for patients with T2DM and ASCVD to reduce cardiovascular and cardiorenal outcomes (class I, level of evidence A), but recommended SGLT2i only (class I, level of evidence A) for patients with T2DM and CKD, and T2DM and HF for these outcomes [43]; the latter two recommendations were different from the more recent 2023 ESC guidelines for patients with T2DM and eGFR $>$ 30 mL/min/1.73 m2, and T2DM and HF [41]. In addition, both SGLT2i and GLP-1RAs may be considered (class IIb, level of evidence B) for patients with T2DM and target organ damage to reduce future CVD and total mortality, and both should be considered (class IIa, level of evidence B) for patients with T2DM without ASCVD, HF, or CKD based on estimated future risks (e.g. using the ADVANCE risk score or DIAL model) for adverse cardiovascular or cardiorenal outcomes [43]. Interestingly, no guideline mentioned the use of GLP-1RA among patients without T2DM to reduce MACE.

5. Strength and limitations

To our knowledge, this is the first meta-analysis to comprehensively report on cardiorenal outcomes in participants receiving GLP-RA across diverse populations and different subgroups. This is a study-level meta-analysis, and we could not access individual patient data. Other limitations include heterogeneity in GLP-1RA studies. Publication bias may be present, the extent of which cannot fully be quantified due to a lack of tools for evaluating this in studies with continuous outcomes. However, we did our best to limit as much bias as possible by utilizing a robust analytical approach to adjust for potential moderators by doing a subgroup analysis.

6. Conclusion

The use of GLP-1RA results in significant MACE reduction in both males and females, with and without CVD history, and on both spectrum of eGFR and BMI. GLP-1RA also reduced the odds of all-cause and CV mortality, fatal and non-fatal stroke, coronary revascularization, and composite kidney outcomes. Thus, our data support the use of GLP-1RA in eligible patients.

Statement of ethics

Ethics approval for this paper is not required because this study is based exclusively on published literature. Patient consent was not needed as this study was based on publicly available data.

Funding

No specific financial support was obtained to prepare this article.

CRediT authorship contribution statement

Frederick Berro Rivera: Writing – review & editing, Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Linnaeus Louisse A. Cruz:** Writing – original draft, Data curation, Conceptualization. **John Vincent Magalong:** Data curation. **Jade Monica Marie J. Ruyeras:** Writing – original draft, Validation. **John Paul Aparece:** Writing – original draft, Methodology. **Nathan Ross B. Bantayan:** Writing – original draft, Resources, Investigation. **Kyla Lara-Breitinger:** Writing – review & editing, Supervision. **Martha Gulati:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100679.

References

[1] Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139(17):2022–31. https://doi.org/10.1161/circulationaha.118.038868. Apr 23.
[2] Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373(23):2247–57. https://doi.org/10.1056/NEJMoa1509225. Dec 3.
[3] Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375(4):311–22. https://doi.org/10.1056/NEJMoa1603827. Jul 28.
[4] Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44. https://doi.org/10.1056/NEJMoa1607141. Nov 10.
[5] Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392(10157):1519–29. https://doi.org/10.1016/s0140-6736(18)32261-x. Oct 27.
[6] Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394(10193):121–30. https://doi.org/10.1016/s0140-6736(19)31149-3. Jul 13.
[7] Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023. https://doi.org/10.1056/NEJMoa2307563. Nov 11.
[8] Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med 2023;389(12):1069–84. https://doi.org/10.1056/NEJMoa2306963. Sep 21.
[9] Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med 2024. https://doi.org/10.1056/NEJMoa2313917. Apr 6.
[10] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj 2009;339:b2700. https://doi.org/10.1136/bmj.b2700. Jul 21.
[11] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71. https://doi.org/10.1136/bmj.n71. Mar 29.
[12] Goldkuhle M, Guyatt GH, Kreuzberger N, et al. GRADE concept 4: rating the certainty of evidence when study interventions or comparators differ from PICO targets. J Clin Epidemiol 2023;159:40–8. https://doi.org/10.1016/j.jclinepi.2023.04.018. Jul.
[13] Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. J Clin Epidemiol 2018;100:103–10. https://doi.org/10.1016/j.jclinepi.2018.01.003. Aug.
[14] Ruff CT, Baron M, Im K, O'Donoghue ML, Fiedorek FT, Sabatine MS. Subcutaneous infusion of exenatide and cardiovascular outcomes in type 2 diabetes: a non-inferiority randomized controlled trial. Nat Med 2022;28(1):89–95. https://doi.org/10.1038/s41591-021-01584-3. Jan.
[15] Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. N Engl J Med 2021;385(10):896–907. https://doi.org/10.1056/NEJMoa2108269. Sep 2.
[16] Marso SP, Baeres FMM, Bain SC, et al. Effects of liraglutide on cardiovascular outcomes in patients with diabetes with or without heart failure. J Am Coll Cardiol 2020;75(10):1128–41. https://doi.org/10.1016/j.jacc.2019.12.063. Mar 17.
[17] Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381(9):841–51. https://doi.org/10.1056/NEJMoa1901118. Aug 29.

[18] Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377(13):1228–39. https://doi.org/10.1056/NEJMoa1612917. Sep 28.
[19] Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7(10):776–85. https://doi.org/10.1016/s2213-8587(19)30249-9. Oct.
[20] Giugliano D, Scappaticcio L, Longo M, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. Cardiovasc Diabetol. 2021;20(1):189. https://doi.org/10.1186/s12933-021-01366-8. Sep 15.
[21] Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. Bmj 2021;372:m4573. https://doi.org/10.1136/bmj.m4573. Jan 13.
[22] Caruso I, Cignarelli A, Sorice GP, Natalicchio A, Perrini S, Laviola L, Giorgino F. Cardiovascular and renal effectiveness of GLP-1 receptor agonists vs. other glucose-lowering drugs in type 2 diabetes: a systematic review and meta-analysis of real-world studies. Metabolites 2022;12(2). https://doi.org/10.3390/metabo12020183. Feb 15.
[23] Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol. 2018;6(2):105–13. https://doi.org/10.1016/s2213-8587(17)30412-6. Feb.
[24] D'Andrea E, Kesselheim AS, Franklin JM, Jung EH, Hey SP, Patorno E. Heterogeneity of antidiabetic treatment effect on the risk of major adverse cardiovascular events in type 2 diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol. 2020;19(1):154. https://doi.org/10.1186/s12933-020-01133-1. Sep 29.
[25] Sharma A, Wood S, Bell JS, De Blasio MJ, Ilomäki J, Ritchie RH. Sex differences in risk of cardiovascular events and mortality with sodium glucose co-transporter-2 inhibitors versus glucagon-like peptide 1 receptor agonists in Australians with type 2 diabetes: a population-based cohort study. Lancet Reg Health West Pac. 2023;33:100692. https://doi.org/10.1016/j.lanwpc.2023.100692. Apr.
[26] Humphries KH, Izadnegahdar M, Sedlak T, et al. Sex differences in cardiovascular disease - Impact on care and outcomes. Front Neuroendocrinol. 2017;46:46–70. https://doi.org/10.1016/j.yfrne.2017.04.001. Jul.
[27] Rivera FB, Cha SW, Aparece JP, et al. Sex differences in permanent pacemaker implantation after transcatheter aortic valve replacement: a systematic review and meta-analysis. Expert Rev Cardiovasc Ther 2023;21(9):631–41. https://doi.org/10.1080/14779072.2023.2250719. Jul-Dec.
[28] Rivera FB, Tang VAS, De Luna DV, et al. Sex differences in cardiovascular outcomes of SGLT-2 inhibitors in heart failure randomized controlled trials: a systematic review and meta-analysis. Am Heart J Plus 2023;26. https://doi.org/10.1016/j.ahjo.2023.100261. Feb.
[29] Frederick Berro Rivera MSWC, MD John Paul Aparece, MD Aubrey Rocimo, MD Bradley Ashley Ong, MD Jem Marie Golbin, MD Pia Gabrielle Alfonso, MD Byambaa Enkhmaa, MD, PhD, MAS Safi U. Khan, MD, MS Miguel Cainzos-Achirica, MD, MPH, PhD Annabelle Santos Volgman, MD Ann Marie Navar, MD, PhD Nishant P. Shah, MD. Sex Differences in Cardiovascular Outcomes and Cholesterol-Lowering Efficacy of PCSK9 Inhibitors: systematic Review and Meta-Analysis. USA: JACC Advances; 2023.
[30] Campesi I, Seghieri G, Franconi F. Type 2 diabetic women are not small type 2 diabetic men: sex-and-gender differences in antidiabetic drugs. Curr Opin Pharmacol 2021;60:40–5. https://doi.org/10.1016/j.coph.2021.06.007. Oct.
[31] Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9(10):653–62. https://doi.org/10.1016/s2213-8587(21)00203-5. Oct.
[32] Rivera FB, Lumbang GNO, Gaid DRM, et al. Glucagon-like peptide-1 receptor agonists modestly reduced blood pressure among patients with and without diabetes mellitus: a meta-analysis and meta-regression. Diabetes Obes Metab 2024. https://doi.org/10.1111/dom.15529. Mar 20.
[33] Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72–130. https://doi.org/10.1016/j.molmet.2019.09.010. Dec.
[34] Lin DS, Lee JK, Hung CS, Chen WJ. The efficacy and safety of novel classes of glucose-lowering drugs for cardiovascular outcomes: a network meta-analysis of randomised clinical trials. Diabetologia 2021;64(12):2676–86. https://doi.org/10.1007/s00125-021-05529-w. Dec.
[35] Wei J, Yang B, Wang R, Ye H, Wang Y, Wang L, Zhang X. Risk of stroke and retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: an eight RCTs meta-analysis. Front Endocrinol (Lausanne) 2022;13:1007980. https://doi.org/10.3389/fendo.2022.1007980.
[36] Margulies KB, Hernandez AF, Redfield MM, et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: a Randomized Clinical Trial. JAMA 2016;316(5):500–8. https://doi.org/10.1001/jama.2016.10260. Aug 2.
[37] Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med 2017;377(9):839–48. https://doi.org/10.1056/NEJMoa1616011. Aug 31.
[38] Virani SS, Newby LK, Arnold SV, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: a Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2023;148(9):e9–119. https://doi.org/10.1161/cir.0000000000001168. Aug 29.
[39] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41(3):407–77. https://doi.org/10.1093/eurheartj/ehz425. Jan 14.
[40] Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44(38):3720–826. https://doi.org/10.1093/eurheartj/ehad191. Oct 12.
[41] Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44(39):4043–140. https://doi.org/10.1093/eurheartj/ehad192. Oct 14.
[42] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368. Sep 21.
[43] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227–337. https://doi.org/10.1093/eurheartj/ehab484. Sep 7.