Glucagon-like Peptide-1 Receptor Agonists and Cardioprotective Benefit in Patients With Type 2 Diabetes Without Baseline Metformin: An Update Meta-analysis

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Abstract

Background: Sodium Glucose Co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) were associated with a reduction in cardiovascular events in cardiovascular outcomes trials (CVOTs) in type 2 diabetes. Most of the patients included in these trials received metformin as background therapy**.** The purpose of this study was to evaluate the effect of glucagon-like peptide-1 receptor agonists on major cardiovascular events (MACE) in metformin-naïve patients with type 2 diabetes.

Methods: A meta-analysis was performed of randomized controlled clinical trials of GLP-1RAs on type 2 diabetes populations, after searching the PubMed/MEDLINE, Embase, Scielo, Google Scholar and Cochrane Controlled Trials databases. The primary endpoint was MACE. The secondary endpoints were cardiovascular death and all-cause mortality. A meta-analysis of time-to-event outcomes was performed.

Results: Six eligible trials, including 10419 patients, were identified and considered eligible for the analyses. GLP-1RAs were associated with a significant reduction in MACE incidence (HR: 0.87, 95% confidence interval: 0.80–0.94; I^2:0%). The analysis of the secondary endpoints showed a non-significant reduction in all-cause mortality (HR: 0.86, 95% confidence interval: 0.73-1.00 I^2:0%) and cardiovascular mortality (HR: 0.81, 95% confidence interval: 0.63–1.05; I^2:0%).

Conclusions: In this meta-analysis, GLP-1RAs reduced the incidence of MACE in patients with type 2 diabetes without metformin at baseline, without significant reduction in all-cause mortality and cardiovascular mortality. These results support the fact that benefit in cardiovascular outcomes is independent of metformin use when GLP-1Ras are administered.

Introduction

People with type 2 diabetes (T2D) are at increased risk for cardiovascular disease (CVD) and have worse outcomes after surviving a cardiovascular event [1–2]. Prevalence of cardiovascular complications in people with T2D is variable. Furthermore, CVD risk is increasing over time. In ZODIAC-13 study, a longitudinal study including 881 patients with T2D over 10 years, the hazard ratio (HR) for death due to CVD was constantly increasing each year [3]. In a recent cross-sectional study of 9823 adults with T2D attending a primary or specialist showed that approximately one in three adults had established CVD [4]. Furthermore, Cebrián Cuenca et al., reported in 373.185 patients with T2D from a Mediterranean region in Spain that 53% of them were classified as very high cardiovascular risk [5]. Regarding antidiabetic treatment new emerging classes of drugs, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been shown to reduce cardiovascular events in patients with T2D and a high cardiovascular risk or established cardiovascular disease [6–14]. Recent 2019 guidelines by the European Society of Cardiology (ESC)/European Association for the study of Diabetes (EASD) on diabetes, prediabetes, and cardiovascular disease recommend SGLT-2 or GLP-1RAs inhibitors as first-line therapies in patients with established cardiovascular disease or high / very high cardiovascular risk. [15]. These recommendations were acquired from data from cardiovascular outcome trials (CVOTs) in which enrolled patients received mostly metformin as background therapy. The question whether the cardiovascular benefits observed in these trials are similar in patients with or without metformin arises from the observation of the contrast between the recommendations of the guidelines and the limited information on subjects who had not received metformin.

Recently subgroups analyses of trials with some of these drugs were published reporting cardiovascular benefits in patients who were not receiving metformin [16–18]. Two previous meta-analysis, using data from a small number of trials, described the reduction of MACE in patients with T2D who received GLP-1RAs regardless of the background use of metformin. [19–20] In this study we included the last three studies published on this topic, and evaluate other endpoints

not previously analyzed such as total and cardiovascular mortality. Therefore, the objective of the present meta-analysis was to evaluate the effect of GLP-1RAs on MACE and other outcomes regardless of background use of metformin.

Material And Methods

Data extraction and quality assessment

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews [21].

A literature search was performed that identified clinical trials of GLP-1RAs published between January 2010 and May 2021. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase, Scielo, Google Scholar and Cochrane Controlled Trials databases using the terms “liraglutide”, “albiglutide”, “exenatide”, “lixisenatide”, “semaglutide”,” dulaglutide”, and “GLP-1RAs”, alone or combined with “cardiovascular disease”, “major cardiovascular events (MACE)”, “mortality”, “cardiovascular mortality”, “stroke”, or “myocardial infarction”.

All the analyzed studies meet the following inclusion criteria: (1) comparisons of efficacy for GLP-1RAs vs. placebo; (2) follow-up duration ≥ 1 year; (3) randomized clinical trials; (4) reporting incidence of MACE; and (5) reporting data from patients without metformin at baseline.

The primary endpoint of the study was MACE incidence (composite of myocardial infarction, stroke, and cardiac death). Cardiovascular mortality and all-cause of mortality were evaluated as secondary endpoints. This meta-analysis was registered in PROSPERO.

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess the potential risk of bias of each included trial [22]. RoB 2 is structured into five distinct domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the outcome measurement and bias in selection of the reported result. Each domain was rated as “low risk of bias,” “high risk of bias” or “some concerns”.

Statistical analysis

Since the number of events in the subgroups with or without metformin were not reported in most studies, a meta-analysis of time-to-event outcomes was performed [23]. Hazard ratios (HRs) and 95% confidence intervals (CIs) were abstracted from each individual study and standard error were calculated. All study-specific estimates were combined using an inverse variance method for pooling. The logarithm of the HRs and their standard errors were used. The summary effect of statin therapy on the endpoints were calculated. Measures of effect size were expressed as HRs, and the I^2 statistic was calculated to quantify between-studies heterogeneity and inconsistency. Because the I^2 was low, a fixed-effects model was chosen. Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages [24]. The level of statistical significance was set at a 2-tailed alpha of .05.

Sensitivity analyses

The sensitivity analysis is carried out by replicating the results of the meta-analysis, excluding at each step one of the studies included in the review. The robustness of the analysis is indicated by the similarity of the results obtained in the direction and magnitude of the effect and the statistical significance. A sensitivity analysis for the primary endpoint was performed.

Analysis of publication bias

A funnel plot using the standard error (SE) for log HR was created. In addition, Egger’s regression intercept tests were done. A p-value less than 0.1 was considered significant for the linear regression test.

Results

Six eligible trials (5 studies of subcutaneous GLP-1RAs and 1 with oral GLP-1RAs), including 10419 patients, were identified and considered eligible for the analyses. A total of 5274 subjects were allocated to receive GLP-1RAs while 5145 subjects were allocated to the respective control arms. A flow diagram of the study's screening process has been shown in **Fig. 1.**

The total of studies evaluated were randomized clinical trials. Overall, the risk of bias was low in all the six studies. The quality of the studies evaluated can be seen in **Fig. 2.**

All studies included patients with T2D. Four studies included more than 80% of patients with a history of cardiovascular disease. Five studies included patients with high cardiovascular risk according to a set of associated cardiovascular risk factors. In addition, two studies considered chronic renal disease as an inclusion criteria. All trials reported MACE, but only four studies reported all-cause of death and three trials cardiovascular death. Data from the semaglutide studies (SUSTAIN-6 and PIONEER) were reported, and consequently included in our analysis jointly. Median follow-up duration ranged from 1.4 to 5.4 years. The characteristics of the studies included in the analysis can be seen in Table 1.

Table 1
Characteristics of the selected randomized controlled trials for analysis.

	EXSCEL[11]	HARMONY[12]	LEADER[17]	REWIND [18]	SUSTAIN 6 [26]	PIONEER 6[26]
Intervention	Exenatide	Albiglutide	Liraglutide	Dulaglutide	Semaglutide	Semaglutide
Patients included	T2D	T2D and ≥ 40 years old with history of cardiovascular disease	T2D and high cardiovascular risk	T2D with history of cardiovascular disease or high cardiovascular risk	T2D and high cardiovascular risk	T2D and high cardiovascular risk
Follow-up, years	3.2	1.6	3.8	5.4	2.1	1.4
Total patients, n	14752	9463	9340	9901	3297	3183
Metformin-naïve patients, n	2261	2495	2196	1864	919	680
Mean age, years	62	64.1	64.3	66.2	64.6	66
Female, %	38	30.6	35.7	46.3	39.3	31.6
Cardiovascular disease, %	73.1	100	81.4	31.4	83	84.7
T2D: type 2 diabetes						

The present meta-analysis revealed that GLP-1RAs drugs were associated with a significant reduction in MACE (HR: 0.87, 95% CI: 0.80–0.94; I^2: 0%). The analysis of the secondary endpoint showed that GLP-1RAs were associated with a non-significant reduction in all-cause mortality (HR: 0.86, 95% CI: 0.73-1.00; I^2: 0%) and cardiovascular mortality (HR: 0.81, 95% CI: 0.63–1.05; I^2: 0%) The graphic representation of the effect of GLP-1RAs on primary and secondary end-point can be seen in **Fig. 3.**

The funnel plot in **Fig. 4** and analytical evaluation do not suggest publication bias (Egger's asymmetry test, p = 0.19). The sensitivity analysis showed the same directionality of results when studies were excluded one by one **(Fig. 5)**,

Discussion

In this meta-analysis, in which only patients without metformin at baseline were included, GLP-1RAs (compared with placebo) were associated with a significant reduction in MACE incidence with a trending forward reduction in all-cause mortality. Metformin has been first line therapy recommended for treatment of patients with T2D for a long time. Results from CVOTs where GLP-1RAs an SGLT2 inhibitors added to standard therapy all have found non-inferiority with many finding superiority respect to placebo [6–14] led to a rethinking of the paradigm of metformin as the first drug choice, and GLP-1RAs arise in some guidelines as the first line therapy in patients with cardiovascular disease o high cardiovascular risk [15, 25].

This discussion is not focused on the glucose lowering effect of metformin or GLP-1RAs but on the impact in terms on reduction in cardiovascular events. Regarding this issue, the supporting data for the cardiovascular benefit of metformin is drawn for the most part from a sub study of the UKPDS trial; all patients included were overweight and control group was usual care (diet, with sulfonylurea or insulin). This study had a small sample size and was not powered to prove cardiovascular benefit [27]. Currently there is no published data from placebo controlled cardiovascular outcomes trials with metformin in patients with T2D. There have been several meta-analyses to investigate the effects of metformin on cardiovascular events, but data have not been particularly conclusive [28–31].

Cardiovascular benefit observed with GLP-1RAs use in CVOTs is overwhelming. However, most of the patients evaluated in these trials received metformin at baseline. An exploratory subgroup analysis was recently performed in some of these trials, reporting that the reduction in MACE was independent of background metformin therapy. Two different meta-analysis including data from 3 GLP-1RAs CVOTs evidenced that GLP1-RAs were associated with a significant reduction in the risk of MACE of 20 % and 23 %, respectively [19–20]. None of the mentioned meta-analyses reported other outcomes than MACE. In this context, the results of this meta-analysis become relevant, since it includes a great number of patients from six different trials.

GLP1-RAs promotes glycemic reduction for the treatment of T2D by glucose-dependent control of insulin and glucagon secretion which results in a low risk of hypoglycemia. GLP1-RAs also decelerate gastric emptying, lower circulating lipoproteins, inflammation, increased satiety and decreased body weight [31]. Furthermore, GLP1-RAs are associated with a variety of positive cardiovascular and renal effects beyond glycemic control. GLP-1RAs improves blood pressure, vascular tone and cardioprotection against myocardial ischemia/stunning [32]. Although improving glycemic control is associated with a reduction of microvascular complications in people with T2D, [33] its impact in reduction of macrovascular complications is not so categorical. Despite a reduction in the incidence of myocardial infarction and death due to an early glycemic control reported in UKPDS, trials like VADT, ADVANCE and ACCORD failed to demonstrate cardiovascular benefit with an intensive glucose control strategy. [34–36]. From the above it follows that cardiovascular benefit exceeds glycemic control, the use of GLP-1RAs could maintain the positive cardiovascular profile regardless use of metformin.

The reduction in MACE observed in this meta-analysis in patients receiving GLP-1RAs without metformin follows the same line as CVOTs. Metformin increases glucagon-like peptide-1 secretion [37]. In patients receiving GLP1-RAs this effect is avoided. This meta-analysis cannot answer the question about what is the mechanism of GLP-1AR that leads to a reduction in MACE, but it may suggest that this benefit does not depend on the use of metformin at baseline.

A meta-analysis of CVOTs, comparing GLP-1RAs and placebo, comprising 56004 patients showed not only a reduction in MACE but also a significant reduction in all-cause mortality and in cardiovascular death [38]. In the present meta-analysis, which only includes patients without baseline metformin, no significant reduction in the mentioned results has been observed. The cause could be the small number of patients included in our study. The total of patients included in our meta-analysis represents 20% of the one mentioned above. The fact that only four studies reported all-cause of death and three trials cardiovascular death, could reduce even more the power to detect a difference between these two groups of

patients. Since metformin trials didn't show a reduction in these endpoints, we don't think that this is the reason why we didn't observe the benefit described before.

This meta-analysis presents several limitations. First, limitations related with clinical heterogeneity (popular characteristics, different schemes of antihyperglycemic drugs, different follow-up). However, the sensitivity analysis showed the same directionality of the results. Second, the analysis included only trial-level data without having the individual data. Consequently, exploratory analysis of certain subgroups according to baseline characteristics could not be performed. Third, the characteristics of patients who were not treated with metformin at baseline may be not necessarily similar to those of the total populations of the included studies. Unfortunately, the characteristics of the subgroups of patients without metformin at baseline have not been published in all included studies. However, the characteristics of the total populations were similar. The reported body mass index ranged between 30.6 and 32.5 kg/m^2 and the baseline HbA1c level ranged between 7.3% and 8.7%. Similarly, the use of statins ranged between 72.2% and 86.4% and the use of insulin ranged between 44.7% and 60.4%. Finally, the number of studies reporting all cause mortality and cardiovascular mortality was small. Therefore, it is necessary to have larger studies to confirm or refute our findings.

In conclusion, in the present meta-analysis GLP-1RAs reduced the incidence of MACE in patients with T2D regardless use of metformin. These results support the fact that metformin would not be needed to obtain positive cardiovascular effects when this class of drugs are administered.

Abbreviations

T2D: Type 2 diabetes

CVD: Cardiovascular disease

HR: Hazard Ratio

SGLT-2: Sodium Glucose co-transporter 2

GLP-1Ras: Glucagon-like peptide-1 receptor agonists

EASD: European Association for the study of diabetes

ESC: European Society of Cardiology

CVOTs: Cardiovascular outcomes trials

MACE: Major adverse cardiovascular events

CI: Confidence interval

SE: Standard error

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

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Authors' contributions: ALC was the main coordinator of the project and was responsible for the study design. ALC and WM drafted the manuscript of the present paper. ML was involved in the supervising of data collection and stratification. ML and GM contributed to data assembly and analysis. GM contributed with manuscript revision. All authors contributed intellectually to this manuscript and have approved this final version.

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Figures

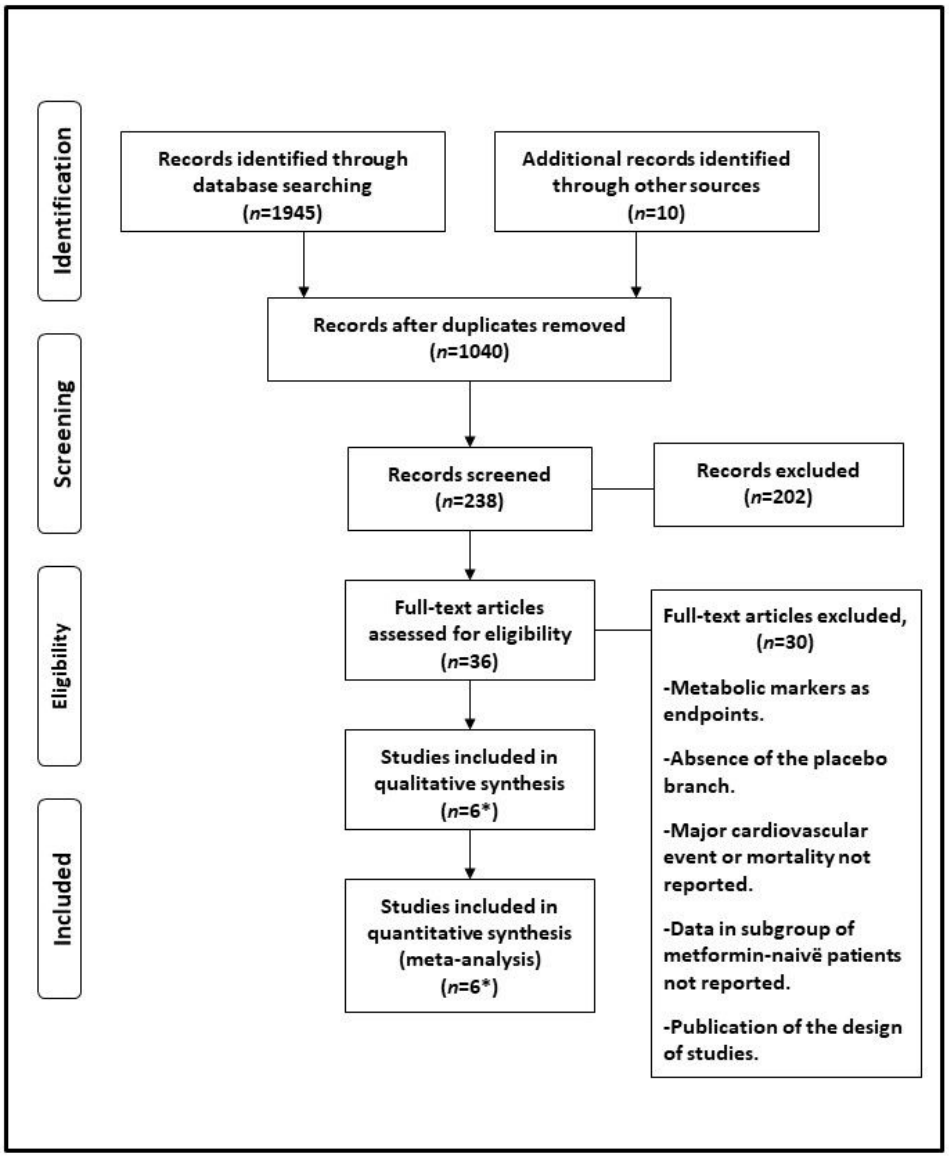

Figure 1

Six eligible trials (5 studies of subcutaneous GLP-1RAs and 1 with oral GLP-1RAs), including 10419 patients, were identified and considered eligible for the analyses. A total of 5274 subjects were allocated to receive GLP-1RAs while 5145 subjects were allocated to the respective control arms. A flow diagram of the study's screening process has been shown in Figure 1.

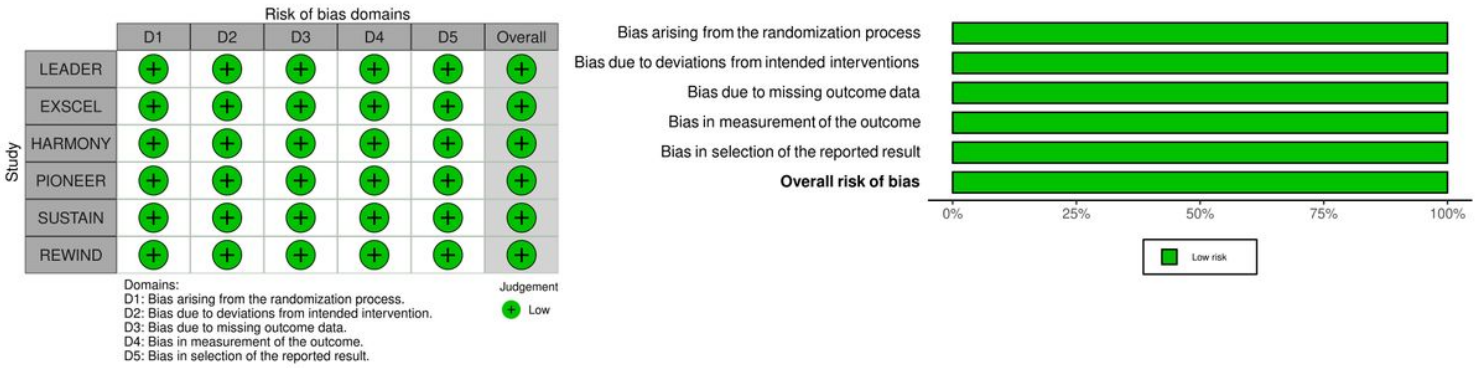

Figure 2

The total of studies evaluated were randomized clinical trials. Overall, the risk of bias was low in all the six studies. The quality of the studies evaluated can be seen in Figure 2.

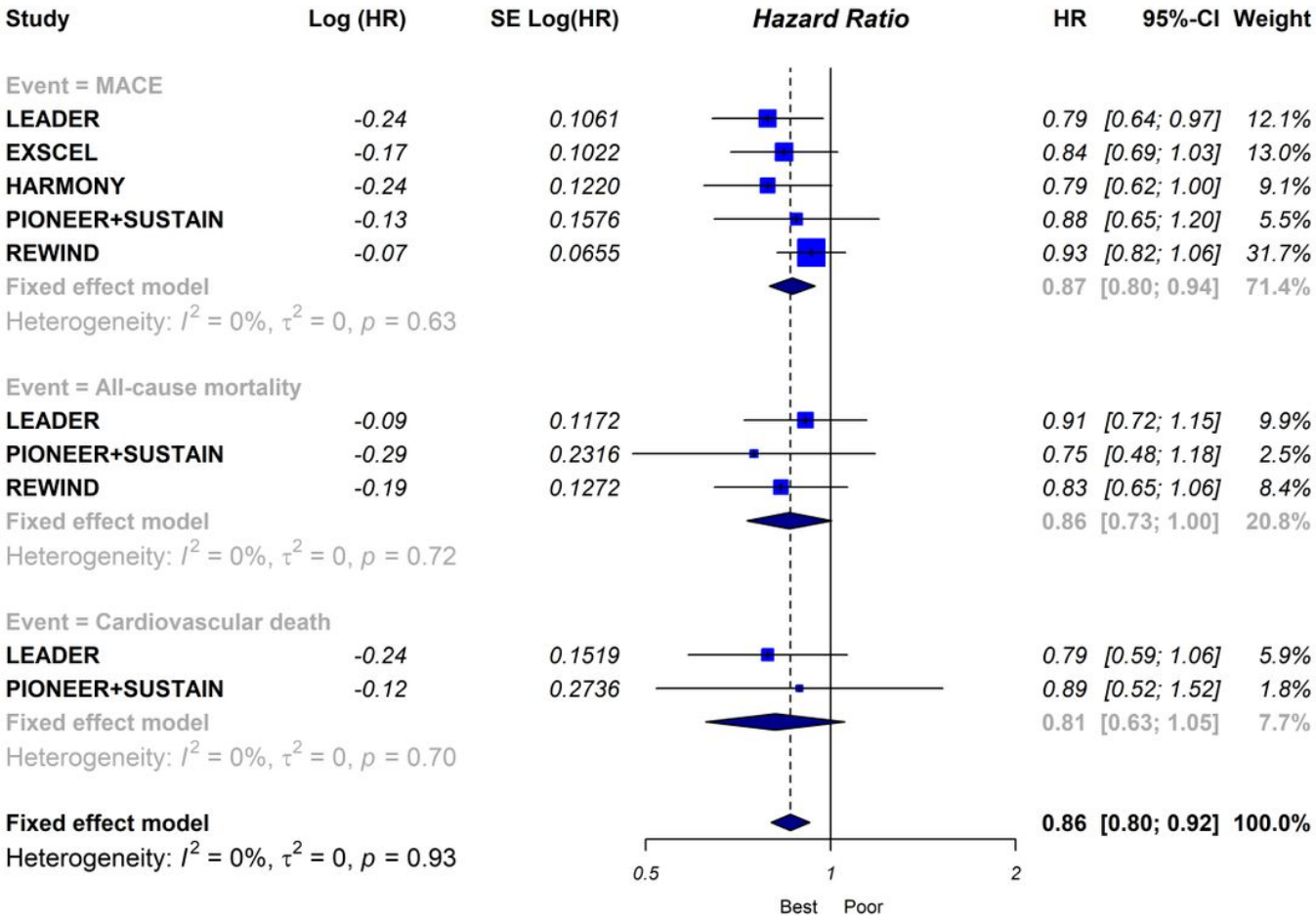

Figure 3

The present meta-analysis revealed that GLP-1RAs drugs were associated with a significant reduction in MACE (HR: 0.87, 95% CI: 0.80–0.94; I2: 0%). The analysis of the secondary endpoint showed that GLP-1RAs were associated with a non-significant reduction in all-cause mortality (HR: 0.86, 95% CI: 0.73-1.00; I2: 0%) and cardiovascular mortality (HR: 0.81, 95%

CI: 0.63–1.05; I2: 0%) The graphic representation of the effect of GLP-1RAs on primary and secondary end-point can be seen in Figure 3.

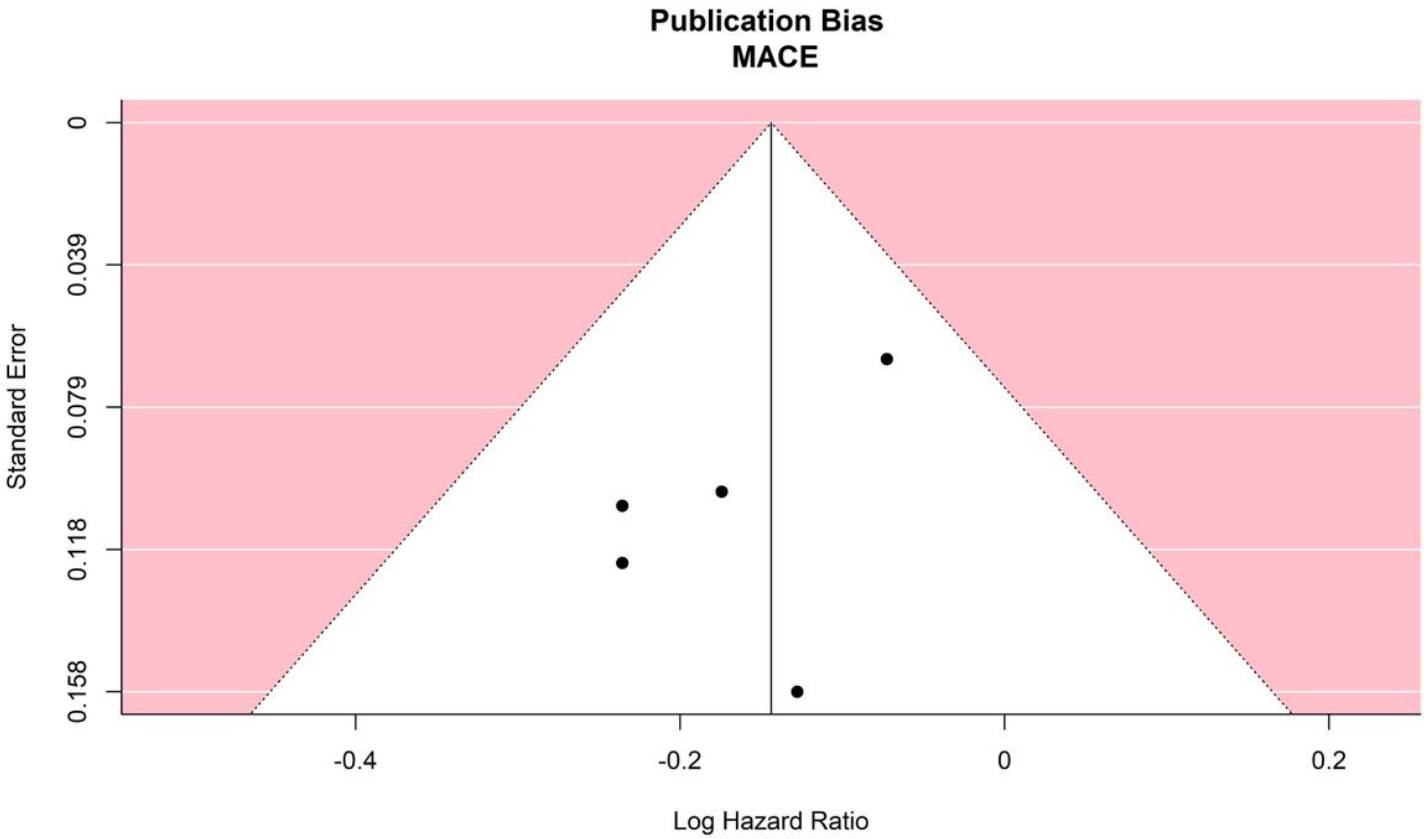

Figure 4

The funnel plot in Figure 4 and analytical evaluation do not suggest publication bias (Egger's asymmetry test, p=0.19).

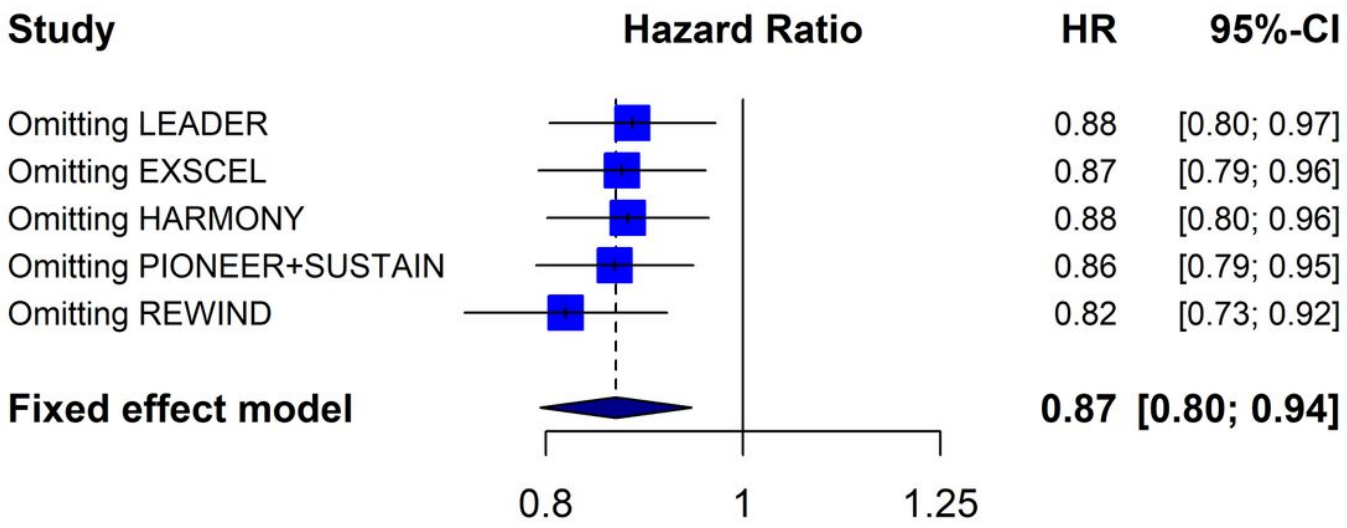

Figure 5

The sensitivity analysis showed the same directionality of results when studies were excluded one by one (Figure 5)