

Original Article

The effects of the baseline characteristics on the efficacy of GLP-1 RAs in reducing cardiovascular events in type 2 diabetes: a meta-analysis

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Abstract: Background: Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been proven to be able to significantly reduce major adverse cardiovascular events (MACE) in type 2 diabetic adults. However, the effects of GLP-1 RAs on MACE in many diabetic subgroups are unestablished. Methods: PubMed and Embase were searched for relevant trials. We conducted a random-effects meta-analysis on MACE in various subgroups defined by seven factors (i.e., sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, antihyperglycemic oral agent therapy, insulin therapy, and DPP-4 inhibitor therapy) to synthesize a hazard ratio (HR). A meta-regression was performed to calculate P_{subgroup} (the P value for subgroup differences). Results: We included seven trials in our analysis. GLP-1 RAs significantly reduced the risk of MACE (HR 0.88, 95% CI 0.83-0.93) in type 2 diabetic adults and significantly reduced this risk in most diabetic subgroups of interest (the HR ranged from 0.77 to 0.89). The relative reductions in the risk of MACE exhibited by the GLP-1 RAs were consistent across the various diabetic subgroups defined by the seven factors of interest (the P_{subgroup} ranged from 0.220 to 0.711). Conclusions: GLP-1 RAs can significantly reduce the risk of MACE in type 2 diabetes regardless of sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, or the baseline use of oral antihyperglycemic agents or insulin.

Keywords: Type 2 diabetes, major adverse cardiovascular events, glucagon-like peptide 1 receptor agonists

Introduction

Large cardiovascular outcome trials have confirmed that glucagon-like peptide 1 receptor agonists (GLP-1 RAs) can significantly reduce major adverse cardiovascular events (MACE) in type 2 diabetic adults. However, the effects of GLP-1 RAs on MACE in many diabetic subgroups are unestablished due to the two main reasons as follows.

First, the efficacy of GLP-1 RAs in reducing MACE in many type 2 diabetic subpopulations is controversial across large randomized trials. For instance, two trials [1, 2] showed that GLP-1 RAs versus a placebo significantly reduced MACE in patients with a diabetes duration ≥ 10 years, but four other trials [3-6] did not show

that. Also, three trials [1, 3, 6] did not show that GLP-1 RAs versus a placebo significantly reduced MACE in patients with a diabetes duration < 10 years but three other trials [2, 4, 5] did show that. Second, individual trials do not have enough statistical power to evaluate the effects of GLP-1 RAs on MACE in some diabetic subgroups. For instance, in three trials [1, 5, 7] GLP-1 RAs were not observed to significantly reduce MACE in the subgroups of diabetic patients with/without prior myocardial infarction or stroke. Moreover, in four trials [1, 2, 4, 5], GLP-1 RAs were not observed to significantly reduce MACE in the subgroup of diabetic patients with a baseline use of insulin.

Thus, we performed this meta-analysis to validate the efficacy of GLP-1 RAs on MACE in dif-

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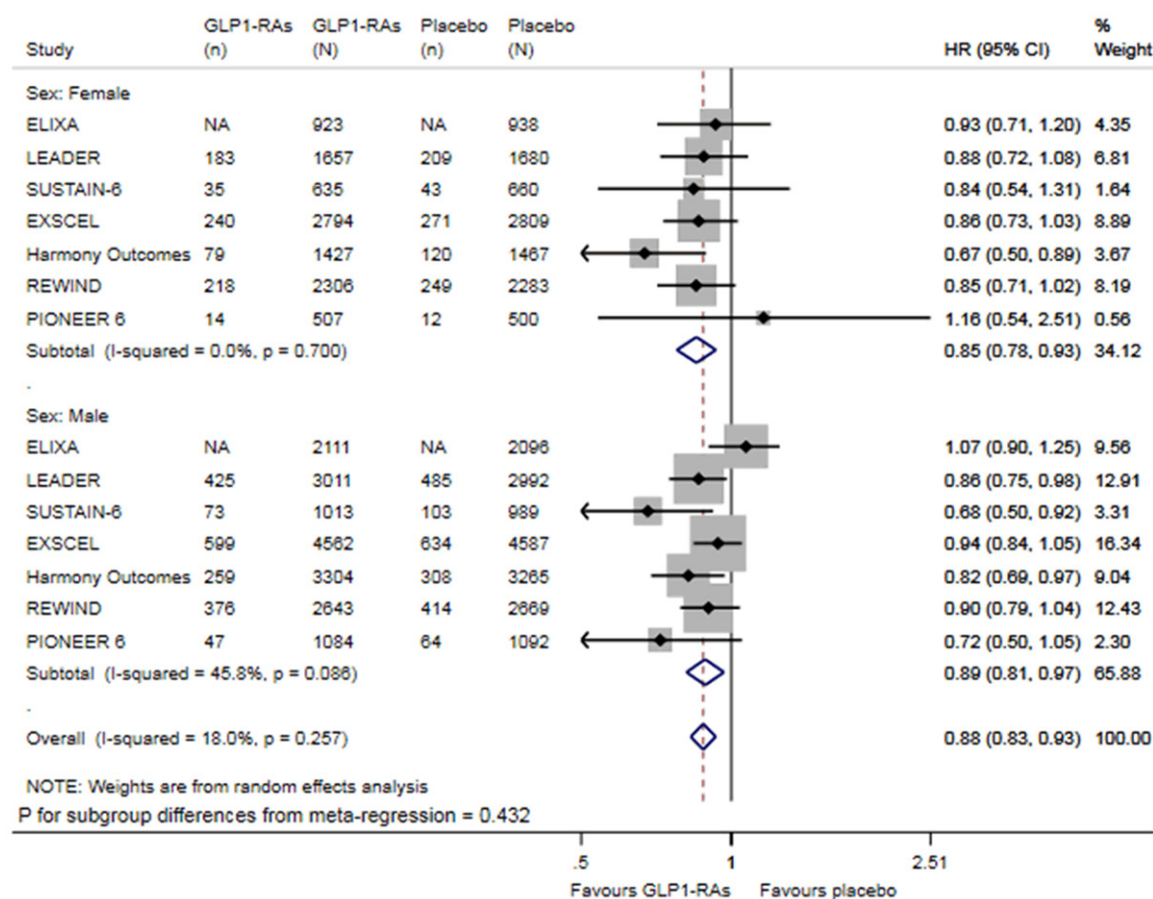


Figure 1. Meta-analysis of GLP-1 RAs on MACE, stratified by sex.

ferent type 2 diabetic subgroups defined by the seven important factors related to patients.

Methods

We report this meta-analysis according to the PRISMA statement, and the PRISMA checklist for the paper is shown in **Appendix A**. The study protocol has been registered (registration number: CRD42020161870) in PROSPERO and is shown in **Appendix B**.

Search strategy

PubMed and Embase were searched up to April 14, 2020 using pre-designed search strategies (**Appendix C**, p 1), for relevant randomized trials.

Inclusion and exclusion criteria

We included randomized, controlled, and cardiovascular outcome trials which assessed the impact of GLP-1 RAs on MACE in one or more

subgroups of type 2 diabetic adults. Our seven factors of interest were sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, antihyperglycemic oral agent therapy, insulin therapy, and DPP-4 inhibitor therapy.

Study selection, data extraction, and quality assessment

Two authors independently performed the study selection, data extraction, and quality assessment for the included trials. The quality assessment was conducted according to the Cochrane risk of bias tool. The involvement of a third author or a discussion between them addressed the disagreements between them.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) from the individual trials were used to perform a random-effects meta-analysis stratified by each factor of interest. Heterogeneity

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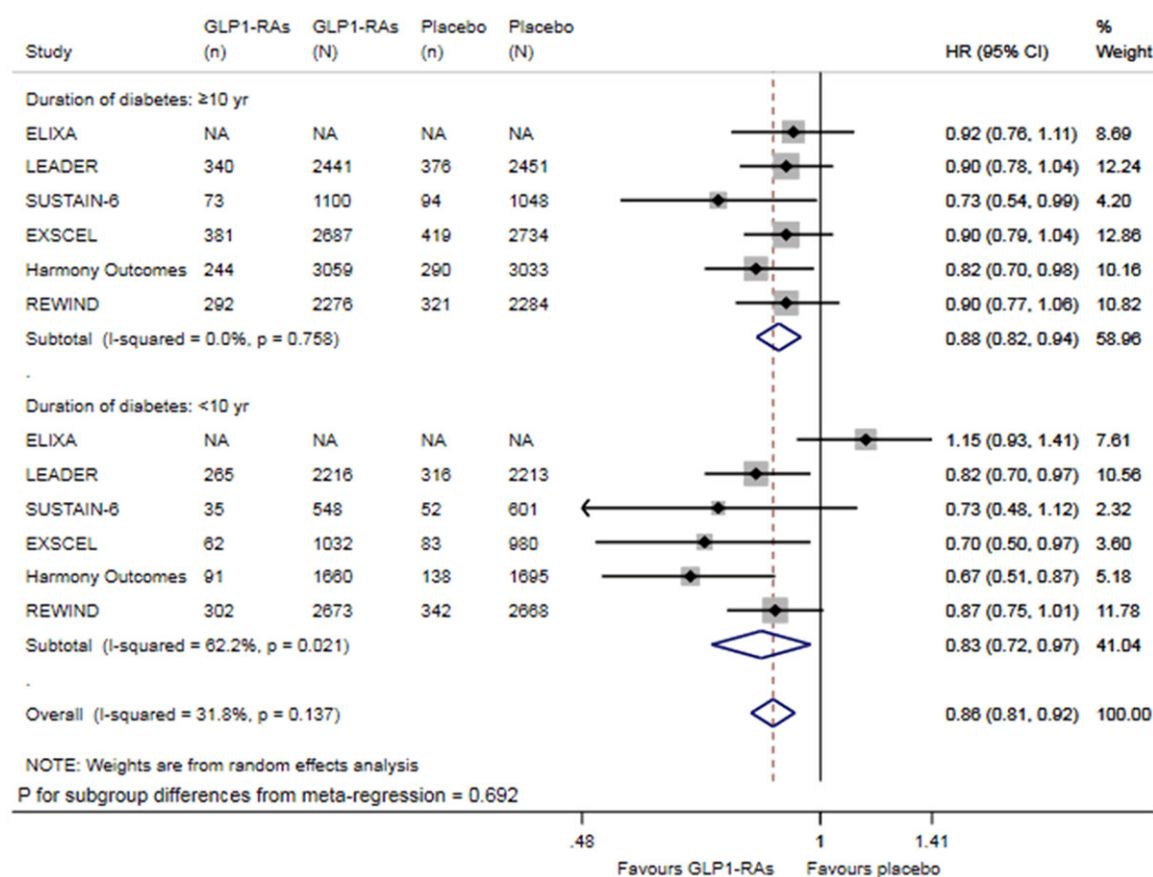


Figure 2. Meta-analysis of GLP-1 RAs on MACE, stratified by duration of diabetes.

was evaluated using the I^2 statistic, and $I^2 > 50\%$ means substantial heterogeneity. Subgroup differences were examined using random-effects meta-regression. Publication bias was determined using funnel plots and Egger tests. $P < 0.05$ represents statistical significance. The statistical analyses were done using Stata (version 15.1).

Results

Characteristics of the included trials

Seven randomized placebo-controlled trials [1-7] were included for analysis (Figure S1 in Appendix C). All the included trials had a low risk of bias (Figures S2 and S3 in Appendix C). The data extracted from trials are provided in Appendix D.

Meta-analyses

Figures 1-7 present the forest plots of the meta-analysis on MACE stratified by sex (Figure

1), duration of diabetes (Figure 2), history of heart failure (Figure 3), prior myocardial infarction or stroke (Figure 4), antihyperglycemic oral agent therapy (Figure 5), insulin therapy (Figure 6), and DPP-4 inhibitor therapy (Figure 7).

Compared with a placebo, GLP-1 RAs significantly reduced the risk of MACE (HR 0.88, 95% CI 0.83-0.93) among the overall diabetic patients in the included trials. Compared with a placebo, GLP-1 RAs significantly reduced the risk of MACE in the subgroups of female diabetic patients (HR 0.85, 95% CI 0.78-0.93), male diabetic patients (HR 0.89, 95% CI 0.81-0.97), patients with a duration of diabetes ≥ 10 years (HR 0.88, 95% CI 0.82-0.94), patients with a duration of diabetes < 10 years (HR 0.83, 95% CI 0.72-0.97), diabetic patients with no history of heart failure (HR 0.87, 95% CI 0.78-0.97), diabetic patients with prior myocardial infarction or stroke (HR 0.89, 95% CI 0.81-0.98), diabetic patients with antihyperglycemic oral agent therapy (HR 0.87,

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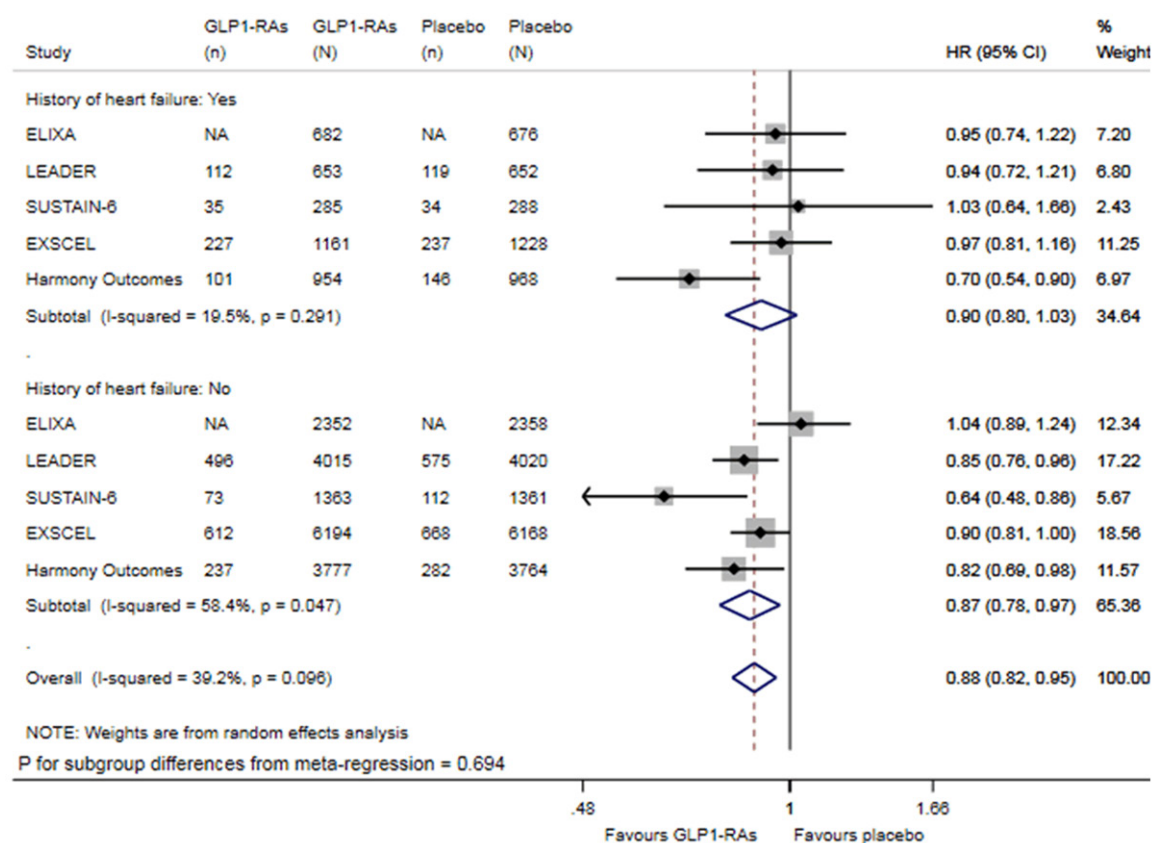
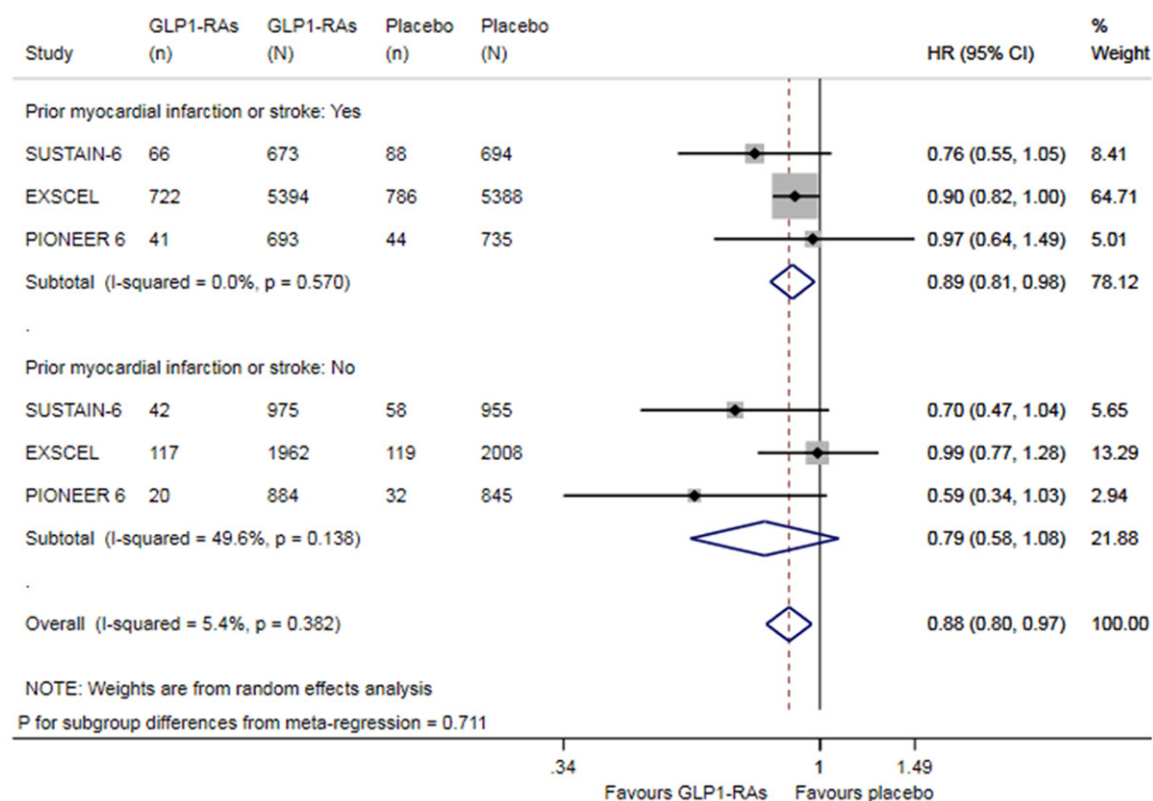


Figure 3. Meta-analysis of GLP-1 RAs on MACE, stratified by history of heart failure.



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Figure 4. Meta-analysis of GLP-1 RAs on MACE, stratified by prior myocardial infarction or stroke.

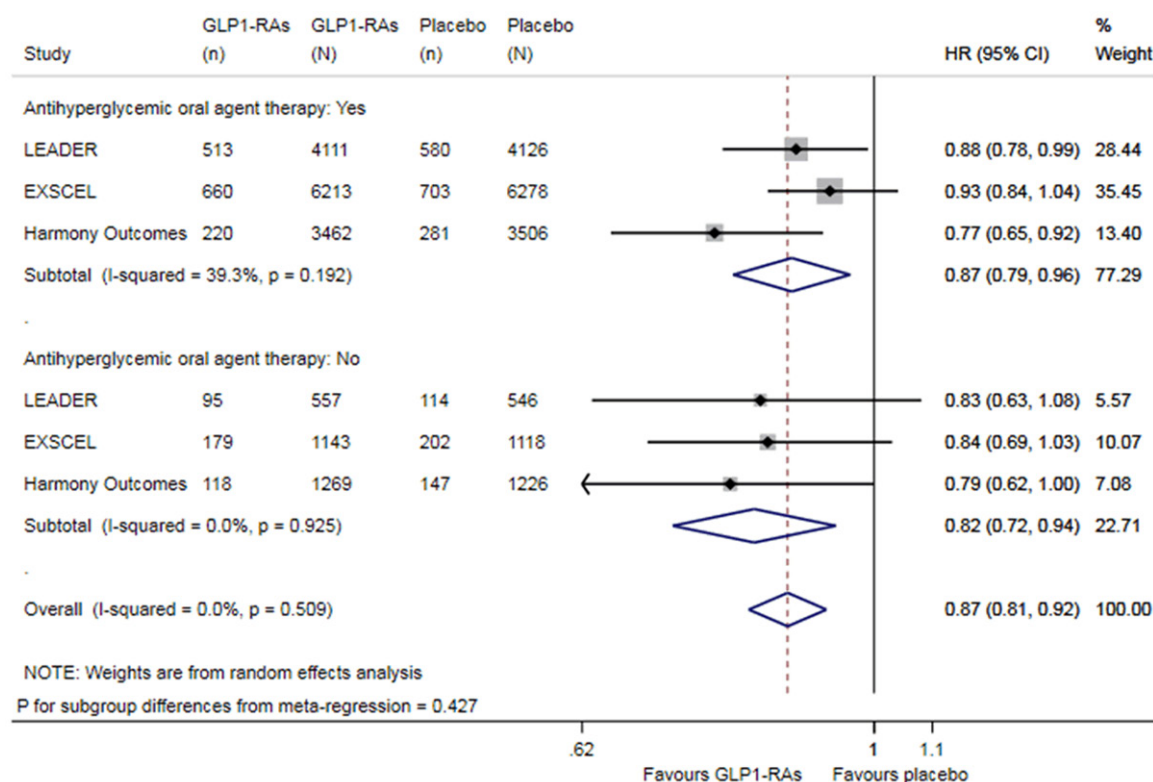


Figure 5. Meta-analysis of GLP-1 RAs on MACE, stratified by antihyperglycemic oral agent therapy.

95% CI 0.79-0.96), diabetic patients with no antihyperglycemic oral agent therapy (HR 0.82, 95% CI 0.72-0.94), diabetic patients with insulin therapy (HR 0.88, 95% CI 0.81-0.95), diabetic patients with no insulin therapy (HR 0.77, 95% CI 0.62-0.95), and diabetic patients with no DPP-4 inhibitor therapy (HR 0.82, 95% CI 0.68-0.98). Compared with a placebo, the GLP-1 RAs showed a reduction trend in the MACE risk in the subgroups of diabetic patients with a history of heart failure (HR 0.90, 95% CI 0.80-1.03) and diabetic patients with no prior myocardial infarction or stroke (HR 0.79, 95% CI 0.58-1.08), and showed an increasing trend in MACE risk in the subgroup of diabetic patients who had undergone DPP-4 inhibitor therapy (HR 1.07, 95% CI 0.87-1.31).

Relative reductions in the risk of MACE exhibited by GLP-1 RAs were consistent across various diabetic subgroups defined by each of the 7 factors of interest (the P_{subgroup} ranged from 0.220 to 0.711). Substantial heterogeneity existed in a few subgroups which were the

subgroups of patients with a duration of diabetes <10 years ($I^2=62.2\%$), diabetic patients with no history of heart failure ($I^2=58.4\%$), diabetic patients with no insulin therapy ($I^2=75.9\%$), and diabetic patients with no DPP-4 inhibitor therapy ($I^2=72.8\%$). Funnel plots and Egger tests (Figures S4, S5, S6, S7, S8, S9, S10, S11, S12, S13, S14, S15, S16, S17 in Appendix C) did not suggest a publication bias in any of the subgroups.

Discussion

In this study, we performed a meta-analysis based on all the diabetic patients from the included trials, and we performed a subgroup meta-analysis stratified using the seven factors of interest related to the patients (i.e. sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, antihyperglycemic oral agent therapy, insulin therapy, and DPP-4 inhibitor therapy). Accordingly, we summarized two main findings as follows.

First, GLP-1 RAs vs. placebo significantly reduced the risk of MACE (HR 0.88, 95% CI

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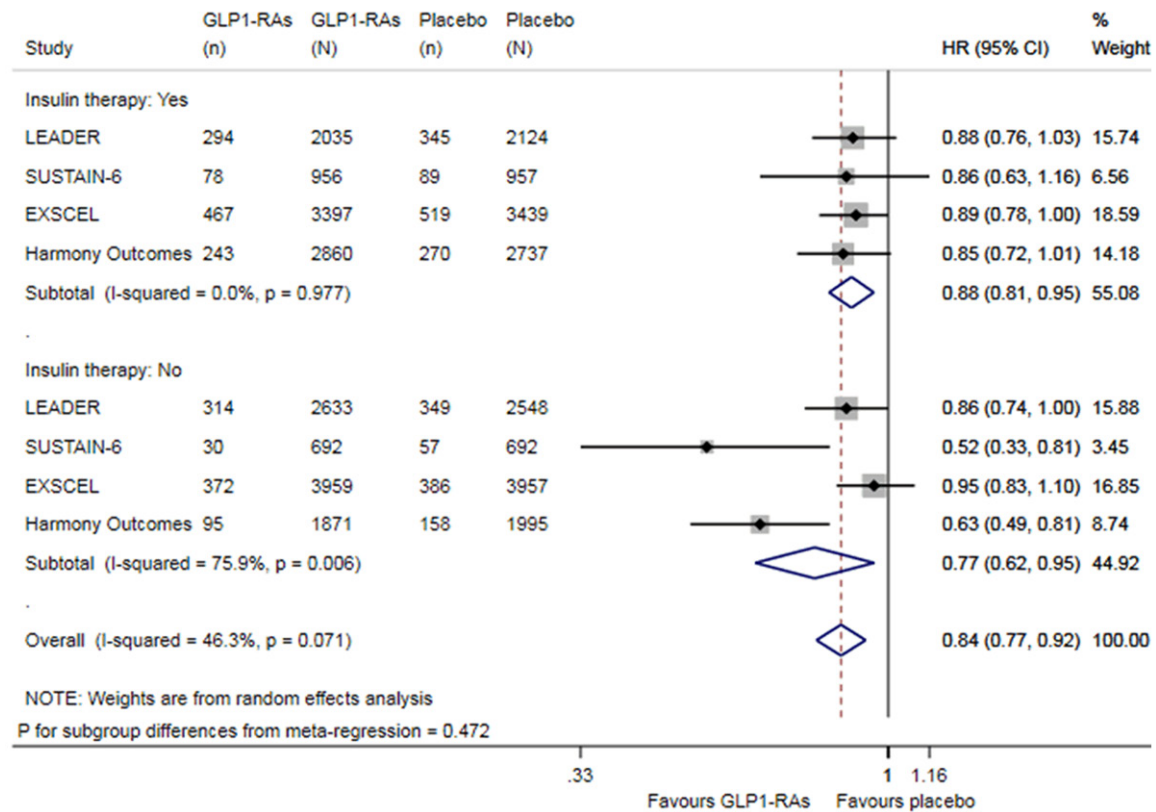


Figure 6. Meta-analysis of GLP-1 RAs on MACE, stratified by insulin therapy.

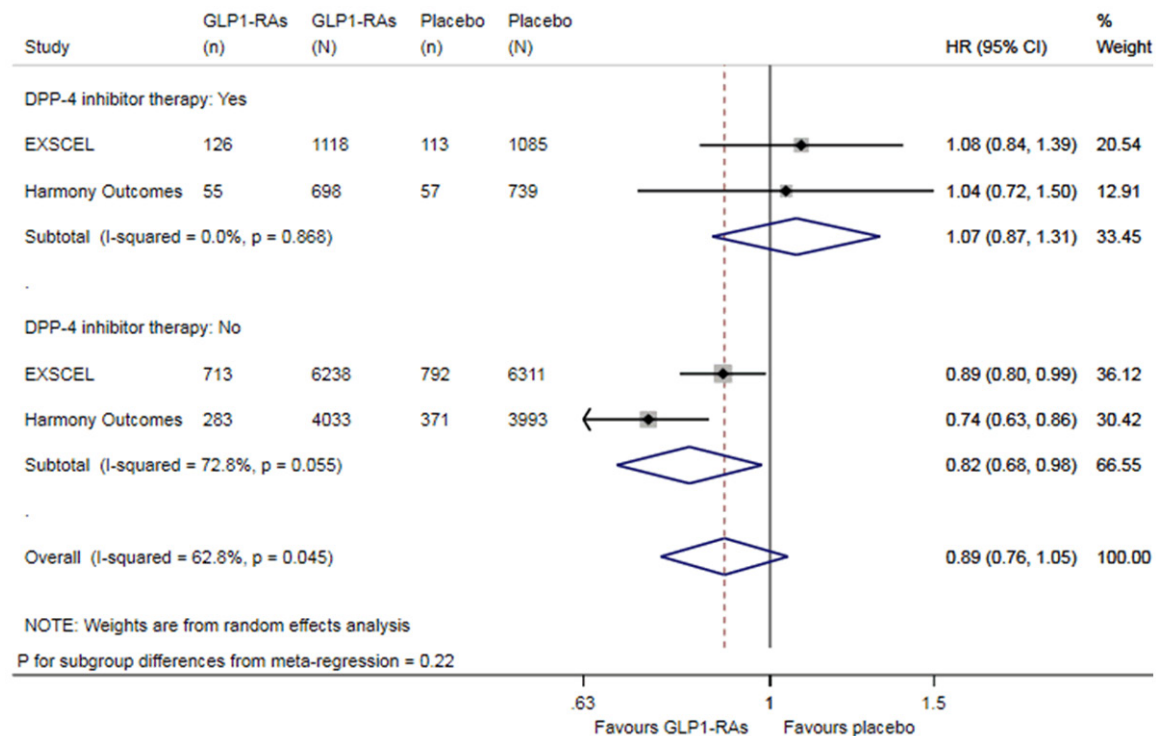


Figure 7. Meta-analysis of GLP-1 RAs on MACE, stratified by DPP-4 inhibitor therapy.

0.83-0.93) in type 2 diabetic adults and significantly reduced this risk in most type 2 diabetic subgroups of interest (the HR ranged from 0.77 to 0.89). Second, the significant reduction in the risk of MACE exhibited by the GLP-1 RAs did not vary across the seven factors of interest (the P_{subgroup} ranged from 0.220 to 0.711).

Similarly, previous meta-analyses [8-15] also confirmed that GLP-1 RAs can significantly reduce the risk of MACE in type 2 diabetic adults. However, these studies [8-15] failed to conduct a subgroup analysis stratified by the different patient characteristics and therefore failed to explore the effects of the baseline characteristics of patients on the efficacy of GLP-1 RAs in reducing MACE. For the first time, our study assessed the effects of seven key factors related to patients (i.e. sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, antihyperglycemic oral agent therapy, insulin therapy, and DPP-4 inhibitor therapy) on the efficacy of GLP-1 RAs and revealed that GLP-1 RAs can significantly reduce the risk of MACE in type 2 diabetic adults regardless of sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, and the baseline use of oral antihyperglycemic agents or insulin. Similarly, Kristensen et al. [16] demonstrated that the benefit of GLP-1 RAs on MACE is consistent across various subgroups defined by five other factors related to patients (i.e. history of cardiovascular disease, BMI, age, baseline HbA_{1c}, and baseline estimated glomerular filtration rate). Moreover, Mannucci et al.'s study [17] shows a significant reduction in the MACE risk with GLP-1 RAs irrespective of age, gender, or obesity.

GLP-1 RAs in the latest consensus report [18] are recommended for type 2 diabetic patients with established cardiovascular disease (ECD) and for type 2 diabetic patients without ECD with high risk indicators, to reduce the risk of MACE. However, the consensus report gives few recommendations about the impact of patient characteristics on the efficacy of this drug class in preventing MACE. Prior studies [19-22] demonstrated that use of GLP-1RAs led to the benefit of reducing the HbA_{1c} levels, weight, and blood pressure in type 2 diabetes. Meanwhile, our study revealed the universality

of the efficacy of GLP-1 RAs in preventing MACE in type 2 diabetes. Thus, the findings in this study will further promote this drug class to be widely used in type 2 diabetes.

This study has two main strengths. First, all the included trials had a low risk of bias. Second, no publication bias was found in any subgroup. As a limitation of this study, the impact of DPP-4 inhibitor therapy on MACE reduced by GLP-1 RAs needs to be further investigated, since in this study the GLP-1 RAs showed an insignificant increasing trend in the risk of MACE in the subgroup of diabetic patients with DPP-4 inhibitor therapy, and substantial heterogeneity was observed in the subgroup of diabetic patients with no DPP-4 inhibitor therapy.

In conclusion, GLP-1 RAs can significantly reduce the risk of MACE in type 2 diabetes regardless of sex, duration of diabetes, history of heart failure, prior myocardial infarction or stroke, and the baseline use of oral antihyperglycemic agents or insulin.

Disclosure of conflict of interest

None.

Abbreviations

GLP-1 RAs, glucagon-like peptide 1 receptor agonists; MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; ECD, established cardiovascular disease.

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