Systematic Review and Meta-Analysis

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# Effects of glucagon-like peptide 1 receptor agonists and sodium glucose cotransporter 2 inhibitors on major adverse cardiovascular events in type 2 diabetes by race, ethnicity, and region

## A meta-analysis

Mei Qiu, MS[a], Liangliang Ding, MS[b], Xubin Wei, MS[c], Wei Wei, MS[d], Hairong Zhou, MD[a,*]

**Abstract**

**Background:** The effects of sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists on major adverse cardiovascular events (MACE) in type 2 diabetic subgroups defined by race, ethnicity, and region are unestablished.

**Methods:** We searched PubMed and Embase for related randomized controlled trials. We conducted random-effects meta-analysis, stratified by drug class, on MACE in various subgroups defined by 3 factors of interest (ie, race, ethnicity, and region) to estimate pooled hazard ratio (HR) and 95% confidence interval. Random-effects meta-regression was conducted to evaluate the differences between 2 drug classes.

**Results:** We included 11 randomized controlled trials for pooled analysis. Compared with placebo, SGLT2is and GLP-1 RAs significantly reduced the risk of MACE (HR ranged from 0.76 to 0.93) in most diabetic subgroups defined by 3 factors of interest. The 2 drug classes did not significantly reduced this risk in the Black race group (HR 0.92, 95% confidence interval 0.70–1.20). The effect of the 2 drug classes on MACE was not significantly different in all diabetic subgroups of interest (*P*-value for subgroup differences ranged from .101 to .971).

**Conclusions:** SGLT2is and glucagon-like peptide 1 receptor agonists can significantly reduce the risk of MACE in most type 2 diabetic subgroups defined by race, ethnicity, and region, whereas they fail to do it in Black individuals.

**Abbreviations:** CI = confidence interval, GLP1-RAs = glucagon-like peptide 1 receptor agonists, HR = hazard ratio, MACE = major adverse cardiovascular events, RCTs = randomized controlled trials, SGLT2is = sodium glucose cotransporter 2 inhibitors.

**Keywords:** cardiovascular events, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes

## 1. Introduction

Although the latest consensus report[1] on the management of hyperglycemia recommends glucagon-like peptide 1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in type 2 diabetic individuals to prevent cardiorenal events, the effects of the 2 drug classes on major adverse cardiovascular events (MACE) in type 2 diabetic subgroups defined by race, ethnicity, and region remain undefined because of the following 2 reasons.

First, the effects of the 2 drug classes on MACE in some diabetic subgroups are not consistent across different trials. As an example, canagliflozin in the CANVAS Program trial[2] and in the CREDENCE trial[3] and albiglutide in the Harmony Outcomes trial[4] showed a significant risk reduction in MACE in the White race group. However, lixisenatide in the ELIXA trial[5] showed a trend for risk increase in MACE and the 2 drug classes in other cardiovascular outcome trials[6–12] showed a trend for risk reduction in MACE in this subgroup, with no statistical significance. Second, there is a lack of statistical power in some diabetic subgroups. As an example, SGLT2is in all SGLT2i trials[2,3,6,7] failed to show a significant risk reduction in MACE in the North America region group and GLP1-RAs in most

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

*The authors report no conflicts of interest.*

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*[a] Department of General Medicine, Shenzhen Longhua District Central Hospital, Shenzhen, [b] Department of Endocrinology, First Affiliated Hospital of Yangtze University, Jingzhou, [c] Department of Cardiology, [d] Department of Pharmacy, The Second Affiliated Hospital of Kunming Medical University, Kunming, China.*

*[*] Correspondence: Hairong Zhou, Department of General Medicine, Shenzhen Longhua District Central Hospital, Shenzhen, China (e-mail: 13798214835@sina.cn).*



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GLP1-RA trials[4,5,8–10,12] also failed to do it, although they significantly reduced MACE in the analysis based on the whole type 2 diabetic population.

Thus, we performed this meta-analysis to investigate the efficacy of the 2 drug classes on MACE in different type 2 diabetic subgroups defined by race, ethnicity, and region.

## 2. Methods

This meta-analysis was performed according to the PRISMA statement,[13] and the PRISMA checklist for this study is presented in Supplementary Material 1, http://links.lww.com/MD/F310. The protocol for this meta-analysis has been published in PROSPERO (Registration Number: CRD42020161830).

### 2.1. Search strategy

PubMed and Embase were searched through February 25, 2020 using a pre-designed search strategy, for English articles reporting related randomized controlled trials (RCTs). The terms searched were: ("Diabetes Mellitus, Type 2"[Mesh] OR "diabetes mellitus type 2"[tiab] OR "type 2 diabetes mellitus"[tiab] OR "T2D*"[tiab]) AND (Sodium-Glucose Transporter 2 Inhibitors [MH] OR "Sodium glucose co-transporter 2*"[TIAB] OR SGLT2*[TIAB] OR "Empagliflozin"[tiab] OR "Dapagliflozin"[tiab] OR "Canagliflozin"[tiab] OR "ertugliflozin"[tiab] OR "glucagon-like peptide 1 receptor agonists"[TIAB] OR lixisenatide[TIAB] OR liraglutide[TIAB] OR semaglutide[TIAB] OR exenatide[TIAB] OR albiglutide[TIAB] OR dulaglutide[TIAB]) AND ("cardiovascular death" [tiab] OR "myocardial infarction"[TIAB] OR stroke[tiab] OR "Cardiovascular Events"[TIAB] OR "cardiac Events"[TIAB] OR "MACE"[tiab] OR "major adverse cardiovascular events"[tiab] OR "major adverse cardiac events"[tiab]) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])). Details of the search strategy are reported in Supplementary Material 2, http://links.lww.com/MD/F311.

### 2.2. Inclusion and exclusion criteria

We included event-driven cardiovascular outcome RCTs in which active drugs (ie, SGLT2is or GLP1-RAs) were compared with other active drugs or placebo in 1 or more type 2 diabetic subgroups of interest. The primary outcome was MACE that was defined as a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.[7,11] Subgroups of interest were the subgroups of type 2 diabetic adults with different race (ie, White, Black, Asian, or Other), ethnicity (ie, Hispanic or Non-Hispanic) and region (ie, North America, Central/South America, Europe, or Asia-Pacific). To avoid biasing the results due to the small sample studies, we excluded those trials in which MACE was not measured as one of the primary outcomes.

### 2.3. Study selection, data extraction, and quality assessment

Two authors independently completed study selection, data extraction, and risk of bias assessment. Two authors independently performed risk of bias assessment for included trials using the Cochrane risk of bias tool.[14] According to the Cochrane tool[14] included trials were assessed in the 7 points as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), selective reporting (reporting bias), incomplete outcome data (attrition bias), and other bias. Any disagreements on study selection, data extraction, and quality assessment for included trials between them were addressed by discussion with a third author.

### 2.4. Statistical analysis

We used the data of hazard ratios (HRs) and 95% confidence intervals (CIs) from eligible trials to conduct meta-analysis stratified by drug class respectively in different subgroups defined by race, ethnicity, and region. The random-effects model was used to conduct meta-analysis, in order to provide a conservative estimate of treatment effect.[15,16] Heterogeneity was examined by $I^2$ statistic,[17] and this value >50% means substantial heterogeneity. Random-effects meta-regression was performed to assess the differences between 2 drug classes, and the $P$-value < .05 denotes statistically significant difference. We used funnel plots and Egger tests to detect publication bias.[18] All analyses were performed in Stata (version 15.1).

### 2.5. Ethical statement

The data analyzed in this study were extracted from previously published studies, and therefore ethical approval was not necessary.

## 3. Results

### 3.1. Characteristics of included trials

After primary screening, 145 full-text articles were assessed for eligibility and 11 articles[2–12] from 11 RCTs were finally included for quantitative synthesis (Supplementary Fig. 1, http://links.lww.com/MD/F306). All the included trials, with low risk of bias (Supplementary Figs. 2, http://links.lww.com/MD/F307 and 3, http://links.lww.com/MD/F308), were placebo-controlled ones, and contained 4 SGLT2i trials[2,3,6,7] with 38,723 participants with 3828 MACE and 7 GLP1-RA trials[4,5,8–12] with 56,004 participants with 6252 MACE. The data analyzed in this study are provided in Supplementary Material 3, http://links.lww.com/MD/F312.

### 3.2. Meta-analyses

The results of meta-analysis stratified by 2 drug classes on MACE in various subgroups defined by race, ethnicity, and region are presented in Figures 1 to 10. The key results of these Figures are shown in Table 1.

Compared with placebo, the 2 drug classes consistently reduced the risk of MACE in the White race group (HR 0.89, 95% CI 0.84–0.95; $P_{subgroup}$ = .631; Fig. 1), in the Asian race group (HR 0.77, 95% CI 0.66–0.89; $P_{subgroup}$ = .622; Fig. 3), in the Other race group (HR 0.84, 95% CI 0.71–1.00; $P_{subgroup}$ = .269; Fig. 4), in the Hispanic Ethnicity group (HR 0.76, 95% CI 0.66–0.86; $P_{subgroup}$ = .119; Fig. 5), in the Non-Hispanic Ethnicity group (HR 0.90, 95% CI 0.84–0.96; $P_{subgroup}$ = .956; Fig. 6), in the North America Region group (HR 0.93, 95% CI

**Table 1**

**Effects of 2 drug classes on MACE in different diabetic subpopulations defined by race, ethnicity, and region.**

| | SGLT2is | | GLP1-RAs | | Overall[†] | | |
|---|---|---|---|---|---|---|---|
| **Subgroups** | **HR (95% CI)** | **$I^2$ (%)** | **HR (95% CI)** | **$I^2$ (%)** | **HR (95% CI)** | **$I^2$ (%)** | **$P^*$** |
| Race | | | | | | | |
| White | 0.88 (0.81, 0.95) | 22.7 | 0.90 (0.83, 0.98) | 51.3 | 0.89 (0.84, 0.95) | 39.3 | .631 |
| Black | 0.87 (0.45, 1.67) | 61.0 | 0.92 (0.67, 1.27) | 49.1 | 0.92 (0.70, 1.20) | 47.2 | .884 |
| Asian | 0.81 (0.61, 1.06) | 33.4 | 0.74 (0.61, 0.90) | 0.0 | 0.77 (0.66, 0.89) | 0.0 | .622 |
| Other | 1.08 (0.69, 1.69) | 0.0 | 0.80 (0.66, 0.97) | 0.0 | 0.84 (0.71, 1.00) | 0.0 | .269 |
| Ethnicity | | | | | | | |
| Hispanic | 0.62 (0.48, 0.79) | 0.0 | 0.82 (0.70, 0.96) | 0.0 | 0.76 (0.66, 0.86) | 0.0 | .119 |
| Non-Hispanic | 0.90 (0.79, 1.03) | 0.0 | 0.89 (0.81, 0.98) | 54.1 | 0.90 (0.84, 0.96) | 31.3 | .956 |
| Region | | | | | | | |
| North America | 0.93 (0.83, 1.03) | 0.0 | 0.93 (0.84, 1.03) | 8.1 | 0.93 (0.87, 0.99) | 0.0 | .971 |
| Central/South America | 0.71 (0.56, 0.91) | 27.5 | 0.89 (0.80, 1.00) | 0.0 | 0.84 (0.75, 0.94) | 18.6 | .101 |
| Europe | 0.93 (0.85, 1.01) | 1.3 | 0.87 (0.74, 1.04) | 77.8 | 0.89 (0.80, 0.99) | 65.6 | .794 |
| Asia-Pacific | 0.87 (0.74, 1.01) | 15.7 | 0.76 (0.62, 0.94) | 0.0 | 0.83 (0.73, 0.94) | 7.9 | .333 |

GLP1-RAs = glucagon-like peptide 1 receptor agonists, MACE = major adverse cardiovascular events, SGLT2is = sodium-glucose cotransporter-2 inhibitors.

[*] The *P*-value for difference in pooled HRs between 2 drug classes was calculated by random-effects meta-regression. HR, hazard ratio of active drugs (ie SGLT2is or GLP1-RAs) versus placebo; CI, confidence interval of HR. $I^2$, the statistic of measuring heterogeneity.

[†] The meta-analysis results with both SGLT2i trials and GLP1-RA trials included.

0.87–0.99; $P_{subgroup} = .971$; Fig. 7), in the Central/South America Region group (HR 0.84, 95% CI 0.75–0.94; $P_{subgroup} = .101$; Fig. 8), in the Europe Region group (HR 0.89, 95% CI 0.80–0.99; $P_{subgroup} = .794$; Fig. 9), and in the Asia-Pacific Region group (HR 0.83, 95% CI 0.73–0.94; $P_{subgroup} = .333$; Fig. 10). Compared with placebo, both of the 2 drug classes failed to reduce the risk of MACE in the Black race group (HR 0.92, 95% CI 0.70–1.20; $P_{subgroup} = .884$; Fig. 2).

Substantial heterogeneity as for meta-analysis was observed only in the Europe Region group ($I^2 = 65.6\%$), but was not observed in all the other groups ($I^2$ ranged from 0% to 47.2%).

### 3.3. Publication bias detection

No dominant publication bias was observed by funnel plots and Egger tests (Supplementary Figs. 4–13, http://links.lww.com/MD/F309) for meta-analysis in all subgroups.

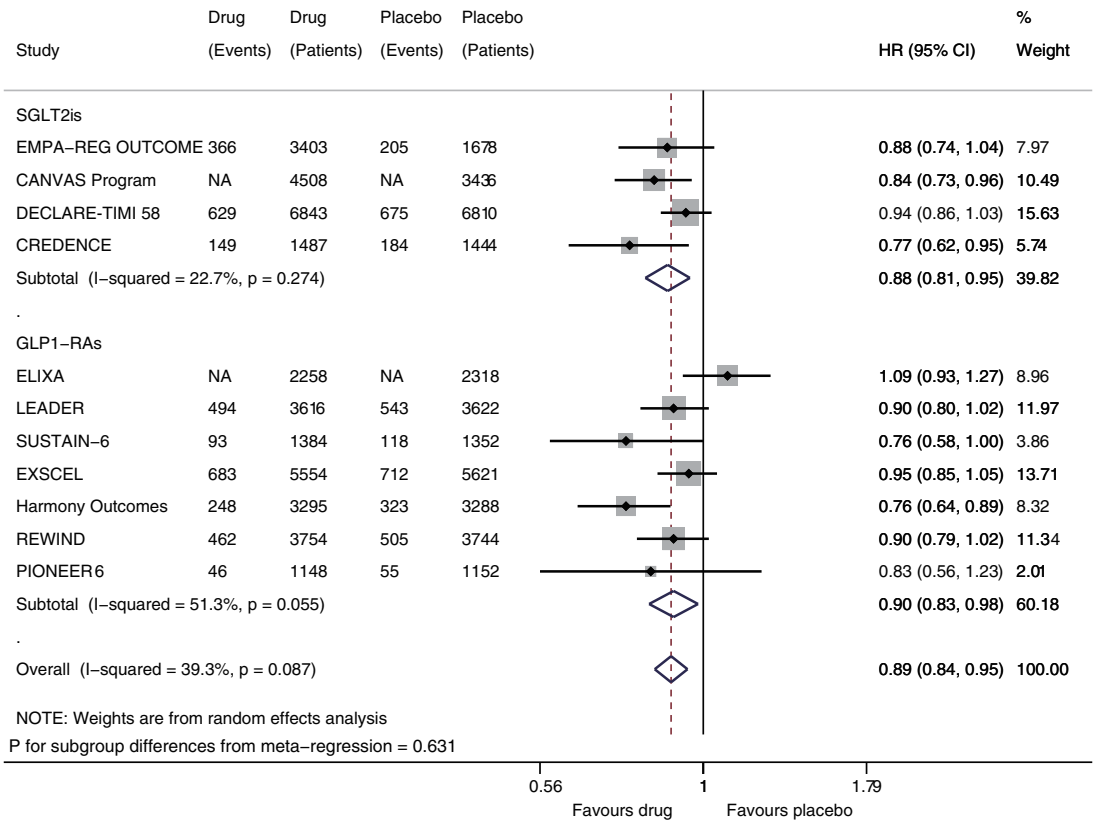


**Figure 1.** Effects of 2 drug classes on MACE in White patients with type 2 diabetes. MACE = major adverse cardiovascular events.

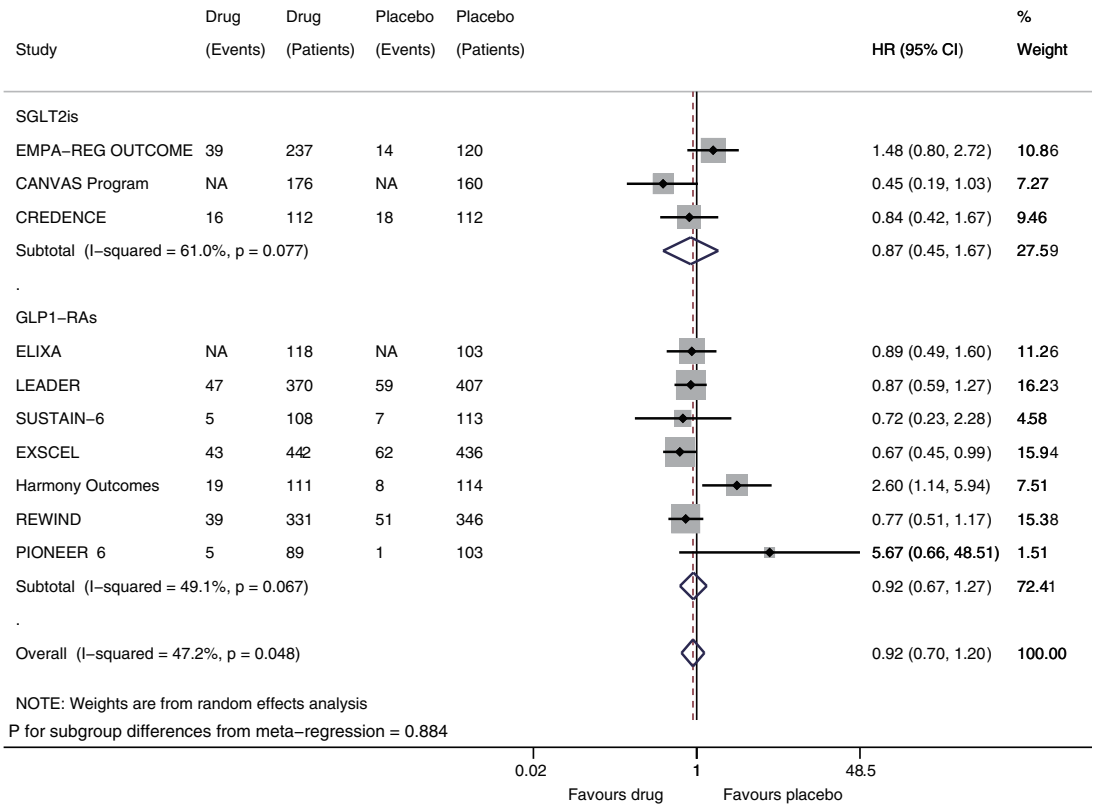


**Figure 2.** Effects of 2 drug classes on MACE in Black patients with type 2 diabetes. MACE = major adverse cardiovascular events.

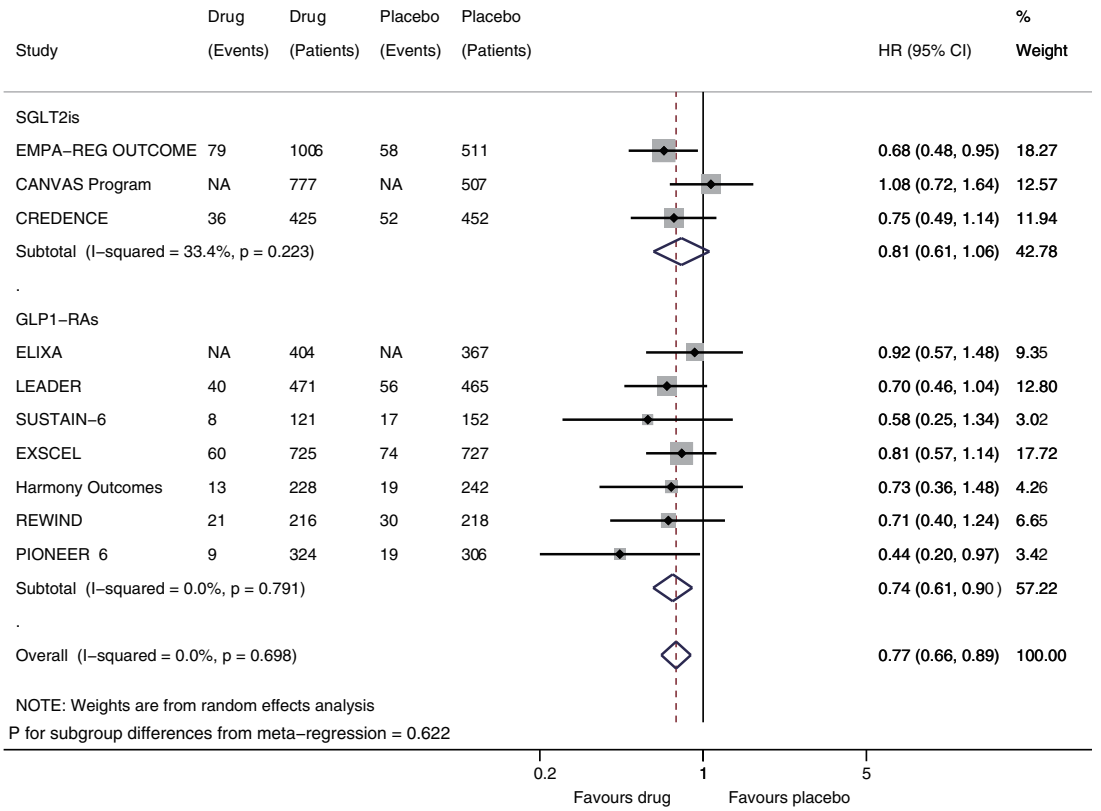


**Figure 3.** Effects of 2 drug classes on MACE in Asian patients with type 2 diabetes. MACE = major adverse cardiovascular events.

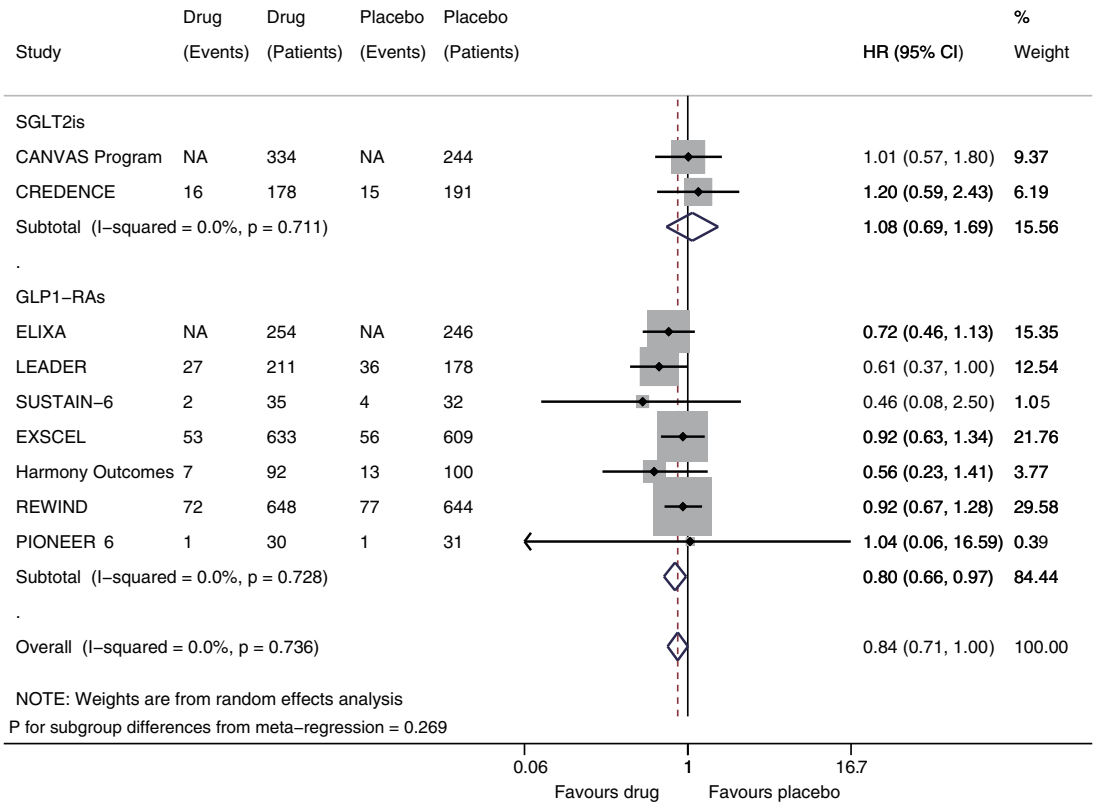


**Figure 4.** Effects of 2 drug classes on MACE in other race patients with type 2 diabetes. MACE = major adverse cardiovascular events.

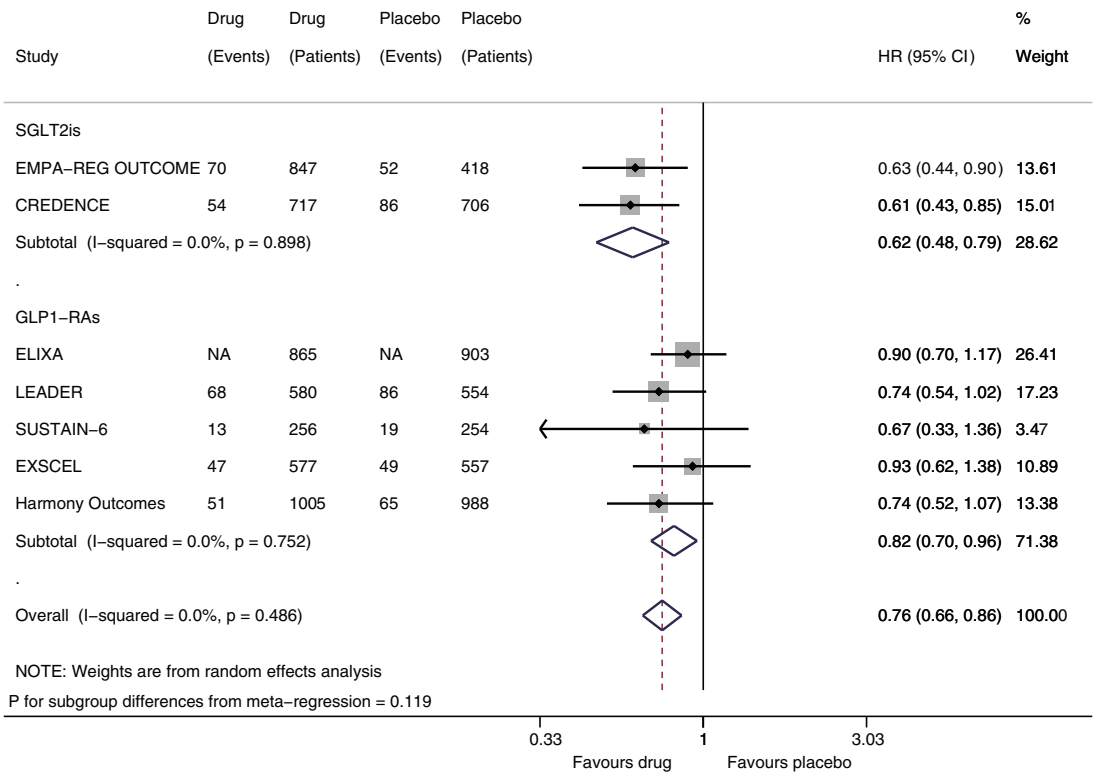


**Figure 5.** Effects of 2 drug classes on MACE in Hispanic patients with type 2 diabetes. MACE = major adverse cardiovascular events.

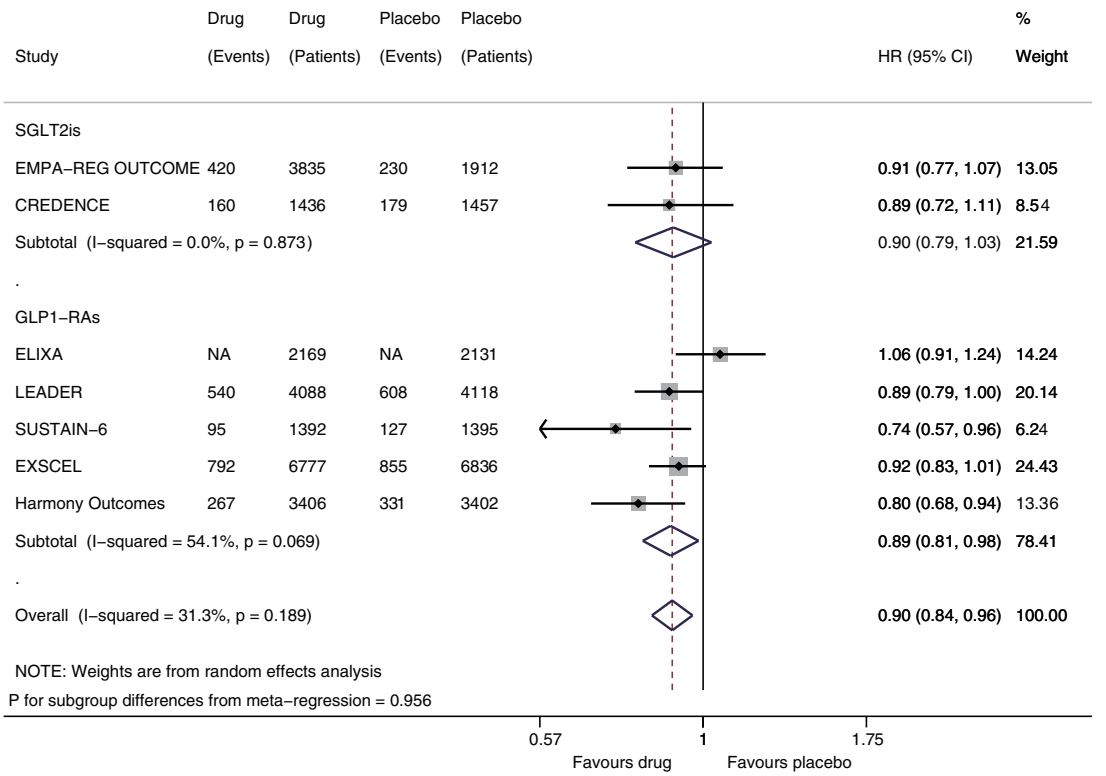


**Figure 6.** Effects of 2 drug classes on MACE in Non-Hispanic patients with type 2 diabetes. MACE = major adverse cardiovascular events.

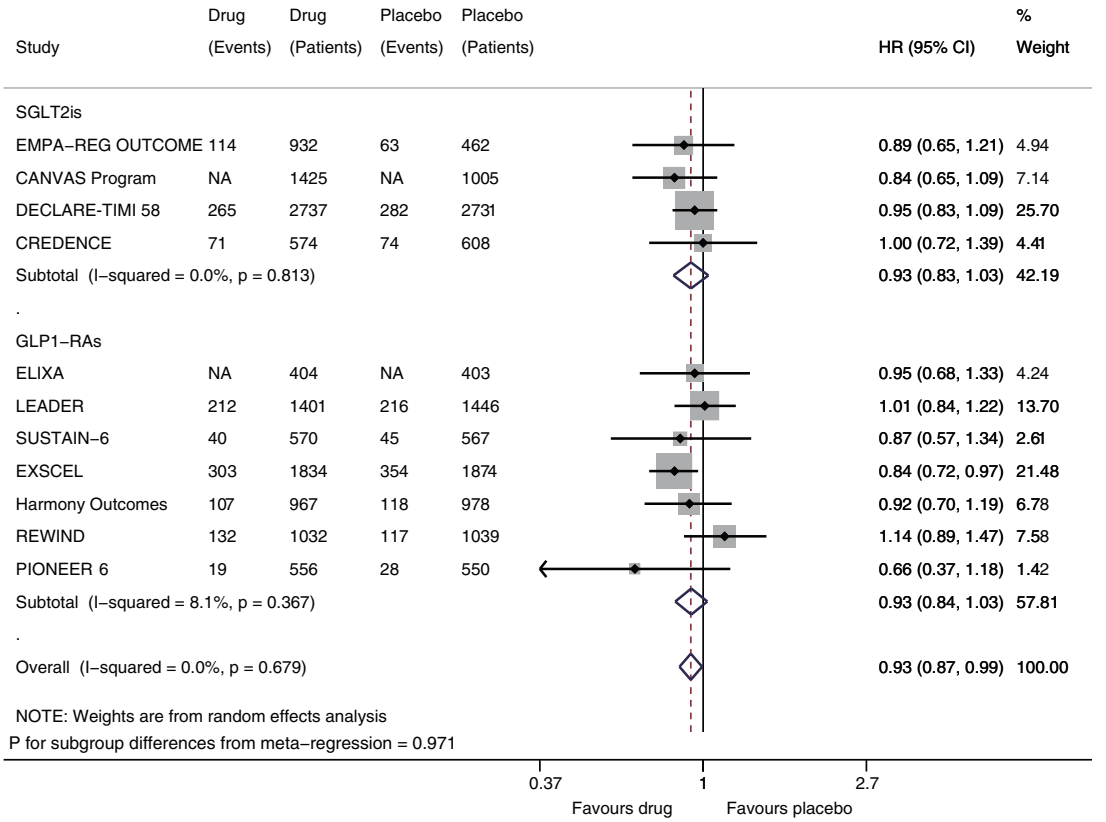


**Figure 7.** Effects of 2 drug classes on MACE in North America patients with type 2 diabetes. MACE = major adverse cardiovascular events.

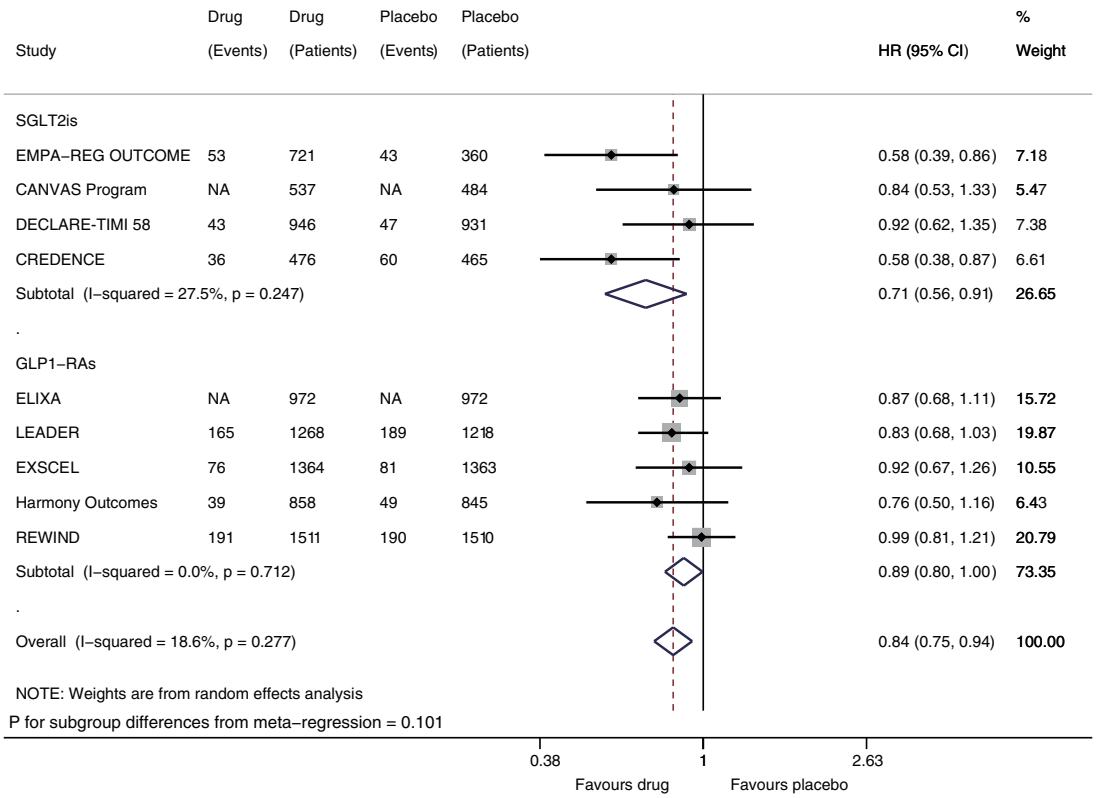


**Figure 8.** Effects of 2 drug classes on MACE in Central/South America patients with type 2 diabetes. MACE = major adverse cardiovascular events.

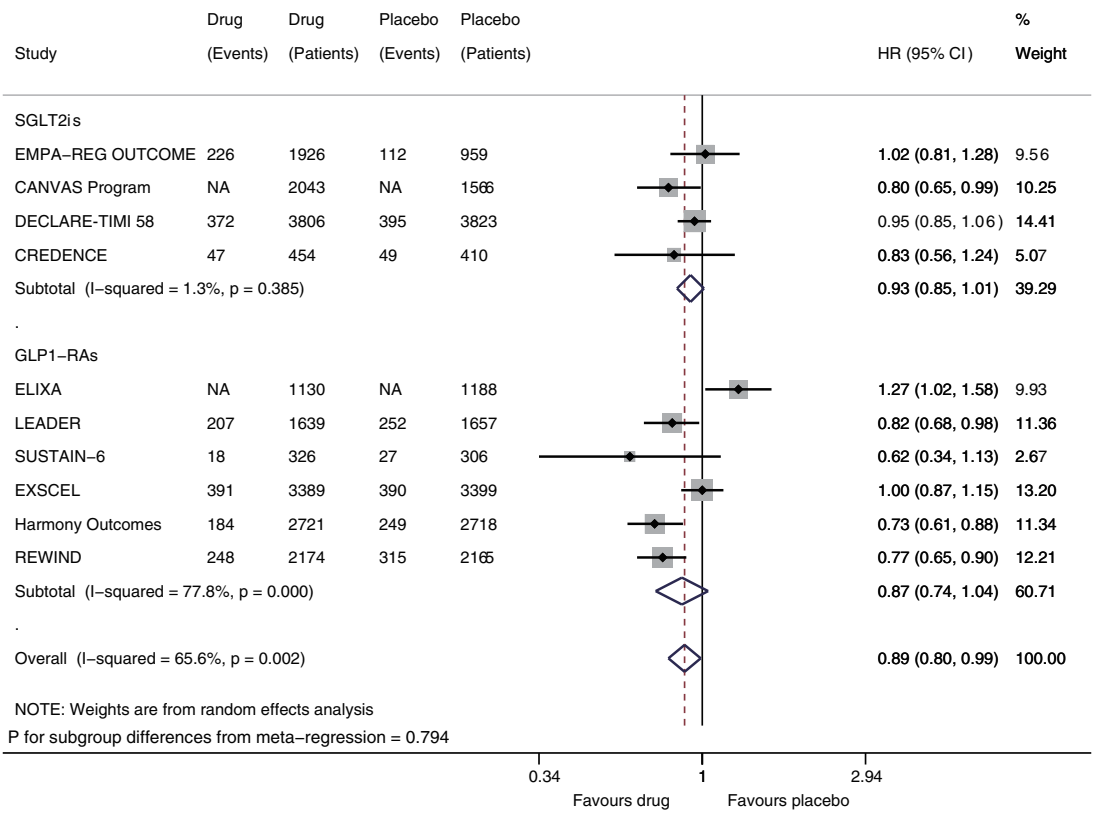


**Figure 9.** Effects of 2 drug classes on MACE in Europe patients with type 2 diabetes. MACE = major adverse cardiovascular events.

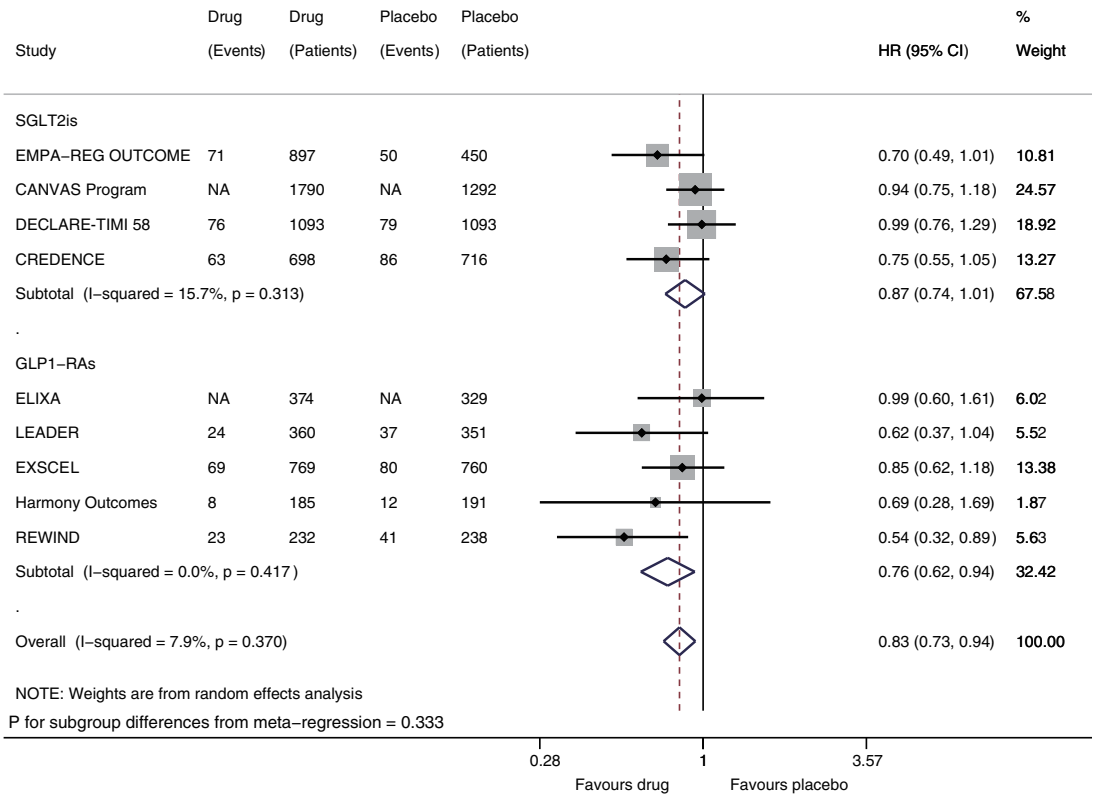


**Figure 10.** Effects of 2 drug classes on MACE in Asia-Pacific patients with type 2 diabetes. MACE = major adverse cardiovascular events.

## 4. Discussion

### 4.1. Main findings and clinical implications

By doing meta-analysis stratified by 2 drug classes in various type 2 diabetic subgroups defined by race, ethnicity, and region, we produced the following findings.

First, SGLT2is and GLP1-RAs consistently reduced the risk of MACE (HR ranged from 0.76 to 0.93, and $P_{subgroup}$ ranged from .101 to .971) compared with placebo in all subgroups defined by race, ethnicity, and region except for the Black race group. Second, both of the 2 drug classes did not reduce the MACE risk (HR 0.92, 95% CI 0.70–1.20, $P_{subgroup}$ = .884) in the Black race group.

The present meta-analysis is the second conventional meta-analysis which assessed the efficacy of both SGLT2is and GLP1-RAs on cardiovascular endpoints in patients with type 2 diabetes. Compared with the first conventional meta-analysis[19] which assessed the efficacy of both SGLT2is and GLP1-RAs on cardiovascular endpoints in patients with type 2 diabetes, our study additionally included 3 new cardiovascular outcome trials[3,10,12] and additionally assessed the efficacy of the 2 drug classes in type 2 diabetic subgroups defined by race, ethnicity, and region.

The findings in this study reveals that SGLT2is and GLP1-RAs are applicable or not applicable to some diabetic subgroups defined by race, ethnicity, and region, which fills the knowledge gaps in the latest consensus report.[1]

In current clinical practice, Black diabetic patients were less likely than White diabetic patients to be prescribed GLP1-RAs and SGLT2is.[20,21] This situation should be kept because the present study revealed the neutral effect of the 2 drug classes on MACE in Black diabetic patients and the 2 drug classes have some safety concerns, such as Fournier gangrene[22] and lower extremity amputation[23] with SGLT2is and gastrointestinal effects[24] with GLP1-RAs.

### 4.2. Strengths and limitations

This study has 2 main strengths. First, all the RCTs included in this study were with low risk of bias. Second, No dominant publication bias was found in meta-analysis for each subgroup.

This study has 2 main limitations. First, the mechanisms of the poor efficacy of SGLT2is and GLP1-RAs on MACE in Black diabetic patients need to be investigated. Second, substantial heterogeneity was observed in few subgroups, which needs to be clarified by further investigation.

### 4.3. Conclusions

SGLT2is and GLP1-RAs can significantly reduce the risk of MACE in most type 2 diabetic subgroups defined by race, ethnicity, and region, whereas they fail to do it in Black individuals.

## Author contributions

**Conceptualization:** Mei Qiu.
**Data curation:** Xubin Wei, Wei Wei, Hairong Zhou.
**Formal analysis:** Liangliang Ding.

**Methodology:** Liangliang Ding.
**Validation:** Xubin Wei, Wei Wei.
**Visualization:** Liangliang Ding.
**Writing – original draft:** Mei Qiu.
**Writing – review and editing:** Hairong Zhou.

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