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ORIGINAL RESEARCH

Subpopulation Differences in the Cardiovascular Efficacy of Long-Acting Glucagon-Like Peptide 1 Receptor Agonists in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: The cardiovascular efficacy of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes mellitus (T2DM) are well documented; however, the differences in cardiovascular efficacy among subpopulations remain unknown. This systematic review and meta-analysis aimed to explore the differences in cardiovascular efficacy of long-acting GLP-1RAs among subpopulations of patients with T2DM and to assess the drug safety.

Methods: Relevant studies up to March 31, 2020 were searched for in six electronic databases, namely PubMed, Cochrane Library, Embase, Clinical Trials, Science Direct, and Web of Science. The primary outcome was three-point major adverse cardiovascular events (including cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke). Subpopulations were defined using ten selected influential factors, and the differences in cardiovascular efficacy in subpopulations stratified by different influential factors were accessed by synthesizing studies with random-effects models one by one.

Results: A total of six cardiovascular outcome trials of long-acting GLP-1RAs, comprising 49,936 participants, were included. Among stratified subpopulations, no significant differences in the cardiovascular efficacy of long-acting GLP-1RAs were observed across the ten characteristics of subjects (all P for interaction > 0.05). Favorable trends were observed in the subpopulation with established cardiovascular disease (CVD) compared to that without ($P = 0.171$). With regards to safety, long-acting GLP-1RAs did not significantly increase the risk of retinopathy (OR 1.09; 95% CI 0.92–1.29; $P = 0.316$), but increase the risk of serious gastrointestinal events (OR 1.37; 95% CI 1.02–1.83; $P = 0.037$). Long-acting GLP-1RAs did not significantly increase the risk of serious adverse events (OR 0.92; 95% CI 0.85–1.00; $P = 0.039$).

Conclusions: Our analysis suggested no subpopulation differences in the cardiovascular efficacy of long-acting GLP-1RAs among stratified subpopulations, and favorable trends were only observed in the subpopulation with established CVD. These findings may have implications for the management of long-acting

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GLP-1RAs across subpopulations of patients with T2DM.

Keywords: Cardiovascular outcome; Long-acting GLP-1 receptor agonists; Meta-analysis; Type 2 diabetes; Safety profiles; Subpopulation differences

Key Summary Points

Why carry out this study?

Many studies reported remarkable cardiovascular efficacy of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in type 2 diabetes mellitus (T2DM), but the differences in cardiovascular efficacy among various subpopulations of patients with T2DM remained unknown.

What were the subpopulation differences in cardiovascular efficacy of long-acting GLP-1RAs among patients with T2DM?

What was learned from the study?

Our studies suggested that the subpopulation differences in cardiovascular efficacy of long-acting GLP-1RAs were insignificant among subpopulations stratified by different influential factors, and only favorable trends were noticed in the subpopulation with established CVD.

Our findings might have implications for the management of long-acting GLP-1RAs treatments across various subpopulations of patients with T2DM, as well as the safety of long-acting GLP-1RAs.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among patients with type 2 diabetes mellitus (T2DM), who are characterized as having a high risk for CVD [1]. As popular antidiabetic agents for patients with T2DM [2], glucagon-like peptide 1 receptor agonists (GLP-1RAs) have attracted increased universal attention for their cardioprotective efficacy, which might be attributed to the pleiotropic effects of ameliorating cardiovascular risk factors [2, 3]. Long-acting GLP-1Ras have shown significant cardiovascular benefits in trials [4], while short-acting GLP-1RAs (lixisenatide) have not shown favorable efficacy in terms of cardiovascular outcomes [5]. This difference might result from the inadequate time of GLP-1R activation with lixisenatide [2, 6]. In addition, diverse characteristics of participants, such as age, sex, and body mass index, might impact the cardiovascular efficacy of antidiabetic drugs. A recent study demonstrated significant differences in the cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) within subpopulations stratified by atherosclerotic cardiovascular disease status [7]. However, as a result of the paucity of relevant investigations and analyses, influential factors and subpopulation differences in cardiovascular efficacy remain unknown and controversial. Exploring subpopulation differences and ascertaining the influence factors could help to optimize the treatments of long-acting GLP-1RAs for patients with T2DM. Intriguingly, subpopulations exhibiting greater cardiovascular efficacy from long-acting GLP-1RAs could be more appropriately recommended for the administration of long-acting GLP-1RAs. Moreover, no up-to-date systematic reviews and meta-analyses have explored subpopulation differences in the cardiovascular efficacy of long-acting GLP-1RAs. Hence, it is necessary to synthesize the results of recently published studies in order to explore the influential factors and subpopulation differences of the administration of long-acting GLP-1RAs.

To address this gap in knowledge, this systematic review and meta-analysis synthesized the randomized controlled cardiovascular outcome trials (CVOTs) of long-acting GLP-1RAs with the intention to explore the differences in cardiovascular efficacy among subpopulations of patients with T2DM, as well as to determine the overall cardiovascular safety of long-acting GLP-1RAs.

METHODS

The present study adhered to the standards of the preferred reporting items for systematic review and meta-analysis (PRISMA) for a meta-analysis and systematic review of randomized clinical trials [8] (Supplementary Appendix). This meta-analysis and systematic review was prospectively registered in PROSPERO (CRD42019132137).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Study Eligibility

Inclusion criteria: (1) randomized controlled clinical trials (RCTs) performed in adults (age $\geq$ 18 years) with T2DM, of any diabetes duration, geographical distribution, countriy, race, follow-up, sample, and any background treatment administrated to participants; (2) including at least one intervention group and one more control; (3) treatment with long-acting GLP-1RAs as the intervention groups; and (4) designed to evaluate the cardiovascular outcome of GLP-1RAs, such as three-point major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) and four-point MACE (including cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina death) for the primary outcome.

Exclusion criteria: (1) non-human studies, such as animal studies; (2) studies with no results of cardiovascular outcomes; (3) studies with insufficient data (without data of subpopulation analysis) or with incomplete trials; and (4) reviews, editorials, commentaries, opinion articles, or conference abstracts without original data.

Study Identification and Selection

PubMed, Cochrane Library, Embase, Clinical Trials, Science Direct, and all databases in Web of Science were scrupulously searched up to March 31, 2020 without limits of language. Full search strategies are listed in the Supplementary Appendix. Two reviewers (LH and HZ) independently conducted systematic literature retrievals for RCTs, and disagreements were settled through discussion with a third reviewer. The major search terms and were as follows: "diabetes mellitus, diabetes," "GLP-1 receptor agonists, exenatide, liraglutide, semaglutide, albiglutide, dulaglutide, taspoglutide," and "cardiovascular outcome, cardiovascular events, cardiovascular diseases, major adverse cardiovascular events, MACE."

On the basis of inclusion and exclusion criteria, two reviewers (LH and NY) screened the titles and abstracts of the retrieved literatures independently. The selection process was repeated twice by each reviewer. The references of the identified literatures were manually searched and screened as an important supplement. Discrepancies were resolved through discussions with other team members until a consensus was reached.

Data Extraction and Quality Assessment

Data were extracted independently by two reviewers (LH and HZ), using standardized predefined data extraction forms. The primary efficacy outcome for this analysis was three-point MACE (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke), and cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, all-cause mortality, and hospitalization for heart failure (HF) were also analyzed individually. Importantly, the characteristics of interest for the stratifications of subpopulations were as follows: age, sex, region, race, diabetes mellitus (DM) duration, history of HF, history of established CVD, body mass index (BMI), glycated hemoglobin levels, and estimated glomerular filtration rate (GFR). The safety endpoints comprised severe hypoglycemia, pancreatitis, pancreatic cancer,

serious gastrointestinal events, retinopathy, adverse events (AEs) leading to drug discontinuation, and serious adverse events (SAE). The definition of primary safety endpoints is outlined in the Supplementary Appendix.

The quality of the enrolled RCTs was assessed with the Cochrane risk of bias assessment tool [9]. All trials met the criteria for being performed well, and had a low risk of bias according to the Cochrane tool for assessing risk of bias in randomized clinical trials (Supplementary Appendix).

Statistical Analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were synthesized for cardiovascular efficacy outcomes with random-effects models. Meta-regression analyses were performed using the residual maximum likelihood method and Hartung–Knapp adjustment for tests of interactions to assess the differences in cardiovascular efficacy across the subpopulations. Overall odds ratios (ORs) with 95% CIs were applied for safety endpoints, which were obtained through inverse-variance weights for the weighted mean logOR estimate, and then exponentiated. Heterogeneity was quantified with Cochrane Q statistic and I^2 statistic, which was judged as low ($I^2 \leq 25\%$), moderate ($25\% < I^2 \leq 50\%$), or high ($I^2 \geq 75\%$). Statistical analyses were conducted with Stata statistical software version 15.0 (Stata Corp, College Station, TX, USA), and P values less than 0.05 were considered statistically significant.

RESULTS

Study Characteristics and Quality Assessment

A total of six CVOTs of long-acting GLP-1RAs [10–15], with 49,936 participants, met the selection criteria in this meta-analysis. The study selection flowchart is shown in Fig. 1. The key design features of the trials and important baseline characteristics of the participants are listed in Table 1. Only the subjects in the Harmony Outcomes trial were 100% with established CVD, while subjects in the REWIND trial were of the lowest proportion (34.3%). Only the PIONEER-6 patients were orally administrated with long-acting GLP-1RAs. The REWIND trial had the longest follow-up time (5.4 years) and the lowest baseline glycated hemoglobin level (7.3%). Participants in the SUSTAIN-6 trial possessed a high proportion of pre-existing retinopathy. The general baseline characteristics of all subjects were generally similar in all included trials (Table S1). All subjects were older than 50 years, with a mean age of 63.2 years, and women accounted for 38.5% of the total. Most of the participants were white, and were from Europe or North America (Table S1).

All included trials had a low risk of bias according to the Cochrane tool for assessing risk of bias in randomized clinical trials (Table S2).

Overall Efficacy of Long-Acting GLP-1RAs

The details of overall efficacy are shown in Table 2 and Fig. S1a–f. For three-point MACE, GLP-1RA treatment generated a significant relative risk reduction of 14% (HR 0.86; 95% CI 0.82–0.91; $P < 0.001$) compared to placebo, similar to that observed for cardiovascular mortality (HR 0.86; 95% CI 0.79–0.95; $P = 0.002$). There were significant risk reductions in non-fatal myocardial infarction of 12% (HR 0.88; 95% CI 0.80–0.98; $P = 0.015$), non-fatal stroke of 18% (HR 0.82; 95% CI 0.74–0.91; $P < 0.001$), all-cause mortality of 12% (HR 0.88; 95% CI 0.81–0.95; $P = 0.001$), and hospitalization for heart failure (HR 0.91; 95% CI 0.83–0.99; $P = 0.036$) compared to placebo.

Analyses of Subpopulation Differences

The data and results of various subpopulations are shown in Tables 3, S3, and S4 and Figs. 2 and S2. There were no significant differences in the cardiovascular benefits among subpopulations classified by various factors during the treatments with long-acting GLP-1RAs (all P for interaction > 0.05) (Table 3, Figs. 2 and S2). The subgroup with previously established CVD

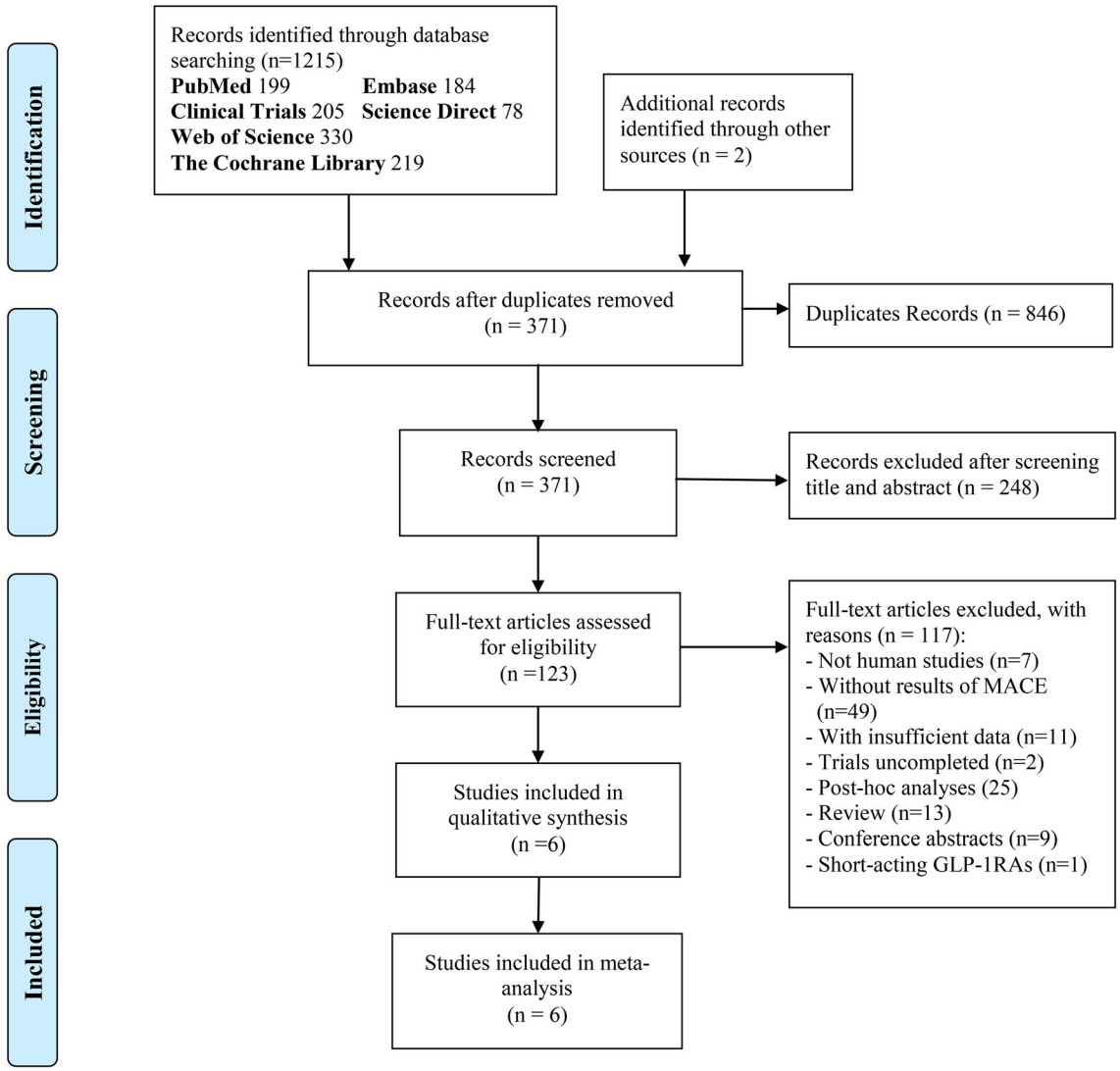


Fig. 1 Flow chart of search strategy. *MACE* major adverse cardiovascular events

showed a clear tendency for greater favorable cardioprotective effects compared to those without established CVD [HR (95% CI) 0.84 (0.80, 0.89) vs. 0.94 (0.82, 1.07); *P* for interaction = 0.171] (Fig. 3), the comparison of which was carried out on the basis of the HRs of the two groups. In the placebo group without established CVD, the incidence of three-point MACE per year was mostly below 1.9%/year, except 2.42%/year in the PIONEER-6 trial (Table S4). Similarly, Asian populations exhibited a slightly favorable tendency for greater cardiovascular benefits in the stratification of race (*P* for interaction = 0.148) (Fig. 4). The subpopulation with baseline BMI $< 30\ kg/m^2$ showed moderate heterogeneity (I^2 = 52.3%) (Fig. 5), while no heterogeneity was observed in the subpopulation characterized with baseline BMI $\geq 30\ kg/m^2$ (I^2 = 0%) (Fig. 5).

Safety Outcomes

With regards to the safety endpoints (Table 4, Fig. S3), there were no significant increases in the risk of severe hypoglycemia (OR 0.95; 95% CI 0.77–1.16; *P* = 0.597), pancreatitis (OR 0.92; 95% CI 0.63–1.34; *P* = 0.657), and pancreatic

Table 1 Key features of cardiovascular outcome trials of long-acting GLP-1RAs

	LEADER (*n* = 9340)	**SUSTAIN-6 (*n* = 3297)**	**EXSCEL (*n* = 14,752)**	**Harmony Outcomes (*n* = 9463)**	**REWIND (*n* = 9901)**	**PIONEER-6 (*n* = 3183)**
ID code	NCT01179048	NCT01720446	NCT01144338	NCT02465515	NCT01394952	NCT02692716
Key inclusion criteria	HbA1c ≥ 7.0%; age ≥ 50 years with CVD, CHF (NYHA class II or III), CKD (stage 3 or higher), or age ≥ 60 years with at least one CV risk factor	HbA1c ≥ 7.0%; age ≥ 50 years with CVD, CHF (NYHA class II or III), CKD (stage 3 or higher), or age ≥ 60 years with at least one CV risk factor	HbA1c 6.5–10.0%; established CVD and primary prevention; age ≥ 18 years	HbA1c ≥ 7.0%; age ≥ 40 years with ASCVD	HbA1c ≤ 9.5%; age ≥ 50 years with established CVD or age ≥ 60 years with at least two CV risk factors; BMI ≥ 23 kg/m^2	Aged ≥ 50 years with established CVD, moderate CKD (stage 3), or aged ≥ 60 years with at least one CV risk factor
Intervention	Liraglutide vs. placebo	Semaglutide vs. placebo	Exenatide vs. placebo	Albiglutide vs. placebo	Dulaglutide vs. placebo	Semaglutide vs. placebo
Usage	SI 1.8 mg, once daily	SI 0.5 or 1.0 mg, once weekly	SI 2 mg, once weekly	SI 30 mg, once weekly	SI 1.5 mg, once weekly	Oral 14 mg, once daily
Dose strategy	Forced increase	Forced increase	Single dose	Clinical titration	Single dose	Increased if tolerated
Follow-up (median)	3.8 years	2.1 years	3.2 years	1.6 years	5.4 years	15.9 months
Phase	III	III	III/IV	IV	III	III
Female sex	3339 (35.7%)	1294 (39.2%)	5605 (38.0%)	2886 (30.5%)	4589 (46.4%)	1005 (31.9%)
White	7430 (79.5%)	2736 (83.0%)	11,175 (75.8%)	8024 (84.8%)	7498 (75.7%)	2300 (72.3%)
Asian	1256 (13.4%)	272 (8.2%)	1453 (9.8%)	464 (4.9%)	4.4%	19.8%
Mean baseline HbA1c (%)	8.7 ± 1.6	8.7 ± 1.5	8.1 ± 1.0	8.7 ± 1.5	7.3 ± 1.1	8.2 ± 1.6
DM duration (years)	12.7 ± 8.0	13.9 ± 8.1	12.0 (7.0, 17.0)	14.1 ± 8.7	10.0 ± 7.2 years	14.9 ± 8.5 years

Table 1 continued

	LEADER (n = 9340)	SUSTAIN-6 (n = 3297)	EXSCEL (n = 14,752)	Harmony Outcomes (n = 9463)	REWIND (n = 9901)	PIONEER-6 (n = 3183)
Baseline BMI (kg/m^2)	32.5 ± 6.3	32.8 ± 6.0	31.8 (28.2, 36.2)	32.3 ± 5.9	32.3 ± 5.7	32.3 ± 6.6
≥ 30 kg/m^2	5753 (61.6%)	2115 (64.1%)	9338 (63.3%)	5834 (61.6%)	6068 (61.3%)	1902 (59.8%)
< 30 kg/m^2	3587 (38.4%)	1182 (35.9%)	5414 (36.7%)	3629 (38.4%)	3833 (38.7%)	1279 (40.2%)
Baseline SBP (mmHg)	135.9 ± 17.7	135.6 ± 17.0	135 (124, 145)	134.7 ± 16.6	137.2 ± 16.8	135.6 ± 17.6
LDL (mmol/L)	2.3 ± 0.9	2.13 ± 1.19	2.4 ± 1.0	2.1	2.56 ± 0.98	2.2 ± 0.9
Prior established CVD	81%	83%	73%	100%	31.4%	84.6%
Prior heart failure[a]	14.0%	23.6%	16.2%	20%	8.6%	12.2%
Pre-existing retinopathy	17%	29.4%	NA	18.5%	9.0%	27.2%
Primary outcome	Three point-MACE	Three point-MACE	Three point-MACE	Three point-MACE	Three point-MACE	Three point-MACE
Number of events in long-acting GLP-1RAs group	608	108	839	334	594	61

Table 1 continued

	LEADER (n = 9340)	SUSTAIN-6 (n = 3297)	EXSCEL (n = 14,752)	Harmony Outcomes (n = 9463)	REWIND (n = 9901)	PIONEER-6 (n = 3183)
HR (95% CI)	0.87 (0.78, 0.97); $P < 0.001$ for non-inferiority; $P = 0.01$ for superiority	0.74 (0.58, 0.95); $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority	0.91 (0.83, 1.00); $P < 0.001$ for non-inferiority; $P = 0.06$ for superiority	0.78 (0.68, 0.90); $P < 0.0001$for non-inferiority; $P = 0.0006$ for superiority	0.88 (0.79, 0.99); $P = 0.026$	0.79 (0.57, 1.11); $P < 0.001$ for non-inferiority
Completion	December 2015	March 2016	May 2017	March 2018	August 2018	September 2018

Data are n, %, or mean (SD), unless otherwise specified. *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *BMI* body mass index, HbA1c glycated hemoglobin, *CVD* cardiovascular disease, *CV* cardiovascular, *CHF* chronic heart failure, *CKD* chronic kidney disease, *ASCVD* arteriosclerotic cardiovascular disease, *SI* subcutaneous injections, *MACE* major adverse cardiovascular events, *HR* hazard ratio, *CI* confidence interval, *NYHA* New York Heart Association functional classification

[a] Heart failure with NYHA II–III

Table 2 Cardiovascular outcomes of long-acting GLP-1RAs across trials

	LEADER (*n* = 9340)			SUSTAIN-6 (*n* = 3297)			EXSCEL (*n* = 14,752)		
	Liraglutide	Placebo	HR (95% CI)	Semaglutide	Placebo	HR (95% CI)	Exenatide	Placebo	HR (95% CI)
3-point MACE	608 (13.0)	694 (14.9)	0.87 (0.78, 0.97)	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95)	839 (11.4)	905 (12.2)	0.91 (0.83, 1.00)
CV mortality	219 (4.7)	278 (6.0)	0.78 (0.66, 0.93)	44 (2.7)	46 (2.8)	0.98 (0.65, 1.48)	340 (4.6)	383 (5.2)	0.88 (0.76, 1.02)
Non-fatal MI	281 (6.0)	317 (6.8)	0.86 (0.73, 1.00)	47 (2.9)	64 (3.9)	0.74 (0.51, 1.08)	455 (6.2)	470 (6.4)	0.95 (0.84, 1.09)
Non-fatal stroke	159 (3.4)	177 (3.8)	0.86 (0.71, 1.06)	27 (1.6)	44 (2.7)	0.61 (0.38, 0.99)	155 (2.1)	177 (2.4)	0.86 (0.70, 1.07)
All-cause mortality	381 (8.2)	447 (9.6)	0.85 (0.74, 0.97)	62 (3.8)	60 (3.6)	1.05 (0.74, 1.50)	507 (6.9)	584 (7.9)	0.86 (0.77, 0.97)
HHF	218 (4.7)	247 (5.3)	0.87 (0.73, 1.05)	59 (3.6)	54 (3.3)	1.11 (0.77, 1.61)	219 (3.0)	231 (3.1)	0.94 (0.78, 1.13)

	Harmony Outcomes (*n* = 9463)			REWIND (*n* = 9901)			PIONEER-6 (*n* = 3183)			HR (95% CI)	*P* values for trend
	Albiglutide	Placebo	HR (95% CI)	Dulaglutide	Placebo	HR (95% CI)	Semaglutide (oral)	Placebo	HR (95% CI)		
3-point MACE	338 (7)	428 (9)	0.78 (0.68, 0.90)	594 (12.0)	663 (13.4)	0.88 (0.79, 0.99)*	61 (3.8)	76 (4.8)	0.79 (0.57, 1.11)	0.86 (0.82, 0.91)	< 0.001***
CV mortality	122 (2.8)	130 (3.0)	0.93 (0.73, 1.19)	317 (6.4)	346 (7.0)	0.91 (0.78, 1.06)	15 (0.9)	30 (1.9)	0.49 (0.27, 0.92)	0.86 (0.79, 0.95)	0.002**
Non-fatal MI	181 (3.8)	240 (5.0)	0.75 (0.61, 0.90)	205 (4.1)	212 (4.3)	0.96 (0.79, 1.16)	37 (2.3)	31 (1.9)	1.18 (0.73, 1.90)	0.88 (0.80, 0.98)	0.015**
Non-fatal stroke	94 (2.0)	108 (2.3)	0.86 (0.66, 1.14)	135 (2.7)	175 (3.5)	0.76 (0.61, 0.95)	12 (0.8)	16 (1.0)	0.74 (0.35, 1.57)	0.82 (0.74, 0.91)	< 0.001***
All-cause mortality	196 (4.1)	205 (4.3)	0.95 (0.79, 1.16)	536 (10.8)	592 (12.0)	0.90 (0.80, 1.01)	23 (1.4)	45 (2.8)	0.51 (0.31, 0.84)	0.88 (0.81, 0.95)	0.001***
HHF	188 (4.0)	218 (5.0)	0.85 (0.70, 1.04)	213 (4.3)	226 (4.6)	0.93 (0.77, 1.12)	21 (1.3)	24 (1.5)	0.86 (0.48, 1.55)	0.91 (0.83, 0.99)	0.036**

Data of long-acting GLP-1RA and placebo are presented as number of patients (%)

GLP-1RAs glucagon-like peptide 1 receptor agonists, *MACE* major adverse cardiovascular events, *3-point MACE* include cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke, *CV mortality* cardiovascular mortality, *HHF* hospitalization for heart failure, *MI* myocardial infarction, *HR* hazard ratio, *CI* confidence interval

P values for trend, $^{**}P \leq 0.05$; $^{***}P \leq 0.001$

Table 3 Subgroup analyses of long-acting GLP-1RAs on three-point MACE

	LEADER (*n* = 9340)		SUSTAIN-6 (*n* = 3297)		EXSCEL (*n* = 14,752)	
	HR (95% CI)	*P*1	HR (95% CI)	*P*1	HR (95% CI)	*P*1
Baseline age						
< 60/65/66 years	0.78 (0.62, 0.97)	0.27	0.74 (0.52, 1.05)	0.95	1.05 (0.92, 1.21)	0.005
≥ 60/65/66 years	0.90 (0.79, 1.02)		0.72 (0.61, 1.02)		0.80 (0.71, 0.91)	
Sex						
Male	0.86 (0.75, 0.98)	0.84	0.68 (0.50, 0.92)	0.45	0.94 (0.84, 1.05)	0.44
Female	0.88 (0.72, 1.08)		0.84 (0.54, 1.31)		0.86 (0.73, 1.03)	
Baseline BMI						
< 30 kg/m^2	0.96 (0.81, 1.15	0.15	0.58 (0.39, 0.87)	0.16	0.94 (0.79, 1.10)	0.59
≥ 30 kg/m^2	0.82 (0.71, 0.94)		0.84 (0.61, 1.16)		0.89 (0.79, 1.00)	
Region						
Europe	0.82 (0.68, 0.98)	0.20	0.62 (0.34, 1.13)	0.58	1.00 (0.87, 1.15)	0.39
North America	1.01 (0.84, 1.22)		0.87 (0.57, 1.34)		0.84 (0.72, 0.97)	
Asia	0.62 (0.37, 1.04)		NA		0.85 (0.62, 1.18)	
Rest of the world	0.83 (0.68, 1.03)		0.68 (0.48, 0.98)		0.92 (0.67, 1.26)	
Race						
White	0.90 (0.80, 1.02)	0.32	0.76 (0.58, 1.00)	0.88	0.95 (0.85, 1.05)	0.61
Black	0.87 (0.59, 1.27)		0.72 (0.23, 2.28)		0.67 (0.45, 0.99)	
Asian	0.70 (0.46, 1.04)		0.58 (0.25, 1.34)		0.81 (0.57, 1.14)	
Others	0.61 (0.37, 1.00)		0.46 (0.008, 2.50)		0.92 (0.63, 1.34)	
Hb1Ac						
< 7.2%/8%/8.3%/8.5%	0.89 (0.76, 1.05)	0.58	0.72 (0.50, 1.03)	0.94	0.91 (0.80, 1.05)	0.97
≥ 7.2%/8%/8.3%/8.5%	0.84 (0.72, 0.98)		0.74 (0.52, 1.04)		0.91(0.80, 1.04)	

Table 3 continued

	LEADER (n = 9340)		SUSTAIN-6 (n = 3297)		EXSCEL (n = 14,752)	
	HR (95% CI)	$P1$	HR (95% CI)	$P1$	HR (95% CI)	$P1$
Duration of DM						
≤ 10/11/15 years	0.82 (0.70, 0.97)	0.42	0.73 (0.48, 1.12)	0.99	0.85 (0.62, 1.18)	0.18
> 10/11/15 years	0.90 (0.78, 1.04)		0.73 (0.54, 0.99)		0.90 (0.79, 1.04)	
Estimated GFR						
≥ 60 ml/min/1.73 m^2	0.94 (0.83, 1.07)	0.01	0.67 (0.48, 0.92)	0.37	0.86 (0.77, 0.97)	0.12
< 60 ml/min/1.73 m^2	0.69 (0.57, 0.85)		0.84 (0.57, 1.25)		1.01 (0.86, 1.19)	
History of HF						
Yes	0.94 (0.72, 1.21)	0.53	1.03 (0.64, 1.66)	0.09	0.97 (0.81, 1.16)	0.50
No	0.85 (0.76, 0.96)		0.64 (0.48, 0.86)		0.90 (0.81, 1.00)	
CVD status						
With established CVD	0.83 (0.74, 0.93)	0.04	0.72 (0.55, 0.93)	0.49	0.90 (0.82, 1.00)	0.50
Without established CVD	1.20 (0.86, 1.67)		1.00 (0.41, 2.46)		0.99 (0.77, 1.28)	

	Harmony Outcomes (n = 9463)		REWIND (n = 9901)		PIONEER-6 (n = 3183)		HR (95% CI)	$P1$
	HR (95% CI)	$P1$	HR (95% CI)	$P1$	HR (95% CI)	$P1$		
Baseline age								
< 60/65/66 years	0.66 (0.53, 0.82)	0.037	0.92 (0.78, 1.09)	0.57	0.51 (0.29, 0.90)	0.05	0.80 (0.67, 0.97)	0.821
≥ 60/65/66 years	0.85 (0.61, 1.17)		0.86 (0.74, 1.00)		1.04 (0.68, 1.59)		0.84 (0.79, 0.91)	
Sex								
Male	0.82 (0.6, 0.97)	0.227	0.90 (0.79,1.04)	0.60	0.72 (0.50, 1.05)	0.28	0.87 (0.81, 0.93)	0.605
Female	0.67 (0.50, 0.89)		0.85 (0.71, 1.02)		1.16 (0.54, 2.51)		0.85 (0.78, 0.92)	
Baseline BMI								
< 30 kg/m^2	0.72 (0.57, 0.91)	0.435	0.91 (0.76, 1.08)	0.67	0.61 (0.36,1.03)	0.20	0.85 (0.74, 0.97)	0.295
≥ 30 kg/m^2	0.81 (0.68, 0.97)		0.86 (0.75, 1.00)		0.95 (0.61, 1.45)		0.82 (0.76, 0.89)	
Region								
Europe	0.73 (0.60, 0.88)	0.691	0.77 (0.65, 0.90)	0.0080	NA		0.82 (0.71, 0.94)	0.967
North America	0.92 (0.70, 1.19)		1.14 (0.89, 1.47)		NA		0.94 (0.84, 1.06)	
Asia	0.69 (0.28, 1.69)		0.54 (0.32, 0.89)		NA		0.72 (0.57, 0.9)	
Rest of the world	0.76 (0.50, 1.16)		0.99 (0.81, 1.21)		NA		0.87 (0.77, 0.98)	

Table 3 continued

	Harmony Outcomes (*n* = 9463)		REWIND (*n* = 9901)		PIONEER-6 (*n* = 3183)		HR (95% CI)	*P*1
	HR (95% CI)	*P*1	HR (95% CI)	*P*1	HR (95% CI)	*P*1		
Race								
White	0.76 (0.64, 0.89)	0.065	0.90 (0.79, 1.02)	0.77	0.83 (0.56, 1.23)	0.14	0.88 (0.82, 0.94)	0.148
Black	2.60 (1.14, 5.94)		0.77 (0.51, 1.17)		5.67 (0.66,48.51)		0.95 (0.65, 1.4)	
Asian	0.73 (0.36, 1.48)		0.71 (0.40, 1.24)		0.44 (0.20, 0.97)		0.71 (0.58, 0.88)	
Others	0.71 (0.51, 1.00)		0.92 (0.67, 1.28)		1.04 (0.06,16.59)		0.81 (0.67, 0.97)	
Hb1Ac								
$<$ 7.2%/8%/8.3%/8.5%	0.94 (0.73, 1.22)		0.90 (0.76, 1.06)	0.75	0.81 (0.53, 1.24)	0.77	0.89 (0.82, 0.97)	0.227
$\geq$ 7.2%/8%/8.3%/8.5%	0.71 (0.60, 0.84)		0.86 (0.74, 1.00)		0.73 (0.42, 1.26)		0.83 (0.76, 0.90)	
Duration of DM								
$\leq$ 10/11/15 years	0.67 (0.51, 0.87)		0.87 (0.75, 1.01)	0.88	NA		0.82 (0.74, 0.90)	0.301
$>$ 10/11/15 years	0.82 (0.70, 0.98)		0.90 (0.77, 1.06)		NA		0.87 (0.81, 0.94)	
Estimated GFR								
$\geq$ 60 ml/min/1.73 m^2	0.72 (0.61, 0.86)		NA		0.81 (0.54, 1.22)	0.80	0.82 (0.73, 0.93)	0.671
$<$ 60 ml/min/1.73 m^2	0.93 (0.73, 1.20)		NA		0.74 (0.41, 1.33)		0.85 (0.71, 1.02)	
History of HF								
Yes	0.70 (0.54, 0.90)	0.278	NA		NA		0.89 (0.75, 1.05)	0.553
No	0.82 (0.69, 0.98)		NA		NA		0.84 (0.76, 0.92)	

Table 3 continued

	Harmony Outcomes (n = 9463)		REWIND (n = 9901)		PIONEER-6 (n = 3183)		HR (95% CI)	$P1$
	HR (95% CI)	$P1$	HR (95% CI)	$P1$	HR (95% CI)	$P1$		
CVD status								
With established CVD	0.78 (0.68, 0.90)	–	0.87 (0.74, 1.02)	0.97	0.83 (0.58, 1.17)	0.44	0.84 (0.80, 0.89)	0.171
Without established CVD	–[a]		0.87 (0.74, 1.02)		0.51 (0.15, 1.68)		0.94 (0.82, 1.07)	

*P*1 the *P* for interaction, referring to the *P* value for subgroup differences; *F* tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung–Knapp adjustment was applied to test subgroup differences

Age < 60/65/66 years: the stratifications for age were done using the cutoff of 60 years or 65 years or 66 years in different trials. LEADER, 60 years; REWIND, 66 years; other trials, 65 years

HbA1c < 7.2%/8%/8.3%/8.5%: the stratifications for HbA1c were done using the cutoff of 7.2% or 8% or 8.3% or 8.5% in different trials. LEADER, HbA1c 8.3%; SUSTAIN-6 and PIONEER-6, HbA1c 8.5%; EXSCEL and Harmony Outcomes, HbA1c 8%; REWIND, HbA1c 7.2%

HR hazard ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *BMI* body mass index, *Hb1Ac* glycated hemoglobin, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *HF* heart failure, *CVD* cardiovascular disease

[a] The proportion of subjects with established CVD in Harmony Outcomes was 100% and none without established CVD

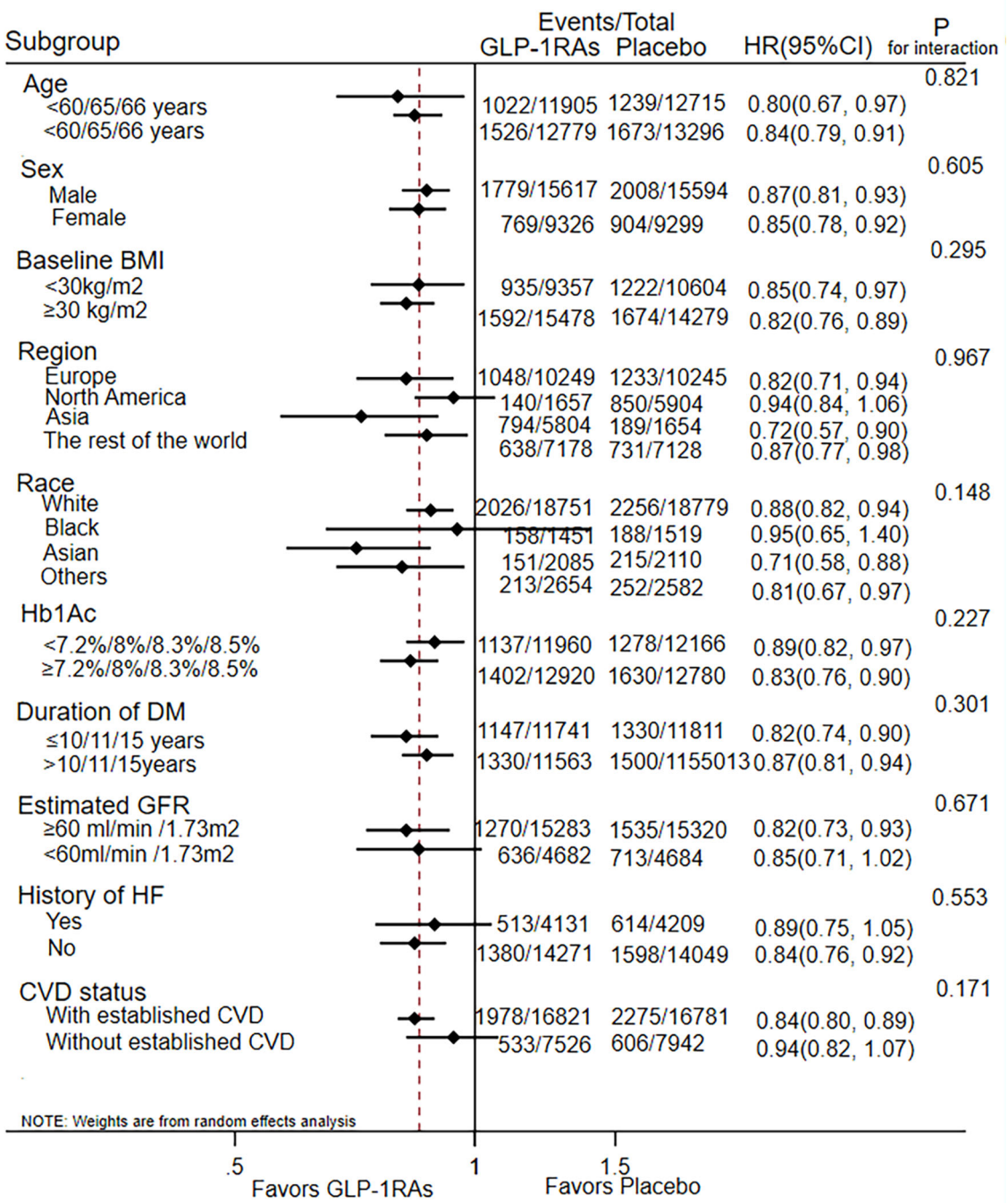


Fig. 2 Forest plot of subgroup analyses. *P* for interaction: the *P* value for differences within subgroups. Age < 60/65/66 years: the stratifications for age were done using the cutoff of 60 years or 65 years or 66 years in different trials. LEADER, 60 years; REWIND, 66 years; other trials, 65 years. HbA1c < 7.2%/8%/8.3%/8.5%: the stratifications for HbA1c were done using the cutoff of 7.2% or 8% or 8.3% or 8.5% in different trials. LEADER, HbA1c 8.3%; SUSTAIN-6 and PIONEER-6, HbA1c 8.5%; EXSCEL and Harmony Outcomes, HbA1c 8%; REWIND, HbA1c 7.2%. *HR* hazard ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *GFR* glomerular filtration rate, *HF* heart failure, *CVD* cardiovascular disease

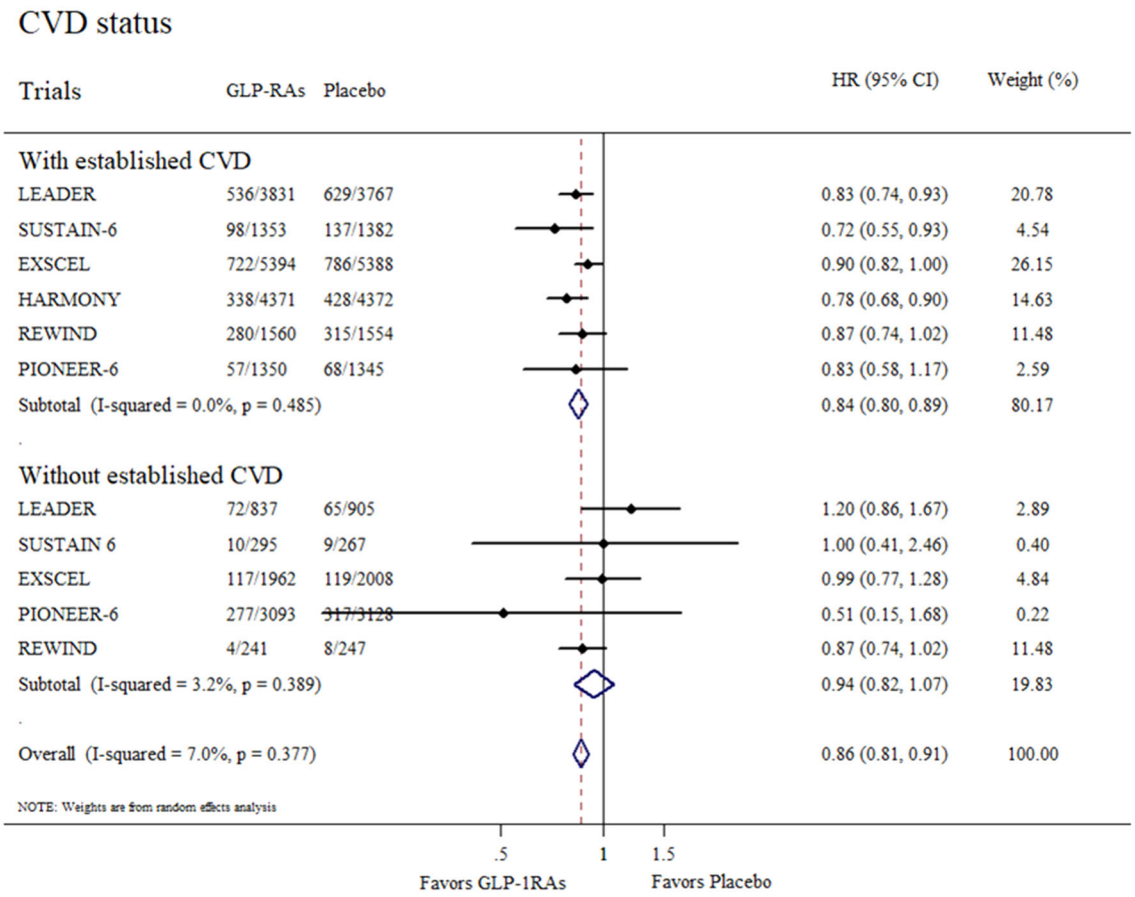


Fig. 3 Long-acting GLP-1RAs on MACE in patients with type 2 diabetes according to cardiovascular disease status. HR hazard ratio, CI confidence interval, GLP-1RAs glucagon-like peptide 1 receptor agonists, CVD cardiovascular disease, *MACE* major adverse cardiovascular events

cancer (OR 1.31; 95% CI 0.79–2.17; $P = 0.300$) with long-acting GLP-1RAs compared to placebo, with low-to-moderate heterogeneity observed between trials. Regardless of the evident increase in the risk of retinopathy in SUSTAIN-6 (semaglutide vs. placebo, 3% vs. 1.8%, $P = 0.02$), no significant increase in risk was found in the overall results of retinopathy (OR 1.09; 95% CI 0.92–1.29; $P = 0.316$). A significantly increased risk of serious gastrointestinal events (OR 1.37; 95% CI 1.02–1.83; $P = 0.037$) and AEs leading to drug discontinuation (OR 1.38; 95% CI 1.01–1.88; $P = 0.039$) were observed, both showing consistent trends (Fig. 6). As shown in Fig. 7, there were no significant differences in SAEs between long-acting GLP-1RAs and placebo (OR 0.92; 95% CI 0.85–1.00; $P = 0.039$). The individual occurrence of SAEs by systemic organ varied, with no significant increase in risk, with the exception of serious gastrointestinal events (Table S5).

DISCUSSION

This systematic review and meta-analysis explored the influential factors and subpopulation differences associated with the cardiovascular efficacy of long-acting GLP-1RAs for patients with T2DM using six recent CVOTs. Among various subpopulations separately stratified by ten factors, there were no significant differences in the cardiovascular efficacy of long-acting GLP-1RAs. There was a favorable trend in the subpopulation with established

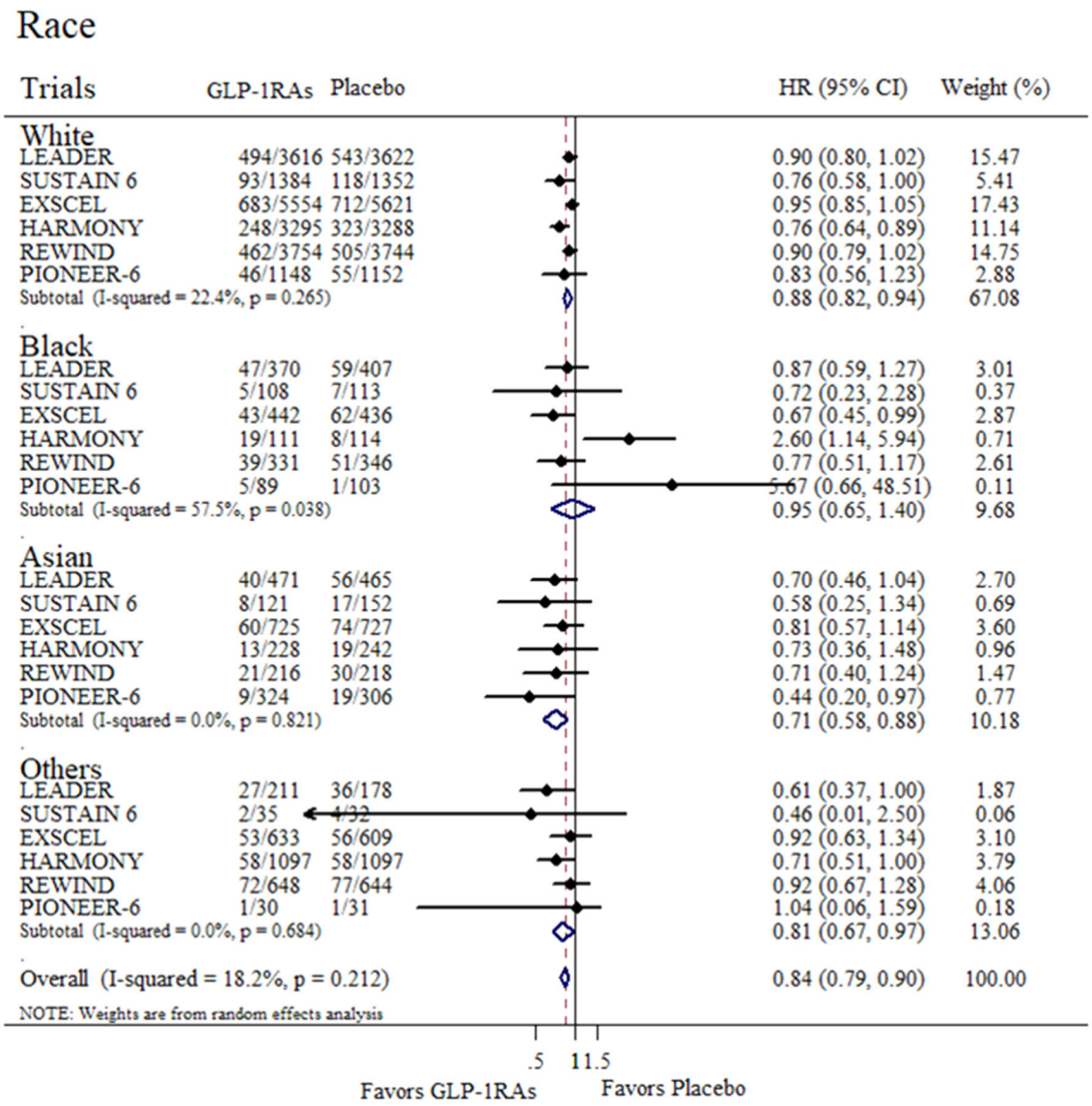


Fig. 4 Long-acting GLP-1RAs on MACE in patients with type 2 diabetes according to race. *HR* hazard ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *MACE* major adverse cardiovascular events

CVD compared to those without established CVD. In addition to remarkable cardiovascular efficacy, treatment with long-acting GLP-1RAs achieved satisfactory safety profiles.

Among the included trials, only the PIONEER trial showed comparative risk reductions in patients without established CVD [15], whereas there were favorable trends towards achieving greater cardiovascular efficacy in the subpopulation with established CVD. However, the *P* value for interaction regarding CVD status was insignificant. Similarly, there were no significant differences between subpopulations with different categories of baseline BMI. Since weight loss contributes to a reduced risk of CVD, and since GLP-1RAs can effectively promote weight loss, the subpopulation with a high baseline BMI was expected to have favorable effects over that with low baseline BMI. Previous studies regarding treatments with liraglutide reported greater effects of weight loss in subpopulations characterized by a high

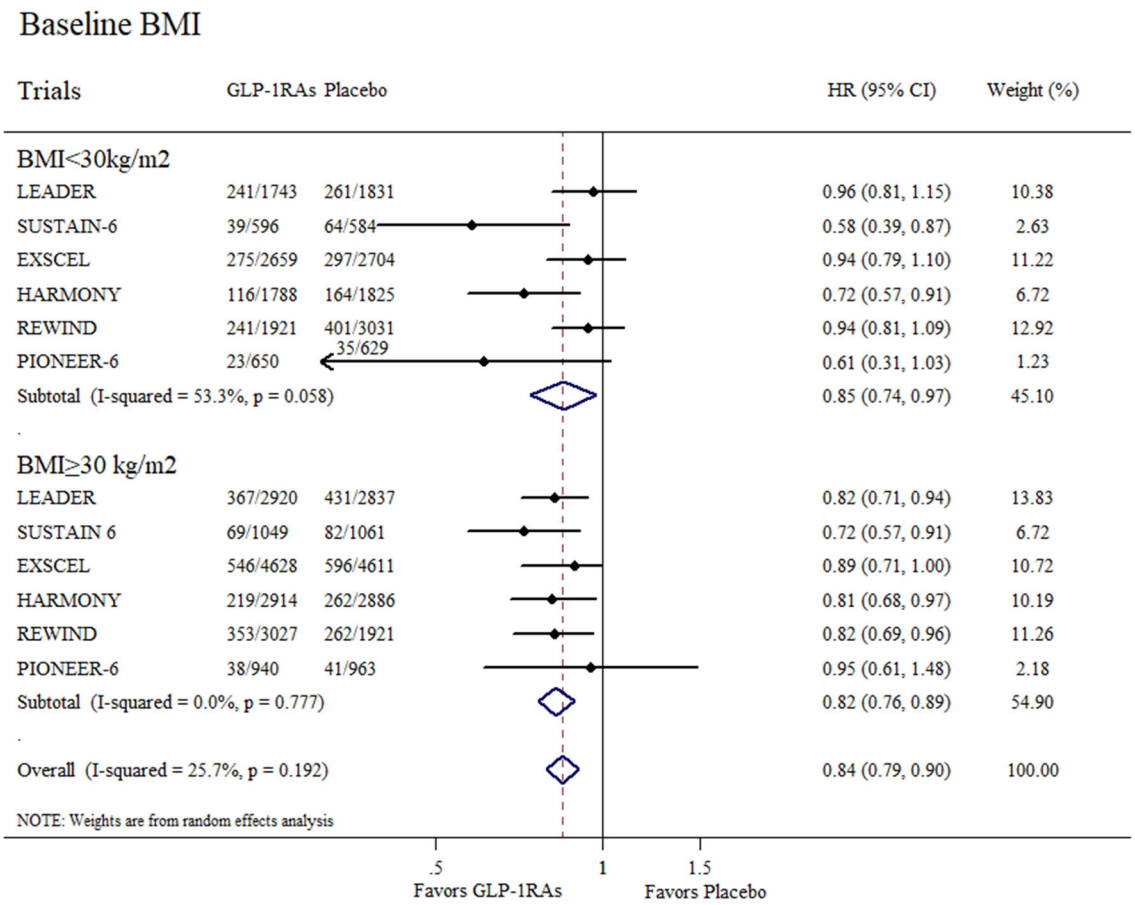


Fig. 5 Long-acting GLP-1RAs on MACE in patients with type 2 diabetes according to baseline BMI. *HR* hazard ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *BMI* body mass index, *MACE* major adverse cardiovascular events

baseline BMI [16]. Therefore, the baseline BMI could not be easily ignored, regardless of the non-significant results observed in the present study.

A previous meta-analysis with only three trials (EXSCEL, LEADER, and SUSTAIN-6) showed significantly greater cardiovascular benefits in an Asian subpopulation [17] than in subpopulations of other races. However, a non-significant *P* value for interaction was observed in our analysis with six trials, including three additional recent trials. Furthermore, the proportion of Asian participants in the overall participants (8.6%) was very small, and only a few Asian subjects were enrolled in each trial, which make the results more ambiguous.

Notably, slight risk reductions in hospitalization for HF were achieved with the use of long-acting GLP-1RAs, while some studies described divergent results [17, 18]. Despite ameliorative cardiac function in patients with T2DM and HF observed in previous nonrandomized pilot studies [19, 20], disappointing effects of GLP-1RA on HF have been reported in recent RCTs [21, 22]. In light of previous studies, GLP-1 therapy might ameliorate advanced HF [23, 24]. Conversely, liraglutide showed no greater benefit in patients with advanced HF in the FIGHT trial [22], and even increased the relative risk of HF readmission. Additionally, according to the LIVE sub-study liraglutide had no obvious effect on myocardial glucose uptake, myocardial blood flow, or myocardial blood flow reserve in patients with chronic HF without diabetes [25]. The exact relationship between long-acting GLP-1RAs and HF requires

Table 4 Selected adverse events of special interests

	LEADER		SUSTAIN 6		EXSCEL	
	Liraglutide (*n* = 4668)	(*n* = 4672)	Semaglutide (*n* = 1648)	(*n* = 1649)	Exenatide (*n* = 7356)	(*n* = 7396)
Severe hypoglycemia	114 (2.4%)	153 (3.3%)	369 (22.4%)	350 (21.2%)	247 (3.4%)	219 (3.0%)
Pancreatitis	18 (0.4%)	25 (0.5%)	9 (0.55%)	12 (0.72%)	26 (0.4%)	22 (0.3%)
Any cancer[a]	296 (6.3%)	279 (6.0%)	66 (4.0%)	70 (4.2%)	355 (4.8%)	361 (4.9%)
Thyroid neoplasms	5 (< 0.1%)	3 (< 0.1%)	1 (< 0.1%)	2 (0.1%)	NA	NA
Pancreatic cancer	13 (0.3%)	5 (0.1%)	1 (0.06%)	4 (0.24%)	15 (0.2%)	16 (0.2%)
Retinopathy	106 (2.3%)	92 (2.0%)	50 (3.0%)	29 (1.8%)	214 (2.9%)	238 (3.2%)
Serious gastrointestinal events[b]	407 (8.7%)	361 (7.7%)	75 (4.5%)	50 (3.0%)	220 (3.0%)	216 (2.9%)
AEs leading to discontinuation	444[c] (9.5%)	339[c] (7.3%)	214[d] (13.0%)	110[d] (6.7%)	108[c] (1.5%)	104[c] (1.4%)
SAE	2320 (49.7%)	2354 (50.4%)	565 (34.3%)	627 (38.0%)	1234 (16.8%)	1222 (16.6%)

	Harmony		REWIND		PIONEER-6		OR (95% CI)	*P* values for trend
	Albiglutide (*n* = 4371)	(*n* = 4372)	Dulaglutide (*n* = 4949)	(*n* = 4952)	Oral Semaglutide (*n* = 1591)	(*n* = 1592)		
Severe hypoglycemia	31 (0.71%)	55 (1.3%)	64 (1.3%)	74 (1.5%)	23 (1.4)	13 (0.8)	0.95 (0.77, 1.16)	0.597
Pancreatitis	10 (0.21%)	7 (0.15%)	23 (0.5%)	13 (0.3%)	1 (0.1)	3 (0.2)	0.92 (0.63, 1.34)	0.657
Any cancer[a]	87 (2.0%)	112 (2.6%)	351 (7.1%)	348 (7.0%)	41 (2.6%)	48 (3.0%)	0.97 (0.89, 1.05)	0.449
Thyroid neoplasms	0	0	7 (0.144%)	3 (0.06%)	NA	NA	–	–
Pancreatic cancer	6 (0.14%)	5 (0.11%)	19 (0.4%)	12 0.2%)	NA	NA	1.31 (0.79, 2.17)	0.300
Retinopathy	78 (1.6%)	89 (1.9%)	95 (1.9%)	76 (1.5%)	113 (7.1)	101 (6.3)	1.09 (0.92, 1.29)	0.316
Serious gastrointestinal events[b]	92 (1.9%)	87 (1.7%)	120 (2.4%)	117 (2.4%)	108 (6.8%)	26 (1.6%)	1.37 (1.02, 1.83)	0.037**
AEs leading to discontinuation	NA	NA	2092[e] (42.3%)	2171[e] (43.8%)	184[c] (11.6%)	104[c] (6.5%)	1.38 (1.01, 1.88)	0.046**
SAE	932 (19.8%)	1022 (21.7%)	NA	NA	301 (18.9%)	358 (22.5%)	0.92 (0.85, 1.00)	0.039**

Data are presented as *n* (%); *n*, number of patients with at least one event. Adverse events were selected on the basis of the safety areas of interest for long-acting GLP-1 receptor agonists

AEs adverse events, *SAE* serious adverse event, *OR* odds ratios, *NA* not available

P values for trend, $^{**}P \leq 0.05$; $^{***}P \leq 0.001$

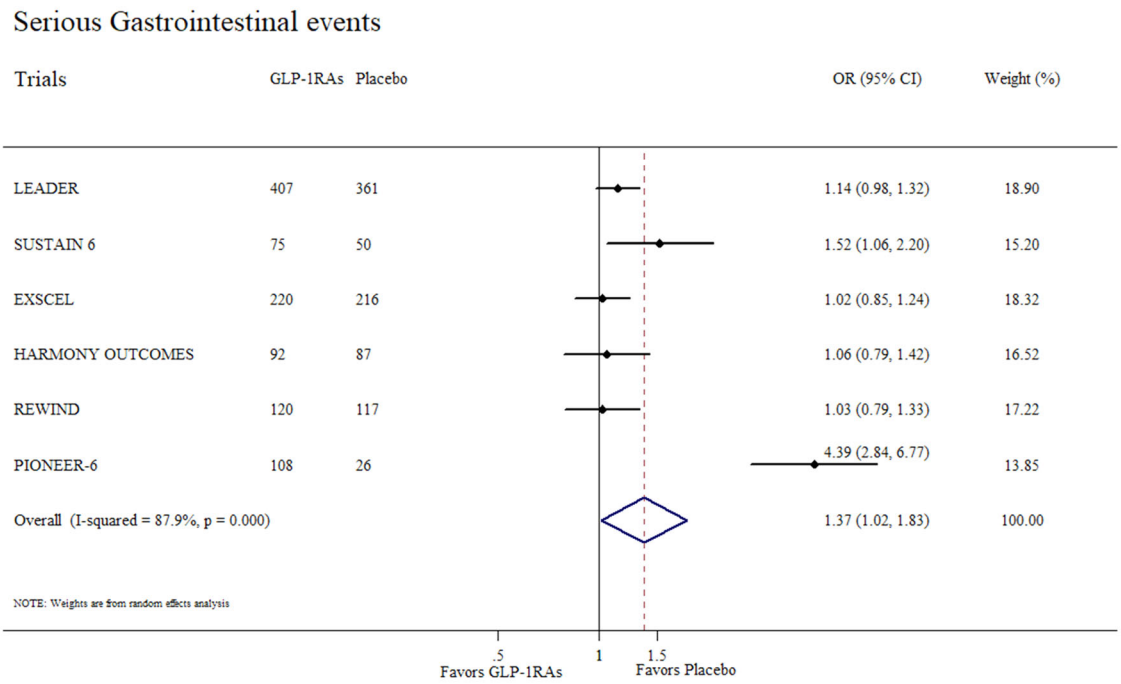
[a] All are malignant neoplasms

[b] Serious gastrointestinal events were those events meeting the definition of a serious adverse event and appearing within the gastrointestinal disorders System Organ Class (SO) of the Medical Dictionary for Regulatory Activities (MedDRA) coding

[c] AEs leading to permanent drug discontinuation

[d] Not stating definitely whether the data was from AEs leading to permanent drug discontinuation

[e] First study drug discontinuation



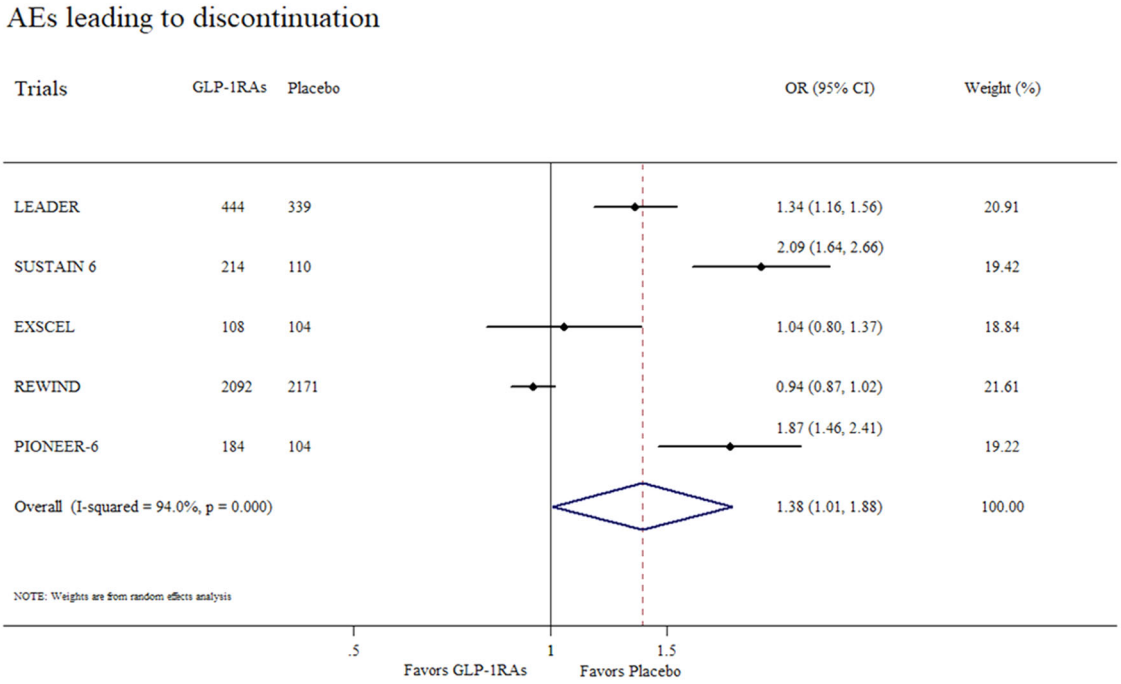


Fig. 6 Forest plot of serious gastrointestinal events and AEs leading to discontinuation. *OR* odds ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *AEs* adverse events

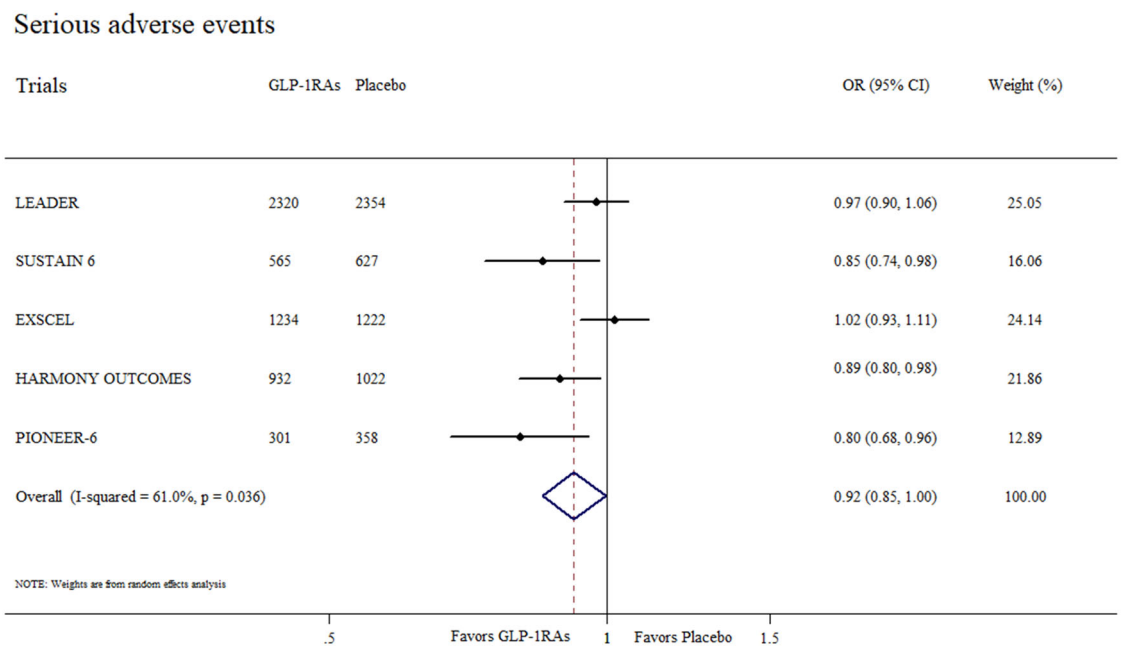


Fig. 7 Forest plot of serious adverse events. *OR* odds ratio, *CI* confidence interval, *GLP-1RAs* glucagon-like peptide 1 receptor agonists

more highly qualified trials for further exploration.

Overall, long-acting GLP-1RAs are well tolerated and are generally safe, regardless of the increased risk of serious gastrointestinal events, which are generally controllable and manageable [26]. The overall results of AEs leading to drug discontinuation were similar to serious gastrointestinal events (Fig. 6), which implied that drug discontinuation was mainly due to serious gastrointestinal events. However, it remains unknown whether semaglutide specifically increases the risk of retinopathy. A recent study reported that the elevated risk of retinopathy was largely dependent on the baseline presence of pre-existing retinopathy, and that the occurrence of retinopathy primarily resulted from the magnitude and rapidity of glycemic reduction [27]. Furthermore, several previous studies reported no association between GLP-1R agonists and diabetic retinopathy [28–30], which is in agreement with the results of the current study.

Among numerous CVOTs, only seven trials have been completed: one trial of short-acting GLP-1Ra (ELIXA) and six trials of long-acting GLP-1RAs (EXSCEL, LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER-6). Several previous meta-analyses [17, 18] have elucidated favorable cardiovascular efficacy of GLP-1RAs without the inclusion of the more recent trials, REWIND and PIONEER-6. A recent updated meta-analysis [31] of GLP-RAs that was published as a brief report simply described the overall cardiovascular efficacy, but did not comprehensively explore the safety endpoints, or the influential factors and subpopulation differences of cardiovascular efficacy. Therefore, focusing on long-acting GLP-1RAs, the present study made comprehensive explorations of influential factors and subpopulation differences in cardiovascular efficacy of long-acting GLP-1RAs, as well as further analysis of the safety profile of GLP-1RAs. Giugliano and colleagues [31] reported that GLP-1RAs reduced three-point MACE by 13%, with seven CVOTs of GLP-1RAs, the results of which supported those of the present study.

Nevertheless, there are some limitations in our study. Firstly, head-to-head trials were lacking, and each trial was conducted with different GLP-RAs. Different GLP-1RAs with varied

properties might have different degrees of cardioprotective efficacy, which would weaken the reliability of the final conclusions to some extent. Secondly, the subjects recruited in each trial were mainly of white race and from Western countries, with very few Asian subjects. Thirdly, the stratifications of various subpopulations in different trials were not completely consistent. For example, the LEADER trial divided age as < 60 years and ≥ 60 years, while other trials chose 65 years as cutoff. Lastly, the duration of the trials might be a potential limitation.

CONCLUSION

There were no significant subpopulation differences in the cardiovascular benefits of long-acting GLP-1RA treatments across various factors. These findings indicate that the administration of long-acting GLP-1RAs is unlikely to differ significantly among T2DM populations with different characteristics. Furthermore, the subpopulation with established CVD showed favorable trends over those without established CVD, which implies a possible propensity to utilize long-acting GLP-1RAs. With remarkable cardiovascular benefits for patients with T2DM, long-acting GLP-1RAs did not significantly increase the risk of retinopathy and SAEs overall. Our findings have implications in the management of long-acting GLP-1RA treatments across various subpopulations of patients with T2DM, and are of clinical importance in the safety of long-acting GLP-1RAs. Further large-scale studies that focus on the exploration of subpopulation differences with respect to the cardiovascular benefits of long-acting GLP-1RAs are required to verify our findings.

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Disclosure. Liyun He, Na Yang, Lingling Xu, Fan Ping, Wei Li, Qi Sun, Yuxiu Li, and Huabing Zhang have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author (Zhang) on reasonable request.

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