

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

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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 metaanalysis, 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, SGLT2 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

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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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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

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

	SGLT2is		GLP1-RAs		Overall [†]		
Subgroups	HR (95% CI)	<i>l</i> ² (%)	HR (95% CI)	l ² (%)	HR (95% CI)	ľ (%)	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

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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. \hat{F} , 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.

	Drug	Drug	Placebo	Placebo				%
Study	(Events)	(Patients)	(Events)	(Patients)			HR (95% CI)	Weight
SGLT2is								
EMPA-REG OUTCOM	/IE 366	3403	205	1678			0.88 (0.74, 1.04)	7.97
CANVAS Program	NA	4508	NA	3436			0.84 (0.73, 0.96)	10.49
DECLARE-TIMI 58	629	6843	675	6810	+++		0.94 (0.86, 1.03)	15.63
CREDENCE	149	1487	184	1444			0.77 (0.62, 0.95)	5.74
Subtotal (I-squared =	22.7%, p =	0.274)			\diamond		0.88 (0.81, 0.95)	39.82
GLP1-RAs								
ELIXA	NA	2258	NA	2318		•	1.09 (0.93, 1.27)	8.96
LEADER	494	3616	543	3622			0.90 (0.80, 1.02)	11.97
SUSTAIN-6	93	1384	118	1352	•		0.76 (0.58, 1.00)	3.86
EXSCEL	683	5554	712	5621			0.95 (0.85, 1.05)	13.71
Harmony Outcomes	248	3295	323	3288	•		0.76 (0.64, 0.89)	8.32
REWIND	462	3754	505	3744			0.90 (0.79, 1.02)	11.34
PIONEER6	46	1148	55	1152			0.83 (0.56, 1.23)	2.01
Subtotal (I-squared =	51.3%, p =	0.055)			\diamond		0.90 (0.83, 0.98)	60.18
					l l			
Overall (I-squared = 3	39.3%, p = 0	.087)			\diamond		0.89 (0.84, 0.95)	100.00
NOTE: Weights are fro	om random e	effects analy	sis					
P for subgroup differen	nces from me	eta-regress	ion = 0.631	l				
				C	.56 1	1.7	9	
					Favours drug	Favours placebo		

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

	Drug	Drug	Placebo	Placebo			%
Study	(Events)	(Patients)	(Events)	(Patients)		HR (95% CI)	Weight
SGLT2is							
EMPA-REG OUTCOME	39	237	14	120		1.48 (0.80, 2.72)	10.8 6
CANVAS Program	NA	176	NA	160		0.45 (0.19, 1.03)	7.27
CREDENCE	16	112	18	112		0.84 (0.42, 1.67)	9.46
Subtotal (I-squared = 61	.0%, p = 0	.077)			\diamond	0.87 (0.45, 1.67)	27.5 9
GLP1-RAs							
ELIXA	NA	118	NA	103		0.89 (0.49, 1.60)	11.26
LEADER	47	370	59	407	-	0.87 (0.59, 1.27)	16.2 3
SUSTAIN-6	5	108	7	113		0.72 (0.23, 2.28)	4.58
EXSCEL	43	442	62	436	-	0.67 (0.45, 0.99)	15.94
Harmony Outcomes	19	111	8	114		2.60 (1.14, 5.94)	7.51
REWIND	39	331	51	346	•	0.77 (0.51, 1.17)	15.38
PIONEER 6	5	89	1	103		5.67 (0.66, 48.51)	1.51
Subtotal (I-squared = 49	.1%, p = 0	.067)			\diamond	0.92 (0.67, 1.27)	72.41
Overall (I-squared = 47.1	2%, p = 0.0	948)			\Diamond	0.92 (0.70, 1.20)	100.00
NOTE: Weights are from	random eff	ects analysis	5				
P for subgroup difference	es from me	eta-regress	ion = 0.884		ıl		
				0.02	1	48.5	
				0.02	Favours drug Favours pla	acebo	

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

E Study (i	Drug	Drug	Placebo	D I I				
Study (/ -		Пасеро	Placebo				%
	(Events)	(Patients)	(Events)	(Patients)		HR (95%	o CI)	Weight
SGLT2is								
EMPA-REG OUTCOME 7	79	1006	58	511		0.68 (0.4	8, 0.95)	18.27
CANVAS Program	NA	777	NA	507		1.08 (0.7	2, 1.64)	12.57
CREDENCE 3	36	425	52	452	-	0.75 (0.4	9, 1.14)	11.94
Subtotal (I-squared = 33.4	4%, p = 0.	223)			\Diamond	0.81 (0.6	1, 1.06)	42.78
GLP1-RAs								
ELIXA N	NA	404	NA	367		0.92 (0.5	7, 1.48)	9.3 5
LEADER 4	40	471	56	465	•	0.70 (0.4	6, 1.04)	12.80
SUSTAIN-6 8	8	121	17	152		- 0.58 (0.2	5, 1.34)	3.0 2
EXSCEL 6	60	725	74	727		0.81 (0.5	7, 1.14)	17.72
Harmony Outcomes 1	13	228	19	242		0.73 (0.3	6, 1.48)	4.26
REWIND 2	21	216	30	218		- 0.71 (0.4	0, 1.24)	6.6 5
PIONEER 6 9	9	324	19	306 -		0.44 (0.2	0, 0.97)	3.42
Subtotal (I-squared = 0.0%	%, p = 0.7	91)			\Diamond	0.74 (0.6	1, 0.9 0)	57.22
Overall (I-squared = 0.0%	%, p = 0.69	8)			\diamond	0.77 (0.6	6, 0.89)	100.00
NOTE: Weights are from ra	andom eff	ects analysis	S					
P for subgroup differences	s from me	ta-regressi	on = 0.622		1 1			
				0.2	2 1	I 5		

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

	Drug	Drug	Placebo	Placebo					%
Study	(Events)	(Patients)	(Events)	(Patients	6)			HR (95% CI)	Weight
SGLT2is						1			
CANVAS Program	NA	334	NA	244			-	1.01 (0.57, 1.80)	9.37
CREDENCE	16	178	15	191			<u> </u>	1.20 (0.59, 2.43)	6.19
Subtotal (I-squared	= 0.0%, p	= 0.711)				\checkmark	>	1.08 (0.69, 1.69)	15.56
•									
GLP1-RAs									
ELIXA	NA	254	NA	246		-		0.72 (0.46, 1.13)	15.35
LEADER	27	211	36	178				0.61 (0.37, 1.00)	12.54
SUSTAIN-6	2	35	4	32	_			0.46 (0.08, 2.50)	1.05
EXSCEL	53	633	56	609				0.92 (0.63, 1.34)	21.76
Harmony Outcomes	7	92	13	100		+ :		0.56 (0.23, 1.41)	3.77
REWIND	72	648	77	644				0.92 (0.67, 1.28)	29.58
PIONEER 6	1	30	1	31	\leftarrow			1.04 (0.06, 16.59)	0.39
Subtotal (I-squared	= 0.0%, p	= 0.728)				\diamond		0.80 (0.66, 0.97)	84.44
Overall (I-squared :	= 0.0%, p =	= 0.736)				\diamond		0.84 (0.71, 1.00)	100.00
		<i></i>							
NUTE: Weights are	from rando	om effects a	nalysis sion – 0.26	20		11			
	1005 110111	ineta-regres	55011 = 0.20		1		I		
					0.06	1	16	.7	

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

Drug Drug Placebo Placebo Study (Events) (Patients) (Events) (Patients) SGLT2is EMPA-REG OUTCOME 70 847 52 418 CREDENCE 54 717 86 706 Subtotal (I-squared = 0.0%, p = 0.898) . . C ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254	% HR (95% CI) Weight 0.63 (0.44, 0.90) 13.61 0.61 (0.43, 0.85) 15.01 0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
Study (Events) (Patients) (Events) (Patients) SGLT2is EMPA-REG OUTCOME 70 847 52 418 CREDENCE 54 717 86 706 Subtotal (I-squared = 0.0%, p = 0.898) . . GLP1-RAs ELIXA NA 865 NA 903 ELIXA NA 865 19 254 SUSTAIN-6 13 256 19 254	HR (95% Cl) Weight 0.63 (0.44, 0.90) 13.61 0.61 (0.43, 0.85) 15.01 0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
SGLT2is EMPA-REG OUTCOME 70 847 52 418 CREDENCE 54 717 86 706 Subtotal (I-squared = 0.0%, p = 0.898) . . GLP1-RAs ELIXA NA 865 NA 903 ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.63 (0.44, 0.90) 13.61 0.61 (0.43, 0.85) 15.01 0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
EMPA-REG OUTCOME 70 847 52 418 CREDENCE 54 717 86 706 Subtotal (I-squared = 0.0%, p = 0.898) . . GLP1-RAS ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.63 (0.44, 0.90) 13.61 0.61 (0.43, 0.85) 15.01 0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
CREDENCE 54 717 86 706 Subtotal (I-squared = 0.0%, p = 0.898) . . GLP1-RAS . . ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.61 (0.43, 0.85) 15.01 0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
Subtotal (I-squared = 0.0%, p = 0.898) GLP1-RAS ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.62 (0.48, 0.79) 28.62 0.90 (0.70, 1.17) 26.41
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GLP1-RAS ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.90 (0.70, 1.17) 26.41
ELIXA NA 865 NA 903 LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	0.90 (0.70, 1.17) 26.41
LEADER 68 580 86 554 SUSTAIN-6 13 256 19 254 EXSCEL 47 577 49 557	
SUSTAIN-6 13 256 19 254 (0.74 (0.54, 1.02) 17.23
EXSCEL 47 577 49 557	0.67 (0.33, 1.36) 3.47
	0.93 (0.62, 1.38) 10.89
Harmony Outcomes 51 1005 65 988	0.74 (0.52, 1.07) 13.38
Subtotal (I-squared = 0.0%, p = 0.752)	0.82 (0.70, 0.96) 71.38
Overall (I-squared = 0.0%, p = 0.486)	0.76 (0.66, 0.86) 100.00
NOTE: Weights are from random effects analysis	
P for subgroup differences from meta-regression = 0.119	
0.33 1	1

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

	Drug	Drug	Placebo	Placebo			%
Study	(Events)	(Patients)	(Events)	(Patients)	HR (95% CI)	Weight
SGLT2is							
EMPA-REG OUTCOM	IE 420	3835	230	1912		0.91 (0.77, 1.07)	13.05
CREDENCE	160	1436	179	1457		0.89 (0.72, 1.11)	8.54
Subtotal (I-squared =	0.0%, p = 0.	873)			$\langle \rangle$	0.90 (0.79, 1.03)	21.59
GLP1-RAs							
ELIXA	NA	2169	NA	2131		1.06 (0.91, 1.24)	14.24
LEADER	540	4088	608	4118		0.89 (0.79, 1.00)	20.14
SUSTAIN-6	95	1392	127	1395		0.74 (0.57, 0.96)	6.24
EXSCEL	792	6777	855	6836		0.92 (0.83, 1.01)	24.43
Harmony Outcomes	267	3406	331	3402		0.80 (0.68, 0.94)	13.36
Subtotal (I-squared =	54.1%, p = 0	0.069)			$\langle \rangle$	0.89 (0.81, 0.98)	78.41
Overall (I-squared = 3	1.3%, p = 0	189)			\diamond	0.90 (0.84, 0.96)	100.00
NOTE: Weights are fro	m random e	ffects analys	is				
P for subgroup difference	es from met	a-regressior	n = 0.956		ı I		
					0.57 1	1.75	
					Favours drug Fa	avours placebo	

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

	Drug	Drug	Placebo	Placebo			%
Study	(Events)	(Patients)	(Events)	(Patients)		HR (95% CI)	Weight
SGLT2is							
EMPA-REG OUTCOM	E 114	932	63	462		0.89 (0.65, 1.21)	4.94
CANVAS Program	NA	1425	NA	1005		0.84 (0.65, 1.09)	7.14
DECLARE-TIMI 58	265	2737	282	2731		0.95 (0.83, 1.09)	25.70
CREDENCE	71	574	74	608		1.00 (0.72, 1.39)	4.41
Subtotal (I-squared =	0.0%, p = 0	.813)			\diamond	0.93 (0.83, 1.03)	42.19
GLP1-RAs							
ELIXA	NA	404	NA	403		0.95 (0.68, 1.33)	4.24
LEADER	212	1401	216	1446		1.01 (0.84, 1.22)	13.70
SUSTAIN-6	40	570	45	567		0.87 (0.57, 1.34)	2.61
EXSCEL	303	1834	354	1874		0.84 (0.72, 0.97)	21.48
Harmony Outcomes	107	967	118	978		0.92 (0.70, 1.19)	6.78
REWIND	132	1032	117	1039	÷. • •	1.14 (0.89, 1.47)	7.58
PIONEER 6	19	556	28	550		0.66 (0.37, 1.18)	1.42
Subtotal (I-squared =	8.1%, p = 0	.367)			\diamond	0.93 (0.84, 1.03)	57.81
Overall (I-squared = 0	.0%, p = 0.6	679)			\diamond	0.93 (0.87, 0.99)	100.00
NOTE: Weights are fro	m random e	ffects analys	sis				
P for subgroup differen	ces from m	eta-regress	ion = 0.97 [.]	1	11		

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

Study	Drug (Events)	Drug (Patients)	Placebo (Events)	Placebo (Patients)			HR (95% CI)	% Weight
SGLT2is						1			
EMPA-REG OUTCOME	53	721	43	360	_			0.58 (0.39, 0.86)	7.18
CANVAS Program	NA	537	NA	484				0.84 (0.53, 1.33)	5.47
DECLARE-TIMI 58	43	946	47	931				0.92 (0.62, 1.35)	7.38
CREDENCE	36	476	60	465				0.58 (0.38, 0.87)	6.61
Subtotal (I-squared = 27	.5%, p = 0.2	247)				$\langle \rangle$		0.71 (0.56, 0.91)	26.65
						-			
GLP1–RAs									
ELIXA	NA	972	NA	972			_	0.87 (0.68, 1.11)	15.72
LEADER	165	1268	189	1218				0.83 (0.68, 1.03)	19.87
EXSCEL	76	1364	81	1363				0.92 (0.67, 1.26)	10.55
Harmony Outcomes	39	858	49	845			_	0.76 (0.50, 1.16)	6.43
REWIND	191	1511	190	1510			<u> </u>	0.99 (0.81, 1.21)	20.79
Subtotal (I-squared = 0.0	0%, p = 0.7 ⁻	12)				\diamond		0.89 (0.80, 1.00)	73.35
						\sim			
Overall (I-squared = 18.6	6%, p = 0.2	77)				\diamondsuit		0.84 (0.75, 0.94)	100.00
NOTE: Weights are from	random effe	ects analysis							
P for subgroup difference	es from me	ta-regressio	on = 0.101			1 I			
		<u> </u>			0.38		°	l 63	
					0.00	Favours drug	Favours placebo		

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

	Drug	Drug	Placebo	Placebo			%
Study	(Events)	(Patients)	(Events)	(Patients)		HR (95% CI)	Weight
SGLT2is							
EMPA-REG OUTCOME	226	1926	112	959		1.02 (0.81, 1.28)	9.56
CANVAS Program	NA	2043	NA	1566		0.80 (0.65, 0.99)	10.25
DECLARE-TIMI 58	372	3806	395	3823	<u>+</u>	0.95 (0.85, 1.06)	14.41
CREDENCE	47	454	49	410		0.83 (0.56, 1.24)	5.0 7
Subtotal (I-squared = 1.3	3%, p = 0.3	385)			\diamond	0.93 (0.85, 1.01)	39.29
GLP1-RAs							
ELIXA	NA	1130	NA	1188		1.27 (1.02, 1.58)	9.93
LEADER	207	1639	252	1657		0.82 (0.68, 0.98)	11.36
SUSTAIN-6	18	326	27	306 —		0.62 (0.34, 1.13)	2.67
EXSCEL	391	3389	390	3399	÷.	1.00 (0.87, 1.15)	13.20
Harmony Outcomes	184	2721	249	2718		0.73 (0.61, 0.88)	11.34
REWIND	248	2174	315	2165		0.77 (0.65, 0.90)	12.21
Subtotal (I-squared = 77	.8%, p = 0	.000)			\diamond	0.87 (0.74, 1.04)	60.71
Overall (I-squared = 65.0	6%, p = 0.0	002)			\Diamond	0.89 (0.80, 0.99)	100.00
NOTE: Weights are from	random of	foote analysi					
P for subgroup difference	s from me	eta-rearessi	on = 0.794		i 1		
		0	-	1			

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

	Drug	Drug	Placebo	Placebo			%
Study	(Events)	(Patients)	(Events)	(Patients)		HR (95% CI)	Weight
SGLT2is							
EMPA-REG OUTCOME	71	897	50	450		0.70 (0.49, 1.01)	10.81
CANVAS Program	NA	1790	NA	1292		0.94 (0.75, 1.18)	24.57
DECLARE-TIMI 58	76	1093	79	1093	<u>+</u>	0.99 (0.76, 1.29)	18.92
CREDENCE	63	698	86	716		0.75 (0.55, 1.05)	13.27
Subtotal (I-squared = 15	.7%, p = 0.	313)			\diamond	0.87 (0.74, 1.01)	67.58
GLP1-RAs							
ELIXA	NA	374	NA	329		0.99 (0.60, 1.61)	6.02
LEADER	24	360	37	351		0.62 (0.37, 1.04)	5.52
EXSCEL	69	769	80	760		0.85 (0.62, 1.18)	13.38
Harmony Outcomes	8	185	12	191		0.69 (0.28, 1.69)	1.87
REWIND	23	232	41	238	•	0.54 (0.32, 0.89)	5.6 3
Subtotal (I-squared = 0.0	0%, p = 0.4	17)			\diamond	0.76 (0.62, 0.94)	32.42
Overall (I-squared = 7.99	%, p = 0.37	0)			\diamond	0.83 (0.73, 0.94)	100.00
NOTE: Weights are from	random eff	ects analysis					
o for subgroup difference	es from me	eta-regressio	on = 0.333				
					0.28 1	і 3.57	
					Favours drug Favours pla	acebo	

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 metaanalysis 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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