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Comparative efficacy of GLP-1 RAs/SGLT-2 inhibitors in reducing cardiovascular events in type 2 diabetes according to baseline use of metformin: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Sodium–glucose transporters 2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are recommended along with metformin for the potential cardiovascular benefits among type 2 diabetes. This meta-analysis aims to evaluate whether the effects of SGLT-2i or GLP-1 RAs on cardiovascular outcomes are consistent with and without baseline metformin use.

Methods PubMed, Cochrane, Web of Science and Embase were searched for randomized placebo-controlled trials with SGLT-2i or GLP-1 RAs as interventions of type 2 diabetes patients up to June, 2024. The main outcomes were major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF) or cardiovascular death. Both random-effects model and fixed model were adopted to estimate pooled hazard ratios (HR) and 95% confidence intervals (95% CI).

Results A total of 81,738 patients (median age: 62–66 years, 53.7–71.5% men, median follow-up: 1.3–5.4 years) from 11 studies (7 studies of SGLT-2i and 4 of GLP-1 RAs) were included in the study. The metformin-naive portions ranged from 28.90% to 81.98%. Among patients using metformin at baseline, SGLT-2i or GLP-1 RAs reduced MACE risk (HR = 0.95, 95% CI 0.91–0.99, $P = 0.02$). In metformin-naive patients, similar reductions were observed (HR = 0.79, 95% CI 0.65–0.95, $P = 0.01$). No statistically significant interaction was found between metformin users and non-users for any outcome (all P values for interaction > 0.05), indicating consistent cardiovascular benefits regardless of baseline metformin therapy.

Conclusions SGLT-2i and GLP-1 RAs have the effects of cardiovascular benefits for T2DM patients regardless of baseline metformin use.

Keywords SGLT-2i, GLP-1 Ras, Cardiovascular disease, Type 2 diabetes, Meta-analysis

†Yuxin Zhang and Zhaoji Li have equally contributed to this work.

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Introduction

Diabetes mellitus (DM) is an increasingly serious burden of global public health. It was assessed that there were 537 million adults (20–79 years) living with diabetes (1 in 10) in 2021, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045 [1]. China has one of the highest numbers of diabetes patients in the world, with over 11% of Chinese adults affected by the disease [2]. Type 2 diabetes (T2DM) is the most common form of diabetes in China, and it is often accompanied by cardiovascular disease, which is the leading cause of death and illness among diabetic patients. Compared to adults without diabetes, those with diabetes have a much higher risk of developing cardiovascular disease, with the risk increasing as blood sugar levels rise [3]. Research by Haffner et al. [4] has shown that the mortality rate due to cardiovascular reasons in T2DM patients is significantly higher than in patients without T2DM. Therefore, it is crucial to control the cardiovascular risk of diabetic patients in the treatment process.

Sodium-dependent glucose transporters 2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are two promising options for the management of type 2 diabetes. SGLT-2i works by reducing the reabsorption of glucose by the kidneys, leading to increased glucose excretion in the urine [5]. On the other hand, GLP-1 RAs not only lower blood sugar levels but also have additional benefits such as weight loss, improved lipid profiles, and reduced blood pressure [6]. These drugs have been shown to significantly reduce cardiovascular risk and improve the prognosis of type 2 diabetes patients, making them attractive options for healthcare professionals to consider.

Metformin is recommended by European Society of Cardiology (ESC), American Diabetes Association (ADA) and Chinese guidelines as the first-line drug while the basic drug in combination therapy [3, 7, 8]. In both European and American guidelines, metformin was no longer recommended as a baseline drug for patients with high cardiovascular risk due to the proven cardiovascular benefits of SGLT-2i and GLP-1 RAs [7, 8]. However, in the latest guideline of American Diabetes Association (ADA 2023), the effect on major cardiovascular episodes (MACE) of metformin remains potential [9]. Furthermore, a new report published in 2023 provided new specific data about Cardio Vascular Outcomes Trials (CVOTs) in patients with or without baseline metformin use from DAPA–CKD (Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease) [10, 11]. In light of this, we did this study to comprehensively evaluate the effects of SGLT-2i or GLP-1 RAs on T2DM patients with or without baseline metformin use in CVOTs.

Methods

Study retrieval and selection

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, our search was conducted on four major databases—PubMed, Cochrane, Web of Science, and Embase—for randomized controlled trials that evaluated the effects of SGLT-2i or GLP-1 RAs on T2DM patients up to June 20th, 2024. We used a combination of keywords, including "SGLT-2 inhibitors", "GLP-1 Ras", "GLP-1 receptor agonist", "GLP1 receptor agonist", "diabetes", "mellitus", "diabetes mellitus", "DM" alone or combined with "randomized controlled trial", "randomized controlled trials as topic", "randomized controlled trials", "randomised controlled trials", "RCT", and "RCTs"to identify relevant studies. In addition, we included various brand names for SGLT-2i and GLP-1 RAs such as "dapagliflozin", "empagliflozin", "canagliflozin", "ertugliflozin", "forxiga", "jardiance", "invokana", "steglatro", "albiglutide", "liraglutide", "exenatide", "dulaglutide", "exendin", "benaglutide", "loxenatide", "lixisenatide"and"semaglutide"in our search to ensure that we did not miss any potentially relevant studies. The detailed search strategies are provided in supplement. This study also adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews and Meta-Analyses to ensure the rigor and reliability of the methodology and results.

Criteria for inclusion and exclusion

This study incorporated only those investigations that fulfilled specific inclusion criteria: publications in the English language, studies involving subjects diagnosed with type 2 diabetes mellitus (T2D), randomized controlled trials (RCTs), interventions that compared the efficacy of SGLT-2 inhibitors or GLP-1 receptor agonists against placebo, and reports on major adverse cardiovascular events (MACE) or hospitalization for heart failure (HHF), as well as cardiovascular outcomes irrespective of baseline metformin usage. Exclusion criteria encompassed animal studies, non-English publications, reviews, corrections, case reports, and correspondence to the editor. Furthermore, trials that did not include T2D subjects, lacked a placebo control, were not designed as randomized controlled trials, did not assess SGLT-2 inhibitors or GLP-1 receptor agonists, or employed combinative antidiabetic therapies were also omitted from this analysis.The primary endpoint for this study was major cardiovascular episodes (MACE), which was defined as cardiovascular death, myocardial infarction or stroke. The secondary endpoint was hospitalization for heart failure. All articles retrieved were independently screened by two researchers (Zhaoji Li and Yuxin

Zhang), and any disagreements were arbitrated by a third researcher (Yongchen Hao).

Data extraction

All the data obtained were independently extracted by two researchers, mainly from the primary trial results, subsequent accompanying publications and accompanying supplementary materials. These data insisted of characteristics of subjects (especially the number or proportion of baseline metformin users), interventions, and the number of endpoints, hazard ratios (HRs) and confidence intervals (CI) for primary and secondary endpoints in both primary trial results and their subgroup results that reported cardiovascular outcomes with or without baseline metformin use.

Study quality assessment

The Cochrane Collaboration Risk-of-Bias tool (RoB 2) and GRADE pro were used to assess the quality of eligible RCTs. The risk of bias was graded as low, unclear or high via a systematic assessment on five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The assessment was conducted independently by two researchers, and any discrepancies were resolved through discussion and consensus. The quality assessment was reported in the final manuscript to ensure transparency and rigor in the analysis.

Statistical analysis

The statistical analysis was conducted using RevMan5.4 software (Cochrane Cooperation Center, 2014). The Q statistics were used to evaluate the statistical heterogeneity between the trials, and a P value of less than 0.1 or an I^2 value greater than 50% was considered to indicate significant heterogeneity between the studies. If significant heterogeneity was found, the random effects model was used to analyze the data, while the fixed model was used if there was no significant heterogeneity. The level of statistical significance was set at $P<0.05$, and all P values were two-sided. In addition, CIs were set at 95% for all analyses. Meta-regression analysis was employed to explore the potential influence of subgroups, such as metformin use, on the overall effect size.

Results

In this study, we conducted a thorough search across four databases and identified a total of 8310 articles. After a rigorous screening process, we selected 11 randomized controlled trials to include in our meta-analysis (Fig. 1). The total sample size included 81,738 patients, who were followed up for a median period ranging from 1.3 to 5.4 years.

Among the selected trials, seven studies used SGLT-2i in the experimental group for treatment, while four studies used GLP-1 RAs. All control groups in the studies were treated with placebo. The proportion of participants receiving metformin treatment varied among the different trials, with metformin-naive portions ranged from 28.90% in DAPA–CKD to 81.98% in DECLARE–TIMI 58. It is worth noting that the CREDENCE trial had a higher proportion of participants with impaired renal function, and the percentage of participants receiving metformin treatment at baseline was lower compared to other trials that enrolled patients with type 2 diabetes. For more detailed information on the basic characteristics of each article, please refer to Table 1.

Seven research reports have been analyzed to determine the impact of SGLT-2i or GLP-1 RAs on MACE events in patients with type 2 diabetes (Fig. 2). The analysis showed a high degree of heterogeneity among the results, and a random effects model was used to analyze the data. The use of SGLT-2i or GLP-1 RAs significantly reduced the risk of MACE (HR 0.88, 95% CI 0.81–0.95), HHF (HR 0.76, 95% CI 0.68–0.84), HHF or CV death (HR 0.79, 95%CI 0.69–0.89), CV death (HR 0.80, 95%CI 0.68–0.94) and stroke (HR 0.80, 95%CI 0.60–1.08) compared to placebo. Further analysis revealed that this reduction in risk was consistent regardless of whether patients were using metformin as a baseline or not. Among patients using metformin at baseline, SGLT-2i or GLP-1 RAs reduced MACE risk (HR 0.95, 95% CI 0.91–0.99, $P=0.02$). In metformin-naive patients, similar reductions were observed (HR = 0.79, 95% CI 0.65–0.95, $P=0.01$). No statistically significant interaction ($P=0.066$) was found between metformin users and non-users for MACE. The result of statistically significant indicates that the study had sufficient power (95.42%) to detect a minimum effect size difference of 0.28 between metformin users and non-users, suggesting that the analysis was well-powered to identify statistically significant differences if they exist. The heterogeneity was high ($I^2=73\%$, $P=0.02$).

Four studies have reported on cardiovascular mortality or heart failure hospitalization, and the results show high heterogeneity between the studies with $P=0.0002$ and $I^2=68\%$, analyzed using a random-effects model. However, a subgroup analysis based on the baseline use of metformin indicates that the use of SGLT-2i or GLP-1 RAs can reduce the risk of cardiovascular mortality or heart failure hospitalization in patients, regardless of whether they are using metformin at baseline. There is no statistical difference between the two, as shown in Fig. 3. These results are consistent with the overall analysis

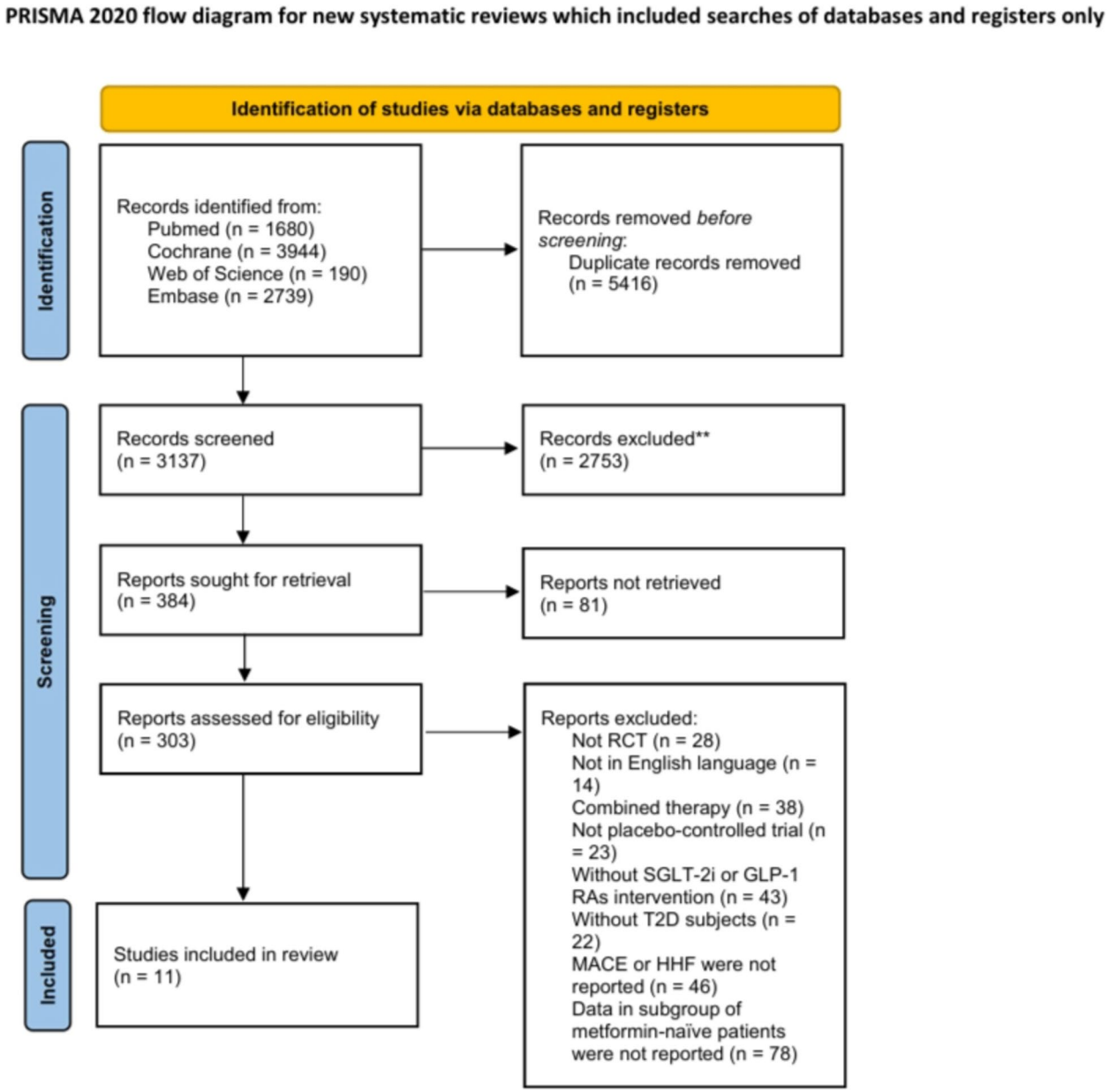

Fig. 1 Document screening process and results base

results, indicating that the use of SGLT-2i or GLP-1 RAs can significantly reduce the risk of cardiovascular mortality or heart failure hospitalization, regardless of whether metformin is used at baseline. The overall analysis results are supported by the subgroup analysis results, as shown in Fig. 3. The results of interaction effect shows that there was no interaction effect between metformin users and non-metformin users ($P=0.560$). The heterogeneity was high ($I^2=68\%$, $P=0.003$).

Furthermore, our analysis also looked at the incidence rates of adverse events such as cardiovascular death, stroke, and heart failure readmission. The findings of both the overall and subgroup analysis show that there is a significant reduction in the incidence of stroke and heart failure hospitalization, regardless of whether metformin is being used or if SGLT-2i or GLP-1 RAs are being used. Please see Figs. 4–6 for more information. Figure 4 shows the results of cardiovascular death. Figure 5 shows the results of stroke. Figure 6 shows the results of heart failure readmission.

Table 1 Characteristics of included studies

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Empa-Reg outcome	2015	Europe North America(plus America and New Zealand) Asia Latin America Africa	Empagli-flozin	≥18 years T2DM CV death	4687	2333	7020	3.1	–	3336 (0.71)	1680 (0.72)	2596 (<65 years) 2091 (>65 years)	1297 (<65 years) 1036 (>65 years)	5193	1827	Primary outcome: MACE Secondary outcome: a composite of the primary outcome plus hospitalization for unstable angina	These conclusions cannot be extrapolated to patient populations with other clinical characteristics
Canvas	2017	North America Central/South America Europe Rest of world	Canagli-flozin	T2DM ≥30 years with a history of symptomatic ASCVD or ≥50 years with two or more of risk factors for CV death	5795	4347	10,142	2.4	13.5	3759 (64.9)	2750 (63.3)	63.2±8.3	63.4±8.2	7825	2317	Primary outcome: MACE Secondary outcomes: death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes and hospitalization for heart failure	The number of events for many important outcomes is not enough, such as end-stage kidney disease. The relatively small proportion of participants with established

Table 1 (continued)

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Declare-Timi 58	2018	North America Europe Latin America Asia–Pacific	Dapagli-flozin	T2DM ≥ 40 years CV death or had multiple risk factors for CVD	8582	8578	17,160	4.2	11.0	5411 (0.63)	5327 (0.62)	63.9 ± 6.8	64.0 ± 6.8	14,068	3092	Primary outcomes: MACE or hospitalization for heart failure Secondary outcomes: renal composite and death from any cause	This trial included a broad population of pa tients with and those without atherosclerotic cardiovascular disease. It is possible that some patients may have had undiagnosed atheroscle rotic cardiovascular disease or heart failure. Given the adherence requirement in the placebo run-in period, patients who found it difficult to adhere to the regimen may have withdrawn from the trial before randomization

Table 1 (continued)

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Credence	2019	–	Canagli-flozin	≥ 30 years type 2 diabetes, diabetic kidney disease	2202	2119	4401	2.6	15.8 ± 8.6	1440 (0.65)	1467 (0.67)	62.9 ± 9.2	63.2 ± 9.2	2543	1858	Primary outcome: a composite of end-stage kidney disease, or death from renal or cardiovascular causes Secondary outcomes: tested hierarchically	Low numbers of events among participants with prior history of HF and considered hypothesis-generating Classification of history of HF was not verified by study investigators, and EF information, echocardiography data, or baseline HF biomarker data were not collected
Dapa-HF	2019	North America South America Europe Asia–Pacific	Dapagli-flozin	≥ 18 years, Heart failure with reduced ejection fraction	2373	2371	4774	1.5	–	1809	1826	66.2	66.5	1020	1119	Primary outcome: hospitalization or an urgent visit resulting in intravenous therapy for heart failure or cardiovascular death	This trial has some limitations. We used spe cific inclusion and exclusion criteria, which may have limited the generalizability of our findings

Table 1 (continued)

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Dapa-CKD	2020	Europe Asia/Pacific North America South America	Dapagliflozin	Adults T2DM	2152	2152	4304	2.4	–	1443 (0.67)	1436 (0.67)	61.8 ± 12.1	61.9 ± 12.1	1244	3060	Primary outcome: a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes	The trial was stopped on the basis of a recommendation from the independent data monitoring committee Estimated GFR values after the completion of the trial was not collected
Vertis-CV	2020	Europe North America South America Asia South Africa Australia New Zealand	Ertugliflozin	≥ 40 years T2DM CVD risk	5499	2747	8246	3.0	13.0	3866 (70.3)	1903 (69.3)	64.4 ± 8.1	64.4 ± 8.0	6292	1954	Primary outcome: MACE: Secondary outcomes: HHF; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level	There is not a clear explanation about why the results did not reach significance
Rewind	2019	–	Dulaglutide	≥ 50 years T2DM and high CV risk	4949	4952	9901	5.4	9.5	2643(0.53)	2669(0.54)	66.2 ± 6.5	66.2 ± 6.5	8037	1846	Primary outcome: MACE Secondary outcomes: a composite clinical microvascular outcome comprising diabetic retinopathy or renal disease	More than 25% of participants were not taking study drug at the time of their last visit

Table 1 (continued)

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Pioneer 6	2019	America Asia Hawaii and other Pacific Latin	Semaglutide	≥50 years with CVD or CKD ≥60 years with at least one cardiovascular risk factor	1591	1592	3183	1.3	14.9±8.5	1591(0.68)	1592(0.69)	66±7	66±7	2463	719	Primary outcome: MACE Secondary outcomes: an expanded composite outcome consisting of the primary outcome; and the individual components of these composite outcomes	More patients received treatment with an SGLT2 inhibitor after randomization in the placebo group than in the oral semaglutide group
Sustain 6	2016	–	Semaglutide	≥50 years with CVD or CKD or CHF ≥60 years with at least one cardiovascular risk factor	1648	1649	3297	2.1	13.9±8.1	1648(0.62)	1649(0.60)	64.7±7.2	64.6±7.5	–	–	Primary outcome: MACE Secondary outcomes: the first occurrence of an expanded composite cardiovascular outcome, an additional composite outcome the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy	Patients were followed for a relatively short duration (2.1 years) and were at high cardiovascular risk. The generalizability of these findings to other populations and a longer duration of treatment is unknown. It is also unknown to what extent the greater glycated hemoglobin reductions in the semaglutide group contributed to the results

Table 1 (continued)

	Publish Year	Area	SGLT-2 inhibitor/ GLP-1RA	Patients included	Number of patients			Median year of follow-up	duration of DM	Male		Age		Metformin use at baseline		Study outcomes	Study limitations
					T	C	ALL			T	C	T	C	Y	N		
Leader	2020	Europe North America Asia Rest of the world	Liraglutide	T2DM ≥ 50 years with at least one cardiovascular coexisting condition ≥ 60 years with at least one cardiovascular risk factor	4668	4672	9340	3.8	12.8	3011(0.65)	2992(0.64)	64.2 ± 7.2	64.4 ± 7.2	7144	2196	Primary outcome: MACE	Patients were followed for only 3.5–5.0 years, so the safety and efficacy data are restricted to that time period

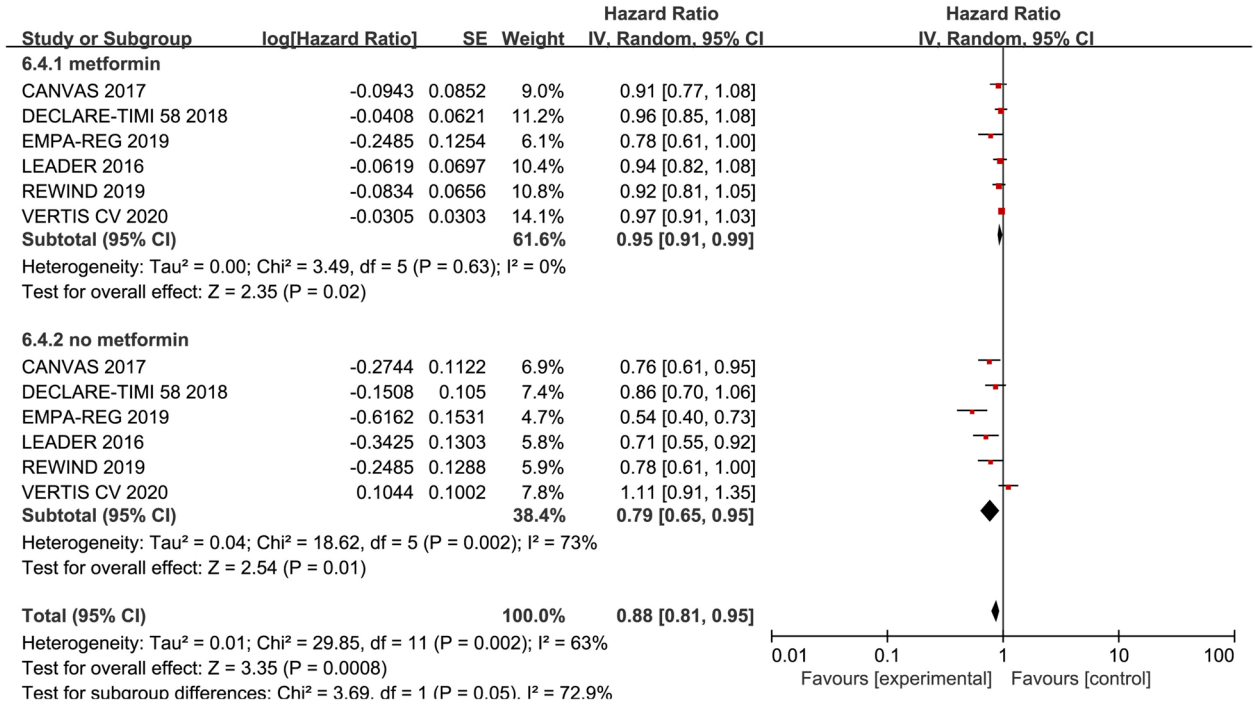

Fig. 2 Forest plots examining the MACE of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 in patients with type 2 diabetes with or without metformin in baseline. CI: confidence interval.MACE, major adverse cardiovascular events. MACE were defined as non-fatal myocardial infarction, nonfatal stroke or cardiovascular death

Subgroup analysis

Subgroup analysis was also conducted based on the incidence of cardiovascular disease. The findings showed that there was little statistical heterogeneity among the studies ($P=0.81$, $I^2=0\%$), and a random-effects model was selected for the meta-analysis. The results indicated that there was no statistically significant difference between follow-up durations greater than 3 years and those less than 3 years (HR = 0.89, 95 CI 0.85–0.93, $P=0.51$). Subgroup analysis was also performed for the five outcomes: MACE events, CV death, stroke, HHF, and a composite of HHF or CV death, based on the presence of baseline ASCVD or HF. The results showed no statistically significant differences between the subgroups for any of the outcomes (all P values > 0.05). These findings suggest that the presence of ASCVD or HF at baseline did not significantly influence the effect on these outcomes. The corresponding results can be found in the attached figures. Please refer to supplement Figure S1 for more information.

In addition, a funnel plot of standard error by log HR of MACE and cardiovascular disease death was created, and it did not suggest publication bias Please refer to supplement Figures S2 and S3 for more information.

Meta-regression

The meta-regression results indicated that the coefficient of MACE for metformin use was estimated as at 0.1436 (95%CI − 0.0095, 0.2967), suggesting a potential positive effect of metformin on the outcome, but did not reach statistical significance ($P=0.0661$). However, baseline ASCVD or HF showed a statistically significant impact on MACE ($P=0.0195$, $I^2=0.00\%$, $R^2=100\%$), indicating that these comorbidities fully accounted for the variability in MACE events, while metformin use had a modest effect.

The interaction effects between metformin users and non-users showed no significant differences ($P>0.05$). The P values for cardiovascular death, stroke, and heart failure were 0.740, 0.052, and 0.715, respectively. Heterogeneity was high, but the statistical power analysis for the stroke subgroup showed sufficient power (97.72%) to detect significant differences, with a minimum effect size of 0.714. However, the power for CV death and HHF subgroups was limited (29.34% and 79.22%, respectively), suggesting smaller effect sizes may not have been detected. For stroke, HHF, CV death, and the composite outcome of HHF or CV death, baseline

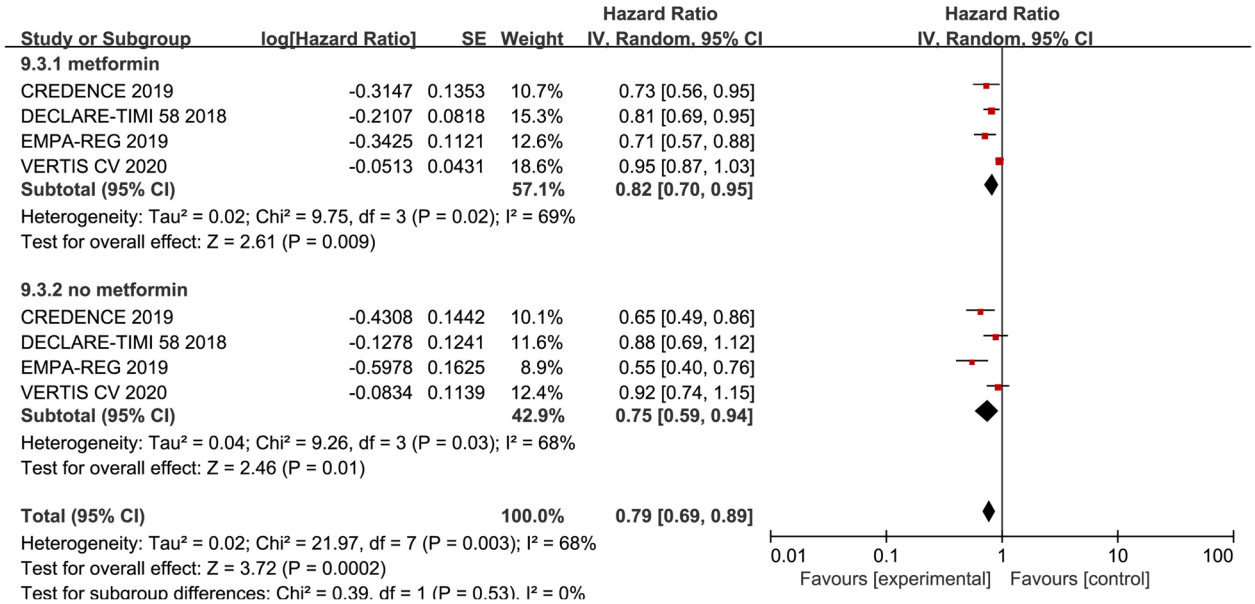

Fig. 3 Forest plots examining the HHF or CV death of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 in patients with type 2 diabetes with or without metformin in baseline. CI: confidence interval

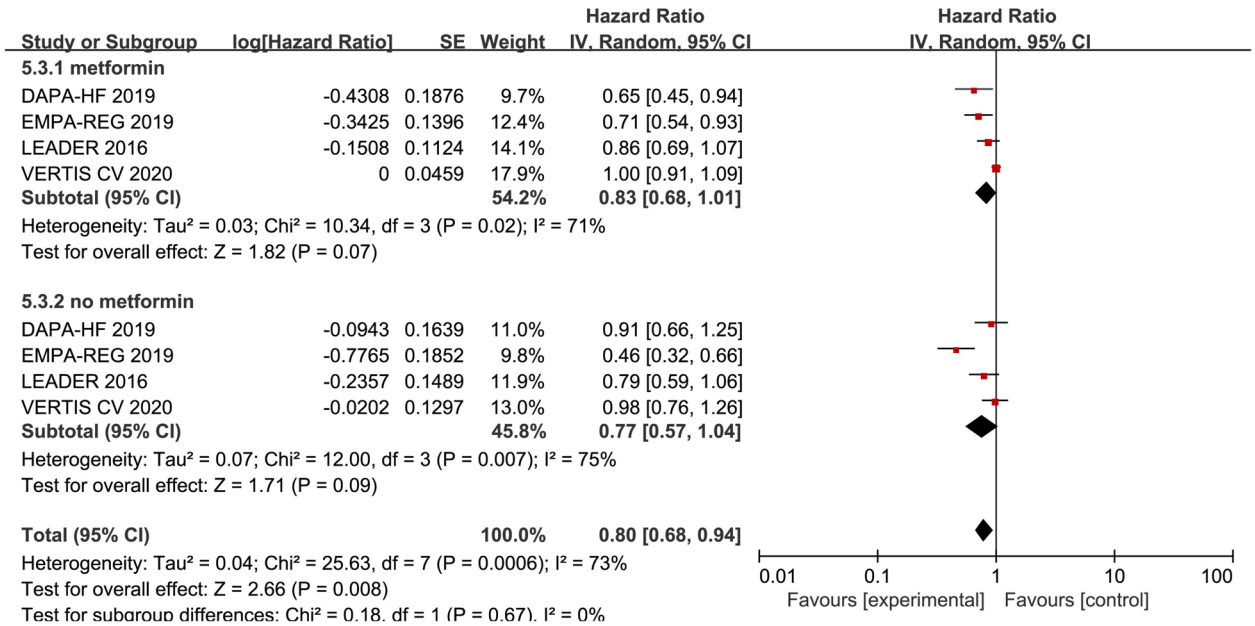

Fig. 4 Forest plots examining the CV death of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 in patients with type 2 diabetes with or without metformin in baseline. CI: confidence interval

ASCVD or HF had no significant effect. I^2 values ranged from 13.47% to 38.31%, indicating moderate to low heterogeneity, with all P values above 0.05. R^2 values were low, suggesting baseline comorbidities explained little of the variability in these outcomes.

Risk of bias

All of the RCTs had a low risk of bias for randomization. The t-statistc of Egger's test was − 1.57 and P value was 0.258, which means there was no significant publication bias. Results of the analyses of risk of bias in these studies were illustrated in supplement Figures S4 and S5.

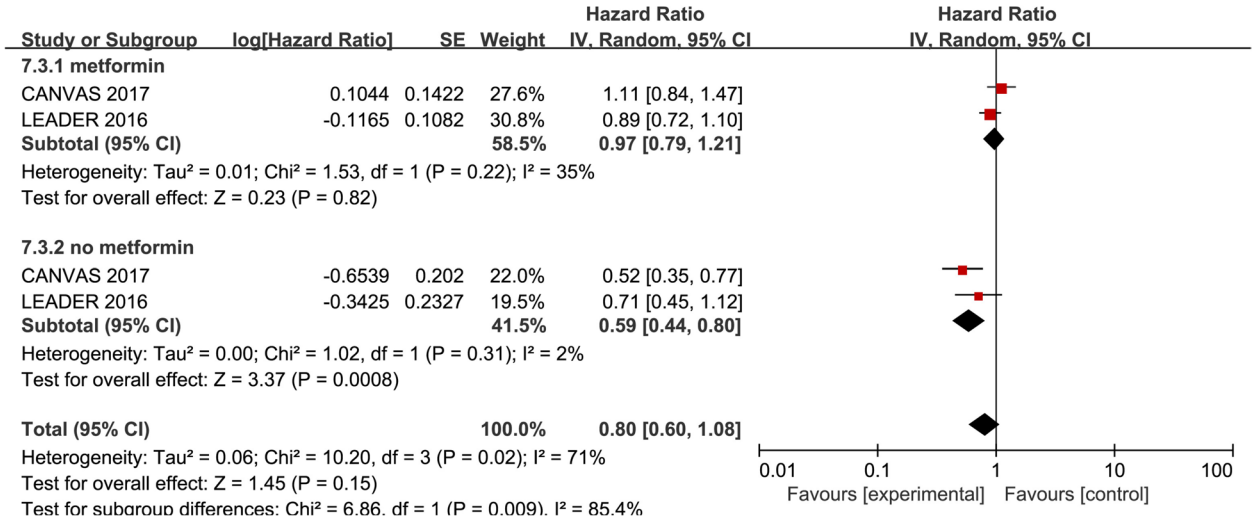

Fig. 5 Forest plots examining the Stroke of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 in patients with type 2 diabetes with or without metformin in baseline. CI: confidence interval

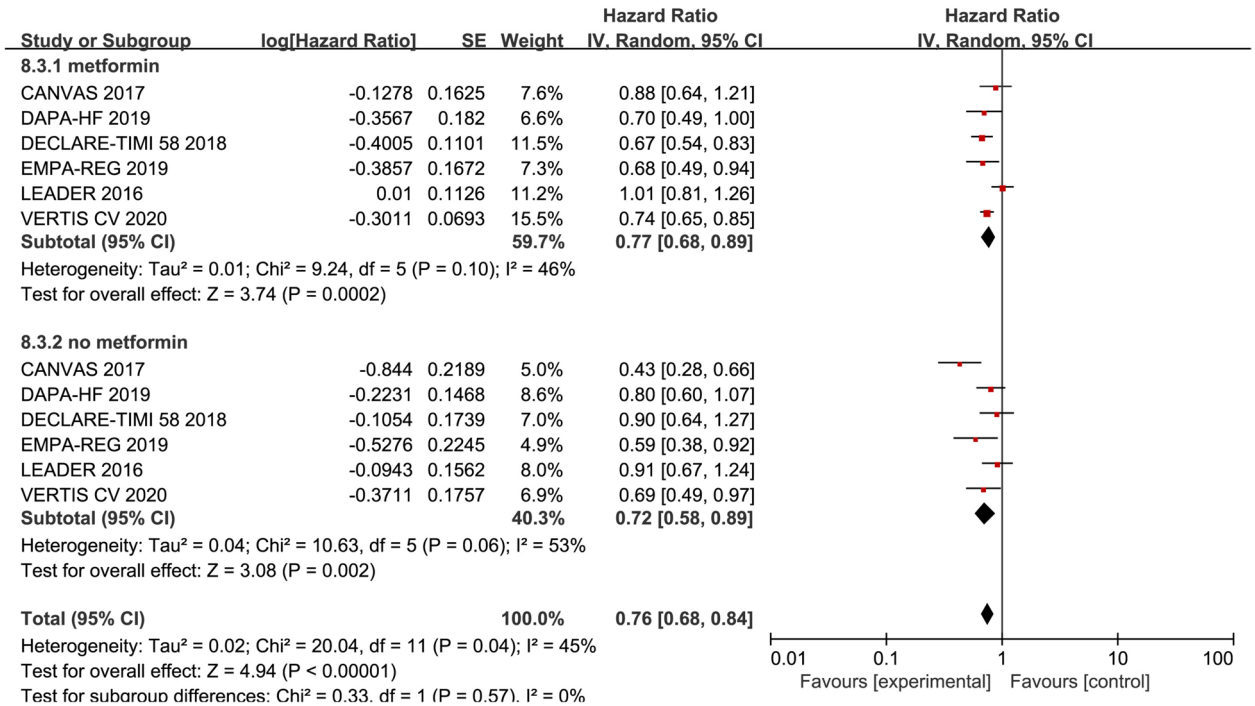

Fig. 6 Forest plots examining the HHF of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 in patients with type 2 diabetes with or without metformin in baseline. CI: confidence interval

Conclusion

SGLT-2 inhibitors and GLP-1 receptor agonists reduce the risk of major cardiovascular events, heart failure, and stroke in type 2 diabetes patients, regardless of metformin use.

Discussion

In this meta-analysis, we aimed to investigate the impact of SGLT-2i or GLP-1 RAs on cardiovascular outcomes, specifically MACE and HHF. Our analysis included a total of 81,738 patients, of which 73,033 (89.4%) had

pre-existing cardiovascular disease or were at high risk of ASCVD. Our findings demonstrated a significant reduction in the risk of MACE and HHF among patients using SGLT-2i or GLP-1 RAs, regardless of whether they were already taking metformin. These results provide further support for the latest recommendations from both the European Society of Cardiology (ESC) [7] and the American Diabetes Association (ADA) [12].

Previously, metformin was recommended as first-line treatment for T2DM patients. Meanwhile, due to increasing observation of cardiovascular benefits of SGLT-2i and GLP-1 RAs, there used to be ambiguity whether these benefits were dependent on background metformin use, because metformin might also have analogous effects. The cardioprotective effects of metformin may date back to over two decades ago, when UKPDS 34 confirmed the reduction of diabetes-related complications, including the risk of cardiovascular events and CV death among overweight T2DM patients [13]. A study conducted in China showed a significant reduction in the recurrence of major cardiovascular events after a median 5.0 years of follow-up with metformin treatment compared to glipizide [14]. However, recent years have seen a shift in this viewpoint, but ongoing studies continue to advance our understanding. Unlike metformin, SGLT-2i and GLP-1 RAs are now recommended as first-line drugs by both ESC and ADA due to their proven cardiovascular benefits [7, 12]. Studies such as EMPA-REG OUTCOME, DECLARE-TIMI 58, EMPEROR-REDUCED and EMPEROR-PRESERVED have demonstrated the benefits of SGLT-2i [15–18], while GLP-1 RAs have evidence from REWIND, EXSCEL, Harmony Outcome, etc [19–21]. Subgroup analyses of CVOTs based on baseline metformin use in two previous meta-analyses, respectively, directed by Brendon L and Apostolos Tsapas have shown that SGLT-2i reduce the risk of MACE, HHF, or CV death, while GLP-1 RAs reduce MACE, cardiovascular mortality, and all-cause mortality regardless of metformin background treatment. The former one which involved 6 COVTs (51,743 patients) showed that SGLT-2 inhibitors reduced the risk of MACE (HR 0.93, 95% CI 0.87–1.00 and HR 0.82, 95% CI 0.71–0.96, respectively; *P*-heterogeneity = 0.14), HHF or cardiovascular death (HR 0.79, 95% CI 0.73–0.86 and HR 0.74, 95% CI 0.63–0.87; *P*-heterogeneity = 0.48), HHF alone and cardiovascular death (*P*-heterogeneity = 0.42 and 0.43) regardless of baseline metformin use. The latter one which included 4 trials (43,456 patients) suggested that GLP-1 RAs reduced MACE by 13% (HR 0.87, 95% CI 0.82–0.93), an effect which was consistent in both subgroups (HR 0.91, 95% CI 0.85–0.97 and HR 0.80, 95% CI 0.72–0.90 with and without metformin, respectively). Presence of metformin at baseline did not affect the overall favorable effect of GLP-1 RAs both on cardiovascular and all-cause mortality [22, 23]. These findings support the cardioprotective benefits of independent SGLT-2i and GLP-1 RAs regardless of baseline metformin use. However, given that both the European Society of Cardiology (ESC) and ADA designated SGLT-2i and GLP-1 RAs as first-line drugs, it was deemed essential and feasible to conduct a comprehensive analysis of these two types of drugs. Therefore, we conducted a systematic evaluation of the effects of SGLT-2i or GLP-1 RAs on MACE and HHF with or without metformin background therapy by combining previous studies. In addition, we included a new report published on January 23rd, 2023, which provided specific data about cardiovascular outcomes in patients with or without baseline metformin use from DAPA–CKD, thereby increasing the size of our study population.

According to current study findings, the guideline from ADA 2023 has designated SGLT-2i and GLP-1 RAs as first-line drugs for T2DM patients with established ASCVD or high cardiovascular risk, and metformin is no longer recommended as first-line therapy for T2DM patients with high cardiovascular risk due to its neutral HF benefits. Nevertheless, ADA 2023 suggests that metformin's benefits on MACE remain potential and dubious [9], indicating that for patients with high risk of MACE, metformin combined with SGLT-2i or GLP-1 RAs with proven cardiovascular benefits may still contribute to the decrease of MACE risk. This study confirms that metformin is unnecessary to decrease the occurrence of MACE among T2DM patients, which provides evidence for both previous conclusions and the more advanced guideline in the future. Recent years, an increasing number of basic studies revealed SGLT-2 inhibitors' cardiovascular benefits. A 5-week double-blind, cross-over study in 2022 found that dapagliflozin treatment for 5 weeks was beneficial to the metabolism of fatty acid and ketone bodies and reduced glycolytic flux; meanwhile, another RCT observed a reduction of epicardial adipose tissue (EAT) thickness and its glucose uptake in T2D patients with SGLT-2i treatment [24, 25]. A post hoc analysis found changes of myocardial iron content after treatment with empagliflozin, which may be an explanation to its cardiovascular benefits. Another study suggested that empagliflozin's function of promoting the recovery of multiple circulating provascular cell subsets may be a mechanism through which SGLT-2i limits the development and progression of cardiovascular diseases [26]. Besides, a sub-analysis of an RCT found a reduction of metabolites that may reduce visceral fat in ipragliflozin treatment patients [27]. While GLP-1 RAs' cardiovascular benefits mainly lie in their antiinflammatory and antiatherogenic effects that restrain atherosclerotic

lesions and affect blood pressure regulation [28–30]. These studies converge on our findings. A recent bioinformatics study on the lncRNA–mRNA co-expression network in type 2 diabetes (T2DM) emphasized the critical role of inflammation in disease progression. The study identified key lncRNAs, including A1BG-AS1, AC084125.4, RAMP2-AS1, FTX, DBH-AS1, LOXL1-AS1, LINC00893, LINC00894, PVT1, RUSC1-AS1, HCG25, and ATP1B3-AS1, which may influence the pathogenesis of T2DM by modulating mRNA pathways associated with inflammation. These findings further support the idea that inflammation is a critical factor in cardiovascular risk in T2DM, providing a biological basis for the independent cardiovascular benefits observed with SGLT-2i and GLP-1 RAs [31]. In conclusion, due to the independent cardiovascular benefits, it is valid to conclude that SGLT-2i and GLP-1 RAs can reduce cardiovascular risks regardless of background metformin treatment. However, we also expect future guidelines to provide more detailed interpretations of the cardiovascular benefits of metformin and peculiar therapy recommendations for T2DM patients with higher risk of MACE, which should be independent of other cardiovascular outcomes.

These conclusions were not persuasive enough to allege that metformin will lose its predominant status in T2DM therapy. In contrast, it is necessary to estimate what role it will play in the future. Recent studies have shown that metformin may have benefits beyond cardiovascular protection, including a potential role in reducing the risk of age-related diseases such as Alzheimer's, cancer and dementia [32–34]. In addition, metformin has no side effects of hypoglycemia [35], which is an independent risk factor for dementia in T2DM patients. Although current guidlines mainly recommend SGLT-2 inhibitors and GLP-1 RAs to be served as first-line drugs to T2DM patients with high cardiovascular risks due to their proven cardiovascular benefits, effects of metformin on MACE still remain potential and dubious according to ADA 2023. Furthermore, the subjects involved are mainly elder people, thus the conclusion is not convincing enough to be applied in practice to all T2DM patients. Besides, not all elder T2DM patients have cardiovascular risks, and there are explicit evidences that SGLT-2 inhibitors can increase the risks of urinary tract infection and genital infection; meanwhile, LEADER reported a potential association between the use of GLP-1 RAs and pancreatitis and pancreatic cancer, so it is not practical to treat every T2DM patients with these two drugs. In that case, due to its cost-effective advantage and potential benefits, metformin should still be considered as a basic therapy for older T2DM patients with a high risk of MACE or amyloid formation. Further research is needed to fully understand the fundamental mechanism of metformin and its therapeutic effects.

There were several limitations in this study. First, we did not attain enough data to analyze myocardial infarction (MI), because among these 11 eligible studies, only leader reported this endpoint based on background metformin use. Furthermore, there is trend for differences between the effects of SGLt2i/GLP1 among those using metformin vs metformin-naive patients, with a trend towards larger benefit among those without metformin. Our conclusions only suggest that naive-metformin therapy is not associated with a reduction in cardiovascular outcomes among patients using SGLT-2i or GLP-1 RAs. The specific effect of metformin on these CVOTs remains unknown, and more research is needed to provide sufficient evidence on this topic. We look forward to more reports on metformin-naive patients in published studies and even more new RCTs to further support our current observations. In addition, data on CVOTs based on background metformin therapy in SUSTAIN 6 and PIONEER 6 were extracted from a pooled analysis [36], which may contribute to data deficiency. We also observed that in these two trials, a small number of patients (5 of 3297 in SUSTAIN 6 & 3 of 3183 in PIONEER 6) were using SGLT-2i at baseline, suggesting that combined use of these two kinds of drugs may exist in these studies. A 2021 study found that adding SGLT-2i to GLP-1 RAs therapy led to additional cardiovascular benefits compared to adding sulfonylurea. However, the study had some limitations due to the lack of randomization [37]. An exploratory analysis of the AMPLITUDE-O Trial published in 2022 showed independent effects of GLP-1 RAs from SGLT-2i [38]. Therefore, the impact in this study is estimated subtle, but it suggests a new research direction to study the efficacy and safety of combining SGLT-2i and GLP-1 RAs. Previous meta-analyses have suggested that GLP-1RA/SGLT2i combination therapy can improve blood glucose levels, reduce HbA1c, body weight, and systolic blood pressure compared to monotherapy in T2DM patients [39, 40]. Further rigorous clinical trials are needed to fully understand the effects of GLP-1RA/SGLT2i combination therapy.

In conclusion, compared with baseline use of metformin, using SGLT-2 inhibitors or GLP-1 RAs only may generate lower risks of MACE, HHF or other relative cardiovascular events. Both SGLT-2 inhibitors and GLP-1 receptor agonists can be effective first-line glucose-lowering drugs for cardiovascular patients, regardless of whether metformin was used at baseline.

Abbreviations

SGLT-2i	Sodium-dependent glucose transporters 2 inhibitors
GLP-1 Ras	Glucagon-like peptide 1
COVTs	Cardiovascular outcomes trials

MACE	Major adverse cardiovascular events
HHF	Hospitalization for heart failure
CV death	Cardiovascular death
HHF or CV death	Hospitalization for heart failure or cardiovascular death
MI	Myocardial infarction
T2DM	Type 2 diabetes mellitus
RoB 2	Risk-of-bias tool
CIs	Confidence intervals
HRs	Hazard ratios

Supplementary Information

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Additional file 1

Additional file 2

Author contributions

Zhang Yuxin and Li Zhaoji wrote the main manuscript text and prepared figures. All authors reviewed the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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