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Contents

Monthly Volume 15 Number 10 October 15, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

World Journal of Diabetes

Monthly Volume 15 Number 10 October 15, 2024

Contents

ABOUT COVER

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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SYSTEMATIC REVIEWS

Combining GLP-1 receptor agonists and SGLT-2 inhibitors for cardiovascular disease prevention in type 2 diabetes: A systematic review with multiple network meta-regressions

Jing-Jing Zhu, John P H Wilding, Xiao-Song Gu

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Abstract

BACKGROUND

Glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT-2I) are associated with significant cardiovascular benefit in type 2 diabetes (T2D). However, GLP-1RA or SGLT-2I alone may not improve some cardiovascular outcomes in patients with prior cardiovascular co-morbidities.

AIM

To explore whether combining GLP-1RA and SGLT-2I can achieve additional benefit in preventing cardiovascular diseases in T2D.

METHODS

The systematic review was conducted according to PRISMA recommendations. The protocol was registered on PROSPERO (ID: 42022385007). A total of 107049 participants from eligible cardiovascular outcomes trials of GLP-1RA and SGLT-2I were included in network meta-regressions to estimate cardiovascular benefit of the combination treatment. Effect modification of prior myocardial infarction (MI) and heart failure (HF) was also explored to provide clinical insight as to when the

combination treatment should be considered.

RESULTS

The estimated hazard ratios (HR)$_{\text{GLP-1RA/SGLT-2I}}$ *vs* $_{\text{Placebo}}$ (0.75-0.98) and HR$_{\text{Combination}}$ *vs* $_{\text{GLP-1RA/SGLT-2I}}$ (0.26-0.86) for primary and secondary cardiovascular outcomes suggested that the combination treatment may achieve additional cardiovascular benefit compared with GLP-1RA or SGLT-2I alone. In patients with prior MI or HF, the monotherapies may not improve the overall cardiovascular outcomes, as the estimated HR$_{\text{MI+/HF+}}$ (0.57-1.52) suggested that GLP-1RA or SGLT-2I alone may be associated with lower risks of hospitalization for HF but not cardiovascular death.

CONCLUSION

Considering its greater cardiovascular benefit in T2D, the combination treatment of GLP-1RA and SGLT-2I might be prioritized in patients with prior MI or HF, where the monotherapies may not provide sufficient cardiovascular protection.

Key Words: Type 2 diabetes; Glucagon-like peptide-1 receptor agonist; Sodium-glucose co-transporter-2 inhibitor; Combination treatment; Cardiovascular outcome; Systematic review; Network meta-regression

Core Tip: Major cardiovascular outcome trials suggest that patients with prior cardiovascular co-morbidities may not gain sufficient cardiovascular protection from glucagon-like peptide-1 receptor agonists (GLP-1RA) or sodium-glucose co-transporter-2 inhibitors (SGLT-2I) alone. This systematic review with network meta-regression demonstrated that the combination treatment may provide greater cardiovascular benefit compared with GLP-1RA or SGLT-2I alone. In patients with prior myocardial infarction or heart failure, the monotherapies may not be associated with consistently improved cardiovascular outcomes, hence the combination treatment might be considered for cardiovascular disease prevention.

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INTRODUCTION

The macro- and micro-vascular benefits of glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter-2 inhibitors (SGLT-2I) are independent of their glucose-lowering effects[1]. In patients with type 2 diabetes (T2D), the major cardiovascular outcome trials (CVOT) showed that dipeptidyl peptidase-4 inhibitors (DPP-4I) did not improve cardiovascular outcomes[2], whereas cardiovascular benefit of GLP-1RA or SGLT-2I was significant[3,4]. Further subgroup analyses indicated that the background cardiovascular risk should be considered when examining the cardiovascular outcomes of these newer glucose-lowering medications. For instance, prevention of major adverse cardiovascular events (MACE) was only seen in those patients with baseline atherosclerotic cardiovascular disease[3,4]. Moreover, a series of CVOT conducted in patients with heart failure (HF) have demonstrated that (compared with placebo) SGLT-2I significantly reduced risk of hospitalization for HF or cardiovascular death, irrespective of their history of T2D[5-8]. However, similar cardiovascular benefits were not observed in those with myocardial infarction (MI)[9,10]. Cardiovascular co-morbidities are not only approximately twice as common but are also associated with disproportionately worse cardiovascular outcomes in patients with T2D, compared to the general population[11]. Therefore, it is of clinical importance to investigate whether the combination treatment of GLP-1RA and SGLT-2I could achieve greater cardiovascular benefit, particularly when considering patients with cardiovascular co-morbidities who may not gain sufficient cardiovascular protection from the monotherapies.

This systematic review with multiple network meta-regressions was mainly aimed to explore whether combining GLP-1RA and SGLT-2I can provide additional cardiovascular benefit in T2D. Cardiovascular outcomes of these newer antidiabetic medications were also estimated under effect modification of prior cardiovascular diseases. This was to provide clinical insight as to when the combination treatment might be prioritized.

MATERIALS AND METHODS

Study search and inclusion

We conducted a comprehensive systematic review with multiple network meta-regressions (and parallel network meta-analyses) according to PRISMA recommendations[12]. The protocol is registered in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022385007). PubMed, Scopus, the ClinicalTrials.gov registry, and Center for Drug Evaluation and Research were searched for eligible CVOT and associated *post-hoc* analyses (Figure 1). The study search was initially performed on October 19, 2023 and further updated on February 12, 2024. Studies included in analysis were those only conducted in adult patients with T2D receiving DPP-4I, GLP-1RA, or SGLT-2I (Table 1 and Supplementary Figure 1). CVOT of these antidiabetic medications while recruiting patients without T2D (which were determined at baseline) were excluded. The Cochrane Collaboration's Risk-of-Bias tool was applied for quality assessment (Supplementary Figure 2).

Data extraction and synthesis

Effect sizes [*i.e.*, hazard ratios (HR)] indicating treatment effects of these newer antidiabetic medications on primary and secondary cardiovascular outcomes, were extracted from the eligible CVOT (Supplementary Figures 3-7), and converted to statistics including mean logHR and their standard errors [calculated using HR and 95% confidence intervals (95%CI)] for network meta-regressions and meta-analyses[13]. Covariates including percentages of patients receiving the co-treatment with GLP-1RA or SGLT-2I and having baseline prior MI or HF in the placebo and treatment groups, were retrieved from the CVOT of GLP-1RA and SGLT-2I for network meta-regressions (Table 1).

Statistical analysis

A set of Bayesian network meta-analyses were initially performed to compare the cardiovascular outcomes among these antidiabetic medications (including DPP-4I). The between-study heterogeneities were assessed using the I^2 and τ^2 statistics (Supplementary Figures 3-7). Surface under the cumulative ranking curve (SUCRA) was also calculated for efficacy comparisons.

Furthermore, we conducted multiple Bayesian network meta-regressions to explore the effect modification of GLP-1RA on treatment efficacies of SGLT-2I and *vice versa*, which is equivalent to answering the main research question of whether the combination treatment of GLP-1RA and SGLT-2I can provide additional cardiovascular benefit. The network meta-regression model was constructed to establish a correlation between the covariate and effect size (*i.e.*, HR) observed in the CVOT. The correlation, namely, effect modification, can be numerically quantified as a coefficient (β)[14]. Given that this statistical model is linear[14], the percentages of patients ever receiving the co-treatment during the CVOT, namely, the postbaseline co-treatment, were incorporated as the covariate. This approach could yield results with more accuracy than those incorporating the baseline co-treatment. $HR_{0/GLP\text{-}1RA/SGLT\text{-}2I\ vs\ Placebo}$ and $HR_{1/Combination\ vs\ GLP\text{-}1RA/SGLT\text{-}2I}$ were thus estimated when assigning covariate = 0 or 1, assuming either 0% or 100% patients receiving the co-treatment in the CVOT, and compared with HR_{NA} from the parallel network meta-analyses (indicating the effect size observed from the CVOT with the actual percentages of patients receiving the co-treatment).

Likewise, cardiovascular outcomes of GLP-1RA or SGLT-2I were explored under effect modification of prior cardiovascular diseases. Percentages of patients having baseline MI or HF were incorporated as the covariates. $HR_{0/Disease-}$ and $HR_{1/Disease+}$, were estimated when assigning covariate = 0 or 1 with the assumption being that either 0% or 100% patients having MI or HF in the CVOT; and compared with HR_{NA} from meta-analyses (indicating the effect size observed from the CVOT with the actual percentages of patients having the co-morbidities).

In addition, I^2 or τ^2 in the network meta-regressions and run-in-parallel network meta-analyses (without covariate incorporation) was compared to determine the covariate effects on between-study heterogeneity. All the analyses were conducted with R version 4.2.3 using the GEMTC packages. We used four Markov chains with 150000 iterations after an initial burn-in of 20000 and a thinning of 1 for all the analyses (Supplementary material). As all the eligible CVOT for analysis were double-blind and randomized placebo-controlled trials, inconsistency was not assessed (Supplementary Figure 1).

Effect modification analysis

The credibility of all the proposed effect modifications was assessed using the instrument for the credibility of effect modification analyses (ICEMAN)[15]. For the credibility question 5, considering a Bayesian network meta-regression model applied in this study, 95%CI of the β (instead of *P* values) was included to indicate the results of the interaction test (Supplementary material).

RESULTS

GLP-1RA or SGLT-2I can improve primary and secondary cardiovascular outcomes in T2D

To determine the cardiovascular benefits of GLP-1RA and SGLT-2I, a total of 150423 participants in the CVOT were incorporated in the overall network meta-analysis to compare primary and secondary cardiovascular outcomes among DPP-4I, GLP-1RA, and SGLT-2I in T2D (Table 1, Supplementary Figure 1, and Figure 2). Based on our preliminary test results (not shown), network meta-analyses using relative risks would significantly underestimate the cardiovascular benefit of SGLT-2I, hence the results using survival (*i.e.*, HR) rather than count statistics have greater robustness. The

Table 1 Study-level characteristics of included major cardiovascular outcome trials and associated *post-hoc* analyses

Year	CVOT	Intervention	Median follow-up (year)	History of MI (yes, %)	History of HF (yes, %)	Post-baseline GLP-1RA/SGLT-2I (yes, %), intervention/placebo
2013	EXAMINE[25]	Alogliptin	1.5	N/A	N/A	N/A
2013	SAVOR-TIMI 53[26]	Saxagliptin	2.1	N/A	N/A	N/A
2015	TECOS[27]	Sitagliptin	3.0	N/A	N/A	N/A
2019	CARMELINA[28]	Linagliptin	2.2	N/A	N/A	N/A
2015	ELIXA[29]	Lixisenatide	2.1	22	22	N/A
2016	SUSTAIN-6[30]	Semaglutide	2.1	32	17[31]	1.5/1.2
2016	LEADER[32]	Liraglutide	3.8	31	18[33]	2.1/2.8[1]
2017	EXSCEL[34]	Exenatide	3.2	32[35]	16	4.4/5.8
2018	HARMONY OUTCOMES[36]	Albiglutide	1.5	47	20	9.7/10.8
2019	REWIND[37]	Dulaglutide	5.4	16[38]	9	5.2/7.3
2019	PIONEER-6[39]	Semaglutide	1.3	36[31]	12[31]	13.5/15.8
2021	AMPLITUDE-O[40]	Efpeglenatide	1.8	N/A	18	17.5/21.2
2015	EMPA-REG OUTCOME[41]	Empagliflozin	3.1	47	10	N/A
2017	CANVAS[42]	Canagliflozin	2.4	29[43]	14	6.2/7.7[2]
2019	DECLARE-TIMI 58 [44]	Dapagliflozin	4.2	21[45]	10	9.5/11.5[19]
2019	CREDENCE[46]	Canagliflozin	2.6	10[47]	15	6.5/6.9
2020	VERTIS CV[48]	Ertugliflozin	3.5	48	24	4.9/5.6

[1]Data kindly provided by Dr. Kajsa Kvist from Novo Nordisk.

[2]Data extracted from the drug approval package (application number: 204042Orig1s027) kindly provided by Dr. Frank Vercruysse from Janssen Pharmaceuticals.

Data for analysis were extracted from 17 primary investigations and 9 *post-hoc* analyses (including a drug approval package retrieved from Center for Drug Evaluation and Research). Covariates of percentages of patients having baseline prior myocardial infarction or heart failure; percentages of patients receiving postbaseline co-treatment with sodium-glucose co-transporter-2 inhibitors (SGLT-2I)/glucagon-like peptide-1 receptor agonists (GLP-1RA) in the placebo and GLP-1RA or SGLT-2I groups of the cardiovascular outcome trials (CVOT), were incorporated into the network meta-regression analyses. The numbers in square brackets denoting the CVOT and data correspond to the cited references. CVOT: Cardiovascular outcome trials; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2I: Sodium-glucose co-transporter-2 inhibitors; MI: Myocardial infarction; HF: Heart failure; N/A: Not applicable.

overall heterogeneities were low, with I^2 of 0% and 19% and τ^2 of 0.001 to 0.005 (Supplementary Figures 3-7). Compared with placebo, DPP-4I demonstrated no risk-reducing effects on any of the cardiovascular outcomes. Both GLP-1RA and SGLT-2I significantly reduced risks of MACE ($HR_{GLP\text{-}1RA\ vs\ Placebo}$ = 0.85, 95%CI: 0.79-0.90; $HR_{SGLT\text{-}2I\ vs\ Placebo}$ = 0.90, 95%CI: 0.83-0.96) and cardiovascular death ($HR_{GLP\text{-}1RA\ vs\ Placebo}$ = 0.87, 95%CI: 0.74-0.95; $HR_{SGLT\text{-}2I\ vs\ Placebo}$ = 0.84, 95%CI: 0.74-0.95). Moreover, GLP-1RA might have modest benefit over SGLT-2I in reducing risks of MACE ($HR_{GLP\text{-}1RA\ vs\ SGLT\text{-}2I}$ = 0.95, 95%CI: 0.86-1.04; $SUCRA_{GLP\text{-}1RA}$ = 0.95, $SUCRA_{SGLT\text{-}2I}$ = 0.70). Whereas for cardiovascular death, SGLT-2I might be associated with lower risk compared with GLP-1RA ($HR_{SGLT\text{-}2I\ vs\ GLP\text{-}1RA}$ = 0.97, 95%CI: 0.83-1.14; $SUCRA_{SGLT\text{-}2I}$ = 0.87, $SUCRA_{GLP\text{-}1RA}$ = 0.77). GLP-1RA also demonstrated significant risk-reducing effects on fatal and non-fatal MI ($HR_{GLP\text{-}1RA\ vs\ Placebo}$ = 0.90, 95%CI: 0.83-0.99), and fatal and non-fatal stroke ($HR_{GLP\text{-}1RA\ vs\ Placebo}$ = 0.84, 95%CI: 0.75-0.93). Compared with the other interventions, SGLT-2I achieved the most significant and superior benefit in reducing risk of hospitalization for HF (*e.g.*, $HR_{SGLT\text{-}2I\ vs\ GLP\text{-}1RA}$ = 0.74, 95%CI: 0.63-0.88; $SUCRA_{SGLT\text{-}2I}$ = 1; Figure 2).

The combination treatment of GLP-1RA and SGLT-2I may provide additional cardiovascular benefit in T2D

Estimation of the combination treatment for cardiovascular disease prevention in T2D was further conducted in 107049 participants only in the CVOT of GLP-1RA and SGLT-2I. Potential effect modification of co-treatment with SGLT-2I on cardiovascular outcomes of GLP-1RA (and *vice versa*) was analyzed using network meta-regressions. The overall negative β (-0.13 to -0.01) indicated that there might be a positive effect modification of the co-treatment on improvement of the primary and secondary cardiovascular outcomes, *i.e.*, the higher the percentages of patients receiving the combination treatment, the lower the HR (Supplementary Table 1), which is in consistent with comparisons among HR_0, HR_1, and HR_{NA} (*e.g.*, $HR_0 > HR_{NA} > HR_{1/Combination\ vs\ GLP\text{-}1RA/SGLT\text{-}2I}$; Table 2). In patients not receiving the co-treatment, GLP-1RA or SGLT-2I (alone) could improve cardiovascular outcomes (compared to placebo). The lack of statistical significance in

Table 2 Effect modification of co-treatment with sodium-glucose co-transporter-2 inhibitors on cardiovascular benefit of glucagon-like peptide-1 receptor agonists and *vice versa* in type 2 diabetes

Cardiovascular outcome	Covariate	Intervention	HR with 95%CI
MACE	NA	GLP-1RA *vs* Placebo	0.84 (0.77-0.90)
MACE	0	GLP-1RA *vs* Placebo	0.89 (0.77-0.99)
MACE	NA	SGLT-2I *vs* Placebo	0.90 (0.82-0.98)
MACE	0	SGLT-2I *vs* Placebo	0.95 (0.82-1.08)
MACE	1	Combination *vs* GLP-1RA	0.51 (0.16-1.65)
MACE	1	Combination *vs* SGLT-2I	0.48 (0.15-1.54)
Cardiovascular death	NA	GLP-1RA *vs* Placebo	0.85 (0.76-0.94)
Cardiovascular death	0	GLP-1RA *vs* Placebo	0.88 (0.73-1.07)
Cardiovascular death	NA	SGLT-2I *vs* Placebo	0.90 (0.79-1.02)
Cardiovascular death	0	SGLT-2I *vs* Placebo	0.93 (0.76-1.16)
Cardiovascular death	1	Combination *vs* GLP-1RA	0.58 (0.08-3.39)
Cardiovascular death	1	Combination *vs* SGLT-2I	0.55 (0.07-3.25)
Fatal and non-fatal MI	NA	GLP-1RA *vs* Placebo	0.89 (0.79-0.98)
Fatal and non-fatal MI	0	GLP-1RA *vs* Placebo	0.94 (0.79-1.09)
Fatal and non-fatal MI	NA	SGLT-2I *vs* Placebo	0.92 (0.81-1.05)
Fatal and non-fatal MI	0	SGLT-2I *vs* Placebo	0.98 (0.81-1.19)
Fatal and non-fatal MI	1	Combination *vs* GLP-1RA	0.45 (0.10-2.18)
Fatal and non-fatal MI	1	Combination *vs* SGLT-2I	0.44 (0.09-2.10)
Fatal and non-fatal stroke	NA	GLP-1RA *vs* Placebo	0.81 (0.72-0.91)
Fatal and non-fatal stroke	0	GLP-1RA *vs* Placebo	0.82 (0.67-1.00)
Fatal and non-fatal stroke	NA	SGLT-2I *vs* Placebo	0.94 (0.82-1.08)
Fatal and non-fatal stroke	0	SGLT-2I *vs* Placebo	0.95 (0.75-1.20)
Fatal and non-fatal stroke	1	Combination *vs* GLP-1RA	0.86 (0.12-6.23)
Fatal and non-fatal stroke	1	Combination *vs* SGLT-2I	0.74 (0.10-5.47)
Hospitalization for HF	NA	GLP-1RA *vs* Placebo	0.90 (0.79-1.02)
Hospitalization for HF	0	GLP-1RA *vs* Placebo	0.97 (0.80-1.19)
Hospitalization for HF	NA	SGLT-2I *vs* Placebo	0.68 (0.59-0.79)
Hospitalization for HF	0	SGLT-2I *vs* Placebo	0.75 (0.59-0.96)
Hospitalization for HF	1	Combination *vs* GLP-1RA	0.26 (0.03-1.88)
Hospitalization for HF	1	Combination *vs* SGLT-2I	0.33 (0.04-2.53)

The covariates of percentages of patients receiving postbaseline co-treatment with sodium-glucose co-transporter-2 inhibitors (SGLT-2I)/glucagon-like peptide-1 receptor agonists (GLP-1RA) were incorporated into the meta-regressions. Hazard ratios (HR)$_{0/\text{GLP-1RA/SGLT-2I}}$ *vs* $_{\text{Placebo}}$ and HR$_{1/\text{Combination}}$ *vs* $_{\text{GLP-1RA/SGLT-2I}}$ with 95% confidence intervals (95%CI) were estimated, assuming either 0% or 100% patients receiving the co-treatment. The network meta-analyses were run in parallel to calculate HR$_{NA}$ with 95%CI. The HR$_{NA}$ indicated effect sizes observed from the cardiovascular outcome trials with the actual percentages of patients receiving the co-treatment. HR: Hazard ratios; 95%CI: 95% confidence intervals; MACE: Major adverse cardiovascular events; CVOT: Cardiovascular outcome trials; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2I: Sodium-glucose co-transporter-2 inhibitors; MI: Myocardial infarction; HF: Heart failure; NA: Not available.

some of the results could stem from EMPA-REG OUTCOME being excluded from the network meta-regressions, as this trial did not report percentages of patients receiving the post co-treatment of GLP-1RA in the placebo and SGLT-2I groups (Table 1). In patients receiving the co-treatment, the combination treatment was estimated to be associated with additional cardiovascular benefit in preventing MACE compared to either GLP-1RA (HR$_1$ = 0.51, 95%CI: 0.16-1.65) or SGLT-2I (HR$_1$ = 0.48, 95%CI: 0.15-1.54) alone. Similar effect sizes were also assessed for cardiovascular death and fatal and non-fatal MI. Although to a lesser extent, the combination treatment might further lower the risk of fatal and non-fatal stroke compared with GLP-1RA (HR$_1$ = 0.86, 95%CI: 0.12-6.23) or SGLT-2I (HR$_1$ = 0.74, 95%CI: 0.10-5.47) alone. Moreover,

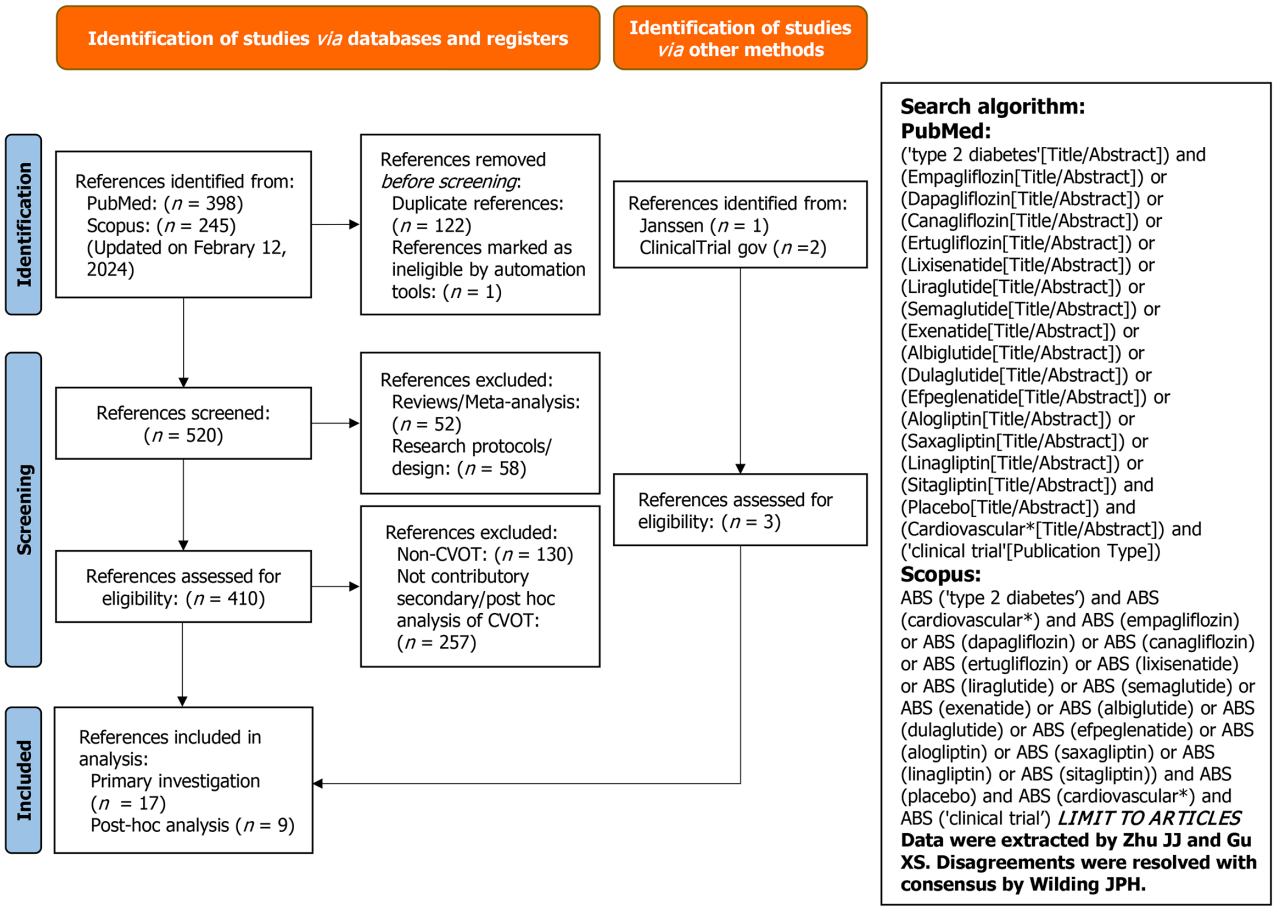

Figure 1 PRISMA flow diagram with search algorithm. CVOT: Cardiovascular outcome trials.

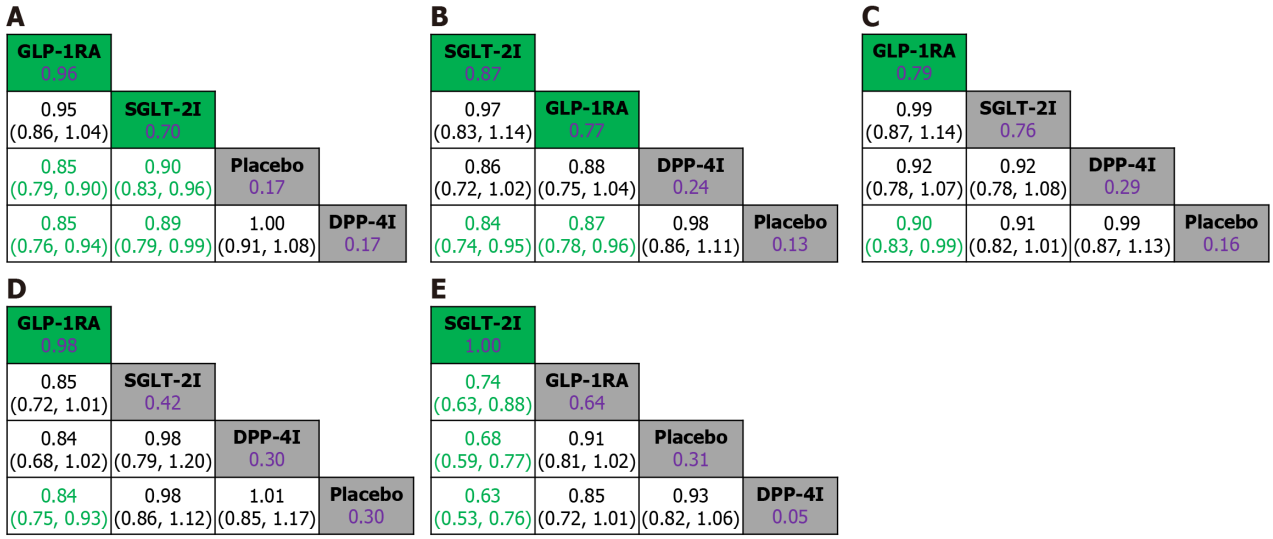

Figure 2 Comparisons of primary and secondary cardiovascular outcomes among newer glucose-lowering medications in type 2 diabetes. A: Major adverse cardiovascular events; B: Cardiovascular death; C: Fatal and non-fatal myocardial infarction; D: Fatal and non-fatal stroke; E: Hospitalization for heart failure. The treatments are reported in order of cardiovascular outcome ranking according to surface under the cumulative ranking curve (indicated in purple). Comparisons in the network meta-analyses should be read from left to right. The results, *i.e.*, hazard ratios (HR) with 95%CI, are located at the intersection of the column-defining treatment and the row-defining treatment (indicated in green and black). For the observed primary and secondary outcomes of the cardiovascular outcome trials, HR (< 1) favors the column-defining treatment. Significant results and treatments of significant cardiovascular benefit are indicated in green.

hospitalization for HF might be prevented to a greater extent in patients receiving the combination treatment rather than receiving GLP-1RA (HR_1 = 0.26, 95%CI: 0.03-1.88) or SGLT-2I (HR_1 = 0.33, 95%CI: 0.04-2.53; Table 2) alone. Taken together, the estimated effect sizes, *i.e.*, HR_1, were all numerically but not significantly favorable to the combination treatment, suggesting that the combination treatment may achieve greater benefit than the monotherapies in preventing cardiovascular diseases in patients with T2D.

Regarding the primary and secondary cardiovascular outcomes, low degrees of variations between I^2 or τ^2 in the meta-regressions and meta-analyses might eliminate the probability of the co-treatments being sources of between-study heterogeneity (Supplementary Table 1). However, for the effect modifications of the co-treatments, the overall credibility ratings ranged from low to moderate (Supplementary material).

Cardiovascular outcomes of GLP-1RA or SGLT-2I could be modified by cardiovascular co-morbidities in T2D

Effect modification of prior MI or HF on cardiovascular outcomes in patients receiving GLP-1RA or SGLT-2I were likewise explored in network meta-regressions. The negative β (-0.07 to -0.01) indicated that GLP-1RA and SGLT-2I might be more effective in prevention of cardiovascular death and hospitalization for HF in trial populations with higher rates of MI and HF, respectively (Supplementary Table 2). In patients without prior MI, GLP-1RA were estimated to be associated with a significant risk reduction in cardiovascular death (HR_0 = 0.88, 95%CI: 0.76-0.99), whereas the effect size might modestly increase in patients with prior MI (HR_1 = 0.74, 95%CI: 0.26-2.01). Similarly, in patients without prior HF, SGLT-2I could significantly reduce the risk of hospitalization for HF (HR_0 = 0.68, 95%CI: 0.60-0.76), and additional risk reduction was estimated in patients with prior HF (HR_1 = 0.62, 95%CI: 0.14-2.80; Table 3). However, the estimated cardiovascular benefit of GLP-1RA and SGLT-2I was numerically but not statistically conclusive in patients with these preexisting cardiovascular co-morbidities.

In contrast, the positive β (0.05-0.08) indicated that GLP-1RA and SGLT-2I might demonstrate reduced effectiveness in preventing cardiovascular death and recurrent MI as the prevalence of MI and HF within trial populations increased (Supplementary Table 2). In patients without prior HF, both GLP-1RA and SGLT-2I could significantly reduce the risk for cardiovascular death ($HR_{0/GLP\text{-}1RA}$ = 0.86, 95%CI: 0.76-0.97; $HR_{0/SGLT\text{-}2I}$ = 0.84, 95%CI: 0.73-0.96). However, these risk reduction effects were estimated to be neutral in patients with prior HF ($HR_{1/GLP\text{-}1RA}$ = 1.52, 95%CI: 0.30-10.07); $HR_{1/SGLT\text{-}2I}$ = 1.51, 95%CI: 0.29-10.38; Table 3).

Compared with fatal and non-fatal MI or hospitalization for HF, cardiovascular death demonstrated the greatest heterogeneities as I^2 = 19% indicated (Supplementary Figures 4, 5, and 7). Notably, the I^2 and τ^2 were reduced when incorporating covariates of prior HF or MI, suggesting that these co-morbidities could be also considered sources of the between-study heterogeneities (Supplementary Table 2). With respect to the effect modifications of these cardiovascular diseases in patients receiving the mono-antidiabetic treatment with GLP-1RA or SGLT-2I, the overall credibility ratings ranged from low to moderate (Supplementary material).

DISCUSSION

The initial network meta-analyses confirmed the cardiovascular benefit of GLP-1RA and SGLT-2I in T2D. GLP-1RA demonstrated remarkable risk reductions in various adverse cardiovascular outcomes. SGLT-2I had superior benefit in preventing cardiovascular death and hospitalization for HF. Compared with previous analyses[16], our study exhibited lower heterogeneities and generated results with higher robustness. These advantages can be attributed to analysis using survival rather than count statistics and incorporation of CVOT exclusively conducted in patients with T2D.

To date, there has not been any systematic review examining whether the combination treatment of GLP-1RA and SGLT-2I can prevent cardiovascular diseases in T2D. It should be noted that running separate subgroup analyses is not a correct method to investigate effect modification in network meta-analysis as it cannot guarantee same estimates of between-trial variation nor produce test of interaction to reject the null hypothesis of equal effects[17]. Therefore, our study used a robust network meta-regression model to explore the cardiovascular benefit of the combination treatment *via* estimating the effect modification of GLP-1RA on treatment efficacies of SGLT-2I (and *vice versa*). Moreover, from a methodological standpoint, covariate incorporation in meta-regression can avoid unbalanced hazards between intervention groups (which can be introduced *via* covariate stratification in sub-group analysis[18-21]), thereby estimating effect sizes with greater precision. Consistent with previous *post hoc* subgroup and propensity score matching analyses [17-21], our results suggest that the combination treatment may achieve additional cardiovascular benefit in T2D[17-21]. A recent published real-world data based study further confirmed that the combination treatment was associated with both lower cardiovascular and risks compared with the monotherapies[22]. Mechanistically, their complementary actions on glucose, blood pressure, and lipid regulation might have contributed to the greater cardiovascular benefits[23].

Cardiovascular co-morbidities have been recognized as risk factors capable of potentially modifying cardiovascular benefit of GLP-1RA and SGLT-2I[3,4]. Our results indicated that SGLT-2I could significantly lower hospitalization for HF but not cardiovascular death in patients with HF, which are consistent with observations from the CVOT conducted in HF with preserved ejection fraction (*e.g.*, EMPEROR-Preserved and DELIVER)[5,7]. In patients with prior MI, the EMPACT-MI trial showed that the SGLT-2I was not associated with improved cardiovascular outcomes[10], whereas our results indicated that the risk of cardiovascular death might be further reduced compared with those without prior MI, but the estimation remains statistically inconclusive as the 95%CI indicated. Similar effect modifications were also estimated in GLP-1RA. As GLP-1RA and SGLT-2I have become the most recommended second-line and, in some cases, first-line antidiabetic treatments, particularly for patients with "high risk" (*e.g.*, atherosclerotic cardiovascular disease) [24], these specific cardiovascular conditions may be considered "above high risk" at which patients should receive the

Table 3 Effect modification of prior cardiovascular diseases on cardiovascular outcomes of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors in type 2 diabetes

Cardiovascular outcome	Covariate		Intervention	HR with 95%CI
Fatal and non-fatal MI	Prior history of MI	NA	GLP-1RA *vs* Placebo	0.91 (0.84-1.01)
Fatal and non-fatal MI	Prior history of MI	0	GLP-1RA *vs* Placebo	1.13 (0.85-1.51)
Fatal and non-fatal MI	Prior history of MI	1	GLP-1RA *vs* Placebo	0.57 (0.30-1.05)
Fatal and non-fatal MI	Prior history of MI	NA	SGLT-2I *vs* Placebo	0.91 (0.82-1.02)
Fatal and non-fatal MI	Prior history of MI	0	SGLT-2I *vs* Placebo	0.84 (0.66-1.07)
Fatal and non-fatal MI	Prior history of MI	1	SGLT-2I *vs* Placebo	1.09 (0.66-1.80)
Cardiovascular death	Prior history of MI	NA	GLP-1RA *vs* Placebo	0.88 (0.76-0.99)
Cardiovascular death	Prior history of MI	0	GLP-1RA *vs* Placebo	0.93 (0.59-1.48)
Cardiovascular death	Prior history of MI	1	GLP-1RA *vs* Placebo	0.74 (0.26-2.01)
Cardiovascular death	Prior history of MI	NA	SGLT-2I *vs* Placebo	0.84 (0.72-0.96)
Cardiovascular death	Prior history of MI	0	SGLT-2I *vs* Placebo	0.92 (0.62-1.32)
Cardiovascular death	Prior history of MI	1	SGLT-2I *vs* Placebo	0.68 (0.32-1.48)
Hospitalization for HF	Prior history of HF	NA	GLP-1RA *vs* Placebo	0.91 (0.82-1.02)
Hospitalization for HF	Prior history of HF	0	GLP-1RA *vs* Placebo	0.93 (0.61-1.42)
Hospitalization for HF	Prior history of HF	1	GLP-1RA *vs* Placebo	0.84 (0.20-3.67)
Hospitalization for HF	Prior history of HF	NA	SGLT-2I *vs* Placebo	0.68 (0.60-0.76)
Hospitalization for HF	Prior history of HF	0	SGLT-2I *vs* Placebo	0.69 (0.52-0.90)
Hospitalization for HF	Prior history of HF	1	SGLT-2I *vs* Placebo	0.62 (0.14-2.80)
Cardiovascular death	Prior history of HF	NA	GLP-1RA *vs* Placebo	0.86 (0.76-0.97)
Cardiovascular death	Prior history of HF	0	GLP-1RA *vs* Placebo	0.77 (0.51-1.08)
Cardiovascular death	Prior history of HF	1	GLP-1RA *vs* Placebo	1.52 (0.30-10.07)
Cardiovascular death	Prior history of HF	NA	SGLT-2I *vs* Placebo	0.84 (0.73-0.96)
Cardiovascular death	Prior history of HF	0	SGLT-2I *vs* Placebo	0.76 (0.52-1.04)
Cardiovascular death	Prior history of HF	1	SGLT-2I *vs* Placebo	1.51 (0.29-10.38)

The covariates of percentages of patients having baseline prior cardiovascular diseases including myocardial infarction and heart failure were incorporated in the network meta-regressions. Hazard ratios $(HR)_{0/Disease-}$ and $HR_{1/Disease+}$ with 95% confidence intervals (95%CI) were estimated with the assumption of either 0% or 100% patients having the co-morbidities in the cardiovascular outcome trials (CVOT). The network meta-analyses were run in parallel to calculate HR_{NA} with 95%CI. The HR_{NA} indicated effect sizes observed from the CVOT with the actual percentages of patients having the co-morbidities. HR: Hazard ratios; 95%CI: 95% confidence intervals; CVOT: Cardiovascular outcome trials; GLP-1RA: Glucagon-like peptide-1 receptor agonists; SGLT-2I: Sodium-glucose co-transporter-2 inhibitors; MI: Myocardial infarction; HF: Heart failure.

combination treatment of GLP-1RA and SGLT-2I to optimize the overall cardiovascular outcomes.

The overall credibility of these effect modifications was rated as low to moderate using ICEMAN. This is considered a major limitation of our study. Factors that underestimated the credibility include the over-specification of the network meta-regression model due to scarcity of the data points (*e.g.*, only 13 available trials/baselines were included for analysis)[14]. Consequently, the β values were generated with less statistical power, which also contributes to the generally low to moderate credibility and may explain the very wide 95%CI of some estimated HR. Multiple interaction models using individual patient data should be undertaken in the future, to investigate cardiovascular and renal benefits of the combination treatment under effect modification of these cardiovascular co-morbidities. Nevertheless, further definitive trials are still in need to be able to support a strong recommendation to this effect.

CONCLUSION

The combination treatment of GLP-1RA and SGLT-2I may achieve additional cardiovascular benefit in T2D. In patients with prior cardiovascular co-morbidities including MI and HF, GLP-1RA or SGLT-2I alone may not significantly improve the overall cardiovascular outcomes, hence the combination treatment can be prioritized in such clinical scenarios.

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FOOTNOTES

Author contributions: Wilding JPH and Gu XS contributed equally to this study as co-corresponding authors. Wilding JPH proposed to investigate cardiovascular benefit of the combination treatment of GLP-1RA and SGLT-2I; Zhu JJ and Gu XS conducted the systematic review; Zhu JJ performed all the statistics and took responsibility for the accuracy of the data analysis; Wilding JPH and Gu XS supervised the findings of this study; all the authors discussed the results, and contributed to and approved the final manuscript (including the registered protocol).

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