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ORIGINAL ARTICLE
Heart failure/cardiomyopathy

Comparative cardiovascular effectiveness of glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter-2 inhibitors in atherosclerotic cardiovascular disease phenotypes: a systematic review and meta-analysis

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Background Atherosclerotic cardiovascular disease (ASCVD) encompasses various phenotypes with elevated risks of major adverse cardiovascular events (MACEs). This study aimed to assess the comparative cardiovascular effectiveness of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT2is) across diverse ASCVD phenotypes.

Methods and results We conducted a systematic review and meta-analysis of randomized controlled trials evaluating GLP-1 RAs or SGLT2is against placebo or standard care in ASCVD patients. Primary outcomes included MACE, defined as cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. Risk ratios (RRs) with 95% confidence interval (CI) were calculated using a random-effects model.

Twenty-six trials (151 789 patients) were included. Both GLP-1 RAs and SGLT2is significantly reduced MACE rates in ASCVD patients (RR 0.85; 95% CI 0.80–0.91 for both). GLP-1 RAs showed significant effectiveness in peripheral artery disease (RR 0.86; 95% CI 0.76–0.98) and post-acute cardiovascular events (RR 0.90; 95% CI 0.83–0.97). In ASCVD with heart failure, both drug classes reduced MACE (GLP-1 RAs: RR 0.73; 95% CI 0.63–0.84; SGLT2is: RR 0.86; 95% CI 0.78–0.95). SGLT2is significantly reduced MACE in ASCVD with chronic kidney disease (RR 0.84; 95% CI 0.72–0.99), particularly in severe albuminuria (RR 0.61; 95% CI 0.37–0.99).

Conclusion GLP-1 RAs and SGLT2is exhibit distinct cardiovascular effectiveness profiles across ASCVD phenotypes. GLP-1 RAs show particular benefits in peripheral artery disease and post-acute cardiovascular events, while SGLT2is demonstrate

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unique advantages in ASCVD with comorbid chronic kidney disease. Both are effective in heart failure. These findings support tailored treatment strategies for diverse ASCVD participants based on specific comorbidities and risk factors.

Keywords Major adverse cardiovascular events • Sodium-–glucose cotransporter-2 inhibitors • Glucagon-like peptide-1 receptor agonists • Atherosclerotic cardiovascular disease • Comparative effectiveness

Introduction

Atherosclerotic cardiovascular disease (ASCVD) encompasses conditions characterized by arterial narrowing, including coronary artery disease, peripheral artery disease, ischaemic stroke, and acute myocardial infarction.[1,2] As a global health concern, ASCVD contributes to higher rates of major adverse cardiovascular events (MACEs) compared to non-ASCVD participants.[3] Its frequent coexistence with heart failure and chronic kidney disease creates diverse phenotypes, complicating clinical management.[4,5]

Recent advancements in diabetes pharmacotherapy, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT2is), have shown promise in reducing MACE rates among ASCVD patients.[6] Network meta-analyses have demonstrated that both drug classes reduce cardiovascular and all-cause mortality, with SGLT2is particularly effective in reducing hospitalization for heart failure and GLP-1 RAs in reducing stroke risk.[7,8] Further studies have shown SGLT2is' positive effects on kidney outcomes and GLP-1 RAs' effectiveness in reducing MACE rates, hospitalization for heart failure, and kidney function deterioration.[9,10]

Current treatment guidelines recommend tailoring diabetes medication based on patient comorbidities, suggesting both SGLT2is and GLP-1 RAs for ASCVD patients, with a preference for SGLT2is in those with chronic kidney disease or heart failure. In cases where SGLT2is are not tolerated in chronic kidney disease patients, GLP-1 RAs are suggested as an alternative.[11] However, managing patients with distinct ASCVD phenotypes, particularly those with peripheral artery disease, acute cardiovascular events, coexisting heart failure, or chronic kidney disease, remains complex due to a lack of robust, evidence-based guidance.

While randomized controlled trials provide valuable insights, their findings can vary in both direction and magnitude, leading to uncertainty in treatment effects. For instance, in patients with ASCVD and chronic kidney disease, one trial showed a neutral effect of GLP-1 RAs on MACE,[12] while another demonstrated a significant reduction.[13] Similarly, in this patient group, two trials reported a neutral effect of SGLT2 inhibitors,[14,15] whereas another showed a reduction in MACE.[16] With the emergence of more recent studies,[17,18] these conflicting results underscore the need for a systematic review and meta-analysis to consolidate the evidence and clarify the overall treatment effects.

According to the Cochrane Handbook, a systematic review is a comprehensive synthesis of existing research and may or may not include a meta-analysis. A meta-analysis specifically refers to the statistical combination of different studies' results to derive pooled effects estimates.[19] To address this knowledge gap and provide more precise treatment recommendations, we conducted a systematic review and meta-analysis to assess the comparative cardiovascular effectiveness of SGLT2is and GLP-1 RAs across diverse ASCVD phenotypes. We aim to provide clinicians with valuable insights for tailoring treatment strategies to meet the specific needs of patients with various ASCVD manifestations.

Methods

Data sources and search strategy

We searched Cochrane Library, Embase, and PubMed databases for articles published up to 13 April 2023, using terms for SGLT2is, GLP-1 RAs, DPP4is, and cardiovascular diseases. (Detailed search strategy is provided in Supplementary material online, Appendix *Table 1*.) DPP4i trials were included for comparison due to their neutral cardiovascular effects. Manual cross-referencing was also performed.

Study selection

We applied pre-specified inclusion criteria to ensure alignment with our research objectives. Eligible studies met the following criteria: (1) randomized controlled trial design; (2) comparison of SGLT2is, GLP-1 RAs, or DPP4is with placebo, standard care, or each other; (3) enrolment of patients with ASCVD; and (4) reporting of MACE as an outcome. ASCVD was defined as the presence of coronary artery disease, peripheral artery disease, stroke, or a history of acute cardiovascular events (defined as acute ischaemic stroke or myocardial infarction in selected studies).

For this study, MACE was considered as one of the following composite endpoints: (1) three-point MACE: cardiovascular mortality, non-fatal stroke, or non-fatal myocardial infarction; (2) four-point MACE: three-point MACE plus hospitalization for unstable angina; (3) cardiovascular mortality or hospitalization for heart failure; or (4) cardiovascular mortality, renal mortality, or progression of renal disease.

We excluded study protocols, conference abstracts, animal studies, comment letters, and observational articles. No language restrictions were imposed.

Data extraction and quality assessment

Data for the meta-analysis were extracted from detailed results reported in the included randomized controlled trials, which provided comprehensive outcome data. Two independent reviewers (Y.-M.L. and J.-Y.W.) extracted key information from eligible studies, including study characteristics (e.g. trial name and publication year), patient demographics (e.g. sample size, age, and comorbidities), intervention details (e.g. dose and frequency), comparison group, and outcome definitions. Discrepancies were resolved through consensus, with a third author (C.-T.L.) arbitrating when necessary.

The risk of bias in included randomized controlled trials was assessed independently by Y.-M.L. and J.-Y.W. using the Cochrane Risk of Bias 2 tool.[20] This tool evaluates five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Based on this assessment, studies were classified as having low, some concerns, or high risk of bias.

Data synthesis and analysis

Meta-analyses are conducted to increase statistical power by pooling results from multiple trials, enabling the detection of smaller effect sizes that may not be evident in individual trials. Our systemic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21] The study protocol was

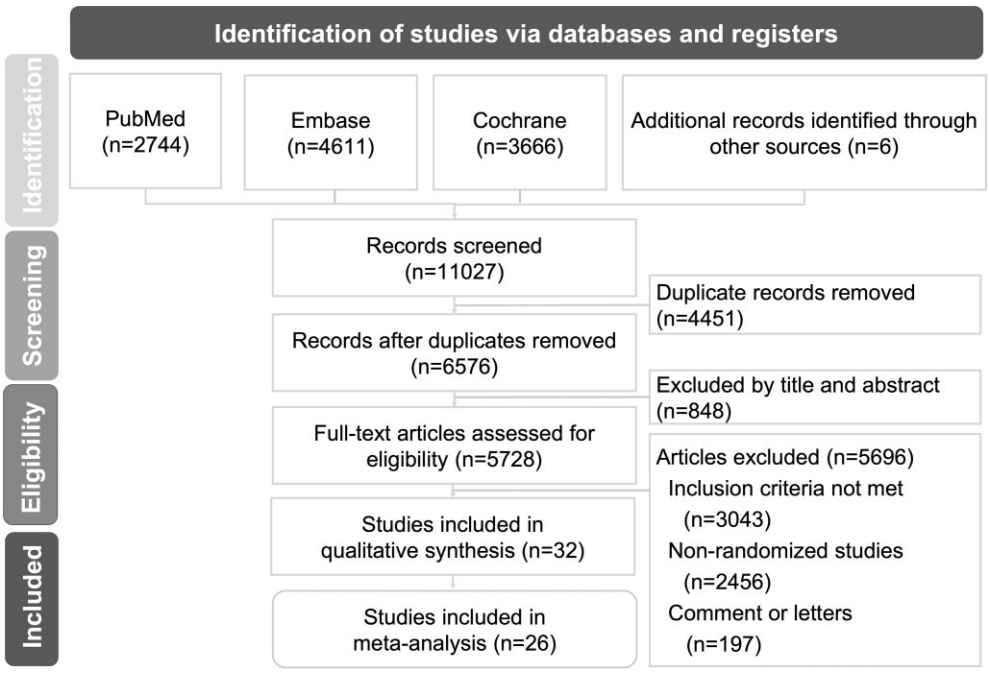

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search and selection process.

registered on PROSPERO (CRD42023493814) to ensure transparency and methodological rigour.

Data analysis was performed using RevMan software (Version 5.4.1). We employed a random-effects model based on the Mantel–Haenszel method. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to quantify the association between interventions and MACE rates.

Heterogeneity was assessed using I^2 statistics, with $I^2 \leq 25\%$, $25\% < I^2 < 75\%$, and $I^2 \geq 75\%$ indicating low, moderate, and high heterogeneity, respectively.[22] We performed a one-by-one exclusion analysis to evaluate the impact of individual studies on our results. We conducted a subgroup sensitivity analysis based on these definitions to account for potential variations in MACE definitions across studies. Additionally, for patients with ASCVD and chronic kidney disease, we performed a separate subgroup analysis based on albuminuria stages (A1: <30 mg/g, A2: 30–299 mg/g, and A3: >300 mg/g) to assess their impact on outcomes in this specific patient participants. A meta-regression analysis was conducted to explore potential sources of heterogeneity.

Sensitivity analysis

To strengthen our conclusions, we performed a network meta-analysis, combining both direct and indirect evidence from trials to offer a more comprehensive assessment of the relative effects of the interventions.

Publication bias assessment

We assessed potential publication bias by visually inspecting funnel plots for asymmetry in the distribution of study effects. Additionally, we conducted Egger's regression test to quantitatively evaluate the likelihood of publication bias in all major outcomes.

Role of the funding source

This research received no external funding or financial support, ensuring independence in study design, data collection, analysis, interpretation, and manuscript preparation.

Results

Characteristics of included trials and study Participants

Our literature search, as shown in *Figure 1*, identified 11 027 articles. After removing duplicates and screening, 32 studies met the inclusion criteria for qualitative synthesis, with 26 studies (151 789 patients) included in the final meta-analysis.

Table 1 summarizes the study participants' characteristics. Participant mean age ranged from 46 to 85 years. Diabetes prevalence varied from 0% to 100%, ASCVD from 26.1% to 100%, peripheral artery disease from 6% to 30%, heart failure from 4% to 100%, and chronic kidney disease from 0% to 100%.

Of the 32 studies, 7 evaluated DPP4is,[23–29] 10 assessed GLP-1 RAs,[12,13,30–37] and 15 investigated SGLT2is.[14–18,38–47] Primary outcomes varied, with most focusing on MACE.

DPP4i trials used three-point MACE (five studies)[23–25,27,29] or four-point MACE (two studies)[26,28] as outcomes. GLP-1 RA trials defined outcomes as three-point MACE (eight studies)[12,13,30–33,36,37] or four-point MACE (two studies).[34,35] SGLT2i trials specified outcomes as three-point MACE (five studies),[14,15,17,39,40] cardiovascular mortality and hospitalization for heart failure (seven studies),[41–47] cardiovascular death and hospitalization for unstable angina (one study),[32] or a composite of cardiovascular mortality, renal death, or kidney disease progression (two studies).[16,18] Kidney disease progression was defined as sustained estimated glomerular filtration rate decline ≥50% or end-stage kidney disease development.

Most studies used placebo as control, with two comparing interventions to glimepiride,[26,29] and one to insulin glargine.[35]

Quality assessment of included studies

Supplementary material online, Appendix *Figures 1–3* present the risk of bias assessment. Most studies showed low risk of bias in

Table 1 Characteristics of included trials and study participants

Study (year)	Patient number	Age (year)	DM(%)	HTN (%)	ASCVD (%)	CAD (%)	PAD (%)	Stroke (%)	HF (%)	¶CKD (%)	BMI (kg/m^2)	Intervention	Comparison	Outcome
SAVOR TIMI 53	I: 8280 C:8212	I:65.1 ± 8 C:65.0 ± 8	100%	I: 81.2% C:82.4%	I: 78.4% C:78.7%	NA	NA	NA	I: 12.8% C:12.8%	§I:15.7% C:15.6%	I: 31.1 ± 5 C:31.2 ± 5	Saxagliptin 5 mg QD PO	Placebo	3P-MACE
Gantz (2017)	I: 2100 C:2102	I:63.7 ± 8 C:63.6 ± 8	100%	I: 95.1% C:95.6%	100%	NA	NA	NA	I: 16.2% C:14.3%	NA	I: 31.2 ± 5 C:31.4 ± 5	Omarigliptin 25 mg QW PO	Placebo	3P-MACE
CARMELINA	I: 3494 C:3485	I:66.1 C:65.6	100%	I:90.8% C:91.2%	100%	I: 58.1% C:58.9%	NA	NA	I: 27.2% C:26.4%	I: 63.0% C:61.6%	I: 31.4 ± 5 C:31.3 ± 5	Linagliptin 5 mg QD PO	Placebo	3P-MACE
Gallwitz (2012)	I: 776 C:775	I:59.8 ± 9 C:59.8 ± 9	100%	NA	NA	NA	NA	NA	NA	NA	I:30.2 ± 4 C:30.3 ± 4	Linagliptin 5 mg QD PO	Glimepiride 1 mg QD PO	4P-MACE
EXAMINE	I: 2701 C:2679	I:61.0 C:61.0	100%	I: 82.5% C:83.6%	100%	100%	I: 9.7% C:9.4%	I: 7.2% C:7.2%	I: 28.0% C:27.8%	I: 28.6% C:29.6%	NA	†Alogliptin 25 mg, 12.5 mg, 6.25 mg QD PO	Placebo	3P-MACE
TECOS	I: 7257 C:7266	65.5 ± 8	100%	86.20%	100%	74%	16.6%	24.50%	18%	2.20%	30.2 ± 5	†Sitagliptin 100 mg or 50 mg QD PO	Placebo	4P-MACE
CAROLINA	I: 3023 C:3010	I:63.9 ± 9 C:64.2 ± 9	100%	I: 90.2% C:89.6%	I: 42.2% C:41.7%	I: 32.1% C:31.2%	I: 6.9% C:6.7%	I: 12.3% C:11.9%	I: 4.1% C:5.0%	I: 19.6% C:17.9%	I: 30.2 ± 5 C:30.0 ± 5	Linagliptin 5 mg QD PO	Glimepiride 1–4 mg QD PO	3P-MACE
EXSCEL	I: 7356 C:7396	I: 62.0 ± 6 C:62.0 ± 6	100%	NA	73%	NA	18.9%	NA	16.1%	71.0%	I: 31.9 ± 4 C:31.7 ± 4	Exenatide 2 mg QW SC	Placebo	3P-MACE
REWIND	I: 4949 C:4952	I: 66.2 ± 6 C:66.2 ± 6	100%	I: 93.0% C:93.3%	I: 31.5% C:31.4%	NA	8.70%	6.90%	I: 8.5% C:8.7%	I:21.8% C:22.6%	I:32.3 ± 5 C:32.3 ± 5	Dulaglutide 1.5 mg QW SC	Placebo	3P-MACE
LEADER	I: 4668 C:4672	I: 64.2 ± 7 C:64.4 ± 7	100%	NA	I: 82.1% C:80.6%	NA	NA	I: 15.6% C:16.6%	I: 17.9% C:17.8%	I:25.4% C:24.0%	I:32.5 ± 6 C:32.5 ± 6	Liraglutide 1.8 mg QD SC	Placebo	3P-MACE
AMPLITUDE-O	I: 2717 C:1359	64.5 ± 8	100%	91.3%	89.6%	NA	NA	NA	18.1%	‡32.6%	32.7 ± 6	Efpeglenatide 4 mg or 6 mg QW SC	Placebo	3P-MACE

Table I Continued

Study (year)	Patient number	Age (year)	DM(%)	HTN (%)	ASCVD (%)	CAD (%)	PAD (%)	Stroke (%)	HF (%)	¶CKD (%)	BMI (kg/m^2)	Intervention	Comparison	Outcome
HARMONY	I: 4732 C:4732	I: 64·1 ± 8 C:64.2 ± 8	100%	I: 86.0% C:87.0%	100%	I: 70.0% C:71.0%	I: 25.0% C:24.0%	I: 17.0% C:18.0%	I: 20.0% C:20.0%	I:19.0% C:18.0%	I: 32.3 ± 5 C:32.3 ± 5	‡Albiglutide 30–50 mg QW SC	Placebo	3P-MACE
ELIXA	I: 3034 C:3034	I: 59.9 ± 9 C:60.6 ± 9	100%	I: 75.6% C:77.1%	100%	100%	I: 7.8% C:7.5%	I: 4.7% C:6.2%	I: 22.5% C:22.3%	I:21.7% C:24.7%	I: 30.1 ± 5 C:30.2 ± 5	Lixisenatide 20 μg QD SC	Placebo	4P-MACE
SUPRASS-4	I: 995 C:1000	63.6 ± 8	100%	NA	87.0%	44.0%	30.0%	12.0%	7.0%	17%	32.6 ± 5	Tirzepatide 5 mg, 10 mg or 15 mg QW SC	Insulin galarine 100 U/mL QD SC	4P-MACE
SUSTAIN-6	I: 1648 C:1649	64.6 ± 7	100%	92.8%	82.9%	60.5%	NA	11.6%	23.6%	28.50%	NA	Semaglutide 0.5 mg, 1.0 mg QW SC	Placebo	3P-MACE
PIONEER-6	I: 1591 C:1592	66.0 ± 7	100%	NA	84.7%	NA	NA	NA	NA	26.90%	32.3 ± 6	Semaglutide 14 mg QD PO	Placebo	3P-MACE
SELECT	I: 8803 C:8801	I: 61.6 ± 8 C:61.6 ± 8	0%	I: 81.9% C:81.6%	100%	I: 82.2% C:82.0%	I: 8.6% C:8.8%	I: 23.4% C:23.3%	I: 24.5% C:24.2%	I:10.9% C:10.6%	I: 33.3 ± 5 C:33.4 ± 5	Semaglutide 2.4 mg QW SC	Placebo	3P-MACE
Adel (2022)	I: 52 C:54	I: 55 ± 9 C:57 ± 9	100%	I: 57.8% C:66.7%	100%	100%	NA	I: 2.2% C:4.2%	NA	I: 8.9% C:6.3%	NA	Empaglifozin 10 mg QD PO	Placebo	CV death, hospitalization due to unstable angina
EMPA-KIDNEY	I: 3304 C:3305	I: 63.9 ± 13 C:63.8 ± 13	I:46.2% C:45.8%	NA	I:26.1% C:27.4%	NA	I: 7.3% C:6.8%	NA	I: 9.8% C:10.1%	#I:78.6% C:79.0%	I: 29.7 ± 6 C:29.8 ± 6	Empaglifozin 10 mg QD PO	Placebo	**CV or renal death, progression of kidney disease
DAPA-CKD	I: 2152 C:2152	I: 61.8 ± 12 C: 61.9 ± 12	67.50%	64.1%	I:37.8% C:37.0%	NA	NA	NA	10.8%	#I:59.1% C:58.1%	I: 29.4 ± 6 C:29.6 ± 6	Dapaglifocin 10 mg QD PO	Placebo	**CV or renal death, progression of kidney disease

Table 1 Continued

Study (year)	Patient number	Age (year)	DM(%)	HTN (%)	ASCVD (%)	CAD (%)	PAD (%)	Stroke (%)	HF (%)	¶CKD (%)	BMI (kg/m^2)	Intervention	Comparison	Outcome
CANVAS	I: 5795 C:4347	I: 63.2 ± 8 C:63.4 ± 8	100%	90.0%	I: 64.8% C:66.7%	56.4%	20.8%	19.3%	14.4%	34.6%	32.0 ± 5	Canagliflozin 300 mg QD PO	Placebo	3P-MACE
CREDENCE	I: 2202 C:2199	I: 62.9 ± 9 C:63.2 ± 9	100%	96.8%	50.4%	NA	NA	NA	14.8%	58.8%	31.3 ± 6	Canaglifozin 100 mg QD PO	Placebo	3P-MACE
EMPA-REG	I: 4687 C:2333	63.1 ± 8	100%	I: 94.9% C:95.2%	100%	I: 75.6% C:75.6%	I: 21.0% C:25.0%	I: 23.1% C:23.7%	I: 9.9% C:10.5%	I: 25.9% C:26.0%	I: 30.6 ± 5 C:30.7 ± 5	Empaglifozin 10 mg or 25 mg QD PO	Placebo	3P-MACE
DECLARE TIMI 58	I: 8582 C:8578	I: 63.9 ± 6 C:64.0 ± 6	100%	NA	I: 40.5 C:40.8%	I: 32.9% C:33.0%	I: 6.1% C:5.9%	I: 7.6% C:7.6%	I: 9.9% C:10.2%	0%	I: 32.1 ± 6 C:32.0 ± 6	Dapaglifozin 10 mg QD PO	Placebo	3P-MACE
VERTIS CV	I: 5499 C:2747	I: 64.4 ± 8 C:64.4 ± 8	100%	NA	100%	I: 75.4% C:76.9%	I: 18.7% C:18.6%	I: 23.2% C:22.3%	I: 23.4% C:24.5%	I: 21.8% C:22.1%	I: 31.9 ± 5 C:32.0 ± 5	Ertuglifozin 5 mg or 15 mg QD PO	Placebo	3P-MACE
EMPEROR-Preserved	I: 2997 C:2991	I: 71.8 ± 9 C:71.9 ± 9	49.0%	I: 90.8% C:90.4%	I: 36.0% C:34.7%	NA	NA	NA	100%	I: 50.2% C:49.6%	I: 29.7 ± 5 C:29.9 ± 5	Empagliflozin 10 mg QD PO	Placebo	CV death, HHF
EMPEROR-Reduced	I: 1863 C:1867	I: 67.2 ± 10 C:66.5 ± 11	49.8%	I: 72.4% C:72.3%	I: 52.8% C:50.7%	NA	NA	NA	100%	I: 48.0% C:48.6%	I: 28.0 ± 5 C:27.8 ± 5	Empagliflozin 10 mg QD PO	Placebo	CV death, HHF
DELIVER	I: 3131 C:3132	I: 71.8 ± 9 C:71.5 ± 9	I: 44.7% C:44.9%	I: 88.0% C:89.3%	NA	NA	NA	NA	100%	I: 48.4% C:49.6%	I: 29.8 ± 6 C:29.9 ± 6	Dapagliflozin 10 mg QD PO	Placebo	CV death, HHF

Table I Continued

Study (year)	Patient number	Age (year)	DM(%)	HTN (%)	ASCVD (%)	CAD (%)	PAD (%)	Stroke (%)	HF (%)	¶CKD (%)	BMI (kg/m^2)	Intervention	Comparison	Outcome
DAPA-HF	I: 2373 C:2371	I: 66.2 ± 11 C:66.5 ± 10	I: 41.8% C:41.8%	74%	I: 55.5% C:57.3%	NA	NA	NA	100%	I: 40.6% C:40.7%	I: 28.2 ± 6 C:28.1 ± 5	Dapagliflozin 10 mg QD PO	Placebo	CV death, HHF
SOLOIST-WHF	I: 608 C:614	I: 69 ± 6 C:70 ± 6	100%	NA	58.2%	NA	NA	NA	100%	69.8%	I: 30.4 ± 4 C:31.1 ± 4	‡Sotagliflozin 200 mg to 400 mg QD PO	Placebo	CV death, HHF
SCORED	I: 5292 C:5292	I: 69 ± 6 C:69 ± 6	100%	NA	NA	NA	NA	I: 8.9% C:9.0%	I: 31.0% C:31.0%	100%	I: 31.9 ± 3 C:31.7 ± 3	‡Sotagliflozin 200 mg to 400 mg QD PO	Placebo	CV death, HHF
EMPA-RESPONSE AHF	I: 40 C:39	I: 79 ± 6 C:73 ± 10	I: 38.0% C:28.0%	I: 68.0% C:56.0%	I: 28.0% C:29.0%	NA	NA	I: 5.0% C:5.0%	100%	NA	NA	Empagliflozin 10 mg QD PO	Placebo	CV death, HHF

Abbreviations: I, intervention; C, comparison; 3P-MACE, non-fatal myocardial infarction, non-fatal stroke, cardiovascular death; 4P-MACE, non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and hospitalization for unstable angina; DM, diabetes mellitus; HTN, hypertension; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; PAD, peripheral artery disease; HF, heart failure; CKD, chronic kidney disease; BMI, body mass index; CV death, cardiovascular death; HHF, hospitalization for heart failure; QD, every day; QW, every week; PO, oral administration; NA, non-applicable; SC, subcutaneous.

†Titrate according to renal function.

‡Titrate according to tolerability to the medication.¶Chronic kidney disease is defined as kidney damage or an estimated glomerular filtration rate (eGFR) <<60 mL/min/1.73 m.

§Chronic kidney disease is defined as an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m.

|Chronic kidney disease is defined as estimated glomerular filtration rate (eGFR) <71.5 mL/min/1.73 m.

#Chronic kidney disease is defined as estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m.

**A sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

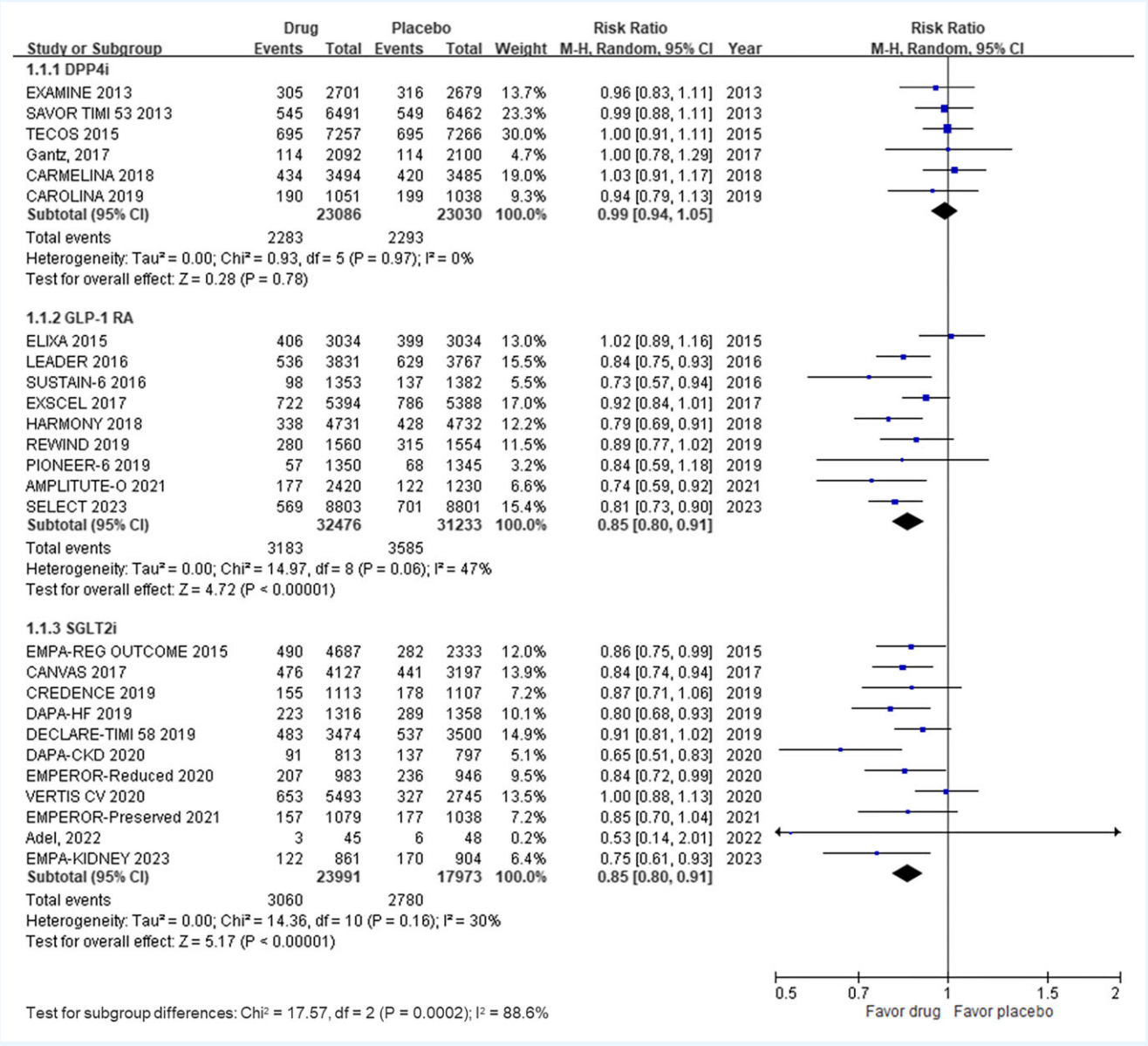

Figure 2 Forest plot: MACE risk in ASCVD patients treated with SGLT2is, GLP-1 RAs, or DPP4is vs. placebo. SGLT2is and GLP-1 RAs significantly reduced risk; DPP4is showed no difference.

randomization (25/32), deviations from intended interventions (28/32), and missing outcome data (28/32). For outcome measurement, 30/32 studies had low risk. In result selection, 28 studies had low risk, 3 had some concerns, and 1 had high risk. Overall, 18 studies were low risk, 11 had some concerns, and 3 were high risk.

Outcomes

MACE in ASCVD patients

Figure 2 shows both GLP-1 RAs and SGLT2is significantly reduced MACE rates in ASCVD patients. GLP-1 RAs (9 studies, $n = 63\,709$): 9.8% vs. 11.4%, RR 0.85, 95% CI 0.80–0.91, $P < 0.001$, $I^2 = 47\%$. SGLT2is (11 studies, $n = 41\,964$): 12.7% vs. 15.4%, RR 0.85, 95% CI 0.80–0.91, $P < 0.001$, $I^2 = 30\%$.

MACE in patients with peripheral artery disease

In peripheral artery disease patients (*Figure 3*), GLP-1 RAs (four studies, $n = 6\,798$) significantly reduced MACE rates: 11.4% vs. 13.4%, RR 0.86, 95% CI 0.76–0.98, $P = 0.02$, $I^2 = 0\%$. SGLT2is (three studies, $n = 3608$) showed a non-significant trend: 13.5% vs. 15.6%, RR 0.89, 95% CI 0.74–1.06, $P = 0.19$, $I^2 = 20\%$.

MACE in patients with history of acute cardiovascular events

GLP-1 RAs (six studies, $n = 25\,372$) significantly reduced MACE rates (*Figure 4*): 13.8% vs. 15.1%, RR 0.90, 95% CI 0.83–0.97, $P = 0.007$, $I^2 = 28\%$.

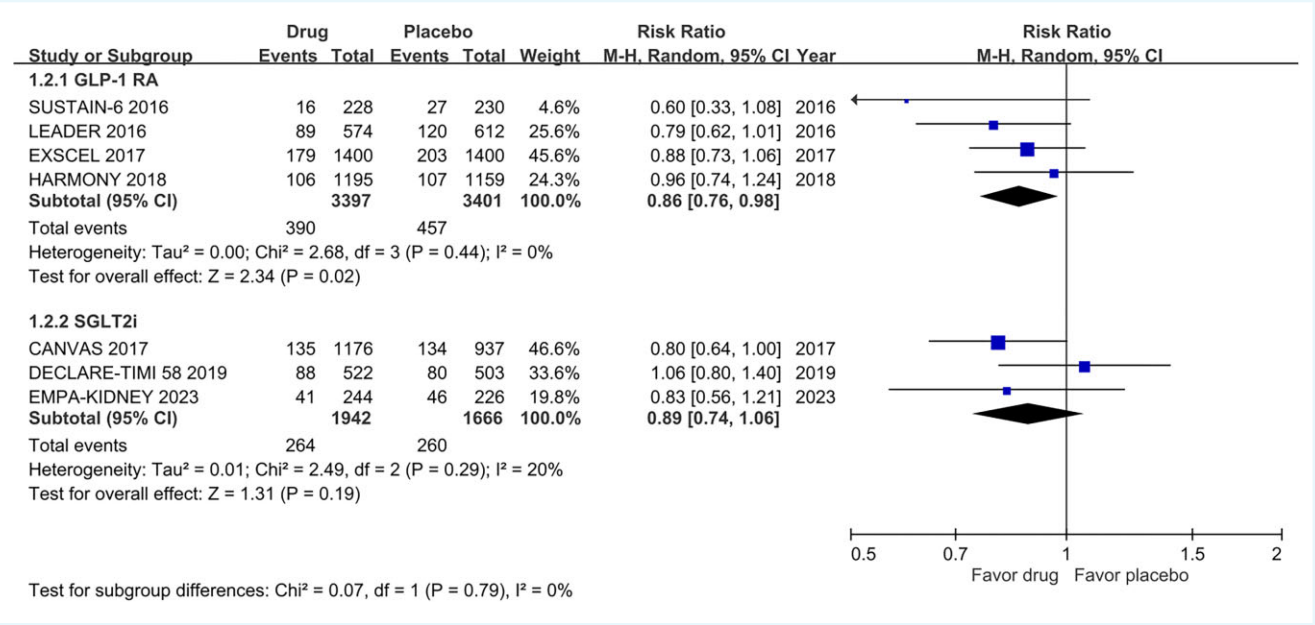

Figure 3 Forest plot: MACE risk in patients with peripheral artery disease treated with GLP-1 RAs or SGLT2is vs. placebo. GLP-1 RAs significantly reduced risk; SGLT2is showed no significant difference.

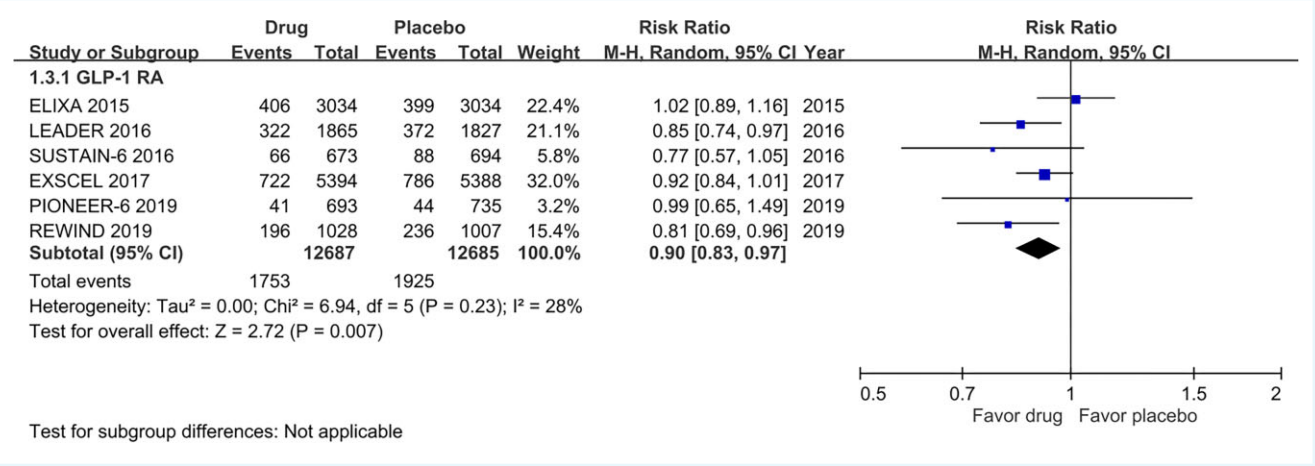

Figure 4 Forest plot: MACE risk in patients with history of acute cardiovascular events treated with GLP-1 RAs vs. placebo. GLP-1 RAs significantly reduced risk.

MACE in ASCVD patients with heart failure

Both drug classes reduced MACE rates in ASCVD patients with heart failure (*Figure 5*). GLP-1 RAs (two studies, $n = 6208$): 9.5% vs. 13.1%, RR 0.73, 95% CI 0.63–0.84, $P < 0.001$, $I^2 = 0\%$. SGLT2is (five studies, $n = 9383$): 16.6% vs. 19.8%, RR 0.86, 95% CI 0.78–0.95, $P = 0.002$, $I^2 = 14\%$.

MACE in ASCVD patients with chronic kidney disease

In ASCVD patients with chronic kidney disease (*Figure 6*), SGLT2is (five studies, $n = 9219$) significantly reduced MACE rates: 14% vs. 16.6%, RR 0.84, 95% CI 0.72–0.99, $P = 0.03$, $I^2 = 61\%$. GLP-1 RAs (two studies, $n = 4120$) did not: RR 0.82, 95% CI 0.64–1.05, $P = 0.12$, $I^2 = 52\%$.

Sensitivity and subgroup analysis

One-by-one exclusion analyses identified ELIXA, DAPA-CKD, and VERTIS CV trials as primary heterogeneity sources.[27,34,39] Results remained consistent after removal (Supplementary material online, Appendix *Tables 2–6*). *Figure 7* shows SGLT2is significantly reduced MACE risk in chronic kidney disease patients with albuminuria stage A3 (RR 0.61, 95% CI 0.37–0.99, $P = 0.05$, $I^2 = 69\%$), but not in stages A1 and A2 (RR 0.82, 95% CI 0.63–1.06, $P = 0.12$, $I^2 = 42\%$). Results were consistent across various MACE definitions (Supplementary material online, Appendix *Table 7*). The meta-regression results showed no statistically significant differences in the comparison between GLP-1 RAs and placebo concerning age ($P = 0.10$), diabetes ($P = 0.56$), or hypertension ($P = 0.15$). Similarly, in the comparison

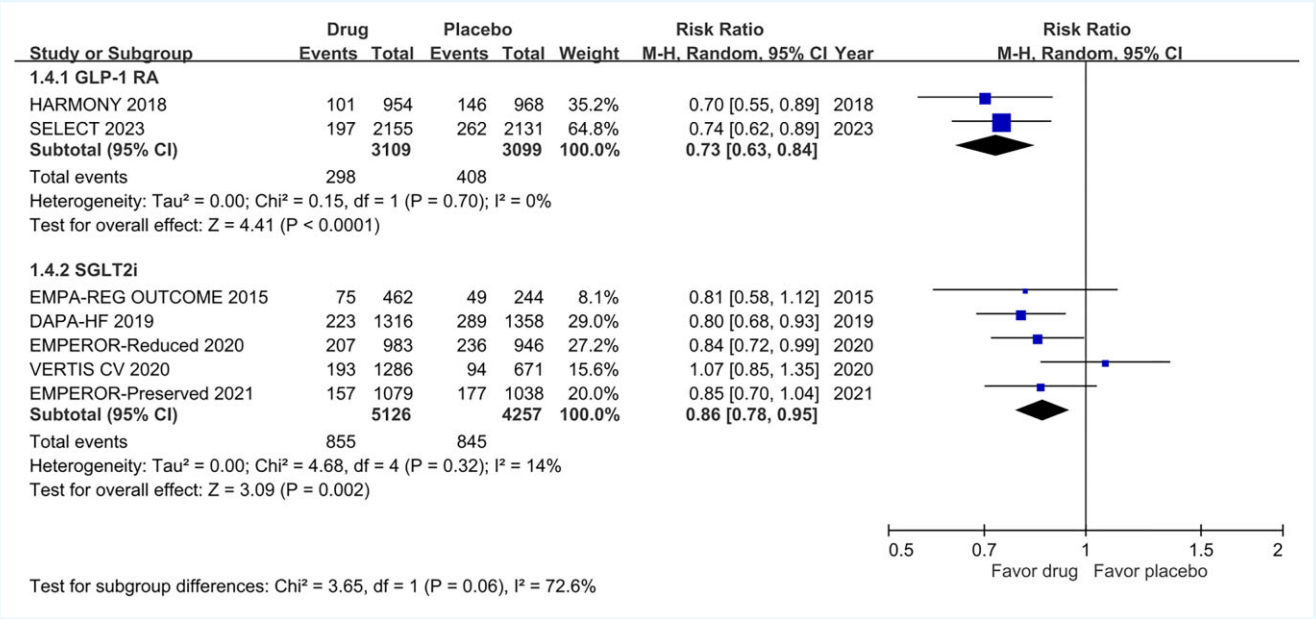

Figure 5 Forest plot: MACE risk in ASCVD and heart failure patients treated with GLP-1 RAs or SGLT2is vs. placebo. Both significantly reduced risk.

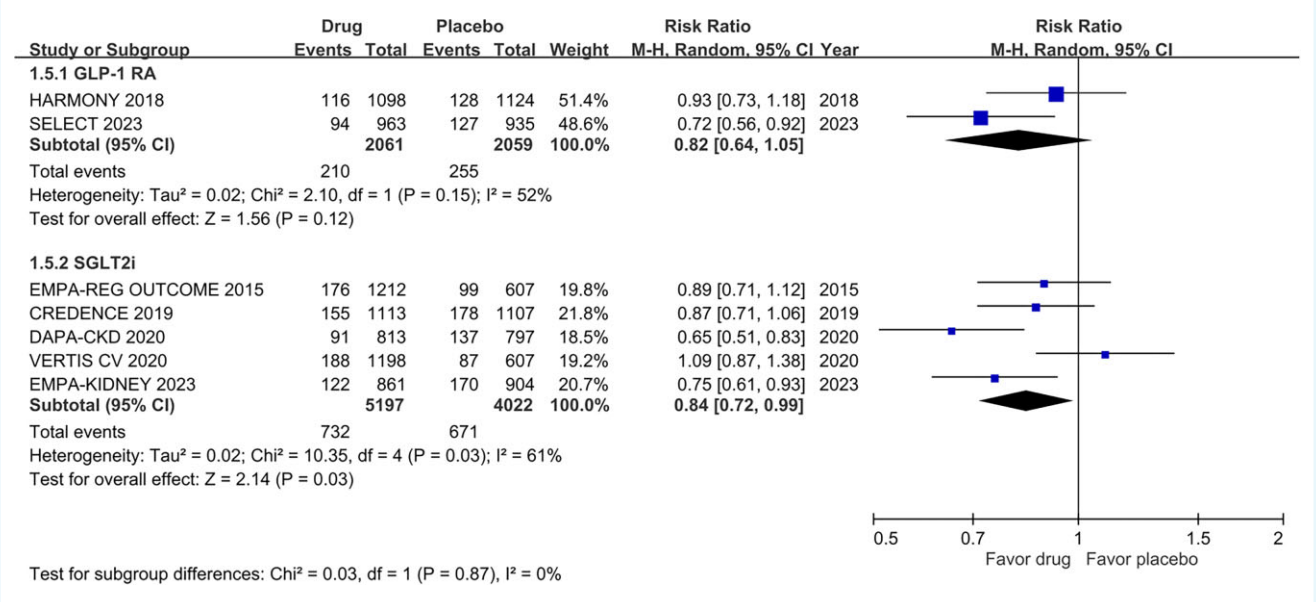

Figure 6 Forest plot: MACE risk in ASCVD and chronic kidney disease patients treated with SGLT2is or GLP-1 RAs vs. placebo. SGLT2is significantly reduced risk; GLP-1 RAs showed no significant difference.

between SGLT2is and placebo, no statistically significant differences were observed for age ($P = 0.68$) or hypertension ($P = 0.11$). However, a statistically significant difference was found for diabetes in the SGLT2i group ($P = 0.04$, slope = 0.20). The results from the network meta-analysis were consistent with the findings from the direct comparisons. (Supplementary material online, Appendix *Figures 4* and *5*.)

Publication bias

The funnel plot analysis revealed no noticeable asymmetry for primary outcomes. (Supplementary material online, Appendix *Figures 6–11*.) Furthermore, Egger's regression test did not indicate any significant evidence of publication bias across the major outcomes, with all p-values >0.05.

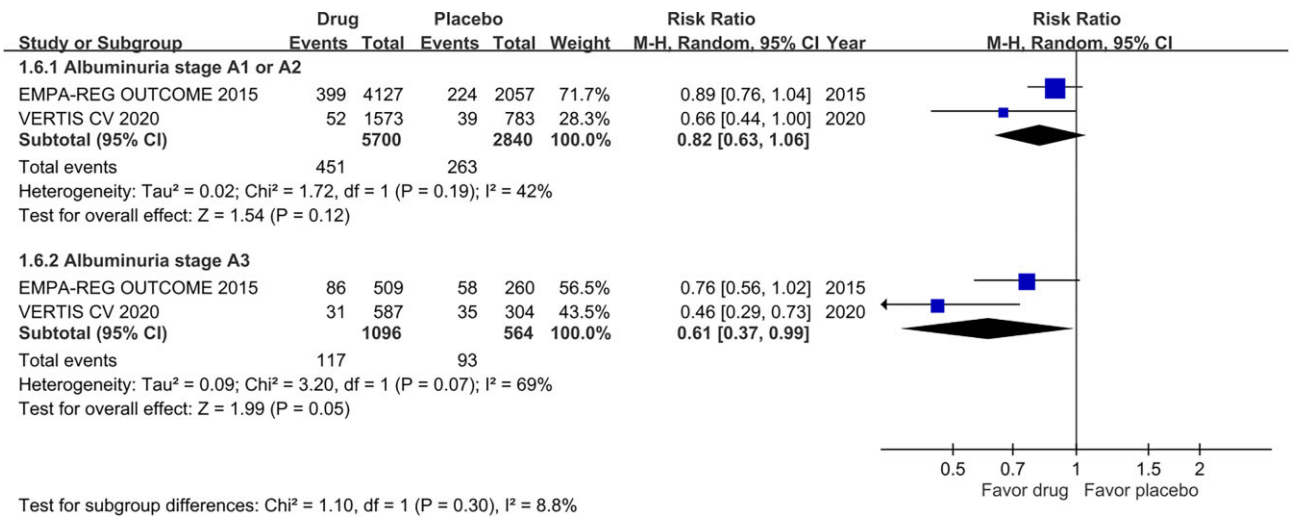

Figure 7 Forest plot: subgroup analysis of MACE risk in ASCVD and chronic kidney disease patients treated with SGLT2is, stratified by albuminuria stages. Significant risk reduction in stage A3; no significant difference in stages A1 and A2.

Discussion

This systemic review and meta-analysis provide robust evidence for the comparative cardiovascular effectiveness of GLP-1 RAs and SGLT2is across various ASCVD phenotypes. Both drug classes significantly reduce MACE rates in ASCVD patients, with comparable overall effectiveness (RR 0.85). However, subgroup and sensitivity analyses revealed important nuances in their effectiveness across different ASCVD participants.

GLP-1 RAs and SGLT2is demonstrated effectiveness in different ASCVD participants. GLP-1 RAs showed particular effectiveness in reducing MACE rates among patients with peripheral artery disease and those with a history of acute cardiovascular events, possibly due to their anti-inflammatory effects and lipid metabolism modification in these patients with severe atherosclerosis.[48] An animal study has shown that liraglutide treatment in ApoE-/- mice led to a significant reduction in aortic plaque area and complexity, suggesting a direct anti-atherogenic effect.[49] Additionally, liraglutide has been found to suppress macrophage foam cell formation, further contributing to the reduction of atherosclerosis.[50] These findings indicate that GLP-1 RAs may not only prevent atherosclerosis progression but potentially reverse existing plaques.

SGLT2is, on the other hand, showed significant MACE reduction in ASCVD patients with concomitant heart failure or chronic kidney disease, especially those with severe albuminuria (stage A3). Their benefits are largely attributed to haemodynamic effects, including natriuresis, glucose elimination, and blood pressure reduction, which may lead to improved ventricular remodelling.[51] Besides, SGLT2is may also contribute to atherosclerosis regression through indirect mechanisms. The randomized trial demonstrated that empagliflozin treatment was associated with a reduction in left ventricular mass index and improved diastolic function.[52] These improvements in cardiac structure and function could lead to reduced mechanical stress on arterial walls, potentially facilitating plaque stabilization and regression. Moreover, the anti-inflammatory effects of SGLT2is, as evidenced by reductions in biomarkers such as high-sensitivity C-reactive protein and interleukin-6,[53] may create a more favourable environment for plaque regression.

For patients with concurrent ASCVD and heart failure, both GLP-1 RAs and SGLT2is showed significant benefits. GLP-1 RAs may be particularly beneficial in heart failure with preserved ejection fraction and ischaemic cardiomyopathy, while SGLT2is may reduce MACE by decreasing afterload and mitigating structural remodelling.[54] These findings align with and extend current treatment guidelines, which suggest considering both drug classes for ASCVD patients, with a preference for SGLT2is in those with chronic kidney disease or heart failure.[55] Our results provide additional granularity, supporting a nuanced approach to treatment selection based on specific ASCVD phenotypes, which may lead to more personalized and effective cardiovascular risk reduction strategies. The meta-regression analysis revealed a statistically significant positive slope for diabetes in the comparison between SGLT2is and placebo, indicating that diabetic patients have a higher cardiovascular risk and event rate. This result aligns with current guidelines, which recommend SGLT2is for reducing cardiovascular risk in patients with diabetes.

Despite the strengths of this meta-analysis, several limitations should be acknowledged. First, the included studies varied in their definitions of MACE and follow-up durations, which may have introduced some heterogeneity. However, our sensitivity analyses demonstrated the robustness of our findings across different MACE definitions. Second, the number of studies for some subgroup analyses was limited, particularly for certain ASCVD phenotypes, which may have affected the statistical power of these analyses. Third, as with all meta-analyses, our study is subject to the limitations of the included trials, including potential publication bias and heterogeneity in study designs and participants. Therefore, we conducted funnel plots and Egger's tests to strengthen our results, both of which indicated no significant publication bias. Additionally, the variability of ASCVD risk factors across different studies contributed to heterogeneity in our results, and the lack of detailed information prevented us from conducting subgroup analyses based on the prevalence of hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, and smoking status. To address this, we conducted a meta-regression analysis based on age, diabetes mellitus, and hypertension to further strengthen our conclusions. Fourth, the possibility that GLP-1 RAs could influence suicidality is reasonable, considering that GLP-1 receptors are found

in the central nervous system, and GLP-1 RAs have been shown to penetrate the blood–brain barrier.[56,57] Earlier studies have associated bariatric surgery and weight-loss medications with an increased risk of suicide and self-harm.[58] A limitation of our study is the absence of data on additional outcomes such as suicidality, depression, and dementia. The randomized controlled trials included in our analysis did not provide relevant information on these outcomes, and further research is needed to explore the potential links between GLP-1 RAs, SGLT2is, and mental health.

Conclusions

This systemic review and meta-analysis demonstrate significant cardiovascular benefits of both GLP-1 RAs and SGLT2is across various ASCVD phenotypes. Our findings support a nuanced approach to treatment selection: GLP-1 RAs show potential value in peripheral artery disease and post-acute cardiovascular events, while SGLT2is offer advantages in ASCVD patients with chronic kidney disease, particularly those with high albuminuria. Both drug classes show notable effectiveness in patients with concurrent ASCVD and heart failure. Future research should focus on direct comparisons of these drug classes in specific ASCVD participants to further refine treatment strategies for these high-risk patients.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Conflict of interest: All authors declare that the research was conducted in the absence of any financial or commercial relationships, which could become a potential conflict of interest.

Data availability

All data generated or analysed during this study are included in this published study and its supplementary information files.

Author contribution

Y.-M.L., J.-Y.W., M.-C.L., C.-L.S., and C.-T.L. were instrumental in this study, participating in the research's conception and design, as well as in the drafting of the manuscript. Y.-M.L. and J.-Y.W. played key roles in extracting and analysing data and interpreting the findings. The manuscript underwent revisions by H.S.T., W.-T.C., S.-Y.C., F.-H.K., H.-J.T., and C.-T.L. All authors have given their final approval and collectively endorse all aspects of the work, thereby guaranteeing its integrity and accuracy.

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