

ORIGINAL ARTICLE

Comparative efficacy of novel antidiabetic drugs on cardiovascular and renal outcomes in patients with diabetic kidney disease: A systematic review and network meta-analysis

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Abstract

Aims: To conduct a systematic review and network meta-analysis to determine the comparative effectiveness of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with diabetic kidney disease (DKD).

Methods: Phase III or IV randomized, placebo-controlled trials evaluating SGLT2 inhibitors, GLP-1RAs or DPP-4 inhibitors in patients with DKD were identified from the MEDLINE database. The outcomes of interest were a kidney-specific composite outcome, kidney disease progression, major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF) and cardiovascular death. A network meta-analysis was conducted to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Sixteen trials representing a total of 46 292 patients were included. SGLT2 inhibitors significantly reduced the risk of the kidney-specific composite outcome by 26% compared to GLP-1RAs (HR 0.74, 95% CI 0.62-0.88) and by 36% compared to DPP-4 inhibitors (HR 0.64, 95% CI 0.52-0.79). The risk of MACE was significantly reduced with SGLT2 inhibitors (by 18%; HR 0.82, 95% CI 0.72-0.93), and with GLP-1RAs (by 18%; HR 0.82, 95% CI 0.69-0.96), compared to DPP-4 inhibitors. SGLT2 inhibitors significantly reduced the risk of HHF by 28% compared to GLP-1RAs (HR 0.72, 95% CI 0.56-0.92) and by 41% compared to DPP-4 inhibitors (HR 0.59, 95% CI 0.49-0.71).

Conclusions: A clear advantage was demonstrated by SGLT2 inhibitors in reducing the risks of CV and renal events in patients with DKD, compared to GLP-1RAs and DPP-4 inhibitors. We recommend that SGLT2 inhibitors be considered the treatment of choice in patients with DKD.

KEYWORDS

diabetic kidney disease, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, network meta-analysis, sodium-glucose cotransporter-2 inhibitors

Hongwei Cao and Tao Liu contributed equally to this work.

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1 | INTRODUCTION

An estimated 463 million people live with diabetes worldwide, with type 2 diabetes mellitus accounting for 90% of that total.¹ Diabetic kidney disease (DKD) is one of the major complications of type 2 diabetes mellitus, occurring in approximately 25% to 50% of adults with type 2 diabetes mellitus.²⁻⁹ DKD manifests clinically as persistent microalbuminuria, reduced glomerular filtration rate (GFR), or both, eventually leading to renal impairment and end-stage kidney disease (ESKD).^{2,10} The incidence of kidney disease in patients with type 2 diabetes mellitus substantially increases both cardiovascular (CV) and all-cause mortality risk; DKD is the primary cause of the excess mortality in patients with type 2 diabetes mellitus.¹¹

Intensive glycemic control has been shown to reduce the risk of development of microalbuminuria; however, there was little or no benefit with regard to the risk of kidney disease progression compared with standard control.¹² The renal protective effects of traditional antidiabetic drugs such as insulin, sulphonylureas and metformin have not been specifically studied in large clinical studies. In the past two decades, only renin-angiotensin-aldosterone system (RAAS) blockade has been shown to be effective for renoprotection in DKD.^{13,14} Consequently, progression to ESKD and CV mortality have been two major unmet medical needs in patients with DKD.¹⁵

There is new evidence that novel antidiabetic drug classes such as sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve CV and renal outcomes in patients with type 2 diabetes mellitus. Several large CV outcome trials (CVOTs) studying new antidiabetic drugs in patients with type 2 diabetes mellitus who were at high risk of CV disease (CVD) or who had existing CVD examined kidney effects as secondary outcomes. In the CVOTs, SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58)¹⁶⁻¹⁸ and GLP-1RAs (LEADER, SUSTAIN-6)^{19,20} significantly reduced the risk of new or worsening nephropathy compared with placebo. In addition, large renal outcomes trials of SGLT2 inhibitors (CREDENCE, DAPA-CKD)^{21,22} have demonstrated significant benefits of SGLT2 inhibitors, on top of RAAS blockade, in reducing the risk of kidney disease progression and development of ESKD. However, it is still unclear which class of drug shows the greatest effectiveness in patients with DKD. Therefore, we performed this systematic review and network meta-analysis to determine the comparative effectiveness of SGLT2 inhibitors, GLP-1RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors on CV and renal outcomes in patients with DKD.

2 | METHODS

This systematic review and network meta-analysis was conducted according to a prespecified protocol (INPLASY registration number: INPLASY2021120070). The results from this network meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

2.1 | Search strategy

We conducted a systematic search of the MEDLINE database (via PubMed) using a predefined search strategy to identify relevant randomized controlled trials (RCTs) reported in English up to July 2021. The following search algorithm was used: (“sodium-glucose transporter 2 inhibitors” OR “dipeptidyl-peptidase IV inhibitors” OR “glucagon-like peptide 1”) AND (“diabetic nephropathies”[MeSH]) OR “chronic kidney disease”) AND (“diabetes mellitus, type 2”[MeSH]) AND (randomized controlled). Each search string also contained the synonyms and related keywords of the search terms mentioned above. The complete search strings are provided in Table S1.

2.2 | Study selection

Studies were included if they met the following inclusion criteria for this network meta-analysis: (a) the trial was a Phase III or IV prospective, randomized, controlled, event-driven CV or kidney outcome trial; (b) patients were adults with type 2 diabetes mellitus and kidney disease; (c) interventions were SGLT2 inhibitors, GLP-1RAs or DPP-4 inhibitors; and (d) the comparator was an active or placebo control.

2.3 | Data extraction

The studies retrieved from the database search were assessed for relevance after screening of titles and abstracts. The full texts of relevant studies were then assessed for final eligibility according to the inclusion and exclusion criteria set for this network meta-analysis. Prespecified data were extracted from each of the included studies using a standardized Excel data extraction sheet by one researcher and were independently reviewed by two researchers. The prespecified data extracted for each eligible study included study design, intervention characteristics, baseline characteristics of interest and study outcomes. Any disagreements during data extraction were resolved by consensus.

2.4 | Study outcomes

The outcomes of interest for this network meta-analysis were: a kidney-specific composite outcome, defined as doubling of serum creatinine or a 40% or greater decline in estimated GFR (eGFR), development of ESKD, or death due to kidney disease; kidney disease progression, defined as a composite of doubling of serum creatinine or 40% or greater decline in eGFR, development of ESKD, or death due to kidney disease or CV disease; major adverse CV events (MACE), defined as a composite of CV death, nonfatal myocardial infarction (MI) or non-fatal stroke; hospitalization for heart failure (HHF); and CV death.

TABLE 1 Study design and patient population of the included studies

Study: first author, year	Intervention (dose)	Number of patients	Patient population (inclusion criteria)	DKD criteria (data inclusion criteria for meta-analysis)	Median follow-up, years
DPP-4 inhibitors					
Udell 2015 ³³	Saxagliptin (2.5 mg OD)	2240	T2DM and renal impairment (eGFR 30-50 mL/min/1.73 m ²)	eGFR 30-50 mL/min/1.73 m ²	2
Cornel 2016 ³⁴	Sitagliptin (100 mg OD)	3301	Age ≥18 years; T2DM with or without CKD	eGFR 45-59 mL/min/1.73 m ² (n = 2518) eGFR 30-44 mL/min/1.73 m ² (n = 783)	3
McGuire 2019 ³⁵ Rosenstock 2019 ³⁶	Linagliptin (5 mg OD)	5147	Age ≥18 years; T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	2.2
Ferreira 2020 ³⁷	Alogliptin (6.25-25 mg OD)	1434	T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	1.5
GLP-1 RAs					
Marso 2016 ²⁰	Semaglutide (0.5-1 mg OW)	939	Age ≥50 years; T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	2.1
Mann 2017 ¹⁹ Mann 2018 ³⁸	Liraglutide (1.8 mg OD)	2158	T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	3.8
Husain 2019 ³⁹	Semaglutide (14 mg OD)	856	Age ≥50 years; T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	1.3
Gerstein 2019 ⁴⁰	Dulaglutide (1.5 mg OW)	2199	Age ≥50 years; T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	5.4
Bethel 2020 ⁴¹	Exenatide (2 mg OW)	3177	T2DM with or without CKD	eGFR <60 mL/min/1.73 m ²	3.2
SGLT2 inhibitors					
Wanner 2016 ⁴² Wanner 2018 ⁴³	Empagliflozin (10-25 mg OD)	1819	T2DM with or without CKD	eGFR <59 mL/min/1.73 m ²	3.1
Neuen 2018 ⁴⁴	Canagliflozin (100-300 mg OD)	2039	T2DM with or without CKD and either age ≥30 years with established atherosclerotic vascular disease or age ≥50 years with 2 or more CV risk factors	eGFR <60 mL/min/1.73 m ²	3.6
Wiviott 2019 ¹⁷	Dapagliflozin (10 mg OD)	1265	Age ≥40 years; T2DM (with a glycated HbA1c of at least 6.5% but below 12.0%), and a creatinine clearance of ≥60 mL per min	eGFR <60 mL/min/1.73 m ²	4.2
Cannon 2020 ⁴⁵ Cherney 2021 ⁴⁶	Ertugliflozin (5-15 mg OD)	1807	Age ≥40 years; T2DM (with a HbA1c level of 7.0%-10.5%) and established atherosclerotic CV disease	eGFR <60 mL/min/1.73 m ²	3
Perkovic 2019 ²²	Canagliflozin (100 mg OD)	4401	Age ≥30 years; T2DM (with HbA1c level of 6.5%-10.5%) and CKD (eGFR of 30 to <90 mL/min/1.73 m ²)	eGFR 30 to <90 mL/min/1.73 m ²	2.62
Heerspink 2020 ²¹	Dapagliflozin (10 mg OD)	2906	CKD (eGFR of 25-75 mL/min/1.73 m ² and UACR of 200-5000 mg/g) with or without T2DM (patients with CKD + T2DM were included)	eGFR 25-75 mL/min/1.73 m ²	2.4
Bhatt 2021 ⁴⁷	Sotagliflozin (200-400 mg OD)	10 584	Age ≥18 years; T2DM with or without CKD	eGFR ≥25 and ≤60 mL/min/1.73 m ²	1.3

Abbreviations: CKD, chronic kidney disease; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; OD, once daily; OW, once weekly; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio.

2.5 | Risk-of-bias and quality assessment

The quality of the included studies and the risk of bias were assessed using the Cochrane Risk-of-Bias tool. Any disagreements during assessment of risk of bias were resolved by consensus.

2.6 | Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each study to assess the effect sizes. Statistical tests were performed using STATA 15.0, as well as the statistical packages “netmeta” for network meta-analysis and “gemtc” for Bayesian analysis in R (version 4.1.2). All tests were two-sided and a P value < 0.05 was considered statistically significant. The net split results were presented as forest plots. The netmeta package on R was used to evaluate the consistency between direct and indirect estimates. Potential publication bias was estimated using funnel plots and Egger tests.

A Bayesian network meta-analysis was employed for the sensitivity analysis to analyse direct and indirect comparisons and to rank the results of the network meta-analysis. A Markov Monte Carlo algorithm was used to derive inferences from the random-effects Bayesian network. A total of 100 000 iterations were run for each chain, and 5000 burn-ins were used for the outcomes. Every 10th data point for 10 000 samples per channel was extracted. Model convergence was measured using trace plots and Gelman-Rubin plots.

3 | RESULTS

3.1 | Studies included in the network meta-analysis

Out of 377 articles identified in the initial database search, a total of 20 publications from 16 studies fulfilled the eligibility criteria and were included in the final analysis (Figure S1), representing a total of 46 292 patients. All studies had placebo as the comparator. The major characteristics of the included studies are summarized in Table 1, including the criteria used to define DKD in each study. The quality evaluation of the included studies is presented in Figure S2. The network profile of the included studies indicates that the SGLT2 inhibitor-placebo arm had the most comparisons, with seven studies, while four studies were included in the DPP-4 inhibitor-placebo arm and five in the GLP-1RA-placebo arm (Figure 1).

3.2 | Network meta-analysis of treatment groups

3.2.1 | Renal outcomes

Ten of the included studies reported a kidney-specific composite outcome (six with SGLT2 inhibitors, three with GLP-1RAs, and one with DPP-4 inhibitors), while only four studies reported kidney disease

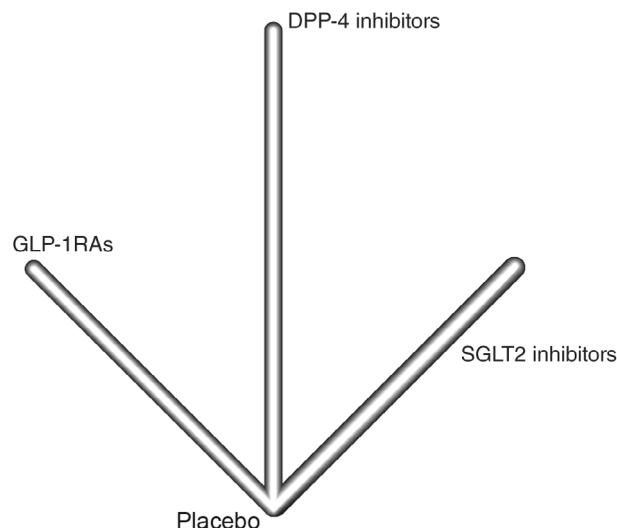


FIGURE 1 Overall network profile. This network meta-analysis included four studies that evaluated dipeptidyl peptidase-4 (DPP-4) inhibitors, five that evaluated glucagon-like peptide-1 receptor agonists (GLP-1RAs) and seven that evaluated sodium-glucose cotransporter-2 (SGLT2) inhibitors

progression (all with SGLT2 inhibitors). The within-design heterogeneity was not significant ($P = 0.6270$), indicating that the network model for a kidney-specific composite outcome was acceptable. No publication bias was found according to the funnel plot (Figure S3A) and Egger test ($P = 0.1716$).

The effect size estimates table and forest plots (Table 2 and Figure 2A) showed that SGLT2 inhibitors and GLP-1RAs significantly reduced the risk of the kidney-specific composite outcome by 36% (HR 0.64, 95% CI 0.57-0.71) and 14% (HR 0.86, 95% CI 0.75-0.99), respectively, compared with placebo. However, DPP-4 inhibitors did not alter the risk of kidney-specific outcome (HR 0.99, 95% CI 0.83-1.18) compared with placebo.

There was strong consistency between direct and indirect evidence for the kidney-specific composite outcome (Figure 3A). SGLT2 inhibitors significantly reduced the risk of the kidney-specific composite outcome by 26% compared to GLP-1RAs (HR 0.74, 95% CI 0.62-0.88) and by 36% compared to DPP-4 inhibitors (HR 0.64, 95% CI 0.52-0.79). GLP-1RAs did not significantly alter the risk of the kidney-specific composite outcome compared to DPP-4 inhibitors (HR 0.87, 95% CI 0.70-1.09; Table 2).

The rankogram (Figure S4A) showed that SGLT2 inhibitors had the highest probability of reducing the risk of the kidney-specific composite outcome (100% probability of being the best treatment), followed by GLP-1RAs (88.5% probability of being the second-best treatment) and DPP-4 inhibitors (10.9% probability of being the second-best treatment, 44.7% probability of being the third-best treatment).

As all four studies that reported kidney disease progression assessed SGLT2 inhibitors versus placebo, a traditional meta-analysis was performed. No publication bias was found according to the funnel plot (Figure S3B) and Harbord test (Egger test, $P = 0.971$). SGLT2 inhibitors reduced the risk of kidney disease

TABLE 2 Network meta-analysis showing effect size (hazard ratio) and 95% confidence interval for the kidney-specific composite outcome, major adverse cardiovascular (CV) events, CV death and hospitalization for heart failure. Comparisons between treatments should be read from left to right, and the hazard ratio is in the cell in common between the column-defining treatment and the row-defining treatment. Hazard ratio <1 favors the column-defining treatment

Kidney-specific composite outcome			
SGLT2 inhibitors			
0.74 (0.62,0.88)	GLP-1RAs		
0.64 (0.52,0.79)	0.87 (0.70,1.09)	DPP-4 inhibitors	
0.64 (0.57,0.71)	0.86 (0.75, 0.99)	0.99 (0.83,1.18)	Placebo
MACE			
SGLT2 inhibitors			
0.95 (0.82,1.10)	GLP-1RAs		
0.81 (0.71,0.92)	0.85 (0.73,0.99)	DPP-4 inhibitors	
0.83 (0.76,0.91)	0.87 (0.78, 0.98)	1.03 (0.93,1.13)	Placebo
CV death			
SGLT2 inhibitors			
0.97 (0.78,1.22)	GLP-1RAs		
0.85 (0.71,1.02)	0.87 (0.69, 1.10)	DPP-4 inhibitors	
0.86 (0.76,0.97)	0.88 (0.73, 1.07)	1.01 (0.89,1.15)	Placebo
HHF			
SGLT2 inhibitors			
0.72 (0.56,0.92)	GLP-1RAs		
0.59 (0.49,0.71)	0.82 (0.64,1.05)	DPP-4 inhibitors	
0.64 (0.56,0.73)	0.88 (0.72,1.09)	1.08 (0.94,1.24)	Placebo

Note: Shaded regions indicate the drug classes being compared, and define the columns and rows.

Abbreviations: CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter 2.

progression by 30% (HR 0.70, 95% CI 0.63-0.77) compared with placebo (Figure S5).

3.2.2 | CV outcomes

Fifteen of the included studies reported outcomes for MACE (six with SGLT2 inhibitors, four with GLP-1RAs and five with DPP-4 inhibitors); 13 studies reported outcomes for CV death (six with SGLT2 inhibitors, two with GLP-1RAs, and five with DPP-4 inhibitors); and 13 studies reported outcomes for HHF (six with SGLT2 inhibitors, two with GLP-1RAs and five with DPP-4 inhibitors). Although the DAPA-CKD study reported outcomes for MACE and HHF, data for the DKD subgroup were unavailable.²¹ Therefore, the MACE and HHF data from the DAPA-CKD study were excluded from the network meta-analysis, resulting in the inclusion of 14 studies for MACE and 12 studies for HHF. The within-design heterogeneity was not significant for MACE ($P = 0.0950$), CV death

($P = 0.5741$) or HHF ($P = 0.1680$). No publication bias was found for any of the three outcomes according to the funnel plots (Figure S3C-E) and Egger tests ($P = 0.7147$ for MACE, $P = 0.5957$ for CV death and $P = 0.5198$ for HHF).

The effect size estimates table and forest plots for each comparison (Table 2, Figure 2B-D) showed that SGLT2 inhibitors significantly reduced the risk of MACE by 17% (HR 0.83, 95% CI 0.76-0.91), the risk of CV death by 14% (HR 0.86, 95% CI 0.76-0.97) and the risk of HHF by 36% (HR 0.64, 95% CI 0.56-0.73) compared with placebo. While GLP-1RAs significantly reduced the risk of MACE by 13% (HR 0.87, 95% CI 0.78-0.98), the risk of CV death (HR 0.88, 95% CI 0.73-1.07) and HHF (HR 0.88, 95% CI 0.72-1.09) was not significantly different compared with placebo. In contrast, the risk of MACE (HR 1.03, 95% CI 0.93-1.13), CV death (HR 1.01, 95% CI 0.89-1.15) and HHF (HR 1.08, 95% CI 0.94-1.24) was comparable between DPP-4 inhibitors and placebo groups.

For all outcomes, there was strong consistency between direct and indirect evidence (Figure 3B-D). As shown in Table 2, the risk of MACE was significantly reduced with SGLT2 inhibitors by 19% (HR 0.81, 95% CI 0.71-0.92) and with GLP-1RAs (by 15%; HR 0.85, 95% CI 0.73-0.99) compared to DPP-4 inhibitors. However, the risk of MACE was comparable between SGLT2 inhibitors and GLP-1RAs (HR 0.95, 95% CI 0.82-1.10). The risk of CV death was not significantly different among all three treatments (HR 0.97, 95% CI 0.78-1.22 between SGLT2 inhibitors and GLP-1RAs; HR 0.85, 95% CI 0.71-1.02 between SGLT2 inhibitors and DPP-4 inhibitors; and HR 0.87, 95% CI 0.69-1.10 between GLP-1RAs and DPP-4 inhibitors). SGLT2 inhibitors significantly reduced the risk of HHF by 28% compared to GLP-1RAs (HR 0.72, 95% CI 0.56-0.92) and by 41% compared to DPP-4 inhibitors (HR 0.59, 95% CI 0.49-0.71). The risk of HHF was comparable between GLP-1RAs and DPP-4 inhibitors (HR 0.82, 95% CI 0.64-1.05).

The rankograms (Figure S4B-D) showed that SGLT2 inhibitors and GLP-1RAs had a similar probability of being the best treatment for reducing the risk of MACE (54.5% and 45.1%, respectively), with DPP-4 inhibitors have a 30.3% probability of being the third-best treatment. Similarly, SGLT2 inhibitors and GLP-1RAs had a 58.2% and 40.4% probability of being the best treatment to reduce risks of CV death, respectively, while there was a 35.0% probability that DPP-4 inhibitors were the third-best treatment. In contrast, SGLT2 inhibitors had the highest probability of being the best treatment for HHF (99.5%), followed by GLP-1RAs (86.1% probability of being the second-best treatment) and placebo (77.3% probability of being the third-best treatment).

Analyses of MACE and HHF outcomes including data from the DAPA-CKD study are shown in Figures S6 to S8. The results were consistent with the main analysis.

3.3 | Sensitivity analyses

The results of the Bayesian sensitivity analyses were consistent with the frequentist analysis. The network plots corresponded with the number of studies included for each outcome (Figure S9A-D). The

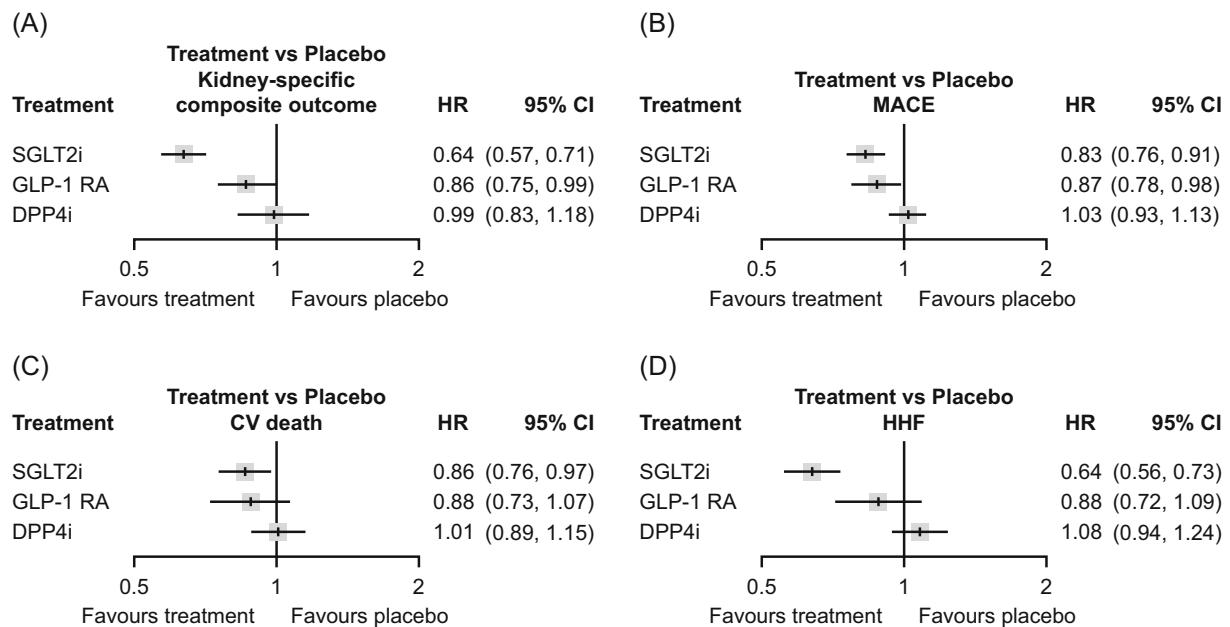


FIGURE 2 Risk of renal and cardiovascular (CV) outcomes with different antidiabetic drug classes. Forest plots comparing the risks of (A) kidney-specific outcome, (B) major adverse cardiovascular events (MACE), (C) cardiovascular (CV) death and (D) hospitalization for heart failure (HHF) with different antidiabetic drug classes compared to placebo. DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2

rankograms showed that SGLT2 inhibitors were the most likely to reduce the risks of the kidney-specific outcome and HHF, followed by GLP-1RAs, while SGLT2 inhibitors and GLP-1RAs had comparable probabilities of reducing the risks of MACE and CV death (Figure S10A-D).

4 | DISCUSSION

This network meta-analysis of 16 RCTs compared SGLT2 inhibitors, GLP-1RAs and DPP-4 inhibitors to identify the drug class that lowers CV and renal risk by the greatest extent in patients with DKD. The inclusion of the latest results from 16 high-quality CV and renal outcome trials encompassing 46 292 patients allowed for better statistical power to compare multiple outcomes and drug classes. The main strength of this study is that the analysis was focused specifically on patients with DKD. This allowed, for the first time, comparison of the efficacy of novel antidiabetic drug classes on CV and renal outcomes in patients with DKD.

The results showed that, in comparison with other treatments, intervention with SGLT2 inhibitors led to the most favourable outcomes. SGLT2 inhibitors significantly lowered the risks of MACE, CV death, HHF and the kidney-specific composite outcome by 17%, 14%, 36% and 36%, respectively, compared with placebo. While GLP-1RAs lowered the risks of MACE and the kidney-specific composite outcome by 13% and 14%, respectively, there was no benefit with regard to the risk of CV death and HHF compared with placebo. In contrast, DPP-4 inhibitors did not significantly alter the risk of kidney-specific outcome and CV outcomes as compared to placebo. These data on

the comparative efficacy of antidiabetic therapies based on the totality of available data will help clinicians make informed treatment decisions for patients with DKD.

4.1 | Advantages of SGLT2 inhibitors and GLP-1RAs

In a comparative analysis, SGLT2 inhibitor therapy was associated with a significantly greater reduction in the risk of the kidney-specific composite outcome and HHF compared with GLP-1RAs in patients with DKD. The results of this network meta-analysis concur with previous meta-analyses that showed the superiority of SGLT2 inhibitors in reducing the risk of renal outcomes compared to GLP-1RAs in patients with type 2 diabetes mellitus.^{23,24} In a previous network meta-analysis of CVOTs in patients with type 2 diabetes, use of SGLT2 inhibitors was associated with a 21% greater reduction in the risk of HHF and a 31% greater reduction in the risk of renal composite outcome compared with GLP-1RAs.²³ Furthermore, in another network meta-analysis in patients with type 2 diabetes and chronic kidney disease (CKD), GLP-1RAs did not reduce the risk of either a CV (MACE) or a renal composite outcome.²⁴ Of note, no trial involving GLP-1RAs has assessed renal outcomes as the primary outcome in patients with type 2 diabetes and CKD. Data pertaining to GLP-1RAs and renal function in patients with CKD have come from CVOTs in which renal outcomes were assessed as secondary or exploratory outcomes. The FLOW trial evaluating the efficacy and safety of semaglutide by injection on primary renal endpoints is currently ongoing and the results are expected in 2024. In the present analysis, we analysed the treatment effects specifically in

patients with type 2 diabetes mellitus and established CKD (DKD). The p-scores and probability rankings confirmed the results from the network meta-analysis. Based on the totality of available evidence, SGLT2

inhibitors had the highest p-rank scores for all outcomes, indicating that they have a greater probability than the other treatments of reducing risks of both CV and renal events.

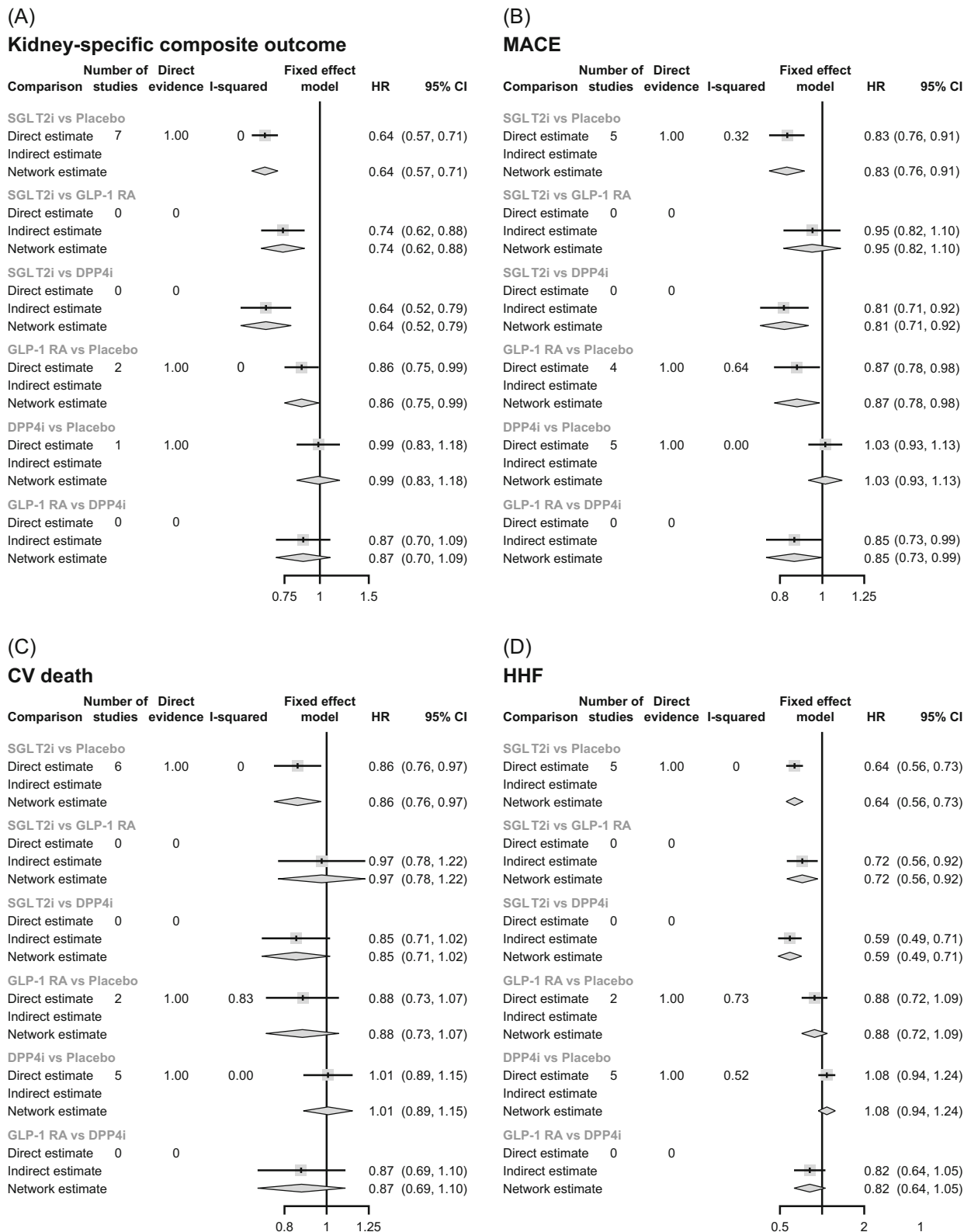


FIGURE 3 Comparison between treatments for (A) kidney-specific composite outcome, (B) major adverse cardiovascular events (MACE), (C) cardiovascular (CV) death and (D) hospitalization for heart failure (HHF). DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2 inhibitor

4.2 | Risks associated with the use of DPP-4 inhibitors

The results presented in this study strengthen the data from previous meta-analyses which showed that DPP-4 inhibitors did not significantly alter CV and renal risks compared to placebo.^{23,25} A comparative cohort study that used data from clinical practice in 13 countries also concluded that SGLT2 inhibitors were associated with improved CV benefits compared to DPP-4 inhibitors.²⁶ Overall, it appears that DPP-4 inhibitors confer limited benefits and may not increase the risk of cardiorenal outcomes in patients with DKD.

4.3 | Mechanism of action of SGLT2 inhibitors

Overall, this study proves the superiority of SGLT2 inhibitors in reducing the risk of CV and renal events, not only compared to placebo, but also compared to GLP-1RAs and DPP-4 inhibitors. Several possible mechanisms have been proposed to explain the benefits of SGLT2 inhibitors. SGLT2 inhibitors block SGLT2 cotransporters in the renal proximal tubule, resulting in increased glycosuria and a mild natriuretic and diuretic effect.²⁷ This leads to metabolic benefits including improved glycemic control, weight loss and blood pressure improvements that confer CV and renal protection.²⁸ It has been proposed that SGLT2 inhibitors improve ventricular loading conditions (due to natriuretic and diuretic effects), optimize cardiac metabolism, thus improving cardiac efficiency and output and inhibit the Na^+/H^+ exchanger (NHE 1) in the myocardium, thus providing favourable effects on the risk of heart failure.^{29,30} The net result of these processes is a reduced risk of CV and renal outcomes with SGLT2 inhibition, as seen in major CVOTs¹⁶⁻¹⁸ and renal outcome trials^{19,20} and confirmed in this meta-analysis. SGLT2 inhibitors also lower the reabsorption of sodium in the renal proximal tubule, thus restoring glomerular feedback and reducing intraglomerular pressure.³¹ While this may result in an acute decrease in eGFR levels, eGFR stability is seen in the long run, leading to a nephroprotective effect.³¹

4.4 | Latest updates in guideline recommendations for the management of DKD

The latest Standards of Medical Care in Diabetes guidelines from the American Diabetes Association (ADA) recommend the use of SGLT2 inhibitors in patients with stage 3 CKD or higher and type 2 diabetes mellitus regardless of glycemic control, to slow the progression of CKD and to reduce CV risks.³² The results of this meta-analysis lend further support to these recommendations. The ADA suggests the use of GLP-1RAs with proven CV benefit if SGLT2 inhibitors are not tolerated or contradicted. GLP-1RAs are suggested “for CV risk reduction if such risk is a predominant problem, as they reduce risks of CV events and appear to possibly slow CKD progression.” The results of this meta-analysis do not confirm

the CV risk reduction benefits of GLP-1RAs in patients with DKD; although GLP-1RAs slightly reduced CV and renal risks compared to placebo, the decrease was not statistically significant for most outcomes.

4.5 | Study limitations

To the best of our knowledge, this is the first analysis to evaluate SGLT2 inhibitors, GLP-1RAs and DPP-4 inhibitors specifically in patients with DKD. This meta-analysis also includes the latest high-quality data from recent CVOTs and renal outcome trials. While results from this network meta-analysis are fairly comprehensive, the study does have some limitations. Firstly, as expected, there may be certain differences across RCTs in the patient population, stage of CKD (although data were specifically extracted for patients with eGFR <90 mL/min/1.73 m²), types of drugs within each drug class, drug dose and duration of treatment. These factors may cause heterogeneity and thus potentially impact results of the meta-analysis. Secondly, as we used data from subgroup analyses of CVOTs, there is a concern that the patients with DKD may not have been fully randomized. Thirdly, the criteria used to define DKD were different in each study included in the analysis.

5 | CONCLUSIONS

SGLT2 inhibitors show a clear advantage in reducing the risks of both CV and renal events in patients with DKD, compared to GLP-1RAs and DPP-4 inhibitors. GLP-1RAs also show CV and renal outcome benefits, compared to placebo, but the benefit was not better than SGLT2 inhibitors or DPP-4 inhibitors for most outcomes. In contrast, DPP-4 inhibitors did not improve either CV or renal outcomes. Based on the results of this meta-analysis, we recommend that SGLT2 inhibitors should be considered the treatment of choice in patients with type 2 diabetes mellitus and kidney disease.

AUTHOR CONTRIBUTIONS

All authors contributed to the meta-analysis design, data analysis and to the drafting, review and final approval of the manuscript.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

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