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Comparative Renal Effects of Dipeptidyl Peptidase-4 Inhibitors and Sodium-Glucose Cotransporter 2 Inhibitors on Individual Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis

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Background: To compare the renal effects of dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors on individual outcomes in patients with type 2 diabetes.

Methods: We searched electronic databases (MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials) from inception to June 2019 to identity eligible randomized controlled trials of DPP-4 inhibitors or SGLT2 inhibitors that reported at least one kidney outcome in patients with type 2 diabetes. Outcomes of interest were microalbuminuria, macroalbuminuria, worsening nephropathy, and end-stage kidney disease (ESKD). We performed an arm-based network meta-analysis using Bayesian methods and calculated absolute risks and rank probabilities of each treatment for the outcomes.

Results: Seventeen studies with 87,263 patients were included. SGLT2 inhibitors significantly lowered the risks of individual kidney outcomes, including microalbuminuria (odds ratio [OR], 0.64; 95% credible interval [CrI], 0.41 to 0.93), macroalbuminuria (OR, 0.48; 95% CrI, 0.24 to 0.72), worsening nephropathy (OR, 0.65; 95% CrI, 0.44 to 0.91), and ESKD (OR, 0.65; 95% CrI, 0.46 to 0.98) as compared with placebo. However, DPP-4 inhibitors did not lower the risks. SGLT2 inhibitors were considerably associated with higher absolute risk reductions in all kidney outcomes than DPP-4 inhibitors, although the benefits were statistically insignificant. The rank probabilities showed that SGLT2 inhibitors were better treatments for lowering the risk of albuminuria and ESKD than placebo or DPP-4 inhibitors.

Conclusion: SGLT2 inhibitors were superior to DPP-4 inhibitors in reducing the risk of albuminuria and ESKD in patients with type 2 diabetes.

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INTRODUCTION

Type 2 diabetes is a main cause of chronic kidney disease (CKD) worldwide [1]. The prevalence of diabetic kidney disease has been reported to be 38% to 68% and is gradually increasing with the global diabetes epidemic [2,3]. Since CKD is closely related to a high risk of morbidity and mortality in type 2 diabetes [4-6], appropriate interventions should be integrated into clinical practice for preventing its development and progression [7].

On the basis of the results from cardiovascular outcome trials, current guidelines for type 2 diabetes prioritize the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with CKD [8-10]. Four large randomized controlled trials (RCTs) have proven that canagliflozin, dapagliflozin, and empagliflozin are beneficial for lowering the risk of hard kidney outcomes compared with placebo [11-14], although three of them [11-13] assessed these outcomes as secondary endpoints. On the other hand, incretin-based drugs have also been reported to be potentially renoprotective in many, but not all, clinical trials for type 2 diabetes [15-18]. Saxagliptin decreased urine albumin-to-creatinine ratio (UACR) regardless of glycemic control in patients with established cardiovascular disease or multiple cardiovascular risk factors [17]. Linagliptin also reduced albuminuria progression in patients with CKD [18]. To date, dipeptidyl peptidase-4 (DPP-4) inhibitors seem to have beneficial renal effects on surrogate markers rather than hard outcomes, especially in the early stages of CKD.

Hence we had a question about whether SGLT2 inhibitors had a comparative advantage over DPP-4 inhibitors for kidney outcomes, especially in the early stages of CKD. Given that there are only a few head-to-head trials of those two classes of drugs, combining evidence from direct and indirect comparisons can provide convincing results. In this regard, we performed a systematic review and network meta-analysis of RCTs to compare the renal effects of DPP-4 inhibitors and SGLT2 inhibitors on individual outcomes in patients with type 2 diabetes.

METHODS

This study was performed according to a prespecified protocol (Appendix S1). The results were reported by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions (Supplemental Table S1) [19].

Data sources and search strategy

The search strategy for the present study has been reported previously [20,21]. Briefly, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched for RCTs of DPP-4 inhibitors or SGLT2 inhibitors (Appendix S1). We retrieved full-text articles without restrictions of language and publication status. Initially, the search period was set from inception to September 2017 but later extended until June 2019 to include more relevant data. We also searched for presentations from scientific conferences to obtain information not described in published articles.

Study selection

We identified eligible trials that compared DPP-4 inhibitors or SGLT2 inhibitors with placebo and/or other antidiabetic drugs in patients with type 2 diabetes. The inclusion criteria were studies that (1) were performed for ≥12 weeks; (2) reported at least one kidney outcome, including microalbuminuria, macroalbuminuria, end-stage kidney disease (ESKD), dialysis, or kidney transplantation. We removed duplicated records and screened titles and abstracts. The details are described in Appendix S1.

Data extraction

The procedure of data extraction has been detailed elsewhere [20,21]. Two authors (J.H.B. and E.G.P.) conducted a standardized data extraction independently (Appendix S1). Outcomes of interest were microalbuminuria (UACR >30 mg/g), macroalbuminuria (UACR >300 mg/g), worsening nephropathy (developing microalbuminuria or macroalbuminuria from normoalbuminuria, or progression from microalbuminuria to macroalbuminuria), and ESKD. The number of study participants reporting kidney outcomes was extracted along with study duration, intervention, comparator, and background antidiabetic drugs.

Quality assessment

Study quality and risk of bias were assessed using the Cochrane Risk of Bias Tool [22]. Four authors (J.H.B., E.G.P., S.K., and N.H.K.) reviewed the studies and evaluated the risk of bias as adequate (low), unclear, or inadequate (high) according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Data synthesis and statistical analysis

Pairwise meta-analyses were conducted using a fixed effect model for direct comparisons of intervention and comparator (DPP-4 inhibitor vs. placebo, SGLT2 inhibitor vs. placebo, and SGLT2 inhibitor vs. DPP-4 inhibitor, respectively). We evaluated statistical heterogeneity using the I^2 statistic, τ^2 statistic, and Cochran's Q test [23]. To combine the direct and indirect estimates of binary outcomes, we performed an arm-based network meta-analysis using Bayesian methods [24]. Before the network meta-analysis, we used a back-calculation method with a fixed effect model to check inconsistency between direct and indirect estimates [25]. We also checked homogeneity in the results of the placebo groups for each outcome. A subgroup analysis was conducted to estimate the risk of ESKD in studies with a duration of ≥52 weeks. The result of pairwise and network meta-analyses was reported as median odds ratio (OR) and its 95% credible interval (CrI). Additionally, the posterior densities of absolute risks and rank probabilities were calculated to confirm the best treatments for each kidney outcome. Statistical analyses were performed using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). P values <0.05 and <0.10 were considered as statistically significant for the outcomes and test for heterogeneity, respectively.

Ethical statement

Ethical approval is not required because this study extracted and synthesized data from previously published articles.

RESULTS

Study characteristics and network geometry

A flow diagram of the study screening and selection is depicted in Supplemental Fig. S1. Of 7,979 initially identified and six additional records, 17 RCTs with 18 publications involving 87,263 patients were finally included: 22,074, 24,262, and 40,943 were the DPP-4 inhibitor, SGLT2 inhibitor, and placebo groups, respectively. Two publications [26,27] reported different kidney outcomes from the same trial. One publication [28] was a pooled analysis of five RCTs [29-33]. The baseline characteristics of the studies are summarized in Table 1 [11,13,14,17,18,26-28,30-39]. The number of study participants ranged from 145 to 17,160. The study duration was varied from 52 weeks to a median of 4.2 years. The mean estimated glomerular filtration rate (eGFR) ranged from 43 to 92 mL/min/1.73 m^2 across the studies. Fig. 1 shows the network of treatment comparisons for each kidney outcome.

Study quality and risk of bias

Supplemental Fig. S2 shows the risk of bias of the studies. Random sequence generation and allocation concealment were not reported in two studies [28,34]. All studies presented adequate blinding of participants, personnel, and outcome assessment. Four studies [17,28,30,32] had incomplete outcome data owing to losses to follow-up. The possibility of selective reporting was found in one study [28] because of a pooled analysis.

Development and progression of albuminuria

A total of nine RCTs evaluated the effects of the drugs on albuminuria (Supplemental Fig. S3A-C). As compared with placebo, SGLT2 inhibitors significantly lowered the risks of microalbuminuria (OR, 0.64; 95% CrI, 0.41 to 0.93), macroalbuminuria (OR, 0.48; 95% CrI, 0.24 to 0.72), and worsening nephropathy (OR, 0.65; 95% CrI, 0.44 to 0.91), whereas DPP-4 inhibitors did not lower the risks. SGLT2 inhibitors did not lower the risks of microalbuminuria (OR, 0.80; 95% CrI, 0.48 to 1.37), macroalbuminuria (OR, 0.59; 95% CrI, 0.27 to 1.07), and worsening nephropathy (OR, 0.79; 95% CrI, 0.50 to 1.36) compared with DPP-4 inhibitors (Table 2, Supplemental Fig. S3A-C). However, SGLT2 inhibitors showed a higher absolute risk reduction in albuminuria and ranked as the best treatment (Fig. 2A-C). These results were more pronounced for macroalbuminuria than for microalbuminuria. Heterogeneity was regarded as considerable only across the studies comparing SGLT2 inhibitors and placebo (Supplemental Fig. S3A-C).

Development of ESKD

Thirteen RCTs assessed ESKD events as an outcome (Supplemental Fig. S3D). SGLT2 inhibitors significantly lowered the risk of ESKD compared with placebo (OR, 0.65; 95% CrI, 0.46 to 0.98). By contrast, DPP-4 inhibitors did not affect the risk of ESKD (OR, 0.97; 95% CrI, 0.71 to 1.40). In indirect comparisons, SGLT2 inhibitors insignificantly lowered the risk of

Table 1. Characteristics of Studies Included in the Network Meta-Analysis

Study	Intervention	Control	Background antidiabetic drugs	Study duration	No. of participants	Mean age of participants, yr	Mean duration of diabetes, yr	Mean baseline eGFR, mL/min/1.73 m^2	History of CVD, n (%)	History of heart failure, n (%)
Cornel et al. (2016) [27][a]	Sitagliptin 25–100 mg/day[b]	Placebo	Any drugs except other DPP-4 inhibitors and GLP-1 RAs	3.0 years (median)	14,671	65.5	11.6	74.9	14,671 (100)	2,643 (18)
Green et al. (2015) [26][a]	Sitagliptin 25–100 mg/day[b]	Placebo	Any drugs except other DPP-4 inhibitors and GLP-1 RAs	3.0 years (median)	14,671	65.5	11.6	74.9	14,671 (100)	2,643 (18)
Mosenzon et al. (2017) [17]	Saxagliptin 2.5–5 mg/day[b]	Placebo	Any drugs except other DPP-4 inhibitors and GLP-1 RAs	2.1 years (median)	16,492	65.0	11.9	72.6	12,929 (78)	2,102 (13)
Rosenstock et al. (2019) [18]	Linagliptin 5 mg/day	Placebo	Any drugs except other DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors	2.2 years (median)	6,979	65.9	14.8	54.6	5,145 (74)	1,873 (27)
White et al. (2013) [34]	Alogliptin 6.25–25 mg/day[b]	Placebo	Any drugs except other DPP-4 inhibitors and GLP-1 RAs	1.5 years (median)	5,380	61.0 (median)	7.3 (median)	71.1 (median)	5,380 (100)	1,501 (28)
Bailey et al. (2015) [35]	Dapagliflozin 10 mg/day	Placebo	None	102 weeks	145	52.2	Intervention: 2.1; control: 2.3	85.8	NA	NA
Barnett et al. (2014) [36]	Empagliflozin 10/25 mg/day	Placebo	Any drugs except other SGLT2 inhibitors	52 weeks	741	63.9	NA	44.9	NA	NA
Cefalu et al. (2015) [33]	Dapagliflozin 10 mg/day	Placebo	Any drugs except rosiglitazone	52 weeks	922	62.9	Intervention: 12.6; control: 12.3	NA	909 (99)	NA
Kohan et al. (2014) [30]	Dapagliflozin 10 mg/day	Placebo	Any drugs except other SGLT2 inhibitors	104 weeks	169	67.0	Intervention: 18.2; control: 15.7	Intervention: 43.9; control: 45.6	NA	NA
Kosiborod et al. (2017) [28][c]	Dapagliflozin 10 mg/day	Placebo	Varying depending on included studies	52 weeks	340	64.2	Intervention: 13.5; control: 14.0	Intervention: 68.8; control: 72.0	320 (100)	320 (100)
Leiter et al. (2014) [31]	Dapagliflozin 10 mg/day	Placebo	Any drugs except rosiglitazone	52 weeks	964	63.8	Intervention: 13.5; control: 13.0	NA	959 (99)	152 (16)
Mosenzon et al. (2019) [13]	Dapagliflozin 10 mg/day	Placebo	Any drugs except other SGLT2 inhibitors, pioglitazone, and rosiglitazone	4.2 years (median)	17,160	63.8	10.5	85.2	6,974 (41)	1,724 (10)
Perkovic et al. (2018) [37]	Canagliflozin 100/300 mg/day	Placebo	Any drugs	188 weeks (mean)	10,142	63.3	13.5	76.5	7,025 (69)	1,460 (15)
Perkovic et al. (2019) [14]	Canagliflozin 100 mg/day	Placebo	Any drugs	2.6 years (median)	4,401	63.0	15.8	56.2	2,200 (50)	653 (15)
Wanner et al. (2016) [11]	Empagliflozin 10/25 mg/day	Placebo	Any drugs (for Japan, except pioglitazone)	3.1 years (median)	7,020	63.1	NA	Intervention: 74.2; control: 73.8	7,018 (99)	706 (10)

(*Continued to the next page*)

Table 1. Continued

Study	Intervention	Control	Background antidiabetic drugs	Study duration	No. of participants	Mean age of participants, yr	Mean duration of diabetes, yr	Mean baseline eGFR, mL/min/1.73 m^2	History of CVD, n (%)	History of heart failure, n (%)
Wilding et al. (2014) [32]	Dapagliflozin 10 mg/day	Placebo	Insulin±oral antidiabetic drugs	104 weeks	393	Intervention: 59.3; control: 58.8	Intervention: 14.2; control: 13.5	NA	75 (19)	NA
DeFronzo et al. (2015) [38]	Empagliflozin 10/25 mg/day	Lina-gliptin 5 mg	Metformin	52 weeks	686	Intervention: 53.9/56.0; control: 53.8	NA	Intervention: 88.4/88.8; control: 89.7	NA	NA
Lewin et al. (2015) [39]	Empagliflozin 10/25 mg/day	Lina-gliptin 5 mg	None	52 weeks	677	Intervention: 56.1/55.5; control: 56.2	NA	Intervention: 91.1/90.2; control: 89.6	NA	NA

eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2; NA, not applicable.
[a]These publications reported different kidney outcomes from the same study; [b]The doses of drugs were modified according to kidney function; [c]This study is a pooled analysis of five randomized controlled trials.

Table 2. Results of the Network Meta-Analysis for Individual Kidney Outcomes

Variable	Placebo	DPP-4 inhibitors	SGLT2 inhibitors
Microalbuminuria			
Placebo	1		
DPP-4 inhibitors	0.80 (0.46–1.24)	1	
SGLT2 inhibitors	0.64 (0.41–0.93)	0.80 (0.48–1.37)	1
Macroalbuminuria			
Placebo	1		
DPP-4 inhibitors	0.82 (0.44–1.33)	1	
SGLT2 inhibitors	0.48 (0.24–0.72)	0.59 (0.27–1.07)	1
Worsening nephropathy			
Placebo	1		
DPP-4 inhibitors	0.82 (0.47–1.23)	1	
SGLT2 inhibitors	0.65 (0.44–0.91)	0.79 (0.50–1.36)	1
End-stage kidney disease			
Placebo	1		
DPP-4 inhibitors	0.97 (0.71–1.40)	1	
SGLT2 inhibitors	0.65 (0.46–0.98)	0.67 (0.42–1.11)	1

Values are expressed as median odds ratios (95% credible intervals).
DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.

ESKD (OR, 0.67; 95% CrI, 0.42 to 1.11) compared with DPP-4 inhibitors (Table 2). However, the subgroup analysis showed that SGLT2 inhibitors were associated with a significantly lower risk of ESKD than DPP-4 inhibitors (OR, 0.60; 95% CrI, 0.34 to 0.91) in the studies longer than 52 weeks (Supplemental Table S2). No studies which directly compared the risk of ESKD between the two drugs were found.

SGLT2 inhibitors showed a higher absolute risk reduction in ESKD than placebo and DPP-4 inhibitors, and thus ranked as the best treatment (Fig. 2D). Heterogeneity was not significant across the studies included in this analysis (Supplemental Fig. S3D). The subgroup analysis revealed similar results for the studies longer than 52 weeks (Supplemental Fig. S4).

Checking consistency in network meta-analysis

The results from checking inconsistency for the network meta-analysis are presented in Supplemental Table S3. There was no substantial inconsistency between the direct and indirect estimates in the network meta-analysis for microalbuminuria (P=0.83), macroalbuminuria (P=0.99), and worsening nephropathy (P=0.69). For ESKD, a statistical inconsistency check was not possible because there was no study of a direct

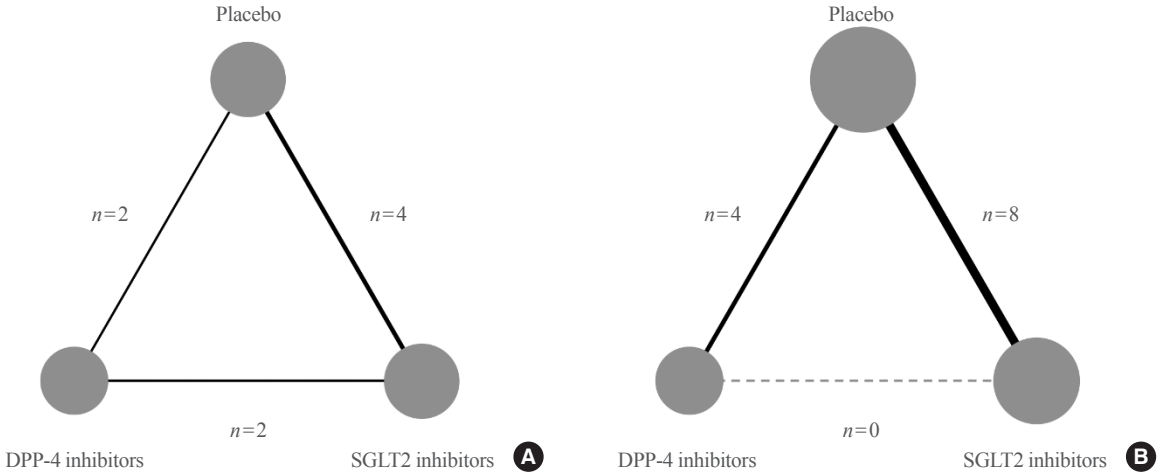

Fig. 1. Network of the treatment comparisons for (A) microalbuminuria, macroalbuminuria, worsening nephropathy, and (B) end-stage kidney disease. Node size is proportional to the number of studies. Lines indicate direct comparisons between the treatments, and their thickness corresponds to the number of studies in each comparison. DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.

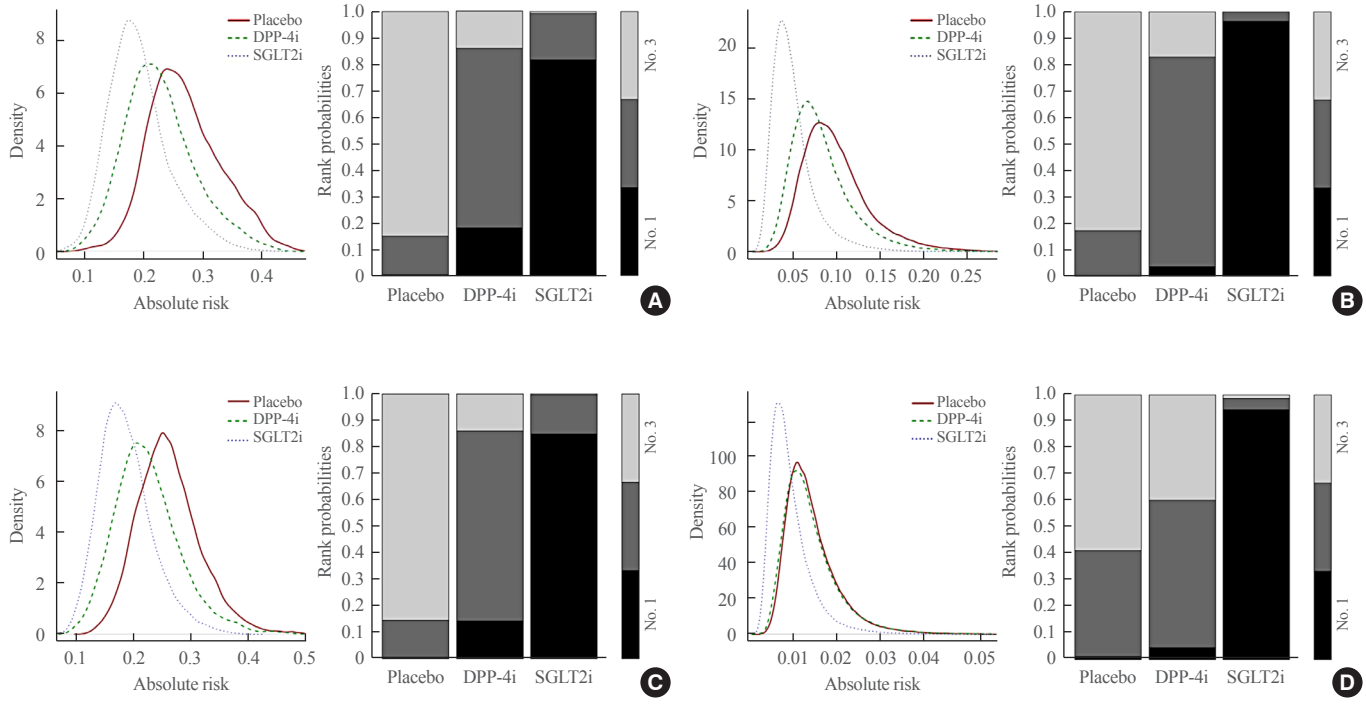

Fig. 2. Absolute risks and rank probabilities of the treatments for (A) microalbuminuria, (B) macroalbuminuria, (C) worsening nephropathy, and (D) end-stage kidney disease. Ranking (no. 1 to no. 3) represents the best, second best, and third best treatment for reducing the risk of each outcome, respectively. DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

comparison between DPP-4 inhibitor and SGLT2 inhibitor for the outcome in this network. On the other hand, we noted an outlying result from one study of SGLT2 inhibitor (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE] trial) [14], with a relatively larger proportion of ESKD events in the placebo group (Supplemental Fig. S5), probably owing to the characteristics of participants who were at high risk of ESKD. However, since a high event rate was also observed in the SGLT2 inhibitor group, this study did not alter direction or heterogeneity in

the treatment effect measure (Supplemental Fig. S3D). Sensitivity analysis with exclusion of the study also demonstrated similar results in absolute risks and rank probabilities (Supplemental Table S4, Supplemental Fig. S6).

DISCUSSION

This network meta-analysis demonstrated that SGLT2 inhibitors were more beneficial for reducing the risk of albuminuria and ESKD than DPP-4 inhibitors in patients with type 2 diabetes. Although the benefits were statistically insignificant, SGLT2 inhibitors had higher absolute risk reductions and ranked as better treatments for all of the individual outcomes than DPP-4 inhibitors.

We found that SGLT2 inhibitors were the most effective treatment for lowering the risk of albuminuria, especially macroalbuminuria, followed by DPP-4 inhibitors and placebo. Given that glucose-lowering efficacy is generally similar between SGLT2 inhibitors and DPP-4 inhibitors [40], the benefits might be owing to the effects beyond glycemic control. As reviewed elsewhere [41], SGLT2 inhibitor could reduce albuminuria by hemodynamic and nonhemodynamic mechanisms. It has been suggested that restoration of tubuloglomerular feedback, which leads to a reduction in intraglomerular pressure, is mainly responsible for the favorable renal effects [42]. In addition, body weight reduction, decrease in systemic blood pressure and vascular stiffness, amelioration of inflammation, fibrosis, and oxidative stress, and reduction in renal workload could improve albuminuria [41]. Several studies reported that DPP-4 inhibitors exerted anti-inflammatory [43], antifibrotic [44], and anti-atherosclerotic [45] properties as well as improved the endothelial function via glucagon-like peptide-1 (GLP-1)-related pathways [46,47]. However, unlike SGLT2 inhibitors, natriuresis and diuresis induced by DPP-4 inhibitors were reduced in type 2 diabetes [48] and caused no significant hemodynamic changes [49]. Moreover, a decrease in the degradation of neuropeptide Y by DPP-4 inhibition promoted sympathetic activation and vasoconstriction via the Y1 receptor in patients using angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) [50]. In the present study, approximately 80% of patients in the DPP-4 inhibitor group were receiving ACEIs/ARBs, and the interaction between these medications could negate the beneficial renal effects. Meanwhile, SGLT2 inhibitor prevented the progression of CKD irrespective of antihypertensive therapy, including ACEIs/ARBs [51]. Therefore, SGLT2 inhibitors could have greater albuminuria-lowering effects than DPP-4 inhibitors by altering renal and systemic hemodynamics.

SGLT2 inhibitors reduced the risk of ESKD compared with DPP-4 inhibitors or placebo, whereas DPP-4 inhibitors did not lower the risk. Cardiovascular outcome trials have shown that SGLT2 inhibitors consistently reduce the composite of doubling of serum creatinine, ESKD, and death from kidney disease by 34% to 47% [11,12,14,52] in both primary and secondary prevention populations [53]. The direct renal hemodynamic effects of these drugs play an important role in slowing the progression of CKD [41]. In our study, the reduction in the risk of ESKD was more pronounced with a longer duration of SGLT2 inhibitor treatment. SGLT2 inhibitors preserved the renoprotective effect even in patients with a low eGFR irrespective of their metabolic effects [42]. A recent meta-analysis suggested that SGLT2 inhibitors produced a greater improvement in kidney outcomes in patients with a higher baseline eGFR [53]. These findings indicate that long-term use of SGLT2 inhibitors from the early stage of CKD is important to delay its progression. On the other hand, DPP-4 inhibitors have favorable effects on risk factors for ESKD, including hyperglycemia [54] and albuminuria [17,18]. Nevertheless, DPP-4 inhibitors have not shown any benefits in ESKD [20]. In the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA) trial, linagliptin decreased the risk of albuminuria progression without affecting a decline in eGFR, ESKD, or death from kidney disease [18]. The beneficial effects of incretin-based drugs on kidney outcomes have been reported in patients with GLP-1 receptor agonists but not in those with DPP-4 inhibitors [55]. The benefits were mainly attributed to a reduction in the progression of albuminuria in patients with relatively normal kidney function [55]. Aside from GLP-1, the complexity of DPP-4 actions on its substrate, such as stromal cell-derived factor-1α [56-58], might influence the effects of DPP-4 inhibitors on the kidney [59,60]. Consequently, SGLT2 inhibitors lowered the risk of ESKD in a broad range of patients with type 2 diabetes as compared with DPP-4 inhibitors.

The present study has several limitations. First, most of the DPP-4 inhibitor studies did not evaluate kidney outcomes as prespecified endpoints. Second, RCTs that directly compared the effects of DPP-4 inhibitors and SGLT2 inhibitors on ESKD were not identified. Therefore, the results for ESKD were from indirect comparisons, which requires careful interpretation. Finally, more detailed analyses according to the baseline risk of CKD could not be conducted owing to the small number of studies and insufficient information.

In conclusion, our network meta-analysis showed that SGLT2

inhibitors were superior to DPP-4 inhibitors in reducing the risk of albuminuria and ESKD in patients with type 2 diabetes. This study warrants further investigation to directly compare the effects of the two classes of drugs on kidney outcomes.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: J.H.B., E.G.P., S.H., N.H.K. Acquisition, analysis, or interpretation of data: J.H.B., E.G.P., S.K., S.G.K., S.H., N.H.K. Drafting the work or revising: J.H.B., E.G.P., S.H., N.H.K. Final approval of the manuscript: J.H.B., E.G.P., S.K., S.G.K., S.H., N.H.K.

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Appendix S1. Study protocol

1. Title: Comparative renal effects of dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter 2 inhibitors on individual outcomes in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized controlled trials

2. Objectives: This study was performed to compare the renal effects of dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors on individual outcomes in patients with type 2 diabetes.

3. Protocol and registration: Methods of database search, study selection, data extraction, assessment of study quality and risk of bias, data synthesis, and statistical analysis were prespecified in the protocol at the beginning of the study.

4. Reporting: This systematic review and network meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) extension statement for reporting systematic reviews incorporating network meta-analyses.

5. Eligible criteria

5.1. Study characteristics

A. Population: patients with type 2 diabetes

B. Intervention: DPP-4 inhibitors or SGLT2 inhibitors

C. Control: placebo and/or other antidiabetic drugs

D. Outcomes of interests

(a) Development of microalbuminuria: defined as urine albumin-to-creatinine ratio (UACR) >30 mg/g

(b) Development of macroalbuminuria: defined as UACR >300 mg/g

(c) Worsening nephropathy: defined as the development of microalbuminuria or macroalbuminuria from normoalbuminuria, or progression from microalbuminuria to microalbuminuria

(d) Development of end-stage kidney disease (ESKD): defined as kidney failure, initiation of renal replacement therapy, or kidney transplantation

E. Study design: randomized controlled trial (RCT)

F. Study duration: 12 weeks or longer

5.2. Report characteristics

A. Years considered: initially published from inception to September 2017, but later extended until June 2019

B. Language: no restriction of language

C. Publication status: full-text articles with no limitation of publication status

5.3. Inclusion and exclusion criteria

A. The study population comprised men and women with type 2 diabetes.

B. We included RCTs comparing the efficacy or safety of DPP-4 inhibitors or SGLT2 inhibitors with placebo and/or other antidiabetic drugs.

C. We included RCTs with a duration of 12 weeks or longer.

D. We included RCTs reporting at least one kidney outcome, including UACR, estimated glomerular filtration rate (eGFR), microalbuminuria, macroalbuminuria, doubling of serum creatinine, kidney failure, ESKD, renal replacement therapy, dialysis, or kidney transplantation.

E. In duplicates or extensions, we only included a study with a longer duration or more information regarding kidney outcomes.

F. Pooled analysis or secondary analysis was included only when it provided more information regarding kidney outcomes than original publications.

G. There was no restriction of language.
H. We included full-text articles with no limitation of publication status.

6. Information sources: We searched the electronic databases of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

7. Search strategy: RCTs of DPP-4 inhibitors or SGLT2 inhibitors in patients with type 2 diabetes were searched using the following search terms.

7.1. DPP-4 inhibitors
A. MEDLINE: (DPP-4 inhibitor OR DPP4 inhibitor OR alogliptin OR anagliptin OR evogliptin OR gemigliptin OR linagliptin OR omarigliptin OR saxagliptin OR sitagliptin OR teneligliptin OR trelagliptin OR vildagliptin) AND (random* OR RCT OR RCTs)
B. Embase: (DPP-4 inhibitor OR DPP4 inhibitor OR alogliptin OR anagliptin OR evogliptin OR gemigliptin OR linagliptin OR omarigliptin OR saxagliptin OR sitagliptin OR teneligliptin OR trelagliptin OR vildagliptin) AND (random* OR RCT*)
C. The Cochrane Central Register of Controlled Trials: DPP-4 inhibitor OR DPP4 inhibitor OR alogliptin OR anagliptin OR evogliptin OR gemigliptin OR linagliptin OR omarigliptin OR saxagliptin OR sitagliptin OR teneligliptin OR trelagliptin OR vildagliptin

7.2. SGLT2 inhibitors
D. MEDLINE: (SGLT2 inhibitor OR SGLT-2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin) AND (random* OR RCT OR RCTs)
E. Embase: (SGLT2 inhibitor OR SGLT-2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin) AND (random* OR RCT*)
F. The Cochrane Central Register of Controlled Trials: SGLT2 inhibitor OR SGLT-2 inhibitor OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin

8. Study selection: All identified records were independently screened and evaluated for eligibility by two reviewers. The titles, abstracts, and full texts of the studies were thoroughly reviewed. Any disagreements were resolved by consensus among investigators of the study.

9. Data extraction: Standardized data extraction was performed independently by two reviewers as follows. Any discrepancies were resolved by consensus among investigators of the study.
9.1. First author
9.2. Publication year
9.3. Intervention
9.4. Comparator
9.5. Number of participants in the analysis
9.6. Age of participants
9.7. Study duration
9.8. Duration of diabetes mellitus
9.9. Background antidiabetic drugs
9.10. Baseline eGFR
9.11. Number of participants reporting microalbuminuria
9.12. Number of participants reporting macroalbuminuria

9.13. Number of participants reporting worsening nephropathy
9.14. Number of participants reporting ESKD

10. Assessment of study quality and risk bias: We assessed quality and risk of bias of the studies using the Cochrane Risk of Bias Tool. Two reviewers independently evaluated each study according to the following aspects of trials.
10.1. Random sequence generation
10.2. Allocation concealment
10.3. Blinding of participants and personnel
10.4. Blinding of outcome assessment
10.5. Incomplete outcome data
10.6. Selective reporting
10.7. Other sources of bias

11. Data synthesis
11.1. Network geometry: Geometry of the network of included studies is presented graphically using nodes and lines.
11.2. Network meta-analysis: We conducted pairwise meta-analyses using a fixed effect model to estimate the effect size of each treatment. We performed an arm-based network meta-analysis for evaluating individual kidney outcomes using Bayesian methods and reported results as median odds ratios and their 95% credible intervals.
A. Subgroup analysis: We conducted a prespecified subgroup analysis to assess the effects of treatments on ESKD for studies with a duration of 52 weeks or longer.
11.3. Absolute risks of the treatments: We calculated the posterior densities of absolute risks of treatments for each kidney outcome.
11.4. Rank probabilities: We evaluated relative rank probabilities to rank the best treatments for each kidney outcome.
11.5. Statistical heterogeneity: We used the I^2 statistic, τ^2 statistic, and Cochran's Q test for testing statistical heterogeneity.
11.6. Checking inconsistency: We checked inconsistency of direct and indirect estimates using a back-calculation method with a fixed effect model.