International Urology and Nephrology (2022) 54:2305–2316
https://doi.org/10.1007/s11255-022-03117-4

NEPHROLOGY - ORIGINAL PAPER

Renal protective effect and safety of sodium-glucose cotransporter-2 inhibitors in patients with chronic kidney disease and type 2 diabetes mellitus: a network meta-analysis and systematic review

Jiaxin Lin[1] · Shanshan Wang[1] · Tong Wen[1] · Xinzhou Zhang[1]

Received: 14 August 2021 / Accepted: 11 January 2022 / Published online: 8 February 2022

Abstract

Purpose A network meta-analysis was conducted to evaluate the renal protective effect and safety of sodium-glucose cotransporter-2 inhibitors in patients with chronic kidney disease and type 2 diabetes mellitus.

Methods PubMed, Embase, Cochrane Library, and Web of Science were searched by two authors using the Cochrane Collaboration risk of bias tool.

Results Compared with controls, luseogliflozin 2.5 mg (MD = − 3.50, 95% CI − 6.65 to − 0.35), bexagliflozin 20 mg (MD = − 3.48, 95% CI − 6.57 to − 0.39), and dapagliflozin 10 mg (MD = − 3.08, 95% CI − 5.09 to − 1.06) reduced the estimated glomerular filtration rate (eGFR). Empagliflozin 25 mg (MD = − 240.43, 95% CI − 414.13 to − 66.73), dapagliflozin 10 mg (MD = − 94.15, 95% CI − 111.72 to − 76.59), and canagliflozin 100 mg (MD = − 193.25, 95% CI − 279.16 to − 107.34) reduced urine albumin-creatinine ratio levels compared with controls. Empagliflozin 25 mg, canagliflozin 100 mg and dapagliflozin 10 mg induced a significant decline in urine albumin-creatinine ratio compared to dapagliflozin 5 mg. In terms of safety, ertugliflozin 5 mg reduced the risk of urinary tract infection. Compared with controls, empagliflozin 10 mg and 25 mg, and canagliflozin 100 mg reduced the risk of any adverse events while canagliflozin 100 mg reduced the risk of serious adverse events. Dapagliflozin 10 mg had a lower risk of treatment discontinuation.

Conclusions Sodium-glucose cotransporter-2 inhibitors have favourable renal protective effect and safety; however, additional randomised clinical trials are needed to validate these findings.

Keywords Chronic kidney disease · Sodium-glucose cotransporter-2 inhibitors · Network meta-analysis

Introduction

Chronic kidney disease (CKD) has become a global public health issue in recent years due to its high prevalence, low awareness, low treatment, and low control rates [1, 2]. Diabetes is a frequently occurring and common disease in the world. It is estimated that more than 400 million people will have diabetes by 2030 [3]. Diabetic nephropathy, a form of CKD, is one of the main complications of diabetes mellitus, and accounts for a large proportion of primary diseases causing end-stage renal disease [4]. Patients with CKD and type 2 diabetes mellitus (T2DM) require more comprehensive management, including the control of urinary protein levels. Albuminuria and microalbuminuria can significantly increase CKD progression and the incidence of cardiovascular complications [5].

The emergence of sodium-glucose co-transporter (SGLT)-2 inhibitors provides a new direction for the treatment of patients with chronic renal disease complicated by diabetes. These inhibitors include empagliflozin, dapagliflozin, canagliflozin, luseogliflozin, ipragliflozin, and ertugliflozin [6]. Typically, 160–180 g of glucose is filtered daily, most of which is recovered by tubular reabsorption. Approximately 90% of this glucose reabsorption is performed by SGLT2, and the remainder by SGLT1. This protects healthy individuals against wide variations in glucose supply and demand, a process essential for life [7]. However, in patients with CKD, glucose handling by the kidneys is compromised, resulting in increased reabsorption. As a result, various SGLT2 inhibitors have been marketed globally for diabetes

✉ Xinzhou Zhang
xinzhouzhang1946@163.com

[1] The Second Clinical Medical College of Jinan University, Shenzhen 518000, Guangdong, People's Republic of China

mellitus treatment. Given these options, clinicians are faced with the problem of drug selection, since there are few randomised control trials (RCTs) that directly compare the efficacy and safety of these drugs.

In this study, we conducted a network meta-analysis to assess and compare the differences in renal protective effect and safety amongst SGLT2 inhibitors including their different doses. Additionally, the differences in renal protective effect and safety between SGLT2 inhibitors and different doses of the same SGLT2 inhibitor were reported.

Methods

The protocol PROSPERO: CRD42021237280 was registered.

Search strategy

PubMed, Embase, Web of Science, and Cochrane Library databases were searched from inception up until 5 March 2021. The search was conducted by two independently reviewers (JXL and SSW), and disagreements were resolved by discussion (JXL, SSW, TW and XZZ). A combination of medical subject headings (MeSH) terms and free text was used for searching. The following search strategies were used: (Sodium-Glucose Transporter 2 Inhibitors OR sodium-glucose cotransporter 2 inhibitors OR sodium-glucose cotransporter type 2 inhibitors OR SGLT2 inhibitors OR SGLT-2 inhibitors OR SGLT2 inhibitors OR bexagliflozin OR canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin OR sergliflozin OR remogliflozin OR sotagliflozin OR tofogliflozin) AND (Renal Insufficiency, Chronic OR chronic kidney disease OR chronic renal insufficiency OR chronic kidney failure OR CKD OR CRF OR CKF OR renal impairment OR renal function OR kidney disease).

The search terms were adjusted according to the corresponding regulations of each database.

Study selection

RCTs that assessed CKD patients with T2DM and compared SGLT2 inhibitors including canagliflozin (100 mg, 300 mg), empagliflozin (10 mg, 25 mg), dapagliflozin (5 mg, 10 mg), sotagliflozin (200 mg, 400 mg), luseogliflozin (2.5 mg), ipragliflozin (50 mg), bexagliflozin (20 mg, and ertugliflozin (5 mg, 15 mg) directly with placebo or usual care were included. To explore the effect of different doses on the protection and safety of renal function, different doses of SGLT2 inhibitors were used as separate groups. Meta-analyses, letters, reviews, uncontrolled trials, conference reports, and case reports were excluded. We set the results of the study with the longest study period as the final endpoint.

Data extraction and quality assessment

Data extraction was independently performed by two reviewers (JXL and SSW), according to the eligibility criteria. The following information was extracted: author, publication year, sample size, trial duration, types of intervention and control, age, efficacy, and safety outcomes. Any discrepancies were resolved by discussion, with involvement of the third and fourth reviewers (TW and XZZ) when necessary. Quality of the included RCTs was assessed using the Cochrane Collaboration Risk of Bias Tool with Cochrane Review Manager software (version 5.3). The assessment included random sequence generation allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias assessments.

Data synthesis and analysis

Meta-analysis and graphics rendering were conducted using Stata software (version 16). A random-effects network meta-analysis within a frequentist framework was performed, and the mean differences (MDs) calculated for the continuous outcomes with 95% confidence intervals (CI) and odds ratios (ORs) for dichotomous data with 95% CI. Statistical heterogeneity was evaluated using the I^2 statistic. $I^2 > 50$ indicated substantial heterogeneity, with the statistics needing to be combined with the DerSimonian–Laird random-effects model or, if $I^2 \leq 50$, the inverse-variance fixed effect model was adopted for all outcomes. To check the consistency, the node splitting method was used to evaluate the presence of inconsistency locally with the P-score. To examine potential small study effects, a comparison-adjusted funnel plot was constructed using Stata (version 16.0). The surface under the cumulative ranking curve (SUCRA) was used to estimate the ranking probabilities for each SGLT2 inhibitor, in terms of renal protective effect and safety in patients with CKD and T2DM. SUCRA is a percentage that is interpreted as the probability of a treatment being most effective. To assess the urine albumin-creatinine ratio (UACR), a cluster rank graph was used to integrate the changes and overall incidence of any adverse events (AEs). A comprehensive comparison was then performed to identify the drugs with superior efficacy and safety.

Results

Search results and study characteristics

A total of 6398 articles were searched using the search strategy. A flow diagram of the search strategy and selection

process is shown in Supplementary Fig. 1. Fifteen RCTs were identified, involving 20,299 patients with 14 interventions; 2719 records were excluded due to duplications and 3541 records, including reviews, conference reports, case reports and meta-analyses, were excluded based on titles and abstracts. Study characteristics are shown in Table 1. All the trials lasting from 1 to 104 weeks were designed as RCTs and included the following drugs: dapagliflozin [13, 16, 21, 22]. Canagliflozin [8, 12, 14], empagliflozin [9, 17], luseogliflozin [11], ipragliflozin [15], sotagliflozin [10, 20], bexagliflozin [18], and ertugliflozin [19].

Risk of bias assessment

The risk of bias was assessed using the Cochrane Collaboration risk of bias tool (Fig. 1). In terms of random sequence generation, four RCTs [11, 12, 20, 22] did not mention specific random methods and were evaluated as unknown risks. Six RCTs [10–12, 15, 20, 22] were evaluated as unclear risks in allocation concealment. In the randomised open-label trial reported by Takashima et al. [12], blinding of participants and personnel was assessed as high risk, and the remaining indicators were assessed as low risk [12].

Network plots and inconsistency

The evidence structures of eligible comparisons for network meta-analysis are shown in Fig. 2, including changes in the estimated glomerular filtration rate (eGFR), UACR, urinary tract infections (UTIs), any AEs, serious adverse effects (SAEs) and treatment discontinuation. The analysis of global inconsistency did not detect any significant differences between the consistency and inconsistency models for all four outcomes ($P=0.3941$ for eGFR, $P=0.4248$ for UACR, $P=0.9442$ for UTIs, $P=0.9321$ for AEs, $P=0.6411$ for serious AEs and $P=0.8313$ for treatment discontinuation). Because there were both direct and indirect comparisons, node splitting analysis was required for eGFR, UACR, UTI incidence, incidence of any AEs, incidence of SAEs and incidence of treatment discontinuation. The results from this analysis suggest that there is no local inconsistency in the results of direct and indirect comparisons between the outcome measures (Supplementary Tables 1–6).

Pairwise meta-analysis and heterogeneity

The pairwise meta-analyses of eGFR, UACR, UTIs, AEs, SAE and treatment discontinuation are shown in Supplementary Tables 7–12. Statistical heterogeneity was examined using the I^2 statistic. Although care was taken in formulating strict and uniform inclusion and exclusion criteria, considering the consistency of research objects and treatment factors, we believe that heterogeneity is inevitable between studies.

Results of network meta-analysis

Changes in eGFR

Thirteen RCTs [8, 10–19, 21, 22] reported changes in eGFR during the trials in patients with CKD and T2DM. Luseogliflozin (2.5 mg, MD = − 3.50, 95% CI − 6.65 to − 0.35), bexagliflozin (20 mg, MD = − 3.48, 95% CI − 6.57 to − 0.39), and dapagliflozin (10 mg, MD = − 3.08, 95% CI − 5.09 to − 1.06) significantly reduced eGFR compared with the control group. As for individual SGLT2 inhibitors, luseogliflozin (2.5 mg, MD = − 4.63, 95% CI − 8.33 to − 0.93), bexagliflozin (20 mg, MD = − 4.61, 95% CI − 8.25 to − 0.96), and dapagliflozin (10 mg, MD = − 4.20, 95% CI − 6.97 to − 1.43) notably reduced eGFR compared with canagliflozin (100 mg). There was no difference in the changes in eGFR between the high and low-dose groups.

Changes in UACR

Ten studies [11–18, 21, 22] reported a change in UACR during the trials in patients with CKD. Empagliflozin (25 mg, MD = − 240.43, 95% CI − 414.13 to − 66.73), dapagliflozin (10 mg, MD = − 94.15, 95% CI − 111.72 to − 76.59), and canagliflozin (100 mg, MD = − 193.25, 95% CI − 279.19 to − 107.34) reduced UACR levels compared with the control ($P<0.05$). In addition, empagliflozin (25 mg, MD = − 245.83, 95% CI − 421.90 to − 69.76), canagliflozin (100 mg, MD = − 198.65, 95% CI − 289.25 to − 108.04), and dapagliflozin (10 mg, MD = − 99.55, 95% CI − 131.13 to − 99.55) reduced UACR levels compared with dapagliflozin (5 mg). Patients in the canagliflozin (100 mg) group had significantly lower UACR than those in the dapagliflozin (10 mg, MD = − 99.09, 95% CI − 186.78 to − 11.40), ipragliflozin (50 mg, MD = − 159.64, 95% CI − 264.64 to − 54.64), and bexagliflozin (20 mg, MD = − 183.79, 95% CI − 270.59 to − 96.98) groups. Patients in the empagliflozin (25 mg) group had significantly lower UACR than those in the ipragliflozin (50 mg, MD = − 206.82, 95% CI − 390.71 to − 22.93) and bexagliflozin (20 mg, MD = − 230.97, 95% CI − 405.11 to − 56.83) groups. No statistically significant differences were observed in the comparison of other SGLT2 inhibitors. The reduction of UACR was statistically significant only in the dapagliflozin high-dose group compared with the low-dose group. The results of network meta-analysis in eGFR and UACR are shown in Fig. 3.

Incidence of UTIs

Thirteen studies [8–13, 15, 15, 17–19, 21, 22] described the incidence of UTIs. Compared with the control group, ertugliflozin (5 mg) reduced the risk of UTIs (OR = 0.36, 95% CI 0.16–0.81, $P<0.05$), while other SGLT2 inhibitors

Table 1 Characteristics of included trials

First author	Year	participants	Design	Duration (weeks)	Study arms	Sample (*n*)	Mean age (years)	Male (%)
Yale et al	2014	T2DM and within a subset of Stage 3 CKD	Randomized, double-blind, placebo controlled	52	Canagliflozin 100 mg Canagliflozin 300 mg Placebo	90 89 90	68.5	60.6
Wanner et al	2017	T2DM and with prevalent kidney disease (defined as eGFR < 60 mL/min/1.73m^2 and/or UACR, > 300 mg/g)	Randomized, double-blind, placebo controlled	48	Empagliflozin 10 mg Empagliflozin 25 mg Placebo	757 741 752	66.1	69.4
Bhatt et al	2020	T2DM (glycated hemoglobin level, ≥ 7), CKD(eGFR 25–60 ml per minute per 1.73 m^2	Randomized, double-blind, placebo controlled	24	Sotagliflozin 200 mg Placebo	5292 5292	69.0	55.0
Haneda et al	2016	Patients with T2DM with eGFR > 30 to < 60 mL/min/1.73 m^2	Randomized, double-blind, placebo controlled	52	Luseogliflozin 2.5 mg Placebo	95 50	68.0	76.6
Takashima et al	2018	T2DM patients with CKD (eGFR of 45–89 mL/min/1.73m^2)	Randomized open-label prospective trial	24	Canagliflozin 100 mg Usual care	20 20	65.1	82.5
Pollock et al	2019	T2DM and moderate-to-severe CKD (20–80 mL/min per 1·73 m^2)	Randomized, double-blind, placebo controlled	24	Dapagliflozin 10 mg Placebo	145 148	64.0	71.0
Perkovic et al	2019	T2DM and albuminuric CKD (GFR of 30 to < 90 ml per minute per 1.73 m^2)	Randomized, double-blind, placebo controlled	42	Canagliflozin 100 mg Placebo	2202 2199	63	66.1
Kashiwagi et al	2014	T2DM and mild to moderate renal impairment(eGFR ≥ 30 to < 90 ml/min/1.73 m^2)	Randomized, double-blind, placebo controlled	52	Ipragliflozin 50 mg Placebo	118 46	64.4	78.0
Fioretto et al	2018	T2DM and moderate renal impairment (eGFR 45–59 mL/min/1.73 m^2; chronic kidney disease [CKD] stage 3A)	Randomized, double-blind, placebo controlled	24	Dapagliflozin 10 mg Placebo	160 161	65.8	56.7
Barnett et al	2014	T2DM and CKD(eGFR ≥ 15 to < 90 mL/min per 1·73 m^2)	Randomized, double-blind, placebo controlled	52	Empagliflflozin 10 mg Empagliflflozin 25 mg Placebo	98 321 319	63.9	58.3
Allegretti et al	2019	T2DM and CKD stages 3a (eGFR, 45- < 60 mL/min/1.73 m^2) and 3b (eGFR, 30- < 45 mL/min/1.73 m^2)	Randomized, double-blind, placebo controlled	24	Bexagliflflozin 20 mg Placebo	157 155	69.6	62.8
Grunberger et al	2017	T2DM and stage 3 CKD(eGFR ≥ 30 and < 60 mL/min/1.73 m^2)	Randomized, double-blind, placebo controlled	52	Ertugliflflozin 5 mg Ertugliflflozin 15 mg Placebo	158 155 154	67.3	49.5
Zambrowicz et al	2015	Patients with T2DM and an eGFR < 60 mL/min/1.73 m^2	Randomized, double-blind, placebo controlled	1	Sotagliflozin 400 mg Placebo	16 15	66.4	54.8

Table 1 (continued)

First author	Year	participants	Design	Duration (weeks)	Study arms	Sample (*n*)	Mean age (years)	Male (%)
Petrykiv et al	2017	Patients with T2DM and eGFR ≥ 45 ml/min/1.73 m^2	Randomized, double-blind, placebo controlled	30	Dapagliflozin 10 mg	16	61.0	78.1
					Placebo	16		
Kohan et al	2013	Patients with T2DM and moderate renal impairment(eGFR ≥ 15 to < 90 mL/min per 1·73 m^2)	Randomized, double-blind, placebo controlled	104	Dapagliflozin 5 mg	83	67.0	65.1
					Dapagliflozin 10 mg	85		
					Placebo	84		

T2DM type 2 diabetes mellitus, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *UACR* urine albumin-creatinine ratio

showed no significant difference. Meanwhile, the risk of UTI incidence with ertugliflozin (5 mg) was lower than that with empagliflozin (10 mg), empagliflozin (25 mg), dapagliflozin (10 mg), canagliflozin (300 mg), bexagliflozin (20 mg), or sotagliflozin (200 mg). Ertugliflozin (5 mg) had a lower risk of UTI incidence compared to ertugliflozin (15 mg, OR = 0.43, 95% CI 0.19–0.99, $P < 0.05$).

Incidence of adverse events

All included articles described the incidence of genital infections. Empagliflozin (10 mg), empagliflozin (25 mg), and canagliflozin (100 mg) reduced the overall risk of AEs compared with the control group (OR = 0.79, 95% CI 0.64–0.68; OR = 0.79, 95% CI 0.65–0.96; OR = 0.78, 95% CI 0.67–0.91). Sotagliflozin (200 mg) was associated with an increased risk of AE incidence compared with the control (OR = 1.32, 95% CI 1.21–1.43). Sotagliflozin (200 mg) was also associated with a higher risk of any AEs than empagliflozin (10 mg), empagliflozin (25 mg), ertugliflozin (15 mg), dapagliflozin (10 mg), canagliflozin (300 mg), and canagliflozin (100 mg, $P < 0.05$). Ertugliflozin (5 mg) had a higher risk of AEs incidence compared to ertugliflozin (15 mg). The risk of any AE was similar in other SGLT2 inhibitor groups. The results of network meta-analysis in UTI and AE are shown in Fig. 4.

Incidence of serious adverse events and treatment discontinuation

Canagliflozin (100 mg, OR = 0.88, 95% CI 0.77–0.99) reduced the overall risk of serious AEs compared with the control group. Patients in the dapagliflozin (10 mg) group had significantly lower incidence of treatment discontinuation than those in the control (OR = 0.49, 95% CI 0.26–0.91), empagliflozin (25 mg, OR = 0.39, 95% CI 0.16–0.97), and ertugliflozin (5 mg, OR = 0.30, 95% CI 0.10–0.90) groups. In addition, there were no statistical differences between the other pairwise comparisons including in the high-dose groups and the low-dose groups. The results of network meta-analysis with respect to SAE and treatment discontinuation are shown in Fig. 5.

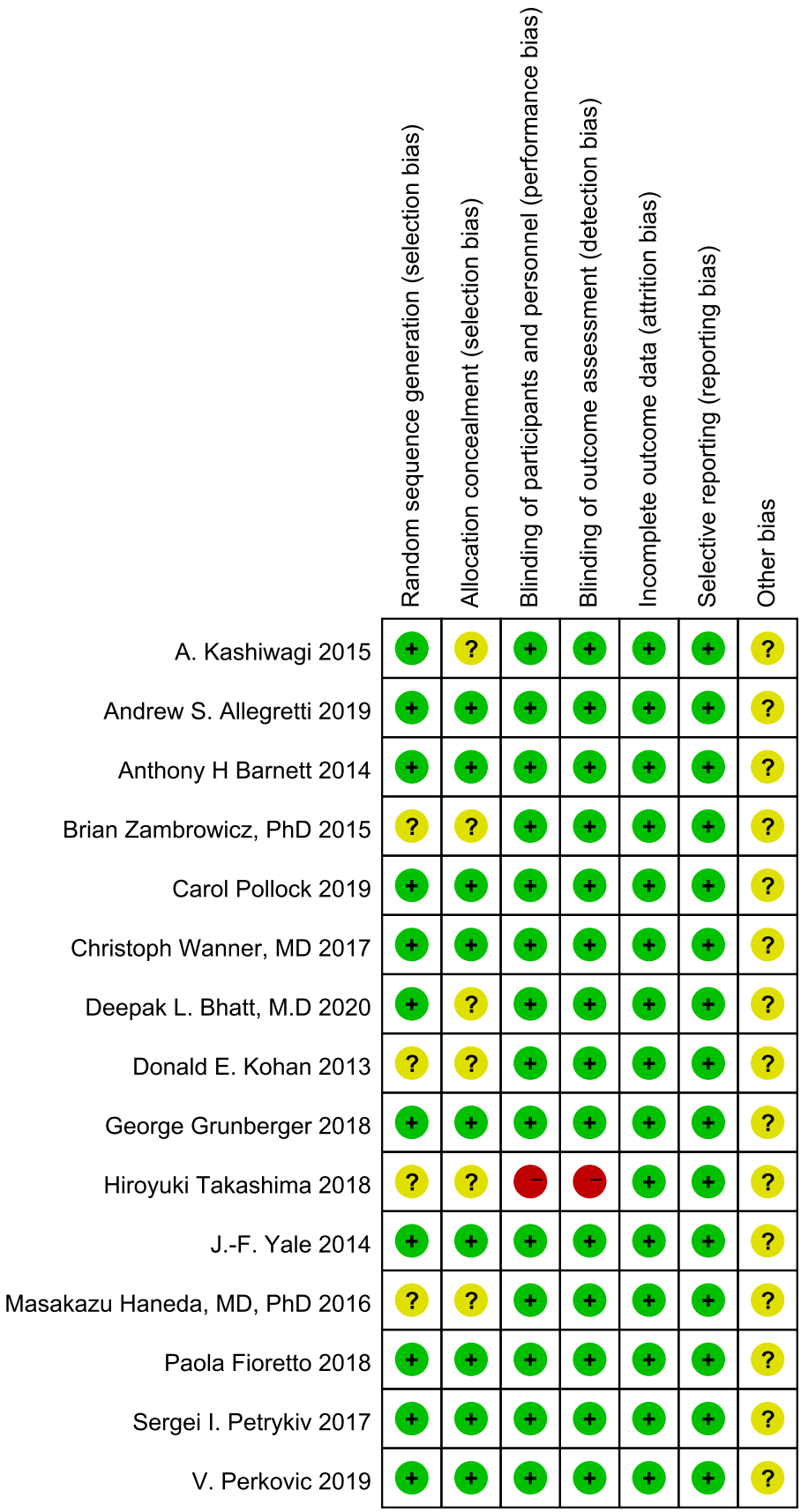
SUCRA and ranking of all treatments

Table 2 shows the mean values of SUCRA, demonstrating the ranking of different treatments based on eGFR, UACR, UTI incidence, incidence of any AEs, incidence of SAE, and incidence of treatment discontinuation. According to the SUCRA values, luseogliflozin (2.5 mg) and bexagliflozin (20 mg) (both with a SUCRA value of 77.8%) ranked first in reduction of eGFR, while canagliflozin 100 mg ranked last (SUCRA: 7.4%). Empagliflozin (25 mg, SUCRA: 93.3%) decreased UACR significantly. Ertugliflozin (5 mg) was associated with an 90.5% probability of having a lower risk of UTIs, whereas luseogliflozin (2.5 mg) was associated with a 14.1% probability of having a lower risk of UTIs. As for the incidence of any AEs, canagliflozin (300 mg) ranked first (SUCRA: 86.5%), while dapagliflozin (5 mg) ranked 14th (SUCRA: 11.3%). Empagliflozin (10 mg, SUCRA: 88.5%) and dapagliflozin (10 mg, SUCRA: 80.7%) ranked first in incidence of SAE and treatment discontinuation. Given that not all trials were included as indicators of eGFR, UACR, UTI incidence, incidence of SAE, and incidence of treatment discontinuation, the rankings and interpretations could not be validated. Two-dimensional graphs of the UACR and AE incidence are shown in Fig. 6. Multiple interventions were divided into four clusters, among which empagliflozin (10 mg), empagliflozin (25 mg), canagliflozin (100 mg), and dapagliflozin (10 mg) showed better renal protection and safety in patients with CKD and T2DM, while dapagliflozin (5 mg) showed the poorest effect.

Publication bias

The comparison-adjusted funnel plot (Fig. 7) was used to evaluate publication bias. In the absence of publication bias

Fig. 1 Risk of bias summary



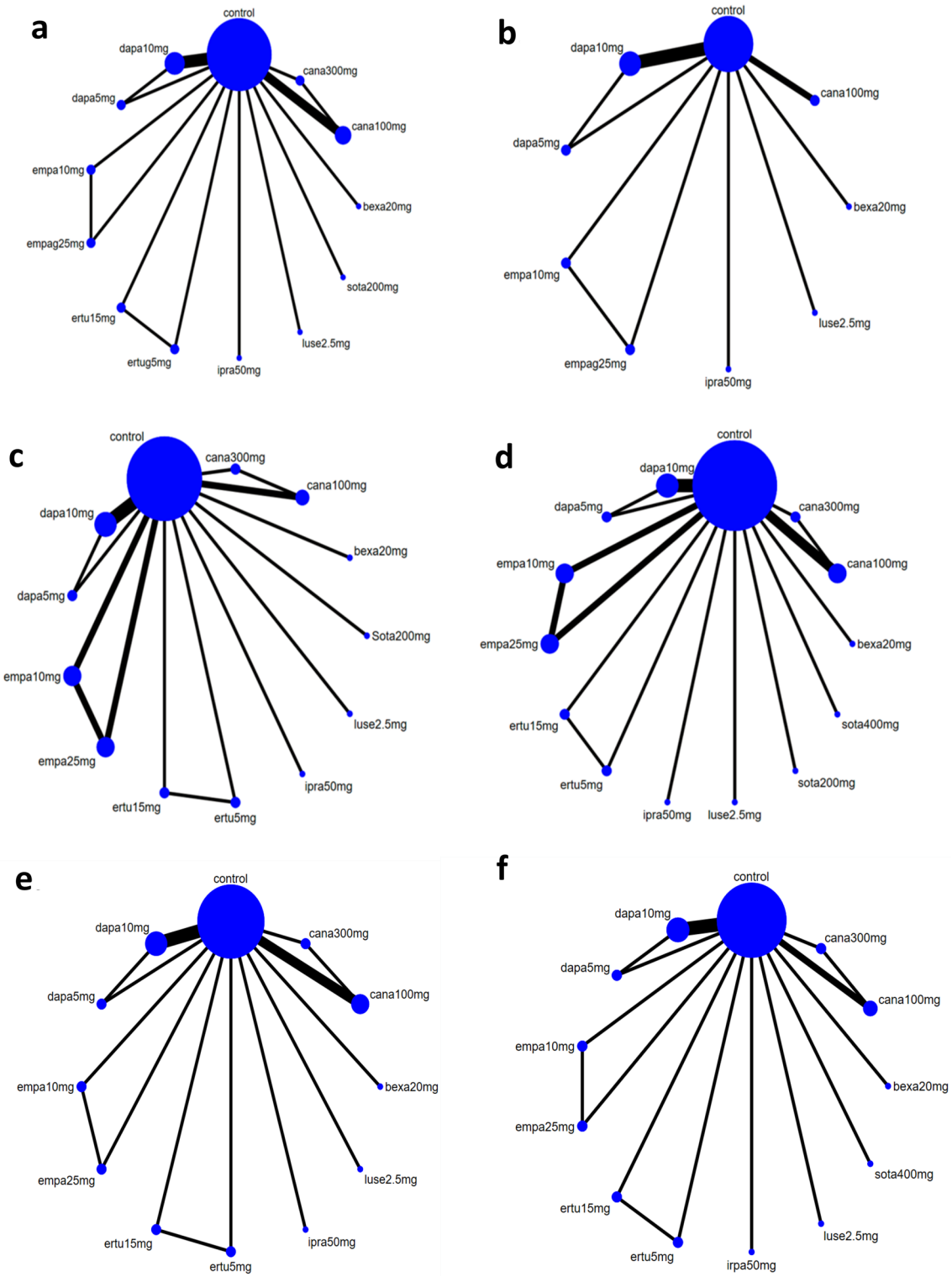


Fig. 2 Network Plots for evidence structure. **a** eGFR. **b** UACR. **c** UTI. **d** Any AEs. **e** SAE. **f** Treatment discontinuation. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible RCTs

luse2.5mg	89.09 (-41.87,220.05)	4.40 (-127.15,135.94)		3.13 (-229.75,236.01)	64.94 (-120.83,250.71)	-141.88 (-359.06,75.30)				103.95 (-29.56,237.46)	98.55 (-31.82,228.92)	-94.70 (-250.83,61.43)
-0.02 (-4.43,4.39)	bexa20mg	-84.69 (-106.22,-63.17)		-85.96 (-279.33,107.41)	-24.15 (-85.78,37.48)	-230.97 (-405.11,-56.83)					9.46 (-2.97,21.89)	-183.79 (-270.59,-96.98)
-0.42 (-4.16,3.31)	-0.40 (-4.09,3.28)	dapa10mg		-1.27 (-195.03,192.50)	60.54 (-2.32,123.41)	-146.28 (-320.86,28.31)				99.55 (67.98,131.13)	94.15 (76.59,111.72)	-99.09 (-186.78,-11.40)
-0.93 (-5.45,3.59)	-0.91 (-5.38,3.56)	-0.51 (-4.32,3.30)	ertu5mg									
-1.47 (-6.16,3.22)	-1.45 (-6.10,3.20)	-1.05 (-5.06,2.97)	-0.54 (-5.29,4.21)	empa10mg	61.81 (-140.38,264.00)	-145.01 (-297.25,7.23)				100.82 (-94.28,295.92)	95.42 (-97.55,288.39)	-97.83 (-309.06,113.40)
-1.60 (-6.35,3.15)	-1.58 (-6.29,3.13)	-1.18 (-5.26,2.91)	-0.67 (-5.48,4.14)	-0.13 (-5.11,4.85)	ipra50mg	-206.82 (-390.71,-22.93)				39.01 (-27.87,105.89)	33.61 (-26.75,93.97)	-159.64 (-264.64,-54.64)
-1.85 (-6.36,2.66)	-1.83 (-6.29,2.63)	-1.43 (-5.23,2.38)	-0.92 (-5.49,3.65)	-0.38 (-3.89,3.13)	-0.25 (-5.05,4.55)	empa25mg				245.83 (69.76,421.90)	240.43 (66.73,414.13)	47.18 (-146.60,240.97)
-1.88 (-6.34,2.59)	-1.86 (-6.27,2.56)	-1.45 (-5.19,2.29)	-0.95 (-5.47,3.58)	-0.41 (-5.11,4.30)	-0.28 (-5.03,4.48)	-0.03 (-4.54,4.49)	cana300mg					
-2.25 (-6.35,1.85)	-2.23 (-6.28,1.82)	-1.83 (-5.13,1.48)	-1.32 (-5.48,2.84)	-0.78 (-5.13,3.57)	-0.65 (-5.07,3.77)	-0.40 (-4.55,3.75)	-0.37 (-4.48,3.73)	sota200mg				
-2.27 (-6.82,2.28)	-2.25 (-6.75,2.25)	-1.85 (-5.69,2.00)	-1.34 (-4.46,1.78)	-0.80 (-5.58,3.98)	-0.67 (-5.51,4.17)	-0.42 (-5.02,4.18)	-0.39 (-4.95,4.16)	-0.02 (-4.22,4.18)	ertu15mg			
-3.14 (-8.79,2.50)	-3.12 (-8.73,2.48)	-2.72 (-7.38,1.94)	-2.21 (-7.91,3.48)	-1.67 (-7.51,4.16)	-1.54 (-7.43,4.34)	-1.29 (-6.98,4.39)	-1.27 (-6.92,4.38)	-0.89 (-6.26,4.47)	-0.87 (-6.59,4.84)	dapa5mg	-5.40 (-34.18,23.38)	-198.65 (-289.25,-108.04)
-3.50 (-6.65,-0.35)	-3.48 (-6.57,-0.39)	-3.08 (-5.09,-1.06)	-2.57 (-4.49,0.67)	-2.03 (-5.51,1.45)	-1.90 (-5.46,1.66)	-1.65 (-4.87,1.57)	-1.62 (-4.79,1.54)	-1.25 (-3.87,1.37)	-1.23 (-4.51,2.05)	-0.36 (-5.04,4.33)	control	-193.25 (-279.16,-107.34)
-4.63 (-8.33,-0.93)	-4.61 (-8.25,-0.96)	-4.20 (-6.97,-1.43)	-3.70 (-7.47,0.08)	-3.16 (-7.14,0.83)	-3.03 (-7.08,1.02)	-2.78 (-6.54,0.99)	-2.75 (-5.91,0.40)	-2.38 (-5.64,0.88)	-2.36 (-6.17,1.45)	-1.48 (-6.54,3.58)	-1.13 (-3.07,0.81)	cana100mg

Fig. 3 MD (mean difference) with 95% CI of network meta-analysis for eGFR and UACR. Results of network meta-analysis for eGFR and UACR were listed in the lower and upper triangle

sota400mg													
0.87 (0.21,3.57)	sota200mg	4.74 (0.25,90.10)	0.18 (0.02,2.02)	0.35 (0.15,0.79)	0.80 (0.41,1.56)	0.94 (0.69,1.29)	1.12 (0.80,1.56)	0.90 (0.39,2.07)	0.99 (0.53,1.84)	0.95 (0.85,1.08)	1.50 (0.60,3.70)	0.53 (0.18,1.59)	2.16 (0.73,6.41)
0.90 (0.19,4.39)	1.04 (0.51,2.14)	luse2.5mg	0.04 (0.00,1.70)	0.07 (0.00,1.54)	0.17 (0.01,3.44)	0.20 (0.01,3.82)	0.24 (0.01,4.56)	0.19 (0.01,4.01)	0.21 (0.01,4.20)	0.20 (0.01,3.82)	0.32 (0.01,6.84)	0.11 (0.00,2.58)	0.45 (0.02,10.45)
0.73 (0.14,3.73)	0.85 (0.38,1.90)	0.81 (0.28,2.38)	ipra50mg	1.94 (0.15,25.07)	4.50 (0.36,55.50)	5.29 (0.46,60.85)	6.30 (0.55,72.65)	5.04 (0.39,65.29)	5.55 (0.46,67.68)	5.36 (0.47,60.64)	8.40 (0.63,111.62)	2.98 (0.21,42.57)	12.12 (0.85,172.48)
0.88 (0.19,4.07)	1.02 (0.56,1.85)	0.98 (0.39,2.47)	1.20 (0.44,3.26)	ertu5mg	2.31 (1.01,5.29)	2.72 (1.15,6.43)	3.24 (1.36,7.72)	2.59 (0.81,8.24)	2.86 (1.04,7.87)	2.76 (1.23,6.20)	4.32 (1.29,14.50)	1.53 (0.39,5.97)	6.24 (1.61,24.08)
1.71 (0.38,7.76)	1.97 (1.14,3.41)	1.90 (0.77,4.65)	2.33 (0.88,6.15)	1.94 (1.10,3.41)	ertu15mg	1.18 (0.57,2.42)	1.40 (0.68,2.90)	1.12 (0.39,3.22)	1.23 (0.50,3.03)	1.19 (0.62,2.31)	1.87 (0.61,5.70)	0.66 (0.19,2.37)	2.70 (0.76,9.56)
1.45 (0.35,6.01)	1.67 (1.34,2.07)	1.60 (0.76,3.36)	1.97 (0.86,4.51)	1.64 (0.88,3.07)	0.84 (0.47,1.50)	empa25mg	1.19 (0.87,1.62)	0.95 (0.40,2.28)	1.05 (0.53,2.06)	1.01 (0.76,1.35)	1.59 (0.62,4.08)	0.56 (0.18,1.74)	2.29 (0.75,7.02)
1.44 (0.35,6.00)	1.66 (1.32,2.08)	1.59 (0.76,3.36)	1.96 (0.85,4.51)	1.63 (0.87,3.06)	0.84 (0.47,1.50)	1.00 (0.81,1.23)	empa10mg	0.80 (0.33,1.93)	0.88 (0.44,1.75)	0.85 (0.62,1.16)	1.33 (0.52,3.45)	0.47 (0.15,1.47)	1.92 (0.62,5.92)
0.46 (0.07,3.08)	0.53 (0.15,1.90)	0.51 (0.12,2.20)	0.63 (0.14,2.83)	0.52 (0.13,2.13)	0.27 (0.07,1.07)	0.32 (0.09,1.16)	0.32 (0.09,1.16)	dapa5mg	1.10 (0.48,2.52)	1.07 (0.47,2.43)	1.67 (0.49,5.66)	0.59 (0.15,2.32)	2.41 (0.62,9.38)
1.24 (0.29,5.25)	1.43 (1.05,1.95)	1.38 (0.63,2.98)	1.69 (0.72,3.99)	1.41 (0.72,2.74)	0.72 (0.39,1.35)	0.86 (0.60,1.23)	0.86 (0.60,1.24)	2.71 (0.76,9.70)	dapa10mg	0.97 (0.52,1.78)	1.51 (0.51,4.49)	0.54 (0.15,1.87)	2.18 (0.63,7.56)
1.14 (0.28,4.68)	1.32 (1.21,1.43)	1.27 (0.62,2.58)	1.56 (0.70,3.48)	1.30 (0.72,2.34)	0.67 (0.39,1.15)	0.79 (0.65,0.96)	0.79 (0.64,0.98)	2.49 (0.69,8.94)	0.92 (0.68,1.24)	control	1.57 (0.64,3.85)	0.56 (0.19,1.65)	2.26 (0.77,6.66)
1.90 (0.40,9.09)	2.19 (1.10,4.35)	2.10 (0.78,5.64)	2.59 (0.90,7.42)	2.15 (0.87,5.31)	1.11 (0.46,2.65)	1.31 (0.65,2.67)	1.32 (0.65,2.69)	4.14 (0.97,17.61)	1.53 (0.73,3.22)	1.66 (0.84,3.28)	cana300mg	0.35 (0.12,1.02)	1.44 (0.35,5.88)
1.46 (0.35,6.04)	1.68 (1.41,2.01)	1.62 (0.78,3.36)	1.99 (0.88,4.52)	1.66 (0.90,3.06)	0.85 (0.49,1.50)	1.01 (0.79,1.30)	1.02 (0.78,1.32)	3.19 (0.88,11.55)	1.18 (0.84,1.65)	1.28 (1.10,1.49)	0.77 (0.39,1.52)	cana100mg	4.07 (0.88,18.90)
1.06 (0.24,4.69)	1.22 (0.75,1.98)	1.17 (0.50,2.76)	1.44 (0.56,3.67)	1.20 (0.56,2.57)	0.62 (0.30,1.27)	0.73 (0.44,1.23)	0.73 (0.43,1.24)	2.30 (0.59,9.02)	0.85 (0.48,1.50)	0.92 (0.57,1.49)	0.56 (0.24,1.28)	0.72 (0.44,1.19)	bexa20mg

Fig. 4 OR (odds ratios) with 95% CI of network meta-analysis for any AEs and UTI. Results of network meta-analysis for any AEs and UTI were listed in the lower and upper triangle

and small sample effect, the points are distributed around the zero line. However, when the sample size is small and the research accuracy low, points are distributed at the bottom of the funnel plot and scattered widely. Results showed that the overall distribution of the studies was unsymmetrical, indicating the risk of publication bias.

Discussion

The network meta-analysis in this study showed that luseogliflozin (2.5 mg) and bexagliflozin (20 mg) decreased eGFR significantly compared with other SGLT2 inhibitors after the trial duration, with a probability of 77.8%. Although the risk of acute kidney injury between the SGLT2 inhibitor groups and placebo groups was similar according to several phase III clinical trials, our findings suggest that there should be increased monitoring of renal function during the treatment with SGLT2 inhibitors. Many RCTs have shown that SGLT2 inhibitors can induce an initial decrease in eGFR, followed by a gradual levelling or increase. It is clear that under hyperglycaemic conditions, the reabsorption of glucose and sodium is increased, which decreases distal sodium delivery to the macula densa at the juxtaglomerular apparatus and triggers the activation of tubuloglomerular feedback (TGF) leading to increased glomerular hypertension [23]. SGLT2 inhibitors lead to afferent renal arterial vasoconstriction, which can decrease glomerular pressure and hyperfiltration. The drop in eGFR is considered as a preservation of kidney function during prolonged treatment

bexa20mg	0.72 (0.19,1.79)	1.16 (0.40,3.35)	0.82 (0.33,2.03)	0.67 (0.24,1.82)	0.56 (0.19,1.70)	0.43 (0.12,1.55)	0.79 (0.28,2.22)	1.06 (0.36,3.15)	0.87 (0.29,2.60)	1.30 (0.21,8.09)	4.20 (0.43,41.21)	
0.55 (0.10,2.97)	cana100mg	1.61 (0.93,2.80)	1.14 (1.01,1.29)	0.93 (0.60,1.45)	0.78 (0.41,1.49)	0.60 (0.24,1.50)	1.10 (0.66,1.84)	1.49 (0.81,2.71)	1.22 (0.66,2.26)	1.81 (0.37,8.91)	5.86 (0.72,47.80)	
0.84 (0.14,5.05)	1.52 (0.42,5.51)	cana300mg	0.71 (0.41,1.23)	0.58 (0.29,1.16)	0.49 (0.21,1.12)	0.37 (0.13,1.07)	0.68 (0.32,1.43)	0.92 (0.41,2.06)	0.75 (0.33,1.71)	1.12 (0.21,6.03)	3.63 (0.42,31.68	
0.55 (0.16,1.93)	1.00 (0.33,3.08)	0.66 (0.18,2.39)	control	0.81 (0.53,1.24)	0.69 (0.37,1.29)	0.53 (0.22,1.30)	0.96 (0.58,1.58)	1.30 (0.72,2.35)	1.07 (0.58,1.95)	1.59 (0.32,7.76)	5.13 (0.63,41.69)	
1.13 (0.28,4.57)	2.05 (0.57,7.40)	1.35 (0.32,5.65)	2.05 (1.09,3.82)	dapa10mg	0.84 (0.45,1.59)	0.65 (0.24,1.76)	1.18 (0.61,2.28)	1.60 (0.77,3.31)	1.31 (0.63,2.75)	1.95 (0.38,10.10)	6.31 (0.74,53.50)	
0.78 (0.18,3.26)	1.40 (0.37,5.29)	0.92 (0.21,4.03)	1.40 (0.69,2.85)	0.69 (0.32,1.49)	dapa5mg	0.77 (0.26,2.31)	1.40 (0.63,3.13)	1.89 (0.80,4.49)	1.55 (0.65,3.72)	2.31 (0.42,12.74)	7.46 (0.84,66.57)	
0.73 (0.14,3.90)	1.32 (0.27,6.43)	0.87 (0.16,4.79)	1.32 (0.43,4.03)	0.65 (0.18,2.32)	0.94 (0.25,3.53)	empa10mg	1.82 (0.74,4.46)	2.46 (0.84,7.19)	2.02 (0.68,5.95)	3.00 (0.48,18.57)	9.69 (0.99,94.70)	
0.44 (0.11,1.82)	0.80 (0.22,2.96)	0.53 (0.12,2.26)	0.80 (0.42,1.55)	0.39 (0.16,0.97)	0.57 (0.22,1.51)	0.61 (0.20,1.82)	empa25mg	1.35 (0.62,2.93)	1.11 (0.51,2.43)	1.65 (0.31,8.72)	5.33 (0.62,45.99)	
0.75 (0.14,3.93)	1.36 (0.29,6.48)	0.90 (0.17,4.83)	1.36 (0.46,4.02)	0.66 (0.19,2.32)	0.97 (0.27,3.53)	1.03 (0.22,4.86)	1.69 (0.48,6.01)	ertu15mg	0.82 (0.46,1.46)	1.22 (0.22,6.64)	3.94 (0.45,34.79)	
0.34 (0.07,1.58)	0.61 (0.14,2.59)	0.40 (0.08,1.95)	0.61 (0.25,1.52)	0.30 (0.10,0.90)	0.44 (0.14,1.38)	0.46 (0.11,1.95)	0.76 (0.25,2.34)	0.45 (0.17,1.21)	ertu5mg	1.49 (0.27,8.13)	4.81 (0.54,42.57)	
0.47 (0.08,2.63)	0.85 (0.17,4.35)	0.56 (0.10,3.23)	0.85 (0.26,2.78)	0.41 (0.11,1.59)	0.61 (0.15,2.41)	0.64 (0.13,3.27)	1.06 (0.27,4.10)	0.62 (0.13,3.11)	1.39 (0.31,6.20)	ipra50mg	3.23 (0.23,44.85)	
0.35 (0.03,4.70)	0.63 (0.05,8.02)	0.41 (0.03,5.71)	0.63 (0.06,6.18)	0.31 (0.03,3.28)	0.45 (0.04,4.90)	0.47 (0.04,6.03)	0.78 (0.07,8.43)	0.46 (0.04,5.79)	1.02 (0.09,12.03)	0.74 (0.06,9.71)	luse2.5mg	
0.59 (0.01,38.16)	1.06 (0.02,66.60)	0.70 (0.01,46.05)	1.06 (0.02,57.01)	0.52 (0.01,29.25)	0.76 (0.01,43.24)	0.80 (0.01,50.21)	1.32 (0.02,74.85)	0.78 (0.01,48.42)	1.74 (0.03,103.38)	1.25 (0.02,79.82)	1.70 (0.02,167.90)	sota400mg

Fig. 5 OR (odds ratios) with 95% CI of network meta-analysis for any SAE and treatment discontinuation. Results of network meta-analysis for any treatment discontinuation and SAE were listed in the lower and upper triangle

Table 2 Surface under the cumulative ranking curve (SUCRA)

Treatment	SUCRA for eGFR (%)	SUCRA for UACR (%)	SUCRA for UTI (%)	SUCRA for AE (%)	SUCRA for SAE (%)	SUCRA for treatment discontinuation (%)
Control	19.8	13.5	51.9	46.0	49.4	42.3
Canagliflozin 100 mg	7.4	87.7	75.9	75.3	67.8	43.9
Canagliflozin 300 mg	49.0		24.4	86.5	27.2	63.0
Empagliflozin 10 mg	55.6	54.9	33.4	73.4	88.5	57.8
Empagliflozin 25 mg	49.4	93.3	52.1	73.7	55.6	30.4
Dapagliflozin 5 mg	32.5	11.0	53.5	11.3	80.0	61.5
Dapagliflozin 10 mg	74.7	62.5	46.7	56.2	70.7	80.7
Ertugliflozin 5 mg	65.4		90.5	29.6	48.3	20.6
Ertugliflozin 15 mg	42.9		60.2	83.5	31.9	60.0
Luseogliflozin 2.5 mg	77.8	61.4	14.1	32.9	8.3	33.1
Bexagliflozin 20 mg	77.8	37.5	14.3	42.0	40.4	70.4
Ipragliflozin 50 mg	54.2	37.5	89.2	22.2	32.1	37.1
Sotagliflozin 200 mg	43.2		43.8	24.0		
Sotagliflozin 400 mg				43.2		49.1

eGFR estimated glomerular filtration rate, *UACR* urine albumin-creatinine ratio, *UTI* urinary tract infection, *AE* adverse events

duration and is reversible once the drug is stopped. In the CANVAS programme, it was found that, after a decrease in eGFR with the use of canagliflozin (76–73 mL/min/1.73 m^2) at 3 months, the eGFR remained stable for six years, while there was a gradual eGFR decline with placebo [24]. EMPA REGOUTCOME study [25] has also shown that patients with diabetic nephropathy will show a short-term mild decline in GFR during the early stages of SGLT-2 inhibitor use. This is similar to the change pattern of glomerular filtration rate after ACER/ARB treatment. Our analysis suggested that canagliflozin (100 mg) may have a greater advantage in maintaining renal function stability. However, to determine whether the decrease of short-term GFR is related to the long-term renal protection of SGLT-2 inhibitors, and whether it can be used as a predictor of efficacy, further studies are required.

Proteinuria is a risk factor for the progression of chronic renal disease and research has shown that positive urine protein at baseline is associated with a significantly increased risk of developing CKD. Higher urine protein

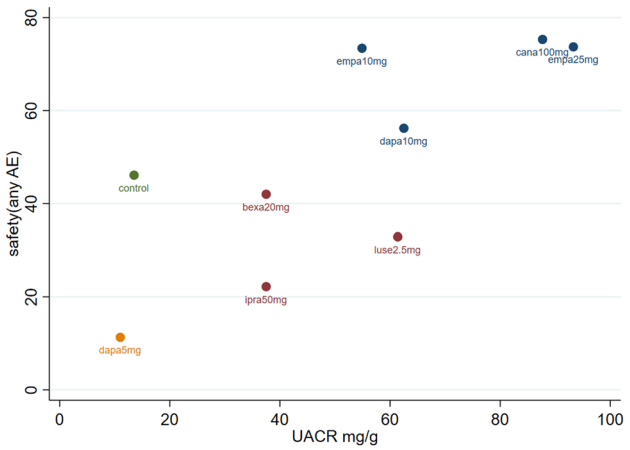


Fig. 6 Clusterank graph: a two-dimensional graphs of the UACR and any AEs. As shown in the figure, different colors represent different clusters

levels are associated with an increased risk of CKD. Empagliflozin 25 mg substantially reduced UACR with a probability of 93.3%, whereas dapagliflozin 5 mg had a probability of 11.1%. Empagliflozin 25 mg, canagliflozin 100 mg, and dapagliflozin 10 mg had a considerably higher renal protective effect than placebo, and no significant effect was found amongst other SGLT2 inhibitors. However, Perkovic et al. [14] and Barnett et al. [17] showed a higher baseline of UACR which made the therapeutic effect more substantial. Treatment with SGLT2 inhibitors significantly reduced albuminuria, and the decrease in urinary protein creatinine ratios was more pronounced in patients with moderately or severely elevated baseline albuminuria, indicating possible bias in the results [26].

SGLT2 inhibitors promote the excretion of large amounts of glucose through the urine and elevate the concentration of glucose locally in the urinary system. This increases the risk of bacterial and fungal infections such as pyelonephritis, cystitis, and vaginal candidiasis, in the genitourinary system. Therefore, it is logical to consider that SGLT2 inhibitors might increase the risk of UTIs, with associated increased risk of severe infections. However, findings on this aspect have been inconsistent. For example, a meta-analysis that including seven randomised controlled trials showed no differences in the rate of UTIs between the group subjected to SGLT2 inhibitors and the control group of patients with stage 3 CKD [27]. Our meta-analysis showed that ertugliflozin 5 mg reduced the risk of UTIs compared with placebo, with a statistically significant difference, and was generally well-tolerated in the overall population. Another study showed that the incidence of UTIs and hypovolemia-related AEs is low and similar across ertugliflozin groups [26]. A population-based study did not identify an increased risk of UTIs but suggested a protective effect for UTIs with incident use of SGLT2 inhibitors [28]. Compared with other SGLT2 inhibitors, ertugliflozin was found to reduce the risk of UTIs in this meta-analysis. Due to the small number of RCTs included, whether ertugliflozin reduces the risk of UTIs remains unknown. In addition, there are no relevant studies to report the biological explanation of reduced incidence of UTIs when SGLT2 inhibitors are used. People with T2DM might be susceptible to an increased risk of UTIs, and for most people with T2DM, the benefits of the SGLT2 inhibitors seem to outweigh the risks of infection.

In terms of overall AEs, sotagliflozin (200 mg) was associated with an increased risk of overall AEs compared with placebo and multiple SGLT2 inhibitors. Sotagliflozin can inhibit gastrointestinal SGLT1 and can delay glucose and reduce postprandial blood glucose. This study suggested a high incidence of adverse reactions associated with sotagliflozin, revealing a need for more large-scale RCTs. In addition, we conducted studies on the incidence of serious AEs and treatment discontinuation. We found that dapagliflozin (10 mg) has a low incidence of treatment discontinuation while empagliflozin (10 mg) has a low incidence of serious AEs.

There are two main limitations of this study. Firstly, only 15 articles were included, which mainly focused on canagliflozin, empagliflozin, and dapagliflozin. Secondly, the time between follow-up was extensive, which may have caused a certain degree of bias in the results. If the results are time-dependent, the length of follow-up may have clinical significance. Different studies using the same drug at the same dose may have different results depending on the length of the study. For example, changes in eGFR may be more consistent with the baseline level over time. Due to the small number of original studies included, we lacked further stratified analysis results, and time-dependent effect could not be evaluated.

In this study, statistical heterogeneity was examined using the I^2 statistic. Although we implemented strict and uniform inclusion and exclusion criteria and considered the consistency of research objects and treatment factors, we believe that heterogeneity is inevitable amongst included studies. From the study, it is clear that more large-scale RCTs are needed to confirm the renal protective effect and safety of

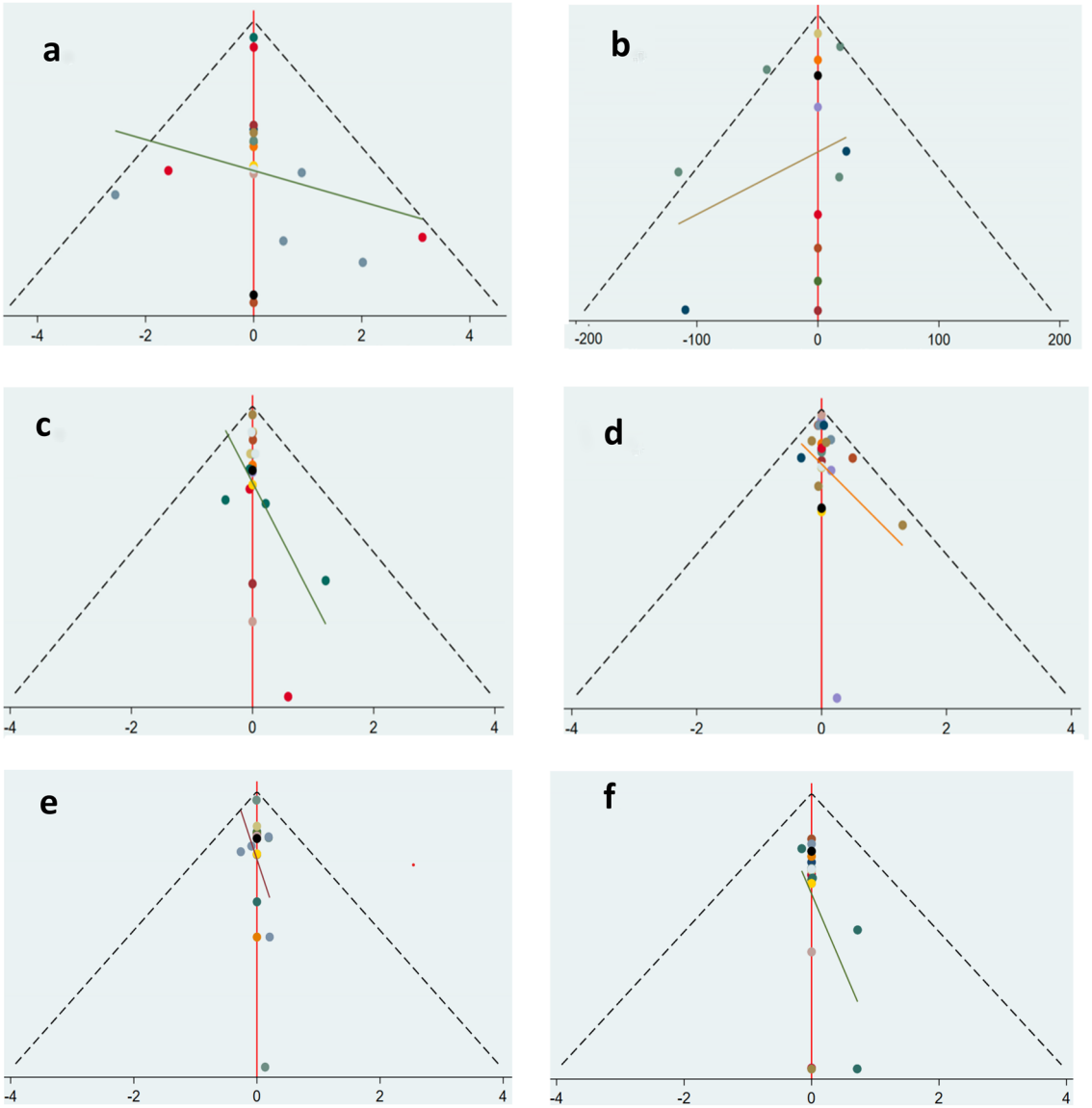


Fig. 7 Comparison-adjusted funnel plot. **a** eGFR. **b** UACR. **c** UTI. **d** any AEs. **e** SAE. **f** treatment discontinuation. Different colored dots represent different direct comparisons of the original studies

SGLT2 inhibitors in patients with chronic renal disease complicated by T2DM, in order to provide evidence-based medicine for clinical use.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-022-03117-4.

Declarations

Conflict of interest All authors have no conflicts of interest to declare.

References

1. Ene-Iordache B, Perico N, Bikbov B et al (2016) Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study. Lancet Glob Health 4:e307–e319
2. Chantrel F, Ott J, Dimitrov Y et al (2020) Blood pressure control in patients with chronic kidney disease according to office and home blood pressures. Blood Press Monit 25:246–251
3. Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 8:228–236
4. Wu L, Liu C, Chang D et al (2021) Annexin A1 alleviates kidney injury by promoting the resolution of inflammation in diabetic nephropathy. Kidney Int 100:107–121

5. Ambarsari CG, Tambunan T, Pardede SO et al (2021) Role of dipstick albuminuria in progression of paediatric chronic kidney disease. J Pak Med Assoc S103-S106.
6. Yamada T, Wakabayashi M, Bhalla A et al (2021) Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. Cardiovasc Diabetol 20:14
7. Lee YJ, Han HJ (2007) Regulatory mechanisms of Na(+)/glucose cotransporters in renal proximal tubule cells. Kidney Int Suppl S27–35.
8. Yale JF, Bakris G, Cariou B et al (2014) Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. Diabetes Obes Metab 16:1016–1027
9. Wanner C, Lachin JM, Inzucchi SE et al (2018) Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 137:119–129
10. Bhatt DL, Szarek M, Pitt B et al (2021) Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 384:129–139
11. Haneda M, Seino Y, Inagaki N et al (2016) Influence of renal function on the 52-week efficacy and safety of the sodium glucose cotransporter 2 inhibitor luseogliflozin in Japanese patients with type 2 diabetes mellitus. Clin Ther 38:66-88.e20
12. Takashima H, Yoshida Y, Nagura C et al (2018) Renoprotective effects of canagliflozin, a sodium glucose cotransporter 2 inhibitor, in type 2 diabetes patients with chronic kidney disease: a randomized open-label prospective trial. Diab Vasc Dis Res 15:469–472
13. Pollock C, Stefánsson B, Reyner D et al (2019) Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 7:429–441
14. Perkovic V, Jardine MJ, Neal B et al (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380:2295–2306
15. Kashiwagi A, Takahashi H, Ishikawa H et al (2015) A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. Diabetes Obes Metab 17:152–160
16. Fioretto P, Del PSt, Buse JB, et al (2018) Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. Diabetes Obes Metab 20:2532–2540
17. Barnett AH, Mithal A, Manassie J et al (2014) Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2:369–384
18. Allegretti AS, Zhang W, Zhou W et al (2019) Safety and effectiveness of bexagliflozin in patients with type 2 diabetes mellitus and stage 3a/3b CKD. Am J Kidney Dis 74:328–337
19. Grunberger G, Camp S, Johnson J et al (2018) Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: the vertis renal randomized study. Diabetes Ther 9:49–66
20. Zambrowicz B, Lapuerta P, Strumph P et al (2015) LX4211 therapy reduces postprandial glucose levels in patients with type 2 diabetes mellitus and renal impairment despite low urinary glucose excretion. Clin Ther 37:71-82.e12
21. Petrykiv SI, Laverman GD, de Zeeuw D et al (2017) The albuminuria-lowering response to dapagliflozin is variable and reproducible among individual patients. Diabetes Obes Metab 19:1363–1370
22. Kohan DE, Fioretto P, Tang W et al (2014) Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 85:962–971
23. Sen T, Heerspink HJL (2021) A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. Cell Metab 33:732–739
24. Seidu S, Kunutsor SK, Cos X et al (2018) SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: a systematic review and meta-analysis. Prim CareDiabetes 12(3):265–283
25. Zinman B, WannerC LJM et al (2015) EMPAREG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373:2117–2128
26. Ji L, Liu Y, Miao H et al (2019) Safety and efficacy of ertugliflozin in Asian patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: VERTIS Asia. Diabetes Obes Metab 21:1474–1482
27. Zhang L, Zhang M, Lv Q et al (2018) Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and moderate renal function impairment: a systematic review and meta-analysis. Diabetes Res Clin Pract 140:295–303
28 Lega IC, Bronskill SE, Campitelli MA et al (2019) Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: a population-based study of older women and men with diabetes. Diabetes Obes Metab 21:2394–2404