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REVIEW ARTICLE

Effects of sodium-glucose co-transporter-2 inhibitors on kidney, cardiovascular, and safety outcomes in patients with advanced chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Aims The overall effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors in patients with advanced chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR), 15–30 ml/min per 1.73 m^2) remain unclear, and we thus conducted a systematic review and meta-analysis to evaluate the effects of SGLT2 inhibitors on kidney, cardiovascular (CV), and safety outcomes in patients with advanced CKD.

Methods The Medline, Embase, and Cochrane Library databases were systematically searched for randomized controlled trials (RCTs) published up to March 3, 2022, and reporting effects of SGLT2 inhibitors on kidney, CV, or safety outcomes in patients with advanced CKD.

Results From 2675 records, six RCTs with 2167 participants were included in the quantitative analyses. In patients with advanced CKD, SGLT2 inhibitors reduced the risk of the primary kidney outcome (a composite of worsening kidney function, end-stage kidney disease (ESKD), or kidney death) by 23% (RR 0.77, 95% CI 0.61–0.98, $p=0.04$, $I^2=0$ for the heterogeneity) and slowed the annual decline in eGFR slope, with the difference between SGLT2 inhibitor group and placebo group being 1.24 mL/min/1.73m^2 per year (95% CI 0.06–2.42, $p=0.04$). SGLT2 inhibitors were also associated with a decreased risk of primary CV outcome (a composite of CV death or hospitalization for heart failure) (HR 0.71, 95% CI 0.53–0.96, $p=0.03$, $I^2=0$ for the heterogeneity) and with similar risks of adverse events (such as acute kidney injury, fracture, amputation, and urinary tract infection).

Conclusions Among patients with advanced CKD, SGLT2 inhibitors reduced the risks of primary kidney and CV outcomes and attenuated the progressive decrease in eGFR compared with placebo, with no evidence of additional safety concerns. These observed benefits may support continuing the use of SGLT2 inhibitors in patients with advanced CKD before initiating maintenance dialysis or kidney transplantation. Future large-scale RCTs are needed to confirm the robustness of these results.

Keywords SGLT2 inhibitors · Chronic kidney disease · Kidney · Cardiovascular · Systematic review · Meta-analysis

Introduction

Chronic kidney disease (CKD) has become a major public health issue consumeing substantial social and financial resources. The global burden of CKD is growing, with approximately 1.2 million deaths attributed to this condition in 2017 [1]. Furthermore, CKD is estimated to become the fifth leading cause of death worldwide by 2040, with the largest projected increase among all leading causes of death [2]. Patients with advanced (stage 4) CKD are more likely to progress to cardiovascular (CV) dysfunction and renal failure. In the last two decades, inhibitors of the

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renin–angiotensin–aldosterone system (RAAS) were widely recommended for the treatment of CKD patients due to their observed benefits in alleviating the progression of CKD [3, 4]. However, the clinical use of RASS inhibitors is often limited by manifestations such as an acute drop in estimated glomerular filtration rate (eGFR) or elevated serum creatinine, which often leads to drug discontinuation, notably in patients with advanced CKD [5]. Promisingly, an increasing number of new drugs have been directed to show a beneficial effect on renal damage in CKD patients, including sodium-glucose co-transporter-2 (SGLT2) inhibitors [6].

SGLT2 inhibitors are a novel class of antihyperglycemic drugs that lower blood glucose levels by inhibiting the reabsorption of glucose in the early proximal tubule, thus increasing glucose excretion in urine [7]. In addition to glycemic control, the use of SGLT2 inhibitors has been demonstrated to reduce CV events as well as body weight and blood pressure [8]. Results from large randomized controlled trials (RCTs) showed that SGLT2 inhibitors could elicit protective effects against major CV and composite kidney events in patients with mild to moderate CKD, but only a few trials reported the application of SGLT2 inhibitors in patients with advanced CKD [9, 10]; as a result, the safety and efficacy of SGLT2 inhibitors in patients with advanced CKD have been controversial.

Recently, two large-scale RCTs comprehensively evaluated the cardiorenal-related outcomes in patients with CKD after treatment with SGLT2 inhibitors [11, 12]. According to the results of the CREDENCE trial [11], canagliflozin significantly reduced the risk of kidney failure and CV outcomes in participants with type 2 diabetes and CKD. According to the data of the DAPA-CKD trial [12], enrolled patients with CKD who received dapagliflozin experienced a lower risk of sustained decline in the eGFR by at least 50%, end-stage kidney disease (ESKD), or death from renal or CV causes compared with patients who received placebo. Considering that the potential benefits of SGLT2 inhibitors in patients with advanced CKD remain unclear, this study aimed to conduct a meta-analysis of RCTs to determine the efficacy and safety of SGLT2 inhibitors in patients with advanced CKD.

Methods

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13], we performed a systematic review and meta-analysis to evaluate the effects of SGLT2 inhibitors in patients with advanced CKD. Through Medline, Embase, and Cochrane Central Register of Controlled Trials, we searched for eligible RCTs that explored the safety and efficacy of SGLT2 inhibitors in individuals with advanced CKD up to March 3, 2022. The search terms were as follows: "Sodium-glucose co-transporter 2 inhibitors" OR "SGLT-2 Inhibitors" OR "Inhibitor, SGLT-2" OR "Tofogliflozin" OR "Ertugliflozin" OR "Gliflozins" OR "Empagliflozin" OR "Sergliflozin" OR "Canagliflozin" OR "Sotagliflozin" OR "Dapagliflozin" OR "Remogliflozin" OR "Ipragliflozin" OR "luseogliflozin" AND "Chronic kidney disease" OR "CKD" OR "renal insufficiency" OR "renal impairment" OR "renal dysfunction" OR "renal inadequacy". There were no criteria regarding publication time or language.

Inclusion and exclusion criteria

The study inclusion criteria were as follows: (1) Adults with or without type 2 diabetes, with advanced CKD (an eGFR of 15–30 mL/min/1.73 m^2). (2) RCTs of SGLT2 inhibitors and placebo. (3) RCTs that lasted at least 24 weeks. Meta-analyses, reviews, letters, case reports, comments, animal experiments, and non-SGLT2 inhibitor trials were excluded.

Prespecified outcomes

The primary kidney outcome was a composite of worsening kidney function (sustained reduction of ≥ 40% in GFR or doubling of serum creatinine), ESKD (defined as requirement for chronic dialysis or chronic transplantation, or sustained GFR ˂ 15 mL/min/1.73m^2), or kidney death. Other kidney outcomes of interest included ESKD or kidney death and eGFR slope. The primary CV outcome was a composite of CV death or hospitalization for heart failure (HHF). Other CV outcomes of interest involved first and recurrent HHF and major adverse CV events (MACE, defined as CV death, myocardial infarction, or stroke). All-cause death and CV or kidney death were also reported. The biomarkers evaluated included glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, and systolic blood pressure (SBP). The parameters that were applied to evaluate the safety outcomes included any adverse event (AE), any serious AE, any severe AE, renal-related AE, any treatment-related AE, acute kidney injury (AKI), fracture, amputation, urinary tract infection, volume depletion, hypoglycemia, hyperkalemia, and discontinuation due to AE.

Data extraction and quality assessment

Two reviewers independently extracted the following information from each article using a customized layout: study characteristics (author, publication year, study design, and period of treatment), participant characteristics (sample size, age, sex, and eGFR), intervention, and outcomes of interest. Any problem encountered with respect to the analysis of the extracted data was discussed among the reviewers or the third author was consulted. The quality of included articles was assessed using the Cochrane

Collaboration's risk of bias tool. The assessment domains included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each item was classified as low, unknown, or high risk. Any discrepancy encountered was resolved by a third reviewer.

Data synthesis and analysis

For CV, kidney and safety, and biomarker outcome data, we calculated the hazard ratio (HR) with 95% confidence intervals (CI), risk ratio (RR) with 95% CI, and mean difference (MD) with 95% CI, respectively, to evaluate the effects of all eligible articles. I^2 statistic values of 0–25%, 26–75%, and 76–100% were regarded as low, moderate, and high heterogeneity [14]. Furthermore, we extracted the data using a random-effect model. Data analysis was completed using the Review Manager 5.3 software, and P-value < 0.05 was considered statistically significant.

Results

A total of 2675 records were obtained after searching different electronic databases. Of them, six trials satisfied our inclusion criteria and were chosen for quantitative analysis [15–20]. The process of study selection is depicted in Fig. 1. A total of 1132 and 1035 patients with advanced CKD were in the SGLT2 inhibitors group (including canagliflozin, empagliflozin, and sotagliflozin) and placebo group, respectively. The eGFR values in the selected articles ranged from 15 to 30 mL/min per 1.73m^2 in four trials [15, 16, 18, 19], 25 to 30 mL/min per 1.73m^2 in one trial [17], and 20 to 30 mL/min per 1.73m^2 in one trial [20]. The mean age of the participants in the articles varied from 61.9 to 70.1 years, and the average treatment period ranged from 16 months to 2.62 years. Table 1 shows the baseline characteristics of the included trials.

Quality evaluation of included studies

Sufficient generation of the random sequence was presented in five trials [15, 16, 18–20]. but not in one trial [17]. Only four articles reported allocation concealment [16, 18–20]. Blinding of participants and personnel, blinding of outcome assessment, and selective reporting were adequate in all included articles. The bias of incomplete outcome data was low in five articles [16–20] and was unclear in one trial [15]. All trials observed unclear risk in other biases (Fig. 2).

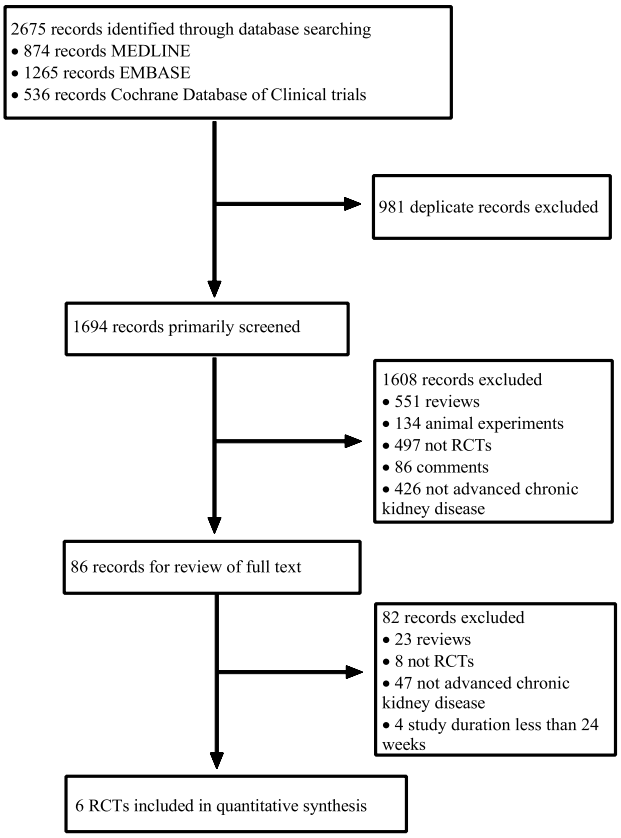

Fig. 1 The process for identifying studies eligible for the meta-analysis

Kidney outcomes

For patients with advanced CKD, SGLT2 inhibitors reduced the risk of primary kidney outcome compared with placebo (RR 0.77, 95% CI 0.61–0.98, $p = 0.04$, $I^2 = 0$ for the heterogeneity). In the random-effect model, SGLT-2 inhibitors were not found to decrease the risk of ESKD or kidney death (RR 0.91, 95% CI 0.65–1.28, $p = 0.59$). Furthermore, no heterogeneity was observed for these outcomes (I^2 of 0%). Based on two trials, SGLT2 inhibitors slowed the decline in eGFR slope, with the difference in eGFR between SGLT2 inhibitor and placebo group being 1.24 mL/min/1.73m^2 per year (95% CI 0.06–2.42, $p = 0.04$) (Fig. 3).

CV outcomes

As shown in Fig. 4, results for primary CV outcome (CV death or HHF) were included from three trials with a total of 1642 individuals. Compared with placebo, SGLT2 inhibitors significantly reduced the risk of primary CV outcome (HR 0.71, 95% CI 0.53–0.96, $p = 0.03$). There was no heterogeneity across the studies for this outcome. In addition, no

Table 1 The baseline characteristics of patients

Study	Study design	Registered number	Baseline GFR	Period of treatment	Intervention	Sample size	Age (mean)	Male (%)	GFR (mean)
Bakris 2020 [15]	RCT	NCT02065791	15–30	2.62 years	Canagliflozin	84	64	64	26
					placebo	90	66	58	27
Barnett 2014 [16]	RCT	NCT01164501	15–30	52 weeks	Empagliflozin 25 mg	37	65.4	56.8	24.4
					placebo	37	62.9	51.4	22
Bhatt2020 [17]	RCT	NCT03315143	25–30	16 months	Sotagliflozin	419	69⊙	55.7⊙	/
					placebo	394	69⊙	54.5⊙	/
Cherney 2021 [18]	RCT	NCT03242018	15–30	52 weeks	Sotagliflozin 200 mg	92	66.8	47.8	23.8
					sotagliflozin 400 mg	92	67.3	53.3	23.9
					placebo	93	68	45.2	24.1
Chertow 2021 [19]	RCT	NCT03036150	15–30	2.4 years	Dapagliflozin 10 mg	293	61.9	64.8	26.8
					placebo	331	62.6	63.1	26.8
Zannad 2021 [20]	RCT	NCT03057977	20–30	16 months	Empagliflozin 10 mg	115	70.4⊙	76.4⊙	/
					placebo	90	70.1⊙	72.6⊙	/

⊙The baseline characteristics can not be acquired in patients with advanced CKD

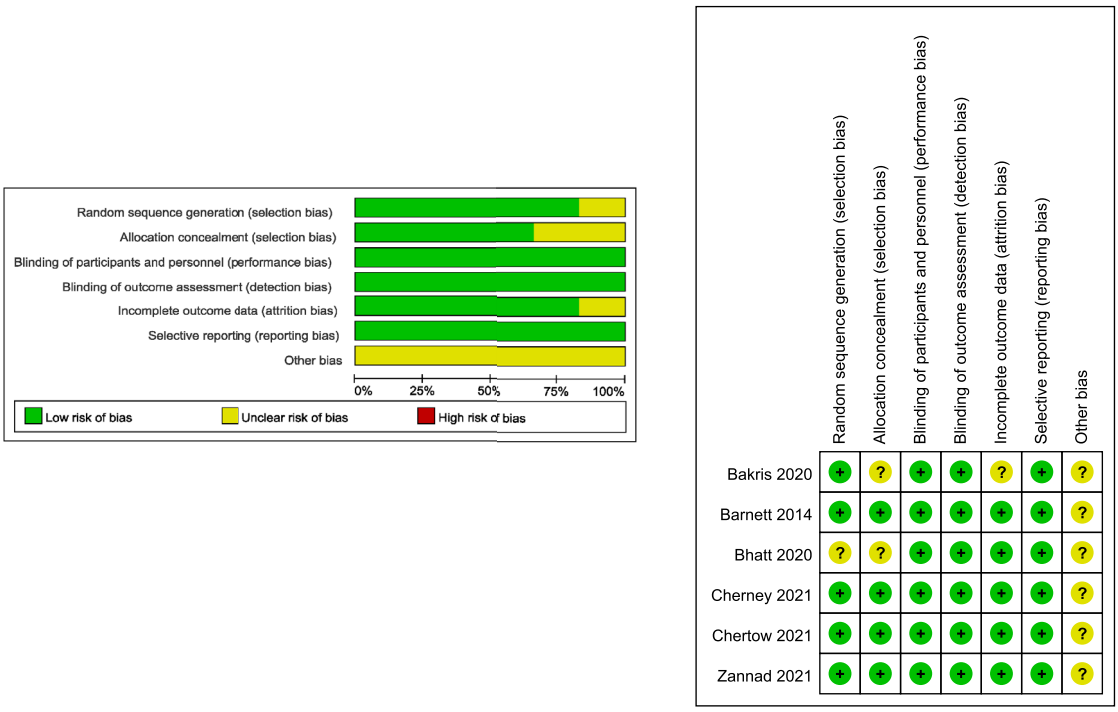

Fig. 2 The quality of each study evaluated by the Cochrane instrument

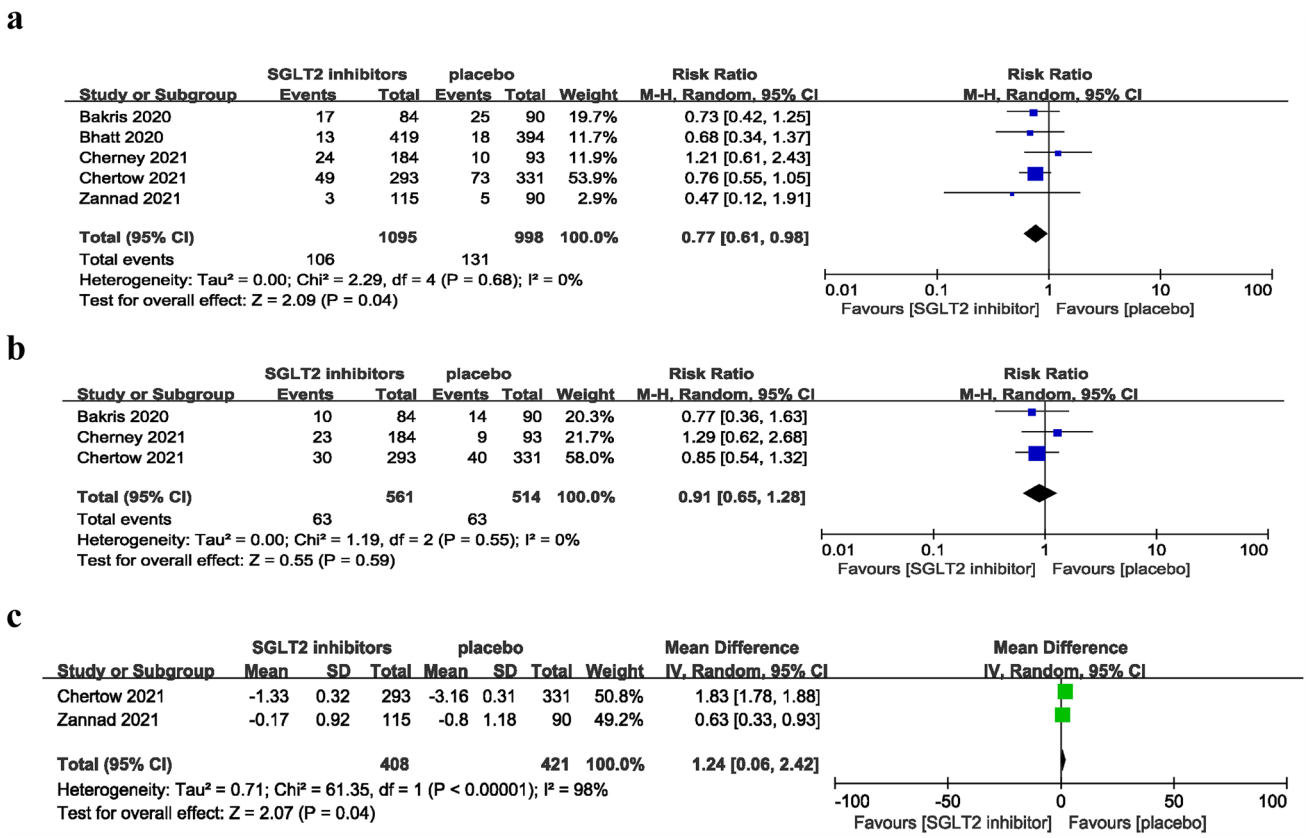

Fig. 3 Effects of SGLT2 inhibitors on the kidney outcomes of the primary kidney outcome (**a**), ESKD or kidney death (**b**), and GFR slope (**c**) among the patients with advanced CKD. Abbreviations SGLT2: sodium-glucose co-transporter 2; ESKD: end-stage kidney disease; GFR: glomerular filtration rate; CKD: chronic kidney disease; CI: confidence interval; MH: Mantel-Haenszel

significant difference in first and recurrent HHF (HR 0.62, 95% CI 0.37–1.04; $p=0.07$, $I^2=0\%$ for the heterogeneity) and MACE (HR 0.78, 95% CI 0.49–1.23; p = 0.29, $I^2=0\%$ for the heterogeneity) was observed between SGLT-2 inhibitor and placebo group.

With regard to the outcomes of CV or kidney death and all-cause death, 5.0% and 6.3% events were observed in participants with advanced CKD, respectively. Nonetheless, there were no obvious differences in the incidence of CV or kidney death and all-cause death (CV or kidney death: RR 0.70, 95% CI 0.29–1.71, $p=0.44$, $I^2=52\%$ for the heterogeneity; all cause death: RR 0.64, 95% CI 0.39–1.04, $p=0.07$, $I^2=0\%$ for the heterogeneity, respectively) (Table 2).

Biomarker outcomes

Based on the data for biomarker outcomes in patients with advanced CKD, we performed four types of biomarker analyses. In summary, SGLT2 inhibitors reduced body weight (MD −0.97, 95% CI −1.18 to −0.76, $p < 0.001$), HbA1c (MD -0.31, 95% CI −0.53 to −0.10, $p < 0.01$), and FPG (MD −1.03, 95% CI −1.50 to −0.57, $p < 0.001$) but had no significant effect on SBP (MD −3.99, 95% CI −9.01 to 1.04, $p=0.12$) (Fig. 5). There was significant evidence of heterogeneity across SGLT2 inhibitor groups for the effect on FPG ($I^2=92\%$, $p<0.01$), HbA1c ($I^2=97\%$, $p<0.01$), and SBP ($I^2=92\%$, $p<0.01$) but no heterogeneity for the effect on body weight ($I^2=0\%$, $p<0.01$).

Safety outcomes

The risks of any AE, any serious AE, and any severe AE were similar between SGLT2 inhibitor and placebo groups (any AE: RR 1.03, 95% CI 0.96–1.10, $p=0.43$, $I^2=0\%$ for the heterogeneity; any serious AE: RR 0.88, 95% CI 0.75–1.04, $p=0.13$, $I^2=0\%$ for the heterogeneity; any severe AE: RR 0.92, 95% CI 0.39 to 2.17, $p=0.86$, $I^2=55\%$ for the heterogeneity, respectively) (Fig. 6). Furthermore, there were no statistically significant differences in the risk of renal-related AE, any treatment-related AE, AKI, fracture, urinary tract infection, volume depletion, hypoglycemia, hyperkalemia, and discontinuation due to AE between patients with advanced CKD receiving SGLT2 inhibitors and those receiving placebo (Table 2, renal-related AE: RR 1.02, 95% CI 0.77–1.35, $p=0.88$; any treatment-related AE: RR 1.16, 95% CI 0.74–1.83, $p=0.52$; AKI: RR 0.96, 95% CI

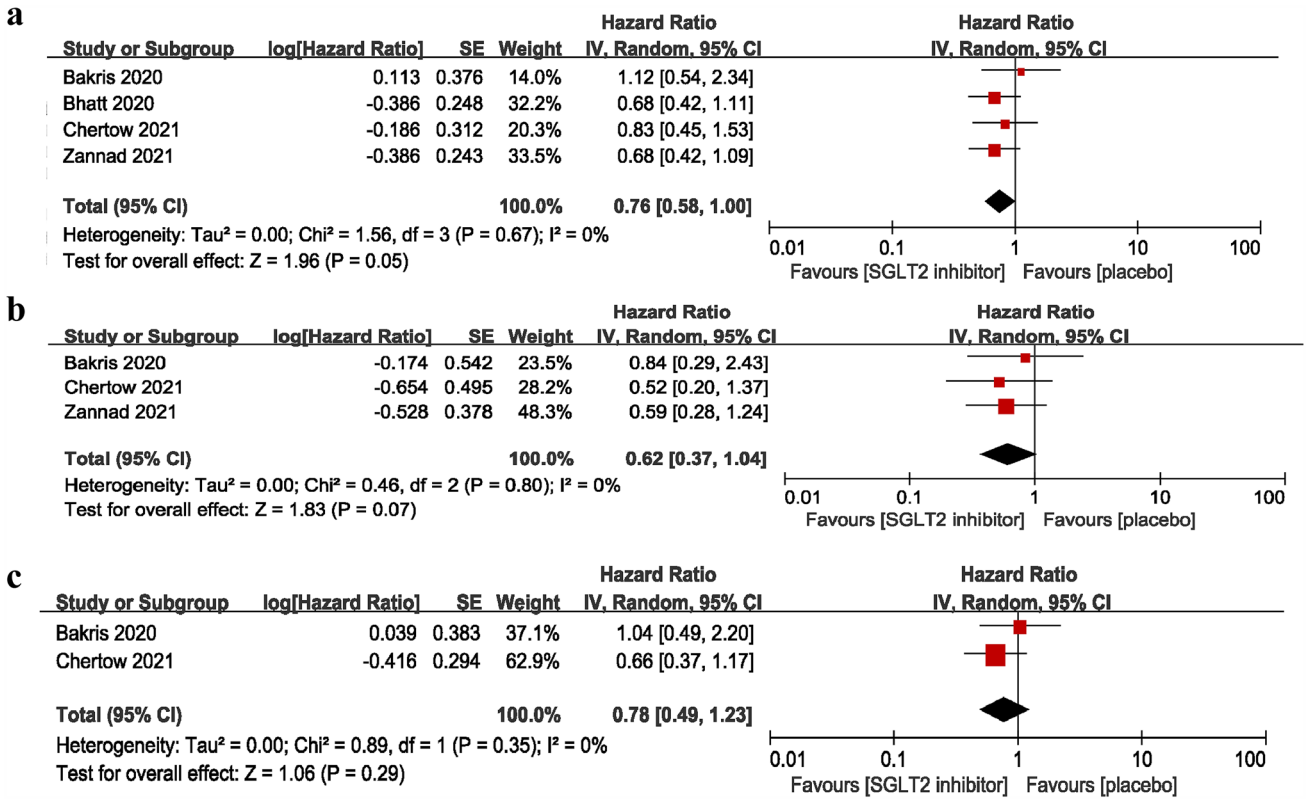

Fig. 4 Effects of SGLT2 inhibitors on the CV outcomes of the primary CV outcome (**a**), first and recurrent HHF (**b**), and MACE (**c**) among the patients with advanced CKD. Abbreviations SGLT2: sodium-glucose co-transporter 2; CV: cardiovascular; HHF: hospitalization for heart failure; MACE: major adverse cardiovascular events; CKD: chronic kidney disease; CI: confidence interval; MH: Mantel-Haenszel

Table 2 Safety events in the included RCTs

	Studies reportings	SGLT2 inhibitors group n/n	placebo group n/n	Relative risk (RR) (95%)	*P* value
CV or kidney death	3	23/561	31/514	0.70(0.29, 1.71)	0.44
All-cause death	3	24/514	38/461	0.64(0.39, 1.04)	0.07
Renal-related AE	2	72/377	77/421	1.02(0.77,1.35)	0.88
Any treatment-related AE	2	45/221	24/130	1.16(0.74–1.83)	0.52
Acute kidney injury	1	9/84	10/90	0.96(0.41, 2.26)	0.93
Fracture	3	17/561	22/514	0.78(0.42, 1.46)	0.44
Amputation	3	9/561	5/514	1.49(0.47, 4.66)	0.50
Urinary tract infection	2	32/221	21/130	1.11(0.35, 3.50)	0.86
Volume depletion	3	23/514	21/461	1.01(0.56, 1.80)	0.98
Hypoglycemia	1	87/221	50/130	1.01(0.77, 1.32)	0.97
Hyperkalemia	2	13/121	16/127	0.64(0.11, 3.72)	0.62
Discontinuation due to AE	3	57/514	54/461	0.93(0.65, 1.32)	0.67

Annotations: CV: cardiovascular; AE: adverse events

0.41–2.26, $p=0.93$; fracture: RR 0.78, 95% CI 0.42–1.46, $p=0.44$; amputation: RR 1.49, 95% CI 0.47–4.66, $p=0.50$; urinary tract infection: RR 1.11, 95% CI 0.35–3.50, $p=0.86$; volume depletion: RR 1.01, 95% CI 0.56–1.80, $p=0.98$; hypoglycemia: RR 1.01, 95% CI 0.77–1.32, $p=0.97$; hyperkalemia: RR 0.64, 95% CI 0.11–3.72, $p=0.62$; discontinuation due to AE: RR 0.93, 95% CI 0.65–1.32, $p=0.67$).

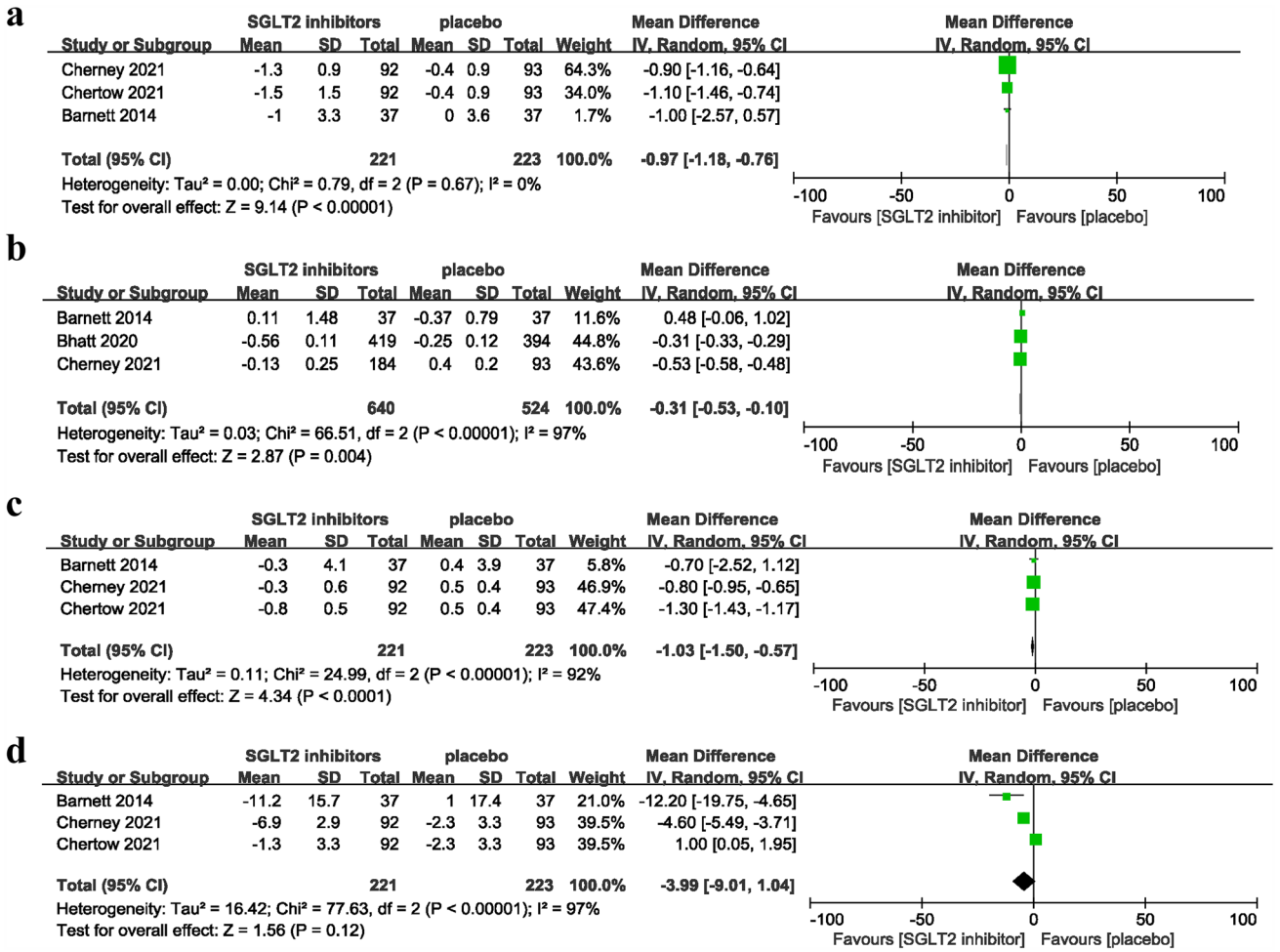

Fig. 5 Effects of SGLT2 inhibitors on the biomarker outcomes of the body weight (**a**), HbA1c (**b**), FPG (**c**), and SBP (**d**) among the patients with advanced CKD. Abbreviations SGLT2: sodium-glucose co-transporter 2; HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; SBP: systolic blood pressure; CKD: chronic kidney disease; CI: confidence interval; MH: Mantel-Haenszel

Discussion

This systematic review and meta-analysis comprehensively summarized evidence on the effects of SGLT2 inhibitors on both kidney and CV outcomes in patients with advanced CKD. In this review of six large-scale RCTs, SGLT2 inhibitors were found to reduce the risk of primary kidney outcome and slow the annual decline in eGFR slope. In addition, the use of SGLT2 inhibitors was associated with a lower risk of primary CV outcome. No additional increase in adverse effects, including any AE and any serious AE, was observed with SGLT2 inhibitors compared with placebo in individuals with advanced CKD. These data support the use and continuation of SGLT2 inhibitors in patients with advanced CKD, thus providing clinicians with an additional treatment opinion for patients with advanced CKD (eGFR 15–30 mL/min/1.73 m^2).

Our findings suggested that the renoprotective effects of SGLT2 inhibitors on the primary kidney outcome and annual eGFR slope extend to the participants with advanced CKD. The observed benefits were consistent with the results from a published meta-analysis of three RCTs, which revealed that SGLT2 inhibitors were associated with a lower risk of primary renal outcome in the sub-populations with advanced CKD [21]. The same renoprotective effects of SGLT2 inhibitors were also observed in populations with type 2 diabetes and stage 3b-4 CKD [22]. Among patients with type 2 diabetes and advanced CKD, the nephroprotective mechanism of SGLT2 inhibitors is more likely to be explained by the synergistic effect with RAS inhibitors on efferent glomerular arterioles to reduce intraglomerular pressure, rather than by rebalancing tubuloglomerular feedback, inducing vasoconstriction of the afferent arteriole, and thus reducing the glomerular hyperfiltration [23]. The researchers conducted

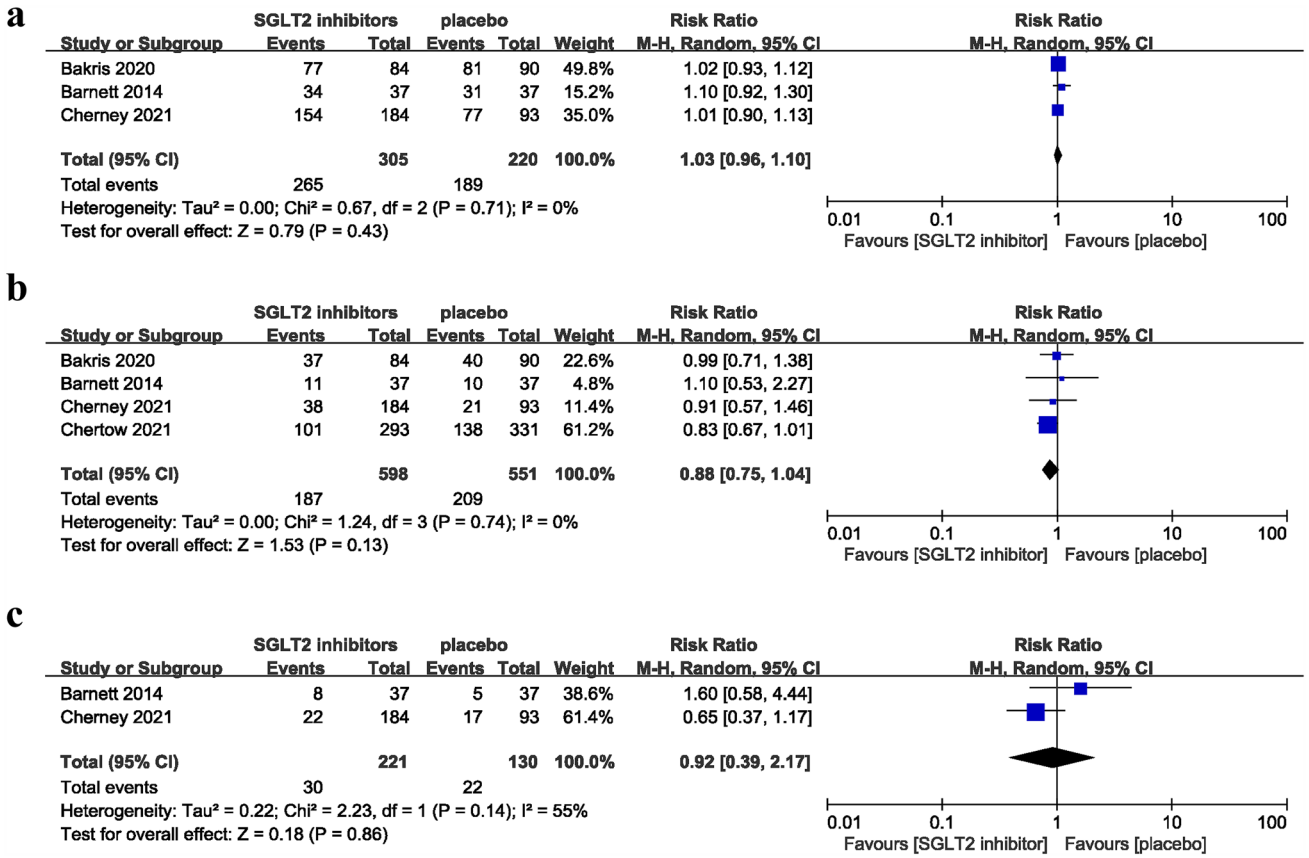

Fig. 6 Effects of SGLT2 inhibitors on the safety outcomes of any AE (**a**), any serious AE (**b**), and any severe AE (**c**) among the patients with advanced CKD. Abbreviations SGLT2: sodium-glucose co-transporter 2; AE: adverse events; CKD: chronic kidney disease; CI: confidence interval; MH: Mantel-Haenszel

pathological studies on diabetic CKD and showed that arteriosclerosis and arteriolohyalinosis of the glomerular afferent arteriole were closely related to the loss of automatic regulation of renal blood flow [24]. This can further result in glomerular ischemia, therefore, the opposite of glomerular hyperfiltration. In addition, non-diabetic patients do not have up-regulated expression levels of SGLT2 and hence do not show inhibition of the tubuloglomerular feedback [23]. The investigators have obtained confirmation with the large-scale trial that the renal protective effect of SGLT2 inhibitors is independent of its hypoglycemic effect [25]. For instance, the beneficial effects of dapagliflozin on the major kidney outcome showed consistency among people with diabetic and non-diabetic CKD [26, 27]. Lastly, during clamped euglycemia (5 mmol/L) and clamped hyperglycemia (15 mmol/L), SGLT2 inhibitors did not increase the renal vascular resistance, suggesting that the reduced GFR and filtration fraction were due to efferent arteriole vasodilation instead of afferent arteriole vasoconstriction [28].

Furthermore, our results indicated that SGLT2 inhibitors reduced the risk of the composite outcome of CV death or HHF in patients with advanced CKD, extending the favorable effects of SGLT2 inhibitors on the major CV outcome to the population with eGFR 15–30 mL/min/1.73 m^2. Besides, this meta-analysis found that SGLT2 inhibitor treatment did not increase the risk of all-cause death and CV or kidney death. The favorable effects on CV outcomes reflect those revealed by Toyama et al., who demonstrated that patients with type 2 diabetes and CKD (eGFR ˂ 60 mL/min/1.73 m^2) had a lower risk of CV events but paid less attention to the population with advanced CKD [29]. Likewise, these results also support the ideas of Malik et al. [30], who suggested that SGLT-2 inhibitors significantly improve CV outcomes in patients with type 2 diabetes and CKD stage 3 or higher. A possible explanation for this might be the reduction in myocardial fibrosis, steatosis, and inflammation [31]. In addition, natriuresis due to osmotic diuresis related to glycosuria is also thought to be a mechanism underlying the decreased duration of hospitalization in these people [32].

Based on the emerged phenomenon that the reduction in the renal function decline is independent of the hypoglycemic effects of SGLT-2 inhibitors, the recent article showed that the benefits on CV outcomes in populations

with diabetes and damaged GFR values are consistent with the benefits in populations with normal GFR values [33]. Given that type 2 diabetes and CKD usually coexist, the cardioprotective effects of SGLT2 inhibitors applied in CKD patients are promising and deserve further exploration. In addition, we discovered that the patients treated with SGLT2 inhibitors had similar risks of MACE and HHF in comparison with those treated with placebo. One possible reason for this result could be the small sample size of the studied population. The recently terminated DIAMOND trial enrolled patients with an eGFR of 25 mL/min per 1.73 m^2 [34]. We believe that the results from the trial will provide a useful insight into the favorable effects of SGLT2 inhibitors on renal and CV outcomes in participants with advanced CKD.

Our results showed that SGLT2 inhibitors significantly reduced HbA1c, FPG, and body weight in patients with advanced CKD. This accords with a prior article, focusing on type 2 diabetic patients with CKD, which indicated that SGLT2 inhibitors reduced HbA1c (0.39–0.19% decrease) and FPG levels (0.94–0.36 mmol/l decrease) [29]. SGLT-2 inhibitors, due to their specific mechanism of increasing natriuresis and diuresis, have the advantage of eliciting favorable effects on the renal and CV outcomes, including decreasing the body weight [35]. Obesity is closely associated with chronic diseases, especially CKD and diabetes [36], and with a growing risk of all cause-deaths [37]. Conventional hypoglycemic agents, such as glinides, insulin, thiazolidinediones, and sulphonylureas, induce weight gain; thus, from this perspective, using SGLT2 inhibitors in CKD patients may be an appropriate choice.

Regarding the safety profile of these agents, the results of our study suggested that SGLT2 inhibitors did not increase the risk of renal-related AE, any treatment-related AE, AKI, fracture, urinary tract infection, volume depletion, hypoglycemia, hyperkalemia, and discontinuation due to AE in patients with advanced CKD. Previously, there were concerns that SGLT2 inhibitors can increase the risk of fracture by changing calcium and phosphate homeostasis. Some investigators also reported an increased risk of fracture when using SGLT2 inhibitors [38, 39]. In contrast, two recent meta-analyses of RCTs revealed that SGLT2 inhibitors did not increase the risk of fracture in participants with type 2 diabetes [40, 41]. Another meta-analysis that focused on CKD patients found that treatment with SGLT2 inhibitors resulted in a similar risk of fracture as with placebo [42]. Our meta-analysis also showed the same result.

Nevertheless, our study has a few limitations. First, the RCTs of SGLT2 inhibitors did not involve an assessment of the efficacy of all relevant outcomes in individuals with advanced CKD (for instance, the included RCTs reported various renal outcomes that may show inconsistency across trials). We were unable to obtain sufficient data that were used to assess the unreported outcomes or perform subgroup analyses even after contacting the authors of the included trials. Second, due to the limited number of available studies, the strength of evidence for beneficial effects on kidney and CV outcomes in patients with advanced CKD may not be reflected well. Third, using different kinds of SGLT2 inhibitors and varied periods of treatment may lead to relatively few events of some safety outcomes. However, despite these limitations, our meta-analysis has several advantages. First, this systematic review and meta-analysis enrich the available data on SGLT2 inhibitors and, for the first time, evaluated their effects on the kidney and CV outcomes and safety events in the population with advanced CKD (eGFR 15–30 mL/min/1.73 m^2). Second, considering the heterogeneity of populations involved in the large trials of SGLT2 inhibitors, we selected the random-effect model instead of the fix-effect model used in previous articles [43]. Third, our meta-analysis is unique in including the placebo-controlled RCTs with high quality.

Conclusion

In conclusion, in patients with advanced CKD, SGLT2 inhibitors reduced the risks of primary kidney and CV outcomes and attenuated the decrease in eGFR compared with placebo, with no evidence of additional safety concerns. These observed benefits may support the continuation of the use of SGLT2 inhibitors in patients with advanced CKD before initiating maintenance dialysis or kidney transplantation. Future large-scale RCTs are needed to confirm the robustness of these results.

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Author contributions D.L designed the study. HY. C and XS.R completed the systematic review, extracted data, and wrote the manuscript. JY.J and TK.Y modified the manuscript. All authors contributed to data interpretation of the manuscript for important intellectual content and approved the final version to be published.

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Data availability The data that support the fndings of this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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