Non comunicable diseases

The Role of SGLT2 Inhibitors in Preventing the Progression of Chronic Kidney Disease in Patients with Type 2 DM: A Systematic Review

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Keywords

SGLT2 inhibitors • Chronic Kidney Disease • Diabetes Mellitus type 2

Summary

Background. *Type 2 diabetes mellitus is the most common type of diabetes and is the leading cause of chronic kidney disease globally. Currently, the medications recommended for treatment are not fully effective for treating CKD. Recent findings from the DAPA-CKD and EMPA-KIDNEY clinical trials have revealed that SGLT-2 inhibitors offer significant benefits in improving kidney function and preventing the progression of kidney disease.*
Objective. *This review aims to evaluate the efficacy and safety of SGLT2 inhibitors in delaying CKD progression and reducing dialysis dependency in patients with type 2 diabetes.*
Methods. *This research is a systematic literature study using PRISMA 2020 Protocols. Article searches were carried out in PubMed, Cochrane Library, Sage Journals, and Europe PMC, covering the period from January 2019 to March 2024. The search strategy used the keywords "SGLT2 Inhibitor" AND "Prevention" AND "Chronic Kidney Disease" AND "Type 2 Diabetes". Articles that met the criteria were assessed for risk of bias using RoB2.*
Results. *From 7 articles with a total of 15,927 participants included in this systematic review, the overall risk of bias was low. Patients with type 2 diabetes and CKD who received SGLT2 inhibitors had a significantly lower risk of renal composite outcomes compared to placebo (e.g. HR 0.70, 95% CI 0.59-0.82). A modest initial decrease in eGFR was observed in the SGLT2i group compared to placebo, followed by stabilization over time.*
Conclusion. *SGLT2 inhibitors can be proposed as an effective treatment option for renal protection in patients with type 2 diabetes mellitus and chronic kidney disease, with moderate certainty of evidence from consistent RCT findings.*

Introduction

Diabetes mellitus or diabetes is a disease that often occurs around the world and still poses a significant threat to health to this day. About 537 million adults (ages 20-79) live with diabetes. The International Diabetes Federation projects that 1 in 8 adults or about 783 million people will live with diabetes by 2045. One in 11 adults (90 million) in Southeast Asia lives with diabetes. Indonesia ranks 5th in the country with the highest diabetic population (19.5 million people) in the world. Type 2 diabetes mellitus is the most common type of diabetes, covering 90-95% of diabetic subjects, and is caused by inadequate insulin secretion combined with insulin resistance [1, 2].

Diabetes and chronic kidney disease (CKD) generally occur together and are associated with a high risk of morbidity and mortality in patients. Diabetes is the leading cause of CKD globally, accounting for nearly half of all cases of kidney failure requiring kidney replacement therapy [3]. Diabetic kidney disease or better known as CKD in diabetes is a common microvascular complication associated with diabetes, affecting about 20-40% of diabetic patients. This condition can develop into *end-stage kidney disease* (ESKD) in some cases. Currently, renin-angiotensin system inhibitors are recommended as the main drug according to guidelines for treating CKD. However, the drug is not completely adequate for the treatment of CKD due to the potential for increased risk of ESKD and acute kidney failure [4, 5].

Glucose-2 glucose-sodium inhibitor (SGLT-2) is a glucose-lowering drug that works by reducing glucose reabsorption by the kidneys in the S1 segment of the proximal tubules in the kidneys. This drug causes glycosuria and natriuresis and is associated with a decrease in glycated hemoglobin (Hb1Ac), blood pressure, albuminuria, and body weight. This class of hypoglycemic drugs works completely without relying on the hormone insulin and functions according to serum glucose levels, so the risk of hypoglycemia can be avoided. Recent findings from the DAPA-CKD and EMPA-KIDNEY clinical trials have revealed that SGLT-2 inhibitors offer significant benefits in improving cardiovascular and renal function, as well as delaying the progression of kidney disease in CKD patients, regardless of their diabetic status. The effectiveness and safety of SGLT-2 inhibitors, have been validated

for the therapy of CKD, so the 2022 KDIGO guidelines recommend its use for PGL patients with a glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2 [1, 6-9].
Slowing the progression of CKD and avoiding dialysis or kidney transplantation is the main goal of all proposed therapeutic modalities, given the impact of dialysis and kidney transplantation on the quality of life and morbidity and mortality of patients, as well as the large costs associated with kidney replacement therapy. Therefore, this systematic review was made to comprehensively review the role of SGLT2 inhibitors in slowing the progression of chronic kidney disease given the high prevalence of diabetes as a major cause of CKD and its impact on quality of life and costs incurred by kidney replacement therapy. Therefore, this systematic review aims to evaluate how SGLT2 inhibitors contribute to delaying CKD progression and reducing dialysis dependency in patients with type 2 diabetes, thereby aligning with preventive medicine and community health priorities. Unlike previous reviews, this study updates and synthesizes recent evidence following the 2022 KDIGO guidelines, providing an up-to-date perspective on the renal-protective role of SGLT2 inhibitors.

Methods

This study is a systematic literature study using data obtained from the search results of related articles using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 Protocols method [10]. Article searches were conducted through four electronic data-based publication centers, namely PubMed, Cochrane Library, Sage Journal, and Europe PMC. The full search string for PubMed was: ("SGLT2 Inhibitor" AND "Chronic Kidney Disease" AND "Type 2 Diabetes") and adapted appropriately for other databases. The search was carried out for articles published between 2019 and 2024.
The articles used in this systematic review must meet the inclusion criteria, including: 1) Studies with populations of individuals aged ≥ 18 years with type 2 diabetes mellitus and chronic kidney disease (CKD defined as *eGFR* < 90 ml/min/1.73 m²); 2) Studies evaluating the use of SGLT2 inhibitors as part of treatment compared to other conventional drugs (such as ACE inhibitors, ARBs) or placebo; 3) Studies that reported relevant clinical outcomes in the form of slowing of kidney disease progression, reduced risk of dialysis or kidney-related mortality; 4) The study is an original article using the Randomized Controlled Trial method; and 5) The article was published in the period 2019-2024, in English, and can be accessed in full. *Two reviewers independently screened titles and abstracts and subsequently reviewed the full texts of potentially eligible studies. Any disagreements were resolved by discussion or by consulting a third reviewer.* The main efficacy outcomes assessed in this systematic review included a slowdown in the progression of chronic kidney disease (decreased glomerular filtration rate/GFR, reduction in albuminuria, reduced risk of kidney failure or transition to end-stage kidney disease (EKSD)), decreased dialysis need, or kidney-related mortality. Given the clinical and methodological heterogeneity across included trials, a narrative synthesis was conducted rather than a meta-analysis. This review was not registered, which is acknowledged as a methodological limitation.

Results

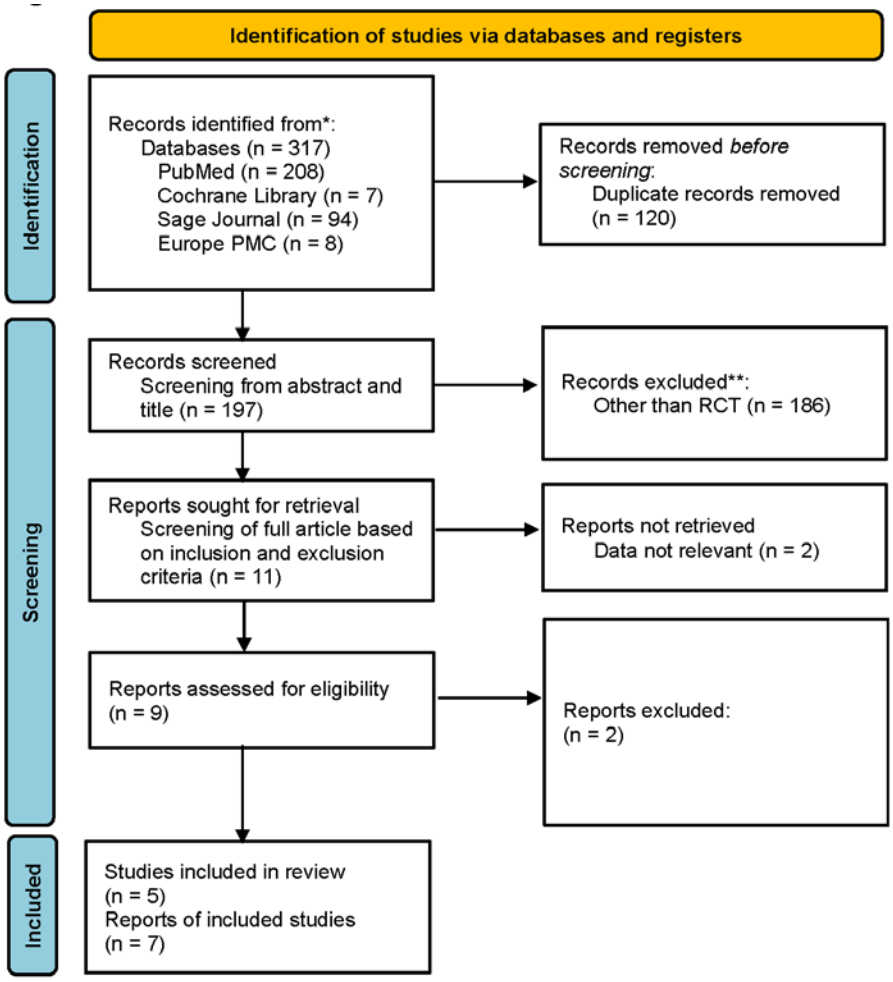
Seven articles from 5 studies that met the inclusion criteria involved a total of 15,927 participants with an average age range of 60-70 years and dominated by male gender. The studies included in this systematic review involved multicenter studies conducted in various countries, including South Africa, the United States, Argentina, Australia, the Netherlands, Belgium, Brazil, the United Kingdom, Bulgaria, Chile, China, Colombia, Denmark, Estonia, the Philippines, Guatemala, Hungary, India, Italy, Israel, Japan, Germany, Canada, South Korea, Latvia, Lithuania, Malaysia, Mexico, Norway, France, Peru, Portugal, Czech Republic, Romania, Russia, New Zealand, Serbia, Slovakia, Spain, Sweden, Taiwan, Turkey, Ukraine, the United Arab Emirates, and Greece. Three SGLT2 inhibitors, namely Canagliflozin, Sotagliflozin, and Ipragliflozin, were used in the 7 articles included in this systematic review. Assessment of study characteristics which include authors, title, study design, study location, study population, intervention, comparison group, assessed findings, and results are presented in Table I. Figure 1 illustrates the study selection process, including screening and eligibility assessment.
In total, 1,234 records were screened, of which 1,180 were excluded after title and abstract review, and 47 were excluded after full-text assessment due to not meeting inclusion criteria. Ultimately, 7 articles were included in the final analysis.
Table II shows the effect of SGLT2 inhibitor on the progression of chronic kidney disease as assessed by the change in eGFR from baseline and composite incidence in the kidneys from the intervention and control groups. Overall, the incidence of renal composite in the intervention group was generally lower when compared to the control group, but did not differ significantly ($p > 0.05$).
The selected articles were then assessed for quality and risk of bias using a risk of bias assessment based on the Revised Cochrane risk-of-bias for randomized trials (RoB2) using the Cochrane Review Manager software (RevMan 5.4). In terms of the assessment of the entire domain, the startification risk of bias of the selected articles is low risk. Figure 2 and 3 presents the risk-of-bias assessment across included studies. Some domains that have high bias risk values are allocation concealment (selection bias) and blinding of participants and personnel (performance bias) domains in the research of Tanaka et al. (2020) and incomplete outcome data (attrition bias)

Tab. I. Characteristics of Enrolled Studies.

Author (Year)	Number of Participants	Intervensi	Outcome
Bakris et al (2020) [11]	A total of 174 participants with type 2 diabetes developed chronic kidney disease and had an eGFR < of 30 ml/min per 1.73 m²	Canagliflozin 100 mg/day	• Canagliflozin did not cause a significant decrease in eGFR in the first week of treatment in this subgroup, in contrast to the general population who showed an initial decrease (Canagliflozin -1.30 ml/min per 1.73 m² per year; Placebo -3.83 ml/min per 1.73 m² per year, Δ = -2.54 ml/min per 1.73 m² per year, 95% CI: 0.9-4.17) • Canagliflozin showed a significant reduction in the risk of renal failure (HR in participants with eGFR < 30 ml/min per 1.73 m² 0.67 (95% CI: 0.35-1.27), for patients with eGFR ≥ 30 ml/min per 1.73 m², HR 0.70 (95% CI: 0.54-0.91)) • Canagliflozin is safe for use in patients with low eGFR, without increasing the risk of adverse side effects, including AKI and the incidence of renal side effects
Bhatt et al (2021) [12]	A total of 10584 participants with type 2 diabetes, HbA1c ≥ 7%, and chronic kidney disease (eGFR 25-60 ml/min/1.73 m²) as well as additional cardiovascular risk factors	Sotaglifozin 200 mg once a day	• Results on renal composites in this study showed that there was no significant difference between the group receiving sotagliflozin and the placebo group (HR 0.71, 95% CI (0.46-1.08) • Although sotagliflozin showed some side effects (diarrhea, genital fungal infections, dehydration, and diabetic ketoacidosis), the overall safety profile did not show significant differences in the incidence of serious side effects between the two groups
Jardine et al (2020) [13]	A total of 4401 participants with type 2 diabetes who also had an eGFR value of 30 - < 90 ml/min/1.73 m²	Canagliflozin 100 mg/day	• Canagliflozin reduced the risk of ESKD by 30% compared to placebo (HR 0.70; 95% CI, 0.59-0.82) • The average decrease in eGFR in the first week was about 2.5 ml/min per 1.73 m², followed by stabilization • The incidence of serious side effects, including urinary tract infections and diabetic ketoacidosis, remained low and comparable between the two groups
Perkovic et al (2019) [14]	A total of 4401 participants with type 2 diabetes mellitus	Canagliflozin 100 mg/day	• The primary composite results of this study included the incidence of end-stage kidney disease (ESKD) or death from renal or cardiovascular causes (HR 0.70 (95% CI, 0.59-0.82), p = 0.00001) • Canagliflozin showed better maintenance of kidney function compared to placebo • Canagliflozin shows an acceptable safety profile in patient populations with type 2 diabetes and nephropathy
Tanaka et al (2020) [15]	A total of 30 participants with type 2 diabetes mellitus	Ipragliflozin 50 mg once a day	• There was a decrease in eGFR in the ipragliflozin group compared to the control group, indicating that ipragliflozin may help maintain kidney function • Ipragliflozin can be safe and effective in improving kidney function and lowering uric acid levels
Wada et al (2022) [16]	A total of 308 CKD patients with type 2 DM	Canagliflozin 100 mg/day	• The incidence of a 30% reduction in eGFR was significantly lower in the canagliflozin group compared to the placebo group, an estimated difference between groups of 5.2% (95% CI 2.3-8.0, $p < 0.001$) • The study reported that the incidence of a 40% decrease in eGFR at week 104 was 10.1% in the canagliflozin group and 13.9% in the placebo group. The estimated difference between groups (placebo - canagliflozin) was 3.8% (95% CI -4.1-11.7, $p = 0.343$) • There were no significant safety concerns associated with the use of canagliflozin in Japanese patients with chronic kidney disease and type 2 diabetes
Wada et al (2022) [17]	A total of 604 participants with type 2 diabetes mellitus and eGFR 30 - < 90 ml/min/1.73 m² were from East and Southeast Asia	Canagliflozin 100 mg/day	Canagliflozin reduced the risk of renal primary composite compared to placebo in EA participants (40.83 *vs.* 73.45 per 1,000-year-patient; HR 0.54, 95% CI 0.35-0.84) Canagliflozin showed significant reductions in UACR and improvements in eGFR Canagliflozin is considered safe for use in patients with type 2 diabetes and nephropathy, with a safety profile comparable to placebo

AKI: acute kidney injury; CI: confidence interval; EA: East Asian and Southeast Asian participants; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HR: hazard ratio; UACR: urine albumin-creatinine ratio.

Fig. 1. PRISMA flowchart.



domains in the research of Bakris et al. (2020), Jardine et al. (2020), and Wada et al. (b) (2020). Importantly, the presence of attrition bias in Bakris et al. (2020) did not alter the overall trend toward renal protection with SGLT2 inhibitors, suggesting robustness of the pooled conclusions.

Discussion

SGLT2 inhibitors are a group of glucose-lowering drugs that inhibit glucose reabsorption in the renal tubules and induce glucose excretion through the urine by lowering the renal glucose threshold. This class of hypoglycemic drugs works completely independently of the hormone insulin and functions according to the existing serum glucose levels, so it has a very low risk of hypoglycemia [1, 18].

Heterogeneity in the included studies arose from differences in the SGLT2 inhibitors evaluated, patient populations, and duration of follow-up, which precluded a formal meta-analysis. Of the 7 articles included in this systematic review, all articles discuss the role of SGLT2 inhibitors in preventing CKD progression, both as the main and secondary findings. The article written by Bakris et al. (2020), Jardine et al. (2020), Perkovic et al. (2019), and Wada et al. (b) (2022) discussed the inhibitory effect of SGLT2 in preventing renal progression as the main finding, with *the end-points* assessed to include the composite of *end-stage kidney disease,* a 2-fold increase in serum creatinine from baseline, a change in eGFR, or death from kidney disease. In this systematic review, it was found that patients with type 2 diabetes and chronic kidney disease who received SGLT2 inhibitors had a lower risk of priner composite outcomes compared to the placebo group. These results suggest that SGLT2 inhibitors can be proposed as an effective treatment option for renal protection in patients with type 2 diabetes and chronic kidney disease.

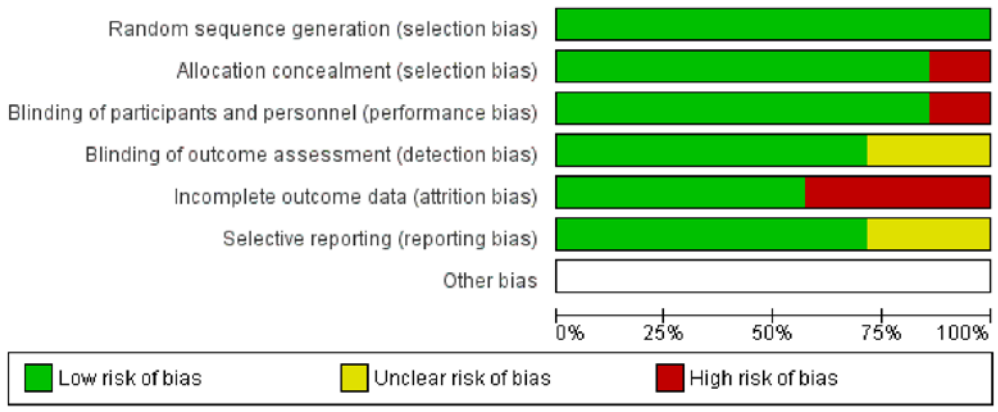
In addition, Bakris et al. (2020) also reported that Canagliflozin, one type of SGLT2 inhibitor, showed a significant reduction in the risk of kidney failure. The hazard ratio (HR) for renal failure in participants with eGFR < 30 ml/min per 1.73 m² was 0.67 (95% CI: 0.35-1.27), for patients with eGFR ≥ 30 ml/min per 1.73 m², HR was 0.70 (95% CI: 0.54-0.91) [11]. Similar

Tab. II. Effect of SGLT2 Inhibitor on Chronic Kidney Disease Progression.

Author (Year)	Type of SGLT2i	Mean baseline eGFR (ml/min/1.73 m²)		Mean change in eGFR from *baseline* (ml/min/1.73 m²)		Effect of SGLT2i on reduction of CKD progression*					
						SGLT2i		Control		HR (95% CI)	*p value***
		SGLT2i	Control	SGLT2i	Control	Participants/events	Events per 1000 patients-year	Participants/events	Events per 1000 patients-year		
Bakris et al. (2020) [11]	Canagliflozin	26 ± 3	27 ± 3	-1.30	-3.38	84/15	75.4	90/25	116.0	0.67 (0.35-1.27	0.77
Bhatt et al. (2021) [12]	Sotaglifozin	44.4	44.5	-0.09	-1.31	5292/37	0.5	5292/52	0.7	0.71 (0.46-1.08)	-
Jardine et al. (2020) [13]	Canagliflozin	56.3 ± 18.2	56.0 ± 18.3	-3.19	-4.71	2202/245	43.2	2199/340	61.2	0.70 (0.59-0.82)	0.0001
Perkovic et al. (2019) [14]	Canagliflozin	56.3 ± 18.2	56.0 ± 18.3	-1.5	-4.5	2202/245	43.2	2199/340	61.2	0.70 (0.59-0.82)	0.0001
Tanaka et al. (2020)	Ipragliflozin	67.3 ± 18.2	67.9 ± 16.9	1.6	-3.5	-	-	-	-	-	-
Wada et al. (2022) [16]	Canagliflozin	56.3 ± 15.5	55.2 ± 13.6	-10.39	-11.49	154/7	24.29	154/11	38.66	0.60 (0.23-1.55)	0.2930
Wada et al. (2022) [17]	Canagliflozin	55.4 ± 16.0	56.1 ± 17.2	-3.38	-5.68	301/31	40.83	303/54	73.45	0.54 (0.35-0.84)	0.2035

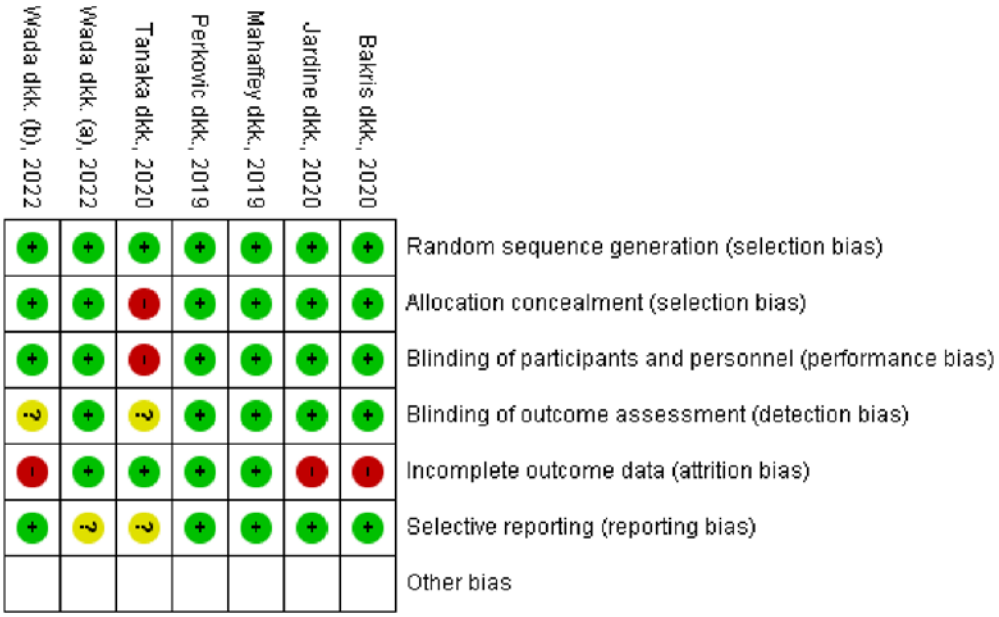
eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor; CI: confidence interval. * Components assessed include the incidence of end-stage kidney disease (ESKD), a 2-fold increase in serum creatinine, kidney failure, kidney death. ** *p* value is considered significant if $p < 0.05$. -: Unreported

Fig. 2. The results of the risk of bias assessment using RoB2 from the included journals.



results were also reported by Jardine et al. (2022) where they found that Canagliflozin reduced the risk of ESKD by 30% compared to placebo (HR 0.70; 95% CI, 0.59-0.82). Perkovic et al. (2019) also reported the results of the primary composite of kidneys including *end-stage kidney disease* (ESKD) or death from renal causes with an HR value for the canagliflozin group compared to placebo of 0.70 (95% CI, 0.59-0.82), *p* value = 0.00001. This suggests that the use of canagliflozin reduces the risk of major composite events by 30% compared to placebo. Perkovic et al. (2019) also reported kidney-specific composite results including a significant decline in kidney function. *The hazard ratio* for this outcome was 0.66 (95% CI, 0.53-0.81), with a *p* value < 0.001 [14]. In a study conducted by Wada et al. (b) (2020) with more demographically specific participants, including participants from East and Southeast Asian countries (China, Philippines,

Fig. 3. Risk of bias summary from the included journals.



Japan, South Korea, Malaysia), canagliflozin reduced the risk of primary outcomes (combined from ESKD, a two-fold increase in serum creatinine, or renal or cardiovascular mortality) compared to placebo in EA participants (40.83 *vs.* 73.45 per 1,000-patient-year-old; HR 0.54, 95% CI 0.35-0.84). In addition, the study also reported that canagliflozin showed a significant reduction in UACR and improvement in eGFR, which showed additional benefits in managing renal risk[17] In contrast to the effects of canagliflozin, Bhatt et al. (2021) reported below results on renal composites in their study showing that there was no significant difference between the group receiving sotagliflozin and the placebo group (HR 0.71, 95% CI (0.46-1.08)) [12].

Six of the 7 articles reported in this systematic review showed a decrease in eGFR in the SGLT2 inhibitor group when compared to the comparison group. However, Bakris et al. (2020) reported that Canagliflozin did not cause a significant decrease in eGFR in the first week of treatment in this subgroup, in contrast to the general population which showed an initial decrease (Canagliflozin -1.30 ml/min per 1.73 m² per year; Placebo -3.83 ml/min per 1.73 m² per year, Δ = - 2.54 ml/min per 1.73 m² per year, 95% CI: 0.9-4.17) [11]. Jardine et al. (2020) also reported canagliflozin causes an acute decrease in eGFR followed by stabilization of eGFR loss. The average decrease in eGFR in the first week was about 2.5 ml/min per 1.73 m², followed by stabilization. The decrease in eGFR in the intervention group had a statistically significant difference when compared to placebo ($p = 0.0001$) [13].

Tanaka et al. (2020) also reported a decrease in eGFR in the ipragliflozin group compared to the control group, indicating that ipragliflozin may help maintain kidney function [15]. The SGLT2 inhibitor inhibits the reabsorption of sodium m and glucose in the proximal tubules, leading to increased delivery of sodium and chloride to the macula densa. This results in vasoconstriction of the afferent arterioles caused by adenosine-mediated myogenic activation, thereby reducing intraglomerular pressure and GFR [19]. Maladaptive glomerular hemodynamics play an important role in the progression of kidney disease. All of the articles used in this systematic review reported similar safety profiles, in both the SGLT2 inhibitor and placebo groups. Bakris et al. (2020) reported that Canagliflozin is safe for use in patients with low eGFR (≤ 30 ml/min/1.73 m^2) without increasing the risk of adverse side effects, including the incidence of AKI and other renal side effects. Jardine et al. (2020) reported the incidence of serious adverse events, including urinary tract infections and diabetic ketoacidosis, remained low and comparable among the SGLT2 and placebo inhibitor groups. Perkovic et al. (2019) [14], Wada et al. (a) (2022) and Wada et al. (b) (2022) reported that Canagliflozin is considered safe for use in patients with type 2 diabetes and nephropathy and there are no significant safety concerns related to the use of this drug in patients with chronic kidney disease and type 2 diabetes. Although sotagliflozin showed some side effects, such as diarrhea, genital fungal infections, dehydration, and diabetic ketoacidosis, Bhatt et al. (2021) reported no significant difference in the incidence of serious side effects in the two groups. Tanaka et al. (2020) reported that Ipragliflozin can be safe and effective in improving kidney function. Using the GRADE approach, the certainty of evidence for renal outcomes was rated as moderate, primarily due to consistency across large multicenter RCTs but with some concerns regarding publication bias. From a public

health perspective, broader implementation of SGLT2 inhibitors could reduce the demand for dialysis and transplantation, particularly in low- and middle-income regions where the burden of diabetic kidney disease is rising. Nonetheless, this review has limitations, including the exclusion of non-English studies, which may limit the generalizability of findings and introduce potential publication bias.

Conclusion

Based on the analysis of seven studies in this systematic review, the authors concluded that patients with type 2 diabetes mellitus and chronic kidney disease who received SGLT2 inhibitors had a lower risk of chronic kidney disease progression compared to those who received a placebo. SGLT2 inhibitors, particularly Canagliflozin, can significantly reduce composite kidney events, including end-stage kidney disease, a two-fold increase in serum creatinine from baseline, changes in eGFR, or death due to kidney disease. These findings suggest that SGLT2 inhibitors could be proposed as an effective treatment option for kidney protection in patients with type 2 diabetes mellitus and chronic kidney disease. Additionally, there were no significant safety issues or adverse effects associated with the use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease, indicating that these medications are safe to use.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare no competing interests. This study did not receive any industry funding and was not produced as part of any grant supported.

Authors' contributions

All authors made substantial contributions to this study. Conceptualization: AAP, AS, IAL. Literature search and study selection: AAP, AS. Data extraction and quality appraisal: AAP, AS, IAL. Data synthesis and interpretation: AAP, AS, IAL. Writing – original draft: AAP. Writing – review & editing: AS, IAL. Supervision: AS, IAL. All authors have read and approved the final version of the manuscript.

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