Sodium-glucose co-transporter 2 inhibitors (SGLT2i); as a preventive factor of kidney failure in patients with type 2 diabetes; a meta-analysis of randomized controlled trials

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a new class of anti-diabetic drugs. SGLT2 inhibitors lower blood glucose levels by decreasing glucose reabsorption in the proximal renal tubule, resulting in increased urinary glucose and sodium excretion.
Objective: This study was conducted to investigate the effects of SGLT2i on individual renal outcomes in diabetic patients.
Methods: This study was a systematic review and meta-analysis of clinical trials. A comprehensive search of Cochrane Central Register of Controlled Trials was conducted in the Cochrane Library and PubMed, to identify relevant articles focusing on SGLT2i and chronic kidney disease (CKD) in diabetic patients. The most recent article search was conducted on July 12, 2021.
Results: Seven randomized controlled trials (RCTs) were included in the meta-analysis. Two trials were comparing dapagliflozin, two comparing empagliflozin, one comparing ertugliflozin, one comparing canagliflozin, and one comparing sotagliflozin. Composite renal outcome and acute kidney injury (AKI) was found in seven and four studies, respectively. Data on end-stage kidney disease (ESKD) and albuminuria or initiation of renal replacement therapy were reported in the two studies. The pooled risk ratio (RR) 95% confidence interval (CI) for the composite renal outcome was 0.54 (0.50–0.59), with 92 % heterogeneity. The pooled RR for AKI was 0.77 (0.66–0.89), with no heterogeneity. A significant lower incidence of albuminuria (RR: 0.69; 95% CI: 0.59–0.81), initiation of renal replacement therapy (RR: 0.71; 95% CI: 0.58–0.87), was observed following the use of SGLT2 inhibitors.
Conclusion: Our findings confirm that the SGLT2 inhibitors can reduce the risk of albuminuria, AKI and renal replacement therapy in ESKD patients with T2D (type 2 diabetes). These meta-analyses provide substantial evidence supporting the beneficial effect of SGLT2 inhibitors on reducing CKD events in individuals with T2D.

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Introduction

Diabetes is a global public health problem and one of the top 10 causes of death in most developed countries that pose a high risk of severe vascular complications (1). Diabetic nephropathy (DN) is a major burden among the chronic complications of diabetes, which develops in approximately 30% of diabetic patients and approaching epidemic proportions globally. Indeed, DN is the leading cause of chronic kidney disease (CKD) in the United States (2). According to International Diabetes Federation, the comparative prevalence of diabetes in 2007 was 8.0%, which is expected to rise to 7.3% by 2025 (3).

The natural history of DN includes glomerular hyperfiltration, progressive albuminuria, decreased glomerular filtration rate (GFR) and eventually end-stage renal disease (ESRD). Further, smoking and obesity are known risk factors for DN. Ethnic, familial, and genetic factors also play a significant role in disease progression (4, 5). There are two distinct pathways, hemodynamic and non-hemodynamic to be involved in the progression of diabetic kidney disease (6). Although the role of hyperglycemia in the pathophysiology of diabetic complications is not fully understood, it has been linked to an increase in intraglomerular pressure, single nephron GFR, and podocyte damage, which further perpetuates renal dysfunction (7). Recently, a study mentioned that metabolic reprogramming is associated with diabetes, leading to tubulointerstitial inflammation and fibrosis (8).

Treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors prevent the major adverse effect of CKD in people with diabetes, and clinical practice guidelines recommend these drugs for the general approach to the all diabetic individuals with kidney disease or at risk for it (9,10).

The recent approval of sodium/glucose co-transporter 2 inhibitors (SGLT2i) creates new therapeutic options for this high-risk diabetes population. SGLT2i are a novel class of diabetes drugs that lower blood glucose levels by decreasing glucose reabsorption in the proximal renal tubule, resulting in increased urinary glucose and sodium excretion (11,12). Recently, SGLT2i have significantly reduced CKD progression in people with diabetes (13, 14). Several clinical trials have found that combining SGLT2 and metformin as an initial treatment for diabetic patients is surprisingly beneficial (15, 16). The American Diabetes Association 2020 guidelines recommend prescribing an SGLT2i after a trial of lifestyle modifications in patients with CKD (17).

The benefits of SGLT2i in diabetic patients overcome the moderate side effects observed in the literature. The SGLT2i have been associated with an increased risk of glycosuria and risk for genital mycotic infections (18). However, in diabetes patients with early signs of DN, the specific role of SGLT2i and risk of acute kidney injury (AKI) needs to be defined. Thus, the present meta-analysis aims to identify the effect of SGLT2i on renal pathophysiological events in seven previous published randomized controlled trials (RCTs).

Materials and Methods

Data sources and search strategy

The present meta-analysis was conducted in accordance with the PRISMA guideline (19) (Figure 1). Two investigators independently searched Cochrane Central Register of Controlled Trials in the Cochrane Library and PubMed for randomized, placebo-controlled studies involving SGLT2i with endpoints such as impaired renal function, acute kidney injury, and composite renal outcome. The keywords searched were "sodium-glucose co-transporter 2 inhibitors", "Sodium-Glucose Transporter 2 Inhibitors", "SGLT2i", "kidney failure", "type 2 diabetes", "T2D", "chronic kidney disease", "CKD", "acute kidney injury", "AKI", "albuminuria", "renal replacement therapy", "RRT", "hemodialysis", "Sotagliflozin", "peritoneal dialysis", "canagliflozin", "metformin", "dapagliflozin", "saxagliptin", "empagliflozin", "ertugliflozin" or a combination of them in the titles or abstracts. The references of the published articles were manually reviewed for additional relevant articles. The duplicate studies were removed by EndNote. No limitations were set on the language, article timeframe or any other trial characteristics; however, the final literature search was conducted on July 12, 2021.

Inclusion and exclusion criteria

Our main aim was to assess the effect of SGLT2 inhibitors on DN outcomes; however, after initial screening, the full
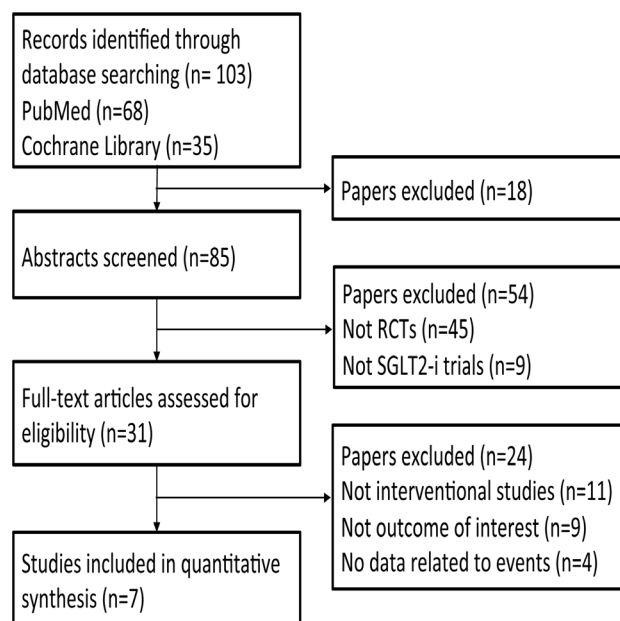

Figure 1. Flow diagram depicting the process of selecting RCTs for inclusion in the meta-analysis.

text of all relevant papers were obtained and were screened based on inclusion criteria; (1) having placebo/control arm in the design (2) presence of association between renal outcomes and SGLT2i in the study (3) adults (>18 years) with type 2 diabetes with detailed information preferred. Exclusion criteria were as follows; (1) duplicate studies (2) letters, case reports, editorials, comments, or animal studies (3) trials on people with type 1 diabetes mellitus.

Outcome definitions

Composite renal outcome is defined as ≥40% reduction in eGFR, the need for renal replacement therapy, doubling serum creatinine or kidney related mortality. AKI is determined by the KDIGO (Kidney Disease: Improving Global Outcomes available at https://web.archive.org/web/20160304025332/http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf) definition. Albuminuria was defined by urine albumin: creatinine ratio (ACR) (moderate: 30–300 mg/g or heavy: >300 mg/g). Serum creatinine criteria (increase in serum creatinine by ≥0.3 mg/dL within 48 h or increase in serum creatinine by ≥1.5 times baseline value in the prior 7 days). End-stage kidney disease (ESKD) is defined as eGFR ≤30 mL/min/1.73 m^2.

Data collection

The renal outcomes studied in this meta-analysis include composite renal outcomes [doubling of serum creatinine or 50% reduction in eGFR (estimated glomerular filtration rate)], AKI, albuminuria, or initiation of renal replacement therapy. Two authors separately collected all data, including date of publication, number of renal outcome events in SGLT2i and placebo groups. The disagreements between the investigators were resolved through discussion with the independent supervisor.

Statistical analysis

Cochrane Collaboration's risk-of-bias tool was used to assess selection, performance, detection, attrition and reporting biases of different trials (20). Heterogeneity was assessed using Cochran's Q test and I^2 statistics and the value with I^2 >50% indicated significance (21). Pooled relative risk (RR) and their 95% confidence interval (CI) were calculated in a fixed-effects model using RevMan version 5.3. Begg's funnel plots were used for assessing publication bias.

Results
Study selection process

The online search strategy retrieved 103 papers from PubMed (n = 68) and Cochrane Library (n = 35). Eighteen papers were excluded due to duplication based on the inclusion and exclusion criteria. Following the review of the title and abstract, 54 papers were ruled out. The full article was obtained for the remaining 31 papers. Furthermore, 24 articles were omitted because they neither

deal with outcome nor events. Seven RCTs were finally included in the meta-analysis. The study selection process and reasons for exclusions were described in Figure 1. The last updated search was conducted in July 2021.

Study characteristics

Finally, seven RCTs were selected for this meta-analysis. A total of 55 265 individuals were identified (30 097 in the SGLT2i group and 25 168 in the control group). There were 2 trials comparing empagliflozin versus placebo (22,23); 2 trials comparing dapagliflozin versus placebo (24,25); 1 trial comparing canagliflozin versus placebo (26); 1 trial comparing ertugliflozin versus placebo (27); 1 trial comparing sotagliflozin versus placebo (28). Characteristics of eligible studies are shown in Table 1. The lower risk of bias indicated that the studies included in this meta-analysis were well-designed and conducted.

Effect of SGLT2i on renal outcomes

Data on composite renal outcomes were available for 55 265 participants (30 097 in the SGLT2i group and 25 168 in the control group) in 7 studies (22-28). AKI was reported in 4 studies with 20 950 patients in the SGLT2i group and 15 844 patients in the placebo group (22,25-27). Data on albuminuria or initiation of renal replacement therapy was reported in 4 studies with 4354 patients in the SGLT2i group and 4351 patients in the placebo group (24,26). Table 2 summarizes the pooled RR with 95% CI for the renal outcomes. The pooled RR for the composite renal outcome was 0.54 (95% CI: 0.50–0.59), with heterogeneity of 92%, while the pooled RR for the AKI was 0.77 (95% CI: 0.66-0.89) with 0% heterogeneity (Figures 2A and 2B). A significant lower incidence of albuminuria (RR: 0.69; 95% CI: 0.59-0.81), initiation of renal replacement therapy (RR: 0.71; 95% CI: 0.58-0.87), was observed without significant heterogeneity (Figures 2C and 2D).

Publication bias

Publication bias statistics determined by the Begg's funnel plot indicated that there is no significant asymmetry in funnel plots for the composite renal outcome and AKI (Figure 3A and 3B). These plots visually indicate that there is no publication bias, due to less number studies included in the meta-analysis. As the coefficients are dependent on number of studies, checking the plots visually is of great importance. We could not conduct a test for publication bias for the remaining outcomes due to less number of studies.

Discussion

The current meta-analysis summarized data on various renal outcomes from seven RCTs involving a range of SGLT2i. The pooled RR indicated that the SGLT2i reduced the incidence of various renal outcomes. Further, Begg's funnel plots demonstrate that there is obvious publication bias. SGLT2 inhibitors protect patients with

Table 1. Characteristics of studies included in the meta-analysis

Study	Clinical trial name	Clinical trial No.	Drug	SGLT2i	Placebo	Age Mean±SD	Diabetic (%)	Women (%)	eGFR <60 ml/min/1.73 m2 % at baseline	HbA1c % baseline	Follow-up time (Median years)
Zinman et al (22)	EMPA-REG OUTCOME	NCT01131676	Empagliflozin	4687	2333	63±9	100	29	25.9	8.1± 0.8	3.1
Packer et al (23)	EMPEROR-REDUCED	NCT03057977	Empagliflozin	1683	1867	67±11	50	24	48	NA	1.3
Cannon et al (27)	VERTIS-CV	NCT01986881	Ertugliflozin	5499	2747	64±8	100	30	21.9	8.2±1	3
Bhatt et al (28)	SCORED	NCT03315143	Sotagliflozin	5292	5292	68.66±8	100	44.3	100	8.3±0.9	1.4
Heerspink et al (24)	DAPA-CKD	NCT03036150	Dapagliflozin	2152	2152	61.8±12	68	33	89.1	NA	2.4
Wiviott et al (25)	DECLARE-TIMI 58	NCT01730534	Dapagliflozin	8582	8578	64±7	100	37	7.4	8.3± 1.2	4.2
Perkovic et al (26)	CREDENCE	NCT02065791	Canagliflozin	2202	2199	63±9	100	34	59.8	8.3± 1.3	2.6

Table 2. Meta-analysis of SGLT2i according to various kidney related outcomes

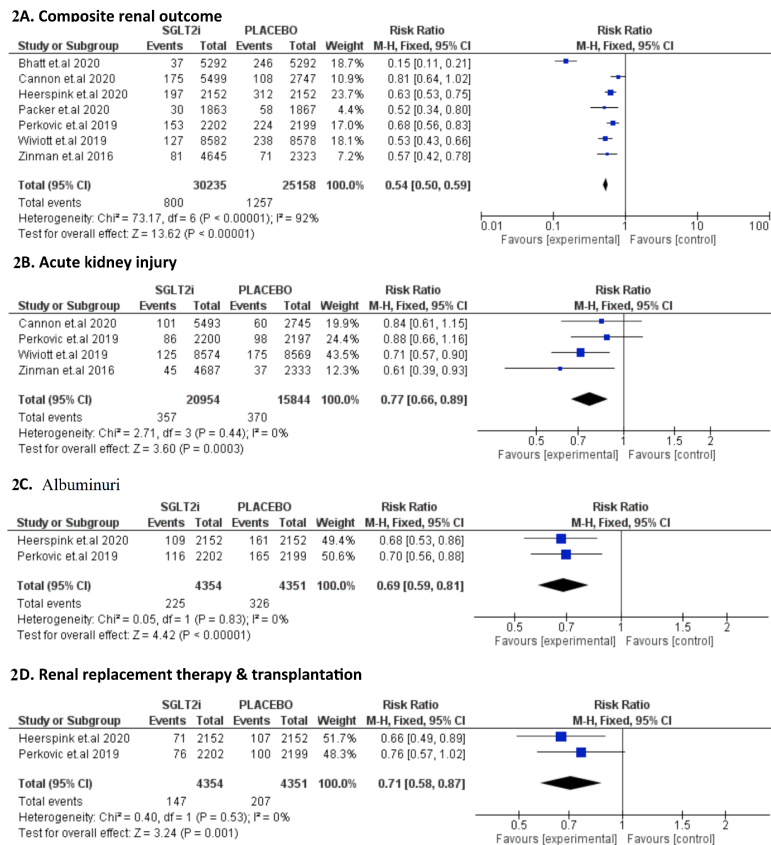| Outcome	Number of studies	Number of Participants	Heterogeneity		Risk ratio (95% CI)	Pooled effect	
			I²%	P value		Z-value	P value
Composite renal Outcome	7	55265	92%	<0.001	0.54 (0.50-0.59)	13.62	<0.001
Acute kidney injury	4	36798	0%	0.44	0.77 (066-0.89)	3.60	<0.001
Albuminuria	2	8705	0%	0.83	0.69 (0.59-0.81)	4.42	<0.001
Initiation of renal replacement therapy	2	8705	0%	0.53	0.71 (0.58-0.87)	3.24	0.001

Figure 2. Forest plots illustrating the pooled analysis for renal outcome .

diabetes and CKD via two distinct mechanisms. First, in diabetic patients, up-regulation of SGLT2 increases sodium and glucose reabsorption by the proximal tubules and lowers blood sugar by inhibition of SGLT2 glucose reabsorption in the renal proximal tubules. Second, SGLT2i inhibit glucose and sodium reabsorption in the proximal tubules while increasing sodium transport to the macula densa, restoring impaired tubuloglomerular feedback. This demonstrates the impact of SGLT2i on renal hemodynamics. This study improves understanding of essential differences in outcomes related to drugs within the class.

Most randomized evidence supporting positive effect of metformin on patient-level outcomes, demonstrating that metformin reduces the risk of major adverse outcomes, including cardiovascular and renal outcomes, when compared to other early glucose-lowering medications (29). However, metformin alone could not achieve adequate glucose control and metformin neither prevents nor delays complications and maintain quality of life. Several lines of evidences indicate that the SGLT2i were associated with a significantly lower risk of development or progression of ESRD. Despite the significant data of clinical benefits of SGLT2 inhibitor, some guidelines recommend them as the preferred second-line therapy in people with concomitant CKD (30). To date, RCTs evaluating the

safety and effectiveness of SGLT2i in patients with T2D have primarily focused on kidney disease outcomes. In this context, it is important to note that SGLT2i was found to be beneficial in trials for dapagliflozin, ertugliflozin, empagliflozin, sotagliflozin, and canagliflozin (22-28). Besides, empagliflozin reduced the urinary albumin to creatinine ratio (UACR) in patients with T2D regardless of hemoglobin HbA1c, blood pressure, and body weight (31). A study also found that dapagliflozin reduced the UACR in stage 3 CKD patients after 2 years of treatment (32). These findings suggested that SGLT2i could reduce albuminuria by affecting the kidney directly through various mechanisms, including decreased glomerular hyperfiltration, improved tubulointerstitial fibrosis, lower systemic blood pressure, changes in plasma volume expansion, and lower uric acid levels (33-35).

In vivo models also demonstrated that SGLT2i reduced albuminuria in diabetic mice by improving intra-glomerular hyperfiltration and tubule-interstitial fibrosis, which are two major contributors to renal damage in diabetic kidney disease (36, 37). In agreement with these findings, our meta-analysis revealed the albuminuria-lowering effects of SGLT2i. However, the accumulation of data suggests that SGLT2i may be beneficial for albuminuria in the ESRD rather than the early stage, which needs to be investigated further. The
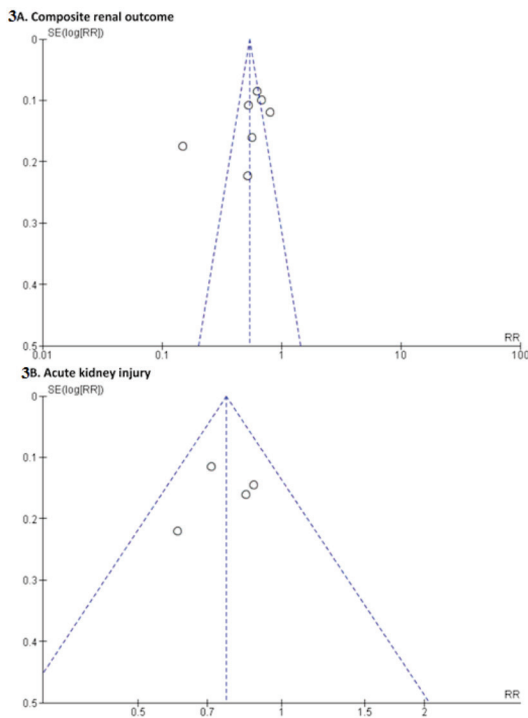
Figure 3. A funnel plot illustrating the publication bias.

overall changes in kidney disease showed a difference between SGLT2 inhibitors and controls. In the subgroup analysis, we discovered that the changes in renal outcome after SGLT2i treatment were characterized by a rapid decline in eGFR within the first 4–5 weeks, followed by progressive recovery over time. Furthermore, the eGFR level was reversible within two weeks of drug discontinuation (38, 39). The evidence from SGLT2i RCT trials significantly reduced the risk of albuminuria, AKI and renal replacement therapy of ESRD compared with placebo. Protection against AKI is a welcome discovery. These findings support a recently published meta-analysis that found SGLT2i protect against the risk of amputation, fracture, hyperkalemia, hypoglycemia, volume depletion, or UTI (40). Despite this, the large number of events and consistency of effect across trials lends credence to the finding that SGLT2i protect against AKI. Further research is needed to understand the mechanism of decreased AKI risk (41, 42).

There are several limitations to this study that should be discussed. First, the analysis included a total of seven RCT studies. Second, the majority of the studies reported incomplete outcome data due to loss to follow-up, which necessitates further investigation. Third, we were unable to assess the renal effects of SGLT2 inhibitors based on CKD risk. In summary, our findings confirm that SGLT2 inhibition can reduce the risk of albuminuria, AKI and renal replacement therapy in ESRD patients with T2D. These meta-analyses provide substantial evidence supporting the beneficial effect of SGLT2 inhibitors on reducing CKD events in individuals with T2D.

Authors' contribution
DJ and HN conducted the primary search. UNP participated in methodological search and data collection. HKV conducted the draft. LVKSB conducted the primary revisions. RV conducted the secondary edit. HN and DJ finalized the manuscript. All authors read and signed the final paper.

Conflicts of interest
The authors declare that there is no potential conflict of interest.

Ethical issues
The institutional ethical committee of Isfahan University of Medical Sciences approved all study protocols (Ethical code# IR.MUI.MED.REC.1400.279). This study was extracted from the M.D., thesis of Dorsa Jahangiri at this university (Thesis # 3400263). Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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