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

Dorsa Jahangiri1,2, Udit Narayan Padhi2, Henu Kumar Verma2, Bhaskar VKS Lakkakula2, Rohollah Valizadeh1,2, Hamid Nasri1,2

1Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2Independent Researcher, 43185 Cardston Place Leesburg Virginia, 20176, USA

A R T I C L E  I N F O
Keywords:
Sodium-glucose transporter 2 inhibitors, Chronic kidney disease, Type 2 diabetes mellitus, Acute kidney injury, Meta-analysis

A B S T R A C T
Introduction: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a new class of antidiabetic 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 sitagliptin. 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.

Implication for health policy/practice/research/medical education: Sodium-glucose co-transporter 2 inhibitors (SGLT2i) lower blood glucose by reducing glucose reabsorption. SGLT2i was found to be beneficial in diabetic patients in randomized controlled trials. The current meta-analysis found that SGLT2 inhibitors may reduce the risk of kidney damage in T2D patients.

Please cite this paper as: Jahangiri D, Padhi UN, Kumar Verma HK, Lakkakula BVKS, Valizadeh R, Nasri H. 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. J Renal Inj Prev. 2021; 10(4): e35. doi: 10.34172/jrip.2021.35.

*Corresponding authors: Prof. Hamid Nasri, hamidnasri@yahoo.com, hamidnasri@med.mui.ac.ir
Jahangiri D et al

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 analysis aims to identify the effect of SGLT2i on renal pathophysiological events in seven previous published randomized controlled trials (RCTs).

Records identified through database searching (n=103)
Papers excluded (n=18)
Abstracts screened (n=85)
Papers excluded (n=54)
Not RCTs (n=45)
Not SGLT2i trials (n=9)
Full-text articles assessed for eligibility (n=31)
Papers excluded (n=24)
Not interventional studies (n=31)
Not outcome of interest (n=9)
No data related to events (n=4)
Studies included in quantitative synthesis (n=7)

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 m².

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 I² statistics and the value with I² >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 55265 individuals were identified (30097 in the SGLT2i group and 25168 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 eugliflozin versus placebo (27); 1 trial comparing otagliflozin 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 55265 participants (30097 in the SGLT2i group and 25168 in the control group) in 7 studies (22-28). AKI was reported in 4 studies with 20950 patients in the SGLT2i group and 15844 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      | NCT011131676       | 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 |
|------------------------------------------|-------------------|------------------------|---------------|---------------------|---------------|
|                                          |                   |                        |               |                     |               |
| Composite renal Outcome                  | 7                 | 55265                  | 92%           | 0.54 (0.50-0.59)    | 13.62 <0.001  |
| Acute kidney injury                      | 4                 | 36798                  | 0%            | 0.77 (0.66-0.89)    | 3.60 <0.001   |
| Albuminuria                              | 2                 | 8705                   | 0%            | 0.69 (0.59-0.81)    | 4.42 <0.001   |
| Initiation of renal replacement therapy  | 2                 | 8705                   | 0%            | 0.71 (0.58-0.87)    | 3.24 0.001    |
SGLT2i in type 2 diabetes

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).

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

### 2A. Composite renal outcome

| Study Subgroup | Events | Total | Placebo | Events | Total | Risk Ratio | Lower 95% CI | Upper 95% CI |
|----------------|--------|-------|---------|--------|-------|------------|--------------|--------------|
| Bhutale 2020   | 37     | 5282  | 246     | 5282   | 10.7% | 0.19 [0.11, 0.31] |
| Cannon 2020    | 175    | 5489  | 106     | 2747   | 10.3% | 0.91 [0.64, 1.29] |
| Hennesey 2019  | 187    | 5212  | 212     | 2932   | 23.7% | 0.63 [0.53, 0.78] |
| Piikari 2009   | 30     | 1862  | 590     | 1217   | 44.4% | 0.67 [0.58, 0.78] |
| Pekuri 2015    | 153    | 2288  | 224     | 2164   | 17.8% | 0.89 [0.79, 1.00] |
| Viikari 2018   | 127    | 882   | 230     | 657    | 17.6% | 0.83 [0.75, 0.95] |
| Zimman 2016    | 84     | 4454  | 71      | 2242   | 7.2%  | 0.87 [0.80, 0.96] |
| Total (95% CI) | 39025  | 25958 | 100%    | 0.54 [0.50, 0.58] |

### 2B. Acute kidney injury

| Study Subgroup | Events | Total | Placebo | Events | Total | Risk Ratio | Lower 95% CI | Upper 95% CI |
|----------------|--------|-------|---------|--------|-------|------------|--------------|--------------|
| Cannon 2020    | 161    | 15482 | 60      | 1527   | 19.9% | 0.84 [0.61, 1.14] |
| Pekuri 2019    | 66     | 2200  | 99      | 2191   | 24.4% | 0.89 [0.66, 1.18] |
| Viikari 2018   | 125    | 8574  | 175     | 869    | 43.5% | 0.71 [0.57, 0.89] |
| Zimman 2016    | 45     | 4667  | 37      | 2333   | 12.3% | 0.81 [0.69, 0.96] |
| Total (95% CI) | 20954  | 15816 | 100%    | 0.77 [0.69, 0.85] |

### 2C. Albuminuria

| Study Subgroup | Events | Total | Placebo | Events | Total | Risk Ratio | Lower 95% CI | Upper 95% CI |
|----------------|--------|-------|---------|--------|-------|------------|--------------|--------------|
| Hennesey 2020  | 108    | 2152  | 181     | 2152   | 43.4% | 0.88 [0.63, 0.98] |
| Pekuri 2019    | 116    | 2282  | 165     | 2199   | 50.6% | 0.70 [0.50, 0.98] |
| Total (95% CI) | 4354   | 4351  | 100%    | 0.63 [0.52, 0.79] |

### 2D. Renal replacement therapy & transplantation

| Study Subgroup | Events | Total | Placebo | Events | Total | Risk Ratio | Lower 95% CI | Upper 95% CI |
|----------------|--------|-------|---------|--------|-------|------------|--------------|--------------|
| Hennesey 2020  | 71     | 2152  | 187     | 2152   | 51.7% | 0.68 [0.40, 0.93] |
| Pekuri 2019    | 79     | 2202  | 140     | 2189   | 46.3% | 0.79 [0.57, 1.02] |
| Total (95% CI) | 4354   | 4351  | 100%    | 0.71 [0.58, 0.87] |

SGLT2i, sodium-glucose cotransporter 2 inhibitors.
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.

Funding/Support
None.

References
1. Lin, X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10:14790. doi: 10.1038/s41598-020-71908-9.
2. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease. Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12:2032-45. doi: 10.2215/cjn.11491116.
3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843.
4. Giralt-Lopez A, Molina-Van den Bosch M, Vergara A, Garcia-Carro C, Seron D, Jacobs-Cacha C, et al. Revisiting experimental models of diabetic nephropathy. Int J Mol Sci. 2020;21:3587. doi: 10.3390/ijms21103587.
5. Natesan V, Kim SJ. Diabetic nephropathy - a review of risk factors, progression, mechanism, and dietary management. Biomol Ther (Seoul). 2021;29:365-72. doi: 10.4062/biomolther.2020.204.
6. Badal SS, Danesh FR. New insights into molecular mechanisms of diabetic kidney disease. Am J Kidney Dis. 2014;63:S63-83. doi: 10.1053/j.ajkd.2013.10.047.
7. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. J Am Soc Nephrol. 2017;28:1023-39. doi: 10.1681/ASN.2016060666.
8. Zheng W, Guo J, Liu ZS. Effects of metabolic memory
on inflammation and fibrosis associated with diabetic kidney disease: an epigenetic perspective. Clin Epigenetics. 2021;13:87. doi: 10.1186/s13348-021-01079-5.

9. Mavrankas TA, Lipman ML. Angiotensin-converting enzyme inhibitors vs. angiotensin receptor blockers for the treatment of hypertension in adults with type 2 diabetes: why we favour angiotensin receptor blockers. Can J Diabetes. 2018;42:118-23. doi: 10.1016/j.cjcd.2017.11.006.

10. Wang K, Hu J, Luo T, Wang Y, Yang S, Qing H, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality and renal outcomes in patients with diabetes and albuminuria: a systematic review and meta-analysis. Kidney Blood Press Res. 2018;43:768-79. doi: 10.1159/000489913.

11. Sorenson J, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413-24. doi: 10.1056/NEJMoa2022190.

12. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-46. doi: 10.1056/NEJMoa2024816.

13. Vlavianos P, Szczepaniak LS, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-57. doi: 10.1056/NEJMoa1812389.

14. Perkovic V, Jardine MJ, Neal B, Bompunto S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-306. doi: 10.1056/NEJMoa1811744.

15. Cannon CP, Pratley R, Doggo-Jack S, Mancuso J, Huyck S, Masuikiewicz U, et al. Cardiovascular outcomes with etogliflozin in type 2 diabetes. N Engl J Med. 2020;383:1425-35. doi: 10.1056/NEJMoa2004987.

16. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384:129-39. doi: 10.1056/NEJMoa2030186.

17. Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647. doi: 10.1093/ndt/gfz264.

18. Craig J, Capuano G, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for Drug-Naïve type 2 diabetes. Diabetes Care. 2016;39:i33-42. doi: 10.2337/dc15-1736.

19. Solomon SD, Zhou Y, Chen D, DeFronzo RA, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality and renal outcomes in patients with diabetes and albuminuria: a systematic review and meta-analysis. Kidney Blood Press Res. 2018;43:768-79. doi: 10.1159/000489913.

20. Petrie JR, Rossing PH, Campbell IW. Metformin and cardiorenal outcomes in diabetes: A reappraisal. Diabetes, Obesity and Metabolism. 2020;22:904-15. doi: 10.1111/dom.13984.

21. Tuttle KR, Brosius FC, Cavender MA, Fioretto P, Fowler KJ, Heerspink HJL, et al. SGLT2 Inhibition for CKD and Cardiovascular Disease in Type 2 Diabetes: Report of a Scientific Workshop Sponsored by the National Kidney Foundation. Diabetes. 2021;70:1-16. doi: 10.2337/db20-0040.

22. Cherney D, Lund SS, Perkins BA, Groop PH, Cooper ME, Kaspers S, et al. The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia. 2016;59:1860-70. doi: 10.1007/s00125-016-4237-7.

23. Panchapakesan U, Pegg K, Gross S, Komala MG, Mudalair H, Forbes J, et al. Effects of SGLT2 inhibition in human kidney proximal tubular cells—renoprotection in diabetic nephropathy? PLoS One. 2013;8:e54442. doi: 10.1371/journal.pone.0054442.

24. Lammers Heerspink HJ, van der Heijden F, Morgenstern B, Boersma E, van der Heijden M, et al. Sodium-glucose co-transporter type 2 inhibitors: extending the indication to non-diabetic kidney disease? Nephrol Dial Transplant. 2020;35:i33-42. doi: 10.1093/ndt/ggz264.

25. Haddad J, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016;39:1718-28. doi: 10.2337/dc16-0522.

26. Rosenstock J, Chuck L, González-Ortiz M, Merton K, Craig J, Capuano G, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for Drug-Naïve type 2 diabetes. Diabetes Care. 2016;39:353-62. doi: 10.2337/dc15-1736.

27. Introduction: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020;43:S1-S2. doi: 10.2337/dc20-S1-S2.
37. Terami N, Ogawa D, Tachibana H, Hatanaka T, Wada J, Nakatsuka A, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One. 2014;9:e100777. doi: 10.1371/journal.pone.0100777.

38. Kohan DE, Fioretto P, Tang W, List JF. 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. 2014;85:962-71. doi: 10.1038/ki.2013.356.

39. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, et al. 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. 2014;2:369-84. doi: 10.1016/S2213-8587(13)70208-0.

40. Bai Y, Jin J, Zhou W, Zhang S, Xu J. The safety outcomes of sodium-glucose cotransporter 2 inhibitors in patients with different renal function: A systematic review and meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases. 2021;31:1365-74. doi: 10.1016/j.numecd.2021.02.006.

41. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney Int. 2018;94:26-39. doi: 10.1016/j.kint.2017.12.027.

42. Chang YK, Choi H, Jeong JY, Na KR, Lee KW, Lim BJ, et al. Dapagliflozin, SGLT2 inhibitor, attenuates renal ischemia-reperfusion injury. PLoS One. 2016;11:e0158810. doi: 10.1371/journal.pone.0158810.

Copyright © 2021 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.