

# Sodium-Glucose Cotransporter 2 Inhibitors and their Renal benefits in type 2 diabetes. A Systematic Review

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Received: June 2020; Accepted: July 2020; Published: August 1, 2020.

Citation: Saad Ur Rehman, Faiqa Rahman. Sodium-Glucose Cotransporter 2 Inhibitors and their Renal benefits in type 2 diabetes. A Systematic Review. World Family Medicine. 2020; 18(8): 57-68 DOI: 10.5742MEWFM.2020.93846

## Abstract

**Background:** Existing studies show that the hyperglycemia-reducing effect of sodium-glucose cotransporter 2 inhibitor (SGLT2i) is dependent on glomerular filtration. Previous studies have shown that SGLT2 are not very effective in controlling blood sugars in patients with impaired renal function. As such, SGLT2i are not recommended for patients with advanced CKD.

**Objective:** This systematic review aims at looking at the effects of SGLT2i in adult patients with Type 2 diabetes and chronic kidney disease.

**Methods:** We searched Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, and Google Scholar to identify various trials, which had reported renal outcome trials for SGLT2i. The reviewers examined renal outcomes, which were end-stage renal disease (ESRD), renal failure, doubling serum creatinine, macroalbuminuria, incident microalbuminuria, alteration in urine albumin-to-creatinine ratio (UACR), estimated glomerular filtrate rate (eGFR), dialysis, kidney transplant, or death related to renal disease. The extracted data were qualitatively synthesized.

**Results:** 18 studies that met the eligibility criteria were selected for review. In line with the strong evidence presented in previous meta-analyses, SGLT2i clearly demonstrated that it lowered the risk of developing ESRD, microalbuminuria, and reduced the levels of eGFR and UACR compared to controls.

**Conclusion:** SGLT2i has positive renoprotective effects in patients with T2DM and CKD by reducing the risk of developing worsening albuminuria and decreasing the risk for ESRD compared to controls.

**Key words:** randomized controlled trial, RCT, type 2 diabetes mellitus, T2DM, sodium-glucose cotransporter 2 inhibitors, SGLT2, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, albuminuria, renal failure, chronic kidney disease, end-stage renal failure

## Background

Diabetes mellitus is a metabolic disorder that results when the body either develops resistance to its own insulin or can't produce enough to help metabolize the glucose in the body. Type 2 Diabetes mellitus, accounts for 90% of all cases and affects at least 463 million people globally, and it is expected that it will effect 578 million and 700 million people worldwide by 2030 and 2045, respectively(1). T2DM is a primary cause for developing chronic kidney failure (CKD) and cardiovascular disease (CVD), as well as a core predictor of frequent hospital admissions, morbidity, and mortality(2, 3). Until relatively recently, the use of pharmacological agents to control blood glucose levels in T2DM patients had limited data on renal and cardiovascular benefits in fact some drugs were associated with adverse effects such as hypoglycemia and cardiovascular-associated fatalities with sulfonylureas, cardiac heart failure (CHF) with thiazolidinediones, and proliferative retinopathy with insulin(4-6). To address the deleterious side effects, the U.S Food and Drug Administration (FDA) devised novel anti-DM medication guidelines in 2008 that necessitated cardiovascular outcome clinical trials (CVOTs) for new hyperglycemic-reducing agents to offer data on safety to make sure that new antihyperglycemic medications do not elevate the risk for ischemic stroke, myocardial infarction, or CVD-associated mortality (7).

A large share of numerous double blind, placebo-controlled clinical trials performed in the last 10-years have reported neutral effects on CV outcomes (8, 9). However some randomized controlled trials (RCTs) lead to the discovery of two medication classes: glucagon-like peptide (GLP)-1 receptor agonist and sodium (Na<sup>+</sup>)-glucose co-transporter-2-inhibitors (SGLT2i) (the focus of the present review) (3). The above drug classes decreased significant CV-related adverse events (10). According to Lo et al., SGLT2i is designed to impair reabsorption of filtered glucose load at the proximal tubule (7). Besides, SGLT2i alters intra-renal hemodynamics, causes intravascular volume contraction, and elevates natriuresis, which is likely to contribute to reducing albuminuria, body weight, and blood pressure (7, 11). Based on the above positive outcomes of SGLT2i, it is clear that its valuable effects cover beyond regulation of glycemia to reducing uric acid levels, body weight, lowering BP and intraglomerular hypotension, and promoting plasma volume contraction. As a result, the FDA has authorized four SGLT2i forms to confer renoprotection in patients with T2DM, including Steglatro (ertugliflozin), Jardiance (empagliflozin), Farxiga (dapagliflozin), and Invokana (canagliflozin) (7).

Numerous investigations have found positive effects of the aforementioned SGLT2i on renal function. Canagliflozin and empagliflozin were evaluated in two large RCTs, and both diminished the risk for albuminuria and the composite of chronic decline in renal function, renal replacement therapy (RRT) or kidney disease-related mortality compared with placebo (12-14). Heerspink et al. investigated the efficacy

of canagliflozin in alleviating renal function impairment and reducing albuminuria independently of its glucose lowering effect in a secondary analysis of an RCT involving n = 1450 patients with T2DM on metformin and randomly allocated to either glimepiride up-titrated to 6-8 mg, canagliflozin 300 mg, or canagliflozin 100 mg once-daily (15). The administration of canagliflozin 300 or 100 mg/day compared to glimepiride 6-8 mg/day showed a deceleration in the progression of kidney disease over 2-years in individuals with T2DM. The authors concluded that canagliflozin confers renoprotective impacts independent of its glycemic effects.

Other large-scale CVOTs of SGLT2i, which were initially intended to fulfill the regulatory standards and guarantee CV safety, have reported promising impacts on an array of serum creatinine-based renal outcomes and albuminuria in patients at increased risk for atherosclerotic CVD (ASCVD) (13, 14, 16-19).

A large proportion of the patients in the above RCT were at low risk of medically significant renal events; consequently, the incidences of CKD were low, with a small number of participants needing RRT or dialysis in all the trails. Besides, since the aforementioned trials were also not primarily aimed to offer definitive data on renoprotective effects, renal endpoints were not explicitly umpired or pre-specified, and the difference between chronic and acute decline in estimated glomerular filtrate rate (eGFR) was not probable in each trial. Thus, it is challenging to conclude that the advantageous kidney effects of SGLT2i apply to all patients, particularly those with low CVD risk.

Moreover, studies examining single renal measures have reported inconsistent results. For instance, in Neal et al. the Canagliflozin Cardiovascular Assessment Study (CANVAS) it revealed the therapeutic effects of canagliflozin on renal, CV and safety outcomes. It was observed that canagliflozin led to a 40% decline in eGFR thus reducing the onset of microalbuminuria (12),(20). Similarly, in the Empagliflozin Cardiovascular Outcome Trial in T2DM Patients (EMPA-REG OUTCOME) trial, empagliflozin substantially diminished the odds for the onset of RRT but it did not show any influence on the initiation of microalbuminuria (13). In the above studies, renal measures were secondary endpoints, and the incidence of adverse events suggestive of ESKD was not enough to confer irrefutable data (12, 13, 20). Furthermore, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) RCT did not look at individual renal outcomes (19). Similarly, a significant number of subjects had normal albuminuria in the CVOTs of SGLT2i and, thus, the consistency of therapeutic effects across various levels of albuminuria remains unknown. In addition to the above concerns, current guidelines in Europe and North America commend metformin as the first-line therapy and SGLT2i as second-line treatment not only for individuals with ASCVD but also for patients with CHF (21, 22).

Furthermore, the hyperglycemia-reducing effect of SGLT2i is dependent on glomerular filtration, and previous evaluations have shown that SGLT2i glycemic effect is reduced in patients with chronic kidney disease (CKD). CKD is described as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m<sup>2</sup> (23, 24). Consequently, SGLT2i agents are not presently prescribed in anyone with an eGFR < 60 mL/min/1.73 m<sup>2</sup> (for ertugliflozin and dapagliflozin) and eGFR < 45 mL/min/1.73 m<sup>2</sup> (for empagliflozin and canagliflozin) (25, 26). On the contrary, the effectiveness of SGLT2i at reducing proteinuria and the risk of worsening renal impairment may be sustained in diabetic patients with CKD (27). Since a large proportion of patients with CKD have the highest odds for ESRD and CVD (28), it is fundamental to understand the reno-protection benefits of SGLT2i. Therefore, the primary aim of the present systematic review is to evaluate the benefits of SGLT2i on kidney function in patients with T2DM and evaluate the influence of the latest evidence on current clinical guidelines when considering treatment for T2DM.

## Methods

### Search strategy

For the present systematic review, the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed accordingly (29). Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases were searched to identify trials with renal outcome for SGLT2i issued between January 1, 2010-March 31, 2020 with full texts. The search terms applied for SGLT2i entailed SGLT2i or SGLT2 inhibitors or ertugliflozin or empagliflozin or dapagliflozin or canagliflozin (Supplementary Table 1). Additionally, the reference lists of the yielded studies were scrutinized for additional RCTs missed during the electronic search.

### Study selection and data extraction

Two reviewers (SR and FR) independently screened the abstracts and titles of the identified studies. Duplicate publications of the original RCTs were eliminated and RCTs reporting one of the following renal outcomes: ESRD, renal failure, doubling serum creatinine, macroalbuminuria, incident microalbuminuria, (UACR) urine albumin-to-creatinine ratio, eGFR, dialysis, kidney transplant, or death due to kidney disease, were selected.

Two authors (SR and FR) individually extracted data from the selected RCTs as per the standardized procedure. Target outcomes of interest encompassed alterations in eGFR and UACR, the occurrence of macroalbuminuria (UACR >300 mg/g), and microalbuminuria (UACR > 30mg/g), incident ESRD, and regression of albuminuria. Any discrepancies were addressed by consensus among the reviewers. Additionally, data about the authors, publication year, mean age and number of the participants, comparison and intervention treatment, and background anti-diabetic medications is summarized on page 65 onward.

### Assessment of study quality and data analysis

The Cochrane Risk of Bias tool was employed to evaluate the quality and risk of bias (30). Two reviewers classified the risk of bias of the sampled RCTs as inadequate (high risk of bias), unclear (unclear risk of bias), and adequate (low risk of bias) grounded on key elements of the clinical trials, namely: selective reporting, incomplete outcome data, blinding of participants and personnel, allocation concealment, random sequence generation, and other potential sources of bias (30). Any conflicts among the reviewers were addressed through consensus. The selected articles were qualitatively synthesized to identify common patterns.

## Results

### Characteristics of included studies

The final search yielded a total of 329 articles. After removing the duplicates, the titles and abstracts of 154 studies were individually screened. A total of 25 RCTs were identified, but 7 were excluded due to their post hoc/sub-analysis nature. Therefore, 18 RCTs that fulfilled the eligibility criteria were included in the study, as illustrated in figure 1 which depicts the PRISMA flow diagram and supplementary Table 2, the summary of papers included in the systematic review. The total number of participants was n = 14,104, including n = 7,366 and n = 5,892 patients randomized into the treatment and control cohorts, respectively. The study population, covered in the systematic review is mainly patients with T2DM with eGFR ≥ 15<90 mL/min/1.73m<sup>2</sup>. The baseline eGFR of the subjects was ≥ 45 mL/min/1.73m<sup>2</sup> in nine studies (31-39), ≥ 30 mL/min/1.73m<sup>2</sup> in seven studies (16, 40-45), ≥ 20 mL/min/1.73m<sup>2</sup> in one study (46), and ≥ 15 mL/min/1.73m<sup>2</sup> in another study (47). The mean age was 49.5-67 years. The number of subjects in each of the RCT varied from n = 42 to n = 4,401. One study was conducted over 2.62 years (16), three over 104 weeks (32, 38, 41), seven were carried out within 52 weeks (31, 36, 39, 42, 44, 47, 48), whereas the remaining had a follow-up period of between 12-28 weeks.

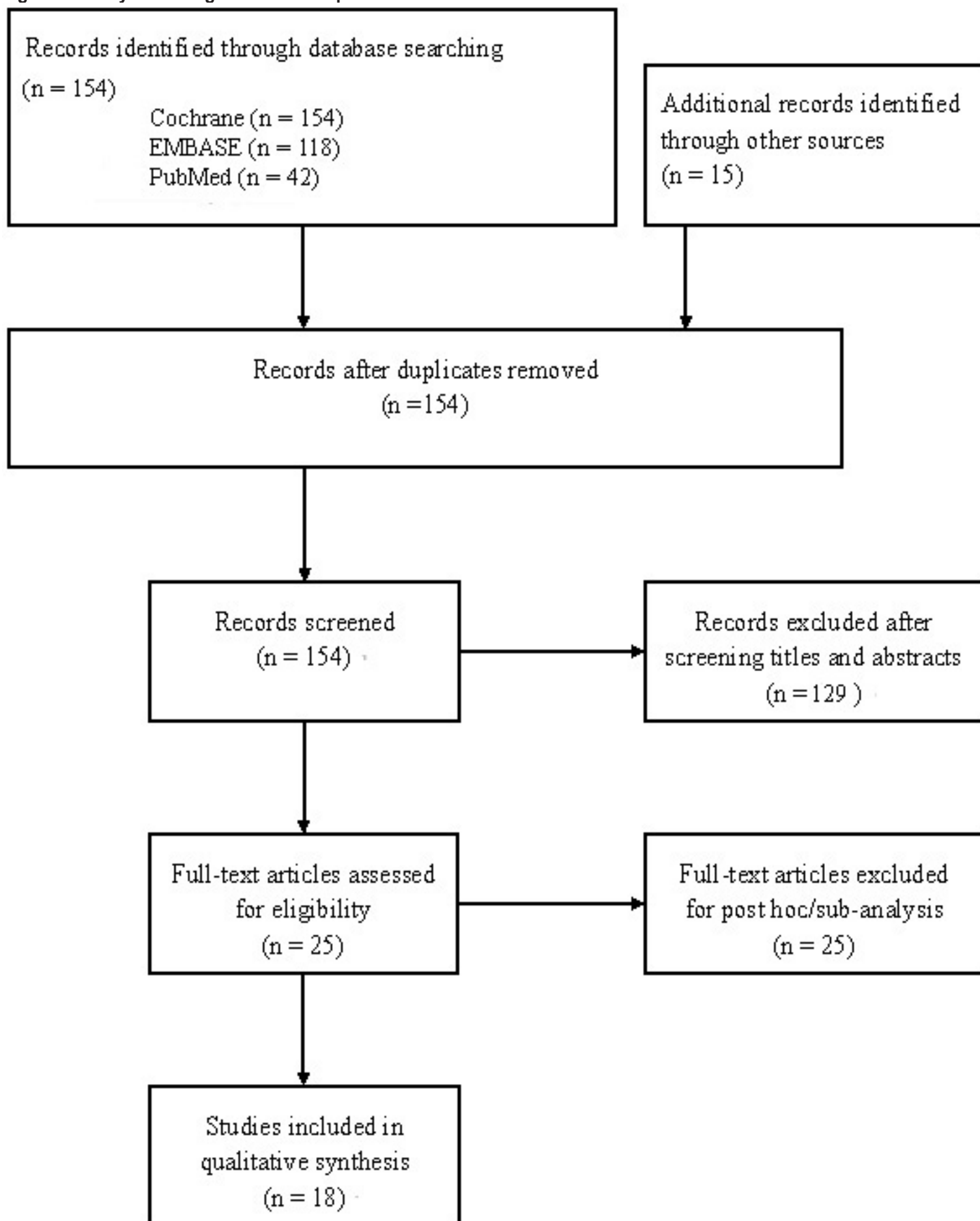
### Assessment of study quality and risk of bias

All the eighteen described sufficient blinding of researchers and participants, and 83% of the selected studies reported sufficient allocation masking and adequate random generation. Three RCTs failed to describe the approach of allocation blinding and sequence generation (39, 41, 44). Furthermore, three RCTs documented incomplete outcome results owing to losses to follow-up (36, 42, 48).

### Renal outcomes

SGLT2i substantially lowered the odds for the occurrence of ESRD, progression of microalbuminuria, and improved the levels of eGFR and UACR compared with the controls, with the beneficial impacts of the SGLT2 inhibitors principally steered by the findings of the largest RCT with canagliflozin (16). In the aforementioned study, SGLT2i substantially reduced the threat of deteriorating nephropathy compared with placebo or other forms of controls, including sitagliptin, exenatide, and glimepiride. A meta-analysis was not performed due to the homogeneity across the reviewed studies.

Figure 1: Study screening and selection process



## Discussion

Overall, this systematic review illustrated that SGLT2i is allied to substantially reduced odds for the onset or worsening of albuminuria, worsening renal function compared to other antidiabetic therapies or placebo in adult patients with T2DM. Nonetheless, a large number of the appraised RCTs, showed improved levels of UACR in patients with a higher baseline compared to those with lower baseline UACR. While there were no substantial alterations in eGFR levels between pre- and post-treatment in both intervention and control cohorts, the various types of SGLT2i decelerated the drop in eGFR in participants with a higher eGFR at the start and over a prolonged research period (16, 41, 47, 48). The observed albuminuria-reducing consequence is clinically significant, and the expected SGLT2i-associated enhancements partly explicate it in variables otherwise linked to declined loss of protein in the urine, including body weight, HbA1c, and BP (49). Findings of pooled analyses attributed the SGLT2i-lowering impacts to a myriad of mechanisms, comprising a drop in uric acid levels, alterations in plasma volume expansion, systemic BP decrease, enhancement in tubule-interstitial fibrosis, and a decline in glomerular hyperfiltration (12, 50-52). In Fioretto et al.'s study, the treatment stage 3 kidney disease diabetics with dapagliflozin for over 52 weeks altered the levels of uric acid, eGFR, BP, and HbA1c (53). Empagliflozin reduced the UACR in patients with T2DM along with either macro- or microalbuminuria independent of body weight, BP, and HbA1c changes (49). Warner et al also reported a preservation of eGFR level in the treatment group with empagliflozin compared to placebo over a period of time (14). In CANVAS trial canagliflozin reduced the risk of albuminuria progression and demonstrated reduction in eGFR, the need for renal replacement therapy, or death due to renal disease (12). A recent review by S Kelly et al. demonstrated that the renal benefits of SGLT2 inhibitors were independent of CKD and reduced incidence of albuminuria (54). DECLARE TIMI 58 trial showed a protective effect in renal outcomes by 24% (19).

The alterations in kidney function after SGLT2i therapy was marked by a fast drop in eGFR in the initial four-five weeks, which gradually recovered back to baseline value over time (35, 41, 47, 48). This effect might be due to the hemodynamic impacts of SGLT2i therapy. Reduced glomerular hyperfiltration might be protective against advancing kidney disease since intraglomerular hyperfiltration has been linked to developing worsening diabetic kidney disease (41). As reported by Lin et al; dapagliflozin reduced the decline of eGFR by 40% from baseline over a 12 month period (55).

SGLT2i substantially decreased the odds for the progression of CKD to late-stage CKD compared to controls. Nonetheless a large proportion of patients in the reviewed articles were at low risk for ESRD; therefore, the impact of SGLT2i on the most critical patient-level renal outcome remains largely unknown. CREDENCE (canagliflozin and renal effects in diabetes with established nephropathy clinical evaluation) was

intended to particularly fill the above evidence gap (16). This RCT illustrated that patients on already established ace inhibitors when given canagliflozin showed slowing of the chronic kidney disease and albuminuria. For the first time, the CREDENCE trial demonstrated that canagliflozin could help halt the progression of renal disease by 30%. This therapeutic approach diminished the need for CKD-associated necessity for dialysis. The trial also demonstrated reduced mortality related to ESRD (15). Recently published meta-analysis on SGLT2i in patients with T2DM reported reduced event rates in both renal and cardiovascular systems and showed that renoprotection effect with this therapy was independent of its cardiovascular effects (56-58). Ongoing trials like DAPA CKD and EMPA-KIDNEY are looking at similar renal outcomes and have enrolled non diabetics as well.

With regards to safety, the reported adverse events (AEs) of interest comprised drug-associated genital infection, lower-extremity amputation, volume depletion events, fractures, and hypoglycemia. Canagliflozin, Ertugliflozin, Empagliflozin were associated with AEs associated with volume depletion and osmotic diuresis plus genital infections (36, 39). Dapagliflozin has been reported to increase risk of fractures (41). These drugs cannot be prescribed in patients with old age, those who have peripheral neuropathy, diabetic foot problems, those with recurrent urinary tract infections (UTI), peripheral vascular disease, osteopenia and/or osteoporosis, and patients with low eGFR at the start of treatment or patients already taking diuretics.

Although, SGLT2i does not currently have the license to be used in patients with  $eGFR < 60 \text{ ml/min/1.73m}^2$ , we believe that recent data supports that SGLT2i can safely be offered to diabetics with underlying CKD with eGFR value as low as  $30 \text{ ml/min/1.73m}^2$  (54, 58).

The current American Diabetic Association and European diabetic society prescribing guidance suggest the use of SGLT2i as the first line agent in T2DM patients, with cardiovascular risk factors, irrespective of their HbA1c level (59).

From the above discussion we suggest using canagliflozin in treatment of type 2 diabetes due to its beneficial effect on the renal system.

## Conclusion

This systematic review reveals that SGLT2i have net protective effects on renal outcomes of patients with T2DM with underlying CKD. Notably, canagliflozin diminishes the risk for stage 4 CKD and the onset and progression of albuminuria over placebo or other antidiabetic medications. We believe that SGLT2i should be the preferred therapy in T2DM patients. The findings support data of recently published meta-analyses that reported strong evidence that SGLT2i decreases the danger of the composite deterioration of renal function, renal mortality, or ESRD in patients with or without ASCVD (54, 50).

Nevertheless, the findings of the systematic review should be interpreted with caution since a large share of the appraised RCTs were initially intended to explore the safety and hyperglycemia-reducing effects of SGLT2 inhibitors.

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**Supplementary Table 1: Search strategy.**

Search strategy	RCTs of SGLT2 inhibitors in patients with type 2 diabetes and CKD were searched using the following key terms
EMBASE	SGLT-2 inhibitor OR SGLT2 inhibitor OR dapagliflozin OR canagliflozin OR ertugliflozin OR empagliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin OR ipragliflozin
MEDLINE	SGLT-2 inhibitor OR SGLT2 inhibitor OR dapagliflozin OR canagliflozin OR ertugliflozin OR empagliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin OR ipragliflozin
The Cochrane Central Register of Controlled Trials	SGLT-2 inhibitor OR SGLT2 inhibitor OR dapagliflozin OR canagliflozin OR ertugliflozin OR empagliflozin OR luseogliflozin OR remogliflozin OR sergliflozin OR tofogliflozin OR ipragliflozin



Supplementary Table 2: Characteristics of selected studies in the systematic review.

Author/ year	Year	Intervention	Control	Background drugs	No age of subjects	follow- up (wks.)	Baseline eGFR mL/min/1.73m <sup>2</sup>	Results
Kohan et al (41).	2014	10mg Dapagliflozin n =172	Placebo n = 84	OADs ± insulin ± GLP- 1 RA ± pramlintide	n = 252 mean age: 67.0	104	≥ 30, ≤ 59	Dapagliflozin did not have a significant influence on glucose control in patients with advanced CKD. There was a moderate decline in FPG and HbA1c in patients with eGFR between 45-59 mL/min/1.73m <sup>2</sup> . Dapagliflozin was associated with increased risk for fractures.
Barnett et al (47).	2014	10/25 mg Empagliflozin n =419	Placebo n = 314	OADs ± insulin ± GLP-1 RA	n = 741 mean = 63.9 years	52	≥15	In patients with stage 2, 3, & 4 CKD, small changes in eGFR occurred in the treatment cohorts but returned to baseline by the 3 <sup>rd</sup> week follow-up after therapy completion. Alterations in UACR and eGFR occurred at follow-up and over the study period in patients with stage 2-4 CKD. Empagliflozin as add-on to prescribed antidiabetic drugs resulted in clinically significant improvement in blood pressure, body weight, and glycemic control in patients with T1DM2 plus stage 2 or 3 CKD. Small alterations in eGFR after a year's therapy reversed to baseline 3 weeks after completion of treatment.
Cefalu et al (48), 48	2015	10 mg Dapagliflozin n = 455	Placebo n = 459	OADs (except TZD) ± insulin	n = 922 m age = 62.9	52 807 complete d	≥60	Dapagliflozin demonstrated efficacy in a large share of patients who had mild (eGFR ≥60 to ≥ 90) or moderate (eGFR ≥ 30 to ≥60) CKD.
Perkovic et al (16).	2019	100 mg Canagliflozin n = 2,202	Placebo n = 2,199	OADs ± insulin ± GLP- 1 RA	n = 4,401 m age – 63.0	2.62 years	≥ 30, < 90	Canagliflozin was associated with 30% reduced risk for ESKD, doubling of creatinine levels and Renal or cardiovascular death in patients with T2DM than those in the placebo.
Roden et al (34).	2013	Empagliflozin 10/25 mg n = 448	100 mg sitaglipti n or Placebo n =551	None	n = 899 m = 54.9	24 weeks	≥ 50	There was no statistically significant change in eGFR or electrolyte concentration in either cohort.
Satrapoj et al (35).	2018	10 mg Dapagliflozin n = 28	Placebo n = 29	None	n = 57 m =57.9	12 weeks	≥ 60	After 12 weeks, the mean UACR reduced significantly from 51.1 to 37.3 mg/g Cr in the treatment group. There was no substantial acute renal injury, hypotension, volume depletion in the treatment group. 10 mg Dapagliflozin exhibited a significant decline in albuminuria and a progressive drop in eGFR after the start of treatment.

Forst et al. (36)	2013	100/300 mg Canagliflozin n = 229	Placebo n = 115	Metformin + TZD	n = 344 m = 57.3 years	52	≥ 55	Canagliflozin 100/300 mg substantially reduced HbA1c than placebo at 26 weeks and the reductions were maintained at 52 weeks. Overall, adverse events (AEs) occurred in 76.5% and 76.3%, and 69.9% in the placebo, 100 mg, and 300 mg Canagliflozin, respectively. AEs associated with volume depletion and osmotic diuresis plus genital mycotic infections were significantly higher in the treatment group than in placebo.
Yale et al. (42)	2014	100/300 mg Canagliflozin n = 179	Placebo n = 90	OADs ± insulin ± GLP-1 RA	n = 272 m = 68.5	52	≥ 30, < 50	HbA1c was substantially lowered from baseline with 100 and 300 mg Canagliflozin compared to placebo at 26 weeks. 100 and 300 mg Canagliflozin resulted in a significant decline in FBG at week 26 with placebo. 100 and 300 mg Canagliflozin resulted in a significant decline in body weight at week 26, while placebo resulted in a moderate rise. Canagliflozin decreased UGE and RT <sub>a</sub> lowering in participants with stage 3 CKD than in subjects with normal renal function. The incidences of AEs did not change across all the groups.
Haring et al. (43)	2014	10 mg/25 mg empagliflozin n = 430	Placebo n = 207	Metformin	n = 638 m = 55.7 years	24	≥ 30	There was no significant change in eGFR levels in either cohorts. Nonetheless, the use of empagliflozin as an add-on drug to metformin enhances glycaemic control with reduced odds for hypoglycemia than placebo. Empagliflozin led to a loss of 2.1-2.5 kg of body weight than a placebo.
Friás et al. (37)	2016	10 mg dapagliflozin or 10 mg dapagliflozin plus exenatide n = 264	Exenatide n = 231	Metformin	n = 695 m = 54.3	28	≥ 60	Dapagliflozin plus exenatide was superior to either dapagliflozin and exenatide in addressing the diverse glycaemic features and CV causal factors poorly controlled T1DM. Nonetheless, it was attributed to slightly higher rates of AEs, mainly UTIs, nausea, and diarrhea. Dapagliflozin plus exenatide led to moderately lower eGFR than either dapagliflozin and exenatide, respectively. However, the change was not clinically significant.

<b>Kashiwagi et al (44).</b>	2015	50 mg Ipragliflozin n = 119	Placebo n = 46	OADs	n = 165 m = 64.4	52	≥ 30, < 90	At 24 weeks, 50 mg Ipragliflozin was allied to significant improvement in body weight and glycemic control than in the placebo.  The effect of treatment in patients with mild CKD on glycemic control was not substantial by week 4. Ipragliflozin-induced glycosuria dropped with diminishing eGFR.  Overall, Ipragliflozin enhanced glycemic control and decreased body weight in diabetic patients with mild or moderate CKD. Thus, Ipragliflozin is a recommended therapeutic option for diabetic patients with normal kidney function or mild CKD, but not for patients with moderate or stage 4 CKD.
<b>Han et al (45).</b>	2018	50 mg Ipragliflozin n = 74	Placebo n = 69	Metformin and sitagliptin	n = 143	24 weeks	≥ 30, < 90	After 24 weeks, Ipragliflozin led to a significant drop in insulin resistance and pattern towards the enhanced beta-cell function.  No significant changes in renal function or electrolyte balance in either groups.
<b>Leiter et al (38).</b>	2015	100/300 mg Canagliflozin n = 968	6 or 8 mg Glimепiri de n = 482	Metformin	n = 1,450 m = 49.5	104	≥ 55	Decreases in eGFR occurred in all cohorts with a significant decline in the glimepiride than canagliflozin. 100/300 mg canagliflozin conferred long-term glycemic improvement in patients with T1DM on Metformin. 100/300 mg canagliflozin resulted in significant weight loss and systolic blood pressure than glimepiride
<b>Stenlofet al (39).</b>	2014	100/300 mg Canagliflozin n = 387	Placebo or sitagliptin n = 192	OAD mono-therapy (except TZD) OR Metformin + SU	n = 587 m = 55.4	52	≥ 50	100/300 mg canagliflozin resulted in a significant decline in systolic blood pressure and improvements in glycemic control over the 52 weeks than placebo or sitagliptin. Genital mycotic infections and AEs associated with osmotic diuresis were more prevalent in the treatment than in the control group. There was a significant drop in eGFR in the treatment cohort was associated with hemodynamic effect and not renal injury.
<b>Pollock et al (46).</b>	2019	10 mg dapagliflozin or 2.5 mg saxagliptin plus 10 mg dapagliflozin n = 308	Placebo n = 153	OADs ± insulin ± GLP-1 RA	n = 461 m = 64.5	24	≥ 20, ≤ 80	In the placebo group, UACR remained relatively stable over the study period. Saxagliptin plus dapagliflozin was more effective than dapagliflozin and placebo alone.

Ridderstråle et al (32).	2014	25 mg Empagliflozin n = 769	1-4 mg Glimepiride n = 780	Metformin	n = 1,549 m = 55.9	104	≥ 60	Empagliflozin substantially reduced FPG over glimepiride at 52 and 104 weeks. Empagliflozin preserved renal function from the start to the completion of the study
Takashima et al (31).	2018	100 mg canagliflozin n = 21	Placebo n = 21	OADs ± insulin	n = 42 m = 60	52	≥ 45, < 90	Treatment with 100 mg canagliflozin led to significant reduction in UACR levels Reductions in eGFR were noted more in the 100 mg canagliflozin than in the placebo cohort.
Lin et al (55).	2019	10-25 mg Empagliflozin n = 7264 10mg Dapagliflozin n = 7264	Placebo none	None	n = 15248 m = 61	78	> 15, < 90	Dapagliflozin lowered the risk of eGFR by 40% in 12 months across all levels of CKD. Also risk of AKI Risk of related hospitalization was lower in patients treated with Dapagliflozin.