REVIEW ARTICLE

SGLT-2 Inhibitors and Renal Outcomes in Non-Diabetic Patients: A Systematic Review

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■ MSS and CA: Were involved in literature research, data extraction and in drafting the manuscript.
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■ IG: Participated in literature search and data extraction, and critical revision of the manuscript.
■ JG: Designed the manuscript, participated in literature search and critical revision of the manuscript.
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■ ABSTRACT

Introduction: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have shown positive renal outcomes in diabetic patients. There is also emerging evidence in non-diabetic patients. This review was conducted to analyse the renal outcomes of SGLT2i in patients without diabetes mellitus (DM).

Methods: A systematic review was performed in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) compliant manner. We included only randomized trials that examined the effect of SGLT2i on renal outcomes in non-diabetic patients.

Results: A total of ten randomized trials were included with a combined cohort of 26 298 patients. There was a tendency for lesser risk of adverse renal outcomes in heart failure (HF) patients with reduced ejection fraction (EF) (hazard ratio (HR) 0.50-0.71). Lesser effect on adverse renal outcomes was seen in HF patients with preserved EF (HR 0.95). For both preserved and reduced EF HF, there was a statistically significant reduction in the rate of decline in estimated glomerular filtration rate (eGFR) ($p<0.001$). On a short follow-up, there was a significant reversible reduction in GFR. In the long term, chronic kidney disease (CKD) proteinuric patients had a statistically significant lesser risk of adverse renal outcomes ($p<0.001$) and a significant reduction in albuminuria ($p=0.0016$). CKD patients, including non-proteinuric, had a significant reduction in the rate of kidney disease progression (HR = 0.71).

Conclusion: Treatment with SGLT2i significantly reduces the rate of kidney disease progression in CKD non-diabetic patients with eGFR ≥ 20 mL/min/1.73 m^2. Benefit seems greater in proteinuric patients. Benefit for eGFR < 20 mL/min/1.73 m^2, dialysis and kidney transplant patients is yet to be defined.

Keywords: Renal Insufficiency, Chronic; Sodium-Glucose Transporter 2 Inhibitors

■ INTRODUCTION

Around 700 million people worldwide have CKD, which is an important cause of morbidity and mortality, partly explained by the prevalence of cardiovascular (CV) disease in this population.[1,2] The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD as reduced glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 and/or albuminuria (≥30 mg/d), persistent for at least 3 months, regardless of the underlying cause.[3,4] Clique ou toque aqui para introduzir texto. Currently, renin-angiotensin system (RAS) blockers are the gold-standard in treatment of CKD progression, by reducing systemic and intraglomerular pressures.[5]

SGLT2i, firstly introduced as therapy for type 2 diabetes (T2D), act by blocking glucose and sodium reabsorption in the renal proximal tubule cells through the SGLT2 transporter, leading to enhanced urinary glucose and sodium excretion. Unexpectedly, recent trials showed that SGLT2i have positive CV and metabolic effects independently of their glucose-lowering outcomes. Accumulating evidence suggests that CV and renal protection associated with SGLT2i is unrelated to the hypoglycaemic effect. Indeed, these have been proven to reduce body weight (BW), systemic blood pressure (BP) and systemic inflammation which impact in these outcomes.[6-12]

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There are several proposed mechanisms underlying renal protection, such as control of glomerular hyperfiltration by decreased sodium reabsorption and subsequent glomerular afferent arteriolar vasoconstriction,[13-15] and reduction in intraglomerular pressure providing an antiproteinuric effect.[16,17]

This systematic review aims to analyse the effect of SGLT2i on renal outcomes in patients without DM.

■ METHODS

This systematic review was performed in a PRISMA compliant manner. PubMed, Medline and CENTRAL (Cochrane Controlled Register of Trials) databases were searched on 30 November 2022. Search was conducted using the terms "Sodium-Glucose Transporter 2 Inhibitors" OR "canagliflozin" OR "dapagliflozin" OR "empagliflozin" AND '"without diabetes" OR "non diabetic".

Fifty results were retrieved from January 2013 to December 2022. We included randomized trials only. Clinical trials were selected to identify if subgroup analysis of patients without diabetes was performed. Inclusion criteria were randomized trials evaluating renal outcomes in patients without DM. Exclusion criteria were studies on diabetic population only, animal or in vitro studies, and protocols or comments on the trials. Of the twenty-two randomized trials found, we included ten.

Renal outcomes included changes in eGFR, albuminuria or proteinuria and progression to end-stage renal disease (ESRD) as detailed in each study. Death from renal or CV causes was also assessed.

Four reviewers independently executed the literature search and data extraction. Data relating to blinding and withdrawals were extracted to assess risk of bias. We collected data on the drug name, dosage and frequency, control group, and length of intervention. This systematic review was not registered.

Population, intervention, comparison, outcome, study design, inclusion and exclusion criteria are detailed in Table 1.

■ RESULTS

■ Study selection

The PRISMA flowchart is presented in Fig. 1. The ten trials comprised a combined cohort of 26 298 patients. Among the ten studies, four included patients with HF, one included patients with obesity and five studies included patients with CKD. Among the SGLT2i used in the trials, five studies used dapagliflozin, four used empagliflozin and one used canagliflozin. Dapagliflozin and empagliflozin were administered at a dosage of 10 mg, while canagliflozin was administered at dosages of 50 mg, 100 mg and 300 mg in the same trial. All regimens were given once daily and placebo controlled.

■ Study characteristics

We collected data of 13 399 patients without DM. Mean age was 59.6±8.3 years, mean GFR was 53.7±11.4 mL/min/1.73 m^2 and mean follow-up was 17.4±10.6 months. The Cochrane risk of bias tool was used to critically evaluate the selected articles.[18] The bias risk assessment looked at six causes of potential bias and a summary for each trial is figured in Table 2. Inclusion and exclusion criteria of the selected studies are detailed in Table 3. Table 4 provides a summary of the studies' characteristics and outcomes.

All studies had a low risk of bias. One study ("Canagliflozin in Overweight and Obese Subjects Without Diabetes Mellitus") contributed to a potential attrition bias due to high dropout rates, as 25% of the participants did not complete the study.[19]

■ Outcomes

In the DAPA-HF trial there was less worsening renal function (defined as a sustained decline in the eGFR of ≥50%), ESRD or death from renal causes on the dapagliflozin group though this difference was not significant (0.8 *vs* 1.2 events/100 patient-year, HR 0.71 (0.44 to 1.16), *p* value not applicable). [10]

Table 1

PICOS criteria for inclusion and exclusion of studies applied to database search

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients without diabetes	Patients with diabetes Studies without subgroup analysis of patients without diabetes
Intervention	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	
Comparison	Comparison of SGLT2 inhibitors with a control group (placebo) on renal outcomes in patients without DM	
Outcome	eGFR, albuminuria, proteinuria, ESRD	
Study design	Randomized trials Year of publication: 2013 to 2022 Database: PubMed	Mixed methods research, meta-analyses, systematic reviews, cohort studies, case-control studies, cross-sectional studies, and descriptive papers, case reports and series, ideas, editorials, and perspectives
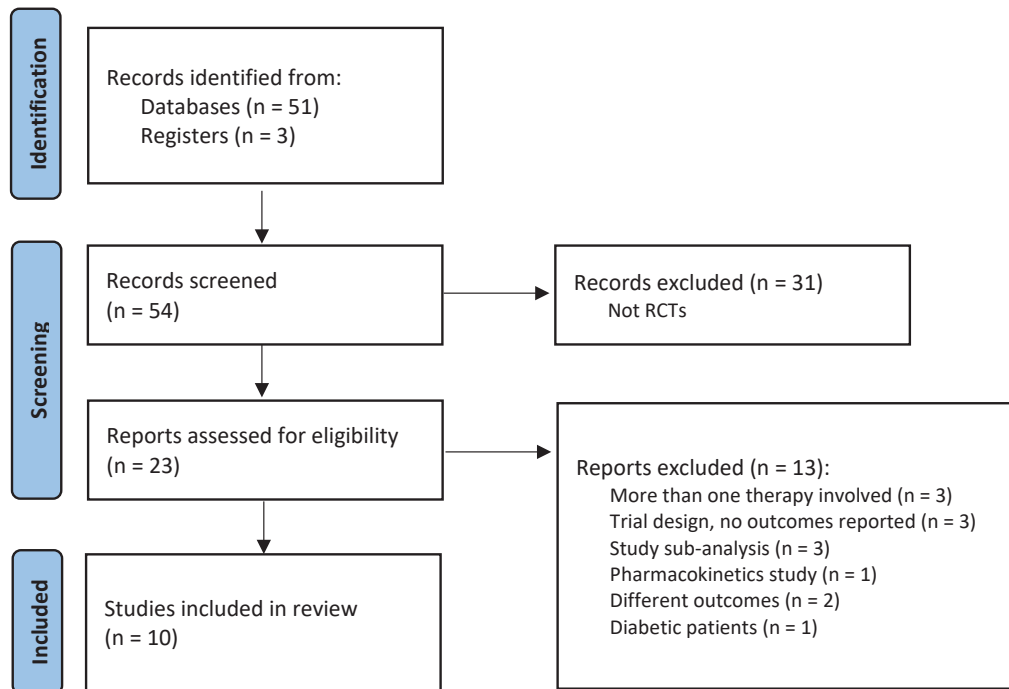
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 1

PRISMA flow diagram of study selection

Table 2

Summary of the trials' bias using the Cochrane assessment tool

COCHRANE APPRAISAL	Random Sequence Generation: Selection bias	Allocation Concealment: Selection bias	Blinding of participants & evaluators: Performance bias	Blinding of outcome assessment: Detection bias	Incomplete outcome data: Attrition bias	Selective reporting: Reporting bias
DAPA-HF	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-CKD	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-CKD – IgA	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-CKD – FSGS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DIAMOND	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EMPEROR-REDUCED	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EMPEROR-PRESERVED	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EMPIRE-HF-RENAL	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Canagliflozin in Overweight and Obese Subjects Without T2D	Low risk	Low risk	Low risk	Low risk	Some concerns	Low risk
EMPA-KIDNEY	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

The DAPA-CKD study demonstrated that dapagliflozin reduced the risk of decline in eGFR of at least 50%, or ESRD or death from renal or CV causes (HR 0.61 (0.51 to 0.72) *p*<0.001), which was lower in the non-diabetic group (HR 0.50 (95% CI, 0.35 to 0.72)). Reduction in eGFR was noticeable in the first two weeks of treatment (-3.97±0.15 *vs* -0.82±0.15 mL/min/1.73 m^2), then, the annual

decline in eGFR was lower with dapagliflozin (-1.67±0.11 *vs* -3.59±0.11 mL/min/1.73 m^2).[16]

An analysis from the DAPA-CKD trial revealed that urine albumin-creatinine ratio (uACR) was reduced with dapagliflozin by 29.3% (95% CI, -33.1 to -25.2, *p*<0.0001).[20] Reduction was higher in patients with

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Table 3

Inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
DAPA-HF	Age ≥ 18, HFrEF ≤ 40%, NT-proBNP ≥ 600 pg/mL HF device therapy and standard drug therapy	Recent treatment with or unacceptable side effects associated with a SGLT2i, type 1 diabetes mellitus (T1D), symptoms of hypotension or a systolic BP of less than 95 mmHg, and an eGFR less than 30 mL/min/1.73 m2 (or rapidly declining renal function).
DAPA-CKD	Age ≥ 18, eGFR 25-75 mL/min, uACR 200-5000 mg/g on stable dose of ACEi or ARB	T1D, polycystic kidney disease, lupus nephritis or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immunotherapy for primary or secondary kidney disease within 6 months before enrolment.
DAPA-CKD – IgA	Same as DAPA-CKD + IgA nephropathy	Same as DAPA-CKD
DAPA-CKD – FSGS	Same as DAPA-CKD + FSGS	Same as DAPA-CKD
DIAMOND	Age ≥ 18, CKD, uPCR 500- 3500 mg/g, eGFR ≥25 mL/min	T1D or T2D, polycystic kidney disease, lupus nephritis or ANCA-associated vasculitis; an indication for or use of immunosuppressants for kidney disease in the last 6 months; peripheral vascular disease; or being at risk of dehydration or volume depletion.
EMPEROR-REDUCED	Age ≥ 18, HF > 3 months, NYHA II- IV, EF ≤ 40%, BMI < 45 kg/m2	Acute CV events, untreated or undertreated CV conditions, significant co-morbid conditions independent of HF and any condition that might jeopardize patient safety.
EMPEROR-PRESERVED	Age ≥ 18, HF EF>40%	Same as EMPEROR-REDUCED
EMPIRE-HF-RENAL	Age ≥ 18, EF ≤ 40%, eGFR > 30 mL/min	Hospital admission for HF within 30 days before randomisation, hospital admission with hypoglycemia within 12 months before randomisation, and symptomatic systolic BP below 95 mmHg
Canagliflozin: Effects in Overweight and Obese Subjects Without Diabetes Mellitus	Age ≥ 18, BMI ≥ 30 and < 50 kg/m2 or ≥ 27 kg/m2 if comorbidities, serum creatinine <1.5 mg/dL (men) and <1.4 mg/dL (women)	History of hereditary glucose-galactose malabsorption, primary renal glycosuria, secondary obesity or clinically significant eating disorder; T1D or T2D; fasting triglycerides >600 mg/dL; previous weight loss surgery or liposuction; or treatment with weight loss medications, glucose-lowering drugs, antiepileptic drugs, systemic corticosteroids, or antipsychotic drugs within 3 months of screening.
EMPA-KIDNEY: Empagliflozin in Patients with Chronic Kidney Disease	Age ≥ 18, eGFR ≥20 and <45 mL/min/1.73 m2 or eGFR ≥45 and <90 mL/min/1.73 m2 with a uACR ≥200 mg/g	Currently receiving SGLT-2 ou SGLT-1/2 inhibitor, combined ACEi and ARB treatment, maintenance dialysis, kidney transplant, polycystic kidney disease, bariatric surgery, ketoacidosis, symptomatic hypotension, ALT or AST >3x ULN at screening, immunosuppression therapy

ACEi – angiotensin-converting enzyme-inhibitor, ALT – alanine transaminase, ARB – angiotensin receptor blocker, AST – aspartate transaminase, BW – body weight, CV – cardiovascular, eGFR – estimated glomerular filtration rate, FSGS – focal segmental glomerulosclerosis, HFrEF – heart failure with reduced ejection fraction RAS – renin-angiotensin system, SGLT – sodium-glucose cotransporter, uACR – urinary albumin-to-creatinine ratio, ULN – upper limit of normal , uPCR – urinary protein excretion.

T2D (-35.1% (95% CI, -39.4 to -30.6, $p<0.0001$) vs -14.8% (95% CI, -22.9 to -5.9, $p=0.0016$)). Additionally, greater reductions in uACR were significantly associated with smaller eGFR decline throughout follow-up (-3.06, 95% CI, -5.20 to -0.90; $p=0.0056$).[16]

In the DAPA-CKD-IgA trial, dapagliflozin reduced the risk of sustained decline in eGFR of at least 50%, ESRD, or death from renal or CV causes in non-diabetic patients (HR 0.42 (95% CI, 0.13 to 0.82, $p=0.013$)). In the first two weeks of treatment there was an eGFR reduction in the dapagliflozin group (-3.4 [±0.4] vs -0.5 [0.4] mL/min/1.73 m2), then, annual eGFR change was lower with dapagliflozin (-2.2 [0.5] and -4.6 [0.47], respectively).[21]

In the DAPA-CKD-FSGS trial, dapagliflozin reduced the risk of sustained ≥40% decline in eGFR, or ESRD or death from renal or CV causes (8.9 vs 11.9%; HR 0.62, [95%CI 0.17-2.17]). Also, dapagliflozin led to an acute decline in eGFR (-4.5, 95% CI, -5.9 to -3.1 vs -0.9, 95% CI, -2.1 to 0.4 mL/min/1.73 m2/two weeks), and lower annual rates of eGFR decline (-1.9 (95% CI -3.0 to -0.9) vs -4.0 (95% CI -4.9 to -3.0) mL/min/1.73 m2/year). Although not statistically significant, the total slope of decline was lower with dapagliflozin (-3.7 (95% CI, -4.8 to -2.6) vs −4.2 (95% CI, -5.2 to -3.3) mL/min/1.73 m2/year).[22]

In the DIAMOND trial, dapagliflozin was associated with a percentage change in 24 hours proteinuria of 0.9% (-16.6 to 22.1, $p=0.93$). Also, there was a reduction of eGFR by -6.6 mL/min per 1.73 m2 (-9.0

to -4.2; $p<0.0001$) at week 6 with dapagliflozin which was reversible six weeks after discontinuation.[7]

In the EMPEROR Reduced trial, empagliflozin was associated with a slower rate of decline in the eGFR, regardless of the presence or absence of diabetes (-0.55 vs -2.28 mL/min/1.73 m2 per year, $p<0.001$). Composite renal outcome (ESRD or sustained reduction in the eGFR) was also less frequent with empagliflozin (HR 0.50; 95% CI, 0.32 to 0.77, p value not shown). Difference between diabetic and non-diabetic patients was not specified.[9]

In the EMPEROR Preserved trial, empagliflozin had a slower rate of decline in eGFR (-1.25 vs -2.62 mL/min/1.73 m2 per year (95% CI, 1.06 to 1.66; $p<0.001$), and was associated with a lesser risk of a composite renal outcome (ESRD or a profound sustained reduction in the eGFR), although not-significant (HR 0.95 (0.73 to 1.24)), which was similar in patients with or without diabetes.[23]

In the EMPIRE-HF-RENAL trial, empagliflozin was associated with a decline in estimated extracellular volume (eECV) (mean difference -0.11L [-0.18 to -0.04]) and eGFR (mean difference -6.7 mL/min [-10.8 to -2.6]) at 12 weeks.[24]

In the canagliflozin in overweight and obese subjects without diabetes trial, treatment with canagliflozin resulted in an increase in urinary glucose excretion (UGE)/creatinine ratio in a dose-dependent manner. Canagliflozin also produced a ≥ 5% loss in BW ($p=0.027$), and

Table 4

Summary of the included studies

Trial	Number of Patients	Mean eGFR	Intervention	Median follow-up	Renal Outcomes
DAPA-HF (2019)	4744 2761 (58.2%) without diabetes	66	Dapagliflozin 10 mg or placebo once daily	18.2 months	Secondary composite outcome: decline in eGFR of ≥ 50%, ESRD or renal death: HR 0.71 (0.44-1.16), p=NA. Dapafliflozin *vs* placebo: Renal SAEs: 1.6% *vs* 2.7%, *p*=0.009; AKI SAE: 1.0% *vs* 1.9%, *p*=0.007
DAPA-CKD (2020)	4304 1399 (32.5%) without diabetes	43	Dapagliflozin 10 mg or placebo once daily	2.4 years	Primary composite outcome: decline in eGFR ≥50%, ESRD or death (non-diabetic): HR 0.50 (0.35-0.72) Secondary outcome: sustained decline in eGFR ≥50%, ESRD or renal death: HR 0.56 (0.45-0.68), *p*<0.001 uACR change of -14.8% (-22.9 - -5.9), *p*=0.0016
DAPA-CKD – IgA nephropathy (2021)	270 232 (86%) without diabetes	44	Dapagliflozin 10 mg once daily or placebo	2.1 years	Primary composite endpoint – decline in eGFR ≥50%, ESRD or renal or CV death: HR 0.42 (0.13-0.82), *p*=0.013
DAPA-CKD – FSGS (2021)	104 84 (80.8%) without diabetes	42	Dapagliflozin 10 mg once daily or placebo	2.4 years	Primary composite endpoint – decline in eGFR ≥40%, ESRD or renal or CV death: HR 0.62 (0.17-2.17)
DIAMOND (2020)	53 All non- diabetic	58	Dapagliflozin 10 mg and then placebo once daily and vice versa	6 weeks	Primary outcome: change in 24h proteinuria: 0.9% (-16.6 - 22.1), *p*=0.93 Secondary outcomes: mGFR -6.6 mL/min/1.73 m2 (-9.0 - -4.2), *p*<0·0001 BW reduction in 1.5 kg (0.03-3.0), *p*=0·046)
EMPEROR-REDUCED (2020)	3730 1874 (50.2%) without diabetes	62	Empagliflozin 10 mg or placebo once daily	1.3 years	Decline in eGFR: -0.55 *vs* -2.28 mL/min/1.73 m2/per year, *p*<0.001 Composite renal outcome (ESRD or a profound sustained reduction in the eGFR): HR 0.50 (0.32-0.77), *p*=NA.
EMPEROR-PRESERVED (2021)	5988 3050 (51%) without diabetes	61	Empagliflozin 10 mg or placebo once daily	26.2 months	Rate of decline in eGFR: -1.25 *vs* -2.62 mL/min/1.73 m2 per year (1.06-1.66), *p*<0.001. Composite renal endpoint (ESRD or a profound sustained reduction in the eGFR): HR 0.95 (0.73-1.24).
EMPIRE-HF-RENAL (2020)	120 105 (88%) without diabetes	70	Empagliflozin 10 mg or placebo once daily	12 weeks	Reductions in eECV (-0.11L [-0.18 - -0.04]), ePV (-6.3% [-9.6 - -3.0]) and mGFR (-6.7 mL/min [-10.8 - -2.6]).
Canagliflozin: Effects in Overweight and Obese Subjects Without Diabetes Mellitus (2014)	376 All non-diabetic	NA	Canagliflozin 50mg, 100mg, 300mg, or placebo once daily	12 weeks	≥5% loss in BW: 13%, 19%, and 17%, *vs* 8%, p=0.027 Uric acid reduction: -1.1, -1.2, -1.3 mg/dL, *vs* -0.1 mg/d Increase in BUN: 0.4, 0.7 *vs* -0.1
EMPA-KIDNEY: Empagliflozin in Patients with Chronic Kidney Disease (2022)	6609 3570 (54%) without diabetes	37.5	Empagliflozin 10 mg once daily or placebo once daily	2.0 years	Primary outcome: decline progression of kidney disease or death from CV causes of 28% with empagliflozin: HR 0.72 (0.64 - 0.82), *p*<0.001.

AKI – acute kidney injury, BW – body weight, BUN – blood urea nitrogen, CV – cardiovascular, eECV – estimated extracellular volume, eGFR – estimated glomerular filtration rate, ePV – estimated plasma volume, ESRD – End-stage renal disease, HR – heart rate, NA – not applicable, SAE – serious adverse event, uACR – urinary albumin-to-creatinine ratio.

reductions in systolic BP in a dose-dependent manner. Also, canagliflozin was associated with modest decreases in eGFR, and increases in blood urea nitrogen (BUN) at a short follow-up.[19]

The EMPA-KIDNEY trial demonstrated a reduction in the risk of progression of kidney disease or death from CV causes of 28% with empagliflozin (*p*<0.001). When these components were analysed separately, empagliflozin remained associated with a significant reduction in the rate of kidney disease progression with relative risk reduction of 29% (HR 0.71; 95% CI, 0.62 to 0.81). There was a consistent benefit of empagliflozin treatment among patients with or without diabetes and regardless of eGFR. Additionally, it seems to suggest a greater risk reduction benefit among patients with higher uACR (> 300 mg/g). In the empagliflozin group there was an acute initial decline in eGFR in the first 2 months. However, the annual rate of eGFR decline was slower with empagliflozin by 0.75 mL/min/1.73 m[2] (95% CI, 0.54 to 0.96), including in the subgroup of patients with a low uACR.[25]

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■ Adverse effects

Concerning adverse effects, in the DAPA-HF trial, dapagliflozin was associated with less renal serious adverse events (SAEs) than placebo 1.6 *vs* 2.7% (*p*=0.009). Acute kidney injury (AKI) was the most common renal SAE.[10]

The incidences of adverse events (AEs) and SAEs were similar overall in the dapagliflozin and placebo groups in the DAPA-CKD trial and subgroup analysis. Neither diabetic ketoacidosis nor severe hypogly-caemia was observed in participants without diabetes.[16,21,22]

In the DIAMOND trial, dapagliflozin resulted in more AEs than placebo, 32% *vs* 25%, respectively. Concerning patients treated with dapagliflozin, one developed AKI, one had urinary tract infection, and another a genital infection. There were two SAEs, one with placebo and the other with dapagliflozin.[7]

SAEs occurred in 41.4% of patients treated with empagliflozin *vs* 48.1% with placebo in the EMPEROR Reduced trial.[9] In the EMPEROR Preserved trial, SAEs occurred in 47.9% patients with empagliflozin and in 51.6% with placebo.[23]

In the EMPA-KIDNEY trial more patients had lower limb amputations and ketoacidosis, however, this just occurred in 0.8% and 0.6% of patients, respectively. Uncomplicated genital and urinary tract infections (UTI) and hypotension were more common in patients treated with empagliflozin.[9,23,25]

In the EMPIRE-HF-RENAL, empagliflozin was associated with SAEs in 8% of patients versus 5% with placebo. The most common AE was UTI (7% *vs* 5%), with one patient in the empagliflozin group requiring hospital admission.[24]

The overall incidence of AEs was comparable in all treatment groups with canagliflozin.[19]

■ DISCUSSION

In this systematic review of randomized trials of patients without DM treated with SGLT2i (dapagliflozin or empagliflozin), there is a tendency for lesser risk of sustained eGFR reduction, progression to ESRD or renal death.

Initially studied in the diabetic population, SGLT2i showed that beside the CV benefit, they could reduce progression to macroalbuminuria, doubling of serum creatinine, ESRD or death from kidney causes by 40% in the EMPA-REG trial.[26] Subsequently, the CREDENCE trial also proved the renoprotective benefits of SGLT2i in a CKD diabetic patient cohort.[27] The trial was terminated early because of significant efficacy of the drug. The relative risk (RR) of the renal composite outcome of ESRD, doubling of the creatinine level and renal death was 34% less (HR 0.66, *p*<0.001), and the RR of ESRD was lower by 32% (HR 0.68, *p*=0.002). CREDENCE, EMPA-REG also reported an early decline in eGFR (3 to 6 mL/min/1.73 m^2) compared to placebo.[26,27] This early reduction was typically observed between the second and fourths weeks of therapy, with partial recovery by week 12, and followed by an attenuation of the slope of eGFR decline compared with placebo after 52 weeks. As what happens with RAS inhibitors, eGFR decline and long-term clinical benefits seem to coexist with SGLT2i.[28,29]

In our analysis, in CKD and proteinuric patients with eGFR ≥ 25 mL/min/1.73 m^2 treated with dapagliflozin there was a statistically significant lesser risk of sustained eGFR reduction, progression to ESRD or death from renal causes in the long-term – DAPA-CKD, which was also evident in subgroup analysis – DAPA-CKD-IgA, DAPA-CKD-FSGS.[16,21,22] Empagliflozin also seems to lead to a statistically significant reduction in the rate of decline in eGFR per year – EMPEROR PRESERVED, EMPEROR REDUCED, EMPA-KIDNEY.[9,23,25] Indeed, the EMPA-KIDNEY trial was stopped early due to clear positive efficacy of empagliflozin in CKD patients. This trial included patients with eGFR ≥ 20 mL/min/1.73 m^2 and wide ranges of albuminuria and demonstrated a significant risk reduction of kidney disease progression or CV death.[32] However, the benefit appears to be higher in patients with uACR > 300 mg/g.

SGLT2i increase the sodium and chloride reaching the *macula densa*, by inhibiting sodium and glucose reabsorption in the proximal tubule. This results in vasoconstriction of the afferent arteriole and a reduction in the intraglomerular pressure and GFR (as seen with RAS inhibitors), and reduction in albuminuria.[8] Natriuresis and intravascular volume reduction also decrease BP and probably contribute to the initial decline in GFR.[30] Indeed, despite the initial decline in GFR, the hemodynamic effects of SGLT2i result in reduction in intraglomerular pressure which may promote long-term renoprotection and lesser risk of CKD progression.[30,31] This initial GFR decline but with long-term benefit was demonstrated in the EMPEROR Reduced, EMPA-KIDNEY and DAPA CKD trials.[16,23,25]

Concerning the antiproteinuric effects, the DIAMOND trial was unsuccessful in achieving a significant decrease in urine protein excretion, but this might be explained by the short duration of treatment – six weeks.[7] In contrast, a sub-analysis from the DAPA-CKD trial reported a significant decline of urine protein excretion with dapagliflozin administered for a mean period of 2.4 years. In patients with CKD, with and without T2D, dapagliflozin was associated with a significant reduction in albuminuria, which was greater in patients with T2D. Greater reductions in albuminuria were associated with a reduced eGFR decline.[20] This was also demonstrated in a pooled analysis of phase three randomized trials. Over 102 weeks, dapagliflozin 5 mg and 10 mg reduced uACR by 47% and 38%, respectively, compared to placebo.[17] Proteinuria reduction may be explained by the reduction of intraglomerular pressure. Also, in an animal study, dapagliflozin was associated with a decrease in proteinuria, glomerular lesions, and foot process effacement. *In vitro*, dapagliflozin decreased albumin-induced cytoskeletal rearrangements in cultured human podocytes.[33]

Weight loss has been consistently observed with SGLT2i therapy. The reduction of BW is about 1.5-2 kg and is dose-dependent.[34-38]. This is resultant from glucose excretion in the kidney (about 60–100 g of glucose per day), resulting in calorie loss and osmotic diuresis.[39] Most important, the weight loss is mainly due to loss in subcutaneous and visceral adipose tissue, rather than lean tissue.[40] In obese individuals without diabetes, co-administration of SGLT2i with a GLP1 receptor antagonist can reduce BW by 4.5 kg, and this can be maintained for up to 1 year.[39] In this systematic review, we report that SGLT2i were

associated with weight loss in patients without DM, treated with dapagliflozin, empagliflozin and canagliflozin.[7,10,19,23,24]

As described in previous studies, uncomplicated genital infections, UTIs and hypotension were more common in patients treated with SGLT2i. Nevertheless, the incidence of AEs was low overall and similar in both groups.

■ Should SGLT2i be given to all CKD patients?

SGLT2 inhibitors, which were originally developed to treat T2D, have demonstrated benefits in patients with albuminuria with or without diabetes including patients with IgA nephropathy, FSGS, and HF. The use of dapagliflozin and empagliflozin can be extended to eGFRs down to 25 and 20 mL/min/1.73 m^2, respectively, although starting at higher eGFRs may result in more beneficial effects. Regarding albuminuria, the benefit appears to be higher with significant risk reduction of kidney disease progression or CV death in patients with uACR > 300 mg/g. In patients with CKD, non-diabetic and without albuminuria, the slope of eGFR was slower. Considering side effects, SGLT2 inhibitors appear to be well tolerated with a low incidence of adverse effects. Also, clinicians should be alert to the initial eGFR decline associated with starting SGLT2 inhibitors to avoid discontinuation. These drugs are modifying the management of CKD patients, and further studies are ongoing to define their role in patients with GFR < 20 mL/min/1.73m2, and in dialysis and kidney transplant patients. The results are encouraging, and the next few years will bring clarity on the effects of SGLT2 in all CKD patients.

This systematic review has several limitations to be noted. Firstly, we used published summary data rather than individual patient data which prevented a statistical analysis. Secondly, the small populations in some studies may have limited their results. The heterogeneity in evaluated outcomes limits the accurate comparison and generalization of the results. Finally, SGLT2i effect on each renal outcome is still missing since most studies focused on a composite renal outcome.

■ CONCLUSION

The impact of SGLT2i in CV outcomes is widely described in patients with and without diabetes. In CKD patients, the beneficial effect in reducing eGFR decline and CV mortality has also been demonstrated but appears to be greater in patients with diabetes or patients with higher degrees of albuminuria.

Further studies, specifically with long-term follow-up, are required to accurately assess the impact of SGLT2i in non-diabetic and non-proteinuric CKD patients, and in end stage kidney disease patients.

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■ Ethical Disclosures

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