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SGLT-2 inhibitors in non-diabetic patients: a systematic review

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Abstract

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have shown positive renal outcomes in diabetic patients. There is also emerging evidence in non-diabetic patients. Since no specific treatment for chronic kidney disease (CKD) exists, there is an urge to find new therapeutic targets. This review was conducted to analyse the renal outcomes of SGLT2i in patients without diabetes mellitus.

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

Results: A total of nine RCTs were included with a combined cohort of 19689 patients. Six studies evaluated a composite renal outcome including sustained estimated glomerular filtration rate (GFR) reduction, progression to ESRD and death from renal causes. Four studies also evaluated effect on GFR and two on proteinuria or albuminuria. There was a tendency for lesser risk of the composite renal outcome in heart failure (HF) patients with reduced ejection fraction (EF) (HR 0.50-0.71, p value not available). Lesser effect on the composite renal outcome 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 eGFR (-0.55 to -1.25 vs -2.28 to 2.62 ml/min/1.73 m^2/per year, p<0.001). On a short follow-up, there was a significant reversible reduction in GFR and no effect in 24h proteinuria. In long term follow-up, CKD proteinuric patients had a statistically significant lesser risk of the composite renal outcome (HR 0.61, p<0.001) and a significant reduction in albuminuria (-14.8% (-22.9 to -5.9, P=0.0016)). The incidence of adverse events was low and severe adverse events were similar in the SGLT2i and placebo groups.

Conclusion: Treatment with SGLT2i appears to lower the risk of sustained eGFR reduction, progression to ESRD or death from renal causes in patients with HF patients and CKD proteinuric patients with eGFR ≥ 25ml/min/1.73m^2. SGLT2i also seem to lower albuminuria in CKD proteinuric patients. Despite the promising results, further studies,

specifically with long-term follow-up are required to accurately assess the impact of SGLT2i in non-diabetic CKD patients.

Keywords

SGLT2 inhibitors; Gliflozins; Chronic Kidney Disease; Non-diabetic; Renal.

Resumo

Contexto: Os inibidores do co-transportador sódio glicose tipo 2 (SGLT2) demostraram ter efeitos positivos a nível renal em doentes diabéticos. Existe ainda evidência recente em não diabéticos. Uma vez que não existe tratamento específico para a doença renal crónica (DRC), há uma grande necessidade de encontrar novos alvos terapêuticos. Esta revisão foi feita para analisar a evidência sobre o uso dos inibidores do SGLT-2 em doentes sem diabetes.

Métodos: Pesquisámos a PubMed para estudos que examinaram o efeito dos inibidores do SGLT2 a nível renal em doentes não diabéticos. Realizámos uma revisão sistemática de acordo com a metodologia PRISMA *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)*. Foram incluídos apenas ensaios clínicos aleatorizados.

Resultados: Um total de nove ensaios clínicos aleatorizados foram incluídos, com uma amostra combinada de 19689 doentes. Seis estudos avaliaram um efeito renal composto, que incluiu a diminuição sustentada da taxa de filtração glomerular (TFG) estimada, progressão para doença renal terminal e morte de causa renal. Quatro estudos avaliaram o efeito na TFG e dois estudos avaliaram o efeito na proteinúria ou albuminúria. Houve uma tendência para menor risco do efeito renal composto em doentes com insuficiência cardíaca (IC) com fração de ejeção (FE) reduzida (HR 0.50-0.71, valor p não disponível). Um efeito menor no efeito renal composto foi observado em doentes com IC com FE preservada (HR 0.95). Em doentes com IC (FE reduzida e preservada) houve uma redução estatisticamente significativa no ritmo de diminuição da TFG (-0.55 a -1.25 vs -2.28 a 2.62 ml/min/1.73 m^2/ano, $p<0.001$). Num seguimento a curto prazo, houve uma redução significativa, mas reversível, da TFG e não houve efeito na proteinúria de 24h. No seguimento a longo prazo de doentes renais crónicos

proteinúricos, houve uma redução estatisticamente significativa do efeito renal composto (HR 0.61, p<0.001) e da albuminúria (-14.8% (-22.9 to -5.9, P=0.0016)). A incidência de efeitos adversos foi baixa e a de efeitos adversos graves foi semelhante nos grupos tratados com inibidores do SGLT2 e placebo.

Conclusão: O tratamento com inibidores do SGLT2 parece diminuir o risco de diminuição sustentada da TFG, progressão para doença renal terminal e morte por causa renal em doentes com IC e DRC proteinúrica com TFG ≥ 25ml/min/1.73m^2. Os inibidores do SGLT2 parecem também diminuir o risco de albuminúria em doentes com DRC proteinúrica. Apesar dos resultados promissores, são necessários mais estudos, principalmente com acompanhamento a longo prazo, para avaliar com precisão o impacto dos inibidores do SGLT2 em doentes não diabéticos com DRC.

Palavras-chave

Inibidores do SGLT2; Gliflozinas; Doença Renal Crónica; Não-diabético; Renal.

Index

Introduction

Chronic kidney disease (CKD) affects about 700 million people worldwide and is an important cause of early morbidity and mortality, which can partly be explained by the prevalence of cardiovascular (CV) disease in this population (Bikbov et al., 2020; Cockwell & Fisher, 2020). 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 (Levin & Stevens, 2014). The disease is often insidious and remains asymptomatic until advanced stages. Consequently, late referral and inadequate diagnosis and treatment are missed opportunities for proper management of CKD, which in turn leads to faster progression towards end stage renal disease (ESRD). Despite different aetiologies, diabetes and hypertension being the main ones, there is a common mechanism that perpetuates and self-sustains the initial damage (Webster et al., 2017). Given these shared mechanisms of progression despite different underlying disease, several nephroprotective agents have been tested and introduced into clinical practice over the years. Since there is no specific treatment for CKD, the main goal is to delay the progression of the disease. Currently, renin-angiotensin system (RAS) blockers are the standard of care in glomerular diseases and provide therapeutic benefits by reducing systemic and intraglomerular pressures (Miyata et al., 2021).

Sodium-glucose cotransporter 2 inhibitors (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 the CV and renal protection offered by SGLT2i is not related to their hypoglycaemic effect. Systemic effects include reduction of body weight (BW), systemic blood pressure (BP) and systemic inflammation (Cherney et al., 2020; Heerspink et al., 2016; Hollander et al., 2017).

SGLT2i dapagliflozin and empagliflozin added to standard therapy reduced the risk of CV death and worsening heart failure (HF) in patients with heart failure with reduced ejection fraction (HFrEF) (McMurray et al., 2019; Packer et al., 2020). The efficacy of

SGLT2i is reflected in the 2021 European Society of Cardiology (ESC) guidelines: unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor neprilysin inhibitor (ARNI), a beta-blocker and a mineralocorticoid receptor antagonist (MRA), regardless the presence of T2D (McDonagh et al., 2021). In the 2019 ESC guidelines, SGLT2i were already considered first-line therapy for patients with T2D and established CV disease (Cosentino et al., 2020).

There are several proposed mechanisms underlying renal protection. The first and most acceptable one is the control of glomerular hyperfiltration by the decreased sodium reabsorption and subsequent glomerular afferent arteriolar vasoconstriction (del Vecchio et al., 2021; Vallon & Thomson, 2020; Wanner et al., 2016). The reduction in intraglomerular pressure explains the antiproteinuric effect and there are already trials done in patients with estimated glomerular filtration rate (eGFR) below 25 ml/min/1.73 m^2 (Dekkers et al., 2018; Heerspink et al., 2020).

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

Methods

This systematic review was performed in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) compliant manner. Medline (via PubMed) was searched on 21 November 2021. Search was conducted using terms “SGLT-2 inhibitors” OR “canagliflozin” OR “dapagliflozin” OR “empagliflozin” AND ‘“without diabetes” OR “non diabetic”.

Fifty results were retrieved from 2013 to 2021. Database filters were applied to include randomized controlled trials (RCTs) only. No dates or language restrictions were applied. In addition, we also screened the reference list of included studies or other relevant publications.

Inclusion criteria were RCTs evaluating renal outcomes in patients without diabetes mellitus. We included all RCTs according to the population, intervention, comparison,

outcome, inclusion and exclusion criteria. Exclusion criteria were studies on diabetic population only, studies without subgroup analysis of patients without diabetes, animal or in vitro studies, and protocols or comments on the trials. Of the twenty-two RCTs found, we included nine in this systematic review.

Renal outcomes included changes in eGFR, albuminuria or proteinuria and progression to ESRD.

Three reviewers independently performed the literature search and data extraction, and all disagreements were solved by mutual consensus. Clinical trials involving SGLT2i were selected for full text review to identify if subgroup analysis of patients without diabetes was performed.

For the SGLT2i regimens, we collected data on the drug name, dosage and frequency, control group, and length of intervention.

Data relating to blinding and withdrawals were extracted to assess risk of bias.

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

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	RCTs Year of publication: 2013 to 2021 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

Table 1. PICOS criteria for inclusion and exclusion of studies applied to database search

Results

Study selection

The PRISMA flowchart is presented in Figure 1. The nine trials comprised a combined cohort of 19689 patients. All the included studies were RCTs. Among the nine studies, four studies included patients with HF, four studies included patients with CKD and one study included patients with obesity. Among the SGLT2i used in the trials, five studies used dapagliflozin, three studies used empagliflozin and one study used canagliflozin. Dapagliflozin and empagliflozin were administered at a dosage of 10 mg throughout the RCTs, 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 compared with a control group receiving placebo. The length of follow-up ranged from six weeks to 2.4 years.

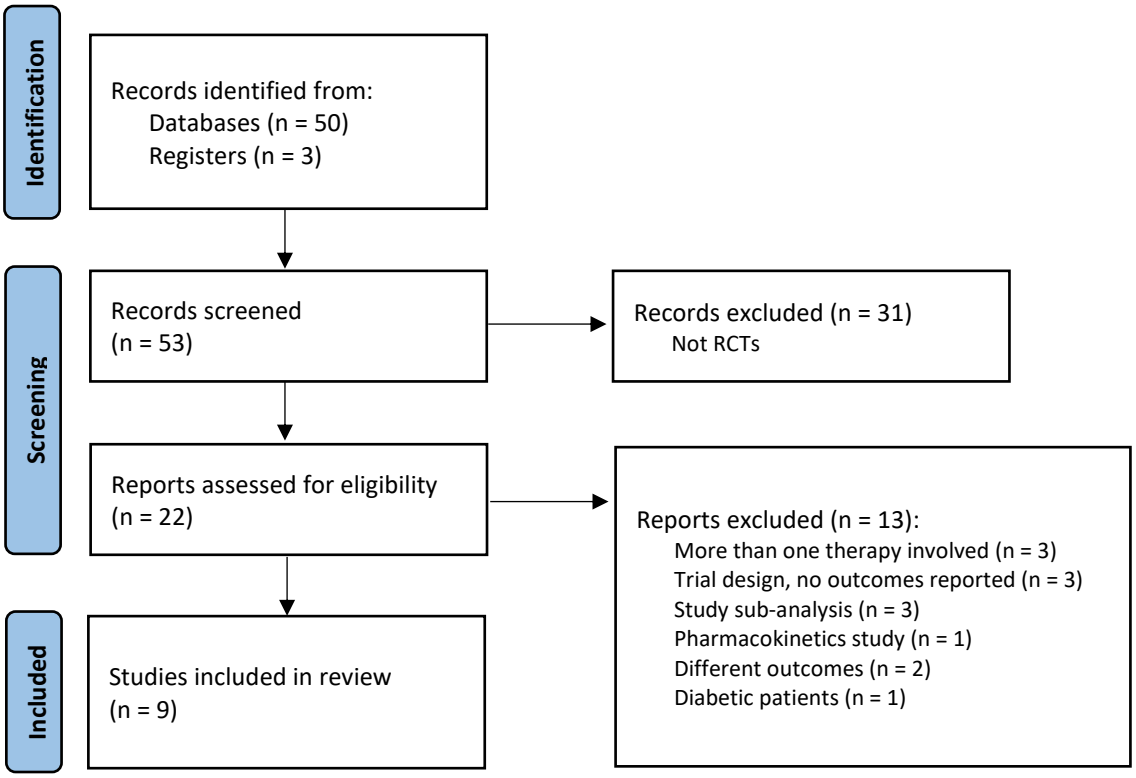

Figure 1. PRISMA flow diagram of study selection

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

Study characteristics

We critically appraised our screened articles using the Cochrane risk of bias tool (Sterne et al., 2019). The bias risk assessment looked at six causes of potential bias, and a summary was given for each clinical trial in this review in Table 2. All studies were assessed to have a low risk of bias. One study (Canagliflozin in Overweight and Obese Subjects Without T2D) experienced high dropout rates, contributing to a potential attrition bias (the authors reported that 25% of the participants did not complete the study).

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

Table 2. Summary of the RCTs bias using the Cochrane assessment tool

Inclusion and exclusion criteria of the selected studies are detailed in table 3.

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 m^2 (or rapidly declining renal function).
DAPA-CKD	Age ≥ 18, eGFR 25-75ml/min, uACR 200-5000mg/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- 3500mg/g, eGFR ≥25mL/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/m^2	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/m^2 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.

uACR - urinary albumin-to-creatinine ratio, ARB - angiotensin receptor blocker, FSGS – focal segmental glomerulosclerosis, uPCR - urinary protein excretion, BW – body weight

Table 3. Inclusion and exclusion criteria

The DAPA-HF trial included 4744 patients, of which 2761 (58.2%) were non-diabetic. Mean eGFR was 66 ml/min/1.73 m^2. Median follow-up was 18.2 months. The secondary outcome was a composite of worsening renal function, defined as a sustained decline in the eGFR of ≥50%, ESRD or death from renal causes. Concerning the secondary renal outcome there were less events on the dapagliflozin group though this difference was not significant (0.8 vs. 1.2 events/100 patient-year, hazard ratio (HR) 0.71 (0.44 to 1.16), p value not applicable). There was a significant weight reduction in the dapagliflozin group (-0.88 ± 3.86 kg vs 0.10 ± 4.09 kg on placebo, HR -0.87 (95% CI, -1.11 to -0.62, p<0.001). Renal serious adverse events (SAEs) occurred in 38 patients (1.6%) in the dapagliflozin group and in 65 patients (2.7%) in the placebo group (p=0.009). Acute kidney injury (AKI), the most common renal SAE, was reported in 23 patients (1.0%) in the dapagliflozin group and in 46 (1.9%) in the placebo group (p=0.007). Findings in patients with diabetes were similar to those in patients without diabetes (McMurray et al., 2019).

The DAPA-CKD trial included 4304 patients, of which 1399 (32.5%) non-diabetic. Mean eGFR was 43 ml/min/1.73 m^2 and the median urinary albumin-to-creatinine ratio (uACR) was 949mg/g. Median follow-up was 2.4 years. Patients treated with dapagliflozin had a lower risk of the primary composite outcome, defined as a sustained decline in the eGFR of at least 50%, or ESRD or death from renal or CV causes (HR 0.61 (0.51–0.72) p<0.001), which was even lower in the non-diabetic group (HR 0.50 (95% CI, 0.35 to 0.72) p value not shown). The dapagliflozin group reduced risk of the composite kidney secondary outcome, defined as a sustained decline in the eGFR of at least 50%, or ESRD or death from renal causes (HR 0.56 (95% CI, 0.45 to 0.68; p<0.001)). The effects of dapagliflozin were similar in participants with T2D and in those without. There was a reduction in the eGFR during the first 2 weeks of dapagliflozin (-3.97±0.15 vs. -0.82±0.15 ml/min/1.73 m^2, then, the annual change in the mean eGFR was smaller with dapagliflozin than with placebo (-1.67±0.11 vs -3.59±0.11 ml/min/1.73 m^2 for a between-group difference of 1.92 ml/min/1.73 m^2 per year (95% CI, 1.61 to 2.24)). The incidences of adverse events (AEs) and SAEs were similar overall in the dapagliflozin and placebo groups. Neither diabetic ketoacidosis nor severe hypoglycemia was observed in participants without diabetes (Heerspink et al., 2020).

On a prespecified analysis from the DAPA-CKD trial, dapagliflozin reduced mean uACR by 29.3% (95% CI -33.1 to -25.2, P<0.0001) (Jongs et al., 2021). Reduction was higher (-35.1% (95% CI -39.4 to -30.6, P<0.0001)) in patients with T2D, when compared to patients without T2D (-14.8% (-22.9 to -5.9, P=0.0016)). Larger reductions in uACR at day 14 during dapagliflozin treatment were significantly associated with attenuated eGFR decline during subsequent follow-up (β per log unit UACR change -3.06, 95% CI -5.20 to -0.90; p=0.0056).

The DAPA-CKD subgroup analysis included a group of patients with IgA nephropathy and another with focal segmental glomerulosclerosis (FSGS).

There were 270 subjects with IgA nephropathy, 232 (86%) non-diabetic. Dapagliflozin reduced the risk of the primary outcome (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 DAPA-CKD-IgA trial, the eGFR reduction during the first 2 weeks was also larger in the dapagliflozin than placebo group (-3.4 [±0.4] vs. -0.5 [0.4]

ml/min/1.73 m^2). Thereafter, annual mean eGFR change was smaller with dapagliflozin compared with placebo (-2.2 [0.5] and -4.6 [0.47], respectively), resulting in a between-group difference of 2.4 ml/min/1.73 m^2 per year (95% CI, 1.08–3.71 ml/min/1.73 m^2 per year). AEs leading to discontinuation of study drug were similar in the dapagliflozin and placebo groups. There were fewer SAEs with dapagliflozin (n = 22; 16%) versus placebo (n = 34; 26%). None of the participants developed major hypoglycemia and there were no events of diabetic ketoacidosis (Wheeler, Toto, et al., 2021).

There were 104 DAPA-CKD participants with biopsy-confirmed FSGS, 84 (80.8%) non-diabetic. The primary outcome was defined as a composite endpoint of sustained ≥40% decline in eGFR, or ESRD or death from renal or CV causes, and occurred in 4 (8.9%) and 7 (11.9%) participants randomised to dapagliflozin and placebo, respectively (HR 0.62, [95%CI 0.17-2.17]). Dapagliflozin led to an initial decline in eGFR between baseline and week 2 compared to placebo (-4.5, 95% CI -5.9 to -3.1 versus -0.9, 95% CI -2.1 to 0.4 ml/min/1.73 m^2/2 weeks). After the second week until end of treatment, the mean annual rates of eGFR decline with dapagliflozin and placebo were -1.9 (95% CI -3.0 to -0.9) and -4.0 (95% CI -4.9 to -3.0) ml/min/1.73m^2/year, respectively (difference 2.0, 95% CI 0.6 to 3.5 ml/min/1.73 m^2/year). The total slope, which combines the acute effect and chronic slope (baseline to end of treatment), was -3.7 (95% CI -4.8 to -2.6) versus −4.2 (95% CI -5.2 to -3.3) ml/min/1.73m^2/year in the dapagliflozin and placebo group, respectively (difference 0.5, 95% CI -0.9, 2.0 ml/min/1.73 m^2/year). Dapagliflozin reduced the rate of chronic decline of eGFR compared to placebo, although this difference was not statistically significant. Data for non-diabetic not specified but most of participants non-diabetic. AEs leading to discontinuation of study drug were similar in the dapagliflozin and placebo groups. There were fewer SAEs with dapagliflozin (n = 9; 20%) versus placebo (n = 16; 28%). None of the participants developed major hypoglycemia and there were no cases of diabetic ketoacidosis (Wheeler, Jongs, et al., 2021).

The DIAMOND trial included 53 non-diabetic patients. Mean eGFR was 58 mL/min/1.73 m^2 and mean 24-h urinary protein excretion 1110 mg. Each treatment period lasted 6 weeks with a 6-week washout period in between. A follow-up visit was scheduled 6

weeks after the last treatment. Primary outcome was the percentage change from baseline in 24-h proteinuria during dapagliflozin treatment relative to placebo with an overall treatment effect 0.9% (–16.6 to 22.1), p=0.93. Secondary outcomes were changes in measured GFR (mGFR), BW, systolic and diastolic BP and neurohormonal biomarkers. On the dapagliflozin group, there was a reduction of mGFR by -6.6 mL/min per 1.73 m2 (-9.0 to -4.2; p<0.0001) at week 6 and BW by 1.5 kg (0.03-3.0; p=0.046). There was no change in the other secondary outcomes (BP and biomarkers). The reduction in mGFR with dapagliflozin was completely reversible within 6 weeks after discontinuation. Regarding safety, 32% participants had one or more AEs during dapagliflozin treatment vs 25% during placebo treatment. No participants had hypoglycaemic events. One participant had a kidney-related AE (AKI) during dapagliflozin treatment. Urinary tract infections (UTI) and genital infections occurred in one patient each during dapagliflozin treatment. There were two SAEs, with one (cellulitis) occurring during placebo treatment and the other (colon cancer) during dapagliflozin treatment (Cherney et al., 2020).

The EMPEROR Reduced trial included 3730 patients, of which 50.2% were non-diabetic. Median follow-up was 1.3 years. Mean eGFR was 62 mL/min/1.73 m^2. The annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group, regardless of the presence or absence of diabetes (–0.55 vs. –2.28 ml/min/1.73 m^2 per year, p<0.001). Composite renal outcome was defined as ESRD or a profound sustained reduction in the eGFR, and occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (HR 0.50; 95% CI, 0.32 to 0.77, p value not shown (not adjusted for multiple comparisons)). Difference between diabetic and non-diabetic patients was not specified. SAEs occurred in 772 patients (41.4%) in the empagliflozin group and in 896 patients (48.1%) in the placebo group. Uncomplicated genital and UTIs and hypotension were more common in patients treated with empagliflozin (Packer et al., 2020).

The EMPEROR Preserved trial included 5988 patients, of which 51% were non-diabetic. Median follow-up was 26.3 months. Mean eGFR was 61 mL/min/1.73 m^2. The rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group

(-1.25 vs -2.62 ml/min/1.73 m² per year (95% CI, 1.06 to 1.66; p<0.001). Treatment with empagliflozin was associated with a lesser not-significant risk of a composite renal outcome, defined as ESRD or a profound sustained reduction in the eGFR (HR 0.95 (0.73 to 1.24)). The effects of empagliflozin appeared consistent in patients with or without diabetes. Empagliflozin decreased uric acid, which was apparent as early as 4 weeks after randomization and maintained for over 24 months (adjusted mean difference 0.80 (-0.88 to -0.72)). SAEs occurred in 47.9% patients in the empagliflozin group and in 51.6% in the placebo group. AE leading to discontinuation of treatment occurred in 19.1% patients in the empagliflozin group and in 18.4% patients in the placebo group. Uncomplicated genital and UTIs and hypotension were more common in patients treated with empagliflozin(Anker et al., 2021).

The EMPIRE-HF-RENAL included 120 patients, of which 88% were non-diabetic. Median follow-up was 12 weeks. Mean eGFR was 70 mL/min/1.73 m². Empagliflozin treatment in non-diabetic patients resulted in reductions in estimated extracellular volume (eECV) (mean difference -0.11L [-0.18 to -0.04]), estimated plasma volume (ePV) (mean difference -6.3% [-9.6 to -3.0]) and mGFR (mean difference -6.7mL/min [-10.8 to -2.6]). Empagliflozin produced a significant reduction in uric acid levels after 12 weeks (adjusted relative difference -20.4% (-25.7 to -15.2; p<0.0001)). In the empagliflozin group, 8% of patients had one or more SAEs, versus 5% of patients in the placebo group. No deaths occurred. The most common AE was UTI, occurring in four (7%) patients in the empagliflozin group and three (5%) in the placebo group, with one event in the empagliflozin group requiring hospital admission. No patients withdrew from their allocated treatment because of AEs or required dose reductions (Jensen et al., 2021).

One trial using canagliflozin in overweight and obese subjects without diabetes included 376 non-diabetic patients. Median follow-up was 12 weeks. There was no data regarding the mean GFR. Canagliflozin increased urinary glucose excretion (UGE)/creatinine ratio in a dose-dependent manner, beginning at week 3 (first assessment) and continuing through week 12. Compared to placebo-treated subjects at week 12, canagliflozin 50, 100, and 300 mg produced a greater proportion of subjects with ≥ 5% loss in BW from baseline (8%, 13%, 19%, and 17%, respectively; p=0.027 for canagliflozin 300 mg vs

placebo). At week 12 compared to baseline, canagliflozin 50, 100, and 300 mg and placebo produced reductions in systolic BP (mean changes of -2.1, -3.3, -2.0 and -1.4 mmHg, respectively), with mean changes in diastolic BP of -1.4, -0.7, -0.5 and -1.8 mmHg, respectively. Canagliflozin 50, 100, and 300 mg were associated with greater reductions in serum urate concentrations compared to placebo (mean changes of -1.1, -1.2, -1.3 and -0.1 mg/dL, respectively). Canagliflozin 50 and 100 mg were also associated with modest decreases in eGFR compared to placebo (mean changes of 21.0, 21.8 and 0.3 mL/min/1.73 m^2, respectively). Unexpectedly, canagliflozin 300 mg was associated with an increase from baseline in eGFR (0.8 mL/min/1.73 m^2). Canagliflozin 100 and 300 mg were associated with increases in blood urea nitrogen (BUN) compared to placebo and canagliflozin 50 mg (mean changes of 0.4, 0.7, -0.1 and -0.2 mg/dL, respectively). The overall incidence of AEs was similar across treatment groups (Bays et al., 2014).

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 the eGFR of ≥ 50%, ESRD or renal death: HR 0.71 (0.44-1.16), p value NA. Dapagliflozin 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 (95% CI, 0.35-0.72) Secondary outcome: sustained decline in eGFR ≥50%, ESRD or renal death: HR 0.56 (95% CI, 0.45 to 0.68; P<0.001) uACR change of -14.8% (-22.9 to -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 (95% CI), 0.13 to 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 (95% CI) 0.17 to 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 24-h proteinuria: 0.9% (-16.6 to 22.1), p=0.93 Secondary outcomes: mGFR -6.6mL/min/1.73 m^2 (-9.0 to -4.2, p<0·0001) reversible; 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 m^2/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 value 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 (95% CI 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 to -0.04]), ePV (-6.3% [-9.6 to -3.0]) and mGFR (-6.7mL/min [-10.8 to -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	Canagliflozin 50, 100, and 300 mg ≥5% loss in BW (13%, 19%, and 17%, respectively (vs. 8% in placebo); p=0.027 for canagliflozin 300 mg vs placebo). Canagliflozin 50, 100, and 300 mg reduced uric acid (mean changes of -1.1, -1.2, -1.3mg/dL, respectively (vs -0.1 mg/dL in placebo)). Canagliflozin 100 and 300 mg increased BUN compared to placebo and canagliflozin 50 mg (mean changes of 0.4, 0.7, -0.1, and -0.2 mg/dL, respectively).

SAE – serious adverse event, AKI - acute kidney injury, NA – not applicable, BW – body weight, eECV - estimated extracellular volume, ePV - estimated plasma volume, BUN - blood urea nitrogen

Table 4. Summary of the included studies

Discussion

In this systematic review of RCTs of patients without diabetes mellitus treated with SGLT2i (Dapagliflozin or Empagliflozin), there is a tendency for lesser risk of sustained eGFR reduction, progression to ESRD or renal death in HFrEF patients – DAPA HF, EMPEROR REDUCED (McMurray et al., 2019; Packer et al., 2020). Lesser effect was seen in patients with HF with preserved EF – EMPEROR PRESERVED (Anker et al., 2021). For

both preserved and reduced EF HF there also seems to be a statistically significant reduction in the rate of decline in eGFR per year – EMPEROR PRESERVED, EMPEROR REDUCED (Anker et al., 2021; Packer et al., 2020).

Initially studied in the diabetic population, SGLT2i showed that beside the CV benefit, they could reduce a composite kidney outcome, including progression to macroalbuminuria, doubling of serum creatinine, ESRD or death from kidney causes by 40% in the EMPA-REG trial (Zinman et al., 2015). Subsequently, the CREDENCE trial, which evaluated the impact of canagliflozin on the primary outcome of composite kidney outcome – doubling of serum creatinine or ESRD – in a CKD diabetic patient cohort, also proved the renoprotective benefits of SGLT2i (Perkovic et al., 2019). The trial was stopped early because of overwhelming efficacy of the drug. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group (HR 0.70, 95% CI, 0.59-0.82, p=0.00001). The relative risk of the renal-specific composite of ESRD, a doubling of the creatinine level, or renal death was lower by 34% (HR 0.66, 95% CI, 0.53-0.81; p<0.001), and the relative risk of ESRD was lower by 32% (HR 0.68, 95% CI, 0.54 to 0.86, p=0.002).

These two trials – CREDENCE, EMPA-REG - also reported an early decline in eGFR (around 3-6 ml/min/1.73 m^2) shortly after initiating these drugs compared with placebo controls (Perkovic et al., 2019; Zinman et al., 2015). These early declines or dips were typically observed at 2-4 weeks after initiation of the SGLT2i, with subsequent partial recovery of the eGFR curve by week 12, and, ultimately, followed by an attenuation of the slope of eGFR decline compared with placebo controls after 52 weeks. The coexistence of eGFR declines and long-term clinical benefits was well described before with RAS inhibitors (Brenner et al., 2001; Jamerson et al., 2008).

In our analysis, in CKD and proteinuric patients with eGFR ≥ 25ml/min/1.73m^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 ((Heerspink et al., 2020; Wheeler, Jongs, et al., 2021; Wheeler, Toto, et al., 2021).

Empagliflozin in patients with HF also seems to lead to a statistically significant reduction in the rate of decline in eGFR per year – EMPEROR PRESERVED, EMPEROR REDUCED (Anker et al., 2021; Packer et al., 2020). In the EMPEROR Reduced trial there was initial eGFR decline within the first 4 weeks of treatment with SGLT2i followed by an attenuation of the slope of eGFR decline (Packer et al., 2020). This was also reported in the DAPA-CKD trial, in which there was a reduction in the eGFR during the first 2 weeks of dapagliflozin, then, the annual change in the mean eGFR was smaller with dapagliflozin than with placebo (Heerspink et al., 2020).

SGLT2i inhibit sodium and glucose reabsorption in the proximal tubule, leading to increased sodium and chloride delivery to the macula densa. This results in afferent arteriolar vasoconstriction secondary to adenosine-mediated myogenic activation, leading to a reduction in the intraglomerular pressure and GFR (as seen in RAS inhibitors), leading to regulation of tubuloglomerular feedback and reduction in albuminuria (Heerspink et al., 2016). Natriuresis and intravascular volume reduction also decrease systemic blood pressure and probably contribute to the initial decline in GFR (Takata & Isomoto, 2021). 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 (Sharaf El Din et al., 2021; Takata & Isomoto, 2021). The EMPA-KIDNEY trial has recently been stopped early due to clear positive efficacy of empagliflozin in adults with CKD (Herrington et al., 2022). The results of this trial are highly anticipated and should be available by the end of this year.

Concerning the antiproteinuric effects, the DIAMOND trial failed to achieve a significant decrease in urine protein excretion, but this might be explained by the short duration of treatment, as this trial was only for 6 weeks (Cherney et al., 2020). In contrast, a prespecified analysis from the DAPA-CKD trial reported a significant decline of urine protein excretion rate with the administration of dapagliflozin for a mean period of 2.4 years. In patients with CKD, with and without T2D, dapagliflozin significantly reduced albuminuria, with a larger relative reduction in patients with type 2 diabetes. Larger reductions in albuminuria were significantly associated with attenuated eGFR decline.

The similar effects of dapagliflozin on clinical outcomes in patients with or without T2D, but different effects on uACR, may suggest that part of the protective effect of dapagliflozin in patients with CKD can be mediated through pathways unrelated to reduction in albuminuria (Jongs et al., 2021) . The anti-proteinuric effect of dapagliflozin was also demonstrated in a pooled analysis of 11 phase 3 RCTs. These studies included 136 diabetic patients having uACR ≥ 30 mg/g that received 5 or 10 mg dapagliflozin in comparison to 69 patients on placebo. The eGFR of these cases ranged between 11 and 45 ml/min/1.73 m^2. Over 102 weeks, dapagliflozin 5 mg and 10 mg reduced uACR by 47% and 38%, respectively, compared to placebo (Dekkers et al., 2018). The reduction of proteinuria can be explained by the reduction of intraglomerular pressure. Also, using mice with protein-overload proteinuria induced by bovine serum albumin, (Cassis et al., 2018) showed that dapagliflozin ameliorated the proteinuria, glomerular lesions, and foot process effacement. In vitro, SGLT2 expression by Western blotting was stimulated by albumin exposure in cultured human podocytes, and dapagliflozin ameliorated albumin-induced cytoskeletal rearrangements in podocytes (Cassis et al., 2018).

The EMPEROR Preserved trial showed that empagliflozin decreased uric acid, which was apparent as early as 4 weeks after randomization and maintained for over 24 months (Anker et al., 2021). The EMPIRE-HF-RENAL trial also showed that, compared with placebo, empagliflozin produced a significant reduction in uric acid levels after 12 weeks and it was the first trial reporting similar reductions in patients with HFrEF without T2D (Jensen et al., 2021). Canagliflozin was also associated with greater reductions in serum urate concentrations compared to placebo in overweight and obese individuals without diabetes (Bays et al., 2014). The observed decreases in serum urate may be mediated by glucosuria facilitating urate efflux into the tubular lumen by the high-capacity urate transporter SLC2A9 (GLUT9) (Caulfield et al., 2008).

Weight loss with SGLT2i therapy has been consistently observed in several studies in T2D, whether patients were taking SGLT2i as monotherapy or in combination with additional glucose-lowering therapies. The results of network meta-analyses show

reductions of body weight compared to placebo for all SGLT2i treatments of about 1.5-2 kg and these effects are dose-dependent (Maruthur et al., 2016; Mearns et al., 2015; Wang et al., 2018; Zaccardi et al., 2016). Inhibition of renal glucose reabsorption is a unique mechanism and has the potential to produce negative caloric balance. SGLT2i directly cause weight loss via glucose excretion in the kidney (about 60–100 g of glucose per day), resulting in calorie loss and osmotic diuresis (Pereira & Eriksson, 2019). Most importantly, the weight loss is mainly due to a reduction in subcutaneous and visceral adipose tissue, rather than lean tissue (Lundkvist et al., 2017). Only a few studies have looked at the effects of SGLT2i in weight loss in obese subjects without diabetes. Co-administration of SGLT2i with a GLP1 receptor agonist reduces body weight by 4.5 kg at 24 weeks of treatment, and this weight loss was maintained for up to 1 year in obese individuals without diabetes (Lundkvist et al., 2017). In this systematic review, we report that SGLT2i were associated with weight loss in patients without diabetes mellitus. The DAPA-HF and DIAMOND trials reported that dapagliflozin led to a significant weight reduction when compared to placebo (Cherney et al., 2020; McMurray et al., 2019). This effect was also demonstrated with empagliflozin, and with canagliflozin. (Anker et al., 2021; Bays et al., 2014; Jensen et al., 2021).

Overall, the incidence of adverse events was low and severe adverse events were similar in the SGLT2i and placebo groups. As described in previous studies, uncomplicated genital infections and UTIs and hypotension were more common in patients treated with SGLT2i.

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. The reduction in the rate of decline in eGFR, one of the most significant renal outcomes, was only evaluated in HF patients. Finally, SGLT2i effect on each renal outcome is still missing since most studies focused on a composite renal outcome.

Conclusion

Treatment with SGLT2i appears to lower the risk of sustained eGFR reduction, progression to ESRD or death from renal causes in patients with HF patients and CKD proteinuric patients with eGFR ≥ 25ml/min/1.73m^2. SGLT2i also seem to lower albuminuria in CKD proteinuric patients.

Despite the promising results, solid data on the renal effects in non-diabetic patients with CKD are still missing, in contrast to the well documented CV effects of SGLT2i in HF patients with or without diabetes. Further studies, specifically with long-term follow-up, are required to accurately assess the impact of SGLT2i on renal outcomes in non-diabetic CKD patients.

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