Kidney Diseases

Review Article

Kidney Dis
DOI: 10.1159/000530395

Received: September 8, 2022
Accepted: March 20, 2023
Published online: April 11, 2023

Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitors in Nondiabetic Patients with Chronic Kidney Disease: A Review of Recent Evidence

Junhao Lv[a, b, c, d] Luying Guo[a, b, c, d] Rending Wang[a, b, c, d]
Jianghua Chen[a, b, c, d]

[a]Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; [b]Key Laboratory of Kidney Disease Prevention and Control Technology, Hangzhou, China; [c]National Key Clinical Department of Kidney Diseases, Institute of Nephrology, Zhejiang University, Hangzhou, China; [d]Zhejiang Clinical Research Center of Kidney and Urinary System Disease, Hangzhou, China

Keywords
Chronic kidney disease · Sodium-glucose cotransporter-2 inhibitors · Clinical trials · Mortality · Outcomes

Abstract
Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) were initially developed as glucose-lowering agents in patients with type-2 diabetes. However, available data from clinical trials and meta-analyses suggest that SGLT2i have pleiotropic benefits in reducing mortality and delaying the progression of chronic kidney disease (CKD) in both diabetic and nondiabetic patients. Thus, we herein review the current evidence regarding the efficacy and safety of SGLT2i in patients with nondiabetic CKD and appraise the recently reported clinical trials that might facilitate the management of CKD in routine clinical practice. ***Summary:*** The benefits of SGLT2i on nondiabetic CKD are multifactorial and are mediated by a combination of mechanisms. The landmark DAPA-CKD trial revealed that dapagliflozin administered with renin-angiotensin system blockade drugs reduced the risk of a sustained decline (at least 50%) in the estimated glomerular filtration rate, end-stage kidney disease, or death from cardiorenal causes. The recent EMPA-KIDNEY trial showed that empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes. These benefits were consistent in patients with and without diabetes. Moreover, a meta-analysis of DAPA-HF and EMPEROR-Reduced trials confirmed reductions in the combined risk of cardiovascular death or worsening heart failure including composite renal endpoint. ***Key Messages:*** Considering the robust data available from DAPA-CKD, EMPA-KIDNEY, and other trials such as EMPEROR-Preserved, DIAMOND that included nondiabetic patients, it may be necessary to update current guidelines to include SGLT2i as a first-line therapy for CKD and reevaluate current CKD therapeutic approaches.

Introduction

Chronic kidney disease (CKD) is the 16th leading cause of mortality worldwide, with an estimated global prevalence of 11–13% [1, 2]. The incidence of CKD and

karger@karger.com
www.karger.com/kdd

Correspondence to:
Jianghua Chen, zjukidney@zju.edu.cn

its contribution to mortality and other cardiovascular outcomes increases with age [3]. Currently, the standard treatment for CKD is renin-angiostatin system blockade by angiostatin receptor blockers and angiostatin-converting enzyme inhibitors [4, 5]. Renin-angiostatin system blockades have a reno-protective effect, thus, although it delays, it does not prevent CKD progression that may lead to end-stage kidney disease (ESKD) [4].

In the past 20 years, no new therapy has slowed the progression of CKD to ESKD [5]. Several studies have shown the potential reno-protective effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) through different diabetic nephropathic animal models of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) [6, 7]. Hence, SGLT2i were initially developed for the treatment of hyperglycemia in patients with T2DM [8, 9]. Various types of SGLT2i are used to control diabetic nephropathy [8–10]. However, the studies of SGLT2i in nondiabetic kidney disease are limited, which instigated more specific and well-powered trials that focused on renal outcomes to obtain better insights into the primary reno-protective mechanisms. In this regard, DAPA-CKD [11] was the first SGLT2i trial in patients with CKD, which demonstrated the efficacy of dapagliflozin to reduce renal function worsening [11]. In April 2021, the FDA expanded indications of dapagliflozin for the treatment of patients with T2DM and heart failure (HF) with reduced ejection fraction, to include reducing the risk of kidney function decline and kidney failure in patients with CKD [12], making it the first SGLT2i to be approved by any regulatory body for patients with CKD, regardless of diabetes.

The kidney disease improving global outcomes (KDIGO) guidelines 2022, recommend SGLT2i in patients with or without T2DM with CKD, having an eGFR >20 mL/min/1.73 m^2. The guidelines recommend using them to delay the progression of CKD [13]. Strategies to prevent CKD progression include primary, secondary, and tertiary methods [14]. In this paper, we aim to review these data to understand the evidence-based benefits of SGLT2i, including potential strategies for how SGLT2i may benefit in delaying the progression of CKD in nondiabetic patients.

Potential Mechanism of SGLT2i in Renal Protection

Tubuloglomerular Feedback

Glomerular hyperfiltration is a common pathway of kidney injury in both diabetic and nondiabetic patients [15, 16]. Higher single-nephron glomerular filtrate rate (GFR) directly leads to higher risk factors for CKD progression [17]. Previous preclinical studies in nephrons of rodent CKD models reported the deactivation of tubuloglomerular feedback (TGF) resulting in abnormal TGF, ultimately leading to the progression of kidney diseases [18]. Several studies have revealed the effects of SGTL2i on glomerular hemodynamic pathways [16, 19]. Previous study has confirmed the acute effects with SGLT2i precursor, phlorizin, and 1 of the SGTL2i such as dapagliflozin on proximal reabsorption and GFR [20]. In addition, continuous treatment with SGLT2i for 2 weeks in diabetic rats normalized the sodium chloride delivery to the macula densa, resulting in attenuation of hyperfiltration [21]. Thus, SGLT2i restore the distal sodium delivery, which results in normalization of TGF and afferent tone, lowering intraglomerular pressure [16]. Various preclinical and clinical studies have shown that dapagliflozin and empagliflozin lower glomerular hyperfiltration without altering the blood glucose levels [21–23]. Canagliflozin has shown to reduce GFR with proteinuria within 3 weeks after treatment in patients with T2DM [24].

Effects of SGLT2i on Erythropoietin

Reabsorption of glucose causes overburden on the proximal tubules of patients with CKD. The excessive quantity of glucose raises oxygen demand in the proximal tubules [19]. SGLT2i can reduce renal oxygen consumption by impeding the active reabsorption of glucose and sodium in proximal tubes, ultimately reducing renal energy consumption and protecting the kidney [25]. On the other hand, oxygen demand rises in the outer medulla due to the shifting of sodium reabsorption to the medullary thick ascending limb of the Henle's loop. This CKD-induced hypoxia renders the tubular segment susceptible to ischemia [20]. Furthermore, hypoxia-inducible factors (HIF-1α) are stimulated by lower medullary oxygen tension in this segment of the tubule, thereby promoting erythropoietin production to improve red cell mass and oxygen-carrying capacity [22]. A previous study with phlorizin has shown to decrease the oxygen levels in an in vivo study [20]. These studies signify the role of SGLT2i in mitigating the metabolic burden on proximal tubules, thereby increasing HIF-1α for erythropoietin production in patients with CKD as shown in Figure 1.

Effects of SGLT2i on Renal Energy Metabolism

In addition to improving renal energy metabolism, SGLT2i enhance oxygen uptake and transformation at the mitochondria level [25]. In contrast to the continuous glucose loss caused by increased glycosuria, SGLT2i improve physiologic adaptive responses [16]. These

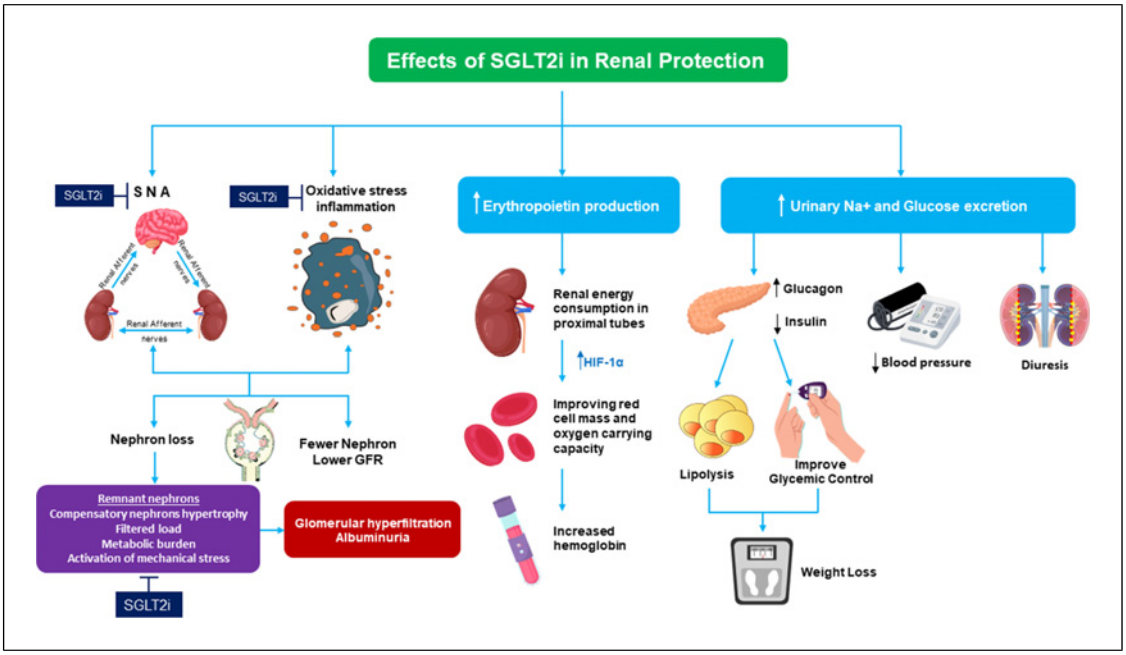

Fig. 1. Schematic diagram representing the effects of SGLT2i in renoprotection. HIF-1α, hypoxia-inducible factor 1-alpha; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SNA, sympathetic nerve activity; GFR, glomerular filtration.

response mechanisms induce an increase in endogenous glucose production by increasing glucagon and reducing insulin levels [16]. These effects stimulate ketogenesis and lipolysis and increase circulating ketone bodies among β-OH-butyrate [26]. This mechanism provides a powerful synergistic effect that could ultimately protect kidney function. Furthermore, blood pressure in nondiabetic patients could be controlled by SGLT2i, reinforcing self-regulation of renal vessels, preserving renal function, and alleviating proteinuria [25].

Effects of SGLT2i on Metabolic Burden in Nephrons

In nondiabetic patients with CKD, 300 g of glucose gets filtered by abundant nephrons, whereas it is filtered by a smaller number of nephrons in non-CKD patients. This indicates that in each nephron, glucose levels increase, leading to TGF deactivation [27]. SGLT2i increase the urinary glucose excretion, to approximately 60–100 g/day from renal proximal tubular, thereby reducing glucose burden [28, 29].

SGLT2i reduce the metabolic burden with respect to reabsorbed excessive sodium, protein, and other solutes in progressive CKD [27]. The SAND trial had promising effects in patients with the syndrome of inappropriate antidiuresis (SIAD). The study showed a significant increase in plasma sodium levels when compared with placebo (10 vs. 7 mmol/L, respectively), indicating the reno-protective effects of empagliflozin [30].

Other Reno-Protective Effects of SGLT2i

The reno-protective effects of SGLT2i can be grouped into direct renal effects and indirect renal effects (Table 1). The previous evidences had shown that SGLT2i can exert nephroprotective effects by reducing oxidative stress, inflammation, fibrosis, sympathetic nervous system activation, intraglomerular hypertension, and improving myocardial efficiency and mitochondrial function [19, 25]. SGLT2i promotes weight loss and a reduction in the abdominal and peripheral fat and body weight through osmotic diuresis [8]. Obesity can affect the hemodynamics of the kidney, which ultimately increases the GFR and glomerular volume [25]. Canagliflozin has shown to reduce weight, glycosylated hemoglobin, and blood pressure [31].

Other mechanisms of renal protection by SGLT2i include decreasing uric acid levels, and hence reducing GFR [25]. In addition, the synergistic effects of SGLT2i and sodium-proton proximal tubule produce diuresis, improving blood pressure and uric acid excretion, ultimately reducing the burden on the kidneys [25].

Table 1. Direct and indirect renoprotective effects by SGLT2 inhibitors

Direct effects	Indirect effects
Renal hemodynamic and non-hemodynamic effects	Blood pressure ↓
Plasma glucose and glycosylated hemoglobin ↓	Plasma glucagon ↑ and insulin↓
Tubular Na+ reabsorption ↓	Weight loss ↓
Tubular excessive energy consumption ↓	Plasma uric acid levels ↓
Intraglomerular pressure by restoring tubuloglomerular feedback ↓	Albuminuria ↓
Inflammatory mediators, and oxidative stress ↓	Hemoglobin ↑ by inducing erythropoietin production

Evidence-Based Benefits of SGLT2i in Nondiabetic Patients with CKD

Administration of SGLT2i facilitates an increase in sodium delivery to the macula densa, which ultimately delays renal function decline in patients with diabetes. Clinical studies demonstrated that these benefits are maintained at lower levels of kidney function, despite attenuation of glycosuric effects, which do not appear to be dependent on ambient hyperglycemia. Thus, more recent clinical trials have rationalized to include both diabetic and nondiabetic patients with HF or CKD. In addition, the most recent meta-analysis has also provided the relevant evidence for both 90,409 participants with diabetes and 15,605 without diabetes to support the use of SGLT2i, irrespective of their diabetic status [32]. The summary of various clinical trials of SGLT2i has been shown in Table 2. The landmark DAPA-CKD [11] was the first exclusive kidney disease outcome trial to include one-third of the total participants without diabetes. The study reported the beneficial effect of dapagliflozin on the primary outcome as compared with the placebo group. Furthermore, the effects of dapagliflozin on kidney, cardiovascular, and mortality outcomes were investigated according to the presence or absence of T2DM, and underlying cause of CKD. The study reported that dapagliflozin reduces the risks of major adverse kidney and cardiovascular events and all-cause mortality in patients with diabetic and nondiabetic CKD [44, 45]. DAPA-CKD trial explicitly indicated that the improved renal, cardiovascular, and mortality outcomes of dapagliflozin were consistent ($p_{\text{interaction}}$ = 0.19) for patients with normoglycemia (hazard ratio, HR = 0.62, 95% confidence interval, CI: 0.39–1.01), prediabetes (HR = 0.37, 95% CI: 0.21–0.66), and T2DM (HR = 0.64, 95% CI: 0.52–0.79), indicating the promising effects of SGLT2i in nondiabetic patients with CKD [46]. Another prespecified analysis demonstrated that dapagliflozin has prolonged survival irrespective of baseline patient characteristics [47]. One study reported a reduced risk of CKD progression among IgA nephropathic patients in the dapagliflozin group as compared with placebo (HR = 0.29, 95% CI: 0.12–0.73) [48]. A recent prespecified study of dapagliflozin and preventing adverse events in patients with focal segmental glomerulosclerosis (DAPA-CKD) has shown nonsignificant reduction in chronic decline of eGFR as compared to placebo [49]. Further, a post hoc analysis of the DAPA-CKD trial had shown reduction in hazard of ≥50% reduction in eGFR, ESKD, and death from a kidney or cardiovascular cause (HR = 0.61; 95% CI: 0.51–0.72) and reduction in all Kidney Disease Improving Global Outcomes (KDIGO) risk categories (all p for interaction >0.09) [50], regardless of background treatment of Mineralocorticoid receptor antagonists (MRAs) [51]. In addition, DAPA-CKD trial also showed promising effects of dapagliflozin on kidney and cardiovascular events and prolonged the survival of patients irrespective of geographic regions [52].

The DAPA-HF phase-3 trial [38] revealed improvement in morbidity, mortality, and symptoms in patients with HF and a reduced ejection fraction (HFrEF). Treatment with dapagliflozin prolonged the rate of decline in eGFR, including in patients without diabetes ($p_{\text{interaction}}$ = 0.92) [53]. The EMPEROR-reduced trial [39, 54] enrolled 3,730 patients with HF. The findings were similar to the DAPA-HF trial, and empagliflozin significantly improved cardiovascular and renal outcomes in patients with HFrEF. It also significantly reduced the risk of the composite kidney endpoint regardless of baseline diabetes status by 50%. Results of a meta-analysis of EMPEROR-Reduced and DAPA-HF indicated that the estimated treatment effect was a 13% and 14% reduction in all-cause and cardiovascular death, respectively [55].

The EMPEROR-Preserved trial that enrolled approximately half nondiabetic patients, has confirmed the benefits of HF complications in patients with HFrEF [41]. In another trial, the EMPA-Response, the effects of empagliflozin were evaluated to be 10 mg/day compared with placebo for 30 days. The study showed exceptional difference with empagliflozin on urinary output (3,449, 95% CI: 578–6,321 mL; N = 28, p = 0.02) and

Table 2. Summary of SGLT2i clinical trials in nondiabetic patients

RCT studies	Size, *n*	Proportion with non-diabetes, *n* (%)	Median follow-up, years	eGFR eligibility criteria, mL/min per 1.73 m^2	Mean (SD) eGFR in nondiabetic group, mL/min per 1.73 m^2	Progression of kidney disease in nondiabetic group, RR (95% CI)	Acute kidney injury in nondiabetic group, RR (95% CI)	Key results
DAPA-CKD [11] (Dapagliflozin 10 mg)	4,304	1,398 (32)	2.4	25–75	42 (12)	0.51 (0.34–0.75)	0.75 (0.39–1.43)	Dapagliflozin significantly lowered risk of CKD progression or death from renal/cardiovascular diseases compared to placebo
EMPA-KIDNEY [33] (Empagliflozin 10 mg)	6,609	3,569 (54)	2.0	20–90	39 (15)	0.74 (0.59–0.95)	0.63 (0.41–0.97)	Empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo
DELIVER [34] (Dapagliflozin 10 mg)	6,263	3,457 (55)	2.3	≥25	63 (19)	1.01 (0.51–1.97)	0.64 (0.41–1.02)	Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction
DIAMOND [35] (Dapagliflozin 10 mg)	53	53 (100)	6 weeks	≥25	58 (23)	NA	△mGFR = −6.6 mL/min per 1.73 m^2 ($p < 0.0001$)	6-week treatment with dapagliflozin did not affect proteinuria but did induce an acute and reversible decline in mGFR and a reduction in body weight
EMPA-TROPISM [36] (Empagliflozin 10 mg)	84	84 (100)	6 months	≥30	81 (22)	NA	△eGFR = −4 mL/min per 1.73 m^2 ($p < 0.01$)	Empagliflozin showed significant effect on LV volumes, mass and systolic function, functional capacity, as compared to placebo in patients with nondiabetic HFrEF

Table 2 (continued)

RCT studies	Size, *n*	Proportion with non-diabetes, *n* (%)	Median follow-up, years	eGFR eligibility criteria, mL/min per 1.73 m^2	Mean (SD) eGFR in nondiabetic group, mL/min per 1.73 m^2	Progression of kidney disease in nondiabetic group, RR (95% CI)	Acute kidney injury in nondiabetic group, RR (95% CI)	Key results
EMPA-RESPONSE-AHF [37] (Empagliflozin 10 mg)	80	54 (68)	30 days	≥30	55 (18)	NA	Not different	Empagliflozin was safe and well tolerated. No significant change in visual analog scale dyspnea, diuretic response, NT-proBNP, and length of hospital stay with the treatment Empagliflozin
DAPA-HF trial [38] (Dapagliflozin 10 mg)	4,744	2,761 (58)	1.5	≥25	68 (19)	0.67 (0.30–1.49)	0.60 (0.34–1.08)	The risk of worsening heart failure or death from cardiovascular causes was lower in dapagliflozin group compared to placebo, regardless of diabetes
SAND [30] (Empagliflozin 25 mg)	87	75 (86)	4 days	≥30	NA	NA	4 patients showed transient renal impairment	The short-term treatment with empagliflozin showed restriction of standard fluid leading to increased plasma sodium concentration as compared to placebo
EMPEROR-reduced trial [39, 40] (Empagliflozin 10 mg)	3,730	1,874 (50)	1.3	≥20	63 (21)	0.50 (0.17–1.48)	0.56 (0.32–0.98)	The study showed significant effect of empagliflozin improving cardiovascular and renal outcomes in heart failure and a reduced ejection fraction patient, regardless of their diabetic status

significant net fluid loss (2,701, 95% CI: −586–8,988 mL, $N = 25$; $p = 0.10$), which strongly supports the effects of empagliflozin treatment on diuretics [37]. Recently, EMPA-KIDNEY trial has included diabetic (including T1DM and T2DM) and nondiabetic patients with small scale or no albuminuria/proteinuria to investigate the effects of 10-mg/day empagliflozin in kidney disease progression or cardiovascular death. Its results have

Table 2 (continued)

RCT studies	Size, *n*	Proportion with non-diabetes, *n* (%)	Median follow-up, years	eGFR eligibility criteria, mL/min per 1.73 m^2	Mean (SD) eGFR in nondiabetic group, mL/min per 1.73 m^2	Progression of kidney disease in nondiabetic group, RR (95% CI)	Acute kidney injury in nondiabetic group, RR (95% CI)	Key results
EMPEROR-Preserved trial [41] (Empagliflozin 10 mg)	5,988	3,050 (51)	2.2	≥20	62 (19)	0.68 (0.33–1.40)	0.80 (0.52–1.23)	Empagliflozin showed reduction in the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, irrespective of diabetes
EMPIRE-HF Renal [42] (Empagliflozin 10 mg)	120	105 (88)	12 weeks	>30	72 (18)	NA	△mGFR = −6.7 mL/min ($p < 0.01$)	Reduction in the estimated extracellular volume, estimated plasma volume, and GFR after 12 weeks in patients with heart failure and reduced ejection fraction with the treatment of empagliflozin
DAPA-MEMRI [43] (NCT04591639)	RCT	HF patients with or without T2DM	Ongoing	≥30	Ongoing	Ongoing	Ongoing	Ongoing

Kidney disease progression was defined as a sustained decrease in eGFR (≥50%), from randomization, a sustained low eGFR, end-stage kidney disease, or death from kidney failure. CKD, chronic kidney disease; eGFR, estimated glomerular filtrate rate; mGFR, measured glomerular filtrate rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; *n*, number of patients; RCT, randomized control trial; RR, relative risk; NA, not available. △ = change from baseline.

further strengthen the role of SGLT2i in significantly reducing the risk of kidney disease progression or cardiovascular death (HR = 0.72, 95% CI: 0.64–0.82; $p < 0.001$) in patients with or without diabetes [33].

Role of SGLT2i in Mitigating Common Risk Factors of CKD Progression

Apart from the direct evidence-based benefits of SGLT2i in patients with nondiabetic CKD, these agents may target common metabolic risk factors that are associated with CKD progression, including obesity, hypertension, dyslipidemia, and hyperuricemia. Therefore, administration of SGLT2i may facilitate early management of risk factors of CKD, which may help prolong ESKD.

Obesity

The KNOW-CKD study [56] demonstrated that obesity is significantly associated with increased risk for CKD progression. In a randomized clinical study with 140 patients with T2DM on metformin [57], patients in the dapagliflozin-treated group exhibited reductions in weight by −4.54 kg, waist circumference by −5.0 cm, and fat mass by −2.80 kg without increasing the rate of

hypoglycemia. In another study including 182 patients with T2DM on metformin [58], administration of dapagliflozin compared with placebo significantly reduced total body weight (−2.08 kg, $p < 0.0001$), waist circumference (−1.52 cm, $p = 0.0143$), dual-energy X-ray absorptiometry total-body fat mass (−1.48 kg, $p = 0.0001$), visceral adipose tissue (−258.4 cm^3, nominal $p = 0.0084$), and subcutaneous adipose tissue (−184.9 cm^3, nominal $p = 0.0385$). Furthermore, the proportion of patients achieving weight reduction of at least 5% increased to 26.2% ($p < 0.0001$).

RESILIENT [59] is an ongoing study that will examine the mechanistic effects of dapagliflozin as monotherapy or as co-therapy with exenatide in obese patients with T2DM. The study will provide insights into the dynamic, adaptive changes in energy balance, total, regional, and organ-specific fat mass along with insulin sensitivity in multiorgan. In DELIVER trial, dapagliflozin has not only improved the cardiovascular events across the different categories of BMI (HR, 95% CI: normal weight: 0.89, 0.69–1.15; overweight: 0.87, 0.70–1.08; obesity grade 1: 0.74, 0.58–0.93; grade 2: 0.78, 0.57–1.08, and grade 3: 0.72, 0.47–1.08, $p_{\text{interaction}} = 0.82$) but also it resulted into promising effect on symptom relief in obese patients as compared to without obese patients along with benefit of weight loss [60]. In addition, a recent trial conducted at 386 sites in 21 countries has also shown significant effects of dapagliflozin among all BMI categories (HR, 95% CI: normal: 0.60, 0.43–0.85; overweight: 0.55, 0.40–0.75; obesity grade I: 0.71, 0.49–1.04; grade II/III: 0.57, 0.37–0.87; $p_{interaction} = 0.72$) [61].

A recent study on obese nondiabetic mice documented that canagliflozin reduced adiposity, and improved glucose tolerance despite a reduction of plasma insulin, increased plasma ketones, and improved plasma lipid profiles [62]. Similarly, another study on mice demonstrated that empagliflozin enhanced metabolism and attenuated inflammation and insulin resistance in high-fat diet-induced obese mice [63].

Hypertension

Hypertension is considered as both a cause and an effect of CKD [64]. Lowering the BP can slow the rate of eGFR decline that delays the progression to ESKD [65]. In a phase-3 study that enrolled patients from 16 countries, the systolic blood pressure (SBP) was significantly reduced in patients administered with dapagliflozin (−11.90 mm Hg) as compared with placebo group (−7.62 mm Hg; $p = 0.0002$) [66]. Another prospective study demonstrated that dapagliflozin treatment for 3 months was significantly associated with reduced 24-h SBP ($p = 0.02$) and reduced daytime SBP ($p = 0.009$). These associations may be related to the drug's effect of increasing 24-h urinary uric acid excretion [67]. The effect of empagliflozin to reduce blood pressure in nondiabetic Ren-2 transgenic rats (TGR) was observed in a study by Hojna et al. [68]. Moreover, a most recent DELIVER trial has shown decreased SBP in 1 month by 1.8 (95% CI: 1.1–2.5) mm Hg as compared to placebo [69].

Dyslipidemia

Few studies revealed the beneficial effects of SGLT2i on increasing high-density lipoprotein cholesterol (HDL-c) levels, thereby regulating dyslipidemia. A post hoc analysis evaluated the effect of dapagliflozin on lipid in patients with and without increased triglyceride and reduced HDL-c levels. A statistically significant increase in HDL-c levels in both lipid groups was seen [70]. Jojima et al. [71] recently reported a randomized, active-controlled, open-label trial including 51 patients. A significantly higher HDL-c, but not low-density lipoprotein (LDL-c), was observed in those receiving empagliflozin between baseline and 12 weeks (54.4 ± 16.3 vs. 58.8 ± 19.6 mg/dL; $p = 0.0006$).

Hyperuricemia

Few studies have reported that elevated serum uric acid independently predicts the development of CKD, and by increasing the levels of uric acid in rats, kidney disease may be induced due to tubulointerstitial fibrosis and glomerular injury [72]. Furthermore, pilot studies indicate that the progression of CKD may be slowed by decreasing plasma uric acid concentrations [72]. The QUARTZ placebo-controlled, randomized study demonstrated that the addition of dapagliflozin to verinurad and febuxostat reduces serum uric acid in patients with asymptomatic hyperuricemia (mean treatment difference −62.3 μmol/L, 95% CI: −82.8 to −41.8) [73]. In a prospective pilot trial, the effects of short-term therapy with dapagliflozin on serum and urinary uric acid were evaluated in patients with T2DM. The serum uric acid levels decreased from 347.75 ± 7.75 μmol/L before treatment to 273.25 ± 43.18 μmol/L after treatment ($p = 0.001$). A meta-analysis of controlled trials indicated that SGLT2i decreased serum uric acid in T2DM and compared with placebo or other active comparators suggested no effects of SGLT2i on the risk of nephrolithiasis [74].

Hyperkalemia

Hyperkalemia is one of the major metabolic complications that frequently occur in CKD [75, 76]. Imbalance of potassium limits the use of renin-angiotensin-

aldosterone inhibitors [77–79] and thus, associated with increase in mortality rate in CKD [76, 80]. Approximately, 2–35% of patients with CKD suffer from incidence of hyperkalemia, which is dependent on GFR [81]. Thus, balancing the potassium levels in patients with CKD becomes challenging.

The studies have shown promising effects of SGLT2i on hyperkalemia without increasing risk of hypokalemia. For instance, CREDENCE trial have shown significant reduction in potassium incidence (HR = 0.77, 95% CI: 0.61–0.98, $p = 0.031$) when treated with canagliflozin in patients with diabetes and CKD [82]. Recently, Neuen et al. [83] have conducted meta-analysis comprising 5 clinical studies, showing the significant effect of SGLT2i on hyperkalemia. The study had shown that SGLT2i not only reduces the serious hyperkalemia (HR = 0.84, 95% CI: 0.76–0.93, $p_{\text{heterogeneity}} = 0.71$) but also incidence of hyperkalemia (HR = 0.80, 95% CI: 0.68–0.93, $p_{\text{heterogeneity}} = 0.21$) in patients with diabetes at high cardiovascular risk or with CKD. However, the role of SGLT2i on hyperkalemia in nondiabetic CKD patients remains to be investigated for developing new strategies to avoid risk of mortality.

Effects of SGLT2i on Surrogate Endpoints of CKD Progression

Although ESKD is the most commonly used clinical endpoint in randomized controlled trials (RCT), it is a fairly late event in the progression course of CKD hampering the feasibility of clinical trials in CKD. Hence, the clinical value of using surrogate endpoints is high, and it is important to understand how SGLT2i affects surrogate endpoints of CKD progression.

Urinary Protein Excretion: Albuminuria

Various trials have validated the benefits of SGLT2i in reducing albuminuria in patients with T2DM. Of the 7,208 patients included in the EMPA-REG outcome, baseline UACR data were available for 6,953 patients. The urinary albumin-creatinine ratios UACR levels were reduced by 7% in the normoalbuminuria group, 25% in the microalbuminuria group, and 32% in the macroalbuminuria group, after 12 weeks of treatment and these reductions were maintained after a median follow-up of 3.1 years. The post hoc analysis from the CANVAS program revealed that canagliflozin lowered albuminuria levels more effectively with higher reductions in those having moderately to severely increased albuminuria levels ($p_{\text{heterogeneity}} < 0.001$). After week 13, canagliflozin slowed the annual loss of kidney function across albuminuria subgroups [84]. In the DELIGHT study [85], the albuminuria-lowering effect of dapagliflozin as monotherapy and in concomitant with saxagliptin was studied. Compared with placebo, dapagliflozin and dapagliflozin-saxagliptin reduced UACR throughout the study period. At week 24, the difference (vs. placebo) in the mean UACR change from baseline was −21.0% (95% CI: −34.1 to −5.2; $p = 0.011$) for dapagliflozin and −38.0% (−48.2 to −25.8; $p < 0.0001$) for dapagliflozin-saxagliptin. Another post hoc analysis characterized the effect of dapagliflozin on albuminuria and eGFR. It was demonstrated that T2DM hypertensive patients receiving dapagliflozin exhibited greater 12-week reductions in albuminuria as compared with placebo (−33.2%, 95% CI: −45.4, −18.2). This reduction in albuminuria was sustained even after adjusting for changes in SBP, body weight, HbA1c, and eGFR, suggesting the beneficial effect of dapagliflozin in reducing long-term renal risks [11]. Yet another small, randomized, crossover trial including 33 patients treated with dapagliflozin demonstrated significant reductions in urinary albumin excretion rate when given as an adjunct to ACEi or angiostatin receptor blocker [86].

A prespecified analysis from the DAPA-CKD trial is the first to demonstrate that dapagliflozin significantly reduced albuminuria in patients with or without T2DM. As compared with placebo, treatment with dapagliflozin resulted in a geometric mean percentage change of −14.8% (−22.9 to −5.9; $p = 0.0016$) in patients without T2DM over the follow-up visits ($p_{\text{interaction}} < 0.0001$) [87]. Further, urine albumin-creatinine ratio decreased in dapagliflozin group as compared to placebo in patients without diabetes and with baseline A2 or A3 stage albuminuria (16% reduction, 95% CI: 221–42 vs. 15%, 95% CI: 5–23; $p_{\text{interaction}} = 0.36$, respectively) indicating renal-protecting effects of dapagliflozin [88].

In a recent prospective study, 42 patients with increased albuminuria (30–300-mg/g creatinine) were included, of which 24 patients had nondiabetic CKD. Interestingly, the study observed a significant reduction of albuminuria after receiving empagliflozin, only in nondiabetic patients with CKD ($p = 0.01$) as compared with those with diabetic CKD [89].

Estimated Glomerular Filtration Rate

In 2020, new well-designed RCTs evaluating SGLT2i in patients with or without T2DM reported beneficial effects in slowing the kidney function decline. A prespecified analysis from the EMPEROR-reduced trial indicated a reduction in the decline of the eGFR slope by 1.11 (0.23–1.98) mL/min/1.73 m^2/year in patients with CKD and by 2.41 (1.49–3.32) mL/min/1.73 m^2/year in patients

without CKD. Furthermore, EMPIRE-HF Renal was a prespecified analysis of renal outcomes of the randomized EMPIRE-HF trial. The double-blinded study revealed that patients administered with 10-mg empagliflozin treatment had significant reductions in measured GFR (−7.5 mL/min, −11.2 to −3.8; $p = 0.00010$) compared with placebo [42]. In addition, the EMPEROR-Preserved trial showed the benefit of renal surrogate outcome: 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 m^2/year; $p < 0.001$) [41].

The effect of dapagliflozin on eGFR was evaluated in the DIAMOND trial [35]. The results revealed that median GFR was changed after 6 weeks of dapagliflozin treatment by −6.6 mL/min/1.73 m^2 (−9.0 to −4.2; $p < 0.0001$) as compared with placebo. Interestingly, this reduction was completely reversed within 6 weeks after dapagliflozin was discontinued. In spite of the reduction in intraglomerular pressure, no effect on proteinuria was observed from the baseline (0.9%, $p = 0.093$). Hence, the effect of SGLT2i on reduction in proteinuria may not be associated with hemodynamic mechanisms. In addition, the DAPA-CKD trial reported that administration of 10-mg dapagliflozin reduces the risk of sustained 50% decline in eGFR, kidney failure, or death due to cardiovascular or kidney disease by 44% in people with CKD (eGFR 25–75 mL/min/1.73 m^2). Patients without T2DM in the dapagliflozin group had an eGFR decline of 2.01 mL/min/1.73 m^2 between baseline and week 2, and the decline of the total eGFR slope was 0.46 mL/min/1.73 m^2/year between baseline and end of treatment [90]. Among the patients in the DAPA-CKD trial, those randomized to the dapagliflozin group underwent a 27% (95% CI: −2–47%) reduction in the primary composite endpoint (time to ≥50% sustained decline in eGFR, ESKD, or kidney or cardiovascular death) as compared with the placebo. The eGFR slope was significantly reduced in the dapagliflozin group as compared with the placebo (2.15 vs. 3.38 mL/min/1.73 m^2/year; $p = 0.005$) [91]. A recent, DAPA-CKD trial showed reduction in eGFR from baseline to 2 weeks (−1.58 mL/min per 1.73 m^2 per year, $p_{interaction} = 0.05$) which is not associated with CKD progression [92]. In addition, a prespecified analysis of DELIVER trial have shown uninfluenced baseline eGFR (eGFR ≥60 mL/min/1.73 m^2: HR: 0.84; 95% CI: 0.70–1.00; eGFR 45–<60 mL/min/1.73 m^2: HR: 0.68; 95% CI: 0.54–0.87; eGFR <45 mL/min/1.73 m^2: HR: 0.93; 95% CI: 0.76–1.14; p for interaction = 0.16) with the treatment of dapagliflozin on cardiovascular death or worsening HF in patients with HF and a mildly reduced or preserved ejection fraction (HFmrEF) [93].

Role of SGLT2i in Eliminating Further CKD Complications

Cardiovascular Diseases

Patients with CKD are 5–10 times more likely to die prematurely due to other complications than they are to progress to ESKD [94]. This increased risk of death greatly rises as kidney function progressively worsens and is characterized by death from cardiovascular diseases.

The DAPA-HF trial [38] enrolled patients with New York Heart Association classification II to IV. The trial revealed the superiority of dapagliflozin in preventing HF events and cardiovascular deaths as compared with the placebo group (HR = 0.74, 95% CI: 0.65–0.85; $p < 0.001$). An exploratory analysis from the DAPA-HF trial indicated that a significantly lower number of patients had an episode of worsened HF or cardiovascular death in the dapagliflozin group as compared with those in the placebo group (13.2% vs. 17.7%, HR = 0.73, 95% CI: 0.60–0.88), and this was not influenced by the presence or absence of diabetes ($p_{interaction} = 0.80$) and age of patient ($p_{interaction} = 0.76$) [95]. Similarly, a prespecified subgroup analysis of patients enrolled in the EMPEROR-reduced trial evaluated the effect of empagliflozin on cardiovascular outcomes in diabetic and nondiabetic patients, and whether the magnitude of SLGT2i benefits on HF is affected by the glycemic status. Among patients without diabetes, the study revealed that the risk of cardiovascular death or HF hospitalization was reduced in those in the empagliflozin group than in the placebo group (HR = 0.78, 95% CI: 0.64–0.97). Like dapagliflozin, the effects of empagliflozin on cardiovascular outcomes were not influenced by the patients' glycemic status ($p_{interaction} = 0.57$).

The EMPEROR-Preserved trial enrolled patients with class II–IV HF and ejection fraction of >40%. A significant decline in the risk of cardiovascular death or hospitalization due to HF was observed over a median of 26.2 months (HR = 0.79, 95% CI: 0.69–0.90, $p < 0.001$). The risk was largely associated with lower hospitalization risk for HF in patients receiving empagliflozin, and the effects of this SGLT2i drug were similar in patients with or without diabetes [41]. The EMPA-TROPISM trial assessed the effect of empagliflozin on left ventricular (LV) function and volumes and functional capacity exclusively in patients without diabetes. A significant decline of LV end-diastolic volume was observed in the empagliflozin group (−25.1 ± 26.0 mL) as compared with the placebo (1.5 ± 25.4 mL, $p < 0.001$), and LV end-systolic volume (−26.6 ± 20.5 mL vs. −0.5 ± 21.9 mL for empagliflozin vs. placebo; $p < 0.001$). The LV mass was

also reduced significantly more in patients receiving empagliflozin (−17.8 ± 31.9 g) as compared with the placebo (4.1 ± 13.4 g, $p < 0.001$), and improvements in LV ejection fraction (6.0 ± 4.2 vs. −0.1 ± 3.9 for empagliflozin vs. placebo, respectively; $p < 0.001$). This trial strongly supported the role of SGLT2i in the treatment of non-diabetic patients with HF with a reduced ejection fraction [36].

The DAPA-MEMRI trial is a double-blinded, placebo-controlled, ongoing trial that will assess the effect of dapagliflozin in myocardial calcium handling in patients with HF, regardless of their diabetes status. Results of this trial are eagerly awaited, as it will provide deeper insights into the mechanisms of action of SGLT2i in HF in even nondiabetic patients, which will facilitate tailor-specific treatments for patients with HF [43]. Another recently published DELIVER study have examined the use of dapagliflozin in patients with HF and reduced ejection fraction. The results implicated that dapagliflozin has reduced the risk of worsening HF (HR: 0.79; 95% CI: 0.69–0.91) or cardiovascular death (HR: 0.88; 95% CI: 0.74–1.05) by 22% and 18% with and without recent hospitalized patients with HFmrEF, respectively, regardless of baseline NT-proBNP [34, 96, 97]. Further, the treatment with dapagliflozin showed consistent results irrespective of atrial fibrillation status of patients [98]. It had also investigated the time to first occurrence of cardiovascular death or worsening HF (13 days, HR: 0.45; 95% CI: 0.20–0.99; $p = 0.046$) in patients with HFmrEF and HR for frailty patients with HFmrEF was observed as frailty class 1–3; 0.85 (95% CI: 0.68–1.06), 0.89 (0.74–1.08), and 0.74 (0.61–0.91), respectively ($p_{\text{interaction}} = 0.40$), indicating early, sustained and consistent decrease in events along with delay in event free survival by 2–2.5 years [99–102]. Furthermore, addition of MRAs in DELIVER trial has not affected the efficacy and safety of dapagliflozin for primary outcomes including composite worsening HF or cardiovascular death (0.86, 95% CI: 0.74–1.01, for MRA nonusers vs. 0.76, 95% CI: 0.64–0.91, for MRA users; $p_{\text{interaction}} = 0.30$) in patients with HFmrEF [103]. Moreover, a recent meta-analysis by Vaduganathan et al. [104] has also suggested promising effects of SGLT2 inhibitors in reducing the risk of composite cardiovascular death or hospitalization for HF (0.77, 95% CI: 0.72–0.82), cardiovascular death (0.87, 95% CI: 0.79–0.95), first hospitalization for HF (0.72, 95% CI: 0.67–0.78), and all-cause mortality (0.92, 95% CI: 0.86–0.99). The results of these trials have complemented previous and ongoing trials evaluating the potential benefits of SGLT2i in cardiovascular diseases [105].

Acute Kidney Injury

Previous studies have shown that CKD is one of the risk factors for acute kidney injury (AKI) due to reduced eGFR and increased proteinuria levels in both [106]. Thus, it is important to study effects of SGLT2i on AKI. Contrary to the initial warning published by the FDA suggesting the risk of AKI in patients administered with SGLT2i [107], a meta-analysis by Menne et al. [108] reported that SGLT2i reduced the odds of AKI with and without hospitalization in both RCTs and real-world settings. In 30 trials, administration of SGLT2i reduced the risk of suffering from AKI by 36% (OR = 0.64, 95% CI: 0.53–0.78, $p < 0.001$). In total, 1089 AKI events of any severity were published in 41 trials (OR = 0.75, 95% CI: 0.66–0.84, $p < 0.001$). An analysis from the real-world observational setting reported a total of 777 AKI events, where the odds of AKI were reduced in patients administered with SGLT2i (OR = 0.40, 95% CI: 0.33–0.48, $p < 0.001$) [108].

A prespecified analysis from DAPA-CKD trial indicated lesser AKI-related serious adverse events in the dapagliflozin group (2.5%) compared with the placebo group (3.2%; HR = 0.77, 95% CI: 0.54–1.10, $p = 0.15$); incidence rate difference 0.35 (95% CI: −0.14–0.86). The study further revealed that dapagliflozin was superior in lowering the risk of an abrupt decline in kidney function, supporting the favorable benefit-risk profile of SGLT2i [109].

In addition, a most recent meta-analysis by Baigent et al. [32], consisting of 13 trials, has shown reduction of 23% (overall relative risk [RR]: 0.77, 95% CI: 0.70–0·84) in the risk of AKI in SGLT2i group as compared to placebo. Interestingly, the similar results were observed in patients without diabetes (RR: 0.6, 0.54–0·81) and with diabetes (RR: 0.79, 0.72–0·88; $p_{\text{heterogeneity}} = 0.12$) [32]. These results indicate that mechanism of SGLT2i on AKI is not influenced by diabetes status of patient.

Anemia

The pragmatic effects of SGLT2i on anemia were observed in 2 independent trials. In the first, the effect of dapagliflozin on the correction of anemia in patients with HF and reduced ejection fraction enrolled in the DAPA-HF was evaluated. Anemia was corrected in 62.2% of the patients in the dapagliflozin group as compared with 41.1% in the placebo group. Dapagliflozin reduced the occurrence of primary composite endpoint (worsening of HF or cardiovascular death) in anemic (HR = 0.68, 95% CI: 0.52–0.88) and non-anemic (HR = 0.76, 95% CI: 0.65–0.89) patients ($p_{\text{interaction}} = 0.44$) [110]. The second trial evaluated the impact of empagliflozin on hematocrit and anemia in a post hoc analysis of the EMPEROR-Reduced trial. Patients receiving empagliflozin experienced an immediate (from

week 4) increase in hematocrit and hemoglobin levels and reduced the rates of new-onset anemia throughout the follow-up (22.6% in placebo vs. 12.3% in empagliflozin; HR = 0.49, 95% CI: 0.41–0.59; $p < 0.001$) [111].

Safety of SGLT2i in Nondiabetic Patients with CKD

The outcome data of SGLT2i have been reported as subgroup analysis in 3 clinical trials according to diabetes status. Since neither of these independent subgroup analyses was substantially powered to assess the effects of SGLT2i in nondiabetic patients, a meta-analysis was performed by Li et al. [112] that incorporated the subgroup data from 3 trials (DAPA-CKD, EMPEROR-Reduced, and DAPA-HF) involving patients without T2DM to assess the safety of SGLT2i. The meta-analysis evaluated 8 safety endpoints. Overall, the meta-analysis reported that the administration of SGLT2i significantly lowered the risk of any serious adverse events (RR = 0.90, 95% CI: 0.84–0.96) and kidney adverse events (RR = 0.82, 95% CI: 0.68–0.99), as compared with placebo.

Hypoglycemia

Hypoglycemia is one adverse reaction reported clinically with SGLT2i, as it renders glucose-lowering effect by stimulating glycosuria via inhibition of glucose reuptake in the proximal tubule. The quantity of glucose filtered by the glomerulus and available for excretion with SGLT2 inhibition is related to the plasma levels of glucose. Because the plasma glucose-lowering effect with SGLT2i is self-limiting, hypoglycemia is uncommon in patients treated with SGLT2i, unless coadministered with insulin and insulin secretagogues (e.g., sulfonylureas and glinides). Hence, since nondiabetic patients may not administer glucose-lowering drugs, hypoglycemia should not be a matter of concern for them. This hypothesis is supported by the outcome data of 12,903 patients without diabetes included in 5 large clinical studies: DAPA-CKD, EMPA-KIDNEY, DELIVER, DAPA-HF, and EMPEROR-Reduced trial, in which no incidence of severe hypoglycemia was reported [10, 112]. Results from the DIAMOND trial showed no hypoglycemic event in nondiabetic patients [35].

Ketoacidosis

Recent cross-sectional, multicenter, retrospective study had shown prevalence of ketoacidosis in diabetic patients who underwent treatment of SGLT2i. The study consisted of total 9,940 patients, among them, the prevalence of diabetic ketoacidosis (DKA), euglycemic DKA (EuDKA), and hyperglycemic DKA (hDKA) was observed as 0.43%, 0.21%, and 0.23%, respectively, in patient treated with dapagliflozin (n = 7,280). With empagliflozin (n = 2,626), the prevalence for DKA, EuDKA, and hDKA was 0.34%, 0.26%, and 0.08%, respectively, while with canagliflozin, total DKA, and EuDKA was 0.21% [113]. Further, another most recent meta-analysis by Baigent et al. [32] 2022 had showed low risk of ketoacidosis in patients with diabetes (0.2 events/1,000 patients years) in placebo, while the RR for ketoacidosis in SGLT2i group was 2.12 (95% CI: 1.49–3.04) as compared to placebo in patients with diabetes. Interestingly, only 1 event of ketoacidosis was observed in patients without diabetes and treated with SGLT2i (n = 30,000 for follow-up) [32]. In addition, there were no reports of ketoacidosis in DAPA-CKD, EMPA-KIDNEY, DELIVER, DAPA-HF, and EMPEROR-Reduced trials [11, 33, 34, 38, 40]. However, more prospective studies are warranted to confirm these results.

Urinary Tract Infections

Since SGLT2i reduce blood glucose by stimulating glucosuria, the risk of urinary tract infections (UTIs) is a major concern in patients with diabetes. Nevertheless, since SGLT2i improves outcomes in patients with CKD, nondiabetic patients may be at a lower risk of developing UTIs. The EMPEROR-Reduced trial showed no significant imbalances in developing UTI events among nondiabetic patients who received empagliflozin (4.2%) compared with placebo (3.6%; $p > 0.05$) [41]. A pooled analysis by Borovac et al. [114] combined safety endpoints from 5 landmark RCTs. These trials examined the use of dapagliflozin, empagliflozin, and sotagliflozin. The analysis reported that the risk of UTI events was similar in patients receiving SGLT2i as compared with placebo (RR: 1.09; 95% CI: 0.94–1.26; $p = 0.24$) and was based on low degree of heterogeneity ($I^2 = 25\%$, $p = 0.25$).

Bone Fractures

Bone mineral losses after SGLT2i administration may result from disturbed calcium-phosphate homeostasis, and may indirectly increase bone turnover by weight loss [115]. Combined data of nondiabetic patients from 3 RCTS (EMPEROR-Reduced, DAPA-HF, and DAPA-CKD) indicated that SGLT2i did not have a significant effect on the risk of study discontinuation due to fracture (RR = 1.23, 95% CI: 0.87–1.72) [112]. On the contrary, the CANVAS trial reported an increase in non-vertebral fractures (HR = 1.56; 95% CI: 1.18–2.06) upon administration of canagliflozin, but this was not confirmed in the sub-study CANVAS-R (HR = 0.76; 95% CI: 0.52–1.12) [116]. This may be due to baseline heterogeneity between the CANVAS trials, and DAPA and EMPEROR trials. Importantly, the CANVAS trial included all patients with T2DM, who are at a higher risk of developing bone fractures.

Conclusion

In conclusion, large well-designed RCTs reveal that along with efficient glycemic control, SGLT2i agents also slow the progression of CKD in patients with or without diabetes. Patients with CKD may not only directly benefit from SGLT2i agents (by improving renal functions) but also indirectly, by targeting other risk factors of CKD progression and mitigating CKD complications (including cardiovascular outcomes and anemia). Approval of dapagliflozin by the FDA was a key milestone in incorporating SGLT2i into clinical practice. The need for renal replacement therapy could be eased by SGLT2i therapy, especially in low- and middle-income countries. Promising results from ongoing clinical trials will guide clinicians in initiating SGLT2i in those with nondiabetic CKD. Furthermore, in the trials reported recently, SGLT2i appear to be much safer than those conducted initially, which may be due to better physician handling of SGLT2i and concomitant drug prescription. Hence, the entire therapeutic approach to CKD may need to be reevaluated based on the evidence-based benefits of SGLT2i reported herein. It may be necessary to update the current guidelines to include SGLT2i as a first-line therapy for the causes of CKD that are tested in the DAPA-CKD trial and EMPA-KIDNEY trial. It is worth mentioning that although these clinical trials were sufficiently powered, they did not include patients with recent immune disorders and polycystic kidney diseases. Therefore, SGLT2i use in such patients is unexplored. Moreover, only 6% of Blacks have been represented in SGLT2i trials [5]. Since they are at a greater risk of developing ESKD, future studies need to be more inclusive of these ethnic populations.

Acknowledgments

The medical writing support was provided by Fatemah Bensaheb, Dr. Priyanka Bhosale, and Dr. Amit Bhat (Indegene Pvt Ltd, Bengaluru, India, funding supported by Clinical Research Foundation of Zhejiang Medical Association (2018ZYC-A12) and Chinese Society of Nephrology).

Statement of Ethics

This was a review of the published literature; no ethical approval was required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by Clinical Research Foundation of Zhejiang Medical Association (2018ZYC-A12) and Chinese Society of Nephrology (Grant No. 18020040783).

Author Contributions

Junhao Lv and Luying Guo were contributed to formulating the concept underlying this article, the identification and interpretation of appropriate data sources, and drafting of the article. Rending Wang and Jianghua Chen were involved in critical revision and approval of the final version for submission.

Data Availability Statement

All data presented has been published previously as cited, and no new data were generated for this manuscript.

References

1 Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019;322(13):1294–304.
2 Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease: a systematic review and meta-analysis. PLoS One. 2016;11(7):e0158765.
3 Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16(5):269–88.
4 Oh YJ, Kim SM, Shin BC, Kim HL, Chung JH, Kim AJ, et al. The impact of renin-angiotensin system blockade on renal outcomes and mortality in pre-dialysis patients with advanced chronic kidney disease. PLoS One. 2017;12(1):e0170874.
5 Jafar TH. FDA approval of dapagliflozin for chronic kidney disease: a remarkable achievement? Lancet. 2021;398(10297):283–4.
6 Kawanami D, Matoba K, Takeda Y, Nagai Y, Akamine T, Yokota T, et al. SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. Int J Mol Sci. 2017;18(5):1083.
7 Chin KL, Ofori-Asenso R, Hopper I, von Lueder TG, Reid CM, Zoungas S, et al. Potential mechanisms underlying the cardiovascular benefits of sodium glucose cotransporter 2 inhibitors: a systematic review of data from preclinical studies. Cardiovasc Res. 2019;115(2):266–76.
8 Brunton SA. The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. Int J Clin Pract. 2015;69(10):1071–87.
9 Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017;24(1):73–9.
10 Staplin N, Roddick AJ, Emberson J, Reith C, Riding A, Wonnacott A, et al. Net effects of sodium-glucose co-transporter-2 inhibition in different patient groups: a meta-analysis of large placebo-controlled randomized trials. EClinicalMedicine. 2021;41:101163.
11 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.

12 Farxiga (dapagliflozin) dosing, indications, interactions, adverse effects, and more. (2021, May 11). Retrieved September 22, 2021, from: https://reference.medscape.com/drug/farxiga-dapagliflozin-999899.
13 KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf.
14 Kalantar-Zadeh K, Li PK. Strategies to prevent kidney disease and its progression. Nat Rev Nephrol. 2020;16(3):129–30.
15 Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol. 2012;8(5):293–300.
16 Sen T, Heerspink HJL. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. Cell Metab. 2021;33(4):732–9.
17 Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-nephron glomerular filtration rate in healthy adults. N Engl J Med. 2017;376(24):2349–57.
18 Lim BJ, Yang JW, Zou J, Zhong J, Matsusaka T, Pastan I, et al. Tubulointerstitial fibrosis can sensitize the kidney to subsequent glomerular injury. Kidney Int. 2017;92(6):1395–403.
19 Mima A. Sodium-glucose cotransporter 2 inhibitors in patients with non-diabetic chronic kidney disease. Adv Ther. 2021;38(5):2201–12.
20 O'Neill J, Fasching A, Pihl L, Patinha D, Franzén S, Palm F. Acute SGLT inhibition normalizes O2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol. 2015;309(3):F227–34.
21 Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol. 2012;302(1):R75–83.
22 Layton AT, Vallon V. SGLT2 inhibition in a kidney with reduced nephron number: modeling and analysis of solute transport and metabolism. Am J Physiol Renal Physiol. 2018;314(5):F969–84.
23 Cherney DZI, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587–97.
24 Yale J-F, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15(5):463–73.
25 Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. Cardiovasc Diabetol. 2020;19(1):98.
26 Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG outcome study? A unifying hypothesis. Diabetes Care. 2016;39(7):1115–22.
27 Rajasekeran H, Cherney DZ, Lovshin JA. Do effects of sodium–glucose cotransporter-2 inhibitors in patients with diabetes give insight into potential use in non-diabetic kidney disease? Curr Opin Nephrol Hypertens. 2017;26(5):358–67.
28 Abdul-Ghani MA, DeFronzo RA, Norton L. Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30–50% of filtered glucose load in humans. Diabetes. 2013;62(10):3324–8.
29 Mima A. Renal protection by sodium-glucose cotransporter 2 inhibitors and its underlying mechanisms in diabetic kidney disease. J Diabetes Complications. 2018;32(7):720–5.
30 Refardt J, Imber C, Sailer CO, Jeanloz N, Potasso L, Kutz A, et al. A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. J Am Soc Nephrol. 2020;31(3):615–24.
31 Cefalu WT, Stenlöf K, Leiter LA, Wilding JPH, Blonde L, Polidori D, et al. Effects of canagliflozin on body weight and relationship to HbA1c and blood pressure changes in patients with type 2 diabetes. Diabetologia. 2015;58(6):1183–7.
32 Baigent C, Emberson J, Haynes R, Herrington WG, Judge P, Landray MJ, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022;400(10365):1788–801.
33 The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–27.
34 Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–98.
35 Cherney DZI, Dekkers CCJ, Barbour SJ, Cattran D, Abdul Gafor AH, Greasley PJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. Lancet Diabetes Endocrinol. 2020;8(7):582–93.
36 Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2021;77(3):243–55.
37 Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020;22(4):713–22.
38 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
39 Zannad F, Ferreira JP, Pocock SJ, Zeller C, Anker SD, Butler J, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-reduced. Circulation. 2021;143(4):310–21.
40 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.
41 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
42 Jensen J, Omar M, Kistorp C, Tuxen C, Gustafsson I, Køber L, et al. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2021;9(2):106–16.
43 University of Edinburgh. An observational cross-sectional study and a double-blind placebo controlled randomised controlled trial to assess the effect of dapagliflozin on myocardial calcium-handling in patients with heart failure- the DAPA-MEMRI trial. Bethesda, Clinicaltrials.gov; 2020.
44 Wheeler DC, Stefánsson BV, Jongs N, Chertow GM, Greene T, Hou FF, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(1):22–31.
45 McMurray JJV, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, et al. Effects of dapagliflozin in patients with kidney disease, with and without heart failure. JACC Heart Fail. 2021;9(11):807–20.
46 Persson F, Rossing P, Vart P, Chertow GM, Hou FF, Jongs N, et al. Efficacy and safety of dapagliflozin by baseline glycemic status: a prespecified analysis from the DAPA-CKD trial. Diabetes Care. 2021;44(8):1894–7.
47 Heerspink HJL, Sjöström CD, Jongs N, Chertow GM, Kosiborod M, Hou FF, et al. Effects of dapagliflozin on mortality in patients with chronic kidney disease: a pre-specified analysis from the DAPA-CKD randomized controlled trial. Eur Heart J. 2021;42(13):1216–27.
48 Wheeler DC, Toto RD, Stefánsson BV, Jongs N, Chertow GM, Greene T, et al. A prespecified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. Kidney Int. 2021;100(1):215–24.
49 Wheeler DC, Jongs N, Stefansson BV, Chertow GM, Greene T, Hou FF, et al. Safety and efficacy of dapagliflozin in patients with focal segmental glomerulosclerosis: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial. Nephrol Dial Transpl. 2022;37(9):1647–56.

50 Waijer SW, Vart P, Cherney DZI, Chertow GM, Jongs N, Langkilde AM, et al. Effect of dapagliflozin on kidney and cardiovascular outcomes by baseline KDIGO risk categories: a post hoc analysis of the DAPA-CKD trial. Diabetologia. 2022;65(7):1085–97.
51 Provenzano M, Jongs N, Vart P, Stefánsson BV, Chertow GM, Langkilde AM, et al. The kidney protective effects of the sodium-glucose cotransporter-2 inhibitor, dapagliflozin, are present in patients with CKD treated with mineralocorticoid receptor antagonists. Kidney Int Rep. 2022;7(3):436–43.
52 Vart P, Correa-Rotter R, Hou FF, Jongs N, Chertow GM, Langkilde AM, et al. Efficacy and safety of dapagliflozin in patients with CKD across major geographic regions. Kidney Int Rep. 2022;7(4):699–707.
53 Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. Circulation. 2021;143(4):298–309.
54 Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the Emperor-reduced trial. Circulation. 2021;143(4):337–49.
55 Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819–29.
56 Yun H-R, Kim H, Park JT, Chang TI, Yoo T-H, Kang S-W, et al. Obesity, metabolic abnormality, and progression of CKD. Am J Kidney Dis. 2018;72(3):400–10.
57 Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16(2):159–69.
58 Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97(3):1020–31.
59 Brown E, Wilton MM, Sprung VS, Harrold JA, Halford JCG, Stancak A, et al. A randomised, controlled, double blind study to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW versus dapagliflozin alone in obese patients with type 2 diabetes mellitus (RESILIENT): study protocol. BMJ Open. 2021;11(7):e045663.
60 Adamson C, Kondo T, Jhund PS, de Boer RA, Cabrera Honorio JW, Claggett B, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. Eur Heart J. 2022;43(41):4406–17.
61 Chertow GM, Vart P, Jongs N, Langkilde AM, McMurray JJV, Correa-Rotter R, et al. Quételet (body mass) index and effects of dapagliflozin in chronic kidney disease. Diabetes Obes Metab. 2022;24(5):827–37.
62 Osataphan S, Macchi C, Singhal G, Chimene-Weiss J, Sales V, Kozuka C, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. JCI Insight. 2019;4(5):e123130.
63 Xu L, Nagata N, Nagashimada M, Zhuge F, Ni Y, Chen G, et al. SGLT2 inhibition by empagliflozin promotes fat utilization and browning and attenuates inflammation and insulin resistance by polarizing M2 macrophages in diet-induced obese mice. EBioMedicine. 2017;20:137–49.
64 Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis. 2010;55(3):441–51.
65 Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. J Am Soc Nephrol. 2017;28(9):2812–23.
66 Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2016;4(3):211–20.
67 Hao Z, Sun Y, Wen Y, Cui L, Li G, Liu Y. Effects and mechanisms of dapagliflozin treatment on ambulatory blood pressure in diabetic patients with hypertension. Med Sci Monit. 2020;26:e925987.
68 Hojná S, Rauchová H, Malínská H, Marková I, Hüttl M, Papoušek F, et al. Antihypertensive and metabolic effects of empagliflozin in Ren-2 transgenic rats, an experimental non-diabetic model of hypertension. Biomed Pharmacother. 2021;144:112246.
69 Selvaraj S, Vaduganathan M, Claggett BL, Miao ZM, Fang JC, Vardeny O, et al. Blood pressure and dapagliflozin in heart failure with mildly reduced or preserved ejection fraction: DELIVER. JACC Heart Fail. 2023;11(1):76–89.
70 Bays HE, Sartipy P, Xu J, Sjöström CD, Underberg JA. Dapagliflozin in patients with type II diabetes mellitus, with and without elevated triglyceride and reduced high-density lipoprotein cholesterol levels. J Clin Lipidol. 2017;11(2):450–8.e1.
71 Jojima T, Sakurai S, Wakamatsu S, Iijima T, Saito M, Tomaru T, et al. Empagliflozin increases plasma levels of campesterol, a marker of cholesterol absorption, in patients with type 2 diabetes: Association with a slight increase in high-density lipoprotein cholesterol. Int J Cardiol. 2021;331:243–8.
72 Johnson RJ, Nakagawa T, Jalal D, Sánchez-Lozada LG, Kang D-H, Ritz E. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transpl. 2013;28(9):2221–8.
73 Stack AG, Han D, Goldwater R, Johansson S, Dronamraju N, Oscarsson J, et al. Dapagliflozin added to verinurad plus febuxostat further reduces serum uric acid in hyperuricemia: the QUARTZ study. J Clin Endocrinol Metab. 2021;106(5):e2347–56.
74 Cosentino C, Dicembrini I, Nreu B, Mannucci E, Monami M. Nephrolithiasis and sodium-glucose co-transporter-2 (SGLT-2) inhibitors: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2019;155:107808.
75 Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. Nephron Clin Pract. 2012;120(1):c8–16.
76 Belmar Vega L, Galabia ER, Bada da Silva J, Bentanachs González M, Fernández Fresnedo G, Piñera Haces C, et al. Epidemiology of hyperkalemia in chronic kidney disease. Nefrologia. 2019;39(3):277–86.
77 Kovesdy CP. Epidemiology of hyperkalemia: an update. Kidney Int Suppl. 2016;6(1):3–6.
78 Hundemer GL, Talarico R, Tangri N, Leon SJ, Bota SE, Rhodes E, et al. Ambulatory treatments for RAAS inhibitor-related hyperkalemia and the 1-year risk of recurrence. Clin J Am Soc Nephrol. 2021;16(3):365–73.
79 Jun M, Jardine MJ, Perkovic V, Pilard Q, Billot L, Rodgers A, et al. Hyperkalemia and renin-angiotensin aldosterone system inhibitor therapy in chronic kidney disease: a general practice-based, observational study. PLoS One. 2019;14(3):e0213192.
80 Cowan ACJ, Gharib EG, Weir MA. Advances in the management of hyperkalemia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2017;26(3):235–9.
81 Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2019;32(4):499–516.
82 Neuen BL, Oshima M, Perkovic V, Agarwal R, Arnott C, Bakris G, et al. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. Eur Heart J. 2021;42(48):4891–901.

83 Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. Circulation. 2022;145(19):1460–70.
84 Neuen BL, Ohkuma T, Neal B, Matthews DR, de Zeeuw D, Mahaffey KW, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: data from the CANVAS program. JASN. 2019;30(11):2229–42.
85 Pollock C, Stefánsson B, Reyner D, Rossing P, Sjöström CD, Wheeler DC, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(6):429–41.
86 Petrykiv SI, Laverman GD, de Zeeuw D, Heerspink HJL. The albuminuria-lowering response to dapagliflozin is variable and reproducible among individual patients: PETRYKIV et al. Diabetes Obes Metab. 2017;19(10):1363–70.
87 Jongs N, Greene T, Chertow GM, McMurray JJV, Langkilde AM, Correa-Rotter R, et al. Effect of dapagliflozin on urinary albumin excretion in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(11):755–66.
88 Heerspink HJL, Chertow GM, Jongs N, Correa-Rotter R, Rossing P, Sjöström CD, et al. Effects of dapagliflozin in people without diabetes and with microalbuminuria. Clin J Am Soc Nephrol. 2022;17(11):1665–8.
89 Masajtis-Zagajewska A, Hołub T, Pęczek K, Makówka A, Nowicki M. Different effects of empagliflozin on markers of mineral-bone metabolism in diabetic and non-diabetic patients with stage 3 chronic kidney disease. Med Kaunas. 2021;57(12):1352.
90 Heerspink HJL, Jongs N, Chertow GM, Langkilde AM, McMurray JJV, Correa-Rotter R, et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021;9(11):743–54.
91 Chertow GM, Vart P, Jongs N, Toto RD, Gorriz JL, Hou FF, et al. Effects of dapagliflozin in stage 4 chronic kidney disease. J Am Soc Nephrol. 2021;32(9):2352–61.
92 Jongs N, Chertow GM, Greene T, McMurray JJV, Langkilde AM, Correa-Rotter R, et al. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. J Am Soc Nephrol. 2022;33(11):2094–107.
93 Mc Causland FR, Claggett BL, Vaduganathan M, Desai AS, Jhund P, de Boer RA, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the DELIVER randomized clinical trial. JAMA Cardiol. 2022:e224210.
94 Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238–52.
95 Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020;141(2):100–11.
96 Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, et al. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. J Am Coll Cardiol. 2022;80(14):1302–10.
97 Myhre PL, Vaduganathan M, Claggett BL, Miao ZM, Jhund PS, de Boer RA, et al. Influence of NT-proBNP on efficacy of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. JACC Heart Fail. 2022;10(12):902–13.
98 Butt JH, Kondo T, Jhund PS, Comin-Colet J, de Boer RA, Desai AS, et al. Atrial fibrillation and dapagliflozin efficacy in patients with preserved or mildly reduced ejection fraction. J Am Coll Cardiol. 2022;80(18):1705–17.
99 Vaduganathan M, Claggett BL, Jhund P, de Boer RA, Hernandez AF, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified secondary analysis of the Deliver randomized clinical trial. JAMA Cardiol. 2022;7(12):1259–63.
100 Vaduganathan M, Claggett BL, Jhund P, de Boer RA, Hernandez AF, Inzucchi SE, et al. Estimated long-term benefit of dapagliflozin in patients with heart failure. J Am Coll Cardiol. 2022;80(19):1775–84.
101 Butt JH, Jhund PS, Belohlávek J, de Boer RA, Chiang CE, Desai AS, et al. Efficacy and safety of dapagliflozin according to frailty in patients with heart failure: a prespecified analysis of the Deliver trial. Circulation. 2022;146(16):1210–24.
102 Ostrominski JW, Vaduganathan M, Claggett BL, de Boer RA, Desai AS, Dobreanu D, et al. Dapagliflozin and New York Heart Association functional class in heart failure with mildly reduced or preserved ejection fraction: the DELIVER trial. Eur J Heart Fail. 2022;24(10):1892–901.
103 Yang M, Butt JH, Kondo T, Jering KS, Docherty KF, Jhund PS, et al. Dapagliflozin in patients with heart failure with mildly reduced and preserved ejection fraction treated with a mineralocorticoid receptor antagonist or sacubitril/valsartan. Eur J Heart Fail. 2022;24(12):2307–19.
104 Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022;400(10354):757–67.
105 Williams DM, Evans M. Dapagliflozin for heart failure with preserved ejection fraction: will the DELIVER study deliver? Diabetes Ther. 2020;11(10):2207–19.
106 Hsu RK, Hsu C. The role of acute kidney injury in chronic kidney disease. Semin Nephrol. 2016;36(4):283–92.
107 Nadkarni GN, Ferrandino R, Chang A, Surapaneni A, Chauhan K, Poojary P, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care. 2017;40(11):1479–85.
108 Menne J, Dumann E, Haller H, Schmidt BMW. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: a systematic review and meta-analysis. PLoS Med. 2019;16(12):e1002983.
109 Heerspink HJL, Cherney D, Postmus D, Stefansson BV, Chertow GM, Dwyer JP, et al. A pre-specified analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial on the incidence of abrupt declines in kidney function. Kidney Int. 2022:101(1):174–84.
110 Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Køber L, et al. Effect of dapagliflozin on anaemia in DAPA-HF. Eur J Heart Fail. 2021;23(4):617–28.
111 Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, et al. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR- Reduced. Eur J Heart Fail. 2022;24(4):708–15; ejhf.2409.
112 Li LF, Ding LL, Zhan ZL, Qiu M. Meta-analysis on the safety and cardiorenal efficacy of SGLT2 inhibitors in patients without T2DM. Front Cardiovasc Med. 2021;8:690529.
113 Ata F, Yousaf Z, Khan AA, Razok A, Akram J, Ali EAH, et al. SGLT-2 inhibitors associated euglycemic and hyperglycemic DKA in a multicentric cohort. Sci Rep. 2021;11(1):10293.
114 Borovac JA, Kurir T, Mustapic I, Kumric M, Bozic J, Glavas D, et al. SGLT2 inhibitors and the risk of urinary tract infections in patients with heart failure: a pooled analysis examining safety endpoints. Kardiol Pol. 2022;80(2):198–201.
115 Ye Y, Zhao C, Liang J, Yang Y, Yu M, Qu X. Effect of sodium-glucose Co-transporter 2 inhibitors on bone metabolism and fracture risk. Front Pharmacol. 2018;9:1517.
116 Zhou Z, Jardine M, Perkovic V, Matthews DR, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and fracture risk in individuals with type 2 diabetes: results from the CANVAS Program. Diabetologia. 2019;62(10):1854–67.