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Emerging Horizons in Diabetic Kidney Disease: Role of Sodium-Glucose Cotransporter 2 Inhibitors

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Abstract

Diabetic kidney disease is the leading cause of kidney failure worldwide and places considerable burdens on health-care systems. The renoprotective effects of renin–angiotensin–aldosterone system (RAAS) inhibitors have been demonstrated in patients with diabetes, especially when the patient has hypertension. The major pharmacological action of sodium-glucose cotransporter 2 (SGLT2) inhibitor is inhibition of glucose reabsorption in the renal proximal tubule, thus enhancing urinary glucose excretion and reducing the glucose level. Landmark kidney outcome trials have demonstrated that apart from their glucose-lowering effect, SGLT2 inhibitors reduce the risk of development or worsening of albuminuria through a range of mechanisms in patients with or without diabetes who have albuminuria and declining renal function. These mechanisms include reduction of intraglomerular pressure through restoration of the tubuloglomerular feedback; reduction of glomerular hyperfiltration through decreased activation of the RAAS; improvement of tubular oxygenation and metabolism; protection against inflammation, oxidative stress, and fibrosis; and lowering of albuminuria and renal decongestion through a diuretic effect. Several cardiovascular outcome trials have discovered the potential renoprotective effects of these agents in patients with or without diabetes. This review analyzes the most recent findings from clinical trials and identifies the mechanisms through which SGLT2 inhibitors exert renoprotective effects in patients with type 2 diabetes and chronic kidney disease.

Key Words: Type 2 diabetes; diabetic kidney disease; sodium-glucose cotransporter 2 inhibitors; renin–angiotensin–aldosterone system inhibitors; mechanisms.

Introduction

Diabetic kidney disease (DKD) is a chronic progressive kidney disease affecting approximately 40% of patients with diabetes and is currently the leading cause of kidney failure worldwide[1]. DKD is characterized by persistent albuminuria and/or impaired glomerular filtration rate (GFR)[2]. The classic pathogenesis of DKD includes diverse structural changes, metabolic alterations, inflammatory processes, and hemodynamic abnormality, leading to a progressive decline in the GFR. DKD is a complex and multifactorial disease, and various

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contributing factors—including aging, obesity, hyperglycemia, dyslipidemia, smoking, hypertension, and other risk factors of chronic kidney disease (CKD)—have been identified[3]. Traditional therapies for DKD aim to reduce the effects of these risk factors. However, DKD pathophysiology has been increasingly investigated and considerable advances in treatment have been made in recent years. Although dialysis is a life-saving treatment, it does not improve quality of life and long-term survival in patients with DKD. Therefore, the main focus of DKD treatment has become preservation rather than replacement of renal function[4].

Studies that have compared the efficiency of specific glucose-lowering drugs with conventional treatment[5,6] or intensive blood-glucose therapy[7-9] in patients with type 2 diabetes (T2D) have consistently demonstrated that correction of hyperglycemia reduces the likelihood of microvascular complications, including DKD. Intensive glucose control was primarily associated with reduced risk of albuminuria but nonsignificantly associated with a reduction in the likelihood of renal endpoints such as end-stage renal disease (ESRD), renal death, and estimated GFR (eGFR) reduction[9]. Although management of the aforementioned risk factors may somewhat delay the progression of renal disease, until recently, renin–angiotensin–aldosterone system (RAAS) inhibitors, mainly angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, were the only drugs that had been shown to be modestly successful in delaying the development or progression of CKD in patients with T2D[10]. Despite the renoprotective potential of these drugs, there remains an unmet need for innovative treatment strategies for preventing, arresting, treating, and reversing DKD.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are novel antidiabetic drugs, reduce glucose levels by inhibiting glucose reabsorption in the renal proximal tubule, thus enhancing urinary glucose excretion. In addition to lowering plasma glucose levels, SGLT2 inhibitors exert renoprotective effects by modifying hemodynamics; maintaining metabolic homeostasis; increasing diuretic actions; and reducing oxidative stress (OS), the production of advanced glycation end-products (AGEs), and inflammation[11,12]. Recent randomized controlled trials (RCTs) of SGLT2 inhibitors have demonstrated their potential to surpass the benefits of RAAS inhibitors in patients with T2D and CKD[13]. Moreover, other emerging agents such as glucagon-like peptide 1 receptor agonists, endothelin-receptor antagonists (ERAs), and mineralocorticoid receptor antagonists (MRAs) offer new hope in terms of preserving renal function and reducing mortality in patients with T2D and CKD. Whether combinations of agents from different classes can have renoprotective effects in patients with T2D and CKD should be elucidated. This review summarizes evidence from the most recent trials and the underlying mechanisms through which SGLT2 inhibitors exert renoprotective effects in patients with T2D and CKD.

Clinical Trials of Renoprotective Effects of SGLT2 Inhibitors

Although SGLT2 inhibitors improve risk factors for kidney disease, the mechanism underlying their renal protection remains unclear.

Early cardiovascular (CV) outcome trials (CVOTs) investigating the effects of SGLT2 inhibitors on patients with T2D and high risk of cardiovascular disease (CVD)—such as the empagliflozin cardiovascular outcomes event trial in type 2 diabetes (EMPA-REG OUTCOME)[14], canagliflozin and cardiovascular and renal events in type 2 diabetes (CANVAS)[15], dapagliflozin and cardiovascular outcomes in type 2 diabetes (DECLARE-TIMI 58)[16], and cardiovascular outcomes with ertugliflozin in type 2 diabetes (VERTIS-CV)[17]—were designed to assess CV outcomes and included definite renal endpoints as secondary outcomes. All trials except

the VERTIS-CV trial revealed that SGLT2 inhibitors prevented the development of CKD and prevented or delayed the worsening of CKD in patients with T2D at any level of renal risk. In the VERTIS-CV trial, the renoprotective effect of ertugliflozin may have been underestimated because prespecified composite renal endpoints were assessed. However, in the prespecified exploratory composite outcome, doubling of serum creatinine level was replaced with a sustained 40% decrease in the eGFR from baseline, and the related finding indicated that ertugliflozin significantly preserved renal function and reduced composite renal outcomes (hazard ratio [HR] = 0.65; $p < 0.01$), consistent with the results of the other 3 SGLT2 inhibitor trials[18]. Moreover, ertugliflozin remarkably reduced the urine albumin-to-creatinine ratio (UACR) in patients with microalbuminuria or macroalbuminuria at baseline and preserved renal function in patients with the highest risk of DKD progression[18].

The aforementioned trials enrolled few patients with baseline nephropathy; however, a recent meta-analysis indicated that SGLT2 inhibitors had robust effects and prevented kidney-related adverse outcomes (HR = 0.62; $p = 0.09$)[19]. Another meta-analysis evaluated data from the 3 large CVOTs—EMPA-REG OUTCOME[14], CANVAS[15], DECLARE-TIMI 58[16]—and reported that SGLT2 inhibitors reduced the incidence of the composite endpoints (renal worsening, ESRD, and renal death) by 44% in patients with established atherosclerotic CVD (HR = 0.56; $p < 0.0001$) and by 46% in patients with multiple CV risk factors (HR = 0.54; $p < 0.0001$)[20].

A similar renal benefit was reported by several trials examining the effect of SGLT2 inhibitors on patients with heart failure (HF) who did or did not have diabetes[21-23]. In the empagliflozin in heart failure with a preserved ejection fraction (EMPEROR-Preserved) trial, empagliflozin significantly reduced the rate of eGFR decline by approximately 50% over time in patients with HF with preserved ejection fraction but did not affect the composite renal endpoints[21]. This pattern of benefits is similar to that reported in the empagliflozin outcome trial in patients with chronic heart failure and reduced ejection fraction (EMPEROR-Reduced) trial, which discovered that the eGFR decline was slower in the empagliflozin group than in the placebo group (−0.55 vs. −2.28 mL/min/1.73 m^2; $p < 0.001$) irrespective of the presence of diabetes and that empagliflozin-treated patients had a lower risk of composite renal outcomes (HR = 0.50; 95% confidence interval [CI] = 0.32 to 0.77; p = not applicable [NA])[22]. In the dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF) trial, the incidence of the prespecified renal composite outcome did not differ between the treatment groups (HR = 0.71; 95% CI = 0.44 to 1.16; $p = 0.17$)[23,24]. Moreover, dapagliflozin reduced the rate of eGFR decline over time, irrespective of the presence of diabetes[24]. A meta-analysis of the DAPA-HF and EMPEROR-Reduced trials reported that SGLT2 inhibitor-treated patients with HF with reduced ejection fraction had a lower risk of composite renal outcomes (HR = 0.62; $p = 0$ .013), although the number of events accrued was limited[25].

However, in these dedicated CVOTs, the reported renoprotective effects of SGLT2 inhibitors were not sufficient for studying renal outcomes and the percentage of patients with baseline nephropathy was relatively low. In addition, whether the renoprotective effects were stronger in those with preserved or reduced renal function remained unclear. Further dedicated renal outcome trials are necessary to verify these results. Studies such as canagliflozin and renal outcomes in type 2 diabetes and nephropathy (CREDENCE)[26], dapagliflozin in patients with chronic kidney disease (DAPA-CKD)[27], sotagliflozin in patients with diabetes and chronic kidney disease (SCORED)[28], and empagliflozin in patients with chronic kidney disease (EMPA-KIDNEY)[29] provide greater insight into

the renoprotective effects of SGLT2 inhibitors in patients with CKD than have the previous CVOTs. Of these, all trials except the SCORED trial were terminated early after a marked clinical benefit was observed in them.

The CREDENCE trial examined the effect of canagliflozin on patients with T2D with a mean eGFR of 56.2 mL/min/1.73 m^2, with a mean UACR of 927 mg/g, and receiving background therapy with an ARB or ACE inhibitor[26]. The relative risk reductions in primary outcomes, composite renal-specific outcomes, and ESRD in the canagliflozin group versus the placebo group were −30% ($p < 0.001$), −34% ($p < 0.001$), and −32% ($p = 0.002$), respectively[26]. Additionally, canagliflozin was found to provide protection against acute kidney injury (AKI). The corresponding number needed to treat (NNT) was 23 for the trial duration[26]. Moreover, subgroup analyses indicated that canagliflozin was safe and effective, regardless of baseline eGFR and albuminuria level, and did not increase the risk of AKI in patients with DKD[26]. Results from the CREDENCE trial indicated that, compared with that in the placebo group, the annual eGFR decline in the canagliflozin group was smaller in each category of acute reductions in eGFR[30]. In contrast to other COVTs and CREDENCE, the DAPA-CKD trial extended these evidences to the broader population of patients with CKD without diabetes, testifying that SGLT2 inhibitors are active in CKD per se through the action of pathophysiologic patterns. In this trial, dapagliflozin significantly improved the renal composite outcome of a sustained decline of at least 50 % in the eGFR, ESRD, and renal or CV death; the relative risk reduction was 39% (HR = 0.61; $p < 0.001$) and corresponding NNT was 19, irrespective of the presence of diabetes[27]. Additionally, for the hard renal endpoint of ESRD, a significant risk reduction of 36% was discovered (HR = 0.64; 95% CI = 0.50 to 0.82; p = NA), with the corresponding NNT being 42 for the trial duration[27]. Furthermore, a prespecified analysis conducted in 624 patients with eGFR of 25-75 ml/min/1.73 m^2 and UACR of 200–5000 mg/g at baseline indicated that dapagliflozin significantly attenuated progressive loss of eGFR compared to placebo with a yearly eGFR slope decline of 2.15 mL/min/1.73 m^2 and 3.38 mL/min/1.73 m^2, respectively ($p = 0.005$)[31]. However, when comparing treatment effects in patients with stage 4 CKD at baseline with those in patients with stages 2/3 CKD, there were no significant differences ($p = 0.13$)[31].

SGLT2 inhibitors exert renoprotective effects in patients with T2D but can also lead to a reversible acute eGFR decline upon treatment initiation[32]. A prespecified analysis from the DAPA-CKD trial revealed that among dapagliflozin-treated patients with CKD and albuminuria, an acute decline in eGFR (from baseline to Week 2) was not associated with higher rates of CKD progression[33]. Moreover, these acute reductions in eGFR after 2 weeks of treatment were not associated with an increased risk of adverse events. These data suggest that in patients with CKD and albuminuria treated with dapagliflozin, a modest acute eGFR decline (from baseline to Week 2) is associated with a lower likelihood of CKD progression and should not be a reason for discontinuation of therapy[33].

A subanalysis of the DAPA-CKD trial, which enrolled 270 patients with immunoglobulin A (IgA) nephropathy already on RAAS blocking therapy, showed that dapagliflozin significantly and substantially reduced the risk of CKD progression, with a 71% risk reduction in the primary composite endpoint (≥50% eGFR decline, ESRD, or renal or CV death; HR = 0.29; $p = 0.005$) and 76% risk reduction in the secondary kidney-specific endpoint (≥50% eGFR decline, ESRD, or renal death; HR = 0.24; $p = 0.002$) as well as an adequate safety profile[34]. Moreover, the aforementioned renoprotective effects were also observed in those with low baseline eGFR and high baseline severity of albuminuria[34]. These

findings may provide early evidence that SGLT2 inhibitors are a safe and effective option among the current standard treatments for IgA nephropathy.

The SCORED trial recruited patients with T2D, CKD (eGFR = 20-60 mL/min/1.73 m^2), and CV risk factors and reported that sotagliflozin improved composite renal outcomes (sustained eGFR decrease of ≥50% for ≥30 days, ESRD, or a sustained eGFR <15 mL/min/1.73 m^2 for ≥30 days), with the relative risk reduction being 29% (HR = 0.71; 95% CI = 0.46 to 1.08; p =NA)[28]. Unfortunately, this trial was prematurely terminated due to loss of funding, and therefore, the intended follow-up duration could not be completed.

The recently published empagliflozin in patients with chronic kidney disease (EMPA-KIDNEY) trial, the largest dedicated SGLT2 inhibitor trial for CKD to date, investigated the cardiorenal benefits of empagliflozin in patients with eGFR as low as 20 mL/min/1.73 m^2 and in those with a low eGFR (20-45 mL/min/1.73 m^2) without albuminuria[29]. This trial revealed that empagliflozin significantly reduced the risk of kidney disease progression or CV death compared with placebo by 28% (HR = 0.72; $p < 0.001$). The results were consistent between patients with versus without diabetes and across subgroups defined in accordance with eGFR ranges. Moreover, empagliflozin led to a 14% reduction in the number of all-cause hospitalizations compared with placebo (HR = 0.86; p = 0.003)[29]. Taken together, these recent trials confirm that the renoprotective effects of SGLT2 inhibitors are applicable to a broad population of patients with CKD, regardless of diabetes status. Table 1 presents a summary of the effects of SGLT2 inhibitors on renal outcomes in RCTs.

Real-World Studies on Renoprotective Effects of SGLT2 Inhibitors

Real-world studies (RWSs) on the renoprotective effects of SGLT2 inhibitors have been limited. Early results from a large Japanese cohort study suggested that, compared with other classes of glucose-lowering drugs (o-GLDs), SGLT2 inhibitors led to a significant annual eGFR decline (−0.86 vs. −2.06 mL/min/1.73 m^2)[35]. Moreover, the incidence of composite renal outcomes was lower in the SGLT2 inhibitor group (HR = 0.70; p = 0.039), although the o-GLDs group exhibited better glycemic control[35]. In a large retrospective cohort study, compared with dipeptidyl peptidase 4 (DPP4) inhibitors, SGLT2 inhibitors were associated with lower risks of ESRD (HR = 0.51; $p < 0.001$) and acute renal failure (HR = 0.59; $p < 0.001$) and a slower eGFR decline[36]. These associations remained significant in patients with or without rapid eGFR decline and patients who added an SGLT2 inhibitor to their treatment or switched to an SGLT2 inhibitor from a DPP4 inhibitor[36]. Similarly, a recent retrospective cohort study demonstrated that SGLT2 inhibitors were associated with a significant reduction in CKD progression (HR = 0.60; $p < 0.001$ for eGFR ≥45 mL/min/1.73 m^2 and HR = 0.43; $p < 0.001$ for 15-44 mL/min/1.73 m^2, respectively)[37]. Moreover, SGLT2 inhibitors reduced the risk of ESRD in the entire cohort (HR = 0.33; p = 0.001) and in those with an eGFR of 15-44 mL/min/1.73 m^2 (HR = 0.24; p =0.006) in a population in which the prevalence of DKD was high. Notably, compared with dapagliflozin and canagliflozin, empagliflozin led to a sustained lower risk of renal endpoints across CKD stages 1 to 4[37]. This RWS indicated that SGLT2 inhibitors might be used to reduce the risks of CKD progression and ESRD in clinical practice, particularly in the treatment of moderate-to-advanced CKD[37].

The dapagliflozin real-world evidence in type 2 diabetes (DARWIN-T2D) study was the first RWS to assess changes in renal endpoints in patients with T2D and reported that compared with o-GLDs, dapagliflozin was strongly associated with lower urinary albumin excretion. Moreover, a mild and marginally significant decline in eGFR was observed after

Table 1. Summary of the Effects of SGLT2 inhibitors on Renal Outcomes in Randomized Clinical Trials

Clinical trial	Year of completion	Intervention (enrollment)	Main inclusion criteria	Median follow-up (years)	Renal outcome (HR [95% CI]; *p* value)	Number needed to treat
CV outcome trials						
EMPA-REG OUTCOME[14]	2015	Empagliflozin (N = 7020)	T2D (%): 100 ASCVD; eGFR ≥ 30 mL/min/1.73 m^2 BMI ≤ 45 kg/m^2 HbA1c: 7.0%-9.0% without GLDs or HbA1c: 7.0%-10.0% with stable GLDs	3.3	Secondary composite renal endpoints (UACR > 300 mg/g; sCr doubling and eGFR ≤ 45 mL/min/1.73 m^2; ESRD; renal death): 0.61 (0.53-0.70); p <0.001	16
CANVAS[15]	2017	Canagliflozin (N = 10 142)	T2D (%): 100 ASCVD or age ≥ 50 years with 2 or more risk factors for CVD	3.6	Secondary: composite renal endpoints (sustained 40% reduction in eGFR; ESRD; renal death): 0.60 (0.47-0.77); p < 0.01	83¶
DECLARE-TIMI-58[16]	2018	Dapagliflozin (N = 17 160)	T2D (%): 100 ASCVD or multiple risk factors for ASCVD eGFR ≥ 60 mL/min/1.73 m^2	4.2	Secondary: composite renal endpoints (sustained ≥ 40% reduction in eGFR to <60 mL/min/1.73 m^2; new ESRD; renal or CV death): 0.53 (0.43-0.66); p < 0.001	77
VERTIS-CV[17]	2020	Ertugliflozin (N = 8246)	T2D (%): 100 CVD Age ≥ 40 years eGFR ≥ 30 mL/min/1.73 m^2	3.5	Secondary: composite renal endpoints (sCr doubling; ESRD; renal death): 0.81 (0.63-1.04); p = 0.08*	134#
SCORED[28]	2020	Sotagliflozin (N = 10 584)	T2D (%): 100 eGFR: 25-60 mL/min/1.73 m^2 Risks for CVD	1.3	Secondary: composite renal secondary endpoints (sustained eGFR decrease of ≥50% for ≥30 days, or long-term dialysis, or renal transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2 for ≥30 days): 0.71 (0.46-1.08)	NA
HF outcome trials						
DAPA-HF[23]	2019	Dapagliflozin (N = 4744)	T2D (%): 45 EF ≤ 40% NYHA class II, III, or IV NT-proBNP ≥ 600 pg/mL eGFR ≥ 30 mL/min/1.73 m^2	1.8	Secondary: composite renal endpoints (sustained ≥50% decline in eGFR; ESRD; renal death): 0.71 (0.44-1.16); p = NA Least-squares mean change in eGFR (mL/min/1.73 m^2): −1.09 (dapagliflozin) vs. −2.85 (placebo)	NA
EMPEROR-Preserved[21]	2020	Empagliflozin (N = 5988)	T2D (%): 49.1 EF ≥ 40% NYHA class II, III, or IV	2.2	Secondary: composite renal endpoints (chronic dialysis or renal transplant ≥ 40% decrease in eGFR or a sustained eGFR < 15 mL/min/1.73 m^2 (if baseline eGFR ≥ 30) or <10 mL/min/1.73 m^2 (if baseline eGFR < 30 mL/min/1.73 m^2): 0.95 (0.73-1.24) Least-squares mean change in eGFR (mL/min/1.73 m^2): −1.25 (empagliflozin) vs. −2.62 (placebo)	NA

Clinical trial	Year of completion	Intervention (enrollment)	Main inclusion criteria	Median follow-up (years)	Renal outcome (HR [95% CI]; *p* value)	Number needed to treat
EMPEROR-Reduced[22]	2020	Empagliflozin (N = 3730)	T2D (%): 49.8 EF ≤ 40% NYHA class II, III, or IV	1.3	Secondary: composite renal endpoints (chronic dialysis or renal transplant ≥40% decrease in eGFR or a sustained eGFR < 15 mL/min/1.73 m^2 (if baseline eGFR ≥ 30) or <10 mL/min/1.73 m^2 (if baseline eGFR < 30mL/min/1.73 m^2): 0.50 (0.32-0.77) Least-squares mean change in eGFR (mL/min/1.73 m^2): −0.55 (empagliflozin) vs. −2.28 (placebo)	NA
CKD outcome trials						
CREDENCE[26]	2019	Canagliflozin (N = 4401)	T2D (%): 100 Age ≥ 30 years eGFR ≥30 to <90 mL/min/1.73 m^2 UACR > 300-5000 mg/g HbA1c: 6.5%-12.0% Required stable dose of ACE inhibitor or ARB	2.6	Primary: ESRD (dialysis or transplantation or sustained eGFR < 15 mL/min/1.73 m^2), sCr doubling or renal or CV death): 0.70 (0.59-0.82); $p = 0.001$ Secondary: sCr doubling or ESRD or renal death): 0.66 (0.53-0.81); $p < 0.001$	23 31
DAPA-CKD[27]	2020	Dapagliflozin (N = 4304)	T2D (%): 67.5 eGFR: 25 to 75 mL/min/1.73 m^2 UACR: 200-5000 mg/g Required stable dose of ACE inhibitor or ARB	2.4	Primary: sustained decline of ≥50% in eGFR (confirmed after ≥28 days), ESRD (dialysis for ≥28 days, transplantation, or eGFR < 15 mL/min/1.73 m^2 confirmed after ≥28 days) or renal or CV death: 0.61 (0.51-0.72); $p < 0.001$ Secondary: composite renal secondary endpoints (≥50% decline in the eGFR, ESRD, or renal death): 0.56 (0.45-0.68); $p < 0.001$	19 21
EMPA-KIDNEY[29]	2022	Empagliflozin (N = 6609)	T2D (%): 44 eGFR ≥20 to <45 mL/min/1.73m^2 or ≥45 to <90 mL/min/1.73m^2 and UACR ≥ 200 mg/g On ACE inhibitor or ARB	2.0	Primary: composite progression of kidney disease (defined as ESRD, a sustained decrease in eGFR to <10 mL/min/1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or renal death) or death from cardiovascular causes: 0.72; 95% (0.64-0.82); $p < 0.001$.	28

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ESRD, end-stage renal disease; GLD, glucose-lowering drug; HF, heart failure; HbA1c, glycated hemoglobin; NA, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; sCr, serum creatinine level; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

¶ calculated per 1000 patient years

* HR = 0.66 [0.50-0.88]; $p < 0.01$ if reduction >40% of eGFR rather than doubling of serum creatinine level in the composite renal outcome

the chosen threshold for eGFR decline was ≥57%, based on doubling of serum creatinine

dapagliflozin treatment at the 6-month follow-up[38]. One possible interpretation of this finding is that a short-term follow-up (~6 months) enables analysis of only acute changes in renal endpoints, and therefore, a longer observation period is required to evaluate treatment benefits over time and trends in eGFR[38]. Interestingly, significantly low urinary albumin excretion was observed only in patients with baseline microalbuminuria and macroalbuminuria treated with dapagliflozin[38]. The comparative effectiveness of cardiovascular outcomes in new users of SGLT-2 inhibitors (CVD-REAL) 3 study was the first multinational RWS to examine the rate of eGFR decline and the composite outcome of 50% eGFR decline or ESRD in patients with T2D receiving SGLT2 inhibitors in comparison with o-GLDs. The mean eGFR of the enrolled population was 90 mL/min/1.73 m^2, with less than 10% of the patients having a baseline eGFR ≤ 60 mL/min/1.73 m^2 [39]. The study reported that SGLT2 inhibitors were strongly associated with a slower eGFR decline (difference in slope = 1.53 mL/min/1.73 m^2; $p < 0$ .001) and a 51% reduction in the composite outcome of 50% eGFR decline or ESRD (HR = 0.49; $p < 0.001$) over a mean follow-up of 14.9 months[39]. The CVD-REAL 3 Korea study enrolled patients with a mean eGFR of 89.2 mL/min/1.73 m^2 and reported that compared with o-GLDs, SGLT2 inhibitors yielded lower risks of ESRD (HR = 0.47; 95% CI = 0.34 to 0.65; p = NA) and all-cause death (HR = 0.82; 95% CI = 0.73 to 0.93; p = NA) over a mean follow-up of 1.49 years[40]. However, a few ESRD events were observed in the subgroup with an eGFR of ≥90 mL/min/1.73 m^2, probably due to the presence of relatively low-risk patients given the clinical natural course of CKD progression[40]. Similarly, scholars used the Scandinavian registry to investigate the association between SGLT2i treatment and the risk of serious renal events and reported that compared with DPP4 inhibitors, SGLT2 inhibitors were strongly associated with lower risks of ESRD (HR = 0.32; 95% CI=0.22 to 0.47; p = NA), renal death (HR = 0.77; 95% CI = 0.26 to 2.23; p = NA), and renal-related admission (HR = 0.41; 95% CI = 0.32 to 0.52; p = NA)[41].

Overall, the retrospective RWSs conducted so far have confirmed that SGLT2 inhibitors yield more favorable renal outcomes than do o-GLDs in patients with T2D. Nevertheless, these studies had a short follow-up duration, and the analysis of surrogate endpoints was subject to inherent bias. Additional evidence from large observational studies is required to identify patients who would benefit the most from the renoprotection offered by SGLT2 inhibitors.

Potential Renoprotective Mechanisms of SGLT2 Inhibitors

The pathogenesis of DKD is multifactorial and involves diverse structural, hemodynamic, physiological, and inflammatory processes that contribute to GFR decline[42]. Apart from the obvious benefits of plasma glucose reduction, body weight loss, and blood pressure (BP) reduction, numerous mechanisms underlying the various beneficial effects of SGLT2 inhibitors on renal problems have been proposed. The potential renoprotective mechanisms of SGLT2 inhibitors are summarized in Figure 1.

4.1 Direct Renal Hemodynamic Effects

Early in the natural course of diabetes, a supraphysiologic increase in GFR occurs, known as glomerular hyperfiltration, and this increase has been hypothesized to predispose a patient to DKD[43]. In diabetes, glomerular hyperfiltration is caused by numerous complex mechanisms and mediators. In response to hyperglycemia, various growth factors and cytokines are secreted, which contribute to nephromegaly (particularly hypertrophy of the proximal tubule) with an increased filtration surface area per nephron; this has been associated

with hyperfiltration[43]. Moreover, this hemodynamic change is believed to be a consequence of an imbalance in vasoactive factors that control either a reduction in afferent arteriolar resistance or increase in efferent arteriolar resistance, leading to increased GFR (known as "vascular theory") or an abnormal interaction between the glomerulus and tubule following hyperglycemia-induced upregulation of SGLT2 and sodium–hydrogen exchanger (NHE) 3 (known as "tubular theory")[43]. Hyperglycemia is associated with increased reabsorption of both glucose and sodium in the proximal tubules through upregulation of SGLT2 receptors. Subsequently, sodium delivery to the macula densa is decreased, an effect that is interpreted as inadequate renal perfusion. This phenomenon then represses the tubuloglomerular feedback (TGF) system through afferent vasodilatation and efferent vasoconstriction caused by the resultant decrease in adenosine, which contributes to a maladaptive increase in the GFR and enhancement of renal plasma flow. The elevated GFR leads to an increase in intraglomerular pressure, associated barotrauma, and, ultimately, hyperfiltration[43]. Overactivation of TGF plays a crucial role in sustained hyperfiltration, which is strongly associated with the incidence of ESRD and with structural changes in DKD through an increase in intraglomerular pressure, enhanced filtration fraction, and vascular changes[44].

SGLT2 inhibition has been shown to attenuate the renal absorption of glucose and sodium in proximal tubules through restoration of TGF signals at the macula densa, contributing to afferent arteriolar vasoconstriction, a decrease in glomerular hyperfiltration, and a reduction of albuminuria severity and tubular transport workload and thus a decrease in renal oxygen consumption, ultimately leading to renoprotective effects in patients with T2D and CKD[45]. An acute decrease in the eGFR is observed after SGLT2i initiation, indicating the direct renal hemodynamic effect of these drugs, as reported by many clinical trials[46]. The exact mechanisms underlying the initial reduction in eGFR upon initiation of SGLT2i treatment appear to differ between type 1 diabetes (T1D) and T2D. In an animal model of T1D, empagliflozin increased adenosine production, which contributed to suppression of hyperfiltration through afferent arteriolar vasoconstriction and stabilization of kidney hemodynamics[47]. Similarly, in young patients with T1D and hyperfiltration, empagliflozin attenuated renal hyperfiltration and restored TGF in association with increased urinary adenosine excretion[48]. An exploratory post hoc analysis suggested that empagliflozin increased urinary adenosine excretion in patients with T1D, an effect that may be associated with the regulation of renal hemodynamic function[49].

However, the renoprotective mechanisms of SGLT2 inhibitors reported in large clinical trials[14-17,26,27] are likely to differ between human and animal studies, given that these clinical trials enrolled patients with T2D, who are older and generally have less hyperfiltration than do patients with T1D. This may have been confirmed by a recent study reporting that in patients with T2D, empagliflozin plus linagliptin combination therapy reduced renal vascular resistance (RVR) and preserved renal perfusion through induction of postglomerular vasodilation[50]. Similarly, another study investigating patients with T2D reported that dapagliflozin attenuated the GFR and filtration fraction without an increase in RVR, suggesting that the renal hemodynamic effects of SGLT2 inhibitors in T2D are caused by postglomerular vasodilation rather than preglomerular vasoconstriction[51]. By contrast, findings from an earlier study concerning patients with T1D suggested that SGLT2 inhibitors caused afferent arteriolar vasoconstriction, contributing to reductions in intraglomerular pressure and hyperfiltration[48]. Aside from differences in the baseline characteristics of the

enrolled patients, the divergent findings from these studies may be attributable to different underlying pathophysiologies of DKD between T1D and T2D. The most crucial structural changes in T2D DKD are tubulointerstitial abnormalities, whereas glomerular alterations are more prominent in T1D[52]. Moreover, glomerular hyperfiltration is more prominent in patients with T1D than in those with T2D in whom the GFR is normal or reduced due to an age-related decline[42]. Thus, the varied responses to SGLT2 inhibitors between these studies may have resulted from different renal histopathologies and baseline renal hemodynamics, suggesting that the pathophysiological abnormalities responsible for DKD may differ between T1D and T2D[42]. The ongoing adolescent type 1 diabetes treatment with SGLT2 inhibitors for hyperglycemia and hyperfiltration (ATTEMPT) trial (NCT04333823) is investigating the physiological impacts of SGLT2 inhibition on the early onset manifestations and progression of diabetes complications in adolescents with T1D.

4.2 Decrease in Renal Hypoxia Effect

SGLT2 upregulation and glomerular hyperfiltration induce sodium and glucose reabsorption in response to hyperglycemia. This is an energy-demanding process for which the proximal tubule requires considerable amounts of oxygen[53]. Animal studies on diabetes have revealed 40% and 16% increases in renal oxygen consumption in the cortical segment and collecting duct, respectively[54]. This mismatch of oxygen demand and supply predisposes patients with DKD to hypoxia[53]. According to the chronic hypoxia hypothesis, this process predisposes a patient to a vicious cycle of hypoxic injury of the glomeruli, nephron ischemia, and progressive renal necrosis[53]. In addition, hypoxia contributes to common pathological abnormalities, including loss of glomerular and peritubular microvasculature as well as the recruitment of inflammatory and immune cells, leading to tubulointerstitial fibrosis and extracellular matrix accumulation[53].

Endothelial dysfunction is also associated with hypoxia in diabetes and activates a cascade of proliferative, inflammatory, and profibrotic responses that contribute to loss of peritubular capillaries and ischemic injury[55]. The hypoxia inducible factors (HIFs; specifically, HIF-1α and HIF-2α) play a critical role in coordinating the metabolic switch from aerobic adenosine triphosphate (ATP) production through oxidative phosphorylation to anaerobic glycolysis to sustain ATP production under hypoxia[56]. Experimental studies have shown that HIF-1α overexpression lead to increased expression of kidney injury markers and that HIF-2α activation can counteract kidney injury markers and alleviate injury in CKD[57,58]. Moreover, HIF-2α expression contributes to increased oxygen supply through the regulation and induction of erythropoietin (EPO) production and through upregulation of the vascular endothelial growth factor[59]. However, HIF-1α overexpression was associated with the development of glomerulosclerosis in an animal model of DKD[42].

SGLT2 inhibition stimulates erythropoiesis through an increase in hematocrit level, and this effect is consistent for all four SGLT2 inhibitors (dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin)[60]. SGLT2 inhibitors appear to activate HIF-2α and suppress HIF-1α expression, potentially by alleviating cellular stress and renal hypoxia and enhancing nutrient deprivation signaling, which may promote erythropoiesis while inhibiting proinflammatory and profibrotic pathways and organellar dysfunction, thereby preventing or slowing the progression of DKD[61]. Clinically, SGLT2 inhibitors contribute to anemia reduction through an increase in hemoglobin, hematocrit, and erythrocyte levels in patients with DKD[62]. Moreover, the effect of SGLT2 inhibitors on erythropoiesis may be caused by an EPO-production-mediated mechanism and be independent of glycemic control[62]. However,

currently, the differential effects of SGLT2 inhibitors on kidney tissue oxygen availability in humans remain poorly understood. The ongoing renal oxygenation, oxygen consumption and hemodynamic kinetics in type 2 diabetes: an ertugliflozin study (ROCKIES, NCT04027530) trial will investigate the role of renal hypoxia in DKD and the effects of SGLT2 inhibition on renal tissue oxygenation and oxygen consumption as well as on changes in intrarenal hemodynamics and perfusion and the shift of fuel metabolites in patients with T2D. The ongoing control of renal oxygen consumption, mitochondrial dysfunction, and insulin resistance (CROCODILE, NCT04074668) trial will assess renal oxygenation, perfusion, and consumption as well as insulin sensitivity and mitochondrial function in patients with T1D and healthy controls. To further investigate the mechanisms of renal damage in T1D, kidney biopsies will be performed.

In addition to the erythropoietic effect of increased oxygen supply, SGLT2 inhibitors may shift renal fuel metabolism from glucose and fat oxidation, which is energy inefficient in the setting of a type 2 diabetic kidney, to an energy-efficient metabolism involving super fuels such as ketone bodies, which improve renal work efficiency and function[55]. Similarly, data obtained from the thrifty fuel hypothesis revealed that the role of SGLT2 inhibitors in promoting ketogenesis may account for their favorable effects on the kidney because enhanced ketone body formation helps meet the energy needs of organs under stress[63]. Notably, contrasting hypotheses have been proposed.[64,65] The first hypothesis suggests that SGLT2 inhibitors change the trajectory of cell response to a toxic environment by modifying a cellular life history program—either the defense program or the dormancy program[64]. The dormancy program represents an energy-preserving status with high resistance to environmental stressors, comparable to animal hibernation, where fuel is stored, metabolism is suppressed, and insulin secretion is reduced, whereas the defense program is characterized by activation of the immune response and anabolic metabolism. SGLT2 inhibitors are similar to the metabolic pattern characteristic of the dormancy program. Therefore, the organ-protective effects of SGLT2 inhibitors may be related to their ability to switch cellular life programming from a defensive to a dormant state[64]. The second hypothesis is that SGLT2 inhibitors activate low-energy sensors-sirtuin 1 (SIRT1) and adenosine monophosphate–activated protein kinase (AMPK), which are responsible for mimicking a fasting transcriptional paradigm to produce renal benefits[65]. SGLT2 inhibitors induce calorie loss through urine, and glycosuria is accompanied by increased glucagon synthesis, enhanced fatty acid oxidation, and shrinkage of adipose tissue depots[45]. Therefore, the ketonemia induced by these drugs is not representative of an efficient source of fuel; instead, it is a biomarker of a fasting-like transcriptional state[65]. Moreover, SGLT2 inhibitors may not only deceive cells into believing that they are fasting but also that they are hypoxic. Oxygen deprivation stimulates AMPK and SIRT1. SIRT1 activates HIF-2α and possibly also HIF-1α under certain conditions; these responses are the principal stimuli for erythropoietin synthesis[65]. Additionally, enhancement of HIF-1α and HIF-2α signaling by SGLT2 inhibitors may amplify the autophagic flux already augmented by AMPK and SIRT1, thereby explaining the remarkable renal benefits of these drugs[65]. Overall, SGLT2 inhibitors appear to reduce renal work through a shift in fuel energetics; however, these hypotheses are largely based on experimental data from animal models, and further studies are warranted to investigate their roles in renal fuel metabolism.

4.3 Reduced Podocyte Loss and Albuminuria

Podocytes, which are firmly attached to the

glomerular basement membrane (GBM), play a crucial role in maintaining the glomerular filtration barrier. Podocyte loss is a major pathological change in DKD and is associated with the development of albuminuria[66].

In an animal model of nondiabetic proteinuric CKD, dapagliflozin ameliorated glomerular lesions, reduced proteinuria, and prevented podocyte dysfunction and loss through a direct effect on podocytes that limited albumin-induced cytoskeletal rearrangement[67]. Notably, this study reported increased podocyte SGLT2 expression in DKD, suggesting that SGLT2 inhibitors may target podocytes and thus indicating a potential therapeutic option for preventing DKD[67]. In in vitro and in vivo models of DKD, dapagliflozin suppressed podocyte epithelial–mesenchymal transition by downregulating insulin-like growth factor-1 receptor/PI3K activity, resulting in remission of glomerulosclerosis, GBM thickening, and glomerular podocyte injury[66]. Empagliflozin increased endogenous ketone body levels, which sequentially attenuated hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1) to reduce podocyte injury and proteinuria in an animal model of DKD[68]. Similarly, empagliflozin augmented podocyte autophagy to attenuate DKD in an animal model of T2D[69]. Acceleration of podocyte autophagy flux was associated with preserved podocyte morphology, attenuated proteinuria, and mitigated glomerulosclerosis[69]. Finally, through glycosuria, SGLT2 inhibitors were found to change carbohydrate utilization into fatty acid oxidation, thereby preventing podocyte damage, reducing proteinuria, and inhibiting the progression of DKD[70]. The ongoing dapagliflozin in nondiabetic stage IV CKD (ADAPT, NCT04794517) trial will investigate whether dapagliflozin ameliorates hyperfiltration and reduces proteinuria compared with placebo in patients with nondiabetic CKD (stage IV CKD) and proteinuria (>0.5 g/24 h).

4.4 Decreased Inflammation, Oxidative Stress, and Fibrosis

The diabetic milieu stimulates OS and triggers inflammatory responses in tissues and organs affected by diabetes. A high glucose level accelerates the production of reactive oxygen species (ROS), which deteriorate the cellular antioxidant systems, resulting in AGE generation and induction of the polyol, protein kinase C, and hexosamine pathways[71]. AGEs are associated with the expression of cytokines (e.g., interleukin [IL]-1 and IL-6) and induce many growth factors (e.g., transforming growth factor-β [TGF-β] and connective tissue growth factor) in DKD[72]. Moreover, another cytokine induced in DKD, IL-18, promotes production of other inflammatory cytokines by mesangial cells and increases the expression of intercellular adhesion molecule-1[72]. The accumulation of AGEs may initiate diabetic macroangiopathy through the receptor for AGE (RAGE), and increased expression of RAGE contributes to the rapid acceleration of diabetic atherosclerosis[73]. AGEs activate nuclear factor-κB (NF-κB) through the RAGE in renal cells[71]. The combination of NF-κB with activator protein-1 regulates the expression of several proinflammatory and profibrotic genes involved in DKD progression, such as the gene encoding monocyte chemoattractant protein-1 (MCP-1)[72]. Moreover, a high glucose level may contribute to an increase in extracellular matrix proteins—such as collagen IV, fibronectin-1, and matrix metalloproteinase (MMP)-7—which are associated with the development of glomerulosclerosis in DKD[72].

Several experimental studies have demonstrated that SGLT2 inhibitors contribute to reductions in circulating inflammatory and fibrotic markers of DKD, particularly IL-6, MCP-1, NF-κB, MMP-7, fibronectin-1, and tumor necrosis factor (TNF) receptor 1[74]. In an animal study of DKD, SGLT2 inhibitors reduced the markers of OS and inflammation as well as improved histological

parameters[42]. In addition, SGLT2 inhibitors were associated with significant reductions in collagen IV expression, macrophage infiltration, and DKD-associated structural changes (e.g., mesangial expansion and interstitial fibrosis) in diabetic rats[71]. Vallon et al. reported that in T1D Akita mice, SGLT2 inhibitors attenuated mRNA levels of IL-6, NF-κB, cytokine CCL2, CD14, and the tissue inhibitor of MMP, which is present during kidney injury[75]. Similarly, Gallo et al. reported that in db/db mice, SGLT2 inhibitors attenuated the renal expression of profibrotic gene markers, TGF-β, and fibronectin[76]. Ojima et al. demonstrated that SGLT2 inhibition exerted anti-inflammatory and antifibrotic effects partly through the suppression of RAGE[77]. They also reported that administration of SGLT2 inhibitors in streptozotocin-induced diabetic rats significantly attenuated expression of the markers of OS and macrophages in DKD[77]. Moreover, markers of inflammation and fibrosis such as TGF-β, MCP-1, plasminogen activator inhibitor-1, connective tissue growth factor, and intercellular adhesion molecule-1, which are enhanced in DKD, were all found to be inhibited by SGLT2 inhibitors[77]. These findings suggest that SGLT2 inhibitors exert renoprotection effects in DKD partly through attenuation of inflammation, extracellular matrix turnover, and fibrosis.

Several clinical studies have indicated that SGLT2 inhibitors are associated with reductions in circulating markers of inflammation and fibrosis. In the CANVAS trial, Sen et al. reported that canagliflozin reduced the urinary level of kidney injury molecule-1 (KIM-1), suggesting attenuated tubular damage, which was partly mediated by MCP-1 reduction, indicative of reduction tubular inflammation[78]. This effect was subsequently mediated by a reduction in the UACR. Dekkers et al. reported that dapagliflozin reduced urinary excretion of a proximal tubular marker (KIM-1), inflammatory markers (MCP-1 and IL-6), and glomerular IgG and IgG4 fractional clearance in patients with T2D[79]. Moreover, a reduction in albuminuria was correlated with improvements in GFR and reduction of KIM-1 excretion[79]. Satirapoj et al. showed that in patients with T2D, dapagliflozin downregulated the proximal tubular injury biomarkers, such as KIM-1 and UACR[80]. Similarly, Heerspink et al. reported that canagliflozin reduced the levels of IL-6, fibronectin-1, TNF receptor 1, and MMP-7 in patients with T2D[74]. These data suggest that canagliflozin contributes to the attenuation of molecular processes related to inflammation, fibrosis, and the extracellular matrix[74].

4.5 Improved Endothelial Dysfunction

Endothelial dysfunction, a hallmark feature of DKD, results from decreased expression of endothelial nitric oxide synthase (eNOS), impaired production of nitric oxide (NO), and increased OS[81]. Hyperglycemia may impair endothelial function through various activated signal pathways such as protein kinase C, the polyol pathway, and TGF-β signaling[82]. eNOS deficiency was associated with accelerated DKD[83]. Moreover, impaired eNOS bioactivity contributes to the accumulation of ROS and superoxides, which induce OS, further resulting in damage to essential cellular components, DNA, and protein[42]. These processes in turn accelerate glomerular injury, leading to glomerulosclerosis and tubular fibrosis[42]. Although preclinical studies of T2D with CKD have supported the positive role of antioxidants, their benefits are limited and are most likely a result of multiple redundant metabolic pathways underlying T2D with CKD and because hyperglycemia, the more proximal inciting event, is not adequately corrected[42].

The impact of SGLT2 inhibitors on endothelial function, as measured by NO production and vasodilation, has been investigated in various preclinical and clinical studies[84-89]. In an in vivo animal model, Salim et al. reported that ipragliflozin pro-

tected against endothelial dysfunction, probably partially through amelioration of OS and reduction of inflammation[84]. Gaspari et al. reported that dapagliflozin reduced endothelial dysfunction partially through attenuation of TNF-α and hyperglycemia-induced adhesion molecule expression[85]. Similarly, Steven et al. indicated that empagliflozin attenuated endothelial dysfunction partially through mediation of metabolic dysfunction, OS, inflammation AGE formation, and AGE/RAGE signaling[86].

Several clinical studies have suggested that SGLT2 inhibitors may improve endothelial function in patients with T2D[87-89]. In an RCT involving 80 patients with early stage T2D and inadequate glycemic control, Shigiyama et al. reported that dapagliflozin protected against endothelial dysfunction[87]. In a nonrandomized controlled study of 54 patients with uncontrolled T2D, Sugiyama et al. revealed that dapagliflozin significantly improved microvascular endothelial function[88]. In a metabolomics-based molecular pathway analysis of kidney biopsies collected from patients with DKD, Mulder et al. discovered that dapagliflozin may upregulate the expression of genes involved in the NOS pathway, leading to improvements in endothelial function[89]. By contrast, in a post hoc analysis of an RCT involving patients with T2D and established CVD, Tanaka et al. reported that empagliflozin was not associated with beneficial effects on endothelial function[90]. This result was attributable to the early phase of treatment, small number of participants, low prevalence of background atherosclerotic CVD, and no measurement of flow-mediated vasodilation, which has been validated as attributable to hard outcomes in several studies[90]. Although the exact mechanism through which SGLT2 inhibitors protect against endothelial dysfunction remains unclear, they may be associated with improved hyperglycemia and mediation of metabolic dysfunction, osmotic diuresis, and changes in sodium homeostasis as a result of increased natriuresis[89]. Moreover, the current evidence suggests that the citrulline pathway is one of the potential mediators of the protective effects of SGLT2 inhibition on kidney function[89].

4.6 Reduced Sodium–Hydrogen Exchanger Activity

In the renal proximal tubule, NHE3 is coexpressed with SGLT2 to reabsorb the majority of filtered sodium, and their activity is crosslinked by membrane associate protein 17 such that positive crosstalk exists between SGLT2 and NHE3[91]. Activation of NHE3 is associated with the development of glomerular hyperfiltration and mesangial proliferation, leading to onset of DKD[42]. Notably, increased NHE3 activity was also implicated in the development of HF and may attenuate the effects of the natriuretic response of peptides in patients with HF[92].

In an animal model of diabetes, both SGLT2 and NHE3 activity were demonstrated to increase the GFR, in line with the diabetic tubular hypothesis of glomerular hyperfiltration and a positive crosslink between proximal tubular reabsorption and GFR through TGF[93]. SGLT2 inhibitors cause blood volume depletion and dehydration at least in part through NHE3 inhibition, which contributes to natriuresis caused by inhibition of sodium reabsorption in the renal proximal tubules[94]. Subsequently, this increases sodium delivery to the macula densa, which would be expected to reset the tubuloglomerular balance, reduce intraglomerular pressure, and reduce hyperfiltration[42]. The positive crosstalk between SGLT2 and NHE3 and the natriuretic effect induced by SGLT2 inhibition facilitate the glomerulotubular balance of glucose, sodium, and bicarbonate when the GFR increases[95]. In a nondiabetic animal model of HF, SGLT2 inhibitors preserved the GFR and prevented renal mass loss and HF-induced renal apoptosis at least in part through the inhibition of NHE3 activity[96]. Hyperglycemia has been shown to induce the expression and

activity of NHE3 in glomerular mesangial cells[97]; hence, SGLT2 inhibitors may inhibit NHE3 activity in mesangial cells through another potential mechanism, thereby ameliorating DKD by preventing glomerulosclerosis[42]. Although the interplay between SGLT2 and NHE3 expression suggests a potential mechanism by which SGLT2 inhibitors may exert renoprotective effects in diabetes, further studies are warranted to investigate this connection.

4.7 Modulation of the RAAS

Hyperglycemia aberrantly activates the intrarenal RAAS, which contributes to overproduction of angiotensin II (Ang II) in renal proximal tubular cells, mesangial cells, and podocytes[72]. In DKD, elevated Ang II levels are responsible for hemodynamic changes in the RAAS, namely renal vasoconstriction, increased glomerular pressure and permeability, and enhanced mesangial cell contraction (leading to a smaller filtration surface area)[98]. Moreover, elevated Ang II levels are associated with the nonhemodynamic changes in the RAAS that are observed in DKD, such as induction of renal hypertrophy and cell proliferation, stimulation of extracellular matrix synthesis, and triggering of proinflammatory production[98]. Thus, RAAS activation plays a crucial role in the pathogenesis of DKD.

For the past 2 decades, RAAS inhibition with an ACE inhibitor or ARB has been demonstrated to exert renoprotective effects in patients with DKD[99]. Nevertheless, RAAS blockade does not completely prevent the progression of DKD, which has been suggested to be a result of aldosterone or angiotensin escape resulting in increased renin activity following long-term RAAS suppression[100]. Notably, the renin inhibitor aliskiren failed to provide any additional beneficial effect on DKD apart from that afforded by RAAS blockade, indicating that mechanisms other than aldosterone or angiotensin escape underlie the incomplete response of DKD to RAAS blockade[42].

RAAS blockade contributes to both afferent and efferent arteriole dilation, although the efferent arteriole dilates more than the afferent arteriole; by contrast, SGLT2 inhibitors lead to constriction of the afferent arteriole and dilation of the efferent arteriole[72]. Hence, SGLT2 inhibitors appear to provide a higher degree of renoprotection than does RAAS blockade and ultimately prevents the progression of DKD to ESRD[72].

A preclinical study on CKD indicated that SGLT2 inhibition reduced urinary angiotensinogen and Ang II levels and the expression of angiotensinogen and Ang II type 1 receptor (AT1R), which are useful biomarkers of RAAS activation in the kidney[101]. In a T2D animal model, canagliflozin reduced the expression of renal angiotensinogen; mitigated renal fibrosis, inflammation, abnormal cell proliferation, and increased BP[102]. A similar study reported that canagliflozin limited hyperglycemia-induced angiotensinogen expression in mouse renal proximal tubular cells, suggesting possible mechanistic explanations for the clinical results of trials such as CANVAS and CREDENCE in which canagliflozin improved renal outcomes to an extent that could be explained by the glucose-lowering properties of the drug[103]. In an animal model of T2D with DKD, dapagliflozin was associated with a reduction in urinary angiotensinogen, Ang II level, the renal expression of AT1R, and OS[71]. Consistent with these findings, in patients with T2D, SGLT2 inhibitors were shown to reduce urinary excretion of total and intact angiotensinogen; however, these changes were not statistically significant[104].

The complementary mechanisms underlying and potential synergistic effects of the SGLT2 inhibitor–RAAS inhibitor combination on the renal system have proven that these drugs are promising choices for the treatment of DKD. Heerspink et al. reported that the addition of an RAAS inhibitor to dapagliflozin therapy led to 33.2% lower albuminuria severity and 3.5-mmHg lower systolic BP

compared with treatment with an RAAS inhibitor alone in patients with DKD[105]. Similar results were reported by two clinical studies conducted by Weber et al. in patients with DKD[106,107]. In the EMPA-REG OUTCOME trial, Mayer et al. reported that, compared with placebo, empagliflozin reduced the risk of incident or worsening, edema, and acute renal failure across the subgroup of RAAS inhibitors users[108]. Moreover, SGLT2 inhibitor–RAAS inhibitor combinations reduced the severity of glomerular injury, tubular necrosis, and renal fibrosis to a greater extent compared with monotherapy with either drug type[109]. This finding may be associated with overexpression of the Ang-(1-7) pathways, leading to vasodilation, anti-inflammation, antioxidation, and antiproliferation effects[110]. However, a post hoc analysis of 13 trials suggested that SGLT2 inhibitor–RAAS inhibitor combinations did not provide added benefits related to cardiorenal clinical outcomes in patients with T2D compared with an SGLT2 inhibitor alone[111]. Nevertheless, the combination of these 2 drug types may improve some renal outcomes and parameters (e.g., uric acid [UA], BP, and body weight) compared with SGLT2 inhibitors alone[111]. Thus, additional studies are required to investigate whether such a combination strategy involving both an SGLT2 inhibitor and an RAAS inhibitor can achieve long-term renoprotection, particularly in patients with T2D and CKD.

4.8 Systemic Effects

Apart from the obvious intrarenal effects, SGLT2 inhibitors have been shown to exert systemic beneficial effects, which may potentially contribute to renoprotection, although the marginal changes in these outcomes could not completely explain the renoprotective effects of SGLT2 inhibitors. First, BP reduction not only attenuates the risk of morbidity and mortality[112] but also exerts renoprotective effects in patients with diabetes[113]. SGLT2 inhibitors induce sustained BP reduction, partly through minimal natriuresis and possibly sympathetic tone reductions[114]. SGLT2 inhibitors could induce volume contraction as a result of osmotic and natriuretic effects[115]. SGLT2 inhibitors contribute to reductions in arterial stiffness and vascular resistance, which may be related to BP reduction[116]. SGLT2 inhibitor-induced arterial stiffness improvement may be associated with reduction of glucose levels, weight loss, and volume contraction as a result of osmotic diuresis or reduced OS[116]. Additionally, SGLT2 inhibitors inhibit RAAS activity and sympathetic nervous system activity through augmented distal sodium chloride delivery to the macula densa, inducing TGF—afferent arteriole narrowing and attenuated hyperfiltration—both of which are important determinants of BP[115]. Next, serum UA levels were demonstrated to be associated with DKD, partly through increased RAAS activity or through induction of inflammatory cascades and endothelial dysfunction[117]. Hence, reduction of UA levels could contribute to renoprotection in diabetes.

Numerous clinical studies on SGLT2 inhibitors have reported that reductions in UA levels are suggestive of improvements in kidney function[118]. Nevertheless, no clinical trial has yet demonstrated a direct beneficial effect of decreased UA level on renal outcomes, and the causal relation remains controversial[119]. Lastly, SGLT2 inhibitors reduce the renal threshold for glucose reabsorption, and subsequent glycosuria reduces the plasma glucose level and ameliorates glucose toxicity, contributing to enhanced insulin sensitivity and improved β-cell function[42], which may also be beneficial for DKD.

Future Perspectives: Roles of MRAs and ERAs

Overexpression of the mineralocorticoid receptor is associated with fibrosis and inflammation, which can damage the heart and kidneys[120]. The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline recom-

mends that a nonsteroidal MRA can be added to first-line therapy for patients with T2D and high residual risks of kidney disease progression and CV events[121]. Finerenone—a novel nonsteroidal, selective MRA—exerted kidney and heart protective effects in both an animal model and clinical study[120]. Mechanistically, MRA—SGLT2 inhibitor combination therapy seems pharmacologically attractive given the action of these two drug types on fibrosis, inflammation, and glomerular hyperfiltration. In a recent randomized open-label crossover trial, combination treatment involving dapagliflozin and the steroidal MRA eplerenone resulted in a robust additive UACR-lowering effect (−53%) at week 4 compared with treatment either dapagliflozin (−19.6%) or eplerenone (−33.7%) alone[122]. Moreover, fewer hyperkalemia events occurred in the dapagliflozin–eplerenone combination group than in the eplerenone-alone group (4.3% vs. 17.4%). No incidence of hyperkalemia was reported in the dapagliflozin treatment group (0%)[122].

In the finerenone in reducing kidney failure and disease progression in diabetic kidney disease (FIDELIO-DKD) trial, compared with placebo, finerenone significantly reduced the risk of a primary renal outcome event (a sustained ≥40% decline in eGFR, ESRD, or renal death; HR = 0.82; $p = 0.001$) in patients with T2D and CKD[123]. Furthermore, the overall frequency of adverse events did not differ between the 2 groups; however, the incidence of hyperkalemia was higher in the finerenone group than in the placebo group (18.3% vs. 9.0%)[123]. A recent subanalysis of the FIDELIO-DKD trial revealed that 259 (4.6%) out of 5674 patients with T2D and CKD already receiving an SGLT2 inhibitor at baseline exhibited significant reductions in UACR and improved renal and CV outcomes, irrespective of the use of an SGLT2 inhibitor at baseline[124]. Moreover, the safety profiles were balanced, irrespective of the use of an SGLT2i at baseline, with fewer episodes of hyperkalemia in the patients treated with finerenone in the SGLT2 inhibitor group (8.1% vs. 18.7% without)[124]. In addition, a recent exploratory post hoc analysis comparing the FIDELIO-DKD and CREDENCE trials suggested that canagliflozin and finerenone are similarly effective in kidney protection when tested in similar patient populations[125].

The FIGARO-DKD trial further revealed similar benefits in a broader population including a moderately elevated UACR of 30 to 300 mg/g (CKD stages 2-4) or severely elevated UACR of 300 to 5000 mg/g (CKD stages 1-2)[126]. Overall, the frequency of adverse events was similar in the 2 groups; however, the incidence of hyperkalemia was higher in the finerenone group than in the placebo group (10.8% vs. 5.3%)[126]. A recent subgroup analysis of the DAPA-CKD trial revealed that dapagliflozin had similar safety and effectiveness profiles in reducing the major renal endpoints in patients with DKD, irrespective of the use of an MRA at baseline[127].

The finerenone in chronic kidney disease and type 2 diabetes: combined FIDELIO-DKD and FIGARO-DKD trial programme analysis (FIDELITY) was a prespecified study investigating the pooled effect of finerenone across the spectrum of CKD in patients with T2D; the results suggested that finerenone reduced the composite renal outcome of eGFR ≥ 57% by 23% (HR = 0.77; $p < 0.001$), eGFR ≥ 40% by 15% (HR = 0.85; $p < 0.001$), and dialysis by 20% (HR = 0.80; $p = 0.04$) compared with placebo[128]. Moreover, finerenone yielded a 32% reduction in the UACR at Month 4 compared with placebo[128].

The study of diabetic nephropathy with atrasentan (SONAR) trial assessed the long-term efficacy of the selective ERA atrasentan in patients with T2D and CKD who received a maximally tolerated RAAS inhibitor selected for a large reduction (≥30%) in UACR without signs of sodium retention during the enrichment period. The result revealed that atrasen-

tan significantly lowered the risk of a primary composite renal endpoint (sustained doubling of serum creatinine, ESRD, or renal death) compared with placebo (HR = 0.65; $p = 0.005$)[129]. Moreover, fluid retention and anemia adverse events were more frequent in the atrasentan group than in the placebo group (36.6% vs. 32.3%, $p = 0.02$; 18.5% vs. 10.3%, $p < 0.001$, respectively)[129]. However, in this trial, only 1.4% of the cohort had received an SGLT2 inhibitor, and the benefit conferred by the atrasentan–SGLT2 inhibitor combination therapy remained unclear. The zibotentan and dapagliflozin for the treatment of CKD (ZENITH-CKD, NCT04724837) trial is evaluating the long-term efficacy of treatment with the combination of selective ERA zibotentan and dapagliflozin compared with that of dapagliflozin alone in patients with CKD and albuminuria, with or without T2D; the results of this trial are expected in 2023. Another double-blind, 3-arm trial (CONFIDENCE, NCT05254002) is assessing the efficacy (change in UACR at 6 months) and safety of finerenone plus empagliflozin compared with either finerenone or empagliflozin alone in patients with DKD; the results of this trial are expected in 2024.

No conclusive evidence indicating the incremental long-term renal benefits of SGLT2 inhibitors combined with MRAs or ERAs compared with monotherapy is available. Additional long-term RCTs on the synergistic renoprotective effects of SGLT2 inhibitor–MRA or SGLT2 inhibitor–ERA combination therapy on DKD are warranted.

Implications of SGLT2 Inhibitor Treatment Effects on DKD Guideline Development

Large RCTs on SGLT2 inhibitors have reported the strong renoprotective effects of these drugs in patients with T2D and CKD[26,27,29]. Developing new therapies involving SGLT2 inhibitors is essential to ensuring that optimal care is provided to patients with T2D and CKD to improve their quality of life outcomes. Metformin is no longer regarded as the first-line therapy for patients with T2D. The unique renoprotective role of SGLT2 inhibitors is emphasized in the international guidelines of many scientific associations, not only those for diabetes[130,131] but also in the fields of nephrology[121] and cardiology[132]. The American Diabetes Association for standards of care in diabetes 2023 guidelines recommend that for T2D and DKD treatment, an SGLT2 inhibitor should be initiated to reduce CKD progression and the likelihood of a CV event in patients with an eGFR of ≥20 mL/min/1.73 m^2 and urinary albumin level ≥ 200 mg/g creatinine, and it should be continued until initiation of dialysis or transplantation[130]. Similar recommendations are made in the 2022 updated guidelines of the American Association of Clinical Endocrinology Clinical Practice[131]. The KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease also provides a first-line therapy indication of an SGLT2 inhibitor for diabetic patients with eGFR ≥ 20 mL/min/1.73 m^2 and recommends continuation of treatment as tolerated, until dialysis or transplantation is initiated[121]. The European Society of Cardiology 2019 guidelines recommend the use of an SGLT2 inhibitor as first-line treatment for patients with T2D at a high risk of CV or atherosclerotic CVD to reduce the likelihoods of a CV event and mortality[132]. These guideline recommendations assist endocrinologists, nephrologists, cardiologists, and primary care physicians in daily clinical practice.

Conclusions

SGLT2 inhibitors have become the treatment of choice for T2D and CKD, including DKD, owing to the large CVOTs and renal outcome trials that have consistently demonstrated that SGLT2 inhibitors not only remarkably reduce albuminuria severity but also significantly lower the risk of composite renal endpoints (sustained decline in eGFR, ESRD,

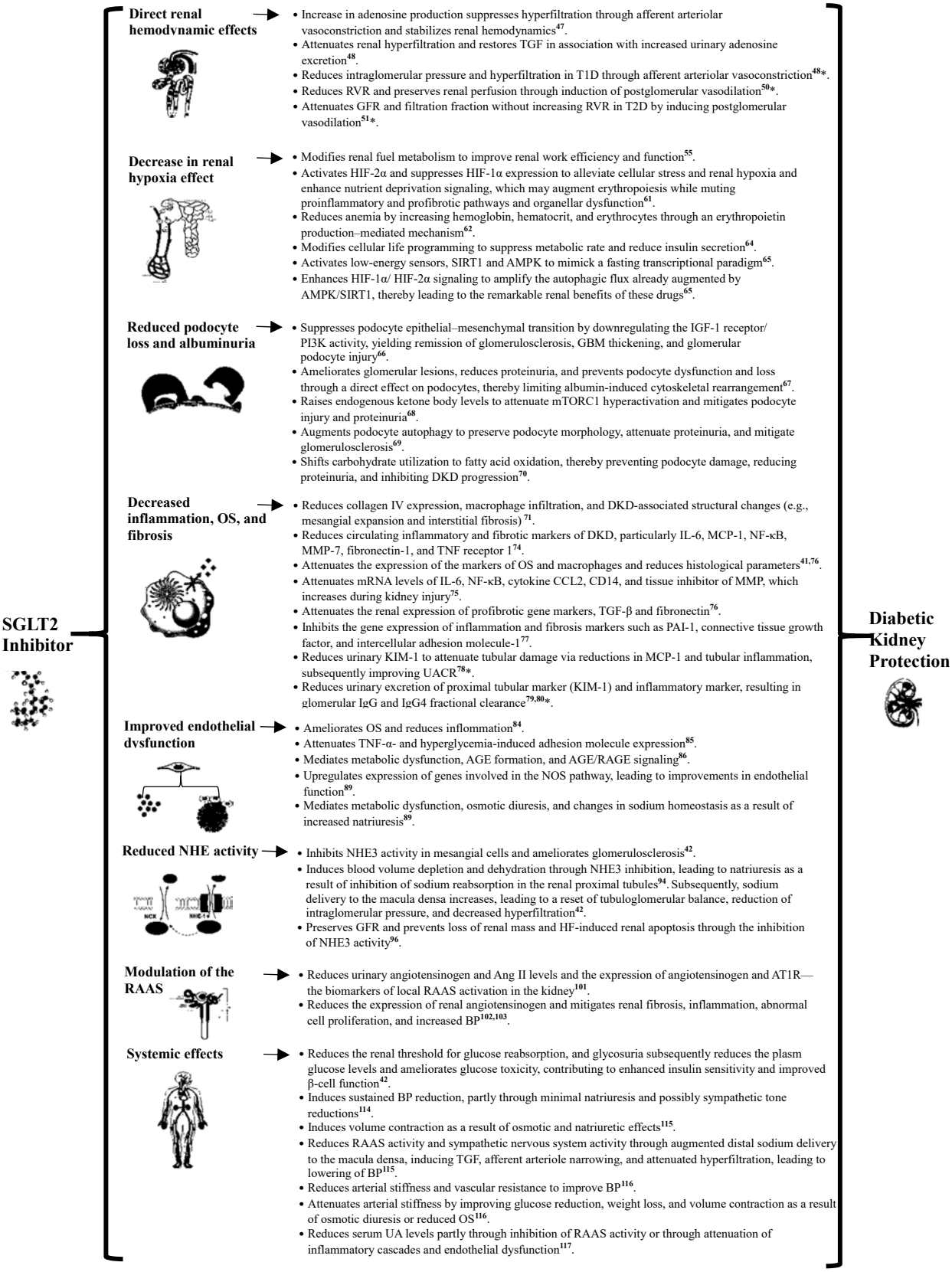

Figure 1. Potential mechanisms implicated in renal protective effects of SGLT2 inhibitors in diabetes

Abbreviations: AGE, advanced glycation end-product; AMPK, adenosine monophosphate-activated protein kinase; Ang II, angiotensin II; AT1R, Ang II type 1 receptor; BP, blood pressure; DKD, diabetic kidney disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; HIF, hypoxia inducible factors; IGF-1, insulin-like growth factor-1; KIM-1, kidney injury molecule-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP-7, matrix metalloproteinase-7; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor-κB; NHE, sodium-hydrogen exchanger; NOS, nitric oxide synthase; OS, oxidative stress; PAI, plasminogen activator inhibitor; RAGE, receptor for advanced glycation end-product; RAAS, renin-angiotensin-aldosterone system; RVR, renal vascular resistance; SGLT2, sodium-glucose co-transporter-2; SIRT1, sirtuin 1; T1D, type 1 diabetes; T2D, type 2 diabetes; TGF, tubuloglomerular feedback; TNF, tumor necrosis factor; TGF-β, transforming growth factor-β; UACR, urine albumin to creatine ratio; UA, uric acid.
*Clinical trial

or renal death) in patients with or without diabetes. SGLT2 inhibitors modulate numerous molecular mechanisms and signaling pathways that contribute to the development and progression of DKD. Numerous RCTs have indicated that the pleiotropic actions of SGLT2 inhibitors probably contribute to their renoprotective effects apart from blood glucose control. Therefore, many international guidelines recommend the use of SGLT2 inhibitors for the management of patients with or at risk of CKD, including those with stage IV CKD with or without diabetes, in whom a favorable benefit–risk ratio has been demonstrated. The potential renoprotective effect exerted by nonsteroidal MRAs has also gained research attention. Numerous clinical trials have suggested that finerenone delays the progression of renal and CV outcomes in patients with T2D and CKD. Although clinical trials have demonstrated the efficacy of ERAs in reducing the risk of composite renal outcomes in patients with T2D and CKD, no conclusive evidence of the incremental long-term renal benefits of SGLT2 inhibitor–ERA combination therapy compared with treatment with an SGLT2 inhibitor or ERA alone is available. Future clinical trials should identify whether a combination strategy involving dual SGLT2 inhibitors and other renoprotective drugs (nonsteroidal MRAs and ERAs) provides added value and has a better safety profile by opposing effects on factors such as BP regulation to yield long-term kidney protection, particularly in patients with T2D and CKD already receiving treatment with an RAAS inhibitor.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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糖尿病腎臟病變治療的新契機：鈉 - 葡萄糖共同轉運器 -2 抑制劑之角色

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摘要

糖尿病腎臟病變是導致世界上腎臟衰竭的主要原因，並且在醫療照護體系方面造成了沉重的負擔。腎素 - 血管張力素 - 醛固酮系統抑制劑之腎臟保護作用於糖尿病人身上已有明顯的效果呈現，尤其是合併有高血壓的病人更為顯著。鈉 - 葡萄糖共同轉運器 -2 抑制劑的主要藥理機轉是藉由抑制腎臟近曲小管對血糖的再吸收，因而增加尿糖的排泄以達到降低血糖的效果。除了降低血糖的效用之外，指標性的腎臟結果試驗顯示，患有蛋白尿和腎臟功能衰竭的患者，無論是否有糖尿病，鈉 - 葡萄糖共同轉運器 -2 抑制劑可以藉由一系列機轉來減少引發或加劇蛋白尿的風險。這些機轉包括藉由腎小管腎絲球回饋的恢復來減低腎絲球的內壓；透過減低腎素 - 血管張力素 - 醛固酮系統的活化來降低腎絲球的高過濾狀態；改善腎小管的氧合和代謝；抵抗發炎、氧化壓力和纖維化以及透過一利尿效應來降低蛋白尿和腎臟去充血化。許多心血管結果試驗也發現這些藥物具有潛在性腎臟保護作用，無論這些病人是否有糖尿病。本篇綜論分析最近關於鈉 - 葡萄糖共同轉運器 -2 抑制劑臨床研究之發現和探討其機轉對於在第二型糖尿病合併有慢性腎衰竭的病人之腎臟保護作用。