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Perspective

A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors

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SUMMARY

Sodium glucose co-transporter (SGLT) 2 inhibitors reduce the risk of kidney failure in patients with and without type 2 diabetes (T2D). Although the precise underlying mechanisms for these nephroprotective effects are incompletely understood, various hypotheses have been proposed including reductions in intraglomerular pressure through restoration of tubuloglomerular feedback, blood pressure reduction and favorable effects on vascular function, reduction in tubular workload and hypoxia, and metabolic effects resulting in increased autophagy. Here, we review these mechanisms, which may also explain the beneficial effects of SGLT2 inhibitors on kidney function in patients without T2D.

INTRODUCTION

The kidney plays an important role in the regulation of glucose. For example, it utilizes glucose as an energy resource, produces glucose under the influence of adrenaline (Gerich et al., 2001; Stumvoll et al., 1995), and reabsorbs glucose in the proximal segment of the nephron via an active sodium-dependent transport process mediated by sodium glucose co-transporters (SGLTs). SGLTs belong to a large family of membrane proteins located in the intestinal tract and proximal tubule and are responsible for the transport of glucose, amino acids, vitamins, and some ions across the membrane of the epithelial intestine and proximal tubule. SGLT1 is predominantly found in the gastrointestinal tract, while SGLT2 is primarily expressed in the proximal tubule and accounts for 80%–90% of glucose reabsorption with the remaining 10%–20% reabsorbed by SGLT1 (Wright et al., 2007). Hence, targeting glucose metabolism in the kidneys seems a logical target to improve glycemic control in patients with T2D.

Studies with inhibitors of the SGLT2 transporter indeed showed that these drugs decrease the glucose reabsorption capacity of the proximal tubule, thereby acutely increasing glycosuria and improving glycemic control over time (DeFronzo et al., 2013). Improved glycemic control has been consistently associated with improved microvascular outcomes (Zoungas et al., 2017). Accordingly, the glucose-lowering properties of these drugs may be one mechanism of their long-term benefit. However, more importantly, SGLT2 inhibitors also decrease other cardiovascular risk factors, such as blood pressure, body weight, and albuminuria. Large cardiovascular outcome trials provided initial proof that SGLT2 inhibitors slow the progression of kidney function decline and reduce the risks of kidney outcomes in patients with T2D of whom the majority had relatively preserved kidney function (Wiviott et al., 2019; Neal et al., 2017; Zinman et al., 2015; Mosenzon et al., 2019). Three dedicated outcome

trials designed to assess the long-term efficacy and safety of the SGLT2 inhibitors, canagliflozin, dapagliflozin, and sotagliflozin, in patients with chronic kidney disease (CKD) are completed (Perkovic et al., 2019; Wiviott et al., 2019; Neal et al., 2017; Zinman et al., 2015; Mosenzon et al., 2019; Heerspink et al., 2020; Bhatt et al., 2021). Canagliflozin and dapagliflozin significantly reduced the risk of kidney failure in the CREDENCE and DAPA-CKD trials, respectively (Perkovic et al., 2019; Heerspink et al., 2020). A similar trend was observed for sotagliflozin, although the effect was not statistically significant in the SCORED trial, probably due to its early termination (Bhatt et al., 2021). Secondary analyses from clinical trials have shown that the benefits on cardiovascular and kidney function are unlikely mediated by the glucose-lowering properties of these agents (Inzucchi et al., 2018; Heerspink et al., 2015). Thus, other non-glycemic pathways appear to be involved. In the last couple of years, experimental and dedicated human mechanistic studies have provided more insight into the underlying molecular mechanisms for how SGLT2 inhibitors may afford cardiovascular and kidney protection. We, here, describe new insights into the mechanisms of action of SGLT2 inhibitors that may explain their favorable effects on kidney function.

TUBULOGLOMERULAR FEEDBACK

A number of studies have evaluated the effects of SGLT2 inhibitors on glomerular hemodynamic pathways. These studies, initially conducted in experimental models or patients with type 1 diabetes (T1D), showed that SGLT2 inhibitors reduce hyperfiltration by inhibiting sodium reabsorption in the proximal tubule (Kidokoro et al., 2019; Cherney et al., 2014b). In brief, under hyperglycemic conditions reabsorption of glucose and sodium is increased, which decreased distal sodium delivery to the macula densa at the juxtaglomerular apparatus. This is inappropriately sensed as a decrease in effective circulating volume and triggers

the activation of tubuloglomerular feedback (TGF). TGF activation causes vasodilation of the afferent renal arteriole and leads to increased glomerular hypertension. An experimental study in Akita mice (a model of T1D) using *in vivo* multiphoton microscope imaging techniques demonstrated that SGLT2 inhibition causes afferent renal arterial vasoconstriction and decreases intraglomerular pressure and hyperfiltration. This effect was abrogated in the presence of an adenosine receptor 1 antagonist, indicating that restoration of TGF and constriction of the afferent renal arteriole following SGLT2 administration is mediated through adenosine-facilitated pathways (Heerspink et al., 2016; Kidokoro et al., 2019). Glomerular hyperfiltration is a common pathway of kidney injury both in diabetic and non-diabetic settings and is associated with progression of kidney function decline (Helal et al., 2012). By inhibiting SGLT2, distal sodium delivery is restored, which normalizes TGF and afferent tone, resulting in a reduction in intraglomerular pressure. Clinically this is manifested by an acute drop in the estimated glomerular filtration rate (eGFR) of approximately 4 to 6 mL/min/1.73m² in the first weeks after initiation of SGLT2 inhibition. Importantly, this drop in eGFR is associated with a preservation of long-term kidney function during prolonged treatment and is reversible soon after discontinuation of SGLT2 inhibitors (Wanner et al., 2018).

The initial studies that described this mechanism of action were performed in the setting of T1D. However, whether this mechanism also accounts for the beneficial effects observed in patients with T2D who participated in large cardiovascular and kidney outcome trials was unknown until early 2020. In a randomized, double-blinded trial with dapagliflozin in patients with T2D, van Bommel et al. demonstrated that dapagliflozin causes an acute fall in GFR that was accompanied by a reduction in renal blood flow and renovascular resistance (van Bommel et al., 2020). This pattern of effect suggests that, in contrast to the effect of the SGLT2 inhibitor empagliflozin in patients with T1D, the acute drop in GFR may be attributed to vasodilation of the renal efferent arteriole similar to how angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce single nephron glomerular hypertension. The differential effects of SGLT2 inhibitors on renal hemodynamic physiology between patients with T1D and T2D are probably explained by differences in patient characteristics, including differences in baseline renal hemodynamic status, such as the degree of vascular resistance, age, diabetes duration, and concomitant medication use; in particular, ACE inhibitors or ARBs and insulin (van Bommel et al., 2020; Cherney et al., 2014a). Thus, while the acute reduction in GFR is consistent in patients with T1D and T2D, the underlying glomerular hemodynamic effectors may differ.

BLOOD PRESSURE EFFECTS

Hypertension is an important risk factor for progressive kidney function loss, and blood pressure lowering has been associated with kidney protection. SGLT2 inhibitors decrease systolic and diastolic blood pressure by approximately 4 and 2 mmHg, respectively. The mechanism by which SGLT2 inhibitors lower blood pressure is likely multifactorial with varying contributing factors. In contrast to other blood pressure-lowering agents (Law et al., 2003), the blood pressure-lowering effect does not

depend on starting blood pressure levels and is also independent of the use of other concomitant blood pressure-lowering agents (Ye et al., 2021). Enhanced natriuresis and osmotic diuresis coupled with reductions in extracellular volume and plasma volume are thought to contribute to the blood pressure-lowering efficacy of SGLT2 inhibitors. Initial clinical studies have indeed suggested that SGLT2 inhibitors increase natriuresis by approximately 40 mEq per 24 h.

Sodium transport in the proximal tubule is to a large extent mediated by the apical Na⁺/H⁺ exchanger 3 transporter (NHE3). Studies in mice have shown a functional relationship between SGLT2 and NHE3 (Onishi et al., 2019). In non-diabetic mice, SGLT2 inhibition with empagliflozin inhibited NHE3 activity and decreased urinary pH and bicarbonate excretion (Figure 1) (Onishi et al., 2020). Notably, chronic empagliflozin treatment in Akita mice increased α -ketoglutarate, which may drive distal sodium chloride reabsorption to compensate for the decreased proximal sodium reabsorption. In accord with these experimental data, results from a large cardiovascular outcome trial demonstrated that the SGLT2 inhibitor canagliflozin compared to placebo decreased urinary pH in patients with T2D at high cardiovascular risk (Li et al., 2020a). The reduction in urinary pH partly explained the kidney-protective effect of canagliflozin (Figure 1).

Although clinical studies demonstrated natriuretic/osmotic diuretic effects of SGLT2 inhibitors, it should be mentioned that these studies did not record or standardize sodium intake (Tanaka et al., 2017; Iijima et al., 2015; Wilcox et al., 2018; Mordi et al., 2020; Griffin et al., 2020). It is therefore possible that changes in sodium excretion could be attributed to changes in sodium intake rather than SGLT2 inhibition. A recent study in patients with T2D and preserved kidney function who adhered to a strict standardized sodium diet showed that the SGLT2 inhibitor dapagliflozin significantly decreased 24 h blood pressure without obvious changes in sodium excretion (Scholtes et al., 2021). This study suggests that other factors may contribute to the blood pressure-lowering effects of SGLT2 inhibitors. A number of natriuretic-independent mechanisms of blood pressure-lowering effects have been proposed. Human clinical trials have shown that SGLT2 inhibitors exert favorable effects on arterial stiffness, vascular resistance, and endothelial and blood pressure variability (Kario et al., 2018; Chilton et al., 2015; Cherney et al., 2014a; Cooper et al., 2019). In addition, the endothelial glycocalyx may also be involved in the blood pressure-lowering effects. The glycocalyx is a gel-like structure that covers the endothelium and is impaired in patients with T2D. SGLT2 inhibitors have been shown to restore the integrity of the glycocalyx both in experimental and in clinical studies (Ikonomidis et al., 2020; Herat et al., 2020). Additional human studies are ongoing to assess effects of SGLT2 inhibitors on natriuresis, plasma volume, and blood pressure in patients with T2D and CKD (NCT04620590).

WORKLOAD AND HYPOXIA

In certain conditions, intraglomerular pressure might decrease too much, resulting in poor renal perfusion, which may lead to acute kidney injury (AKI) through renal ischemia. SGLT2 inhibitor use could also lead to AKI, in particular in settings of reduced

circulating volume (e.g., intercurrent illness). Post-marketing surveillance reports from clinical practice have indeed suggested that SGLT2 inhibitors may increase the risk of AKI (FDA, 2016). On the contrary, large clinical trials and meta-analyses have demonstrated that SGLT2 inhibitors reduce the incidence of AKI (Neuen et al., 2019). These benefits are likely explained by reductions in tubular workload and hypoxia. Increased expression of SGLT2 under hyperglycemic conditions increases glucose and sodium reabsorption and therefore increases ATP-dependent tubular workload and oxygen requirements, which can lead to hypoxia. By decreasing glucose and sodium reabsorption, SGLT2 inhibitors decrease tubular workload and oxygen consumption and alleviate hypoxia, which may explain why SGLT2 inhibitors decrease proximal biomarkers of AKI such as kidney injury molecule-1 and decrease the risk of AKI events (Neuen et al., 2019; Dekkers et al., 2018). However, shifting sodium reabsorption to the medullary thick ascending limb of the loop of Henle raises oxygen demand in the outer medulla, rendering this tubular segment vulnerable to ischemia (O'Neill et al., 2015). Lower medullary oxygen tension in this segment of the tubule stimulates hypoxia-inducible factors, particularly HIF-2 α , which promotes erythropoietin production to improve red cell mass and oxygen-carrying capacity (Layton and Vallon, 2018). Clinical studies have indeed shown transient increases in EPO following SGLT2 inhibition (Lambers Heerspink et al., 2013; Mazer et al., 2020). It is therefore perhaps not a surprise that in a large multi-national kidney outcome trial with canagliflozin (namely, the CREDENCE trial), the risk of anemia, which was an independent predictor of renal and cardiovascular outcomes, and initiation of treatments for anemia were markedly reduced with canagliflozin (Oshima et al., 2020). Ongoing observational studies and randomized controlled studies in patients with diabetes and varying degrees of kidney function will assess oxygenation tension in the kidney using oxygen or carbon-labeled PET imaging and will provide additional insight into the interplay between insulin resistance, kidney oxygenation, mitochondrial dysfunction, glomerular hemodynamics, and impact of SGLT2 inhibitors (e.g., ROCKIES and CROCODILE studies; clinical trial registration numbers: NCT04027530 and NCT04074668).

NUTRIENT DEPRIVATION AND KETOGENESIS

Apart from these physiological effects caused by downstream mediators of proximal sodium inhibition, emerging studies provide novel insights into metabolic alterations and changes in fuel utilization that can explain effects of SGLT2 inhibitors in preventing kidney failure. Because of continuous glycosuria, SGLT2 inhibitors cause physiological adaptive responses to counter the continuous glucose loss. These compensatory mechanisms include an increase in endogenous glucose production, partly through an increase in glucagon, and decrease in insulin levels. These effects stimulate ketogenesis and lipolysis and increase circulating ketone bodies among β -OH-butyrate, which is an efficient energy source in addition to glucose (Mudaliar et al., 2016). This mechanism would cooperate with other SGLT2 inhibitor-induced mechanisms, as described above, and would provide a powerful synergistic effect that could ultimately protect kidney function. Indeed, urinary β -OH-butyrate concentrations were significantly increased following treatment with the SGLT2 inhib-

itors dapagliflozin, and the rise in β -OH-butyrate correlated with changes in erythropoietin and hematocrit in patients with T2D and CKD (Kim et al., 2019a; Mulder et al., 2019). Additionally, increased levels of ketone bodies inhibit the Nod-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome and reduce production of interleukin-1 β in monocytes (Youn et al., 2015; Goldberg et al., 2017). These inflammatory mediators represent important pathways of inflammation and may play an important role in the development and progression of kidney disease in the setting of diabetes (Kim et al., 2019b). Furthermore, ketone bodies possibly reduce mechanistic target of rapamycin complex 1 (mTORC1)-regulated proximal tubular epithelial cell and podocyte damage by inhibiting hyperactive mTORC1 due to a hyper-nutrient state, which may ameliorate kidney function (Tomita et al., 2020; Kogot-Levin et al., 2020). However, several arguments against the fuel shift hypothesis have been published. These reports challenge the notion that ketones are “super fuels” in the setting of diabetes and question whether increases in β -OH-butyrate result from increased production or decreased clearance (Lopaschuk and Verma, 2016). Moreover, instead of enhancing fuel supply, it has been hypothesized that SGLT2 inhibitors may induce “a state of dormancy” mimicking a state of hibernation, as seen in hibernating animals. According to this hypothesis, SGLT2 inhibitors switch cell life programs from defense to dormancy by downregulating mTOR and upregulating AMP-activated protein kinase (AMPK) and fibroblast growth factor 21 (FGF21), resulting in energy conservation (Avogaro et al., 2020). It should be mentioned that most of the studies conducted to date are experimental studies largely performed in animal models. Future clinical mechanistic studies are required to assess if these findings have direct human relevance in the heart and kidney. Such studies should measure *in vivo* ketone oxidation rates and endogenous glucose production in the kidney, and assess relationships with cardiac and kidney structure and function.

Although the theory on changes in fuel utilization is an attractive hypothesis to explain the mechanism of action of SGLT2 inhibitors, it should be noted that ketonemia promotes glomerular hyperfiltration along with other potential deleterious effects (Nosadini et al., 1989). This questions whether ketogenesis, as an additional energy supply, has direct favorable effects on the kidney. It is also possible that ketogenesis is an indicator of a transcriptional change that mimics a deprived nutrient state and activates a diverse range of molecular and physiological changes that ultimately protect the kidney (Packer, 2020). According to this hypothesis, in the setting of SGLT2 inhibition, ketogenesis is a result of activation of sirtuin-1 (SIRT1), AMPK, and HIF. Due to glycosuric effects, SGLT2 inhibition mimics a state of starvation that stimulates SIRT1, a nicotinamide adenine dinucleotide-dependent deacetylase activator. SIRT1 in turn activates AMPK. Both are master regulators of various genes important in the regulation of cellular glucose and energy homeostasis. SIRT1 increases ketone body production and facilitates energy transfer. Interplay of SIRT1 with AMPK along with their downstream effectors, peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), a master regulator of mitochondrial biogenesis, and FGF21, a regulator of energy balance, is thought to reduce cellular stress and promote cell survival (Ren et al., 2020; Wei et al., 2018; Hu et al., 2017; Lempiäinen et al.,

Figure 1. SGLT2 inhibitors reduce NHE3 transporter activity

SGLT2 inhibition decreases urinary pH in (A) non-diabetic mice and (B) patients with T2D at high cardiovascular risk. Left panel in (B) shows the urinary pH in the placebo and canagliflozin groups at baseline of the CANVAS trial; right panel shows the difference between canagliflozin and placebo during follow-up. The data presented are a reanalysis of the data from Onishi et al. (2020) and Li et al. (2020a). BL, baseline; EMPA, empagliflozin; ko, knockout.

2013; Kume et al., 2010). Furthermore, both SIRT1 and AMPK act in a coordinated manner to activate autophagy, which is responsible for the degradation of damaged mitochondria and peroxisomes, thereby abrogating inflammatory processes and reducing oxidative stress. Another nutrient and oxygen deprivation transcription factor is HIF-2 α , which is activated during SGLT2 inhibition, either directly or indirectly via SIRT1. HIF-2 α promotes autophagy and degradation of peroxisomes and erythropoiesis, and in combination with SIRT1 and AMPK activation, attenuates oxidative stress, hypoxia, and organelle damage, which collectively may preserve kidney function. That the molecular SIRT1-AMPK-HIF-2 α axis is likely involved in the mechanism of action of SGLT2 inhibitors is supported by mediation analyses from the EMPAREG-OUTCOME and CANVAS program trials, which showed that markers of volume and hemopoiesis (i.e., hemoglobin, hematocrit, reticulocyte count) and uric acid, as a proxy of oxidative stress, are the most important mediators of the cardiovascular and kidney benefits of SGLT2 inhibitors (Li et al., 2020a, 2020b; Fabbrini et al., 2014). Further evidence that SGLT2 inhibition exerts antioxidant effects has been shown in an animal study demonstrating that canagliflozin stimulates antioxidant pathways involving AMPK, Akt, and endothelial nitric oxide synthase (Hasan et al., 2020).

OTHER PROTECTIVE MECHANISMS

Apart from the mechanisms described above, there are many other effects of SGLT2 inhibitors that may contribute to long-term nephron protection. Hyperuricemia has been associated with kidney inflammation, and various observational studies documented a strong linear association between higher plasma uric acid levels and progressive kidney function loss (Zoppini et al., 2012). SGLT2 inhibitors reduce uric acid, and post hoc analyses from SGLT2 inhibitor clinical trials suggest that the reduction in uric acid at least partly explains their long-term effects (Zhao et al., 2018). Experimental studies have demonstrated that in non-diabetic mice, URAT-1, a highly specific urate transporter located on the apical membrane of the proximal tubular cell, is required for the uricosuric effect of SGLT2 inhibitors (Novikov et al., 2019). It is interesting to note that a recent clinical study demonstrated that adding the SGLT2 inhibitor dapagliflozin to verinurad, a URAT-1 inhibitor, further reduced uric acid without increased rates of adverse events, suggesting that

both agents can be combined to achieve desired uric acid targets (Stack et al., 2020). The diuretic effects of SGLT2 inhibitors are the most likely mechanism for their blood pressure-lowering effects. The lack of a compensatory increase in heart rate suggests there may be commensurate blunting of sympathetic nervous system (SNS) activity, which may contribute to the salutary effects of SGLT2 inhibitors compared with other diuretics (Gueguen et al., 2020). The relation between increased SNS activity and increased blood pressure and impaired glycemic control has been well described (Schlaich et al., 2015). Hence, blunting of SNS activity through SGLT2 inhibition could contribute to kidney protection. The interaction between SGLT2 inhibition and SNS activity has been studied in human kidney cells and mice models of obesity. In human kidney cells, the neurotransmitter noradrenaline increased SGLT2 expression and promoted SGLT2 translocation to the cell membrane. Further studies in obese mice revealed that SGLT2 inhibition with dapagliflozin leads to significant reductions of intrarenal tyrosine hydroxylase, a marker of sympathetic nerve innervation, and norepinephrine (Matthews et al., 2017). The crosstalk between SNS activity and SGLT2 inhibitors was further studied in a neurogenic hypertensive mouse model (Herat et al., 2020). In this model, chemical denervation of the SNS reduced SGLT2 expression evidenced by reductions in tyrosine hydroxylase staining in kidney tissues. Importantly, treatment with dapagliflozin reduced tyrosine hydroxylase and norepinephrine, indicating reduced SNS innervation and activity, concomitant with glycosuria and improvements in blood pressure and endothelial function (Herat et al., 2020). These data illustrate that sympathoinhibition is a possible mediator of the kidney, and possibly cardiovascular, protective effects of SGLT2 inhibitors. Another study in a diabetes-induced rabbit model demonstrated that the SGLT2 inhibitor empagliflozin reduced the hyperactive sympathetic response caused by diabetes to similar levels as in non-diabetic rabbits and suppressed the renal sympathetic baroreflex (Gueguen et al., 2020). These reductions were also observed with another proximal diuretic, namely acetazolamide, but not with insulin or perindopril. The lack of effect in SNS activity during treatment with insulin and perindopril suggests that specific proximal natriuretic effects are involved to blunt SNS activity (Gueguen et al., 2020). Further clinical research is needed to confirm these findings and to investigate whether blunting of SNS activity is causal to kidney benefits seen with SGLT2 inhibitors.

In addition, local and systemic effects on inflammation and fibrosis may contribute to beneficial kidney outcomes with

Figure 2. Mechanisms of action for how SGLT2 inhibitors protect kidney function

(A) The beneficial effects of SGLT2 inhibitors on kidney function can be explained by multiple pathways, which include favorable effect on glomerular hemodynamics by adenosine-mediated tubuloglomerular feedback, which is associated with long-term preservation of kidney function.

(B) Experimental studies have shown that SGLT2 inhibition inhibits NHE3, which contributes to the diuretic properties of SGLT2 inhibitors.

(C) Reduced fibrosis by inhibiting fibrosis-mediating factors such as nuclear factor-κB (NF-κB), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and mammalian target of rapamycin complex 1 (mTORC1).

(D) Metabolic alterations and activation of transcriptional factors such as Sirtuin 1 (SIRT1), 5' adenosine monophosphate-activated protein kinase (AMPK), and hypoxia-inducible transcription factor-2α (HIF-2α), which may drive autophagy and ultimately kidney protection.

effects of the SGLT2 inhibitor dapagliflozin in patients with CKD with or without T2D (Heerspink et al., 2020; Wheeler et al., 2021). These results also extend previous findings from the DECLARE TIMI-58 trial, in which the vast majority of patients did not have CKD, to patients with impaired kidney function (Mosenzon et al., 2019). The DAPA-CKD trial showed reduced risk of kidney failure, death from cardiovascular causes or heart failure hospitalization, and all-cause mortality in these patients with CKD with statistically significant effects in reducing the risks of

SGLT2 inhibitors. SGLT2 inhibitors reduce nuclear factor-κB, interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and other inflammatory factors implicated in DKD pathogenesis in experimental models of diabetes (Dekkers et al., 2019; Mancini et al., 2018). Similar effects on inflammatory mediators, including reductions in urinary IL-6 and MCP-1 and serum tumor necrosis factor receptor 1 and IL-6, were observed in clinical trials of SGLT2 inhibitors in patients with T2D (Mancini et al., 2018). Whether these effects represent direct effects or whether they are secondary to increased glycosuria and reduced plasma glucose levels is unknown. In this respect it is interesting to note that a head-to-head study comparing canagliflozin with glimepiride demonstrated that at equal glycemic control canagliflozin reduced pro-inflammatory mediators, suggesting that direct anti-inflammatory effects may be involved (Heerspink et al., 2019).

SGLT2 INHIBITION IN PATIENTS WITHOUT DIABETES

The above-mentioned mechanisms of SGLT2 inhibitors could also be relevant for the treatment of CKD in patients without diabetes as these mechanisms are largely independent of improvements in glycemic control. Recent findings of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial support this notion by demonstrating beneficial

kidney failure both in the subgroup of patients with and without T2D (Heerspink et al., 2020). In addition, the EMPEROR-Reduced and DAPA-HF trials demonstrated that in patients with heart failure and reduced ejection fraction with and without T2D, SGLT2 inhibitors reduce the risk of heart failure hospitalizations or cardiovascular death and slow the progression of kidney function decline (Packer et al., 2020; Jhund et al., 2021). These three clinical trials demonstrate that the beneficial effects of SGLT2 inhibitors extend beyond patients with T2D and, if implemented in clinical practice, may transform the management of a broad range of high-risk patients with CKD.

SUMMARY AND FUTURE PERSPECTIVES

Large clinical trials in patients with T2D with established cardiovascular disease or cardiovascular risk factors, patients with heart failure, and patients with CKD have shown that SGLT2 inhibitors confer cardiovascular and kidney protection. These clinical benefits can only be realized if SGLT2 inhibitors are now implemented in clinical practice. Unfortunately, history has taught us that implementation of new therapies in clinical practice is a slow process. For example, although the renoprotective effects of ACE inhibitors and ARBs were demonstrated in the late 1990s and early 2000s, only 21% of patients with CKD receive these drugs in the United States (Tuttle et al.,

2019). Improving awareness among physicians and patients about the benefits of SGLT2 inhibitors is necessary to implement them in practice. In this respect, it is important to explain how SGLT2 inhibitors afford renoprotection as this will help physicians to master competency in prescribing and managing SGLT2 inhibitors.

Several theories have emerged that could explain the molecular mechanism underlying the protective effects of SGLT2 inhibitors in the heart and kidney. In our view, the reduction in intraglomerular pressure is the most important mechanism responsible for the clear effects of SGLT2 inhibitors. Several mechanistic pathways targeted by SGLT2 inhibitors may result in reductions in intraglomerular pressure and GFR. Restoration of TGF through adenosine-mediated pathways is a plausible mechanism and has been studied in humans and animals (Kido-koro et al., 2019; Rajasekeran et al., 2017). However, other mechanisms may be involved as well. The hypothesis that SGLT2 inhibitors may modify the trajectory of cell response from a defense to a dormancy program as it occurs during hibernation in animals may also explain reductions in renal blood flow and GFR (Zancanaro et al., 1999; Suh et al., 2014). In addition to the reduction in intraglomerular pressure, other effects such as reduction in hypoxia as well as changes in renal metabolism and transcription factors may be involved. However, mechanistic clinical studies are required as most of the evidence to date is derived from experimental cell or animal studies. Thus, dedicated mechanistic human studies are vital to educate physicians and patients about the effective and safe use of these drugs in various clinical settings in order to rapidly facilitate these drugs in clinical practice.

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Figure 2 was created with [biorender.com](https://www.biorender.com).

DECLARATION OF INTERESTS

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