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Renal physiology of glucose handling and therapeutic implications

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ABSTRACT

The rationale for using sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes (T2D) has evolved over the last decade. Due to the effects on glucosuria and body weight loss, SGLT2 inhibitors were originally approved for glycemic control in T2D. Since glucosuria is attenuated in chronic kidney disease (CKD) Stages 3–5, initial regulatory approval for SGLT2 inhibitor use was limited to patients with T2D and preserved estimated glomerular filtration rate. Over time, however, it has become increasingly apparent that these therapies have a variety of important pharmacodynamic and clinical effects beyond glycemic lowering, including antihypertensive and antialbuminuric properties, and the ability to reduce glomerular hypertension. Importantly, these sodium-related effects are preserved across CKD stages, despite attenuated glycemic effects, which are lost at CKD Stage 4. With the completion of cardiovascular (CV) outcome safety trials—EMPA-REG OUTCOME, CANVAS Program and DECLARE TIMI-58—in addition to reductions in CV events, SGLT2 inhibition consistently reduces hard renal endpoints. Importantly, these CV and renal effects are independent of glycemic control. Subsequent data from the recent CREDENCE trial—the first dedicated renal protection trial with SGLT-2 inhibition—demonstrated renal and CV benefits in albuminuric T2D patients, pivotal results that have expanded the clinical importance of these therapies. Ongoing trials will ultimately determine whether SGLT2 inhibition will have a role in renal protection in other clinical settings, including nondiabetic CKD and type 1 diabetes.

Keywords: cardiovascular disease, diabetes, diabetic kidney disease, heart failure

INTRODUCTION

Hyperglycemia is a pivotal factor in the cascade of events leading to the initiation and progression of renal and cardiovascular (CV) complications in patients with diabetes. Despite this mechanistic paradigm, maintenance of tight glycemic control, paradoxically, has little or no impact on CV event reduction [1] and has modest protective effects on renal complications [2]. Specifically, for effects in the kidney, tight glycemic control consistently reduces albuminuria progression as a surrogate of diabetic kidney disease (DKD) worsening. In contrast, protective effects on 'hard' renal endpoints such as end-stage kidney disease have been relatively limited to long-term follow-up of the ADVANCE-ON trial—a benefit that was seen beyond the duration of the trial [3]. The physiological mechanisms responsible for this lack of benefit with intensive control are not known. Some older-generation glucose-lowering therapies used in previous trials, such as sulfonylureas, are associated with weight gain, hypertension, significant hypoglycemic risk or retention of salt and water, which may offset any potential benefits associated with concomitant improvements in glycemic control with these agents [4–7]. Regardless of the mechanism, patients with diabetes remain at high risk for the development of CV and renal complications despite achievement of glycemic and blood pressure (BP) targets, the use of renin–angiotensin–aldosterone (RAS) inhibitors and achievement of lipid control with statins. There is therefore a large unmet need to identify effective and safe glucose-lowering agents to improve glycemic control, while avoiding the potential pitfalls of older-generation glucose-lowering agents.

Due to effects on glucosuria resulting in hemoglobin A1c (HbA1c) reduction, sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed exclusively for targeting glycemic control in patients with type 2 diabetes (T2D). However, the

rationale for using SGLT2 inhibitors in T2D patients has evolved over time. Since glucosuria is attenuated with chronic kidney disease (CKD) Stages 3–5, SGLT2 inhibitors initially had regulatory approval only in patients with preserved renal function. Over time, however, it became increasingly apparent that these therapies modify a variety of important nonglycemic pathways, including natriuresis-related physiological and clinical effects, thereby contributing to antihypertensive and antialbuminuric properties and the ability to reduce glomerular hypertension. In contrast with attenuation of glycemic-lowering effects in parallel with glomerular filtration rate (GFR) decline, the sodium-related effects of SGLT2 inhibition are preserved across CKD stages and persist down to Stage 4 [8–11]. Furthermore, exploratory analyses from CV outcome trials (CVOTs) have been most closely linked with clinical markers of plasma volume contraction, such as increases in hemoconcentration and hematocrit, rather than improvements in HbA1c, with respect to CV benefits [12]. Therefore there is a striking discordance between the effects of SGLT2 inhibitors on glucosuria versus natriuresis-related pharmacodynamic effects in the setting of diabetes. These observations likely have implications for the benefits of SGLT2 inhibitors in renal outcome trials, in which patients experienced only modest changes in HbA1c. Accordingly, it is important for clinicians to appreciate not only the glycemic but also the nonglycemic, natriuresis-based effects of SGLT2 inhibitors, especially in patients with renal function impairment where glucosuria can be modest or even lost, even though cardiorenal clinical benefits—especially for heart failure and DKD progression—are still robust.

SGLT2 INHIBITION, GLYCEMIC CONTROL AND BODY WEIGHT LOSS

SGLT2 inhibition, used alone or in combination with older-generation glucose-lowering therapies, improves glycemic control and, in the absence of insulin secretagogues such as sulfonylureas or insulin itself, has a low risk of hypoglycemia. Fortunately, based on limited available data, SGLT2 inhibitors can safely be used with newer glucose-lowering therapies such as glucagon-like peptide-1 receptor agonists (GLP-1RA), resulting in additive metabolic and BP-lowering effects [13]. Although beyond the scope of this review, there is also significant interest in potential additive end-organ benefits with a combination of SGLT2 inhibitors and GLP-1RA, as described elsewhere, due to DKD and heart failure protection with the former and lower atherosclerotic CV risk with the latter [14]. SGLT2 inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors can similarly be used safely together for additional HbA1c lowering, although this combination has not been shown to lead to additive albuminuria lowering and DPP4 inhibition does not have any known end-organ protective benefits [15]. In patients with preserved renal function, SGLT2 inhibitors induce a glucosuric response, leading to HbA1c reductions of ∼0.6–0.8% in T2D patients on average and can have more pronounced effects on hyperglycemia in patients with poor glycemic control at baseline (HbA1c >10%) [16] due to the increased filtered glucose load. As kidney function declines in the setting of DKD, however, the glucosuric effects of SGLT2 inhibitors also gradually decrease, leading to more modest HbA1c reductions [0.3–0.4% in CKD Stage 3A (45–59 mL/min/1.73 m^2), 0.2–0.3% in CKD Stage 3B (30–44 mL/min/1.73 m^2) and no effect in CKD Stage 4 (<30 mL/min/1.73 m^2)] [8–11]. As discussed in another chapter in this supplement, comparable glucose-lowering effects also occur in patients with type 1 diabetes (T1D), albeit with an increase in the risk for diabetic ketoacidosis versus T2D on the basis of lowered insulin doses and perhaps an increase in glucagon secretion [17].

In contrast with many other antihyperglycemic agents, which are associated with body weight gain, SGLT2 inhibitors have a favorable effect on the loss of body weight, an effect that is observed with all agents in this class [18]. Body weight loss starts within 3 days of starting SGLT2 inhibition, likely on the basis of natriuretic/diuretic effects and increased urine excretion, resulting in fluid loss and mild contraction of plasma volume [19]. This acute natriuresis tends to attenuate after 3–4 days of administration but body weight loss continues, likely because of a reduction in adipose tissue [19, 20]. During chronic treatment, the net effect of SGLT2 inhibition on body weight loss is, based on mechanistic body composition studies, ∼2–3 kg, consisting of 60–70% loss of adipose tissue and the remainder due to loss of fluid [20, 21]. The nadir in body weight loss occurs after ∼6 months, and ongoing weight loss is not achieved despite ongoing glucosuria, possibly due to increased hunger and/or changes in hepatic gluconeogenesis [20–22]. From a clinical perspective, SGLT2 inhibition in T2D patients decreases abdominal circumference, body weight [23] and body mass index [24], effects that are also observed in the setting of T1D [25], which makes these agents a preferred treatment option for coadministration with certain classes of glucose-lowering therapies that are associated with either fluid retention or body weight gain.

SGLT2 INHIBITION AND ORGAN-SPECIFIC CHANGES IN ADIPOSE TISSUE CONTENT

In addition to the loss of body weight, caloric loss induced with SGLT2 inhibition reduces organ-specific fat content, including in the liver and the heart, which may ultimately contribute to cardiorenal benefits by, for example, suppressing systemic inflammation. In the liver, steatohepatitis is a novel area of potential benefit for SGLT2 inhibitors in T2D (Figure 1). In T2D patients, canagliflozin significantly reduced body weight, liver enzymes and bilirubin at 26 weeks [26]. Similarly, in a retrospective analysis of nonalcoholic fatty liver disease (NAFLD) patients with concomitant T2D treated with SGLT2 inhibition, serum aminotransferases decreased over time [24]. In a separate study, when added to incretin-based therapies, SGLT2 inhibition with ipragliflozin decreased HbA1c levels and serum alanine aminotransferase levels in T2D patients with NAFLD [27]. Interestingly, other glucose-lowering therapies with a similar range of HbA1c reduction are not associated with improvements in levels of NAFLD markers. In addition to effects on liver enzymes, SGLT2 inhibition reduced histological evidence of steatohepatitis, with reductions in steatosis, inflammation, hepatocyte ballooning and 3-point NAFLD activity score in a case report [28], and histological evidence of improvement of

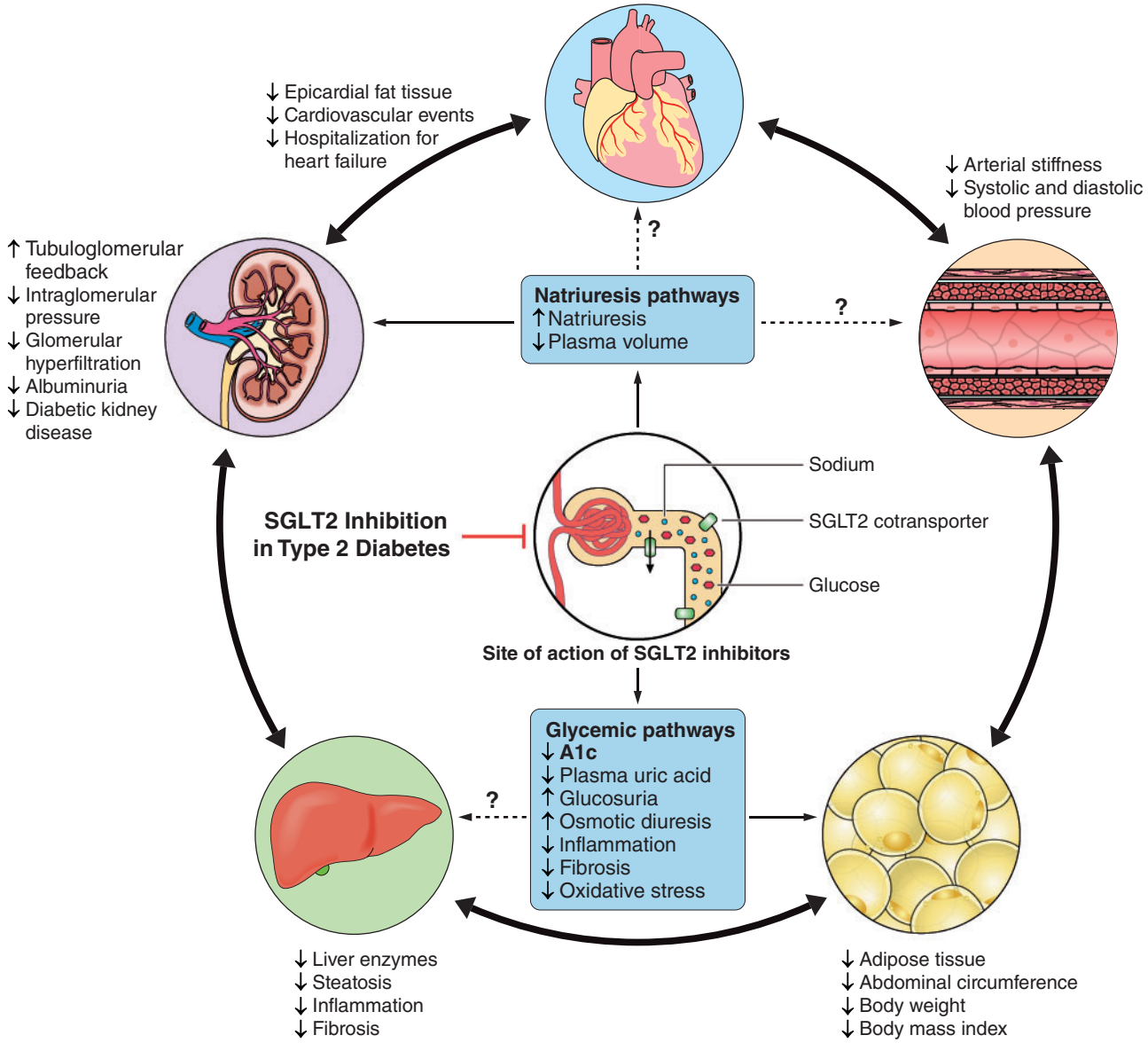

FIGURE 1: Metabolic and cardiorenal protective effects of SGLT2 inhibitors.

NAFLD was also reported in a pilot study involving patients with T2D [29]. While SGLT2 inhibition may be beneficial for fatty liver disease associated with T2D, it remains incompletely understood whether these effects are related to glycemic responses or are due to adipose-lowering or other pathways that remain to be identified. Furthermore, it is not yet known whether improvements in NAFLD result in protection from CV or renal complications. Accordingly, more research is merited in this area in order to evaluate these potential effects, ideally in larger, dedicated NAFLD studies in T2D.

NAFLD is perhaps the most well-recognized consequence of excess adiposity at the organ-specific level in patients with either obesity or T2D. However, epicardial adipose tissue has also been associated with inflammation, impaired cardiac contractility, heart failure and an increased risk of CV complications [30–32]. In addition to a decrease in total body weight and liver fat, SGLT2 inhibition reduces epicardial fat in patients with T2D at 12 weeks when evaluated by magnetic resonance imaging [31], independent of glycemic lowering, even in the absence of systemic obesity [33, 34]. While the clinical implications of changes in epicardial fat with SGLT2 inhibition are not yet known, these observations highlight a potential role for suppressing inflammation in the CV system leading to better outcomes.

SGLT2 INHIBITION AND BP LOWERING

T2D is associated with elevated systolic BP in >70% of individuals and contributes to the development of CV and cerebrovascular events and to the initiation and progression of DKD [35]. SGLT2 inhibitors uniformly decrease office BP in hypertensive adults with T2D by ∼3–5 mmHg systolic and ˋ1–2 mmHg diastolic [35], regardless of baseline kidney function. Accordingly, while the clinical consequences of glucosuria—HbA1c and body weight reductions—are attenuated with estimated GFR (eGFR) <60 mL/min/1.73 m^2, natriuresis-related effects—such

as BP lowering—are preserved in the setting of impaired kidney function in several separate analyses in T2D patients [36]. In addition, in 24-h ambulatory BP monitoring studies in T2D patients, systolic BP decreases by −3.76 mmHg and 24-h ambulatory diastolic BP by −1.83 mmHg [37]. Overall, BP lowering with SGLT2 inhibition is modest, but clinically significant, and could be beneficial for reducing heart failure and CV risk in selected patients [38]. BP-lowering effects of the same magnitude observed in adults with T2D occur in the setting of T1D and have the potential to positively impact cardiorenal risk—a possibility that warrants further clinical investigation [39]. This is particularly relevant given the overlapping benefits on other clinical parameters in patients with T1D versus T2D.

While it is not yet established how BP lowering occurs with SGLT2 inhibition, several factors may be involved (Figure 1). First, diuretic effects are likely involved [40], leading to natriuresis, osmotic diuretic effects and a contraction in plasma volume [41, 42]. A reduction in plasma volume of ∼7% was reported at 12 weeks, measured with radiolabeled albumin methods, and occurs in the context of modest BP lowering (5 mmHg) that is comparable with the impact of traditional thiazide diuretics [40]. Interestingly, in most studies, the initial decline in plasma volume measures with thiazides tends to return to baseline by Week 8, whereas the effect persists with SGLT2 inhibitors [40]. While the relative contribution of natriuretic versus osmotic pathways to BP lowering is controversial, relatively little data have been published in humans—especially with end-organ disease such as heart failure and/or DKD—and longer-term systemic hemodynamic changes are most closely associated with natriuresis [43]. Other supportive evidence for a contraction of plasma volume with these agents includes an increase in circulating and urinary levels of RAS hormones, at least in the short term [19, 44, 45], and increases in serum albumin and hematocrit that are thought to reflect hemoconcentration [12]. Others have reported that sodium content in skin, an important reservoir for sodium in humans, also decreases with SGLT2 inhibition, suggesting a reduction in total body sodium content, which may be beneficial for reducing the risk of being hospitalized for heart failure [46]. Importantly, plasma volume contraction with SGLT2 inhibition is not associated with sympathetic nervous system activation or a reflex tachycardia [47], for reasons that are not yet understood, whereas older generation thiazide diuretics modestly raise heart rate [48, 49]. Additional insights into acute versus chronic natriuretic and volume effects of SGLT2 inhibitors will hopefully be obtained from the ongoing DAPASALT trial (NCT03152084) in patients with T2D with and without kidney disease, as well as a cohort of nondiabetic individuals with kidney disease.

In addition to effects on plasma volume, BP lowering may be achieved by reducing peripheral vascular abnormalities associated with diabetes such as arterial stiffness and endothelial dysfunction [50], including in the coronary arteries in animals [51]. If these changes are direct rather than a consequence of BP lowering due to lowering of plasma volume, then arterial vasorelaxation could lower systemic BP. From a metabolic perspective, it has been hypothesized that SGLT2 inhibitors reduce BP by reducing body weight and HbA1c. Given the multiple pathways involved, further mechanistic studies are warranted to elucidate the antihypertensive effects of SGLT2 inhibitors, especially in T2D patients with kidney disease and/or CV disease and in patients without diabetes.

Regardless of the mechanism, the impact of SGLT2 inhibitors on BP has several specific clinical implications. First, the diuretic effects of SGLT2 inhibitors may permit a reduction in the dose of other diuretic agents such as loop diuretics [52]. Second, given their BP-lowering and natriuretic effects, SGLT2 inhibitors should be part of the 'sick day' management advice given to T2D patients and are medications that should be held during significant intercurrent illness or hospitalization. Third, BP lowering with SGLT2 inhibitors is modest, but is also not associated with changes in electrolytes such as hyponatremia or hyperkalemia, which can occur with diuretics and RAS inhibitors, respectively. Accordingly, in RAS inhibitor–intolerant patients with hyporeninemic hypoaldosteronism, SGLT2 inhibition may be a reasonable alternative therapy for cardiorenal protection since patients in completed CVOTs benefitted from SGLT2 inhibition regardless of background RAS inhibitor use [53].

SGLT2 INHIBITION AND KIDNEY PROTECTION

The renal protective effects of SGLT2 inhibitors have been the topic of significant discussion, and it is likely that, as with the CV benefits, salutary effects in the kidney are derived on the basis of many converging factors related to both sodium and glucose (Figure 1). From a natriuretic perspective, it is increasingly clear from models of diabetes-related hyperfiltration that augmented increased distal natriuresis to the macula densa in response to SGLT2 inhibition activates a reflex called tubuloglomerular feedback [54, 55]. Tubuloglomerular feedback is a minute-by-minute autoregulatory feedback system by which GFR is maintained at a constant level despite minor changes in BP and volume. Tubuloglomerular feedback is based on the concept that if sodium delivery to the kidney, and hence filtration by the glomerulus, is reduced for any reason, then sodium delivery to the macula densa at the juxtaglomerular apparatus is also decreased. This would normally occur under conditions of volume depletion or hypotension and results in afferent arteriolar vasodilatation—likely via adenosine-related mechanisms discussed below—in an attempt to regulate and keep renal perfusion and GFR constant [55]. In the context of diabetes, proximal sodium and glucose reabsorption is enhanced, leading to diminished distal delivery. As a consequence, the same tubuloglomerular feedback pathways are suppressed, leading to afferent vasodilatation, renal hyperperfusion and hyperfiltration. SGLT2 inhibition is associated with a restoration of distal sodium delivery, which causes an increase in sodium reabsorption at the macula densa [9]. This sodium reabsorption process is energy dependent and leads to adenosine triphosphate breakdown to adenosine, which then binds to the adenosine-1 receptor at the afferent arteriole and induces renal vasoconstriction [56]. Using *in vivo* intrarenal imaging, this sequence of events was visualized in recent preclinical experimental studies and directly verified that SGLT2 inhibitor–

mediated afferent vasoconstriction is dependent on adenosine signaling [57]. In clinical practice, this hemodynamic effect may be responsible for the characteristic acute dip in eGFR with SGLT2 inhibition—an effect that occurs even after a single dose [58]—which is reversible after cessation of the drug. This decrease in intraglomerular pressure is also thought to account for the substantial albuminuria-lowering effect of SGLT2 inhibitors [59], which occurs independently of other clinical factors that impact urine albumin excretion [60, 61]. As an important caveat, physiological effects suggestive of afferent vasoconstriction leading to reduced hyperfiltration have been demonstrated in experimental work in animals and in patients with T1D with hyperfiltration. While recent work in nonhyperfiltering, older patients with T2D has similarly shown acute decreases in measured GFR, this may be related to other efferent vasodilatory mechanisms, including alteration in the RAS or renal prostanoid system—hypotheses that require further investigation [62].

Aside from hemodynamic mechanisms, SGLT2 inhibition impacts a variety of other factors linked with CKD progression. It has been recognized for >10 years that the inhibition of glucose reabsorption at the proximal tubule suppresses pathways linked with inflammation and fibrosis [63], including cytokines and chemokines *in vitro* and *in vivo*, the intrarenal RAS and markers of oxidative stress [64, 65] and uric acid [66–68]. Anti-inflammatory effects have also been replicated in humans with T2D [69]. While these anti-inflammatory and antifibrotic effects may be due to suppression of hyperglycemia-related pathways, it is also possible that a decline in intraglomerular pressure via tubuloglomerular feedback attenuates shear stress and wall tension in the glomerulus, thereby reducing renal inflammation/fibrosis. Moreover, a decrease in renal hypoxia—due to less proximal tubular demand for both sodium and glucose reabsorption—may prevent the activation of proinflammatory and profibrotic pathways [70]. Additional anti-inflammatory benefits may be derived at the level of both the heart and the kidney via changes in energy substrate utilization and/or delivery [71] through decreases in organ-specific adiposity described above that attenuate fibrosis [72] and by lowering uric acid [68]. Interestingly, SGLT2 inhibitors lower uric acid by inducing a uricosuric effect, as described elsewhere [68]; uric acid lowering has been linked with CV benefits in CVOTs with SGLT2 inhibition and with protection against DKD progression [12, 73]. The distinction between sodium versus glucose-related cardiorenal protection is of interest beyond simply understanding physiological principles, due to the potential for future use of these agents in normoglycemic, nondiabetic individuals, which will ultimately be determined in ongoing trials such as Dapa-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) (NCT03036150) and EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) (NCT03594110). To this point, experimental work has shown benefits in mesangial cells, human proximal tubule cells and in nondiabetic experimental animal models independent of hyperglycemia [70, 74]. Furthermore, in *post hoc* analyses of EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)] (NCT01131676), kidney protective effects of SGLT2 inhibitors are observed regardless of baseline HbA1c or changes in HbA1c over time [75]. Together, this work suggests more ubiquitous protective applications for these agents (Figure 2).

To date, however, cardiorenal benefits have only been reported in patients with T2D. Three CVOTs with SGLT2 inhibitors, including EMPA-REG OUTCOME [76], CANVAS (CANagliflozin cardioVascular Assessment Study) (NCT01032629), DECLARE-TIMI58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) (NCT01730534) have been completed in T2D participants at high CV risk. The majority of participants had preserved renal function (60–90 mL/min/1.73 m^2) and only a small minority had macroalbuminuria. In both EMPA-REG OUTCOME and CANVAS, consistent effects of SGLT2 inhibition were observed for superiority in reducing CV events, including major adverse cardiovascular events (MACEs) and hospitalization for heart failure. In DECLARE-TIMI58, dapagliflozin reduced the coprimary endpoint of CV death or hospitalization for heart failure. From a cardiorenal perspective, it is important to emphasize that the magnitude of glycemic reduction and body weight loss was minimal in these trials, by design, suggesting that clinical benefits were on the basis of natriuretic/osmotic, hemodynamic or other pharmacodynamic effects rather than improvements in hyperglycemia. While EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI58 were not dedicated renal outcome studies, favorable effects on secondary renal endpoints, including 40–50% reductions in eGFR (depending on the trial), renal replacement therapy or death from renal causes, were observed in these trials.

The CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial (NCT02065791) is the first dedicated renal protection study reported with SGLT2 inhibitors in patients with T2D with DKD (eGFR 30–90 mL/min/1.73 m^2) and macroalbuminuria (urine 300–500 mg/g) on a background of maximally tolerated angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment. Canagliflozin was associated with an expected early dip in eGFR, likely as a consequence of tubuloglomerular feedback pathways described above. In keeping with reduced intraglomerular pressure, there is a concomitant reduction in urine albumin excretion and a modest but clinically significant 3.30 mmHg reduction in systolic BP. The rate of decline in kidney function was significantly different in the canagliflozin versus placebo-treated groups, with an eGFR slope difference of −2.74 mL/min/1.73 m^2/year in the two groups. In this trial, the primary endpoint (end-stage kidney disease, doubling of serum creatinine or renal or CV death) was reduced by 30% and end-stage kidney disease was reduced by 32%. CV death or hospitalization for heart failure was reduced by 31%, MACE reduced by 20%, hospitalization for heart failure by 39% and the composite of end-stage kidney disease, doubling of serum creatinine or renal death reduced by 34%. Importantly, trial participants continued on canagliflozin, even if eGFR was <30 mL/min/1.73 m^2, until CKD Stage 5 or

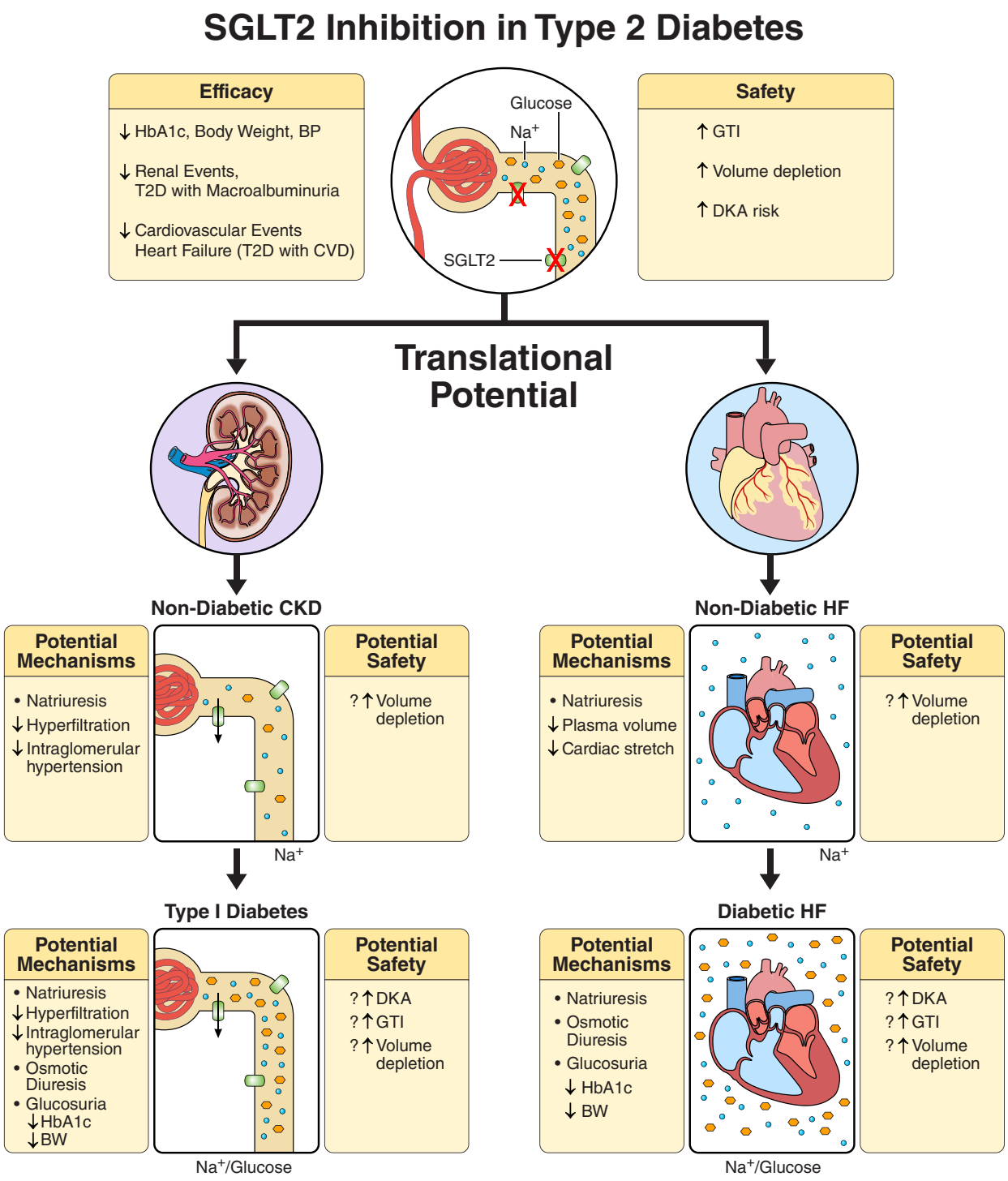

FIGURE 2: SGLT2 inhibition and potential for translation to use in other conditions. GTI, genital tract infection; DKA, diabetic ketoacidosis; CVD, cardiovascular disease; HF, heart failure; Na^+, sodium; BW, body weight.

renal replacement therapy occurred, which may have implications for its safe and effective use beyond current regulatory restrictions down to 30 mL/min/1.73 m^2 in some jurisdictions. Finally, for safety, beyond the known risks of genital mycotic infections and diabetic ketoacidosis, there was no increase in the risks of either amputation or fracture in CREDENCE. These concerns with canagliflozin had arisen due to significant increases in these adverse events in the CANVAS program. Observations from CREDENCE are therefore reassuring and demonstrate safety around these issues in a high-risk renal cohort.

In summary, it is increasingly clear that although SGLT2 inhibitors have a major impact on renal glucose handling and improve glycemic control, long-term benefits in CVOTs and in CREDENCE were likely unrelated to improvements in glycemic control. This hypothesis is predicated on several

Table 1. Clinical and physiological parameters that are impacted by SGLT2 inhibitors in patients with both T1D and T2D

Physiological parameter	Magnitude of effect	Possible clinical benefit
↓Hyperglycemia	↓HbA1c ∼0.7%	↓Microvascular risk
↑Natriuresis	Acute (24-h urine): absolute ↑fractional excretion of sodium 0.8% [58], 24-h sodium effect variable, generally no change [79, 80]	↓BP, body weight along with eGFR dip, ↓albuminuria
	Chronic (24-h urine): no change [81–83]	Acute natriuresis, along with osmotic effects, establishes a new steady state of relative euvolemia, which may reduce heart failure risk.
↓Body weight	↓2–3 kg weight loss	↓BP, improved metabolic profile
↓Insulin requirements[a]	↓10–15%	↓Hypoglycemia risk, ↓weight gain, ↑ natriuresis
↓BP	↓3–5 mmHg SBP, 1–2 mmHg DBP	↓Micro- and macrovascular risk
↑Hemoconcentration	↑3–7% hematocrit	↓BP, ↓risk of heart failure
↓Renal hyperfiltration	↓20% in hyperfiltration	↓Albuminuria and DKD risk
↓Plasma uric acid [68, 84]	↓10–15% uric acid	↓Possible BP, renal and CV benefits

[a]Most data around changes in insulin dosing with SGLT2 inhibitors have been described in patients with T1D. Similar approaches may be used in patients with T2D with tight glycemic control. For natriuresis, chronic treatment in most studies was >4–7 days.

Table 2. Clinical scenarios when SGLT2 inhibitor use should be avoided

Scenario	Potential risk
Perioperative setting	Volume depletion, ketoacidosis
Intravenous contrast study	Acute kidney injury
Dynamic volume status (e.g. gastrointestinal loss, sepsis syndrome)	Volume depletion, acute kidney injury
History of ketoacidosis	Recurrent ketoacidosis
Severe and/or recurrent genital tract infections	Genital tract infection
Active limb ischemia, gangrene	Risk of amputation in the CANVAS program
Acute decompensated heart failure	Hypotension, prerenal ischemia
Urological conditions such as chronic bladder catheterization, bladder outlet obstruction	Unknown, potential for urinary tract infection

factors, including known pharmacodynamic effects of SGLT2 inhibitors, whereby glucosuria attenuates with declining kidney function; clinical cardiorenal benefits extend to patients across CKD Stages 1–3; mild glucose-lowering achieved by these agents in CVOTs and in CREDENCE, which is not sufficient to produce such robust cardiorenal protection; and the lack of interaction with baseline HbA1c or changes in glycemic control with protective effects in long-term trials.

SGLT2 INHIBITION AND THERAPEUTIC IMPLICATIONS

In light of emerging evidence from CVOTs and a dedicated renal outcome study, CREDENCE, there is increasing enthusiasm for reevaluating the positioning of SGLT2 inhibitor therapies in clinical practice toward the use of these therapies as both glucose-lowering therapies and cardiorenal protective agents, with protective effects extending to patients with CKD in whom HbA1c lowering may not even be relevant. This transition has already begun, with several major international diabetes, nephrology and cardiology associations advocating to prioritize the use of SGLT2 inhibition after metformin in patients with T2D patients with heart failure or DKD [77, 78].

Since the cardioprotective effects of SGLT2 inhibitors are predominantly associated with reductions in hospitalizations for heart failure, coupled with mechanistic observations on plasma volume reduction, hematocrit and natriuresis, there is both clinical and mechanistic rationales to pursue SGLT2 inhibition in the setting of acute and chronic heart failure with and without T2D. Accordingly, as reviewed elsewhere, ongoing prospective heart failure trials with SGLT2 inhibitors are enrolling patients with and without diabetes and will ultimately clarify the role of SGLT2 inhibition in the setting of heart failure with both reduced and preserved ejection fraction [49]. Mechanistically, however, many unanswered questions remain, since SGLTs are not present in the heart. It is not known whether SGLT2 inhibitors directly impact cardiac physiology or instead modify heart function via sodium–hydrogen exchangers, calcium-binding proteins, energy substrate utilization or other factors that have yet to be identified [49]. It is therefore unclear whether these same pathways will be relevant outside the setting of T2D.

While the mechanisms and clinical efficacy for SGLT2 inhibition in heart failure remain unknown, the renal protective effects observed with canagliflozin in CREDENCE are unequivocal. Indeed, the results of the CREDENCE trial are pivotal and practice-changing for albuminuric patients with T2D. Observations from this trial have also, finally, demonstrated an effective adjunctive renoprotective therapy to RAS blockade after a long period of neutral CKD trials dating back to the Reduction of Endpoints in Noninsulin-dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study and the Irbesartan Diabetic Nephropathy Trial. Importantly, in CVOTs with SGLT2 inhibitors and in CREDENCE, CV and renal benefits are seen regardless of the use of RAS blockers at baseline. While many mechanisms may be at play for renoprotection with SGLT2 inhibitors in DKD, natriuresis may be a mechanism that explains both early protective effects, as well as benefits in patients with established DKD, and the reduction in hospitalization for heart failure. Ongoing renal protection trials such as EMPA-KIDNEY and Dapa-CKD with further

knowledge in this field by assessing whether or not benefits from CREDENCE extend to other CKD populations, including those with nondiabetic CKD, to patients with lower eGFR and no albuminuria and, in the case of EMPA-KIDNEY, patients with T1D (Figure 2). Nevertheless, despite these benefits, until further data are available, there are some clinical conditions in which SGLT2 inhibitor use should be avoided, as listed in Table 2.

CONCLUSION

The available clinical evidence for renal glucose handling with SGLT2 inhibition confirms not only effective glucose lowering in patients with preserved renal function, but also ancillary reductions in body weight loss and a favorable metabolic profile in T2D. Regardless of glucose lowering, the associated natriuretic properties of SGLT2 inhibition may, in fact, be of far greater importance for cardiorenal protection, independent of glucose-lowering or eGFR level. In the future, based on nonglycemic effects, the use of SGLT2 inhibition for cardiorenal protection may extend beyond patients with T2D—a possibility that will ultimately be determined in the course of ongoing clinical trials.

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AUTHORS' CONTRIBUTIONS

All authors contributed to authorship, critically reviewed the manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

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