Published in final edited form as:

Annu Rev Physiol. 2021 February 10; 83: 503–528. doi:10.1146/annurev-physiol-031620-095920.

Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function

Volker Vallon[1,2,3], **Subodh Verma**[4,5]

[1]Division of Nephrology and Hypertension, Department of Medicine, University of California, San Diego, La Jolla, California 92093, USA

[2]Department of Pharmacology, University of California, San Diego, La Jolla, California 92093, USA

[3]VA San Diego Healthcare System, San Diego, California 92161, USA

[4]Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario M5B 1W8, Canada

[5]Departments of Surgery and Pharmacology and Toxicology, University of Toronto, Toronto, Ontario M5S 1A8, Canada

Abstract

SGLT2 inhibitors are antihyperglycemic drugs that protect kidneys and the heart of patients with or without type 2 diabetes and preserved or reduced kidney function from failing. The involved protective mechanisms include blood glucose–dependent and –independent mechanisms: SGLT2 inhibitors prevent both hyper- and hypoglycemia, with expectedly little net effect on HbA1C. Metabolic adaptations to induced urinary glucose loss include reduced fat mass and more ketone bodies as additional fuel. SGLT2 inhibitors lower glomerular capillary hypertension and hyperfiltration, thereby reducing the physical stress on the filtration barrier, albuminuria, and the oxygen demand for tubular reabsorption. This improves cortical oxygenation, which, together with lesser tubular gluco-toxicity, may preserve tubular function and glomerular filtration rate in the long term. SGLT2 inhibitors may mimic systemic hypoxia and stimulate erythropoiesis, which improves organ oxygen delivery. SGLT2 inhibitors are proximal tubule and osmotic diuretics that reduce volume retention and blood pressure and preserve heart function, potentially in part by overcoming the resistance to diuretics and atrial-natriuretic-peptide and inhibiting Na-H exchangers and sympathetic tone.

Keywords

SGLT2 inhibitor; diabetic nephropathy; heart failure; HFrEF; HFpEF; chronic kidney disease

vvallon@ucsd.edu.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide growing public health problem that is associated with a rising prevalence and a high mortality rate. Good blood glucose control early in the disease can reduce the risk of micro- and macrovascular complications, including cardiovascular disease (CVD), diabetic nephropathy, and mortality (1). However, for many current blood glucose–lowering drugs, including insulin, adequate glycemic control may be difficult to establish without clinically relevant unwanted side effects, such as weight gain and hypoglycemia, and these strategies may not reduce the risk of cardiovascular complications (2).

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) are a new class of antihyperglycemic drugs recently approved in T2DM (3). These drugs inhibit renal glucose reabsorption in the early proximal tubule, thereby enhancing urinary glucose excretion and lowering the glucose burden on the organism. Since 2008, the US Food and Drug Administration (FDA) has required proof of cardiovascular safety for new glucose-lowering therapies (4). SGLT2 inhibitors were in development when the guidance came into effect. Hence, there are data from large-scale clinical trials designed to confirm cardiovascular safety, but some also acquired data on microvascular complications, including diabetic kidney disease, which were reported as secondary outcomes. It was observed in three large clinical outcome trials in patients with T2DM that the SGLT2 inhibitors empagliflozin, dapagliflozin, and canagliflozin reduced the incidence of heart failure and induced salutary effects on the kidney, including lower hazard ratios for major decline in estimated glomerular filtration rate (eGFR) (5–8). Since the primary objective of these trials was to document cardiovascular safety, enrollment was targeted toward subjects at high cardiovascular risk. Furthermore, because SGLT2 inhibitors are predictably less effective at lowering blood glucose levels when GFR is low (see below), the initial trials were conducted in patients with relatively well-preserved kidney function. However, subanalyses indicated that the beneficial effects may extend to patients with chronic kidney disease (CKD) (9). The first demonstration that SGLT2 blockade slows the progression of established diabetic kidney disease and lowers the risk of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure in patients with T2DM was provided by the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial (10). These results are consistent with a previous systematic review and meta-analysis of multiple randomized controlled trials that included patients with T2DM and CKD treated with various SGLT2 inhibitors (11). Based on the findings of the CREDENCE trial, the FDA approved canagliflozin to treat diabetic kidney disease and reduce the risk of hospitalization for heart failure in patients with T2DM and diabetic kidney disease. More recently, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial showed that the SGLT2 inhibitor dapagliflozin improved relevant renal and cardiovascular outcomes in patients with CKD, regardless of the presence or absence of T2DM (12), indicating the therapeutic potential of these drugs also in the nondiabetic setting.

In the following review, we briefly introduce the physiology and regulation of SGLT2 in the kidney, followed by a discussion of potential mechanisms to explain the renoprotective and cardioprotective effects of SGLT2 inhibitors.

2. THE PHYSIOLOGY OF SGLT2 IN THE KIDNEY AND ITS UPREGULATION IN DIABETES

The daily glomerular filtrate of a normal human adult contains ~180 g of glucose, which is equal to approximately one-third of the body's caloric expenditure. In euglycemia and with normal GFR, the proximal tubule reabsorbs almost all of the filtered glucose and thereby prevents glucose from being lost into the urine. The bulk of tubular glucose uptake occurs in the "early" proximal tubule (S1/S2 segments) via high-capacity SGLT2 (Figure 1), whereas lower-capacity SGLT1 "mops up" most of the remaining luminal glucose in the "late" proximal tubule (S2/S3 segments) (for a review, see 13). Glucose then exits the cell passively through glucose transporter 2 (GLUT2) in the basolateral membrane (Figure 1). Renal clearance and micropuncture studies in knockout mice for *Sglt1* and *Sglt2* indicated that SGLT2 accounts for all glucose reabsorption in the early proximal tubule (14) and for ~97% of total renal glucose reabsorption, while SGLT1 reabsorbs the remaining ~2–3% under normoglycemic conditions (14–16). In accordance, individuals with loss-of-function mutations in SGLT1 (*SLC5A1*) excrete relatively little glucose in the urine, though they suffer intestinal glucose and galactose malabsorption (13). In contrast, individuals with loss-of-function mutations in the gene for SGLT2 (*SLC5A2*, or a condition known as familial renal glucosuria) excrete large amounts of glucose (60–120 g/day) in the urine (13).

Hyperglycemia increases the amounts of filtered glucose. At the same time, the tubular glucose reabsorption capacity increases from ~400–450 g/day to ~500–600 g/day in patients with T2DM and T1DM (13). This helps to conserve this valuable energy substrate but becomes maladaptive by sustaining hyperglycemia (Figure 1).

SGLT2 uses one sodium ion per glucose molecule and SGLT1 uses two sodium ions per glucose (13). Thus, SGLT2 uses less energy than SGLT1 by a factor of two, but SGLT1 can drive the tubular glucose concentration lower than SGLT2 by a power of two. Hence, the most energy-efficient adaptation to hyperglycemia is to increase the amount of SGLT2. Indeed, studies in humans with T2DM (17–19) and genetic rodent models of T2DM and T1DM (17, 20–22) support an upregulation of renal SGLT2 protein expression.

This upregulation is in part the consequence of the overall growth and hypertrophy of the diabetic proximal tubule (23) (Figure 1). This process is likely exaggerated on the single-nephron level in CKD when nephrons are lost and the remaining nephrons compensate by hyperfiltration and tubular growth (24). Upregulation of SGLT2 expression in the diabetic rat kidney has been linked to activation of angiotensin II (Ang II) AT1 receptors (25) and the transcription factor hepatocyte nuclear factor HNF-1α (26), which may respond to basolateral hyperglycemia sensed through GLUT2 (17) (Figure 1). HNF-1α and HNF-3β have been implicated in GLUT2 upregulation (27). Moreover, insulin phosphorylates SGLT2, thereby increasing Na^+-glucose transport (28). Thus, postprandial insulin release may increase proximal tubular SGLT2 activity to retain increased amounts of filtered

glucose, but SGLT2 activity may also be enhanced by hyperinsulinemia associated with obesity and T2DM (Figure 1).

SGLT2 protein expression is also increased by pharmacologic inhibition of SGLT2 (20, 29), suggesting negative feedback regulation by intracellular glucose. In contrast, conditions associated with enhanced proximal tubule gluconeogenesis reduced SGLT2 expression (30). As a consequence, renal SGLT2 expression could be unchanged or reduced in some individuals with T2DM as a consequence of enhanced gluconeogenesis, e.g., due to metabolic acidosis, but also due to severe tubular hypoxia or injury (13) (Figure 1).

3. SGLT2 INHIBITION IMPROVES METABOLIC CONTROL

The logic of inhibiting SGLT2 as a therapeutic strategy in diabetes starts with the role of SGLT2 in maintaining hyperglycemia (Figure 1). SGLT2 inhibitors induce a sustained urinary glucose loss of 40–80 g/day, which in patients with T2DM decreases glycated hemoglobin (HbA1C) levels by 0.5–0.7% (3). The higher the blood glucose level and GFR, the more glucose is filtered and thus excreted in response to SGLT2 blockade. The glucosuric effect also explains the main side effect of SGLT2 inhibitors, namely an increased risk of genitourinary infections (3).

SGLT2 inhibitors act on their target from the extracellular surface of the brush border membrane (31), which they reach by glomerular filtration and, as indicated for empagliflozin, also by tubular secretion (32). In the small intestine, SGLT1 may sense increases in luminal glucose concentrations to enhance the apical insertion of GLUT2 and facilitate glucose uptake (33). If, by analogy, the apical GLUT2 expression observed in the proximal tubule in experimental diabetes (13) is driven by SGLT2, then SGLT2 inhibitors may lower renal glucose reabsorption in part by inhibiting apical GLUT2 translocation (Figure 1). SGLT2 inhibition can also increase renal expression of genes involved with gluconeogenesis, bicarbonate regeneration, and ammonium formation (34). While this could reflect compensatory responses to acidification of proximal tubular cells resulting from reduced sodium/hydrogen exchanger 3 (NHE3) activity (see below), these effects were at least in part independent of tubular NHE3 and potentially indicated renal metabolic adaptations to urinary glucose loss. Alternatively, glucose may leak back into the lumen via apical GLUT2, and the resulting apical recycling of glucose promotes sodium reabsorption via SGLTs.

The beneficial renal and cardiac effects of SGLT2 inhibitors that have been observed within a few months after onset of therapy in large cardiovascular outcome trials seem not to be explained by the small effect on blood glucose control alone, and other mechanisms likely contribute. On the other hand, SGLT2 inhibitors may not induce the deleterious effects described for other antihyperglycemic drugs that can offset the benefits of improved blood glucose control on the cardiovascular system, including an increase in body weight and, particularly, an increase in hypoglycemic episodes (35). SGLT2 inhibitors do not increase the hypoglycemia risk (3) because they stop lowering blood glucose levels once the filtered glucose load falls to ~80 g/day, which can be reabsorbed by downstream SGLT1 (13, 15); in addition, metabolic counterregulation remains intact in response to SGLT2 inhibitors, which

increase plasma glucagon concentrations and thereby hepatic gluconeogenesis (3) (Figure 2). Thus, SGLT2 inhibitors may improve renal and cardiovascular outcome by simultaneously preventing blood glucose highs and lows, which results in relatively small effects on HbA1C values.

Furthermore, SGLT2 inhibition reduces body weight, initially due to the diuretic effect and subsequently by shifting substrate utilization from carbohydrates to lipids, thereby reducing body fat, including visceral and subcutaneous fat (3) (Figure 2). The released free fatty acids are also used for hepatic formation of ketone bodies, which provide additional energy substrates to improve the performance of cardiac myocytes and kidney epithelia (36–38) (Figure 2). By lowering blood glucose levels and body weight, SGLT2 inhibitors induce an improvement in beta-cell function and insulin sensitivity that is sustained (3).

Thus, spilling glucose and calories into the urine, which mimics fasting and triggers counterregulatory metabolic readjustments, provides unique benefits as an antihyperglycemic approach. This is because the body's responses to environments with scarce energy resources have been intensively tested and refined during evolution for the survival of the organism (3). In the following sections, we discuss direct and indirect kidney and heart protecting effects of SGLT2 inhibition that are, at least in part, independent of blood glucose lowering and thus have the potential to be relevant also in nondiabetic settings. In fact, the recent DAPA-CKD trial showed that the SGLT2 inhibitor dapagliflozin reduced the risk of hard clinical renal and cardiac outcomes (a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes) in patients with chronic kidney disease, regardless of the presence or absence of T2DM (12).

4. SGLT2 INHIBITION PRESERVES KIDNEY FUNCTION

4.1. SGLT2 Inhibition Lowers Glomerular Filtration Rate Initially and Preserves It in the Long Term

As the proximal tubule in the diabetic kidney grows and reabsorbs more glucose through SGLT2 and SGLT1, it also reabsorbs more sodium, followed by chloride and fluid. This causes the luminal concentration and delivery of Na, Cl, and K to the macula densa (MD_{NaClK}) to decline. This decline is mitigated, in turn, by the tubuloglomerular feedback (TGF), which causes single-nephron GFR (SNGFR) to increase and partially restore fluid and NaCl excretion. In addition, the hyperreabsorption of fluid reduces the tubular back pressure in Bowman's space (P_{Bow}), thereby increasing filtration pressure and SNGFR. These mechanisms form the basis for the tubular hypothesis of glomerular hyperfiltration in the diabetic kidney (23).

In accordance with the tubular hypothesis, SGLT2 inhibition attenuates proximal tubule hyperreabsorption in the diabetic kidney and thereby lowers diabetic glomerular hyperfiltration (Figure 2). Micropuncture studies in hyperfiltering streptozotozin (STZ)-diabetic rats with superficial glomeruli allowed for tubular fluid collection from sites near the MD while drugs were being delivered into Bowman's space of the same nephron without changing blood glucose levels (39). Concentrations of sodium, chloride, and potassium in

tubular fluid at the MD were ~25% lower in diabetic rats compared with nondiabetic controls, consistent with a primary increase in reabsorption upstream of the MD. Perfusing phlorizin into Bowman's space, which inhibits SGLT2 and to a lesser extent SGLT1, increased the MD electrolyte concentrations to normal levels, and the SNGFR declined to normal values. Similar effects on SNGFR and early distal chloride concentrations were obtained in diabetic rats by acute or chronic systemic application of a selective SGLT2 inhibitor (40). Furthermore, pharmacologic or genetic inhibition of SGLT2 reduced glomerular hyperfiltration in diabetic mice (20, 21, 41). The lowering of diabetic hyperfiltration in response to SGLT inhibition is associated with and in part the consequence of an increase in P_{Bow} (39), and the effect is independent of lowering blood glucose levels (21, 39, 40).

The described GFR-lowering effect of short-term SGLT2 inhibition has been confirmed in humans. Moreover, SGLT2 inhibition induces a biphasic GFR profile: An initial GFR reduction is followed by long-term GFR preservation. T1DM patients with baseline hyperfiltration responded to treatment with empagliflozin for 8 weeks with a decrease in GFR, which was independent of lowering blood glucose levels (42). Based on estimation of glomerular hemodynamics the authors proposed a dominant effect on the afferent arteriole (42), whereas the authors of a recent study in patients with T2DM proposed that the SGLT2 inhibitor dapagliflozin lowered measured GFR by reducing efferent arteriolar resistance (43). Tubuloglomerular feedback–induced ATP release from MD cells and subsequent adenosine formation constricts the afferent arteriole via adenosine A1 receptors (44) and dilates the efferent arteriole via adenosine A2 receptors (45) (Figure 2). Both effects are expected to lower glomerular capillary pressure (P_{GC}), while the net effect of efferent dilation on GFR is less predictable due to the increase in plasma flow. Studies in mice confirmed a role of adenosine A1 receptor-mediated afferent arteriolar vasoconstriction in the GFR-lowering effect of empagliflozin (46) (Figure 2). Preliminary micropuncture studies in STZ-diabetic rats confirmed that the SGLT2 inhibitor ipragliflozin reduced P_{GC} by a tubuloglomerular feedback–dependent mechanism (47); moreover, and consistent with the asymmetry of afferent and efferent arteriolar tubuloglomerular feedback responses and their consequences for GFR and P_{GC} (48), the changes in these two parameters in response to SGLT2 inhibition were not strictly correlated; in other words, SGLT2 inhibition can induce a robust reduction in P_{GC} even when GFR decreases only slightly (47).

In the EMPA-REG OUTCOME trial involving patients with T2DM and preserved kidney function, empagliflozin treatment for 4 weeks also reduced eGFR versus placebo, consistent with the abovementioned short-term studies. During the follow-up until week 192, eGFR remained stable with SGLT2 inhibitor treatment but decreased progressively in the placebo group, such that kidney function was better preserved with the SGLT2 inhibitor (7). A similar GFR time course was observed in clinical studies with canagliflozin (10, 49, 50) and dapagliflozin (51). Most importantly, after discontinuation of treatment, eGFR increased to baseline in the SGLT2 inhibitor groups while eGFR remained unchanged at reduced levels in placebo groups (7, 49). Even though blood glucose effects of SGLT2 inhibitors are attenuated in patients with T2DM and CKD (level 2/3) due to lesser-filtered glucose, the short-term GFR-lowering effect (10, 12, 52, 53), the long-term GFR preservation (10, 12), and the full reversibility after discontinuation of the SGLT2 inhibitor (53) remained. The

preserved effect on GFR in CKD is consistent with the assumption that remaining nephrons show compensating tubular growth and hyperfiltration (24) and thus maintain a high glucose load and reabsorption on the single-nephron level.

Two recent studies implicated a SGLT1–nitric oxide synthase 1 (NOS1) pathway in the MD in diabetic glomerular hyperfiltration (41, 54): The MD senses an increased glucose delivery via luminal SGLT1, which then activates NOS1, and the resulting increase in NO formation blunts the vasoconstrictor effect of tubuloglomerular feedback and thereby contributes to diabetic hyperfiltration. In accordance, absence of SGLT1 prevents the increase in MD-NOS1 expression in T1DM Akita mice and in response to a glucosuric dosage of dapagliflozin in nondiabetic mice (41). Thus, an increase in MD glucose delivery and the resulting activation of the MD-SGLT1-NOS1 pathway may explain a blunted GFR reduction in response to initiation of an SGLT2 inhibitor (for further discussion, see 23). It is also possible that the MD-SGLT1-NOS1 pathway contributes to the proposed efferent dilation of SGLT2 inhibition in T2DM, potentially due to a rather low endogenous NO tone in the efferent arteriole in this setting.

4.2. How Can Lowering Glomerular Filtration Rate Protect the Kidney in the Long Term?

By reducing GFR and P_{GC} (and increasing P_{Bow}), SGLT2 inhibition reduces the physical stress placed on glomerular capillaries and diminishes the glomerular filtration of tubulo-toxic factors (e.g., albumin, growth hormones, advance glycation end products). The interaction of these factors with the tubular system requires energy and promotes hypoxia, impairs autophagy, and triggers renal oxidative stress, inflammation, and fibrosis, and thereby triggers the development and progression of diabetic kidney disease (23) (Figure 2). A proposed role of SGLT2 expression in podocytes in protein overload conditions remains to be confirmed (55).

GFR is the primary determinant of renal NaCl reabsorption and, thus, of renal transport work and oxygen consumption. The proximal tubule segments reabsorb most of the glomerular filtrate and thus are predicted to show the largest increases in oxygen consumption when GFR increases (56, 57). According to the tubular hypothesis of diabetic kidney disease, lowering single-nephron glomerular hyperfiltration and thereby the oxygen-consuming transport work has the potential to preserve the integrity of the remaining nephrons and overall kidney function in the long term (23) (Figure 2). This has been previously proposed for blockers of Ang II and now for SGLT2 inhibitors, and the clinical trials provided evidence that the two strategies are additive and apply to patients with initial GFRs of at least 30 mL/min/1.73 m^2 of body surface area (23). Mathematical modeling predicted that SGLT2 inhibition in the diabetic kidney reduces oxygen consumption in the proximal convoluted tubule and renal cortex, in large part by lowering GFR (56, 57). The predicted increase in cortical O_2 pressure has been observed in a diabetic rat model using phlorizin (58). SGLT2 inhibition attenuated the cortical tubular expression of hypoxia-induced factor HIF-1α in *db*/*db* mice (59). Moreover, preserving renal cortical oxygenation appears critical to preserve kidney function in patients with CKD (60).

Meta-analyses of clinical studies indicate that SGLT2 inhibition induces small increases in serum creatinine but reduces the incidence of acute kidney injury (AKI) (61, 62).

Dapagliflozin treatment decreased urinary levels of markers of glomerular and tubular injury in T2DM patients (63, 64). Along these lines, luseogliflozin reduced hypoxia and fibrosis and prevented renal capillary rarefaction in a murine model of renal ischemia-reperfusion (IR) (65). Unexpectedly, *SGLT2* gene knockout in mice did not affect the initial IR injury or the subsequent kidney recovery in the bilateral renal artery clamping model of IR injury (66), whereas *SGLT1* gene knockout improved recovery (67).

Preliminary data from studies in T1DM Akita mice and patients with T2DM suggested that diabetes increased the urinary ratio of lactate to pyruvate, which may indicate a metabolic shift from mitochondrial oxidation to glycolysis, and this effect was reversed by SGLT2 inhibition (68). In patients with T2DM and albuminuria, dapagliflozin increased urinary metabolites linked to mitochondrial metabolism, indicating that dapagliflozin may improve mitochondrial function in the diabetic kidney (69). Similar findings were made in T1DM Akita mice with empagliflozin, which also enhanced urinary α-ketoglutarate in nondiabetic mice (34). The first evidence that SGLT2 inhibition may improve autophagy in the diabetic kidney was provided by studies in Akita mice, in which empagliflozin reduced the renal accumulation of p62 (20) (Figure 1). Azelaic acid, a compound that reduces adiposity by rewiring fuel preference to fats and promotes mitochondrial biogenesis and autophagy, was increased in the urine of T1DM Akita mice but also of nondiabetic mice in response to empagliflozin (34). Empagliflozin also improved mitochondrial fragmentation and enhanced renal proximal tubule autophagic activity under high-glucose conditions and in STZ-diabetic mice; this potentially involved effects on AMPK and the mTOR pathway, which may be affected by ketone bodies (38) and reduced apoptosis and tubulointerstitial fibrosis (70). Along these lines, a high-fat diet caused tubular and mitochondrial damage in mice, an effect reversed by the SGLT2 inhibitor ipragliflozin, independent of effects on blood glucose control (71). Thus, SGLT2 inhibitors may protect the kidney by reducing GFR, the filtration of albumin and other tubulo-toxic compounds, and the tubular transport work, enhancing ketone bodies and potentially azelaic acid, and lowering blood glucose levels and glucose toxicity in the early proximal tubule, thereby improving tubular energetics and preserving mitochondrial function and autophagy (Figure 1).

4.3. Potential Coupling of SGLT2 to Other Transporters in the Early Proximal Tubule

Beneficial renal and cardiovascular effects of SGLT2 inhibition include a uricosuric and plasma uric acid–lowering effect: Studies using nondiabetic gene-targeted mouse models proposed an inhibitory effect on the luminal urate transporter URAT1 (72). SGLT2 inhibition may increase urate excretion through increased tubular or urinary glucose delivery (72–74) and inhibit URAT1 through reduced insulin activity (75) or through other coupling mechanisms between SGLT2 and URAT1 (Figures 1 and 2). SGLT2 is also functionally coupled to NHE3, such that pharmacological blockade of SGLT2 partially inhibits NHE3 activity, potentially involving the scaffolding protein MAP17 and NHE3 phosphorylation (34, 76–78) (Figures 1 and 2). Tubular NHE3 determined the acute natriuretic and chronic volume effect of empagliflozin in nondiabetic mice (34). SGLT2 inhibition in nondiabetic mice increased renal expression of genes involved with gluconeogenesis, bicarbonate regeneration, and ammonium formation, which could reflect metabolic adaptations to urinary glucose loss as well as compensatory responses to reduced NHE3 activity (34). In

contrast, tubular knockdown of NHE3 reduces SGLT2 expression (30). Hyperinsulinemia costimulates SGLT2, NHE3, and URAT1 (13) (Figure 1). This may facilitate glomerulotubular balance in response to a postprandial increase in GFR and insulin but also lead to renal NaCl and urate retention in obesity and T2DM (13) (Figure 1). Coinhibition of NHE3 would enhance the natriuretic and uricosuric effect of SGLT2 inhibition. Moreover, upregulation of renal NHE3 in heart failure and remnant nephrons in CKD could enhance the natriuretic efficacy and renal hemodynamic effect of SGLT2 inhibition and thereby contribute to kidney and cardioprotection in nondiabetic patients.

4.4. SGLT2 Inhibition Enhances the Delivery of Glucose, NaCl, and Fluid Downstream of the Early Proximal Tubule: More Equal Distribution of Transport Work and Mimicking Systemic Hypoxia at the Renal Oxygen Sensor

As mentioned above, the early proximal tubule reabsorbs most of the glomerular filtrate and thus is predicted to show the largest absolute increase in oxygen consumption when GFR increases (56, 57). Therefore, by shifting some of the glucose, NaCl, and fluid reabsorption downstream, SGLT2 inhibition more equally distributes the transport burden along the tubular and collecting duct system, which may help to preserve tubular function in the long term.

On the other hand, the shift in transport to the S3 segment and thick ascending limb in the renal outer medulla may reduce the already physiologically low O_2 availability in this region (56–58) (Figure 2). As discussed above, SGLT1 in the S3 segment uses double the energy per glucose compared with SGLT2, and the downregulation of renal SGLT1 protein expression observed in response to SGLT2 inhibition (20) may serve to protect the S3 segment from excessive transport burden (3). The observed increased urinary adenosine excretion in patients with T1DM (79) and T2DM (43) in response to SGLT2 inhibition likely reflects an increase in transport work in the downstream segments, which enhances ATP consumption and adenosine formation and release (44). Furthermore, the net increase in downstream transport is mitigated by the concomitant reduction in blood glucose and GFR (56, 57) (Figure 2). Moreover, the lesser oxygen pressure in the deep cortex and outer medulla may be a stimulus for hypoxia-inducible factors HIF-1 and HIF-2. Mice lacking SGLT2 have higher renal mRNA expression of hemoxygenase 1 (21), a tissue-protective gene that is induced by HIF-1α. Moreover, SGLT2 inhibitor-induced HIF-2 activation may enhance erythropoietin expression (34) and release from renal interstitial cells, which, together with the diuretic effect of the drugs, may contribute to the clinically observed modest increase in hematocrit and hemoglobin (80). This can improve the oxygenation of renal outer medulla and cortex and facilitate oxygen delivery to the heart and other organs (Figure 2). In this regard, 51.8% and 48.9% of the effect of the SGLT2 inhibitor empagliflozin on the risk of cardiovascular death were explained by changes in hematocrit and hemoglobin from baseline, respectively (80). Thus, it has been proposed that, in addition to its volume effect, the transport shift induced by SGLT2 inhibition may simulate systemic hypoxia at the oxygen sensor in the deep cortex and outer medulla of the kidney, and the induced response then helps the kidney and failing heart (81). Modeling studies indicate that these effects of SGLT2 inhibition can be preserved in CKD (81). Moreover, the latter studies indicated that the natriuretic and diuretic effect of SGLT2 inhibition is preserved in CKD

due to a high glucose load on the single-nephron level (facilitated by lesser blood glucose–lowering effect), which induced paracellular sodium secretion in the proximal tubule, thereby preserving a natriuretic, kaliuretic, and diuretic effect despite the reduced nephron number (81). This may contribute to the preserved protective effects of SGLT2 inhibitors on heart and kidney failure in patients with CKD. Recent mediation analyses of the CANVAS program indicated a similarly strong association between effects of canagliflozin on markers of plasma volume and hematopoiesis and its protective effects on both the failing kidney (82) as well as on the failing heart (83). Notably, the runner-up factors in both mediation analyses were also the same, namely a reduction in albuminuria and in serum urate levels, with lesser contributions from systolic blood pressure and effects on acid base status, which may reflect the discussed interactions with NHE3 (82, 83).

5. SGLT2 INHIBITORS AFFORD CARDIAC PROTECTION

5.1. What Do We Need to Explain Mechanistically?

The exercise of exploring and refining the mechanisms of cardiac protection must first start by setting the clinical context. As discussed earlier, the completed SGLT2 inhibitor trials were initially conducted in patients with T2DM with either established atherosclerotic cardiovascular disease or multiple risk factors and in enrolled patients across the renal spectrum (eGFR ≥30 mL/min/1.73m^2, and in some cases with overt macroalbuminuria) (5, 6, 8, 10, 84–87). A minority of patients in these trials had a history of heart failure at baseline. These studies revealed that SGLT2 inhibitors were associated with a marked reduction in the incidence of hospitalization for heart failure and the composite of cardiovascular death and hospitalization for heart failure (5, 6, 8, 10, 84–89). While prevention of heart failure was clearly demonstrated, an important unanswered question was whether these agents could treat prevalent heart failure. In this regard, recent data from the first completed study in patients with heart failure with reduced ejection fraction (HFrEF) were reported (90–94). This study demonstrated that treatment of HFrEF patients with dapagliflozin, in addition to excellent background therapy, was associated with a significant 26% reduction in the primary outcome of cardiovascular death or worsening heart failure and a marked improvement in quality of life parameters. Importantly, these benefits were observed equally in those with and without diabetes and across the entire range of baseline HbA1C (90). A similar benefit was observed with empagliflozin in patients with more advanced HFrEF in the EMPEROR-Reduced trial (95). Therefore, as we explore the mechanism(s) of cardiac protection of SGLT2 inhibitors, we must consider that these must help explain the following clinical observations: (*a*) prevention and treatment of heart failure; (*b*) rapid benefit, which appears to emerge within weeks of treatment initiation; (*c*) efficacy that is independent of glycemia; (*d*) reduction in hospitalization for heart failure on top of excellent background therapy [beta-blockers, blockers of the renin-angiotensin-aldosterone system (RAAS)]; (*e*) close association with renal protection; and (*f*) modest benefits on atherosclerotic outcomes. While no single cogent mechanism exists to explain all of these observations, some of the most plausible theories that have been put forward are discussed below (Figures 2 and 3) (96–103).

5.2. The Reno-Cardiac Axis

Heart failure and renal disease are closely related, both clinically and pathophysiologically (104). Numerous studies have shown that declining renal function is strongly associated with an increased incidence of heart failure, and this relationship is particularly prominent in those with coexistent diabetes (105). As renal disease develops, volume is retained, which in turn promotes the development and worsening of heart failure. The changes in central venous pressure and arterial blood pressure reduce renal perfusion pressures and thereby worsen renal function. This vicious cycle leads to the stimulation of many cytokines, inflammatory markers, and neurohumoral mediators, which worsen cardiac function in part through enhancing endoplasmic reticulum stress (106). As described above, SGLT2 inhibitors reduce the physical glomerular stress and the renal cortical transport burden and improve or preserve renal function. Improving and preserving renal function, through both hemodynamic and nonhemodynamic mechanisms, is important for SGLT2 inhibitors to protect the heart (107) (Figures 2 and 3).

5.3. SGLT2 Inhibitors Induce a Fasting Response

As mentioned above, by spilling glucose into the urine and making use of the metabolic responses, SGLT2 inhibitors may provide unique benefits (3). An emerging theory links this to autophagy stimulation, including in the kidney and heart (20, 70, 97) (Figures 1 and 3). According to this paradigm, SGLT2 inhibitors reduce cellular glucose availability and stimulate a starvation-like response, which occurs without the need for basal hyperglycemia per se. The response includes activation of SIRT1/AMPK and inhibition of AKT/mTOR signaling, thereby inducing autophagy, which serves the systemic cellular defense and prosurvival mechanism. Autophagy improves energy metabolism and fuel supply and reduces oxidative stress, cytotoxicity, and inflammation (Figure 3). Such a mechanism may also lead to a reduction in visceral/epicardial fat, which has been implicated in the pathophysiology of heart failure (103, 108).

5.4. The Osmotic Diuresis and Natriuresis Hypothesis

SGLT2 inhibitors promote mild osmotic diuresis and natriuresis, and these hemodynamic effects may afford protection against heart failure by improving filling conditions and reducing whole-body sodium content (Figures 2 and 3). Ferrannini et al. (109) documented some of the earliest hemodynamic consequences of SGLT2 inhibition in humans. In their study, one dose of empagliflozin given to individuals with T2DM led to a mild diuresis and a drop in blood pressure within 1 hour of treatment. This was coupled with a drop in creatinine clearance, indicating a fall in GFR. In another study, the same group demonstrated that acute SGLT2 inhibitor treatment promoted an increase in sodium excretion by 15–20% and provided evidence that such an effect was sustained during chronic treatment and resulted in a reduction in the whole-body pool of sodium (110). Compared to other diuretics, SGLT2 inhibitors have been suggested to differentially regulate the interstitial versus intravascular volume. In studies comparing dapagliflozin with the loop diuretic bumetanide, a more sustained natriuresis was observed, with dapagliflozin associated with relatively more reduction in interstitial versus intravascular volume (111) (Figure 3). This may be due to osmotic diuresis and a greater electrolyte-free water clearance in response to SGLT2

inhibitors compared with traditional diuretics, which produces a greater clearance of fluid from the interstitial fluid space versus the circulation (111). Compared to hydrochlorothiazide, it has been proposed that SGLT2 inhibitors may result in a more sustained volume contraction associated with a rise in hematocrit (112).

In patients with heart failure, the increased delivery of NaCl and fluid downstream of the early proximal tubule in response to SGLT2 inhibition may also enhance the responsiveness and potentially help overcome the resistance to endogenous atrial natriuretic peptide (ANP) as well as to diuretics, which act in these distal tubular segments (Figures 2 and 3), thereby reducing volume overload. The osmotic effect of SGLT2 inhibition is reminiscent of the ANP-sensitizing effect of mannitol in patients with cirrhosis and ascites (113). In accordance, a reduction in natriuretic peptides in response to empagliflozin was observed in a nonhyperglycemic zebrafish model of heart failure (114).

5.5. SGLT2 Inhibition Stimulates Erythropoietin Production

As mentioned above, mediation analyses from EMPA-REG OUTCOME indicated that the rise in hematocrit was a key determinant of the cardiovascular death benefit (80). An important question is whether this rise in hematocrit is secondary to volume contraction, or whether it may also represent a primary erythropoietic response. Some translational insights were provided by the DAPA-HF trial (90). First, the rise in hematocrit in DAPA-HF was observed consistently and to a similar degree in individuals with and without diabetes. Furthermore, the increase in hematocrit appeared to peak after 4 months of treatment, i.e., later than what would be expected based on the diuretic effect alone. The change in blood pressure and body weight appeared to occur earlier than the rise in hematocrit, again pointing toward a partial temporal dissociation between the diuresis and the increase in hematocrit. Additionally, it would be reasonable to expect that individuals without T2DM have less osmotic diuresis than hyperglycemic individuals with T2DM, at least initially before good blood glucose control is established, and hence, a similar rise in hematocrit might not be expected on the basis of diuresis-induced volume contraction alone. Therefore, SGLT2 inhibitors have been proposed to actually promote the production of erythropoietin (EPO) and thereby further increase hematocrit and help improve heart failure outcomes (Figures 2 and 3). As such, two recent studies on humans have demonstrated an early stimulatory effect of empagliflozin and dapagliflozin on EPO production. In the EMPA-HEART CardioLink-6 trial, treatment with empagliflozin significantly increased EPO levels after 1 month of treatment, and this was associated with an increase in hematocrit by 2.34% (115). This occurred in the setting of reduced ferritin levels and mean cell hemoglobin concentration. Dapagliflozin was also shown to increase erythropoiesis, EPO, and hematocrit in individuals with T2DM, an effect associated with suppression of hepcidin and modulation of iron regulatory proteins (116). Empagliflozin also increased renal EPO mRNA expression in nondiabetic mice (34).

EPO is known to be a pleiotropic factor that can promote increased oxygen delivery and improve cardiovascular outcomes through both hematopoietic and nonhematopoietic mechanisms (Figure 3). EPO is also known to be a stimulus of bone marrow progenitor cells, and this may explain recent observations suggesting that SGLT2 inhibitors favorably

affect regenerative provascular progenitor cells in individuals with diabetes (117). The potential intrarenal mechanism of EPO stimulation by SGLT2 inhibition is discussed in Section 4.4 and illustrated in Figure 2.

5.6. SGLT2 Inhibitors Improve Cardiac Energetics

SGLT2 inhibitor treatment can increase circulating ketone bodies (118), which by improving cardiac energetics and efficiency has been proposed as a mechanism to protect the failing heart (119, 120). Ketone oxidation has been shown to improve heart failure outcomes (when infused) in patients with heart failure (121). Recent studies indicated that this mechanism activated by SGLT2 inhibition does improve energy supply in the failing diabetic murine heart (122) and also improves cardiac energetics in a porcine model of heart failure (123). Notably, the increase in cardiac ketone oxidation in the cardiomyopathic heart in response to SGLT2 inhibition was not associated with a decrease in glucose or fatty acid oxidation (122). The authors therefore proposed that SGLT2 inhibitors do not necessarily increase cardiac efficiency in the failing heart but provide an extra fuel source in the form of ketone bodies (Figures 2 and 3). Whether this mechanism is operative in humans and also occurs in the absence of hyperglycemia needs to be confirmed. Other mechanisms involving a stimulating effect of SGLT2 inhibitors on glucose uptake via GLUT1 (124) or on branched-chain amino acid metabolism and their use as a source for ketone bodies (125) have also been put forward and require further confirmation.

5.7. SGLT2 Inhibitors Can Inhibit the Sympathetic Nervous System

The sympathetic nervous system (SNS) plays a critical role in the pathogenesis of heart failure, and various therapies that reduce outcomes do so, in part, through inhibiting SNS activity. There is both indirect and direct evidence for an attenuation of SNS activity with SGLT2 inhibitors. In a recent study, the interplay between the kidney, SGLT2 inhibition, and SNS was examined. In these studies, chemical denervation in BPH/2J mice led to a reduction in the SGLT2 protein expression in the kidney (126, 127). Additionally, dapagliflozin treatment reduced markers of SNS activity (tyrosine hydroxylase and norepinephrine). Therefore, SGLT2 inhibitors may reduce SNS activity by attenuating the stimulation of the afferent sympathetic nerve activity (Figure 3). In another study, which employed microneurography, the effects of a 4-day treatment with empagliflozin were studied in patients with T2DM (128). Empagliflozin had no significant effect on muscle sympathetic nerve activity despite a numerical increase in urine volume, numerical reductions in blood pressure, and significant weight loss. There were no clinically relevant changes in heart rate, indicating that empagliflozin was not associated with clinically relevant reflex-mediated sympathetic activation, in contrast to increases observed with diuretics in other studies. The data suggest that SGLT2 inhibition can affect human autonomic cardiovascular regulation. In a preliminary subanalysis of the EMPA-HEART CardioLink-6 trial, we have attempted to evaluate this construct with Holter monitoring analyses (129). Automated algorithms were used to determine changes in time and frequency heart rate variability domain measures over 6 months and suggested that the observed cardiac benefits of empagliflozin are not associated with positive modulation of autonomic tone. Finally, acute studies in mice have shown that dapagliflozin can significantly suppress norepinephrine turnover in brown adipose tissue and c-fos expression

in the rostral raphe pallidus nucleus, which contains the sympathetic premotor neurons responsible for thermogenesis (130). This effect may be secondary to nutrient deprivation. Intriguingly, a greater absolute benefit of the SGLT2 inhibitor empagliflozin for renal and heart failure–related events has been observed in individuals with a history of atrial fibrillation (131), suggesting potential antiarrhythmic effects.

5.8. Do SGLT2 Inhibitors Have an Off-Target Effect on the Cardiac Sodium-Hydrogen Exchanger?

Cardiomyocytes express SGLT1 but not SGLT2. Nevertheless, in vitro data have suggested that SGLT2 inhibitors lower intracellular Na^+ concentrations in mouse cardiomyocytes, and that this effect was due to inhibiting the activity of a Na-H-exchanger, potentially NHE1 (132). The studies compared empagliflozin (1 μmol/L), dapagliflozin (1 μmol/L), and canagliflozin (3 μmol/L) with vehicle; the IC50 values of these compounds for SGLT2 and SGLT1 are in the single-digit nanomolar and micromolar ranges, respectively. The authors also performed NHE docking simulation studies to explore potential binding sites for SGLT2 inhibitors. When NHE activity was evaluated by pH recovery after a NH_4^+ pulse, all three agents modestly reduced the recovery as well as intracellular Na^+ concentrations. These effects on cytosolic Na^+ and NHE flux occurred in the absence of extracellular glucose. Moreover, based on the simulation experiments, the authors concluded that these agents may bind the extracellular Na^+-binding site of NHE1. In additional constant-flow Langendorff-perfused mouse hearts, empagliflozin and canagliflozin, but not dapagliflozin, were reported to induce coronary vasodilation of the intact heart (132).

A recent study has employed artificial intelligence (AI) to evaluate cellular mechanism of SGLT2 inhibitors in heart failure (133). The authors concluded based on the AI analysis that inhibition of NHE1, potentially through restoration of the antiapoptotic activity of X-linked inhibitor of apoptosis (XIAP) and baculoviral IAP repeat-containing protein 5 (BIRC5), may explain the cardioprotective effect independent of diabetes. Complementary in vivo studies in heart failure models in rats showed that empagliflozin enhanced the cardiac expression of XIAP and BIRC5, again independent of diabetes. The described cardiac NHE hypothesis relies on in vitro studies and mathematical modeling and includes very limited in vivo data sets. Nonetheless, the proposed glucose independent efficacy of SGLT2 inhibition makes this a theory that deserves further in vivo studies and validation.

5.9. SGLT2 Inhibitors Modulate Cardiac Inflammation and Fibrosis

Inflammation is a central mechanism involved in the pathobiology of cardiovascular events in individuals with diabetes and heart failure. The efficacy of SGLT2 inhibitors has been studied in rodent models of HFrEF and heart failure with preserved ejection fraction (HFpEF) without diabetes, and these studies provide some evidence of the potential modulatory role on cardiac inflammation and fibrosis. Byrne et al. studied nondiabetic rodent models of heart failure that were treated with empagliflozin (134): Although ketone bodies can induce anti-inflammatory effects on the heart (135), the cardiac benefits were observed without any changes in the levels of circulating ketone bodies or ketone oxidation or an increase in cardiac ATP generation. Nevertheless, there was a reduction in the NLRP3 inflammasome activation in the heart in the HFrEF model in response to SGLT2 inhibition,

which also appeared to occur in animals with HFpEF (Figure 3). These benefits seemed to be reliant on regulation of cytoplasmic calcium, since they were attenuated in the presence of a calcium ionophore. On the other hand, studies in murine myocytes and human failing ventricular myocytes suggested that empagliflozin reduces Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity and CaMKII-dependent sarcoplasmatic reticulum calcium leak (124) (Figure 3).

Cardiac fibroblasts play an integral role in the progression of structural cardiac remodeling and heart failure, in part, by regulating extracellular matrix homeostasis. In this regard, in vitro studies in human cardiac fibroblasts demonstrated that the SGLT2 inhibitor empagliflozin attenuated transforming growth factor (TGF)-β1-induced fibroblast activation (136). In addition, the fibroblasts that were treated with high concentrations of empagliflozin (5 μM) were smaller in size, with reduced cell extension length, and total number of extensions, consistent with a quiescent phenotype. Furthermore, empagliflozin reduced the extracellular matrix remodeling response and reduced the profibrotic markers COL1A1, ACTA2, CTGF, and MMP2 (136). In comparison, in mice subjected to transverse aortic banding (a model of HFrEF), treatment with empagliflozin prevented the reduction in ejection fraction in the absence of effects on collagen content or markers of fibrosis (137). In a rodent model of HFpEF, empagliflozin also improved measures of diastolic function and reduced wall stress without affecting collagen I/IV (138). It appears that the improvement in cardiac function by SGLT2 inhibitors does not require an antifibrotic effect.

5.10. SGLT2 Inhibitors May Promote Cardiac Reverse Remodeling

SGLT2 inhibitors improve cardiovascular outcomes consistently in individuals with and without a history of left ventricular hypertrophy (139) and improve functional capacity as assessed by cardiopulmonary exercise testing (140). An important question that has remained unanswered is whether these therapies will promote cardiac reverse remodeling. In this regard, the recently completed EMPA-HEART CardioLink-6 trial provides some insights (141). Specifically, we conducted a randomized double-blind trial of individuals with T2DM and concomitant coronary artery disease treated with either 10 mg of empagliflozin or placebo. The primary outcome was the change over six months in left ventricular mass indexed to body surface area from baseline as measured by cardiac magnetic resonance imaging. The regression in this parameter was 2.6 g/m^2 and 0.01 g/m^2 for those assigned empagliflozin and placebo, respectively, and thus significantly greater with the SGLT2 inhibitor (adjusted difference −3.35 g/m^2; 95% CI, −5.9 to −0.81g/m^2, P = 0.01). No changes in systolic or diastolic function were observed in the echocardiographic substudy (142). Another study in subjects with T2DM and established cardiovascular disease confirmed that treatment with empagliflozin for three months reduced left ventricular mass, in this case associated with beneficial effects on diastolic function (143). These data provided important translational insights into the ability of SGLT2 inhibitors to potentially promote reverse cardiac remodeling (Figure 3), an effect that was not entirely explained by reductions in blood pressure per se.

5.11. SGLT2 Inhibitors Can Improve Vascular Function

Diabetes causes detrimental effects on the vasculature (144–146). There have been many in vitro and in vivo experimental studies that suggested a benefit of SGLT2 inhibitors on measures of endothelial dysfunction, vascular smooth muscle cell homeostasis, and vascular stiffness (102, 103, 126, 147–152). Recent randomized clinical trial data evaluating endothelial function in humans with empagliflozin did not show any benefit per se (153). The EMPA-HEART CardioLink-6 trial, however, found that six-month treatment with empagliflozin was associated with an increase in the frequency of proangiogenic myeloid and progenitor cells, an increase in proangiogenic M2 polarized macrophages, and an increase in the concentration of antioxidant catalase with stabilization of the superoxide generating enzyme NOX1 (117). Simultaneously, there was a reduction in the frequency of proinflammatory granulocyte precursor cells and M1 polarized macrophages. In preliminary studies, the SGLT2 inhibitor canagliflozin ameliorated arterial stiffness in patients with T2DM in part through reducing urate levels (154), an emerging biomarker of vascular risk in diabetes (155). We have also shown that canagliflozin is associated with an improved angiogenic function and promotes recovery of blood flow after hindlimb ischemia (156). Empagliflozin therapy also improved arterial function, including central pulse pressure, forward pressure wave amplitude, and backward pulse wave amplitude (157). All of these vascular effects may contribute toward improving filling conditions and reducing the outcomes of heart failure (Figure 3). To which extent these mechanisms contribute to the cardioprotective effect and/or are observed in people without diabetes remains unclear.

6. PERSPECTIVES

Much needs to be learned about the mechanisms involved in the renal and cardioprotective effects of SGLT2 inhibitors and which patient populations benefit from treatment. It is likely that the cardiac benefits are a culmination of both primary myocardial and secondary metabolic/renal benefits, as outlined above. Currently, the randomized placebo-controlled CKD outcome trial EMPA-KIDNEY (ClinicalTrials.gov identifier NCT03594110) is conducted in patients with established kidney disease, with or without diabetes. Likewise, several heart failure trials in patients with HFrEF and HFpEF are being conducted in patients with and without diabetes, including the EMPEROR-Preserved (NCT03057951), DELIVER (NCT03619213), and SOLOISTWHF (NCT03521934) studies. The results of these trials will critically refine our understanding of the therapeutic potential of SGLT2 inhibitors and guide further mechanistic studies.

ACKNOWLEDGMENTS

V.V. is supported by US National Institutes of Health (NIH) grants R01DK112042, R01DK106102, R01HL139836, and RF1AG061296; the UAB/UCSD O'Brien Center of Acute Kidney Injury grant NIH-P30DK079337; and the Department of Veterans Affairs. S.V. is supported by grants from the Canadian Institutes of Health Research (CIHR) and the Heart and Stroke Foundation of Canada.

DISCLOSURE STATEMENT

Over the past 36 months, V.V. has served as a consultant and received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Merck, and Retrophin, and received grant support for investigator-initiated research from AstraZeneca, Bayer, Boehringer Ingelheim, Fresenius Medical Care, Novo Nordisk, and Janssen Pharmaceuticals. S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery and

reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, EOCI Pharmacomm Ltd., HLS Therapeutics, Janssen Pharmaceuticals, Merck, Novartis, Novo Nordisk, PhaseBio, Sanofi, Sun Pharma, and the Toronto Knowledge Translation Working Group. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization.

LITERATURE CITED

1. Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, et al. 2019. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). Diabetes Care 42:416–26 [PubMed: 30104301]
2. Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, et al. 2008. Effects of intensive glucose lowering in type 2 diabetes. N. Engl. J. Med 358:2545–59 [PubMed: 18539917]
3. Vallon V, Thomson SC. 2017. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 60:215–25 [PubMed: 27878313]
4. Food US and Admin Drug. 2008. Guidance for industry on diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes; availability. Fed. Regist 73. https://www.govinfo.gov/content/pkg/FR-2008-12-19/pdf/E8-30086.pdf
5. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, et al. 2019. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med 380:347–57 [PubMed: 30415602]
6. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, et al. 2015. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med 373:2117–28 [PubMed: 26378978]
7. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, et al. 2016. Empagliflozin and progression of kidney disease in type 2 diabetes. N. Engl. J. Med 375:323–34 [PubMed: 27299675]
8. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, et al. 2017. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med 377:644–57 [PubMed: 28605608]
9. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, et al. 2019. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 7:606–17 [PubMed: 31196815]
10. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, et al. 2019. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N. Engl. J. Med 380:2295–306 [PubMed: 30990260]
11. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, et al. 2019. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diabetes Obes. Metab 21:1237–50 [PubMed: 30697905]
12. Heerspink HJL, Stefánsson BV, Correa-Rotter MDR, Chertow GM, Greene T, et al. 2020. Dapagliflozin in patients with chronic kidney disease. N. Engl. J. Med 383:1436–46 [PubMed: 32970396]
13. Vallon V 2020. Glucose transporters in the kidney in health and disease. Pflügers Arch. 472:1345–70 [PubMed: 32144488]
14. Vallon V, Platt KA, Cunard R, Schroth J, Whaley J, et al. 2011. SGLT2 mediates glucose reabsorption in the early proximal tubule. J. Am. Soc. Nephrol 22:104–12 [PubMed: 20616166]
15. Rieg T, Masuda T, Gerasimova M, Mayoux E, Platt K, et al. 2014. Increase in SGLT1-mediated transport explains renal glucose reabsorption during genetic and pharmacological SGLT2 inhibition in euglycemia. Am. J. Physiol. Ren. Physiol 306:F188–93
16. Gorboulev V, Schurmann A, Vallon V, Kipp H, Jaschke A, et al. 2012. Na^+-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes 61:187–96 [PubMed: 22124465]
17. Umino H, Hasegawa K, Minakuchi H, Muraoka H, Kawaguchi T, et al. 2018. High basolateral glucose increases sodium-glucose cotransporter 2 and reduces Sirtuin-1 in renal tubules through glucose transporter-2 detection. Sci. Rep 8:6791 [PubMed: 29717156]

18. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. 2005. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 54:3427–34 [PubMed: 16306358]
19. Wang XX, Levi J, Luo Y, Myakala K, Herman-Edelstein M, et al. 2017. SGLT2 expression is increased in human diabetic nephropathy: SGLT2 inhibition decreases renal lipid accumulation, inflammation and the development of nephropathy in diabetic mice. J Biol. Chem 292:5335–48 [PubMed: 28196866]
20. Vallon V, Gerasimova M, Rose MA, Masuda T, Satriano J, et al. 2014. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. Am. J. Physiol. Ren. Physiol 306:F194–204
21. Vallon V, Rose M, Gerasimova M, Satriano J, Platt KA, et al. 2013. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. Am. J. Physiol. Ren. Physiol 304:F156–67
22. Wen L, Zhang Z, Peng R, Zhang L, Liu H, et al. 2019. Whole transcriptome analysis of diabetic nephropathy in the db/db mouse model of type 2 diabetes. J. Cell Biochem 120:17520–33 [PubMed: 31106482]
23. Vallon V, Thomson SC. 2020. The tubular hypothesis of nephron filtration and diabetic nephropathy. Nat. Rev. Nephrol 16:317–36 [PubMed: 32152499]
24. Fattah H, Layton A, Vallon V. 2019. How do kidneys adapt to a deficit or loss in nephron number? Physiology 34:189–97 [PubMed: 30968755]
25. Osorio H, Bautista R, Rios A, Franco M, Santamaria J, Escalante B. 2009. Effect of treatment with losartan on salt sensitivity and SGLT2 expression in hypertensive diabetic rats. Diabetes Res. Clin. Pract 86:e46–49 [PubMed: 19800706]
26. Freitas HS, Anhe GF, Melo KF, Okamoto MM, Oliveira-Souza M, et al. 2008. Na^+-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1α expression and activity. Endocrinology 149:717–24 [PubMed: 17962340]
27. Freitas HS, Schaan BD, David-Silva A, Sabino-Silva R, Okamoto MM, et al. 2009. SLC2A2 gene expression in kidney of diabetic rats is regulated by HNF-1α and HNF-3β. Mol. Cell. Endocrinol 305:63–70 [PubMed: 19433262]
28. Ghezzi C, Wright EM. 2012. Regulation of the human Na^+ dependent glucose cotransporter hSGLT2. Am. J. Physiol. Cell Physiol 303:C348–54 [PubMed: 22673616]
29. Masuda T, Watanabe Y, Fukuda K, Watanabe M, Onishi A, et al. 2018. Unmasking a sustained negative effect of SGLT2 inhibition on body fluid volume in the rat. Am. J. Physiol. Ren. Physiol 315:F653–64
30. Onishi A, Fu Y, Darshi M, Crespo-Masip M, Huang W, et al. 2019. Effect of renal tubule-specific knockdown of the Na^+/H^+ exchanger NHE3 in Akita diabetic mice. Am. J. Physiol. Ren. Physiol 317:F419–F34
31. Ghezzi C, Hirayama BA, Gorraitz E, Loo DD, Liang Y, Wright EM. 2014. SGLT2 inhibitors act from the extracellular surface of the cell membrane. Physiol. Rep 2:e12058 [PubMed: 24973332]
32. Fu Y, Breljak D, Onishi A, Batz F, Patel R, et al. 2018. The organic anion transporter OAT3 enhances the glucosuric effect of the SGLT2 inhibitor empagliflozin. Am. J. Physiol. Ren. Physiol 315:F386–94
33. Kellett GL, Brot-Laroche E, Mace OJ, Leturque A. 2008. Sugar absorption in the intestine: the role of GLUT2. Annu. Rev. Nutr 28:35–54 [PubMed: 18393659]
34. Onishi A, Fu Y, Patel R, Darshi M, Crespo-Masip M, et al. 2020. A role for the tubular Na^+-H^+-exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. Am. J. Physiol. Ren. Physiol 319:F712–28
35. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. 2015. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 38:316–22 [PubMed: 25492401]
36. Qiu H, Novikov A, Vallon V. 2017. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: basic mechanisms and therapeutic perspectives. Diabetes Metab. Res. Rev 33:e2886

37. Ferrannini E, Mark M, Mayoux E. 2016. CV Protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. Diabetes Care 39:1108–14 [PubMed: 27289126]
38. Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, et al. 2020. SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mTORC1 inhibition. Cell Metab. 32:404–19.e6 [PubMed: 32726607]
39. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. 1999. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J. Am. Soc. Nephrol 10:2569–76 [PubMed: 10589696]
40. Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, et al. 2012. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am. J. Physiol. Regul. Integr. Comp. Physiol 302:R75–83 [PubMed: 21940401]
41. Song P, Huang W, Onishi A, Patel R, Kim Y, et al. 2019. Knockout of Na-glucose-cotransporter SGLT1 mitigates diabetes-induced upregulation of nitric oxide synthase-1 in macula densa and glomerular hyperfiltration. Am. J. Physiol. Ren. Physiol 317:F207–17
42. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, et al. 2014. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129:587–97 [PubMed: 24334175]
43. van Bommel EJM, Muskiet MHA, van Baar MJB, Tonneijck L, Smits MM, et al. 2020. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. Kidney Int. 97:202–12 [PubMed: 31791665]
44. Vallon V, Muhlbauer B, Osswald H. 2006. Adenosine and kidney function. Physiol. Rev 86:901–40 [PubMed: 16816141]
45. Ren Y, Garvin JL, Carretero OA. 2001. Efferent arteriole tubuloglomerular feedback in the renal nephron. Kidney Int. 59:222–29 [PubMed: 11135074]
46. Kidokoro K, Cherney DZI, Bozovic A, Nagasu H, Satoh M, et al. 2019. Evaluation of glomerular hemodynamic function by empagliflozin in diabetic mice using in vivo imaging. Circulation 140:303–15 [PubMed: 30773020]
47. Thomson SC, Vallon V. 2020. Effects of acute SGLT2 blockade and dietary NaCl on glomerular hemodynamics in diabetic rats. FASEB J. 34(Suppl. 1):1 (Abstr.)
48. Thomson S, Vallon V, Blantz RC. 1996. Asymmetry of tubuloglomerular feedback effector mechanism with respect to ambient tubular flow. Am. J. Physiol 271:F1123–30 [PubMed: 8997385]
49. Perkovic V, Jardine M, Vijapurkar U, Meininger G. 2015. Renal effects of canagliflozin in type 2 diabetes mellitus. Curr. Med. Res. Opin 31:2219–31 [PubMed: 26494163]
50. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. 2018. Canagliflozin slows progression of renal function decline independently of glycemic effects. J. Am. Soc. Nephrol 28:368–75
51. Kohan DE, Fioretto P, Johnsson K, Parikh S, Ptaszynska A, Ying L. 2016. The effect of dapagliflozin on renal function in patients with type 2 diabetes. J. Nephrol 29:391–400 [PubMed: 26894924]
52. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, et al. 2013. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes. Metab 15:463–73 [PubMed: 23464594]
53. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, et al. 2014. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2:369–84 [PubMed: 24795251]
54. Zhang J, Wei J, Jiang S, Xu L, Wang L, et al. 2019. Macula densa SGLT1-NOS1-TGF pathway—a new mechanism for glomerular hyperfiltration during hyperglycemia. J. Am. Soc. Nephrol 30:578–93 [PubMed: 30867247]
55. Cassis P, Locatelli M, Cerullo D, Corna D, Buelli S, et al. 2018. SGLT2 inhibitor dapagliflozin limits podocyte damage in proteinuric nondiabetic nephropathy. JCI. Insight 3:e98720

56. Layton AT, Vallon V, Edwards A. 2015. Modeling oxygen consumption in the proximal tubule: effects of NHE and SGLT2 inhibition. Am. J. Physiol. Ren. Physiol 308:F1343–57
57. Layton AT, Vallon V, Edwards A. 2016. Predicted consequences of diabetes and SGLT inhibition on transport and oxygen consumption along a rat nephron. Am. J. Physiol. Ren. Physiol 310:F1269–83
58. Neill O, Fasching A, Pihl L, Patinha D, Franzen S, Palm F. 2015. Acute SGLT inhibition normalizes oxygen tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am. J. Physiol. Ren. Physiol 309:F227–34
59. Bessho R, Takiyama Y, Takiyama T, Kitsunai H, Takeda Y, et al. 2019. Hypoxia-inducible factor-1α is the therapeutic target of the SGLT2 inhibitor for diabetic nephropathy. Sci. Rep 9:14754 [PubMed: 31611596]
60. Pruijm M, Milani B, Pivin E, Podhajska A, Vogt B, et al. 2018. Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease. Kidney Int. 93:932–40 [PubMed: 29325997]
61. Gilbert RE, Thorpe KE. 2019. Acute kidney injury with sodium-glucose co-transporter-2 inhibitors: a meta-analysis of cardiovascular outcome trials. Diabetes Obes. Metab 21:1996–2000 [PubMed: 31050116]
62. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, et al. 2019. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 7:845–54 [PubMed: 31495651]
63. Dekkers CCJ, Petrykiv S, Laverman GD, Cherney DZ, Gansevoort RT, Heerspink HJL. 2018. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. Diabetes Obes. Metab 20:1988–93 [PubMed: 29573529]
64. Satirapoj B, Korkiatpitak P, Supasyndh O. 2019. Effect of sodium-glucose cotransporter 2 inhibitor on proximal tubular function and injury in patients with type 2 diabetes: a randomized controlled trial. Clin. Kidney J 12:326–32 [PubMed: 31198224]
65. Zhang Y, Nakano D, Guan Y, Hitomi H, Uemura A, et al. 2018. A sodium-glucose cotransporter 2 inhibitor attenuates renal capillary injury and fibrosis by a vascular endothelial growth factor-dependent pathway after renal injury in mice. Kidney Int. 94:524–35 [PubMed: 30045814]
66. Nespoux J, Patel R, Zhang H, Huang W, Freeman B, et al. 2020. Gene knockout of the Na^+-glucose cotransporter SGLT2 in a murine model of acute kidney injury induced by ischemia-reperfusion. Am. J. Physiol. Ren. Physiol 318:F1100–12
67. Nespoux J, Patel R, Hudkins KL, Huang W, Freeman B, et al. 2019. Gene deletion of the Na^+-glucose cotransporter SGLT1 ameliorates kidney recovery in a murine model of acute kidney injury induced by ischemia-reperfusion. Am. J. Physiol. Ren. Physiol 316:F1201–10
68. Darshi M, Onishi A, Kim JJ, Pham J, Van Espen BF, et al. 2017. Metabolic reprogramming in diabetic kidney disease can be restored via SGLT2 inhibition. J. Am. Soc. Nephrol 28(Abstr. Suppl.):439 (Abstr.) [PubMed: 27297947]
69. Mulder S, Heerspink HJL, Darshi M, Kim JJ, Laverman GD, et al. 2019. Effects of dapagliflozin on urinary metabolites in people with type 2 diabetes. Diabetes Obes. Metab 21:2422–28 [PubMed: 31264758]
70. Lee YH, Kim SH, Kang JM, Heo JH, Kim DJ, et al. 2019. Empagliflozin attenuates diabetic tubulopathy by improving mitochondrial fragmentation and autophagy. Am. J. Physiol. Ren. Physiol 317:F767–80
71. Takagi S, Li J, Takagaki Y, Kitada M, Nitta K, et al. 2018. Ipragliflozin improves mitochondrial abnormalities in renal tubules induced by a high-fat diet. J. Diabetes Investig 9:1025–32
72. Novikov A, Fu Y, Huang W, Freeman B, Patel R, et al. 2019. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. Am. J. Physiol. Ren. Physiol 316:F173–85
73. Lytvyn Y, Skrtic M, Yang GK, Yip PM, Perkins BA, Cherney DZ. 2015. Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated type 1 diabetes mellitus. Am. J. Physiol. Ren. Physiol 308:F77–83

74. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi JI, et al. 2014. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm. Drug Dispos 35:391–404 [PubMed: 25044127]
75. Toyoki D, Shibata S, Kuribayashi-Okuma E, Xu N, Ishizawa K, et al. 2017. Insulin stimulates uric acid reabsorption via regulating urate transporter 1 and ATP-binding cassette subfamily G member 2. Am. J. Physiol. Ren. Physiol 313:F826–34
76. Pessoa TD, Campos LC, Carraro-Lacroix L, Girardi AC, Malnic G. 2014. Functional role of glucose metabolism, osmotic stress, and sodium-glucose cotransporter isoform-mediated transport on Na^+/H^+ exchanger isoform 3 activity in the renal proximal tubule. J. Am. Soc. Nephrol 25:2028–39 [PubMed: 24652792]
77. Coady MJ, El TA, Santer R, Bissonnette P, Sasseville LJ, et al. 2017. MAP17 is a necessary activator of renal Na^+/glucose cotransporter SGLT2. J. Am. Soc. Nephrol 28:85–93 [PubMed: 27288013]
78. Fu Y, Gerasimova M, Mayoux E, Masuda T, Vallon V. 2014. SGLT2 inhibitor empagliflozin increases renal NHE3 phosphorylation in diabetic Akita mice: possible implications for the prevention of glomerular hyperfiltration. Diabetes 63(S1):A132
79. Rajasekeran H, Lytvyn Y, Bozovic A, Lovshin JA, Diamandis E, et al. 2017. Urinary adenosine excretion in type 1 diabetes. Am. J. Physiol. Ren. Physiol 313:F184–91
80. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, et al. 2018. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 41:356–63 [PubMed: 29203583]
81. Layton AT, Vallon V. 2018. SGLT2 inhibition in a kidney with reduced nephron number: modeling and analysis of solute transport and metabolism. Am. J. Physiol. Ren. Physiol 314:F969–84
82. Li J, Neal B, Perkovic V, de Zeeuw D, Neuen BL, et al. 2020. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. Kidney Int. 98:769–77 [PubMed: 32470492]
83. Li J, Woodward M, Perkovic V, Figtree GA, Heerspink HJL, et al. 2020. Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. JACC Heart Fail. 8:57–66 [PubMed: 31676303]
84. Verma S, Mazer CD, Fitchett D, Inzucchi SE, Pfarr E, et al. 2018. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME(R) randomised trial. Diabetologia 61:1712–23 [PubMed: 29777264]
85. Verma S, Mazer CD, Al-Omran M, Inzucchi SE, Fitchett D, et al. 2018. Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. Circulation 137:405–07 [PubMed: 29133602]
86. Savarese G, Sattar N, Januzzi J, Verma S, Lund LH, et al. 2019. Empagliflozin is associated with a lower risk of post-acute heart failure rehospitalization and mortality. Circulation 139:1458–60 [PubMed: 30855996]
87. Stone JA, Houlden RL, Lin P, Udell JA, Verma S. 2018. Cardiovascular protection in people with diabetes. Can. J. Diabetes 42(Suppl. 1):S162–69 [PubMed: 29650091]
88. Cherney DZI, Odutayo A, Verma S. 2019. A big win for diabetic kidney disease: CREDENCE. Cell Metab. 29:1024–27 [PubMed: 31067448]
89. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, et al. 2019. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 393:31–39 [PubMed: 30424892]
90. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, et al. 2019. Dapagliflozin in patients with heart failure and reduced ejection fraction. N. Engl. J. Med 381:1995–2008 [PubMed: 31535829]
91. Verma S 2020. The DAPA-HF trial marks the beginning of a new era in the treatment of heart failure with reduced ejection fraction. Cardiovasc Res. 116:e8–10 [PubMed: 31850505]
92. O'Meara E, McDonald M, Chan M, Ducharme A, Ezekowitz JA, et al. 2020. CCS/CHFS heart failure guidelines: clinical trial update on functional mitral regurgitation, SGLT2 inhibitors, ARNI in HFpEF, and tafamidis in amyloidosis. Can. J. Cardiol 36:159–69 [PubMed: 32036861]

93. Docherty KF, Jhund PS, Inzucchi SE, Kober L, Kosiborod MN, et al. 2020. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. Eur. Heart J 41:2379–92 [PubMed: 32221582]

94. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, et al. 2020. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation 141:90–99 [PubMed: 31736335]

95. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, et al. 2020. Cardiovascular and renal outcomes with empagliflozin in heart failure. N. Engl. J. Med 383:1413–24 [PubMed: 32865377]

96. Lam CSP, Chandramouli C, Ahooja V, Verma S. 2019. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. J. Am. Heart Assoc 8:e013389 [PubMed: 31607208]

97. Packer M 2020. SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: a paradigm shift in understanding their mechanism of action. Diabetes Care 43:508–11 [PubMed: 32079684]

98. Ferrannini E 2017. Sodium-glucose co-transporters and their inhibition: clinical physiology. Cell Metab. 26:27–38 [PubMed: 28506519]

99. Verma S, McMurray JJV. 2019. The serendipitous story of SGLT2 inhibitors in heart failure. Circulation 139:2537–41 [PubMed: 30882236]

100. Lopaschuk GD, Verma S. 2020. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC Basic Transl. Sci 5:632–44 [PubMed: 32613148]

101. Verma S 2019. Potential mechanisms of sodium-glucose co-transporter 2 inhibitor-related cardiovascular benefits. Am. J. Cardiol 124(Suppl. 1):S36–44 [PubMed: 31741439]

102. Butler J, Handelsman Y, Bakris G, Verma S. 2020. Use of sodium–glucose co-transporter-2 inhibitors in patients with and without type 2 diabetes: implications for incident and prevalent heart failure. Eur. J. Heart Fail 22:604–17 [PubMed: 31926059]

103. Verma S, McMurray JJV. 2018. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 61:2108–17 [PubMed: 30132036]

104. Verma S, Sharma A, Kanumilli N, Butler J. 2019. Predictors of heart failure development in type 2 diabetes: a practical approach. Curr. Opin. Cardiol 34:578–83 [PubMed: 31219877]

105. Verma S, Wanner C, Zwiener I, Ofstad AP, George JT, et al. 2019. Influence of microvascular disease on cardiovascular events in type 2 diabetes. J. Am. Coll. Cardiol 73:2780–82 [PubMed: 30885684]

106. Dickhout JG, Carlisle RE, Austin RC. 2011. Interrelationship between cardiac hypertrophy, heart failure, and chronic kidney disease: endoplasmic reticulum stress as a mediator of pathogenesis. Circ. Res 108:629–42 [PubMed: 21372294]

107. Opingari E, Verma S, Connelly KA, Mazer CD, Teoh H, et al. 2020. The impact of empagliflozin on kidney injury molecule-1: a subanalysis of the Effects of Empagliflozin on Cardiac Structure, Function, and Circulating Biomarkers in Patients with Type 2 Diabetes CardioLink-6 trial. Nephrol. Dial Transplant 35:895–97 [PubMed: 32159783]

108. Patel VB, Shah S, Verma S, Oudit GY. 2017. Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease. Heart Fail Rev. 22:889–902 [PubMed: 28762019]

109. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, et al. 2014. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J. Clin. Investig 124:499–508 [PubMed: 24463454]

110. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Barsotti E, et al. 2017. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care 40:771–76 [PubMed: 28325783]

111. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. 2018. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes. Metab 20:479–87 [PubMed: 29024278]

112. Heerspink HJL, de Zeeuw D, Wie L, Leslie B, List J. 2013. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes. Metab 15:853–62 [PubMed: 23668478]
113. Abraham WT, Lauwaars ME, Kim JK, Pena RL, Schrier RW. 1995. Reversal of atrial natriuretic peptide resistance by increasing distal tubular sodium delivery in patients with decompensated cirrhosis. Hepatology 22:737–43 [PubMed: 7657277]
114. Shi X, Verma S, Yun J, Brand-Arzamendi K, Singh KK, et al. 2017. Effect of empagliflozin on cardiac biomarkers in a zebrafish model of heart failure: Clues to the EMPA-REG OUTCOME trial? Mol. Cell. Biochem 433:97–102 [PubMed: 28391552]
115. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, et al. 2019. Effect of empagliflozin on erythropoietin levels, iron stores and red blood cell morphology in patients with type 2 diabetes and coronary artery disease. Circulation 141:704–7 [PubMed: 31707794]
116. Ghanim H, Abuaysheh S, Hejna J, Green K, Batra M, et al. 2020. Dapagliflozin suppresses hepcidin and increases erythropoiesis. J. Clin. Endocrinol. Metab 105:e1056–63
117. Hess DA, Terenzi DC, Trac JZ, Quan A, Mason T, et al. 2019. SGLT2 inhibition with empagliflozin increases circulating provascular progenitor cells in people with type 2 diabetes mellitus. Cell Metab. 30:609–13 [PubMed: 31477497]
118. Goldenberg RM, Berard LD, Cheng AYY, Gilbert JD, Verma S, et al. 2016. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin. Ther 38:2654–64.e1 [PubMed: 28003053]
119. Lopaschuk GD, Verma S. 2016. Empagliflozin's fuel hypothesis: not so soon. Cell Metab. 24:200–2 [PubMed: 27508868]
120. Ferrannini E, Mark M, Mayoux E. 2016. Response to Comment on Ferrannini et al. CV protection in the EMPA-REG OUTCOME Trial: a "thrifty substrate" hypothesis. Diabetes Care 39:e226 [PubMed: 27879364]
121. Nielsen R, Møller N, Gormsen LC, Tolbod LP, Hansson NH, et al. 2019. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation 139:2129–41 [PubMed: 30884964]
122. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, et al. 2018. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. JACC Basic Transl. Sci 3:575–87 [PubMed: 30456329]
123. Santos-Gallego CG, Requena-Ibanez JA, San AR, Ishikawa K, Watanabe S, et al. 2019. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J. Am. Coll. Cardiol 73:1931–44 [PubMed: 30999996]
124. Trum M, Wagner S, Maier LS, Mustroph J. 2020. CaMKII and GLUT1 in heart failure and the role of gliflozins. Biochim. Biophys. Acta Mol. Basis Dis 1866:165729 [PubMed: 32068116]
125. Kappel BA, Lehrke M, Schutt K, Artati A, Adamski J, et al. 2017. Effect of empagliflozin on the metabolic signature of patients with type 2 diabetes mellitus and cardiovascular disease. Circulation 136:969–72 [PubMed: 28874423]
126. Verma S 2020. Are the cardiorenal benefits of SGLT2 inhibitors due to inhibition of the sympathetic nervous system? JACC Basic Transl. Sci 5:180–82 [PubMed: 32142070]
127. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, et al. 2020. SGLT2 inhibitor-induced sympathoinhibition: a novel mechanism for cardiorenal protection. JACC Basic Transl. Sci 5:169–79 [PubMed: 32140623]
128. Jordan J, Tank J, Heusser K, Heise T, Wanner C, et al. 2017. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. J. Am. Soc. Hypertens 11:604–12 [PubMed: 28757109]
129. Garg V, Verma S, Connelly KA, Yan AT, Sikand A, et al. 2020. Does empagliflozin modulate the autonomic system among patients with type 2 diabetes and coronary artery disease? The EMPA-HEART CardioLink-6 Holter analysis. Metab. Open 7:100039
130. Chiba Y, Yamada T, Tsukita S, Takahashi K, Munakata Y, et al. 2016. Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, acutely reduces energy expenditure in BAT via neural signals in mice. PLOS ONE 11:e0150756 [PubMed: 26963613]

131. Bohm M, Slawik J, Brueckmann M, Mattheus M, George JT, et al. 2020. Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. Eur. J. Heart Fail 22:126–35 [PubMed: 31820559]

132. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JWT, et al. 2018. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na^+/H^+ exchanger, lowering of cytosolic Na^+ and vasodilation. Diabetologia 61:722–26 [PubMed: 29197997]

133. Iborra-Egea O, Santiago-Vacas E, Yurista SR, Lupon J, Packer M, et al. 2019. Unraveling the molecular mechanism of action of empagliflozin in heart failure with reduced ejection fraction with or without diabetes. JACC Basic Transl. Sci 4:831–40 [PubMed: 31998851]

134. Byrne NJ, Matsumura N, Maayah ZH, Ferdaoussi M, Takahara S, et al. 2020. Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure. Circ. Heart Fail 13:e006277 [PubMed: 31957470]

135. Byrne NJ, Soni S, Takahara S, Ferdaoussi M, Al Batran R, et al. 2020. Chronically elevating circulating ketones can reduce cardiac inflammation and blunt the development of heart failure. Circ. Heart Fail 13. 10.1161/CIRCHEARTFAILURE.119.006573

136. Kang S, Verma S, Hassanabad AF, Teng G, Belke DD, et al. 2020. Direct effects of empagliflozin on extracellular matrix remodelling in human cardiac myofibroblasts: novel translational clues to explain EMPA-REG OUTCOME results. Can. J. Cardiol 543–53 [PubMed: 31837891]

137. Byrne NJ, Parajuli N, Levasseur JL, Boisvenue J, Beker D, et al. 2017. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. JACC Basic Transl. Sci 2:347–54 [PubMed: 30062155]

138. Connelly KA, Zhang Y, Visram A, Advani A, Batchu SN, et al. 2019. Empagliflozin improves diastolic function in a nondiabetic rodent model of heart failure with preserved ejection fraction. JACC Basic Transl. Sci 4:27–37 [PubMed: 30847416]

139. Verma S, Mazer CD, Bhatt DL, Raj SR, Yan AT, et al. 2019. Empagliflozin and cardiovascular outcomes in patients with type 2 diabetes and left ventricular hypertrophy: a subanalysis of the EMPA-REG OUTCOME trial. Diabetes Care 42:e42–44 [PubMed: 30674547]

140. Kumar N, Garg A, Bhatt DL, Sabongui S, Gupta N, et al. 2018. Empagliflozin improves cardiorespiratory fitness in type 2 diabetes: translational implications. Can. J. Physiol. Pharmacol 96:1184–87 [PubMed: 30265814]

141. Verma S, Mazer CD, Yan AT, Mason T, Garg V, et al. 2019. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation 140:1693–702 [PubMed: 31434508]

142. Bami K, Gandhi S, Leong-Poi H, Yan AT, Ho E, et al. 2020. Effects of empagliflozin on left ventricular remodeling in patients with type 2 diabetes and coronary artery disease: echocardiographic substudy of the EMPA-HEART CardioLink-6 randomized clinical trial. J. Am. Soc. Echocardiogr 33:644–46 [PubMed: 32199780]

143. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, et al. 2016. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: An important clue to the EMPA-REG OUTCOME trial? Diabetes Care 39:e212–13 [PubMed: 27679584]

144. Verma S, Maitland A, Weisel RD, Li SH, Fedak PW, et al. 2002. Hyperglycemia exaggerates ischemia-reperfusion-induced cardiomyocyte injury: reversal with endothelin antagonism. J. Thorac. Cardiovasc. Surg 123:1120–24 [PubMed: 12063458]

145. Connelly KA, Yan AT, Leiter LA, Bhatt DL, Verma S. 2015. Cardiovascular implications of hypoglycemia in diabetes mellitus. Circulation 132:2345–50 [PubMed: 26667098]

146. Verma S, Mazer CD, Bhatt DL. 2018. The perils of polyvascular disease in type 2 diabetes. Lancet Diabetes Endocrinol. 6:914–16 [PubMed: 30396866]

147. Chowdhury B, Luu AZ, Luu VZ, Kabir MG, Pan Y, et al. 2020. The SGLT2 inhibitor empagliflozin reduces mortality and prevents progression in experimental pulmonary hypertension. Biochem. Biophys. Res. Commun 524:50–56 [PubMed: 31980166]

148. Cooper S, Teoh H, Campeau MA, Verma S, Leask RL. 2019. Empagliflozin restores the integrity of the endothelial glycocalyx in vitro. Mol. Cell. Biochem 459:121–30 [PubMed: 31127491]

149. Cherney DZI, Perkins BA, Soleymanlou N, Har R, Fagan N, et al. 2014. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc. Diabetol 13:28 [PubMed: 24475922]

150. Pfeifer M, Townsend RR, Davies MJ, Vijapurkar U, Ren J. 2017. Effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on blood pressure and markers of arterial stiffness in patients with type 2 diabetes mellitus: a post hoc analysis. Cardiovasc. Diabetol 16:29 [PubMed: 28241822]

151. Mancini SJ, Boyd D, Katwan OJ, Strembitska A, Almabrouk TA, et al. 2018. Canagliflozin inhibits interleukin-1β-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-activated protein kinase-dependent and -independent mechanisms. Sci. Rep 8:5276 [PubMed: 29588466]

152. Behnammanesh G, Durante ZE, Peyton KJ, Martinez-Lemus LA, Brown SM, et al. 2019. Canagliflozin inhibits human endothelial cell proliferation and tube formation. Front. Pharmacol 10:362 [PubMed: 31057401]

153. Tanaka A, Shimabukuro M, Machii N, Teragawa H, Okada Y, et al. 2019. Effect of empagliflozin on endothelial function in patients with type 2 diabetes and cardiovascular disease: results from the multicenter, randomized, placebo-controlled, double-blind EMBLEM trial. Diabetes Care 42:e159–61 [PubMed: 31533913]

154. Sanchez RA, Sanchez MJ, Ramirez AJ. 2018. Canagliflozin ameliorates arterial stiffness by reducing serum uric acid in type 2 diabetic patients. Diabetes 67(Suppl. 1):1216–P (Abstr.) [PubMed: 29769238]

155. Verma S, Ji Q, Bhatt DL, Mazer CD, Al-Omran M, et al. 2020. The association between uric acid levels and cardio-renal outcomes and death in patients with type 2 diabetes: a subanalysis of EMPA-REG OUTCOME. Diabetes Obes. Metab 22:1207–14 [PubMed: 32030863]

156. Sherman SE, Bell GI, Teoh H, Al-Omran M, Connelly KA, et al. 2018. Canagliflozin improves the recovery of blood flow in an experimental model of severe limb ischemia. JACC Basic Transl. Sci 3:327–29 [PubMed: 30062217]

157. Striepe K, Jumar A, Ott C, Karg MV, Schneider MP, et al. 2017. Effects of the selective sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function and central hemodynamics in patients with type 2 diabetes mellitus. Circulation 136:1167–69 [PubMed: 28923906]

SUMMARY POINTS

1. SGLT2 inhibitors reduce the risk of renal and heart failure in individuals with preserved and reduced kidney function and in the presence and absence of T2DM; the pleiotropic effects include blood glucose–dependent and –independent mechanisms.
2. SGLT2 inhibitors prevent both hyper- and hypoglycemia, and the metabolic adaptation to urinary glucose loss includes enhanced lipolysis, which reduces fat mass and enhanced ketone bodies, which act as additional fuel; these metabolic changes have little net effect on HbA1C values but the potential to contribute to kidney and heart protection.
3. SGLT2 inhibitors lower glomerular capillary hypertension and hyperfiltration at the onset of therapy, thereby reducing the physical stress on the filtration barrier, albuminuria, and the oxygen demand for reabsorbing the filtered load; this improves cortical oxygenation and potentially tubular mitochondrial function and autophagy, which can preserve tubular function and GFR in the long term.
4. SGLT2 inhibitors better distribute and shift reabsorption downstream of the early proximal tubule, which may mimic systemic hypoxia at the kidney oxygen sensors in the deeper cortex and outer medulla, thereby stimulating erythropoiesis and, together with their diuretic effect, enhance hematocrit and improve oxygen delivery to kidneys, heart and other organs. Delivering more NaCl and fluid downstream of the early proximal tubule may also help to overcome the resistance to endogenous atrial natriuretic peptide and diuretics observed in heart failure.
5. SGLT2 inhibitors have marked effects to prevent heart failure in individuals with T2DM and treat heart failure with reduced ejection fraction in people with and without T2DM.
6. Several mechanisms have been suggested to mediate the heart failure benefits, including diuresis and natriuresis, changes in myocardial energetics, increased EPO production and erythropoiesis, changes in reno-cardiac signaling, inhibition of the sympathetic nervous system, inhibition of NHE1, inhibition of the NLRP3 inflammasome, and potential vascular effects.
7. The EMPA-HEART CardioLink-6 trial has demonstrated the efficacy of SGLT2 inhibition to cause a regression in left ventricular mass index in patients with T2DM over a period of six months.
8. Ongoing studies in patients with and without diabetes with HFrEF and HFpEF will provide further insights into the heart failure treatment paradigm.

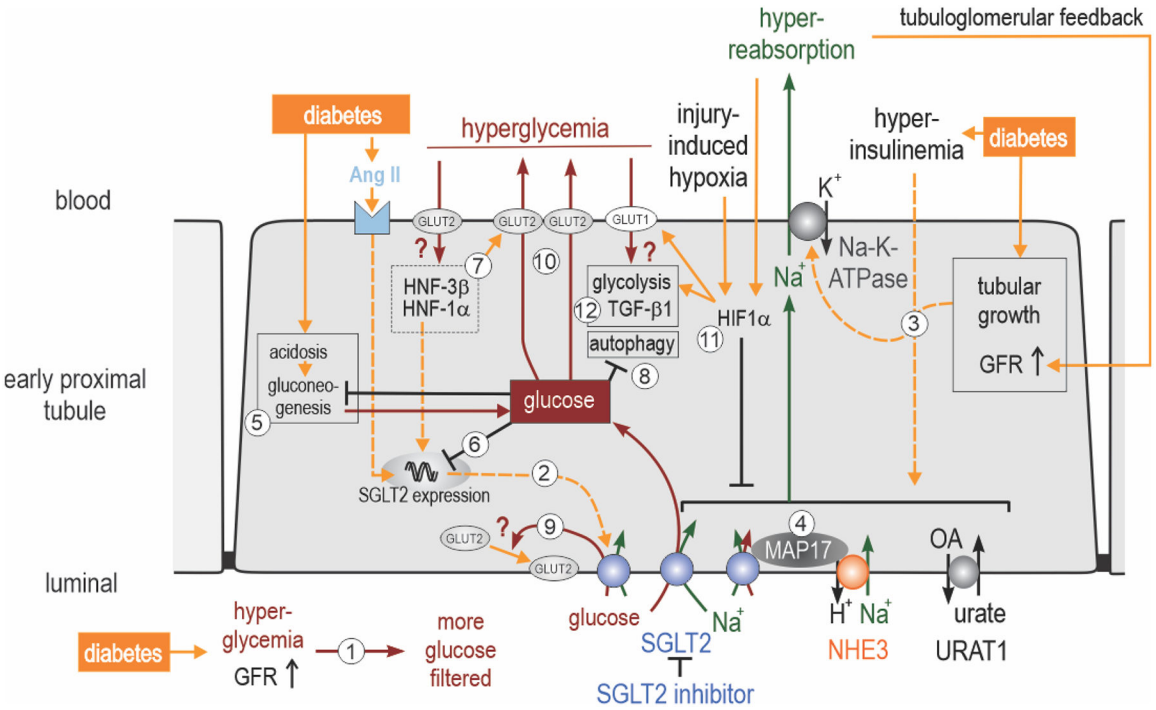

Figure 1.

Cellular processes linked to SGLT2 and its inhibition in the early proximal tubule. Hyperglycemia enhances filtered glucose and, via SGLT2, the reabsorption of glucose and Na^+ (1). Diabetes can increase SGLT2 expression (2); proposed mechanisms include tubular growth, Ang II, and HNF-1α, which may respond to basolateral hyperglycemia sensed by GLUT2. Hyperinsulinemia and tubular growth upregulate proximal tubular transport systems, including SGLT2, NHE3, URAT1, and Na-K-ATPase (3). The apical transporters may be functionally coupled via scaffolding proteins, such as MAP17 (4). The resulting proximal tubular Na^+ retention enhances the GFR via tubuloglomerular feedback, which by increasing brush border torque can further increase transporter density in the luminal membrane. Diabetes, in part due to the associated acidosis, can enhance gluconeogenesis (5). The increase in intracellular glucose may lower SGLT2 expression via negative feedback (6). HNF-1α and HNF-3β upregulate GLUT2 and thereby the basolateral exit of glucose (7). Excessive SGLT2-mediated glucose uptake may attenuate autophagy (8) and trigger apical translocation of GLUT2 (9). Increased glucose reabsorption maintains hyperglycemia (10). Hypoxia due to diabetes-induced hyperreabsorption or kidney injury may induce HIF-1α, which enhances basolateral glucose uptake via GLUT1, induces a metabolic shift to glycolysis, and inhibits apical transport (11). Induction of TGF-β1 and tubular growth may be particularly sensitive to basolateral glucose uptake via GLUT1 (12). Abbreviations: Ang II, angiotensin II; GFR, glomerular filtration rate; GLUT, facilitative glucose transporter; HIF-1α, hypoxia-inducible factor 1 alpha; HNF, hepatic nuclear factor; MAP17, 17-kDa membrane-associated protein; NHE3, Na-H-exchanger 3; OA, organic anion; TGF-β1, transforming growth factor β1; URAT1, urate transporter 1. Figure adapted with permission from Reference 23.

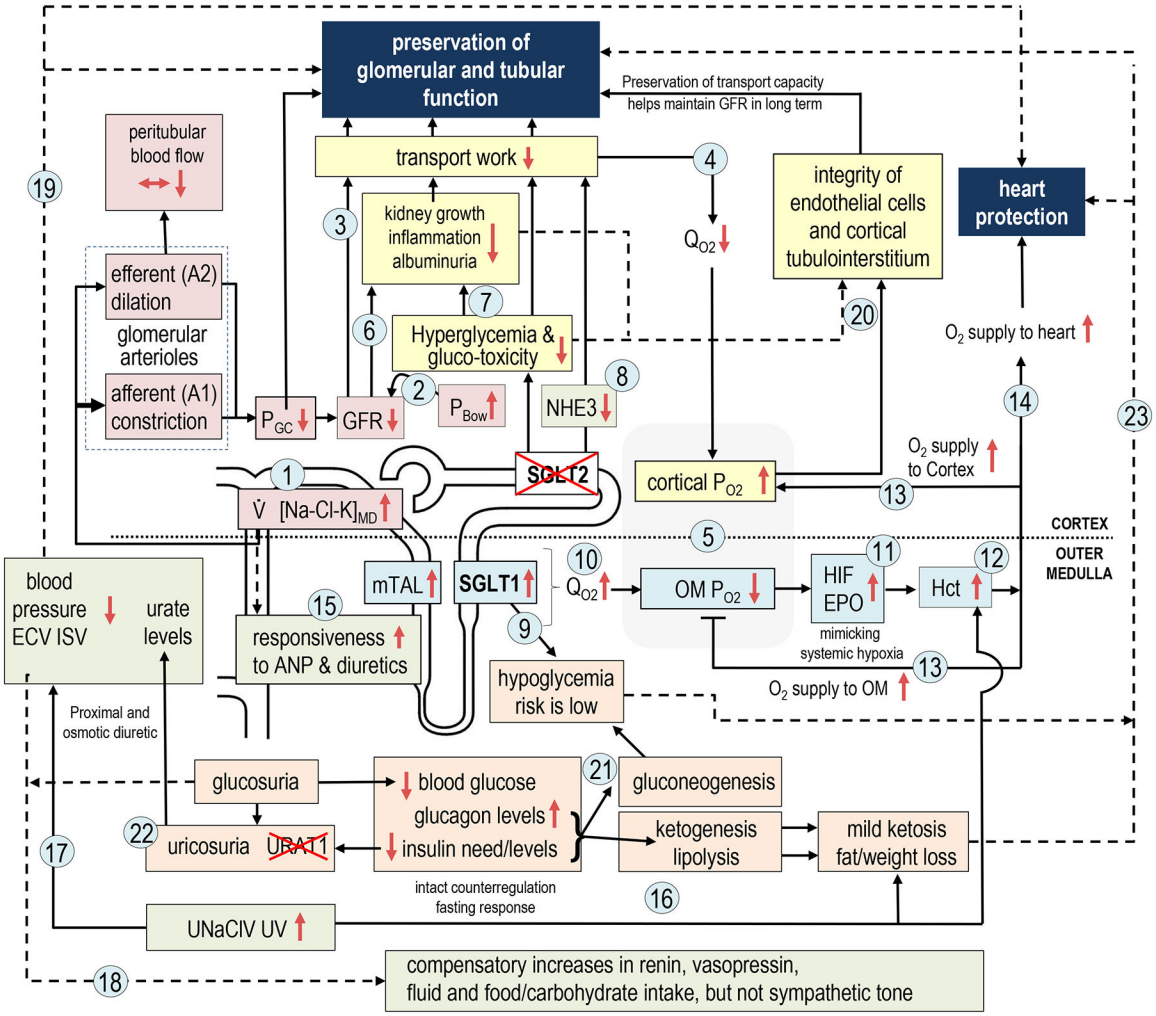

Figure 2.

Potential kidney-protective effects of SGLT2 inhibition. SGLT2 inhibition counteracts the diabetes-induced hyperreabsorption of glucose and Na^+ in the early proximal tubule and lowers blood glucose levels. This also increases the NaCl and K concentration ($[Na\text{-}Cl\text{-}K]_{MD}$) and fluid delivery (V) to the macula densa, which lowers glomerular filtration rate (GFR) through the physiology of tubuloglomerular feedback (1) and by increasing hydrostatic pressure in Bowman's space (P_{Bow}) (2). The GFR-lowering effect of tubuloglomerular feedback includes afferent arteriole constriction (via adenosine A1 receptor) and potentially efferent arteriole dilation (via adenosine A2 receptor), which both reduce glomerular capillary pressure (P_{GC}). Lowering of GFR reduces tubular transport work (3), thereby lowering cortical oxygen demand (Q_{O2}) (4) and increasing cortical oxygen tension (P_{O2}) (5). Lowering GFR (6) and hyperglycemia (7) attenuates filtration of tubulo-toxic compounds, including albumin, and reduces tubular growth and kidney inflammation. Tubular transport work is further reduced by lowering blood glucose and by cellular SGLT2 blockade itself, which reduces tubular gluco-toxicity and has also been linked to inhibition of the Na-H-exchanger NHE3 (8). SGLT2 inhibition shifts glucose reabsorption downstream where SGLT1 compensates and reduces the risk of hypoglycemia (9). Shifting glucose and

Na^+ reabsorption downstream to S3 and mTAL segments increases Q_{O2} (10) and lowers P_{O2} in the outer medulla (OM) (5). Furthermore, lower medullary P_{O2} may activate hypoxia-inducible factor (HIF) and enhance erythropoietin (EPO) release (11). The latter increases hematocrit (Hct) (12) and improves O_2 delivery to kidney medulla and cortex (13) and the heart (14). Enhanced delivery of NaCl and fluid downstream of early proximal tubule enhances responsiveness to atrial natriuretic peptide (ANP) and diuretics (15). The diuretic and natriuretic effects of SGLT2 inhibition further increase Hct (16) and reduce extracellular (ECV) and interstitial (ISV) volume and blood pressure (17). These effects, which are also evident by compensatory upregulation of renin and vasopressin levels (18), can help protect the failing kidney and heart (19). The increased cortical oxygen availability together with lesser hyperglycemia, tubular gluco-toxicity, filtered albumin, and tubulointerstitial inflammation improves the integrity of the tubular and endothelial system, thereby allowing a higher tubular transport capacity and GFR to be maintained in the long term (20). The glucosuric effect lowers therapeutic and/or endogenous insulin levels and increases glucagon concentrations (21). This induces compensatory lipolysis and hepatic gluconeogenesis and ketogenesis. SGLT2 inhibitors are uricosuric, potentially involving urate transporter 1 (URAT1) inhibition and their glucosuric and insulin-lowering effect (22). These metabolic adaptations reduce urate levels, the hypoglycemia risk, and body and organ fat mass, which together with the resulting mild ketosis have the potential to further protect the kidney and heart (19, 23). Other abbreviations: UNaClV, urinary salt excretion; UV, urinary flow rate. Figure adapted with permission from Reference 13; copyright 1999 Portland Press, Ltd.

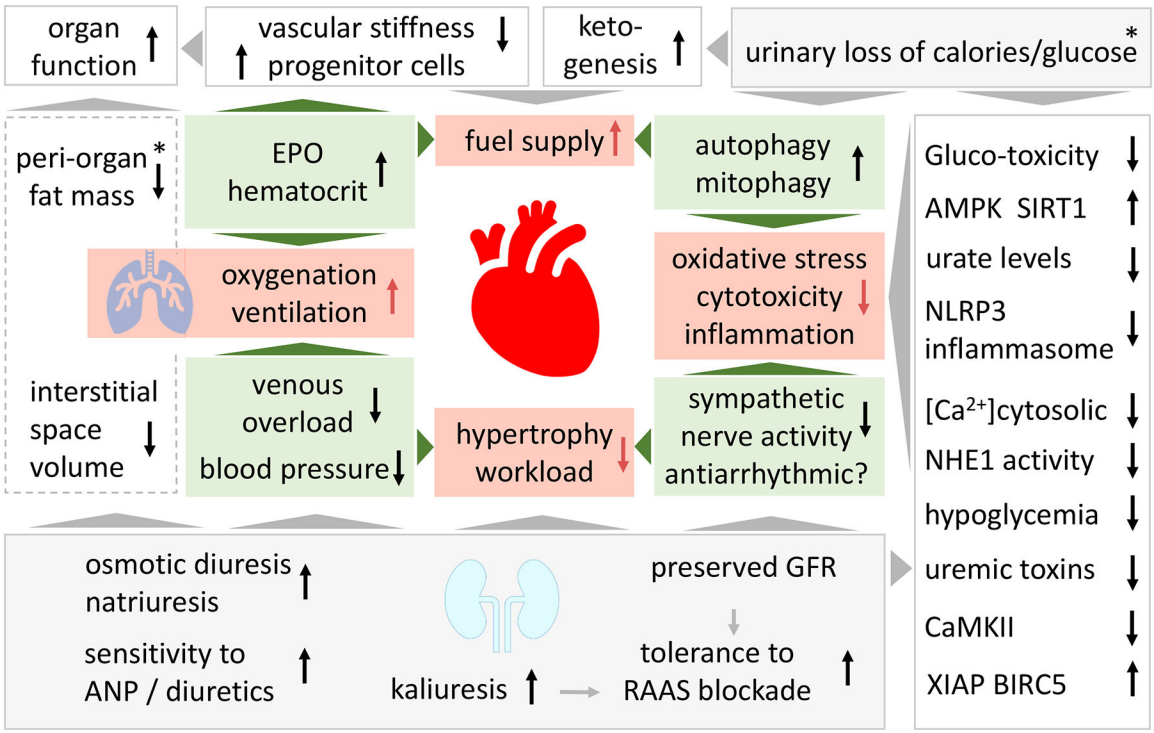

Figure 3.

Potential cardioprotective effects of SGLT2 inhibition. SGLT2 inhibitors enhance the cardiac oxygen and fuel supply while simultaneously reducing cardiac workload and cytotoxic and proinflammatory influences. The involved mechanisms are illustrated. Asterisks (*) denote urinary loss of calories, and glucose enhances lipolysis and thereby reduces peri-organ fat mass. Figure integrated and further developed from References 3, 97, 100, 115, 126. Abbreviations: AMPK, AMP-activated protein kinase; ANP, atrial natriuretic peptide; BIRC5, baculoviral IAP repeat-containing protein 5 or survivin; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; GFR, glomerular filtration rate; NLRP3, NLR family pyrin domain-containing 3; RAAS, renin-angiotensin-aldosterone system; SIRT1, Sirtuin 1; XIAP, X-linked inhibitor of apoptosis.