Sodium-glucose cotransporter-2 inhibitors: Understanding the mechanisms for therapeutic promise and persisting risks

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In a healthy person, the kidney filters nearly 200 g of glucose per day, almost all of which is reabsorbed. The primary transporter responsible for renal glucose reabsorption is sodium-glucose cotransporter-2 (SGLT2). Based on the impact of SGLT2 to prevent renal glucose wasting, SGLT2 inhibitors have been developed to treat diabetes and are the newest class of glucose-lowering agents approved in the United States. By inhibiting glucose reabsorption in the proximal tubule, these agents promote glycosuria, thereby reducing blood glucose concentrations and often resulting in modest weight loss. Recent work in humans and rodents has demonstrated that the clinical utility of these agents may not be limited to diabetes management: SGLT2 inhibitors have also shown therapeutic promise in improving outcomes in heart failure, atrial fibrillation, and, in preclinical studies, certain cancers. Unfortunately, these benefits are not without risk: SGLT2 inhibitors predispose to euglycemic ketoacidosis in those with type 2 diabetes and, largely for this reason, are not approved to treat type 1 diabetes. The mechanism for each of the beneficial and harmful effects of SGLT2 inhibitors—with the exception of their effect to lower plasma glucose concentrations—is an area of active investigation. In this review, we discuss the mechanisms by which these drugs cause euglycemic ketoacidosis and hyperglucagonemia and stimulate hepatic gluconeogenesis as well as their beneficial effects in cardiovascular disease and cancer. In so doing, we aim to highlight the crucial role for selecting patients for SGLT2 inhibitor therapy and highlight several crucial questions that remain unanswered.

SGLT2, also known as SLC5A2, is the primary glucose transport protein in the proximal segment of the proximal tubule of the nephron (1). SGLT2, found at the apical membrane of the brush border in renal proximal tubule cells (2), is a low-affinity (K_m ~0.4 mM (3)), high-capacity (filtering ~180 g of glucose/day) glucose transporter that is traditionally considered responsible for 80–97% of renal glucose reabsorption (4–7) (Fig. 1). SGLT2 inhibitors (gliflozins) are a unique class of diabetes drug: these agents are the only approved agents that waste glucose through the urine rather than reducing hepatic glucose output (biguanides), increasing tissue glucose uptake (insulin, sulfonylureas, thiazolidinediones, incretins), or inhibiting intestinal carbohydrate uptake (α-glucosidase inhibitors). Gliflozins are highly selective, competitive inhibitors, offering great promise for treatment of diabetes. However, the use of these agents has been complicated by clinical side effects that can be traced to a lack of full understanding of the corresponding biology. This review explores the current state of the field, capturing open biological and medical questions as well as emerging applications of SGLT2 inhibitors.

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History and mechanism of SGLT2 inhibitors

Seemingly paradoxically, pharmacokinetics data would suggest that at the concentrations of SGLT2 inhibitors achieved *in vivo* (<0.5–1.5 μM (8), 3 orders of magnitude higher than the IC_{50} of ~1.5 nM (9)), glucose reuptake through SGLT2 would be totally inhibited (predicting an 80–97% reduction in renal glucose reabsorption) (10, 11); however, SGLT2 inhibitors have been shown to inhibit only 30–50% of glucose reabsorption in clinical studies (12). It is likely that increased glucose reabsorption by SGLT1 contributes substantially when SGLT2 is inhibited; the maximal glucose transport capacity of SGLT1 is approximately one-third to one-half that of SGLT2 (3), suggesting that when more glucose is presented in the distal nephron because of SGLT2 inhibition, SGLT1 has the capacity to increase glucose reabsorption. In support of this hypothesis, Powell *et al.* (13) demonstrated that mice lacking both SGLT1 and SGLT2 exhibited 3-fold greater glycosuria than mice lacking SGLT2 alone. However, the reason for the marked reduction in glycosuria in those treated with these agents, as compared with what would be predicted by pharmacokinetic data on these agents, remains an important unanswered question.

The first SGLT inhibitor, phlorizin, which was later found to inhibit both SGLT1 and SGLT2, was a natural product isolated more than 175 years before the first agent in this class of drugs was approved by the Food and Drug Administration (FDA) to treat diabetes. Phlorizin was first derived by de Koninck from the bark of the apple tree (*Malus domestica*) in 1835 (14). Due to its bitter taste and the previously observed antimalarial properties of extracts from the bark of other trees (*Salix alba*, the white willow, and *Cinchona rubra*, from which quinine was isolated), it was first surmised that phlorizin would have antipyretic, antipathogenic properties (15). Subsequent studies failed to confirm this presumption but quickly identified a highly reproducible effect of phlorizin: it increased glucose clearance markedly, causing subjects to produce high volumes of glucose-containing urine (16–18) and lowering blood glucose concentrations in subjects with diabetes (19). Phlorizin was listed in the Merck manual as a glycoside from the 1880s onward. Thus,

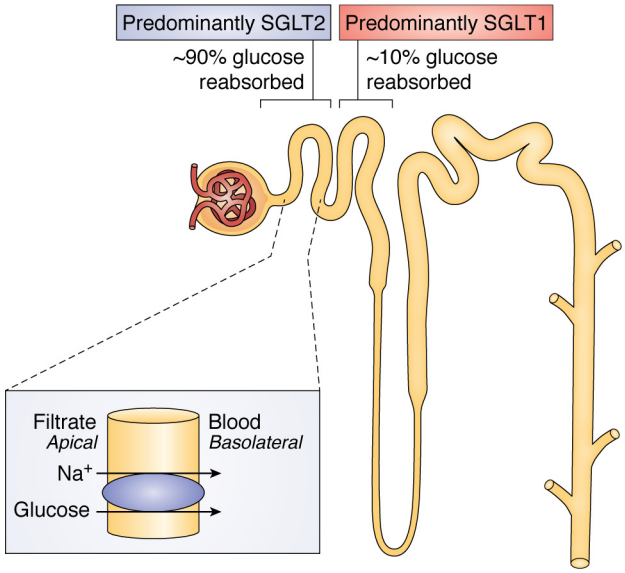

Figure 1. The location of SGLT1 and SGLT2 transporters in the nephron and the mechanism by which SGLT2 inhibitors promote renal glucose wasting.

the discovery of phlorizin and its capacity to promote glycosuria and glucose clearance preceded even the discovery of insulin as a glucose-lowering agent in 1921.

Subsequent studies on phlorizin's mechanism of action demonstrated that the drug inhibits glucose uptake into renal tubule cells (20), suggesting that this agent may exert its antihyperglycemic effect by reducing glucose reabsorption in the kidney. Indeed, phlorizin competitively inhibits SGLT2 at the brush border on the luminal membrane of renal proximal tubular cells, with an affinity for SGLT2 more than 1000 times that of glucose (21), while also inhibiting SGLT1 (22, 23), thereby reducing glucose reuptake throughout the proximal tubule.

These mechanistic insights into the action of phlorizin reinvigorated interest in developing SGLT-inhibiting agents to lower blood glucose in diabetes. Glucose toxicity on the β-cell (*i.e.* damage to the insulin-producing cells in the pancreas as a consequence of chronically high circulating glucose, which often occurs concordantly with lipotoxicity resulting from increased circulating lipids) has been identified as a key driver of the transition from insulin resistance to diabetes (24, 25). In support of this hypothesis, Rossetti *et al.* (26, 27) demonstrated that lowering the glucose load presented to the body, and thereby reducing systemic glucose toxicity, improved β-cell function and reversed insulin resistance in partially pancreatectomized, streptozotocin-treated diabetic rats. Subsequent studies of mice with a global genetic knockout of SGLT2 showed similar improvements: db/db SGLT2$^{-/-}$ mice exhibited lower plasma glucose concentrations, improved insulin sensitivity, and enhanced β-cell function (28, 29), which could be attributed to reductions in glucose toxicity without differences in body weight.

These data demonstrating the effect of SGLT inhibition or ablation to reverse systemic glucose toxicity refocused attention on their clinical development. Phlorizin's potential for clinical use was limited by its effects to reduce glucose uptake in the brain (30)—whether by inhibition of SGLTs (31, 32) or SGLT-like channels (33) or by its poor oral bioavailability (34–36). To address these limitations, investigators developed inhibitors specific to SGLT2, the expression of which is confined to the kidney (37). Canagliflozin, the first SGLT2 inhibitor on the market in the United States, was approved by the FDA for type 2 diabetes (T2D) in 2013. This agent and two other SGLT2 inhibitors developed later lower hemoglobin A1c by an average of 0.8 and 0.6% when used as monotherapy and added to combination therapy, respectively (38), in those with poorly controlled T2D. Pharmacokinetic and clinical parameters of the currently approved SGLT2 inhibitors are shown in Table 1.

SGLT2 inhibitor–induced euglycemic ketoacidosis

The major risk of serious adverse events in those treated with SGLT2 inhibitors is ketoacidosis, a metabolic acidosis in which unrestrained production of ketone bodies, which are generated in a largely unregulated process through hepatic mitochondrial β-oxidation that occurs primarily as a consequence of increases in white adipose tissue (WAT) lipolysis, promotes a potentially lethal decrease (acidification) in blood pH. Treatment with an SGLT2 inhibitor increases the risk of ketoacidosis by 1.5–5-fold (39–41), with a recent meta-analysis finding an odds ratio for ketoacidosis of 2.13 (42). Notably, up to 70% of ketoacidosis episodes are euglycemic (43, 44), and the fatality rate for euglycemic ketoacidosis precipitated by SGLT2 inhibitors is 3-fold higher than that of all DKA (45, 46). Therefore, the risk of euglycemic ketoacidosis represents a significant, treatment-limiting risk of this class of agents.

Due in large part to the risk of ketoacidosis, SGLT2 inhibitors are prescribed with caution in those with T2D and are not FDA-approved for type 1 diabetes. To reap the glucose-lowering benefits of SGLT2 inhibitors—which avoid the risks of hypoglycemia that exist with insulin and sulfonylureas and the gastrointestinal side effects that can accompany metformin and glucagon-like peptide-1 agonists—there is great interest in understanding the mechanism by which SGLT2 inhibitors predispose to ketoacidosis. Early work focused on a potential role for glucagon in this process. Indeed, hyperglucagonemia—which is a hallmark of diabetic ketoacidosis (47–49)—has been observed in both humans (50–52) and rodents (53–56) following treatment with an SGLT2 inhibitor and has been suggested to play a major role in causing both ketoacidosis and increased hepatic glucose production. The putative role of glucagon in both processes is logical, given glucagon's clearly documented effects to promote hepatic gluconeogenesis (57–60), glycogenolysis (61–63), and intrahepatic lipolysis (57), but the mechanisms by which SGLT2 inhibitors increase circulating glucagon concentrations remains unclear. Whereas some early studies found that dapagliflozin increased glucagon release from the islet due to a direct effect on the α-cell (9, 54, 64), subsequent studies failed to replicate this finding and observed no significant effect of SGLT2 inhibitors to alter glucagon release from isolated islets *in vitro* (53, 65–67). In concert with this finding, isolated perfused islets from whole-body SGLT2 knockout mice did not exhibit any difference in glucagon secretion (28). These data represent a case in which *in vivo* data showing an increase in plasma glucagon concentrations in those treated

Table 1

Pharmacokinetic and clinical parameters of the three currently approved SGLT2 inhibitors

A1c-lowering effects refer to studies in which the SGLT2 inhibitor was given as an add-on to metformin (compared with metformin alone).

Drug	Bioavailability (187)	$t_{½}$	Route of excretion	A1c lowering
	%	*h*		%
Canagliflozin	65	10–13 (188)	Urine, feces	0.8–1.0 (189, 190)
Dapagliflozin	78	13 (191)	Urine	0.7–0.8 (192, 193)
Empagliflozin	90	13 (194)	Urine, feces	0.6–0.8 (195, 196)

with an SGLT2 inhibitor are dissociated from *in vitro* data documenting the lack of an effect of SGLT2 inhibitors to promote glucagon secretion from isolated islets and highlight the important of *in vivo* studies to assess the mechanism(s) by which SGLT2 inhibitors may regulate endocrine function.

WAT lipolysis and SGLT2 inhibitor–induced euglycemic ketoacidosis

An alternative mechanism for the effects of SGLT2 inhibitors to promote ketoacidosis is through stimulation of WAT lipolysis—an effect that likely could not be attributable to hyperglucagonemia, as numerous human (68–73) and rodent studies (57, 74) have argued against direct stimulation of white adipose tissue lipolysis by physiological and pathophysiological, as opposed to pharmacological, doses of glucagon when β-cell function is intact. However, increased WAT lipolysis is a hallmark of diabetic ketoacidosis (49, 75–78). WAT lipolysis promotes ketone production by supplying fatty acids that generate β-hydroxybutyrate, acetoacetate, and acetone as they are oxidized and increase gluconeogenesis due to increased supply of both glycerol (a gluconeogenic precursor that drives gluconeogenesis by a substrate push mechanism (79–81)) and acetyl-CoA (the end product of β-oxidation and an allosteric activator of the rate-controlling gluconeogenic enzyme pyruvate carboxylase (82–84)). Given that both ketogenesis (44, 53, 85–88) and increased rates of endogenous glucose production (51–53, 89–92) are observed after SGLT2 inhibitor treatment in humans and rodents, increased rates of lipolysis are a logical upstream explanation of both phenomena. Indeed, in a recent study, we observed that dapagliflozin more than doubled rates of *in vivo* WAT lipolysis in awake rats (53).

A critical question therefore is how do SGLT2 inhibitors activate WAT lipolysis. It is unlikely that SGLT2 inhibitor–induced WAT lipolysis occurs due to a direct effect of these agents on the adipose tissue, because SGLT2 is not expressed significantly in human adipose tissue (37, 93). We recently hypothesized an alternative mechanism for SGLT2 inhibitor–induced increases in WAT lipolysis causing euglycemic ketoacidosis (53).

We reasoned that dehydration (as occurs in a number of the precipitating causes of DKA, including alcohol use and gastrointestinal illness) may promote WAT lipolysis as a result of increased plasma catecholamine and/or corticosterone concentrations, which, in the setting of insulinopenia (as is expected in those on a low-carbohydrate diet and those experiencing an unplanned interruption of insulin delivery due to an insulin pump malfunction or those who substantially reduce their daily insulin dose due to the glucosuric effect of the SGLT2 inhibitor), results in increased WAT lipolysis, driving both increased gluconeogenesis and ketoacidosis (Fig. 2). Indeed, we found that dehydration increased both plasma catecholamine and corticosterone concentrations, resulting in increased rates of WAT lipolysis and endogenous glucose production (EGP) in both healthy control and diabetic rats—but that the increases in both WAT lipolysis and EGP required concomitant reductions in plasma insulin concentrations. Consistent with this two-hit hypothesis, rats treated with furosemide, which caused diuresis but did not lower plasma glucose or insulin concentrations, did not manifest increased rates of WAT lipolysis or ketogenesis or become ketoacidotic, despite equivalent weight loss due to dehydration. Infusing glucose to normalize plasma insulin concentrations to levels measured in control rats prevented increased rates of WAT lipolysis, increased ketogenesis, and ketoacidosis in dapagliflozin-treated rats (53).

Increases in rates of endogenous glucose production, which have been documented in rodents (53, 89, 90) and humans (50, 51, 91, 92), are an expected consequence of the increases in plasma glucagon concentrations that have been documented following acute and chronic SGLT2 inhibitor treatment. The increase in plasma glucagon following treatment with an SGLT2 inhibitor, which data reviewed in the previous section argue does not occur due to a direct effect on the α-cell, has been attributed to the glucose-lowering effect of these drugs (94) and may also be attributable to a direct effect of SGLT2 inhibition in the ventromedial hypothalamus, the activity of which has been shown to be critical to the hormonal counterregulatory response to hypoglycemia (95). Consistent with this possibility, blocking glucose utilization via injection of the nonmetabolizable glucose analog 2-deoxyglucose directly into the ventromedial hypothalamus promoted both glucagon and catecholamine secretion in rats (96). These data suggest that increased plasma glucagon concentrations could contribute to increased rates of gluconeogenesis by stimulating intrahepatic lipolysis (57) in this setting. However, a recent study in which subjects were treated with somatostatin to inhibit pancreatic islet hormone secretion of insulin and glucagon and were given an intravenous infusion of replacement basal insulin and glucagon demonstrated an insulin- and glucagon-independent effect of dapagliflozin to increase EGP in humans with T2D (97). In contrast, either blocking catecholamine and corticosterone action or infusing with saline to prevent dehydration fully abrogated the effect of dapagliflozin to increase EGP in rats, despite a lack of any difference in plasma glucagon concentrations (53). Taken together, these data point to a mechanism for SGLT2 inhibitor–induced diabetic ketoacidosis explained by the two-hit hypothesis: dehydration provokes increases in glucocorticoid and catecholamine concentrations, leading to WAT lipolysis in the setting of insulinopenia resulting from lower plasma glucose concentrations as a result of SGLT2 inhibitor–induced glucosuria. Consistent with this hypothesis, Blau *et al.* (44) found that viral illness (commonly gastroenteritis), alcohol use or abuse, and insulin pump malfunction or insulin dose reduction—each of which can lead to reduced caloric intake and insulin dose reduction—were observed in more than 70% of those who develop euglycemic ketoacidosis on an SGLT2 inhibitor

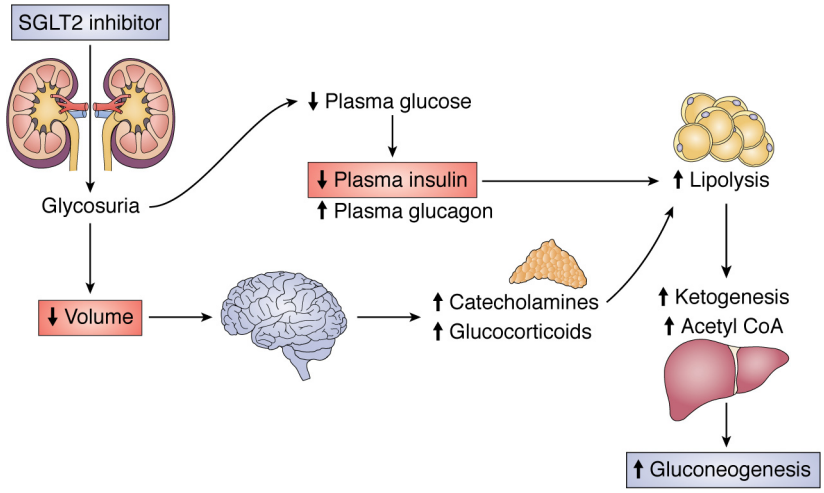

Figure 2. Two-hit hypothesis for the effect of SGLT2 inhibitors to promote euglycemic ketoacidosis via both predisposing to volume depletion and lowering plasma insulin concentrations.

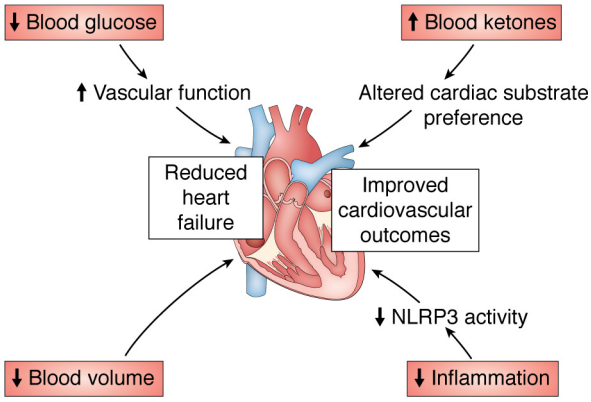

Figure 3. Proposed mechanisms by which SGLT2 inhibitors may reduce heart failure and improve cardiovascular outcomes.

(98–100). However, future studies will be required to mechanistically test whether two hits (insulinopenia and dehydration) are necessary and/or sufficient to promote ketoacidosis in humans treated with SGLT2 inhibitors.

SGLT2 inhibitors and heart failure

Perhaps the largest potential benefit of SGLT2 inhibitors in terms of morbidity and mortality benefits may be reduced heart failure and cardiovascular death. The EMPA-REG trial first identified an effect of the SGLT2 inhibitor empagliflozin to reduce heart failure incidence and mortality (101–103). This result, although surprising, is consistent with the fact that volume overload is a—if not the—critical predisposing factor to heart failure (104, 105). Encouragingly, multiple trials have demonstrated an effect for SGLT2 inhibitors to reduce overall mortality—and, in particular, both hospitalization and mortality from cardiovascular events—among patients with heart failure (39, 41, 106–113). Multiple hypotheses have emerged to explain the beneficial effect of SGLT2 inhibitors on cardiovascular outcomes (Fig. 3). Diabetes *per se* increases the risk of cardiovascular events and mortality (114–118), and poorer glucose control in those with diabetes predicts worse heart failure incidence and mortality (119, 120); thus, it is conceivable that the improved glycemic control observed in those on SGLT2 inhibitors could independently contribute to reduced cardiovascular mortality. However, the improvement in cardiovascular outcomes was observed very quickly after initiation of an SGLT2 inhibitor (generally between 3 months and 1 year) (39, 41, 103, 106, 108–111, 113), a time frame likely incompatible with either glucose-lowering or reversal of atherosclerosis as the primary beneficial mechanism. In addition, most studies (107, 112, 113, 121), with one exception (122), indicated that hemoglobin A1c did not correlate with cardiovascular outcomes in those treated with an SGLT2 inhibitor, and cardiovascular benefits were observed in nondiabetic humans (110) and rodents (123–125). These data, in concert with the fact that an SGLT2 inhibitor, canagliflozin, was more effective to improve cardiac outcomes than dipeptidyl peptidase-4 inhibitors, sulfonylureas, and GLP-1 agonists (112) despite similar glucose-lowering effects to dipeptidyl peptidase-4 inhibitors (38, 126–129) and less efficacy to lower glucose as compared with sulfonylureas (128, 130) and GLP-1 agonists (131, 132), argue against glycemic control as the primary mechanism by which SGLT2 inhibitors reduce cardiovascular risk. It remains an open question—with tremendous clinical relevance—how SGLT2 inhibitors improve cardiovascular function in individuals with diabetes.

Several competing hypotheses have emerged to explain the efficacy of SGLT2 inhibitors in reducing cardiovascular events and mortality. One intriguing explanation highlights the impact of SGLT2 inhibitors to generate a shift in substrate utilization systemically. Due to the glucose-wasting effect of these agents, SGLT2 inhibitors cause a shift in systemic glucose to fat utilization, as reflected by a decreased respiratory exchange ratio (87, 133–135). A related consequence of increased hepatic fat oxidation is the generation of ketones, which opens the intriguing possibility—which has been speculated about in the literature (136–138)—that a shift to increased ketone metabolism in the heart may yield direct cardiovascular benefits by modulating cardiomyocyte energy metabolism. This idea is supported by the fact that ketone perfusion improves energy generation (139, 140), a finding duplicated in diabetic mice treated with empagliflozin (140). Alternatively, recent work has

highlighted an indirect mechanism by which SGLT2 inhibition may achieve improvements in cardiac function: Kim *et al.* (141) demonstrated that SGLT2 inhibitors reduce activity of the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome, and that this anti-inflammatory effect may be attributable to increased ketones in concert with reduced insulin concentrations. As activation of the NLRP3 inflammasome worsens heart failure mortality (142), the effects of SGLT2 inhibition to suppress NLRP3 inflammasome activation secondary from reduced insulin and increased ketone concentrations would be predicted to improve outcomes. However, the substantial cardiac benefits observed with SGLT2 inhibitor treatment, despite the rare incidence of clinically significant ketosis, and the fact that ketone metabolism is already high in the failing heart, even without SGLT2 inhibitor treatment (143), highlight the high likelihood that additional mechanisms may also play a role. Because of the diuretic effect and consequent ability to lower blood pressure (129, 144–152), which may occur, at least in part, due to down-regulation of catecholamine activity in renal tissue (152), the clinical data suggest that reductions in blood pressure can partially—but not completely—explain improved cardiovascular outcomes in those on an SGLT2 inhibitor (153).

In concert with the cardiovascular benefits with SGLT2 inhibitor treatment, recent studies have also identified renal benefits associated with these agents. Improved glomerular filtration rates and urine albumin/creatinine ratio, a marker of renal function, have been observed in diabetic human subjects treated for 12–104 weeks with SGLT2 inhibitors (154–157). Additionally, those treated with SGLT2 inhibitors manifest lower rates of acute kidney injury in heart failure (154) and after a myocardial infarction (158). Whereas it is possible, given their mechanism, that the chronic effects of SGLT2 inhibition to improve cardiovascular outcomes are partially dependent on their ability to improve glycemic control in individuals with diabetes, the renal benefits were observed independent of any glucose-lowering effect (154, 156, 157) and, in the acute setting, are likely in large part attributable to the diuretic effect of SGLT2 inhibitors.

SGLT2 inhibitors and cancer

In recent years, investigators have also begun to study the potential effects of SGLT2 inhibitors on cancer in preclinical studies. *In vitro* studies have demonstrated that SGLT2 inhibitors, at high doses, inhibit cell division in liver (159–161), lung (162, 163), kidney (164), prostate (163), and breast cancer (165, 166) potentially by inhibiting tumor cell glucose uptake (161) and/or oxidation (167). Even more exciting, SGLT2 inhibitors inhibit tumor growth *in vivo* (159, 161, 164, 166, 168–172) by a mechanism that remains under debate. The finding that primary lung tumors—a tumor type in which SGLT2 inhibitors have been shown to slow tumor growth both *in vitro* (162, 163) and *in vivo* (171)—express SGLT2 (173, 174) suggests the possibility of a direct effect of SGLT2 inhibitors to inhibit tumor glucose uptake. Similarly, use of an SGLT-specific radioactive glucose analog, α-methyl-4-deoxy-4-[^{18}F]fluoro-D-glucopyranoside,

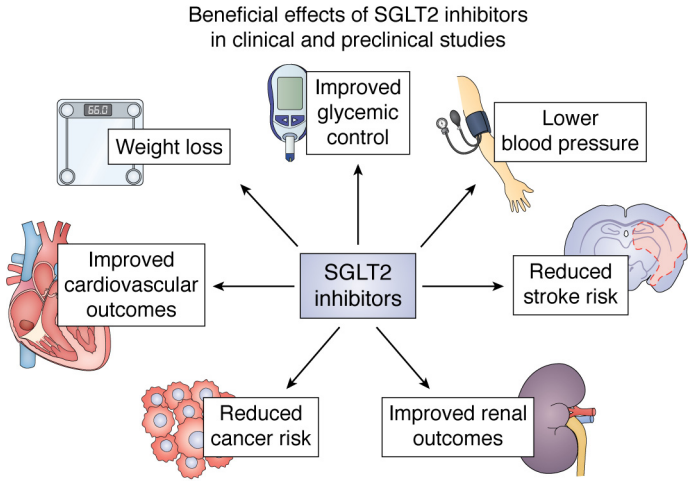

Figure 4. Beneficial effects of SGLT2 inhibitors that have been observed in clinical and preclinical studies. Mechanistic trials to explain how these improvements may occur and how they may be interrelated are ongoing.

demonstrates functional SGLT activity in pancreatic and prostate tumors (175), tumor types in which, again, SGLT inhibitors have been shown to reduce cell proliferation *in vitro* (163, 176). These data suggest that, at least in these tumor types, SGLT2 inhibitors may act directly to reduce tumor glucose uptake. In addition, there is likely an indirect effect of SGLT2 inhibition to slow tumor growth *in vivo* by reducing circulating insulin as a result of its glucose-lowering effects. We recently showed that treatment with dapagliflozin slows colon and breast tumor growth in obese mice, associated with a 50% reduction in plasma insulin concentrations (168). As high circulating insulin (177) and exogenous insulin treatment (178) have been shown in meta-analyses to correlate with increased cancer risk in humans, and overexpression of the insulin receptor is a marker of cancer and a poor prognostic factor (179–186), the ability of SGLT2 inhibitors to reduce circulating insulin concentrations would be expected to slow tumor growth via this mechanism. Consistent with this hypothesis, chronic subcutaneous insulin infusion abrogated the effect of dapagliflozin to slow tumor growth in both models in our recent mouse study (168). These data do not necessarily contradict the possibility that SGLT2 inhibitors may also directly reduce tumor glucose uptake: it is possible that both mechanisms may be at play, but insulin infusion could compensate for the reduction in tumor glucose uptake through SGLT2, by promoting increases in glucose uptake via GLUT4. Regardless of the mechanism, there is clear justification for a clinical trial to explore the impact of SGLT2 inhibitors on cancer, particularly obesity-associated, insulin-responsive tumors. Surprisingly, at this time, there are only two trials posted on clinicaltrials.gov treating cancer patients with an SGLT2 inhibitor currently recruiting. Based on the wealth of preclinical data suggesting that SGLT2 inhibitors are effective against multiple cancer types with minimal toxicity, this represents an area of as-yet untapped potential to generate a new adjuvant therapeutic approach to cancer treatment.

Conclusion

In summary, SGLT2 inhibitors are uniquely well-positioned to improve not only glycemic control in diabetes, but also, and

likely independently of a direct effect of hyperglycemia, cardiovascular and renal health and perhaps cancer incidence and outcomes (Fig. 4). Whereas the risk of diabetic ketoacidosis must be considered, advances in understanding the pathogenesis of DKA in those taking an SGLT2 inhibitor as well as patient selection based on those at highest risk of this serious side effect will likely limit its incidence. However, as with any class of therapy, SGLT2 inhibitors must be prescribed carefully while considering potential risks as well as benefits. Mechanistic studies are needed to better understand how SGLT2 inhibitors yield their beneficial effects as well as how and in whom they may cause adverse events.

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Conflict of interest—G. I. S. serves on the advisory boards for Merck, AstraZeneca, and Janssen Research and Development and receives investigator-initiated support from Merck and AstraZeneca, who manufacture SGLT2 inhibitors. G. I. S. is also a Scientific Co-Founder of TLC, Inc.

Abbreviations—The abbreviations used are: SGLT, sodium-glucose cotransporter; FDA, Food and Drug Administration; DKA, diabetic ketoacidosis; T2D, type 2 diabetes; WAT, white adipose tissue; EGP, endogenous glucose production.

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