Sodium–Glucose Cotransporter Inhibitors: Effects on Renal and Intestinal Glucose Transport

From Bench to Bedside

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REVIEW

Type 2 diabetes is a chronic disease with disabling micro- and macrovascular complications that lead to excessive morbidity and premature mortality. It affects hundreds of millions of people and imposes an undue economic burden on populations across the world. Although insulin resistance and insulin secretory defects play a major role in the pathogenesis of hyperglycemia, several other metabolic defects contribute to the initiation/worsening of the diabetic state. Prominent among these is increased renal glucose reabsorption, which is maladaptive in patients with diabetes. Instead of an increase in renal glucose excretion, which could ameliorate hyperglycemia, there is an increase in renal glucose reabsorption, which helps sustain hyperglycemia in patients with diabetes. The sodium–glucose cotransporter (SGLT) 2 inhibitors are novel antidiabetes agents that inhibit renal glucose reabsorption and promote glucosuria, thereby leading to reductions in plasma glucose concentrations. In this article, we review the long journey from the discovery of the glucosuric agent phlorizin in the bark of the apple tree through the animal and human studies that led to the development of the current generation of SGLT2 inhibitors.

It took nearly 200 years from the isolation of phlorizin, a chemical found in apple tree bark that inhibits sodium–glucose cotransporters (SGLTs) (1), to the approval of the first medications inhibiting SGLTs for treatment of type 2 diabetes (T2D). During this time, several SGLTs were discovered and the roles of SGLT1 and SGLT2 in intestinal and renal glucose reabsorption have been elucidated in studies in genetically manipulated rodents, humans with SGLT gene mutations, healthy humans, and humans with diabetes (Fig. 1). This review provides an overview of the basic and clinical research that led to the translation of the initial findings of increased glucosuria with phlorizin to the development and approval of SGLT inhibitors and a summary of the clinical trial results obtained to date.

Identification, Distribution, and In Vitro Characterization of the SGLT Inhibitors

In the 1980s and 1990s, Wright and colleagues cloned SGLT1 (2) and SGLT2 (2,3) and did much of the in vitro characterization, demonstrating that SGLT1 has a higher affinity for glucose than SGLT2 (K_m for glucose ~0.4 mmol/L and 2 mmol/L, respectively), whereas SGLT2 has a higher capacity (4). SGLT1 is expressed at high levels in the intestine and is also expressed in the kidney, heart, and skeletal muscle, whereas SGLT2 is expressed almost exclusively in the kidney (4). Renal SGLT2 expression is increased in hyperglycemic rodents (5,6) and in humans with T2D (7). Intestinal SGLT1 expression is regulated by diet and other factors (8) and is

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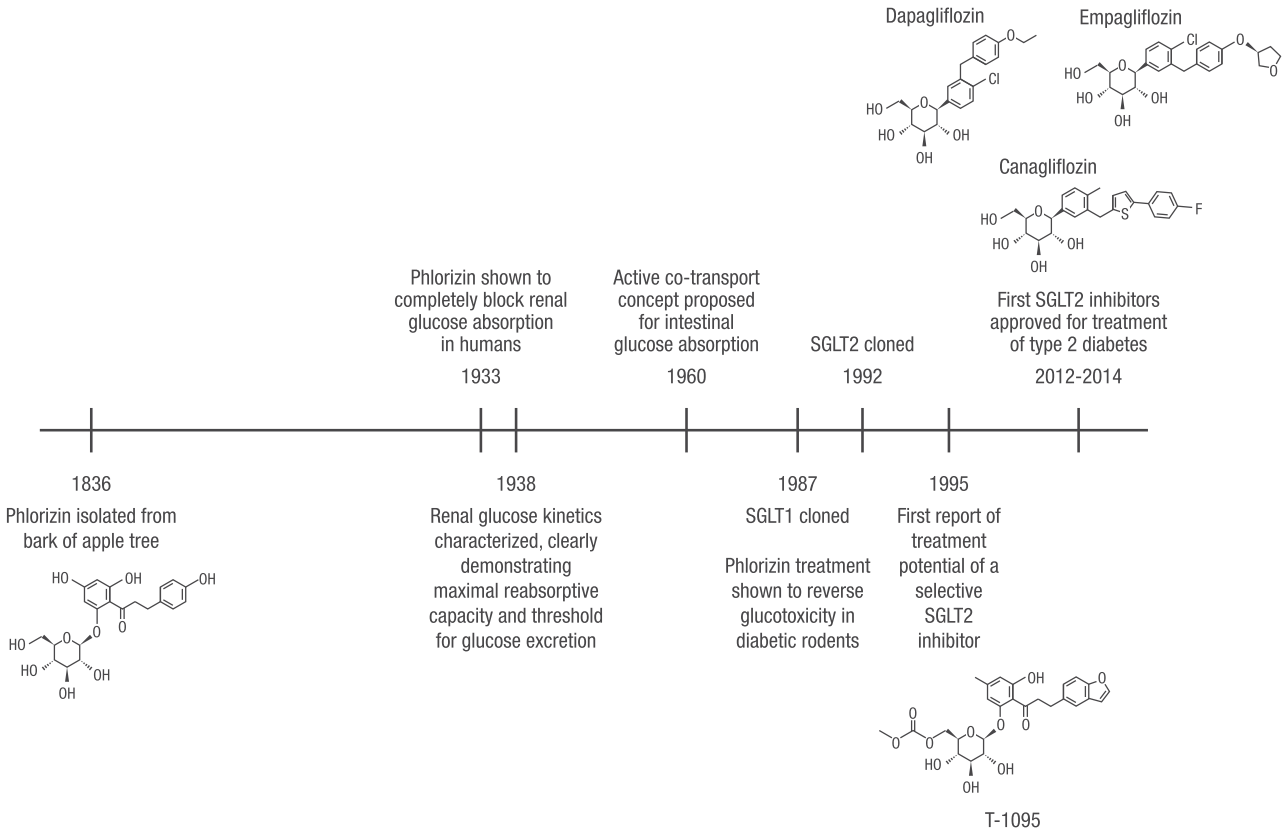

Figure 1—Time line of some key developments in the understanding of SGLT-mediated glucose uptake and the development of SGLT inhibitors.

increased in subjects with T2D (9). Further details on the structure and function of the transporters can be found in ref. 4.

Role of SGLT2 and SGLT1 in Renal Glucose Reabsorption

In the 1930s, Shannon and Fisher elucidated the renal glucose reabsorption kinetics in dogs (10). Their work showed that *1*) there is a maximum capacity for renal tubular glucose transport (the tubular maximum glucose reabsorption rate) (T_mG), *2*) nearly all filtered glucose is reabsorbed when plasma glucose (PG) concentrations remain below a threshold value called the renal threshold for glucose (RT_G), and *3*) urinary glucose excretion (UGE) increases nearly linearly with PG when PG is above RT_G.

In the early 1970s, Vick, Diedrich, and Baumann demonstrated that glucose reabsorption occurred in the proximal tubule (11), and Turner and Moran later demonstrated that this occurs through two distinct sodium-dependent glucose transport systems, one with relatively low affinity and high capacity and one with higher affinity and lower capacity (12). Wright and colleagues later demonstrated that these two systems were accounted for by SGLT2 and SGLT1, respectively (4).

The effects of SGLT2 inhibitors on renal glucose kinetics were assessed using controlled glucose infusion experiments in rats (13) and humans (14,15). These experiments showed that SGLT2 inhibition leads to a reduction in T_MG and RT_G while maintaining a threshold-like relationship between PG and the UGE rate (Fig. 2). Importantly, in subjects with T2D treated with SGLT2 inhibitors, the UGE rate is high when PG is high but diminishes as PG approaches hypoglycemic levels, suggesting a low risk of treatment-induced hypoglycemia. The SGLT2 inhibitor–induced increases in UGE are sustained at similar levels with long-term treatment (16).

The roles of SGLT2 and SGLT1 in renal glucose reabsorption were further confirmed through human and rodent genetic studies. In humans, familial renal glucosuria is a rare, benign condition arising from SGLT2 mutations that reduce renal glucose reabsorption and lead to UGE ranging from 1 to 170 g/day, whereas SGLT1 mutations only mildly increase UGE (17). Similarly, only minimal UGE is observed in SGLT1 knockout (KO) mice, whereas high UGE is seen in SGLT2 KO mice (17,18).

While it is often stated that SGLT2 accounts for 90% of glucose reabsorption, SGLT2 and SGLT1 appear sequentially in the proximal tubule, so it is an oversimplification to provide a single value to describe their relative contribution to glucose reabsorption. For example, under normoglycemic conditions, there is sufficient SGLT2 capacity to reabsorb virtually all filtered glucose, and only minimal UGE is observed in humans or rodents lacking SGLT1. However, maximally effective SGLT2 inhibitor doses typically prevent ~50% of the filtered glucose from being reabsorbed, suggesting that SGLT1 has considerably greater capacity for glucose reabsorption than expected based on the commonly quoted 90% value for SGLT2. This is supported by data from genetic models, since SGLT2 KO mice exhibit only about 30% of the UGE observed in SGLT1/SGLT2 double KO mice (17). These data, combined with human

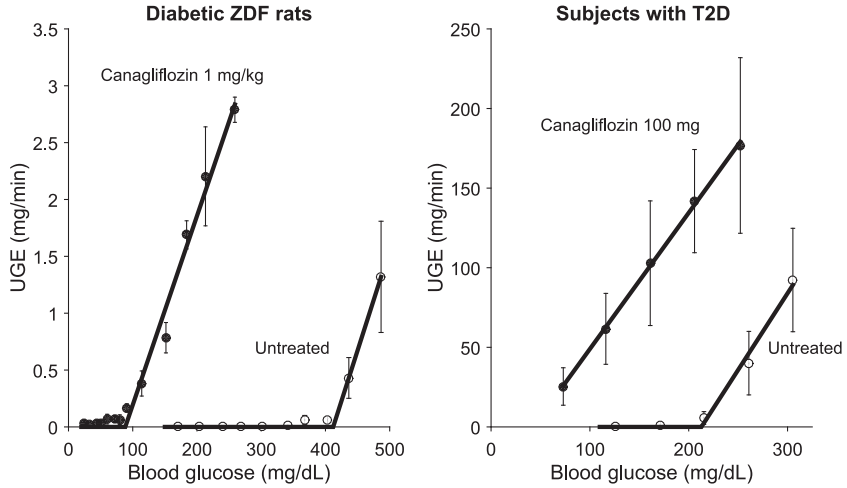

Figure 2—Relationship between blood glucose concentrations and UGE rates in rodents and humans treated with the SGLT2 inhibitor canagliflozin. Left panel: Results (mean ± SE) from a graded glucose infusion study in Zucker diabetic fatty (ZDF) rats (13). Right panel: Results (mean ± SD) from a stepwise hyperglycemic clamp study in human subjects with T2D (15). In both studies, canagliflozin treatment produces a left shift in the relationship between blood glucose and UGE with no apparent change in the slope, leading to a reduction in RT_G.

data showing that phlorizin can block virtually all renal glucose reabsorption (19), suggest that dual SGLT1/2 renal inhibitors might achieve considerably greater UGE than selective SGLT2 inhibitors.

Role of SGLT1 in Intestinal Glucose Absorption

SGLT1 is essential for intestinal glucose/galactose absorption and represents the primary mechanism of glucose/galactose uptake from the lumen into enterocytes (4). The essential nature of SGLT1 is confirmed by the rare genetic disease glucose-galactose malabsorption (GGM), which arises from missense mutations in SGLT1 (19). This condition causes severe diarrhea if glucose or galactose is consumed and can be fatal unless glucose and galactose are removed from the diet. SGLT1 KO mice develop a similar glucose-galactose malabsorption syndrome when fed glucose but thrive normally when fed a glucose- and galactose-free diet (18).

Studies in KO animals have further elucidated the role of intestinal SGLT1. SGLT1 KO mice exhibited elevated glucose in the distal small intestine and colon and decreased cecal pH when challenged with a meal containing glucose (17,20). Reductions in serum total glucagon-like peptide 1 (GLP-1) have been reported 5 min after a meal challenge (17,20), but serum GLP-1 was increased from 30 min to 6 h after the meal (20), indicating that SGLT1 may be required for the early GLP-1 response and that there is a second more predominant phase of GLP-1 release that does not require SGLT1 and is enhanced in the absence of SGLT1. The increased GLP-1 seen in SGLT1 KO mice may be due to increased glucose reaching the distal small intestine and colon where it, or its metabolites, can trigger GLP-1 release (21,22). SGLT1 heterozygous mice thrived normally on a regular diet but also exhibited elevated glucose in the distal small intestine and cecum and elevated postmeal GLP-1 levels (17), indicating that partial SGLT1 inhibition might provide benefits without GI intolerability observed in the absence of SGLT1 activity.

Development of Pharmaceutical SGLT Inhibitors as Treatment for T2D

Although phlorizin was known to increase UGE and was demonstrated to completely inhibit renal glucose reabsorption in the 1930s (23), the potential for using increased UGE as a means to regulate PG was not demonstrated until the 1980s. Experiments by Rossetti and colleagues in diabetic rats demonstrated that sustained phlorizin treatment normalized blood glucose concentrations resulting in reduced "glucotoxicity" and improvements in β-cell function and insulin sensitivity (24,25). However, phlorizin was not a suitable therapeutic agent due to poor absorption, metabolism to phloretin, which inhibits GLUTs, and potential intestinal malabsorption with SGLT1 inhibition. This led to the pursuit of selective SGLT2 inhibitors with improved properties. The first publication demonstrating the potential of a selective SGLT2 inhibitor (T-1095) as a treatment for diabetes in rodent models appeared in 1999 (26). Since then, several SGLT2 inhibitors have been developed and three compounds are currently approved for use in the U.S. and Europe (dapagliflozin, canagliflozin, and empagliflozin) (Table 1). Additionally, luseogliflozin, topogliflozin, and ipragliflozin have been approved in Japan and other compounds are in late-stage clinical trials. While these compounds have been primarily designed to be highly selective for SGLT2 compared with SGLT1, there is variability in the selectivity, most notably for sotagliflozin, which is only 20-fold selective for SGLT2 compared with SGLT1. A selective SGLT1 inhibitor was tested in a phase 1 study in 12 subjects and showed that SGLT1 inhibitors block intestinal glucose absorption, reduce GIP secretion, and enhance GLP-1 and peptide YY (PYY) secretion (27).

Effects of SGLT2 Inhibitors on Glycemia

SGLT2 inhibitors are effective in lowering PG when used as monotherapy or in combination with other oral agents/insulin. These effects have been demonstrated in large multicenter, multinational, placebo- and active-controlled studies. Due to limited space, efficacy studies summarized are limited to those at least 24 weeks long with compounds approved for use in the European Union (EU) and U.S.

Monotherapy

Although metformin is the first choice pharmaceutical treatment for T2D, it causes intolerable gastrointestinal (GI) side effects in occasional patients. In such patients, SGLT2 inhibitors can be used as monotherapy, and in clinical trials, compared with placebo/active comparator, they lowered fasting PG (FPG) by 20–46 mg/dL and HbA_{1c} by 0.54–1.45% in patients with baseline HbA_{1c} 7.9–9.1%. Those with higher baseline HbA_{1c} had greater glycemic benefits, as did those on higher doses of SGLT2 inhibitors (Supplementary Table 1).

Table 1—Summary of the most advanced SGLT2 inhibitor compounds (refs. 28–31)

Compound	SGLT2 IC_{50} (nmol/L)	SGLT1 IC_{50} (nmol/L)	SGLT2/SGLT1 selectivity	Highest approved dose (mg)[a]	Status
Canagliflozin	4.2	663	160	300	Approved in U.S., EU, Japan, other countries
Dapagliflozin	1.2	1,400	1,200	10	Approved in U.S., EU, Japan, other countries
Empagliflozin	3.1	8,300	2,700	25	Approved in U.S., EU
Ipragliflozin	5.3	3,000	570	50	Approved in Japan
Luseogliflozin	2.3	3,990	1,770	5	Approved in Japan
Tofogliflozin	6.4	12,000	1,875	20	Approved in Japan
Ertugliflozin	0.9	1,960	2,200	25	Phase 3
LX-4211 (sotagliflozin)	1.8	36	20	400	Completed phase 2

[a]Highest approved dose or the highest dose still in development for compounds that have not yet been approved.

Dual Oral Combination Therapy

SGLT2 Inhibitor and Metformin Combination. Over time, due in part to disease progression, there is worsening glycemia in metformin-treated patients. These patients are often treated with the addition of sulfonylureas or dipeptidyl peptidase-4 (DPP-4) inhibitors. In metformin-treated patients, adding an SGLT2 inhibitor results in additional glycemic benefit with low potential for hypoglycemia (unlike sulfonylureas) and modest reductions in weight and blood pressure (not seen with DPP-4 inhibitors or sulfonylureas). The addition of SGLT2 inhibitors as add-on to metformin results in FPG lowering by 15–40 mg/dL and HbA_{1c} by 0.54–0.77% compared with placebo in patients with mean baseline HbA_{1c} between 7.9 and 8.2%. Compared with sulfonylureas, placebo-subtracted FPG is lowered by 20–27 mg/dL and HbA_{1c} by 0.52–0.93% in patients with baseline HbA_{1c} 7.7–7.9%. Compared with DPP-4 inhibitors, placebo-subtracted FPG is lowered by 27–36 mg/dL and HbA_{1c} by 0.73–0.88% in patients with baseline HbA_{1c} 7.9–8%. Of note, while dapagliflozin 10 mg, empagliflozin 25 mg, and canagliflozin 100 mg were associated with equivalent glycemic control, canagliflozin 300 mg achieved superior glycemic control compared with glimepiride and sitagliptin (Supplementary Table 2).

SGLT2 Inhibitors and Nonmetformin Oral Combination. In patients treated with nonmetformin oral agents (sulfonylureas, DPP-4 inhibitors, or glitazones), the addition of SGLT2 inhibitors results in improved glycemia with placebo-subtracted FPG lowered by 10–40 mg/dL and HbA_{1c} lowered by 0.4–0.9% in patients with baseline HbA_{1c} 8.0–8.4%. Higher doses of SGLT2 inhibitors resulted in greater HbA_{1c} lowering, and combining SGLT2 inhibitors with DPP-4 inhibitors/pioglitazone has a low potential for hypoglycemia (Supplementary Table 3).

Triple Oral Combination

The SGLT2 inhibitors are also effective in improving glycemia in triple combination with metformin and either sulfonylureas, DPP-4 inhibitors, or glitazones, with placebo-subtracted FPG lowered by 20–38 mg/dL and HbA_{1c} lowered by 0.4–1.03% in patients with mean HbA_{1c} 7.8–8.1%. Of note, higher doses of SGLT2 inhibitors resulted in greater HbA_{1c} lowering and canagliflozin 300 mg had superior HbA_{1c} lowering compared with sitagliptin 100 mg in patients on metformin and sulfonylurea combination (Supplementary Table 4).

SGLT2 Inhibitor and Insulin Combination

Most patients with T2D eventually require exogenous insulin therapy to achieve and maintain glycemic goals. The addition of insulin is associated with weight gain and increased hypoglycemia risk. The addition of SGLT2 inhibitors in patients inadequately controlled with insulin and mean HbA_{1c} 8.3–8.5% is associated with improved glycemic control with placebo-subtracted FPG lowered by 6–63 mg/dL and HbA_{1c} lowered by 0.39–1.27% in the setting of modest weight loss (1.31–3.5 kg) and lower insulin requirements (9–19 units), without increasing major hypoglycemic episodes (Supplementary Table 5).

Effects of Dual SGLT1/2 Inhibitors on Glycemia

Combined renal SGLT2 and intestinal SGLT1 inhibition have the potential to increase renal glucosuria and delay/reduce dietary glucose absorption, albeit with a potential for diarrhea, bloating, and GI discomfort due to intestinal glucose/galactose malabsorption. Both sotagliflozin and canagliflozin have been associated with some intestinal SGLT1 inhibition, but neither is believed to have any meaningful renal SGLT1 inhibition. Hence, it is not currently known what the efficacy and safety profile would be for a dual inhibitor that also provides renal SGLT1 inhibition.

In clinical studies, sotagliflozin has been shown to improve glycemia without any clinically significant increase in GI side effects. As monotherapy in T2D, sotagliflozin 150/300 mg once daily for 28 days lowered placebo-subtracted FPG by 39 and 55 mg/dL and HbA_{1c} by 0.66 and 0.76%, respectively, in patients with baseline HbA_{1c} 8.1% (31). Of note, in another study, sotagliflozin 400 mg QD in combination with metformin resulted in greater reductions in FPG and HbA_{1c} compared with sotagliflozin 200 mg QD despite similar amounts of UGE (32). This suggests that part of the efficacy with 400 QD is through SGLT1 inhibition in the GI tract.

The 300-mg dose of canagliflozin also has transient intestinal SGLT1 inhibition and reduces postprandial PG excursions in the meal after dosing in both healthy subjects and subjects with T2D (14,33,34) through a non-UGE-associated mechanism. This additional effect on postprandial glucose is postulated to be due to transient proximal intestinal SGLT1 inhibition.

Effects of SGLT2 Inhibitors in Type 1 Diabetes

Currently, SGLT2 inhibitors are not approved in type 1 diabetes (T1D). However, given their insulin-independent mechanism of action, there is potential

to use these agents in T1D. In small pilot studies, use of SGLT inhibitors in addition to insulin increased UGE and modestly improved glycemia and body weight with lower insulin doses, less glucose variability, and no increase in hypoglycemia (35–37). Longer-term studies are in progress to characterize the efficacy and importantly the safety of these agents, especially regarding potential development of diabetic ketoacidosis (DKA).

Metabolic, Renal, Cardiovascular, and GI Effects of SGLT Inhibitors

In addition to lowering PG by increasing UGE, SGLT2 inhibitor treatment is associated with additional metabolic, renovascular, GI, and cardiovascular effects.

Insulin Secretion

Consistent with the improvements in β-cell function observed in rats treated with phlorizin, improvements in measures of β-cell function have been observed in patients with T2D treated with SGLT2 inhibitors. Improvements in model-based measures of β-cell glucose function obtained from mixed-meal tolerance tests were observed in subjects treated with empagliflozin (38) and canagliflozin (39). These improvements were observed within the first day of treatment (38) and with treatment of 6–12 months (39). With use of the frequently sampled intravenous glucose tolerance test method, numerical improvements were observed in the acute insulin response to glucose in subjects treated with dapagliflozin for 3 months, although the increase relative to placebo did not reach statistical significance (P = 0.06). Longer studies are needed to assess whether SGLT2 inhibitors slow the progressive decline in β-cell function that occurs in diabetes.

Peripheral Insulin Sensitivity

Improvements in peripheral insulin sensitivity have also been observed in patients treated with SGLT2 inhibitors. In two hyperinsulinemic-euglycemic clamp studies ranging from 2 weeks to 3 months after treatment with dapagliflozin, increases in glucose disposal rate of ~15–20% occurred relative to placebo (40,41). With use of mixed-meal tolerance test–based measurements of insulin sensitivity in patients treated with empagliflozin and canagliflozin, numerical increases in insulin sensitivity measures were observed in multiple studies (38,39), although the changes did not always reach statistical significance. Potential mechanism(s) leading to improved insulin sensitivity include amelioration of glucotoxicity and body weight reduction.

Endogenous Glucose Production

Treatment with SGLT2 inhibitors increases endogenous glucose production (EGP). EGP increased after a single dose of canagliflozin in healthy subjects (14) and increased by ~17–25% after single and multiple doses of empagliflozin and dapagliflozin in patients with T2D (38,41). Despite this increase in EGP, SGLT2 inhibitors still lower fasting and postprandial glucose and improve glycemia in T2D patients. Although an increase in EGP appears paradoxical, it is possible that this is a physiological response to counter the acute glucosuric effect of SGLT2 inhibition. Notably, in the above studies, increases in plasma glucagon and decreases in plasma insulin were observed, leading to an increased glucagon-to-insulin ratio that may be responsible for the observed EGP increase. Recent work documenting expression of SGLT1/2 in human pancreatic α-cells suggests that SGLT2 inhibitors may act directly on these cells to increase glucagon secretion (42). Preliminary studies indicate that combining an SGLT2 inhibitor with a DPP-4 inhibitor blunts the glucagon increase seen with SGLT2 inhibitor monotherapy and further improves glycemic control (43). However, it is not known whether the combination of SGLT2 inhibitors with GLP-1 receptor agonists blunts the increase in EGP.

Body Weight/Body Composition

Increased UGE with SGLT2 inhibition results in caloric loss and osmotic diuresis leading to transient fluid loss that appears largely attenuated with sustained treatment (44). Both processes can lead to weight loss, particularly during the early treatment period. In patients treated with SGLT2 inhibitors, a progressive reduction in body weight is typically observed over the first 12–26 weeks, followed by maintenance of the reduced body weight with minimal further reduction after 26 weeks. In the phase 3 clinical studies, SGLT2 inhibition typically provided mean placebo-subtracted weight loss of ~2–5% (~1.5–6 kg) (45–47).

While fluid loss may contribute to the initial weight loss with SGLT2 inhibitor treatment, the majority of the steady-state weight loss appears to be due to fat loss. In studies with DEXA measurement of body composition, ~70% of weight loss was attributed to fat and numerically greater reductions occurred in visceral compared with subcutaneous adipose tissue (48,49). Interestingly, treatment with empagliflozin or dapagliflozin also shifted substrate utilization from carbohydrate to lipid metabolism (38,39).

Renovascular Effects of SGLT Inhibitors

In addition to increasing UGE, inhibiting SGLT2-mediated renal glucose and sodium reabsorption leads to changes in fluid balance, blood pressure, and renal function.

Urine Volume

Although the magnitude of UGE is generally sustained with continued treatment, the increases in urine volume appear to be largely attenuated after multiple dosing. No significant changes in urine volume were noted after 2 or 12 weeks of treatment with canagliflozin (44) or after 4 weeks of treatment with empagliflozin (50) in phase 1 studies, and only modest increases in mean daily urine volume (~100–500 mL/day) were reported with SGLT2 inhibitors in phase 3 studies (45–47).

Plasma Volume

Given the mechanism of action of SGLT2 inhibitors to produce osmotic diuresis, it is expected that there would be changes in plasma volume. In a 12-week study with dapagliflozin, plasma volume was measured in a subset of subjects using ^{125}I-labeled human serum albumin. After 12 weeks' treatment, median plasma volume decreased by ~7% with dapagliflozin compared with an increase of 5% with placebo. However, these results were based on a small sample size of 8–10 subjects/group (51). In a 12-week study with canagliflozin in patients with T2D, plasma volume measured using indocyanine green dilution decreased ~10% compared with placebo after 1 week of treatment, and this effect was largely attenuated with sustained treatment (44). In phase 3 clinical studies, volume-related adverse events were generally higher in the SGLT2 inhibitor groups, particularly in elderly subjects, those with low estimated glomerular filtration rate (eGFR), or those on diuretics (especially loop diuretics).

Glomerular Filtration Rate

Since SGLT2 inhibitors cause osmotic diuresis and small reductions in plasma volume and blood pressure, it is important to document their effects on renal function (Table 2). In the study with dapagliflozin in patients with moderate renal impairment (52), mean eGFR and creatinine clearance fell by ~3–5 mL/min/1.73 m^2 after 1 week of treatment but stabilized thereafter through 104 weeks of therapy, whereas these parameters slowly declined in the placebo group. Similar changes have been seen with canagliflozin where the reductions in eGFR were largest at week 3 (the first postbaseline measurement) and trended back toward baseline over the 26-week treatment period (53). Similarly, with empagliflozin treatment in patients with stage 2, 3, or 4 chronic kidney disease (CKD), initial small decreases in eGFR returned to baseline by the end of the 3-week follow-up after treatment completion at 52 weeks (54). The initial eGFR reduction with SGLT2 inhibition may be related not only to antihypertensive and diuretic effects but also to increased tubulo-glomerular feedback (55).

Effects on Glycemia in Patients With CKD

With decreasing eGFR, there is lower glycemic efficacy of SGLT2 inhibitors due to a lesser filtered load of glucose. In studies in patients with T2D and moderate renal impairment, SGLT2 inhibition was associated with approximately a 0.3–0.45% fall in HbA_{1c} compared with baseline (52–54). Though modest compared with placebo, these reductions reached statistical significance for canagliflozin and empagliflozin but not for dapagliflozin (where the placebo group experienced an HbA_{1c} decrease of 0.32%). Of note, in the empagliflozin study, significant lowering was only seen in patients with CKD2 and CKD3 but not in those with CKD4. Current clinical guidelines for SGLT2 inhibitor use in renal impairment are listed in Table 3.

Hemoglobin and Hematocrit

Small increases in hemoglobin and hematocrit are consistently seen in phase 3 studies with SGLT2 inhibitors. While these increases are consistent with small reductions in fluid volume, small increases in reticulocytes, erythropoietin, and red cell mass were reported in a 12-week study with dapagliflozin (51), suggesting that changes in hematopoiesis may contribute to changes in hemoglobin and hematocrit.

Electrolytes/Uric Acid

In clinical studies, changes in mean serum electrolytes were infrequent. With dapagliflozin, there were no changes from baseline levels of mean serum sodium, potassium, bicarbonate, calcium, or chloride at week 24 and up to 102 weeks. There were small increases in mean serum inorganic phosphorus levels from baseline (46). SGLT2 inhibitor use is associated with decreases in serum uric acid (56). Hyperuricemia is known to be associated with an increased risk of gout, kidney stones, and cardiovascular disease. Whether lowering uric acid has beneficial effects on renal or cardiovascular complications will require evaluation in longer-term studies.

Renal Hyperfiltration and Diabetic Nephropathy

Glomerular hyperfiltration is an early renal hemodynamic abnormality reflecting increased intraglomerular pressure. Studies suggest that in hypertensive subjects with T2D with normo- or microalbuminuria, persistent hyperfiltration is an independent risk factor for accelerated renal function loss and development or progression of nephropathy, whereas amelioration of hyperfiltration is renoprotective (56). In a recent study in patients with T1D and no macroalbuminuria, treatment with empagliflozin for 8 weeks improved HbA_{1c} by 0.5% with lower insulin requirements and was associated with a significant attenuation of renal hyperfiltration (55). The authors concluded that although several factors may have contributed to the decrease in glomerular filtration rate to near-normal levels, they postulated that activation of tubulo-glomerular feedback by empagliflozin made a substantial contribution. They speculated that long-term SGLT2 inhibitor use could be renoprotective by reducing intraglomerular pressure, thereby reducing the risk of developing overt diabetic nephropathy. Existing data from phase 3 studies in patients with T2D and CKD show modest improvements in albuminuria progression with SGLT2 inhibitor treatment compared with placebo (52–54). Long-term studies are being conducted to determine whether the SGLT2 inhibitors retard/prevent the development and progression of diabetic nephropathy.

Cardiovascular Effects of SGLT Inhibitors

Blood Pressure

SGLT2 inhibitor treatment is associated with reductions in blood pressure that are likely attributable to both an osmotic diuretic effect and weight loss. In a

Table 2—Changes in renal function with SGLT2 inhibitors (refs. 45–47)

		Canagliflozin (mg)			Dapagliflozin (mg)			Empagliflozin (mg)	
	Placebo	100	300	Placebo	5	10	Placebo	10	25
n	90	90	89	84	83	85	87	90	89
eGFR (mL/min/1.73 m^2)									
Baseline	40.0	39.8	38.8	45.6	44.2	43.9	CKD2 71.8 CKD3 44.3 CKD4 22.0	CKD2 70.8 NA NA	CKD2 72.3 CKD3 45.4 CKD4 24.4
Change from baseline to 6 months	−1.4	−3.6	−3.9	−0.25	−2.38	−4.80	NA	NA	NA
Change from baseline to 1 year	NA	NA	NA	−2.58	−2.08	−4.46	CKD2 −0.71 CKD3 −0.3 CKD4 −1.1	CKD2 −2.04	CKD2 −2.47 CKD3 −2.8 CKD4 −1.4
Change from baseline to 2 years	NA	NA	NA	−2.38	−1.71	−3.50	NA	NA	NA

Table 3—Dose adjustment with renal function when using SGLT2 inhibitors (refs. 45–47)

	eGFR (mL/min/1.73 m^2)			
Drug	<30	30–45	45–60	>60
Dapagliflozin	- Do not start drug - D/C if on drug	- Do not start - D/C if on drug	- Do not start drug - D/C if on drug and eGFR persistently <60	- Start at 5 mg QD - Increase to 10 mg QD as needed to decrease glucose
Canagliflozin	- Do not start drug - D/C if on drug	- Do not start drug - D/C if on drug and eGFR persistently <45	- Start at 100 mg QD - Do not increase dose - If on 300 mg, decrease dose to 100 mg	- Start at 100 mg QD - Increase to 300 mg QD as needed to decrease glucose
Empagliflozin	- Do not start drug - D/C if on drug	- Do not start - D/C if on drug and eGFR <45 persistently	- Start at 10 mg and increase to 25 mg QD as needed to decrease glucose	- Start at 10 mg and increase to 25 mg QD as needed to decrease glucose

D/C, discontinued.

prespecified pooled analysis of 12 placebo-controlled studies (46), treatment with dapagliflozin 10 mg for 24 weeks resulted in a systolic blood pressure (SBP)/diastolic blood pressure change from baseline of −4.4/−2.1 mmHg vs. −0.9/−0.5 mmHg with placebo. Similar placebo-corrected changes from baseline in SBP have been seen with canagliflozin 100/300 mg of −3.7/−5.4 mmHg and empagliflozin 10/25 mg of −3.35/−3.93 (45,47). In a recent meta-analysis of >50 studies, compared with other glucose-lowering agents, SGLT2 inhibitors reduced mean SBP by −4.45 mmHg (57). Although these changes in blood pressure are favorable, longer-term studies are needed to determine whether these changes are sustained and, importantly, lead to lower cardiovascular morbidity and mortality.

Lipids

LDL cholesterol (LDL-C) is a major cardiovascular disease risk factor, and reduction of LDL-C is a primary component of cardiovascular disease risk reduction strategies. SGLT2 inhibitor treatment is associated with small increases in LDL-C and HDL cholesterol. In long-term data over 2 years, the placebo-subtracted increases in LDL-C with dapagliflozin, canagliflozin, and empagliflozin were ~5, 3, and 6 mg/dL in patients with a baseline LDL-C of ~103, 92, and 93 mg/dL, respectively. For HDL cholesterol, the placebo-subtracted increase from a baseline of ~47 mg/dL was ~1, 0.6, and 3.5 mg/dL with dapagliflozin, canagliflozin, and empagliflozin, respectively (45–47).

Data from the first cardiovascular outcome study with an SGLT2 inhibitor were recently reported and demonstrated that empagliflozin treatment reduced a composite measure of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke by 16% compared with placebo, with much of the benefit driven by a 38% reduction in cardiovascular death (58). Notably, reductions in the risks of death from cardiovascular causes and from any cause occurred early in the trial, and these benefits continued throughout the study. Further research is needed to understand the mechanisms responsible for the reduction in cardiovascular events. Cardiovascular outcome studies with canagliflozin and dapagliflozin are still ongoing (59,60) and will provide further information on the effects of SGLT2 inhibitors on cardiovascular outcomes.

GI Effects of Dual SGLT1/2 Inhibitors

Intestinal Glucose Absorption and Incretin/PYY Secretion

Gut hormones (GLP-1, GIP) play an important role in glucose homeostasis. Growing evidence suggests that SGLT1 transport plays a role in entero-endocrine hormone release. In human studies, treatment with sotagliflozin increased GLP-1 and PYY levels after meals and reduced blood GIP levels after breakfast in patients with T2D (31) and increased GLP-1 and PYY in healthy subjects (61). Similar gut hormone changes have been seen in healthy subjects after single 300-mg doses of canagliflozin (14). Transient effects on intestinal glucose absorption with canagliflozin are believed to be due to locally high intestinal drug concentrations occurring shortly after dosing. However, virtually all of the ingested glucose is absorbed over a 6-h period.

There is a potential opportunity to combine dual SGLT1/2 inhibitors with DPP-4 inhibitors based on their complementary mechanisms of action. In a small pilot study, combination sotagliflozin and sitagliptin treatment elevated active GLP-1 levels after meals above levels achieved with sitagliptin alone (62). Whether this combination results in greater glycemic benefit remains to be determined.

Long-term Efficacy of SGLT2 Inhibitors

At 208 weeks, in metformin-treated patients, dapagliflozin compared with glipizide produced sustained reductions in HbA_{1c} (−0.30%), body weight (−4.38 kg), and SBP (−3.67) with lower hypoglycemia rates (5.4 vs. 51.5%). Of note, glycemic control gradually deteriorated over time in both study arms but was slower with dapagliflozin. At 52 weeks, mean HbA_{1c} reduction was 0.5% and similar in both arms (baseline mean 7.7%). At 208 weeks, the HbA_{1c} decrease from baseline was 0.10 with dapagliflozin versus a 0.20% increase with glipizide (16).

Side Effects and Safety Profile

Urinary Tract and Genital Infections

SGLT2 inhibitor use is associated with increased incidence of both urinary tract infections (UTIs) and genital tract infections (GTIs) (45–47). UTIs occurred more frequently in female patients, and most diagnosed infections were mild/moderate and responded to standard antimicrobial treatment. There was no increase in serious or upper UTIs. In the phase 3 studies, the incidence of UTIs was 4.0, 5.9, and 4.3% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively; 3.7, 5.7, and 4.3% with placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively; and 7.6, 9.3, and 7.7% with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Most GTIs in the clinical studies were mild to moderate and resolved spontaneously or responded to standard antifungal therapy. Infections rarely led to treatment discontinuation. A small minority of patients experience recurrent events. In some studies, male genital mycotic infections occurred more commonly in uncircumcised males and those with a prior history of balanitis/balanoposthitis. These patients were more likely to experience recurrent infections. In the phase 3 studies, the incidence of female GTIs was 3.2, 10.4, and 11.4% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively; 0.9, 5.7, and 4.8% with placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively; and 1.5, 5.4, and 6.4% with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

The incidence of male GTIs was 0.6, 4.2, and 3.7% with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively; 0.3, 2.8, and 2.7% with placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively; and 0.4, 3.1, and 1.0% with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

DKA

Some cases of DKA have recently been reported with SGLT2 inhibitor use in clinical practice (63–65). Many of these occurred in patients with T1D in whom the drug was used off-label, although some cases have occurred in patients with T2D. In most cases, there were other contributing factors including acute illness, infections, reduced carbohydrate intake, missed insulin doses/pump failures, recent surgery, and alcohol use. In several patients the blood glucose level was lower than commonly seen in DKA and in rare cases in the euglycemic range. All patients recovered with intravenous fluids along with insulin and glucose infusions and discontinuation of the SGLT2 inhibitor. Potential mechanisms that may make patients taking SGLT2 inhibitors more susceptible to developing DKA include an increase in the glucagon-to-insulin ratio, increased free fatty acids, a shift in substrate oxidation from carbohydrate to fat, and possibly reductions in ketone body clearance (66).

Skeletal Effects

The SGLT2 inhibitors may potentially affect calcium and phosphorus homeostasis leading to adverse skeletal effects (67). In clinical studies, there have been minimal changes in serum calcium, phosphorus, magnesium, 25-OH-vitamin D, and parathyroid hormone that appear to be clinically insignificant. In a randomized, double-blind, placebo-controlled study, dapagliflozin treatment over 2 years did not affect markers of bone turnover or bone mineral density in patients with T2D inadequately controlled on metformin (48). In studies with canagliflozin, there have been small changes in bone markers and bone mineral density that appear to be clinically insignificant (49). Of note, there is a numerical excess of bone fractures in some studies with canagliflozin and dapagliflozin (45,46). A more definitive answer to the deleterious effects of SGLT2 inhibitors on bone should become available from the results of the large cardiovascular outcome trials currently in progress (58–60).

Hypoglycemia

Due to the insulin-independent mechanism of action of the SGLT2 inhibitors, hypoglycemia incidence rates are low with SGLT2 inhibitor use, except when they are used in combination with sulfonylureas and insulin, the doses of which may need to be lowered to avoid hypoglycemia (45–47).

Malignancies

In the preapproval clinical studies, there was an excess of bladder cancers with dapagliflozin treatment. However, there were too few cases to determine relationship to the drug. Hence, until additional data become available dapagliflozin should not be used in patients with known bladder cancer (46).

Conclusions

T2D is a chronic disease with significant morbidity and mortality. The introduction of SGLT2 inhibitors has provided a paradigm shift in diabetes management. Glucosuria, once considered a manifestation of poor glycemic control, is now being used to lower blood glucose levels. Increased glucosuria with SGLT2 inhibition improves glycemia and leads to caloric loss and modest weight reduction, small decreases in blood pressure (mainly SBP), and a low incidence of hypoglycemia. These properties have led to the increasing use of these agents in clinical practice in combination with metformin and other agents including insulin. The insulin-independent mechanism of action of these agents means that these drugs could also be of glycemic benefit in T1D. However, recent reports of DKA with SGLT2 inhibitors in T2D and in T1D with off-label use mandate further detailed study, especially in T1D. Other side effects include an increase in the incidence of GTIs and in some studies a numerical excess of UTIs and bone fractures. Dual SGLT1/2 inhibition is also emerging as a viable therapeutic option without an increase in GI symptoms associated with more extensive SGLT1 inhibition. The potential for benefit due to the effects of SGLT1 on gut hormones remains to be determined. The long-term implications of increased glucosuria in patients with diabetes are not known. Early data suggest that SGLT2 inhibition leads to increased glucosuria and increased delivery of sodium to the distal tubule, which may modulate tubulo-glomerular feedback and reduce glomerular hyperfiltration. The benefits of such effects require long-term studies that are in progress to evaluate the consequences of SGLT2 inhibitors on cardiovascular disease, a major contributor to disease burden in patients with diabetes.

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