Review

SGLT2 inhibitors: a promising new therapeutic option for treatment of type 2 diabetes mellitus

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Abstract

Background Hyperglycemia is an important pathogenic component in the development of microvascular and macrovascular complications in type 2 diabetes mellitus. Inhibition of renal tubular glucose reabsorption that leads to glycosuria has been proposed as a new mechanism to attain normoglycemia and thus prevent and diminish these complications. Sodium glucose cotransporter 2 (SGLT2) has a key role in reabsorption of glucose in kidney. Competitive inhibitors of SGLT2 have been discovered and a few of them have also been advanced in clinical trials for the treatment of diabetes.

Objective To discuss the therapeutic potential of SGLT2 inhibitors currently in clinical development.

Key findings A number of preclinical and clinical studies of SGLT2 inhibitors have demonstrated a good safety profile and beneficial effects in lowering plasma glucose levels, diminishing glucotoxicity, improving glycemic control and reducing weight in diabetes. Of all the SGLT2 inhibitors, dapagliflozin is a relatively advanced compound with regards to clinical development.

Summary SGLT2 inhibitors are emerging as a promising therapeutic option for the treatment of diabetes. Their unique mechanism of action offers them the potential to be used in combination with other oral anti-diabetic drugs as well as with insulin.

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by the failure of body tissues to respond to insulin (insulin resistance) and by β-cell dysfunction that results in hyperglycemia. Untreated hyperglycemia leads to tissue damage that results in micro- and macrovascular pathologies (coronary heart disease, retinopathy, nephropathy, neuropathy and stroke).[1] It also inhibits wounds healing, thereby promoting lower limb infections and gangrene. High glucose levels exacerbate insulin resistance and promote β-cell damage, leading to their apoptosis.[2,3] Even with the availability of multiple antidiabetic drugs, including metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, glucagon like peptide-1 agonists and dipeptidyl-peptidase-IV inhibitors, many patients do not achieve glycemic targets. These drugs also have numerous side effects, such as weight gain, hypoglycemia, fluid retention and gastrointestinal side effects (nausea, abdominal discomfort and diarrhoea).[4] Hence, the search for novel efficacious and safer treatment strategies is ongoing.

Sodium glucose co-transporters 2 (SGLT2) inhibitors represent a new strategy in the treatment of diabetes. These drugs inhibit glucose reabsorption from renal tubules, thereby promoting urinary glucose excretion and decreasing plasma glucose levels. These drugs have a unique mechanism

of action that is independent of pancreatic β-cell function or modulation of tissue insulin sensitivity. Thus, they have the potential to be used as combination therapy with other oral antidiabetic drugs as well as insulin. A number of SGLT2 inhibitors are in various phases of preclinical and clinical development, and dapagliflozin is the furthest advanced compound. This article reviews the role of SGLT2 in glucose homeostasis, SGLT2 inhibitors currently under clinical development, their therapeutic potential and safety concerns in the treatment of diabetes.

Glucose transport across biological membranes

Glucose absorption at the enterocytes, reabsorption at the renal tubules, transport across the blood–brain barrier and uptake and release by all cells in the body is mediated by two groups of transporters. These include glucose transporters (GLUTs) and sodium-glucose co-transporters (SGLTs).[5]

GLUTs are facilitative or passive transporters that transport glucose along the concentration gradient. They belong to the solute carrier family 2 (SLC2) gene family, which has 13 members: GLUT1-12 and the H+-myoinositol
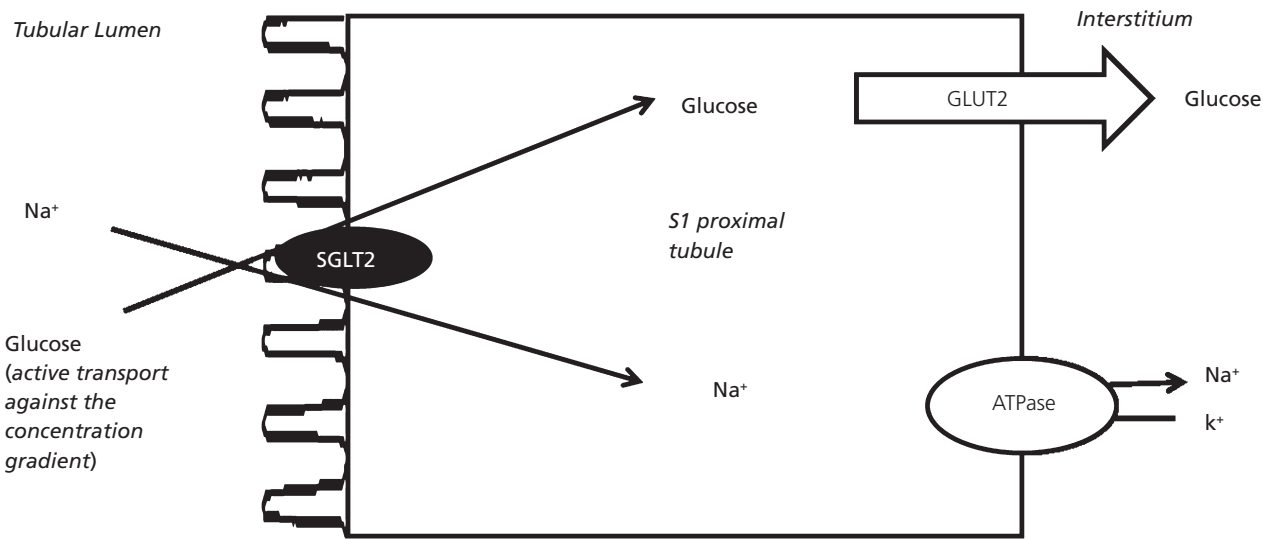
Figure 1 Diagram of proximal renal tubular cell showing secondary active transport of glucose by SGLT2. The Na+/K + ATPase pump present at baso-lateral memebrane produces the electrochemical gradient that is used for sodium and glucose cotransport. Glucose is transported passively by GLUT2 into the interstitium. SGLT2, sodium glucose co transporter; GLUT2, glucose transporter 2.

Table 1 Comparison of SGLT1 and SGLT2 (7–16)

	SGLT1	SGLT2
Site	Mainly intestine, other sites include brain, skeletal and heart muscle, liver, lungs, kidneys	Kidney
Gene encoding	SLC5A1	SLC5A2
Substrate	Glucose or galactose	Glucose
Affinity for glucose	High	Low
Capacity for glucose transport	Low	High
Main function	Dietary glucose absorption	Renal glucose reabsorption
Renal location	Late proximal straight tubule (S3)	Early proximal convoluted tubule (S1 and S2)
Percentage of renal glucose reabsorption	10%	90%
Mutation of encoding gene	Glucose/galactose malabsorption, leading to fatal diarrhoea*	Familial renal glucosuria, a benign condition
Inhibitors of transporter	Selective SGLT1 inhibitors: KGA2727 (Kessei Pharmaceutical Co. Ltd) GSK1614235/ KGA3235 (Kissei Pharmaceuticals Co. Ltd, GlaxoSmithKline plc)	Dapagliflozin, canagliflozin, empagliflozin etc. advanced in clinical trials

*The gastrointestinal side effects have not been reported in clinical studies. SGLT1, sodium glucose co-transporter 1; SGLT2, sodium glucose co-transporter 2; SLC, solute carrier family.

co-transporters. GLUTs are expressed in every cell of the body.[5–7]

SGLTs transport sodium and glucose into cells using the sodium gradient produced by sodium/potassium ATPase pump at the basolateral cell membrane (Figure 1). These transporters belong to the solute carrier family 5 (SLC5) gene family, which has nine members with known functions.[7,8] Of these, SGLT1 and SGLT2 are primarily responsible for renal glucose reabsorption. These transporters are compared in Table 1.[7–16]

SGLT1 is chiefly responsible for the absorption of dietary glucose from enterocytes and accounts for only 10% of renal glucose reabsorption. SGLT1 gene mutations lead to glucose–galactose malabsorption, which results in potentially fatal diarrhoea,[11,12] but such adverse effects were not observed with the SGLT1 inhibitors currently in clinical testing.[15]

SGLT2 plays a major role in renal glucose reabsorption and accounts for approximately 90% of renal glucose reabsorption. The evidence for SGLT2 being a major pathway for renal glucose reabsorption has been derived from the genetic studies of individuals with familial renal glycosuria. Mutations in the SLC5A2 gene encoding SGLT2 lead to familial renal glycosuria.[17,18] This benign disorder is inherited as an autosomal recessive trait and is characterized by isolated

persistent glycosuria with normal blood glucose levels and normal oral glucose tolerance test results.[7,17,19–21] Analyses of 23 families with index cases of renal glycosuria demonstrated that each family had a unique mutation in the SGLT2 gene.[18] Individuals who were found to be carriers of two mutated alleles showed severe glycosuria.[18,22] Apart from isolated persistent glycosuria, these patients were asymptomatic and did not develop hypoglycemia, hypovolemia or electrolyte imbalance. They had normal renal function tests and normal life expectancies.[10,13,21] This benign genetic disorder is a potential demonstration of the safety of SGLT2 inhibitors.

Renal glucose transport in health and disease

The renal system plays a very important role in glucose homeostasis. Blood glucose is freely filtered by the glomeruli and is completely reabsorbed from the proximal tubules via SGLTs in the brush border membrane. Glomeruli filter about 144 gm of glucose per 24 hours, nearly 100% of which is reabsorbed in the renal tubules. Glycosuria develops when the blood glucose level reaches the renal threshold for reabsorption, which is about 8–10 mmol/l (180 mg/dl).[7]

Renal tubular reabsorption is known to undergo adaptations in uncontrolled diabetes. There is an up-regulation of both GLUT2 and SGLT2 in diabetes to maintain renal tubular glucose reabsorption.[23,24] SGLT2 mRNA expression is up-regulated in the kidneys of diabetic rats, and reversed by lowering blood glucose levels.[7,24] In comparison to the cells of healthy individuals, the exfoliated proximal tubular epithelial cells from the fresh urine of diabetic patients express significantly higher levels of SGLT2 and GLUT2.[25] The increased expression of SGLT2 in uncontrolled diabetes has practical significance, as SGLT2 inhibitors are likely to produce a greater degree of glycosuria in the presence of higher prevailing plasma glucose levels.[7]

Therapeutic potential of SGLT2 inhibitors

A number of SGLT2 inhibitors are in various stages of clinical development for the treatment of diabetes. SGLT2 inhibitors interfere with the function of SGLT2 in proximal convoluted tubules of kidney and induce glycosuria. Animal studies and clinical trials have revealed that SGLT2 inhibition benefits the diabetic state by lowering plasma glucose levels, decreasing glucotoxicity and reducing plasma insulin and glycosylated hemoglobin levels.[26–28] Reduction in the plasma glucose level improves liver sensitivity to insulin. This suppresses hepatic glucose production, leading to an improvement in the diabetic state.[29] By causing glycosuria, SGLT2 inhibitors not only reduce plasma glucose levels, but also cause a net loss of calories from the body and maintain overall negative energy balance. This results in a reduction in adiposity and weight

loss.[30–35] In addition, these inhibitors also have a blood pressure lowering effect, which might be related to their mild diuretic and weight-reducing action.[30–32,35] As compared to currently used antidiabetic drugs, SGLT2 inhibitors do not stimulate insulin secretion or pose the risk of hypoglycemia or cause gastrointestinal side effects.[28,31] The convenience of oral administration is another advantage of this new class of antidiabetic drugs. The novel mechanism of action suggests their potential use in combination with other antidiabetic agents to exert additive or synergistic effects in lowering glucose levels in T2DM.

The efficacy of SGLT2 inhibitors is dependent on the amount of glucose filtered through the glomeruli. As the glomerular filtration rate (GFR) declines in renal impairment, the efficacy of the SGLT2 inhibitors decreases.[36] Renal dysfunction is a common complication of T2DM, with 35.2% of patients having evidence of moderate to end-stage renal impairment.[37] This implies that the therapeutic efficacy of SGLT2 inhibitors would be limited to diabetic patients with normal renal function or with mild renal impairment at best. There would be a need to monitor the renal function prior to giving this drug and during the course of therapy.[38] The drug might even undergo a therapeutic failure with progressive deterioration of renal function during the course of treatment.[38]

Early drugs

Phlorizin, a naturally occurring β-glucoside isolated from the bark of apple trees in 1835, was the first known SGLT inhibitor.[39] It acts as a potent non-selective competitive inhibitor of both SGLT1 and SGLT2. The principal pharmacological action of phlorizin is to produce renal glycosuria and block intestinal glucose absorption through the inhibition of SGLT located in the proximal renal tubule and mucosa of the small intestine. It has been used as a pharmaceutical tool for physiology research for over 150 years.[39] Using euglycaemic hyperinsulinaemic clamp studies, phlorizin was found to normalize insulin sensitivity in pancreatectomized diabetic rats. Administration of phlorizin caused glycosuria in these rats, which normalized both the fasting and fed plasma glucose levels and completely reversed insulin resistance. When phlorizin was discontinued, hyperglycemia and insulin resistance recurred. This was the first study which demonstrated that hyperglycemia alone can lead to the development of insulin resistance via glucotoxicity.[40] Phlorizin was used in multiple studies that helped to establish that hyperglycemia contributes to the development of insulin resistance and T2DM.[10,24] However, it was not developed further because of its non-selective SGLT inhibition and low oral bioavailability, resulting from rapid in-vivo β-glucosidase-mediated intestinal degradation.[39] Subsequently developed SGLT2 inhibitors were more SGLT2 selective and resistant to intestinal

degradation. All of these are phlorizin derivatives that are structurally modified to increase SGLT2 selectivity and improve oral bioavailability.

The first orally available phlorizin derivative reported was T-1095. This drug was not progressed further because of its non-selective SGLT inhibition.[10,41] Sergiflozin and remigliflozin, the potent SGLT2 inhibitors subsequently synthesized, were tested in preclinical and clinical studies. Both these drugs were progressed to phase 1 clinical testing, but their further development was not pursued because of their unfavourable pharmacokinetic profile.[42] These drugs contained O-glucoside linkages that made them susceptible to hydrolysis by intestinal β-glucosidase, thus reducing their plasma half-life.[42] Oral administration of a single dose of sergiflozin etabonate to healthy volunteers and T2DM patients produced a dose-related glycosuria under fasting conditions as well as following glucose loading, without affecting urinary electrolyte excretion or fluid balance.[43] This single dose of sergliflozin did not significantly affect fasting plasma glucose levels but produced transient attenuation of the plasma glucose area under the curve (AUC) following glucose challenge.[43] Sergiflozin treatment for 14 days also produced a significant weight reduction as compared to placebo (sergliflozin 500 mg three times a day = −1.55 kg and 1000 mg three times a day = −1.74 kg) in healthy obese or overweight individuals.[44] Remogliflozin etabonate administration for 12 days in patients with T2DM produced a significant reduction in fasting plasma glucose levels (remigliflozin 1000 mg twice a day = −2.3 mmol/l) and weight (remigliflozin 1000 mg four times a day = −2.6 kg) as compared to placebo.[31,45]

Drugs currently in clinical trials

Dapagliflozin

Dapagliflozin (developed by Bristol – Myers Squibb and AstraZeneca) is the furthest advanced compound in clinical development belonging to the SGLT2 inhibitor class. It has favourable pharmacokinetic profile as compared to earlier agents. The C-aryl glycosidic linkage present in dapagliflozin confers resistance to degradation by intestinal β-glucosidase enzymes.[46] Consequently, it is orally effective and has a long duration of action that suppresses both postprandial and fasting hyperglycemia for 24 h on once-daily dosing.[42,46] It also has approximately 1200 times more selectivity for SGLT2 than SGLT1.[27]

Dapagliflozin has shown promising results in various preclinical and clinical studies of T2DM. Administration of a single dose of dapagliflozin induced renal glucose excretion in normal and diabetic rats without causing hypoglycemia.[27] It also improved glucose tolerance in normal rats, and reduced hyperglycemia in Zucker diabetic fatty (ZDF) rats.[27] Chronic treatment with dapagliflozin for 2 weeks significantly lowered fasting and fed glucose levels in ZDF rats and

resulted in a significant increase in glucose utilization rate, accompanied by a significant reduction in hepatic glucose production.[27] This promising evidence of efficacy in animal models led to further clinical investigations in humans.

In clinical studies, treatment with oral dapagliflozin (either as monotherapy or in combination with other antidiabetic drugs) significantly reduced fasting plasma glucose levels, improved glycemic control and decreased weight in T2DM patients (Table 2[30–35,47–50]). There was also a reduction in mean systolic and diastolic blood pressure due to its diuretic action.[30–32,35] This reduction in blood pressure was seen without an increased incidence of orthostatic hypotension.[30–32,35] In a few studies, dapagliflozin treatment also increased plasma high density lipoprotein (HDL) cholesterol levels and decreased plasma triglyceride levels.[30,32]

Dapagliflozin was well tolerated in clinical trials. The most common side effect of dapagliflozin was an increased incidence of genital infections and urinary tract infections (UTI).[30–35,47–50] Genital infections were dose dependent. The incidence rates of genital infections with dapagliflozin dose 2.5, 5 and 10 mg were 5.8%, 7% and 7%, respectively, as compared to only 2.3% with placebo.[51] These were more common in females in the form of vulvovaginal mycotic infection.[38] Genital infections responded satisfactorily to standard treatment and led to discontinuation of study medication only in a few patients. More patients in the dapagliflozin group reported events suggestive of UTI as compared to those treated with placebo. The risk of UTI was not related to dose and duration of the treatment. The incidence rates of UTI with dapagliflozin dose 2.5, 5 and 10 mg were 4.2%, 7.3% and 6.5%, respectively, as compared to 4.5% with placebo.[51] Like genital infections, UTIs were also more common in females. Most cases were mild to moderate in intensity and resolved with standard medication. Pyelonephritis was an uncommon event and occurred at equal rates in both placebo and dapagliflozin-treated groups (0.1% in both groups).[38] Although these common side effects of dapagliflozin were not serious in nature, their long-term effect on renal function and reproduction remains to be investigated.

Serious but rare side effects of dapagliflozin include cancer development and hepatotoxicity.[38] The safety data pooled from T2DM patients enrolled in phase 2b and 3 clinical trials revealed an increased incidence of bladder and breast cancer.[38] A total of 9 cases of bladder cancer were reported out of 5478 patients in the study group, as compared to 1 case out of 3156 patients in the control group (0.3% of patients in dapagliflozin group as compared to 0.05% of patients in the control group). Also, there were 9 cases of breast cancer out of 2223 women in the study group as compared to 1 case in 1053 women in the control group (0.4% of women on dapagliflozin as compared to 0.1% of women in the control group). Given the lack of statistical significance of the breast and bladder cancer observation ($P = 0.15$ and $P = 0.27$, respectively) at this

Table 2 Clinical trials of dapagliflozin

References	Study population/duration	Study drugs	ΔHbA1c%	ΔFBG (mg/dl unless defined otherwise)	Change in weight (kg)	Other parameters	Adverse drug reaction
Komoroski et al. (2009)[49]	T2DM drug-naïve patients or patients on stable dose of MET (n = 47) DOS = 2 weeks	DP = 5 mg/25 mg/ 100 mg or PL		Percentage reduction from baseline: DP: −11.7% to −21.8% (DP 5 mg/25 mg, P < 0.05 vs PL; DP 100 mg, P < 0.001 vs PL)		ΔSBP: −2.6 to −6.4 mm Hg	• No serious ADRs or discontinuations due to AEs
List et al. (2009)[47]	T2DM drug-naïve patients (n = 389) with inadequate glycemic control (HbA1c = 7–10%) DOS = 12 weeks	DP = 2.5 mg/5 mg/ 10 mg/20 mg 50 mg or MET 750–1500 mg or PL	−0.55% to −0.90% (DP 2.5 mg/5 mg/ 10 mg/50 mg, P < 0.001 vs PL)	−16 to −31 mg/dl (DP 5 mg/10 mg, P < 0.01; DP20 mg/50 mg, P < 0.001)	% body weight reduction with DP = −2.5% to −3.4%		• AEs rate similar across all groups • Similar rate of UTI & hypoglycemia • Higher incidence of genital infections with high dose of DP • Small increases in hematocrit, BUN, serum phosphate, serum magnesium, PTH, & decreases in serum uric acid
Wilding et al. (2009)[48]	T2DM patients (n = 71) on high dose of insulin and stable dose of insulin-sensitizing therapy with Hba1c = 7.5–10% DOS = 12 weeks	DP = 10 mg/20 mg or PL + 50% of insulin dose and OADs	DP = −0.61% to −0.69% vs +0.09% by PL	DP 10 mg = 2.4 mg/dl DP 20 mg = −9.6 mg/dl vs PL = 17.8 mg/dl	−4.3 to −4.5 kg	ΔSBP/ΔDBP = DP: −6.1 to −7.2 mm Hg/−1.2 to −3.9 mm Hg	• Similar rates of AEs across all groups • Genital infections: DP 10 mg: DP 20 mg : PL = 0%: 20.8%: 4.3%
Ferrannini et al. (2010)[35]	T2DM patients (n = 485) with inadequate glycemic control (HbA1c = 7–10%) on diet and exercise DOS = 24 weeks	Baseline HbA1c = 7–10%: DP = 2.5 mg/5 mg/ 10 mg or PL	Baseline HbA1c = 7–10%: DP = −0.58% to −0.89% (DP 5 mg, P < 0.001 vs PL; DP 10 mg, P < 0.0001 vs PL)	Baseline HbA1c = 7–10%: DP = −15.2 to −29.6 mg/dl (DP 5 mg, P < 0.001 vs PL; DP 10 mg, P < 0.0001 vs PL)	−2.2 to −3.8 kg	ΔSBP/ΔDBP = DP: −2.3 to −5.2 mm Hg/−1 to −3.2 mm Hg DP treatment caused slight increase in HDL-C	• No major episodes of hypoglycemia in both groups • Increased incidence of UTI & genital infections with DP • Small increases in hematocrit and decreases in serum uric acid
Bailey et al. (2010)[30]	T2DM patients (n = 546) receiving metformin>1500 mg/day and having inadequate glycemic control ((HbA1c = 7–10%) DOS = 24 weeks	DP = 2.5 mg/5 mg/ 10 mg or PL	DP = −0.67% to −0.84% (DP 2.5 mg, P < 0.001; DP 5 mg/10 mg, P < 0.0001 vs PL)	Value in mmol/l: DP = −0.99 to −1.30 (DP 5 mg/10 mg, P < 0.0001 vs placebo)	−2.2 to −3 kg (all doses of DP P < 0.0001 vs placebo)	ΔSBP/ΔDBP = DP: −2.1 to −5.1 mm Hg/−1.8 to −2.5 mm Hg No orthostatic hypotension DP : increase in HDL-C by 1.8% to 4.4% and decrease TGs by 2.4% to 6.2%	• Hypoglycemic rates similar in all groups • No major hypoglycemic event • Rate of genital infections 8–13% in DP vs. 5% in placebo • Similar rates of UTI in all groups • Small increase in BUN, hematocrit and decrease in serum uric acid in DP
Strojek et al. (2011)[32]	T2DM patients (n = 597) with inadequate glycemic control (HbA1c = 7–10%) having at least half maximal recommended dose of glimepiride DOS = 24 weeks	DP 2.5 mg/5 mg/ 10 mg or PL + glimepiride	−0.58% to −0.82% (DP all doses P < 0.0001 vs PL)	−16.8 to −28.5 mg/dl (DP 5 mg/10 mg, P < 0.0001 vs PL)	−1.18 to −2.26 kg (DP 5 mg, P < 0.01; DP 10 mg, P < 0.0001 vs PL)	ΔSBP/ΔDBP = DP: −4 to −5 mm Hg/−1.1 to −2.8 mm Hg. No orthostatic hypotension Significant reductions from baseline in OGTT by DP 5 mg/10 mg	• Similar AEs in all groups • Genital infections with DP 3.9 to 6.6% vs. 0.7% with PL
Kipnes (2010)[31]	T2DM patients (n = 800) with inadequate control of diabetes (HbA1c = 7.5–10%) with mean insulin dose> 30 IU for at least 8 weeks with or without OADs DOS = 24 weeks	DP = 2.5 mg/5 mg/ 10 mg or PL	−0.75% to −0.90% (DP all doses P ≤0.0001 vs PL)	−12.5 to −21.7 mg/dl (DP 2.5 mg, P = 0.0008; DP 10 mg, P < 0.0001 vs PL)	−0.98 to −1.67 kg (DP all doses P ≤0.0001 vs PL)	DP: reduction in insulin daily dose = −0.61 to −1.8 IU/day vs PL: increase in insulin dose of 5.08 IU/day	• Similar AE & discontinuations in all groups • UTI & genital infections more in DP • UTI: DP = 5.9 to 7.7% vs 2% in PL • Genital infections: DP = 5.4% to 9.2% vs. 2% PL
Nauck et al. (2011)[34]	T2DM patients (n = 814) with inadequate glycemic control (HbA1c = 6.5–10%) on 1500 mg/day MET alone DOS = 52 weeks	DP + MET vs MET + glipizide (glipizide median dose = 20 mg; DP median dose = 10 mg)	Identical reductions in HbA1c = −0.52%		DP + MET = −3.22 kg vs MET + glipizide = +1.44 kg (P < 0.0001)	ΔSBP/ΔDBP = DP + MET = −4.3 mm/−1.6 mm Hg vs MET + glipizide = +0.8 mm/−0.4 mm Hg	• Hypoglycemic events DP + MET : 3.5% vs. MET + Glipizide 40.8% (P < 0.0001) • AEs similar • UTI = DP+MET : 10.8% vs. Glipizide + MET : 6.4% • Genital infections: DP + MET : 12.3% vs. glipizide + Met : 2.7%
Nauck et al. (2011)[50]	52-week extension study 52-week extension phase in T2DM patients on DP + MET or glipizide + MET (n = 624) DOS = 52 weeks to 104 weeks	DP + MET vs MET + glipizide (MET = 1500 mg/day; glipizide median dose = 20 mg; DP median dose = 10 mg)	At 104 weeks = DP+ MET = −0.32% vs glipizide + MET = −0.14%		At 104 weeks = DP + MET = −3.7 kg vs MET+ glipizide = +1.36 kg		• Incidence of hypoglycemic episodes were 4.2% in DP + MET group as compared to 45.8% in glipizide + MET group • Frequency of UTI & genital infections more in DP • UTI: DP + MET group = 13.5% vs. 9.1% in glipizide + MET group • Genital infections: DP + MET group = 14.8% vs. 2.9% in glipizide + MET group

ΔDBP, change in diastolic blood pressure; ΔFBG, change in fasting blood glucose level from baseline at end of study; ΔHbA1c%, change in glycosylated haemoglobin from baseline at end of study; ΔSBP, change in systolic blood pressure; ADRs, adverse drug reactions; AEs, adverse events; BUN, blood urea nitrogen; DOS, duration of study; DP, dapagliflozin; HDL-C, high-density lipoprotein cholesterol; MET, metformin; OADs, oral antidiabetic drugs; OGTT, oral glucose tolerance test; PL, placebo; PTH, parathyroid hormone; T2DM, type 2 diabetes mellitus; TGs, triglycerides; UTI, urinary tract infection; vs, versus.

time, it is still unclear whether this is due to the carcinogenic potential of the drug or an imbalance of some baseline risk factor between the study and control groups.[52] These findings require further investigation as neither bladder nor breast tissue express SGLT2 transporters.[16] Moreover, rigorous 2-year carcinogenic studies in animals failed to demonstrate any neoplastic activity.[16] Breast and especially bladder cancers take many years to develop, whereas the exposure to dapagliflozin was short (generally ≤1 year).[16] In addition, there could have been a detection bias for bladder cancer, as frequent urine analyses in the treatment group (due to increased incidence of UTI) may have led to the discovery of microscopic hematuria.[52] Similarly, weight loss in the treatment group may have lead to a relatively easier location of breast lump, thus increasing the rate of diagnosis of carcinoma breast.[52]

Five cases in the Phase 2b and 3 clinical trial data pool were found to have elevated values of liver enzymes suggesting liver injury (laboratory values of aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal in addition to elevation of total bilirubin greater than twice the upper limit of normal).[38] An adequate explanation for these biochemical abnormalities could be identified in only one case. This was classified as a 'probable diagnosis of mild to moderately severe dapagliflozin-induced liver injury'.[38]

In clinical trials of dapagliflozin, a low risk of hypoglycemic episodes has been reported since this group of drugs acts selectively targeting the renal glucose transporters without affecting the counter regulatory hormones.[30–35,50] In a meta-analysis of randomized controlled trials of dapagliflozin, it was found that the overall incidence of major hypoglycemic events did not exceed 1% and was not significantly increased by dapagliflozin treatment.[53] However, the risk of mild hypoglycemic events, generally not leading to the discontinuation of the drug, was reported more frequently with dapagliflozin compared to placebo. Further analysis of data revealed that this increased risk was not dose related and could only be explained by co-administration of insulin.[48,53] These results imply that although the risk of hypoglycemia with use of these drugs is low, it is important to investigate this risk when these drugs are administered in combination with other antidiabetic agents.

Dapagliflozin treatment was associated with a dose-dependent increase in hematocrit and blood urea nitrogen levels, suggesting volume depletion.[30,35,47] Dehydration and hypovolemia might put the patients at increased risk of thromoembolic events.[38] The clinical relevance of this side effect is yet to be established, especially in elderly patients and patients on antihypertensive therapy and diuretics.[38] There was also a dose-dependent decrease in serum uric acid levels with dapagliflozin treatment reported in few clinical trials.[30,35,47] The clinical relevance of this finding is unknown, although an association between glucosuria and increased renal uric acid clearance has been reported in some studies.[54]

The finding of increased trabecular bone mass by dapagliflozin in animal studies led to a more critical assessment of the risk of fractures in clinical trials.[36] The data gathered from phase 2b and 3 clinical trials demonstrated no significant effect on bone loss or increased risk of fracture.[36,38] In a few studies, an increase in levels of serum magnesium, phosphate and parathyroid hormone was found.[30,35,47] These electrolyte changes were statistically insignificant. The long-term effect of dapagliflozin on bone health remains to be investigated.

Dapagliflozin has completed phase 3 clinical trials as a once-daily oral treatment for T2DM. Its New Drug Application (NDA) has recently been reviewed by the US Food and Drug Administration (FDA). Citing fears of cancer development, the Endocrinologic and Metabolic Drugs Advisory Committee of FDA has voted against the approval of the drug.[55] The FDA panel stated that 'based on evaluation of the Surveillance Epidemiology and End Results (SEER) database and review of the literature on the incidence of these cancers in T2DM, it was determined that the number of observed breast and bladder cancers in the dapagliflozin-treated group exceeded the expected number of cases in the general T2DM population'.[38] Other safety issues reviewed by the FDA panel included a possible hepatotoxicity risk and increased incidence of genitourinary infections by the drug.[38]

The FDA advisory panel also questioned the efficacy of the drug in renal impairment.[38] Patients with severe renal impairment (GFR<30 ml/min/1.73 m²) were excluded from large controlled clinical trials. Hence, the efficacy and safety data could not be extracted from these patients. Clinical trials conducted to assess the efficacy of dapagliflozin in patients with moderate renal impairment (GFR = 30 ml/min/1.73 m² to 59 l/min/1.73 m²) demonstrated no statistical significant difference in attaining glycemic control by either placebo or dapagliflozin at the end of the treatment period.[36,38] These observations restrict the use of dapagliflozin to diabetic patients with normal renal function or patients with mild renal impairment. The FDA panel discussed the need for monitoring the renal function prior to or during the course of therapy. They also argued that as T2DM patients are at risk of worsening renal function over the course of their disease, the secondary failure of glycemic control might reflect a failure of dapagliflozin efficacy and require discontinuation of drug. This would be in contrast to the common practice of adding drugs with complementary effects in uncontrolled diabetes.[38]

Based on these safety and efficacy concerns, the FDA advisory panel has delayed the approval of the drug, asking the manufacturers to submit the additional clinical data of dapagliflozin to allow a better assessment of its benefit–risk profile.[56]

Despite a setback from the FDA, dapagliflozin has received a positive opinion from the Committee for Medicinal Products (CHMP) of the European Medicine Agency (EMEA),

which will now be reviewed by the European commission.[57] Dapagliflozin (Forxiga 5 mg/10 mg once daily) is intended to be approved for adult patients with type 2 diabetes to improve glycaemic control, as a monotherapy in metformin-intolerant patients as an adjunct to diet and exercise, and in combination with other glucose-lowering drugs, including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.[57]

Other SGLT 2 inhibitors in clinical trials

A number of SGLT2 inhibitors are currently in phase 2/3 clinical trials, including canagliflozin, empagliflozin (BI 10773), ipragliflozin (ASP 1941), luseogliflozin (TS 071), LX4211, tofogliflozin (CSG 452), ertugliflozin (PF04971729) and EGT 1474 (Tables 3 and 4).[15,58–75] LX4211 is a dual SGLT2/ SGLT1 inhibitor (lesser extent of SGLT1 inhibition as compared to SGLT2).[15] It inhibits both glucose reabsorption by the kidney and glucose absorption by the small intestine. It thus produces rapid and robust decreases in fasting plasma glucose, improvements in postprandial glycemic control and reductions in haemoglobin A1c (HbA1c).[15] The HbA1c reductions achieved with LX4211 after 4 weeks of treatment were comparable to those achieved by other SGLT2 inhibitors at 12 weeks of treatment.[15,52] In this short-term clinical trial there were no reports of severe gastrointestinal adverse effects due to SGLT1 inhibition.[15]

SGLT 2 antisense oligonucleotide

ISIS – 388626 (developed by Isis Pharmaceuticals) represents a novel approach to SGLT2 inhibition. It is an antisense oligonucleotide (ASO) designed to block the expression of the SGLT2 gene *in vivo*. Administration of ISIS – 388626 once weekly yielded an approximately 80% reduction of renal SGLT2 mRNA expression without affecting SGLT1 expression.[76] It was safe and effective during 6-week studies in dogs, 3-month studies in Sprague–Dawley (SD) rats and 6-month studies in ZDF rats. In ZDF rats a marked decrease in plasma glucose was attained after once-a-week injection for 4 weeks and this effect was maintained throughout the 6-month study (saline: 695 ± 46 mg/dl; ASO-treated: 382 ± 48 mg/dl), with a significant reduction in HbA1c (saline: 10.9 ± 0.3%; ASO-treated: 6.3 ± 0.8%). ISIS 388626 also slowed progression of ocular cataract formation, glomerular kidney and pancreatic islet cell deterioration.[10,76] This drug is in the early phase of clinical testing.[75] The current clinical development of ISIS 388626 is not known.

Conclusion

Inhibition of SGLT2 glucose transporter is a new therapeutic approach for the treatment of T2DM. Administration of SGLT2 inhibitors reduces both preprandial and postprandial blood glucose levels, decreases glucotoxicity, reduces glycosylated hemoglobin and causes weight reduction. The clinical trials of the most advanced SGLT2 inhibitor, dapagliflozin, have shown therapeutic benefits in attaining glycemic control, lowering plasma glucose levels and reducing weight in T2DM patients. Apart from these effects, there is also a positive beneficial effect on blood pressure and lipid profile. A unique mechanism of action of SGLT2 inhibitors offers them a potential to be used in combination with other oral antidiabetic drugs and with insulin. However, as the efficacy of these drugs is dependent on glomerular filtration, these therapeutic benefits are limited to a subset of diabetic patients with normal renal function or patients with mild renal dysfunction. Increased incidence of breast and bladder cancer and its hepatotoxic potential are safety concerns overshadowing the potential therapeutic benefits of the drug. However, further investigations are required to confirm these safety issues. Notwithstanding these issues, a number of SGLT2 inhibitors currently in clinical trials are showing promising efficacy and safety profile.

Declarations

Conflict of interest

Table 3 SGLT2 inhibitors currently in clinical development (58–66)

Drug candidate	Manufacturing company	Clinical development phase
Canagliflozin	Johnson & Johnson	NDA submitted to US-FDA
Empagliflozin (BI 10773)	Boehringer Ingelheim	Phase 3
Ipragliflozin (ASP 1941)	Astella Pharma. Inc.	Phase 2/3
LX 4211*	Lexicon Pharmaceuticals	Phase 2
Luseogliflozin (TS071)	Taisho Pharmaceuticals Co. Ltd	Phase 3
Tofogliflozin (CSG452)	Chugai Pharmaceuticals	Phase 3
Ertugliflozin (PF 04971729)	Pfizer	Phase 2
EGT1474	Theracos Inc.	Phase 1
ISIS 388626	Isis Pharmaceuticals	Phase 1

*Lx4211 is a dual sodium- glucose co-transporter 1 and SGLT2 inhibitor. FDA, Food and Drug Administration; NDA, New Drug Application.

Table 4 Effects of the SGLT2 inhibitors (currently in phase 2/3 clinical trials) on HbA1c, fasting plasma glucose and body weight in patients of T2DM

References	Study population/duration	Study drugs	ΔHbA1c%	ΔFPG (mg/dl unless defined otherwise)	Change in weight (kg)	Adverse drug reaction
Devineni et al.(2012)[67]	T2DM patients not optimally controlled on insulin and up to one oral antihyperglycemic drug (n = 29) DOS = 28 days	CANA 100 mg once daily or 300 mg twice daily or PL	CANA (100 mg once daily) = −0.73%; CANA (300 mg twice daily) = −0.92 PL = −0.19%	CANA (100 mg once daily) = −38.1 mg/dl CANA (300 mg twice daily) = −42.4 mg/dl PL = +8.7 mg/dl	CANA (100 mg once daily) = 0.73 kg CANA (300 mg twice daily) = 1.19 kg PL = +0.03	• No deaths, serious adverse events or severe hypoglycaemic episodes • Similar adverse events across all groups
Rosenstock et al. (2010)[68]	T2DM patients not adequately controlled on metformin (n = 451) DOS = 12 weeks	CANA = 50 mg/100 mg/200 mg/ 300 mg once daily or 300 mg twice daily or PL or SITA = 100 mg/daily	CANA = −0.45% to −0.73% (P ≤ 0.001 vs PL for all dose regimens); SITA = −0.56% (P ≤ 0.001 vs PL)	CANA = −16.2 to −32.4 mg/dl (P ≤ 0.001 vs PL for all dose regimens) SITA = −18.0 mg/dl (P ≤ 0.001 vs PL)	Percentage reduction from BL = CANA = −1.3% to 2.3% (P ≤ 0.01 for 50 mg/100 mg of CANA vs PL; P ≤ 0.001 for 200 mg/300 mg CANA vs PL) No statistical significance seen with SITA vs PL	• Similar incidence of AEs across all groups • Frequency of symptomatic genital infection :CANA = 3–8%; PL = 2%; SITA = 2% • Frequency of UTI: CANA = 3–9%, PL = 6%; SITA = 2% • Frequency of hypoglycemia events: CANA = 0–6%; PL = 2%; SITA = 5%
Inagaki et al. (2011)[69]	T2DM Japanese patients (n = 383) DOS = 12 weeks	CANA = 20 mg/100 mg/200 mg/ 300 mg once daily or PL	−0.61% to −0.88% (significant reduction vs PL at all doses)	−24.7 to −38.8 mg/dl (significant reduction vs PL at all doses)	CANA = −1.98 to −3.19 kg PL = −0.78 kg	• Similar incidences of AEs across all groups • All ADRs were mild to moderate in intensity • Most frequently reported ADR = nasopharyngitis • Genital infections: two female patients in CANA • Pollakiuria = one patient in each CANA 50 mg/100 mg/300 mg
Rosenstock et al. (2011)[70]	T2DM patients not controlled on metformin (n = 495) DOS = 12 weeks	EMP = 1 mg/5 mg/10 mg/25 mg/ 50 mg/100 mg once daily or PL or SITA = 100 mg once daily	EMP = −0.24% to −0.71% (P < 0.05 vs PL for EMP 1 mg; P < 0.001 vs PL for 5 mg EMP; P < 0.0001 vs PL for 10 mg/25 mg/ 50 mg EMP and SITA)	EMP = −1.7 to −27.9 mg/dl (P < 0.0001 vs PL for EMP 5 mg/10 mg/25 mg/50 mg; P < 0.001 vs PL for SITA)	EMP = −1.55 to −2.85 kg SITA = −0.84 kg (P < 0.01 vs PL for EMP 5 mg; P < 0.001 for EMP 10 mg/25 mg; P < 0.0001 for EMP 50 mg) No statistical significance observed with SITA vs PL	• Frequency of AEs was similar in all groups (EMP: 38.5%, PL: 36.6%, SITA: 35.2%) • Most frequently reported AEs in the EMP groups vs PL were: UTI (3.1% vs 2.8%), pollakiuria (2.5% vs 1.4%), genital infections (2.5% vs 0%) • Incidence of hypoglycemia were similar between groups
Ferrannini et al. (2010)[71]	T2DM patients with HbA1c = 7% to 10% (n = 408) DOS = 12 weeks	EMP = 5 mg/10 mg/25 mg or MET = 500 mg or 1000 mg twice daily or PL	EMP = 0.52% to −0.72% (P < 0.001 vs PL); MET = −0.82% (P < 0.001 vs PL)	EMP = −23.3 to −31.1 mg/dl (P < 0.001 vs PL); MET = −29.7 mg/dl (P < 0.001 vs PL)	EMP = −1.81 to −2.33 kg (P < 0.001 vs PL); MET = −1.32 kg (P < 0.05 vs PL)	• Similar rates of hypoglycemia in all groups • Pollakiuria, thirst and nasopharyngitis were the most frequently reported adverse events in as a result of EPA
Kashiwagi et al. (2010)[72]	T2DM Japanese patients (baseline HbA1c = 8%) (n = 361) DOS = 12 weeks	IPR = 12.5 mg/25 mg/50 mg /100 mg once daily or PL	Dose-dependent reduction at all doses; maximum reduction with 50 mg = −0.8 ± 0.6% (<0.001 vs PL)	NA	Dose-dependent reduction at all doses; maximum reduction up to 2 kg with 100 mg (<0.001 vs PL)	• No hypoglycemia was observed except one mild symptomatic hypoglycemia in the 100 mg group • Five UTI and five genital infections were reported — all events were mild in severity and not significantly different between IPR and placebo groups
Kashiwagi et al. (2011)[73]	T2DM Japanese patients (n = 129) DOS = 16 weeks	IPR = 50 mg once daily or PL	IPR = −1.23% (P < 0.001 vs PL)	−45.8 mg/dl (P < 0.001 vs PL)	−1.47 kg (0.001 vs PL)	• One mild case of symptomatic hypoglycemia in the IPR group • One UTI case observed in the PL group but none in IPR group • Two genital infection cases were observed in the IPR group but none in PL group
Seino et al. (2011)[74]	T2DM Japanese patients (n = 236) DOS = 12 weeks	TS071 = 0.5 mg/2.5 mg/5 mg once daily or PL	−0.43% to 0.82% (significant at all doses vs PL)	−14.6 to −27.9 mg/dl (significant at all doses vs.PL)	−1.8 kg (significant at 2.5 and 5 mg doses)	• No hypoglycemia was observed in either group • Six pollakiuria cases reported in 2.5 and 5 mg groups; but all events were mild in severity
Freiman et al. (2010)[15]	T2DM patients (n = 36) DOS = 28 days	LX4211 = 150 mg once daily or 300 mg once daily or PL	−1.15% (150 mg/day); −1.25% (300 mg/day) (P < 0.05 vs PL)	−52.3 mg/dl (150 mg/day); −67.8 mg/dl (300 mg/day) (P < 0.05 vs PL)	NA	• ADRs were mild and evenly distributed across all treatment groups • No serious adverse events or dose-limiting toxicities
Nucci et al. (2011)[75]	T2DM patients not adequately controlled on metformin (n = 328) DOS = 12 weeks	PF04971729 = 1 mg/5 mg/ 10 mg/25 mg once daily or SITA = 100 mg once daily or PL	PF04971729 = −0.56 to −0.83%; SITA = −0.87% (P < 0.05 vs PL for PF04971729 all doses and SITA)	PF04971729 = −18.3 to −31.47 mg/dl; SITA = −17.29 mg/dl (P < 0.05 vs PL for PF04971729 all doses and SITA)	PF04971729 = −1.9 to −2.9 kg; SITA = −0.30 kg (P < 0.05 vs PL for PF04971729 all doses) No statistical significance observed with SITA vs PL	• ADRs were mild and evenly distributed across all treatment groups • No case of pyelonephritis reported • Frequency of symptomatic UTI: 2.3% with PF04971729 vs 3.7% with PL • Frequency of genital fungal infections: 3.6% with PF04971729 vs 1.8% with PL

ΔHbA1c%, change in glycosylated haemoglobin from baseline at end of study; ΔFPG, change in fasting plasma glucose level from baseline at end of study; ADR/ADRs, adverse drug reaction/adverse drug reactions; AEs, adverse events; CANA-, canagliflozin; DOS, duration of study; EMP-, empagliflozin; IPR, ipragliflozin; MET, metformin; NA, data not available; PL, placebo; SITA, siatgliptin; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection; vs, versus.

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