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REVIEW

Sodium Glucose Co-transporter Type 2 (SGLT2) Inhibitors: Targeting the Kidney to Improve Glycemic Control in Diabetes Mellitus

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ABSTRACT

Although hyperglycemia is a key therapeutic focus in the management of patients with type 2 diabetes mellitus (T2DM), many patients experience sub-optimal glycemic control. Current glucose-lowering agents involve the targeting of various body organs. Sodium glucose co-transporter type 2 (SGLT2) inhibitors target the kidney, reduce renal glucose reabsorption, and increase urinary glucose elimination, thus lowering glucose blood levels. This review examines some of the key efficacy and safety data from clinical trials of the main SGLT2 inhibitors approved or currently in development, and provides a rationale for the use of SGLT2 inhibitors in the treatment of T2DM.

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INTRODUCTION

Cardiovascular disease (CVD) is the major cause of death in patients with diabetes mellitus (DM); however, microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) cause significant morbidity and disability, such as visual impairment/blindness, progressive renal impairment, and non-traumatic amputations. Hyperglycemia increases the risk of microvascular complications, and improved control of hyperglycemia reduces the risk of microvascular complications. Adiposopathy (i.e., positive caloric balance leading to adipocyte hypertrophy, visceral fat accumulation, "lipotoxicity", and subsequent pathogenic adipocyte and adipose tissue endocrine and immune responses) is often the initial promoter of insulin resistance and, therefore, of hyperglycemia [1]. However, once

elevated glucose levels are present, chronic hyperglycemia itself may worsen glucose control by further promoting insulin resistance and impairing pancreatic beta-cell function (via a reduced beta-cell survival and mass, decreased insulin gene transcription, and decreased insulin synthesis and secretion) [2, 3], through a process often termed glucotoxicity. Hyperglycemia may also promote macrovascular complications via direct and indirect effects on vasculature similar to those observed in atherosclerosis [4–7]. Finally, hyperglycemia may further worsen the adiposopathic dyslipidemia often associated with type 2 DM (T2DM) [8–11].

DM is defined by hyperglycemia and, given the proven health benefits of reducing hyperglycemia, glucose control remains a key therapeutic focus for the treatment of DM [12–19], with glycosylated hemoglobin A_{1c} (HbA_{1c}) being a commonly used measure of longer-term glycemic control. Some studies are inconclusive in determining the efficacy of intensive versus standard glycemic control in reducing macrovascular disease in T2DM [20–23]. However, one interpretation of the existing data is that the potential benefit of intensive versus less intensive (or "standard") glucose control is dependent on the mechanism of action of the antidiabetes agent, as well as the speed and extent by which glucose lowering is achieved [24]. The greatest potential for macrovascular CVD benefit seems to be achieved with antidiabetes agents having the most favorable effects on CVD risk factors and the least potential to promote hypoglycemia, as well as when aggressive therapy is implemented early in the disease process in younger individuals with limited comorbidities.

The recommended HbA_{1c} target of the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation is <7.0% (53 mmol/mol) [25–27], which is applicable to many non-pregnant adults with DM [25]. However, it is increasingly recognized that the best health outcomes are often achieved via individualization of DM treatment objectives [26]. Less stringent HbA_{1c} goals (such as <8.0%) may be appropriate for some patient groups, such as DM patients with hypoglycemia unawareness, as well as individuals with repeated bouts of severe hypoglycemia, comorbid conditions, and advanced microvascular/macrovascular complications [25]. Conversely, if significant hypoglycemia or other treatment side effects can reasonably be avoided, then more stringent HbA_{1c} goals (such as 6.0–6.5%) might be considered in selected patients with short disease duration, minimal to no DM complications, and otherwise good health [25].

The key point is that improved glucose control in DM patients can reduce the risk of microvascular disease, and possibly reduce macrovascular disease in selected individuals. However, in clinical practice, glycemic control remains sub-optimal in many patients [28–32]. Data from the 2004 US National Health and Nutrition Examination Survey revealed that approximately 43% of DM patients had HbA_{1c} >7.0% [33]. Reasons for the failure to achieve glycemic targets are multifactorial, and may include issues relating to the health-care provider (e.g., failure to sufficiently instruct on lifestyle changes, reluctance to intensify antidiabetes drugs, complexity of antidiabetes drug management, or lack of expertise) [34], and to the patient (e.g., non-adherence to favorable lifestyle habits and other therapies, lack of attendance at clinic, lack of understanding of the disease, reluctance to use insulin when required, longer duration of DM, or younger age [<40 years]) [30, 31, 35, 36].

Lifestyle modifications, such as nutritional and physical activity interventions, remain important toward improving both the glucose levels and overall health of DM patients. However, the reality is that the majority of patients with DM are managed with glucose-lowering therapeutic agents. Some examples of target organs for agents that lower glucose levels in DM include the pancreas, liver, muscle, adipose tissue, gastrointestinal system, and central nervous system. Due to the potential DM complication of nephropathy, the kidney has historically been regarded solely as a "victim" in DM management. With the development of the sodium glucose co-transporter type 2 (SGLT2) inhibitors, the kidney is now recognized as a potential "ally" in the management of DM [37]. Specifically, SGLT2 inhibitors reduce renal glucose reabsorption and promote urinary glucose excretion, thus lowering glucose blood levels. This supports the concept of the kidney as a target organ in the treatment of DM.

This review examines kidney glucose management and literature supporting SGLT2 inhibitors as a therapeutic approach to treating hyperglycemia.

METHODS

The literature search involved review and original articles published up to July 11, 2013 using PubMed, with key search terms including *SGLT2 inhibitors*, *sodium glucose co-transporter 2 inhibitors*, *glucose and kidney*, and the individual drug names (*dapagliflozin or BMS-512148*; *canagliflozin or JNJ-24831754*; *empagliflozin or BI10773*; *luseogliflozin or TS-071*; *tofogliflozin or CSG452*; *ipragliflozin or ASP1941*; *LX4211*; *EGT0001442*; and *ertugliflozin or PF04971729*). Other sources of information for this review included abstracts from the American Diabetes Association (2010–2013) and the European Association for the Study of Diabetes (2010–2012), and clinical trial listings of SGLT2 inhibitors posted on *ClinicalTrials.gov*.

GLUCOSE REABSORPTION IN THE KIDNEY

Overview of Renal Structure and Function

The anatomy of the kidney is shown in Fig. 1. The main structural and functional unit of the kidney is the nephron. A normal human kidney contains approximately 1 million nephrons, with the majority located in the renal cortex and the remainder situated near the cortico-medullary junction. Each nephron consists of a glomerulus, containing afferent and efferent capillaries, and a renal tubule, which includes the glomerular (or Bowman's) capsule, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and the collecting duct. Higher positive pressure in the glomerular blood vessels forces fluid and solutes from the plasma into the glomerular capsule (filtration), and this filtrate then flows through the renal tubule. Much of this glomerular filtrate undergoes reabsorption into capillary blood via the proximal convoluted tubule. Nitrogenous and other waste products largely remain in the filtrate and pass into the collecting duct, eventually leading to urinary excretion. Other substances (e.g., hydrogen ions, potassium ions, ammonia, and drugs) undergo transport from peritubular capillaries into the renal tubule cells, and then into the filtrate for ultimate urinary excretion via the ureter, bladder, and urethra.

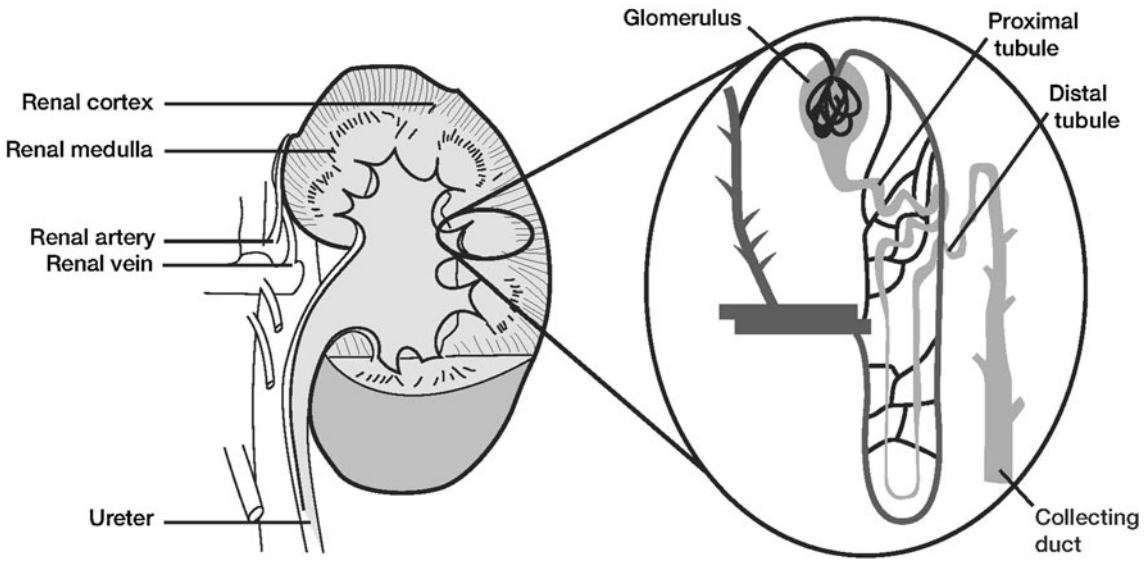

Fig. 1 Renal anatomy. Nephrons are predominantly located in the renal cortex, with the remainder at the cortico-medullary junction. Each nephron consists of a glomerulus, containing afferent and efferent capillaries, and a renal tubule, including proximal and distal sections and a collecting duct

Physiology of Renal Glucose Transport

Key kidney functions that help achieve glucose homeostasis involve renal gluconeogenesis, glucose uptake from the circulation, and glucose reabsorption from the glomerular filtrate [38]. Given an average plasma glucose concentration of approximately 100 mg/dL (5.5 mmol/L) and a normal glomerular filtration rate of approximately 180 L/day, healthy individuals filter in the region of 180 g/day of glucose. Virtually all glucose is reabsorbed in the proximal convoluted tubule and returned to the circulation, so that effectively no glucose is excreted in the urine of an otherwise healthy individual. This system is highly efficient and allows conservation of glucose, which is a valuable energy source. Given the figure of 180 g/day of glucose reabsorbed, and the fact that the kidneys produce 15–55 g/day of glucose via gluconeogenesis and metabolize 25–35 g/day, renal absorption is a primary mechanism by which the kidney influences glucose homeostasis [38].

To retrieve glucose in the filtrate, the kidney utilizes two types of membrane-bound carrier proteins: SGLTs (sometimes described as symporters because they transport both glucose and sodium) and the facilitated glucose transporters (GLUTs, sometimes described as uniporters because they only transport glucose) [39, 40]. Details of the SGLT and GLUT families are given in Table 1 [40, 41]. Reabsorption of glucose from the glomerular filtrate is mediated by SGLTs in the proximal convoluted tubule (Fig. 2), in a process that is independent of insulin. Approximately 90% of filtered renal glucose is reabsorbed in the first segment (S1) of the proximal convoluted tubule by SGLT2, a low-affinity high-capacity transporter, and the remaining 10% is removed in the distal segment (S3) by SGLT1, a high-affinity low-capacity transporter [39, 40]. In the kidney, SGLT2 and SGLT1 are located on the luminal surface of epithelial cells lining the proximal convoluted tubule [40]. SGLT2 is expressed to a lower extent in other organs, including the liver, while SGLT1 is extensively

Table 1 Glucose transporters

Transporter protein	Distribution in human tissue	Known function	Associated disease
Sodium glucose co-transporters (SGLT)			
SGLT1	Intestine, trachea, kidney, heart, brain, testis, prostate	Active co-transport of sodium, glucose, and galactose across intestinal brush border and S3 segment of kidney proximal tubule	SGLT1 mutations associated with congenital glucose–galactose malabsorption
SGLT2	Kidney, brain, liver, thyroid, muscle, heart	Active co-transport of sodium and glucose in S1 segment of kidney proximal tubule	SGLT2 mutations associated with familial renal glucosuria
SGLT3	Intestine, testis, uterus, lung, brain, thyroid	Not a glucose transporter in humans—probable glucosensor	Unknown
SGLT4	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas	Unknown—glucose, mannose substrates	Unknown
SGLT5	Kidney cortex	Unknown—glucose, galactose substrates	Unknown
SGLT6	Brain, kidney, spinal cord, small intestine	Unknown—d-chiro-inositol substrate	Unknown
Facilitated glucose transporters (GLUT)			
GLUT1	Ubiquitous	Glucose transport	GLUT1 deficiency contributes to De Vivo disease (low cerebrospinal fluid glucose levels)
GLUT2	Pancreas, liver, kidney, small intestine	Glucose transport (low affinity) and fructose	GLUT2 mutations associated with Fanconi–Bickel syndrome
GLUT3	Neurons, lymphocytes, monocytes/macrophages, platelets	Glucose transport in neurons (high affinity)	Unknown
GLUT4	Skeletal muscle, heart, adipose tissue	Glucose transport (high affinity)	GLUT4 deficiency may cause insulin resistance and diabetes mellitus, as well as cardiac hypertrophy
GLUT5	Intestine (kidney, brain, fat, testis, muscle—lower levels)	Fructose transport (and very low-affinity glucose transport)	Unknown
GLUT6	Spleen, leukocytes, brain	Glucose transport	Unknown
GLUT7	Small and large intestine	Unknown	Unknown
GLUT8	Testis, blastocyst, brain, muscle, adipocytes	Glucose transport	Unknown

Table 1 continued

Transporter protein	Distribution in human tissue	Known function	Associated disease
GLUT9	Liver, kidney, intestine (chondrocytes—low levels)	Urate transporter	Inactivating mutations of GLUT9 cause hypouricemia
GLUT10	Liver, pancreas	Glucose transport	GLUT10 mutations cause arterial tortuosity syndrome
GLUT11	Heart, skeletal muscle	Fructose and glucose transport	Unknown
GLUT12	Heart, skeletal muscle, small intestine, prostate, adipose tissue, mammary gland	(Probable glucose homeostasis)	Unknown
GLUT13 (HMIT)	Brain	Myoinositol transport	Unknown
GLUT14	Testis	Probable glucose transport	Unknown

Source: Information taken from Wright et al. [40] and Thorens and Mueckler [41]

expressed in the small intestine, where it has a significant role in glucose absorption [40]. SGLTs actively transport glucose against its concentration gradient via coupling to the electrochemical sodium gradient, using energy from a sodium/potassium adenosine triphosphatase pump [39, 40]. Glucose is released from the proximal convoluted tubule and returned to the bloodstream via GLUT2 in the S1/S2 segment and via GLUT1 in the S3 segment of the proximal convoluted tubule [39, 40]. This is a passive process requiring no energy (adenosine triphosphatase) input.

The amount of glucose filtered in the kidney increases linearly with increasing plasma glucose concentration until the transport maximum for glucose is reached (abbreviated as TM_G and often expressed as mg glucose/min). Beyond the level of the TM_G, the glucose transport system becomes saturated; therefore, any excess glucose remains in the filtrate and is excreted in the urine (i.e., glucosuria). In healthy, glucose-tolerant individuals, TM_G is equivalent to a filtration rate of 260–350 mg/min [42]. The plasma glucose concentration at which TM_G is reached is called the renal threshold, and occurs at approximately 200 mg/dL (11.0 mmol/L) [43]. This threshold may vary between individual nephrons due to variation in their activity and actual reabsorption capacity, which may be below the TM_G level; the difference between the theoretical and actual renal thresholds is called "splay" [44].

Renal Glucose Handling in T2DM

In T2DM patients, glucose handling by the kidney may be altered, with an increase in TM_G and urinary glucose excretion (UGE; i.e., glucosuria) at more elevated plasma glucose levels [38]. Mean TM_G may increase to up to 20% or higher in those with DM, compared with healthy individuals [45]. Furthermore, SGLT2 and GLUT2 expression may be up-regulated in T2DM [46, 47]. These processes

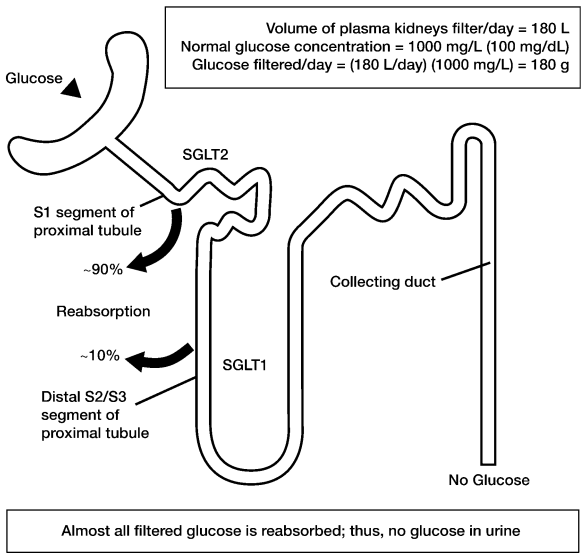

Fig. 2 Glucose transporters in the renal proximal tubule. Data suggest approximately 90% of filtered glucose is reabsorbed in the first part (S1) of the proximal tubule and is mediated by SGLT2. The remaining 10% is reabsorbed in the distal (S2/S3) part of the tubule and this is mediated by SGLT1. This process is extremely efficient and virtually no glucose escapes into the urine of a healthy individual. Glucose is returned to the bloodstream via GLUT2 in the S1/S2 segment and via GLUT1 in the S3 segment of the proximal tubule

might be considered maladaptive in that they attenuate glucosuria, resulting in enhanced glucose reabsorption and further worsening hyperglycemia [37]. Inhibiting this cycle would be expected to increase glucose excretion in the urine, and thus reduce plasma glucose concentrations.

TARGETING RENAL GLUCOSE REABSORPTION WITH SGLT2 INHIBITORS

Inhibiting SGLT2 provides an attractive addition to the DM treatment armamentarium. SGLT2 inhibitors reduce the TM_G, so less glucose is reabsorbed in the proximal convoluted tubule; they also lower the renal threshold, so UGE occurs at a lower plasma glucose concentration (Fig. 3 [48]). The net result is increased UGE and decreased hyperglycemia. In addition to potentially improving hyperglycemic symptoms and DM disease complications, normalization of plasma glucose concentration may improve the adverse effects of glucotoxicity, which may contribute to DM itself, by reducing insulin resistance, decreasing hepatic gluconeogenesis, and potentially improving pancreatic beta-cell function [49].

Genetic models can often provide insight into what might be expected with therapeutic interventions. Individuals with familial renal glucosuria (FRG) have mutations in the gene encoding SGLT2 that cause loss of function. FRG is characterized by UGE, varying from a few grams to >200 g/day, depending on the presence of a homozygous or heterozygous mutation, in the presence of normal plasma glucose concentrations and without evidence of renal tubular dysfunction [50]. Most individuals affected by FRG have no symptoms and only rarely suffer from hypoglycemia or hypovolemia [50]. The lack of adverse events experienced by individuals with FRG due to

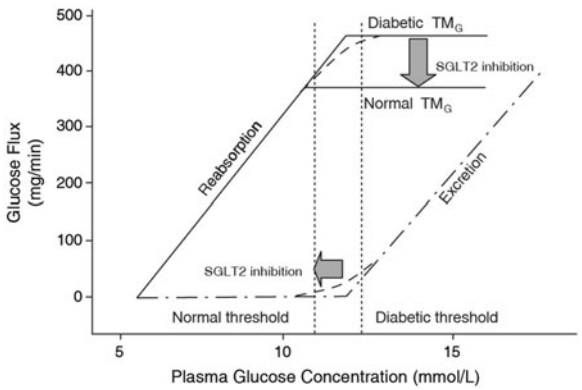

Fig. 3 Renal glucose handling before and after SGLT2 inhibition. SGLT2 inhibition reduces the transport maximum for glucose (TM_G), which decreases glucose reabsorption in the proximal renal tubule, and lowers the renal threshold so that urinary glucose excretion (i.e., glucosuria) occurs at a lower plasma glucose concentration (reproduced with permission from [48])

persistent UGE suggests that long-term UGE induced by pharmacologic inhibition of SGLT2 may also be well tolerated. However, the number of FRG patients studied to date is small and these patients typically did not have DM. Therefore, while intriguing, long-term safety data for any therapeutic agents based upon this mechanism (i.e., SGLT2 inhibitors) are required before any conclusions can be made regarding the potential value of such agents in the clinical management of DM.

SGLT2 INHIBITORS

Phlorizin is a naturally occurring glucoside found in various plants, such as the root bark of apple and other fruit trees, and was the prototype SGLT2 inhibitor. The structure of phlorizin is shown in Fig. 4. First isolated in the 1800s, research into phlorizin provided the evidence that altered renal glucose excretion could improve glycemic control [51, 52]. Studies from the 1950s revealed that phlorizin blocked sugar transport in several tissues, including the kidney and small intestine [53], and this was subsequently found to be due to inhibition of SGLT proteins. Phlorizin was ultimately found to be a competitive inhibitor of SGLT1 and SGLT2, but with a greater affinity for SGLT2 [40, 51]. In the 1980s, investigators found that phlorizin-induced UGE was effective in reducing hyperglycemia via an insulin-independent mechanism, without causing hypoglycemia [54, 55]. Animal studies also supported the use of phlorizin in improving insulin sensitivity without affecting insulin action in healthy control animals, with hyperglycemia and insulin resistance both returning after phlorizin discontinuation [54].

Unfortunately, phlorizin was unsuitable for clinical development as a therapeutic agent for a number of reasons. Firstly, phlorizin has a low selectivity for SGLT2 versus SGLT1, resulting in the inhibition of SGLT1 as well as SGLT2. As SGLT1 is primarily expressed in the small intestine, where it is responsible for the absorption of glucose and galactose from the diet, SGLT1 inhibition can result in gastrointestinal side effects such as severe diarrhea, dehydration, and malabsorption [40]. Secondly, phlorizin has a low oral bioavailability and is metabolized to phloretin by glucosidase enzymes in the gut, which means it must be given parenterally. Lastly, the phlorizin metabolite phloretin is a potent inhibitor of GLUT1 [51], which may lead to interference with glucose uptake in various tissues (e.g., the central nervous system [41]).

Nonetheless, phlorizin served as a model demonstrating how SGLT2 inhibition may become a therapeutic target for hyperglycemia [51]. Subsequent pharmacology research focused on phlorizin derivatives that possess increased stability, better bioavailability, more potent SGLT2 selectivity, and which were more suitable for once daily oral dosing with acceptable tolerability. Such investigations have included both O- and C-glucoside compounds. The first reported SGLT2 inhibitor was T-1095, an orally administered O-glucoside pro-drug that was metabolized in the liver into its active form, T-1095A [56]. Although T-1095 demonstrated increased SGLT2 selectivity and a dose-dependent glucosuric effect in preclinical studies [56], its non-selective SGLT1 inhibition led to discontinuation. Other O-glucoside compounds, such as sergliflozin, were discontinued during phase 2 studies. Attention then turned to the C-glucoside compounds, which had the advantage of increased metabolic stability (see below) [57].

SGLT2 inhibitor compounds in clinical development are shown in Table 2 and the chemical structures of those in phase 3 trials

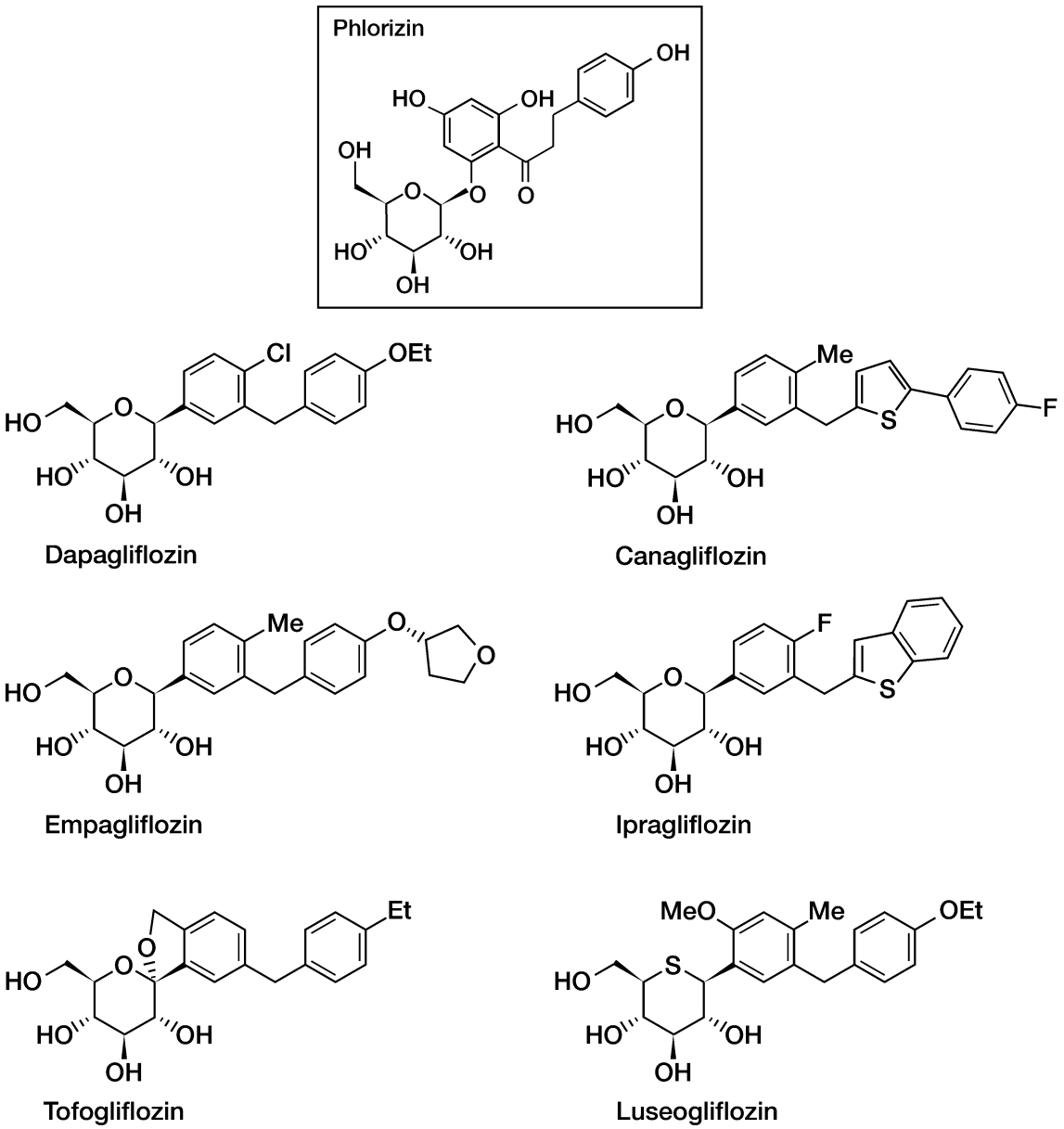

Fig. 4 SGLT2 inhibitors in late phase clinical development

are shown in Fig. 4. Dapagliflozin was approved in the European Union in 2012, and is awaiting the outcome of resubmission of an application to the US Food and Drug Administration (FDA) following a complete response letter. The FDA approved canagliflozin in March 2013 and the submission made to the European Medicines Agency (EMA) is still under consideration. Marketing applications for empagliflozin were submitted to the FDA and EMA in March 2013, while marketing applications for ipragliflozin, luseogliflozin, and tofogliflozin were also recently submitted to the Japanese regulatory body.

Dapagliflozin is the most advanced of the SGLT2 inhibitors in terms of clinical development and, thus, has the largest amount of published clinical data.

Table 2 SGLT2 inhibitors in clinical development

Compound	Sponsor	Development phase	Expected approval/launch date
Dapagliflozin	Bristol Myers Squibb, AstraZeneca	3	EMA approval given in November 2012; recent NDA resubmission to FDA
Canagliflozin	Janssen (Johnson & Johnson), Mitsubishi Tanabe	3	FDA approval given in March 2013; EMA decision awaited
Empagliflozin	Boehringer Ingelheim, Lilly	3	Applications filed with FDA (NDA) and with EMA (MAA) in March 2013
Ipragliflozin	Astellas, Kotobuki	3	Marketing approval filed with Japanese regulatory body in March 2013
Luseogliflozin	Taisho	3	Marketing approval filed with Japanese regulatory body in April 2013
Tofogliflozin	Chugai, Kowa, Sanofi	3	Marketing approval filed with Japanese regulatory body in June 2013
Ertugliflozin (PF04971729)	Pfizer, Merck & Co.	2	Not applicable
LX4211	Lexicon Pharmaceuticals	2	Not applicable
EGT0001442	Theracos	2	Not applicable

EMA European Medicines Agency, *FDA* Food and Drug Administration (United States), *MAA* marketing authorization application, *NDA* New Drug Application, *SGLT2* sodium glucose co-transporter

Publications for the other SGLT2 inhibitors are more limited and largely consist of data presented in scientific abstracts. A summary of key efficacy data from completed phase 3 trials and larger phase 2 trials using SGLT2 inhibitors developed in the US/Europe are presented in Table 3.

Dapagliflozin Overview

Dapagliflozin 1–50 mg orally once daily was evaluated as monotherapy in previously untreated patients with T2DM [58–60], or as add-on combination therapy with metformin [59, 61, 62], other oral anti-hyperglycemic agents [63–65], or insulin-based therapy [66–68]. Dapagliflozin significantly reduced HbA_{1c} and fasting plasma glucose (FPG) levels (Table 3), with longer-term extension studies (≥100 weeks) supporting maintained efficacy [61, 63, 68]. Dapagliflozin monotherapy (2.5–50 mg/day for 12 weeks) in T2DM patients resulted in the urinary excretion of 52–85 g/day glucose at the end of the study period, compared with a loss of 6 g/day with placebo or metformin [69]. Dapagliflozin also reduced body weight, with an approximate 2 kg loss versus placebo after 12 weeks [66] or 24 weeks [58, 61], 1–2 kg loss versus comparator after 24 weeks [59], and 4 kg loss versus comparator after 52 weeks [63]. Although body weight increased when dapagliflozin was co-administered with pioglitazone, the increase was smaller than that of the placebo plus pioglitazone group (0.69–1.35 kg vs. 2.99 kg, respectively) [65].

Table 3 Key efficacy data from clinical trials of SGLT2 inhibitors in development in the USA and Europe

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
Dapagliflozin														
Ferrannini 2010 [58] NCT00528372	Phase 3, 24 weeks	Drug naïve	485										Seated	
			75	Pbo	−0.23	[0.10]	−4.1	[3.9]	−0.23	[0.22]	−2.2	[0.4]	−0.9	[1.8]
			65	2.5 a.m.	−0.58	[0.11]	−15.2	[4.2]	−0.84	[0.23]	−3.3	[0.5]	−4.6	[1.8]
			64	5 a.m.	−0.77	[0.11]	−24.1	[4.3]	−1.34	[0.24]	−2.8	[0.5]	−2.3	[1.9]
			70	10 a.m.	−0.89	[0.11]	−28.8	[4.0]	−1.60	[0.22]	−3.2	[0.5]	−3.6	[1.9]
			67	2.5 p.m.	−0.83	[0.11]	−25.6	[4.1]	−1.42	[0.23]	−3.8	[0.5]	−4.0	[2.3]
			68	5 p.m.	−0.79	[0.11]	−27.3	[4.2]	−1.52	[0.23]	−3.6	[0.5]	−5.2	[1.7]
			76	10 p.m.	−0.79	[0.11]	−29.6	[4.0]	−1.64	[0.22]	−3.1	[0.4]	−2.3	[1.4]
			34	5 (HbA$_{1c}$ ≥ 10.1)	−2.88	1.41	−77.1	53.4	−4.28	2.96	−2.1	3.4	−5.7	[2.1]
			39	10 (HbA$_{1c}$ ≥ 10.1)	−2.66	1.26	−84.3	61.0	−4.68	3.39	−1.9	3.5	−2.5	[2.1]
Bailey 2010 [61] NCT00528879	Phase 3, 24 weeks	MET	546										Seated	
			137	Pbo	−0.30	(−0.44, −0.16)	−5.95	(−11.17, −0.72)	−0.33	(−0.62, −0.04)	−0.9	(−1.4, −0.4)	−0.2	[1.2]
			137	2.5	−0.67	(−0.81, −0.53)	−17.83	(−23.06, −12.43)	−0.99	(−1.28, −0.69)	−2.2	(−2.7, −1.8)	−2.1	[1.1]
			137	5	−0.70	(−0.85, −0.56)	−21.44	(−26.85, −16.22)	−1.19	(−1.49, −0.90)	−3.0	(−3.5, −2.6)	−4.3	[1.3]
			135	10	−0.84	(−0.98, −0.70)	−23.42	(−28.83, −18.02)	−1.30	(−1.60, −1.00)	−2.9	(−3.3, −2.4)	−5.1	[1.3]
Wilding 2012 [67] NCT00673231	Phase 3, 48 weeks	OADs + INS	800				Not reported							
			193	Pbo	−0.47	–	–	–	–	–	0.82	–	−1.49	(−3.55, 0.57)
			202	2.5	−0.79	–	–	–	–	–	−0.96	–	−5.30	(−7.25, −3.34)
			211	5	−0.96	–	–	–	–	–	−1.00	–	−4.33	(−6.28, −2.38)
			194	10	−1.01	–	–	–	–	–	−1.61	–	−4.09	(−6.09, −2.09)

Table 3 continued

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
Wilding 2013 [68] NCT00673231	Phase 3, 104 weeks	OADs + INS	808										Not reported	
			197	Pbo	−0.43	(−0.58, −0.28)	−18.0	(−25.8, −10.1)	−1.0	(−1.43, −0.56)	1.83	(1.05, 2.61)	–	–
			203	2.5	−0.64	(−0.78, −0.50)	−20.5	(−27.7, −13.3)	−1.14	(−1.54, −0.74)	−0.99	(−1.71, −0.27)	–	–
			212	5/10	−0.82	(−0.96, −0.68)	−34.1	(−41.3, −26.8)	−1.89	(−2.29, −1.49)	−1.03	(−1.75, −0.31)	–	–
			196	10	−0.78	(−0.92, −0.65)	−23.4	(−30.5, −16.4)	−1.30	(−1.69, −0.91)	−1.50	(−2.21, −0.78)	–	–
Nauck 2011 [63] NCT00660907	Phase 3, 52 weeks	MET												
			406	2.5–10 DAPA	−0.52	(−0.60, 0.44)	−22.34	(−25.59, −19.28)	−1.24	(−1.42, −1.07)	−3.22	(−3.56, −2.87)	−4.3	–
			408	5–20 GLIPZ	−0.52	(−0.60, 0.44)	−18.74	(−21.98, −17.66)	−1.04	(−1.22, −0.98)	1.44	(1.09, 1.78)	0.8	–
Strojek 2011 [64] NCT00680745	Phase 3, 24 weeks	GLIMP	597										Seated	
			145	Pbo	−0.13	–	−1.98	–	−0.11	–	−0.72	–	−1.2	–
			154	2.5	−0.58	–	−16.76	–	−0.93	–	−1.18	–	−4.7	–
			142	5	−0.63	–	−21.26	–	−1.18	–	−1.56	–	−4.0	–
			151	10	−0.82	–	−28.47	–	−1.58	–	−2.26	–	−5.0	–
Bolinder 2012 [62] NCT00855166	Phase 3, 24 weeks	MET	182										Seated	
			91	Pbo	−0.10	–	2.4	–	0.13	–	−0.88	(−1.43, −0.34)	0.1	–
			91	10	−0.39	–	−14.7	–	−0.82	–	−2.96	(−3.51, −2.41)	−2.7	–
Rosenstock 2012 [65] NCT00683878	Phase 3, 48 weeks	PIO											Seated	
			139	Pbo	−0.54	[0.08]	−13.1	[3.6]	−0.73	[0.20]	2.99	[0.41]	2.0	[1.2]
			141	5	−0.95	[0.08]	−22.8	[3.2]	−1.27	[0.18]	1.35	[0.38]	−1.0	[1.1]
			140	10	−1.21	[0.07]	−33.1	[3.0]	−1.84	[0.17]	0.69	[0.36]	−2.2	[1.2]

Table 3 continued

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
Henry 2012 [59] NCT00643851 NCT00859898	Phase 3, 24 weeks (each)	MET XR	–											
			201	Pbo + MET	−1.35	(−1.53, −1.18)	−33.51	(−38.92, −28.29)	−1.86	(−2.16, −1.57)	−1.29	(−1.76, −0.82)	−1.8	[0.9]
			194	5 + MET	−2.05	(−2.23, −1.88)	−61.09	(−66.49, −55.68)	−3.39	(−3.69, −3.09)	−2.66	(−3.14, −2.19)	−2.9	[0.9]
			203	5 + Pbo	−1.19	(−1.36, −1.02)	−41.98	(−47.39, −36.76)	−2.33	(−2.63, −2.04)	−2.61	(−3.07, −2.15)	−4.2	[0.9]
			208	Pbo + MET	−1.44	(−1.59, −1.29)	−34.78	(−39.82, −29.73)	−1.93	(−2.21, −1.65)	−1.36	(−1.83, −0.89)	−1.2	[1.0]
			211	10 + MET	−1.98	(−2.13, −1.83)	−60.36	(−65.23, −55.32)	−3.35	(−3.62, −3.07)	−3.33	(−3.80, −2.86)	−3.3	[0.9]
			219	10 + Pbo	−1.45	(−1.59, −1.31)	−46.49	(−51.35, −41.44)	−2.58	(−2.85, −2.30)	−2.73	(−3.19, −2.27)	−4.0	[0.9]
Canagliflozin														
Stenlof 2013 [76] NCT01081834	Phase 3, 26 weeks	Drug naïve	584											
			192	Pbo	0.14	–	9.00	–	0.5	–	−0.5	–	0.4	[0.8]
			195	100	−0.77	–	−27.03	–	−1.5	–	−2.5	–	−3.3	[0.8]
			197	300	−1.03	–	−34.23	–	−1.9	–	−3.4	–	−5.0	[0.8]
Cefalu 2013 [79] NCT00968812	Phase 3, 52 weeks	MET	1,450											
			483	100	−0.82	[0.04]	−25.2	[1.80]	−1.35	[0.1]	−3.7	[0.2]	−3.3	[0.6]
			485	300	−0.93	[0.04]	−27.0	[1.80]	−1.52	[0.1]	−4.0	[0.2]	−4.6	[0.6]
			482	GLIMP 1–8	−0.81	[0.04]	−18.0	[1.80]	−1.02	[0.1]	0.7	[0.2]	0.2	[0.6]
Schernthaner 2013 [80] NCT01137812	Phase 3, 52 weeks	MET + SU	755											
			377	300	−1.03	–	−28.7	–	−1.7	–	−2.3	–	−5.1	[0.7]
			378	SITA 100	−0.66	–	−2.2	–	−0.3	–	0.1	–	0.9	[0.7]
Wilding 2012 [78] NCT01106625	Phase 3, 26 weeks	MET + SU	469											
			156	Pbo	−0.13	[0.08]	3.60	[3.60]	0.2	[0.2]	−0.7%	[0.3]	−2.7	[1.0]
			157	100	−0.85	[0.08]	−18.02	[3.60]	−1.0	[0.2]	−2.1%	[0.3]	−4.9	[1.0]
			156	300	−1.06	[0.08]	−30.63	[3.60]	−1.7	[0.2]	−2.6%	[0.3]	−4.3	[1.0]

Table 3 continued

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
Bode 2013 [82] NCT01106651	Phase 3, 26 weeks (elderly)	AHAs	714											
			237	Pbo	−0.03	–	7.4	–	0.4	–	−0.1	–	1.1	[1.0]
			241	100	−0.60	–	−18.1	–	−1.0	–	−2.2	–	−3.5	[1.0]
			236	300	−0.73	–	−20.3	–	−1.1	–	−2.8	–	−6.8	[1.1]
Matthews 2012 [85] NCT01032629	CANVAS sub-study	INS	1,708											
			565	Pbo	Δ vs. Pbo	–	Δ vs. Pbo	–	Δ vs. Pbo	–	Δ vs. Pbo	–	Δ vs. Pbo	–
			566	100	−0.65	(−0.73, −0.56)	−22.52	(−27.93, −17.30)	−1.25	(−1.55, −0.96)	−1.9%	(−2.2, −1.6)	−2.6	(−4.1, −1.1)
			587	300	−0.73	(−0.81, −0.65)	−29.01	(−34.23, −23.60)	−1.61	(−1.90, −1.31)	−2.4%	(−2.7, −2.1)	−4.4	(−5.9, −2.9)
Forst 2013 [83] NCT01106690	Phase 3, 52 weeks	MET + PIO	275											
			N/s	100	−0.98	[0.07]	−28.8	[2.8]	−1.60	[0.16]	−2.9%	[0.5]	−3.5	[1.1]
			N/s	300	−1.07	[0.07]	−33.4	[2.9]	−1.85	[0.16]	−4.0%	[0.5]	−4.3	[1.1]
Lavalle González 2013 [108] NCT01106677	Phase 3, 52 weeks	MET	–											
			368	100	−0.73	[0.05]	−26.2	[1.8]	−1.45	[0.10]	−3.8%	[0.2]	−3.5	[0.6]
			367	300	−0.88	[0.05]	−35.2	[1.8]	−1.95	[0.10]	−4.2%	[0.2]	−4.7	[0.6]
			366	SITA 100 mg	−0.73	[0.05]	−17.7	[1.8]	−0.98	[0.10]	−1.3%	[0.2]	−0.7	[0.6]
Empagliflozin														
Ferrannini 2013 [90] NCT00789035	Phase 2b, 12 weeks	Drug naïve	406										Not reported	
			82	Pbo	0.1	(−0.09, 0.27)	0.72	(−6.31, −7.75)	0.04	(−0.35, 0.43)	−0.75	(−1.26, −0.23)	–	–
			81	5	−0.4	(−0.61, −0.25)	−23.24	(−30.45, −16.22)	−1.29	(−1.69, −0.90)	−1.81	(−2.32, −1.29)	–	–
			81	10	−0.5	(−0.66, −0.30)	−29.00	(−36.04, −21.80)	−1.61	(−2.00, −1.21)	−2.33	(−2.84, −1.82)	–	–

Table 3 continued

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
			82	25	−0.6	(−0.81, −0.45)	−30.99	(−38.20, −24.14)	−1.72	(−2.12, −1.34)	−2.03	(−2.54, −1.52)	–	–
			80	MET	−0.7	(−0.92, −0.57)	−29.91	(−38.02, −21.80)	−1.66	(−2.11, −1.21)	−1.32	(−1.84, −0.81)	–	–
Rosenstock 2013 [92] NCT00749190	Phase 2b, 12 weeks	MET	495											
			71	Pbo	0.15	(−0.00, 0.30)	5	(−2, 12)	0.28	(−0.11, 0.67)	-1.2	(−1.8, −0.5)	−2.23	14.84
			71	1	−0.09	(−0.24, 0.07)	−2	(−9, 5)	−0.11	(−0.50, 0.28)	−1.6	(−2.2, −0.9)	−2.17	12.11
			71	5	−0.23	(−0.39, −0.08)	−16	(−23, −9)	−0.89	(−1.28, −0.50)	−2.3	(−2.9, −1.7)	−3.03	14.58
			71	10	−0.56	(−0.71, −0.41)	−22	(−29, −16)	−1.22	(−1.61, −0.89)	−2.7	(−3.4, −2.1)	−4.39	13.09
			70	25	−0.55	(−0.70, −0.40)	−27	(−34, −20)	−1.50	(−1.90, −1.11)	−2.6	(−3.2, −2.0)	−8.51	12.82
			70	50	−0.49	(−0.64, −0.33)	−28	(−35, −21)	−1.55	(−1.94, −1.17)	−2.9	(−3.5, −2.2)	−3.16	15.26
			71	SITA 100	−0.45	(−0.65, −0.25)	−13	(−22, −3)	−0.72	(−1.22, −0.17)	−0.8	(−1.5, −0.2)	−1.79	11.65
Woerle 2012 [93] NCT00881530	Phase 2b, 78-week open-label extension	Monotherapy or MET	–											
			80	10	−0.34	(−0.54, −0.14)	−30.4	(−37.1, −23.7)	−1.69	(−2.06, −1.32)	−2.24	(−3.12, −1.36)	0.120	(−3.18, 3.42)
			88	25	−0.47	(−0.66, −0.27)	−27.8	(−34.3, −21.3)	−1.54	(−1.90, −1.82)	−2.61	(−3.46, −1.77)	−1.66	(−4.87, 1.56)
			56	MET	−0.56	(−0.79, −0.33)	−26.0	(−33.5, −18.4)	−1.44	(−1.86, −1.02)	−1.28	(−2.30, −0.26)	1.96	(−1.77, 5.70)
			137	10 + MET	−0.34	(−0.47, −0.21)	−21.3	(−26.4, −16.2)	−1.18	(−1.47, −0.90)	−3.14	(−3.89, −2.38)	−3.28	(−5.66, −0.91)
			139	25 + MET	−0.63	(−0.76, −0.50)	−31.8	(−36.8, −26.7)	−1.76	(−2.04, −1.48)	−4.03	(−4.77, −3.29)	−2.97	(−5.30, −0.64)
			56	SITA + MET	−0.40	(−0.60, −0.20)	−15.6	(−23.6, −7.62)	−0.87	(−1.31, −0.42)	−0.41	(−1.49, 0.67)	1.83	(−1.50, 5.15)

Table 3 continued

Reference and NCT ID	Study details	Background therapy	*n*	SGLT2i dose (mg/day)	ΔHbA$_{1c}$ from baseline (%)		ΔFPG from baseline (mg/dL)		ΔFPG from baseline (mmol/L)		ΔBody weight from baseline (kg)		ΔSBP from baseline (mmHg)	
					Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]	Mean	SD or (95% CI) or [SEM]
Häring 2013 [94] NCT01159600	Phase 3, 24 weeks	MET + SU	666											
			225	Pbo	−0.17	[0.05]	5.52	[1.96]	0.31	[0.11]	−0.39	[0.15]	−1.4	[0.7]
			225	10	−0.82	[0.05]	−23.30	[1.95]	−1.29	[0.11]	−2.16	[0.15]	−4.1	[0.7]
			216	25	−0.77	[0.05]	−23.27	[2.00]	−1.29	[0.11]	−2.39	[0.16]	−3.5	[0.7]
Roden 2013 [91] NCT01177813	Phase 3, 24 weeks	Drug naïve	899											
			228	Pbo	0.08	(−0.03, 0.18)	11.7	(7.92, 15.7)	0.65	(0.44, 0.87)	−0.33	(−0.67, 0.00)	−0.3	(−1.9, 1.3)
			224	10	−0.66	(−0.76, −0.56)	−19.5	(−23.2, −15.7)	−1.08	(−1.29, −0.87)	−2.26	(−2.60, −1.92)	−2.9	(−4.5, −1.3)
			224	25	−0.78	(−0.88, −0.67)	−24.5	(−28.3, −20.5)	−1.36	(−1.57, −1.14)	−2.48	(−2.82, −2.14)	−3.7	(−5.3, −2.1)
			223	SITA	−0.66	(−0.76, −0.56)	−6.85	(−10.8, −3.06)	−0.38	(−0.60, −0.17)	0.18	(−0.16, 0.52)	0.5	(−1.1, 2.1)
Häring 2013 [95] NCT01159600	Phase 3, 24 weeks	MET	637											
			207	Pbo	−0.13	[0.05]	6.38	[1.77]	0.35	[0.10]	−0.45	[0.17]	−0.4	[0.7]
			217	10	−0.70	[0.05]	−20.04	[1.73]	−1.11	[0.10]	−2.08	[0.17]	−4.5	[0.7]
			213	25	−0.77	[0.05]	−22.28	[1.75]	−1.24	[0.10]	−2.46	[0.17]	−5.2	[0.7]
Rosenstock 2013 [97] NCT01011868	Phase 2b, 78 weeks	INS	494											
			170	Pbo	−0.02	[0.09]	3	[3]	0.17	[0.17]	0.7	[0.5]	0.1	[1.0]
			169	10	−0.48	[0.08]	−10	[3]	−0.55	[0.17]	−2.2	[0.5]	−4.1	[1.0]
			155	25	−0.64	[0.09]	−15	[3]	−0.83	[0.17]	−2.0	[0.5]	−2.4	[1.1]
Kovacs 2013 [96] NCT01210001	Phase 3, 24 weeks	PIO ± MET	498											
			165	Pbo	−0.11	[0.07]	6.47	[2.61]	0.36	[0.14]	0.34	[0.21]	0.7	[0.9]
			165	10	−0.59	[0.07]	−17.00	[2.63]	−0.94	[0.15]	−1.62	[0.21]	−3.1	[0.9]
			168	25	−0.72	[0.07]	−21.99	[2.59]	−1.22	[0.14]	−1.47	[0.21]	−4.0	[0.8]

Δ Change (in), *AHA* antihyperglycemic agent, *CANVAS* canagliflozin cardiovascular assessment study; *CI* confidence interval, *DAPA* dapagliflozin, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *FPG* fasting plasma glucose, *GLIMP* glimepiride, *GLIPZ* glipizide, *HbA$_{1c}$* glycated hemoglobin, *INS* insulin, *MET* metformin, *NCT ID* National Clinical Trials (US) identification (number), *N/s* not stated, *OAD* oral antidiabetes drug, *Pbo* placebo, *PIO* pioglitazone, *SBP* systolic blood pressure, *SD* standard deviation, *SEM* standard error of the mean, *SGLT2* sodium glucose co-transporter type 2, *SGLT2i* sodium glucose co-transporter type 2 inhibitor, *SITA* sitagliptin, *SU* sulfonylurea, *XR* extended release

In terms of safety and tolerability, dapagliflozin was associated with a small increase in the incidence of minor hypoglycemic events (0–10.0%) compared with the control group (placebo/comparator, 0.7–9.0%), although this was not statistically significant [59, 63–65]. A trial using dapagliflozin in combination with insulin (with/without ≤2 oral anti-hyperglycemic agents) reported slightly higher rates of hypoglycemic events (dapagliflozin [total groups] 56.6% vs. placebo 51.8%), but major hypoglycemic episodes were comparable between groups (dapagliflozin [total groups] 1.3% vs. placebo 1.0%) [67]. In another trial report, patients receiving dapagliflozin added to metformin experienced significantly fewer hypoglycemic events (3.5%) compared with glipizide plus metformin (40.8%; $P < 0.0001$) [63]. A safety analysis of 12 pooled placebo-controlled trials ($n > 4{,}500$) reported that hypoglycemia was more common with dapagliflozin than with placebo (10.7–16.3% vs. 8.0%, respectively), and that imbalances in individual studies were only observed when dapagliflozin was combined with a sulfonylurea or insulin [70, 71].

Dapagliflozin reduced systolic blood pressure (SBP) by up to 5 mmHg, with no significant increase in heart rate or occurrence of orthostatic hypotension [58, 61–65, 67].

Rates of hypotension, dehydration, and hypovolemia were similar in dapagliflozin groups (1–2%) to those in the placebo/comparator groups (0–1%) [58, 67, 70]. Dapagliflozin treatment was not associated with an increased risk of acute renal toxicity or deterioration of renal function [72]. The dapagliflozin Summary of Product Characteristics advises against its use in patients receiving loop diuretics or who are volume depleted, and recommends appropriate monitoring if volume depletion is likely to occur [73].

Symptoms suggestive of genital infection, such as cutaneous fungal infections, and lower urinary tract infection (UTI) were common adverse events with dapagliflozin and were reported more frequently compared with placebo/comparator. Genital infection occurred in 2–13% of patients receiving dapagliflozin compared with 0–5% of those receiving placebo/comparator, with women affected more commonly than men [58, 61–65, 67]. Most cases were not severe and responded well to standard therapy. Lower UTIs also occurred more frequently with dapagliflozin (3.0–12.5%) than with placebo/comparator (0–9.0%) [58, 61–65, 67]. None of these events were serious, and all cases resolved with standard antibiotic therapy. The pooled safety analysis ($n = 4{,}545$) reported that genital infections and UTIs were more common with dapagliflozin than placebo, and between-group differences were less marked for UTIs (genital infection: 4.1–5.7% dapagliflozin vs. 0.9% placebo; UTIs: 3.6–5.7% dapagliflozin vs. 3.7% placebo) [74, 75].

Canagliflozin Overview

Canagliflozin 50–300 mg once daily and 300 mg twice daily was evaluated as monotherapy in previously untreated patients with T2DM [76], or as add-on combination therapy with metformin [77–79], other oral anti-hyperglycemic agents [80–83], or insulin-based therapy [84, 85]. Canagliflozin significantly reduced HbA_{1c} and FPG levels from baseline in studies of 12–52 weeks' duration, as shown in Table 3, and modestly reduced body weight (up to 2.9 kg compared with control groups) [76, 77, 84]. Reductions in SBP with canagliflozin, when used as monotherapy and in combination,

ranged from −0.8 to −6.8 mmHg [76, 78, 79, 82]. A recent pooled analysis of six phase 3 studies ($n = 4,158$; treatment duration not stated) revealed that canagliflozin produced modest reductions in SBP (−3.3 and −4.5 mmHg for 100 and 300 mg, respectively) relative to placebo [86].

The overall incidence of hypoglycemia was low and rates were similar across canagliflozin (2–6%), placebo (2–3%), and comparator (5%) groups [76, 77, 84]; however, canagliflozin groups (4.9–5.6%) reported lower rates of hypoglycemia compared with glimepiride (34.2%) [79]. Prescribing information for canagliflozin states that rates of hypoglycemia were higher when canagliflozin was administered with insulin or sulfonylureas [87]. Genital mycotic infections were higher with canagliflozin (3–15%) versus placebo/comparator (0–6%); these events were mild to moderate in severity and none led to study discontinuation [76, 77, 79–81]. As with dapagliflozin, genital mycotic infections were more common in women. Genital mycotic infections with canagliflozin were also assessed in a pooled analysis of four 26-week phase 3 studies ($n = 2,313$) [88]. Genital mycotic infections were more common in canagliflozin groups than placebo, occurring in 11% of women and 4% of men, versus 3% and 1% in the placebo groups, respectively. These events were generally mild or moderate in severity and were managed with standard treatments; in addition, few such events led to study discontinuation [10 cases, canagliflozin groups (6 cases 100 mg, 4 cases 300 mg)]. In a larger data set of eight phase 3 studies ($n = 9,439$) with longer mean exposure (68 weeks of canagliflozin, 64 weeks of placebo), the rate of male genital mycotic infection was higher (8% canagliflozin, 2% placebo) and was more common in uncircumcised men (11% vs. 3% in circumcised men) [88]. Reported UTI events showed a similar trend. Higher rates of UTI occurred in the canagliflozin groups (2.3–12.0%) versus the placebo/comparator groups (2.1–8.0%); the events were mild to moderate in severity and responded to standard treatment [76–82]. The pooled analysis of four 26-week phase 3 studies ($n = 2,313$) stated that UTIs occurred in 5.1% of patients receiving canagliflozin (100 mg plus 300 mg groups) and in 4.0% of those receiving placebo [89].

Empagliflozin Overview

Empagliflozin 1–50 mg once daily was evaluated as monotherapy in previously untreated patients with T2DM [90, 91], or as add-on combination therapy with metformin [92–95], other oral anti-hyperglycemic agents [96], or insulin-based therapy [97]. As shown in Table 3, empagliflozin significantly lowered HbA_{1c}, reduced FPG, and decreased body weight (up to 2 kg vs. placebo). Empagliflozin 10 and 25 mg produced placebo-corrected reductions in SBP of approximately 2–5 mmHg after 24 weeks [91, 94, 95].

The rate of hypoglycemia was low with empagliflozin monotherapy (0.4–1.8%), and was comparable to placebo (0.4%) and comparator (sitagliptin monotherapy 0.4%, metformin monotherapy 7.1%) [91, 93]. The rate of hypoglycemia was higher when empagliflozin was given in combination therapy, particularly in regimens containing sulfonylurea or insulin (empagliflozin + metformin 2.4–3.6% vs. sitagliptin + metformin 5.4% [93]; empagliflozin + metformin 1.4–1.8% vs. placebo + metformin 0.5% [95]; empagliflozin + metformin + sulfonylurea 11.5–16.1% vs. placebo + metformin + sulfonylurea 8.4% [94]; and

empagliflozin + insulin 36.1% vs. placebo + insulin 35.3% [97]).

UTI events after 24 weeks were reported in 8.3–10.3% of empagliflozin patients versus 8.0% of those on placebo, and the rates of genital infection events were 2.3–2.7% for empagliflozin and 0.9% for placebo [94]. A pooled analysis of safety data from four 24-week phase 3 trials ($n = 2,477$) examined the effect of empagliflozin on UTIs and genital infections [98]. The percentage of patients with events consistent with a UTI was similar across all groups (7.5% and 9.3% for empagliflozin 10 and 25 mg, respectively, vs. 8.2% for placebo); however, more patients receiving empagliflozin reported events consistent with genital infection (4.2% and 3.6% for empagliflozin 10 and 25 mg, respectively, vs. 0.7% for placebo) [98]. Both types of event were more common in women than in men, and were more common in patients with a history of UTI or genital infection [98]. Nevertheless, of those who reported events consistent with UTI or genital infection, most experienced only one episode; the episodes were generally mild in severity, and very few led to study discontinuation [4 cases of UTI (placebo: 1 case; empagliflozin: 2 cases, 10 mg and 1 case, 25 mg); 3 cases of genital infection (empagliflozin: 1 case, 10 mg; 2 cases, 25 mg)] [98].

Ipragliflozin Overview

Ipragliflozin is currently being developed in Japan (Table 2). Ipragliflozin 50–300 mg once daily was evaluated as monotherapy in previously untreated patients with T2DM [99, 100], or as add-on combination therapy with metformin [101] and other oral anti-hyperglycemic agents [102], and showed significant decreases in HbA_{1c} and FPG versus placebo over periods of 12–24 weeks. Ipragliflozin monotherapy produced a placebo-corrected weight loss of −1.47 kg after 16 weeks [100]. After 12–16 weeks, SBP was reduced by −3.2 to −4.3 mmHg with ipragliflozin compared with placebo [100, 101].

Hypoglycemia was reported in 1.0–5.9% of ipragliflozin dose groups versus 0–3.0% in the placebo/comparator groups [101, 102]. During a 12-week study, UTIs were infrequent and were reported in all treatment groups (placebo 6.1% vs. ipragliflozin 1.4–6.9%) [101]. Genital infections occurred with greater frequency in the ipragliflozin versus placebo groups (3.0–4.3% vs. 1.5%, respectively) [101].

Other SGLT2 inhibitors in clinical development had few publications available at the time of this review.

Other Issues

Currently available information on outcomes such as stroke, heart attack, and other vascular complications is limited, but larger studies with cardiovascular end points are ongoing and will provide data in 2017 onwards [103, 104]. The Canagliflozin Cardiovascular Assessment Study (CANVAS; NCT01032629) has recruited more than 4,000 patients with T2DM and elevated risk of CVD, while the Empagliflozin Cardiovascular Outcome Event Trial (NCT01131676) has recruited an estimated 7,000 patients to date and the Dapagliflozin Effect on Cardiovascular Events (NCT01730534) study has recently begun recruitment (for further details of these trials see ClinicalTrials.gov).

The potential relationship between SGLT2 inhibitors and neoplasia is also being investigated. Although the overall proportion of patients with malignant or unspecified tumors was similar between those treated with dapagliflozin (1.43%) and placebo/comparator (1.30%), breast and bladder cancer events were

more common with dapagliflozin [71]. The FDA regulatory submission for dapagliflozin stated that 9 cases of breast cancer were reported out of 4,287 patients receiving dapagliflozin compared with no cases out of 1,941 patients in the placebo/comparator group, and 7 cases of bladder cancer were reported out of 4,310 patients receiving dapagliflozin compared with no cases out of 1,962 patients in the placebo/comparator group [105]. Hematuria was documented before exposure to dapagliflozin in 4 of the patients later found to have bladder cancer, and the patients with breast cancer had received dapagliflozin for <1 year (2/9 cases were diagnosed within 6 weeks of dapagliflozin treatment initiation). Whether these are chance findings or clinically relevant concerns requires further study.

The incidence of breast or bladder tumor events was low for canagliflozin and occurred at a similar rate across treatment groups (breast cancer 0.41% vs. 0.39% and bladder cancer 0.07% vs. 0.11% for canagliflozin vs. non-canagliflozin groups, respectively) [106]. No data on cancer cases from other SGLT2 inhibitor studies are currently available.

This overview was limited to major data from late phase and/or large trials of those compounds that are the most advanced along the drug development pathway. Due to the emerging nature of this field, full text journal publications are limited for many of these agents.

CONCLUSIONS

SGLT2 inhibitors represent a therapeutic approach in the treatment of T2DM that is independent of insulin secretion and activity. Clinical trials have supported the efficacy of SGLT2 inhibitors as add-on therapy with metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin. SGLT2 inhibitors may also have a role as monotherapy in patients who are intolerant to metformin (e.g., due to gastrointestinal side effects), as well as to potentially facilitate the use of triple combinations of oral anti-hyperglycemic agents (e.g., metformin + DPP-4 inhibitor + SGLT2 inhibitor).

SGLT2 inhibitors improve glycemic control in T2DM, reducing HbA_{1c} and FPG levels, and are somewhat effective in reducing body weight and blood pressure, which are also CVD treatment targets for many patients with T2DM. SGLT2 inhibitors are generally well tolerated with few serious adverse events reported to date. When evaluated versus comparator groups, the hypoglycemic episodes associated with SGLT2 inhibitors were mostly mild in severity and not statistically significant. Among the more common adverse events of these agents is an increased risk of genital infections, which appears to be more common in women.

Some data regarding SGLT2 inhibitors are lacking. For example, little data exist on the use of SGLT2 inhibitors in debilitated older patients (especially those with central nervous system dysfunction, decreased cognition, and/or impaired thirst mechanisms) who may be at risk of volume depletion, hypotension, and electrolyte disturbances. Additional studies of interest would also include patients with varying degrees of renal impairment, given that the action of these drugs depends upon mechanisms involving glomerular filtration rate and renal function, and data from several such studies have been published or presented at congresses [72, 81, 107].

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