DAPAGLIFLOZIN: NEWER MOLECULE FOR TREATMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT
Type 2 diabetes mellitus is a common chronic disease that causes significant morbidity and mortality worldwide. Diabetes results from a combination of increased hepatic glucose production, decreased insulin secretion from beta cells, and insulin resistance in the peripheral tissues. Currently available antidiabetic agents work by different mechanisms to lower blood glucose levels. Available treatments (such as metformin, sulfonylureas, glitazones, and insulin) have proven unsatisfactory in producing a long-lasting impact on glycemic control. In addition, most of these treatments have undesirable side effects such as weight gain and hypoglycemia. As a result, exploring new treatment targets and new therapies is mandatory in order to treat this condition. Sodium dependent glucose cotransporters couple the transport of glucose against a concentration gradient with the simultaneous transport of Na+ down a concentration gradient. The sodium-dependent glucose cotransporter pathway plays an important pathological role in the Type 2 diabetes mellitus, and treatments targeting the system have recently become available. Dapagliflozin is a potent and specific inhibitor of sodium-dependent glucose cotransporter. Current data suggests that dapagliflozin as monotherapy or in combination with metformin results in significant reductions in fasting and postprandial plasma glucose and glycosylated hemoglobin level. Dapagliflozin is well tolerated and does not increase hypoglycemia compared with the placebo, and use of dapagliflozin is associated mainly with weight loss. Dapagliflozin, a sodium-dependent glucose cotransporter inhibitor, offer a novel treatment option for patients with type 2 diabetes mellitus.

KEY WORDS: Type 2 diabetes mellitus, sodium dependent glucose cotransporter inhibitors, dapagliflozin, metformin, hypoglycemia.

INTRODUCTION
As early as the 1930s, it was recognized by Himsworth that two types of diabetes mellitus exist. One was shown to be attributable to an insufficiency of insulin (type 1); the other to resistance to the action of insulin (type 2). Nevertheless, until recently, thinking with regard to these two disparate types of diabetes has tended to consider them as one1. Type 2 diabetes mellitus (T2DM) is the most common endocrine disorder worldwide2, characterized by fasting and postprandial hyperglycemia and relative insulin insufficiency. If left untreated, then hyperglycemia may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and atherosclerosis and is associated with co morbidities, such as obesity, hypertension, hyperlipidemia (increased VLDL, triglycerides and decreased HDL cholesterol), and cardiovascular disease, which taken together, comprise the ‘Metabolic Syndrome’3. This disease causes significant morbidity and mortality at considerable expense to patients, their families and society4. In 2007, type 2 diabetes represents a major public health issue all over the world, becoming a “diabetes epidemic” as stated by Zimmet. A few years ago, the concern of the “diabetes epidemic” was restricted...
to the US while the other parts of the world were not considered as threatened. Unfortunately, the picture has moved and nowadays no country escapes the diabetes invasion. According to International Diabetes Federation (IDF) the enormity of the T2DM epidemic, disease now affects a staggering 246 million people worldwide, with 46% of all those affected in the 40-59 age group and the total number of people living with diabetes will skyrocket to 380 million within 20 years if nothing is done. There are two primary underlying causes associated with type 2 diabetes are the body does not produce enough insulin (insulin deficiency), and the cells ignore the insulin (insulin resistance). Symptoms of T2DM develop gradually, and their onset is not as sudden as in type I diabetes. Symptoms may include fatigue, frequent urination, increased thirst and hunger, weight loss, blurred vision, and slow healing of wounds or sores.

Type 2 diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity and certain ethnicities. People with type 2 diabetes often are characterized with insulin resistance, abdominal obesity, a sedentary lifestyle, having low HDL-C cholesterol levels and high triglyceride levels and hypertension.

The kidneys play a key role in the overall regulation of blood glucose levels in the body. Normally, in healthy individuals, the kidneys filter a large volume of glucose and actively reabsorb virtually all of it. In patients with type 2 diabetes that have hyperglycemia, a greater amount of glucose is filtered and reabsorbed by the kidneys despite the fact that this perpetuates the hyperglycemia. Over time, the factors that contribute to sustained hyperglycemia lead to glucotoxicity, which worsens insulin resistance and contributes to dysfunction in the beta cells of the pancreas. In this way, hyperglycemia appears to perpetuate a vicious cycle of deleterious effects that exacerbate type 2 diabetes.

The pathogenesis of type 2 diabetes mellitus is multifactorial and complex, resulting from insulin resistance in target tissues and impairment of pancreatic insulin secretion and unrestrained hepatic glucose production. The natural history of diabetes usually begins with obesity leading to insulin resistance. Insulin resistance in turn promotes a state of compensatory hyperinsulinemia that leads to other adverse sequelae. Once hyperglycemia develops in the insulin-resistant patient, increased mobilization of fatty acids occurs, glucose metabolism decreases, insulin secretion is impaired, and insulin resistance becomes even more pronounced. Initially, normoglycemia is maintained because of compensatory increase in insulin secretion by the β-cell. Ultimately insulin secretion and insulin concentration fall leading to increased hepatic glucose production and overt diabetes. β-cell function continues to decline in the presence of continued insulin resistance making treatment complex and achievement of therapeutic targets difficult. Hence, the failure of β-cells to secrete sufficient insulin to overcome insulin resistant (IR) (i.e., β-cell dysfunction) is the crucial step in the development and progression of T2DM. In addition to β-cell dysfunction, patients with T2DM have α-cell dysfunction, which manifests as elevated glucagon secretion in the presence of hyperglycemia. Based on the current understanding of the pathophysiology of T2DM, multiple pharmacological and nonpharmacological interventions have been developed over the past five decades to improve glycemic control and slow disease progression. However, gradual loss in drug efficacy over time due to progressive deterioration in β-cell function is the main limitation as most of the observed initial improvements in glycemic control are not sustained.

Furthermore, most of these treatments have undesired side effects: sulfonylureas (SUs) increase insulin secretion, but are associated with hypoglycemia and weight gain. Metformin reduces hepatic glucose output, with no weight gain, and is not associated with hypoglycemia, but has a relatively high frequency of gastrointestinal side effects. Thiazolidinediones (TZDs) improve β-cell function and reduce IR, but are associated with weight gain and can cause peripheral edema; meglitinides improve insulin secretion from β-cells, but increases the incidence of hypoglycemia and weight gain compared with metformin. Finally, insulin therapy produces sustainable glycosylated hemoglobin A1c (HbA1c) reductions and might improve β-cell function, but causes hypoglycemia and weight gain. Hence, interventions that can slow and/or reverse β-cell decline, which result in weight loss and do not result in hypoglycemia, might be expected to have a significant sustained impact in patients with T2DM.

The development of alternative agents acting by novel mechanisms has become necessary in order to control glucose levels in patients with progressing hyperglycemia. Some emerging small molecules primarily lower blood glucose levels by modulating targets that affect glucose metabolism or by regulating glucose homeostasis (AMP activated protein kinase). One such novel mechanism by which
blood glucose levels could be lowered is by removing glucose from the bloodstream via inhibition of the sodium glucose co-transporter (SGLT)\(^1\). Thus, SGLTs inhibitors-based therapies are a new class of antidiabetic medication that may address some of the above mentioned shortfalls of current treatments\(^9\). Dapagliflozin is a newer SGLT inhibitor. The major advantage of dapagliflozin over the other antidiabetic agents is to improvement in both fasting and postprandial hyperglycaemia without increasing insulin secretion or causing weight gain, hypoglycaemia, gastrointestinal side effects or fluid retention.

**TREATMENT OF T2DM WITH SODIUM GLUCOSE CO TRANSPORTER**

Sodium-glucose cotransporter 2 (SGLT\(_2\)) inhibitors represent a new strategy in the treatment of diabetes by inhibiting glucose reabsorption in kidneys, thereby prompting glucose urinary excretion\(^11,12\). Concentration gradient across the cell membrane drives the entry of glucose into the cell via diffusion. Diffusion reaches equilibrium and stops as the inner and outer concentrations equalize. If the cell’s energy demand requires additional glucose, glucose transporter units (GLUT) are mobilized. At present, there are 13 types of known GLUTs. Some GLUTs, such as GLUT4 in muscle, require insulin to mediate transmembrane glucose transport. Others, such as GLUT1 in brain, accomplish glucose transport without the aid of insulin. As for intestinal cells and renal cells, particularly the proximal tubule cells of the kidney, glucose is transported via SGLT. The kidney filters 160 g glucose daily, with 90% reabsorbed by SGLT\(_2\) and 10% by SGLT\(_1\) in the renal tubules\(^13\). At present, there are six types of known SGLTs. SGLT\(_1\) and SGLT\(_2\) have been more extensively studied. SGLT\(_1\) is particularly abundant in the cells and membranes of the renal proximal tubule at the S\(_2\) site. SGLT\(_1\) has a stronger affinity for glucose but less transporting capacity than SGLT\(_2\). It is therefore unlikely to become a target for new drug development. SGLT\(_2\) is found in the proximal tubule membranes at the S\(_1\) site. It has lower affinity but greater capacity for transporting glucose. About 90% of glucose reabsorbed in the proximal tubule is mediated by SGLT\(_2\), and the remaining 10% is by SGLT\(_1\)\(^14,15\). The regulatory mechanisms of SGLT\(_2\) are still under investigation but according to Lee et al., it appears that the activity of renal SGLT can be regulated by hyperglycemia through the ROS-NF-k (reactive oxygen species-nuclear factor-k) pathways, as well as being inhibited by angiotensin II (ANGII) and epidermal growth factor (EGF). Hypothetically, high glucose levels activate protein kinase C (PKC), which induces the formation of ROS that subsequently stimulate the nuclear translocation of NF-k. PKC also induces activation of Ca\(^{2+}\)-dependent cytotoxic phospholipase A\(_2\) (cPLA\(_2\)), which leads to the release of arachidonic acids (AA). ANGII and EGF work through a tyrosine kinase (TK), protein kinase C, mitogen activated protein kinase (MAPK)-cPLA\(_2\) signal transduction cascade, which results in the release of AA and the subsequence downregulation in expression of SGLT\(_2\). Due to inhibition of SGLT\(_2\), glucose reabsorption from the renal filtrate is reduced and the bulk of the glucose appears in the urine. Therefore, SGLT\(_2\) is a potential drug target for the treatment of diabetes mellitus\(^12,14\).

**DAPAGLIFLOZIN**

The selective sodium glucose cotransporter 2 inhibitor is a new class of agent. The sodium glucose cotransporter type 2 (SGLT\(_2\)) located in the plasma membrane of cells lining the proximal tubule mediates the majority of renal glucose reabsorption from the tubular fluid. Blood glucose is continuously filtered by the renal glomeruli and then reabsorbed in the renal proximal tubules by SGLT\(_2\), and to a lesser extent SGLT\(_1\), preventing the loss of glucose in the urine. Competitive inhibitors of SGLT\(_2\) provoke renal excretion of glucose, potentially lowering elevated blood glucose levels in patients with diabetes. Dapagliflozin is the first in a new class of oral selective sodium-glucose cotransporter 2 (SGLT\(_2\)) inhibitors designed for treating type 2 diabetes\(^9\). These agents are expected to improve plasma glucose levels and decrease body weight in patients with type 2 diabetes without causing hypoglycemia. The selectivity of dapagliflozin for SGLT\(_2\) allows for decreased renal reabsorption of glucose without a discernable effect on the function of SGLT\(_1\) in the small intestines; thus, gastrointestinal adverse events (AEs) are theoretically minimized with this agent\(^11\). Figure 1 clearly represents the mechanism of action of dapaglifazone.

**CHEMISTRY, SYNTHESIS and SAR**

Dapagliflozin (Fig. 2), which was known earlier as BMS 512148 (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl) tetrahydro-2H pyran-,4,5-triol), is the SGLT2 inhibitor\(^12\). Figure 2 represents chemical structure of dapagliflozin.
The synthesis of Caryl glucoside compounds containing a direct carbon-carbon bond between the glucose and aglycone moieties culminated in the discovery of dapagliflozin. Caryl glucosides are more metabolically stable than O-glucosides (e.g., phlorizin) because they are resistant to degradation by intestinal beta-glucosidases. A SAR evaluation of Caryl glucosides indicated that meta-substituted diarylmethanes, such as dapagliflozin, were preferred SGLT2 ligands compared with their biphenyl or 1,2-diarylmethane equivalents.

Dapagliflozin was synthesized via C-arylation of 2,3,4,6-tetra-O-trimethylsilyl-1-d-glucolactone with a benzophenone derivative. Commercially available glucolactone was silylated with trimethylsilyl chloride in N-methylmorpholine and tetrahydrofuran (THF) to produce the persilylated glucolactone (99% yield). The starting benzophenone derivative, 5-bromo-2-chloro-4'-ethoxybenzophenone, was prepared via Friedel Crafts acylation of phenetole with 5-bromo-2-chlorobenzoyl chloride under standard conditions. The benzophenone was reduced with triethylsilane and boron trifluoride. The observed oral plasma clearance was 4.9 mL/min/kg. The amount of total radioactivity recovered in urine was 1.6%. The unchanged dapagliflozin recovered in urine was 1.6%. The rate of clearance was 5.6 mL/min and GFR+fu was 10.8 mL/min.

**PHARMACOKINETICS**

Dapagliflozin is predominantly metabolized to an inactive metabolite by UGT1A9 (UDP glycosyltransferase 1 family polypeptide A9), although the compound can be catabolized with a low turnover by multiple cytochrome P450 (CYP) enzymes, including CYP1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6 and CYP3A4. Dapagliflozin displayed a selectivity of approximately 1200-fold for hSGLT2 compared with hSGLT1 (EC50 = 1.1 nM versus 1.4 microM), whereas selectivity for rSGLT2 was 200-fold greater than for rSGLT1. Dapagliflozin has a half-life of approximately 17 h and almost a maximal SGLT2 blockade for at least 24 h following doses of 25–50 mg, making this suitable for once-daily dosing. It causes dose-dependent glycosuria in healthy subjects and patients with T2DM.

**PRECLINICAL DEVELOPMENT**

Dapagliflozin demonstrated an EC50 value of 22 nM against SGLT2 with a selectivity of 600-fold against hSGLT1. In a study of in vivo SGLTs inhibitory activity, healthy Sprague-Dawley rats (food-restricted for 5 h post-dose) were orally administered dapagliflozin (0.1, 1 and 10 mg/kg), resulted in significant dose-dependent increases in glucosuria and urine volume. Specifically, the 1-mg/kg dose produced a 400-fold increase in glucosuria (0.0001) and a 3-fold increase in urine volume (0.0005) compared with vehicle. Treatment with dapagliflozin resulted in 24-h renal glucose losses of 550, 1100 and 1900 mg/200 g of body weight at doses of 0.1, 1 and 10 mg/kg, respectively. In one study, single dose of dapagliflozin 50mg orally administered. Dapagliflozin was rapidly absorbed after oral administration of the 50 mg dose with maximum plasma concentrations (Cmax) attained within 1 hour after administration in a fasted state. The mean terminal half-life (T1/2) value for dapagliflozin was 13.8 h. The observed oral plasma clearance was 4.9 mL/min/kg. The amount of total radioactivity recovered in the urine was 75.2%; the amount of unchanged dapagliflozin recovered in urine was 1.6%. The rate of clearance was 5.6 mL/min and GFR+fu was 10.8 mL/min.

**CLINICAL DEVELOPMENT**

**Phase I Trials**

The pharmacokinetic and Pharmacodynamic properties of dapagliflozin were investigated in randomized, double-blind, placebo-controlled, two-period, sequential, single-ascending-dose clinical trial, healthy individuals were assigned to either single-dose dapagliflozin (2.5, 5, 10, 20, 50, 100, 250 or 500 mg po, after a 10-h fast [n = 6 per dose level]) or placebo (n = 2 per dose level). Glucosuria was dose-dependent and, at doses of 20- to 50-mg, a near-maximum rate of glucose excretion (approximately 3 g/h) was sustained for a minimum of 24 h. Mean serum glucose AUC0-4 h values after a midday meal ranged from
In these healthy individuals, dapagliflozin was associated with a decrease of 7% (on average) in the mean serum glucose AUC0-4 h value compared with the value with placebo.

In other randomized, double-blind, placebo-controlled, sequential, multiple-ascending-dose clinical trials, healthy individuals received diets containing fixed amounts of calcium and sodium chloride and were assigned to receive dapagliflozin (2.5, 10, 20, 50 or 100 mg po, qd for 14 days [n = 6 per dose level]) or placebo (n = 2 per dose level). Similar to single-dose treatment, a near maximum glucosuric effect was achieved with the 20-mg dose. Cumulative daily glucose excretion displayed dose-dependency, with 17.7, 40.0, 58.0, 62.0 and 58.3 g excreted on day 1 and 20.4, 33.6, 49.2, 53.3 and 55.4 g on day 14 for doses of 2.5, 10, 20, 50 or 100 mg, respectively. This excretion equates an inhibition of renal glucose reabsorption of approximately 20 to 30% on day 1 and approximately 16 to 50% on day 14. The highest three doses of dapagliflozin (20, 50 and 100 mg) inhibited reabsorption of approximately 50% of the filtered glucose, resulting in an excretion of 60 g/day, which was significantly less than that observed in individuals with severe FRG who displayed massive glucosuria of 125 g/day. A trend toward lower glucose excretion was observed at the end of the trial, possibly reflecting a reduction in the overall glucose load. However, serum levels of glucose, insulin and C-peptide were unaltered, suggesting that changes in the filtered glucose load had not occurred.

In 4 completed phase I, randomized, open-label, active controlled, crossover clinical trials, dapagliflozin was assessed in combination with other agents in healthy volunteers. These trials assessed the pharmacokinetics and pharmacodynamics of dapagliflozin monotherapy. A non-randomized, open-label, parallel-assignment trial assessed single-dose dapagliflozin (50 mg) and multiple-dose dapagliflozin (20 mg, for 7 days) in healthy volunteers and patients with T2DM with and without mild, moderate or severe renal impairment (n = 40); a randomized, double-blind, placebo-controlled, single-group-assignment trial assessed multiple ascending doses of dapagliflozin (2.5, 10 and 20 mg, for 14 days) in Japanese patients with diabetes (n = 36); and an open-label, single-group-assignment trial assessed the oral bioavailability of dapagliflozin (10 mg, and 100 microg iv) in healthy volunteers (n=7).

**Phase II Trials**

The efficacy and safety of dapagliflozin monotherapy was investigated in a IIa, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter, multiple-dose clinical trial was conducted in patients with an established diagnosis of T2DM who received dapagliflozin (5 [n = 11], 25 [n = 12] or 100 mg [n = 16] po, qd for 14 days) or placebo (n = 8); a total of 18 patients (all of whom were randomly assigned to the dapagliflozin dosing groups) continued to receive stable doses of metformin. Dapagliflozin induced a dose-dependent reduction in fasting serum glucose (FSG); on day 13, FSG was reduced from baseline by 11.7 (0.05), 13.3 (0.05) and 21.8% (0.0001) for the 5-, 25- and 100-mg doses, respectively. An analysis of AUC0-4 h values following an oral glucose tolerance test indicated that overall glucose excursion was reduced more substantially on day 13 than on day 2; the greatest reduction from baseline (22.6%) was observed for the 25-mg dose at day 13. Daily urinary glucose excretion increased in a dose-dependent manner; however, despite the prediction of similar or slightly increased SGLT2 inhibition at the end of the study (44% at day 13 versus 36% at day 2), the amount of glucosuria after 2 weeks treatment was inferior (69.9 g/day for the 100-mg dose) compared with day 2 (81.3 g/day for the 100-mg dose). A comparable level of SGLT2 inhibition was associated with greater glucosuria in patients with T2DM compared with healthy individuals, and was attributed to the higher glycemic values in the former group. Body weight was unaltered after 14 days of dapagliflozin treatment. In another, randomized, double-blind, placebo-controlled, parallel-assignment, multicenter, prospective clinical trial, drug-naive patients with T2DM received dapagliflozin (2.5 [n = 53], 5 [n = 55], 10 [n = 40], 20 [n = 55] or 50 [n = 50] mg po, qd), extended-release metformin (750 mg force titrated at week 2 to 1500 mg [n = 51]) or placebo (n = 44) for 12 weeks including a 2-week lead-in period. All analyses were reported for week 12. A significant reduction from baseline in mean HbA1c levels was observed in all dapagliflozin groups compared with the placebo group. However, although the highest reduction occurred in the 50-mg dapagliflozin group (0.9%, compared with 0.18% in the placebo and 0.73% in the metformin groups), no clear dose-response relationship was observed. In contrast, a dose dependent lowering of FPG occurred; reductions from baseline ranged from 16 to 31 mg/dl in the 2.5- to 50-mg dapagliflozin groups,
respective, while reductions of 6 and 18 mg/dl were observed in the placebo and metformin groups, respectively. Adjusted mean reductions in postprandial glucose (PPG) AUC from baseline were 10,149 mg.min/dl for the 10-mg dapagliflozin dose (no dose-dependent relationship), compared with 3182 mg.min/dl for placebo and 5891 mg.min/dl for metformin. HbA1c levels 7% were attained by 40 to 59% of patients in the dapagliflozin groups, compared with 32 and 54% in the placebo and metformin groups, respectively; however, significance was only achieved with the 50-mg dose versus placebo (0.01). Urinary glucose excretion had increased in all dapagliflozin groups versus placebo (0.001 for each dapagliflozin group), and the total mean urinary glucose excreted per 24 h reached a peak of 85 g for the 20-mg dose of dapagliflozin. Importantly, mean weight loss was higher in all dapagliflozin groups (maximum reduction of 3.4% in both the 20- and 50-mg dose groups) compared with either placebo (1.2%) or metformin (1.7%). Visual analog scale evaluations suggested that dapagliflozin did not alter appetite.  

**Phase III Trials**

There have been several phase III trials assessing dapagliflozin-based therapy in groups of patients with T2DM. The efficacy and safety of dapagliflozin in drug-naive patients with T2DM was investigated in a randomized, double-blind, placebo-controlled, multicenter clinical trial assessed the effects of open-label metformin (1500 mg/day) plus either dapagliflozin (2.5 [n = 137], 5 [n = 137] or 10 mg [n = 135] po, qd for 24 weeks) or placebo (n = 137), in patients with T2DM that was inadequately controlled with metformin alone (1500 mg/day). At week 24, mean reductions from baseline in HbA1c and FPG levels were significant in all dapagliflozin groups compared with placebo (0.005 for all treatment groups for both measures); baseline-adjusted mean reductions in HbA1c were 0.67, 0.70 and 0.84% in the 2.5-, 5- and 10-mg dapagliflozin groups, respectively. The percentage of patients with HbA1c values, 7% at 24 weeks was significant in the 5- and 10-mg dapagliflozin groups (0.05 for both doses versus placebo), but not in the 2.5-mg dose group. Dapagliflozin induced progressive and continuing weight loss during the trial, and a greater proportion of patients in the dapagliflozin groups experienced weight losses of 5% compared with placebo (24 to 28% of patients in the dapagliflozin groups compared with 5.9% in the placebo group). Significant decreases in total body weight were also observed at 24 weeks in the dapagliflozin groups (0.0001 versus placebo).  

**TOLERABILITY AND SIDE EFFECTS**

Although long-term safety data are lacking, studies to date have generally found dapagliflozin to be safe and well tolerated. It is useful to note that genetic mutations involving SGLT2 cause isolated glucosuria, with individuals affected not experiencing significant morbidity or a decreased life expectancy. Reported adverse events in clinical trials were most often gastrointestinal in nature and appear to occur more commonly in patients receiving concomitant metformin therapy.

**Hypoglycaemia**

SGLT2 inhibition is generally not associated with hypoglycaemia. Two episodes of hypoglycaemia, defined as symptomatic hypoglycaemia and/or a blood glucose level <50mg/dL on multiple occasions, were reported in one phase II study in dapagliflozin-treated patients. Another phase II study reported hypoglycaemia in 6–10% of dapagliflozin-treated patients, compared with 4% in the placebo group and 9% in those receiving metformin. When used as add-on therapy in patients inadequately controlled with metformin monotherapy, hypoglycaemia was reported in 2.2–3.7% of patients receiving dapagliflozin, compared with 2.9% of placebo treated patients over 24 weeks of treatment. In contrast, the incidence of hypoglycaemia appears to be increased when dapagliflozin is used as add-on therapy to insulin plus oral anti diabetic therapy, with 25.0–29.2% of dapagliflozin-treated patients reporting hypoglycaemia compared with 13.0% of those receiving placebo.

**Renal Function**

Given the mechanism of SGLT2 inhibitors, renal monitoring has been performed in clinical trials to identify any potential changes in renal function resulting from therapy. Short-term trials with dapagliflozin have not identified any clinically significant changes in renal function or electrolyte levels to date. Fourteen days of treatment showed no clinically meaningful changes in estimated glomerular filtration rate or in 24-hour urine excretion of electrolytes. Dapagliflozin has demonstrated a diuretic effect in clinical trials as evidenced by an increased 24-hour urinary output volume ranging from 107 to
470ml above baseline in dapagliflozin-treated patients. The diuretic effect of dapagliflozin has been associated with an observed mean decrease in systolic blood pressure ranging from -2.6 to -6.4 mm Hg in one study. Although this could be a theoretical benefit in patients with T2DM, hypotension is a potential concern, with up to 2% of dapagliflozin-treated patients reporting a hypotensive event. However, it is important to note that in this study 2% and 4% of placebo and metformin treated individuals, respectively, experienced a hypotensive event. Increased magnesium and decreased uric acid levels have also been reported with treatment. Safety data from long-term clinical trials are needed to further determine the safety of SGLT2 inhibition in terms of renal function.

Other Potential Events
Other potential adverse events associated with SGLT2 inhibition are urinary tract infections (UTIs) and genital infections secondary to increased glucosuria. In the study conducted by List and colleagues, 5–12% of dapagliflozin-treated patients reported a UTI, compared with 6% of placebo treated and 9% of metformin-treated patients. Genital infections occurred in 2–7% of those in the dapagliflozin group, with no infections reported in placebo-treated participants and 2% of those receiving metformin reporting such an event. In a 24-week study, UTI rates were similar in dapagliflozin treated patients (4.4–8.1%) when compared with those receiving placebo (8.0%). However, genital infections occurred more frequently in those receiving dapagliflozin versus placebo (8–13.1% vs 5.1%, respectively). The relationship between SGLT2 inhibitors and such infections warrants further study in long-term trials to determine the risk of UTI and genital infections with prolonged therapy.11

CONCLUSION
SGLTs inhibitor represents a highly promising, novel class of oral agents for the treatment of T2DM. SGLTs inhibitors may occupy a unique position as antidiabetic drugs. Their unique mechanism of action provides an improvement in both fasting and postprandial hyperglycaemia without increasing insulin secretion or causing weight gain, hypoglycaemia, gastrointestinal side effects or fluid retention. SGLT2 inhibitors would be expected to be beneficial in the treatment of type 2 diabetes as monotherapy or in combination with other hypoglycemic agents or insulin. Furthermore, because of their potential role in weight loss, they would be very appealing to patients and medically useful in the treatment of type 2 diabetes and associated comorbid conditions such as hypertension and dyslipidaemia. An effective and highly specific inhibition of SGLTs, of dapagliflozin making once daily treatment feasible, effective and safe. Hence, these agent should be considered as alternative to the second-line diabetes therapies in patients with inadequately controlled glycemia treated with monotherapy.

REFERENCES


Figure 1: Angiotensin II, Epidermal Growth Factor And Sodium-Hypothetical Role of Glucose Transporter

ANG II = Angiotensin II, DAG = diacylglycerol, EGF = epidermal growth factor, PIP2 = phosphatidylinositol 4, 5-bisphosphate.

Figure 2: Chemical Structure of Dapagliflozin