Glucuretic effects and renal safety of dapagliflozin in patients with type 2 diabetes

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Abstract: Dapagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor approved as a treatment for type 2 diabetes mellitus (T2DM) in the United States, the European Union and other countries. Dapagliflozin increases renal glucose excretion in an insulin-independent manner, and its mechanism of action is complementary to those of other antidiabetes medications. When used as monotherapy or in combination with other oral antidiabetes medications or insulin, dapagliflozin improves glycemic measures in patients with T2DM. Dapagliflozin treatment is also associated with weight reduction and a decrease in blood pressure, both of which may be beneficial in patients with T2DM. Because of its mechanism of action, dapagliflozin has a low intrinsic propensity to cause hypoglycemia. Overall, dapagliflozin is well tolerated, with the frequency of most adverse events similar to that seen with placebo. Cases of genital infections and, in some studies, urinary tract infections have been more frequent in dapagliflozin-treated groups compared with placebo groups. In the clinical development program, more cases of newly diagnosed bladder cancer were reported for patients treated with dapagliflozin (0.17%) compared with placebo or comparator (0.03%). Although there were not enough cases to determine causality, dapagliflozin should not be used in patients with bladder cancer and should be used with caution in patients with a history of bladder cancer. Dapagliflozin may decrease glomerular filtration rate (GFR), especially in elderly patients and patients with impaired renal function. Renal function should be monitored before initiation of dapagliflozin. Dapagliflozin should not be used in patients with an estimated GFR <60 mL/min/1.73 m². No cardiovascular safety signals have been detected for dapagliflozin, and a long-term cardiovascular outcomes study is ongoing. Evidence from clinical trials suggests that dapagliflozin is a promising new treatment option for T2DM.

Keywords: dapagliflozin, diabetes, glucose, kidney, SGLT2 inhibitors

Introduction

Diabetes is a complex disease that affects 382 million adults worldwide [International Diabetes Federation, 2013] and 29 million in the United States [Centers for Disease Control and Prevention, 2014]. Type 2 diabetes mellitus (T2DM) accounts for >90% of newly diagnosed cases of diabetes and is a major cause of heart disease, stroke and kidney failure [Centers for Disease Control and Prevention, 2011]. Although there are numerous classes of antidiabetes drugs, 47% of US adults with diabetes do not attain a glycated hemoglobin (HbA1c) of <7% [Stark Casagrande *et al.* 2013], a goal proposed by some national and international medical societies for

many patients with T2DM [American Diabetes Association, 2014]. Owing to the progressive nature of T2DM [Fonseca, 2009], most patients will eventually require pharmacotherapy in addition to diet and exercise modification to achieve and maintain personal glycemic goals [Inzucchi *et al.* 2012]. Pharmacotherapy should be individualized based on efficacy, cost, side effects, comorbidities, potential for hypoglycemia and patient preference. Therapy will likely need to be intensified with additional complementary acting antidiabetes agents during the course of the disease to achieve and maintain glycemic control [American Diabetes Association, 2014; Garber *et al.* 2013].

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In recent years, several new treatments have been developed that provide additional options for the individualized treatment of patients with T2DM [Garber *et al.* 2013]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, exemplified by three recently approved drugs – canagliflozin, dapagliflozin and empagliflozin – are the newest class of antidiabetes drugs [Bays, 2013]. Unlike other major antidiabetes drug classes, SGLT2 inhibitors act independently of insulin secretion or action [List and Whaley, 2011] and are therefore complementary to existing insulin-dependent therapies.

The purpose of this review is to discuss the mechanism of action of SGLT2 inhibitors and the efficacy of dapagliflozin in patients with T2DM. Because the mechanism of action of SGLT2 inhibitors is to inhibit glucose reabsorption by the kidney, the renal safety of dapagliflozin is discussed here as well.

Mechanism of action of SGLT2 inhibitors

SGLT2 is a sodium-dependent glucose transporter that is located in the proximal tubule of the kidney (Figure 1) and is responsible for the reabsorption of

Normal physiology of renal glucose reabsorption

SGLT2 inhibitors reduce renal glucose reabsorption

Figure 1. Mechanism of action of SGLT2 inhibitors.
SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2.
Reproduced with permission from Freeman [2013].

the majority (~90%) of the glucose that is filtered by the kidneys [Bakris *et al.* 2009]. The kidneys play an important role in glucose homeostasis. At normal plasma glucose concentrations, the kidneys reabsorb virtually all of the glucose that is filtered, such that urinary excretion of glucose is near zero [Bakris *et al.* 2009]. As plasma glucose concentration rises above ~180 mg/dl, more glucose is filtered, the reabsorptive capacity of the kidneys is exceeded, and glucose that is not reabsorbed is excreted in the urine [DeFronzo *et al.* 2013]. Interestingly, in individuals with T2DM, the kidneys' capacity to reabsorb glucose is increased [DeFronzo *et al.* 2013], which further contributes to the existing hyperglycemia. Thus, inhibition of SGLT2 represents a novel mechanism to reduce hyperglycemia by increasing renal glucose excretion. Because renal glucose excretion depends on both glomerular filtration rate (GFR) and plasma glucose concentrations, the ability of SGLT2 inhibitors to increase glucose excretion in the urine, and thus decrease plasma glucose concentrations, is attenuated in patients with reduced GFR [Barnett *et al.* 2014; Kohan *et al.* 2014; Yale *et al.* 2013].

The mechanism of action of SGLT2 inhibitors does not depend on insulin secretion or action [List and Whaley, 2011], which offers a number of potential benefits. First, there is less risk of hypoglycemic events with this drug class compared with, for example, the sulfonylureas (SUs), which are insulin secretagogues [Vasilakou *et al.* 2013]. Second, because they do not depend on β -cell function or tissue insulin sensitivity, SGLT2 inhibitors are effective throughout the progression of T2DM, from patients newly diagnosed with T2DM to those with long-standing disease, as long as there is adequate renal function [Zhang *et al.* 2010]. Additional benefits of SGLT2 inhibitors include body weight reduction [Vasilakou *et al.* 2013], associated with the loss of calories through increased renal excretion of glucose [Bolinder *et al.* 2012] and blood pressure reduction, possibly the result, at least in part, of a combination of weight loss and mild osmotic diuresis [Lambers Heerspink *et al.* 2013]. However, the pharmacologically induced excretion of urine with high concentrations of glucose may increase the risk of genital and urinary tract infections (UTIs) in patients with T2DM [Vasilakou *et al.* 2013].

Dapagliflozin efficacy in patients with T2DM

Dapagliflozin was approved in the EU in 2012 and in the US in 2014 as an adjunct to diet and

exercise to improve glycemic control in adults with T2DM. In the US, the recommended starting dose is 5 mg/day, which can be increased to 10 mg/day in patients who require additional glycemic control [Bristol-Myers Squibb and AstraZeneca, 2014]. In the EU, the recommended dose is 10 mg/day. Dapagliflozin should not be used in patients with an estimated GFR (eGFR) <60 ml/min/1.73 m² [Bristol-Myers Squibb and AstraZeneca, 2014]. No important drug interactions have been observed with other oral antidiabetes drugs (OADs) such as metformin, pioglitazone, sitagliptin and glimepiride [Kasichayanula *et al.* 2011], or with the cardiovascular (CV) drugs valsartan, simvastatin, warfarin and digoxin, when co-administered with dapagliflozin [Kasichayanula *et al.* 2012]. No adjustment in dapagliflozin dose is required in patients with mild renal impairment (eGFR 60–90 ml/min/1.73 m²) [Bristol-Myers Squibb and AstraZeneca, 2014].

In the clinical development program, the effects of dapagliflozin on glycemic parameters when used as monotherapy in treatment-naïve patients [Ferrannini *et al.* 2010] and as add-on therapy to other antidiabetes drugs, including metformin [Bailey *et al.* 2010], SUs [Strojek *et al.* 2011], thiazolidinediones (TZDs) [Rosenstock *et al.* 2012], dipeptidyl peptidase-4 (DPP-4) inhibitors [Jabbour *et al.* 2014] and insulin [Wilding *et al.* 2012], were measured. Dapagliflozin was compared with the SU glipizide as add-on therapy to metformin [Nauck *et al.* 2011]. Dapagliflozin was also compared as an initial combination therapy with metformin extended release (XR) *versus* dapagliflozin or metformin XR alone [Henry *et al.* 2012]. A summary of these clinical trials is presented in Table 1.

In treatment-naïve patients with inadequate glycemic control with diet and exercise modification, monotherapy with dapagliflozin 5 and 10 mg/day significantly reduced HbA1c (placebo corrected) by 0.54% and 0.66%, respectively, after 24 weeks [Ferrannini *et al.* 2010]. Fasting plasma glucose (FPG) was reduced by 20 and 25 mg/dl by dapagliflozin 5 and 10 mg/day, respectively, compared with placebo. In other studies, initial therapy with dapagliflozin 5 or 10 mg/day alone, metformin XR alone, or the combination of dapagliflozin and metformin XR was assessed in treatment-naïve patients. The combination of dapagliflozin and metformin XR significantly reduced HbA1c by 0.70% with dapagliflozin 5 mg/day + MET and 0.54% with dapagliflozin 10 mg/day + MET

Table 1. Placebo- or control-corrected adjusted mean changes from baseline to study end in HbA1c, FPG and body weight with dapagliflozin in phase III trials of glycemic efficacy.

Trial*	n	Duration of T2DM, years	HbA1c, %	FPG, mg/dl			PPG, mg/dl			Body weight, kg (lb)				
				DAPA, mg/day			DAPA, mg/day			DAPA, mg/day				
				Baseline	5	10	Baseline	5	10	Baseline	5	10		
Monotherapy [Ferrannini <i>et al.</i> 2010] [NCT00528372]	485 [§]	0.3–0.5	7.84–8.01	–0.54	–0.66	160–167	–20	–25	ND	ND	ND	88–94	–0.6 [–1.3]	–1.0 [–2.2]
Add-on to MET [Bailey <i>et al.</i> 2010] [NCT00528879]	546	5.8–6.4	7.92–8.17	–0.40	–0.54	156–169	–15	–17	ND	ND	ND	85–88	–2.1 [–4.6]	–2.0 [–4.4]
Add-on to glimepiride [Strojek <i>et al.</i> 2011] [NCT00680745]	597	7.2–7.4	8.07–8.15	–0.49	–0.68	172–174	–19	–26	324–330	–43	–49	81	–0.8 [–1.8]	–1.5 [–3.3]
Add-on to pioglitazone [Rosenstock <i>et al.</i> 2012] [NCT00683878]	420	5.1–5.8	8.34–8.40	–0.40	–0.55	161–169	–19	–24	285–308	–51	–53	85–88	–1.5 [–3.3]	–1.8 [–4.0]
Add-on to sitagliptin ± MET [Jabbour <i>et al.</i> 2014] [NCT00984867]	451	5.6–5.7	7.9–8.0	NA	–0.50	162–163	ND	–28	226–228	ND	–43	89–91	NA	–1.9 [–4.2]
Add-on to insulin [Wilding <i>et al.</i> 2012] [NCT00673231]	808	13.1–14.2	8.47–8.62	–0.49	–0.57	171–185	–20	–20	ND	ND	ND	93–95	–1.4 [–3.1]	–2.0 [–4.4]
Add-on to MET versus glipizide add-on to MET [Nauck <i>et al.</i> 2011] [NCT00660907]	814	6.1–6.6	7.69–7.74	NA	0	162–164	ND	–4	ND	ND	ND	88	NA	–4.7 [–10.4]
Add-on to MET + SU [Matthaei <i>et al.</i> 2013] [NCT01392677]	216	9.3–9.6	8.08–8.24	NA	–0.69	167–180	ND	–33	ND	ND	ND	89–90	NA	–2.1 [–4.6]
DAPA 5 mg/day combined with MET XR as initial therapy [Henry <i>et al.</i> 2012] [NCT00643851]	603	0.3–0.6	9.2	–0.70	NA	194–197	–28	NA	ND	ND	ND	84–86	–1.4 [–3.1]	ND
DAPA 10 mg/day combined with MET XR as initial therapy [Henry <i>et al.</i> 2012] [NCT00859898]	641	0.5–0.6	9.1	NA	–0.54	189–190	NA	–26	ND	ND	ND	87–88	NA	–2.0 [–4.4]

*Primary treatment period was 24 weeks for all trials except for the add-on to MET versus glipizide add-on to MET trial, which was 52 weeks.

[§]Main cohort included 274 patients.

DAPA, dapagliflozin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; MET, metformin; NA, not applicable; ND, not determined; PPG, postprandial glucose; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; XR, extended release.

and FPG by 27 and 26 mg/dl, respectively, *versus* metformin XR alone. Dapagliflozin 10 mg/day alone was noninferior to metformin XR alone in reducing HbA1c [Henry *et al.* 2012]. Body weight was significantly reduced with dapagliflozin 5 or 10 mg/day plus metformin XR by 1.4 and 2.0 kg (3.1 and 4.4 lb), respectively, compared with metformin XR alone. In patients with more advanced disease (T2DM duration of 5.1–14.2 years), dapagliflozin, when used as add-on therapy to other OADs or insulin [Bailey *et al.* 2010; Jabbour *et al.* 2014; Rosenstock *et al.* 2012; Strojek *et al.* 2011; Wilding *et al.* 2012], reduced HbA1c compared with placebo by 0.40% to 0.69%, FPG by 15 to 33 mg/dl, and body weight by up to approximately 2.0 kg (4.4 lb) (Table 1). Dapagliflozin also reduced 2-hour postprandial glucose (PPG) compared with placebo by –43 to –53 mg/dl when used as add-on to glimepiride [Strojek *et al.* 2011], add-on to pioglitazone [Rosenstock *et al.* 2012] or add-on to sitagliptin with or without metformin [Jabbour *et al.* 2014]. Long-term extensions of the add-on to metformin [Bailey *et al.* 2013] and add-on to insulin studies [Wilding *et al.* 2014] showed that the improvements in glycemic parameters and reduction in body weight were maintained for up to 2 years.

In a study designed to compare the efficacy of dapagliflozin at a maximum dose of 10 mg/day with glipizide at a maximum dose of up to 20 mg/day in patients inadequately controlled with metformin [Nauck *et al.* 2011], the reduction in HbA1c after 52 weeks of treatment was identical (0.52%) in both treatment groups, and there was no difference in the decrease in FPG between the groups. Notably, body weight increased with glipizide by 1.4 kg (3.1 lb) and decreased by 3.2 kg (7.1 lb) with dapagliflozin, resulting in a difference of 4.7 kg (10.4 lb) between treatment groups.

National and international diabetes societies recommend that addition of a third noninsulin agent be considered as a treatment option in some patients when dual therapy fails to achieve or maintain glycemic control [Garber *et al.* 2013; International Diabetes Federation, 2012; Inzucchi *et al.* 2012]. The efficacy of dapagliflozin 10 mg/day *versus* placebo as add-on therapy in patients poorly controlled on metformin (≥ 1500 mg/day) and a maximum tolerated dose of an SU was assessed [Matthaei *et al.* 2013]. Compared with placebo, after 24 weeks, dapagliflozin significantly reduced HbA1c (0.69%), FPG (33 mg/dl) and body weight [2.1 kg (4.6 lb)]. Another study

compared the dual addition of dapagliflozin 10 mg/day and the DPP-4 inhibitor saxagliptin 5 mg/day *versus* the addition of dapagliflozin 10 mg/day and placebo or saxagliptin 5 mg/day and placebo to metformin XR in patients inadequately controlled with metformin XR alone (Rosenstock *et al.* 2015). After 24 weeks, the adjusted mean change from baseline in HbA1c was significantly greater with saxagliptin and dapagliflozin add-on (–1.47%) than with saxagliptin add-on alone (–0.88%, $p < 0.0001$) or dapagliflozin add-on alone (–1.20%, $p < 0.02$). Changes in FPG were –38 mg/dl with saxagliptin and dapagliflozin add-on, –14 mg/dl with saxagliptin add-on and –32 mg/dl with dapagliflozin add-on. There was no change in body weight in the saxagliptin add-on group, whereas body weight was reduced by 2.1 kg (4.6 lb) in the saxagliptin and dapagliflozin group and 2.4 kg (5.3 lb) in the dapagliflozin group.

In patients with T2DM and moderate renal impairment (89–94% of patients in the 3 study arms had an eGFR ≥ 30 and < 60 ml/min/1.73 m²) who continued on their existing antidiabetes medications, the change in HbA1c after 24 weeks with dapagliflozin 5 mg/day (–0.41%) and 10 mg/day (–0.44%) was not statistically different from that with placebo (–0.32%) [Kohan *et al.* 2014]. Body weight was reduced by 1.3 to 1.7 kg (2.9 to 3.7 lb) in patients treated with dapagliflozin and was increased by 0.7 kg (1.5 lb) in the placebo group. A *post hoc* analysis found larger adjusted mean (SE) change from baseline compared with placebo in HbA1c [–0.37% (0.23%) and –0.33% (0.24%)] for dapagliflozin 5 and 10 mg/day, respectively) and FPG [–24.8 (12.4) and –24.4 (12.7) mg/dl] in patients with eGFR of ≥ 45 and < 60 ml/min/1.73 m² than for those with eGFR ≥ 30 and < 45 ml/min/1.73 m² [HbA1c, 0.05% (0.21%) and 0.07% (0.21%); FPG, –2.7 (12.1) and –1.5 (11.8) mg/dl]. The observed decrease in dapagliflozin efficacy with worsening renal function is characteristic of SGLT2 inhibitors [Barnett *et al.* 2014; Yale *et al.* 2013] owing to their mechanism of action.

As noted above, moderate weight reduction has been a consistent finding in patients treated with dapagliflozin. Because dapagliflozin appears to have a mild diuretic effect [Lambers Heerspink *et al.* 2013], the weight loss could result from fluid loss secondary to osmotic diuresis; it could also be attributed to caloric loss resulting from increased glucose excretion or to both. A study

was performed to determine whether body weight reduction with dapagliflozin was the result of changes in body composition [Bolinder *et al.* 2012]. Patients with T2DM were treated with dapagliflozin 10 mg/day or placebo in addition to open-label metformin. Change in fat mass was assessed by dual-energy X-ray absorptiometry. At the end of 24 weeks, placebo-corrected change in body weight with dapagliflozin was -2.1 kg (-4.6 lb; $p < 0.0001$). A reduction in fat mass accounted for approximately two-thirds of the total weight loss. The changes in body weight and fat mass with dapagliflozin were sustained for a total of 102 weeks of treatment, at which time placebo-corrected weight loss was 2.4 kg (5.3 lb) and reduction in fat mass accounted for 68% of the reduction in body weight [Bolinder *et al.* 2014]. These results suggest that, although the initial reduction in body weight may be due, in large part, to osmotic diuresis, the gradual continuous reduction and subsequent stabilization of body weight is likely the result of caloric loss *via* increased glucose excretion [Lambers Heerspink *et al.* 2013].

In most studies with dapagliflozin, modest reductions in blood pressure have been reported, probably the result of a mild diuretic-like effect of dapagliflozin [Lambers Heerspink *et al.* 2013]. In patients with T2DM and hypertension being treated with OADs and an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), dapagliflozin 10 mg/day significantly reduced seated systolic blood pressure *versus* placebo by 3.1 mm Hg after 12 weeks of treatment [Weber *et al.* 2013a]. In a similarly designed 12-week study in patients with hypertension and T2DM receiving OADs, an ACEi or ARB, and a second antihypertensive agent, dapagliflozin 10 mg/day significantly reduced seated systolic blood pressure *versus* placebo by 4.3 mm Hg [Weber *et al.* 2013b]. In both studies, asymptomatic orthostatic hypotension occurred in $<3.5\%$ of patients.

Overall safety

In the studies listed in Table 1, the proportion of patients reporting ≥ 1 adverse event (AE) was similar to or slightly higher in patients treated with dapagliflozin compared with those receiving placebo or a comparator drug [Bailey *et al.* 2010; Ferrannini *et al.* 2010; Henry *et al.* 2012; Jabbour *et al.* 2014; Matthaei *et al.* 2013; Nauck *et al.* 2011; Rosenstock *et al.* 2012; Strojek *et al.* 2011;

Wilding *et al.* 2012]. The most common AEs included nasopharyngitis, diarrhea, headache and upper respiratory tract infections.

Hyperglycemia and diabetes are associated with an increased risk of genital and urinary tract infections [Benfield *et al.* 2007; De Leon *et al.* 2002]. Because glucosuria may play a role in the development of genital and urinary tract infections [Geerlings *et al.* 2014], patients were actively monitored throughout dapagliflozin clinical trials for signs and symptoms suggestive of UTI and genital infections [Bailey *et al.* 2010]. In data pooled from 12 double-blind clinical trials of dapagliflozin, confirmed cases of genital infections were more frequent in patients receiving dapagliflozin 5 mg/day (6%) and 10 mg/day (5%) than in those receiving placebo or comparator (1%) [Johnsson *et al.* 2013a]. In the dapagliflozin 5 and 10 mg/day groups, genital infections were more common in women (8% and 7%, respectively) than in men (3% and 3%). For all groups, diagnosis of genital infections was more prevalent in patients with a history of recurrent genital infections. Confirmed cases of UTI in the 12-study pool were somewhat more frequent in the dapagliflozin 5 mg/day group (6%), but similar in the dapagliflozin 10 mg/day group (4%) to the placebo or comparator groups (4%) [Johnsson *et al.* 2013b]. The increase in genital infections and, in some studies, UTIs has been reported for other SGLT2 inhibitors [Häring *et al.* 2013; Nicolle *et al.* 2014; Nyirjesy *et al.* 2012] and appears to be a class effect. Patients, especially those with a history of genital infections, should be informed of the increased risk of genital mycotic infections and should be monitored and treated accordingly [Bristol-Myers Squibb and AstraZeneca, 2014].

The incidence of hypoglycemia with dapagliflozin was low and similar to that with placebo in most studies. Hypoglycemic events were reported more frequently with dapagliflozin 5 and 10 mg/day than with placebo when dapagliflozin was added on to insulin (56% and 54% *versus* 52%, respectively) [Wilding *et al.* 2012] or glimepiride (7% and 8% *versus* 5%) [Strojek *et al.* 2011] or with dapagliflozin 10 mg/day added on to metformin plus an SU (13% *versus* 4%) [Matthaei *et al.* 2013]. Of note, hypoglycemia was approximately 10-fold less frequent with dapagliflozin (3.4%) compared with glipizide (39.7%) as add-on therapy to metformin [Nauck *et al.* 2011].

Major hypoglycemic episodes, defined as symptomatic episodes in which the patient required external assistance owing to severe impairment in consciousness or behavior, had plasma glucose concentration <54 mg/dl, and promptly recovered after receiving glucose or glucagon, were rare with dapagliflozin. One major hypoglycemic episode occurred with dapagliflozin 10 mg/day *versus* none with placebo during the 48 weeks of treatment in the add-on to sitagliptin study [Jabbour *et al.* 2014]. In the add-on to insulin study, there were 2 (0.9%) major episodes with dapagliflozin 5 mg/day plus insulin, 3 (1.5%) with dapagliflozin 10 mg/day plus insulin, and 2 (1%) with placebo plus insulin.

In 13 phase IIb and III placebo-controlled trials, events of volume depletion (e.g. orthostatic hypotension, syncope, dehydration) were infrequent but slightly more common with dapagliflozin 10 mg/day (1.9%) than with placebo (1.4%) [Food and Drug Administration, 2013]. Events were more frequent with either dapagliflozin or placebo in patients ≥ 65 years old (2.3% and 1.7%, respectively), those receiving loop diuretics (3% and 2.7%), and those with moderate renal impairment (3.2% and 2.4%). Volume status should be assessed and corrected in elderly patients, patients with renal impairment or low systolic blood pressure, and patients taking diuretics before initiating dapagliflozin therapy [Bristol-Myers Squibb and AstraZeneca, 2014].

In this same placebo-controlled trial pool, the proportion of patients with AEs leading to discontinuation was slightly higher with dapagliflozin (8.5%) than with placebo (7.4%) [Food and Drug Administration, 2013]. AEs leading to discontinuation that were more frequent in dapagliflozin-treated patients than in those receiving placebo included changes in renal function and genital infections or UTIs.

In data from the dapagliflozin clinical development program presented to the US Food and Drug Administration (FDA) in 2013, an imbalance in bladder cancer was observed with dapagliflozin. In 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 1/3512 patients (0.03%) receiving placebo or comparator and in 10/6045 patients (0.17%) treated with dapagliflozin [Food and Drug Administration, 2013]. There were 6 cases of bladder cancer with dapagliflozin and 1 case with placebo or comparator in patients who were exposed to study drug

for <1 year at the time of diagnosis of bladder cancer; the remaining 4 cases occurred within 1–2 years of initiation of dapagliflozin treatment. There were too few cases and insufficient data to determine causality [Food and Drug Administration, 2013]. Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in those with a history of bladder cancer, taking into consideration the benefits of glycemic control *versus* unknown risks for cancer recurrence [Bristol-Myers Squibb and AstraZeneca, 2014].

A meta-analysis of 21 phase IIb/III trials was performed to assess the CV safety of dapagliflozin as per the 2008 FDA guidance on CV safety in anti-diabetes drug development [Food and Drug Administration, 2008]. The prespecified primary endpoint was a composite of the time to first event of CV death, myocardial infarction, stroke, or hospitalization for unstable angina. As per the guidance criteria, there was no unacceptable increase in CV risk with dapagliflozin compared with placebo or comparator [Food and Drug Administration, 2013]. A secondary analysis of CV major AEs (MACE) (a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke) also showed no increased risk with dapagliflozin. A long-term CV outcomes trial to assess the effect of dapagliflozin on the incidence of CV events in patients with T2DM and at high risk for CV events is ongoing [ClinicalTrials.gov identifier: NCT01730534].

Renal safety

Because the mechanism of action of SGLT2 inhibitors is to inhibit glucose reabsorption in the kidney, renal safety is of special interest. In an exploratory study in patients with T2DM and $\text{eGFR} > 60$ ml/min/1.73 m², dapagliflozin 10 mg/day for 12 weeks reduced GFR as measured by the plasma disappearance of iothexol from baseline by 10.8% compared with 2.9% with placebo [Lambers Heerspink *et al.* 2013]. Mean eGFR decreased from baseline up to week 2 and, unlike measured GFR, returned to values close to baseline by 12 weeks (mean change -0.5 *versus* 2.0 ml/min/1.73 m² with dapagliflozin *versus* placebo). In an analysis of 12 placebo-controlled randomized trials involving >4000 patients, most of whom had either normal renal function (37–40% of patients, $\text{eGFR} > 90$ ml/min/1.73 m²) or mild renal impairment (53–54% of patients; eGFR 60–90 ml/min/1.73 m²), dapagliflozin was

associated with a small reduction in eGFR at week 1 that returned to baseline by week 24 and was maintained at baseline values for up to 2 years [Ptaszynska *et al.* 2014]. It has been postulated that the acute reductions in eGFR may reflect reversible hemodynamic effects, such as a decrease in plasma volume or blood pressure, or autoregulation through tubuloglomerular feedback due to increased delivery of sodium to the macula densa rather than permanent changes in renal function [Lambers Heerspink *et al.* 2013]. Acute reductions in eGFR followed by stabilization have been shown with other SGLT2 inhibitors [Cefalu *et al.* 2013] and appear to be a class effect.

In the aforementioned 12 clinical trials, there were no changes from baseline in serum sodium, potassium, bicarbonate, chloride or calcium with dapagliflozin or placebo. Small increases in serum magnesium and phosphate were reported. There were no changes in albumin excretion (expressed as the urinary albumin/creatinine ratio) [Ptaszynska *et al.* 2014], a marker of kidney functional damage [Heerspink *et al.* 2011].

In a study in patients with T2DM and moderate renal impairment (eGFR 30–60 ml/min/1.73 m²), dapagliflozin 5 and 10 mg/day caused a decline in eGFR over the first 1–2 weeks, followed by stabilization or small increases in eGFR through 104 weeks of therapy (albeit with no return to baseline values), whereas in the placebo group, eGFR appeared to decline over this period [Kohan *et al.* 2014]. The change from baseline in eGFR at 104 weeks was similar across groups (placebo, –2.4 ml/min/1.73 m²; dapagliflozin 5 mg/day, –1.7 ml/min/1.73 m²; dapagliflozin 10 mg/day, –3.5 ml/min/1.73 m²). No changes from baseline were observed for mean serum sodium, potassium, bicarbonate, chloride or calcium. There was a higher incidence of hyperphosphatemia in patients treated with dapagliflozin 5 mg/day (16%) and 10 mg/day (14%) compared with those receiving placebo (8%). Urinary albumin/creatinine ratio increased from baseline with dapagliflozin 5 mg/day (78 mg/g) and placebo (70 mg/g) and decreased with dapagliflozin 10 mg/day (–12 mg/g).

In 13 phase IIb and III placebo-controlled trials with durations from 12 to 104 weeks ($n = 3982$), AEs related to renal function (e.g. decreased creatinine clearance, increased blood creatinine, decreased urine flow, anuria) were more common

in patients treated with dapagliflozin 10 mg/day (7%) than in those receiving placebo (4%) [Food and Drug Administration, 2013]. Patients ≥ 65 years old were at an increased risk for AEs related to renal function (dapagliflozin 10 mg/day, 14%; placebo, 8%), as were those with moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m²; dapagliflozin 10 mg/day, 28%; placebo, 16%). Renal function should be assessed before initiating dapagliflozin. Dapagliflozin should not be used in patients with an eGFR <60 ml/min/1.73 m² [Bristol-Myers Squibb and AstraZeneca, 2014].

Across all phase IIb and III clinical trials ($n = 9339$), serious AEs (SAEs) of renal impairment occurred in 9 (0.2%) dapagliflozin-treated patients and in 5 (0.1%) patients receiving placebo or control [Food and Drug Administration, 2013].

Summary

Dapagliflozin is a member of a new class of anti-diabetes agents, the SGLT2 inhibitors, that reduce plasma glucose concentrations by inhibiting renal glucose reabsorption. Because the efficacy of dapagliflozin is not affected by either β -cell dysfunction or insulin resistance, it improves glycemic control in a wide range of patients, from treatment-naïve patients to those with long-standing disease, as long as renal function is adequate. Moreover, dapagliflozin can be used with other OADs and with insulin to gain additional efficacy.

Dapagliflozin is associated with weight reduction that is maintained for at least 2 years, which may be a benefit for overweight and obese patients with T2DM as well as a means to mitigate the weight gain usually seen with SU and insulin therapy. Reduction in blood pressure with dapagliflozin is an additional potential benefit in view of the high prevalence of hypertension in patients with T2DM.

In clinical trials, dapagliflozin was generally well tolerated, with genital infections and UTIs being the most common AEs. Patients should be informed of the signs and symptoms of these infections and the need to seek treatment should they occur. Dapagliflozin has a low intrinsic propensity to cause hypoglycemia. However, hypoglycemic events were more frequent when dapagliflozin was added to insulin or SU therapy.

In a meta-analysis of short-term clinical trials, there was no increased risk of adverse CV events with dapagliflozin treatment. Dapagliflozin can

decrease eGFR, especially in elderly patients and in patients with impaired renal function. Renal function should be monitored before initiation of dapagliflozin. Volume-related AEs were infrequent with dapagliflozin. The volume status of elderly patients and those receiving diuretics or with renal impairment should be monitored. Dapagliflozin should not be used in patients with bladder cancer, and caution should be exercised in patients with a history of bladder cancer.

Conclusion

Dapagliflozin is an SGLT2 inhibitor that improves glycemic control in patients inadequately controlled by diet and exercise modification or anti-diabetes medications. Additional benefits of dapagliflozin include reductions in body weight and blood pressure. Dapagliflozin poses a low risk of hypoglycemia, except when used with insulin or insulin secretagogues. The most common AEs in clinical trials were genital and urinary tract infections. No increase in CV risk was detected during the clinical development program, and an outcomes study is being conducted to assess the effects of dapagliflozin on CV events. Evidence from clinical trials suggests that dapagliflozin is a promising new treatment option for T2DM.

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