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Dapagliflozin for the treatment of type 2 diabetes: a review of the literature

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Objective: Dapagliflozin was the first drug in a class of therapies that took a new approach to glycemic control in adults with type 2 diabetes (T2D). It is an inhibitor of the sodium glucose cotransporter, resident in the proximal nephron, which is responsible for the recovery of filtered glucose back into circulation. Inhibiting this cotransporter reduces glucose recovery, increases glucose excretion, and reduces hyperglycemia. Here, we review some of the literature relating to the action, efficacy, and clinical use of dapagliflozin.

Materials and methods: A Medline search was conducted within date, animal, and language limits, and relevant papers were selected for review. Conference proceedings were reviewed to obtain up-to-date literature on this drug. Clinical trial websites were reviewed for ongoing studies.

Results: On average, treatment with dapagliflozin results in improvement in glycated hemoglobin by 0.50%, fasting plasma glucose by 1 mmol/L, weight by 2 kg, body mass index by 1.1%, and systolic/diastolic blood pressure by 4/2 mmHg over 24–52 weeks. The weight benefit is greater when used in association with sulfonylureas. It is generally well tolerated, but comes with an increased risk of genitourinary and urinary tract infections. In addition, it is associated with reversible changes to renal function that need to be explored. Early reports of an association with cancer also need to be carefully monitored.

Conclusion: Dapagliflozin is a useful therapy for adult patients with T2D. It also holds potential for a broader range of patients with T2D (such as the elderly and pediatric populations), as well as those with other forms of diabetes, such as type 1 diabetes. While longer-term outcome studies of safety and efficacy are awaited, dapagliflozin forms a very useful and welcome addition to our armamentarium for managing patients with T2D.

Keywords: diabetes, dapagliflozin, SGLT2, SGLT2 inhibitor, review

Introduction

Diabetes is a significant international health care problem. There are currently 382 million people with diabetes, a staggering 8.3% or one in 12 of the adult population. This figure is estimated to rise to 592 million people by 2035.¹ The disease comes with a financial burden. An estimated US\$548 billion was spent on this condition in 2013. The vast majority of this cost relates to the management of diabetic complications. These complications include renal replacement therapy, cardiovascular disease, diabetic retinopathy, and diabetic foot disease.

Optimized glucose control reduces the risk of diabetic complications.^{2,3} Several glycated hemoglobin (HbA_{1c}) glycemic targets have been proposed for the management of diabetes, ranging from 6.0% to 8.5% (42–69 mmol/mol).^{4–10} While the last few years have seen an improvement in glucose control and generally in diabetes care, significant further improvement is urgently required. It is estimated that only about half of the diabetic population reach the proposed glycemic targets.¹¹ Reasons for

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failure are complex, but there is little doubt that identifying the right therapy for the patient will go some way to improve their glycemic control.

A number of factors need to be considered when individualizing first-line therapy. These are outlined in Table 1. Tolerability and side effects in particular significantly contribute to noncompliance and therapy failure. It is therefore important to have access to a range of therapies that can be trialed for individual patients.

Furthermore, type 2 diabetes (T2D) is a progressive condition with a gradual and continuing loss of β -cell function.^{13,14} This results in deterioration in glycemic control and eventually for the need for insulin-replacement therapy.¹⁵ This long-term requirement for the escalation of therapy provides additional pressure to have access to a range of therapies. Additionally, excess adiposity is seen in most T2D patients¹⁶ and is associated with insulin resistance,¹⁷ and targeting it is an important consideration in diabetes management.

The twenty-first century has seen the emergence of several new classes of antidiabetic drugs. One is the sodium glucose cotransporter (SGLT)-2 inhibitors. Dapagliflozin is the first in this class of new therapies. It is currently licensed by the US Food and Drug Administration (FDA; in January 2014),¹⁸ the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA; in April 2012)¹⁹ and the Medicines and Healthcare Products Regulatory Agency in the UK, the Ministry of Health, Labour, and Welfare (MHLW) in Japan (March 2014),²⁰ and by the Scottish Medicines Consortium (in January 2013).²¹

The aim of this article is to review the literature on dapagliflozin with regard to its mechanism of action, efficacy, side

effects, drug interaction, contraindications, and cost. We also review its place in the treatment of T2D.

Materials and methods

An Ovid Medline (1946 to September 2014) search was carried out using the terms “diabetes” and “dapagliflozin”. Papers and abstracts on animal studies and not in English were excluded, including any duplicates (Figure 1). Any useful references cited in these papers/abstracts were also reviewed. A search on ClinicalTrials.gov using the search term “dapagliflozin” was also made to find information on past and ongoing studies. Other sources included the World Health Organization, the FDA, Centers for Disease Control and Prevention, clinical guidelines (including National Institute for Health and Care Excellence technology appraisal), FDA/EMA/UK labeling of summary of product characteristics, briefings, press releases, and Google searches. Conference abstracts were also used.

Mechanism of action

The human nephron reabsorbs almost all of the glucose present in the filtrate, and can do so from as early as 34 weeks of gestation.^{22,23} This comprises 180 g of glucose per day.^{24,25} Only 1% of the filtered glucose makes its way into the urine, and 90% of the filtered glucose is reabsorbed by SGLT2 expressed by epithelial cells lining the first segment of the proximal convoluted tubule. The remaining 10% is reabsorbed by SGLT1 lower in the nephron.^{26,27}

The process of glucose reabsorption^{28–31} starts at the luminal surface of the proximal tubular epithelium, where SGLT2 actively moves glucose from the glomerular filtrate into the epithelial cells (Figure 2). The cotransporters move glucose along with sodium, which is in turn driven by the active transport of sodium out of the basolateral cells by the Na⁺/K⁺-adenosine triphosphatase pump. Glucose transporters (GLUTs) are passive transporters that move glucose out of the cell across the basolateral membrane. This happens along the concentration gradient. This entire process results in glucose being moved from the proximal tubule back into the circulation.

Two genetic disorders²³ have helped our understanding of the working of the SGLT2/GLUT2 transporter molecules: familial renal glycosuria and Fanconi–Bickel syndrome.

Familial renal glycosuria

This autosomal-recessive condition occurs due to mutations in the *SLC5A2* gene, which encodes SGLT2. Persistent glycosuria is present, but without significant disturbance in plasma

Table 1 Some factors to consider while managing patients with diabetes

Factors	Considerations
Age	Licensed indications (eg, dapagliflozin licensed for use in patients 18–75 years of age)
Weight	Weight-neutral or promotion of weight loss in overweight/obese patients
Pregnancy	Contraindications exist for most oral hypoglycemic agents
Renal/hepatic dysfunction	Metabolism of the drug and/or route of excretion
Ease of use	Frequency and timing of medication
Polypharmacy	This can lead to poor patient adherence ¹²
Occupation	HGV drivers and the risk of hypoglycemia
Costs	Individual, national, or insurance costs can dictate medication choice
Side effects	Hypoglycemia, weight gain, gastrointestinal disturbance, edema, etc

Abbreviation: HGV, heavy goods vehicle.

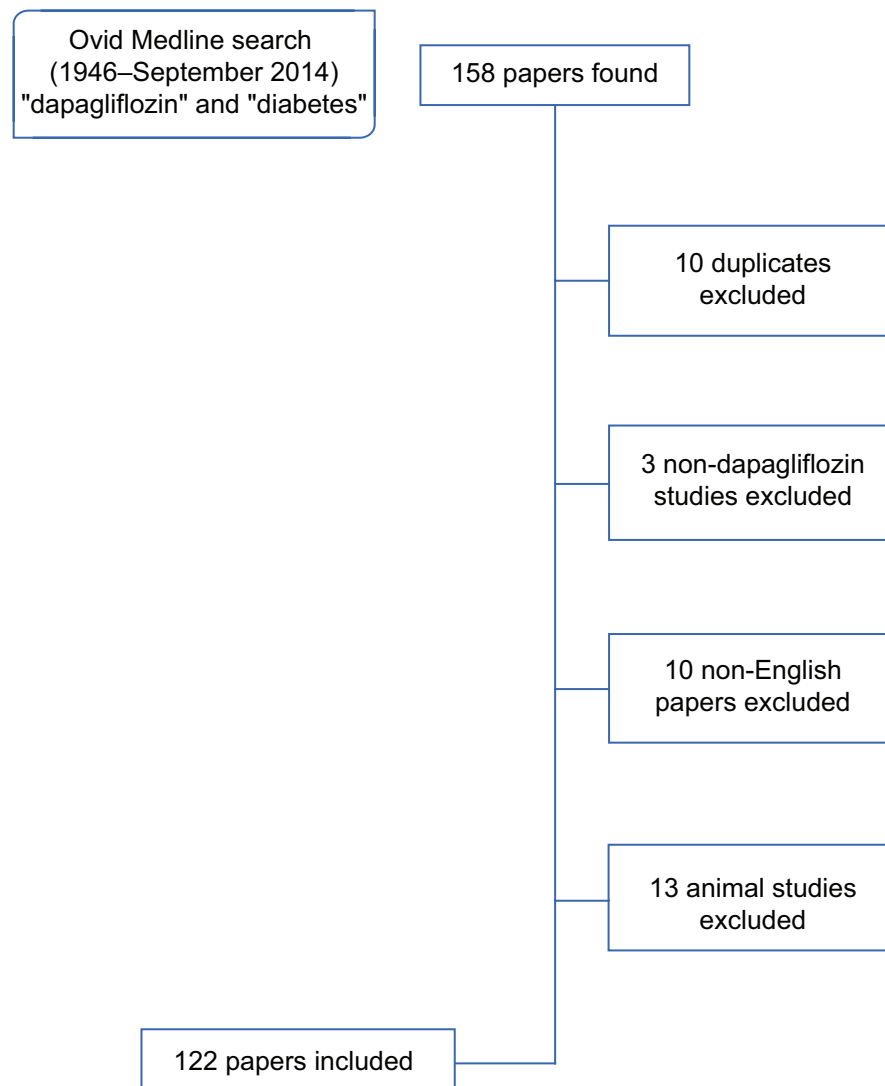


Figure 1 Flow diagram of search process.

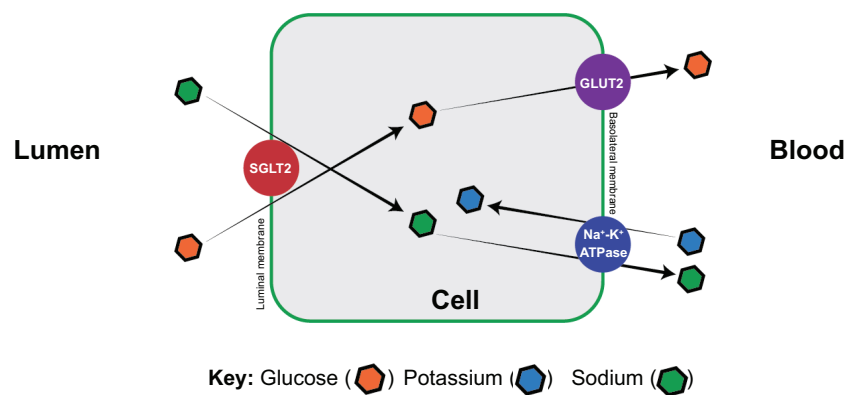


Figure 2 S1 segment of the proximal convoluted tubule of the nephron.

Notes: SGLT2 located on the luminal membrane of the S1 segment of the proximal convoluted tubule of the nephron actively transports glucose from the lumen into the cell against a concentration gradient. The glucose is then transported out through the basolateral side via GLUT2. Na⁺-K⁺ ATPase actively excretes sodium from the cell in exchange for potassium.

Abbreviations: SGLT, sodium glucose cotransporter; GLUT, glucose cotransporter; ATPase, adenosine triphosphatase.

glucose, glucose tolerance, or insulin. This is considered to be a benign condition, and urinary tract infections are only occasionally seen in severe forms of this condition.³²

Fanconi–Bickel syndrome

This is a rare autosomal condition characterized by a mutation in the *SLC2A2* gene, which encodes the GLUT2 transporter, and which results in glycosuria.³³

Phlorizin,^{30,34} first isolated from the root bark of the apple tree in 1835, is an inhibitor of SGLTs. However, this was not used therapeutically due to its nonspecificity for SGLT2. The use of this drug resulted in blockade of intestinal SGLT1, poor intestinal absorption of glucose, and thus led to diarrhea and dehydration. Dapagliflozin, however, is a highly selective competitive and reversible inhibitor of SGLT2,³⁵ and can achieve increased urinary excretion of glucose without the gastrointestinal side effects associated with nonspecific SGLT therapy.

While the mechanism of action of dapagliflozin is primarily through SGLT2 blockade, this may be complicated by the concurrent secretion of glucagon. Recent data³⁶ indicate that SGLT2 is also expressed in human pancreatic α -cells, and therapy with dapagliflozin is described to increase circulating glucagon.³⁷ This increased glucagon potentially dampens the efficacy of SGLT2 inhibitors and needs further examination. This potentially is also protective against hypoglycemia.

Pharmacokinetics

Dapagliflozin (Figure 3) is rapidly and well absorbed after oral administration.^{38,39} Maximum dapagliflozin plasma concentrations occur within 2 hours of administration (in the fasted state). Bioavailability is 78% with the 10 mg once-daily (OD) dosing. It can be taken with or without food.⁴⁰ It is 91% protein-bound, and this is not affected by hepatic or renal disease.

Dapagliflozin is metabolized to its inactive metabolite – dapagliflozin 3-*O*-glucuronide – in the liver and kidney by the enzyme uridine diphosphate-glucuronosyltransferase 1A9. The mean plasma terminal half-life for dapagliflozin is 13 hours (10 mg dosing). Dapagliflozin and its metabolites are mainly excreted via the urine, and the excretion is impaired in

the presence of renal disease;⁴¹ 15% is excreted unaltered via the feces and 2% excreted unaltered via the urine.

There do not appear to be any ethnic variations in the pharmacokinetics or pharmacodynamics of dapagliflozin, though to date this has only been examined in studies in Chinese⁴² and Japanese⁴³ populations.

Pharmacodynamics

Dapagliflozin is associated with dose-dependent glycosuria and increased diuresis averaging 375 mL/day.^{38,39,44,45} There is a transient increase in urinary sodium excretion, but this does not appear to affect serum sodium. There is a transient increase in urinary uric acid excretion, but a sustained reduction in serum uric acid levels. The mechanism of reduced serum uric acid levels is unclear, but was recently proposed to be due to glycosuria-induced uric acid secretion via GLUT9 isoform 2 in the proximal tubule or inhibition of uric acid uptake at the collecting duct of the renal tubule.⁴⁶ Additionally, this could be due to the weight reduction associated with dapagliflozin.

Place in management

Dapagliflozin can be used as monotherapy or in combination with other oral hypoglycemic agents and insulin.⁴⁷ It can be used at any stage of the natural history of T2D.⁴⁸ It has now been placed within clinical guidelines⁸ as monotherapy and in combination therapy where the renal function is not chronic kidney disease (CKD) stage 3 or lower (<60 mL/min/1.73 m²).

While studies have used various doses of dapagliflozin, for the purposes of this review we only report the results of the 5 and 10 mg doses, because only these are currently licensed for therapy.

Monotherapy

Dapagliflozin has been studied as a monotherapy against placebo^{49–53} and versus metformin or placebo.⁵⁴ In these studies, the mean HbA_{1c} reduction compared to placebo at 24 weeks was 0.66–1.45%, and weight reduction was 1.0–2.73 kg. There was a reduction in fasting glucose, and more patients achieved an HbA_{1c} $<7\%$ in at least one study. Genital and urinary infections are more common (3.7% and 2.3% difference, respectively) compared to placebo.⁵³

Dual therapy

In dual therapy, dapagliflozin has been studied (against placebo) with metformin,^{55–60} metformin slow/extended release,^{51,54} glimepiride,^{61,62} pioglitazone,⁶³ sitagliptin,⁶⁴ and exenatide.⁶⁵

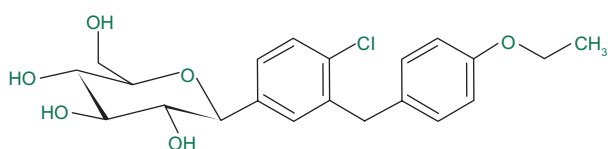


Figure 3 Chemical structure of dapagliflozin.

The highest reduction in HbA_{1c} was seen when dapagliflozin was combined with metformin. Here, HbA_{1c} reduced by 0.8% following 102 weeks of therapy,⁵⁶ compared to 0.5%–0.68% when combined with the other agents. The highest reduction in weight was seen when combined with sulfonylureas (SUs). When combined with glipizide, an average 4.4 kg in weight was lost compared to glipizide alone.^{58–60} In comparison, weight loss of 1.74 kg with metformin⁵⁶ and 1.8 kg with sitagliptin has been reported.⁶⁴ Across all studies, a 5%–10% increase in genital infections was reported. There are no human studies of dapagliflozin with glucagon-like peptide-1 analog therapy.

Triple therapy

Dapagliflozin has been used with metformin and sitagliptin,^{64,66} metformin and saxagliptin,⁶⁷ and metformin and an SU,⁶⁸ in triple combinations. HbA_{1c} reduction of up to 0.6% and body weight reductions of 2.2 kg were reported. Genital and urinary infections were higher than in control groups.⁶⁰

With insulin

A number of studies of dapagliflozin in combination with insulin have been undertaken, and a further study is ongoing (ClinicalTrials.gov identifier: NCT02096705). Studies to date demonstrate benefits in HbA_{1c} (–0.4%), weight (–3.33 kg), along with a stable insulin dose (–19.2 units when compared to increased requirements in the placebo group) at 104 weeks. Increased hypoglycemia rates were noted at 48 weeks, which leveled out by 104 weeks. There were higher rates of genital and urinary infections.^{69–71}

Meta-analyses of dapagliflozin efficacy

There have been several meta-analyses on dapagliflozin to date.^{72–76} They suggest that treatment with dapagliflozin results in average improvement in HbA_{1c} by 0.50%, fasting plasma glucose by 1.1 mmol/L, weight by 2 kg (4.5 kg when used with SUs), body mass index by 1.1%, and systolic/diastolic blood pressure (BP) by 4/2 mmHg, but is associated with an increased risk of genitourinary (odds ratio 3.50) and urinary tract (odds ratio 1.40) infections. These analyses are summarized in Table 2 and show placebo-subtracted data from randomized controlled trials. By way of illustration, in one meta-analysis, study durations ranged between 12 and 104 weeks, with about 4,000 patients randomized across these randomized controlled trials (n=12).⁷²

Benefits other than glucose Weight

Weight loss is a benefit of therapy with dapagliflozin. It is thought to be through fluid loss in the initial phase of

treatment, and then a more gradual loss through the net calorie deficit (typically 200–300 kcal per day). More recently, it has been shown that dapagliflozin therapy also reduces fat mass.^{77,78} Meta-analyses (Table 2) show about a 1–2 kg weight reduction with this agent, and up to 5 kg when used in combination with SUs.

Hypertension

Investigators have noted a lowering of both systolic and diastolic BP in patients, and this is thought to be due to a combination of the diuretic effect of glycosuria, a natriuretic effect,⁷⁹ as well as via weight loss. The BP lowering is noted as early as 1–2 weeks of treatment initiation, and averages 4/2 mmHg.²⁹ The BP-lowering effects of dapagliflozin also manifest in patients on established antihypertensive therapy.⁸⁰

Sjöström et al⁸¹ pooled safety data from 13 placebo-controlled Phase IIB/III studies, and found a slightly higher cumulative frequency of orthostatic reactions over 24 weeks with dapagliflozin (13.1% versus 11.3% with placebo), although adverse events due to orthostatic hypotension were rare (0.1%) and not serious.

Lipids

Dapagliflozin 10 mg OD has shown a mean change compared to placebo in total cholesterol of 2.5%, high-density lipoprotein of 3.3%, low-density lipoprotein of 3.9%, and triglycerides of –2.0%.³⁸ Meaningful long-term data are required to understand if this has any clinical impact.

Quality of life

Dapagliflozin-treated patients have been shown to have a high health-related quality-of-life (HRQOL, EQ-5D) score in several domains. This persisted for 102 weeks.⁸² In a triple-therapy regimen, dapagliflozin showed greater improvement over placebo in weight change-related QOL, similar obesity-specific QOL, and greater treatment satisfaction.⁸³

Side effects

Genital (vulvovaginitis and balanitis) infections

Genital infections are by far the commonest side effect of dapagliflozin. Pooled data from 12 studies⁸⁴ suggest infection rates of 5.7%, 4.8%, and 0.9% of study subjects treated with dapagliflozin 5 mg (n=1,145), 10 mg (n=1,193), or placebo (n=1,393), respectively. These were mainly mild or moderate infections that occurred in the first 6 months with low risk of recurrence or new emergent infections with prolonged therapy. Those with a previous history of these

Table 2 Meta-analyses of dapagliflozin

Study	Year published	RCTs included, n	Theme of the meta-analysis	Summary
Musso et al ¹⁵	2012	13	Efficacy and safety of dapagliflozin	<ul style="list-style-type: none"> ↓ HbA_{1c} (−0.52%, 95% CI −0.46% to −0.57%; $P<0.00001$) ↓ FPG (−18.28 mg/dL [1.01 mmol/L], 95% CI −20.66 [−1.15 mmol/L] to −15.89 [0.88 mmol/L]; $P<0.00001$) ↓ BMI (−1.17%, 95% CI −1.41 to −0.92; $P<0.00001$) ↓ SBP (−4.08 mmHg, 95% CI −4.91 to −3.24) ↓ DBP (−1.16 mmHg, 95% CI −1.67 to −0.66) ↓ Serum uric acid (−41.50 μmol/L, 95% CI −47.22 to −35.79) ↑ Risk genital infections (OR 3.57, 95% CI 2.59–4.93) ↑ Risk of UTIs (OR 1.34, 95% CI 1.05–1.71) ↑ Hypoglycemia (mild) when added to insulin (OR 1.27, 95% CI 1.05–1.53)
Vasilakou et al ¹⁶	2013	3 ^a	Efficacy and safety of SGLT2 inhibitors	<ul style="list-style-type: none"> ↓ HbA_{1c} (−0.59%, 95% CI −0.67% to −0.50% versus placebo) ↓ BW (−1.92 kg, 95% CI −2.23% to −1.60%; $P<0.00001$ versus placebo) ↓ SBP/DBP ↓ CV events (OR 0.73, 95% CI 0.46–1.16) ↑ Genital infections (OR 3.48, 95% CI 2.33–5.20 versus placebo; OR 4.81, 95% CI 2.97–7.81 versus active agent) ↑ UTIs (OR 1.43, 95% CI 1.05–1.94 versus placebo; OR 1.69, 95% CI 1.19–2.40 versus active agent) ↑ Hypoglycemia (OR 1.20, 95% CI 0.88–1.64 versus placebo; OR 0.49, 95% CI 0.18–1.39 versus active agent) ↑ Hypotension
Goring et al ¹⁴	2014	6	Adding dapagliflozin versus other OHAs to metformin monotherapy (1-year data)	<ul style="list-style-type: none"> Similar efficacy Similar or reduced hypoglycemic episodes Added benefit of weight reduction (versus DPP-4 inhibitors, −2.74 kg, 95% CI −5.35 to −0.10); versus SUs, −4.67 kg, 95% CI −7.03 to −2.35)
Sun et al ⁷²	2014	12	Synergism of dapagliflozin in combination with other OHAs	<ul style="list-style-type: none"> ↓ HbA_{1c} (−0.52%, 95% CI −0.60% to −0.45%; $P<0.001$) ↓ FPG (−1.13 mmol/L, 95% CI −1.33 to −0.93; $P<0.001$) ↓ BW (−2.10 kg, 95% CI −2.32 to −1.88; $P<0.001$)
Zhang et al ⁷³	2014	10	Efficacy and safety of dapagliflozin	<ul style="list-style-type: none"> ↓ HbA_{1c} (−0.53%, 95% CI −0.58% to −0.47%; $P<0.00001$) ↓ FPG (−1.06 mmol/L, 95% CI −1.20 to −0.92; $P<0.00001$) ↓ BW (−1.63 kg, 95% CI −1.83 to −1.43; $P<0.00001$) No hypoglycemia as monotherapy ↑ Hypoglycemia (RR 1.16, 95% CI 1.05–1.29; $P=0.005$) when added to a hypoglycemic agent ↑ Risk of UTIs (RR 1.33, 95% CI 1.10–1.60; $P=0.004$) ↑ Risk of genital infections (RR 3.23, 95% CI 2.50–4.18; $P=0.00001$)

Note: ^aSeveral studies used.

Abbreviations: BMI, body mass index; BW, body weight; CI, confidence interval; DBP, diastolic blood pressure; DPP, dipeptidyl peptidase; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; OHAs, oral hypoglycemic agents; OR, odds ratio; RCTs, randomized controlled trials; RR, relative reduction; SBP, systolic blood pressure; SGLT, sodium glucose cotransporter; SUs, sulfonylureas; UTIs, urinary tract infections.

infections were at higher risk. These infections responded to standard oral antibiotic therapy. Therapy discontinuation was rare.

Urinary tract infections

Urinary tract infections have also been reported.⁸⁵ For dapagliflozin 5mg, 10 mg, or placebo, urinary tract infections were reported in 5.7%, 4.3%, and 3.7% of patients, respectively. Again, these were mild or moderate infections that responded to standard oral antibiotic therapy. Therapy discontinuation for this reason was also rare (0.3% with dapagliflozin and 0.1% with placebo). There was no increase in serious infections, eg, pyelonephritis.

Hypoglycemia

Hypoglycemia is not associated with dapagliflozin monotherapy, nor with dual therapy with metformin. It is associated with less hypoglycemia than SUs.⁶⁰ Dapagliflozin is however associated with an increased risk of hypoglycemia when used with other hypoglycemic agents, such as insulin and SUs.⁷³ It is advisable that the dose of these agents are downtitrated at initiation of dapagliflozin in order to reduce the risk of hypoglycemia at the onset of therapy.

Dehydration

Volume depletion (dehydration, hypotension, or hypovolemia) appears uncommon with dapagliflozin therapy. These were reported at 0.8% versus 0.4% for dapagliflozin 10 mg OD versus placebo (not statistically significant).

Other side effects

Some common side effects of dapagliflozin include back pain, dyslipidemia, dizziness, and hematocrit increase.³⁸

Potential for “off-target” effects that need further monitoring

Renal dysfunction

Mean estimated glomerular filtration rate (GFR) and creatinine clearance appear to fall in the first week with dapagliflozin therapy, but remain stable thereafter up to 104 weeks and return back to baseline after 2–6 months, whereas there is a continual slow decline seen with placebo. The changes in the first week are felt to be due to the diuretic and antihypertensive effect and a possible enhanced tubuloglomerular feedback.^{86,87} The creatinine changes are reversible,⁸⁸ and therefore do not appear to demonstrate an irreversible damage to the nephrons.

Cancer

The FDA had highlighted increased signals for cancer seen in early studies.⁸⁹ These were bladder and breast cancer. For bladder cancer, there were nine patients on dapagliflozin and one on placebo (0.3% versus 0.05%, respectively). All patients were male, and most were aged ≥ 60 years. There was a current or past smoking history in six patients, and five had microscopic hematuria at baseline from the dapagliflozin group.

There were nine patients who developed breast cancer (compared to one in the control group; 0.4% versus 0.1%, respectively). All were aged over 50 years (seven were over 60 years in age), all diagnoses were made within the first year of exposure, and two diagnoses were made within the first 8 weeks of exposure to dapagliflozin.

The duration of exposure to dapagliflozin was too short to be attributable to these cancers. The cancer risk was subsequently reevaluated⁸⁹ and license-authorized by the FDA.¹⁸

The safety of dapagliflozin has been examined in animal studies and also the effects of dapagliflozin and increased glucose on human bladder transitional cell carcinoma cell lines and in vivo xenograft models. There was no increased cancer with dapagliflozin in either of these models.⁹⁰ Furthermore, canagliflozin, a comparator medication, has not shown a higher incidence in these cancers, but this could be due to different monitoring precautions. However, longer-term human safety data are awaited.

Dosage

Dapagliflozin is marketed under the trade names of Forxiga[®] in the EU⁹¹ and in the US as Farxiga[®].¹⁸ It is available in 5 mg or 10 mg strengths. It is also available in combination with metformin, under the trade name of Xigduo[®], in 5 mg/850 mg or 10 mg/850 mg (dapagliflozin/metformin) strengths.⁹²

Contraindications

Age

Due to comorbidities, concurrent medication, and risk of volume depletion, dapagliflozin is to be used with caution in the ≥ 65 -year age group; it is not recommended in those aged ≥ 75 years (Table 3). Barring these considerations, a placebo-controlled pool of nine double-blind Phase IIB/III studies shows dapagliflozin is safe and well tolerated in old patients with T2D up to 104 weeks of studied data.⁹³

Pregnancy

There are no trials to support the use of dapagliflozin in pregnancy. The manufacturers advise to discontinue

Table 3 Differentiating features between dapagliflozin/empagliflozin

Drug	Age of patient (years)	Renal impairment (eGFR: mL/min/1.73 m ²)	Severe hepatic impairment	Side effects
Dapagliflozin	≥65: volume depletion should be taken into account ≥75: not recommended	<60: not recommended	Start at 5 mg OD; if tolerated, can use 10 mg OD	–
Empagliflozin	≥75: volume depletion should be taken into account ≥85: not recommended	<60: do not initiate; if eGFR falls to this level, maintain or reduce to 10 mg OD when already on <45: do not use, and stop when already on	Do not use	–
Canagliflozin	≥65: volume depletion should be taken into account	<60: do not initiate; if eGFR falls to this level, maintain or reduce to 100 mg OD when already on <45: do not use, and stop when already on	Do not use	Vulvovaginal candidiasis appears to have a higher incidence ^b compared to dapagliflozin and empagliflozin)

Notes: ^aSafety data in chronic kidney disease 3A (45–59 mL/min/1.73 m²) is available for both canagliflozin¹⁴ and empagliflozin¹⁵; ^bdescribed as “very common” (> 1/10 frequency) in canagliflozin versus “common” (≥ 1/100 to < 1/10) in dapagliflozin and empagliflozin (based on information available in the summary of product characteristics for each drug).

Abbreviations: eGFR, estimated glomerular filtration rate; OD, once daily.

treatment if pregnancy is detected.³⁸ In rat studies, toxicity to the developing kidney was observed in the time period corresponding to the second and third trimesters.

Use of dapagliflozin in the presence of renal, liver, and cardiovascular disease

Renal disease

The glycemic benefit of dapagliflozin persists in renal disease at least down to the level of CKD stage 3 (≥60 mL/min/1.73 m²).⁸⁷ It has not been tested in patients with more significant renal disease. Therapy also induces weight loss (–1.33 and –1.68 kg for 5 and 10 mg, respectively) and lowers BP. Importantly, there is no further deterioration in renal function in these patients. Therefore, there is potentially some benefit in CKD stage 3A (45–59 mL/min/1.73 m²) patients, but only of a modest nature. Longer-term studies are required.

Liver disease

T2D is associated with liver disease.^{94,95} Dapagliflozin has been tested in patients with varying degrees of liver disease at a dose of 10 mg. It was well tolerated, and there was no change in liver-function tests.⁹⁶ In clinical practice, no dosage modification is necessary with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended by the manufacturers, and if the medication is well tolerated, the dose may be increased to 10 mg.³⁸

Cardiovascular disease

Dapagliflozin has been shown to be safe and efficacious in a large (964 patients) study of older T2D patients with coexistent cardiovascular disease.⁹⁷ Dapagliflozin improved glycemic control without an increase in hypoglycemia, promoted weight loss, and was well tolerated in the study subjects, and these benefits persisted for 2 years.⁹⁸

There is an ongoing study (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events [DECLARE-TIMI58], ClinicalTrials.gov identifier: NCT01730534), further evaluating this subject and due to end in April 2019.

There is a 20-year simulation study⁹⁹ estimating the long-term cardiovascular and microvascular outcomes that found relative reductions in the incidence of myocardial infarction, stroke, cardiovascular death, and all-cause death of 13.8%, 9.1%, 9.6%, and 5.0%, respectively, and relative reductions in

the incidence of end-stage renal disease, foot amputation, and diabetic retinopathy of 18.7%, 13.0%, and 9.8%, respectively, when compared with standard care, thereby potentially showing additional benefits with adding dapagliflozin to standard therapy in reducing diabetes-related complications.

Use of dapagliflozin in other contexts

Ethnicity

Studies have now shown efficacy of dapagliflozin in Chinese^{42,53} and Japanese^{41,43,100} populations. These studies demonstrated that it is as effective at lowering glucose in these populations as it is in the white Caucasian population. There is, however, a need for studies in other ethnicities.

Type I diabetes

There is currently one study that has examined dapagliflozin in type 1 diabetes (T1D). This was a randomized, double-blind, placebo-controlled, parallel-group, Phase II trial (ClinicalTrials.gov identifier: NCT01498185). It was designed to explore dapagliflozin (1, 2.5, 5, 10 mg OD) as an add-on to insulin therapy in subjects with T1D. A dose-dependent increase in urinary glucose and a reduction in glycemic levels/variability and total daily dose of insulin was noted with dapagliflozin. Hypoglycemia was noted to be common in all treatment groups, and led to discontinuation in one patient on dapagliflozin 10 mg OD due to a major hypoglycemic event.¹⁰¹

Another gliflozin, empagliflozin, has been studied¹⁰² in an open-label 8-week trial at a dose of 25 mg OD on renal hyperfiltration in T1D. Patients were divided into those with renal hyperfiltration ($\text{GFR} \geq 135 \text{ mL/min/1.73m}^2$, $n=27$) or normal GFR ($\text{GFR} 90\text{--}134 \text{ mL/min/1.73m}^2$, $n=13$). A statistically significant reduction in total daily dose of insulin and in HbA_{1c} was observed in both study groups. There is therefore proof of concept for the use of SGLT2 inhibitors for the therapy of T1D.

Drug–drug interactions

Dapagliflozin and loop diuretics are advised not to be used together, in order to avoid hypotension and dehydration. Lack of interaction has been shown between dapagliflozin and simvastatin, valsartan, warfarin, digoxin, rifampin, or mefenamic acid.^{103,104}

Other considerations

Cost

Dapagliflozin is a cost-effective treatment when used in combination with insulin in patients with T2D. Van Haalen et al¹⁰⁵

used the Cardiff Diabetes Model to show a lower incidence of both micro- and macrovascular complications, a greater life expectancy, and an incremental benefit of 0.42 quality-adjusted life-years (QALYs). They conclude that the lifetime incremental cost per patient in those taking dapagliflozin was €2,293, with a €27,779 incremental cost-effectiveness ratio per life-year gained and a €5,502 incremental cost-utility ratio per QALY gained.

Sabale et al¹⁰⁶ studied the cost-effectiveness of dapagliflozin added to metformin compared to an SU added to metformin in patients with T2D and inadequate diabetes control. In this 52-week Scandinavian study, there was a gain in cost per QALY ranging between €4,769 and €7,944. The QALY gains for the dapagliflozin group were reported to be between 0.236 and 0.278, with incremental costs between €1,125 and €1,962.

In the UK, the National Institute for Health and Care Excellence has undertaken a technology appraisal (TA288) to evaluate the cost-effectiveness of dapagliflozin.¹⁰⁷

What does the future hold for the SGLT2 inhibitors?

Competition within this class of drug is proving to be fierce,¹⁰⁸ with several other SGLT2 inhibitors on the market: canagliflozin, developed by Janssen-Cilag (approved by the FDA in March 2013 and EMA in November 2013); empagliflozin, developed by Boehringer Ingelheim and Eli Lilly (approved by the EMA in March 2014 and the FDA in August 2014); ipragliflozin,¹⁰⁹ developed by Astellas Pharma and Kotobuki Pharmaceutical (approved by the MHLW, Japan in January 2014); tofogliflozin,¹¹⁰ developed by Chugai Pharmaceutical (approved by the MHLW, Japan in March 2014), and luseogliflozin,¹¹¹ developed by Taisho Pharmaceutical (approved by the MHLW, Japan in March 2014).

There are yet more molecules, including ertugliflozin¹¹² and remogliflozin,¹¹³ that have undergone development through Phase I, II, and III trials, with some, including remogliflozin, that have been discontinued. While the currently available SGLT2 inhibitors are broadly similar, there are some differentiating features (Table 3).

Conclusion

Dapagliflozin is the first class SGLT2 inhibitor licensed for use in adult patients with T2D. Large studies have demonstrated glycemic benefit with this therapy without significant hypoglycemia. There are also benefits with BP, weight, and lipids that may translate to cardiovascular benefit.

However, a number of important clinical questions remain to be answered, and we require further reassurance on issues relating to safety. Specifically, we see these as being:

1. the safety profile in patients over the age of 75 years and in pediatric patients
2. the efficacy profile in estimated GFR <60 mL/min/1.73 m², particularly when other agents have these data already available
3. the long-term cardiovascular safety and risk-modification profile
4. cancer safety data, particularly bladder cancer, in view of the increased glucose load passing through the urinary system
5. combination use with glucagon-like peptide-1 agonists
6. use in T1D, pregnancy, monogenic forms of diabetes, and other conditions resulting in hyperglycemia
7. efficacy across different ethnicities.

Regardless, dapagliflozin makes a significant contribution to the range of therapies we require for the optimal management of patients with T2D. Its action is not affected by where a patient lies in the natural history of diabetes and regardless of residual β -cell function. It is also independent of the mechanisms through which other oral hypoglycemic agents work, such as increasing insulin or decreasing glucagon secretion, reducing gluconeogenesis or insulin resistance, slowing intestinal carbohydrate digestion/absorption, or increasing glucose deposition into liver, muscle or fat tissues. This allows for a versatile therapy that can be used in patients who are drug-naïve, as well as those on established blood glucose-lowering therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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