REVIEW

Patient considerations in the management of type 2 diabetes – critical appraisal of dapagliflozin

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Abstract: Type 2 diabetes affects more than 350 million people worldwide, and its prevalence is increasing. Many patients with diabetes do not achieve and/or maintain glycemic targets, despite therapy implementation and escalation. Multiple therapeutic classes of agents are available for the treatment of type 2 diabetes, and the armamentarium has expanded significantly in the past decade. Selective sodium glucose co-transporter 2 inhibitors, including dapagliflozin, represent the latest development in pharmacologic treatment options for type 2 diabetes. This class has a unique mechanism of action, working by increasing glucose excretion in the urine. The insulin-independent mechanism results in decreased serum glucose, without hypoglycemia or weight gain. Dapagliflozin is a once-daily oral therapy. Expanding therapy options for a complex patient population is critical, and dapagliflozin has a distinct niche that can be a viable option for select patients with diabetes.

Keywords: SGLT2 inhibitor, selective sodium glucose co-transporter 2 inhibitors, pharmacological treatment

Introduction

Type 2 diabetes affects more than 350 million people worldwide, with increasing prevalence due to the aging population, increasing obesity rates, and greater representation of high-risk ethnic groups.[1] The pathophysiology of diabetes is multifactorial, with elements of insulin resistance, insulin deficiency, progressive beta cell decline, and dysregulation of incretin hormones. The resultant hyperglycemia is a known contributor to multiple chronic complications, including cardiovascular disease, retinopathy, neuropathy, and nephropathy. Goals for glycemic indices have been established using clinical evidence, and endorsed by expert guidelines and position statements. Yet, these goals prove difficult to achieve and maintain in clinical practice.[2–4] Evidence indicates that only about half of adult patients with type 2 diabetes achieve glycemic goals.[5,6] For those patients who do reach the recommended hemoglobin A_{1c} (A_{1c}) goal, control is lost at a rate of 5%–10% per year.[7,8] Adequate management of the condition is complex, requiring a combination of lifestyle modifications and pharmacological therapy.[3] The progressive nature of diabetes results in the need for more intensive approaches to glycemic control over time, and the majority of patients require multiple medications with complementary mechanisms of action.[3]

There are multiple therapeutic classes of agents available for the treatment of type 2 diabetes, and the armamentarium has expanded significantly in the past decade. Available therapeutic agents vary in mechanism, efficacy, safety, and route of administration. Metformin, one of the oldest therapeutic agents, works primarily by limiting hepatic glucose

production, via an increase in hepatic insulin sensitivity; it has a long record of clinical efficacy. As the most consistently recommended first-line agent, metformin is not without disadvantages. Although it is weight neutral, with a low risk of hypoglycemia, the risk of rare (but potentially fatal) lactic acidosis requires careful patient selection, avoiding those with renal insufficiency and unstable heart failure.[3] Additionally, gastrointestinal side effects can limit its use for some patients.[3] Insulin secretagogues, including sulfonylureas and meglitinides, have demonstrated clinical efficacy in the short term, but do not demonstrate durability over time.[3] In addition, these work by stimulating endogenous insulin secretion. Thus, they carry a high risk of hypoglycemia, contribute to weight gain for most patients, and depend upon functional beta cells for efficacy.[3] Thiazolidinediones increase insulin sensitivity in the periphery, and demonstrate clinical efficacy that is sustainable over time.[9] Hypoglycemia is not common when they are used as monotherapy. However, fluid retention and weight gain limit their use, especially in combination with insulin, or in patients with heart failure.[9] Alpha-glucosidase inhibitors delay the breakdown and absorption of glucose, thereby decreasing postprandial glucose following oral administration.[10] This class requires multiple daily dosing, and slow dose titration is necessary to improve tolerability.[10] Intolerable gastrointestinal side effects are common, and the overall efficacy of this class is minimal. Newer pharmacological classes include therapies that target incretin hormones, such as glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl-peptidase-IV (DPP-IV) inhibitors. The GLP-1 agonists promote glucose-dependent insulin secretion, inhibition of inappropriate post-prandial glucagon secretion, and slowed gastric emptying.[3] Available agents within this class are administered via subcutaneous injection, and range from twice-daily to once-weekly dosing frequency. Hypoglycemia is uncommon when they are used as monotherapy, and significant weight loss often results with continued use.[11,12] Side effects common to this class include nausea, which is often limiting; pancreatitis and acute renal changes are emerging risks.[11,12] A US Food and Drug Administration (FDA) boxed warning is in place for this class, due to the risk of medullary thyroid cancer, identified in animal studies; the class is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[11,12] DPP-IV inhibitors block the enzyme responsible for degradation of endogenous GLP-1, thereby exerting a mechanism of action similar to GLP-1 agonists.[3] Clinical efficacy is less robust than with direct GLP-1 agonists. However, this class is administered orally once-daily, which is often considered more desirable by patients. DPP-IV inhibitors are very well

tolerated, with minimal hypoglycemia, and a potential for weight loss.[3] Exogenous insulin therapies are the most effective pharmacological agents, with no dose limitations, and a mechanism that directly addresses insulin deficiency.[3] Newer insulin analogues provide enhanced pharmacokinetic profiles that more closely mimic natural physiology, thereby minimizing hypoglycemia. Nonetheless, hypoglycemia remains a significant concern, and weight gain is a near certain result of dose titration.[3]

Evidence-based and expert consensus guidelines and position statements have been published in an effort to guide clinicians in patient-centered therapy selection, given the growing number of pharmacologic categories. The position statement of the American Diabetes Association and European Association for the Study of Diabetes endorses metformin as a first-line recommendation, followed by patient-specific selection for add-on therapy, considering clinical efficacy, risk of hypoglycemia, effects on weight, and cost.[3] The American Association of Clinical Endocrinologists, in 2013, also recommended a patient-centered approach to therapy selection, including metformin as an option for first-line therapy, but also including GLP-1 agonists, DPP-IV inhibitors, and alpha-glucosidase inhibitors as alternate first-line options.[4] Although the guideline recommendations differ in some specific instances, recognition of therapy limitations remains the same. Common side effects, such as hypoglycemia, weight gain, and gastrointestinal issues, as well as safety concerns over renal and/or hepatic dysfunction, limit the use or dose maximization of available medications. Additionally, the progressive nature of the disease necessitates additional therapies targeting the multifaceted pathophysiology. Selective sodium glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin, represent the latest development in pharmacologic treatment options for type 2 diabetes. This class offers some unique advantages, when compared with other classes available, including low risks of hypoglycemia and weight gain, once-daily dosing, and a minimal side effect profile. Dapagliflozin is currently approved in Australia, Brazil, Mexico, New Zealand, the European Union, and the United States.[13,14]

Pharmacology

Healthy kidneys reabsorb nearly 99% of filtered plasma glucose, leaving only 1% to be excreted in the urine.[15,16] Sodium glucose co-transporters (SGLTs) mediate this reabsorption. SGLT2 functions within the proximal convoluted tubule, and is responsible for approximately 90% of renal glucose reabsorption, while SGLT1 is expressed within

the gastrointestinal tract, as well as the renal tubules, and is responsible for reabsorbing the remaining 10%.[17–19] In the setting of hyperglycemia (plasma glucose >200 mg/dL), the overall amount of glucose excreted in the urine is increased. However, the SGLTs become saturated, leading to inability of the kidneys to effectively sustain enough glucose excretion to maintain euglycemia.[20] Inhibition of SGLT2 blocks sodium and glucose reabsorption, thereby increasing urinary glucose excretion, and decreasing plasma glucose concentration.[21,22] The transport of sodium and glucose by the SGLT2 protein is driven by the sodium gradient between the proximal tubule and the tubular epithelial cells.[19,21] Therefore, in addition to induction of glycosuria, additional fluid is excreted due to the reduction in sodium reabsorption.[19,21]

Because the mechanism of action is independent of insulin secretion, the SGLT2 class does not require functioning beta cells in order to be effective, and has limited risk of hypoglycemia and weight gain.[23,24] Dapagliflozin is a selective, competitive, reversible inhibitor of SGLT2.[14] Selectivity for SGLT2 is an important advantage of the class, because SGLT1 is expressed to a greater extent in the gastrointestinal tract, and has demonstrated in animal studies an increased likelihood of gastrointestinal side effects, such as diarrhea and dehydration.[25] Additionally, SGLT1 is responsible for only 10% of urinary glucose excretion, making it a less effective target for therapy.[23]

Pharmacokinetics

Taken orally, dapagliflozin has a bioavailability of >75%, and is rapidly absorbed into systemic circulation.[26] A dose–response relationship has been observed: glycosuria is induced after the initial dose; maximum plasma concentration is demonstrated within 2 hours.[23] The mean elimination half-life is 12.9 hours, and dapagliflozin is 91% bound to plasma proteins.[23] Metabolism to inactive metabolites occurs primarily via glucuronidation and, the cytochrome P450 (CYP) enzyme pathway is a minor clearance pathway.[26] Elimination occurs primarily via renal excretion of inactive metabolites.[14] Dapagliflozin does not induce or inhibit CYP isoenzymes.[23] The pharmacokinetic profile of dapagliflozin is not significantly affected by age, sex, ethnicity, or the timing of administration.[23]

Drug interactions

Since the metabolism of dapagliflozin does not induce or inhibit CYP isoenzymes, there are minimal potential drug interactions.[23] Pharmacokinetic analyses have been conducted, to include potential drug interactions with other common antidiabetic and cardiovascular agents.[27,28] The first analysis found no concern, or need for dose adjustments, when used in combination with pioglitazone, metformin, glimepiride, or sitaglipitin.[27] The second analysis expanded the list, to find no concerns with administering dapagliflozin in combination with simvastatin, valsartan, warfarin, or digoxin.[28] The drugs assessed in the two analyses included a range of metabolic pathways.

Dapagliflozin may increase the risk of volume depletion, so its use with loop diuretics is not recommended. Additional caution is warranted for patients at risk for volume depletion and/or hypotension, such as those with acute illness, cardiovascular disease, concomitant antihypertensive therapy (especially thiazide diuretics), history of hypotension, and the elderly. Volume depletion may be more evident in patients with very high blood glucose levels. Careful monitoring of volume status and electrolytes is recommended when using dapagliflozin.[26]

Efficacy

Dapagliflozin is indicated for the treatment of type 2 diabetes as monotherapy, and as add-on therapy with many other antidiabetic agents. US prescribing information supports the combination of dapagliflozin with metformin, pioglitazone, glimepiride, sitagliptin (with or without metformin), and insulin (with or without other oral antidiabetic agents).[14]

Current European prescribing information does not recommend the combination of dapagliflozin and pioglitazone, as a precautionary measure, because studies are ongoing to evaluate pioglitazone and the risk of bladder cancer.[26] Dapagliflozin has not been studied in combination with GLP-1 agonists.[14,26] Phase III clinical trials, highlighting its use as monotherapy and add-on therapy, are summarized in Table 1.

Limited head-to-head studies have been performed with dapagliflozin. A 52-week randomized, multi-site, double-blind, parallel-group, active controlled, non-inferiority study compared dapagliflozin with glipizide in patients inadequately controlled on metformin. The study included 814 patients who had A_{1c} 6.5%–10% while on metformin or metformin plus one additional oral antidiabetic medication (up to half-maximal dose). The study began with an 8-week period, when other antidiabetic agents were discontinued and patients were stabilized on metformin 1,500–2,000 mg/day. Level 1 of the study included randomization, in a 1:1 fashion, to dapagliflozin 2.5 mg or glipizide 5 mg. Doses were titrated up to dapagliflozin 10 mg and glipizide 20 mg, as tolerated. The primary endpoint resulted in statistical

Table 1 Phase III clinical trials of dapagliflozin as monotherapy or add-on therapy

Study	Methods	A$_{1c}$ reduction (% adjusted mean change from baseline)[a]	Other statistically significant[b] findings
Dapagliflozin monotherapy[29]	24-week, placebo-controlled RCT 485 treatment-naïve patients	AM 2.5 mg: not statistically significant AM 5 mg: −0.77% ($P<0.0005$) AM 10 mg: −0.89% ($P<0.0001$) Placebo: −0.23% PM doses had similar reductions (−0.79% to −0.83%) (extrapolated data) Patients with baseline A$_{1c}$ ≥10% had mean change in A$_{1c}$ of −2.88% (for 5 mg) and −2.66% (for 10 mg) (extrapolated data)	FPG reductions: AM 2.5 mg: −15.2 mg/dL AM 5 mg: −24.1 mg/dL AM 10 mg: −28.8 mg/dL PM dose reductions (−26 to −30 mg/dL) (extrapolated data) Patients with baseline A$_{1c}$ ≥10% had FPG reductions of −77 to −84 mg/dL (extrapolated data)
Dapagliflozin monotherapy[30]	24-week, double-blind, placebo-controlled RCT 282 treatment-naïve patients	5 mg: −0.82% 2.5 mg: −0.72% 1 mg: −0.68% Placebo: 0.02% ($P<0.0001$, for all doses)	FPG reductions 1 mg: −11 mg/dL 2.5 mg: −22 mg/dL 5 mg: −28 mg/dL OGTT reductions (with all doses): −33 to −52 mg/dL
Dapagliflozin + metformin vs placebo + metformin[31,32]	24-week, double-blind, placebo-controlled RCT Extension study to 102 weeks 546 patients inadequately controlled on metformin monotherapy (≥1,500 mg/day)	2.5 mg: −0.65% ($P=0.0008$) 5 mg: −0.67% ($P<0.0001$) 10 mg: −0.82% ($P<0.0001$) Placebo: −0.31% At 102 weeks, reductions were maintained: −0.48% to −0.78%	FPG reductions: 5 mg: −26 mg/dL 10 mg: −24 mg/dL
Dapagliflozin + metformin vs placebo + metformin[33]	24-week double-blind, placebo-controlled RCT 182 patients inadequately controlled on metformin	10 mg: −0.39% Placebo: −0.10% ($P<0.0001$)	FPG reductions: 10 mg: −15 mg/dL
Dapagliflozin + glimepiride vs placebo + glimepiride[34]	24 week double-blind, placebo-controlled RCT 597 patients inadequately controlled on SU (≥ half the maximum recommended dose)	2.5 mg: −0.58% 5 mg: −0.63% 10 mg: −0.82% Placebo: −0.13% $P<0.0001$, for all doses Hypoglycemic episodes were more frequent in the dapagliflozin arm (6.9%–7.9% vs 4.8% placebo)	FPG reductions: 5 mg: −21 mg/dL 10 mg: −28 mg/dL OGTT reductions (−32 to −35 mg/dL) were statistically significant for 5 mg and 10 mg
Dapagliflozin + insulin vs placebo + insulin[35]	24-week, placebo-controlled RCT with blinded oral administration 808 patients inadequately controlled on insulin (≥30 units/day) Mean daily insulin dose was 77.1 units/day, with 17% using basal insulin and 83% using sliding-scale	2.5 mg: −0.79% 5 mg: −0.89% 10 mg: −0.96% Placebo: −0.39% $P<0.0001$, for all doses After 48 weeks, A$_{1c}$ reduction was maintained with all doses (−0.79% to −1.01%) ($P<0.001$) Hypoglycemic episodes were 53.6% for dapagliflozin 10 mg vs 51.8% with placebo	FPG reductions: 2.5 mg: −12 mg/dL 5 mg: −20 mg/dL 10 mg: −20 mg/dL At 48 weeks, FPG reduction was −12 to −17 mg/dL Patients continued usual daily dose of insulin with titrations, and up to two existing oral antidiabetic drugs (>50% on existing orals, mostly metformin)
Dapagliflozin + pioglitazone vs placebo + pioglitazone[36]	24 week, placebo-controlled RCT 480 patients inadequately controlled on pioglitazone 30–45 mg/day	5 mg: −0.82% ($P=0.0007$) 10 mg: −0.97% ($P<0.00001$) Placebo: −0.42% After 48 weeks, A$_{1c}$ reductions were maintained (−0.95% to −1.21%). However, statistical tests were not performed	FPG reductions: 5 mg: −24.9 mg/dL 10 mg: −29.6 mg/dL
Dapagliflozin + sitagliptin vs placebo + sitagliptin[37]	24-week, placebo-controlled RCT 451 patients inadequately controlled on sitagliptin 100 mg/day ± metformin ≥1,500 mg/day	Without metformin: 10 mg: −0.5% Placebo: −0.1% ($P<0.0001$) With metformin: 10 mg: −0.4% Placebo: 0.0% ($P<0.0001$) Patients with baseline A$_{1c}$ ≥8% had mean change in A$_{1c}$ of −0.8% compared to 0.0% ($P<0.0001$)	FPG reductions (combined ± metformin) 10 mg: −24.1 mg/dL Placebo: 3.8 mg/dL

Notes: [a]Versus placebo; [b]statistical significance at $P<0.05$.
Abbreviations: A$_{1c}$, hemoglobin A$_{1c}$; RCT, randomized controlled trial; AM, morning; PM, evening; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; vs, versus; SU, sulfonylureas.

non-inferiority, with both arms demonstrating an adjusted mean A_{1c} change of −0.52% from baseline. Key secondary outcomes looked at change in total body weight (TBW), hypoglycemia episodes, and proportion of patients achieving a decrease of ≥5% of TBW. Hypoglycemic events occurred in 3.4% of the dapagliflozin group, compared with 39.7% of the glipizide group. There were no major hypoglycemic events (requiring external assistance, with blood glucose <54 mg/dL) in the dapagliflozin group, and only three episodes in the glipizide group. Minor hypoglycemia was defined as blood glucose <63 mg/dL. The absolute mean change in weight loss between the groups at week 52 was −4.65 kg ($P<0.0001$), with 33.3% of dapagliflozin patients losing ≥5% of TBW, compared to −2.5% of the patients in the glipizide group. Overall, glipizide had more hypoglycemic events and weight gain; whereas, dapagliflozin had more weight loss, urinary infections (10.8% vs 6.4%; $P<0.05$, in post-hoc analysis), and reduced renal function (5.9% vs 3.4%). The dapagliflozin group had one episode of acute renal failure, and 13 patients discontinued from the study due to decrease in estimated creatinine clearance (compared to 6 patients in the glipizide group).[38]

Another set of trials assessed initial treatment for patients with type 2 diabetes. Both were 24-weeks in length, double-blind, active-controlled, randomized, controlled trials, comparing dapagliflozin, metformin XR, or both. Enrolled patients had an A_{1c} of 7.5%–12% and were treatment-naïve. Patients were randomly assigned in a 1:1:1 ratio to metformin XR monotherapy, dapagliflozin monotherapy, or combination therapy. Study 1 used dapagliflozin 5 mg, while Study 2 used dapagliflozin 10 mg. Metformin XR was titrated, as tolerated, up to 2,000 mg/day, in all arms of both studies. At 24 weeks, mean A_{1c} reductions from baseline were greater with combination therapy. Results from Study 1 included A_{1c} reductions as follows: dapagliflozin 5 mg + metformin (−2.05%) vs dapagliflozin 5mg (−1.19%) vs metformin monotherapy (−1.35%). Results from Study 2 included the following A_{1c} reductions: dapagliflozin 10 mg + metformin (−1.98%) vs dapagliflozin 10 mg (−1.45%) vs metformin monotherapy (−1.44%). The A_{1c} reductions demonstrated for combination vs either agent monotherapy, in both studies, were statistically significant ($P<0.0001$). Secondary endpoints included change in fasting blood glucose (FPG) at 24 weeks, proportion of patients achieving A_{1c} <7%, A_{1c} in those with baseline ≥9%, TBW, and the proportion of patients discontinued or failed. Study 2 also looked at non-inferiority and weight reduction. Fasting plasma glucose was lowest in the combination group, for both studies, compared to each agent alone ($P<0.0001$). Both studies

found more patients at A_{1c} goal <7% in the combination group, compared with either agent alone ($P<0.05$, for each). In those patients with baseline A_{1c} ≥9%, combination therapy reduced A_{1c} by −3.01% in Study 1, compared with −1.67% for dapagliflozin 5 mg ($P<0.0001$) and −1.82% for metformin ($P<0.0001$). Study 2 found A_{1c} reductions of −2.59% in the combination group, −2.14% for dapagliflozin 10 mg ($P=0.0133$), and −2.05% for metformin ($P=0.0036$). Weight loss was statistically greater for dapagliflozin 10 mg ($P<0.0001$, compared with metformin) and combination therapy yielded more weight loss than metformin monotherapy in both studies ($P<0.0001$). No major hypoglycemic events occurred, with seven mild events in Study 2 with combination therapy, compared to six events with metformin monotherapy. Dapagliflozin 10 mg was found to be non-inferior to metformin at lowering A_{1c}, and superior at lowering FPG ($P=0.0012$).[39]

Additionally, on 24 September 2013, Bristol-Myers Squibb announced that new Phase III data showed significantly reduced A_{1c}, compared with placebo, at 24 weeks, in patients inadequately controlled with metformin plus sulfonylurea. Results of this study were presented at the 49th Annual Meeting of the European Association for the Study of Diabetes, in Barcelona, Spain. Results revealed that patients treated with dapagliflozin 10 mg, in addition to metformin and a sulfonylurea, had a mean decrease in A_{1c} of −0.86%, compared with placebo (−0.17%) ($P<0.0001$). This study has an ongoing 28-week extension to continue efficacy and safety evaluations.[40]

Overall, Phase III studies have demonstrated the effectiveness of dapagliflozin as both monotherapy and add-on therapy. When used as monotherapy, dapagliflozin 5–10 mg lowered FPG (24–28 mg/dL) and reduced the plasma glucose following the 2-hour oral glucose tolerance test (OGTT) (33–52 mg/dL).[29,30] When used as add-on therapy, dapagliflozin lowered FPG an additional 15–29 mg/dL, and reduced plasma glucose following the OGTT (32–35 mg/dL).[31–37] In treatment-naïve patients, dapagliflozin, combined with metformin, provided additional lowering of A_{1c}, FPG, and weight, compared with either agent alone.[39] In patients inadequately controlled on metformin, dapagliflozin provided equal A_{1c} lowering to glipizide, with less hypoglycemia and weight gain.[38] Dapagliflozin also provided additional A_{1c} lowering in patients already receiving metformin and sulfonylurea, or metformin and sitagliptin.[37,40]

Based on efficacy data, patients have another effective oral agent to consider in the treatment of their diabetes. Dapagliflozin can be considered as initial therapy in combination with metformin, or when metformin is not

optimal. Due to dapagliflozin's unique mechanism of action, it also proves to be an effective add-on option to existing therapy, including metformin, sulfonylureas, DPP-IV inhibitors, pioglitazone, and insulin. Patients should expect to see reductions in A_{1c}, FPG, and OGTT. Although effectiveness is of utmost importance, it provides half of the consideration in the patient-centered approach to the treatment of diabetes. The remaining half is safety and tolerability.

Safety and tolerability

When considering drug therapy, side effect profiles assist in guiding patient-specific drug therapy selection, and this is no different for a patient's consideration of dapagliflozin. Dapagliflozin's unique mechanism results in numerous benefits, including increases in the excretion of glucose, sodium, and fluid, reduced plasma glucose, total caloric availability, and blood pressure.[23,24,41] However, its use does not come without potential side effects.

Given its mechanism of action, dapagliflozin therapy results in increased urinary glucose excretion of 20.4–53.3 g/day, compared with placebo. However, no apparent changes in sodium, potassium, chloride, magnesium, or albumin were noted.[42] A clinically insignificant increase in blood urea nitrogen (1.5–1.8 mg/dL), compared with placebo (0.3 mg/dL), was noted at 24 weeks with dapagliflozin therapy.[43] There was also a slight increase in serum creatinine, and a decrease in estimated glomerular filtration rate (eGFR), following initiation of therapy. However, both returned to baseline at 24 weeks.[43]

Dapagliflozin's efficacy is dependent upon renal function. Studies have shown that as renal function declines, so does the change in A_{1c}. With an eGFR >90 mL/min/1.73 m², A_{1c} decreased by 0.69% compared with 0.54%, with an eGFR of 60–90 mL/min/1.73 m². A lesser decrease in A_{1c} (0.39%) was noted with an eGFR <60 mL/min/1.73 m².[44] Thus, dose adjustment is not necessary for mild renal impairment (eGRF >60 mL/min/1.73 m²). Initiation of therapy is not recommended in patients with an eGFR <60 mL/min/1.73 m². Furthermore, therapy should be discontinued if eGFR is persistently <60 mL/min/1.73 m². Baseline and ongoing assessment of renal function is recommended while taking dapagliflozin.[14] Due to the increased risk of reduced renal function and volume depletion in the elderly (age ≥65 years), caution is warranted when using dapagliflozin in these patient populations.[14]

Studies including dapagliflozin therapy note genital and urinary tract infections for both men and women. The occurrence of genital myotic infections is 2%–13%, with a

mean of 7.9% and a standard deviation of ±3.7%, compared with placebo (up to 5%).[27,31,34,36,45,46] The common types of infections in women include vulvovaginal myotic infections, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. In men, they include balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. Increased occurrence of genital mycotic infection was noted in women, and associated with the higher dose (10 mg) of dapagliflozin.[14,29,31,34,38] The occurrence of signs and symptoms of a urinary tract infection (UTI) varied between dapagliflozin (mean: 5.6%; standard deviation: ±3.6%) and placebo (up to 8%).[29,31,34,36,45] Urinary tract infections include cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.[14,29,31,34,36,45] This is an important patient consideration in drug therapy selection, as recent findings indicate that adults with diabetes are more likely to experience a UTI (9.4%) compared to those without diabetes (5.7%).[47]

Since dapagliflozin does not cause insulin secretion, it has a lesser potential for hypoglycemia. When evaluating the final results of studies, fewer than 10% of individuals receiving dapagliflozin as monotherapy, or in combination with metformin, experienced hypoglycemia.[29,31,39,45] No severe hypoglycemic events occurred – defined as symptomatic hypoglycemia with a plasma blood glucose <54 mg/dL, requiring third party assistance, or with confusion, disorientation, abnormal behavior, unconsciousness, or glucagon administration.[31,39] When dapagliflozin was studied as add-on therapy with a sulfonylurea (glipizide), the occurrence of hypoglycemia was 6.9%–7.9%, compared with 4.8% with monotherapy.[34] In combination with insulin, the risk of hypoglycemia increases. In one study, dapagliflozin 10 mg, in combination with pre-study insulin use, resulted in nearly 30% of participants experiencing hypoglycemia.[45] Caution should be exercised when using dapagliflozin in combination with medications known to increase the risk of hypoglycemia, such as insulin, glinides, and sulfonylureas. Prescribing information suggests lowering the dose of insulin, or medications known to cause insulin secretion, upon initiation of dapagliflozin therapy.[14]

In July 2011, the FDA Advisory Committee requested further investigation of dapagliflozin's risk–benefit profile, given an observed increase in the incidences of bladder and breast cancers. Bladder cancer occurred in 9 out of 5,478 patients treated with dapagliflozin, compared with 1 out of 3,136 control patients.[43] Breast cancer occurred in 9 out

of 2,223 patients treated with dapagliflozin, compared with 1 out of 1,053 control patients.[43] However, 2-year carcinogenic studies in animals failed to demonstrate any pre-neoplastic or neoplastic activity.[48] Another noteworthy concern is the occurrence of five cases of elevated aspartate transaminases (AST) or alanine transaminases (ALT), greater than three times the upper limit of normal levels found in dapagliflozin trials. Of the total, two could not be attributed to another cause, resulting in possible dapagliflozin-induced hepatic injury.[43] Results of one study indicate dapagliflozin was well tolerated by individuals with mild and moderate hepatic impairment; while those with severe hepatic impairment experienced greater dapagliflozin exposure. Therefore, its use should be individualized in those with severe hepatic impairment, as its efficacy and safety profile have not been fully studied.[49] Given the current findings, dose adjustment is not necessary with mild or moderate hepatic impairment, and dapagliflozin should not be used in patients on dialysis.[14,26,49]

Given the diuretic effect of dapagliflozin, hypotension is a reported side effect. However, studies do not indicate significant hypotension or orthostatic hypotension, when compared with placebo.[29,46] For some patients, blood pressure reduction may be a favorable side effect. Studies indicate a 2.1–6.4 mmHg and 1.7–3.3 mmHg reduction in systolic and diastolic blood pressure, respectively.[29,42,45,46] Furthermore, an increase in urine volume and sodium excretion was noted within the first 2–3 days of initiating dapagliflozin.[50] Assessment of volume status and correction is warranted prior to initiation of therapy.[14]

In addition to its A_{1c} and blood pressure lowering potential, dapagliflozin has other positive outcomes that make it a favorable choice for select patients with diabetes. Weight loss is noted in numerous dapagliflozin trials.

Table 2 Comparison of dapagliflozin and canagliflozin

	Dapagliflozin[14]	Canagliflozin[51]
Approved indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Starting dose	5 mg once-daily in the morning	100 mg once-daily
Dose titration	May increase to 10 mg for additional glycemic control	May increase to 300 mg with an eGFR ≥60 mL/min/1.73 m², for additional glycemic control
A_{1c} reduction	Monotherapy: −0.8% (5 mg) and −0.9% (10 mg)	Monotherapy: −0.77% (100 mg) and −1.03% (300 mg)
	With metformin: −0.7% (5 mg) and −0.8% (10 mg)	With metformin: −0.79% (100 mg) and −0.94% (300 mg)
	With glimepiride: −0.6% (5 mg) and −0.8% (10 mg)	With sulfonylurea: −0.70% (100 mg) and −0.79% (300 mg)
	With pioglitzone: −0.8% (5 mg) and −1.0% (10 mg)	
	With sitagliptin: NS (5 mg) and −0.45% (10 mg)	
Administration	With or without food	Before the first meal of the day
Contraindications	Hypersensitivity, severe renal impairment, end stage renal disease, on dialysis	Hypersensitivity, severe renal impairment, end stage renal disease, on dialysis
Warning and precautions	Hypotension, increased serum creatinine, decrease in eGFR, hypoglycemia with insulin and insulin secretagogues, genital mycotic infections, increase in LDL, bladder cancer	Hypotension, increased serum creatinine, decrease in eGFR, hyperkalemia, hypoglycemia with insulin and insulin secretagogues, genital mycotic infections, increase in LDL
Common side effects (5% or greater incidence)	Female genital mycotic infections, nasopharyngitis, urinary tract infections	Female genital mycotic infections, urinary tract infections, increased urination
Drug interactions (avoid use)	None reported	Pimozide
Drug interactions (monitor concomitant use)	May increase effect of hypoglycemia agents and hypotensive agents	Digoxin (increased AUC and C_{max}) UGT enzyme inducers* (decrease AUC of canagliflozin)
Renal impairment	Do not initiate if eGFR <60 mL/min/1.73 m² Discontinue if eGFR is persistently <60 mL/min/1.73 m²	Do not initiate if eGFR <45 mL/min/1.73 m² Discontinue if eGFR falls below 45 mL/min/1.73 m² 100 mg daily is maximum dose with eGFR 45–60 mL/min/1.73 m²
Hepatic impairment	Assess risk: benefit with severe hepatic impairment	Not recommended with severe hepatic impairment
Special populations	Pregnancy category: C Breastfeeding: unknown excretion in breast milk Pediatrics: not studied Geriatrics: higher incidence of ADRs; similar A_{1c} reduction compared to those <65 years old	Pregnancy category: C Breastfeeding: unknown excretion in breast milk Pediatrics: not studied Geriatrics: higher incidence of ADRs; less A_{1c} reduction compared to those <65 years old
How supplied	5 mg and 10 mg tablets	100 mg and 300 mg tablets

Note: *Rifampin, phenytoin, phenobarbital, ritonavir.
Abbreviations: eGFR, estimated glomerular filtration rate; NS, not studied; LDL, low-density lipoprotein; AUC, area under the curve; C_{max}, peak drug concentration; UGT, UDP-glucuronosyltransferase; ADRs, adverse drug reactions.

Treatment with dapagliflozin resulted in a weight loss of approximately 2–3 kg, compared with a ~1 kg loss with metformin or placebo after 12–24 weeks of therapy.[39,46] When dapagliflozin was used as add-on therapy with metformin, glimepiride, and insulin, a statistically significant weight loss occurred at 24 weeks, with mean changes of –2.9 kg, –2.3 kg, and –1.7 kg, respectively.[31,34,35] Weight loss was maintained at 48 weeks when combined with insulin, and at 102 weeks when combined with metformin.[32,35] In a 24-week trial, dapagliflozin 10 mg, used in combination with pioglitazone (a medication known to increase the risk of weight gain), resulted in a –0.14 kg weight loss, compared with a 1.64 kg weight gain with pioglitazone monotherapy.[36]

Patients treated with dapagliflozin also saw improvement in triglyceride levels, compared with placebo, with reductions of –2.4%, –6.2%, and –2.1%, respectively.[31] Additionally, there was improvement of 1.8%–4.4% in high-density lipoprotein levels.[29,31,42] Future studies are needed to assess the benefits of dapagliflozin's weight and blood pressure reductions and lipid improvements, in light of cardiovascular events. According to the FDA's mandate, all new oral antidiabetic medications are required to demonstrate no increased risk in cardiovascular events. Data from clinical trials to date do not indicate any increased risk. However, further studies are needed.[43]

Place in therapy – conclusion

With an ever-growing demand for oral antidiabetic medications, dapagliflozin, acting through a unique mechanism, reduces blood glucose and provides a favorable tolerability profile. With recent FDA approval for its use as monotherapy and add-on therapy, dapagliflozin is now a second-in-class agent. Table 2 compares and contrasts dapagliflozin with canagliflozin.[14,51] The occurrence of genital mycotic infections and urinary tract infections associated with SGLT2s may pose limitations for use. The risks should be considered for each patient when selecting drug therapy.

While an array of oral antidiabetic medications are available, few favorably impact on comorbidities such as obesity and hypertension, which are often found in patients with diabetes. Dapagliflozin's noted blood pressure reduction, weight loss, and low potential to cause hypoglycemia are advantageous, when compared with currently available oral medications. Long-term clinical trials and post-marketing studies are needed to further investigate dapagliflozin's cardiovascular profile, and its impact on morbidity and mortality.

It is critical to expand therapy options for a complex patient population. Dapagliflozin has a distinct niche that can be a viable option for select patients with diabetes.

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