PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

www.pacjmedsci.com. Email: pacjmedsci@gmail.com.

DAPAGLIFLOZIN REVIEW: MORE THAN AN ANTI-DIABETIC DRUG

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Submitted May 2021; Accepted: August 2021

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ABSTRACT:
Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. DM is a significant health care concern. Worldwide, the prevalence is increasing at an alarming rate despite using different classes of anti-hyperglycemic agents. Although several treatment options reduce hyperglycemia, only half the patients achieve desirable glycemic targets. Newer treatments that significantly reduce hyperglycemia with novel mechanism of action and acceptable safety profiles are warranted to reduce complications associated with type 2 DM. Sodium-glucose cotransporter-2 inhibitors are anti-hyperglycemic agents with unique mechanism of action that lower blood glucose level independent of insulin. Recent findings on efficacy and safety establish their role in the treatment of DM. Sodium-glucose cotransporter-2 inhibitors may be an option in type 2 DM patients not willing or not ready to start insulin, those requiring additional glucose lowering and in those with acceptable risk factor profiles. Dapagliflozin (Farxiga) can be used at any stage of type 2 DM as a mono-therapy or in combination with other oral hypoglycemic agents and insulin. This review highlights the efficacy and safety of dapagliflozin as an anti-hyperglycemic agent and its use in co-morbid conditions like chronic kidney disease and cardiovascular diseases.

Keywords: Dapagliflozin, Sodium-glucose cotransporter-2 Inhibitors, Insulin, Type 2 Diabetes Mellitus

INTRODUCTION:

Diabetes Mellitus (DM) is a significant international health care concern that is growing in prevalence [1]. In 2019, approximately 463 million adults (20-79 years) were living with diabetes worldwide; by 2045 this will rise to about 700 million [1]. The proportion of people with type 2 diabetes mellitus (T2DM) is increasing in most countries with 79% adult diabetics living in low- and middle-income countries [1]. In 2019, 1 in 2 or 232 million people with diabetes were undiagnosed and 374 million people were at increased risk of developing T2DM [1]. People with T2DM are at risk of developing complications, including macrovascular (cardiovascular disease (CVD), strokes, and heart failure (HF)) and microvascular (chronic

kidney disease (CKD) and damage to the eyes and nerves) complications [2]. Furthermore, T2DM is a progressive disease characterized by a gradual and continuing loss of pancreatic β-cell function. This results in deterioration in glycemic control and eventually for the need for insulin-replacement therapy. This long-term requirement for the escalation of therapy exerts additional pressure to have access to a wide range of therapies. Optimized glycemic control reduces the risk of diabetic complications. Several glycated hemoglobin (HbA1c) glycemic targets have been proposed for the management of diabetes, ranging from 6.0% to 8.5% (42–69 mmol/L) [3]. Significant improvement in glycemic control is urgently required as it is estimated that only about half of the diabetic population reach the proposed glycemic targets [3].

Current T2DM management guidelines recommend initiating lifestyle modifications and metformin as first-line therapy, but beyond that, anti-hyperglycemic therapy becomes very patient specific [4, 5]. Even when patients are able to achieve a target goal of less than <7% (53 mmol/L) HbA1c, it is difficult to maintain this long term as their disease progresses [6, 7]. Anti-hyperglycemic agents with novel mechanisms and synergistic effects when used in combination with other anti-hyperglycemic agents are necessary to expand the number of treatment options available to patients with T2DM [8]. The aim of this article is to review the literature on dapagliflozin use as monotherapy and in combination with other oral hypoglycemic agents and insulin. This review also highlights the use of dapagliflozin in CKD with or without diabetes, in CKD with and without cardiovascular disease, in heart failure and CKD with or without T2DM and in type 1 diabetes mellitus (T1DM).

Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor

The SGLT-2 inhibitors are a new class of oral anti-hyperglycemic agents for the treatment of T2DM that improve glycemic control by insulin-independent mechanisms. SGLT-2 inhibitors increase glucosuria by reducing reabsorption of glucose from the proximal tubule of the kidneys. This unique mechanism of action of SGLT-2 inhibitors complements that of other classes of anti-hyperglycemic agents, allowing for their use as combination therapy with other anti-hyperglycemic agents including insulin [9]. SGLT-2 inhibitors also exhibit natriuretic effect by reducing sodium reabsorption, which may partially explain the observed reduction in blood pressure (BP). These reductions in BP are not accompanied by increases in heart rate, indicating a lack of reflex sympathetic nervous system activation [2]. The natriuretic effects of SGLT-2 inhibitors, which may lead to reductions in plasma volume and cardiac preload, also occur without activation of the renin–angiotensin–aldosterone (RAA) system. This therapeutic class includes agents like

canagliflozin, dapagliflozin, empagliflozin, remogliflozin and ertugliflozin [2].

Dapagliflozin:

Dapagliflozin competitively, reversibly, and highly selectively inhibits SGLT2. There are two isoforms of the Sodium-Glucose Co-transporter (SGLT). They are SGLT-1 and SGLT-2. Both are expressed in the kidneys and on the epithelial lining of the proximal convoluted tubules (PCT). SGLT-2 is located in the cells of the S1 and S2 segments of the PCT and has a high capacity but low affinity for glucose transport [10]. Physiologically, in healthy individuals, these transporters are responsible for approximately 90% of renal glucose absorption [10]. Dapagliflozin is a highly potent SGLT-2 inhibitor that is over 1400 times more selective for SGLT-2 than SGLT-1, which is one of the transporters responsible for glucose absorption in the intestine [9].

By blocking SGLT-2, dapagliflozin promotes glucose filtration through the kidneys and into the urine to be eliminated from the body. To quantify the degree of glucose excretion that occurs with dapagliflozin, studies have examined 24 h glucose excretion amounts in healthy subjects as well as in patients with T2DM given a range of dapagliflozin doses [8]. Dapagliflozin doses of 20–100 mg have resulted in urinary glucose excretion of approximately 60 g over 24 h in healthy volunteers. In subjects with T2DM who received dapagliflozin doses between 2.5 and 20 mg, the 24 h glucose excretion after 1 day ranged from 38 to 77 g; after 14 days the range was from 42 to 73 g [8]. In comparison, patients who have a mutation of the SGLT-2 gene *SLC5A2* can excrete up to 125 g per day of glucose with no clinically relevant adverse outcomes [8]. Other studies [11] have demonstrated that the 24 h urine glucose excretion with dapagliflozin represents about 40–50% of the human-filtered glucose load. One of the potential reasons proposed for this ceiling effect was that when SGLT-2 is inhibited, SGLT-1 may compensate by increasing reabsorption of glucose [8].

Dapagliflozin is usually administered with a starting dose of 5 mg orally in the morning, which can be increased to 10 mg orally in the morning based on the response of the patient and the decision of the clinician [8]. Dapagliflozin is 78% bioavailable and rapidly absorbed [8]. Its half-life is 12.9 h, qualifying for once-daily dosing. Dapagliflozin is not known to have any meaningful drug–drug interactions. It is predominantly metabolized by UDP-glucuronosyltransferase enzyme (UGT1A9) and has minor cytochrome 450-mediated metabolism [8]. Dapagliflozin has been evaluated in combination with glimepiride, metformin, pioglitazone, and sitagliptin. It does not affect the metabolism of these anti-hyperglycemic agents nor is its metabolism affected by them, and there are no known pharmacokinetic (PK) alterations [8]. Dapagliflozin can cause decreases in systolic

BP *via* its osmotic diuretic effect, therefore patients receiving antihypertensive agents (especially loop diuretics) or those known to experience hypotension should be closely monitored when using dapagliflozin [8].

Pharmacological properties of dapagliflozin

Pharmacodynamic [9] and pharmacokinetic [12] properties of dapagliflozin are summarized below:

Pharmacodynamic properties [9]

- Highly potent, selective and reversible inhibitor of SGLT-2 (K_i=0.55 nM)
- Glucose excretion is observed after the first dose, is continuous over the 24-h dosing interval and is sustained over the course of treatment
- Urinary glucose excretion induced by dapagliflozin is associated with body weight reduction

Pharmacokinetic properties [12]

- Similar pharmacokinetics in type 1 and 2 diabetes
- Dose-linear pharmacokinetics over 0.1–500 mg; pharmacokinetics does not change after repeated daily dosing for 24 weeks
- Mean steady-state volume of distribution is 118 L; ≈91% bound to plasma proteins (protein binding unchanged by renal or hepatic impairment)
- Extensively metabolized in the liver and kidney to form an inactive metabolite (dapagliflozin 3-O-glucuronide)
- Mean steady-state AUC is estimated to be ≈22% higher in females than males
- No clinically relevant differences in systemic exposure among white, black or Asian races
- In patients with severe hepatic impairment, the mean C_{max} and AUC are 40% and 67% higher than matched healthy controls

Clinical Efficacy

Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It can be employed as a monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin. Dapagliflozin is currently approved to improve glycemic control in adults with T2DM and to reduce the risk of hospitalization for heart failure in patients with T2DM and established cardiovascular disease or multiple cardiovascular risk factors [9]. It is also approved to reduce the risk of cardiovascular mortality and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (HFrEF) with or without T2DM [9].

Mono-therapy

Dapagliflozin has been evaluated as a monotherapy against placebo [13-17] and versus metformin or placebo [18]. In these studies, the mean HbA1c reduction was 0.66–1.45%, and weight reduction was 1.0–2.73 kg compared to placebo at 24 weeks. There was a reduction in fasting glucose and more patients achieved an HbA1c of 7%. Genital and urinary infections were more common (3.7% and 2.3% difference, respectively) compared to placebo [17].

Dual therapy

In dual therapy, dapagliflozin has been studied with metformin [19], glimepiride [20], pioglitazone [21] and sitagliptin [22]. Dapagliflozin when combined with metformin reduced HbA1c by 0.8% following 102 weeks of therapy, compared to 0.5%–0.68% when combined with the other agents [19]. When combined with glipizide, an average 4.4 kg in weight was lost compared to glipizide alone [23-25]. In comparison, weight loss of 1.74 kg with metformin [19] and 1.8 kg with sitagliptin has been reported [22].

Triple therapy

Dapagliflozin has been used in triple combinations with metformin and sitagliptin [22], metformin and saxagliptin [26] and metformin and a sulfonylurea [27]. Triple therapy has shown HbA1c reductions of up to 0.6% and body weight reductions of 2.2 kg. Urinary and genital infections were higher than in control groups.

Newer avenues of Dapagliflozin

Dapagliflozin in patients with CKD with or without T2DM

Dapagliflozin and other SGLT-2 inhibitors were initially developed for patients with T2DM, but the drugs have shown far-reaching benefits in different patient populations, specifically patients with HFrEF with or without T2DM. Based on the results of Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, which was presented at European Society of Cardiology Congress, dapagliflozin is now indicated to reduce the risk of declining kidney function, kidney failure, cardiovascular mortality, and hospitalization for heart failure in adults with CKD [28].

In the DAPA-CKD trial, dapagliflozin added to usual care reduced the primary composite endpoint, one that included renal and cardiovascular events and mortality, by 39% when compared with usual care alone. The trial was unique in that one-third of patients did not have T2DM, and yet these patients derived the same benefit as those with T2DM. This makes dapagliflozin the first SGLT2 inhibitor to be approved for the treatment of CKD regardless of diabetes status.

The DAPA-CKD study concluded that among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained

decline in the estimated glomerular filtration rate (GFR) of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo [28].

Dapagliflozin in patients with CKD with and without CVD

The combined cardio-renal benefits of SGLT-2 inhibitors in patients with CKD, with and without T2DM, are substantial; whether there is a history of CVD or not. Dapagliflozin reduces risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure and prolonged survival in people with CKD, independently of the presence of concomitant CVD. In a pre-specified secondary analysis from the DAPA-DKD trial, the authors observed that treatment with dapagliflozin reduced the absolute risk of cardiovascular or renal death or a renal event by 6% and 5% over a period of 32 months in patients with and without CVD, respectively [29]. The absolute risk of all-cause death (−3.3% and −1.4%) and a heart failure hospitalization (−3.2% and −0.7%) were also reduced by dapagliflozin compared with placebo in both groups with acceptable safety.

The study compared outcomes in 4304 patients with chronic kidney disease who were randomized to treatment with dapagliflozin or placebo. In a pre-specified subgroup analysis, they examined whether these outcomes were influenced by the presence or absence of CVD. Of the total study population, 37.4% were secondary prevention patients, and these patients were more often male and more likely to have T2DM. Additionally, the secondary prevention group had a higher BMI and higher blood pressures versus other participants [29]. The primary and secondary prevention groups had similar estimated GFR and median urinary albumin-to-creatinine ratio. Rate of kidney failure was similar between the two groups, but the secondary prevention group had higher rates of adverse cardiovascular outcomes. The primary composite outcome (which included a sustained decline in e-GFR of 50% or lower, end-stage kidney disease, and kidney or cardiovascular death) was significantly reduced by dapagliflozin treatment in both the primary and secondary prevention groups. Additionally, dapagliflozin treatment yielded similar reductions in both groups in a composite outcome of heart failure hospitalization and cardiovascular death and in all-cause mortality [29]. No differences in rates of adverse events were detected between the groups.

Based on these data, benefits from dapagliflozin are present in patients with and without CVD. The study adds information to existing knowledge, and it may now be suggested that SGLT-2 inhibitors prevent progression of renal disease and heart failure, and improve survival in a broad clinical spectrum, including patients with T2DM, CKD, and heart failure. The clinical implications of the study are that physicians should be aware of estimated glomerular filtration rate (e-GFR) and

albumin excretion (spot urine) in patients with T2DM, hypertension, atherosclerotic disease, and CKD to initiate SGLT2 inhibition to improve primary and secondary "cardio-renal prevention" [29].

Dapagliflozin in Heart Failure and CKD with or without T2DM

Dapagliflozin slows the rate of decline in e-GFR in patients with heart failure with reduced ejection fraction both in patients with and without T2DM. There is no effect on the efficacy of dapagliflozin by baseline kidney function in preventing the risk of cardiovascular death or worsening heart failure [30].

The authors assessed the safety and efficacy of dapagliflozin in patients with HFrEF, according to baseline kidney function, in the Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial [30]. The effect of dapagliflozin on kidney function after randomization was also assessed. HFrEF patients with or without T2DM and an e-GFR over 30 ml/min/1.73m^2 were enrolled in DAPA-HF trial. The incidence of the primary outcome (CV death or worsening HF) according to e-GFR category at baseline (<60 and ≥60 ml/min/1.73m^2) as well as using e-GFR at baseline as a continuous measure were calculated. Secondary cardiovascular outcomes and a pre-specified composite renal outcome (≥ 50% sustained decline e-GFR, end stage renal disease (ESRD) or renal death) were also examined, along with decline in e-GFR over time.

According to the authors [30], of the 4742 patients with baseline e-GFR, 41% had e-GFR over 60 ml/min/1.73m^2. The effect of dapagliflozin on the primary and secondary outcomes did not differ by e-GFR category or examining e-GFR as a continuous measurement. The composite renal outcome was not reduced by dapagliflozin (HR=0.71, 95% CI 0.44, 1.16; p=0.17) but the rate of decline in e-GFR between day 14 and 720 was less with dapagliflozin, -1.09 vs. placebo -2.87 ml/min/1.73m^2 per year (p<0.001) and was observed in those with and without T2DM (p = 0.92).

Dapagliflozin slows the progression of kidney dysfunction, including in patients without T2DM and the benefits on morbidity and mortality in HFrEF were not modified by baseline kidney function [30].

Dapagliflozin in patients with T1DM

Insulin replacement therapy is the mainstay of treatment for patients with T1DM. Despite the improvements over the years in insulin delivery and glucose monitoring systems, glycemic control in patients with T1DM is often suboptimal, with less than a third of this population achieving optimal glycemic control (with HbA1c below 7%) [31]. Although intensive insulin treatment may be used to improve poor glycemic control, its therapeutic potential is limited by the increased risk of hypoglycemia

and weight gain, which are associated with a greater risk of adverse cardiovascular outcomes. Severe hypoglycemic episodes may also lead to events such as seizures, coma or death. Furthermore, glycemic variability (the fluctuations in blood glucose levels throughout the day) is an independent risk factor for hypoglycemia in T1DM. Obesity and insulin resistance are also associated with intensive insulin therapy and have become more prevalent in T1DM [31]. Therefore, improving glycemic control without increasing the risk of hypoglycemia and other related comorbidities is an important objective in the management of T1D [31].

Dapagliflozin, an SGLT2 inhibitor, is the first oral treatment approved in T1DM in the EU where it is indicated as an adjunct to insulin in adults with T1DM and BMI of above 27 kg/m^2, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy [31].

Adverse effects and warnings

Genital Infections

One of the most common adverse effects appear to be genital infections; because high concentrations of glucose in the urine facilitates the onset of mycotic infections [32]. Volume depletion has been reported. This may be due to osmotic diuresis induced by glycosuria resulting from SGLT-2 inhibition. This is usually accompanied by increased urinary frequency, thirst, and rarely orthostatic hypotension [32]. Risk factors for volume depletion include, age over 75 years, GFR below 60 mL/min/1.73m^2, and use of loop diuretics [32].

Ketoacidosis

Pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse may predispose patients to developing ketoacidosis. A possible explanation suggests that by lowering serum glucose levels through the inhibition of glucose reabsorption in the kidneys, SGLT2 inhibitors lead to decreased insulin release and increased glucagon secretion in the pancreatic cells. Glucagon stimulates production of ketone bodies via the beta-oxidation of free fatty acids in the liver. Additionally, SGLT-2 inhibitors directly stimulate glucagon release from the pancreas, which results in increased production of the ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone).

Indeed, in normal physiology, glucose stimulation of insulin release by the beta cells, coupled with subsequent insulin-induced inhibition of glucagon secretion, leads to a high insulin-to-glucagon ratio in the pancreatic venous flow and portal circulation, promoting glycogenesis. The renal glucose loss observed with SGLT-2 inhibitors decrease insulin stimulation and insulin-to-glucagon ratio, leading to decreased glycogenesis, and in the setting of prolonged glucose deprivation, increased gluconeogenesis, and glycogenolysis [33]. The lack of circulating glucose results in an increased production of

glucagon and ketoacids. Another possible mechanism of ketoacidosis is an SGLT2 inhibitor-induced starvation state that results in increased renal reabsorption of ketone bodies. Eventually, there will be a buildup of ketosis in the presence of lower glucose levels, which is exacerbated in acute stress or lower carbohydrates availability [33].

SGLT-2 inhibitors and lower limb complications

A meta-analysis by *Lin et al* [34] examined the associations between the use of SGLT-2 inhibitors and the risk of lower limb complications. The analysis concluded that risks of amputation and peripheral arterial disease (PAD) are slightly increased in patients with canagliflozin treatment. Reductions in body weight and blood pressure were associated with lower limb complications in patients with SGLT-2 inhibitor treatment [34].

Summary

Dapagliflozin lowers glucose levels independently of insulin action. Dapagliflozin provides effective glycemic control and reduces bodyweight and blood pressure. It reduces rate of cardiovascular death or hospitalization for heart failure, does not adversely affect major adverse cardiovascular events and reduces progression of renal disease. There is low risk of hypoglycemia with dapagliflozin, while genital infections and DKA are more common than with placebo. Dapagliflozin is also used as an adjunct to insulin in adults with T1DM and a BMI more than 27 kg/m^2 in whom insulin alone does not provide adequate glycemic control. Dapagliflozin is generally well tolerated with manageable safety profile. Also, dapagliflozin is effective in chronic kidney disease with or without diabetes, chronic kidney disease with or without T2DM, independently of the presence of concomitant cardiovascular disease, chronic kidney disease and heart failure with or without T2DM and in T1DM. Further studies are warranted for its pleotropic effects which extend beyond diabetes management.

Acknowledgement

Author acknowledges the contribution of Mr. Rafique Sheikh, M. Pharm (Pharmacology) for his contribution in doing literature search & helping with the preparation of manuscript.

Financial Disclosure or Funding-Nil

REFERENCES:

1. Diabetes facts & figures [Internet]. International Diabetes Federation. www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html
2. Handelsman Y. Rationale for the Early Use of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Type 2 Diabetes. Adv Ther. 2019 Oct;36(10):2567-2586. www.ncbi.nlm.nih.gov/pmc/articles/PMC6822830/pdf/12325_2019_Article_1054.pdf
3. Saeed MA, Narendran P. Dapagliflozin for the treatment of type 2 diabetes: a review of the literature. Drug Des Devel Ther. 2014 Dec 10;8:2493-505.

www.ncbi.nlm.nih.gov/pmc/articles/PMC4267514/pdf/dddt-8-2493.pdf

4. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014 Jan;37 Suppl 1:S14-80.https://care.diabetesjournals.org/content/37/Supplement_1 /S14.full-text.pdf
5. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012 Jun;55(6):1577-96. https://doi.org/10.1007/s00125-012-2534-0
6. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ. 1995 Jan 14;310(6972):83-8. www.bmj.com/content/310/6972/83.long
7. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes. 1995 Nov;44(11):1249-58. https://diabetes.diabetesjournals.org/content/44/11/1249.full-text.pdf
8. Anderson SL. Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf.2014 Dec; 5(6):242-54. https://journals.sagepub.com/doi/pdf/10.1177/2042098614551938
9. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019 Jul;79(10):1135-1146. www.ncbi.nlm.nih.gov/pmc/articles/PMC6879440/pdf/40265_2019_Article_1148.pdf
10. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014 Jan;32(1):4-11. www.ncbi.nlm.nih.gov/pmc/articles/PMC4521423/pdf/4.pdf
11. DeFronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, Pfister M, Morrow LA, Leslie BR, Boulton DW, Ching A, LaCreta FP, Griffen SC. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care. 2013 Oct;36(10):3169-76. https://care.diabetesjournals.org/content/36/10/3169.full-text.pdf
12. Paik J, Blair HA. Dapagliflozin: A Review in Type 1 Diabetes. Drugs. 2019 Nov;79(17):1877-1884. www.ncbi.nlm.nih.gov/pmc/articles/PMC6881422/pdf/40265_2019_Article_ 1213.pdf
13. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010 Oct;33(10):2217-24. https://care.diabetesjournals.org/content/33/10/2217.full-text.pdf
14. Bailey CJ, Iqbal N, T'joen C, List JF. Dapagliflozin monotherapy in drug-naïve patients with diabetes: a randomized-controlled trial of low-dose range. Diabetes Obes Metab. 2012 Oct;14(10):951-9. https://doi.org/10.1111/j.1463-1326.2012.01659.x
15. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012 May;66(5):446-56. https://doi.org/10.1111/j.1742-1241.2012.02911.x
16. Kaku K, Inoue S, Matsuoka O, Kiyosue A, Azuma H, Hayashi N, Tokudome T, Langkilde AM, Parikh S. Efficacy and safety of dapagliflozin as a monotherapy for type 2 diabetes mellitus in Japanese patients with inadequate glycaemic control: a phase II multicentre, randomized, double-blind, placebo-

controlled trial. Diabetes Obes Metab. 2013 May;15(5):432-40. https://doi.org/10.1111/dom.12047

17. Ji L, Ma J, Li H, Mansfield TA, T'joen CL, Iqbal N, Ptaszynska A, List JF. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther. 2014 Jan 1;36(1):84-100.e9. www.clinicaltherapeutics.com/action/showPdf?pii=S0149-2918%2813%2901071-0
18. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009 Apr;32(4):650-7. https://care.diabetesjournals.org/content/32/4/650.full-text.pdf
19. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013 Feb 20;11:43. https://bmcmedicine.biomedcentral.com/track/pdf/10.1186/1741-7015-11-43.pdf
20. Strojek K, Yoon KH, Hruba V, Sugg J, Langkilde AM, Parikh S. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. Diabetes Ther. 2014 Jun;5(1):267-83.
21. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012 Jul;35(7):1473-8. www.ncbi.nlm.nih.gov/pmc/articles/PMC4065289/pdf/13300_2014_Article_72.pdf
22. Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37(3):740-50. https://care.diabetesjournals.org/content/37/3/740.full-text.pdf
23. Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, Parikh SJ. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011 Sep;34(9):2015-22. https://care.diabetesjournals.org/content/34/9/2015.full-text.pdf
24. Nauck MA, Del Prato S, Durán-García S, Rohwedder K, Langkilde AM, Sugg J, Parikh SJ. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab. 2014 Nov;16(11):1111-20. https://doi.org/10.1111/dom.12327
25. Langkilde AM, Nauck MA, Prato SD, et al. Durability of dapagliflozin vs glipizide as add-on therapies in T2DM inadequately controlled on metformin: 4-year data. Diabetologia. 2013;56(1):S374. www.easd.org/virtualmeeting/home.html#!resources/durability-of-dapagliflozin-vs-glipizide-as-add-on-therapies-in-type-2-diabetes-inadequately-controlled-on-metformin-4-year-data--2
26. Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, Iqbal N. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care. 2015 Mar;38(3):376-83. https://care.diabetesjournals.org/content/38/3/376.full-text.pdf

27. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S; Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015 Mar;38(3):365-72.https://care.diabetesjournals.org/content/38/3/365.full-text.pdf
28. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. www.nejm.org/doi/pdf/10.1056/NEJMoa2024816?articleTools=true
29. McMurray JJV, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, Chertow GM, Greene T, Held C, Hou FF, Mann JFE, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Heerspink HJL; DAPA-CKD Trial Committees and Investigators. Effect of Dapagliflozin on Clinical Outcomes in Patients With Chronic Kidney Disease, With and Without Cardiovascular Disease. Circulation. 2021 Feb 2;143(5):438-448. www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.120.051675
30. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, Chopra V, de Boer RA, Desai AS, Ge J, Kitakaze M, Merkley B, O'Meara E, Shou M, Tereshchenko S, Verma S, Vinh PN, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Bengtsson O, Langkilde AM, Sjöstrand M, McMurray JJV. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. Circulation. 2021 Jan 26;143(4):298-309. www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.120.050391
31. Paik J, Blair HA. Dapagliflozin: A Review in Type 1 Diabetes. Drugs. 2019 Nov;79(17):1877-1884. www.ncbi.nlm.nih.gov/pmc/articles/PMC6881422/pdf/40265_2019_Article _1213.pdf
32. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):73-79. www.ncbi.nlm.nih.gov/pmc/articles/PMC6028052/pdf/nihms941349.pdf
33. Osafehinti DA, Okoli OJ, Karam JG. A Case of SGLT2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis Following Coronary Artery Bypass Surgery. AACE Clin Case Rep. 2020Dec 28;7(1):20-22. www.ncbi.nlm.nih.gov/pmc/articles/PMC7924150/pdf/main.pdf
34. Lin C, Zhu X, Cai X, Yang W, Lv F, Nie L, Ji L. SGLT2 inhibitors and lower limb complications: an updated meta-analysis. Cardiovasc Diabetol. 2021 Apr 28;20(1):91. https://cardiab.biomedcentral.com/track/pdf/10.1186/s12933-021-01276-9.pdf