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REVIEW ARTICLE **OPEN ACCESS**

A Detailed Study On The Safety, Efficacy, And Effect Of Dapagliflozin : A Review Article

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ABSTRACT

A very effective, reversible, and selective sodium-glucose cotransporter-2 (SGLT2) inhibitor called dapaglifozin has been recommended all over the world for the treatment of T2DM. Majority of renal glucose reuptake is performed by SGLT2, which can be inhibited to enhance renal glucose excretion and, as a result, lower plasma glucose levels. In the EU, oral dapaglifozin has been approved for usage as a monotherapy for those patients that are intolerable to metformin as well as an add-on combination treatment with insulin for T2DM if diet and exercise are insufficient for glycemic control. According to studies, dapagliflozin is effective both when used alone and when combined with insulin and oral antihyperglycemic drugs. Through glucose independent mechanisms, SGLT2 inhibitors lower The risk of being hospitalised for heart failure in people with T2DM. Female genital mycotic infections and urinary tract infections (UTI) were the most often reported adverse responses of dapagliflozin in clinical studies. The Long-term effectiveness and safety of dapagliflozin, a new oral medication for type 2 diabetes, remain uncertain although its short-term effectiveness is comparable to that of a dipeptidyl peptidase 4 inhibitor.

Keywords *: Dapagliflozin, Hypoglycemic agents, sodium-glucose transporter 2 (SGLT2) inhibitors , Type 2 diabetes mellitus (T2DM), Urinary tract infection (UTI).*

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INTRODUCTION

According to studies, dapagliflozin works effectively both alone and in combination with other medications including insulin and oral antihyperglycemics. SGLT2 inhibitors lower the likelihood of a first heart failure hospitalisation in type 2 diabetics through mechanisms independent of glucose. The most often reported adverse reactions to dapagliflozin in clinical studies were genital mycotic infections in women and UTI. Dapagliflozin, a new oral treatment for type 2 diabetes, is equally effective in the short term as a dipeptidyl peptidase 4 inhibitor, but its long term efficacy and safety are unknown.(1–3) SGLT2 inhibitors mechanism of action complements those of other kinds of AHAs, making it possible to utilise them in combination treatment with other AHAs, such as insulin.(4,5)One such SGLT2 inhibitor is dapaglifozin, which was previously approved and is used in 38 other nations, including Europe, and received US approval on January 8, 2014 under the brand name Forxiga. Dapagliflozin and metformin were recently approved as a fixed dosage combination in Europe under the name xigduo. (6)

PHARMACOLOGICAL PROPERTIES

SGLT2 is severely inhibited by dapagliflozin in a reversible, highly competitive manner.Type 2 SGLT2s are expressed by both the kidney and the epithelial lining of the S1 segment of the proximal convoluted tubule. These transporters are responsible for around 90% of renal glucose absorption in terms of physiology. (7) In T2D patients, dapaglifozin reduced fasting and post-prandial plasma glucose levels while increasing the volume of glucose urine excretion. (8) According tp the study of komoroski 24 hour glucose excretion quantities in both healthy participants and T2DM patients given a range of dapagliflozin doses to measure the quantity of glucose excretion that happens with dapagliflozin. In healthy individuals, dosages of 20–100 mg of dapagliflozin caused urine glucose excretion of about 60 g in the course of 24 hour. (9) Defronzo Studies found that the 24-hour urine glucose excretion with dapagliflozin expressed only around 40–50%

of the human-filtered glucose load. The ceiling effect may have been caused by SGLT1 improving glucose absorption to make up for SGLT2 being inhibited, which is one explanation for the occurrence. (10) According to the study of Bristol-Myers Squibb Company the recommended dose of dapagliflozin is 5 mg taken orally early in the morning, and if required, it may be increased to 10 mg. It is quickly absorbed and has a 78% bioavailability. Due to its 12.9-hour half-life, it can be administered once a day. Dapaglifozin also caused a slight drop in blood pressure (BP), which could be attributed to the drug's diuretic/natriuretic effects, which produce a decrease in ciculating volume. Patients using antihypertensive medications or those with a history of hypotension should be cautiously monitored before starting or titrating dapagliflozin since it has the potential to lower systolic BP through its osmotic diuretic effect. (11–13) The usual steady-state volume of distribution for dapaglifozin is 118 L and is 91% protein bound. UGT1A9, an enzyme found in the liver and kidneys, metabolises dapaglifozin primarily into the primary inactive metabolite 3-O-glucuronide, which is not involved in the drug's effects on blood sugar levels. Dapaglifozin and its metabolites are mostly excreted in the urine, where 75% of a dosage is recovered (less than 2% of which is the parent drug unchanged) and 21% of which is recovered (less than 15% of which is the parent drug uchanged). After a single dosage of 10 mg, dapaglifozin's mean plasma elimination half-life in healthy patients was 12.9 hours. Dapagliflozin has been tested in combinations with glimepiride, metformin, pioglitazone, and sitagliptin; neither its metabolism nor that of these antihyperglycemic medications is impacted by them, and no pharmacokinetic (PK) changes are known to have occurred. (13)
Dapagliflozin improve glycaemic control and lowers bodyweight and blood pressure in a variety of T2D patients, including those with high baseline HbA1c (9%) and the elderly (aged 65 years), in numerous randomised, double-blind, multicentre, phase 3 trials. (14)

CLINICAL EFFICACY OF DAPAGLIFLOZIN

Clinical efficacy of dapagliflozin as monotherapy:

Five clinical trials involving dapagliflozin as a monotherapy have been conducted. Its monotherapy was added to diet and exercise in 2 of the trials, metformin monotherapy was compared in two more, and dapagliflozin was administered as monotherapy in both patients who had never received treatment before and those who had.(6) Add-on dapaglifozin significantly decreased bodyweight compared to placebo in a randomised, double-blind, international, phase 3 research in patients with metformin-insufficient control (n = 182), with the amount of fat accounting for approximately two-thirds of the overall weight reduction. (15) Bailey and associates studied dapagliflozin 1, 2.5, or 5 mg/day for 24 weeks in 282 drug-naive T2DM patients with poorly managed diabetes. When compared to the patients who received placebo, patients who received dapagliflozin experienced greater decreases in HbA1c (-8 mmol/mol for 1 mg, 8 mmol/mol for 2.5 mg, 9 mmol/mol for 5 mg, and +0.2 mmol/mol for placebo), and also in weight (-2.69 kg for 1 mg, 2.64 kg for 2.5 mg, 2.69 kg for 5 mg, and 0.96 kg for placebo).(16)

Clinical efficacy of dapagliflozin as adjunctive therapy:

A randomised, double-blind, placebo-controlled experiment was conducted by Bailey and colleagues in 546 T2DM patients using metformin (>1500 mg daily) with inadequate glycemic control (baseline HbA1c from 63 mmol/mol to 66 mmol/mol). Dapagliflozin dosages of 2.5, 5 or 10 mg were given daily to these patients, or a placebo, in a random order. All three dapagliflozin groups observed larger HbA1c improvements in 24 weeks than were observed with placebo. The HbA1c level was decreased by an additional 4-6 mmol/mol with dapagliflozin medication as compared to metformin therapy alone. Patients taking dapagliflozin in addition to metformin saw higher reductions in FPG (-17.8 to 23.4 mg/dl) and weight (-2.2 to 3.0 kg) compared to metformin alone (-5.9 mg/dl and 0.9 kg).(11)
According to the study conducted by Strojek and colleagues patients were chosen at random to receive either a placebo or dapagliflozin 2.5, 5 or 10 mg added to open-label glimepiride 4 mg in a 24-week randomised, double-blind, placebo-controlled experiment. All groups receiving dapagliflozin experienced significant reductions in HbA1c (-6 mmol/mol to 9 mmol/mol versus 1 mmol/mol for glimepiride alone) and FPG (-16.8 to 28.5 mg/dl versus 2.0 mg/dl for glimepiride alone) after 24 weeks. The doses of dapagliflozin of 5 mg and 10 mg decreased FPG in a statistically significant manner in comparison to glimepiride alone. Patients in the dapagliflozin 5 mg and 10 mg groups observed continued weight reduction.(17)

Clinical efficacy of dapagliflozin in patient with hypertension:

In phase 3 studies involving patients with inadequately controlled T2D and hypertension despite receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy alone or in combination with one other antihypertensive), dapaglifozin 10 mg once daily decreased SBP and enhanced glycemic control. At week 12, dapaglifozin significantly reduced mean SBP and HbA1c compared to placebo in both studies. According to the analysis of one research, participants taking a beta-

blocker or calcium-channel blocker as their supplemental antihypertensive medication saw lower SBP with dapaglifozin than those on a thiazide diuretic.(18,19)

Clinical efficacy of dapagliflozin in patients receiving insulin:

In a trial by Zhang and colleagues, 58 patients were randomised to receive placebo, dapagliflozin 10 mg, or dapagliflozin 20 mg for 12 weeks and had late stage T2DM despite rigorous insulin and insulin-sensitizing drug treatment for at least 6 weeks. Stable dosages of metformin larger than 1000 mg daily, pioglitazone daily dosage of more than 30 mg, or 4 mg of rosiglitazone each day are examples of insulin sensitizers. Patients in this group received a prophylactic 50% dose of insulin to lower their risk of hypoglycemia, but other prescription dosages were left unchanged. The late-stage patients had baseline HbA1c values between 64 mmol/mol and 68 mmol/mol, and their T2DM duration ranged from 11.1 to 19.3 years. Compared to those not taking dapagliflozin, participants in the late-stage dapagliflozin group had a HbA1c reduction of between 7 and 9 mmol/mol after 12 weeks. Patients who received late-stage dapagliflozin also had greater weight losses (-4.3 to 5.05 kg) in comparison to individuals who didn't get drugs. (–1.55 kg). (20)

Clinical efficacy of dapagliflozin inpatients with heart failure and reduced ejection fraction:

SGLT2 inhibitors have been shown to decrease the risk of being admitted to the hospital for heart failure in large-scale clinical studies including patientss with type 2 diabetes. Most patients in this studies did not have heart failure at baseline, the benefit of therapy with an SGLT2 inhibitor was primarily to prevent the incidence of heart failure. (21)

A total of 4744 patients with New York Heart Association classifications II, III, or IV heart failure with an ejection fraction of 40% or less received dapagliflozin (at a dosage of 10 mg once day) or a placebo in addition to prescribed medication. The main outcome was a composite of cardiovascular death (386 of 2373 patients receiving dapagliflozin and 502 of 2371 patients receiving a placebo) or worsening heart failure (hospitalisation or urgent visit requiring IV heart failure medication). Compared to 326 participants receiving a placebo, 237 patients on dapagliflozin suffered their first episode of heart failure that worsened. 276 and 329 patients, respectively, died from any cause whereas 227 patients in the dapagliflozin group and 273 in the placebo group died away due to cardiovascular causes. Patients without diabetes and those with diabetes both had comparable outcomes. Adverse events related to fluid depletion, renal failure, and Hypoglycemia was the same in frequency across treatment groups. (21)

In those with heart failure and a low ejection fraction, dapagliflozin therapy decreased the risk of cardiovascular-related death or worsening heart failure no matter if they had diabetes or not.(21)

Clinical efficacy of dapagliflozin in patients with chronic kidney disease:

In extensive clinical trials involving type 2 diabetes patients, SGLT2 inhibitors reduced glycated haemoglobin levels and had positive impacts on renal and cardiovascular outcomes. (22–24)

Benefits of SGLT2 Inhibitors might be mediated through natriuresis and glucose-induced osmotic diuresis, which would lower intraglomerular pressure, and appear to be independent of their blood glucose-lowering effects. Those who have renal disease caused by factors other than type 2 diabetes may still retain kidney function as a result of this beneficial hemodynamic effect. (25–27)

10 mg of Dapagliflozin once daily or placebo was given to a total of 4304 participants with estimated glomerular filtration rates (GFR) of 25 to 75 ml a minute per 1.73 m2 of body surface area. and urinary albumin-to-creatinine ratio (with albumin measured in milligram and creatinine measured in grammes of 200 to 5000. The primary result was a composite of end-stage kidney disease, mortality from the cardiovascular or renal causes, and a prolonged fall in estimated GFR of at least 50%.The independent data monitoring group advised ending the trial due to its effectiveness.The primary outcome event was experienced by 197 of the 2152 patients who were given dapagliflozin and 312 of the 2152 participants in the placebo group. Heart failure-related hospitalisations or cardiovascular deaths had a hazard ratio of 0.71, whereas end-stage renal disease, an ongoing decrease in estimated GFR of at least 50%, or death from renal causes had a hazard ratio of 0.56. Dapagliflozin caused the deaths of 101 individuals were in the dapagliflozin group and 146 individuals were in the placebo group. Participants without type 2 diabetes and those with type 2 diabetes experienced the same effects from dapagliflozin.(28)

Regardless of whether they had diabetes or not, patients with chronic kidney disease who took dapagliflozin had a considerably lower chance of developing end-stage kidney disease, dying from cardiovascular or renal causes, or both, than those who took a placebo. (28)

Dapagliflozin effect on risk of urinary tract infection in patient with diabetes:

Urinary tract infections are common in patient with type 2 diabetes. One of the most likely contributing factors is glucosuria, a side effect of therapy with SGLT2 inhibitors. Dapagliflozin has shown glycemic benefit in diabetic patients.(29)

Utilising safety data from 12 randomised, placebo-controlled studies, the relationship between glucosuria and UTI was evaluated in patients with poorly managed diabetes (HbA1c > 6.5%–12%). For 12 to 24 weeks, patients were given dapagliflozin (2.5, 5, or 10 mg) or a placebo, either as Monotherapy or in combination with metformin, insulin, or sulfonylurea, or thiazolidinedione. Clinical diagnoses and circumstances that might indicate UTI were quantified.

In this study, 3152 patients received dapagliflozin as monotherapy or as an additional medicine (2.5 mg or 10 mg) were included together with 1393 patients who got a placebo. 3.6%, 5.7%, 4.3%, and 3.7% of patients receiving dapagliflozin 2.5 mg, 5 mg, 10 mg, and placebo, respectively, reported having infections that were officially diagnosed. Urine glucose levels were gradually increasing, but UTI occurrence did not rise at the same time. Most of the infections identified were ones that were known to be typical among diabetics. An uncommon discontinuation caused by a UTI was observed in eight patients receiving dapagliflozin and one patient receiving a placebo. Most infections were mild to severe and responded to treatment with standard antibiotics. (30)

Treatment of T2DM with dapagliflozin 5 or 10 mg has been associated to a slightly increased incidence of UTI. Most infections were mild to severe and treated clinically. (30)

CONCLUSION

Dapagliflozin, one of the SGLT2 inhibitors, lowers HbA1C in T2DM both by alone and in combination with other antihyperglycemic drugs. When dapagliflozin was added to oral therapies with metformin, glimepiride, pioglitazone, and sitagliptin, compared to placebo, HbA1c, FPG, and body weight considerably reduced. Patients who use dapagliflozin and oral antihyperglycemic drugs concurrently with or without insulin treatment see an additional glycemic effect. Patients receiving dapagliflozin are less likely to get worsening heart failure or death from cardiovascular causes and reduces the risk of end-stage kidney disease, an extended decrease in estimated GFR, and death from renal and cardiovascular causes in patients with CKD.The most severe adverse effect of dapagliflozin, which is normally well tolerated, is presently genitourinary infections. Dapagliflozin and other SLGT2 inhibitors provide an effective new oral therapy option for T2DM patients, although their long-term consequences are unknown.

REFERENCES

1. Hsia, D. S., Grove, O., & Cefalu, W. T. (2016). An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. Current Opinion in Endocrinology & Diabetes and Obesity, 23(4), 1.
2. Wilding, J., Fernando, K., Milne, N., Evans, M., Ali, A., Bain, S., et al. (2018). SGLT2 Inhibitors in Type 2 Diabetes Management: Key Evidence and Implications for Clinical Practice. Diabetes Therapy, 9(5), 1757–73.
3. Scheen, A. J. (2015). Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. Drugs, 75(1), 33–59.
4. Plosker, G. L. (2012). Dapagliflozin. Drugs, 72(17), 2289–312.
5. Plosker, G. L. (2014). Dapagliflozin: A Review of Its Use in Patients with Type 2 Diabetes. Drugs, 74(18), 2191–209.
6. Anderson, S. L. (2014). Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf, 5(6), 242–54.
7. Turk, E., & Wright, E. M. (2004). The sodium/glucose cotransport family SLC5. Pflügers Archiv European Journal of Physiology, 447(5), 510–8.
8. Komoroski, B., Vachharajani, N., Feng, Y., Li, L., Kornhauser, D., Pfister, M., et al. (2009). Dapagliflozin, a Novel, Selective SGLT2 Inhibitor, Improved Glycemic Control Over 2 Weeks in Patients With Type 2 Diabetes Mellitus. Clin Pharmacol Ther, 85(5), 513–9.
9. Komoroski, B., Vachharajani, N., Boulton, D., Kornhauser, D., Geraldes, M., Li, L., et al. (2009). Dapagliflozin, a Novel SGLT2 Inhibitor, Induces Dose-Dependent Glucosuria in Healthy Subjects. Clin Pharmacol Ther, 85(5), 520–6.
10. DeFronzo, R. A., Hompesch, M., Kasichayanula, S., Liu, X., Hong, Y., Pfister, M., et al. (2013). Characterization of Renal Glucose Reabsorption in Response to Dapagliflozin in Healthy Subjects and Subjects With Type 2 Diabetes. Diabetes Care, 36(10), 3169–76.
11. Bailey, C. J., Gross, J. L., Pieters, A., Bastien, A., & List, J. F. (2010). Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. The Lancet, 375(9733), 2223–33.
12. Petrykiv, S., Sjöström, C. D., Greasley, P. J., Xu, J., Persson, F., & Heerspink, H. J. L. (2017). Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function. Clinical Journal of the American Society of Nephrology, 12(5), 751–9.
13. Anderson, S. L. (2014). Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf, 5(6), 242–54.
14. Skolnik, N., Bonnes, H., Yeh, H., Katz, A. (2016). Dapagliflozin in the treatment of patients with type 2 diabetes presenting with high baseline A1C. Postgraduate Medicine, 128(4), 356-363.
15. Bolinder, J., Ljunggren, Ö., Kullberg, J., Johansson, L., Wilding, J., Langkilde, A. M., & Sugg, J. (2012). Effects of Dapagliflozin on Body Weight, Total Fat Mass, and Regional Adipose Tissue Distribution in Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin. The Journal of Clinical Endocrinology & Metabolism, 97(3), 1020-1031.

16. Bailey, C. J., Iqbal, N., T'joen, C., List, J. F. (2012). Dapagliflozin monotherapy in drug-naïve patients with diabetes: A randomized-controlled trial of low-dose range. Diabetes, Obesity and Metabolism, 14(10), 951-959.
17. Weber, M. A., Mansfield, T. A., Alessi, F., Iqbal, N., Parikh, S., Ptaszynska, A. (2016). Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin–angiotensin system blockade. Blood Pressure, 25(2), 93-103.
18. Weber, M. A., Mansfield, T. A., Alessi, F., Iqbal, N., Parikh, S., & Ptaszynska, A. (2016). Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin–angiotensin system blockade. Blood Pressure, 25(2), 93–103.
19. Weber, M. A., Mansfield, T. A., Cain, V. A., Iqbal, N., Parikh, S., & Ptaszynska, A. (2016). Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes & Endocrinology, 4(3), 211–220.
20. Zhang, L., Feng, Y., List, J., Kasichayanula, S., & Pfister, M. (2010). Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes, Obesity & Metabolism, 12(6), 510–516.
21. McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., & Boulton, A. J. M. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine, 381(21), 1995–2008.
22. Wanner, C., Inzucchi, S. E., Lachin, J. M., Fitchett, D., von Eynatten, M., Mattheus, M., & Koitka-Weber, A. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine, 375(4), 323–334.
23. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. (2017). New England Journal of Medicine, 377(21), 2097–2099.
24. Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., & Braunwald, E. (2019). Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine, 380(4), 347–357.
25. Cherney, D. Z. I., Dekkers, C. C. J., Barbour, S. J., Cattran, D., Abdul Gafor, A. H., Greasley, P. J., & Sharma, K. (2020). Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. Lancet Diabetes & Endocrinology, 8(7), 582–593.
26. Heerspink, H. J. L., Kosiborod, M., Inzucchi, S. E., Cherney, D. Z. I., & Koitka-Weber, A. (2018). Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney International, 94(1), 26–39.
27. van Bommel, E. J. M., Muskiet, M. H. A., van Baar, M. J. B., Tonneijck, L., Smits, M. M., Emanuel, A. L., & van Raalte, D. H. (2020). The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. Kidney International, 97(1), 202–212.
28. Heerspink, H. J. L., Stefánsson, B. V., Correa-Rotter, R., Chertow, G. M., Greene, T., Hou, F. F., & McMurray, J. J. V. (2020). Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine, 383(15), 1436–1446.
29. Schiff, M. A., & Holt, V. L. (2005). Pregnancy outcomes following hospitalization for motor vehicle crashes in Washington State from 1989 to 2001. American Journal of Epidemiology, 161(6), 503–510.
30. Johnsson, K. M., Ptaszynska, A., Schmitz, B., Sugg, J., Parikh, S. J., & List, J. F. (2013). Urinary tract infections in patients with diabetes treated with dapagliflozin. Journal of Diabetes and Its Complications, 27(5), 473–478.

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