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An Overview of Dapagliflozin

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Abstract:- Type 2 diabetes, a chronic, progressive condition, causes hyperglycemia in the heart, liver, skeletal muscle, and adipose tissue. The latest forecasts show 592 million diabetics globally by 2035, up from 382 million in 2013. A new line of medicines blocks the kidney-based transporter protein sodium glucose co-transporter-2 (SGLT2) independently of insulin, complementing insulin treatment. Dapagliflozin (Forxiga) is a new EU-approved type 2 diabetes medication. This insulin-dependent process boosts urine glucose excretion. By specifically and potentially inhibiting SGLT2, dapagliflozin decreases blood glucose without insulin. Dapagliflozin had no clinically meaningful pharmacokinetic interactions with metformin, pioglitazone, sitagliptin, or glimepiride in healthy volunteers. The principal findings of clinical trials employing dapagliflozin to treat type 2 diabetes showed that the prescribed dosage (10 mg/day) was beneficial. Dapagliflozin works best with type 2 diabetes and cardiovascular disease or risk factors.

Keywords:- *Dapagliflozin, Type 2 Diabetes, SGLT-2 Inhibitor.*

I. INTRODUCTION

Type 2 diabetes, a chronic, progressive condition, causes hyperglycemia in the heart, liver, skeletal muscle, and adipose tissue [1]. Every country has a significant diabetes disease burden due to the rise in unhealthy lifestyles and obesity. The latest forecasts show 592 million diabetics globally by 2035, up from 382 million in 2013. The aetiological classification of diabetes is widely accepted. Diabetes is divided into type 2 and type 1, with type 2 prevalent (>85%) [2,3]. Growing obesity rates and Western lifestyle choices such as poor eating and lack of exercise are expected to raise these numbers, especially in developing nations, in the next decades [1,3]. Diabetes causes morbidity, death, and social and economic problems. Diabetes is a primary cause of disability worldwide, and the latest estimates place its annual mortality at 4–4.6 million [4]. Diabetes treatment cost about 11% of worldwide healthcare spending in 2011 [5]. Poorly treated diabetes causes permanent eyesight loss, stroke, kidney failure, heart attack, and lower limb amputation. Eighteen percent of type 2 diabetes patients in the UK Prospective Diabetes Study (UKPDS) 16 had diabetes-related issues within six years. Since several studies—including UKPDS 35—have linked poor glycaemic control to microvascular and macrovascular complications, HbA1c management is a crucial therapeutic target [3'4]. Based on clinical trials that showed better clinical outcomes in patients with better glycaemic control, current guidelines recommend treating diabetic patients with lifestyle changes and medication to achieve a HbA1c value below 7.0% in a patient-centered approach that allows for some flexibility. UKPDS 49 shows that most patients need combination treatment since single-antidiabetic medicine glycaemic control is rarely acceptable. Only over half of adult diabetics attain their HbA1c goals, underscoring the necessity for combination regimens [5,6]. Most oral antidiabetic medicines increase insulin production or make target tissues more insulin-sensitive. New medicines that block the kidney-based transporter protein sodium glucose co-transporter-2 (SGLT2) independently of insulin complement insulin treatment [3,4,6]. This article focuses on SGLT2 inhibitors, specifically dapagliflozin (Forxiga), a novel type 2 diabetes medicine licensed in the EU [2,7]. Farmiga (dapagliflozin) is an SGLT2 inhibitor used to treat type 2 diabetes, chronic kidney disease, and heart failure. The first-in-class SGLT2 inhibitor Farxiga (dapagliflozin) is taken orally daily. Farxiga protects the heart, kidneys, and pancreas from cardiorenal disease, which is important given their interconnectedness. T2D, HF, and CKD are the leading causes of death worldwide, and damage to one can induce the other to fail [4,5,8].

II. PHARMACOLOGY

- *Mechanism Of Action*

Since over 99 percent of the glucose filtered by the average adult kidney is reabsorbed, just around one percent is excreted in urine. SGLTs help the kidneys, intestines, and heart reabsorb glucose. The SLC5A2 gene family has seven SGLTs, including the notable SGLT1 and SGLT2. Dapagliflozin targets SGLT2, which reabsorbs 90% of renal glucose. It is mostly expressed on proximal convoluted tubule S1 epithelial cells. Mutations in the SGLT2 gene cause persistent glucosuria, confirming that SGLT2 is important in renal glucose reabsorption. SGLT1 reabsorbs the remaining 10% of renal glucose after SGLT2 on the S3 proximal tubule [8,9]. Dapagliflozin, a competitive, reversible, and highly selective SGLT2 inhibitor, prevents glucose reabsorption into the circulation, causing glucosuria. Glucosuria is more affected by dapagliflozin in patients with higher blood glucose levels due to renal function and glycemic management. Dapagliflozin's ability to function without insulin production and sensitivity is crucial. Patients with impaired β cell function can use dapagliflozin, which

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does not require functioning pancreatic β cells. Dapagliflozin interacts synergistically with other oral medications and has a minimal additional risk of hypoglycemia. [6,10]

➢ *Pharmacokinetics*

After Phase 1 and 2 dapagliflozin trials, 651 people were examined. The drug's pharmacokinetics remained unaffected by factors such as age, type 2 diabetes, weight/BMI, sex, race, genetic polymorphisms (involving UGT1A9), mild liver impairment (class A or B according to Child-Pugh), or mild renal impairment (CrCl >50 to <80 mL/min) [3,11]. A1C change of -0.1% at 24 weeks was the study's major goal, although patients with moderate renal impairment (estimated glomerular filtration rate 30-59 mL/min/1.73 m2) who received 5 mg or 10 mg dapagliflozin daily did not meet it. This shows the medicine is less effective in this population [11]. Within 30–120 minutes, dapagliflozin achieves peak plasma concentrations and is 78% bioavailable. The main metabolite of dapagliflozin generated by UGT1A9 is 3-O-glucuronide. Due to its protein binding affinity, dapagliflozin is removed in the urine in less than 2%. The kidneys remove fewer than 70% of metabolites. At 10 mg, dapagliflozin has a half-life of 12–13 hours, making it suitable for once-daily use [12].

➢ *Pharmacodynamics*

In the proximal renal tubule and intestinal epithelium, SGLT proteins transport glucose, amino acids, and other substances. A complex mechanism involving several transport systems reabsorbs nearly all of the glucose filtered daily in the glomeruli in healthy adult kidneys. SGLTs help tubular epithelial cells absorb glucose from the tubule. The proximal tubule reabsorbs about 10% of glucose, while SGLT1 absorbs glucose in the gut. SGLT2 is a key kidney SGLT transporter. By specifically and potentially inhibiting SGLT2, dapagliflozin decreases blood glucose without insulin. This reduces renal glucose reabsorption and increases urine glucose excretion [11,13]. SGLT2, which reabsorbs 90% of renal glucose, is predominantly expressed in the kidney. However, SGLT2 has low affinity but great capacity. For secondary active transport of glucose, the SGLT2 protein co-transports the two substances via the brush-border membrane of the proximal renal tubule into the tubular epithelial cells in response to a sodium gradient. A glucose transporter protein permits glucose to be passively reabsorbed into the interstitium from epithelial cells [14,15]. In vitro, dapagliflozin demonstrated 1,200 times the selectivity for human SGLT2 over human SGLT1, the gut's principal glucose transporter. Human SGLT2 and SGLT1 had 50% dapagliflozin inhibitory values of 1.1 and 1,390 nmol/L. An abstract from a recent study shows that SGLT1 inhibits 3000-fold less than SGLT2 [16]. Dapagliflozin caused dose-dependent glucosuria in healthy volunteers and type 2 diabetics in short-term studies. [17]. Healthy volunteers' 24-hour glucose excretion was 20.4, 33.6, 49.2, 53.3, and 55.4 g after two weeks of consuming 2.5, 10, 20, 50, or 100 mg dapagliflozin daily. The cumulative urine glucose excretion on days 1 and 14 was similar, suggesting that the first dosage induces glucosuria [10,17]. After 2 weeks of treatment with 10 mg dapagliflozin daily, type 2 diabetes patients' 24-hour urine glucose levels jumped from 11g/24 hours to 68g/24 hours. Day 14 results for 2.5-50 mg dapagliflozin patients were 52 to 85 g/24 hours. In the placebo-controlled trial, dapagliflozin improved HbA1c, FPG, and PPG. In another 2-week randomized, placebo-controlled experiment on type 2 diabetics, glucosuria increased dose-dependently, and glycaemic indicators improved [17]. An abstract from a study of renal glucose kinetics in response to dapagliflozin 10 mg/day in healthy volunteers and type 2 diabetics found that a significantly lower renal blood glucose threshold was the main mechanism for glucosuria [18]. In 12-week trials, type 2 diabetics were administered dapagliflozin to induce glucosuria lost weight, and had moderate diuresis. Over time, scientific investigations demonstrated weight loss owing to calorie loss, not fluid loss. At week 12, 2.5-50 mg dapagliflozin daily patients had dose-dependent 24-hour urine volumes of 107 to 470 milliliters greater than baseline. Despite no change in potassium, calcium, or sodium levels, magnesium rose slightly and uric acid dropped steadily, returning to baseline after the medicine was withdrawn. In healthy individuals given 2.5-100 mg dapagliflozin daily for two weeks, baseline, 8-, and 13-day urine sodium excretion levels were comparable [19,20].

➢ *Drug Interactions*

Overall, dapagliflozin has few pharmacokinetic drug interactions. Dapagliflozin had no clinically meaningful pharmacokinetic interactions with metformin, pioglitazone, sitagliptin, or glimepiride in healthy volunteers. Dapagliflozin should not influence CYP substrate pharmacokinetics. Rifampin, an enzyme inducer, reduced dapagliflozin's systemic exposure slightly [15,21]. No clinically meaningful pharmacokinetic interactions were observed in healthy patients using dapagliflozin with simvastatin, valsartan, warfarin, or digoxin. The study found no therapeutic significance in the »50% increase in dapagliflozin exposure from taking it with the UGT1A9 inhibitor mefenamic acid. Several pharmacodynamic interactions between dapagliflozin and other medications may affect patient care. When loop diuretics are administered concurrently, volume depletion is a danger, and insulin or insulin secretagogues such as sulfonylureas can cause hypoglycemia [22].

➢ *Therapeutic Efficacy*

The analyses of the important findings of clinical trials utilizing dapagliflozin to treat type 2 diabetes in phase III studies that used the recommended dosage (10 mg/day) and had the same primary efficacy outcome. Several recent presentations of pooled analyses or extension studies of key phase III trials or other relevant clinical trial data are also included, along with several other dapagliflozin type 2 diabetes trials. This section shows glucose levels in mmol/L; mg/dL data was converted using 0.0555. Except for insulin, which was subcutaneously administered, other drugs were oral. Study techniques occasionally included dietary and exercise guidance, but abstracts may not have stated so [18,23].

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➢ *Dosage And Administration*

Adults (18 years old) with type 2 diabetes can use dapagliflozin alone, with metformin, or with additional glucose-lowering drugs like insulin. It can also be used in conjunction with a good diet and regular exercise. Dapagliflozin 10 mg once a day is recommended alone or with other oral antidiabetics, insulin, or both [23]. Dapagliflozin can be taken with or without food. Dapagliflozin alone or with metformin has a low risk of hypoglycemia, but it increases when taken with an insulin secretagogue or insulin, which may require a lower background medication dose [24]. Dapagliflozin is not recommended for those with moderate to severe renal impairment, as indicated by creatinine clearance below 60mL/min or an estimated glomerular filtration rate below 60mL/min/1.73m2. Patients with severe hepatic impairment should start at 5 mg/day and increase to 10 mg/day if tolerated. Modest renal impairment or mild to severe hepatic impairment do not require dapagliflozin dose changes [25,26]. See the local prescribing information for adverse effects, precautions, drug interactions, and how to use the medication in certain patient populations.

➢ *Side Effects*

Ketoacidosis characterises diabetes mellitus. Patients with type 1 or 2 diabetes have developed ketoacidosis from dapagliflozin. Ketoacidosis has also occurred in diabetics using dapagliflozin during illness or surgery. Ketoacidosis may require hospitalisation. Death from ketoacidosis. Dapagliflozin can cause ketoacidosis in people with blood sugar < 250 mg/dL. Stop dapagliflozin and consult your doctor if you experience nausea, vomiting, abdominal pain, excessive exhaustion, or trouble breathing [6,9,11]. If any of these symptoms occur while taking dapagliflozin, check for urine ketones even if your blood sugar is below 250 mg/dL [25]. Dapagliflozin users have had severe UTIs that require hospitalization. Urgency to pee, burning feeling when passing urine, frequent or urgent urination, pelvic discomfort, or blood in the urine may indicate a urinary tract infection. High fever, backache, nausea, and vomiting may develop. Patients with diabetes have hypoglycemia. Taking dapagliflozin with insulin or sulfonylureas increases your risk of low blood sugar. While using dapagliflozin, you may need to lower your insulin or sulfonylurea dose. A racing heart, trembling or jitteriness, irritability, weakness, lethargy, sweating, disorientation, vertigo, and an intense need to eat are indications of dangerously low blood sugar [27,29]. A rare and potentially fatal bacterial illness that affects perineal subcutaneous tissue (the space between the anus and the genitalia) is necrotizing fasciitis. Male and female diabetics using dapagliflozin are at risk of perineal necrotizing fasciitis. Necrotizing fasciitis of the perineum can cause death, hospitalization, and many surgeries. Consult a doctor immediately if you have a fever, excessive exhaustion, generalized malaise, discomfort or soreness, edema, or erythema between and around the anus and genitals [28]. The most common side effects of dapagliflozin include penile and vaginal yeast infections, nose and throat congestion, urine output abnormalities, and urgency [30].

➢ *Indication*

Prolonged eGFR reduction in chronic kidney disease patients reduces the risk of end-stage renal disease, cardiovascular mortality, and heart failure hospitalization. Reduce cardiovascular mortality, heart failure hospitalizations, and emergency department visits in heart failure patients. People with type 2 diabetes and cardiovascular disease or multiple risk factors should have a lower risk of heart failure hospitalization. Farxiga belongs to the SGLT2 inhibitor family [29,30]. Along with diet and exercise, it helps type 2 diabetics control their blood sugar. Drugs that inhibit SGLT2 reduce filtered glucose reabsorption and increase urine glucose excretion. Dapagliflozin decreases sodium reabsorption and increases distal tubule sodium transport. One Farxiga tablet is swallowed daily. Farxiga warns against hypoglycemia, genital mycotic infections, Fournier's Gangrene, volume depletion, urosepsis, and pyelonephritis. The most prevalent side effects are nasopharyngeal, urinary, and female genitourinary infections [30].

III. CONCLUSION

Dapagliflozin, a new SGLT-2 inhibitor, was approved by the FDA in December 2017 to treat adult type 2 diabetes. It was authorized on January 8, 2014. This insulin-dependent process boosts urine glucose excretion. Clinical research shows it improves A1C and weight reduction safely. The kidneys and heart are the key objectives for diabetic complications prevention. Dapagliflozin reduces adverse events in cardiovascular disease and chronic renal disease patients. If you have heart disease or renal illness, dapagliflozin won't worsen it.

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