



## Review Article

# A Review of Dapagliflozin Effect On Disease Conditions Like Diabetes Mellitus, Heart Failure, Renal Failure

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### ABSTRACT

In these studies, Dapagliflozin action was seen in different disease conditions like Diabetes mellitus, Heart failure, and Renal failure. The class of Dapagliflozin is sodium-glucose cotransporter 2 inhibitors, it shows major action in the kidneys. It blocks the reabsorption of filtered glucose in the kidney, increases urinary glucose excretion, and reduces blood glucose levels. By this mechanism, it maintains the blood glucose level and excretes the excess amount of water through urine. Dapagliflozin is used in the treatment of reduced ejection fraction in heart failure patients for better improvement in the condition. In renal failure also these drugs are used for the improvement in the excretion of urine.

### INTRODUCTION

Diabetes mellitus is a collection of metabolic illnesses characterized by chronic hyperglycemia caused by deficiencies in insulin secretion, action, or both. The relevance of insulin as an anabolic hormone causes metabolic irregularities in carbohydrates, lipids, and proteins. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and, to a lesser extent, the liver, are responsible for these metabolic abnormalities at the level of insulin receptors,

signal transduction system, and/or effector enzymes or genes<sup>(1)</sup>

It has many subclassifications

- Type 1 diabetes.
- Type 2 diabetes,
- Maturity-onset diabetes of the young (MODY),
- Gestational diabetes,
- Neonatal diabetes,
- Steroid-induced diabetes is all subtypes.

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The two most common kinds of diabetes are type 1 and type 2.

T1DM is defined by the loss of beta cells in the pancreas, which is usually the result of an autoimmune disease. As a result, beta cells are destroyed, and insulin is either absent or extremely low.

T2DM has a more gradual start, with an imbalance between insulin levels and insulin sensitivity resulting in an insulin functional deficit. Insulin resistance is complex, however, it is most typically caused by fat and aging.<sup>(2)</sup>

T2DM is characterized by a more intricate combination of genetics and lifestyle. There is compelling evidence that T2DM has a greater genetic profile than T1DM. The majority of patients with T2DM have at least one parent who has the illness.<sup>(3)</sup>

Systemic arterial hypertension (also known as hypertension) is defined by persistently high blood pressure (BP) in the systemic arteries. The ratio of systolic BP (the pressure that the blood exerts on the artery walls when the heart contracts) to diastolic BP (the pressure when the heart relaxes) is widely used to express blood pressure.<sup>(4)</sup>

Renal failure is defined as the kidneys' inability to conduct excretory functions, resulting in the retention of nitrogenous waste products in the blood. The two types of kidney failure are acute and chronic renal failure<sup>(5)</sup>

#### **Acute Renal Failure (ARF)**

ARF is a reversible syndrome in which glomerular filtration drops abruptly (hours to days). AKI can be diagnosed using any of the following criteria, according to the KDIGO criteria in 2012:

- (1) a 0.3 mg/dL increase in 48 hours
- (2) a 1.5 times baseline increase in the last 7 days
- (3) a urine volume less than 0.5 mL/kg per hour for 6 hours.

#### **chronic Renal Failure (CRF)**

CRF, also known as chronic kidney disease (CKD), is defined as a chronic impairment of

kidney function, characterized by excessively increased serum creatinine for more than 3 months or a calculated glomerular filtration rate (GFR) of less than 60 ml per minute / 1.73m<sup>2</sup>. It is frequently characterized by a progressive decrease in kidney function that necessitates renal replacement therapy (dialysis or transplantation). End-stage renal disease (ESRD) is a condition in which a patient requires renal replacement therapy.

CKD classified based on grade:

- Grade 1: GFR greater than 90
- Grade 2: 60 to 89
- Grade 3a: 45 to 59
- Grade 3b: 30 to 44
- Grade 4: 15 to 29
- Grade 5: Less than 15<sup>(6)</sup>

#### **DAPAGLIFLOZIN ACTION IN DIABETES**

Dapagliflozin is a sodium-glucose cotransporter-2 inhibitor that is extremely effective, reversible, and selective in the treatment of type 2 diabetes (T2D). In the European Union, oral dapagliflozin is approved as monotherapy (in patients who are intolerant of metformin) and as add-on combination therapy (with additional glucose-lowering medicines, including insulin) for T2D when diet and exercise alone do not offer acceptable glycemic control.<sup>(8)</sup>

#### **PHARMACODYNAMICS**

1. Dapagliflozin is a selective and reversible SGLT2 transporter inhibitor. SGLT2 proteins are found in the kidney's proximal convoluted tubule (PCT), where they are important for glucose and salt reabsorption from the glomerular filtrate. Approximately 180 g of glucose is filtered and subsequently reabsorbed daily, the majority via SGLT2 and the balance by SGLT1. As a result, no glucose is excreted in healthy people's urine. During hyperglycemia (as in type 2 diabetes) Upregulation of SGLT2 leads to increased glucose reabsorption, adding to



hyperglycemia, although the capacity is finally exhausted, resulting in glycosuria. SGLT2 inhibitors prevent glucose reabsorption, resulting in glycosuria of around 80 g per day, which directly lowers glucose in an insulin-independent manner.(8)

2. Dapagliflozin is a selective and reversible SGLT2 inhibitor that reduces glucose reabsorption and blood glucose concentrations in an insulin-independent manner.(9)
3. Dapagliflozin increases insulin sensitivity while increasing endogenous glucose production in T2DM patients. Dapagliflozin's reduction in glucose reabsorption has been linked to a loss of body weight, presumably due to a reduction in body calories.(10)

#### **DAPAGLIFLOZIN ACTION ON HEART FAILURE**

SGLT2 inhibitors, which were initially developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus, reduce the risk of death and other adverse outcomes in patients with chronic heart failure and a reduced ejection fraction (i.e., a left ventricular ejection fraction of 40%) and in those with chronic kidney disease, regardless of the presence or absence of type 2 diabetes mellitus. SGLT2 inhibitors are strongly recommended by current clinical guidelines in patients with persistent heart failure and a decreased ejection fraction. In individuals with heart failure and a modestly reduced or retained ejection fraction, dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death.(11) Molecular Mechanisms of Dapagliflozin in heart failure Reduction in preload and afterload (leading to improved ventricular loading), improvement in myocardial metabolism, and changes in cardiac fibrosis are among these. SGLT2 inhibitors have been demonstrated to inhibit the sodium proton channel (NHE) in cardiac myocytes, resulting in a decrease

in intracellular calcium and mitochondria-induced cellular damage, which is at the heart of myocardial remodeling.(12)

#### **DAPAGLIFLOZIN ACTION ON RENAL FAILURE**

In extensive clinical trials involving type 2 diabetes patients, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduced glycosylated hemoglobin levels and improved renal and cardiovascular outcomes.

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) experiment found that long-term canagliflozin medication provided renal and cardiovascular protection in type 2 diabetes patients with chronic kidney disease. The advantages of SGLT2 inhibitors appear to be independent of their blood glucose-lowering effects and may be mediated through natriuresis and glucose-induced osmotic diuresis, resulting in a decrease in intraglomerular pressure.

This beneficial hemodynamic effect may also preserve renal function in people who have kidney disease from sources other than type 2 diabetes.(13) Dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival in people with chronic kidney disease, with or without type 2 diabetes, independently of the presence of concomitant cardiovascular disease.(14) The combination of dapagliflozin and metformin is used to treat type 2 diabetes, along with a healthy diet and exercise. It is also used to reduce the risk of heart failure hospitalization in individuals with type 2 diabetes and cardiovascular disease (heart or blood vessel disease) or multiple cardiovascular risk factors. This medication is also used to reduce the risk of cardiovascular death and hospitalization in people who have heart failure with a poor ejection fraction (the heart is weak and cannot pump enough blood to the rest of the body). In patients with chronic



kidney disease, the combination of dapagliflozin and metformin is also used to reduce the risk of kidney disease deteriorating, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure. Dapagliflozin works in the kidneys to prevent glucose (blood sugar) absorption. This aids in the reduction of blood sugar levels. Metformin inhibits sugar absorption from the stomach, decreases the release of stored sugar from the liver, and improves the utilization of sugar<sup>(15)</sup>

## **DAPAGLIFLOZIN DRUG**

### **Class of Dapagliflozin Drug**

Sodium-glucose co-transporter 2 (SGLT2) inhibitors. <sup>(7)</sup>

### **Dosage Forms & Strengths of Dapagliflozin .**

- 5mg
- 10mg

### **Type 2 Diabetes Mellitus**

➤ Improve glycemic control

Used in conjunction with diet and exercise to improve glycemic control in people with type 2 diabetes mellitus (T2DM).

- Start with 5 mg PO Day in the morning.
- May be increased to 10 mg Day in patients who tolerate 5 mg/day but more glycemic control.

➤ Reduce the risk of hospitalization for heart failure

Indicated to lower the risk of heart failure hospitalization in individuals with T2DM and existing cardiovascular disease (CVD) or multiple CV risk factors.

- 10 mg PO Day in the morning

### **Heart Failure**

Indicated to lower the risk of heart failure hospitalization in individuals with T2DM and existing cardiovascular disease (CVD) or multiple CV risk factors.

- 10 mg PO Day in the morning

### **Chronic Kidney Disease**

Indicated to minimize the risk of long-term eGFR decline, end-stage kidney disease (ESKD), cardiovascular death, and HF hospitalization in people with chronic kidney disease (CKD) at risk of progression.

- 10 mg PO once a day<sup>(16)</sup>

## **PHARMACOLOGY**

### **Mechanism of Action**

SGLT-2 inhibitors reduce glucose reabsorption and lower the renal threshold for glucose, resulting in increased urinary glucose excretion. SGLT-2, which is expressed in the proximal renal tubules, is responsible for the majority of reabsorption of filtered glucose from the tubular lumen; SGLT2 inhibitors reduce glucose reabsorption and lower the renal threshold for glucose, resulting in increased urinary glucose excretion.

Reduces sodium reabsorption while boosting sodium availability to the distal tubule; this may affect a variety of physiological activities, including decreasing cardiac pre- and afterload and downregulating sympathetic activity.

### **Absorption**

- 78% bioavailability
- Peak plasma time: 2 hours (fasting); 3 hours (high-fat meal).
- Peak plasma concentration can be reduced by up to 50% after consuming a high-fat meal.

### **Distribution**

- 91%protein bound

### **Metabolism**

In humans, metabolism mediated predominantly by UGT1A9 CYP-mediated metabolism is a minor clearance mechanism. Dapagliflozin 3-O-glucuronide (inactive metabolite) is extensively metabolized.

### **Elimination**

- The half-life is 12.9 hours.
- 75% urine; 21% faeces excretion<sup>(16)</sup>

### **Side Effect**

Dapagliflozin may have unwanted side effects. Symptoms are strong or persistent

- frequent urination, even during the night
- increased thirst

Some of the negative effects can be severe.

- frequent, urgent, burning, or painful urination
- cloudy, red, pink, or brown urine
- strong-smelling urine
- decrease in urine amount
- pelvic or rectal pain
- vaginal odor, white or yellowish vaginal discharge (may be lumpy or look like cottage cheese), or vaginal itching
- (in men) penis redness, itching, or swelling; rash
- on the penis or pain in the skin around the penis
- fatigue, weakness, or discomfort, as well as a temperature and pain, soreness, redness, or swelling of the genitals or the area between the genitals and the rectum
- edema of the legs or feet<sup>(19)</sup>

## WARNINGS

Dapagliflozin should not be given in these disease conditions

- severe renal illness (requiring dialysis)
- diabetic ketoacidosis
- polycystic kidney disease
- liver disease
- bladder infections or other urinary difficulties
- pancreas disorders, including surgery
- alcoholism or current heavy alcohol consumption
- on a low-salt diet.<sup>(18)</sup>

## CONCLUSION

Dapagliflozin reduced the risk of kidney failure, death from cardiovascular causes or hospitalization for heart failure, and prolonged survival in people with chronic kidney disease, with or without type 2 diabetes. Nowadays dapagliflozin is used as a drug of choice in uncontrolled diabetes mellitus. And it is also used

in reduced ejection fraction in heart failure patients for better improvement in their condition. Dapagliflozin shows positive effects in Heart failure, Diabetes Mellitus, and Renal failure.

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