CLINICAL BENEFITS AND TOLERABILITY OF DAPAGLIFLOZIN IN PATIENTS WITH REDUCED EJECTION FRACTION

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ABSTRACT

Heart failure is a progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body's metabolic needs. Heart failure (HF) with reduced systolic function (i.e., reduced left ventricular ejection fraction, LVEF) is referred to as HF with reduced ejection fraction (HFrEF). Based on the measurement of LVEF, HF is divided into three distinct types:

- Patients with LVEF ≤40% (reduced LV systolic function): HFrEF
- Patients with LVEF between 41% and 49% (mildly reduced LV systolic function): HFmEF
- Patients with LVEF ≥50% (preserved ejection fraction): HFpEF

The signs and symptoms of heart failure includes primary symptoms like dyspnoea and fatigue which lead to exercise intolerance, other pulmonary symptoms include orthopnoea, paroxysmal nocturnal dyspnoea, tachypnoea, and cough. Fluid overload can result in pulmonary congestion and peripheral edema. Basic tests such as serum urea and electrolytes, creatinine, complete blood count, and liver and thyroid function tests are recommended to differentiate HF from other conditions, provide prognostic information, and guide potential therapy. Echocardiography is recommended as the key research tool to assess cardiac function and to provide information on other parameters such as chamber size, eccentric or concentric LVH, regional wall motion abnormalities (RWMA), RV function, pulmonary hypertension, valvular function, and markers of diastolic function.

SGLT2 inhibitors are a class of prescription medicines that are FDA approved for use along with diet and exercise to lower blood sugar in adults with type 2 diabetes. It promotes osmotic diuresis and natriuresis in patients with and without diabetes, and thus may reduce preload. Among that, Dapagliflozin reduced death and hospitalizations, and improved symptoms in HFrEF patients. The common side effects may include acute kidney injury, electrolyte imbalance, bone fracture, genito- urinary fungal infection, urinary tract infection, hypovolemia, backpain etc. Dapagliflozin does not cause any serious drug interaction, but the effect should be monitored with other antidiabetic drugs, lithium etc. Among patients with heart failure and a mildly reduced or preserved ejection fraction, dapagliflozin resulted in a lower risk of the primary outcome (worsening heart failure or cardiovascular death, CV), in fewer worsening heart failure events and cardiovascular deaths.

AIM

To investigate the clinical benefits of dapagliflozin in patients with reduced ejection fraction and to analyze the tolerability of dapagliflozin.

OBJECTIVE

Primary objective:

1. To identify the clinical benefits of dapagliflozin in the symptomatic treatment of HFrEF.
2. To document the incidence of re-admission in HF patients on dapagliflozin.
3. To determine the effect on blood sugar levels.

Secondary objective:

1. To identify the adverse effects (if any) and tolerability of dapagliflozin.
2. To analyze the effect of dapagliflozin on body weight.

METHODOLOGY:

STUDY DESIGN

- An ambispective study from January 2022 to April 2023.
- Data was collected using a specially designed data collection form.
- Patients were selected based on inclusion and exclusion criteria.
- 85 patients of heart failure being managed in the hospital with standard HF treatment including the retrospective group from Jan 2022 to Nov 2022 and newly diagnosed HF patients from December 2022 were included in the study.
- These patients as per indication were started on dapagliflozin by the treating Cardiologist.
- The patients were followed up for 2 months after starting dapagliflozin.
- They were evaluated for the clinical benefits.
- Symptomatic improvement in patients were analyzed by using KCCQ 12, and recorded the symptoms of patients during the initial phases of heart failure and during the follow up time.
- Effect of dapagliflozin on the blood sugar levels and body weight were analyzed.

- The incidence of re hospitalization and the safety and tolerability of the drug were also documented.
- The study was done by taking details of patients from the medical records and the Mediware system available in the Lourdes Hospital, Kochi.

STUDY PERIOD

- The study period was from January 2022 to April 2023.
- Patients who were diagnosed with heart failure from Echo scan with EF less than 50 were identified from January 2022 to November 2022 and when they came for follow-up they were started on dapagliflozin and they were also included in our study and were prospectively analyzed along with the others.
- The study was done by taking details of patients from the medical records and the Mediware system available in the Lourdes Hospital, Kochi.

STUDY SETTING

This study was carried out in the department of Cardiology, Lourdes Hospital, Post Graduate Institute of Medical Science and Research, Ernakulam, Kochi - 682 012, Kerala, India, which is a 600 bedded multi-specialty tertiary care referral teaching hospital with a wide range of amenities. The institution is equipped with 7 super speciality department and 22 other departments with facilities comprising 12 operation theatres, 10 intensive care units and a computerized Lourdes Mediware system. Clinical laboratories with ISO standards. It is one of the top most hospitals in Kerala where even the poor have access to advanced medical care in an atmosphere of love and compassion.

STUDY POPULATION

All the patients who met the inclusion and exclusion criteria and gave consent to participate were selected in the study.

SAMPLE SIZE

- As suggested by the Statistician, sample size for the study was calculated to be 72.
- We included a total of Eighty-five patients in our study.

The sample size was calculated by the formula,

$$n \geq \frac{Z^2 P Q}{E^2}$$

Where, Z = 1.96, P = 46

- ✓ Where n is the sample size, Z is the statistic corresponding to level of confidence (95%)
- ✓ P is expected prevalence, E is the allowable error 10%.

METHOD OF SELECTION

Patients were selected based on inclusion and exclusion criteria.

INCLUSION CRITERIA

- Patients aged above 18 years, irrespective of gender.
- Patients initiated on dapagliflozin and are on standard heart failure treatment (Aspirin ± clopidogrel, Beta-blockers, ACEi/ARBs. Diuretics, Statins, Digoxin) with or without diabetes.
- Patients with reduced ejection fraction (<50%).

EXCLUSION CRITERIA

- Patients who had a history of type 1 diabetes mellitus.
- Pregnant and lactating women.
- Patients with malignancy.

DATA COLLECTION

The data were collected using specially designed data collection form. Prospective patient demographic details, pertinent laboratory as well as treatment details were extracted from medical records and Lourdes Mediware system.

DATA COLLECTION TOOL

- Medical records of patients
- Lourdes Mediware system
- KCCQ-12 questionnaire
- Clinician Rating Scale

DATA COLLECTION METHOD

Details of patients were collected from the medical records and the Mediware system available in the Lourdes Hospital, Kochi. The selected cases were then analysed by obtaining those files from medical records department and subsequently entered into data collection forms. The collected data were verified before entering on the terms of inclusion and exclusion criteria. The data entered were subsequently entered into Microsoft excel and further analysis done using SPSS statistical software.

STATISTICAL ANALYSIS

The data were tabulated, analyzed and compared with relevant studies. The collected data were compiled using Microsoft Excel and were presented using tables and graphs. The data were tabulated, analyzed and compared with relevant studies. Analyses were carried out at 10% level of statistical significance. Mean, standard deviation, paired t-test were done using statistical calculators. The statistical software SPSS was used for analysis of the data.

RESULTS AND DISCUSSION

We included a total of 85 patients, where most of the patients were in the age category 61-70 years (41.2%) and most of participants were men (81.2%). The clinical benefits of dapagliflozin were studied using KCCQ 12 questionnaire. Of these 85.9% of the patients had shown significant improvement in their physical function, symptoms and quality of life. The incidence of readmission after initiating dapagliflozin were compared with another study and concluded that dapagliflozin had shown a reduction in re-hospitalization. Our study population included 66 diabetic patients among them 84.8 % showed a significant reduction in their blood sugar level along with other antidiabetic drugs. The study also shows that dapagliflozin is not associated with reduction in the blood sugar levels in patients without diabetes. 13 patients had shown side effects to dapagliflozin along with standard heart failure therapy and among that Hyponatremia was seen in 3 patients, hypokalemia and AKI in 4 patients, and in 2 patients' hypotension was observed. Patients' tolerability on dapagliflozin in association with adherence

were studied using the clinician rating scale and 74.1 % passively accepted to continue taking the drug. Dapagliflozin also shows reduction in the body weight of patients. 34.1% of the patients showed a reduction in their body weight. Our study also shows that dapagliflozin used along with standard heart failure treatment and revascularization procedures was noted to have improvement in the ejection fraction of heart failure patients with reduced ejection fraction mostly within a period of 1 year.

CONCLUSION

The study concluded the various clinical benefits and tolerability of dapagliflozin in heart failure patients with reduced ejection fraction who are on standard treatment for heart failure. The study shows that dapagliflozin along with standard HF therapy significantly improves the symptoms of HF as well as reduces the incidence of hospitalization. The study also concludes that dapagliflozin has significantly reduced the blood sugar levels in diabetic patients and had no effect on blood sugar levels of non-diabetic patients. Dapagliflozin also shows benefits in reducing the body weight, and improving the ejection fraction along with other revascularization and therapy in patients with reduced ejection fraction. The safety and tolerability of dapagliflozin along with patience adherence were also studied and concludes that dapagliflozin is safe and is tolerated by the patients.

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INTRODUCTION

Heart failure is not just a single pathological diagnosis but a clinical syndrome consisting of cardinal symptoms like dyspnoea, orthopnoea, and fatigue. Heart failure (HF) is accompanied by symptoms like elevated jugular venous pressure and peripheral oedema. Heart failure is defined as a structural or functional abnormality of the heart that results in elevated intracardiac pressure and inadequate cardiac output (at rest or during exercise)[1]. Heart failure develops when the heart via an abnormality of cardiac function, fails to pump blood at a rate that is commensurate with the requirements of the metabolizing tissues or is able to do so only with an elevated diastolic filling pressure. Heart failure often causes circulatory failure, but not necessarily the other way around, because various noncardiac conditions (eg, hypovolemic shock, septic shock) can produce circulatory failure in the presence of mild, moderately impaired, or severe heart failure. To maintain the heart's pumping function, compensatory mechanisms increase the blood volume, cardiac filling pressure, heart rate, and cardiac muscle mass. However, despite these mechanisms, still there is a progressive decline in the heart's ability to contract and relax, resulting in worsening heart failure.

A healthy heart is a strong, muscular pump about the size of a fist. It circulates blood through the circulatory system continuously. The heart has 4 chambers, two on the right and two on the left, two upper chambers known as atria (one is called an atrium), and two lower chambers called ventricles. The right atrium receives oxygen-depleted blood from the rest of the body and sends it to the right ventricle, where it is oxygenated in the lungs. The Oxygen-rich blood flows from the lungs to the left atrium, then to the left ventricle, sending it to the rest of the body. The heart circulates blood to the lungs and all of the body's tissues through a series of highly organised contractions in the four chambers.

CLASSIFICATION

Heart failure can be classified according to a variety of factors. Based on the measurement of left ventricular ejection fraction (LVEF) heart failure is divided into three distinct types:

i. Patients with LVEF $\leq$40 % (reduced LV systolic function): HFrEF

ii. Patients with LVEF between 41 % and 49% (mildly reduced LV systolic function): HFmEF

iii. Patients with LVEF $\geq$ 50% (preserved ejection fraction): HFpEF

The New York Heart Association (NYHA) classification for heart failure comprises four classes, based on the relationship between symptoms and the amount of effort required to provoke them, as follows:

i. Class I patients have no limitation of physical activity

ii. Class II patients have slight limitations in physical activity

iii. Class III patients have marked limitations in physical activity

iv. Class IV patients have symptoms even at rest and are unable to carry on any physical activity without discomfort

Class I	No limitation on physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitation
Class II	Slight limitations to physical activity. Comfortable at rest but ordinary physical activity results in undue breathlessness, fatigue or palpitation
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in undue breathlessness, fatigue or palpitation
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

Table 1.1: New York Heart Association Functional Classification of Heart Failure

The incidence of HF seems to be 1-2% in adults. The incidence increases with age: from around 1% for those aged < 55 years to > 10% for those aged 70 years or over. Considering patients having HF, about 50% have HFrEF and 50% have HFpEF or HFrEF. According to ESC (European Society of Cardiology), Long Term Registry reports that 60% have HFrEF, 24% have HFrEF and 16% have HFpEF.

The American College of Cardiology/American Heart Association (ACC/AHA) heart failure guidelines complements the NYHA classification to reflect the progression of the disease, divided into four stages, as follows[3]:

i. Stage A patients are at high risk for heart failure but have no structural heart disease or symptoms of heart failure

ii. Stage B patients have structural heart disease but have no symptoms of heart failure

iii. Stage C patients have structural heart disease and have symptoms of heart failure

iv. Stage D patients have refractory heart failure requiring specialized interventions[2].

More recently, the ACC/AHA and Heart Failure Society of America (HFSA) introduced additional disease-staging terminology to characterize the syndrome of heart failure as a continuum, as follows:

i. "At risk for HF" for stage A: Applied to asymptomatic patients with risk factors such as diabetes or hypertension but no known cardiac changes

ii. "Pre-HF" for stage B: Adds cardiac structural changes or elevated natriuretic peptides, still in the absence of symptoms

iii. "Symptomatic HF" for stage C: Structural disease with current or previous symptoms

iv. "Advanced HF" for stage D: Characterized by severe debilitating symptoms or repeated hospitalizations even with guideline-directed medical therapy (GDMT)[3].

SYSTOLIC HEART FAILURE: The pumping action of the heart is reduced because of an abnormality in the myocardium.

DIASTOLIC HEART FAILURE: Because of the abnormality in myocardial relaxation which results in poor ventricular filling.

LEFT VENTRICULAR FAILURE: Dysfunction of the left ventricle causing insufficient delivery of blood to vital body organs. Hypertension & aortic valve stenosis most common causes of LVH.

RIGHT VENTRICULAR FAILURE: when there is pressure or volume overload or myocardial diseases such as RV infarction or cardiomyopathy. The most common cause is pulmonary hypertension.

ETIOLOGY

From a clinical standpoint, the causes of heart failure can be classified into four categories:

- Underlying causes: Underlying causes of heart failure include structural abnormalities (congenital or acquired) that affect the peripheral and coronary arterial circulation, pericardium, myocardium, or heart valves, thus leading to increased hemodynamic burden or myocardial or coronary insufficiency.
- Fundamental causes: Fundamental causes include biochemical and physiologic mechanisms, through which either an increased hemodynamic load or a reduction in myocardial oxygen supply results in the impairment of myocardial contraction.
- Precipitating causes: Overt heart failure may occur by the progression of the underlying heart disease (for eg, further narrowing of a stenotic aortic valve or mitral valve) or various conditions (fever, anemia, infection) or medications (chemotherapy, nonsteroidal anti-inflammatory drugs [NSAIDs]) which alters the homeostasis in heart failure patients.
- Genetics of cardiomyopathy: Dilated, arrhythmic right ventricular and restrictive cardiomyopathies are known genetic causes of heart failure[4].

Heart failure is caused by a variety of conditions that damage the heart muscle, including;

Coronary artery disease: A disease of the arteries that supply blood and oxygen to the heart, resulting in reduced blood flow to the heart muscle. When the arteries are blocked or severely narrowed, the heart become deprived of oxygen and nutrients.

Heart attack: A heart attack occurs when a coronary artery becomes suddenly blocked, preventing the blood from flowing to the heart muscle. A heart attack damages the heart muscle, leaving a scar.

Cardiomyopathy: Damage to the heart muscle caused by factors other than artery or blood flow problems, such as infections, and drug or alcohol abuse.

Conditions that overwork the heart: Heart failure can be caused by conditions such as high blood pressure, valve disease, thyroid disease, kidney disease, diabetes or congenital heart disease[5].

SIGNS AND SYMPTOMS OF HEART FAILURE WITH REDUCED EJECTION FRACTION

Typical symptoms

- Dyspnoea
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Fatigue
- Reduced exercise tolerance
- Ankle swelling

Less typical symptoms

- Cough
- Abdominal distension
- Wheezing
- Abdominal bloating

More specific signs

- Elevated jugular venous pressure
- Positive abdominojugular reflux
- Laterally displaced apical impulse

Less specific signs

- Weight gain
- Lung rales

- Peripheral edema
- Ascites
- Weight loss and cachexia[6].

DIAGNOSIS

The European Society of Cardiology (ESC) recommendations for the diagnosis of HF include the following:

- The diagnosis of heart failure with preserved ejection fraction (HFpEF) requires evidence of cardiac structural or functional abnormalities as well as high plasma NP (natriuretic peptide) concentrations consistent with LV diastolic dysfunction and elevated LV filling pressures.
- A chest x-ray is recommended to rule out any other potential causes of breathlessness, such as pulmonary disease.
- If the patient has a normal ECG, the diagnosis of HF is unlikely. The ECG shows abnormalities such as AF, Q waves, LV hypertrophy (LVH), and a widened QRS complex, which increases the likelihood of HF.
- Basic tests such as serum urea and electrolytes, creatinine, complete blood count, and liver and thyroid function tests are recommended to differentiate HF from other conditions, to provide prognostic information, and to guide potential therapy.
- Echocardiography is recommended as the key research tool to assess cardiac function and to provide information on other parameters such as chamber size, eccentric or concentric LVH, regional wall motion abnormalities (RWMA), RV function, pulmonary hypertension, valvular function, and markers of diastolic function.

Laboratory studies should include a complete blood cell (CBC) count, serum electrolyte levels (including calcium and magnesium), and renal and liver function tests. Other additional tests may be indicated in specific patients. An assessment for iron deficiency should be considered; about one-third of heart failure, patients are also iron deficient, which is associated with poor cardiac function and can worsen outcomes in these individuals. Iron deficiency appears to affect the contractility of human cardiomyocytes by impairing mitochondrial respiration and reducing contractility and relaxation. These effects can be reversed by restoring intracellular iron levels. The rapid measurement of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels helps to differentiate between cardiac and noncardiac causes of dyspnoea. That is, BNP is often limited to differentiate heart failure from other causes of dyspnoea in patients with an atypical presentation.

PHARMACOTHERAPY

The goals of pharmacotherapy for patients with HF with reduced ejection fraction;

i. Reduction in the mortality

ii. Prevention of recurrent hospitalizations due to worsening HF

iii. Improvement of clinical conditions, functional capacity, and quality of life

GENERAL MEASURES

DIET AND FLUID RESTRICTION

Sodium restriction (2–3 g daily) is generally recommended in patients with symptomatic heart failure, based on the notion that salt and fluid retention is a major part of HF pathogenesis. Although total sodium restrictions have long been recommended for HF therapy, the amount of evidence on which these recommendations are based is limited, and the level of evidence for fluid restriction in recent guidelines is primarily dependent on expert opinion (class IIa recommendation, level of evidence C). Indeed, many of the studies imply that sodium restriction alters the neurohormonal profile, resulting in inferior results. In most individuals, severe fluid restriction is recommended unless the patient is hyponatremic (130mEq/L), a condition that can develop due to renin-angiotensin system activation (RAAS), excessive secretion of arginine vasopressin (AVP), or salt loss in excess of water following a diuretic therapy. In hyponatremia patients or in those whose fluid retention is difficult to control despite the high doses of diuretics and sodium restriction, fluid restriction (2 L per day) should be considered.

ACTIVITY

According to the current ACC-AHA guidelines, patients with heart failure should engage in regular physical activity or exercise training (class 1, level of evidence A). A large randomized outcome trial in HFrEF showed that exercise training improves functional capacity, quality of life, and clinical outcomes in people with heart failure, according to research and meta-analysis.

THERAPIES TO AVOID

Several common medications have been shown to worsen heart failure symptoms and may accelerate the progression of the disease; thus, they should be avoided in heart failure patients. NSAIDs (Nonsteroidal anti-inflammatory drugs) blocks the prostaglandin synthesis, resulting in salt and fluid retention and possibly exacerbating heart failure. Thiazolidinedione is an anti-diabetic drug class that

can cause fluid retention and has an increased risk of heart failure. The DPP-4 inhibitor, saxagliptin has also been associated with an increase in Heart Failure hospitalization[7].

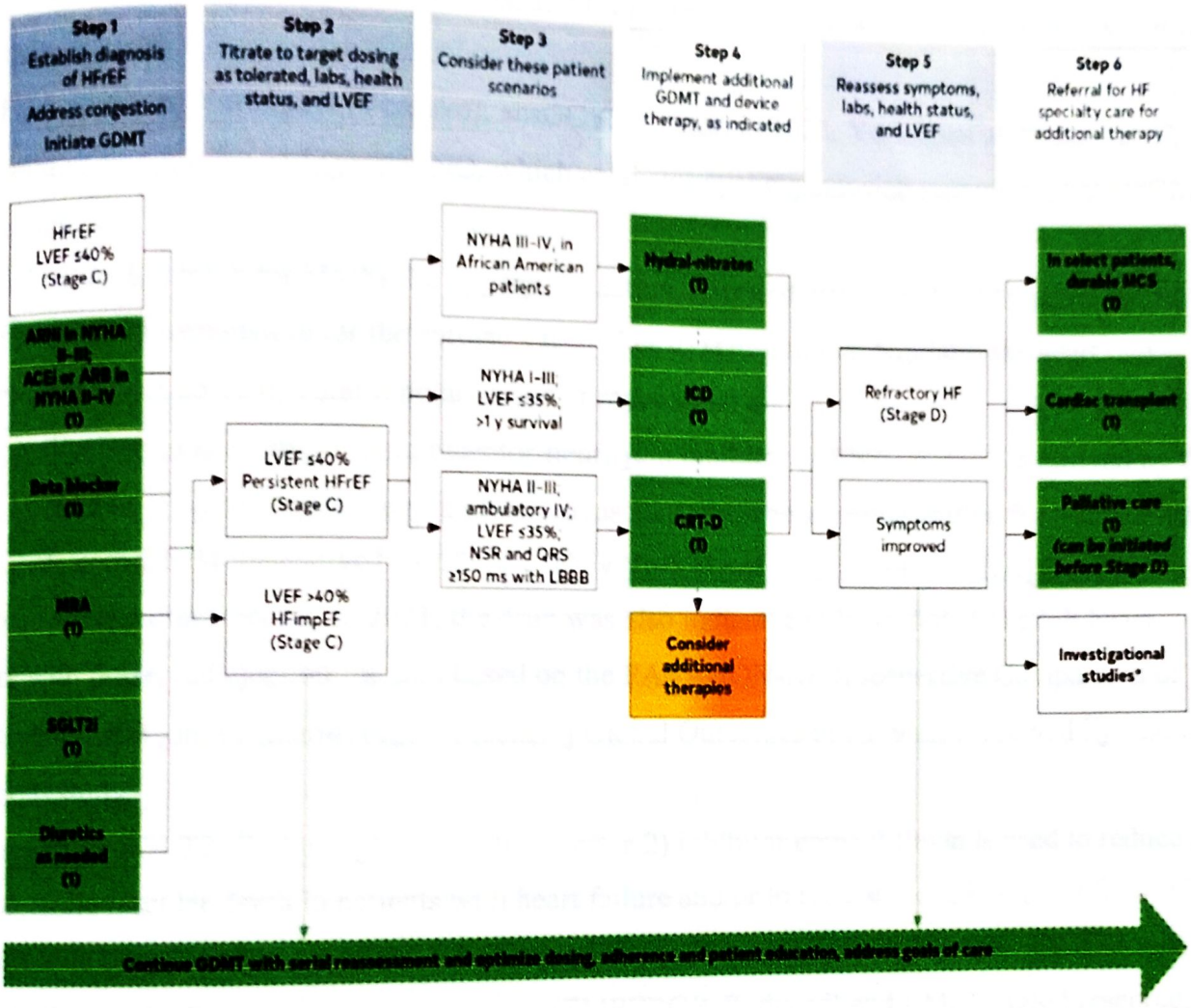

FIG 1.1: AHA Treatment Recommendations for Patients with HFrEF

In patients with HFrEF, symptom reduction is achieved by the modulation of renin-angiotensin-aldosterone (RAAS) and the sympathetic nervous system using angiotensin-converting enzyme Inhibitors (ACEI) or angiotensin receptor neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonist (MRA) as the foundation of pharmacotherapy. Along with oxygen, drugs that reduces symptoms include Diuretics- which reduce edema by reducing the blood volume and venous pressure, Vasodilators- to reduce the preload and the afterload, Digoxin- which causes a small increase in cardiac output, Inotropic agents- that help to restore organ perfusion and reduce congestion, Anticoagulants- in order to decrease the risk of thromboembolism, Beta-blockers, for neurohormonal modification, left ventricular ejection fraction

(LVEF) improvement, arrhythmia prevention, and ventricular rate control, Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs)- both for the neurohormonal modification, vasodilatation, and LVEF improvement, and lastly Analgesics- for the pain management.

The FDA approved Vericiguat (Verquvo), ansGC stimulator, in 2021. Vericiguat stimulates sGC, the intracellular receptor for endogenous NO, which catalyzes cyclic guanosine monophosphate (cGMP) production.

Ivabradine, an I(f) inhibitor blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel which is responsible for the cardiac pacemaker I(f) current, that regulates the heart rate without any effect on ventricular repolarization or myocardial contractility.

Sacubitril/valsartan is an angiotensin receptor-neprilysin inhibitor (ARNI), that was approved by the FDA in 2015 in order to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with CHF (congestive heart failure, New York Heart Association [NYHA] class II-IV) and reduced ejection fraction. In 2021, the drug was also indicated to be included in adult heart failure with preserved ejection fraction based on the PARAGON-HF (Prospective Comparison of ARNI with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction) study.

The selective SGLT2 (Sodium-glucose cotransporter-2) inhibitor empagliflozin is used to reduce the risk of cardiovascular death in patients with heart failure and/or to reduce the risk of heart failure in patients with type 2 diabetes mellitus. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) and EMPEROR-Preserved, provide evidence for the FDA approval of empagliflozin to reduce the risk of CV death or hospitalization in patients with HFrEF or HFpEF.

Dapagliflozin is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with HFrEF. The approval is based on the results from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) phase 3 clinical trial. The Clinical trials (PRESERVED-HF, DELIVER) for dapagliflozin in HFpEF are ongoing[8].

DAPAGLIFLOZIN IN MANAGEMENT OF HEART FAILURE

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, which were originally developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus, reduce the risk of death and other adverse outcomes among 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. Current clinical guidelines strongly recommend the use of SGLT2 inhibitors in patients with chronic heart failure and a reduced ejection fraction Few pharmacologic treatment options exist for patients with heart failure and a mildly reduced or preserved left ventricular ejection fraction.

Recently, treatment with the SGLT2 inhibitor Dapagliflozin was shown to reduce the combined risk of hospitalization due to the worsening heart failure or cardiovascular death among patients with heart failure and a left ventricular ejection fraction of more than 40%, a finding that suggests that the benefits of sodium glucose co transporter 2 inhibition may extend to all patients with heart failure, regardless of the left ventricular ejection fraction but are now commonly prescribed in patients with reduced ejection fraction.

The benefit, which was driven by a reduction in hospitalization for heart failure, appeared to be attenuated in patients with ejection fractions in the highest part (=65%) of the range. Among patients with heart failure and a mildly reduced or preserved ejection fraction, dapagliflozin resulted in a lower risk of the primary outcome (worsening heart failure or cardiovascular death), in fewer worsening heart failure events and cardiovascular deaths, and in a lower symptom burden, with no excess of adverse events[9].

The Sodium-glucose cotransporter 2 (SGLT2) is responsible for reabsorption of approximately 90% of the urinary glucose in the proximal tubule of the nephron. The inhibition of SGLT2 induces glucosuria, which is more noticeable in hyperglycemic individuals owing to the higher amounts of glucose filtered into the urine. The effect of glucosuria diminishes with the normal of blood glucose levels. Among individuals with HFrEF, with or without DM, the addition of dapagliflozin has been associated with decreased rates of cardiovascular death or worsening heart failure and hospitalization as well as all-cause mortality.

In addition to lowering blood glucose, the SGLT2 inhibitors such as dapagliflozin also enhance natriuresis, change tissue sodium handling, lower systolic blood pressure and reduce the body mass. Early decreases in systolic blood pressure, weight and estimated glomerular filtration rate (eGFR), as well as increase in haematocrit are consistent with a diuretic action. According to the established side effect profile like electrolyte imbalances, acute kidney injury, volume depletion, etc. dapagliflozin is associated with significantly higher rates of urinary tract infections, urinary urgency, frequency, and genital mycotic infections in females and in males[10].

MOLECULAR MECHANISM OF DAPAGLIFLOZIN

Regarding outcomes relating to CV benefit, specific mechanisms have not been fully explained, but several presumes mechanisms have been proposed. Among these are reduction in preload and afterload (resulting in improvement in ventricular loading), improvement in myocardial metabolism and alterations of cardiac fibrosis. SGLT2 inhibitors have been shown to inhibit the sodium proton channel (NHE) in the cardiac myocytes that eventually leads to the reduction in intracellular calcium and mitochondria-induced cellular damage that lies at the heart of myocardial remodeling. At the level of the kidneys, in addition to glucosuria by direct inhibition of glucose reabsorption in the proximal convoluted tubules (PCT), the SGLT2 inhibitors have also been demonstrated to have anti-inflammatory activity. Dapagliflozin also reduces the sodium reabsorption and increases the delivery of sodium to the distal convoluted tubule (DCT), this may influence several physiological functions such as lowering both preload and afterload of the heart and downregulating the sympathetic activity. The blockade of SGLT2 channels causes a decrease in intraglomerular pressure and subsequently decreases in glomerular filtration rate and tubular hypertrophy.

This consequence is further amplified by afferent vasoconstriction mediated by direct action. The potential mechanisms by which the SGLT2 Inhibition is Cardioprotective and a considerable number of theories have been proposed to explain the beneficial effects of SGLT2 inhibitors.

These include beneficial effects of SGLT2 inhibition on the following:

1) blood pressure lowering, 2) increasing diuresis/natriuresis, 3) improving cardiac energy metabolism, 4) preventing inflammation, 5) weight loss, 6) improving glucose control, 7) inhibiting the sympathetic nervous system, 8) preventing adverse cardiac remodeling, 9) preventing ischemia/reperfusion injury, 10) inhibiting the cardiac Na+/H+ exchanger, 11) inhibiting SGLT-1, 12) reducing hyperuricemia, 13) increasing autophagy and lysosomal degradation, 14) decreasing epicardial fat mass, 15) increasing erythropoietin (EPO) levels, 16) increasing circulating pro-vascular progenitor cells, 17) decreasing oxidative stress, and 18) improving the vascular function[11].

FDA APPROVES DAPAGLIFLOXIN FOR TREATMENT OF HFrEF

The Food and Drug Administration (FDA) has approved dapagliflozin for the treatment of heart failure with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes (T2D) on 2014, marking the first time a drug in a class developed for diabetes was approved for heart failure even if diabetes is not present. The oral tablets are already indicated for adults to reduce the risk of

cardiovascular (CV) death and hospitalization for heart failure. But with this step, dapagliflozin is now the first sodium-glucose co-transporter 2 (SGLT2) inhibitor to be approved to treat adults with heart failure with reduced ejection fraction[12].

On May 5th, 2020, the FDA announced the approval of dapagliflozin oral tablets in order to reduce the risk of cardiovascular death and hospitalization for adults with heart failure with reduced ejection fraction (HFrEF). Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor typically used for the treatment of Type II diabetes, is the first in its class to be approved for New York Heart Association's functional class II-IV heart failure with reduced ejection fraction despite a patient's diabetes status. It has been proposed that in addition the SGLT2's effects on antidiuretic hormone, it has effects on myocardial metabolism, ion transporters, fibrosis, adipokines, and vascular function, but the mechanism of their cardiac effects are not fully known. A randomized, double-blind, placebo-controlled study of 4,744 participants with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less evaluating 10 mg dapagliflozin compared to placebo showed the dapagliflozin group experienced less cardiovascular deaths, hospitalizations, and urgent heart failure visits.

HFrEF is initiated by an event that impairs the heart's ability to contract and relax leading to a decrease in cardiac output. This results in the activation of several compensatory mechanism that the body employs to maintain circulation: sympathetic nervous system activation leading to tachycardia and increased contractility, increases in preload, vasoconstriction, and ventricular hypertrophy and remodeling. When activated over long periods of time, these mechanisms result in detrimental effects including increased myocardial volume oxygen (MVO)2, increased afterload, systemic congestion and pulmonary edema, decreased B1 sensitivity, diastolic/systolic dysfunction, risk of arrythmias, and risk of myocardial cell death.

Patients with heart failure can present with a variety of symptoms ranging from asymptomatic to cardiogenic shock. Patients are typically presenting with the symptoms like fatigue and dyspnoea which leads to exercise intolerance and pulmonary edema. There is no test to confirm the diagnosis of heart failure but rather identification of a clinical syndrome with specific signs and symptoms. The echocardiogram (ECG) is the most useful evaluation tool to assess the cardiac abnormalities. A thorough history, physical examination, and laboratory testing can also provide useful insight on the underlying cause. As heart failure contributed to 1 out of 8 deaths in the US in 2017, researchers are looking for more ways to treat the disease and prevent disease progression. The SGLT2 inhibitors is the new treatment option for the patients who are diagnosed with heart failure with reduced ejection

fraction and among the sodium glucose co transporter 2 inhibitors, dapagliflozin serves as the foremost option in the treatment of heart failure with reduced ejection fraction[13].

PHARMACOKINETICS

The pharmacokinetics of dapagliflozin are:

Absorption

Bioavailability: 78%

Peak plasma time: 2 hr (fasting); ~3 hr (with high fat meal)

High fat meal decreases peak plasma concentration by up to 50%

Distribution

Protein bound: 91%

Metabolism

Metabolism primarily mediated by UGT1A9

CYP-mediated metabolism is a minor clearance pathway in humans

Extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide (inactive metabolite)

Elimination

Half-life: 12.9 hr

Excretion: 75% urine; 21% faeces.

ADVERSE EFFECTS

Renal impairment (>10%) occur mostly in patients with an eGFR 30-60 mL/min and elderly patients > 65 yrs. Other side effects observed include the female genital mycotic infections (6%), urinary tract infections (4.3-5.7%), Back pain (3.1-4.2%), increased urination (2.9-3.8%), Male genital mycotic infection (2%), nausea (2%), extremity pain (1.7%) etc.

Hypoglycaemic episodes were reported in 6% to 10% of patients. Renal impairment and volume depletion with dapagliflozin are similar to that of placebo. Dapagliflozin showed more adverse effects of hypotension, dehydration, genital infections, and renal impairment (in pre-existing mild/moderate renal disease) as compared to other drugs. More research is needed to assess the efficacy and safety of dapagliflozin regarding the renal profile. Volume depletion may also occur (0.6-1.1%), and for patients on loop diuretics is 1.8-2.5%, for patients with moderate renal impairment, GFR 30-60 mL/min 0.9-1.9%. Hypersensitivity reactions are rare (0.3%). Some of the post marketing reports shows the incidence of rash, ketoacidosis, acute kidney injury and renal impairment, urosepsis and pyelonephritis, necrotizing fasciitis of perineum and hypoglycaemia[14].

Ketoacidosis in people with diabetes mellitus (increased ketones in your blood or urine) is a serious and potentially life-threatening acute complication of diabetes mellitus. Euglycemic diabetic ketoacidosis (eDKA) is condition where the marked hyperglycaemia is absent often leading to delayed diagnosis and treatment. eDKA has been recently found to be in association with sodium-glucose cotransporter 2 inhibitors, though there are very limited reports implicating dapagliflozin as the offending agent. Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with dapagliflozin. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Symptoms of ketoacidosis may include

- nausea,
- vomiting,
- abdominal pain,
- tiredness,
- trouble breathing.

Serious urinary tract infections. Serious urinary tract infections that may lead to hospitalization have happened in people who are taking dapagliflozin. Serious urinary tract infections (UTI): The common signs and symptoms of UTI include a burning feeling while passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine with or without fever, back pain, nausea, or vomiting.

Low blood sugar (hypoglycaemia) in patients with diabetes mellitus. Taking dapagliflozin with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, risk of getting low blood sugar is higher. Hypoglycaemia can occur on taking dapagliflozin with other antidiabetic drugs such as sulfonylureas or insulin. Symptoms of low blood sugar include shaking, sweating, fast heartbeat, dizziness, hunger, headache, and irritability. The dose of sulfonylurea medicine or insulin may need to be lowered while taking dapagliflozin. The signs and symptoms of low blood sugar may include: Headache, shaking or feeling jittery, irritability, fast heartbeat, weakness, drowsiness, sweating, confusion, dizziness, hunger etc.

A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum). Necrotizing fasciitis of the perineum has happened in women and men with diabetes mellitus who take dapagliflozin. The necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. Seek medical attention immediately if you have fever or you are feeling very weak, tired, or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around the anus and genitals: pain or tenderness, swelling, redness of skin (erythema)[15].

Dehydration: The loss of body water and salt, which may cause dizzy, faint, lightheaded, or weak, (orthostatic hypotension). There have been reports of sudden kidney injury in people with type 2 diabetes who are taking dapagliflozin. Higher risk of dehydration may occur while taking along with diuretics, patients who are at the age of 65 or older; who are on a low salt diet, or have any kidney related problems.

Genital infections: Symptoms include vaginal odour, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), or vaginal itching. Yeast infection of skin around the penis (balanitis) in men who take dapagliflozin. Certain uncircumcised men may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. The most common side effects of dapagliflozin include yeast infections of the vagina or penis, and changes in urination, including urgent need to urinate more often, in larger amounts, or at night[16].

WARNINGS

The use of dapagliflozin is contraindicated in patients who have serious hypersensitivity to the drug like anaphylaxis, angioedema etc. and also to patients on dialysis. Special caution should be taken in patients with history of genital mycotic infections. Patients with diabetes and renal impairment may be more likely to experience hypotension and may be at a higher risk for acute kidney injury secondary to volume depletion. Symptomatic hypotension may occur after initiating, particularly in patients with renal impairment (eGFR<60 mL/min/1.73m^2), with low systolic blood pressure, taking loop diuretics or who are elderly.

Before initiating therapy, factors that predispose ketoacidosis should be considered, including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. Temporary discontinuation of therapy for at least 3 days before undergoing surgery to avoid euglycemic ketoacidosis should also be considered.

Urine glucose tests is not recommended in patients taking SGLT2 inhibitors, as they increase the urinary excretion of glucose and leads to positive urine glucose tests.

The drug should be stores at room temperature at 20-25^{0}C.

INTERACTIONS

Dapagliflozin does not has any serious interactions with any drugs, but the effect of drug along with other antidiabetic drugs such as chlorpropamide, meglitinides, glimepiride, insulin etc, lithium, letermovir should be closely monitored.

INDICATIONS

Dapagliflozin is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes. Now a days the drug is commonly prescribed to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes or without diabetes, who also have known cardiovascular disease or multiple cardiovascular risk factors to reduce the risk of cardiovascular death, hospitalization for heart failure in adult patients with heart failure, when the heart is weak and cannot pump enough blood to the rest of your body. To reduce the risk of further worsening of your kidney disease, end-stage kidney disease (ESKD), death due to cardiovascular disease, and hospitalization for heart failure in adults with chronic kidney disease.

Dapagliflozin is not for people with type 1 diabetes. Dapagliflozin may increase the risk of diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 diabetes. Dapagliflozin is not for use to improve blood sugar (glucose) control in adults with type 2 diabetes who have moderate to severe kidney problems, because it may not work. Dapagliflozin is not for people with certain genetic forms of polycystic kidney disease, or who are taking or have recently received immunosuppressive therapy to treat kidney disease. Dapagliflozin is not expected to work if you have these conditions. It is not known if dapagliflozin is safe and effective in children younger than 18 years of age[17].

AIM AND OBJECTIVES

AIM

To investigate the clinical benefits of Dapagliflozin in patients with reduced ejection fraction and to analyze the tolerability of Dapagliflozin.

OBJECTIVES:

PRIMARY OBJECTIVES

- To identify the clinical benefits of Dapagliflozin in symptomatic treatment of HFrEF.
- To document the incidence of readmission in HF patients on dapagliflozin.
- To determine the effect on blood sugar level.

SECONDARY OBJECTIVES

- To identify the adverse effects (if any) and tolerability of Dapagliflozin.
- To analyze the effect of Dapagliflozin on body weight.