Pattern of Use of SGLT2 Inhibitors In Patient With Chronic Heart Failure In A Tertiary Care Hospital In South India 2021-22

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ABSTRACT:

AIM: To assess the efficacy, safety & tolerability of SGLT2 inhibitors in chronic heart failure, as well as their impact on patient symptoms and QOL. To investigate the reasons for therapeutic discontinuance.

Objectives: To evaluate the Indian population's safety, efficacy & tolerability. The assessment of patient quality of life is as important as the treatment outcome. The cost-effectiveness of the treatment should be considered for the patient's convenience.

Materials and methods: The study is conducted as a Prospective Observational study in the Department of Out-patient Unit of Cardiology at Krishna Institute of Medical Sciences (KIMS) hospital in Secunderabad. The study duration is 6 months, and the sample size consists of 103 adult patients.

Results and discussion: In our study, a total of 103 patients were included, from the age of 20 to 89 years. Of those, the males were 65 and the females were 38, and the mean age was 54.85 years. Most (93.3%) of the patients had no complaints when they were on SGLT2 among them, 6.7% had complaints of burning micturition and dysuria. The number of pus cells in the urine increased by an average of 18, while serum creatinine increased by an average of 0.9 in the patients showing adverse effects in their review 1. An average of 15 and 0.6 changes were in pus cells and serum creatinine respectively in the patients showing adverse during their review 2. The effectiveness of SGLT2 in HF management is seen comparing the ejection fraction improvement from each and every review to baseline visit. The average improvement in EF at the first review of each patient is 1.96% and the average EF improvement on review 2 is 3.26%.

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Conclusion: The heart failure patients, regardless of their diabetes state, can be prescribed SGLT2 inhibitors. Both empagliflozin and dapagliflozin show positive results in HF management. The chances of adverse effects like urinary tract infections, urogenital infections, and nausea occurring are very low. Our study also concluded the improvement of ejection fraction in patients on SGLT2 inhibitors, which is proven by LVEF 2D echo reports. As India is lacking information regarding how SGLT2 inhibitor drugs act and help in HF management in the Indian population.

Key words: SGLT2 inhibitors, empagliflozin, dapagliflozin, LVEF 2D echo reports.

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1. INTRODUCTION:

Definition:

Heart failure (HF) is a chronic progressive disease that shows intense changes in cardiac functions and a slew of anatomical and physiological alterations in the heart that degrade systolic and diastolic characters.[1] Heart failure is diagnosed when the heart is unable to pump and fill the blood at a sufficient rate to meet metabolic demands of human body due to abnormal cardiac functions. It is a chronic progressive disease with an average survival of 2.1 years after diagnosis.[2]

Heart failure is caused by many underlying diseases that affect the heart anatomy. [3]. The underlying causes may include heart inflammation, cardiomyopathy, coronary vascular disease, hypertension, pulmonary hypertension, and arrhythmia. Heart failure may ultimately result in kidney and liver failure.[4]

Heart failure may not develop symptoms immediately. It is one of the leading causes of morbidity & mortality globally, with an estimated prevalence of 1–2% and >10% for patients overthe age of 70 years.[5,6] According to a study men have a 33% lifetime risk of developing HF, while women have a 28% chance.[7]

Heart failure is a commonly occurring cardiac functional impairment caused by many undefined factors, and heart failure patients suffer from a variety of symptoms that alarmingly impact their quality of life, like shortness of breath, fluid accumulation, tiredness, and decreased exercise tolerance.

Classification:

Types of Heart Failure: A, B, and C When HFpEF is present, the heart's ability to pump blood around the body is maintained. If the heart's ability to pump blood around the body is diminished, however, the patient has heart failure (table.1)

A) Heart failure with preserved ejection fraction (HFpEF):

In addition to having an ejection fraction (EF) higher than 50%, this condition is characterized by a number of pro-inflammatory and metabolic complications. When the left ventricle fails to relax correctly due to structural and cellular abnormalities such as cardiomyocyte hypertrophy, fibrosis, and inflammation, it is known as hypertrophic cardiomyopathy (HCM).
B) Heart failure with reduced ejection fraction (HFrEF):

To put it another way: Systolic dysfunction, or the inability to contract the left ventricle normally, is a symptom of hypertrophic cardiomyopathy (HFrEF), which has an EF of less than 40%.

C) Heart failure with mid range ejection fraction (HFmrEF):

This intermediate category, which has certain characteristics with the patients with HFrEF, was defined by American College of Cardiology/American Heart Association (ACC/AHA) guidelines from 2013 as HFmrEF. A borderline HFpEF (LVEF 41–49 percent) was also recognized, as was an improved HFpEF (LVEF >40 percent).

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2013 ACC/AHA Guidelines. This group of heart failure sufferers is known as the HFP EF subgroup. [10]

<table>
<thead>
<tr>
<th>Type of heart failure</th>
<th>LVEF (Left Ventricle Ejection Fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>LVEF &lt;40%</td>
</tr>
<tr>
<td>HfmrEF</td>
<td>LVEF 40% to 49%</td>
</tr>
<tr>
<td>HFP EF</td>
<td>LVEF ≥ 50%</td>
</tr>
</tbody>
</table>

Table 1.1 Classification of heart failure based on ejection fraction

Heart failure (HF) with preserved ejection fraction (HFpEF) currently accounts for about half of all HF patients, and its incidence is growing by 1% every year (HFrEF). By 2020, the prevalence of HFpEF in individuals over 65 is predicted to reach 8%, with HFpEF and HFrEF having relative prevalence of 69% and 31%, respectively, making HFpEF the most frequent HF phenotype. Both HFpEF and HFrEF patients have similar prognosis, with 5-year mortality rates of up to 75% in both HF categories. [11]

Patients with HFrEF are often more likely to have had surgery, such as a pacemaker or other heart rhythm control device implanted. Most people with HFpEF, on the other hand, have never undergone surgery or had a device installed to treat their heart failure. [12]

When it comes to heart failure, Type-2 Diabetes mellitus (T2DM) is the most common cause of both HFrEF and HFpEF as well as cardiovascular disease. [13]

**Stages of heart failure:**

Depending on where you are on the "high risk of developing heart failure" continuum to where you are in "advanced heart failure," four stages of heart failure may be identified (A, B, C, and D). [14]

**Etiology:**

Heart failure typically has conditional causes. Cardiovascular disease (CVD), a narrowing of the blood vessels that supply the heart with blood and oxygen, is a leading cause of cardiac failure. Table no.2 [15] contains additional risk factors for heart failure.

It is more common in older women who have high blood pressure, atrial fibrillation, and hypertrophied left ventricles than in younger women without a history of coronary artery disease. [3].

When you become older, even if you do not have any other heart problems, your diastolic performance deteriorates. [16].
Pathophysiology:

Heart failure will be detected only after observing the initial reduction in heart pumping capacity, which in turn activates a number of mechanisms.

![Pathophysiology of HF](https://www.slideshare.net/samghany/management-of-heart-failure)

Figure 1.2: Pathophysiology of Heart Failure (https://www.slideshare.net/samghany/management-of-heart-failure)

Being overweight and having high blood pressure are other risk factors for developing heart failure, which is becoming more common with age. Patients with type 2 diabetes are 2.5 times more likely to develop heart failure than those who do not suffer from the condition.” [17].

About 60% to 70% of people with systolic heart failure have CAD, which is a predictor of progress from asymptomatic to symptoms of left ventricular systolic dysfunction. If you have high blood pressure, you are more likely to suffer from heart failure than someone who doesn't.[18]

Factors that may raise the risk for heart failure include a person's age, gender, race, and sex, among others. The following are known or suspected risk factors for congestive heart failure:

**Major clinical risk factors:**

- Older age; male sex; high blood pressure; diabetes mellitus; obesity; LV hypertrophy; myocardial infarction; and valvular disease.

**Minor clinical risk factors:**

- Smoking and obesity are both known diabetes risk factors, as are a sedentary lifestyle, mental stress, and a lack of physical activity.

**Signs and symptoms:**

- Ascites, shortness of breath, edema, an irregular or fast heartbeat, cyanosis, a chronic cough or wheezing, and a diminished capacity to exercise are all indications of clinical heart failure (listed below in Table.3). Heart failure has sometimes been referred to as a clinical end point that cannot be reversibly reversed. [20,21].
- End stage heart failure is defined as a condition in which a patient's symptoms of shortness of breath and
weariness at rest persist after getting appropriate medical care.[2]

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS</th>
<th>CARDIAC FAILURE PATIENTS EXPERIENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath (also called dyspnea)</td>
<td>Breathlessness that occurs during physical activity (such as running or walking) but not at rest or while sleeping. Paroxysmal dyspnea (shortness of breath which may occur suddenly during sleep and wakes you up). Tiredness, anxiety, or restlessness when you wake up.</td>
</tr>
<tr>
<td>Continuous coughing or wheezing</td>
<td>Continuous coughing with white or pink blood-tinged mucus.</td>
</tr>
<tr>
<td>Increased heart rate</td>
<td>Heart palpitations lead to a reduction in pumping capacity.</td>
</tr>
<tr>
<td>Edema (excessive fluid builds up in the body tissues)</td>
<td>Fluid accumulation causes swelling of feet, ankles, limbs, and abdomen.</td>
</tr>
<tr>
<td>Tiredness, fatigue</td>
<td>Feeling tired all of the time or having difficulty performing daily activities such as climbing, walking, etc.</td>
</tr>
<tr>
<td>Nausea and lack of appetite</td>
<td>Low blood flow to the stomach may cause a feeling of fullness or sickness in the stomach.</td>
</tr>
<tr>
<td>Impaired thinking and confusion</td>
<td>Memory loss and confusion caused by electrolyte imbalances such as sodium and other electrolytes</td>
</tr>
</tbody>
</table>

Table 1.3. Clinical features of the heart failure patients

**Diagnosis:**

Types of Heart Failure: A, B, and C When HFpEF is present, the heart's ability to pump blood around the body is maintained. If the heart's ability to pump blood around the body is diminished, however, the patient has heart failure (table 1)
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Patients with heart failure can be initially diagnosed by observing:
Epidemiology:

Because of an expanding population of older persons, the number of HF patients has increased, while the incidence of HF has decreased with time. [14] With decreasing and growing incidence, those with HFrEF have showed diverse patterns in the occurrence of heart failure (HF); nonetheless, HFpEF has demonstrated an increasing incidence; (increasing incidence). Those with type 2 diabetes are 2.5 times more likely to suffer from heart failure than those who do not have diabetes. [17]

Study participants were divided into two groups: black and white. Those who were more likely to be diagnosed with heart disease were more likely to be found in the black group; those who were less likely to be diagnosed were found in the white group. [18]
Surprisingly, gender differences in HFrEF and HFpEF diagnoses are revealed by survey responses. The majority of HFrEF survey participants are men who reside in rural areas. However, the majority of people with HFpEF are women who live in cities.[19]

Management:

First, patients with clinical heart failure should begin with prevention, which focuses on reducing the risk factors that may be managed. Structural heart disease and symptoms of heart failure need the following therapy.

1) Diuretics
2) Renin angiotensin-aldosterone pathway inhibitors
3) Beta-Blockers
4) Digitalis
5) Cardiac resynchronization Therapy
6) LV Assist Devices and Cardiac Transplantation.[20]

Patients with comorbid disorders should be treated with a triple neuro hormonal blockade, which comprises ACEI, ARB, beta-blocker and a mineralocorticoid receptor antagonist, with particular recommendations based on their underlying health issues. [21]

Sodium Glucose Co-transporter Inhibitors (SGLT2 Inhibitors):

Type of active glucose transporter protein are sodium-dependent glucose co-transporters. This enzyme is present in many different organs (such as the heart and liver), although SGLT2 is most often located in the proximal tubule of the kidney. It is usual for the enzymes SGLT2 (90%) and SGLT1 (10) to re-absorb glucose in the proximal tubule under normal conditions (the remaining 10 percent)

Oral anti-diabetic drugs known as SGLT2 inhibitors have been demonstrated to enhance urine glucose excretion by blocking renal tubule glucose and salt reabsorption. Patients with type 2 diabetes are being evaluated for their cardiovascular safety and effectiveness in a number of big randomized controlled studies including a variety of medications. In diabetic patients, Traditional antihyperglycemic medications have focused on restoring cell function, tissue glucose absorption, insulin sensitivity, or, but SGLT2 inhibition offers an alternative. SGLT2 inhibitors are typically well tolerated, and the risk of hypoglycemia is minimal due to the fact that their effectiveness in boosting glucose excretion reduces as plasma glucose levels fall. [22]

Despite the fact that certain glucose medicines seem to be more successful than SGLT2 inhibitors, they fail to limit cardiovascular risk, especially in the event of cardiac failure. As a result, even in individuals with renal impairment, SGLT2 inhibitor therapy's glucose-lowering efficacy declines but its cardiovascular benefits remain intact. [23] Data on SGLT2 inhibitors comes mostly from the West, where these drugs have been studied extensively. Studying how SGLT2 inhibitors are used and accepted by a subset of the Indian population will help fill in the gaps left by other studies.

Patients who were treated with either SGLT-2 inhibitors alone or in combination with other diabetes medications experienced lower rates of cardiovascular outcomes, hospitalizations for heart failure, and associated cardiovascular deaths than those who were treated with only other anti-diabetic medications. SGLTI inhibitors revealed remarkable improvements in T2DM patients with prior atherosclerosis and a history of MI. Non-MI patients and those with risk factors did not show any improvement in their health.
Type 2 diabetes patients' glycaemic control, blood pressure reduction, weight management, and reduction of heart-related hospitalizations and fatalities were all helped by SGLT-2 inhibitors.[24]

An increase in blood pressure was seen in individuals with a greater BMI and pre-existing high blood pressure (BPP). Diabetes nephropathy must be treated with SGLT2 inhibitors, which block sodium-glucose co-transporter 2.

Several landmark clinical trials have demonstrated their role in lowering the mortality associated with congestive heart failure and improving glomerular filtration rate (GFR) decline.[25]

How SGLT2 inhibitors help in treating heart failure:

1. Improved myocardial energetics:

In Heart Failures, there is a dysregulation of fatty acid and glucose uptake in myocardial cells, which are important sources of energy for heart cells. SGLT2 inhibitors drugs produce ATP for heart cells by using ketone bodies as super fuel. Thereby, improving cardiac energies[26]

2. Improved Ionic Hemostasis in the myocardium:

SGLT-2 inhibitors disrupt the activity of the sodium/hydrogen exchanger 1 (NHE1) in cardiomyocytes, resulting in lower cytoplasmic sodium and calcium levels and higher mitochondrial calcium levels. Overall, cardiac muscle cells have a lower concentration of salt. [26]

Sodium hydrogen exchanger 1 (SHE1) and sodium glutamate transporter 1 (SGLT1) are both significantly upregulated in people with T2DM & HF. Thereby calcium ions are promoted by sodium calcium exchanger transporters. This elevates intracellular calcium content, which inhibits contractile function of heart cells. The SGLT2 inhibitor therapy downs cardiac systolic sodium levels and promotes heart cell contraction.

3. Altered Adipokine regulation:

SGLT2 inhibitors lower leptin levels while raising adiponectin levels. Offering the possibility of cardioprotection.

4. Autophagy:

SGLT2 inhibitors upregulate the expression of AMPK, SLRT1, HIF1, which are responsible for autophagy induction. Autophagy is important for removal of potentially dangerous constituents and cellular debris to keep cardiac cells healthy.[27]

5. Altered Renal function:

As a result, these medications also inhibit NHE3 in proximal renal tubules as well as diminish communication between renal tubules and the glomerulus. If the retinal macula densa detects sodium chloride in the tube fluid, this might be taken as a sign that the kidneys are working efficiently. Suppressing NHE3 raises the concentration of NaCl in tubular fluids, preventing it from being reabsorbed in the proximal tubule as a consequence. As NaCl is excreted in the urine, the body begins to lose fluid, which is referred to as natriuresis.
Patients with Type 2 Diabetes Mellitus (T2DM) should expect to benefit from all of these benefits, which improve left ventricular diastolic performance, cardiac muscle cell function, and ventricular volume burden. [26] Some side effects or adverse effects of SGLT2:

These are the common side effects:

1. Acute cystitis & pyelonephritis.
2. Urogenital yeast infections in both genders.
3. Nausea
4. Constipation [28]

Numerous side effects have been linked to case reports by regulatory bodies, such as acute renal damage, diabetic ketoacidosis and other infections of the urinary system as well as amputations of the lower legs and fractured bones. [25].

In studies, SGLT2 inhibitors increased the risk of vaginal infections, although they were generally well tolerated. An increased awareness is needed in the presence of euglycemic ketoacidosis, soft tissue and vaginal infections, as well as the adjustment of any essential hydration therapy in order not to deplete the body's water supply. [14]

**Pharmacokinetics of SGLT2 inhibitors:**

<table>
<thead>
<tr>
<th>S No.</th>
<th>KINETIC PROPERTIES OF EMPAGLIFLOZIN</th>
<th>OBSERVED PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>ABSORPTION</td>
<td>Peak plasma concentration is observed in 1.5 hours (Tmax) of oral administration</td>
</tr>
<tr>
<td>2.</td>
<td>DISTRIBUTION</td>
<td>Vd: Observed apparent volume of distribution is 73.8 litres</td>
</tr>
<tr>
<td>3.</td>
<td>METABOLISM</td>
<td>EMPA undergoes minimum metabolism in human body. It is basically undergoes glucuronidation metabolism in liver by enzyme called 5-disphopho-glucuronosyltransferases</td>
</tr>
<tr>
<td>Table 1.4. Pharmacokinetic properties of SGLT2 inhibitors.</td>
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<td>----------------------------------------------------------</td>
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</table>

**Review of Literature:**

Matthew griffin., et.al., 2020 sep. Researchers found that empagliflozin, especially when paired with loop diuretics, resulted in large amounts of diuresis. However, electrolyte loss, renal failure, and neurohormonal activation were not ingested. Patients with heart failure may benefit greatly from this diuresis activity in terms of controlling their volume profile. After a washout period of two weeks, patients were switched to an alternative treatment for heart failure patients with type 2 diabetes, which included a baseline study. [30]
Mikhail Kosiborod., et. al., Hospitalization, heart failure, and death rates dropped when SGLT2 inhibitors were used. There was no substantial variability in findings by country in international studies. To see how well SGLT-2 inhibitors stack up against other diabetes medications in terms of heart failure hospitalizations and overall mortality, Kosiborod and colleagues conducted the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors). [31]

Felipe A Martinez., et. al., This Randomized controlled study (DAPA-HF trial) found that dapagliflozin decreased mortality and worsening heart failure and improved symptoms across the wide range of ages. Dapagliflozin and placebo were found to be indistinguishable in terms of tolerability and safety in older people. A clinically significant benefit was discovered in heart failure patients with low ejection fraction, including a reduction in cardiovascular mortality and an improvement in symptoms, physical performance, and quality of life. [32]

Katrine M. Lauritsen., et. al., Studying the effects of SGLT2 inhibition on myocardial oxygen consumption, efficiency, and perfusion was the focus of this randomized, controlled crossover study. They could not find any differences worth mentioning. There was some evidence that SGLT2 inhibitors reduced resting MBF and diverted myocardial substrate use away from glucose in this EMPA-REG OUTCOME study, although the changes were small, and only a small fraction of the cardioprotective impact of SGLT2 inhibitors was likely explained by these effects. The EMPA treatment was compared to a placebo in this research. There was a one-week washout period between each study period of four weeks. [33]

Scott D Solomon., et. al., 2020 Oct. recruited and randomly assigned 4744 patients to participate in a clinical investigation. There was no difference in efficacy or safety between patients on dapagliflozin and those who were not taking sacubitril/valsartan. They argued that taking both medicines combined might further reduce morbidity and death in patients with HfrEF.

– 508 individuals (10%) were given valsartan/sacubitril as part of the DAPA-HF research, which had 4744 patients in total. Patients using Dapagliflozin or a placebo, whether they were also taking sacubitril/valsartan as a preventative, had the same levels of safety. [34]

Manasvi Gupta., et. al., 2021 Aug. With this medicine, doctors may use it even in patients with poor renal function, as long as they have a creatinine clearance of 25 ml/min/1.73 sqm. This research has made dapagliflozin a more plausible therapy choice for those with end-stage renal failure. [35]

Foote C., et. al., SGLT-2 inhibitors' impact on cardiovascular events and death in people with type 2 diabetes was examined in 42 randomized clinical trials, according to specialists (T2DM). There was a reduction in cardiovascular events and mortality in patients with type 2 diabetes who were using SGLT-2 inhibitors as compared to other ADAs. [36]

David C Wheeler., et. al., Researchers conducted a study and found that dapagliflozin lowered the risk of kidney failure and increased survival in patients with kidney failure and type 2 diabetes, as well as those with IgA nephropathy. Dapagliflozin has only been associated with a few significant side effects thus far. [37]

Javed butler, et. al., One research found a link between type 2 diabetes and an increased risk of heart failure. Heart failure hospitalizations, cvd hospitalizations, and renal hospitalizations may all be reduced with SGLT2i s, which have been shown in a number of randomized controlled studies (CVOTs). Atherosclerotic cvd patients with Type 2 diabetes may benefit most from starting sglt2i treatment sooner rather than later, according to multiple studies.

Awadesh Kumar Singh., et. al., Study results showed that SGLT2 inhibitors reduced the risk of cardiovascular mortality or heart failure by 26% relative risk in patients with heart failure. Hf patients with HFrEF and HfPefEF exhibited comparable advantages in the composite of CV death or HfF. These data
demonstrate that SGLT2 inhibitors may reduce the risk of cardiovascular mortality and heart failure in both types of heart failure when administered in combination. [39]

Robert Puckrin., et, al., SGLT2 inhibitors were shown to increase the risk of urogenital infections in a meta-analysis of randomized clinical trials. UTIs were shown to be more common in patients using the medicine dapagliflozin 10 mg per day, according to one research (UTI). Respiratory tract infections were not linked to SGLT2 inhibitors despite a reduced incidence of gastroenteritis. [40]

Fei Y., et, al., conducted a meta-analysis which combined the findings of 14 clinical studies that was done to compare the advantages of other ADA classes. In comparison to other ADA, sglt-2 inhibitors showed significantly lower rates of heart failure hospitalization and a clear superiority over all the others. [41]

Yang DY., et, al., An extensive meta-analysis done in China examined the rankings of several AAScombinations for one particular cardiovascular outcome: heart failure. Research undertaken during the preceding 19 years (from 1980 to 2019) yielded 92 randomized clinical trials that explored the particular advantages of heart failure drugs, compared them, and assessed their impact on those at high risk of heart failure. The sglt-2 inhibitors and metformin were shown to be much more efficacious than the other ADAs tested. [42].

Vasiliki Tsampasian., et, al., conducted a meta analysis and concluded that sglt2 inhibitorsshowed a favorable profile in treating hf patients regardless of their diabetes status. [43]

Giuseppe Palmiero.et, al., stated in their studied conclusion that sglt2 inhibitors should be introduced in the first step of the hf treatment, regardless of concomitant medications. [44]

David M., et, al., In their article on hfpef treatment with dapagliflozin (deliver studied) delivered clinically meaningful outcomes and stated that it was needed to added dapagliflozin to the treatment chart of hfpef as it improved qol, reduces hospitalization, and lowers financial costed. It also stated its effects in hfpef were associated with other clinical burdens and added a statement saying further studied were needed to evaluate the add-on effect of other antidiabetic drugs with sglt2is. [45]

Heidi Storgaard., et, al., There was an increased risk of urinary and vaginal tract infections, as well as elevated serum creatinine levels, when the sglt2i medications (empagliflozin 25 mg/dapagliflozin 10 mg/canagliflozin 300 mg) were studied for more than 12 weeks at the maximum therapeutic dosage that were authorized. They had proven that sglt2is reduces hba1c levels too

NEED FOR STUDY:-

The goal of this study was to evaluate the Indian population's safety, efficacy & tolerability. The assessment of patient quality of life is as important as the treatment outcome. The cost-effectiveness of the treatment should be considered for the patient's convenience.

Because there was limited data available in India for SGLT2 inhibitors, which are prescribed for people with heart failure to reduce risk of mortality and hospitalization. Majority of the data with SGLT2 inhibitors is from the Western world. Our study intends to fill this gap in the literature by investigating the pattern of usage and acceptance of SGLT2 inhibitors in a segment of the Indian population.

3.AIM:
To assess the efficacy, safety & tolerability of SGLT2 inhibitors in chronic heart failure, as well as their impact on patient symptoms and QOL. To investigate the reasons for therapeutic discontinuance.
MATERIALS AND METHODS: Method and collection of Data:

STUDY LOCATION: This research is being carried out at the Krishna Institute of Medical Sciences (KIMS) hospital in Secunderabad Out-patient Unit of Cardiology.

STUDY DESIGN: The study was conducted after the approval of the institutional ethics committee. Confidentiality of the patient and the prescriber was maintained. Permission from the head of the department was obtained prior to the study.

STUDY DESIGN: This is a Prospective Observational study.

STUDY PERIOD: This study lasted six months.

SAMPLE SIZE: 103 (Confidence level - 95%)

STUDY EXCLUSION AND INCLUSION CRITERIA:

INCLUSION CRITERIA:

- Adults.
- Patients with and without diabetes.
- Both Male & Female Patients.
- Outpatient data.
- Heart Failure (stable NYHA Class: I-III)
- Patients giving their consent.

EXCLUSION CRITERIA:

- Pregnant and lactating women.
- Pediatric & young adults < 18 years.
- Patients not giving consent.
- Acutely decompenated heart failure patients (NYHA Class- IV)

SOURCE OF DATA:

- All essential and useful data was gathered from outpatient department patient records, lab reports, and medications.
- Communicated with healthcare professionals.
PROPOSED PLAN OF WORK:-

1. Literature
2. Preparation of protocol and data
3. Getting permission from the ethical board

All those patients who meet the study criteria will be included in the study after obtaining the informed consent.

During the initial visit, collection of baseline information of the patients by applying exclusion and inclusion criteria was collected and documented as well.

Patient’s demographic data, other comorbid conditions, the medication details, and treatment outcome of the patients, with all the required data have been collected from.

The primary parameters such as BP and ADR Report were documented for the analysis.

The obtained data is analysed using suitable statistical methods.

Results

Conclusion → Report
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Results

Conclusion
Fig. Flow chart of heart failure & treatment algorithm.

STATISTICAL ANALYSIS:

Appropriate statistical methods like Paired t test, Analysis of variance, Analysis of covariance, F-test and Correlation analysis were applied to analyze the data at the end to achieve the objective of the study.

**Paired t test:** Pre- and post-test scores, for example, were utilized in this test to determine whether the means of the two measures vary.

\[
t = \frac{\sum d}{\sqrt{n \left( \sum d^2 \right) - (\sum d)^2}}
\]

where \(d\): difference per paired value

\(n\): number of samples
ANOVA: In order to assess the equality of different means, we utilized ANOVA to compare the variation across groups and within groups

ETHICAL CONSIDERATIONS:

There will be an institutional human ethics committee approval process. Each participant must provide written agreement before they may participate in the research, and only those who agree will be included. The study participants' confidentiality will be protected.

With the ethical committee approval number: KIMS/ECBMHR/2021/27-3.

5. RESULTS:

In our study, a total number of 103 heart failure subjects who were prescribed with SGLT2 inhibitors were enrolled as per inclusion and exclusion criteria from the outpatient unit - Krishna Institute of Technology, Secunderabad.

DEMOGRAPHIC DETAILS:

6.1. GENDER WISE DISTRIBUTION OF HEART FAILURE PATIENTS:

Total no. 103 patients included, 65 (63.1%) were male and 38(36.8%) were female. This study shows male predominance.

FIG 6.1: PIE CHART REPRESENTING PATIENTS PERCENTAGE ACCORDING TO SEX.

AGE WISE GENDER DISTRIBUTION:

Both male and female patients were distributed accordingly age wise in fig 6.2.
<table>
<thead>
<tr>
<th>AGE</th>
<th>MALE</th>
<th>FEMALE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>40-49</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>50-59</td>
<td>27</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>60-69</td>
<td>16</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>70-79</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>80-89</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Fig.6.2: SUBJECTS DISTRIBUTION BASED ON AGE GROUPS AND SEX.**
AGE WISE DISTRIBUTION OF PATIENTS:

In our study the patients' age ranges between 20 to 89 years. The average age of subjects included is 54.85. Subject's age majorly lies in between 50-59 years (30.7%).

<table>
<thead>
<tr>
<th>AGE</th>
<th>NO. OF PATIENTS (n= 103)</th>
<th>PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>1</td>
<td>0.97</td>
</tr>
<tr>
<td>30-39</td>
<td>7</td>
<td>6.79</td>
</tr>
<tr>
<td>40-49</td>
<td>17</td>
<td>16.5</td>
</tr>
<tr>
<td>50-59</td>
<td>40</td>
<td>38.3</td>
</tr>
<tr>
<td>60-69</td>
<td>25</td>
<td>24.2</td>
</tr>
<tr>
<td>70-79</td>
<td>10</td>
<td>9.7</td>
</tr>
<tr>
<td>80-89</td>
<td>2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Fig 6.3: SUBJECTS DISTRIBUTION BASED ON AGE GROUPS
PATIENTS DISTRIBUTION BASED ON TYPE OF HF:

Considering the 2D ECHO as a standard diagnostic tool for HF patients were categorized either into HFrEF (EF<=40%) or HfPEF (EF>=60%).

<table>
<thead>
<tr>
<th>Type of HF</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>92</td>
</tr>
<tr>
<td>HfPEF</td>
<td>11</td>
</tr>
</tbody>
</table>

DISTRIBUTION OF PATIENTS BASED ON THE TYPE OF SGLT2 INHIBITORS THEY WERE ON:

Out of 103 patients in study 42 (40.7%) were on EMPAGLIFLOZIN and 61 (59.2%) were on DAPAGLIFLOZIN.
FIG. 6.5: DISTRIBUTION OF PATIENTS BASED ON TYPE OF SGLT2 INHIBITORS

DRUG WISE DISTRIBUTION OF HFrEF AND HFpEF PATIENTS:

In our study, HFrEF and HFpEF patients were mostly prescribed with dapagliflozin rather than empagliflozin.

<table>
<thead>
<tr>
<th>HF Classification</th>
<th>Empagliflozin</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td>HFpEF</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

: DISTRIBUTION OF PATIENTS BASED ON ADRs OBSERVED:

Out of 103 HF patients on SGLT2is we studied, only 7 had shown adverse effects like cystitis, pyelonephritis, and other UTIs.
After one month of treatment with SGLT2 inhibitors, 5 of the 103 patients developed UTIs (i.e. a complaint was filed on their review – 1). Their PUS cells, as well as the serum creatinine level in their blood, had significantly increased (observations from urine examination and renal function test).

**Review-1:**

: Pus cells findings of five patients who experienced adverse effects:

<table>
<thead>
<tr>
<th>Baseline visit (pus cells count/hpf)</th>
<th>Review 1 (pus cells count/hpf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>
The average increase in pus cells in patients presented with a UTI is 18.

**Serum creatinine observations from RFT of patients with side effects:**

<table>
<thead>
<tr>
<th>Baseline visit S.creatinine level (mg/dl)</th>
<th>Review 1 S.creatinine level (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>1.76</td>
</tr>
<tr>
<td>0.9</td>
<td>1.82</td>
</tr>
<tr>
<td>0.8</td>
<td>1.87</td>
</tr>
<tr>
<td>1.23</td>
<td>1.93</td>
</tr>
<tr>
<td>0.6</td>
<td>1.95</td>
</tr>
</tbody>
</table>

An average increase in serum creatinine in patients with renal effect is 0.9.

**Review-2:**

After three months of SGLT2 inhibitors treatment, 2 patients developed UTI. Their observations of pus cells are as follows:

**Pus cell observations in UTI infected individuals:**

<table>
<thead>
<tr>
<th>Pus cell in baseline visit</th>
<th>Review 1</th>
<th>Review 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

After one month, no significant changes in CUE were seen, however after three months of therapy (i.e. on review 2), the pus cell count had increased dramatically.

Average increase in pus cells for these patients is 15.
Serum creatinine levels in their baseline - review 1 - review 2 are:

<table>
<thead>
<tr>
<th></th>
<th>Baseline visit</th>
<th>Review 1</th>
<th>Review 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>1.10</td>
<td>1.14</td>
<td>1.74</td>
</tr>
<tr>
<td></td>
<td>1.04</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The average increase in serum creatinine levels from baseline visit to review-2 is 0.6.

: PATIENTS DISTRIBUTION BASED ON MEDICATION HISTORY:

Some of the subjects in the study were already on SGLT2 inhibitors while others were newly prescribed.

<table>
<thead>
<tr>
<th>USAGE STATUS</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Already on SGLT2 inhibitors</td>
<td>11</td>
</tr>
<tr>
<td>Newly prescribed</td>
<td>92</td>
</tr>
</tbody>
</table>

FIG 6.8: PIE CHART REPRESENTING SGLT2 USAGE STATUS
REASONS FOR DISCONTINUATION OF DRUGS:

Few patients had to discontinue the drug during the study period. The following are the reasons for the discontinuation:

<table>
<thead>
<tr>
<th>REASON FOR DISCONTINUATION</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRS observed</td>
<td>7</td>
</tr>
<tr>
<td>Unavailability of prescribed brand</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REASON FOR DISCONTINUATION</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRS observed</td>
<td>7</td>
</tr>
<tr>
<td>Dispensing error at Pharmacy</td>
<td>1</td>
</tr>
</tbody>
</table>

PATIENTS DISTRIBUTION BASED ON THEIR DIABETIC STATUS:

Based on the diabetic history of the subjects in our study, we discovered that 67 were diabetic and the remaining 36 were non-diabetic.

<table>
<thead>
<tr>
<th>Patients with diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>36</td>
</tr>
</tbody>
</table>
EJECTION FRACTION OBSERVED DURING BASELINE VISIT, REVIEW - 1 AND REVIEW - 2:

Average improvement in the EF in review 1 is : 1.961 The p value observed in applying paired t test is : 0.003163 P value is less than less than α So there is a significant difference between EF of baseline visit and EF of review 1.

Average improvement in EF in review 2 is : 3.26
P value : 0.00000997
Here p value is less than α
So there is a significant difference between EF of review 1 and EF of review 2.

Discussion:

All the researchers have suggested that the add-on therapy of SGLT2 inhibitor drugs in the heart failure management protocol (both reduced ejection fraction and preserved ejection fraction) along with other cardiac drugs has shown an abrupt decrease in the hospitalization chances of patients.

Majority of the data with SGLT2 inhibitors is from the Western world. Our study aims to bridge the gap in literature by studying the pattern of use & acceptability of SGLT2 inhibitors in a segment of the Indian population for heart failure management. In our study, a total of 103 patients were included, from the age of 20 to 89 years. Of those, the males were 65 and the females were 38, and the mean age was 54.85 years. Most (93.3%) of the patients had no complaints when they were on SGLT2. Among them, 6.7% had complaints of burning micturition and dysuria. The major negative effect, as described in multiple clinical trials is an increased risk of UTIs.

Changes in pus cells and serum creatinine levels were observed in urine examination (CUE) and renal function test (RFT) of patients who experienced adverse effects. Thenumber of pus cells in the urine increased by an average of 18, while serum creatinine increased by an average of 0.9 in the patients showing adverse effects in their review 1.

FIG 6.10: PIE CHART REPRESENTING DIABETIC STATUS OF PATIENTS
An average of 15 and 0.6 changes were in pus cells and serum creatinine respectively in the patients showing adverse during their review 2.

The effectiveness of SGLT2 in HF management is seen comparing the ejection fraction improvement from each and every review to baseline visit.

The average improvement in EF at the first review of each patient is 1.96 % and the average EF improvement on review 2 is 3.26%.

Robert Puckrin.,et.,al.in their study concluded that SGLT2i increases the risk of urogenital infections. In this study, only mild to moderate UTI infections were reported. The conclusion of our study to the reference study’s was not matched.

Mikhail Kosiborod.,et.,al.,in their study concluded that SGLT2is in HF management were associated with lesser chances of hospitalization of patients.In this study reports were similar to our reports.No hospitalization of our subjects were reported.

Javed butler. ,et.al., concluded that the major risk factor of HF is the presence of diabetes. From our study, we concluded the same. Of the total number of subjects included in our study, 65.04% of them have a history of diabetes.

In a meta-analysis conducted by Vasiliki Tsampasian and team, it was concluded SGLT2 inhibitors show a positive effect in treating HF patients both with and without diabetes. Our study included heart failure patients with and without diabetes history, and we observed of course not limitations in the effectiveness of treatment for either group.

Giuseppe Palmiero.et.,al., in their article proposed addition of SGLT2 inhibitors drugs in the first line treatment of heart failure. Presently, both Empagliflozin and Dapagliflozin showed upright effectiveness in EF improvement and no major side effects in our study. Hence our reports support their article.

David M Williams.,et.al in their study conclusion stated it's important to add Dapagliflozins to themanagement of HFpEF as they improved QOL, decreased the frequency of hospitalization, and improved the financial cost of disease control. Our study also aimed at SGLT2 inhibitors inclusion in HF(HFrEF/HFpEF)management protocol. 9 hfpef cases were studied for 3 months and their EF for 3 visits were noted and compared for any improvement. Dapagliflozin was used in 7 of the 9 HFPEF patients. In these patients the EF improvement was observed improving standardly.

Heidi Storgaard.,al.,in their systematic review analysis concluded that SGLT2 inhibitors drugs at their highest approved doses showed an increase in serum creatinine levels. In our study serum creatinine levels were recorded for patients showing UTIs and the comparison was done among them in their baseline :review 1:review 2 visits and we observed rise in serum creatinine levels i.e an average rise observed was 0.9 in their review 1 and 0.6 in their review 2.

Conclusion:

Our study has concluded that heart failure patients, regardless of their diabetes state, can be prescribed SGLT2 inhibitors. Both empagliflozin and dapagliflozin show positive results in HF management. The chances of adverse effects like urinary tract infections, urogenital infections, and nausea occurring are very low. Our study also concluded the improvement of ejection fraction in patients on SGLT2 inhibitors, which is proven by LVEF 2D echo reports.

As India is lacking information regarding how SGLT2 inhibitor drugs act and help in HF management in the Indian population, we need more studies to fill this gap.
References:


12. Living with heart failure: Reduced ejection fraction vs. Preserved ejection fraction [Internet]. Heart-Failure.net. [cited 2022 May 2]. Available from: https://heart-failure.net/living/ejection-fraction-differences


29. HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use JARDIANCE safely and effectively. See full prescribing information for JARDIANCE. JARDIANCE ® (empagliflozin tablets), for oral use Initial U.S. Approval: 2014 [Internet]. Boehringer-Ingelheim.com. [cited 2022 May 6]. Available from: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf


