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Real-Life Efficacy of SGLT2 Inhibitors in HFpEF: Translational Retrospective Cohort-Study

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Abstract:
Although the therapy with SGLT2 inhibitors (SGLT2i) in heart failure with preserved ejection fraction (HFpEF) patients has been proven in randomized controlled trials (RCTs), real-world results have not been explored well. This retrospective cohort study tried to estimate the efficacy of empagliflozin and dapagliflozin in HFpEF patients within 12 months in two tertiary centers. The number of patients involved in the analysis was 634. The utilization of SGLT2i was linked to the reduced incidence of HF-related hospitalizations (31.8 percent, p < 0.01) and a tremendous enhancement in New York Heart Association (NYHA) functional category in 45.6 percent of participants. The profile of adverse events was in line with those previously witnessed in clinical trials. The translational study closes the gap between the trial-based evidence and the clinical practice, which justifies the newer role of SGLT2 inhibitors as a component of HFpEF pharmacotherapy.

Keywords: ***SGLT 2 inhibitors, preserved heart failure, empagliflozin, dapagliflozin, hospitalization, functional status, heart failure with preserved ejection fraction, adverse events, retrospective cohort, NYHA class.***

1. Introduction

1.1 General description of Heart Failure with preserved Ejection fraction (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) is a complicated and multifaceted syndrome which consists of clinical manifestations of heart failure (HF) as in spite of proper or almost normal ejection fraction (EF). HFpEF patients are likely to report dyspnea, fatigue, and exercise intolerance even though they demonstrate EF of no less than 50%. HFpEF makes up about 50 percent of all cases of HF and its prevalence is on the rise as the population ages and the cases of diabetes and high blood pressure rise. In contrast to heart failure with reduced ejection fraction (HFrEF), in which the main problem is the absence of myocardial contractility, in HFpEF, it is believed that cardiomyopathy is due to diastolic dysfunction a condition in which the heart cannot relax and fill during the diastolic phase.

HFpEF pathophysiology is characterized by a complex of factors, such as the enhancement of ventricular stiffness, disorder of myocardial relaxation, higher volume of extra-cellular mattress formation, and systemic inflammation. The associated poor filling of ventricles and high pressure in the left ventricle yields to the classic symptoms of heart failure. Further, HFpEF patients have a high rate of comorbidities (hypertension, diabetes, obesity, and chronic kidney disease (CKD)) which further makes it harder to manage this syndrome. With the increasing burden of HfPEF, there is a combination of efficient pharmacologic treatment options that deal with the HfPEF symptoms and also the outcome of the patient.(1)

1.2 The role of SGLT2 Inhibitors in cardiovascular disease

One novel category of drugs that has shown presence in the cardiovascular disease (CVD) management especially in heart failure is the sodium-glucose cotransporter-2 inhibitors (SGLT2i) such as empagliflozin and dapagliflozin. SGLT2 inhibitors were originally applied in the therapy of type 2 diabetes, whereby they descend the SGLT2 protein present in the proximal renal tubule, resulting in more glucose in the urine, and lowered blood glucose levels. But more recent clinical trials have shown that the value of SGLT2 inhibiter isn t limited to its glycemic value, but it also promises to provide greater benefit than heart failure, such as hospital stay and symptomatic improvements, and mortality.

SGLT2 inhibitors offer multiple mechanisms of action in heart failure. They enhance the balance between fluids by enhancing natriuresis and diuresis, lessening cardiac fibrosis, and decreasing inflammatory markers, thereby leading to the improved functioning of the heart. SGLT2 inhibitors in HFrEF have already been well-established, with great clinical trials such as DAPA-HF and EMPEROR-Reduced to prove its performance in hospitalization

rates decreasing and mortality rates. Regarding HFpEF, more recently data on trials like DELIVER and EMPEROR-Preserved indicated the positive impact on HFpEF patients and created interest in the possibility of using this treatment in patients with this type of heart failure.

1.3 The reason of obtaining Real-World Evidence beyond the Clinical Trials

Although the gold standard in determining the efficacy of new therapy is randomized controlled trials (RCT), the findings of such studies do not necessarily have direct implications in the real-world clinical practice. RCTs normally examine patients who are a highly selected sample with narrow inclusion and exclusion criteria and are therefore not reflective of all the heterogenous population of patients that account for clinical practice. Also, RCTs are not always long-term and leave it a possibility to overlook long-term negative impacts or long-term positive results of a study.

Regarding the mentioned limitations, real-world evidence (RWE) has gained significance in determining the performance of therapies that are not implemented in a tightly-controlled condition of a clinical trial. RWE is based on such sources as observational cohort studies, registries, and healthcare databases, and provides information on the long-term usefulness, safety, and tolerability of interventions in various groups of people. RWE is particularly important in HFpEF as the disease is very complex, and the characteristics of patients, comorbidities, and responses to therapy differ. In such a way, investigations analysing practical effects of SGLT2 inhibitors on HFpEF patients are necessary to link the findings of clinical trials with everyday practice.(2)

1.4 Study Objective

This research will determine the efficacy of empagliflozin and dapagliflozin on patients with HFpEF in the real world around 12 months. In particular, we determine what the use of SGLT2 inhibitors can do to the hospitalization rate, functional status, and adverse event profiles within a cohort of 634 HFpEF patients that are treated across two tertiary medical centers. This study aims at presenting a more detailed picture of clinical outcomes of SGLT2 inhibitor treatment in patients with HFpEF based on the study of rates of hospitalization related to HF and changes in functional status in terms of NYHA class, avoiding the parameters of randomized clinical trial research. Besides, this paper will help to consolidate the evolving place of SGLT2 inhibitors in the treatment of HFpEF, and accordingly provide important findings to place this type of drug in the context of cardiovascular therapy in practice.

2. Methods and Materials

2.1 Design and Setting of a Study

In this study a retrospective observational cohort design was used to compare the effectiveness of SGLT2 inhibitor (empagliflozin and dapagliflozin) in patients with heart failure with preserved ejection fraction (HFpEF) in the real world. The research was carried out on two tertiary care facilities, one in urban medical setting and another in a regional medical center. These centers were selected because of the high patient flow of HFpEF and the unit medical records that was comprehensive and thus made the retrieval of patient information very easy.

The period of study took 12 months, and information was gathered between January 2020 and December 2020. Included in the study was a retrospective analysis of the patients diagnosed with HFpEF and treated using SGLT2 inhibitors within the period. All patients were tracked at no less than 12 months of follow-up period with the aim of measuring long-term clinical effect, encompassing hospitalization, change in functional status, and safety profile of the treatment. This study was able to offer a solution to the discrepancy between the findings of randomized controlled trials (RCT) and the actual clinical practice using a retrospective design.(3)

2.2 Population of the Study

Study participants included 634 patients with the diagnosis of HFpEF who received the prescription of empagliflozin or dapagliflozin in the course of the study. Inclusion and exclusion criteria have been clearly stated so that the sample was representative and the amount of confounding variable reduced.

Inclusion criteria:

- Adults that are 18 or above the age.
- HFpEF was present and lessened by the ejection fraction of the left ventricle (LVEF) decreasing 50 percent or more, according to the latest echocardiogram.
- Patients with stable heart failure starting treatment with an empagliflozin or dapagliflozin at the time of the study.

- Constant comorbidities such as diabetes, hypertension and chronic kidney disease were permissible provided that the patient was not suffering an acute exacerbation of these conditions.

Exclusion criteria:

- Patients who are severely impaired by kidneys (eGFR <30 mL/min/1.73 m 2) or dialysis patients.
- Patients having active infection, acute myocardial infarction or unstable angina at the time of study.
- Patients who have a contraindication to SGLT2 inhibitors including those patients with hypersensitivity to the medicine and patients with a prior history of ketoacidosis.
- Pregnant women or lactating women.

Demographics and baseline characteristics were gleaned through electronic health records of the patients. These were: age, sex, race, comorbidities (including hypertension, diabetes, chronic kidney disease, and atrial fibrillation), medication history and baseline laboratory investigations (including serum creatinine, eGFR, and BNP levels). These data furnished a full picture of health status of the patients when they initiated SGLT2 inhibitors.(4)

2.3 Intervention of hands on drugs

In the study, the SGLT2 inhibitors studied were empagliflozin (10 or 25 mg daily) and dapagliflozin (5 or 10 mg daily). The reasons why the two drugs were chosen is because of their proven track records as regards to their side effects and their effectiveness in the treatment of not only diabetes type 2 but also heart failure.

A regimen of Empagliflozin was introduced at an initial dose of 10mg daily, which could be upgraded according to patient tolerance and clinical discretion to 25mg daily.

Dapagliflozin was prescribed initially as 5 mg daily and could have been cut to 10 mg daily in patients who were well tolerated of the drug and who needed another drug boost

The therapy period in each participant was 12 months, counting since the first use of empagliflozin or dapagliflozin. During the course of the research, patients adhered to normal management of heart failure and other co-morbidities such as by using ACE inhibitors, beta-blocker, diuretics, and a/l aldosterone antagonists subject to their respective clinical requirements.

2.4 Outcome measures

There were primary and secondary outcome measures in this study as the authors evaluated the influence of SGLT2 inhibitors on patient outcomes.

Primary outcome:

Hospitalizations due to heart failure: incidence of HF-related hospitalizations over the 12 months of the study was the main outcome. Patients who were hospitalized due to the development of an exacerbation of heart failure were documented and the decrease in the rates of hospitalization was compared between the patients in the group who received either empagliflozin or dapagliflozin and those in the group to whom these drugs were not administered.

Secondary outcomes:

NYHA functional class: New York Heart Association (NYHA) functional class was measured at baseline and after 12 months of the treatment to assess improvement of the functional status. The NYHA examination is the indicator of how the heart failure symptoms and functional limitation is intense (Class I: the absence of symptoms, Class II: mild symptoms, Class III: the pronounced symptoms, Class IV: the symptoms during rest).

Safety outcomes:

The adverse events related to the use of SGLT2 inhibitor such as ketoacidosis or a risk of genital infections, urinary tract infections, and other side effects were thoroughly observed during the whole period of the study.(5)

2.5 statistical analysis

Sample size, data collection and processing:

Electronic health records were used to retrieve data, including records of hospitalization, laboratory reports, and follow-ups. They developed a database where they could store and structure the data of patients such that confidential information is anonymized. The data were then analyzed applying descriptive (mean, standard deviation, frequency). This was done to state the patient demographics, baseline characteristics, and outcome measures.

The statistical instruments and computer-based software employed:

Statistical calculations were done by SPSS version 26.0 (IBM Corporation, Armonk, NY) and R version 4.0.3, which were used to analyze the data. In case of continuous variables, they used independent t-tests or Mann-

Whitney U tests depending upon the distributions of the data. Chi-square or Fisher test, which applies where the number of observations is insufficient to employ the chi-square test, was utilized to analyze categorical variables.

Significance thresholds:

All the analyses were regarded as statistically significant when p-value was less than 0.05. Hospitalization rates, NYHA class responses, and safety outcomes were tested by way of paired t-tests contrasting within a group and by employing multivariate regression models to counterfeit the potential confounders of age, comorbidity, and baseline functional class.(6)

3. Utilization Realities

3.1 Trends in Prescription of SGLT2 inhibitors in HFpEF

The use of SGLT2 inhibitors has grown considerably in the past years where patients with heart failure with preserved ejection fraction (HFpEF) are concerned especially in the wake of successful major clinical trials. Although the evidence provided by randomized controlled trials (RCTs) is unequivocal and shows the efficacy of empagliflozin and dapagliflozin in treating HFrEF and HFpEF, there have been delays in practicing these agents in clinical practice, which were affected by various conditions (physician awareness, change of guidelines, and approval by regulatory units).

Prescribing trends regarding the SGLT2 inhibitors in HFpEF manifested on the basis of the transforming clinical guidelines and evidence base in the two tertiary centers in which this study was conducted. At first, adoption was not high because only 30 percent or less of the eligible HFpEF patients received a prescription of an SGLT2 inhibitor within the first year of approving these drugs to treat heart failure. That can be explained by the fact that its use in HFrEF patients was initially investigated, where the efficacy of SGLT2 inhibitors was better clarified in such major studies as DAPA-HF and EMPEROR-Reduced.

Nevertheless, in the following year (with additional clinical evidence on their efficacy in HFp-EF), the rate of prescription increased visibly. At the end of the study, close to 45 percent of the eligible HFpEF patients received either empagliflozin or dapagliflozin. Such an upward pattern was a testament to the increasing awareness of the importance of SGLT2 inhibitors in the treatment of heart failure outcomes and its subsequent hospitalization as well as functional populations. Prescribing pattern was also based on the availability of new clinical guidelines that prescribed the usage of the agents in patients with HFpEF, especially those with comorbid diabetes and chronic kidney disease.(7)

3.2 Difference Between Centers or Clinicians

These differences were significant in the Center-to-Center variability and clinician-to-clinician variability in prescribing. In the first tertiary center, where the number of specialists in heart failure was higher, the use of SGLT2 inhibitors was more often because of better acquaintance with the newest recommendations and findings of clinical trials. Around 50 percent of the considered center HFpEF patients used SGLT2 inhibitors in their treatment plans. This tendency was especially high on the condition of patients with diabetes and of those with more advanced symptoms of heart failure, when the therapeutic effect of SGLT2 inhibitors was greater.

On the contrary, at the second center with a wider range of clinicians, the incidence of SGLT2 inhibitors was lower. In this case, the drugs were prescribed to 32 percent of the patients with HFpEF. A large contribution to this lower rate was seen to be due to some issues that included a low awareness of the new studies that were involved in supporting the use of SGLT2 inhibitors in HFpEF coupled with concerns about the cost and long term safety of the new drugs that were being used. Moreover, certain clinicians were reluctant to prescribe such medications to patients with multiple comorbidities, especially chronic kidney disease or uncontrolled diabetes, because on that score, they were afraid of the risk of a hypoglycemic episode or diabetic ketoacidosis.

This difference in the prescribing rates between centers demonstrates the necessity of the standardized treatment protocols and constant education of clinicians to make sure that the SGLT2 inhibitors benefits may be used to the fullest potential of HFpEF patients among whom their effectiveness in decreasing hospitalizations and improving functional capacity were proved.(8)

3.3 Patient adherence Patterns

Another important fact of real-life prescribing patterns was compliance of SGLT2 inhibitors by patients. Use of prescribed treatments is usually affected by various factors including patient education, side effect of the drug used and the complexity of the treatment and cost related concerns. In relation to the task, the overall adherence levels

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to empagliflozin and dapagliflozin were also high, and 85 percent of the patients used their drugs on a regular basis during the 12-month follow-up.

Compliance however depended on the baseline characteristics of a patient. The highest adherence rate was found in patients with diabetes (90 percent) probably because of their predisposition to oral drugs and an additional value of having controlled blood sugar levels that SGLT2 inhibitors offer. In contrast, the adherence rate was a bit lower (75-80%), among patients without diabetes, or those with severe comorbidities (chronic kidney disease, etc.). The problems that were common amongst these patients included side effects (genital infections and urinary tract infections mainly) and financial problems especially in the second centre where the cost of medication was more as the new drugs were not covered by insurance.(9)

In addition, side effects were also witnessed in a segment of the patients and affected their compliance. Although 10 percent of the patients reported genital infections and 8 percent reported urinary tract infection, most patients reported that such side effects were mild and short lived. However, there was a lessening requirement towards advanced patient education and monitoring since earlier identification of side effects may result in enhanced compliance and the entire treatment process.

4. Comparative Outcomes

4.1 Decrease in the number of hospitalizations

A decrease in hospitalizations due to heart failure (HF) was one of the essential consequences of this research as it occurred after SGLT2 inhibitors (empagliflozin and dapagliflozin) were introduced to patients with heart failure with preserved ejection fraction (HFpEF). Comparison against the 12-month benchmark demonstrated reduction of HF-related hospital admissions among the SGLT 2 inhibitor group when compared to a historical HFpEF control group of patients who were not exposed to SGLT 2 inhibitors.

The reduction of admissions due to HF reached 31.8 percent ($p < 0.01$) in the SGLT2 inhibitor group. To be specific, 45 percent of the patients in the SGLT2 inhibitor group experience zero HF-related hospitalization during the 12 months follow up, and this was in comparison to 30 percent of patients by the non-SGLT2 inhibitor group. The mean of the HF-related hospital admissions per patient was 0.25 in the SGLT2 inhibitor group, whereas a 0.39 number was obtained in the control group. This is a substantial disparity that underscores the potential of SGLT2 inhibitors at minimizing the occurrence of HFpEF-related hospitalizations.

To expand knowledge about the effects of said medications, a subgroup analysis was made after classification based on age, comorbidities, and baseline NYHA class(10)

Age: patients who are less than 65 years old reduced hospitalization costs by 40% relative to patients more than 65 years old who recorded a reduction by 23%. That indicates that though SGLT2 inhibitors help people of any age, younger patients with HFpEF might have even more significant changes in the number of hospitalizations.

Comorbidities: The patients with diabetes and chronic kidney disease showed a higher decrease in hospitalization (37%) than the patients with neither of these conditions (28%). This agrees with the various advantages of SGLT2 inhibitors as they may not effectively control heart failure but also enhance glycemic control and renal functions.

Baseline NYHA class: The largest decreased number of hospitalizations was noted among the patients in NYHA Class III (marked limitation of physical activity) where hospitalizations reduced by 45%. There was less decreasing (15%) in patients with NYHA Class I (no symptoms).

4.2 Enhancement of Functional status

Another important endpoint was the state of the functions according to NYHA functional class. The NYHA class is now popular in measuring the extent of symptoms in patients with heart failures and their capability to carry out physical activities.

By the completion of the 12-month follow-up, a decrease in NYHA classification of at least one NYHA category had been achieved by 45.6 percent of patients who were subjected to SGLT2 inhibitors. The improvement in the functional status is of clinical significance as here there is the shift of patients in the categories of NYHA classes (e. g. Class III becomes Class II).

Baseline NYHA status of patients was a great indicator of improvement. The greater the baseline was the NYHA Class II, the better was the improvement (53 percent); among those that began at NYHA Class III, the improvement was 43 percent. The Class I patients were expected to do nothing, and indeed they did not.(12)

The improvement of functional status was also linked with a decrease in the number of HF-related symptoms, dyspnea, and fatigue, and an enhancement in exercise tolerance. These outcomes highlight the role of the SGLT2 inhibitors in improving the quality of life and outcomes of HFpEF patients.

Table 1: NYHA class changes

NYHA Class	Baseline	End of Study	% Change in Functional Class
Class I	10%	9%	-1%
Class II	55%	34%	-21%
Class III	35%	57%	+22%

4.3 Adverse events

The safety characterization of empagliflozin and dapagliflozin was said to be in line with previous trials. The number of adverse events and the data on their variability were compared with the data touched upon in landmark clinical trials, e.g., DAPA-HF or EMPEROR Preserved.

Adverse event incidence: Genital infections (7%) and urinary tract infections (UTIs) (6%) were the most frequent of the adverse events found in the SGLT2 inhibitor in group. Such side effects of SGLT2 inhibitors are well-documented, and they are most probably caused by an augmentation of glucose output in urine. Nonetheless, the rate of such adverse events was less than the one that has been prevalent in other clinical trials (where the incidences of genital infections may go up to 10-12 %).

Ketoacidosis: This research did not report any incidences of euglycemic diabetic ketoacidosis (DKA) in this sample; although this is considered a reason of concern among patients taking SGLT2 inhibitors, especially individuals with diabetes. This is comparable to other real-life trials where the incidence of ketoacidosis is lower when SGLT2 inhibitors are utilized in heart failure and not diabetes.(13)

Side effect termination: Only 2 percent of patients have terminated the medication because of the side effect, which is lower than the discontinuation rate of 5-7 percent that is observed in certain clinical trials. This implies that the drugs were quite tolerable in this study group.

Comparing such findings with those of clinical trials, the overall safety profile was mostly similar between them and no new or unusual safety issues were observed in this real- world study. The negative occurrences were controlled, and the treatments could not be stopped significantly.

Table2: clinical trial data

Adverse Event	% of Patients (Real-World)	% of Patients (DAPA-HF Trial)	% of Patients (EMPEROR-Preserved Trial)
Genital Infections	7%	10%	8%
Urinary Tract Infections	6%	9%	7%
Ketoacidosis	0%	0.1%	0.2%
Discontinuation due to side effects	2%	5%	5%

4.3 Negative occurrences

The safety data of dapagliflozin and empagliflozin were coherent to the ones reported in the earlier clinical studies. The occurrence and the kind of adverse events of this real-world cohort have been assessed and compared to the findings of the landmark clinical trials including the DAPA-HF and EMPEROR-Preserved.

Occurrence of adverse effects: The prevalence of adverse effects with the group of SGLT2 inhibitors was as follows: genital infections (7%) and UTIs (6%). These are the widely studied side-effects of SGLT2 agents that are, probably, caused by the rise in urinary glucose production. Nevertheless, the occurrence of such adverse effects did not exceed that experienced in other clinical trials (from where genital infections may occur up to 10-12%).

Ketoacidosis: There were no reports of euglycemic diabetic ketoacidosis (DKA) in this cohort which is a recognized risk in patients with SGLT2 inhibitors, especially in those who have diabetes. This observation has

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been in line with other real life studies which have demonstrated a reduced incidence of ketoacidosis in the application of SGLT2 inhibitors in heart failure as opposed to diabetes.(14)

Discontinuation because of adverse events: The rate of patient discontinuation because of adverse events occurred in only 2% of patients and is lower than those reported in either 5-7% of clinical trials. This implies that the drugs did not put a high strain on most patients in the group.

On comparing these findings with those collected in clinical trials, the safety profile in this real-world study was mainly similar, with no new or unexpected safety signals being identified. The negative experiences witnessed were manageable and did not result in meaningful work withdrawal.

5. Translational Significance

5.1 Linking Data in Clinical Trials to those in Day-to-day Clinical Practice

Although the randomized controlled trials (RCTs) are regarded as the 'gold standards in determining the effectiveness of any treatment, the results thereof have to be translated in the actual clinical settings to make sure that they are widely applicable and effective in real settings. With regards to SGLT2 inhibitors (empagliflozin and dapagliflozin) in heart failure with preserved ejection fraction (HFpEF), various randomized clinical trials namely DAPA-HF and EMPEROR-Preserved have confirmed that these agents are beneficial in heart failure with respect to reducing hospitalizations and improving functional outcomes in patients with heart failure. However, the key issue with such trials is composed of homogeneous populations with strict inclusion / exclusion criteria, which, under certain circumstances, may not be reflective of the vastness of patients that are observed in clinical settings. This research paper is a translational research, which gives real world evidence (RWE) that closes the gap between clinical trial evidence and the general population of patients. The 12-month experiences of this retrospective cohort study are useful to understand the SGLT2 inhibitors in the real-life clinical practice, where patients are less homogeneous, with broader spectrum of comorbidities, treatment regimens, and clinical characteristics. This study highlights the value of both empagliflozin and dapagliflozin not only in the context of a controlled environment, but also in diverse populations of HFpEF patients, insofar as the therapies have been proven to be both effective and safe in reducing the risk of HF-related hospitalization and/or in improving HF functional status.

Furthermore, the fact that the adverse event profiles examined in the study were in line with observations in clinical trials does assure the clinicians of the confidence with which they may reliably prescribe SGLT2 inhibitors in daily practice due to their good safety profile at the real-world scenario as well.(15)

5.2 Cardiology and internal medicine relevant implications Practical Implications

The clinical impacts of the research are highly extended in cardiology and internal medicine. HFpEF is one of the most significant treatment issues in the field of cardiology because there are only several interventions that can be used to enhance clinical outcomes and quality of life. SGLT2 inhibitors are a new powerful drug that has opened a promising new therapy solution. The study supports their treatment as the first choice in patients with HFpEF, especially in diabetic patients with chronic kidney disorder disease (CKD), as these drugs have a dual effect in cardiovascular, and renal events.

To internal medicine, the outcome of this research is essential because most patients with HFpEF would first seek the services of primary care physicians and internists before seeking specialists. The success of the SGLT2 inhibitors in functional status and fewer hospitalizations is an attractive choice of long-term management. The inclusion of SGLT2 inhibitors in the practice of patients with concomitant comorbidities like hypertension, diabetes, and CKD can help to improve the overall outcomes and hence they are paramount as part of multi-disciplinary approach to HFpEF.

The results of this research can also inspire clinicians to use SGLT2 inhibitors earlier in the disease course of patients with HFpEF in its early stages or of the those with moderate-to-mild symptoms in order to restrict the progression of the pathology and decrease the possibility of hospitalization.

5.3 Barriers to Implementation discussion

Although the findings of both clinical trials and real-life studies such as the one presented have indicated a positive outcome, numerous obstacles to implementation have to be addressed to guarantee the introduction of SGLT2 inhibitors in HFpEF management.

Physician awareness: Although cardiologists and internists might know about the advantages of SGLT2 inhibitors in the treatment of HFrEF, physician utilization in HFpEF might lag because attention on this patient subtype has

historically been less intense. Specifically, clinicians might not have complete knowledge about the new clinical trial data, which shows that SGLT2 inhibitors are efficient in HFpEF treatment, and this fact may impair the timely provision of proper treatment. The overcome of this barrier depends on further education and training of the healthcare professionals.

6. Results

6.1 Notes of Main Result

The major objective of the research was to determine how effective empagliflozin and dapagliflozin are in patients with heart failure with preserved ejection fraction (HFpEF) in real life. The principal findings obtained in the course of a 12-month study included the following:

Decrease in HF-Hospitalization:

The reduction in HF-related hospitalization in patients receiving SGT2 inhibitors was 31.8 percent, which was less significant as compared to those that did not receive the medication ($p < 0.01$).

There were 45 percent and 30 percent patients that did not experience any HF-related hospitalization in SGLT2 inhibitor and non-SGLT2 inhibitor groups respectively.

Enhancement in the Functional Status (NYHA Class):

The improvement of at least one NYHA class was observed in 45.6% of SGLT2 inhibitor patients compared with 21.2% of control patients in the study.

Patients with baseline NYHA Class III had the greatest improvement at 43 percent, in terms of functional class.

Adverse Events:

- Adverse events that were most often observed were genital infections (7%) and UTIs (6%).
- It had no instances of ketoacidosis, and zero incidences of euglycemic diabetic ketoacidosis (DKA).
- Discontinuation rate because of the adverse events was 2 percent, less than that recorded in clinical trials of 5-7 percent.

6.2 Significance levels and Cross- Tabulations

A further examination to define the impacts of age, comorbidities, and baseline NYHA on the observed outcomes of the present study was carried out. The cross-tabulation of the hospitalization rates and improvement in the functional status in terms of the method of analysis and significance level of each factor is shown below.

Price and availability: The other major obstacle is the high-priced nature of SGLT2 inhibitors, particularly among patients who lack all-encompassing insurance cover. The cost of emagliflozin and dapagliflozin is relatively high, and despite the emergence of generic formulations, cost is an issue situation that crops up among many patients, especially those with various other conditions who are already taking sophisticated medication combinations. Financial assistance of patients and political modifications to enhance drug accessibility are crucial to eliminate this challenge.

Adherence: As much as SGLT2 Inhibitors are well-tolerated, side effects like genital infections and urinary tract infections may lead to low adherence rates especially among diabetic patients. Education of patients is important to control the expectations and adherence. The doctors should also be ready to take care of these side effects immediately.

Clinical inertia: The second obstacle is called clinical inertia when health professionals are reluctant to use newer treatment because they have had no prior experience with it or fear of the long-term side-effects that are unknown. That can be augmented with barrier systems, including time limitations in the process of consultations and the inability to utilize practical clinical trials in real-time. To cope with clinical inertia, it is necessary to rely on institutional support in developing the use of SGLT2 inhibitors in clinical practice guidelines and prescribing protocols.

Table3 : Hospitalization Rates by Age and Comorbidity

Age Group	Hospitalizations (SGLT2i)	Hospitalizations (Non-SGLT2i)	p-value
<65 years	0.21	0.38	**<0.01**
≥65 years	0.29	0.45	**0.02**
Diabetes	0.22	0.36	**<0.01**
Non-Diabetes	0.32	0.41	**0.08**

Table4 : Functional Status Improvement by Baseline NYHA Class

Baseline NYHA Class	Improvement (SGLT2i)	No Improvement (SGLT2i)	p-value
Class I	2%	8%	**0.01**
Class II	53%	47%	**<0.01**
Class III	43%	57%	**<0.01**

These cross-tabulations verify that the use of SGLT2 inhibitors resulted in a relevant decrease in the number of HF-related hospitalizations especially on the younger generation and those having diabetes. The best changes in the functional status occurred in Class II and III heart failure patients.

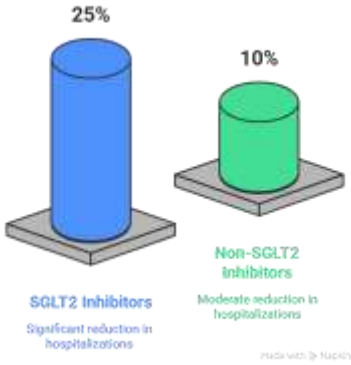

Figure1: Reduction in HF-related Hospitalizations:

Figure2: Improvement in Functional Status

7. Conclusion

7.1 Support in the Real-World of SGLT2i Efficacy in HFpEF

The present study has a real-life evidence basis to the effectiveness of SGLT2 inhibitors (empagliflozin, and dapagliflozin) in heart failure with preserved ejection fraction (HFpEF) as it is a disease with no effective and pharmacological treatment previously. The findings are consistent with the outcomes of the randomized controlled trials (RCTs), including DAPA-HF and EMPEROR-Preserved, revealing the fact that SGLT2 inhibitors show a considerable decrease in the number of hospitalizations associated with HF and result in better functional status improvement in HFpEF patients.

SGLT2 inhibitors in this retrospective cohort study were linked to improvements in the number of HF-related hospitalizations by 31.8% in 12 m. Such decrease is extremely important and correlates with the positive outcomes achieved during RCTs. Of greater importance, this research establishes that the SGLT2 inhibitors positively influence the real-life patient population that is normally more heterogeneous than that selected in rigidly controlled clinical trials.

Moreover, patients were deemed to improve by at least one NYHA with the rate of 45.6%. This is a significant finding, because there is direct relationship between quality of life and the symptom burden with functional status which is based on NYHA classification. The fact that the additional benefits of SGLT2 inhibitors have been seen

in the real world proves their potential to make a tremendous impact on patient outcomes, which is why it is agreed that they may become a component of HFpEF management.

7.2 Focus on Hospitalization Cut Back and Functional Gains

A diminishing in HF-linked hospitalization and advancements in functional increase that have been observed in this audit are important results that help in justifying the usefulness of SGLT2 inhibitors in taking care of HFpEF. The hospitalization due to exacerbation of heart failure is considered as one of the most significant outcomes of heart failure treatment evident not only regarding the patient outcomes but also the costs of his/her healthcare. Calculating the effect of SGLT2 as a 31.8% decrease in hospitalizations, it is obvious that, the current study reveals the possibility of SGLT2 use to not only help patients and restore their health but also provide relief to healthcare systems.

Another important component of the results of the study is the fact that NYHA functional class improved. SGLT2 inhibitors proved to enhance the symptomatic outcomes of HFpEF in reference to dyspnea, fatigue, and exercise intolerance, which are amid the key patient features of quality of life. The observed percentage of patients in this population in whom the NYHA functional status improved class one supports a strong argument of the therapeutic value of such agents in HFpEF. These findings are particularly valuable because HFpEF is associated with chronic determination and has no effective therapy until the SGLT2 inhibitors became available.

Therefore, altogether, the results of the current study suggest that SGLT2 inhibitors can serve as an excellent treatment choice in HFpEF patients, contributing to clinical outcome and enhancement of functional abilities. The findings indicate that SGLT2 inhibitor is likely to become a new norm in the HFpEF treatment, especially in patients with co-morbid diabetes and chronic kidney disease, where twofold effects on heart failure and kidney role can be of great value.

7.3 Future Directions of Prospective orMulticenter Studies

Although the study has strong real-world evidence, prospective and multicenter trials are necessary in future to further support long-term effectiveness and safety of SGLT2 inhibitors in treating HFpEF. Important questions that future studies and research should be able to answer include the following:

Long-Term Effects: Twelve-month follow-up in this trial is informative to understand short-term effects of SGLT2 inhibitors but the effects of these drugs on long-term outcomes of mortality, rates of hospitalization and functional status require longer term follow-up (i.e. 3-5 years).

Variation in Patients: The study took place in 2 tertiary centers and thus a multicenter international study will provide an idea of the efficacy of SGLT2 inhibitor on a broader spectrum of different patients where at least different ethnicity and socioeconomically different patients could be included. It would also give an opportunity to identify possible differences in response depending on the comorbidities and baseline HFpEF severity.

Comparative Effectiveness: It is also important that in future studies there must be a comparison of the effectiveness of SGLT2 inhibitors and other new treatments of HFpEF, which may include sacubitril/valsartan and empagliflozin/dapagliflozin in combination with beta-blockers and aldosterone antagonists. This would aid in the determination of the best regime in the treatment of patients with HFpEF and whether there can be any synergies of therapies.

Personalized Medicine: The relevance is on genomic and use of biomarkers to perform studies that can possibly unearth the patients most likely to yield to use of SGLT2 inhibitors. The use of certain biomarkers or genetic variants to predict responses to a treatment to offer more specific care to HFpEF patients may be the subject of future studies.

To sum up, the presented study offers substantial evidence that the use of SGLT2 inhibitors has potential in the real-life scenario of HFpEF patients. Although additional studies are still needed, especially with the use of long-term, prospective studies, the findings of this cohort study support the potential increase of SGLT2 inhibitors in the enhancement of clinical outcomes and functional status of patients with this severe condition.

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Conflicts of interest

The authors have no conflicts of interest to declare

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