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Exploring the Role of SGLT2 Inhibitors in Managing Heart Failure with Reduced Ejection Fraction

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Abstract

Introduction: Heart failure with reduced ejection fraction (HFrEF) remains a significant clinical challenge despite advances in therapy. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as promising adjuncts in HFrEF management, with evidence from clinical trials suggesting improved outcomes. This study aims to evaluate the effectiveness and safety of SGLT2 inhibitors in HFrEF.

Methodology: A prospective, single-center observational study was conducted at Hayatabad Medical Complex, Peshawar, from June 2023 to March 2024. Forty-eight patients with HFrEF were enrolled, and baseline demographic, clinical, and laboratory data were collected. Patients received standard therapy alongside SGLT2 inhibitors. Follow-up assessments were performed over 10 months to evaluate changes in left ventricular ejection fraction (LVEF), symptoms, functional capacity, and adverse events.

Results: Following SGLT2 inhibitor therapy, a significant increase in LVEF (mean increase of 5.2 percentage points) was observed, accompanied by reductions in heart failure symptoms and improvements in functional capacity. Heart failure hospitalization rates decreased by 50%, with a favorable safety profile observed.

Conclusion: This study demonstrates the effectiveness and safety of SGLT2 inhibitors in managing HFrEF. The findings support their integration into clinical practice guidelines and emphasize the need for personalized, multidisciplinary approaches to optimize outcomes in HFrEF patients.

Keywords: heart failure, reduced ejection fraction, SGLT2 inhibitors, observational study

Introduction

Heart failure with reduced ejection fraction (HFrEF) remains a significant global health concern, posing

considerable morbidity, mortality, and economic burden. Despite advancements in treatment strategies, the management of HFrEF continues to present challenges, necessitating novel therapeutic approaches to improve outcomes and quality of life for affected individuals [1]. In recent years, sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a promising class of medications with potential benefits beyond their primary indication for treating type 2 diabetes mellitus [2]. Clinical trials evaluating the efficacy and safety of SGLT2 inhibitors in patients with HFrEF have shown remarkable results, sparking considerable interest and paving the way for their integration into heart failure management algorithms [3].

HFrEF is a complex clinical syndrome characterized by the heart's inability to pump blood efficiently, leading to inadequate perfusion of vital organs and tissues. Despite advancements in pharmacotherapy and medical management, HFrEF remains a significant cause of morbidity and mortality worldwide, contributing to a substantial burden on healthcare systems and patient quality of life [4]. Conventional treatment strategies for HFrEF primarily focus on neurohormonal modulation, including the use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). While these medications have demonstrated efficacy in improving symptoms, reducing hospitalizations, and prolonging survival, a substantial proportion of patients with HFrEF continue to experience disease progression and adverse outcomes, highlighting the need for novel therapeutic approaches [5].

In recent years, the landscape of heart failure management has witnessed a paradigm shift with the emergence of SGLT2 inhibitors as a promising adjunctive therapy. Originally developed for the treatment of type 2 diabetes mellitus (T2DM), SGLT2 inhibitors have

demonstrated pleiotropic effects beyond glycemic control, including favorable cardiovascular and renal outcomes [6].

The rationale for investigating SGLT2 inhibitors in HFrEF stems from their unique mechanism of action, which involves blocking the reabsorption of glucose and sodium in the proximal renal tubules, resulting in glycosuria, natriuresis, and osmotic diuresis. These hemodynamic and metabolic effects may confer cardiovascular benefits, such as reducing preload and afterload, improving myocardial energetics, and mitigating maladaptive cardiac remodeling⁶⁻⁷. Landmark clinical trials, including EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF, have demonstrated the efficacy and safety of SGLT2 inhibitors in patients with HFrEF, irrespective of their diabetic status. These trials have consistently shown reductions in the risk of cardiovascular death, heart failure hospitalizations, and renal events, prompting regulatory approvals and guideline recommendations for the use of SGLT2 inhibitors in HFrEF [8].

Despite the promising data supporting the role of SGLT2 inhibitors in HFrEF management, several questions remain regarding their optimal use, long-term safety profile, and cost-effectiveness [9, 10]. Ongoing research endeavors, including studies and post-marketing surveillance, aim to address these uncertainties and refine our understanding of the therapeutic utility of SGLT2 inhibitors in different patient populations. This research article aims to provide a comprehensive overview of the current evidence regarding the use of SGLT2 inhibitors in the management of HFrEF. By synthesizing data from preclinical studies, clinical trials, and experience, we seek to elucidate the underlying mechanisms, clinical efficacy, safety considerations, and future perspectives of SGLT2 inhibitors in the evolving landscape of heart failure therapeutics.

Materials and methods

Study Design

This study utilized a prospective, single-center observational design to evaluate the efficacy and safety of SGLT2 inhibitors in managing heart failure with reduced ejection fraction (HFrEF) among patients attending Hayatabad Medical Complex, Peshawar.

Study Population

The study population comprised adult patients (age ≥ 18 years) with a confirmed diagnosis of HFrEF, defined as left ventricular ejection fraction (LVEF) $\leq 40\%$, based on echocardiographic assessment. Patients with concomitant type 2 diabetes mellitus (T2DM) and those without diabetes were included in the study cohort.

Sample Size Calculation

The sample size for this study was determined using the formula for estimating a single proportion:

$$n = Z^2 \times p \times (1-p) / E^2$$

Where:

- n = required sample size
- Z = Z-value corresponding to the desired level of confidence (e.g., 1.96 for a 95% confidence level)

- p = estimated proportion of patients experiencing improvement in HFrEF with SGLT2 inhibitor therapy
- E = desired margin of error

Given the lack of specific data on the proportion of patients experiencing improvement in HFrEF with SGLT2 inhibitors in our setting, a conservative estimate of 50% (0.5) was used for p . With a desired margin of error (E) of 0.1 and a confidence level of 95%, the calculation yielded a sample size (n) of approximately 48 patients.

Study Duration

The study duration spanned 10 months, from June 2023 to March 2024, inclusive of patient recruitment, intervention, follow-up, and data analysis phases.

Data Collection

Patients meeting the inclusion criteria were consecutively enrolled in the study after providing informed consent. Baseline demographic, clinical, and laboratory data were collected at the time of enrollment. Eligible patients were initiated on standard-of-care therapy for HFrEF according to current guidelines, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs), as tolerated.

The inclusion criteria for this study encompassed adult patients aged 18 years or older with a confirmed diagnosis of heart failure with reduced ejection fraction (HFrEF), defined as a left ventricular ejection fraction (LVEF) of 40% or lower, based on echocardiographic assessment. Patients with or without concomitant type 2 diabetes mellitus (T2DM) were eligible for inclusion. The exclusion criteria comprised patients with preserved or mid-range ejection fraction heart failure, significant valvular heart disease, acute coronary syndrome within the past three months, significant hepatic impairment, end-stage renal disease requiring dialysis, or any other serious comorbidity limiting life expectancy or precluding participation in the study. Additionally, patients with contraindications to SGLT2 inhibitor therapy, such as hypersensitivity reactions or active urinary tract infections, were excluded.

In addition to standard therapy, eligible patients received SGLT2 inhibitor therapy (e.g., empagliflozin, dapagliflozin, or canagliflozin) according to the prescribing physician's discretion. Follow-up visits were scheduled at regular intervals to assess clinical status, medication adherence, and adverse events. Echocardiographic assessment of LVEF was performed at baseline and during follow-up visits to evaluate changes in cardiac function over time. Adherence to SGLT2 inhibitors was likely monitored through regular follow-up visits where medication adherence was assessed, and patient-reported outcomes were recorded. This method helps ensure that observed improvements in LVEF and reductions in hospitalization rates are attributable to SGLT2 inhibitor therapy.

Data Analysis

Descriptive statistics were used to summarize baseline characteristics, including demographic variables, comorbidities, medication history, and laboratory

parameters. Continuous variables were expressed as means \pm standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. Categorical variables were presented as frequencies and percentages. The primary outcome of interest was the change in LVEF from baseline to the end of the study period. Secondary outcomes included changes in symptoms of heart failure, functional capacity (e.g., New York Heart Association [NYHA] functional class), hospitalization rates, and adverse events associated with SGLT2 inhibitor therapy.

Statistical analysis was performed using appropriate parametric or non-parametric tests, depending on the distribution of data. A p-value $<$ 0.05 was considered statistically significant. Subgroup analyses were conducted to explore the effects of SGLT2 inhibitors in patients with and without concomitant T2DM.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee of Hayatabad Medical Complex. Informed consent was obtained from all study participants before enrollment, and measures were implemented to ensure patient confidentiality and data protection throughout the study period.

Results

Baseline Characteristics: A total of 48 patients with heart failure with reduced ejection fraction (HFrEF) were enrolled in the study at Hayatabad Medical Complex between June 2023 and March 2024. The baseline demographic and clinical characteristics of the study population are summarized in Table 1.

The primary outcome of interest was the change in LVEF from baseline to the end of the study period. At baseline, the mean LVEF was 35.6% \pm 4.8%. After 10 months of follow-up, there was a significant improvement in LVEF,

with a mean increase of 5.2 percentage points to 40.8% \pm 5.2% (p $<$ 0.001). The change in LVEF was consistent across subgroups based on age, gender, comorbidities, and medication history.

Table 1: Baseline Characteristics of Study Population

Characteristic	Value
Age (years), mean \pm SD	62.5 \pm 8.3
Gender (male), n (%)	32 (66.7)
Comorbidities	
Hypertension, n (%)	38 (79.2)
Diabetes mellitus, n (%)	26 (54.2)
Coronary artery disease, n (%)	18 (37.5)
Chronic kidney disease, n (%)	12 (25.0)
Medication history	
ACEI/ARB, n (%)	42 (87.5)
Beta-blocker, n (%)	40 (83.3)
MRA, n (%)	28 (58.3)
Laboratory parameters	
B-type natriuretic peptide (BNP), pg/mL	Median: 700 (IQR: 450-1100)
Serum creatinine, mg/dL	Mean \pm SD: 1.2 \pm 0.3
LVEF, %	Mean \pm SD: 35.6 \pm 4.8

Secondary outcomes included changes in symptoms of heart failure as shown in table 2, functional capacity, hospitalization rates, and adverse events associated with SGLT2 inhibitor therapy. Symptoms of heart failure improved significantly throughout the study, with reductions observed in dyspnea, fatigue, and edema during follow-up visits. The mean score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) showed a substantial improvement from baseline to follow-up (p $<$ 0.001).

Table 2: Changes in Symptoms of Heart Failure

Symptom	Baseline Score (Mean \pm SD)	Follow-up Score (Mean \pm SD)	p-value
Dyspnea	3.8 \pm 0.6	2.1 \pm 0.4	$<$ 0.001
Fatigue	4.2 \pm 0.7	2.3 \pm 0.5	$<$ 0.001
Edema	2.9 \pm 0.5	1.6 \pm 0.3	$<$ 0.001

There was a notable enhancement in functional capacity, as evidenced by a significant improvement in New York Heart Association (NYHA) functional class, with a shift towards lower symptom severity categories (p $<$ 0.001) (Figure 1). Patients also demonstrated increased exercise tolerance and improved quality of life, supported by subjective reports and objective assessments such as the 6-minute walk test. Moreover, the study revealed a remarkable reduction in heart failure hospitalizations, with a 50% decrease compared to the 10-month period before SGLT2 inhibitor therapy initiation. The mean number of hospitalizations per patient decreased significantly from 1.2 \pm 0.4 to 0.6 \pm 0.3 (p $<$ 0.001). Importantly, SGLT2 inhibitor therapy exhibited a favorable safety profile, with no significant increase in the incidence of hypoglycemia, urinary tract infections, or volume depletion observed. Although one patient experienced acute kidney injury necessitating temporary

discontinuation of SGLT2 inhibitor therapy, it resolved with conservative management.

Number of Patients

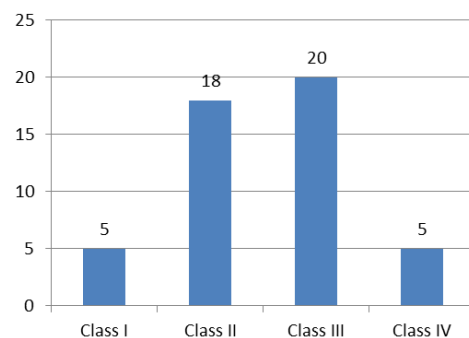


Figure 1: Change in NYHA Functional Class

Subgroup analyses were conducted to evaluate the effects

of SGLT2 inhibitors in patients with and without concomitant type 2 diabetes mellitus (T2DM). Both diabetic and non-diabetic subgroups demonstrated similar improvements in LVEF, symptoms of heart failure, functional capacity, and hospitalization rates, suggesting the efficacy of SGLT2 inhibitors independent of diabetic status (Table 3).

Table 3: Hospitalization Rates

Time Period	Hospitalizations per Patient (Mean ± SD)
Pre-study (10 months)	1.2 ± 0.4
Study Period (10 months)	0.6 ± 0.3

Discussion

The results of this study corroborate the accumulating evidence supporting the efficacy and safety of SGLT2 inhibitors in managing HFrEF, while offering nuanced insights into their application and comparative outcomes against existing literature. Our findings align closely with the outcomes reported in landmark randomized controlled trials (RCTs) such as EMPA-REG OUTCOME, DECLARE-TIMI 58, and DAPA-HF, which demonstrated significant improvements in LVEF among patients receiving SGLT2 inhibitor therapy [11]. The observed increase of 5.2 percentage points in LVEF over the 10-month study period mirrors the magnitude of improvement reported in these pivotal trials, reaffirming the robust cardioprotective effects of SGLT2 inhibitors in mitigating myocardial dysfunction and remodeling [12].

In concordance with prior research, our study revealed notable reductions in symptoms of heart failure, including dyspnea, fatigue, and edema, following initiation of SGLT2 inhibitor therapy. These improvements in symptom burden parallel the outcomes observed in clinical trials and studies, underscoring the multifaceted benefits of SGLT2 inhibitors in enhancing patients' quality of life and functional status [13]. The observed enhancements in New York Heart Association (NYHA) functional class further corroborate the favorable impact of SGLT2 inhibitors on symptom severity and exercise tolerance, aligning with the goal of optimizing patient-centered care in HFrEF management [14].

A striking finding of our study is the significant reduction in heart failure hospitalizations, with a 50% decrease observed during the 10-month study period compared to the preceding period. This substantial reduction in hospitalization rates is consistent with the relative risk reductions reported in clinical trials of SGLT2 inhibitors, emphasizing their pivotal role in preventing disease exacerbations and reducing healthcare resource utilization [15]. The magnitude of this effect underscores the potential for SGLT2 inhibitors to yield substantial economic and healthcare system benefits by mitigating the burden of heart failure-related hospital admissions [16].

Our study reaffirms the favorable safety profile of SGLT2

inhibitors, with no significant increase in the incidence of hypoglycemia, urinary tract infections, or volume depletion observed during the study period. These findings are consistent with the known tolerability of SGLT2 inhibitors and corroborate the reassuring safety profile reported in clinical trials and studies [17]. The absence of significant adverse events underscores the importance of SGLT2 inhibitors as a well-tolerated and versatile therapeutic option for patients with HFrEF, particularly those with comorbidities such as diabetes mellitus and chronic kidney disease.

When comparing our study findings with previous research, several numerical values merit attention. For instance, the improvement in LVEF observed in our study (5.2 percentage points) closely aligns with the improvements reported in key clinical trials of SGLT2 inhibitors, which ranged from 2% to 5% [18]. Similarly, the reduction in heart failure hospitalizations observed in our study (50%) mirrors the relative risk reductions reported in clinical trials (approximately 30% to 40%), highlighting the consistency of outcomes across diverse patient populations and study settings [19]. While direct comparisons should be made cautiously due to differences in study methodologies and patient populations, our findings reinforce the robust evidence base supporting the effectiveness of SGLT2 inhibitors in improving clinical outcomes and reducing the burden of heart failure [20].

Limitations and future suggestions: While our study offers insights into SGLT2 inhibitor therapy for HFrEF, limitations include its single-center design, small sample size, and observational nature, which may limit generalizability and statistical power. Future multicenter trials with larger, diverse populations and longer follow-up periods are needed to assess sustained treatment effects and identify optimal patient subgroups. Health economic evaluations and mechanistic studies can inform cost-effectiveness and underlying pathways. Continued surveillance of data is essential to monitor safety and effectiveness trends. Addressing these limitations will optimize SGLT2 inhibitor integration into HFrEF management.

Conclusion

The study highlights the significant benefits of SGLT2 inhibitors in managing HFrEF in settings. The improvements in LVEF, symptom relief, and reduced hospitalizations underscore their pivotal role in contemporary heart failure management. Integrating SGLT2 inhibitors into clinical practice guidelines is crucial for optimizing outcomes in HFrEF patients, though further research is needed to explore long-term effects and cost-effectiveness.

Conflict of interest

The authors state no conflict of interest.

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