ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 11 | November - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF ROLE OF SGLT2 INHIBITORS IN HEART FAILURE WITH REDUCED EJECTION FRACTION AT A TERTIARY HEALTH CENTER

Clinical Science

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) is a major cause of hospitalization and mortality in India. Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors have emerged as a foundational therapy for HFrEF globally, independent of diabetes status. However, real-world data validating their efficacy and safety in Indian tertiary care settings remains vital. Present study was aimed to study role of SGLT2 inhibitors in heart failure with reduced ejection fraction at a tertiary health center. This was a single-center, prospective, comparative, and observational study conducted over 6 months of follow-up (July 2022 to June 2024). 100 eligible HFrEF patients (LVEF≤40%) were divided into two well-matched groups: Group A (n=50, SMT+SGLT2i) and Group B (n=50, SMT only). Primary endpoints included changes in LVEF, NT-proBNP, and NYHA functional class. Statistical analysis used independent and paired t-tests, with $p<0.05$ considered significant. At 6 months, the SGLT2i group showed significantly superior outcomes compared to the control group. Mean LVEF change was substantially greater (+5.1%±2.5 vs +1.5%±1.8; $p<0.001$). NT-proBNP reduction was nearly four-fold greater (−620±210 pg/ml vs −180±90 pg/ml; $p<0.001$). A greater percentage of patients improved by ≥1 NYHA class (76.0% vs 30.0%; $p<0.001$) and the 6MWT distance improved significantly more (+52.6±28.7 meters vs +12.6±15.3 meters; $p<0.001$). All-cause hospitalization was significantly lower in the SGLT2i group (8.0% vs 24.0%; $p=0.021$). The drug was well-tolerated with no discontinuations due to adverse events. The integration of SGLT2 inhibitors into standard care for HFrEF patients in this Indian tertiary setting provides significant benefits in terms of cardiac remodelling, functional capacity, and reduction in hospitalizations. SGLT2 inhibitors are an essential and effective therapeutic component for HFrEF.

KEYWORDS

Heart Failure; HFrEF; SGLT2 Inhibitor; Dapagliflozin; LVEF; NT-proBNP.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a significant contributor to impaired quality of life, hospitalizations and mortality, globally as well as in India.[1,2,3] HFrEF is defined by an LVEF of [7]≤40% and is typically managed with an established regimen of beta-blockers, ACE inhibitors/ARBs/ARNI, and mineralocorticoid receptor antagonists (MRAs).[4,5] Despite optimal standard care, residual risk of hospitalization and death remains high.

The therapeutic landscape for HFrEF has been transformed by the emergence of Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors (e.g., Dapagliflozin, Empagliflozin).[6] Initially developed for Type 2 Diabetes Mellitus (T2DM), large-scale cardiovascular outcome trials (e.g., DAPA-HF, EMPEROR-Reduced) demonstrated their unprecedented efficacy in reducing cardiovascular death and HF hospitalizations in patients with HFrEF, regardless of the presence of T2DM. The mechanism of action is thought to be multifaceted, involving not just glucosuria and natriuresis, but also improved cardiac energy metabolism, reduction in pre- and afterload, and anti-inflammatory/anti-fibrotic effects.[7]

Given the high prevalence of HF in the Indian population, often presenting with advanced disease and multiple comorbidities, it is crucial to assess the real-world effectiveness and safety profile of SGLT2 inhibitors in a tertiary care setting in India. This study was conducted to evaluate the clinical and echocardiographic benefits of adding an SGLT2 inhibitor to standard care in patients with HFrEF at a tertiary health center.

MATERIAL AND METHODS

The present study was a single-center, prospective, comparative, study, conducted in the Department of General Medicine at Government Medical College & Hospital (GMC), Chhatrapati Sambhajinagar, India. The study duration was 24 months spanning from July 2022 to June 2024. The study protocol was reviewed and approved by the Institutional Ethics Committee of GMC, Chhatrapati Sambhajinagar (IEC/2018/GMCSNB/05).

Inclusion Criteria

Patients Age ≥18 years, clinical diagnosis of chronic Heart Failure, Left Ventricular Ejection Fraction (LVEF) ≤ 40% (determined by 2D echocardiography), NYHA functional class II or III, On optimal standard medical therapy (ACEi/ARB/ARNI, beta-blocker, MRA) for at least 3 months, willingness to provide informed consent and comply with follow-up.

Exclusion Criteria

1. Acute decompensated heart failure requiring intravenous inotropes.
2. Recent myocardial infarction (within the last 3 months).
3. Severe renal impairment (eGFR<30ml/min/1.73m2).
4. Type 1 Diabetes Mellitus or recurrent episodes of Diabetic Ketoacidosis.
5. Severe hepatic impairment (Child-Pugh Class C).
6. Known hypersensitivity to SGLT2 inhibitors.
7. Pregnant or lactating women.

All participants provided written informed consent prior to enrolment. Patients diagnosed with HFrEF (LVEF≤40%) were screened. Eligible patients were divided into two comparative groups:

1. **Group A (SGLT2i Group):** Patients receiving SGLT2 inhibitor (Dapagliflozin 10mg OD) added to optimal standard medical therapy (SMT).
2. **Group B (Control Group):** Patients receiving optimal SMT only.

The primary endpoints were changes in LVEF, NT-proBNP levels, and NYHA functional class at 6-month follow-up. Secondary endpoints included changes in 6-Minute Walk Test (6MWT) distance, all-cause hospitalization, and adverse event profiles.

Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and as frequency and percentage (%) for categorical variables. Chi-square test or Fisher's exact test was used to compare categorical data. Independent samples t-test was used to compare continuous data between the two groups at baseline. Paired t-test was used to compare pre- and post-treatment parameters within each group. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 120 patients were screened, and 100 eligible patients with HFrEF were enrolled and completed the 6-month follow-up (n=50 in Group A and n=50 in Group B). The baseline characteristics, including age, gender distribution, etiology of HF, prevalence of T2DM, baseline LVEF, and NYHA class, were well-matched between the SGLT2i Group and the Control Group. The p-values for all parameters were >0.05, confirming homogeneity between the two groups at the start of the study.

Table 1: Baseline Characteristics Of Study Subjects

Characteristic	SGLT2i Group (Group A, n=50)	Control Group (Group B, n=50)	p-value
Age (Years), Mean ±SD	58.1±9.4	59.5±8.8	0.48
Male Subjects, n (%)	35 (70.0%)	33 (66.0%)	0.66
Etiology: Ischemic, n (%)	28 (56.0%)	26 (52.0%)	0.68
Comorbidity: T2DM, n (%)	24 (48.0%)	22 (44.0%)	0.71
Baseline LVEF (%), Mean ±SD	31.5±3.8	32.0±4.0	0.54
NYHA Class III, n (%)	30 (60.0%)	28 (56.0%)	0.67

The SGLT2i Group demonstrated a significantly greater improvement in both LVEF and reduction in NT−proBNP levels at the 6-month follow-up compared to the Control Group. The mean increase in LVEF in the SGLT2i group (+5.1%) was substantially larger than the control group (+1.5%), with a highly significant p-value (<0.001). Similarly, the mean reduction in NT-proBNP was nearly four-fold greater in the SGLT2i group, confirming a robust positive effect on cardiac remodelling and neurohormonal activation.

Table 2: Comparison Of Primary Efficacy Endpoints At 6 Months

Parameter	SGLT2i Group (n=50)	Control Group (n=50)	Change in SGLT2i Group (Post - Pre)	Change in Control Group (Post - Pre)	p-value (Group A vs B Change)
LVEF (%)					
Baseline	31.5±3.8	32.0±4.0	+5.1±2.5	+1.5±1.8	<0.001
6 Months	36.6±4.5	33.5±3.9			
NT-proBNP (pg/ml)					
Baseline	1580±450	1610±480	−620±210	−180±90	<0.001
6 Months	960±350	1430±450			

SGLT2 inhibitor therapy was associated with a statistically significant and clinically meaningful improvement in functional status. 76.0% of patients in the SGLT2i Group showed an improvement of at least one NYHA functional class, compared to only 30.0% in the Control Group (p<0.001). This highlights a significant clinical benefit in terms of quality of life and symptom burden.

Table 3: Change in NYHA Functional Class at 6 Months

NYHA Class	SGLT2i Group (n=50)	Control Group (n=50)	p-value
Patients Improved by ≥1 Class	38 (76.0%)	15 (30.0%)	<0.001
NYHA Class I	12 (24.0%)	3 (6.0%)	0.011
Class II	31 (62.0%)	35 (70.0%)	0.370
Class III	7 (14.0%)	12 (24.0%)	0.198

The 6MWT distance, a measure of exercise capacity, showed a highly significant improvement in the SGLT2i Group (+52.6 meters) compared to the Control Group (+12.6 meters), with p<0.001. This reinforces the objective evidence of improved functional capacity, consistent with the observed NYHA class improvement.

Table 4: Comparison of 6-Minute Walk Test (6MWT) Distance

Parameter	SGLT2i Group (n=50)	Control Group (n=50)	p-value (Group A vs B Change)
Baseline 6MWT (m)	325.4±45.1	328.9±42.6	0.66
6 Months 6MWT (m)	378.0±40.5	341.5±41.2	
Change in 6MWT (m)	+52.6±28.7	+12.6±15.3	<0.001

The rate of all-cause hospitalization was significantly lower in the SGLT2i Group (8.0%) compared to the Control Group (24.0%), with a p-value of 0.021. While the reduction in HF-specific hospitalization and all-cause mortality showed a trend favoring SGLT2i use, these differences did not reach statistical significance, likely due to the limited sample size and short follow-up duration.

Table 5: All-Cause Hospitalization and Mortality at 6 Months

Outcome	SGLT2i Group (n=50)	Control Group (n=50)	p-value
All-Cause Hospitalization	4 (8.0%)	12 (24.0%)	0.021
HF Hospitalization	2 (4.0%)	8 (16.0%)	0.053
All-Cause Mortality	1 (2.0%)	3 (6.0%)	0.305

The SGLT2 inhibitor was generally well-tolerated. The incidence of genital mycotic infections was numerically higher in the SGLT2i Group (6.0%) but did not reach statistical significance compared to the Control Group (p=0.078). The rates of UTI and symptomatic hypotension were comparable between the groups, and no patient in either group discontinued the study drug due to adverse events.

Table 6: Adverse Events Profile at 6 Months

Adverse Event	SGLT2i Group (n=50)	Control Group (n=50)	p-value
Genital Mycotic Infections	3 (6.0%)	0 (0.0%)	0.078
Urinary Tract Infections (UTI)	1 (2.0%)	1 (2.0%)	1.000
Symptomatic Hypotension	2 (4.0%)	1 (2.0%)	1.000
Discontinuation due to AE	0 (0.0%)	0 (0.0%)	1.000

DISCUSSION

HFpEF is recognized as a heterogeneous syndrome of multiple discrete phenotypes, such as diabetes mellitus (DM), obesity and hypertension.[8] Given the rising aging population in many countries and increasing prevalence of DM/obesity or hypertension, the proportion of HFpEF is also rapidly rising in comparison to HFrEF.1 Unlike HFrEF or HFmrEF, the evidence of clear benefits of standard of care HF therapy (angiotensin receptor blockers/ARBs, mineralocorticoid receptor agonists/MRA, beta blockers, angiotensin receptor neprilysin inhibitors/ARNi) have been debatable in HFpEF.[9]

Gupta A et al.,[10] showed Dapagliflozin resulted in a mean LVEF increase of 4.8% at 6 months, mirroring our observed 5.1% increase, validating the LVEF recovery potential. Khatri K et al.,[11] in their registry of HF patients found a 65% relative risk reduction in HF hospitalization with SGLT2 inhibitor use. Our study's 66% relative reduction in all-cause hospitalization (24%24%−8%) is highly consistent, demonstrating the impact on resource utilization.

In study by Bhavsar A et al.,[12] they focused on NT-proBNP in T2DM and HF patients, reporting a 35−40% reduction in NT-proBNP with Dapagliflozin. Our study showed a ∼39% reduction (1580620) in NT-proBNP in the SGLT2i group, supporting the robust neurohormonal modulatory effect.

Reddy S et al.,[4] reported a significant improvement in NYHA class in over 70% of SGLT2i-treated patients at 6 months. Our finding of 76.0% NYHA improvement confirms the substantial symptomatic relief. Dutta P et al.,[13] emphasized the SGLT2i benefit in non-diabetic HFrEF patients, reporting improved quality of life scores. Our study, which included both diabetic and non-diabetic patients, echoes this functional improvement via the 6MWT gain of over 50 meters.

Singh V et al.,[5] evaluated the safety of SGLT2 inhibitors in a multi-centric setting, noting a low incidence of AEs and no increase in major hypoglycemia (even in diabetic patients). Our data are consistent, showing a manageable safety profile with no discontinuations due to AEs. Jain M et al.,[14] conducted a retrospective analysis & found that the addition of SGLT2i was associated with superior renal outcomes and less eGFR decline. While our study did not focus on eGFR, the observed clinical benefits are consistent with the known cardio-renal protective effects. Vaidya R et al.,[15] highlighted the high cost-effectiveness of SGLT2 inhibitors in India due to reduced hospitalization, supporting their widespread adoption in public health centers.

Akash Jaiswal et al.,[16] conducted a meta-analysis of randomised controlled trials, 6 studies with a total of 15,989 total patients were included in the final analysis. The mean age of patients enrolled in SGLT2 inhibitors and placebo was 69.13 and 69.37 years, respectively. The median follow-up duration was 2.24 years. SGLT2 inhibitors reduced composite cardiovascular mortality or first hospitalization for heart failure (HR, 0.80 [95% CI: 0.74–0.87], P < .001, I2 = 0%), heart failure hospitalization (HR, 0.74 [95% CI: 0.67–0.82], P < .001, I2 = 0%) compared with placebo. However, all-cause mortality (HR, 0.97

[95% CI: 0.89–1.06], P = .54, I2 = 0%) and cardiovascular mortality (HR, 0.96 [95% CI: 0.82–1.13), P = .66, I2 = 35.09%] were comparable between both groups. Study finding shows that SGLT2 inhibitors significantly reduced the risk of first HF hospitalization or cardiovascular death and HF hospitalization; however, all-cause mortality was comparable between the groups.

In a systematic review and meta-analysis by Rahil AI et al.,[17] total of seven trials were included. SGLT2 inhibitors were associated with decreased all-cause mortality (RR = 0.61, 95% CI = 0.40, 0.95; P = 0.03), worsening of HF (RR = 0.59, 95%CI = 0.36, 0.97;P = 0.04), and GFR (MD: 1.05, 95% CI = 0.68, 1.43; P < 0.00001) compared with the control group. There were no significant differences between the two groups regarding readmission for HF, cardiovascular mortality, AKI, hypoglycemia, hypotension, and diuretic efficiency. SGLT2 inhibitors were associated with improved KCCQ-CSS scores (MD: −3.82, 95% CI = −7.51, −0.13; P = 0.04). SGLT2 inhibitors demonstrate overall clinical benefits and a favorable safety profile in acute heart failure, although their impact on readmission rates is limited. Further research is needed to refine patient selection and optimize treatment strategies.

Present observational study confirms the substantial benefits of adding an SGLT2 inhibitor to standard medical therapy for patients with HFrEF. The most compelling findings are the highly significant improvements in LVEF (+5.1% vs +1.5% change), NT−proBNP reduction, and functional status (76.0% NYHA improvement), along with a significantly lower rate of all-cause hospitalization (8.0% vs 24.0%). These results underscore that the cardiorenal benefits observed in large global trials are reproducible and clinically relevant in the Indian real-world setting. The findings align with and strengthen evidence from recent studies conducted in the Indian subcontinent:

The study is limited by its single-center, observational nature and relatively small sample size, which may affect the generalizability and power to detect rare events or differences in mortality. The short follow-up of 6 months is insufficient to assess long-term HF outcomes and sustained effects on mortality.

CONCLUSIONS

The addition of an SGLT2 inhibitor to standard medical therapy in patients with HFrEF at our tertiary health center in Chhatrapati Sambhajinagar demonstrated significant clinical superiority over standard therapy alone. This included a highly significant increase in LVEF, a robust reduction in NT−proBNP, substantial improvement in NYHA functional class and 6MWT distance, and a significant decrease in all-cause hospitalization. The drug was well-tolerated. SGLT2 inhibitors should be considered an essential component of the therapeutic regimen for all eligible HFrEF patients in the Indian healthcare setting.

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