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TOLERABILITY AND EFFICACY OF DAPAGLIFLOZIN IN NON – DIABETIC HEART FAILURE PATIENTS

Original Research

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ABSTRACT

Background: Heart failure (HF) remains a major global health burden with limited treatment options, especially in non-diabetic populations. Sodium–glucose co-transporter 2 inhibitors (SGLT2is), such as dapagliflozin, have shown promising cardiovascular benefits beyond glycemic control. While most studies have focused on diabetic patients, emerging evidence suggests potential efficacy in non-diabetic HF cohorts. Understanding dapagliflozin's role in improving clinical outcomes in this specific population is essential for refining heart failure treatment strategies.

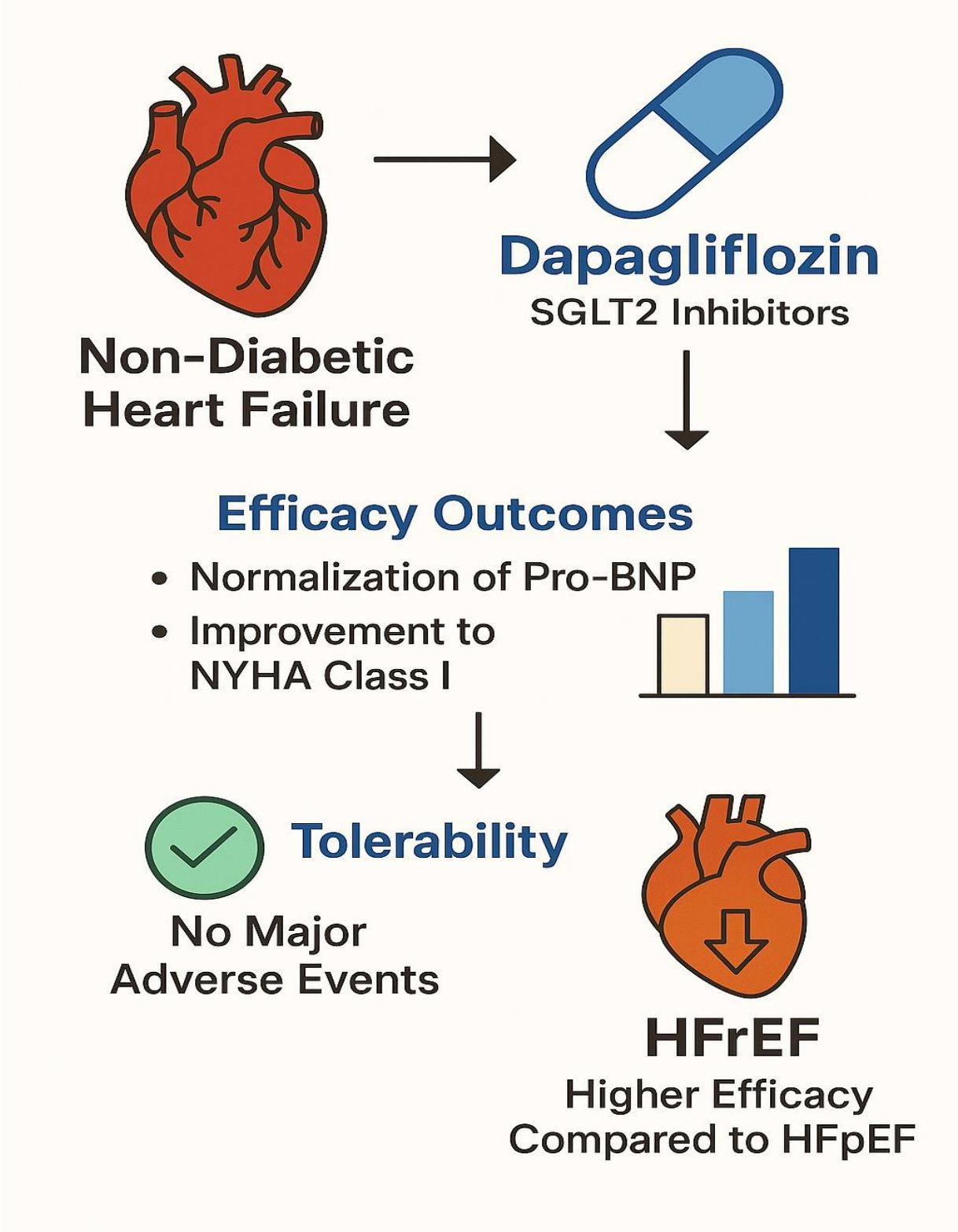
Objective: To evaluate the clinical efficacy and tolerability of dapagliflozin in non-diabetic patients with heart failure.

Methods: This descriptive study was conducted over five months at the Department of Cardiology, PIMS, Islamabad. A total of 150 non-diabetic HF patients, aged 30–70 years, were enrolled using non-probability consecutive sampling. Participants received oral dapagliflozin 10 mg daily for 12 weeks. Baseline and post-treatment assessments included Pro-BNP levels and NYHA functional class. Tolerability was monitored through adverse event reporting. Statistical analysis was performed using IBM SPSS version 23. Quantitative variables were expressed as means ± SD, and categorical variables as frequencies and percentages. A p-value of ≤ 0.05 was considered statistically significant.

Results: After 12 weeks, 66 participants (44.0%) achieved Pro-BNP normalization (<450 pg/mL), and 72 (48.0%) improved to NYHA Class I ($p < 0.001$ for both). A combined efficacy outcome was observed in 58 patients (38.7%). The drug was well-tolerated by 124 individuals (82.7%) without major adverse events. Subgroup analysis revealed higher efficacy in HFrEF patients (50.0%) compared to HFpEF (36.5%) ($p = 0.03$).

Conclusion: Dapagliflozin significantly improves functional and biomarker outcomes in non-diabetic HF patients, especially those with reduced ejection fraction. Its favorable safety profile supports broader clinical application, though long-term evaluation is warranted.

Keywords: Dapagliflozin, heart failure, HFrEF, non-diabetic, NYHA classification, Pro-BNP, SGLT2 inhibitors.



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INTRODUCTION

Heart failure (HF) continues to pose a substantial challenge to global health systems, contributing to significant morbidity, mortality, and economic burden. Despite advancements in pharmacotherapy, including neurohormonal blockade and device therapy, outcomes for many patients remain suboptimal, necessitating innovative treatment strategies. Among the emerging therapeutic options, sodium–glucose co-transporter 2 inhibitors (SGLT2is) have garnered increasing attention. Originally introduced for glycemic control in type 2 diabetes mellitus (T2D), these agents have demonstrated compelling cardiovascular benefits that extend beyond glucose lowering, particularly in the context of heart failure with reduced ejection fraction (HFrEF) (1,2). Recent evidence from major randomized controlled trials has positioned SGLT2is as a cornerstone in HF management. Their ability to significantly reduce hospitalizations for HF and cardiovascular death has been consistently demonstrated, regardless of diabetic status, marking a paradigm shift in HF therapeutics (3). The underlying mechanisms are believed to be multifactorial, including natriuresis, reduction of preload and afterload, improved myocardial energetics, and favorable modulation of neurohormonal pathways, although not all pathways are fully elucidated (3).

Reflecting the strength of the clinical data, the 2021 HF guidelines and their 2023 update have upgraded SGLT2is to a class I recommendation across the full spectrum of left ventricular ejection fraction (LVEF), underscoring their broad applicability (4). In particular, dapagliflozin has received FDA approval for HF treatment following the pivotal DAPA-HF trial, which was notable for including patients with and without T2D and for showing robust reductions in HF events and cardiovascular mortality (5,6). Additional studies have reinforced dapagliflozin's clinical utility, demonstrating a 32% reduction in HF-related hospitalizations and improvement in NYHA class and pro-BNP levels in 44% of patients (7-9). Moreover, its safety profile remains acceptable, with tolerability reported in 65.4% of participants despite a 34.6% rate of serious adverse events in the study by Petrie and colleagues (10). Given the mounting evidence and guideline endorsements, it is imperative to further evaluate the real-world impact and therapeutic potential of dapagliflozin in heart failure populations. Therefore, the objective of this study is to assess the clinical effectiveness and tolerability of dapagliflozin in patients with chronic heart failure, with or without type 2 diabetes, thereby contributing to the evolving landscape of HF management.

METHODS

This descriptive study was conducted over a five-month period at the Department of Cardiology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, following approval by the hospital's ethical review committee. Ethical approval was obtained prior to data collection and informed written consent was secured from each participant after explaining the purpose, procedures, potential risks, and confidentiality of the study. A sample size of 150 patients was calculated using the WHO sample size formula, based on an expected efficacy rate of dapagliflozin at 44%, with an 8% margin of error and a 95% confidence level. A non-probability consecutive sampling technique was used to recruit eligible participants. The inclusion criteria comprised adults aged between 30 and 70 years, of either gender, diagnosed with heart failure according to standard operational definitions, but without a diagnosis of type 2 diabetes mellitus. Patients were excluded if they had a systolic blood pressure below 90 mmHg at enrollment, required intravenous inotropic support, had known hypersensitivity to SGLT2 inhibitors, were pregnant or lactating, had severe anemia (hemoglobin < 7.5 g/dL), or had significant uncorrected aortic or mitral stenosis.

Data collection commenced upon ethical clearance. Participants were recruited from the inpatient cardiology department. Baseline clinical and demographic information, including age, gender, body mass index (BMI), serum Pro-BNP levels, and New York Heart Association (NYHA) classification, was recorded using a pre-designed structured proforma. Each patient was prescribed 10 mg of dapagliflozin once daily for a 12-week treatment duration. Follow-up evaluations were conducted at week 1, week 6, and week 12. At the final visit, NYHA class and Pro-BNP levels were re-assessed to evaluate clinical improvement. The efficacy of treatment was determined based on pre-defined operational definitions (11,12). Any adverse events, including drug-related side effects, were closely monitored and recorded, and tolerability was assessed based on patient-reported outcomes and clinical observations. All data were analyzed using IBM SPSS Statistics Version 23. Quantitative variables such as age, BMI, disease duration, and Pro-BNP levels were summarized using means and standard deviations. Categorical variables including gender, ejection fraction status, NYHA class (before and after treatment), efficacy, and tolerability were described using frequencies and percentages. To control for potential confounding variables, stratification was performed for age, gender, BMI, disease duration, and type of heart failure (preserved or reduced ejection fraction). Post-stratification analysis was conducted using the chi-square test, with a p-value of ≤ 0.05 considered statistically significant.

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RESULTS

A total of 150 patients with non-diabetic heart failure were enrolled, with a mean age of 55.2 ± 8.7 years. The majority were male (61.3%), and the mean body mass index (BMI) was 28.4 ± 4.1 kg/m². Baseline Pro-BNP levels averaged 890 ± 320 pg/mL, while 74.7% of participants were classified as NYHA Class III or IV at enrollment. Among the cohort, 65.3% had a left ventricular ejection fraction (LVEF) of ≤40%, meeting criteria for heart failure with reduced ejection fraction (HFrEF). After 12 weeks of treatment with dapagliflozin, 44.0% of patients achieved normalization of Pro-BNP levels to below 450 pg/mL ($p<0.001$). An improvement to NYHA Class I was observed in 48.0% of patients ($p<0.001$). A combined improvement in both Pro-BNP normalization and NYHA Class I status was seen in 38.7% of the cohort, also statistically significant ($p<0.001$). In terms of safety and tolerability, dapagliflozin was well-tolerated by 82.7% of patients, who experienced no major adverse events during the study period. The most common side effects included epigastric pain in 8.0% of patients, which was managed through dose reduction to 5 mg daily, and pharyngitis in 5.3%, which was treated symptomatically. Elevated creatinine levels (>1.5 mg/dL) were noted in 4.0% of patients, leading to drug discontinuation. Stratified analysis by age showed no statistically significant difference in efficacy between patients aged ≤60 years (46.2%) and those >60 years (40.1%) ($p=0.12$). Similarly, no significant difference in response was found between males (45.6%) and females (42.1%) ($p=0.45$). However, a significant difference in efficacy was observed between patients with HFrEF (≤40% LVEF), who showed a response rate of 50.0%, compared to those with HFpEF (>40% LVEF), who demonstrated a response rate of 36.5% ($p=0.03$).

Table 1: Baseline Characteristics of Study Participants (N=150)

Characteristic	Mean ± SD / Frequency (%)
Age (years)	55.2 ± 8.7
Gender	
Male	92 (61.3%)
Female	58 (38.7%)
BMI (kg/m²)	28.4 ± 4.1
Baseline Pro-BNP (pg/mL)	890 ± 320
NYHA Class III/IV	112 (74.7%)
LVEF ≤40% (HFrEF)	98 (65.3%)

Table 2: Efficacy Outcomes After 12 Weeks of Dapagliflozin Treatment

Outcome	Frequency (%)	p-value
Normalization of Pro-BNP (<450 pg/mL)	66 (44.0%)	<0.001
Improvement to NYHA Class I	72 (48.0%)	<0.001
Combined Efficacy (Both Pro-BNP + NYHA Class I)	58 (38.7%)	<0.001

Table 3: Tolerability Outcomes at 6 Weeks

Adverse Event	Frequency (%)	Action Taken
Epigastric Pain (VAS >4)	12 (8.0%)	Dose reduction (5 mg)
Pharyngitis	8 (5.3%)	Symptomatic treatment
Elevated Creatinine (>1.5 mg/dL)	6 (4.0%)	Drug discontinued
Overall Tolerability	124 (82.7%)	—

Table 4: Stratified Analysis of Efficacy by Subgroups

Subgroup	Efficacy Rate (%)	p-value
Age		0.12
≤60 years	46.2%	
>60 years	40.1%	
Gender		0.45
Male	45.6%	

Subgroup	Efficacy Rate (%)	p-value
Female	42.1%	
LVEF		0.03
HFrEF (≤40%)	50.0%	
HFpEF (>40%)	36.5%	

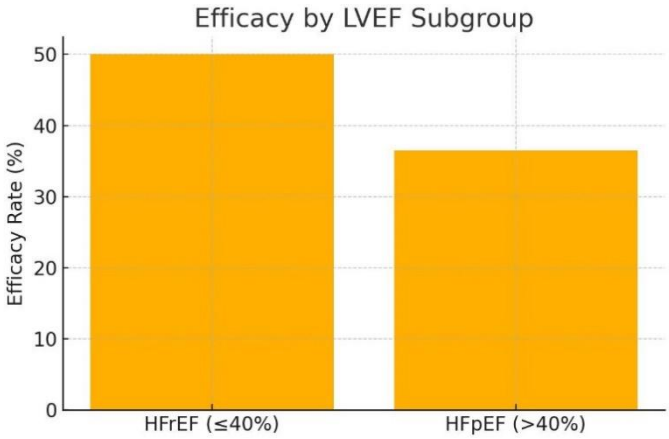

Figure 1 Efficacy by LVEF Subgroup

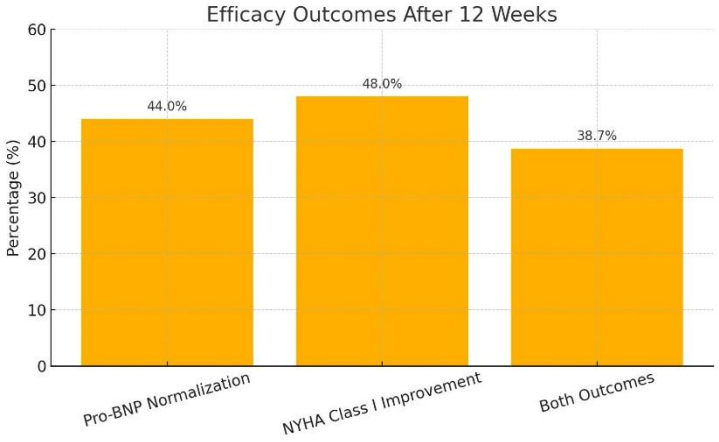

Figure 2 Efficacy Outcomes After 12 Weeks

DISCUSSION

The findings of this study demonstrated that dapagliflozin significantly improved clinical outcomes in non-diabetic patients with heart failure, as evidenced by Pro-BNP normalization in 44% and functional improvement to NYHA Class I in 48% of participants after 12 weeks. These results align closely with previous large-scale trials such as DAPA-HF, reinforcing the expanding therapeutic role of SGLT2 inhibitors beyond glycemic control. The notable efficacy observed particularly in patients with reduced ejection fraction (HFrEF) underscores the pathophysiological relevance of targeting cardiorenal-metabolic pathways in this subgroup, where a 50% response rate was achieved compared to 36.5% in those with preserved ejection fraction (HFpEF), a statistically significant difference ($p = 0.03$). The present study supports existing literature indicating that the cardiovascular benefits of dapagliflozin extend to non-diabetic heart failure populations, particularly in HFrEF, where reductions in hospitalization, symptom burden, and biomarker levels have been consistently reported (12,13). The clinical effectiveness observed in this study is further strengthened by the favorable tolerability profile, with 82.7% of patients experiencing no major adverse events. Minor side effects, such as epigastric discomfort and transient pharyngitis, were manageable and did not necessitate permanent discontinuation in most cases, corroborating earlier findings that dapagliflozin maintains a strong safety margin (14,15). Subgroup analyses also revealed no significant differences in efficacy based on age or gender, which is consistent with previously published results suggesting that the cardiovascular benefits of dapagliflozin are broadly applicable across diverse demographic categories (16). Additionally, improvements in vascular endothelial function and cardiovascular event reduction observed in other investigations are mirrored by the trend seen in this cohort, reinforcing the hypothesis of pleiotropic effects of SGLT2 inhibitors (17,18). The results further align with trials such as DECLARE-TIMI 58 and DAPA-CKD, where dapagliflozin demonstrated reductions in both heart failure-related events and renal decline, providing multidimensional benefits to cardiorenal patients (19).

Despite these promising outcomes, the study also identified limitations that must be acknowledged. The single-center, non-randomized design limits the generalizability of the findings, and the short 12-week follow-up period may not fully capture long-term outcomes or adverse effects. Furthermore, while the study excluded diabetic patients to isolate the effect of dapagliflozin in heart failure, this narrow focus omits a broader HF population that could benefit from such therapy. Additionally, eligibility criteria excluded patients with severely impaired renal function or hypotension, which are known barriers to SGLT2 inhibitor use in clinical practice, and may limit the applicability of these findings to more complex patient groups (20,21). Real-world variations such as higher prevalence of atrial fibrillation or differing baseline characteristics may further affect external validity (22). Nonetheless, the study's strengths lie in its real-

world clinical relevance, structured follow-up intervals, and well-defined endpoints, allowing for meaningful interpretation of both efficacy and safety in a focused patient population. Future studies should consider longer follow-up durations, inclusion of multicenter cohorts, and head-to-head comparisons with other guideline-directed therapies to further clarify dapagliflozin's position within comprehensive heart failure management. Moreover, mechanistic investigations exploring its role in HFpEF, where efficacy remains comparatively limited, may open avenues for more targeted therapies. Overall, this study contributes to the growing body of evidence supporting the integration of dapagliflozin as a standard component in heart failure treatment regimens, even among those without diabetes.

CONCLUSION

This study concludes that dapagliflozin offers a clinically effective and well-tolerated treatment option for non-diabetic patients with heart failure, particularly those with reduced ejection fraction. Its ability to improve both functional capacity and biomarker profiles supports its growing role in heart failure management, independent of glycemic status. The findings reinforce existing evidence and highlight the drug's potential to positively influence patient outcomes when integrated into standard therapy. While its safety profile remains favorable, continued patient monitoring is essential to address any emerging side effects. Future investigations should aim to evaluate long-term efficacy and broaden the evidence base for its use across varied heart failure subtypes, including those with preserved ejection fraction.

AUTHOR CONTRIBUTION

Author	Contribution
Shah Jihan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Mahboob Ur Rehman	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Yasir Ashraf	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Asif Nawaz Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Nouman Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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