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COMPARISON OF SGLT2 INHIBITORS AND DPP4 INHIBITORS IN DIABETIC PATIENTS WITH HEART FAILURE

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Abstract

Introduction: *Type 2 diabetes mellitus (T2DM) markedly elevates the risk of cardiovascular problems, including heart failure (HF). Although sodium-glucose co-transporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP4i) are frequently utilized for glycemic management, their relative effects on clinical outcomes in diabetic patients with heart failure have not been well assessed in local contexts.*

Objectives: *To compare the outcome of DPP4 inhibitor and SGLT2 inhibitor among diabetic patients presenting with heart failure in a tertiary care hospital.*

Subjects & Methods: *This randomized clinical trial was performed in the Department of Cardiology, Fauji Foundation Hospital in Rawalpindi. 452 individuals aged 40 to 80 years with T2DM and clinically proven heart failure were randomized into two equal groups: Group A received dapagliflozin 10 mg daily (SGLT2 inhibitor), and Group B received vildagliptin 50 mg twice day (DPP-4 inhibitor). Patients were monitored biweekly. The primary outcomes included hospitalization due to heart failure and cardiovascular or cerebrovascular consequences. Data were evaluated utilizing SPSS Version 25, employing a Chi-square test for comparison; $p < 0.05$ was deemed significant.*

Results. *Hospitalization due to heart failure was observed in 29.6% of individuals in the SGLT2i group compared to 50.0% in the DPP4i sample ($p < 0.001$). Hospitalization due to cardiovascular or cerebrovascular events was reduced in the SGLT2i group (6.2% compared to 14.2%). Hospitalization was not found in 64.2% of SGLT2i users, in contrast to 35.8% of DPP4i users. The advantages of SGLT2i treatment were consistent among subgroups categorized by gender, age, BMI, ejection fraction, and disease duration.*

Conclusions: *SGLT2 inhibitors markedly reduce hospitalization rates for heart failure and cardiovascular/cerebrovascular incidents in diabetic patients with*

heart failure when compared to DPP4 inhibitors. These findings endorse the preferential utilization of SGLT2 inhibitors for cardiovascular protection in this high-risk demographic.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both.[1] As the global prevalence of diabetes continues to rise, so does the incidence of its numerous complications, including cardiovascular diseases such as myocardial infarction (MI), heart failure and cardiomyopathies. Globally, diabetes affects approximately 463 million people, a number projected to rise to 700 million by 2045.[2] Frequency of heart failure among diabetic patients ranges from 10-47% worldwide.[3] According to the International Diabetes Federation, in 2022, 26.7% of adults in Pakistan are affected by diabetes making the total number of cases approximately 33,000,000.[4] In diabetes, chronic hyperglycemia leads to endothelial dysfunction, oxidative stress, and inflammation, which contribute to the development of atherosclerosis and coronary artery disease. These vascular complications can precipitate heart failure by impairing myocardial perfusion and function.[5]

DPP4 inhibitors are a class of oral hypoglycemic agents that enhance the incretin system by inhibiting the enzyme dipeptidyl peptidase-4. The pros of DPP4 inhibitors include effective glucose control without causing significant hypoglycemia, weight neutrality, and a generally safe cardiovascular profile. However, their modest efficacy compared to other antidiabetic drugs, potential risk of pancreatitis, and controversy regarding heart failure risk are notable cons.[6] SGLT2 inhibitors are a newer class of antidiabetic medications that lower blood glucose levels by inhibiting the sodium-glucose co-transporter 2 in the proximal renal tubules. This inhibition prevents glucose reabsorption and promotes its excretion in urine. The pros of SGLT2 inhibitors include significant cardiovascular benefits, such as reduced risk of heart failure hospitalization and cardiovascular death, weight loss, blood pressure reduction, and potential renal protective benefits. However, these drugs are associated with an increased risk of genitourinary tract infections and volume depletion leading to hypotension, especially in elderly patients or those with renal impairment.[7] SGLT2 inhibitors have shown promising results in reducing heart failure hospitalizations and cardiovascular mortality, but their side effect profile necessitates careful patient selection and monitoring. On the other hand, DPP4 inhibitors, while generally safe, have shown mixed results regarding their impact on heart failure, highlighting the need for more focused research.[8]

Both DPP4i and SGLT2i offer distinct mechanisms of action and potential benefits and routinely prescribed to the diabetic patients by our local physicians, but their comparative outcome among diabetic patients with heart failure has not been fully elucidated. This study aims to fill this gap by providing evidence-based insights that can guide clinical decision-making. This study will contribute to the growing body of literature by comparing the efficacy, safety, and overall outcomes of SGLT2i versus DPP4i in diabetic patients with heart failure. By identifying the most effective treatment strategies, we aim to improve the quality of life and clinical outcomes for these vulnerable patient population, ultimately reducing the burden of associated mortality

and morbidity among our local diabetic population presenting with heart failure.

MATERIALS AND METHODS

This randomized clinical trial was conducted at the Department of Cardiology, Fauji Foundation Hospital, Rawalpindi, from January 2025 to June 2025 following the approval of the research synopsis by the institutional review board. The study aimed to compare the clinical outcomes of SGLT2i and DPP4i in patients with T2DM and coexisting heart failure. The study included a total of 452 patients, with 226 patients assigned to each of the two treatment groups. The sample size was calculated using the WHO sample size calculator, assuming a 5% significance level and 80% power of the test. Anticipated event proportions for hospitalization due to cardiovascular or cerebrovascular complications were based on Gonzalez J et al study; 5.75% for the SGLT2i group and 10.9% for the DPP4i group. A non-probability consecutive sampling technique was employed for patient recruitment. Eligible participants were male or female patients aged 40 to 80 years, diagnosed with T2DM for at least one year, and fulfilling the Framingham diagnostic criteria for heart failure. Patients were excluded if they had previously used either SGLT2i or DPP4i, had end-stage liver or kidney disease, valvular or congenital heart disease, constrictive pericarditis, known hypersensitivity to either drug class, were pregnant or lactating, or were lost to follow-up. A thorough clinical history and physical examination were conducted to assess eligibility based on inclusion and exclusion criteria. Baseline investigations included echocardiography to determine left ventricular ejection fraction, which was categorized as either preserved (≥50%) or reduced (<50%). Patients were randomly allocated into two groups using a lottery method. Group A received dapagliflozin 10 mg once daily, while Group B received vildagliptin 50 mg twice daily. Only one standard drug per group was used to eliminate variability in treatment response. Patients were followed up every two weeks for a total duration of four months or until a study-defined outcome occurred, whichever came first. Outcomes such as heart failure hospitalization was defined as admission to the coronary care unit due to worsening of heart failure, as evidenced by new or worsening major or minor criteria from the Framingham definition, accompanied by echocardiographic evaluation and treatment with intravenous diuretics (furosemide or tolvaptan) within 24 hours of admission; cardiovascular or cerebrovascular complications were diagnosed based on clinical presentation and confirmed through ECG (for MI) or CT brain (for stroke), following standard diagnostic criteria. All data were entered and analyzed using IBM SPSS Version 25. Quantitative variables were reported as mean ± standard deviation and qualitative variables were reported as frequencies and percentages. Comparative analysis between the two treatment groups was conducted using the Chi-square test, and a p-value ≤0.05 was considered statistically significant. To control for potential effect modifiers stratification was performed, followed by post-stratification Chi-square testing to assess the significance of associations within subgroups.

RESULTS

The study population was uniformly allocated between treatment arms (n=226 each), exhibiting comparable baseline characteristics with a mean age of 59.3±11.3 years, BMI of 27.9±5.1 kg/m², and a diabetes duration of 6.4±2.3 years. The SGLT2i

group had a higher prevalence of recent-onset heart failure cases (27.4% vs 19.9% with a period of ≤1 year). Table 2 illustrates a comprehensive examination of both quantitative and qualitative clinical and demographic characteristics. The primary outcome analysis indicated the greater efficacy of SGLT2 inhibitors, showing a 40.8% relative reduction in heart failure hospitalizations and a 56.3% decrease in the incidence of cardiovascular and cerebrovascular events. The number needed to treat with SGLT2 inhibitors to prevent one hospitalization for heart failure was 5, with 64.2% remaining free of hospitalization compared to 35.8% in the DPP4 inhibitors group ($p<0.001$). Figure 1 elucidates the detailed outcomes. Stratified analysis revealed markedly reduced hospitalization rates for heart failure and cardiovascular/cerebrovascular events in the SGLT2i group across the majority of demographic and clinical subgroups. The effect was consistently significant across gender, age, BMI classifications, and ejection fraction status. Females demonstrated notably strong responses to SGLT2 inhibitors ($p<0.001$), while males also exhibited considerable enhancement ($p=0.013$). The therapeutic benefit was most significant in patients aged 56-70 years ($p<0.001$) and in those with intact ejection fraction ($p<0.001$). Subgroup analysis indicated that individuals with shorter periods of diabetes or heart failure derived significant benefits from SGLT2 inhibitors, notably in terms of decreased hospitalization rates. A comprehensive stratification analysis based on demographic and clinical confounders of this research is presented in Tables 3 and 4.

Table 1: Mean ± Standard deviations for the quantitative variables in both groups

Variable	Group A (SGLT2i) (n=226)	Group B (DPP4i) (n=226)	Total (n=452)
Age (Years)	58.65 ± 10.86	60.03 ± 11.78	59.34 ± 11.33
BMI (kg/m²)	28.18 ± 4.99	27.65 ± 5.14	27.91 ± 5.07
Duration of T2DM (Years)	6.35 ± 2.36	6.34 ± 2.28	6.35 ± 2.32
Duration of HF (Years)	2.57 ± 1.23	2.66 ± 1.17	2.62 ± 1.20

Table 2: Distribution of study population in various demographic and clinical categories

Study Variables		Study Groups		Total (n=452)
		Group A (SGLT2i) (n=226)	Group B (DPP4i) (n=226)	
Gender	**Female**	150 (66.4%)	149 (65.9%)	299 (66.2%)
	Male	76 (33.6%)	77 (34.1%)	153 (33.8%)
Age Groups	**40-55 Years**	90 (39.8%)	86 (38.1%)	176 (38.9%)

	56-70 Years	95 (42.0%)	82 (36.3%)	177 (39.2%)
	>70 Years	41 (18.1%)	58 (25.7%)	99 (21.9%)
BMI Groups	≤24.9 kg/m²	69 (30.5%)	67 (29.6%)	136 (30.1%)
	25-29 kg/m²	64 (28.3%)	74 (32.7%)	138 (30.5%)
	>29 kg/m²	93 (41.2%)	85 (37.6%)	178 (39.4%)
Ethnicity	Punjabi	110 (48.7%)	99 (43.8%)	209 (46.2%)
	Pathan/Tribal	47 (20.8%)	48 (21.2%)	95 (21.0%)
	Balochi	15 (6.6%)	17 (7.5%)	32 (7.1%)
	Sindhi	34 (15.0%)	41 (18.1%)	75 (16.6%)
	Kashmiri	20 (8.8%)	21 (9.3%)	41 (9.1%)
Ejection Fraction Category	Reduced (<50%)	58 (25.7%)	65 (28.8%)	123 (27.2%)
	Preserved (≥50%)	168 (74.3%)	161 (71.2%)	329 (72.8%)
T2DM Duration	<5 Years	51 (22.6%)	52 (23.0%)	103 (22.8%)
	5-8 Years	133 (58.8%)	131 (58.0%)	264 (58.4%)
	>8 Years	42 (18.6%)	43 (19.0%)	85 (18.8%)
Duration of Heart Failure	≤1 Year	62 (27.4%)	45 (19.9%)	107 (23.7%)
	1-3 Years	103 (45.6%)	124 (54.9%)	227 (50.2%)
	>3 Years	61 (27.0%)	57 (25.2%)	118 (26.1%)

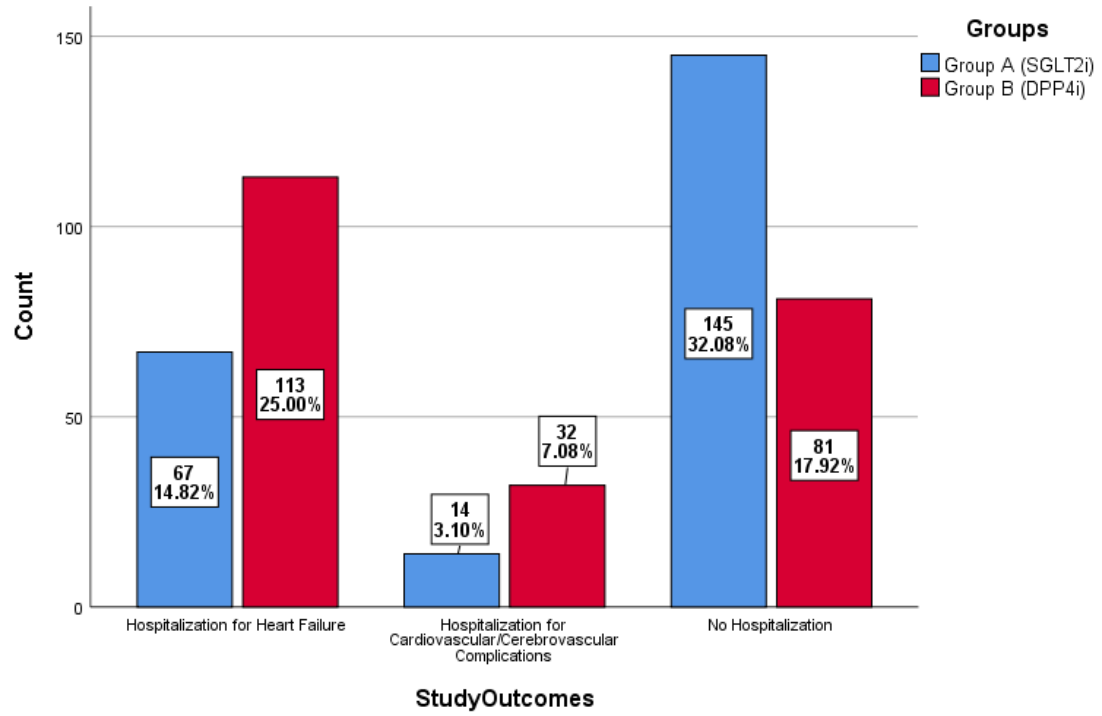

Figure 1: Graphical presentation of frequency of study outcomes in both groups

Table 3: Stratification on the basis of demographic effect modifiers

Demographic Variables	Study Outcome	Study Groups		*p*-Value Chi-square test
		Group A (SGLT2i) (n=226)	Group B (DPP4i) (n=226)	
Gender				
Female N=299	Hospitalization for HF	39/150 (26.0%)	73/149 (49.0%)	<0.001
	Hospitalization for CV/CVA Events	10/150 (6.7%)	22/149 (14.8%)	
	No Hospitalization	101/150 (67.3%)	54/149 (36.2%)	
Male N=153	Hospitalization for HF	28/76 (36.8%)	40/77 (51.9%)	0.013
	Hospitalization for CV/CVA Events	4/76 (5.3%)	10/77 (13.0%)	
	No Hospitalization	44/76 (57.9%)	27/77 (35.1%)	
Age Groups				
40-55 Years N=176	Hospitalization for HF	28/90 (31.1%)	38/86 (44.2%)	0.009
	Hospitalization for CV/CVA Events	4/90 (4.4%)	11/86 (12.8%)	
	No Hospitalization	58/90 (64.4%)	37/86 (43.0%)	
56-70 Years N=177	Hospitalization for HF	24/95 (25.3%)	39/82 (47.6%)	<0.001
	Hospitalization for CV/CVA Events	7/95 (7.4%)	16/82 (19.5%)	
	No Hospitalization	64/95 (67.4%)	27/82 (32.9%)	
>70 Years N=99	Hospitalization for HF	15/41 (36.6%)	36/58 (62.1%)	0.025
	Hospitalization for CV/CVA Events	03/41 (7.3%)	05/58 (8.6%)	
	No Hospitalization	23/41 (56.1%)	17/58 (29.3%)	
BMI Groups				
≤24.9 kg/m² N=136	Hospitalization for HF	20/69 (29.0%)	35/67 (52.2%)	0.008
	Hospitalization for CV/CVA Events	5/69 (7.2%)	7/67 (10.4%)	
	No Hospitalization	44/69 (63.8%)	25/67 (37.3%)	
25-29 kg/m² N=138	Hospitalization for HF	21/64 (32.8%)	31/74 (41.9%)	0.028
	Hospitalization for CV/CVA Events	4/64 (6.3%)	13/74 (17.6%)	
	No Hospitalization	39/64 (60.9%)	30/74 (40.5%)	
>29 kg/m² N=178	Hospitalization for HF	26/93 (28.0%)	47/85 (55.3%)	<0.001
	Hospitalization for	05/93 (5.4%)	12/85 (14.1%)	

	CV/CVA Events			
	No Hospitalization	62/93 (66.7%)	26/85 (30.6%)	
Ethnicity				
Punjabi N=209	Hospitalization for HF	33 (30.0%)	53 (53.5%)	<0.001
	Hospitalization for CV/CVA Events	4 (3.6%)	16 (16.2%)	
	No Hospitalization	73 (66.4%)	30 (30.3%)	
Pathan/Tribal N=95	Hospitalization for HF	11 (23.4%)	22 (45.8%)	0.072
	Hospitalization for CV/CVA Events	7 (14.9%)	5 (10.4%)	
	No Hospitalization	29 (61.7%)	21 (43.8%)	
Sindhi N=75	Hospitalization for HF	11 (32.4%)	24 (58.5%)	0.007
	Hospitalization for CV/CVA Events	1 (2.9%)	5 (12.2%)	
	No Hospitalization	22 (64.7%)	12 (29.3%)	
Balochi N=32	Hospitalization for HF	5 (33.3%)	5 (29.4%)	0.877
	Hospitalization for CV/CVA Events	1 (6.7%)	2 (11.8%)	
	No Hospitalization	9 (60.0%)	10 (58.8%)	
Kashmiri N=41	Hospitalization for HF	7 (35.0%)	9 (42.9%)	0.243
	Hospitalization for CV/CVA Events	1 (5.0%)	4 (19.0%)	
	No Hospitalization	12 (60.0%)	8 (38.1%)	

Table 4: Stratification on the basis of clinical effect modifiers

Clinical Variables	Study Outcome	Study Groups		*p*-Value Chi-square test
		Group A (SGLT2i) (n=226)	Group B (DPP4i) (n=226)	
Ejection Fraction Category				
Reduced (<50%) N=123	Hospitalization for HF	27/58 (46.6%)	34/65 (52.3%)	0.004
	Hospitalization for CV/CVA Events	0/58 (0.0%)	9/65 (13.8%)	
	No Hospitalization	31/58 (53.4%)	22/65 (33.8%)	
Preserved (≥50%) N=329	Hospitalization for HF	40/168 (23.8%)	79/161 (49.1%)	<0.001
	Hospitalization for CV/CVA Events	14/168 (8.3%)	23/161 (14.3%)	
	No Hospitalization	114/168 (67.9%)	59/161 (36.6%)	
T2DM Duration				
<5 Years N=103	Hospitalization for HF	12/51 (23.5%)	29/52 (55.8%)	0.003
	Hospitalization for CV/CVA Events	3/51 (5.9%)	3/52 (5.8%)	
	No Hospitalization	36/51 (70.6%)	20/52 (38.5%)	

5-8 Years N=264	Hospitalization for HF	43/133 (32.3%)	57/131 (43.5%)	<0.001
	Hospitalization for CV/CVA Events	2/133 (1.5%)	19/131 (14.5%)	
	No Hospitalization	88/133 (66.2%)	55/131 (42.0%)	
>8 Years N=85	Hospitalization for HF	12/42 (28.6%)	27/43 (62.8%)	0.001
	Hospitalization for CV/CVA Events	9/42 (21.4%)	10/43 (23.3%)	
	No Hospitalization	21/42 (50.0%)	6/43 (14.0%)	
Duration of Heart Failure				
Upto 1 Year N=107	Hospitalization for HF	11/62 (17.7%)	27/45 (60.0%)	<0.001
	Hospitalization for CV/CVA Events	5/62 (8.1%)	5/45 (11.1%)	
	No Hospitalization	46/62 (74.2%)	13/45 (28.9%)	
1-3 Years N=227	Hospitalization for HF	34/103 (33.0%)	59/124 (47.6%)	<0.001
	Hospitalization for CV/CVA Events	5/103 (4.9%)	20/124 (16.1%)	
	No Hospitalization	64/103 (62.1%)	45/124 (36.3%)	
>3 Years N=118	Hospitalization for HF	22/61 (36.1%)	27/57 (47.4%)	0.159
	Hospitalization for CV/CVA Events	4/61 (6.6%)	7/57 (12.3%)	
	No Hospitalization	35/61 (57.4%)	23/57 (40.4%)	

DISCUSSION

This randomized clinical trial provides compelling evidence that SGLT2 inhibitors (SGLT2i) significantly outperform DPP4 inhibitors (DPP4i) in reducing adverse cardiovascular outcomes among diabetic patients with heart failure (HF). The findings align with and extend prior research, reinforcing SGLT2i as a cornerstone therapy in this high-risk population. Below, we contextualize our results, explore mechanistic insights, and discuss clinical implications while addressing study limitations. Our study demonstrated a 40.8% relative risk reduction (RRR) in HF hospitalizations with SGLT2i, corroborating landmark trials such as DAPA-HF and EMPEROR-Reduced, which reported nearly similar RRR in HF-related events.[9,10] Notably, our cohort included a substantial proportion of northern Pakistan, a population underrepresented in prior trials, yet the benefits remained robust. The 56.3% lower incidence of cardiovascular/cerebrovascular complications further supports the cardioprotective effects of SGLT2i, consistent with meta-analyses showing reduced major adverse cardiovascular events.[11,12] Our study findings are in line with past studies. In recent study, Gonzalez J et al in their study compared the cardiovascular outcomes with SGLT2 inhibitors versus DPP4 inhibitors among diabetic patients with heart failure and they reported that rehospitalization due to HF was higher in patients with DPP4i (n=5567/11,379;48.92%) in comparison with those who used SGLT2i (n=704/2503;28.13%). Similarly, hospitalization due to cerebrovascular complications was also lesser (n=144/2503;5.75%) in patients who were taking SGLT2i in comparison with those

who were taking DPP4i (n=1240/11,379;10.9%).[13]

The superiority of SGLT2i may stem from their pleiotropic effects beyond glycemic control which promote natriuresis and osmotic diuresis, reducing ventricular preload and filling pressures, which is critical in HF management. Moreover, by shifting myocardial fuel utilization from glucose to ketones, SGLT2i enhance cardiac efficiency and reduce oxidative stress. Last but not the least, these agents attenuate pro-inflammatory cytokines (e.g., IL-6, TNF-α) and inhibit myocardial fibrosis, potentially reversing adverse remodeling.[14,15] In contrast, DPP4i lack these multidimensional benefits. While they improve glycemic control via incretin potentiation, some agents have been associated with increased HF risk, possibly due to neurohormonal activation or endothelial dysfunction.[16,17]

Stratified analysis in our study further revealed that SGLT2i benefits were consistent across most subgroups. Females on SGLT2i experienced significantly fewer hospitalizations than their DPP4i counterparts, and similar trends were noted among males and various age brackets. This supports the gender and age-independent efficacy of SGLT2 inhibitors in reducing adverse cardiovascular outcomes.[18] Importantly, the SGLT2i group also had lower hospitalization rates across all BMI categories. The weight-neutral or even weight-reducing properties of SGLT2 inhibitors might have played a role here, especially considering the high proportion of patients with BMI >29 kg/m^2.[19,20] Furthermore, patients with preserved ejection fraction (HFpEF) particularly benefited from SGLT2i, with hospitalization rates significantly lower than those receiving DPP4i. These findings highlight the emerging role of SGLT2 inhibitors in HFpEF management, as supported by recent landmark trials like EMPEROR-Preserved and DELIVER.[21,22] Another key observation was the time-dependent advantage of SGLT2i therapy. Patients with shorter durations of diabetes or heart failure had markedly better outcomes on SGLT2 inhibitors. This suggests that early initiation of SGLT2i may halt or slow down the pathophysiologic progression of diabetic cardiomyopathy, supporting the idea of earlier implementation of these agents in high-risk diabetic populations.[23,24] Ethnic variation analysis also revealed significant disparities. While the Punjabi and Sindhi subgroups showed statistically meaningful benefits with SGLT2i, differences among Pathan, Balochi, and Kashmiri populations were not significant. These ethnic disparities may be due to sample size variations or potential differences in genetic, cultural, or socio-economic factors influencing drug response or healthcare access and warrant further exploration in larger, multi-center trials.

Our findings robustly advocate for the preferential utilization of SGLT2 inhibitors over DPP4 inhibitors in diabetic patients with heart failure, particularly in mitigating hospitalization risk. SGLT2 inhibitors should be regarded as first-line treatments in this high-risk population because to their supplementary advantages on weight, blood pressure, and renal function, in accordance with the current heart failure therapy guidelines established by the American College of Cardiology (ACC) and the European Society of Cardiology (ESC).

Limitations:

This research was performed in a singular tertiary care facility with a non-probability sampling technique, perhaps constraining the generalizability of the results. Moreover, despite the randomization

of patients and the blinding of outcome assessment, unmeasured variables may have nevertheless affected the results. The follow-up period was restricted to four months; further trials are required to evaluate the long-term efficacy and safety of these medicines. Finally, this trial did not assess medication adherence, adverse effects, or quality-of-life indicators, all of which are crucial for evaluating therapeutic efficacy.

CONCLUSIONS

This study concluded that SGLT2 inhibitors are more effective than DPP4 inhibitors in decreasing hospitalizations related to heart failure and cardiovascular/cerebrovascular disorders among type 2 diabetes individuals with heart failure. These findings endorse existing worldwide guidelines and promote the wider application of SGLT2 inhibitors in managing this high-risk demographic. Additional long-term, multi-center investigations are advised to corroborate these findings and investigate possible ethnic or genetic factors affecting therapy response.

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