

Dapagliflozin's impact on health-related quality of life and mortality in patients of chronic heart failure with reduced ejection fraction: A randomized controlled trial

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Abstract

Objective: To explore the impact of dapagliflozin on health-related quality of life, functional status and mortality in chronic heart failure with reduced ejection fraction patients.

Method: The randomized controlled trial was conducted from April 2023 to May 2024 at the Department of Pharmacology and Therapeutics, Wah Medical College, National University of Medical Sciences, Islamabad, Pakistan, in collaboration with the National Institute of Heart Diseases, Rawalpindi, and the Pakistan Ordinance Factories Hospital, Wah Cantt, and comprised chronic heart failure with reduced ejection fraction patients who were randomised into two equal groups, with control group A receiving conventional therapy alone, and intervention group B receiving oral dapagliflozin 10mg daily in addition to the conventional therapy. At 3-month follow-up, each patient was subjected to Kansas City Cardiomyopathy Questionnaire for health-related quality of life, the New York Heart Association classification for functional status, and mortality check. Data was analysed using SPSS 31.

Results: Of the 170 patients, 136(80%) were male and 34(20%) were female. There were 85(50%) patients in group A with mean age 64.71 ± 10.07 years and 85(50%) in group B with mean age 62.67 ± 9.75 years. Both the groups showed improvement post-intervention, but group B had significantly more improvement in quality of life ($p=0.048$) and overall summary scores ($p=0.037$). Functional status was better in group B, but the difference was non-significant ($p=0.320$). The trial was completed by 83(98%) patients in group B and 80 (94%) in group A. Mortality was lower in group B 2(2.4%) than in group A 5(5.9%).

Conclusion: Dapagliflozin led to marked improvement in health-related quality of life and reduced mortality in chronic heart failure with reduced ejection fraction patients.

Trial Registration: The trial was registered with the Iranian clinical trial registry under registration number IRCT20230331057788N1 at 2023-04-04.

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Introduction

Heart failure (HF), being a chronic medical illness, is linked to considerable mortality, morbidity and diminished health-related quality of life (HRQoL).¹ The estimated count of congestive heart failure (CHF) patients is 28 million in Pakistan. Besides the prevalence of coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM), South Asian nations are more likely to experience HF at an earlier age than other racial/ethnic groups.² Patients with chronic HF

reduced ejection fraction (CHFrEF) usually suffer from various symptoms, including fatigue, oedema, dyspnoea, orthopnoea and decreased exercise tolerance, which can have noteworthy effects on their daily functioning and health status.³ Although traditional pharmacotherapies have majorly focussed on improving clinical outcomes, there is a growing trend towards recognition of patient-reported symptoms, physical limitations and overall HRQoL as essential components in comprehensive HF management. Improving HRQoL is a fundamental goal in CHF management.⁴

The conventional Guideline Directed Medical Therapy (GDMT) for CHFrEF patients include angiotensin converting enzyme inhibitor (ACEi)/Angiotensin receptor blockers (ARBs)/Angiotensin receptor-neprilysin inhibitor (ARNi), diuretics, beta-blockers (β -blockers), mineralocorticoid receptor antagonists (MRAs), hydralazine, long-acting nitrates and ivabradine. The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study revealed a promising role of dapagliflozin treatment in

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significant reduction of mortality and recurrent hospitalisations in CHF_{REF} patients, and the latest American Heart Association (AHA) guidelines also give recommendation for use of dapagliflozin in CHF_{REF} patients.⁵

Dapagliflozin is a promising sodium-glucose co-transporter-2 inhibitor (SGLT2i) initially developed for managing DM. Regardless of patients' DM status, dapagliflozin has shown great cardiovascular benefits in CHF_{REF}, and a significant impact on glycaemic control.⁶ Dapagliflozin has shown beneficial cardiovascular outcomes, including reduction in HF hospitalisations and cardiovascular mortality, as proven by landmark trials.^{6,7} Despite the fact that such trials have provided invaluable insights concerning the overall safety and clinical efficacy of dapagliflozin, scarcity of data is present regarding its effect on health status, patient-reported outcomes (PROs) and HRQoL in CHF_{REF} patients, mainly in diverse races, such as those in Pakistan and South Asia at large. Given the socioeconomic, cultural and healthcare system variations in Pakistan, it is crucial to evaluate the impact of dapagliflozin on PROs and HRQoL in patients having CHF_{REF}.

Kansas City Cardiomyopathy Questionnaire (KCCQ-23) is a standardised tool to record and assess HF patients' symptoms, PROs and HRQoL.⁸ Despite its proven effectiveness in clinical practice and research, no data exists, to our knowledge, about the use of the KCCQ-23 questionnaire to evaluate the efficacy of dapagliflozin on PROs, QoL and mortality in CHF_{REF} patients in Pakistan. The current study was planned to fill the gap in literature by exploring the impact of dapagliflozin on HR-QoL, functional status and mortality in CHF_{REF} patients.

Patients and Methods

The prospective, randomised controlled trial (RCT) was conducted from April 2023 to May 2024 at the Department of Pharmacology and Therapeutics, Wah Medical College, National University of Medical Sciences (NUMS), Islamabad, Pakistan, in collaboration with the National Institute of Heart Diseases NIHD), Rawalpindi, and the Pakistan Ordinance Factories Hospital (POFH), Wah Cantt. Each enrolled participant was followed up for a fixed duration of 3 months. After approval from the institutional ethics review committee, the sample size was calculated in the light of literature which suggests that HF prevalence ranges from 1% to 12% in different populations, and the risk increases among those aged >65 years.⁹ The calculation was based on the primary outcome of change in HRQoL assessed by the KCCQ-23 overall summary (KCCQ-OS) score. Presuming a minimal clinically important intergroup

difference (MCID) of 5 points, a standard deviation (σ) of change of around 15 points based on earlier HF studies, a two-sided alpha (α) of 0.05, and 80% power, approximately 71 patients in each group were required. Keeping in view potential attrition, 85 CHF_{REF} patients were enrolled in each group.^{6,10}

The sample size formula used was:
$$= \frac{2SD^2 (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

in which standard deviation (SD) was based on previous studies^{6,7,11,12} $Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (From the Z table) at type 1 error of 5%; $Z_{\beta} = Z_{0.20} = 0.842$ (From the Z table) at 80% power; and d = effect size = difference between mean values = 5.

Inclusion criteria comprised both diabetic and non-diabetic, male and female Pakistani patients aged >18 years who had been diagnosed with symptomatic HF with New York Heart Association (NYHA) class 1-IV¹³ during the preceding 12 months and had an EF of $\leq 40\%$ on imaging, and had received conventional HF therapy for ≥ 4 weeks. Pregnant and nursing mothers, people with type-1 diabetes or patients with any history of diabetic ketoacidosis (DKA), systolic blood pressure (SBP) <95mmHg, estimated glomerular filtration rate (eGFR) <25ml/min/1.73m² [Calculated using Chronic Kidney Disease Epidemiology Collaboration, (CKD-EPI) formula],¹⁴ myocardial infarction (MI), unstable angina, stroke, any malignancy, hepatic impairment, severe Chronic Obstructive Pulmonary disease (COPD) leading to dyspnoea, acute HF or hospitalisation for acute HF within four weeks preceding enrolment were excluded.¹¹ The criteria¹⁵ outlined by the Declaration of Helsinki were followed, and the randomization and allocation procedures were in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.¹⁶ The random allocation sequence was generated using computer-generated random numbers by an independent investigator not involved in patient recruitment or outcome assessment. Participants fulfilling the eligibility criteria were enrolled by the attending physician. Intervention assignment and randomisation into either control or dapagliflozin group was carried out after enrollment according to the pre-generated randomisation list by the attending physician and a research assistant.

Patients in control group A received only conventional therapy as per the recommended clinical guidelines,⁵ while patients in dapagliflozin group B received 10 mg dapagliflozin along with conventional therapy. Demographic data, personal medical history, baseline laboratory investigations, and EF on echocardiography were recorded on day 0.

The principal investigator followed up the patients after three months by conducting interviews to assess improvements in HRQoL and PROs using KCCQ-23¹² and NYHA functional classification to evaluate changes in functional symptoms.¹³

The KCCQ-23 evaluates PROs and HRQoL in HF patients. It is a valid and reliable tool that assesses physical limitations, symptoms' stability, burden and frequency, self-efficacy as physical limitation score (PLS), social restriction as social limitation score (SLS), and QoL domains. The total symptom score (TSS) is derived from the symptoms' frequency and burden domain. The clinical summary score (CSS) comprises TSS and PLS. The overall summary score (OSS), which reflects the primary health status, combines scores of TSS, CSS, QoL and SLS. It is a standardised, self-administered, patient-reported outcome measure, thereby minimising assessor-related bias.¹²

The primary outcome was changes from baseline in pre-specified KCCQ-23 domains of PLS, TSS, CSS, QoL and OSS. The secondary outcome was to evaluate the changes in the NYHA functional class, and to record the mortality rate of patients in the two groups. The recall period for all patients was standardised to the preceding two weeks. On a 0-100 scale, the KCCQ-23 evaluates PROs and HRQoL, with higher scores indicating better HRQoL.¹²

Data was analysed using SPSS 31. Numerical variables were summarised using median with interquartile range (Q1,Q3) and mean $\pm$ standard deviation (SD). Categorical variables were presented as frequencies and percentages. Histogram and Shapiro-Wilk tests were applied to assess data normality. Comparisons between the groups were done using chi-square tests for categorical variables, independent sample *t*-tests for normally distributed data, and Mann-Whitney U tests for non-normally distributed data. A responder analysis was performed by applying ordinal logistic regression for each KCCQ-23 domain to compare the groups. The treatment effect was mentioned as common odds ratio (OR) with 95% confidence interval (CI). NYHA class was also analysed using ordinal logistic regression. Improvement in NYHA class was compared by using Pearson chi-square test. Mortality was reported using Fisher's Exact test. Additionally, a general linear model (GLM) procedure was applied to evaluate the efficacy of dapagliflozin compared to the control group on KCCQ-OS score over 3 months among different subgroups, including clinical and demographic characteristics in terms of treatment-by-subgroup interaction. The results were presented using a forest plot to illustrate the mean effects and 95% CIs. All tests were two-tailed, and $p \leq 0.05$ was considered statistically significant.

Results

Of the 440 patients screened, 170(%) were included; 85(50%) in each group (Figure 1).

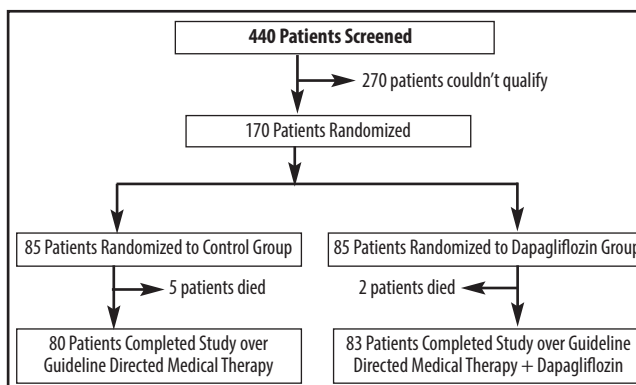


Figure-1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

The overall mean age was 63.69 ± 9.94 years, with 98(57.6%) patients aged ≤ 65 years and 72(42.4%) aged > 65 years. Of the 170 patients, 136(80%) were male and 34(20%) were female. The mean age in group A was 64.71 ± 10.07 years and it was 62.67 ± 9.75 years in group B. This sample comprised various ethnicities, with the majority being Punjabis 127(74.7%), followed by Pathans 16(9.4%), Kashmiris 11(6.5%) and Urdu-speaking 10(5.9%). Among the participants, 131(77%) patients had a history of hypertension (HTN), 151(88.8%) had ischaemic heart disease (IHD), 18(10.6%) had stroke, and 54(31.8%) had TDM. Regarding smoking status, 28(16.5%) were current smokers, 14(8%) were former smokers, and 128(75%) were non-smokers. Median body mass index (BMI) was 27kg/m² (23.85, 29.15). There were 53(31%) patients with normal weight, and 117(68.85%) were overweight/obese. Median pulse was 74 (72, 80), SBP 122 (110,130), diastolic blood pressure (DBP) 80 (70, 80), left ventricular ejection fraction (LVEF) 30 (25,35), Haemoglobin A1c (HbA1c) 5.90 (5.40, 7.20), creatinine 1.08 (0.90, 1.40), eGFR 72.95 (52, 92.25), B-type natriuretic peptide (BNP) 113 (30.50, 328) and N-Terminal pro B-type natriuretic peptide (NT-pro BNP) 769 (282, 20250). NYHA class II symptoms were found to be present in the majority of patients 101(59.4%), followed by class III symptoms 40(23.5 %), class I symptoms 26(15%) and class IV symptoms 3(1.8 %) (Table 1). The trial was completed by 80(94.1%) patients in group A and 83(97.6%) patients in group B (Figure 1). No patient was lost to follow-up except for the 7(4.1%) who died during the trial period.

The primary endpoint was achieved in 83(97.6%) patients in group B and 80(94.1%) patients in the group A at 12 weeks. QoL score showed significant improvement by effect size with 0.15 points ($p=0.048$), and OSS improved by effect size of 0.16 points ($p=0.037$). However, no significant

Table-1: Baseline patient characteristics (n=170).

Baseline Characteristics	Control (n=85) n (%)	Dapagliflozin (n=85) n (%)
Mean Age -(years)	64.71±10.07	62.67±9.75
≤ 65-	45 (52.9)	53 (62.4)
>65	40 (47.1)	32 (37.6)
Gender		
Male	70 (82.4)	66 (77.6)
Female	15 (17.6)	19 (22.4)
Ethnicity		
Punjabi	66 (77.6)	61 (71.8)
Pathan	5 (5.9)	11 (12.9)
Sindhi	0 (0.0)	1 (1.2)
Balochi	0 (0.0)	1 (1.2)
Kashmiri	6 (7.1)	5 (5.9)
Urdu Speaking	7 (8.2)	3 (3.5)
Others	1 (1.2)	3 (3.5)
Medical History		
Hypertension (HTN)	67 (78.8)	64 (75.3)
Ischaemic Heart Disease (IHD)	75 (88.2)	76 (89.4)
Stroke	10 (11.8)	8 (9.4)
Type 2 Diabetes	23 (27.1)	31 (36.5)
Smoking Status		
Current	13 (15.3)	15 (17.6)
Former	7 (8.2)	7 (8.2)
Never	65 (76.5)	63 (74.1)
Physical examination		
Median (Q1, Q3)		
Pulse	72 (70.50, 80)	76 (72, 82)
Systolic BP	120 (110,130)	127(110,130)
Diastolic BP	80 (70,80)	80 (70,80)
BMI, kg/m ²	27 (23.85, 29.15)	27(24.80, 29.79)
BMI Class		
Normal	28(32.9)	25(29.4)
Overweight/Obese	57(67.1)	60(70.6)
Baseline laboratory parameters		
Median (Q1, Q3)		
LVEF, %	33 (25,35)	30 (25,35)
HbA1c, %	5.80 (5.40, 6.85)	5.90(5.50,7.74)
Creatinine, (mg/dl)	1.13 (0.94, 1.45)	1.0 (0.84, 1.35)
eGFR, (ml/min/1.73m ²)	71(50.50, 89.50)	77(56.50, 95)
BNP (pg/ml)	83.50(28, 273.68)	159 (32, 356)
NT-proBNP (pg/ml)	622(285, 1492)	1014(276, 2391)
NYHA Functional Class		
I	12 (14.1)	14 (16.5)
II	53 (62.4)	48 (56.5)
III	19 (22.4)	21 (24.7)
IV	1 (1.2)	2 (2.4)
KCCQ -Median (Q1, Q3)		
KCCQ-PLS	50 (33,58)	50 (33,58)
KCCQ-TSS	75 (60,85)	78 (60,89)
KCCQ-CSS	60 (47.50, 70.50)	63 (50.75,78.75)
KCCQ-QoL	66 (50,75)	66 (50,75)
KCCQ-SLS	50 (50,75)	50 (31, 68)
Mean KCCQ-OSS)	59.74±16.08	58.74±16.71
Baseline CV/HF medicines		
ACEi	14(16.5)	14(16.5)
ARBs	36 (42.4)	26 (30.6)
ARNI	23 (27.1)	28 (32.9)
β-blockers	65 (76.5)	67 (78.8)
Hydralazine	1 (1.2)	0 (0.0)
Long-acting nitrates	42 (49.4)	38(44.7)
MRA	69 (81.2)	68 (80.0)
Loop diuretics	80(94.1)	75(88.2)

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Table-1: Continued from previous column.

Baseline Characteristics	Control (n=85) n (%)	Dapagliflozin (n=85) n (%)
Other diuretics	4(4.7)	3(3.5)
Lipid lowering drugs	76(89.4)	73(85.9)
Anticoagulants	6(7.1)	2(2.4)
Digoxin	2 (2.4)	0(0.0)
Ivabradine	4 (4.7)	3 (3.5)
Glucose lowering drugs in type 2 diabetes patients		
Metformin	5 (5.9)	7 (8.2)
Sulfonylureas	3(3.5)	0 (0.0)
DPP4i	3 (3.5)	5 (5.9)
Insulin	4 (4.7)	5 (5.9)

LVEF: Left ventricular ejection fraction, BMI: Body mass Index, HbA1c: Haemoglobin A1c, BNP: B-type natriuretic peptide, eGFR: Estimated glomerular filtration rate, NT-pro BNP, N-Terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, ACEi: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin receptors blockers, ARNI: Angiotensin receptor neprilysin inhibitor, β-blockers: Beta-blockers, MRA: Mineralocorticoid receptor antagonist, DPP4: Dipeptidyl peptidase-4 inhibitors.

Table-2A: Intergroup comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ) domain scores.

KCCQ Domain	Control Median (Q1,Q3)	Dapagliflozin Median (Q1,Q3)	Effect size (r)	p-value
Δ Physical Limitation Score	12 (-8, 42)	20(0, 50)	0.12	0.106
Δ Clinical Summary Score	0 (-23, 16.5)	0(-13, 18)	0.11	0.169
ΔQuality of Life Score	4(-12, 26)	11(-2, 29)	0.15	0.048*
ΔSocial Limitation Score	0.00(-24, 25)	9(0.00, 29)	0.12	0.106
ΔOverall Summary Score	22(-6, 43.50)	25(0.00,50)	0.160	0.037*

Mann-Whitney u test applied to calculate p-value,
* significant p-value; Values mentioned are median (IQR),

KCCQ Domain	Control (Mean±SD)	Dapagliflozin (Mean±SD)	Effect size (Cohen's d)	p-value
ΔTotal Symptom Score	-4.48±34.49	1.46±31.99	0.18	0.246

t-test applied to calculate p-value; Values mentioned are mean±S.D

Table-2B: Intergroup comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ) domain scores.

KCCQ Domain	Control Median (Q1,Q3)	Dapagliflozin Median (Q1,Q3)	Effect size (r)	p-value
Δ Physical Limitation Score	12 (-8, 42)	20(0, 50)	0.12	0.106
Δ Total Symptom Score	0 (-23, 16.5)	0(-13, 18)	0.08	0.308
Δ Clinical Summary Score	4(-12, 26)	11(-2, 29)	0.11	0.169
ΔQuality of Life Score	0.00(-24, 25)	9(0.00, 29)	0.15	0.048*
Δ Social Limitation Score	22(-6, 43.50)	25(0.00,50)	0.12	0.106
ΔOverall Summary Score	8(-5,24)	18(0.00, 34)	0.16	0.037*

Values mentioned are median (IQR); Mann-Whitney u test applied to calculate p-value, * significant p-value

differences were observed in PLS, TSS, CSS and SLS even though group B showed more improvement compared to Group A (Table 2, Central illustration). These results were consistent among both diabetic and non-diabetic patients as well as across all other subgroups (Figure 2).

Responder analysis for KCCQ-23 domains showed trends favouring dapagliflozin across PLS, CSS, TSS, QoL, SLS and OSS, but ordinal logistic regression analysis revealed that dapagliflozin was not a significant predictor of PLS, TSS, CSS, SLS and OSS outcomes (Table 3, Figure 3). Only QoL

score showed a significant difference, with fewer patients experiencing deterioration in group B 19 (22%) compared to group A 34(40%) ($p=0.014$, OR: 0.48, 95%CI: 0.27-0.86, $\beta=-0.730$). Similarly, higher proportion of patients showed improvement in group B 50 (59%) compared to group A 36 (42%) (Table 3, Figure 3). The proportional odds assumption was satisfied ($p=0.512$), establishing the appropriateness

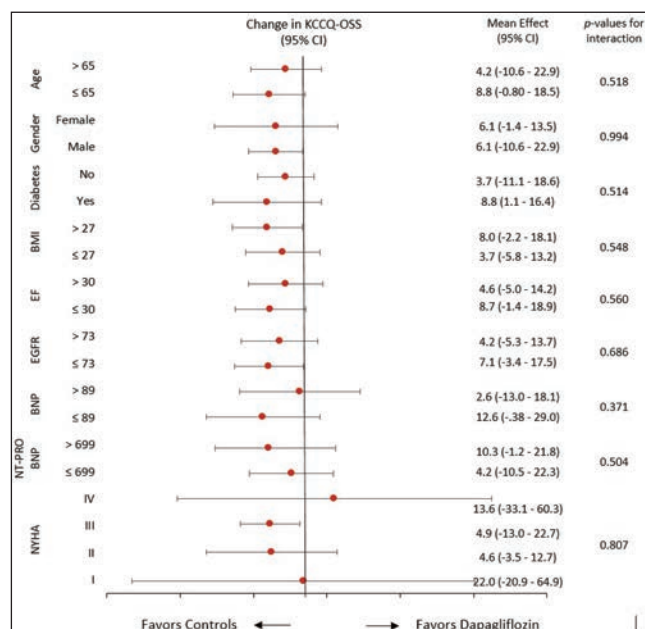


Figure-2: Intergroup comparison of Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS) across various patient subgroups: BMI: Body mass index, LVEF: Left ventricular ejection fraction, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, NT-pro BNP: N-Terminal pro B-type natriuretic peptide, BNP: B-type natriuretic peptide, NYHA: New York Heart Association.

Table-3 Responder analysis for Kansas City Cardiomyopathy Questionnaire (KCCQ) domain between the groups.

KCCQ Domain	Responder Status	Control n(%)	Dapagliflozin n(%)	OR (95% CI)	p-value
Physical Limitation Score	>5 Deterioration	24 (28)	14 (17)	0.64(0.35 – 1.19)	0.158
	No change	11 (13)	14 (17)		
	5+ Improvement	50 (59)	57 (67)		
Total Symptom Score	>5 Deterioration	38 (44.7)	29 (34)	0.69 (0.39 – 1.20)	0.189
	No change	18 (21)	21 (25)		
	5+ Improvement	29 (34)	35 (41)		
Clinical Summary Score	>5 Deterioration	30 (35)	20 (24)	0.62 (0.35 – 1.11)	0.106
	No change	14 (17)	15 (18)		
	5+ Improvement	41 (48)	50 (59)		
Quality of Life Score	>5 Deterioration	34 (40)	19 (22)	0.48 (0.27-0.86)	0.014*
	No change	15 (18)	16 (19)		
	5+ Improvement	36 (42)	50 (59)		
Social Limitation Score	>5 Deterioration	22 (26)	15 (18)	0.63 (0.34 – 1.16)	0.137
	No change	13 (15)	11 (13)		
	5+ Improvement	50 (59)	59 (70)		
Overall Summary Score	>5 Deterioration	23 (27)	19 (22)	0.65 (0.36–1.19)	0.165
	No change	15 (18)	9 (11)		
	5+ Improvement	47 (55)	57 (67)		

Ordinal logistic regression applied, * significant p -value; OR: Odds ratio, CI: Confidence interval.

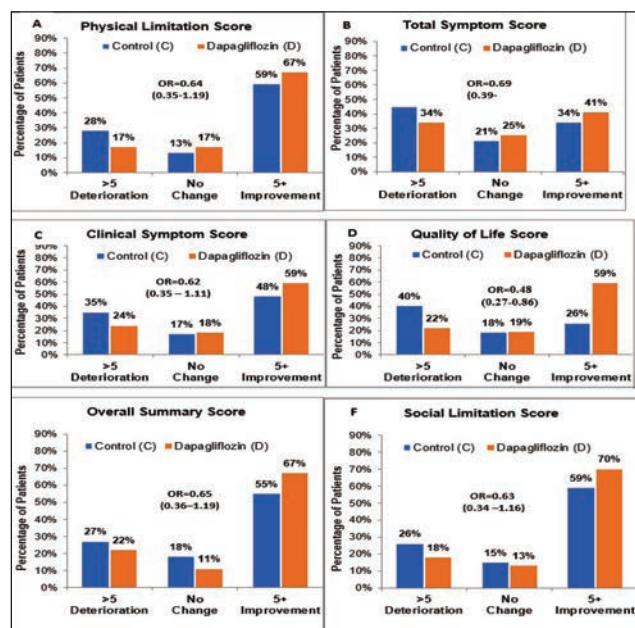


Figure-3: Responder analysis across Kansas City Cardiomyopathy Questionnaire (KCCQ) at 3 months. of the model.

The distribution of CHF_{rEF} patients in the two groups according to NYHA classification was comparable and non-significant at baseline ($p=0.851$) (Table 4). The majority of the participants in both the groups were in NYHA class II (Table 4) at baseline. Ordinal logistic regression revealed no significant difference in NYHA class at 3 months between the groups ($p=0.320$). The calculated OR was non-significant 1.34 (95% CI: 0.75-2.41, $\beta=0.296$). However, a greater proportion of participants in group B improved towards lower NYHA classes, with NYHA I cases being 47(57%) in group B compared to 37 (46%) in group A (Table 4, Figure 4).

There was non-significant association between group B and NYHA improvement ($p=0.357$) even though, a higher percentage of patients improved in group B 44(52%) compared to group A 38 (45%) (Table 4, Figure 4).

There was a non-significant association between group A and mortality ($p=0.443$) even though the mortality rate was lower in group B 2 (2.40%) compared to 5(5.9%) in group A (Table 4).

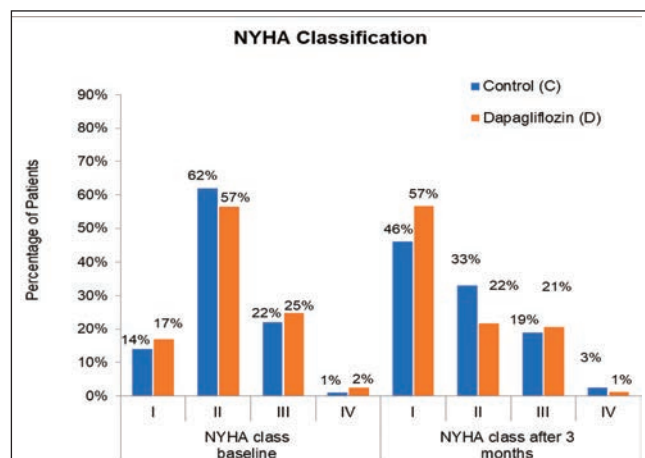
Discussion

The primary goal in managing CHF is improving PROs and HRQoL. The current study, to our knowledge, is the first RCT conducted in Pakistan and Asia to explore health-related symptoms with dapagliflozin using the KCCQ-23 questionnaire in

Table-4: Comparison of death and improvement in New York Heart Association (NYHA) class between the groups.

Parameter	Status	Control n(%)	Dapagliflozin n(%)	p-value
NYHA class baseline	I	12(14)	14 (17)	0.851
	II	53 (62)	48 (57)	
	III	19 (22)	21 (25)	
	IV	1 (1)	2 (2)	
NYHA class after 3 months	I	37 (46)	47 (57)	0.320
	II	26(33)	18 (22)	
	III	15(19)	17 (21)	
	IV	2 (3)	1 (1)	
Improvement in NYHA class	No	47 (55)	41 (48)	0.357
	Yes	38 (45)	44 (52)	
Death	No	80 (94)	83 (98)	0.443
	Yes	5 (6)	2 (2)	

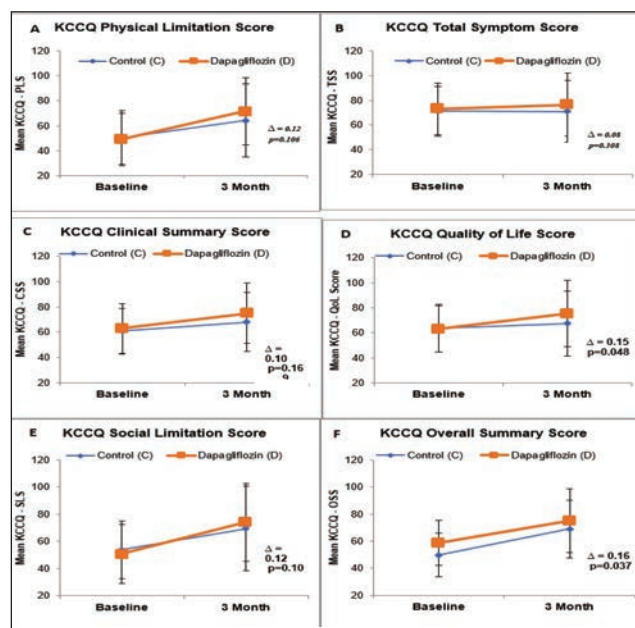
Values mentioned are n (%); Ordinal logistic regression applied for NYHA class comparison; Pearson Chi-square test applied for NYHA improvement as all expected cell counts were ≥ 5 ; Fisher's Exact test applied for mortality as few expected cell counts were < 5 .

**Figure-4:** Effect of dapagliflozin on New York Heart Association NYHA classification at 3 months.

CHF/EF patients. Recently, a study in Pakistan on acute HF patients showed significant improvement in physical limitations and PROs with the addition of 10 mg oral dapagliflozin to baseline therapy.¹⁷

In the current multicentre, open-label, RCT, the dapagliflozin group revealed greater improvement in QoL compared to the control group, as measured by KCCQ-23, at 12 weeks in patients with CHF/EF, including both diabetics and non-diabetics. Specifically, the KCCQ-QoL significantly improved by an effect size of 0.15 points, and the KCCQ-OS by 0.16 points, which included overall physical function, social function and QoL.

The current findings align closely with those of a trial, which was a moderately sized RCT conducted across different areas in the United States for 3 months, and reported significant betterment in KCCQ-QoL, KCCQ-CS and KCCQ-OS.¹¹ Similarly, the current results also confirmed the findings of another landmark trial which demonstrated

**Figure-5:** CENTRAL ILLUSTRATION: Intergroup comparison of efficacy related to Kansas City Cardiomyopathy Questionnaire (KCCQ) domains at 3 months.

improvement in KCCQ-CS and KCCQ-OS scores.¹⁸

Despite the significant improvement in patients' QoL and OS score (OSS) with dapagliflozin, the current study did not show a statistically significant difference in KCCQ-PLS, which measures the degree of limitation that patients experience while performing daily activities, such as dressing up, showering, walking, climbing stairs, or cleaning the house.

The finding aligns with other trials in which where KCCQ-PLS was not significantly different between other interventions and dapagliflozin.^{19,20} On the contrary, the finding of no improvement in KCCQ-PLS does not align with some trials in which dapagliflozin showed statistically significant improvement in KCCQ-PLS.^{11,18,21}

The current trial did not show a significant difference in KCCQ-TSS between dapagliflozin and the control group. This is a novel finding that no other trial has yet reported. Notably, the KCCQ-TSS finding contradicts all other dapagliflozin-related trials in HF/EF patients.^{4,6,22} Furthermore, the finding is also inconsistent with those of other SGLT2i interventions, such as empagliflozin, which showed improvement in KCCQ-TSS.^{23,24}

The KCCQ-SLS specifically evaluates the patients' hobbies, performing household chores, visiting friends or family, and intimate relationships with loved ones. The current trial revealed a non-significant difference in KCCQ-SLS between dapagliflozin and control groups. This confirms the finding of a trial.¹¹ It may reflect the multifactorial nature of social

outcomes, which are influenced by social factors beyond pharmacological treatment. However, the findings contradict other large trials which revealed significant improvement in KCCQ-SLS by dapagliflozin.^{18,19}

The NYHA classification is a globally recognised criterion for assessing the degree of functional limitations and symptoms in HF patients.¹³ The current study evaluated changes in NYHA functional class between dapagliflozin and the control group. At baseline, the functional class distribution in both groups was similar in both males and females, with no significant difference. However, following 3 months of intervention, patients in the dapagliflozin group showed a distinctive improvement, shifting from class II, III and IV to NYHA class I. The results are in line with recent research conducted in Pakistan in patients with acute HF, which showed improvement of NYHA class by using dapagliflozin compared to controls.¹⁷

The current findings align with a trial which investigated dapagliflozin's efficacy in HF with mildly reduced EF.⁷ Similarly, the results also complement the findings of a trial which showed that addition of 10mg of dapagliflozin to conventional therapy for the treatment of refractory HF patients significantly improved their NYHA class.²⁵

Unlike traditional analyses, which assess the mean changes in scores, responder analysis facilitates a more patient-centred interpretation of therapy by focussing on the percentage of patients who experience clinically meaningful improvement or no change or deterioration in the health status of patients.¹¹ The current findings showed trends favouring dapagliflozin across PLS, TSS, CSS, QoL, SLS and OSS. Although most results did not reach statistical significance, the QoL showed a significant difference favouring dapagliflozin, with lower odds of deterioration (22% vs 40% patients). Moreover, the CSS showed a trend favouring dapagliflozin, with a higher proportion of patients experiencing improvement (59% vs 48%). However, the difference was not statistically significant. Therefore, the current findings partially support the published trials conducted in CHF_rEF where the responder analysis of most of the KCCQ domains showed improvement with dapagliflozin.^{11,22}

However, the findings are complementary to those of a trial which also revealed non-significant improvement in PLS, suggesting the smaller sample size of the trial may have restricted the power to find significant differences between the groups.¹⁹ Furthermore, the current results are in line to some extent with the published data from another trial which revealed that patients at a higher range of LVEF showed less improvement in KCCQ.²⁶

By addressing social functionality, the KCCQ-SLS highlights the importance of holistic management that focuses on improving survival and the everyday QoL for HF patients. The non-significant findings of the current study regarding KCCQ-SLS in the two groups are in line with a trial in which all KCCQ domains showed significant improvement with dapagliflozin except the KCCQ-SLS.¹¹

In the current study, there was lower mortality in the dapagliflozin group compared to the control group. The findings are in line with a phase 3 RCT done in 2020.²⁷ The current findings also confirmed those of a post-hoc analysis revealing a decline of sudden death in patients using dapagliflozin added to conventional medical therapy.²⁸

Though the exact mechanism of cardiovascular benefits by SGLT2i, like dapagliflozin, is still not confirmed, a plausible mechanism has been proposed, suggesting that SGLT2i leads to modest osmotic diuresis by preventing glucose reabsorption in the proximal tubule, leading to decreased preload and workload on the heart.¹¹ It leads to decreased blood pressure and improved myocardial energetics, improving patient-reported outcomes and QoL.¹⁷

The strength of the current study is that, as per protocol analysis, 100% of the patients completed the study except those who died during the follow-up period. The findings confirm the efficacy of dapagliflozin as an add-on to conventional therapy in CHF_rEF patients in the shape of improved HRQoL and minimised functional limitations, which are significant targets of HF management supported by the American Heart Association (AHA) guidelines.²⁹

The current study has a number of limitations. The sample size was small, and the number of female patients was less than desired. The follow-up duration was very short (3 months), providing limited information regarding dapagliflozin's long-term effects on QoL. The majority of the patients had Punjabi ethnicity, with only a limited representation of other ethnicities of Pakistan, limiting the generalisability of the results. Also, KCCQ scores were standardized on a scale ranging from 0 to 100, where higher scores reflected better health status. Therefore, the scores exceeding the 100 were capped at 100 to maintain consistency and uniformity across all over patients.

Finally, the study was conducted using an open-label design and the outcome assessors were not blinded.

Conclusion

Evidence supported that SGLT2i, specifically dapagliflozin, had a great clinical impact in terms of improving HRQoL and functional status, and reducing mortality in CHF_rEF patients.

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SR: Concept, data acquisition, analysis, interpretation, drafting, revision and agreement to be accountable for all aspects of the work.

KF, MN & AAC: Concept, data analysis, interpretation, revision and final approval.

AR & RI: Concept, data acquisition and interpretation.