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ORIGINAL ARTICLE

Evaluating the impact of Dapagliflozin on outcomes in systolic heart failure.

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ABSTRACT… Objective: To determine the efficacy of dapagliflozin in reducing cardiovascular events and improving clinical outcomes in patients with systolic heart failure. **Study Design:** Randomized Controlled Trial. **Settings:** Department of Internal Medicine and Cardiology, PAF Hospital, Islamabad. **Study Period:** November 2022 to April 2024. **Method:** A total of 1470 systolic heart failure (HF) patients aged ≥ 18 years with symptoms of New York Heart Association class (NYHA) II, III or IV, ejection fraction ≤ 40% and raised levels of plasma pro-B-type natriuretic peptide (pro-BNP) were enrolled in the study and randomized in 2 equal groups of 735 patients each. In Group-A, patients received dapagliflozin 10 mg once daily while the patients in Group-B received a matching placebo, over a period of one year. The primary outcome was set as worsening of HF (unplanned consultation/hospitalization due to HF). The secondary outcome was a change in the Kansas City Cardiomyopathy Questionnaire (KCCQ). **Results:** The mean age of participants in this study was 64.81±7.98 years. The results showed that worsening of heart failure (19.05% Vs 26% respectively, p-value=0.001), unplanned hospital visits due to HF (10.34% Vs 14.1% respectively, p-value=0.031), hospitalization due to HF (8.84% Vs 12.65% respectively, p-Value=0.032) was significantly lower and statistically significant change in KCCQ score (5.2±17.6 Vs 3.1±18.4 respectively, p-value=0.026) was observed in Group-A compared to Group-B. **Conclusion:** In systolic heart failure patients with reduced ejection fraction, dapagliflozin lowered the risk of worsening of heart failure and improved the symptoms of heart failure.

Key words: Dapagliflozin, Ejection Fraction, Systolic Heart Failure.

INTRODUCTION

The incidence of heart failure (HF) is on rise and the global number of patients suffering from HF is reported to be more than 64 million. HF is thus becoming a leading cause of global morbidity and mortality. In USA, the approximate number of hospitalization due to HF is 1 Million.[1] It is also reported that 50% of these patients are with systolic HF with a reduced Ejection Fraction having EF ≤ 40%.[2] The classical medical treatment for systolic HF targets the inhibition of renin angiotensin-aldosterone system, sympathetic pathways and neprilysin. Hence the drugs recommended include angiotensin-converting enzyme inhibitors /angiotensin II receptor blockers, β-blockers, angiotensin receptor-neprilysin inhibitors and mineralocorticoid receptor antagonists.[3]

Type II diabetes is the leading risk factor for HF that increases the risk of mortality in these patients. Hence a treatment addressing both Type II diabetes and HF, will offer a valuable advantage for these patients.[4]

A recently developed class of drugs used for control of blood glucose, Sodium–glucose cotransporter-2 inhibitors (SGLT-2 I) has shown cardiovascular (CV) benefits besides glycemic control. SGLT-2 inhibitors lower the blood glucose levels by modulating the sodium-glucose cotransporter preventing the reabsorption of glucose and increasing its renal excretion.[5] Additionally SGLT2 inhibitors also play a role in preventing myocardial remodeling by inhibiting sodium proton channel at the level of cardiomyocytes hence leading to reduced intracellular calcium.[6] This class of drugs has been reported to reduce the symptoms of HF which was found to be independent of lowering HbA_1C levels.

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Starting treatment with a SGLT2 inhibitor is reported to be beneficial even in patients without diabetes.[7] Researchers have discussed that these cardioprotective effects are beyond their effect on glycemic control.[8,9,10] These cardioprotective effects are also found in form of lowering of blood pressure and decreasing body weight.[11,12,13] Yurista SR, Garg V and Santos-Gallego CG in three different clinical trials have shared their results concluding that cardio protective benefits of SGLT2 inhibitors are beyond the changes of blood glucose levels.[8,14,15] In HF patients, a major concern is the reduction of exercise capacity resulting from inability of CV system to ensure appropriate oxygen supply during exercise, and therefore making it difficult for HF patients to perform daily life physical activities. Dapagliflozin is one among the SGLT-2 inhibitors that has shown to benefit the patients of HF in this regard in recently done trials.[12,13] Dapagliflozin has got the US FDA approval for indication of lowering the risk of hospitalization in patients of HF with diabetes.[7]

These studies have shown clinical benefits of dapagliflozin in form of providing CV benefits, safety and reduced need for hospitalization due to HF both in diabetics and non-diabetics.[7,13,16] Hence, irrespective of presence of diabetes, dapagliflozin has shown the benefits like decrease in CV mortality, prevention in HF progression and incidence of mortality.[13]

An important study with Dapagliflozin on this subject is the DAPA-HF trial which studies the HF patients having reduced ejection fraction. The outcomes showed reduction of worsening HF events, improvement in HF symptoms and reduction of CV mortality irrespective of presence of diabetes.[12,17] International studies have focused on benefits of Dapagliflozin in systolic HF during past few years, however, there is lack of data in Pakistani population regarding this important indication. This study was therefore planned to determine the efficacy of dapagliflozin in reducing cardiovascular events and improving clinical outcomes in patients with systolic heart failure in Pakistani population. The results of the study will be helpful in setting up the rationale for systolic HF treatment regimen in our local population.

METHODS

Study Design & Setting

This randomized controlled study was conducted at the department of Internal Medicine and Cardiology, PAF hospital, Islamabad from November 2022 to April 2024, over a period of 1.5 years. Approval for conducting the study was obtained from ethical committee of the hospital (MED-2021-258-18013).

Sample Size

The sample size was 735 per group. Total 1470 participants were included in this study.

Sampling Technique and Patient's Randomization

A total of 1470 systolic HF patients were enrolled in the study using consecutive sampling. Participants were equally randomized into Group A and Group B through a computer-generated randomization sheet. Stratification during randomization was performed based on the presence of type 2 diabetes (defined as HbA1C levels $\geq$6.5%).

Inclusion Criteria

Patients aged $\geq$ 18 years with systolic heart failure, exhibiting symptoms of New York Heart Association (NYHA) class II, III, or IV, with left ventricular ejection fraction (EF) $\leq$40% and elevated plasma pro-B-type natriuretic peptide (pro-BNP) levels were included in this study.

Exclusion Criteria

Patients with Type 1 diabetes mellitus, an eGFR $\leq$ 30 ml/min/1.73 m^2 and systolic blood pressure $<$ 95 mmHg were excluded. Additionally, patients recently treated with SGLT2 inhibitors or reporting intolerance to these medications were also excluded from study population.

The purpose of study was explained, and written consent was obtained from the patients.

Confounding Factors

Potential confounding factors, such as the presence of type 2 diabetes, were managed through stratification during randomization based

on HbA1C levels ≥6.5%, ensuring balanced distribution of participants with type 2 diabetes across study groups.

Intervention and Follow-up Protocol

In Group-A, patients received once daily dose of dapagliflozin 10 mg over a period of 1 year, while the patients in Group-B received a matching placebo. Dose of dapagliflozin was allowed to be reduced to 5 mg or temporarily discontinued if there was decline in eGFR, hypotension or volume depletion. The standard drug treatment for HF was continued in these patients. Similarly, patients with type 2 diabetes were continued with their treatment, however doses were allowed to be readjusted to avoid any risk of hypoglycemia.

First and second follow-up visits were arranged at day 14 and 60 respectively in order to assess volume status, renal functions or any other adverse event after the start of treatment. Further follow-up visits were advised at the completion of 6 months and then last visit at 12 months of treatment.

Outcome Measures

The primary outcome was set as worsening of HF (assessed in form of unplanned hospital consultation/hospitalization due to HF). The secondary outcome was a change in the KCCQ score where significant clinical change was considered if ≥ 5-point change was observed.

Data Analysis

Data analysis was conducted using SPSS version 25. The mean and standard deviation were calculated for quantitative variables, while qualitative variables were presented as frequencies and percentages. Chi-square tests and independent t-tests were used to compare outcomes between the two groups, with statistical significance defined as p value ≤ 0.05.

RESULTS

The mean age in our study was 64.81±7.98 years with a range of 50 to 82 years. Male gender was 1088 (74%) while the number of female patients was 382 (26%) in overall study population. Details of demographics and clinical characteristics of patients in Group A and Group B are shown in Table-I.

The patients were continued on their existing therapies for HF and diabetes as required. The details of these medications are given in Table-II.

The results show that worsening of HF was significantly less in Group A compared to Group B. Similarly, unplanned hospital visits due to HF and hospitalization due to HF was significantly less in Group A compared to Group B. The details of primary and secondary outcomes are given in Table-III.

DISCUSSION

The clinical data of our study showed that the patients predominantly comprised NYHA class II patients (71.22%), followed by class III (27.07%) and class IV (1.7%). The diabetic population was similarly distributed between Group-A (36.2%) and Group-B (35.5%). Primary outcome of the study i.e. the worsening of HF (assessed in form of unplanned hospital consultation /hospitalization due to HF) was reported in 19.05% patients in Group-A while in 26% patients in Group-B (p-value=0.001). There was statistically significant difference between the two groups in unplanned hospital visits (10.34% in Group-A Vs 14.1% in Group-B, p-value=0.031) and hospitalization due to HF (8.84% in Group A Vs 12.65% in Group B, p-Value=0.032). In the secondary outcome, there was a significant improvement in KCCQ score in Group A compared to Group B (5.2±17.6 Vs 3.1±18.4 respectively, p-value=0.026).

The therapeutic potential of SGLT2 inhibitors in the management of HF has been discussed in various clinical studies. The two drugs in this class, dapagliflozin and empagliflozin have specifically given positive results in this regard. Lopaschuk GD and Verma S explained the overall mechanism through which the dapagliflozin may benefits the CV system. It includes diuresis, natriuresis, blood pressure lowering, sympathetic nervous system suppression, minimizing the inflammatory mediators and preventing the cardiac remodeling.

Demographics		Group-A (n=735)	Group-B (n=735)
Age (years) Mean±SD		64.77±7.99	64.85±7.97
Gender	Male n (%)	551 (74.97)	537 (73.06)
	Female n (%)	184 (25.03)	198 (26.94)
NYHA Class n (%)	II	518 (70.5)	529 (72)
	III	206 (28)	192 (26.1)
	IV	11 (1.5)	14 (1.9)
Principal Cause of HF n (%)	Ischemic	404 (55)	394 (53.6)
	Non-Ischemic	271 (36.8)	278 (37.82)
	Unknown	60 (8.2)	63 (8.6)
BMI Mean±SD		29.41±4.3	28.38±4.3
Heart Rate/Min Mean±SD		71.92±7.43	70.86±7.55
Systolic BP Mean±SD (mmHg)		119.72±5.58	120.1±5.83
LVEF Mean±SD (%)		31.81±3.28	32.25±3.17
Pro-BNP Mean±SD (pg/mL)		1464.63±423.19	1504.53±547.62
eGFR Mean±SD mL/min/1.73m2		64.46±14.80	64.64±15.04
Hospitalization due to HF n (%)		338 (46)	357 (48.57)
Atrial Fibrillation n (%)		312 (42.45)	299 (40.7)
Diabetes n (%)		266 (36.2)	261 (35.5)

Table-I. Details of demographics and clinical characteristics. n=1470

Medication at the Time of enrolment	Group-A n=735	Group-B n=735
Diuretics n (%)	688 (93.6)	692 (94.12)
ACEI/ARB n (%)	631 (85.9)	609 (82.9)
Sacubitril–valsartan n (%)	86 (11.7)	68 (9.3)
B-blockers n (%)	705 (95.92)	697 (94.83)
Mineralocorticoid receptor antagonist n (%)	530 (72.11)	511 (69.52)
Digitalis n (%)	133 (18.1)	147 (20)
Biguanides n (%)	259 (35.24)	241 (32.8)
Sulfonylureas n (%)	147 (20)	158 (21.5)
DPP-4 I n (%)	114 (15.5)	108 (14.7)
GLP-1 receptor agonist n (%)	37 (0.5)	28 (0.38)
Insulin n (%)	183 (25)	193 (26.3)

Table-II. Details of medication at time of enrolment n=1470

Out Comes	Group-A (n=735)	Group-B (n=735)	P-Value
Primary Outcomes			
Worsening of heart failure n (%)	140 (19.05)	191 (26)	0.001
Unplanned hospital visit n (%)	76 (10.34)	103 (14.1)	0.031
Hospitalization due to HF n (%)	63 (8.84)	88 (12.65)	0.032
Secondary Outcome			
Changes in KCCQ Mean±SD	5.2±17.6	3.1±18.4	0.026

Table-III. Treatment outcomes in both the groups n=1470

Dapagliflozin is presumed to work on cardiac cell functions and overall cardiac physiology in HF patients with reduced ejection fraction. The result of all these natriuretic and diuretic effects ultimately provides reduction in the preload.[18]

SD Wiviott et al., studied the CV outcomes of dapagliflozin in type II diabetic patients with the outcomes set as a composite of major adverse CV events, CV mortality or hospitalization due to HF. The results of this study concluded that in type II diabetics with high risk of atherosclerotic CV disease, dapagliflozin lowers the risk of CV mortality or hospitalization due to HF.[7] JJV McMurray et al., studied the effects of SGLT2 inhibitors in HF patients with reduced ejection fraction irrespective of the presence of type II diabetes. In this comprehensive work on this topic, 4744 HF patients with EF ≤ 40% received once daily dose of dapagliflozin 10mg or a matching placebo on top of their existing therapies. The primary outcome of the study was set as worsening of HF (composite of urgent visit or hospitalization due to HF) and CV mortality. In 18 months follow up, primary outcomes were significantly in the favor of dapagliflozin group compared to placebo (16.3% Vs 21.2% in Dapagliflozin Vs placebo, p-value□0.001). There was also improvement in KCCQ score in dapagliflozin group which indicates the decrease in HF symptoms compared to placebo. Benefits of dapagliflozin were reported in patients irrespective of presence of diabetes.[13] An analysis of a randomized trials published in JAMA, discussed the effects of dapagliflozin on worsening of HF and CV mortality in HF patients with or without diabetes. The primary outcome of the study was the composite of worsening of HF or CV mortality. The results of this analysis in patients given once daily dapagliflozin (10mg) in addition to existing therapy, Dapagliflozin showed significant reduction in the risk of worsening of HF or CV mortality irrespective of presence of diabetes.[19] A retrospective research work done in Pakistan by Kamin M et al. assessed the effects of dapagliflozin on blood pressure control, weight control and safety, besides its ability of lowering the blood sugar levels. The results showed that in addition to blood glucose control, dapagliflozin significantly lowered body weight, diastolic and systolic blood pressure.[20] Mahaffey KW studied the efficacy of Canagliflozin, an SGLT2 inhibitor, in reducing CV death, myocardial infarction, stroke, and hospitalization due to HF in patients with type 2 diabetes and high CV risk. The study demonstrated consistent CV benefits across primary/secondary prevention groups. It is important that higher baseline CV risk yielded greater absolute reductions, demonstrating broad efficacy in at-risk populations.[21] A comprehensive review by Marilly E concluded that for 1000 individuals treated with SGLT2i over 3.5 years, reduce deaths from 70 to 61, prevent nine Major Adverse Cardiovascular Events (MACE), and avoid 11 hospitalizations for HF.[22]

The findings of our study align with previous research, particularly the work discussed above, demonstrating significant reductions in worsening of HF and hospitalization due to HF with dapagliflozin therapy, while also showing consistent benefits in KCCQ scores across both diabetic and non-diabetic populations.

We worked on limited parameters and only selected outcomes, which are the major limitations of this study. Future work taking more baselines parameters and working on broader range of outcomes will add up in this useful data for HF patients.

CONCLUSION

In patients with systolic HF and reduced ejection fraction, dapagliflozin demonstrated significant benefits by reducing the risk of worsening of HF and hospitalization due to HF. The therapy improved HF symptoms, with benefits observed regardless of diabetic status.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. **American heart association council on epidemiology and prevention statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics-2020 update: A report from the American heart association.** Circulation. 2020; 141(9):e139-e596. doi: 10.1161/CIR.0000000000000757.

2. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. **Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes.** J Am Coll Cardiol. 2017; 70(20):2476-86. doi: 10.1016/j.jacc.2017.08.074.

3. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. **Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry.** J Am Coll Cardiol. 2018; 72(4):351-66. doi: 10.1016/j.jacc.2018.04.070.

4. Kenny HC, Abel ED. **Heart failure in type 2 diabetes mellitus.** Circ Res. 2019; 124(1):121-41. doi: 10.1161/CIRCRESAHA.118.311371.

5. Thomas MC, Cherney DZI. **The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure.** Diabetologia. 2018; 61(10):2098-2107. doi: 10.1007/s00125-018-4669-0.

6. Hou YC, Zheng CM, Yen TH, Lu KC. **Molecular mechanisms of SGLT2 inhibitor on cardiorenal protection.** Int J Mol Sci. 2020; 21(21):7833. doi: 10.3390/ijms21217833.

7. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. **DECLARE–TIMI 58 investigators. dapagliflozin and cardiovascular outcomes in type 2 diabetes.** N Engl J Med. 2019; 380(4):347-57. doi: 10.1056/NEJMoa1812389.

8. Yurista SR, Silljé HHW, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, et al. **Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction.** Eur J Heart Fail. 2019; 21(7):862-73. doi: 10.1002/ejhf.1473.

9. Garg V, Verma S, Connelly K. **Mechanistic insights regarding the role of SGLT2 inhibitors and GLP1 agonist drugs on cardiovascular disease in diabetes.** Prog Cardiovasc Dis. 2019; 62(4):349-57. doi: 10.1016/j.pcad.2019.07.005.

10. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, et al. **Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics.** J Am Coll Cardiol. 2019; 73(15):1931-44. doi: 10.1016/j.jacc.2019.01.056.

11. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM et al. **DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF).** Eur J Heart Fail. 2019; 21(5):665-75. doi: 10.1002/ejhf.1432.

12. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE et al. **Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: The DEFINE-HF Trial.** Circulation. 2019; 140(18):1463-76.

13. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA et al. **DAPA-HF Trial committees and investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction.** N Engl J Med. 2019; 381(21):1995-2008.

14. Garg V, Verma S, Connelly K. **Mechanistic insights regarding the role of SGLT2 inhibitors and GLP1 agonist drugs on cardiovascular disease in diabetes.** Prog Cardiovasc Dis. 2019; 62(4):349-57.

15. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. **Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics.** J Am Coll Cardiol. 2019; 73(15):1931-44. doi: 10.1016/j.jacc.2019.01.056.

16. Zhang Y, Lin X, Chu Y, Chen X, Du H, Zhang H et al. **Dapagliflozin: a sodium-glucose cotransporter 2 inhibitor, attenuates angiotensin II-induced cardiac fibrotic remodeling by regulating TGFβ1/Smad signaling.** Cardiovasc Diabetol. 2021; 20(1):121.

17. Seferović PM, Fragasso G, Petrie M, Mullens W, Ferrari R, Thum T, et al. **Sodium-glucose co-transporter 2 inhibitors in heart failure: Beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology.** Eur J Heart Fail. 2020; 22(9):1495-1503. doi: 10.1002/ejhf.1954.

18. Lopaschuk GD, Verma S. **Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) Inhibitors: A state-of-the-art review.** JACC Basic Transl Sci. 2020; 5(6):632-44. doi: 10.1016/j.jacbts.2020.02.004.

19. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, et al. **Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes.** JAMA. 2020; 323(14):1353-68.

20. Kamin M, Ishtiaq O, Raashid K, Wahab MU, Khan SA, Raja U. **The Outcomes of Dapagliflozin Use in Real-Life Clinical Settings in Endocrinology Clinics of Islamabad, Pakistan.** Cureus. 2020; 12(6): e8565. doi: 10.7759/cureus.8565.

21. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, et al. **CANVAS program collaborative group. Canagliflozin for primary and secondary prevention of cardiovascular events: Results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study).** Circulation. 2018; 137(4):323-34. doi: 10.1161/CIRCULATIONAHA.117.032038.

22. Marilly E, Cottin J, Cabrera N, Cornu C, Boussageon R, Moulin P, et al. **SGLT2 inhibitors in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials balancing their risks and benefits.** Diabetologia. 2022; 65(12):2000-10. doi: 10.1007/s00125-022-05773-8.

AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ayesha Salim:** Conception, design of study, acquisition, analysis, manuscript writing, critical review.
2	**Muhammad Tahir:** Conception, design of study, acquisition, analysis, manuscript writing, critical review.
3	**Muhammad Zuhair Tahir:** Interpretation of data, design of study.
4	**Muhammad Zubair Tahir:** Concept, design, results, discussion.
5	**Afrah Malik:** Critical analysis, final approval, manuscript writing.
6	**Hifza Shahid:** Conception, design.