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Research Article

Effectiveness of Empagliflozin in Patients with Heart Failure Having Type-2 Diabetes

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ABSTRACT
Introduction: Heart failure with reduced ejection fraction (HFrEF) is a significant cause of morbidity and mortality in patients with diabetes mellitus type 2 (T2DM). Although international trials have shown the cardiovascular benefits of empagliflozin, there is limited local data for the effectiveness of empagliflozin in Pakistani patients. This research intended to compare the effectiveness of empagliflozin versus placebo, as well as standard medical therapy, in patients with T2DM and HFrEF.
Methods: This randomized, double-blind, placebo-controlled trial was conducted at Allama Iqbal Memorial Teaching Hospital, Sialkot, from June to December 2025. A total of 170 patients aged 20–75 years with T2DM and LVEF <50% were enrolled and randomized (1:1) to receive empagliflozin 10 mg/day or matching placebo along with guideline-directed medical therapy. Echocardiographic assessment was performed at baseline and after 3 months. Effectiveness was defined as improvement in left ventricular ejection fraction (LVEF) to ≥50%. Data were analyzed using SPSS v27.0, with p ≤0.05 considered significant.
Results: Baseline characteristics were comparable between groups. Treatment efficacy was achieved in 78.8% of patients receiving empagliflozin versus 54.1% in the placebo group (p=0.001).
Conclusion: In addition, empagliflozin significantly improved left ventricular function when compared to placebo in patients with T2DM and HFrEF when added to standard therapy. These findings support its usefulness in improving cardiac outcomes in this high-risk population.

Keywords: Empagliflozin, Type 2 Diabetes Mellitus, Heart Failure, Reduced Ejection Fraction, Left Ventricular Ejection Fraction.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that is characterised by the inability of the heart to pump enough blood to meet the metabolic demands of the body. It represents a significant burden of global public health, with over 64 million individuals worldwide affected, contributing to a substantial burden of morbidity, mortality and healthcare spending.[1] The prevalence of HF is continuing to increase as a result of aging populations and enhanced survival after acute cardiovascular events. In South Asia including Pakistan, HF is becoming more and more common, with an earlier age of onset and poorer prognosis than Western populations and is mainly due to high rates of ischemic heart disease, hypertension and diabetes mellitus.[2-3]

Type 2 diabetes mellitus (T2DM) has been identified as one of the most important risk factors for developing HF as it confers a two- to fourfold higher risk through mechanisms including diabetic cardiomyopathy, accelerated atherosclerosis, endothelial dysfunction and renal impairment.[4] Coexistence of HF and T2DM is linked to a poorer prognosis, increased hospitalization rates, and cardiovascular mortality.[5] Management includes an integrated approach to both glycemic control and cardiovascular risk reduction through GDMT using ACEIs, ARBs, ARNIs, beta-blockers, MRAs and diuretics.[6]
In patients with T2DM metformin remains the first line medication unless contraindicated, but concerns of fluid retention have restricted the use of certain glucose-lowering

medications like thiazidinedines, in patients with HF.[7] Recent cardiovascular outcome trials have modified treatment paradigms by showing that sodium-glucose cotransporter-2 (SGLT2) inhibitors not only improve glycemic control, but also significantly reduce HF hospitalisations and cardiovascular death, even in patients without diabetes. This dual cardiometabolic benefit has empowered SGLT2 inhibitors as cornerstone therapy in HF management guidelines.[8-9]

Among the SGLT2 inhibitors, empagliflozin has had especially-strong evidence in those with T2DM with established cardiovascular disease. The EMPA-REG OUTCOME trial first demonstrated a significant reduction of cardiovascular mortality and of hospitalisation for HF with empagliflozin in patients with T2DM with high cardiovascular risk.[10] Subsequent trials with EMPEROR-Reduced and EMPEROR-Preserved confirmed the efficacy of empagliflozin in decreasing HF hospitalizations and improving clinical outcomes across the spectrum of EF, regardless of diabetic status.[8-9]

Despite robust international data for empagliflozin's use in heart failure with reduced ejection fraction (HFrEF) the lack of systematic clinical trials investigating use of empagliflozin in Pakistan. Local research is generally limited to small observational studies only looking at glycemic, rather than cardiac, outcomes. Given how common type 2 diabetes and HFrEF are in Pakistan, there are regional factors that could affect treatment response and safety. Thus, global data may not accurately represent outcomes for a locality. This study aims to evaluate the efficacy of empagliflozin in patients with type 2 diabetes and HFrEF in Pakistan, bridging the knowledge gap and also ensuring better evidence-based cardiometabolic care for the region.

METHODS

This randomized, double-blind, placebo-controlled, was performed in the Outpatient Department of Internal Medicine at Allama Iqbal Memorial Teaching Hospital, Sialkot, from June 10, 2025 to December 9, 2025. A total of 170 patients were recruited using non-probability consecutive sampling method with 85 patients assigned to each group. The sample size was based on a 95% confidence level, with a 80% statistical power, an efficacy rate of 78% for the empagliflozin and 58% for the placebo group.[11]

Eligible for study were adults from 20 to 75 years with type 2 diabetes mellitus on at least one anti-diabetic medication other than an SGLT2 inhibitor for more than six months and with heart failure, ejection fraction less than 50%. Patients were excluded if they had insulin-dependent type 2 diabetes, severe renal impairment or renal transplantation, hypotension, metabolic acidosis or diabetic ketoacidosis, active malignancy or chemotherapy use in the past 5 years, or were pregnant or lactating.

After obtaining informed consent, study participants were allocated in a 1:1 ratio by the lottery by allocation schedule to receive either empagliflozin 10 mg once daily or matching placebo, plus standard heart failure therapy. Baseline evaluations included physical examination, echocardiography, complete blood count, and lipid profile, which were repeated after 3 months of treatment. Clinical parameters: weight, heart rate and blood pressure were recorded.

Echocardiographic assessment was performed in accordance with the guidelines of the American Society of Echocardiography, and comprised measurement of LVEF, left ventricular mass index (LVMI), left ventricular end-systolic and end-diastolic volumes, left atrial volume index (LAVI), and the ratio of mitral peak E-wave velocity to early diastolic tissue Doppler velocity (E/e').

Effectiveness was considered defined as improvement in left ventricular systolic function measured by echocardiography. After a 3-month treatment period, left ventricular ejection fraction (LVEF) [?]50% was considered an indicator of effective treatment. Treatment efficacy was determined by change in LVEF from baseline to 3 months according to the predefined operational definition.

All the data collected were processed and analysed using the version 27.0 of the statistical analysis software package, the Statistical Package for Social Sciences (SPSS). Continuous variables (like age) were summarised with mean and standard deviation and categorical variables like gender and treatment efficacy values were converted to frequency and percentage. The difference in efficacy between the two groups over the three months period was assessed using the chi-square test. Data were further stratified according to age, gender, and baseline LVEF, and analysis in post stratum was accomplished by the chi-square test, with a cut-off for statistical significance set at <0.05.

RESULTS

A total of 85 patients were included in each group. The gender distribution was comparable, with males comprising 58.8% in the empagliflozin group and 57.6% in the placebo group. The majority of participants in both groups were aged 51–75 years (54.1% vs. 58.8%), and the mean age was similar (52.42 ± 12.80 years in Group A vs. 53.64 ± 11.54 years in Group B).

Baseline LVEF was nearly identical between groups (33.33 ± 2.69% vs. 33.04 ± 2.72%). After three months, mean LVEF improved to 56.01 ± 6.21% in the empagliflozin group compared to 50.31 ± 6.59% in the placebo group. The mean change in LVEF was greater in Group A (22.68 ± 7.03%) than in Group B (17.27 ± 7.04%). Most patients had baseline LVEF ≤35% (71.8% in Group A and 74.1% in Group B), indicating comparable severity of systolic dysfunction at baseline.

Treatment efficacy between the two groups is compared in table 2. A significantly higher proportion of patients with in the empagliflozin group achieved effective treatment (LVEF >50% at 3 months) as compared to the placebo group (78.8% vs. 54.1%) and difference was statistically significant (p = 0.001), demonstrating superior efficacy of empagliflozin when added to standard medical therapy.

Stratified analysis revealed that empagliflozin was significantly superior to placebo regardless of gender, age groups, and baseline LVEF categories (p <0.05). The superiority of empagliflozin was consistent in all subgroups including patients with lower baseline LVEF (>35%).

Table-1: Comparison of distribution of different variables between groups

		Groups	
		Group-A (Empagliflozin)	**Group-B (Placebo)**
Gender	Male	50(58.8%)	49(57.6%)
	Female	35(41.2%)	36(42.4%)
Age groups	20-30 years	9(10.6%)	5(5.9%)
	31-50 years	30(35.3%)	30(35.3%)
	51-75 years	46(54.1%)	50(58.8%)
	Mean age (years)	52.42±12.80	53.64±11.54
Baseline LVEF (%)		33.33±2.69	33.04±2.72
LVEF after 3 months (%)		56.01±6.21	50.31±6.59
Change in LVEF (%)		22.68±7.03	17.27±7.04
Baseline LVEF (%)	LVEF ≤35%	61(71.8%)	63(74.1%)
	LVEF >35%	24(28.2%)	22(25.9%)

Table-2: Comparison of efficacy between groups

Efficacy	**Groups**		**P-Value**
	Group-A (Empagliflozin)	Group-B (Placebo)	
Yes	67(78.8%)	46(54.1%)	0.001
No	18(21.2%)	39(45.9%)	

Table-3: Stratification of efficacy between groups with respect to different variables

Variables	**Efficacy**	**Groups**		**P-Value**
		Group-A (Empagliflozin)	Group-B (Placebo)	
Gender				
· Male	Yes	40(80.0%)	22(44.9%)	0.001
	No	10(20.0%)	27(55.1%)	
· Female	Yes	27(77.1%)	24(66.7%)	0.032
	No	8(22.9%)	12(33.3%)	
Age groups				
· 20-30 years	Yes	8(88.9%)	3(60.0%)	0.050
	No	1(11.1%)	2(40.0%)	
· 31-50 years	Yes	19(63.3%)	13(43.3%)	0.021
	No	11(36.7%)	17(56.7%)	
· · 51-75 years	Yes	40(87.0%)	30(60.0%)	0.003

	No	6(13.0%)	20(40.0%)	
Baseline LVEF				
· LVEF ≤35%	Yes	49(80.3%)	32(50.8%)	0.001
	No	12(19.7%)	31(49.2%)	
· LVEF >35%	Yes	18(75.0%)	14(63.6%)	0.040
	No	6(25.0%)	8(36.4%)	

DISCUSSION

The current randomised, double-blind, placebo-controlled trial established that empagliflozin when added to guideline-directed medical therapy led to significantly greater treatment efficacy compared to placebo in patients with type 2 diabetes mellitus (T2DM) and heart failure with reduced ejection fraction (HFrEF). In our study, 78.8% of patients in the empagliflozin group achieved effective improvement in left ventricular ejection fraction (LVEF >50%) compared to 54.1% among the placebo group (p=0.001).

This statistically significant difference shows the additive benefit of empagliflozin over standard therapy with ACE inhibitors/ARNIs, beta-blockers, and diuretics. These findings are in keeping with a landmark trial, known as EMPEROR-Reduced, which showed empagliflozin reduced significantly the composite endpoints of cardiovascular death or hospitalization for heart failure in patients with HFrEF regardless of whether they had diabetes.[8,12]

While the main endpoints in EMPEROR-Reduced were clinical endpoints, not echocardiographic endpoints, the extent of the benefit observed in our study is consistent with the significant protection against cardiovascular events seen in earlier studies.

Subsequent analyses of the EMPEROR program have added support for the beneficial effects of empagliflozin on cardiac structure and function. Ferreira et al (2025) demonstrated favourable biomarker changes and mechanistic signal implying reverse cardiac remodeling with empagliflozin therapy.[13] Similarly, Doehner et al (2022) demonstrated that empagliflozin improved metabolic and biochemical profile, which contributed to the occurrence of less unfavourable cardiovascular events in HFrEF patients.14[14]

Contemporary reviews and updates between 2024 and 2026 have continued to consider SGLT2 inhibitors as foundational therapy in HFrEF because of their sustained benefit in decreasing hospitalisation and cardiovascular mortality.[15-16] Alfieri et al. (2024) detailed SGLT2 inhibitors as part of the core pharmacotherapy of contemporary heart failure, notably for their pleiotropic impacts in HFrEF, including natriuresis, optimal heart myocardial energetics, decreased preload and afterload and attenuation of maladaptive ventricular hypertrophy.[15]

Furthermore, Lauretti et al. (2024) showed that empagliflozin could improve the stability of the electrical signals in the ventricles of the heart and help reduce the risk of arrhythmias, providing more mechanistic note for the improved outcomes.[17]

Systematic reviews performed in recent years have confirmed these results. Ansar et al. (2025), in a systematic overview and meta-analysis of randomised controlled trials, identified that empagliflozin significantly slows the progression of HF and cardiovascular events in both diabetic and non-diabetic populations.[18] Recent updated guideline statements from major cardiology societies between 2023 and 2025 have taken on board these results and suggest the use of SGL2 inhibitors, including empagliflozin, as Class I therapy in patients with HFrEF.[16,19]

These recommendations are based on the consistency and strength of accumulated evidence. Importantly, while most international trials assessed hard clinical endpoints such as cardiovascular death and hospitalisation, our study presents supportive evidence at the echocardiographic level, showing noteworthy improvement in systolic function within quite a short time, three months. This early improvement in LVEF indicates possible reverse remodeling that is consistent with mechanistic analyses from the EMPEROR-Reduced trial in terms of structural and functional benefits to the heart.[20]

Our results thus not only corroborate the findings from other parts of the world but also add important local evidence from a Pakistani population, where large scale randomised evidence has been limited. Considering regional variations in demographics, comorbid burden, and access to healthcare, the demonstration of significant efficacy in our cohort adds to the robust external validity of the benefits of empagliflozin in South Asian patients with diabetes Mellitus (T2DM) and

Heart Failure with Reduced Ejection Fraction (HFrEF).

Despite these promising findings, there are some limitations to note. This study was done at one tertiary care centre and may limit the generalizability of findings to more general populations. The follow-up duration of 3 months was relatively short and failed to allow for assessment of the long-term adverse outcomes such as cardiovascular mortality, recurrent hospitalization, or long-term remodeling effects. Larger, multicenter trials with longer follow-up periods are needed to validate these results and evaluate long-term safety and cardiovascular outcome.

CONCLUSION

In addition, empagliflozin significantly improved left ventricular function when compared to placebo in patients with T2DM and HFrEF when added to standard therapy. These findings support its usefulness in improving cardiac outcomes in this high-risk population.

REFERENCES

1. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: an updated review. Cardiac Failure Review. 2023;9(1):11-20.
2. Yaqoob S, Shaikh GA, Shah HH, Zuberi MA, Rauf SA, Tariq H, et al. Assessing the Real-World Impact of Empagliflozin on Heart Failure with Reduced Ejection Fraction (HFrEF) Outcomes Irrespective of Diabetes Status. Pak Heart J. 2025;58(3):297-304.
3. Liew A, Bavanandan S, Hao CM, Lim SK, Prasad N, Sahay M, et al. Executive summary of the asian pacific society of nephrology clinical practice guideline on diabetic kidney disease—2025 update. Nephrology (Carlton, Vic.). 2025;30(5):e70031.
4. Agress S, Sheikh JS, Perez Ramos AA, Kashyap D, Razmjouei S, Kumar J, et al. The interplay of comorbidities in chronic heart failure: challenges and solutions. Current Cardiol Reviews. 2024;20(3):13-29.
5. Zhang A, Kalil R, Marzec A, Coulter SA, Virani S, Patel KV, et al. Cardiovascular disease management with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes: a cardiology primer. Texas Heart Institute J. 2024;51(1):250-5.
6. Anker SD, Khan MS, Shahid I, Filippatos G, Coats AJ, Butler J. Sodium–glucose co-transporter 2 inhibitors in heart failure with preserved ejection fraction: reasons for optimism. Eur J Heart Fail. 2021;23(8):1250-5.
7. Stompor T, Adamczak M, Kurnatowska I, Naumnik B, Nowicki M, Tylicki L, et al. Pharmacological nephroprotection in non-diabetic chronic kidney disease—clinical practice position statement of the Polish Society of Nephrology. J Clin Med. 2023;12(16):5184-90.
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. New Engl J Med. 2020;383(15):1413-24.
9. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-preserved trial. Circulation. 2021;144(16):1284-94.
10. Inzucchi SE, Khunti K, Fitchett DH, Wanner C, Mattheus M, George JT, et al. Cardiovascular benefit of empagliflozin across the spectrum of cardiovascular risk factor control in the EMPA-REG OUTCOME trial. J Clin Endocrinol Metabol. 2020;105(9):3025-35.
11. Anker SD, Butler J, Usman MS, Filippatos G, Ferreira JP, Bocchi E, et al. Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction: a pre-specified analysis of EMPEROR-Preserved. Nature medicine. 2022;28(12):2512-20.
12. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, et al. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. European heart journal. 2021;42(13):1203-12.
13. Ferreira JP, Anker SD, Butler J, Filippatos G, Januzzi Jr JL, Schueler E, et al. Effect of empagliflozin on

the mechanisms driving erythropoiesis and iron mobilization in patients with heart failure: the EMPEROR program. J Am Coll Cardiol. 2025;85(18):1757-70.

14. Doehner W, Anker SD, Butler J, Zannad F, Filippatos G, Ferreira JP, et al. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. Eur Heart J. 2022;43(36):3435-46.
15. Alfieri M, Bruscoli F, Di Vito L, Di Giusto F, Scalone G, Marchese P, et al. Novel medical treatments and devices for the management of heart failure with reduced ejection fraction. J Cardiovasc Development Dis. 2024;11(4):125-30.
16. Beghini A, Sammartino AM, Papp Z, Von Haehling S, Biegus J, Ponikowski P, et al. 2024 update in heart failure. ESC heart failure. 2025;12(1):8-42.
17. Lauretti C, Antonio GL, Fernandes AE, Stocco FG, Girardi AC, Verrier RL, et al. Empagliflozin's role in reducing ventricular repolarization heterogeneity: insights into cardiovascular mortality decline from the EMPATHY-HEART trial. Cardiovasc Diabetol. 2024;23(1):221-25.
18. Ansar F, Azzam A, Zafar U, Ahmed S, Ghauri FK, Khan AM, et al. Empagliflozin and cardiovascular outcomes: a systematic review of randomized controlled trials in populations with diabetes and heart failure. Cureus. 2025;17(8):e394397.
19. Valente V, Beer BN, Savarese G. Advances in the Pharmacological Treatment of Heart Failure With Preserved Ejection Fraction. Int J Heart Failure. 2026;8(1):24-42.
20. Ferreira JP, Anker SD, Butler J, Vasques-Nóvoa F, Marques P, Pocock S, et al. Serum Magnesium and the Effect of Empagliflozin in Heart Failure With Reduced Ejection Fraction: Findings From EMPEROR-Reduced. Heart Failure. 2026;14(2):102751.