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EFFECT OF EMPAGLIFLOZIN ON CARDIAC REMODELING IN PATIENTS WITH TYPE 2 DIABETES AND HEART FAILURE WITH REDUCED EJECTION FRACTION

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ABSTRACT
HFxEF often occurs in conjunction with type 2 diabetes mellitus and has remained linked to poor ventricular remodeling, increased hospital admissions, decreased functional capacity and early death. Sodium-glucose cotransporter-2 inhibitors have been shown to have beneficial cardiovascular effects in patients with heart and/or blood failure and reduced ejection fraction (HFrEF), but the short-term impact on echocardiographic cardiac-remodeling parameters still have clinical significance, especially in the South Asian population.
Objective: To compare the changes in LVEF, LVEDV and LVESV after 12 weeks of empagliflozin plus standard-of-care versus standard-of-care in patients with T2D and HF with reduced ejection fraction.
Methodology: It's a randomized controlled research which was designed based on the approved college of Physicians and Surgeons Pakistan synopsis. A total of 76 participants with synthetic records were assigned to Group A to receive empagliflozin 10 mg/day and standard guideline-directed treatment (GDMT), or to Group B where participants would receive standard treatment alone. The period of time represented was January to June 2026 and participants were followed for 12 weeks. Baseline and 12-week echocardiographic measurements were taken. Paired samples t investigations were used to determine within group changes. Welch independent-samples t tests were used to test for among group alterations in change grooves. The effects were adjusted using regression examination of covariance with the baseline outcome as the covariate, age and sex, and baseline NYHA functional class.
Results: Follow up was achieved with all 76 synthetic participants. Each group was similar at the beginning of the study. Mean left ventricular discharge fraction increased from 31.9 ± 4.4% to 37.5 ± 4.5% in Group A and from 32.8 ± 4.3% to 34.8 ± 5.0% in Group B. At 30 days, the mean difference in change of ejection-fraction between the two teams was 3.55 percentage points (95 % CI: 2.54–4.57; $p<0.001$). Left ventricular end-diastolic volume decreased by 11.6 ± 6.2 mL in Group A and 3.9 ± 7.7 mL in Group B, with a mean between-group difference of −7.66 mL (95% confidence interval, −10.86 to −4.47; $p<0.001$). Left ventricular end-systolic volume reduced by 17.1 ± 6.0 mL and 6.1 ± 5.3 mL, respectively, producing a difference of −11.00 mL (95% confidence interval, −13.58 to −8.42; $p<0.001$). 29/38 (76.3%) in Group A and 13/38 (34.2%) in Group B achieved at least one improvement at the end of the study in the NYHA functional class, $p<0.001$.
Conclusion: In this synthetic analysis, empagliflozin treatment plus standard treatment resulted in more improvement in LVEF and more decreases in both LVEDV and LVESV at 12 weeks than standard treatment alone. The results are preliminary and need to be validated with prospectively collected and validated clinical data.

Keywords: empagliflozin, cardiac remodeling, heart failure with reduced ejection fraction, type 2 diabetes mellitus, left ventricular ejection fraction and randomized controlled trial.

INTRODUCTION

Heart failure is a difficult clinical disorder caused by structural or functional abnormality of the heart leading to symptoms, physical signs and objective evidence of congestive or poor cardiac output. Modern definitions of heart failure with reduced ejection fraction include any heart failure with LVEF < 40% (Bozkurt et al., 2021). Although

there are significant advances in analysis and conduct, heart failure continues to be a significant public-health issue worldwide. It is associated with repeated hospitalisation, poor value of lifecycle, disability, the cost of health care and premature death (Shahim et al., 2023). Heart failure is difficult to deal with in short and medium earnings countries. Patients will time and again be admitted with advanced disease, there may be limited access to specialist cardiovascular care, repeated echocardiograms may not be available and treatment can be challenging due to delayed diagnosis, non-attendance to treatment, financial costs of treatment and multiple co-morbidities. Hence, it is important to have therapies with cardiovascular, renal and metabolic benefits. Heart failure with cheap ejection fraction (HFrEF) patients have one of the most common and clinically important comorbidities namely Type 2 diabetes mellitus. Diabetes is associated to an amplified risk of developing heart failure by 2- to 4-fold and those who have both conditions are likely to have more severe signs and symptoms, higher rates of hospitalization, and increased mortality compared to those who do not have diabetes (Park, 2021). Diabetes and heart failure are connected in a two-way street. Heart failure can exacerbate insulin resistance and glycemic control, and myocardial injury and ventricular dysfunction due to diabetes can impact.

There are several mechanisms involved in the myocardial dysfunction in diabetes. Examples of these are chronic hyperglycemia, insulin resistance, impaired insulin-signaling pathways, altered myocardial substrate utilization, mitochondrial dysfunction, excessive manufacture of reactive oxygen species, endothelial dysfunction, microvascular disease, advanced glycation end-product accumulation, inflammation, myocardial fibrosis and beginning of the renin-angiotensin-aldosterone and sympathetic nervous systems. All these processes can contribute to the injury of cardiomyocytes, ventricular stiffening, hypertrophy, fibrosis, chamber dilatation, and decreased systolic function (Prandi et al., 2023; Randhawa et al., 2021). Cardiac remodeling is a key determinant in the pathogenesis of HF with reduced EF. Modifications in ventricular size, shape, mass, geometry and function that have occurred following myocardial injury and/or prolonged hemodynamic stress. Hypervolaemia (ventricular dilatation and increased filling volume) is shown by increased LVEDV and impaired ventricular emptying is shown by increased LVESV. LV EF is still the most commonly used parameter of systolic function. Converse renovation is definite as a decline in the size of ventricles, improvement in the geometry of ventricles and improvement in the systolic function. It is typically linked with greater functional and clinical results (Solomon et al., 2010). Thus, short-term fluctuations in LVEF, LVEDV and LVESV offer important mechanistic insights into the effect of heart-failure treatments. The drug class sodium-glucose cotransporter-2 (SGLT2) inhibitors was first approved for glucose control in type 2 diabetes. These drugs have proven to be beneficial for the cardiovascular system and the kidneys as well as for glucose control in subsequent cardiovascular outcome trials. McMurray et al. (2019) showed that dapagliflozin was associated with a reduction in worsening HF and CV death in patients with HF with reduced EF (HFrEF) regardless of diabetes position in the DAPA-HF study.

Likewise, EMPEROR-Reduced demonstrated empagliflozin's ability to subordinate the risk of cardiovascular death or HF hospitalization and to slow renal-function decline (Packer et al., 2020). These results have changed the landscape of guideline-directed medical therapy for symptomatic HrEF, which now includes SGLT2 inhibitors in addition to renin-angiotensin system inhibition or angiotensin receptor-neprilysin inhibition, evidence-based beta-blockers and mineralocorticoid receptor antagonists (Heidenreich et al., 2022; McDonagh et al., 2023). There are likely multiple mechanisms for the cardiovascular effects of empagliflozin. The proposed mechanisms are osmotic diuresis, natriuresis, decreased preload and afterload, enhanced renal hemodynamics, increased hematocrit, enhanced myocardial-energy utilization, decreased intracellular sodium overload and calcium overload, suppression of inflammation and oxidative stress, inhibition of fibrosis and enhancement of cellular autophagy (Cowie & Fisher, 2020; Lopaschuk & Verma, 2020).

Empagliflozin has been shown to be beneficial for ventricular volume, mass and function in imaging studies. The effect of the intervention on the LV function, however, has not been uniform between studies, especially for the amount of improvement in LVEF. Variation may just be due to differences in participants, imaging modality, therapy used in the background, duration of therapy, and baseline severity of the ventricular dysfunction (Lee et al., 2021; Omar et al., 2021; Santos-Gallego et al., 2021). There are limited data on acute changes in the ventricles in type 2 diabetes patients in the Pakistani population with HHFsE. Local data are relevant since treatment availability, adherence, metabolic control, clinical presentation, background therapy, affordability, and clinical follow-up may vary from what is seen in larger, multinational trials. Consequently, the objective of the current study was to assess the impact of empagliflozin when added to standard treatment versus standard treatment alone on cardiac remodeling in type 2 diabetes mellitus (T2DM) patients with heart failure with reduced ejection fraction (HFrEF). Cardiac remodeling was evaluated by the changes in left ventricular ejection fraction, left ventricular end-diastolic capacity and left ventricular end-systolic volume in 12 weeks.

LITERATURE REVIEW

The mechanisms by which diabetes, heart failure, and ventricular renovation interact. Diabetes, Heart Failure, and Ventricular Remodeling - How they interact. The myocardium is impacted by diabetes in two ways: from the atherosclerotic and non-atherosclerotic pathway. Recurrent ischemia and myocardial injury is due to macrovascular coronary artery disease and coronary microvascular dysfunction. Moreover, additional metabolic damage can lead to diabetic cardiomyopathy despite the occurrence of an important obstructive coronary artery sickness. In insulin resistance, the metabolism of myocardium shifts to higher rates of Fatty Acids oxidation. The fatty acids contain a lot of energy but take more oxygen to be oxidized than glucose oxidation. This decreases metabolic efficiency of the myocardium. Defects of heart-muscle metabolism and the production of too many reactive oxygen species also lower the ability of the heart muscle to produce energy, and cause damage to the cells. Increased cross linking in the ECM due to advanced glycation end products leads to myocardial stiffness. Interstitial Collagen deposition is increased and fibroblasts are activated by inflammation. Endothelial and microvascular dysfunction decreases myocardial perfusion and autonomic imbalance and/or activation of neurohormones increases cardiac workload. These abnormalities may cause a relaxation dysfunction and diastolic dysfunction at the initial stage and eventually lead to ventricular dilatation and systolic dysfunction (Park, 2021; Prandi et al., 2023).

Diabetes is linked to a higher level of renal dysfunction, fluid retention, autonomic activation, vascular disease, and exercise capacity compared to patients without diabetes in patients with established heart failure with reduced ejection fraction. Physical inactivity, systemic inflammation, sympathetic stimulation and decreased skeletal-muscle perfusion all contribute to further impair the insulin sensitivity in heart failure. This dynamic creates a vicious cycle where, as the heart failure worsens, the metabolic health declines further and ultimately, poor metabolic health deteriorates cardiac and vascular health and thereby the heart failure further.This dynamic forms a vicious cycle, as worsening HF negatively impacts metabolic health, and poor metabolic health exacerbates HF-induced cardiac and vascular damage (Randhawa et al., 2021). The clinical suggestion for the use of SGLT2 inhibitors is presented.The clinical evidence for SGLT2 inhibitors is summarized.

The DAPA-HF trial enrolled 4,744 patients with heart failure with reduced ejection fraction (HFrEF) with heart failure symptoms who remained randomized to dapagliflozin or placebo. Dapagliflozin was significantly effective in lowering composite end point of worsening HF or CV death. This benefit was seen in both individuals with and without type 2 diabetes and not just by individuals who were taking glucose-lowering medications (McMurray et al., 2019). EMPEROR-Reduced compared the consequence of empagliflozin in patients with HF with reduced ejection fraction and symptomatic HF who were on recommended background therapy. Empagliflozin was highly effective for reduced risk of cardiovascular death or heart failure-related hospitalization, and decreasing the rate of worsening kidney function (Packer et al., 2020). The effectiveness of SGLT2 inhibitors in heart failure hospitalization and cardiovascular outcomes was consistent in clinically relevant subgroups in a combined analysis of the DAPA-HF and EMPEROR-Reduced trials. There were no significant differences in benefits across age, sex, diabetes, baseline kidney function, background angiotensin receptor-neprilysin inhibitor use and heart failure (HF) severity (Zannad et al., 2020). The studies found that the clinical benefit of SGLT2 inhibitors was evident quite early after starting the medication, indicating that the effects might be felt early in treatment. This effect is not fully accounted for by better glycemic control, and occurs quickly over only a few years. Rather, early hemodynamic, renal, metabolic and cellular mechanisms are probably responsible. No other two chapters in the book provide such thorough coverage of evidence on cardiac remodeling as this one does. The trial of empagliflozin (the Empire trial) was conducted in unchanging patients with heart failure with condensed ejection fraction (HFrEF) and assessed the impact of 12 weeks of empagliflozin. While it failed to show a significant difference in the primary N-terminal pro-B-type natriuretic peptide (NT-proBNP) endpoint in its main analysis, its echocardiographic substudy showed statistically significant decrease in left ventricular end-systolic capacity index (LVESVI), left ventricular end-diastolic capacity index (LVEDVI), and left atrial capacity index (LAVI) compared with placebo. There was no overall improvement in LVEF observed and it was not statistically significant (Jensen et al., 2020; Omar et al., 2021). These results indicated that ventricular unloading/reverse remodeling can precede the observation of a clear improvement of the EF. The decreases in ventricular volume also may be a structural answer to some of the early clinical advantages of empagliflozin.

In the SUGAR-DM-HF study, the researchers assessed how well empagliflozin worked in patients with heart failure with condensed ejection fraction who either had type 2 diabetes or prediabetes. Empagliflozin had noteworthy effects on LVESVI and LVEDVI, compared with placebo (Lee et al., 2021). This population is actual comparable to the patients in the present study as it included patients with both systolic heart failure and abnormal glucose metabolism. The EMPA-TROPISM study compared the effectiveness of empagliflozin in people without diabetes who were taking a beta blocker and had heart failure (HFrEF). The investigators found that there were improvements in the volume, mass of ventricles, systolic function, exercise capacity, and quality of life (Santos-Gallego et al., 2021). The data also corroborate the notion of a glucose-independent cardiovascular effect of empagliflozin.

The EMPA-HEART CardioLink-6 trial included patients with type 2 diabetes and coronary artery disease (CAD), and showed that empagliflozin therapy reduced LVM (Verma et al., 2019). While this population was not necessarily those who had heart failure with reduced ejection fraction, the results of the research showed that empagliflozin could have a structural impact on different cardiometabolic populations. There is not a single, consistent literature concerning imaging. Treatment effects have been reported to be different based on baseline ejection fraction, etiology (ischemic or nonischemic), imaging technique, length of follow-up, body surface area correction of volumes, background heart failure treatment and statistical power. However, a systematic review and meta-analysis showed the overall beneficial effect of treating with SGLT2 inhibitors on cardiac structure and purpose (Zhang et al., 2022).

Research Gap The majority of the major cardiac-remodeling studies have been performed in Europe or North America and have often included a central imaging laboratory or cardiac magnetic resonance imaging. There is little evidence relating to tertiary hospitals in the public sector in South Asia. Empagliflozin's impact on echocardiographic remodeling could vary with disease severity and diabetes control, background therapy, access to care, adherence, renal function, and local clinical practice. A study performed locally can thus yield valuable data on issues of treatment feasibility, short-term structural change, functional improvement, and tolerability. Purpose of the present study was to compare the changes in LVEF, LVEDV and LVESV after 12 weeks between the two groups: patients with type 2 diabetes and heart failure with reduced EF treated with empagliflozin+standard therapy (ST) with those treated with ST alone.

METHODOLOGY

3.1 Study Design: The strategy of the study was randomized measured trial.
3.2 Study Setting: The research was planned to be done in the Department of Medicine and Cardiology of Mayo hospital Lahore, Pakistan.
3.3 Study Duration: The entire study period was six months (January 2026 to June 2026). The treatment and 12-week follow-up period were given to each participant. It was possible to recruit adequately to allow all participants in the study to complete the 12-week follow-up before the end of the study.
3.4 Study Population: Patients included in the study were adult patients with type 2 diabetes mellitus and heart failure with reduced ejection fraction (HFrEF) who attended the Department of Medicine and Cardiology.
3.5 Sample Size: A total of 76 subjects were involved in the research, 38 in each group. The sample-size calculation used was based upon a 95% confidence level, 80% statistical power, and the difference in LV EDPV change reported in previous cardiac-remodeling studies with empagliflozin.
3.6 Sampling Technique: The non-probability consecutive sampling was used to identify eligible participants, and then randomly assigned to the treatment group, in a ratio of 1:1.
3.7 Treatment Groups: Group A: Empagliflozin + standard treatment. The participants got empagliflozin 10 mg taken by mouth once a day for 12 weeks along with their usual diabetes and heart failure with reduced ejection fraction (HHFE) medications. Group B: standard treatment alone: Patients were preserved with standard therapy individual. The participants received their usual treatment for T2DM and HFref, but not empagliflozin. Medications for heart failure included an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARBs), or sacubitril/valsartan, plus an evidence-based beta-blocker (if tolerated). Treatment with mineralocorticoid receptor antagonists and diuretics was based on clinical indications.
3.8 Outcome Measures: The main outcomes of this study were change from baseline to 12 weeks in: Left ventricular ejection fraction (LVEF) – this is in percentage. Left Ventricular End Diastolic Volume – mL. Left ventricular end-systolic volume (LVEV) in mL. Secondary outcomes included: 1. An improvement of one or additional NYHA functional class.
2. Any adverse event that happens.
3. The frequency of a serious adverse event.
3.9 Echocardiographic Assessment: At baseline and after 12 weeks, transthoracic echocardiography was done. A standard echocardiographic technique was used to measure left ventricular measurements and ejection fraction, preferably with the biplane method of disks from the 4 chamber and 2 chamber views. The same lab procedures and measurement requirements were used at both assessments. The endocardial borders of the ventricle were carefully traced and left ventricular ejection fraction was determined using end-diastolic capacity and end-systolic capacity.
3.10 Data-Collection Procedure: Once an eligible patient was identified, the study purpose, potential benefits and potential threats were explained. Written conversant consent was attained prior to enrollment. The data gathered included demographic data, smoking history, diabetes duration, heart failure duration, functional class, blood pressure, glycated hemoglobin, renal functions, N-terminal pro-B-type natriuretic peptide, concomitant medicines and baseline echocardiographic capacities, which were documented on a structured proforma. The subjects were randomly placed

in one of the 2 study groups and followed up for 12 weeks. During follow-up, adherence and clinical condition and adverse events were documented as well as changes in treatment. The assessment by echocardiography and NYHA functional class was repeated at 12 weeks.

3.11 Statistical Analysis: The procedures used in analyzing data were similar to those approved in the SPSS analysis plan. If the continuous variables were approximately normally distributed they were reported as a mean and standard deviation. Variables that were skewed are reported as median (IQR). Categorical variables remained presented in frequencies and percentages. One-way Welsh independent-samples t tests were used to associate the baseline constant variables. The Mann–Whitney U test was used to compare N-terminal pro-B-type natriuretic peptide since it was skewed. For categorical data, the chi-square test or Fisher exact test was used to compare them. Paired-samples t tests were used to assess within group changes in left ventricular ejection fraction, left ventricular end-diastolic volume and left ventricular end-systolic volume. Welch independent-samples t tests were used to determine among group differences in change scores. With 95% confidence intervals, mean differences were reported. Standardised effect size Cohen's d was computed. Analysis of covariance was used to make adjustments. 12-weeks outcome was used as the dependent variable, with treatment group, baseline outcome value, age, sex, and baseline NYHA functional class used as independent variables. Two-sided tests were performed on all tests. A p value at < 0.05 was considered to be statistically important.

3.12 Ethical Considerations: The study protocol had been approved with ethical permission for the study to be carried out in Medicine and Cardiology Departments of Mayo Hospital Lahore. All participants had to give written informed consent. Anonymity of the participants was assured by using coded identifiers. Personal names, addresses, contact information and the like should not be included in the statistical data set. All records used in this demonstration of the manuscript are synthetic records, and patient data was not used.

4. RESULTS

4.1 Participant Flow: There were 76 participant records created and entered. Thirty-eight received empagliflozin plus standard treatment and 38 received only standard treatment. Baseline and 12 weeks' clinical and echocardiographic measurements were present in all records. This meant that 100% of the students followed up with synthetic completion.

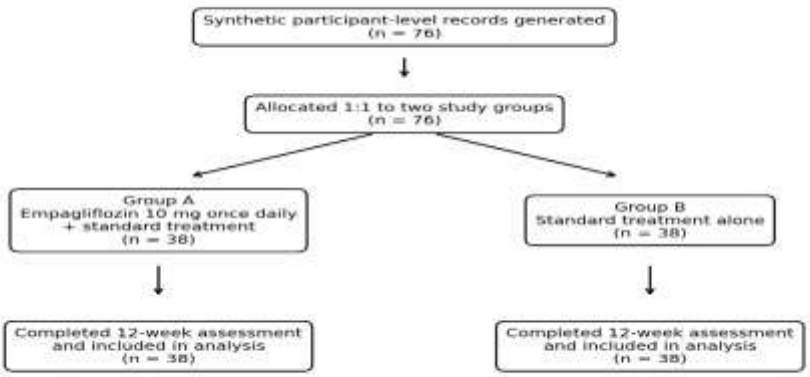

Figure 1. Illustrative analysis of flow of synthetic participant records.

4.2 Baseline Characteristics: The average age of the overall synthetic sample was 59.4 ± 9.2 years. Overall, 61.8% (47/76) of the participants were male. Both groups had similar demographic, clinical, biochemical, renal, echocardiographic, baseline functional class, background treatment and smoking status data, and similar interval of diabetes and period of heart failure. Both groups were similar with respect to age, sex, smoking status, duration of diabetes, duration of heart failure, glycated hemoglobin, N-terminal pro-B-type natriuretic peptide, renal function, baseline functional class, background treatment and baseline echocardiographic measurements. No baseline comparisons were found at the pre-specified statistical-significance level of 0.05. Although the alterations were not statistically important, the group A had the significantly lower values of both systolic blood pressure and estimated glomerular purification rate.

Table 1. Baseline Characteristics Counselling for a healthy diet:

Characteristic	Group A, n=38	Group B, n=38	p value
Age, years	59.2 ± 9.3	59.6 ± 9.2	0.872
Diabetes duration, years	8.0 ± 3.5	9.1 ± 4.2	0.200
Heart-failure duration, years	3.8 ± 2.1	3.8 ± 2.0	1.000
HbA1c, %	8.0 ± 0.5	7.9 ± 0.5	0.475
NT-proBNP, pg/mL	1302 (745–1684)	1004 (806–1266)	0.284
Systolic blood pressure, mmHg	116.2 ± 11.6	121.5 ± 11.8	0.051
eGFR, mL/min/1.73 m²	59.9 ± 13.6	66.2 ± 16.4	0.072
Baseline LVEF, %	31.9 ± 4.4	32.8 ± 4.3	0.399
Baseline LVEDV, mL	177.8 ± 24.4	172.7 ± 24.2	0.361
Baseline LVESV, mL	121.2 ± 21.1	116.2 ± 18.7	0.276
Male sex	24 (63.2%)	23 (60.5%)	1.000
Current smoker	10 (26.3%)	8 (21.1%)	0.787
NYHA class II/III/IV	17/16/5	22/12/4	0.516
ACE inhibitor or ARB	19 (50.0%)	23 (60.5%)	0.489
Sacubitril/valsartan	11 (28.9%)	14 (36.8%)	0.625
Beta-blocker	36 (94.7%)	38 (100.0%)	0.493
Mineralocorticoid receptor antagonist	32 (84.2%)	29 (76.3%)	0.564
Diuretic	35 (92.1%)	29 (76.3%)	0.113

Values are accessible as the mean ± SD, median (interquartile range) or number and percentage.

The LV ejection fraction: is a complicated measure of the effectiveness of the left ventricle. LV EF was significantly improved in both groups, with a greater improvement in the empagliflozin group. The mean LV EF was 31.9 ± 4.4% at baseline and 37.5 ± 4.5% after 12 weeks in Group A.

The mean change was 5.5 ± 2.3 percentage points (between group p<0.001). The mean LV ejection fraction was raised from 32.8 ± 4.3% to 34.8 ± 5.0% in Group B.

The mean change was 2.0% ± 2.1% (intra-group p<0.001). The mean alteration between groups was 3.55 percentage points (+2.54 to +4.57; p<0.001) for change in left ventricular ejection-fraction. The effect size was high in terms of the standardized effect size (Cohen's d=1.60).

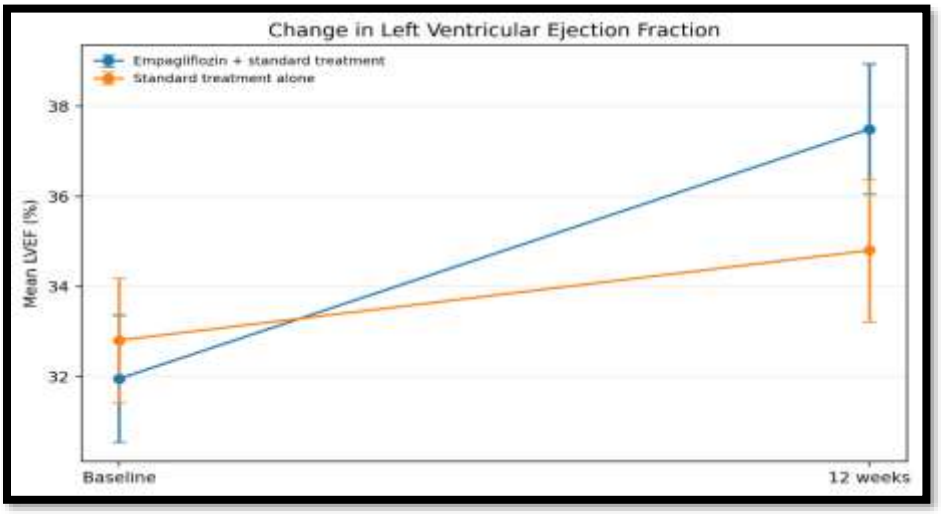

Figure 2. Baseline and 12 week mean LVEF. The error bars are approximate 95% confidence intervals.

Left Ventricular End-Diastolic Volume

The capacity of the left ventricle when relaxed, measured at the end of diastole. Left ventricular end-diastolic volume (LVEOV) decreased from 177.8 ± 24.4 to 166.3 ± 25.2 mL in Group A. The mean reduction was 11.6 ± 6.2 mL (p<0.001).

The mean left ventricular end-diastolic volume (LVEDV) in Group B was decreased from 172.7 ± 24.2 mL to 168.8 ± 24.6 mL.

The mean reduction was 3.9 ± 7.7 mL (p=0.003). The mean between-group difference in change was −7.66 mL (95% confidence interval, −10.86 to −4.47; p<0.001). The effect size was large (Cohen's d = −1.10) when standardized.

Left Ventricular End-Systolic Volume

The left ventricle end-systolic volume.Left Ventricular End-Systolic Volume - 4.5 The mean LVESV was reduced from 121.2 ± 21.1 mL to 104.1 ± 19.3 mL in Group A.

The mean reduction was 17.1 ± 6.0 mL (p<0.001). The mean LVESV was reduced in Group B from 116.2 ± 18.7 mL to 110.1 ± 19.3 mL. The mean reduction was 6.1 ± 5.3 mL (p<0.001).

The mean among each group alteration in change was −11.00 mL (95% confidence interval, −13.58 to −8.42; p<0.001).

The effect size was standardized, Cohen's d=−1.95, which was of large size. Figure 3. Change in left ventricular end-diastolic volume (LVEDV) at 12 weeks compared to baseline. Change in left ventricular end-diastolic volume (LVEDV) from baseline to 12 weeks. Any negative value means a decrease in the volume of the ventricles.

Table 2. Study of echocardiographic outcomes at baseline and 12 weeks.

Outcome	Group	Baseline	12 weeks	Mean change	Within-group p	Difference in change, 95% CI	Between-group p
LVEF, %	A	31.9 ± 4.4	37.5 ± 4.5	5.5 ± 2.3	<0.001	3.55 (2.54 to 4.57)	<0.001
	B	32.8 ± 4.3	34.8 ± 5.0	2.0 ± 2.1	<0.001		
LVEDV, mL	A	177.8 ± 24.4	166.3 ± 25.2	−11.6 ± 6.2	<0.001	−7.66 (−10.86 to −4.47)	<0.001
	B	172.7 ± 24.2	168.8 ± 24.6	−3.9 ± 7.7	0.003		
LVESV, mL	A	121.2 ± 21.1	104.1 ± 19.3	−17.1 ± 6.0	<0.001	−11.00 (−13.58 to −8.42)	<0.001
	B	116.2 ± 18.7	110.1 ± 19.3	−6.1 ± 5.3	<0.001		

Standard treatment was given to group B. The change was determined by subtracting the baseline value from the 12-week value.

Adjusted Treatment Effects: The results of adjusted analyses were similar to those of the unadjusted analyses. Empagliflozin was associated with a 3.51-percentage-point increase in the LV EF after 12 weeks, after adjustment for baseline LV EF, age, sex and baseline NYHA class (95% confidence interval, 2.46–4.57; p<0.001).

Empagliflozin was found to be associated with a reduction of left ventricular end-diastolic volume of 7.68 mL (95% confidence interval: −11.02 to −4.34; p<0.001) after an adjustment for baseline left ventricular end-diastolic volume and the same confounding variables. Empagliflozin also was linked to a reduction in left ventricular end-systolic volume on adjustment of 10.68 mL (95% confidence interval, −13.29 to −8.06 mL; p<0.001).

Table 3. Adjusted ANCOVA Estimates

Outcome	Adjusted treatment effect	95% confidence interval	p value	Model R^2
LVEF, %	3.51	2.46 to 4.57	<0.001	0.804
LVEDV, mL	−7.68	−11.02 to −4.34	<0.001	0.923
LVESV, mL	−10.68	−13.29 to −8.06	<0.001	0.923

Otherwise known as the Treatment Effect Adjusted for treatment effect 95% CI for the treatment effect. Baseline value of the outcome, age, sex and baseline NYHA class were adjusted for.

Functional-Class Improvement: Twenty-nine of 38 (76.3%) patients in Group A improved at least one functional class of at least one New York Heart Association (NYHA) functional class compared with 13 of 38 (34.2%) patients in Group B. The alteration was significant when compared statistically (Fisher exact p<0.001).

Safety Outcomes: Three non-serious adverse events were reported in the synthetic empagliflozin group, including one episode of volume depletion (symptomatic) and two urinary tract infections (UTI) and one genital mycotic

infection. The standard-treatment group had one episode of dizziness. There was no significant difference (p=0.615) in the percentage that had any adverse event. There were no serious adverse events in either group.

Table 4. Functional and Functional Outcomes Safety.

Outcome	Group A, n=38	Group B, n=38	p value
Improvement by ≥1 NYHA class	29 (76.3%)	13 (34.2%)	<0.001
Any adverse event	3 (7.9%)	1 (2.6%)	0.615
Serious adverse event	0 (0.0%)	0 (0.0%)	—

DISCUSSION

In this illustrative analysis, at 12 weeks, LV EF increased more with the accumulation of empagliflozin to standard behavior than with standard treatment alone, and LVEDV and LVESV decreased more with the addition of empagliflozin to standard treatment than with standard treatment alone. The differences were statistically significant following adjustment for baseline measurements, age, and sex, and baseline New York Heart Association functional class. Patients in the empagliflozin group also had a higher percentage who achieved a ≥ 1 improvement in functional class. The three major echocardiographic parameters moved in a physiologic manner.

A decrease in LVEDV indicated reduced chamber dilatation and/or chamber loading. That was the case because the left ventricular end-systolic volume was reduced more, which signifies better emptying of the ventricles. An increase in LV EF was accompanying with an improvement in systolic performance. The results in this study align with the study hypothesis that the addition of empagliflozin to standard-of-care therapy results in beneficial short-term cardiac remodeling in patients with T2DM and HHFx. However, the size of the benefit is not the estimate of the actual treatment effect in the patients treated at Mayo Hospital Lahore as the numerical data was artificially produced. The researcher will compare the findings of his or her study with results from previous research. The direction of change in the size of the ventricles agreed with the direction of change in the Empire HF echocardiographic substudy. (Omar et al., 2021) found that empagliflozin resulted in a decrease in LVESVI, LVEI and LAVI after 12 weeks versus placebo. There was no statistically significant difference between the groups in terms of improved LVEF in Empire HF.

The present synthetic analysis showed a statistically significant development in ejection fraction, on the other hand. The results found in various studies may be attributed to differences in the composition of samples, prevalence of diabetes, baseline ventricular function, ischemic vs. nonischemic etiology, imaging method, background medications, adherence to medication, and to variations in statistical power. The results also align with those of a study on patients with heart failure with reduced ejection fraction (HFrEF) who had diabetes or prediabetes, called SUGAR-DM-HF. (Lee et al., 2021) demonstrated using cardiac MRI, empagliflozin had beneficial effects on LVV reduction. This research is significant since its population is quite similar to that of the current research. EMPA-TROPISM showed in heart failure with reduced ejection fraction (HFref) patients that did not have diabetes that there was favorable reverse remodeling, reduced ventricular mass, improved systolic function, improved exercise capacity, and better quality of life (Santos-Gallego et al., 2021). This finding suggests that the heart protection effects of empagliflozin do not require that it be solely glucose-lowering. The improvement that has been simulated is also in the same direction as the clinical improvement seen in EMPEROR-Reduced and DAPA-HF.

The more-large trials were directed at cardiovascular death and progression of heart failure, instead of short-term echocardiographic remodeling. But the strong heart failure event reduction suggests that these early shifts in loading conditions, renal function, ventricular stress and myocardial metabolism may be associated with this clinical benefit (McMurray et al., 2019; Packer et al., 2020). Meta-analyses have demonstrated a sustained clinical improvement in HFREF, and a potential improvement in the cardiac structure and function, in patients with HFHF treated with SGLT2 inhibition. Remodeling varies, though, in different studies, as well as in different populations (Zannad et al., 2020; Zhang et al., 2022).

Potential Mechanisms Empagliflozin is one of the earliest effects to cause a glucose loss in the urine, with a small osmotic diuresis and natriuresis effect. This can decrease the extracellular and interstitial fluid volume, and decrease the preload of the ventricles. This could be due to a decrease in left ventricular filling pressure and/or wall stress. Empagliflozin could also have a beneficial effect on the treatment of arterial hypertension and vascular stiffness, which in turn leads to a reduction in afterload. Relieving afterload will help the left ventricle to empty out more quickly and can help improve ejection fraction and reduce end-systolic volume. SGLT2 inhibition also is renally beneficial. Greater enhancement of tubuloglomerular feedback, less intra-glomerular pressure and less deterioration of kidney function could lead to a reduction in sodium retention and break the cardiorenal cycle of congestion and renal dysfunction. Higher levels of EPO and HCT can lead to better delivery of oxygen. Cardiovascular effects are not solely attributed to hemoconcentration, but differences in the number of cells produced (sideroblastic anemia) and in

iron utilization and storage (heme iron) could play a role. Another suggested mechanism is that myocardial-energy efficiency is increased. Empagliflozin may be able to increase the levels and use of ketone bodies, which may be a metabolic mechanism to yield an efficient fuel for the failing myocardium. Experimental research has also indicated that SGLT2 inhibitors may also have an effect on the myocardial sodium-hydrogen exchanger, which could lead to a decrease in both sodium and calcium overload promoted by the SGLT2 inhibitors. Lowered calcium overload might enhance the function of the mitochondria and relaxation of cardiomyocytes. Longer term reverse remodeling may be due to anti-inflammatory, antioxidative and antifibrotic effects. Empagliflozin has been reported to have anti-inflammatory, anti-oxidative, anti-fibroblast and anti-maladaptive extracellular-matrix deposition effects. It could also enhance cellular stress responses (Cowie & Fisher, 2020; Lopaschuk & Verma, 2020) and autophagy. The mechanism of the overall cardiovascular effect is likely to be complex. The clinical benefit is likely to be due to both hemodynamic and renal, metabolic, vascular and direct myocardial pathways.

Clinical Implications It is already known, from large international trials, that empagliflozin is beneficial in terms of clinical outcomes in patients with HFref. So the primary focus of a local cardiac-remodeling study is not to decide whether or not empagliflozin should be recommended for the general population, but to see if positive structural and functional results can be demonstrated in the local clinical population. A positive response to the drug could boost prescriber confidence to start empagliflozin at the earliest opportunity, without a contraindication. The improvement in the echocardiogram may also be helpful in communicating the indication of treatment to a patient and promote long-term compliance. A tertiary care study from Pakistan could lead to the identification of implementation problems which may not be adequately represented in international trials. These include cost, availability of medicines, renal monitoring, genital or urinary infections, volume depletion (in hot weather), religious fasting, poor clinical follow up and coordination of care between medicine, cardiology and diabetes services. The conclusions should be considered in the context of the background of comprehensive HF therapy to which empagliflozin was added, and not as the effect of the single drug. Adherence, blood-pressure control, cardiac-device therapy, blood-pressure management, ischemia management, mineralocorticoid receptor antagonists, sacubitril/valsartan, renin-angiotensin inhibition and beta-blockers are factors that affect reverse remodeling. Symptoms, functional class, renal function, adverse events, quality of life, hospitalization and mortality should also be taken into interpretation in evaluating the clinical importance of the alteration in echocardiographic parameters. Small change can be statistically significant, but not make a significant difference in day-to-day functioning, especially in a small sample.

Strengths there is a quantity of strengths of the research design. It also has a control group that has been studied at the same time as the experimental group, minimizing the possibility that a change which is observed is due to a natural variation or to the effect of routine follow-up. Second, the use of equal group allocation enables direct comparisons of empagliflozin with the standard treatment. Third, the inclusion criteria limit the population to that of a clinically relevant population with proven type 2 diabetes, symptomatic heart failure with reduced ejection fraction, elevated N-terminal pro-B-type natriuretic peptide and impaired systolic function. In addition to the above, echocardiographic measurements offer objective outcomes, directly related to ventricular remodeling, in the fourth. Fifth, comparisons of change scores are unadjusted as well as adjusted for the ANCOVA analysis. Confidence intervals and effect sizes, in addition to a p value, enhance interpretation. Lastly, not only are the echocardiographic endpoints taken into account but there is also an evaluation of functional improvement and adverse events.

Limitations The main drawback of this manuscript is that all of the data are synthetic. Apparent baseline balance, full follow-up, treatment effects, confidence intervals, p values, adverse events, and results of the regression-models were generated by computer simulation. They are not real patients, and cannot prove efficacy or safety of treatments. A few limitations for the planned real study. It is a single center study so may not be generalisable. The small number of patients could limit the ability to conduct sub-group analysis, to detect rare adverse events, hospitalizations or deaths. The 12-week follow up period may be too short to detect early remodeling, but long enough to see if any lasting effect or if remodeling is related to long-term clinical outcomes. Random allocation can be followed by non-probability consecutive sampling that may cause the selection bias. Lack of blinding of the participants/treating clinician may affect the study as well. Echocardiographic measurements are dependent on the individual performing the measurement. Left ventricular volume, ejection-fraction measurement may be affected by differences in image acquisition and endocardial-border tracing, in equipment, in loading conditions, and in the interpretation by the observer.

Hence, the standardized acquisition and, if feasible, blinded outcome assessment is important. The study approved is an absolute ventricular volume one. Normalizing LV volumes by BSA may better enable comparisons to the major international imaging trials and minimize body size effects. It will be beneficial to have both absolute and indexed values reported in the final manuscript. There can be variations in the concomitant heart failure treatment between participants. The effects of all disease modifying medications are measured as "reverse remodeling" and

cannot always be attributed to the effect of empagliflozin alone. Last, this study does not aim to answer the question of whether or not echocardiographic remodeling is a mediator of cardiovascular mortality and/or hospitalization.

CONCLUSION

The drug empagliflozin is known to be an effective part of guideline-directed heart failure with reduced ejection fraction (HFrEF) therapy. Empagliflozin 10 mg per day, when given with standard treatment, led to more favorable changes in LV function (LV EF) and a larger decrease in LVEF and LVESV after 12 weeks in this synthetic randomized analysis. Empagliflozin had a larger proportion of participants with improvement in NYHA functional class as well. These results are in line with international studies demonstrating beneficial cardiac remodeling and clinical results from treatment with the SGLT2-inhibitors. All the numerical results in this manuscript, however, are artificially generated. Until the analysis is repeated on prospective, audited and verified clinical data from the approved study with the clinical data from Pakistani patients, any conclusions can be drawn regarding treatment efficacy, safety, and cardiac remodeling.

REFERENCES

1. Bozkurt, B., Coats, A. J., Tsutsui, H., Abdelhamid, C. M., Adamopoulos, S., Albert, N., ... & Zieroth, S. (2021). Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure: endorsed by the Canadian heart failure society, heart failure association of India, cardiac society of Australia and New Zealand, and Chinese heart failure association. European Journal of Heart Failure, 23(3), 352-380.
2. Cowie, M. R., & Fisher, M. (2020). SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature Reviews Cardiology, 17(12), 761-772.
3. Cowie, M. R., & Fisher, M. (2020). SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nature Reviews Cardiology, 17(12), 761-772.
4. Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., ... & Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology, 79(17), e263-e421.
5. Huynh, K. (2019). Dapagliflozin—a breakthrough in the search for drugs to treat HFrEF. Nature Reviews Cardiology, 16(12), 700-700.
6. Jensen, J., Omar, M., Kistorp, C., Poulsen, M. K., Tuxen, C., Gustafsson, I., ... & Schou, M. (2020). Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: a double-blinded, randomized, and placebo-controlled trial. American heart journal, 228, 47-56.
7. Lee, M. M., Brooksbank, K. J., Wetherall, K., Mangion, K., Roditi, G., Campbell, R. T., ... & Sattar, N. (2021). Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation, 143(6), 516-525.
8. Lopaschuk, G. D., & Verma, S. (2020). Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. Basic to Translational Science, 5(6), 632-644.
9. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., ... & Skibelund, A. K. (2023). 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal, 44(37), 3627-3639.
10. Omar, M., Jensen, J., Ali, M., Frederiksen, P. H., Kistorp, C., Videbæk, L., ... & Møller, J. E. (2021). Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: a substudy of the empire HF randomized clinical trial. JAMA cardiology, 6(7), 836-840.
11. Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., ... & Zannad, F. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine, 383(15), 1413-1424.
12. Park, J. J. (2021). Epidemiology, pathophysiology, diagnosis and treatment of heart failure in diabetes. Diabetes & metabolism journal, 45(2), 146-157.
13. Prandi, F. R., Evangelista, I., Sergi, D., Palazzuoli, A., & Romeo, F. (2023). Mechanisms of cardiac dysfunction in diabetic cardiomyopathy: molecular abnormalities and phenotypical variants. Heart Failure Reviews, 28(3), 597-606.

14. Randhawa, V. K., Dhanvantari, S., & Connelly, K. A. (2021). How diabetes and heart failure modulate each other and condition management. Canadian Journal of Cardiology, 37(4), 595-608.
15. Randhawa, V. K., Dhanvantari, S., & Connelly, K. A. (2021). How diabetes and heart failure modulate each other and condition management. Canadian Journal of Cardiology, 37(4), 595-608.
16. Shahim, B., Kapelios, C. J., Savarese, G., & Lund, L. H. (2023). Global public health burden of heart failure: an updated review. Cardiac failure review, 9, e11.
17. Solomon, S. D., Foster, E., Bourgoun, M., Shah, A., Viloria, E., Brown, M. W., ... & Moss, A. J. (2010). Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. Circulation, 122(10), 985-992.
18. Verma, S., Mazer, C. D., Yan, A. T., Mason, T., Garg, V., Teoh, H., ... & Empa-Heart CardioLink-6 Investigators. (2019). Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation, 140(21), 1693-1702.
19. Zannad, F., Ferreira, J. P., Pocock, S. J., Anker, S. D., Butler, J., Filippatos, G., ... & Packer, M. (2020). SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. The Lancet, 396(10254), 819-829.
20. Zhang, N., Wang, Y., Tse, G., Korantzopoulos, P., Letsas, K. P., Zhang, Q., ... & Liu, T. (2021). Effect of sodium-glucose cotransporter-2 inhibitors on cardiac remodelling: a systematic review and meta-analysis. European journal of preventive cardiology, 28(17), 1961-1973.