

Original Article

SGLT-2 inhibitor dapagliflozin improves left ventricular diastolic function and reduces circulating inflammatory markers in HFpEF patients: a retrospective cohort study

Jian-Feng Ye^{1*}, Jian Zhang^{1*}, Xu Wang¹, Guang-Quan Yang², Min-Fang Yao², Wei Liu¹, Lin-Lin Pei¹

¹Department of Cardiovascular Medicine, The Second People's Hospital of Kunshan, Kunshan 215300, Jiangsu, China; ²Department of Ultrasound, The Second People's Hospital of Kunshan, Kunshan 215300, Jiangsu, China.
*Co-first authors.

Received March 23, 2026; Accepted July 10, 2026; Epub September 15, 2026; Published September 30, 2026

Abstract: Objective: This study sought to evaluate the efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitor Dapagliflozin in ameliorating left ventricular diastolic function (LVDF) and attenuating systemic inflammatory biomarkers in patients with heart failure with preserved ejection fraction (HFpEF). Methods: A total of 114 patients diagnosed with HFpEF were retrospectively enrolled and allocated into either the SGLT-2 inhibitor group (Dapagliflozin combined with standard guideline-directed therapy; n = 58) or the Control group (standard guideline-directed therapy alone; n = 56). Echocardiographic parameters at baseline and 6-month follow-up were measured, including early diastolic transmitral flow velocity/early diastolic mitral annular velocity ratio (E/e') and left atrial volume index (LAVI). Circulating inflammatory markers comprising high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were examined. In addition, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores were collected for functional and symptomatic assessments. Results: After six months of treatment, the SGLT-2 inhibitor group exhibited significant improvements in cardiac diastolic parameters. E/e' ratio decreased significantly from 14.8 ± 3.2 to 12.1 ± 2.7 ($P < 0.001$), and LAVI decreased from 38.6 ± 8.4 to 34.2 ± 7.1 mL/m² ($P = 0.003$). Consistently, systemic inflammation was markedly alleviated. hs-CRP decreased from 4.82 ± 1.73 to 2.94 ± 1.28 mg/L ($P < 0.001$), IL-6 decreased from 8.46 ± 2.91 to 5.73 ± 2.14 pg/mL ($P = 0.002$), and TNF-α decreased from 12.8 ± 4.6 to 9.4 ± 3.8 pg/mL ($P = 0.011$). Moreover, NT-proBNP levels in the SGLT-2 inhibitor group exhibited a substantial 28.4% reduction, which was significantly greater than the 8.7% reduction observed in the Control group ($P = 0.004$). There was also a striking reduction in MLHFQ scores in the SGLT-2 inhibitor group (average reduction: -8.6 ± 4.2 points, $P < 0.001$), demonstrating significant symptomatic improvement. Conclusion: SGLT-2 inhibitor Dapagliflozin effectively improved LVDF and reduced systemic inflammatory burden in patients with HFpEF. These findings support the role of Dapagliflozin as a promising disease-modifying therapeutic agent for HFpEF.

Keywords: SGLT-2 inhibitor, dapagliflozin, heart failure with preserved ejection fraction, diastolic function, inflammation, E/e' ratio

Introduction

Heart failure (HF) represents one of the most pressing cardiovascular health challenges worldwide. It affects approximately 64 million individuals globally, imposing substantial burdens on healthcare systems [1]. Heart failure with preserved ejection fraction (HFpEF) accounts for nearly half of all HF cases, characterized by preserved left ventricular systolic function (LVSF) but impaired diastolic filling, elevated filling pressures, and reduced cardiac

output during exertion [2]. The prevalence of HFpEF continues to rise. Primary drivers include population aging and increasing burden of cardiometabolic comorbidities (e.g., hypertension, obesity, diabetes mellitus, and chronic kidney disease) [3]. Additionally, HFpEF has been historically termed "therapeutic orphan" due to the paucity of clinically effective pharmacological interventions.

The pathophysiology of HFpEF is notably complex and multifactorial, involving a constella-

tion of abnormalities that extend beyond simple diastolic dysfunction to encompass systemic inflammation, endothelial dysfunction, microvascular abnormalities, and myocardial fibrosis [4]. The systemic proinflammatory state defines HFpEF pathogenesis. In this state, levels of circulating inflammatory mediators, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), are increased. Such increases promote coronary microvascular endothelial dysfunction, reduce nitric oxide bioavailability, and ultimately lead to cardiomyocyte hypertrophy and interstitial fibrosis [5]. This inflammation-driven paradigm has fundamentally shifted our understanding of HFpEF from a purely hemodynamic disorder to a systemic inflammatory condition with cardiac manifestations. The resultant myocardial stiffness and impaired relaxation lead to elevated left ventricular filling pressures, which manifest clinically as dyspnea, exercise intolerance, and fluid retention [6]. Moreover, left atrial remodeling, pulmonary hypertension, and right ventricular dysfunction frequently accompany left ventricular diastolic abnormalities, creating a complex hemodynamic milieu that has historically proven resistant to pharmacological intervention.

For decades, the therapeutic landscape for HFpEF has remained disappointingly barren. Numerous large-scale randomized controlled trials have demonstrated the efficacy of pharmacological agents against heart failure with reduced ejection fraction (HFrEF). Unfortunately, these trials failed to demonstrate significant benefits of such treatment in HFpEF populations [7]. Various pharmacological agents, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and even angiotensin receptor-neprilysin inhibitors, have yielded largely neutral or only modestly positive results when applied to patients with truly preserved ejection fractions [8]. This therapeutic void has prompted intense investigation into novel pharmacological targets and mechanisms that may address the unique pathophysiological features of HFpEF. Moreover, HFpEF represents a heterogeneous syndrome with multiple distinct phenotypes, which has further complicated therapeutic development. It has been established that interventions that benefit certain patient sub-

groups may prove ineffective or even harmful in others [9].

The emergence of sodium-glucose cotransporter 2 (SGLT-2) inhibitors represents a paradigm shift in the treatment of HF across the ejection fraction spectrum. SGLT-2 inhibitors were originally developed as glucose-lowering agents for type 2 diabetes mellitus (T2DM). Recently, trials with SGLT-2 inhibitors have demonstrated remarkable cardiovascular and renal protective effects that extend far beyond their glucose-lowering effects [10]. The landmark EMPEROR-Preserved and DELIVER trials confirmed that SGLT-2 inhibitors Empagliflozin and Dapagliflozin significantly reduced the composite endpoint of cardiovascular death and HF hospitalization in patients with HFpEF, irrespective of diabetes status [11, 12]. These findings have fundamentally transformed the treatment paradigm for HFpEF. SGLT-2 inhibitors have currently been incorporated into major international guidelines as Class I recommendations for management of patients with HFpEF [13].

The clinical benefits of SGLT-2 inhibitors appear to be multifactorial, involving favorable effects on preload reduction, natriuresis, blood pressure, weight, cardiac metabolism, myocardial energetics, and inflammation [14]. Despite these encouraging clinical outcomes, the precise mechanism by which SGLT-2 inhibitors exert their cardioprotective effect in patients with HFpEF remains incompletely elucidated. Current preclinical and translational studies have suggested that SGLT-2 inhibitors may improve myocardial energetics through a shift toward ketone body utilization, reduce myofibrillar stiffness, attenuate cardiac fibrosis, and diminish systemic and myocardial inflammation [15]. However, clinical data on related echocardiographic diastolic function parameters and circulating inflammatory biomarkers in HFpEF patients remain limited. A deeper understanding of the underlying pathophysiological mechanisms, not confined to clinical endpoints, is desirable to optimize therapeutic strategies and identify patient populations most likely to derive benefit. Moreover, the associations among diastolic function, inflammation, and clinical outcomes in patients with HFpEF warrant further investigation to help establish

SGLT-2 inhibitor improves diastolic function and inflammation in HFpEF

mechanistic links and potential surrogate endpoints.

The innovation of the present study is three-fold. First, this study provided mechanistic insights into the effect of SGLT-2 inhibitor therapy on left ventricular diastolic function (LVDF) using comprehensive echocardiographic parameters including early diastolic transmitral flow velocity/early diastolic mitral annular velocity ratio (E/e') and left atrial volume index (LAVI). This is different from previous large-scale trials that primarily focused on clinical hard endpoints such as cardiovascular death and HF hospitalization. Second, multiple circulating inflammatory markers, including high-sensitivity CRP (hs-CRP), IL-6, and TNF- α , were simultaneously measured, providing direct evidence for the anti-inflammatory property of SGLT-2 inhibitor therapy in HFpEF patients. Third, the potential link between inflammation reduction and cardiac benefit in this population was explored. To our knowledge, this is one of the few studies to comprehensively assess both diastolic function and inflammatory profile in HFpEF patients receiving SGLT-2 inhibitor therapy.

This retrospective cohort study was designed to evaluate the efficacy of SGLT-2 inhibitor therapy in improving LVDF and reducing circulating inflammation levels in patients with HFpEF. Meanwhile, the potential mechanistic links were evaluated. This study hopes to provide more evidence for the clinical application of SGLT-2 inhibitors in the treatment of HFpEF.

Methods

Patient selection

This retrospective cohort study was conducted at the Department of Cardiology of the Second People's Hospital of Kunshan. Consecutive patients diagnosed with HFpEF and receiving medical care between November 2024 and October 2025 were enrolled. The study protocol was approved by the Institutional Ethics Committee of the Second People's Hospital of Kunshan. Due to the retrospective nature of the study and data anonymization prior to analysis, the requirement for informed consent was waived. All procedures were conducted in accordance with the Declaration of Helsinki.

Inclusion criteria: (1) age ≥ 18 years; (2) HFpEF defined as symptomatic HF with New York Heart Association (NYHA) functional class II-IV, left ventricular ejection fraction (LVEF) $\geq 50\%$, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 300 pg/mL (or ≥ 900 pg/mL in patients with atrial fibrillation); (3) structural heart disease with echocardiographic evidence (left atrial enlargement or left ventricular hypertrophy) and/or left ventricular diastolic dysfunction; (4) a history of standardized HF medication for at least 4 consecutive weeks before enrollment, with stable clinical condition; (5) complete baseline clinical, laboratory and echocardiographic data, and valid 6-month follow-up data.

Exclusion criteria: (1) LVEF $< 50\%$ at any time during observation; (2) acute decompensated HF, cardiogenic shock or acute myocardial infarction within 4 weeks prior to enrollment; (3) severe valvular heart disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, or other primary myocardial diseases requiring surgical or interventional treatment; (4) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m², or end-stage renal disease; (5) active malignant tumors, severe liver dysfunction, autoimmune diseases, or severe infectious diseases; (6) pregnancy or lactation; (7) history of recurrent diabetic ketoacidosis, repeated genital or urinary tract infections, or clear contraindications to SGLT-2 inhibitor therapy; (8) combined use of other novel anti-HF drugs that may interfere with study outcomes; (9) loss to follow-up or incomplete key research data during the 6-month follow-up period.

A total of 138 patients with HFpEF were initially enrolled. One hundred and fourteen patients met all inclusion and exclusion criteria and were included in the final analysis (**Figure 1**). Participants were retrospectively categorized into the Control group ($n = 56$) or the SGLT-2 inhibitor group ($n = 58$) based on their treatment regimen during the study period. The Control group received standard guideline-directed medical therapy for HFpEF, which included diuretic Furosemide (Sanofi-Aventis, Paris, France), angiotensin receptor-neprilysin inhibitors Sacubitril/Valsartan (Novartis Pharmaceuticals, Basel, Switzerland), beta-blocker Bisoprolol (Merck KGaA, Darmstadt, Germany), and mineralocorticoid receptor antagonist Spi-

SGLT-2 inhibitor improves diastolic function and inflammation in HFpEF

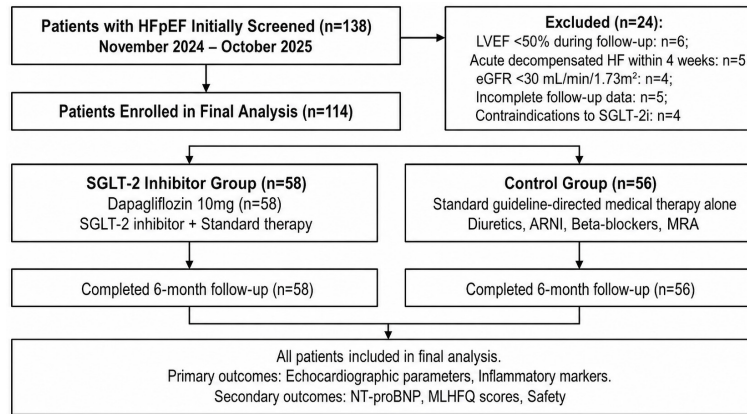


Figure 1. Flowchart of patient enrollment following CONSORT guidelines.

ronolactone (Pfizer Inc., New York, NY, USA). The SGLT-2 inhibitor group received standard guideline-directed medical therapy combined with SGLT-2 inhibitor Dapagliflozin 10 mg once daily (AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA).

All treatment decisions were made by the attending physicians following a comprehensive assessment of patients' clinical characteristics, comorbidity profiles, laboratory findings, and individual preferences. The decision to initiate SGLT-2 inhibitor (Dapagliflozin) therapy was based on the physicians' clinical judgment, considering the presence of T2DM (indication for SGLT-2 inhibitors) and absence of contraindications. Before treatment initiation, all patients or their legal guardians were fully informed about the potential benefits (e.g., improvement in HF prognosis, reduction in cardiovascular events) and possible adverse effects (e.g., genital infections, urinary tract infections) produced by SGLT-2 inhibitor therapy. Patients made their own choices after fully understanding the strengths and limitations of each treatment option. Due to the retrospective nature of this study, treatment assignment was not randomized.

Data extraction

Data were extracted from the electronic medical records by two independent investigators using a standardized data collection form. Demographic and clinical characteristics included age, sex, body mass index (BMI), comorbidities, NYHA functional class, and vital signs. Laboratory parameters comprised NT-proBNP,

hs-CRP, IL-6, TNF- α , hemoglobin A1c, serum creatinine, eGFR, and lipid profiles. Echocardiographic parameters were composed of LVEF, E, e', E/e' ratio, LAVI, and tricuspid regurgitation velocity. Clinical outcomes encompassed the Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, NYHA class at follow-up, body weight, blood pressure, HF hospitalization, and adverse events. Data completeness was verified by cross-referencing with original medical

records. Attempts were made to retrieve missing data for patients with incomplete baseline or 6-month follow-up data. Patients with missing data required for primary outcome analysis were excluded. A random sample of patients was re-extracted by a third investigator to assess data accuracy.

Materials and reagents used in this study were commercially available. hs-CRP was measured using an immunofluorescence dry quantitative assay kit (Getein Biotech, Nanjing, China). IL-6 and TNF- α were quantified using a chemiluminescence immunoassay kit (Siemens Healthineers, Erlangen, Germany). NT-proBNP was measured using an electrochemiluminescence immunoassay kit (Roche Diagnostics, Basel, Switzerland). Echocardiographic examinations were performed using the EPIQ5 2.1.1 ultrasound system (Philips Ultrasound, Washington, USA).

Outcome measures

All outcome measures were assessed at baseline and at the 6-month follow-up.

Primary outcomes were changes in echocardiographic LVDF parameters (E/e' ratio and LAVI) and circulating inflammatory markers (hs-CRP, IL-6, and TNF- α) from baseline to 6 months.

Secondary outcomes were changes in NT-proBNP level, eGFR, MLHFQ score and NYHA functional class, HF hospitalization during the 6-month follow-up period, and adverse events (e.g., genital infections, urinary tract infections, symptomatic hypotension, acute kidney injury).

Statistical analysis

Sample size estimation was performed based on the primary endpoint of the change in E/e' ratio from baseline to 6 months between the two groups. Assuming a clinically meaningful between-group difference of 2.0 units and a standard deviation of 3.0 units based on previous literature, with a two-sided α of 0.05 and a statistical power of 80%, the minimum required sample size was calculated as 36 patients per group using the formula for two independent means ($n = 2 \times (Z_{\alpha/2} + Z_{\beta})^2 \times SD^2 / \Delta^2$, where $Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.84$, $SD = 3.0$, and $\Delta = 2.0$). Considering a potential dropout rate of 20%, this study aimed to recruit at least 45 patients per group (total ≥ 90 patients). Ultimately, 114 patients were included in this study (58 in the SGLT-2 inhibitor group and 56 in the Control group), which met the minimum requirement.

Statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Shapiro-Wilk test was used to assess the normality of data distribution. For continuous variables that followed a normal distribution, Levene's test was applied to evaluate the homogeneity of variances. When the assumptions of both normality and homogeneity of variances were satisfied, parametric tests were employed: independent samples t-test for between-group comparisons and paired t-test for within-group comparisons. If the assumption of normality was violated, non-parametric tests were used instead: Mann-Whitney U test for between-group comparisons and Wilcoxon signed-rank test for within-group comparisons. Normally distributed continuous variables were presented as means $\pm$ standard deviations, while non-normally distributed continuous variables were expressed as medians (inter-quartile range). Categorical variables were presented as frequencies and percentages, and between-group comparisons were performed using chi-square test.

Pearson correlation coefficients (r) (normally distributed variables) or Spearman correlation coefficients (r) (non-normally distributed variables) were calculated to assess the correlation between changes in echocardiographic parameters and inflammatory markers.

Uni- and multi-variate logistic regression analyses were performed to identify independent

predictors of diastolic function improvement ($\geq 15\%$ reduction in E/e' ratio from baseline to 6 months). Variables with $P < 0.05$ in univariate analysis were entered into the multivariate model. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). A two-tailed P -value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 138 patients with HFpEF were initially screened, of whom 114 met all inclusion and exclusion criteria and were included in the final analysis (**Figure 1**). The mean age was approximately 68 years, with a slight female predominance. Hypertension and T2DM were present in over 80% and 50% of patients, respectively. Based on treatment regimen, participants were assigned to receive Dapagliflozin (SGLT-2 inhibitor group, $n = 58$) or standard therapy (Control group, $n = 56$). Baseline demographic, clinical, echocardiographic, and laboratory characteristics of both groups are presented in **Table 1**.

The two groups were well-balanced at baseline without statistically significant differences in age, sex, BMI, comorbidities, NYHA functional class, renal function, cardiac biomarkers, or echocardiographic parameters (all $P > 0.05$).

Effect on echocardiographic parameters of diastolic function

At 6-month follow-up, the SGLT-2 inhibitor group demonstrated much more significant improvements in echocardiographic parameters of LVDF than the Control group (**Table 2; Figure 2**).

The SGLT-2 inhibitor group showed a significant reduction in E/e' ratio from baseline 14.8 ± 3.2 to 6-months 12.1 ± 2.7 ($P < 0.001$), representing an 18.2% improvement. However, the Control group showed only a modest, non-significant change (from baseline 14.4 ± 3.5 to 6-months 13.8 ± 3.3 , $P = 0.142$). Between-group difference was highly significant ($P < 0.001$). In addition, both septal and lateral e' velocities were improved significantly in the SGLT-2 inhibitor group at the 6-month follow-up (both $P < 0.001$), indicating enhanced early diastolic relaxation. **Supplementary Figure 1** provides representative paired mitral inflow

Table 1. Baseline characteristics of the study population

Variable	SGLT-2 Inhibitor Group (n = 58)	Control Group (n = 56)	Statistical value	P-value
Age, years	68.4 ± 9.7	67.2 ± 10.3	t = 0.640	0.521
Female, n (%)	33 (56.9)	30 (53.6)	χ ² = 0.127	0.717
BMI, kg/m ²	28.6 ± 4.3	27.9 ± 4.8	t = 0.540	0.412
Hypertension, n (%)	48 (82.8)	45 (80.4)	χ ² = 0.110	0.738
Type 2 diabetes, n (%)	31 (53.4)	28 (50.0)	χ ² = 0.136	0.712
Atrial fibrillation, n (%)	22 (37.9)	19 (33.9)	χ ² = 0.198	0.652
Coronary artery disease, n (%)	18 (31.0)	16 (28.6)	χ ² = 0.083	0.774
NYHA class II/III, n (%)	41/17 (70.7/29.3)	38/18 (67.9/32.1)	χ ² = 0.107	0.743
eGFR, mL/min/1.73 m ²	62.4 ± 18.7	64.8 ± 17.2	t = 1.259	0.473
NT-proBNP, pg/mL	1284 ± 743	1196 ± 682	t = 1.284	0.498
LVEF, %	58.3 ± 5.8	57.6 ± 6.2	t = 0.273	0.532
E/e' ratio	14.8 ± 3.2	14.4 ± 3.5	t = 0.432	0.519
LAVI, mL/m ²	38.6 ± 8.4	37.2 ± 9.1	t = 0.687	0.393

Abbreviations: SGLT-2, sodium-glucose cotransporter 2; BMI, body mass index; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; E/e' ratio, ratio of early mitral inflow velocity (E) to early diastolic mitral annular velocity (e'); LAVI, left atrial volume index.

Table 2. Changes in echocardiographic parameters from baseline to 6 months

Parameter	SGLT-2 Inhibitor Group			Control Group			Between-group
	Baseline	6 months	Within-group P (t value)	Baseline	6 months	Within-group P (t value)	P-value (t value)
LVEF, %	58.3 ± 5.8	59.1 ± 5.4	P = 0.287 (t = 0.236)	57.6 ± 6.2	57.4 ± 6.5	P = 0.814 (t = 0.236)	P = 0.186 (t = 1.452)
E/e' ratio	14.8 ± 3.2	12.1 ± 2.7	P < 0.001 (t = 9.364)	14.4 ± 3.5	13.8 ± 3.3	P = 0.142 (t = 1.482)	P < 0.001 (t = 3.018)
e' septal, cm/s	6.4 ± 1.6	7.9 ± 1.5	P < 0.001 (t = 5.215)	6.6 ± 1.8	6.9 ± 1.7	P = 0.218 (t = 1.241)	P = 0.008 (t = 2.756)
e' lateral, cm/s	8.2 ± 2.1	9.6 ± 1.9	P < 0.001 (t = 5.087)	8.4 ± 2.3	8.7 ± 2.4	P = 0.312 (t = 1.018)	P = 0.016 (t = 2.328)
LAVI, mL/m ²	38.6 ± 8.4	34.6 ± 7.2	P = 0.003 (t = 5.190)	37.2 ± 9.1	36.4 ± 8.7	P = 0.428 (t = 0.796)	P = 0.009 (t = 2.328)
TR velocity, m/s	2.72 ± 0.38	2.51 ± 0.34	P = 0.027 (t = 2.372)	2.68 ± 0.41	2.64 ± 0.39	P = 0.476 (t = 0.715)	P = 0.042 (t = 2.098)

Abbreviations: e', early diastolic mitral annular velocity; TR, tricuspid regurgitation.

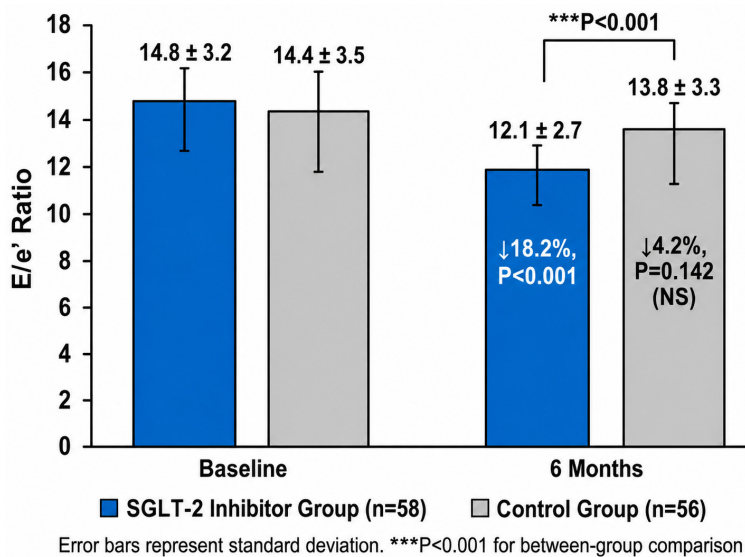


Figure 2. Changes in E/e' ratio from baseline to 6 months in the SGLT-2 inhibitor group versus the Control group. Bar chart shows a significant reduction in E/e' ratio in the SGLT-2 inhibitor group with error bars representing standard deviation. *P < 0.001 for between-group comparison.

and tissue Doppler spectra from one patient per group to visually illustrate the distinct longitudinal changes in E/e' ratio between the two groups. Consistent with the overall group statistical trend, the representative cases from the SGLT-2 inhibitor group displayed an obvious decline in E/e' ratio at the 6-month follow-up; while the representative cases from the Control group showed only a minor variation in E/e' ratio over the 6-month observation window.

With respect to LAVI, a significant decline from baseline 38.6 ± 8.4 to 6-months 34.6 ± 7.2 mL/m² was observed in the SGLT-2 inhibitor group (P =

SGLT-2 inhibitor improves diastolic function and inflammation in HFpEF

Table 3. Changes in inflammatory markers and cardiac biomarkers from baseline to 6 months

Parameter	SGLT-2 Inhibitor Group			Control Group			Between-group
	Baseline	6 months	Within-group P (t value)	Baseline	6 months	Within-group P (t value)	P-value (t value)
hs-CRP, mg/L	4.82 ± 1.73	2.94 ± 1.28	P < 0.001 (t = 9.599)	4.56 ± 1.84	4.21 ± 1.76	P = 0.218 (t = 1.243)	P < 0.001 (t = 4.312)
IL-6, pg/mL	8.46 ± 2.91	5.73 ± 2.14	P < 0.001 (t = 8.638)	8.12 ± 3.08	7.64 ± 2.87	P = 0.347 (t = 0.946)	P = 0.004 (t = 3.156)
TNF-α, pg/mL	12.8 ± 4.6	9.4 ± 3.8	P < 0.001 (t = 5.870)	12.2 ± 4.9	11.6 ± 4.7	P = 0.428 (t = 0.796)	P = 0.023 (t = 3.156)
NT-proBNP, pg/mL	1284 ± 743	983 ± 512	P < 0.001 (t = 4.245)	1196 ± 682	1092 ± 624	P = 0.214 (t = 1.256)	P = 0.004 (t = 3.045)
HbA1c, % (diabetic patients)	7.64 ± 1.23	7.12 ± 1.08	P = 0.001 (t = 0.236)	7.48 ± 1.31	7.36 ± 1.24	P = 0.412 (t = 0.826)	P = 0.086 (t = 3.045)

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HbA1c, hemoglobin A1c.

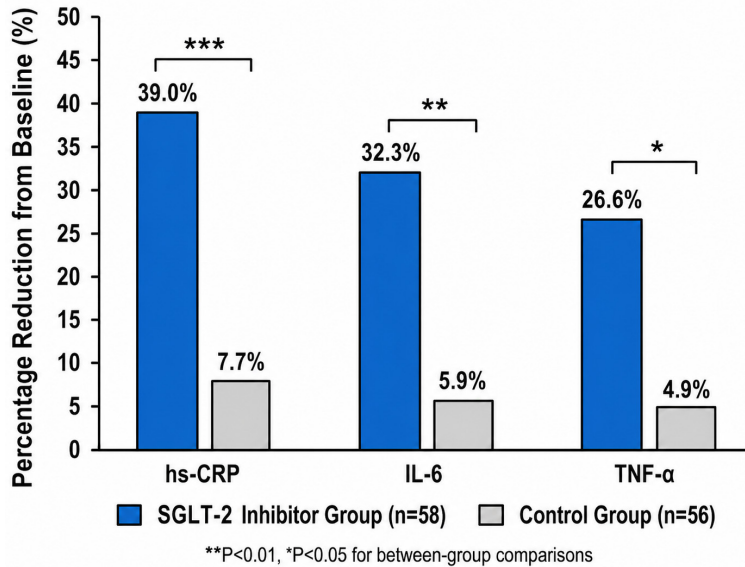


Figure 3. Comparison of changes in inflammatory markers (hs-CRP, IL-6, TNF-α) between the SGLT-2 inhibitor and Control groups at 6-month follow-up. Bar chart with error bars shows percentage reduction from baseline. **P < 0.01, *P < 0.05 for between-group comparisons.

0.003); no significant change was noted in the Control group. Tricuspid regurgitation velocity was also decreased in the SGLT-2 inhibitor group at the 6-month follow-up ($P = 0.027$), suggesting reduced pulmonary pressure. LVEF remained stable in both groups after 6 months of intervention, without significant changes.

Effect on inflammatory markers

At the 6-month follow-up, significant reductions in circulating inflammatory markers were observed in the SGLT-2 inhibitor group (**Table 3; Figure 3**).

The SGLT-2 inhibitor group reported a remarkable decrease in hs-CRP by 39.0% (from baseline 4.82 ± 1.73 to 6-months 2.94 ± 1.28 mg/L, $P < 0.001$), much more significant than the 7.7% in the Control group ($P = 0.218$ for within-group comparison). IL-6 levels in the SGLT-2 inhibitor group were decreased by 32.3% (from baseline 8.46 ± 2.91 to 6-months 5.73 ± 2.14 pg/mL, $P < 0.001$). No significant change was observed in IL-6 levels after 6 months of follow-up in the Control group. TNF-α levels demonstrated a significant reduction by 26.6% in the SGLT-2 inhibitor group (from baseline 12.8 ± 4.6 to 6-months 9.4 ± 3.8 pg/mL, $P < 0.001$). NT-proBNP levels were found to decrease by 28.4% in the SGLT-2 in-

hibitor group, which was greater than the 8.7% in the Control group ($P = 0.004$ for between-group comparison).

Clinical outcomes and functional status

At the 6-month follow-up, significant improvements in both patient-reported health status and functional capacity were observed in the SGLT-2 inhibitor group (**Table 4**).

At the 6-month follow-up, the MLHFQ total score was decreased by 8.6 ± 4.2 points in the SGLT-2 inhibitor group versus 2.1 ± 3.8 points in the Control group ($P < 0.001$), indicating greater improvement in quality of life after SGLT-2 inhibitor therapy. Clinically me-

aningful improvement (≥ 5 -point decrease) was achieved by 65.5% of patients in the SGLT-2 inhibitor group, much higher than the 21.4% in the Control group ($P < 0.001$). Regarding NYHA functional class, 41.4% of patients receiving SGLT-2 inhibitor therapy improved by at least 1 NYHA functional class, notably higher than the 14.3% in the Control group ($P = 0.001$). BMI also demonstrated a significant reduction after SGLT-2 inhibitor therapy (-2.4 ± 1.6 kg, $P < 0.001$). Only a modest reduction was noted in systolic blood pressure in the SGLT-2 inhibitor group at the 6-month follow-up. No statistically significant difference was found in HF hospitalization between the SGLT-2 inhibitor group and the Control group (5.2% vs. 14.3%, $P = 0.099$). Kaplan-Meier analysis demonstrated a numerical but not statistically significant difference in freedom from heart failure hospitalization between the two groups over the 6-month follow-up (log-rank $P = 0.089$), as shown in **Figure 4**.

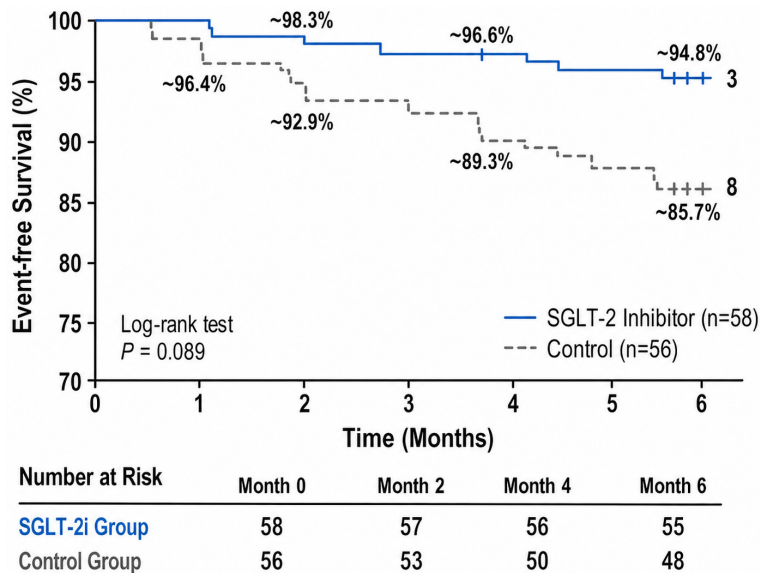
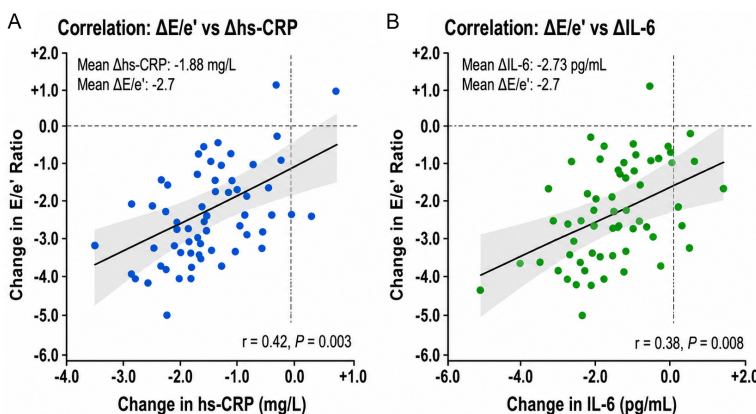
Correlation analysis and predictors of response

Correlation analysis revealed significant associations between the changes in echocardiographic parameters and inflammatory markers (**Figure 5**). The change in E/e' ratio was posi-

Table 4. Changes in clinical outcomes and functional status

Parameter	SGLT-2 Inhibitor Group	Control Group	Statistical value	P-value
MLHFQ score change, points	-8.6 ± 4.2	-2.1 ± 3.8	t = 8.734	< 0.001
MLHFQ ≥ 5-point improvement, n (%)	38 (65.5)	12 (21.4)	$\chi^2 = 22.491$	< 0.001
NYHA class improvement ≥ 1 class, n (%)	24 (41.4)	8 (14.3)	$\chi^2 = 10.361$	0.001
Body weight change, kg	-2.4 ± 1.6	+ 0.3 ± 1.2	t = 10.213	< 0.001
Systolic BP change, mmHg	-6.8 ± 8.4	-1.2 ± 7.6	t = 3.782	0.018
Heart failure hospitalization, n (%)	3 (5.2)	8 (14.3)	$\chi^2 = 2.714$	0.099

Abbreviations: MLHFQ, Minnesota Living with Heart Failure Questionnaire; BP, blood pressure.

**Figure 4.** Kaplan-Meier curves show freedom from heart failure hospitalization in the SGLT-2 inhibitor group versus the Control group over the 6-month follow-up period.**Figure 5.** Scatter plots demonstrate correlations between changes in E/e' ratio and inflammatory markers (A: hs-CRP, B: IL-6) in the SGLT-2 inhibitor group, with regression lines and correlation coefficients.

tively associated with the changes in hs-CRP ($r = 0.42$, $P = 0.003$), IL-6 ($r = 0.38$, $P = 0.008$),

(-0.6 ± 4.2 vs. -1.2 ± 4.8 mL/min/1.73 m², $P = 0.468$).

and NT-proBNP ($r = 0.51$, $P < 0.001$). In addition, the change in LAVI also significantly correlated with the change in NT-proBNP ($r = 0.46$, $P = 0.002$).

Safety outcomes

The safety profiles of both groups are summarized in **Table 5**. Overall, SGLT-2 inhibitor therapy was well-tolerated. No significant between-group differences were observed in the incidence of adverse events.

Genital mycotic infections occurred exclusively in the SGLT-2 inhibitor group ($n = 4$, 6.9%), while the between-group difference was not statistically significant ($P = 0.120$). All 4 cases were mild and resolved with topical antifungal therapy, and no patient required treatment discontinuation. The incidence of urinary tract infections was comparable between the two groups (5.2% vs. 3.6%, $P = 0.678$). No cases of diabetic ketoacidosis, severe hypoglycemia, Fournier's gangrene, or acute kidney injury were observed in either group. eGFR remained stable from baseline to 6 months in both groups, and no significant between-group difference in eGFR change was reported

SGLT-2 inhibitor improves diastolic function and inflammation in HFpEF

Table 5. Adverse events and renal safety during the 6-month follow-up period

Adverse Event	SGLT-2 Inhibitor Group (n = 58)	Control Group (n = 56)	Statistical value	P-value
Genital mycotic infections, n (%)	4 (6.9)	0 (0.0)		0.120 [†]
Urinary tract infections, n (%)	3 (5.2)	2 (3.6)		0.678 [†]
Symptomatic hypotension, n (%)	2 (3.4)	1 (1.8)		1.000 [†]
Diabetic ketoacidosis, n (%)	0 (0.0)	0 (0.0)		-
Severe hypoglycemia, n (%)	0 (0.0)	0 (0.0)		-
Fournier's gangrene, n (%)	0 (0.0)	0 (0.0)		-
Acute kidney injury, n (%)	0 (0.0)	0 (0.0)		-
Treatment discontinuation due to AE, n (%)	0 (0.0)	0 (0.0)		-
Renal function				
eGFR at baseline, mL/min/1.73 m ²	62.4 ± 18.7	64.8 ± 17.2	t = 0.720	0.473 [‡]
eGFR at 6 months, mL/min/1.73 m ²	61.8 ± 17.9	63.6 ± 17.8	t = 0.553	0.582 [‡]
ΔeGFR, mL/min/1.73 m ²	-0.6 ± 4.2	-1.2 ± 4.8	t = 0.728	0.468 [‡]

[†]Fisher's exact test; [‡]Independent samples t-test. Abbreviations: AE, adverse event.

Table 6. Uni- and multi-variate logistic regression analysis for diastolic function improvement

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
SGLT-2 inhibitor treatment	4.85 (2.56-9.18)	< 0.001	4.26 (2.18-8.32)	< 0.001
Age	1.02 (0.99-1.05)	0.184	-	-
Gender	1.15 (0.64-2.07)	0.632	-	-
BMI	1.03 (0.95-1.12)	0.417	-	-
Hypertension	1.22 (0.61-2.44)	0.57	-	-
Type 2 diabetes	2.13 (1.18-3.84)	0.012	1.65 (0.87-3.13)	0.120
Atrial fibrillation	1.33 (0.72-2.46)	0.358	-	-
Coronary artery disease	1.18 (0.60-2.31)	0.625	-	-
NYHA class	1.42 (0.78-2.59)	0.251		
eGFR	1.00 (0.98-1.02)	0.814	-	-
Baseline NT-proBNP	1.01 (1.00-1.02)	0.023	1.01 (1.00-1.02)	0.071
Baseline LVEF	0.98 (0.93-1.03)	0.412		
Baseline LAVI	1.04 (1.00-1.08)	0.058		
Baseline E/e' ratio	1.38 (1.21-1.58)	< 0.001	1.32 (1.14-1.53)	< 0.001
Baseline hs-CRP	1.27 (1.12-1.44)	< 0.001	1.21 (1.06-1.38)	0.005

Abbreviations: OR, odds ratio; CI, confidence interval.

Uni- and multivariate logistic regression analysis

All categorical variables in the logistic regression model were assigned a value of 0 or 1 indicating different conditions: SGLT-2 inhibitor treatment (0 = Control group, 1 = SGLT-2 inhibitor group); sex (0 = female, 1 = male); hypertension (0 = no, 1 = yes); T2DM (0 = no, 1 = yes); atrial fibrillation (0 = no, 1 = yes); coronary artery disease (0 = no, 1 = yes); and NYHA class (0 = II, 1 = III). All continuous variables

(age, BMI, eGFR, baseline NT-proBNP, LVEF, and LAVI, baseline E/e' ratio, baseline hs-CRP) were entered as continuous measurements, with ORs representing the change in odds per 1-unit increment. The results of uni- and multivariate logistic regression analyses are presented in **Table 6**. Univariate analysis demonstrated that SGLT-2 inhibitor treatment, baseline E/e' ratio, baseline hs-CRP, T2DM, and baseline NT-proBNP were associated with diastolic function improvement (all P < 0.05), whereas age, sex, BMI, hypertension, atrial

fibrillation, coronary artery disease, eGFR, NYHA class, LVEF, and LAVI showed no significant associations. In the multivariate model, after adjusting for all the above covariates, SGLT-2 inhibitor treatment (OR = 4.26, 95% CI: 2.18-8.32, $P < 0.001$), higher baseline E/e' ratio (OR = 1.32, 95% CI: 1.14-1.53, $P < 0.001$), and higher baseline hs-CRP (OR = 1.21, 95% CI: 1.06-1.38, $P = 0.005$) remained independent positive predictors of significant diastolic function improvement. T2DM and baseline NT-proBNP did not retain statistical significance in the multivariate model ($P = 0.120$ and $P = 0.071$, respectively), suggesting their predictive effects were attenuated after adjustment for other clinical covariates.

Discussion

The present retrospective cohort study demonstrated that SGLT-2 inhibitor Dapagliflozin significantly improved LVDF and reduced circulating inflammatory markers in patients with HFpEF. It was noted that 6-months of SGLT-2 inhibitor therapy contributed to substantial improvements in E/e' ratio, tissue Doppler velocities, and LAVI, accompanied by meaningful reductions in circulating hs-CRP, IL-6, TNF- α , and NT-proBNP levels. Moreover, these echocardiographic and biochemical improvements were paralleled by the significant enhancement in patient-reported health status and functional capacity, supporting the clinical value of SGLT-2 inhibitor Dapagliflozin as a disease-modifying therapeutic agent for HFpEF.

This study observed a reduction by approximately 18.2% in E/e' ratio after SGLT-2 inhibitor therapy (from baseline 14.8 ± 3.2 to 6-month 12.1 ± 2.7), which aligns with and extends previous observations from the EMPEROR-Preserved and DELIVER trials [16, 17]. The difference is that these landmark trials primarily focused on clinical hard endpoints, while the present study provided mechanistic insights by demonstrating direct improvement in echocardiographic LVDF. In addition, this result is also comparable to that reported by Nassif and colleagues [16], who found that Dapagliflozin improved the health status and exercise function in HFpEF patients. Our finding also corroborates the experimental data from the animal study by Santos-Gallego *et al.* [17], where

Empagliflozin was found to reduce myocardial stiffness and improve diastolic function through mechanisms independent of its diuretic effects.

Circulating inflammatory markers were observed with significant reductions following SGLT-2 inhibitor therapy in this study, providing important mechanistic insights into the cardioprotective effect of SGLT-2 inhibitors in HFpEF patients. Previous preclinical studies demonstrated that SGLT-2 inhibitors attenuated NLRP3 inflammasome activation and reduced secretion of proinflammatory cytokines through multiple mechanisms, including inducing AMPK activation, improving mitochondrial function, and reducing oxidative stress [18]. The present study also found a significant correlation between the reduction in inflammatory markers and the improvement in E/e' ratio ($r = 0.42$ for hs-CRP, $r = 0.38$ for IL-6). This suggests that the anti-inflammatory effect of SGLT-2 inhibitor Dapagliflozin may contribute directly to improvement in diastolic function. Research found that SGLT-2 inhibitors exerted pleiotropic benefits through improvement in cardiac energetics (ketone utilization), diuresis/natriuresis enhancement, oxidative stress reduction, and suppression of inflammatory pathways [14].

Findings of the present study are consistent with the emerging recognition that immune dysregulation plays a central role in the pathophysiology of HFpEF. Immune dysregulation can lead to myocardial remodeling, endothelial dysfunction, and comorbidity-driven inflammation, which are hallmarks of HFpEF [19]. The reductions in TNF- α and IL-6 levels observed in our study are particularly noteworthy. These cytokines have been implicated in increased cardiomyocyte passive stiffness (F_{passive}) in diabetic HFpEF patients, as well as in inspiratory muscle dysfunction and reduced forced vital capacity (FVC) in HFpEF. These associations provide a mechanistic link between systemic inflammation and both myocardial remodeling and exercise intolerance [20, 21]. Our findings extend previous work by Van Tassell and colleagues [22], who demonstrated that IL-1 blockade with Anakinra improved exercise capacity in HFpEF patients. Targeting inflammatory pathways, therefore, may represent a therapeutic strategy for this syndrome.

LAVI in this study was observed with a significant reduction following SGLT-2 inhibitor therapy, which has important implications for HFpEF management. Left atrial enlargement is a marker of chronically elevated filling pressures and an independent predictor of adverse outcomes in HFpEF patients [23]. The 11.4% reduction in LAVI suggests favorable reverse remodeling and may contribute to a reduced risk of atrial arrhythmias [24]. With respect to MLHFQ assessment, the improvement in MLHFQ total score by 8.6 ± 4.2 points found in this study exceeds the threshold of 5 points, which is clinically meaningful and consistent with the health status benefits reported by existing large randomized trials [25].

Several limitations of this study warrant acknowledgment. First, the retrospective design introduces potential selection bias and confounding. Patients receiving SGLT-2 inhibitor therapy may differ from controls in unmeasured characteristics with potential influence on outcomes. Although baseline characteristics were found to be well-balanced between groups, the possibility of residual confounding cannot be excluded. Second, this was a single-center study with a relatively small sample size ($n = 114$). While the sample size met the pre-specified requirement for the primary endpoint, it may have been underpowered for certain secondary endpoints, particularly HF hospitalizations (5.2% vs. 14.3%, $P = 0.099$) that showed a numerical reduction without statistical significance. Third, the follow-up period was only 6 months, which may not capture longer-term benefits or risks of SGLT-2 inhibitor therapy. Fourth, due to the retrospective nature of the study, operators were not blinded to treatment allocation during echocardiographic assessments. Fifth, potentially relevant biomarkers, such as galectin-3, soluble ST2, or cardiac troponins, were not analyzed in this study, although these biomarkers may provide additional mechanistic insights. Sixth, the generalizability of our findings to other SGLT-2 inhibitors (e.g., Empagliflozin, Ertugliflozin) remains to be established. Finally, as with all observational studies, causation cannot be definitively established from the observed associations.

In conclusion, this study demonstrated that SGLT-2 inhibitor Dapagliflozin significantly im-

proved LVDF and reduced circulating inflammatory markers in patients with HFpEF. The observed improvements in E/e' ratio, LAVI, circulating inflammatory biomarkers, and patient-reported functional status support the clinical value of SGLT-2 inhibitor Dapagliflozin as a disease-modifying therapy targeting the underlying pathophysiology of HFpEF. These findings provide a mechanistic context for the clinical benefits observed in large randomized trials and support guideline recommendations for use of SGLT-2 inhibitors in HFpEF patients. Future prospective studies should further elucidate the mechanisms underlying these benefits and identify patient subgroups most likely to derive optimal benefit from this therapeutic class.

Acknowledgements

This study was supported by Gusu Health Talent Plan Talent Research Project GSWS2023077.

Disclosure of conflict of interest

None.

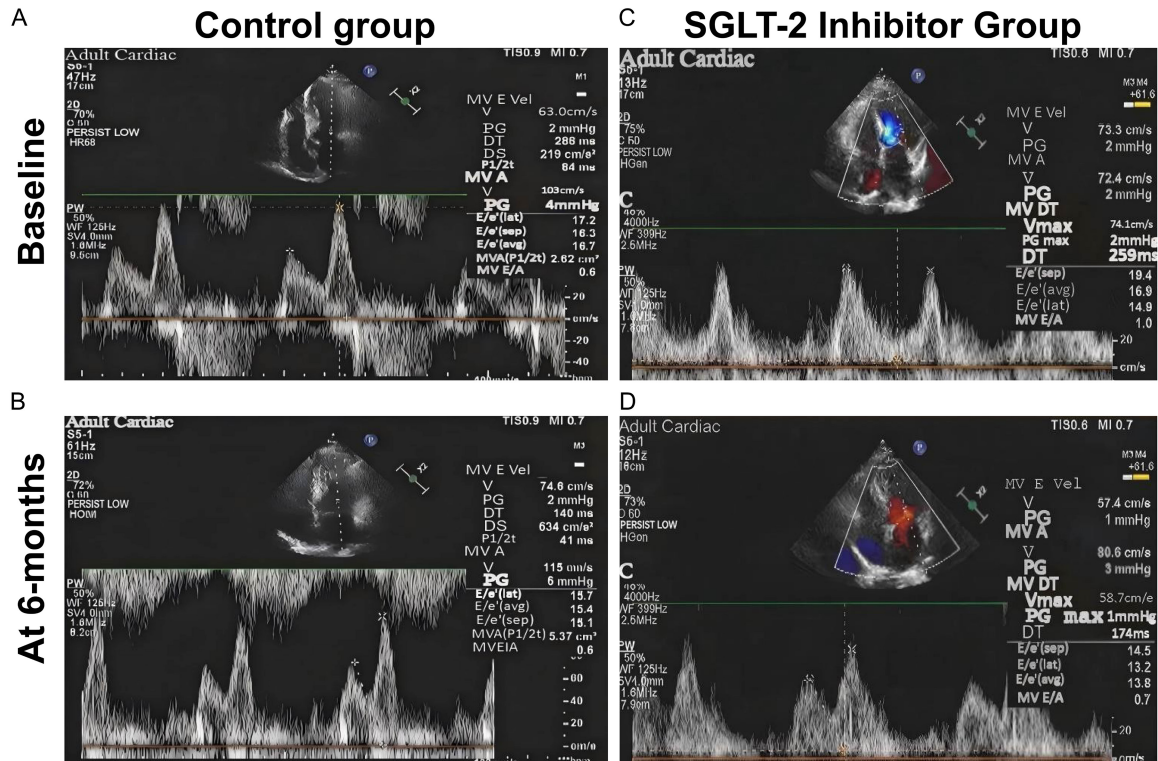
Address correspondence to: Dr. Xu Wang, Department of Cardiovascular Medicine, The Second People's Hospital of Kunshan, No. 91, Qianjin West Road, Kunshan 215300, Jiangsu, China. Tel: +86-0512-36922907; E-mail: wangxu197301@163.com

References

- [1] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC and Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res* 2022; 118: 3272-3287.
- [2] Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020; 17: 559-573.
- [3] Dunlay SM, Roger VL and Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017; 14: 591-602.
- [4] Paulus WJ and Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; 62: 263-271.
- [5] Hage C, Michaëlsson E, Linde C, Donal E, Daubert JC, Gan LM and Lund LH. Inflammatory biomarkers predict heart failure severity and prognosis in patients with heart failure

- with preserved ejection fraction: a holistic proteomic approach. *Circ Cardiovasc Genet* 2017; 10: e001633.
- [6] Redfield MM and Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA* 2023; 329: 827-838.
- [7] Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA and Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation* 2016; 134: 73-90.
- [8] Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Gonçalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC and Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; 381: 1609-1620.
- [9] Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, Gao Q, Hasenfuß G, Kahwash R, Kaye DM, Litwin SE, Lurz P, Massaro JM, Mohan RC, Ricciardi MJ, Solomon SD, Sverdlow AL, Swarup V, van Veldhuisen DJ, Winkler S and Leon MB; REDUCE LAP-HF II investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet* 2022; 399: 1130-1140.
- [10] Zelniker TA and Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; 75: 422-434.
- [11] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F and Packer M; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; 385: 1451-1461.
- [12] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozd J, Fang JC, Alcocer-Gamba MA, Al Habib W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M and Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; 387: 1089-1098.
- [13] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F and Skibellund AK; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023; 44: 3627-3639.
- [14] Lopaschuk GD and Verma S. Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci* 2020; 5: 632-644.
- [15] Pandey AK, Bhatt DL, Pandey A, Marx N, Cosentino F, Pandey A and Verma S. Mechanisms of benefits of sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction. *Eur Heart J* 2023; 44: 3640-3651.
- [16] Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S, Sharma K, Khan SS, Chandra L, Gordon RA, Ryan JJ, Chaudhry SP, Joseph SM, Chow CH, Kanwar MK, Pursley M, Siraj ES, Lewis GD, Clemson BS, Fong M and Kosiborod MN. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med* 2021; 27: 1954-1960.
- [17] Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, Flores E, Garcia-Ropero A, Sanz J, Hajjar RJ, Fuster V and Badimon JJ. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. *J Am Coll Cardiol* 2019; 73: 1931-1944.
- [18] Kim SR, Lee SG, Kim SH, Kim JH, Choi E, Cho W, Rim JH, Hwang I, Lee CJ, Lee M, Oh CM, Jeon JY, Gee HY, Kim JH, Lee BW, Kang ES, Cha BS, Lee MS, Yu JW, Cho JW, Kim JS and Lee YH. SGLT2 inhibition modulates NLRP3 inflammatory activity via ketones and insulin in diabe-

- tes with cardiovascular disease. *Nat Commun* 2020; 11: 2127.
- [19] Wang B, Jankauskas SS, Mone P, Varzideh F and Santulli G. Immunology of heart failure with preserved ejection fraction. *Expert Rev Clin Immunol* 2025; 21: 1725-1739.
- [20] Delalat S, Sultana I, Osman H, Sieme M, Zha-zykbayeva S, Herwig M, Budde H, Kovács Á, Kaçmaz M, Göztepe E, Borgmann N, Shahriari G, Sasko B, Wintrich J, Haldenwang P, Schmidt WE, Fenske W, Khan M, Jaquet K, Mügge A, Máthé D, Tóth VE, Varga ZV, Ferdinandy P, El-Battrawy I, van Heerebeek L and Hamdani N. Dysregulated inflammation, oxidative stress, and protein quality control in diabetic HFpEF: unraveling mechanisms and therapeutic targets. *Cardiovasc Diabetol* 2025; 24: 211.
- [21] Spießhöfer J, Kabitz HJ, Tuleta I, Fröb E and Boentert M. Inspiratory muscle dysfunction with restrictive lung disease in heart failure: association with exercise intolerance and relation to IL-6 and TNF-alpha. *Pneumologie* 2020; 74: FV22.
- [22] Van Tassel BW, Arena R, Biondi-Zoccai G, Can-ada JM, Oddi C, Abouzaki NA, Jahangiri A, Fal-cao RA, Kontos MC, Shah KB, Voelkel NF, Din-arello CA and Abbate A. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and pre-served ejection fraction (from the D-HART pilot study). *Am J Cardiol* 2014; 113: 321-327.
- [23] Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G and Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015; 8: 295-303.
- [24] Bhm M, Anker S, Mahfoud F, Lauder L, Filippa-tos G, Ferreira JP, Pocock SJ, Brueckmann M, Saloustros I, Schler E, Wanner C, Zannad F, Packer M and Butler J. Empagliflozin, irrespec-tive of blood pressure, improves outcomes in heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. *Eur Heart J* 2023; 44: 396-407.
- [25] Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Køber L, Martinez FA, Ponikowski P, Sabatine MS, Solo-mon SD, Bengtsson O, Lindholm D, Niklasson A, Sjöstrand M, Langkilde AM and McMurray JJV. Effects of dapagliflozin on symptoms, func-tion, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation* 2020; 141: 90-99.



Supplementary Figure 1. Representative echocardiographic images of diastolic function parameters at baseline and 6-month follow-up. A and B show a representative patient from the Control group at baseline (A: $E/e' = 16.7$) and 6-month follow-up (B: $E/e' = 15.4$), demonstrating only modest improvement with standard therapy alone. C and D show a representative patient from the SGLT-2 inhibitor group at baseline (C: $E/e' = 16.9$) and 6-month follow-up (D: $E/e' = 13.8$), demonstrating marked improvement in diastolic function after Dapagliflozin treatment.