

Early Changes in Left Atrial Mechanics During Sodium–Glucose Cotransporter-2 Inhibitor Therapy in Heart Failure with Preserved Ejection Fraction

ABSTRACT

Background: Conventional echocardiographic improvements after sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy have been reported in heart failure with preserved ejection fraction (HFpEF), but data on novel composite indices of atrial mechanics, particularly the left atrial (LA) stiffness index and the left atrioventricular coupling index (LACI), remain poorly characterized. The authors evaluated early changes in conventional diastolic parameters and atrial mechanics following initiation of SGLT2 inhibitor therapy.

Methods: In this prospective, single-center observational cohort study, patients with HFpEF in sinus rhythm who were naive to SGLT2 inhibitors received empagliflozin or dapagliflozin. Clinical assessment, laboratory testing, and comprehensive echocardiography were performed at baseline and after 3 months. Echocardiographic evaluation included LA reservoir and pump strain, the LA stiffness index (E/e' /LA reservoir strain), and LACI (minimum LA volume/LV end-diastolic volume $\times 100$).

Results: Fifty patients completed follow-up (70% women; mean age, 63.9 ± 8.1 years). New York Heart Association functional class improved and N-terminal pro–brain natriuretic peptide levels decreased significantly (347 [134.8 – 524.8] vs. 257 [161.3 – 427.5] pg/mL; $P = .007$). Left atrial volume index and E/e' decreased significantly (34.6 ± 5.5 to 32.6 ± 5.7 mL/m² and 12.1 ± 3.2 to 9.8 ± 2.8 , respectively; both $P < .001$). Left atrial reservoir and pump strain increased, whereas the LA stiffness index and LACI decreased significantly (all $P < .001$).

Conclusions: In this prospective observational cohort of patients with HFpEF, initiation of SGLT2 inhibitor therapy was associated with early changes in conventional diastolic parameters and LA mechanics. Composite atrial indices, particularly the LA stiffness index and LACI, changed in parallel with established clinical and echocardiographic markers, suggesting that they may provide complementary information for monitoring early atrial remodeling during SGLT2 inhibitor therapy.

Keywords: Echocardiography, heart failure with preserved ejection fraction, left atrioventricular coupling index, left atrial stiffness index, SGLT2 inhibitors

INTRODUCTION

Heart failure (HF) is a heterogeneous clinical syndrome characterized by structural and functional cardiac abnormalities that result in elevated cardiac filling pressures and neurohormonal activation.¹ Among its clinical phenotypes, HF with preserved ejection fraction (HFpEF) currently accounts for nearly half of all HF cases, and its prevalence continues to rise. This trend largely reflects population aging together with the growing burden of cardiometabolic disorders, particularly obesity, diabetes mellitus (DM), and hypertension.² Heart failure with preserved ejection fraction is increasingly recognized as a multisystem disorder involving not only impaired left ventricular (LV) filling but also atrial, vascular, renal, and metabolic dysfunction.³ This complex pathophysiology contributes to the persistent diagnostic and therapeutic challenges associated with the syndrome.

ORIGINAL INVESTIGATION

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The diagnosis of HFpEF remains challenging because symptoms such as dyspnea are nonspecific and frequently occur in the presence of multiple comorbidities. Although natriuretic peptides, including brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), provide important diagnostic information, their concentrations may be relatively low in younger individuals and in patients with obesity.⁴ Consequently, echocardiography remains the cornerstone of HFpEF assessment. Beyond conventional Doppler-derived indices of diastolic function, parameters such as left atrial (LA) volume index (LAVI), tricuspid regurgitation velocity (TRV), and LA strain have substantially improved the evaluation of LV filling pressure and diastolic dysfunction.⁵ Increasing evidence suggests that the LA is more than a passive marker of chronically elevated filling pressures. Structural remodeling and impaired atrial function may reflect underlying atrial myocardial disease and contribute directly to HF progression.⁶ Accordingly, early identification of atrial dysfunction has become an important component of HFpEF evaluation.⁷ Among currently available imaging markers, LA reservoir strain has emerged as a sensitive indicator of atrial performance and LV filling pressure.^{8,9} More recently, composite indices such as the LA stiffness index (E/e' divided by LA reservoir strain) and the left atrioventricular coupling index (LACI, defined as LA minimum volume/LV end-diastolic volume $\times 100$) have attracted increasing interest. Although these indices are not yet incorporated into contemporary guidelines, accumulating evidence, including recent HFpEF studies, indicates that they may provide incremental diagnostic and prognostic information.¹⁰⁻¹²

For many years, effective pharmacological treatment options for HFpEF remained limited. This changed with the EMPEROR-Preserved and DELIVER trials, which demonstrated that sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of cardiovascular death or hospitalization for patients with HFpEF.^{13,14} Importantly, clinical benefits emerged soon after treatment initiation, suggesting mechanisms beyond glucose lowering.¹⁵ In addition to their metabolic effects, SGLT2 inhibitors favorably influence cardiac loading conditions.¹⁶ Several echocardiographic studies have also demonstrated early improvements in conventional markers of diastolic function, including reductions in E/e' and favorable changes in LA strain within the first few months of therapy.^{17,18}

HIGHLIGHTS

- Early changes in left atrial (LA) mechanics were evaluated during sodium-glucose cotransporter-2 inhibitor therapy in heart failure with preserved ejection fraction (HFpEF).
- Left atrial stiffness index and left atrioventricular coupling index showed coordinated changes over 3 months.
- Novel atrial indices changed in parallel with clinical and conventional echocardiographic markers.
- Serial assessment of atrial mechanics may complement routine echocardiographic follow-up in HFpEF.

Despite these encouraging findings, evidence regarding the response of newer composite atrial indices to SGLT2 inhibition remains limited. In particular, changes in the LA stiffness index and LACI following initiation of SGLT2 inhibitor therapy have not been adequately characterized in patients with HFpEF. Because atrial and ventricular function are tightly interconnected, evaluating these indices may provide additional insight into atrioventricular remodeling during treatment.

Therefore, the authors investigated the early effects of SGLT2 inhibitor therapy (empagliflozin or dapagliflozin) on conventional diastolic parameters together with multiple measures of atrial mechanics, including LA reservoir strain, LA pump strain, the LA stiffness index, and LACI, in patients with HFpEF. By integrating these complementary atrial indices, the authors sought to provide a more comprehensive characterization of atrial remodeling and atrioventricular interaction following the initiation of SGLT2 inhibitor treatment.

METHODS

The authors conducted a prospective, single-center cohort study to evaluate the 3-month effects of SGLT2 inhibitor initiation on clinical and echocardiographic parameters in patients with HFpEF. The study adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent. The study protocol was approved by the Institutional Ethics Committee of the authors' University Hospital.

Study Population, Design, and Follow-up

Between April 2024 and April 2025, consecutive patients were recruited at the cardiology outpatient clinics of the authors' university hospital. Patients with compensated HFpEF, either newly diagnosed or under follow-up, who were naive to SGLT2 inhibitors and had adequate echocardiographic image quality for LA strain assessment, were included. Patients were eligible if they were ≥ 18 years of age, in sinus rhythm, and had an LVEF $\geq 50\%$. Heart failure with preserved ejection fraction was diagnosed according to the 2021 European Society of Cardiology (ESC) Heart Failure Guidelines, based on symptoms and/or signs of HF and objective evidence of cardiac structural or functional abnormalities consistent with LV diastolic dysfunction or elevated LV filling pressures. Echocardiographic findings and natriuretic peptide levels were considered together with the clinical findings when establishing the diagnosis.¹⁹ Exclusion criteria were as follows: LVEF $< 50\%$, history or presence of atrial fibrillation (AF), acute decompensated HF requiring hospitalization, history of HF hospitalization or myocardial revascularization in the previous 3 months, contraindications to SGLT2 inhibitors (estimated glomerular filtration rate [eGFR] < 20 mL/min/1.73 m², type 1 DM, and known hypersensitivity), history of use of a SGLT2 inhibitor, scheduled major surgery requiring temporary discontinuation of SGLT2 inhibitor, significant angina requiring coronary angiography, moderate-to-severe aortic or mitral valvular disease, any degree of mitral annular calcification, having prosthetic or repaired valves, pacemaker implantation, and congenital heart

disease. Patients with mild congestion who were managed in the outpatient setting were included only after achieving clinical stability and decongestion on a stable diuretic regimen.

At baseline, demographic characteristics, comorbidities, medications, laboratory data, and comprehensive echocardiographic parameters were recorded. Functional status was assessed using the New York Heart Association (NYHA) classification. Estimated glomerular filtration rate was calculated from the serum creatinine level closest to the clinical evaluation using the Modification of Diet in Renal Disease equation and venous blood samples for NT-proBNP were obtained on the day of the index echocardiography. Following baseline evaluation, SGLT2 inhibitor treatment was initiated (empagliflozin 10 mg daily or dapagliflozin 10 mg daily). All clinical, laboratory, and echocardiographic assessments were repeated at 3-month follow-up. During follow-up, adherence, symptoms, and adverse events were assessed, and medications were adjusted by the attending physician in accordance with guideline recommendations when necessary.

A total of 78 patients were screened. Fourteen were excluded due to inadequate image quality, and 5 declined to initiate therapy. Fifty-nine patients were initially enrolled; during follow-up, 4 patients underwent coronary revascularization, 3 discontinued treatment, and 2 were lost to follow-up. Ultimately, 50 patients completed the study protocol and were included in the final analysis (Figure 1).

Echocardiographic Assessment

Transthoracic echocardiography was performed at baseline and repeated after 3 months of SGLT2 inhibitor therapy using a Vivid E9 system (GE Healthcare, Horten, Norway). All studies were obtained by experienced echocardiographers according to routine laboratory practice. Digital images were stored for offline analysis using EchoPAC software (GE Healthcare, Milwaukee, WI). Measurements were independently performed by 2 observers who were blinded to the baseline results. All examinations and measurements were performed following the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging.^{20,21}

Standard parameters, including LV volumes and LVEF, were obtained using the modified Simpson's method. Peak TRV was measured using continuous-wave Doppler from the acoustic window providing the highest quality and most complete tricuspid regurgitation spectral envelope. Mitral inflow velocities (E and A waves) were measured by pulsed-wave Doppler in the apical 4-chamber view, and the E/A ratio was derived accordingly. Early diastolic annular velocity (e') was measured at both the septal and lateral mitral annulus using tissue Doppler imaging, and the average of these values was used to calculate the E/ e' ratio. Left atrial volume was measured at end-systole in apical 4- and 2-chamber views using the biplane disk summation method and indexed to body surface area to obtain LAVI.

Left atrial strain analysis was performed using 2-dimensional speckle-tracking echocardiography with automated function imaging software. Left atrial-focused apical 4- and 2-chamber views were used for strain assessment. Reservoir and pump strain values were derived with R-wave gating, and the zero reference was set at end-diastole²² (Figure 2). Previously reported cut-off values for elevated LV filling pressure (PCWP >12 mm Hg) were <18% for LA reservoir strain and <8% (absolute value) for LA pump strain.²³ The LA stiffness index was calculated as the ratio of averaged E/ e' (derived from septal and lateral annular velocities) to peak LA reservoir strain and a LA stiffness index > 0.26 was shown to optimally identify high risk HFpEF patients.¹⁰ Left atrioventricular coupling index was defined as the ratio of minimum LA volume to LV end-diastolic volume, multiplied by 100, and expressed as a percentage. For LACI, values > 30% were shown to be associated with adverse prognosis in HF.²⁴

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 30.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ SD when normally distributed and as median with interquartile range when the distribution was non-normal. Categorical variables are expressed as number and percentage. The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test.

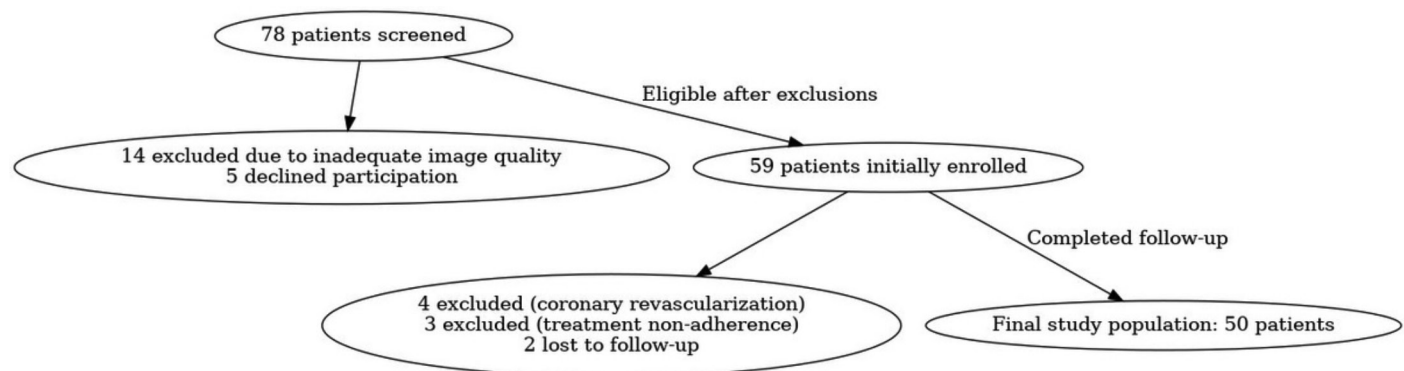


Figure 1. Patient flow diagram.

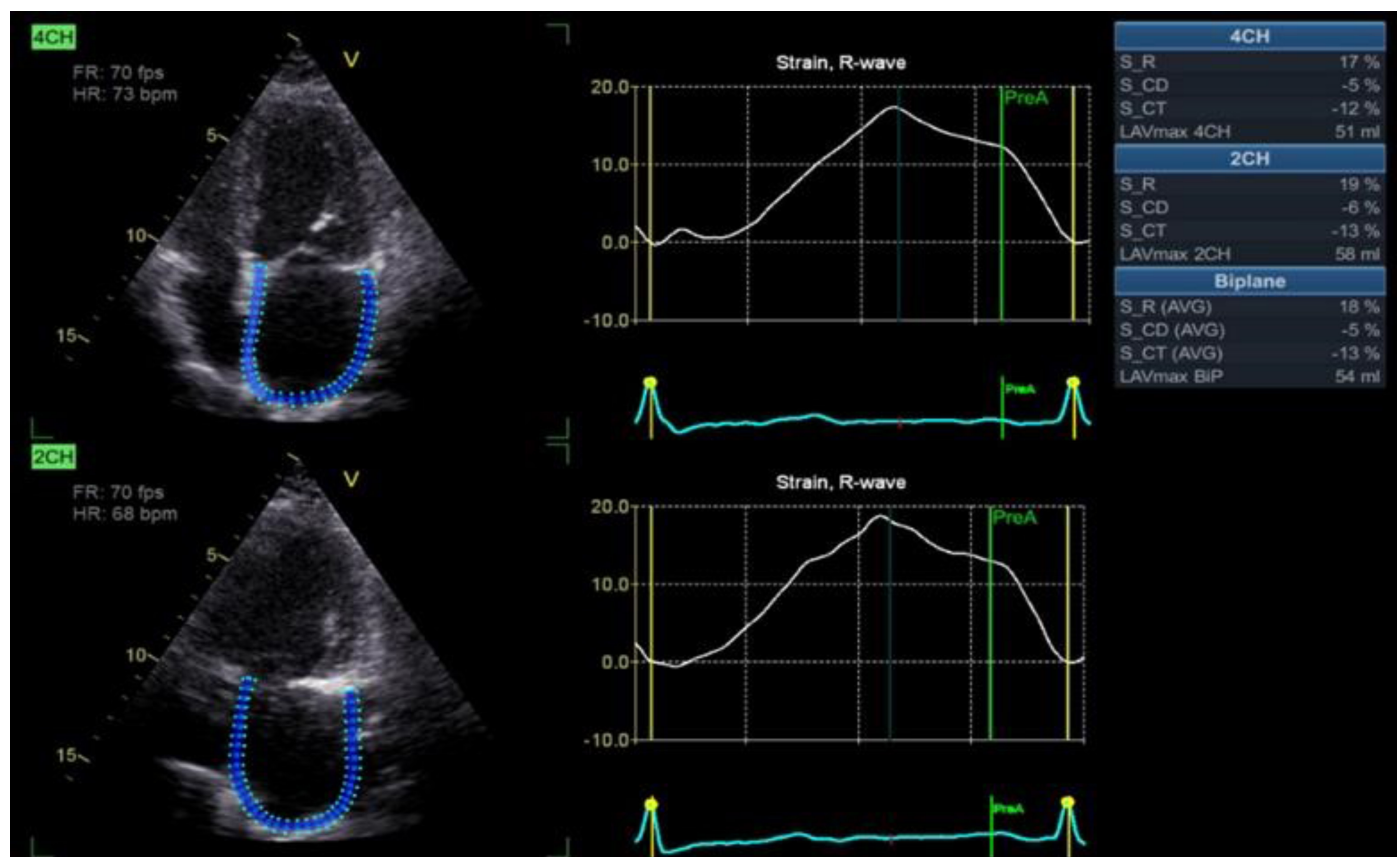


Figure 2. Left atrial strain measurements of a representative patient before initiation of SGLT2 inhibitor therapy. SGLT2, sodium–glucose cotransporter-2.

Changes between baseline and 3-month follow-up were assessed according to data distribution. For normally distributed variables, paired-sample *t*-tests were used. When variables were non-normally distributed or ordinal in nature (including NYHA class), comparisons were performed using the Wilcoxon signed-rank test.

For subgroup analyses (sex, diabetes status, and SGLT2 inhibitor type), change values (Δ = follow-up – baseline) were calculated for LA reservoir strain, LAVI, LACI, LA stiffness index, and E/e' . The normality of change scores was assessed using the Shapiro–Wilk test. Between-group comparisons were performed using independent-samples *t*-tests when assumptions were met, with Welch's correction in cases of unequal variances; otherwise, the Mann–Whitney *U*-test was used. In an additional exploratory analysis, patients were categorized according to loop diuretic dose modification during follow-up (increased, decreased, or unchanged), and changes in these echocardiographic parameters were compared across the 3 groups using the Kruskal–Wallis test.

All statistical tests were 2-sided, and a *P* value <.05 was considered statistically significant.

To assess measurement reproducibility, echocardiographic datasets from 20 randomly selected patients were reanalyzed. For interobserver variability, a second blinded observer repeated the measurements independently. For

intraobserver variability, the initial observer repeated measurements after an interval of at least 4 weeks. Agreement was quantified using intraclass correlation coefficients (ICC). As the LA stiffness index and LACI are derived from strain and Doppler parameters, their reproducibility reflects the reliability of these primary measurements.

RESULTS

Fifty patients with HFpEF who initiated SGLT2 inhibitor therapy (78% dapagliflozin and 22% empagliflozin) completed the study and were included in the final analysis. Baseline clinical characteristics are summarized in Table 1. The mean age was 63.9 ± 8.1 years, 70% ($n=35$) were women, mean BMI was 30.7 ± 3.9 kg/m², mean eGFR was 69.8 ± 19.2 mL/min/1.73 m², median NT-proBNP was 347 (134.8–524.8) pg/mL, and mean LVEF was $56.2\% \pm 4.3\%$.

Loop diuretic therapy (oral furosemide in all cases) was adjusted according to clinical judgment during follow-up. At baseline, 39 patients (78%) were receiving oral furosemide compared with 43 (86%) at 3 months. The median weekly furosemide dose remained unchanged (120 [IQR 25–140] vs. 120 [IQR 65–160] mg/week, *P* = .095), whereas MRA therapy also remained unchanged. Detailed data on loop diuretic and MRA use are presented in Supplementary Table 1. No significant differences were observed among the increased, decreased, and unchanged loop diuretic dose groups for

Table 1. Baseline Clinical Characteristics of the Patients

Clinical Characteristics	Patients (n = 50)
Age (years)	63.9 ± 8.1
Female, n (%)	35 (70)
BMI (kg/m ²)	30.7 ± 3.9
NYHA Class (I-II-III)	2.24 ± 0.63
Type 2 DM	36 (72)
Hypertension	46 (92)
Coronary artery disease	21 (42)
Current smokers	19 (38)
Dapagliflozin	39 (78)
Empagliflozin	11 (22)
Beta-blocker	31 (62)
ACEi/ARB	38 (76)
Loop diuretic (furosemide)	39 (78.0)
MRA	8 (16.0)
Insulin	8 (16)
Metformin	36 (72)
GLP-1RA	2 (4)
Statin	35 (70)

Data are expressed as mean ± SD, as n (%).

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; GLP-1RA, glucagon-like peptide-1 receptor agonists; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

ΔLACI ($P=.15$), ΔLA reservoir strain ($P=.83$), ΔLAVI ($P=.71$), ΔLA stiffness index ($P=.41$), or ΔE/e' ($P=.60$) using the Kruskal–Wallis test (Supplementary Table 2).

Baseline and 3-month clinical, laboratory, and echocardiographic findings are presented in Table 2. New York Heart Association functional class improved and NT-proBNP levels decreased significantly ($P < .001$ and $P=.007$, respectively). Uric acid levels decreased ($P < .001$), while hemoglobin increased ($P=.007$), whereas eGFR remained unchanged ($P=.331$).

At 3 months, LAVI, E/e', LA stiffness index, and LACI decreased significantly, while LA reservoir and pump strain increased (all $P < .001$) (Figure 3). No significant change was observed in TRV ($P=.218$).

Reproducibility analysis demonstrated excellent agreement, with intraobserver and interobserver ICCs of 0.97 (95% CI = 0.93–0.98) and 0.94 (95% CI = 0.88–0.96), respectively.

Subgroup analyses were exploratory because of the small and unequal treatment groups (empagliflozin $n=11$ and dapagliflozin $n=39$). Changes in LA reservoir strain, LAVI, LACI, LA stiffness index, and E/e' were similar according to sex and diabetes status (all $P > .05$). A nominal between-group difference was observed only for ΔLACI between the dapagliflozin and empagliflozin groups (between-group difference -2.17 [95% CI = -4.18 to -0.16]; $P=.045$), whereas no significant differences were found for the remaining echocardiographic parameters. Given the exploratory nature of these analyses, this finding should be considered

Table 2. Baseline and Third Month Values of Clinical, Laboratory, and Echocardiographic Parameters

Clinical and Laboratory Parameters	Baseline	Third month	P
BMI (kg/m ²)	30.7 ± 3.9	30.2 ± 3.3	.08
NYHA class	2.24 ± 0.63	1.92 ± 0.60	<.001
Furosemide dose (mg/week)	120 (25–140)	120 (65–160)	.095
Fasting glucose (mg/dL)	125.2 ± 25.4	120.4 ± 22.5	.031
HbA1c (%)	7.5 ± 1.8	7.3 ± 1.5	.084
Hemoglobin (g/dL)	12.6 ± 1.8	12.8 ± 1.8	.007
Hematocrit (%)	38.2 ± 5.7	39.1 ± 5.3	.008
Creatinine (mg/dL)	1.01 ± 0.31	0.94 ± 0.26	.158
eGFR (mL/min/1.73 m ²)	69.8 ± 19.2	71.0 ± 20.4	.331
NT-proBNP (pg/mL)	347 (134.8–524.8)	257 (161.3–427.5)	.007
Uric acid (mg/dL)	5.7 ± 1.5	5.0 ± 1.6	<.001
Echocardiographic Parameters			
LVEF (%)	56.2 ± 4.3	56.4 ± 4.1	.190
E/A ratio	1.06 ± 0.41	0.92 ± 0.34	<.001
E/e' ratio	12.1 ± 3.2	9.8 ± 2.8	<.001
TRV (m/s)	2.53 ± 0.36	2.55 ± 0.31	.218
LAVI (mL/m ²)	34.6 ± 5.5	32.6 ± 5.7	<.001
LA reservoir strain (%)	18.6 ± 4.2	20.9 ± 5.0	<.001
LA pump strain (%)*	9.2 ± 3.2	11.6 ± 3.1	<.001
LA stiffness index	0.64 ± 0.26	0.47 ± 0.20	<.001
LACI (%)	32.4 ± 7.4	29.0 ± 6.6	<.001

Data are presented as mean ± SD or median (interquartile range), as appropriate.

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LA, left atrium; LACI, left atrioventricular coupling index; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TRV, tricuspid regurgitation velocity.

*LA pump strain values are reported as absolute percentages.

hypothesis-generating. Detailed subgroup results are presented in Supplementary Table 3.

DISCUSSION

The principal finding of this prospective observational cohort is that initiation of SGLT2 inhibitor therapy in stable patients with HFpEF was accompanied by coordinated early improvements across multiple markers of LA remodeling during the first 3 months of treatment. Alongside favorable changes in LA reservoir and pump strain, both the LA stiffness index and LACI declined, paralleling improvements in symptoms, NT-proBNP concentrations, and conventional diastolic indices. Rather than assessing the therapeutic efficacy of SGLT2 inhibitors themselves, this study was designed to characterize the behavior of emerging atrial imaging markers following guideline-directed treatment. The consistent direction

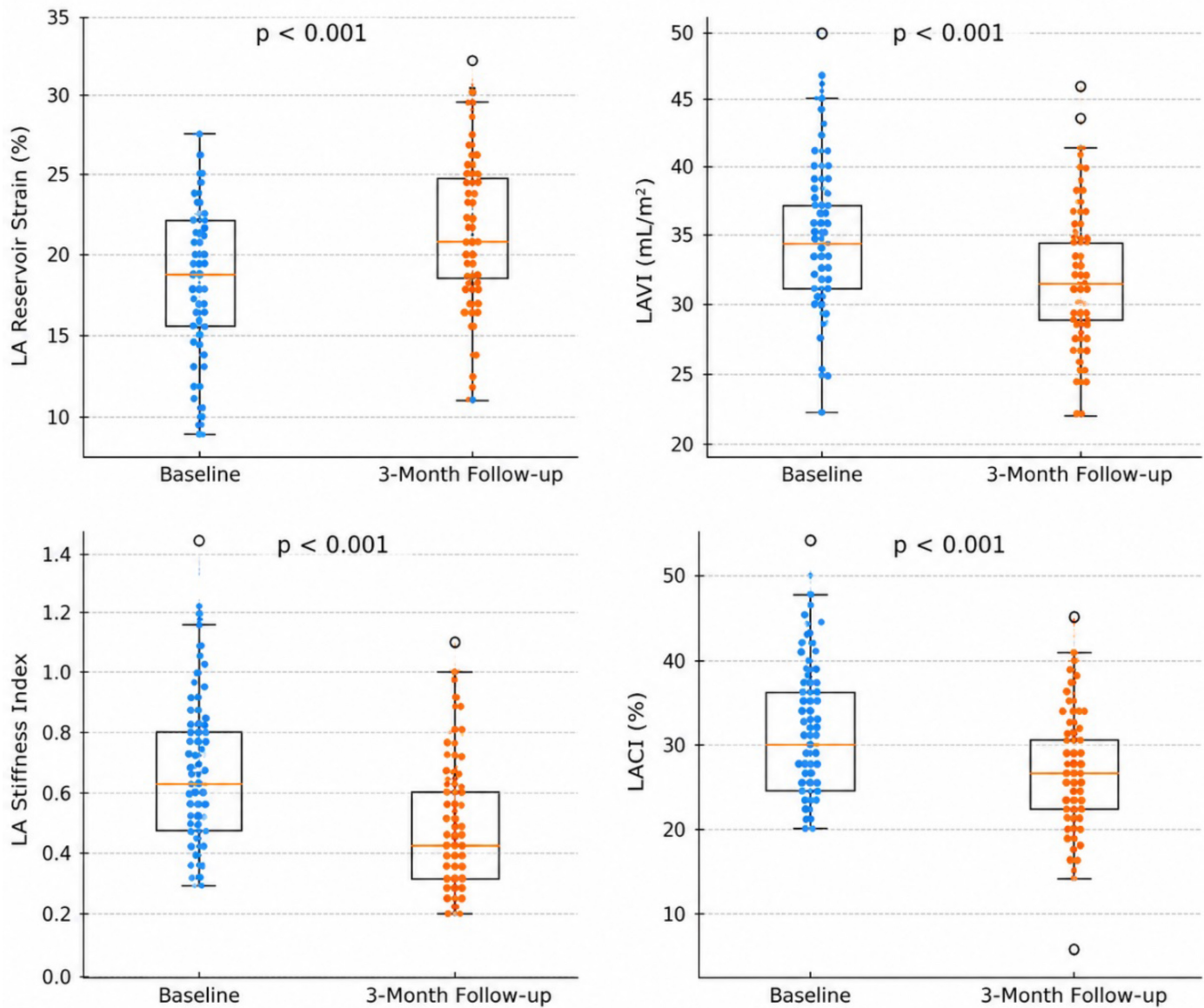


Figure 3. Changes in left atrial echocardiographic parameters from baseline to 3-month follow-up. Boxplots show the distribution of LA reservoir strain, LAVI, LA stiffness index, and LACI at baseline and after 3 months of SGLT2 inhibitor therapy. Individual patient values are superimposed. All comparisons were significant at $P < .001$ LA, left atrium; LACI, left atrioventricular coupling index; LAVI, left atrial volume index; SGLT2, sodium–glucose cotransporter-2.

of change across these complementary indices supports that they may provide incremental information beyond conventional echocardiographic parameters for monitoring atrial remodeling in HFpEF.

Heart failure with preserved ejection fraction remains challenging to diagnose and treat because of its heterogeneous presentation and frequent comorbidities. Among currently available therapies, SGLT2 inhibitors are the first pharmacological agents to consistently improve clinical outcomes in this population.^{13,14} Several echocardiographic studies have also demonstrated favorable changes in conventional indices of diastolic function, particularly E/e' , following SGLT2 inhibitor therapy, findings that are consistent with this study's observations.^{25,26} In an exploratory physiological

study, empagliflozin reduced E/e' as early as the first day after treatment initiation despite the absence of measurable systemic hemodynamic changes, suggesting that improvements in ventricular filling may occur rapidly.²⁷ Likewise, reductions in LAVI have been reported after approximately 6 months of dapagliflozin therapy.^{28,29} In this study's cohort, LAVI improved after only 3 months. Although the absolute reduction was modest, it is biologically plausible because atrial enlargement may regress as LV filling pressures decline. Exclusion of patients with AF may also have facilitated detection of these initial structural changes before more advanced atrial remodeling became established.

The influence of SGLT2 inhibitors on pulmonary hemodynamics and right-sided cardiac function remains less well

established than their effects on left-sided filling pressures. Although dapagliflozin has been shown to reduce pulmonary capillary wedge pressure, corresponding improvements in right ventricular performance or pulmonary vascular load have not been consistently demonstrated.³⁰ No significant change was observed in TRV during follow-up.

Growing evidence indicates that HFpEF should not be viewed solely as a disorder of ventricular diastolic dysfunction but also as a disease involving progressive atrial remodeling.^{6,31} In this setting, atrial dysfunction is increasingly considered an active component of disease pathophysiology rather than simply a consequence of chronically elevated filling pressures. Mechanisms including inflammation, fibrosis, and epicardial adiposity may contribute to the development of atrial cardiomyopathy.^{6,32} In this study, following initiation of SGLT2 inhibitor therapy, the authors observed parallel improvements in LA strain together with reductions in both the LA stiffness index and LACI. Because AF was excluded, these findings probably reflect an earlier phase of atrial remodeling, during which atrial function may remain responsive to treatment. The concordant changes across these atrial indices suggest that atrial-focused echocardiographic markers may provide complementary information beyond conventional diastolic parameters during follow-up.

Left atrial strain has become an established echocardiographic marker for evaluating atrial function and estimating LV filling pressure, and is increasingly incorporated into contemporary approaches to HFpEF assessment.^{5,33} Among its functional components, reservoir strain appears to provide the greatest prognostic information, whereas pump strain has been linked to relatively preserved filling pressures.^{23,34} In the present study, both parameters improved after 3 months of SGLT2 inhibitor therapy, supporting the concept that atrial function may respond early during treatment. The increase in LA pump strain despite reductions in LAVI and LA stiffness may reflect the complex determinants of atrial contractile function. Left atrial pump strain is influenced not only by intrinsic atrial properties but also by LV filling pressure and longitudinal function. Inoue et al²³ demonstrated an inverse relationship between LA pump strain and LV filling pressure, with higher pump strain values associated with normal filling pressures in patients with preserved LV systolic function. In this study's cohort, the parallel reduction in E/e' may therefore indicate lower atrial afterload, allowing improved atrial contractile function. However, because LV-GLS was not assessed, the contribution of changes in LV longitudinal function cannot be determined. Previous studies evaluating LA strain after SGLT2 inhibitor therapy have reported heterogeneous findings.^{17,26,35} While several investigations demonstrated favorable changes similar to those observed in this study's cohort, the DAPA-MODA did not detect significant improvement in LA strain. Differences in baseline patient characteristics may partly explain these discrepant results, as participants in DAPA-MODA had substantially larger LA (mean LAVI ≈ 48 mL/m²) and a high prevalence of permanent AF, features consistent with more advanced and potentially less reversible atrial remodeling.²⁸ A recent meta-analysis has shown that SGLT2 inhibitors can promote

reverse cardiac remodeling compared with placebo in HF populations, although LA strain parameters were not specifically evaluated.³⁶ The findings of this study add prospective observational evidence suggesting that atrial strain may serve as an early imaging marker of reverse atrial remodeling in stable HFpEF patients in sinus rhythm.

The LA stiffness index combines information derived from atrial deformation and LV filling pressure into a single composite parameter and therefore provides a more integrated assessment of atrioventricular interaction than either measurement alone.³⁷ Previous studies have highlighted the diagnostic and prognostic value of the LA stiffness index. Lin et al³⁸ reported that combining LA reservoir strain with E/e' improved identification of elevated LV filling pressure compared with LA strain alone. Similarly, the LA stiffness index has been reported to identify HFpEF with good diagnostic accuracy, performing at least as well as conventional echocardiographic parameters.³⁹ Furthermore, the inclusion of the LA stiffness index in the recent European Association of Cardiovascular Imaging and the European Heart Rhythm Association consensus document underscores its growing clinical relevance in the multimodality assessment of LA function.⁴⁰ In the present study, baseline LA stiffness index values were markedly abnormal and decreased significantly following SGLT2 inhibitor therapy. Because this parameter reflects both atrial compliance and ventricular loading conditions, its improvement may indicate favorable early changes in atrioventricular interaction rather than isolated changes in atrial mechanics. To the authors' knowledge, prospective data evaluating changes in the LA stiffness index during SGLT2 inhibitor therapy in HFpEF remain very limited. The findings of this study therefore indicate that this composite index may represent a useful adjunct to conventional echocardiographic parameters when monitoring treatment-related remodeling in HFpEF.

Conventional echocardiographic parameters typically describe structural or functional characteristics of either the LA or the LV separately, whereas HFpEF is characterized by impaired interaction between these 2 chambers. Because the LA is directly exposed to LV end-diastolic pressure, changes in atrial size reflect the cumulative burden of diastolic loading, supporting the concept of a composite index that incorporates both atrial and ventricular volumes.²⁴ The LACI, defined as the ratio of minimum LA volume to LV end-diastolic volume, was proposed to capture this interaction.⁴¹ Previous studies have demonstrated excellent diagnostic performance of LACI for identifying HFpEF.⁴² Beyond its diagnostic utility, LACI has also been linked to the severity of diastolic dysfunction and to adverse clinical outcomes in HF.⁴³ More recently, findings from the multicenter PURSUIT HFpEF study (Clinical characteristics and prognostic impact of pulmonary hypertension in heart failure with preserved ejection fraction) confirmed that higher LACI values independently predicted cardiovascular death or HF rehospitalization, highlighting its potential role in risk stratification.¹² In the present study, LACI decreased significantly after three months of SGLT2 inhibitor therapy. Because patients with AF were excluded, these changes were observed in a population

likely representing an earlier phase of atrial remodeling, in which atrioventricular interaction may remain more responsive to therapeutic intervention. Although evidence regarding the behavior of LACI during SGLT2 inhibitor therapy remains scarce, the findings of this study suggest that it may represent a useful imaging marker for monitoring atrioventricular remodeling following initiation of SGLT2 inhibitor therapy in HFpEF.

The reduction in LAVI observed in this study was modest but directionally consistent with the favorable changes in LA strain, the LA stiffness index, LACI, and E/e' . Although structural remodeling generally evolves more slowly than functional improvement, the parallel changes across these complementary parameters support the presence of early reverse atrial remodeling rather than isolated variation in chamber size.

In parallel with the echocardiographic findings, NT-proBNP and uric acid levels decreased, whereas hemoglobin increased during follow-up. These changes are consistent with the pleiotropic effects attributed to SGLT2 inhibitors beyond their hemodynamic actions.⁴⁴ Previous studies evaluating the effects of SGLT2 inhibitors on NT-proBNP have reported heterogeneous results.^{28,45} In this study's cohort, the reduction in NT-proBNP paralleled the improvements in echocardiographic parameters and NYHA functional class, supporting the overall pattern of short-term clinical and functional improvement observed during follow-up.

Subgroup analyses were exploratory and limited by the small and unequal treatment groups (empagliflozin, $n=11$ and dapagliflozin, $n=39$). Although a nominal between-group difference was observed for LACI, with a greater reduction in the dapagliflozin group, this finding should be interpreted cautiously and considered hypothesis-generating. No significant between-group differences were observed for LA strain, LA stiffness index, LAVI, or E/e' . Overall, the similar direction of change across most echocardiographic parameters is more consistent with a class-related effect than with clear drug-specific differences, although the study was not designed to compare individual SGLT2 inhibitors.

Heart failure with preserved ejection fraction is increasingly recognized as a syndrome involving both ventricular and atrial remodeling rather than isolated left ventricular diastolic dysfunction.^{46,47} Impaired myocardial energetics and systemic metabolic abnormalities have been proposed as key mechanisms contributing to this process, while SGLT2 inhibitors may modulate several of these pathways.^{16,48} In this prospective observational cohort of stable HFpEF patients in sinus rhythm, initiation of SGLT2 inhibitor therapy was associated with coordinated changes across multiple indices of atrial mechanics, including LA strain, the LA stiffness index, and LACI, accompanied by favorable changes in E/e' and LAVI. Patients were enrolled after achieving clinical stability and adequate decongestion, and although loop diuretic therapy was adjusted when clinically indicated, the overall median diuretic dose remained unchanged. Furthermore, changes in atrial and diastolic parameters did not differ significantly according to loop diuretic dose modification. Taken

together, these observations suggest that the changes in atrial mechanics are unlikely to be explained solely by pre-load reduction and support the potential value of serial assessment of novel atrial imaging markers during SGLT2 inhibitor therapy in HFpEF.

Study Limitations

Several limitations should be considered when interpreting these findings. Because this study was designed as a prospective observational cohort without a randomized control group, causal inferences regarding the effects of SGLT2 inhibitor therapy cannot be made. Accordingly, the findings should be interpreted as exploratory and hypothesis-generating. In addition, the single-center design, relatively small sample size, and short follow-up period limit the assessment of long-term clinical outcomes such as hospitalization and mortality. Patients with AF were intentionally excluded to allow accurate assessment of atrial strain parameters; therefore, the findings are primarily applicable to stable HFpEF patients in sinus rhythm. Although this approach limits generalizability, it enabled evaluation of atrial mechanics in a more homogeneous population. Left ventricular global longitudinal strain was not systematically assessed; therefore, the authors cannot exclude the possibility that changes in subtle LV systolic function contributed to the observed changes in LA reservoir and pump strain. Functional capacity was assessed using NYHA functional class rather than objective exercise-based measures. Finally, the modest sample size reduced statistical precision, particularly in the exploratory subgroup analyses. Nevertheless, the concordant changes observed across clinical status, laboratory markers, and multiple independent echocardiographic parameters support the biological plausibility of these observations. Larger multicenter studies with longer follow-up are warranted to determine the clinical significance of these changes.

CONCLUSION

In this prospective observational cohort of patients with HFpEF, initiation of SGLT2 inhibitor therapy was associated with early changes in both conventional diastolic indices and LA mechanics. Composite atrial indices, particularly the LA stiffness index and LACI, changed in parallel with established clinical and echocardiographic markers, suggesting that they may facilitate monitoring atrial remodeling during SGLT2 inhibitor therapy in HFpEF. Whether these early alterations in atrial mechanics translate into improved long-term clinical outcomes remains to be established.

Ethics Committee Approval: This study was approved by the Ethics Committee of Ankara University (Approval No: I03-200-24, Date: March 28, 2024).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Supplementary Table 1. Loop Diuretic and MRA Use

Variables	Value (total patients = 50)
Loop diuretic use at baseline, n (%)	39 (78%)
Diuretic-naïve at baseline, n (%)	11 (22%)
Loop diuretic use at 3 months, n (%)	43 (86%)
No loop diuretic at 3 months, n (%)	7 (14%)
New initiation during follow-up, n (%)	4 (8%)
Dose increased during follow-up, n (%)	14 (28%)
Dose decreased during follow-up, n (%)	7 (14%)
Dose unchanged during follow-up, n (%)	29 (58%)
Furosemide dose at baseline (mg/week), median (IQR)*	120 (25-140)
Furosemide dose at 3 months (mg/week), median (IQR)*	120 (65-160)
MRA use at baseline, n (%)	8 (16%)
MRA use at 3 months, n (%)	8 (16%)

*Median dose was calculated across the entire cohort, including patients not receiving loop diuretics (0 mg/week).
Data are presented as n (%) or median (interquartile range).
MRA, mineralocorticoid receptor antagonist

Supplementary Table 2. Association Between Loop Diuretic Dose Change* and Echocardiographic Parameters

Outcome	Kruskal–Wallis P
Δ LACI	0.15
Δ LA reservoir strain	0.83
Δ LAVI	0.71
Δ LA stiffness index	0.41
Δ E/e'	0.60

*Patients were categorized according to loop diuretic dose change during follow-up (increased, decreased, unchanged).
LA, left atrium; LACI, left atrioventricular coupling index; LAVI, left atrial volume index

Supplementary Table 3. Exploratory Subgroup Analyses of Changes in Echocardiographic Parameters

A. According to sex			
Parameter	Female (n=35)	Male (n=15)	P
ΔLACI (%)	-2.97 ± 2.93	-4.33 ± 5.11	0.237
ΔLA reservoir strain (%)	2.29 ± 1.89	2.27 ± 1.62	0.897
ΔLAVI (mL/m ²)	-1.66 ± 2.43	-2.91 ± 3.39	0.144
ΔLA stiffness index	-0.17 ± 0.19	-0.18 ± 0.19	0.772
ΔE/e'	-1.86 ± 2.23	-1.82 ± 2.55	0.956
B. According to diabetes status			
Parameter	Diabetes (n=36)	No diabetes (n=14)	p value
ΔLACI (%)	-3.56 ± 3.90	-2.56 ± 2.79	0.593
ΔLA reservoir strain (%)	2.20 ± 1.81	2.67 ± 1.80	0.487
ΔLAVI (mL/m ²)	-2.14 ± 2.97	-1.56 ± 1.69	0.612
ΔLA stiffness index	-0.15 ± 0.19	-0.27 ± 0.14	0.079
ΔE/e'	-1.68 ± 2.42	-2.61 ± 1.57	0.282
C. According to SGLT2 inhibitor type			
Parameter	Dapagliflozin (n=39)	Empagliflozin (n=11)	p value
ΔLACI (%)	-3.85 ± 3.88	-1.68 ± 2.51	0.045
ΔLA reservoir strain (%)	2.21 ± 1.88	2.55 ± 1.51	0.738
ΔLAVI (mL/m ²)	-2.07 ± 2.78	-1.91 ± 2.89	0.860
ΔLA stiffness index	-0.16 ± 0.20	-0.21 ± 0.17	0.510
ΔE/e'	-1.63 ± 2.40	-2.65 ± 1.79	0.196

Changes (Δ) represent 3-month follow-up minus baseline values.
Data are presented as mean $\pm$ SD for descriptive purposes. Between-group comparisons were performed using independent-samples t tests (with Welch's correction when appropriate) or Mann–Whitney U tests according to the distribution of change scores
LA, left atrium; LACI, left atrioventricular coupling index; LAVI, left atrial volume index; SGLT2, sodium–glucose cotransporter 2.