

Influence of the Angiotensin Receptor Neprilysin Inhibitor Compared with Perindopril on Left Atrial Strain and Prognosis in Heart Failure

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Abstract

Backgrounds

Contemporary guidelines lack support for the therapies of left atrial (LA) dysfunction. The objective of this study is to compare the effects of angiotensin receptor–neprilysin inhibitor (ARNI) therapy and perindopril on left atrial (LA) strain assessed by three-dimensional speckle-tracking echocardiography (3D-STE) in patients with heart failure with reduced ejection fraction (HFrEF).

Methods

This single-centre retrospective observational study included patients with HFrEF who received either ARNI therapy or perindopril. The primary endpoint was the change in LA reservoir strain (LASr), LA conduit strain (LAScd), and LA booster strain (LASct) from baseline to 6 months. The secondary endpoint was the occurrence of major adverse cardiovascular events (MACEs).

Results

Among the 159 enrolled patients, 135 completed the 6-month follow-up (ARNI, $n = 80$; perindopril, $n = 55$). Baseline characteristics were comparable between the two groups. After adjustment for potential confounders, ARNI therapy was associated with significantly greater improvement in LASr than perindopril (adjusted mean difference, 4.31%; 95% confidence interval [CI], 3.02–5.60; $P < 0.05$). Similar benefits were observed for LAScd and LASct (both $P < 0.05$). MACEs occurred in 6 patients (6.1%) in the ARNI group and 17 patients (28.3%) in the perindopril group (log-rank $P < 0.05$).

Conclusions

In patients with HFrEF, ARNI therapy was associated with greater improvement in LA strain and a lower incidence of MACEs than perindopril over 6 months.

1. Introduction

During the cardiac cycle, the left atrium (LA) contributes to left ventricular (LV) filling through its reservoir, conduit, and booster pump functions, thereby maintaining an adequate stroke volume. LA function reflects LV filling pressure and is closely influenced by LV performance. In addition, the LA acts as a reservoir that buffers volume overload, particularly in conditions such as functional mitral regurgitation^[1–4]. These pathophysiological mechanisms frequently coexist in heart failure (HF), especially in heart failure with preserved ejection fraction (HFpEF)^[5]. In patients with heart failure with reduced ejection fraction (HFrEF), impaired LA mechanical function, particularly as assessed by LA strain, has emerged as an important predictor of adverse clinical outcomes^[6].

Neurohormonal modulation is the cornerstone of pharmacological therapy for HFrEF. Angiotensin receptor–neprilysin inhibitors (ARNIs), one of the most important recent advances in HFrEF treatment, simultaneously inhibit the renin–angiotensin–aldosterone system (RAAS) and reduce the degradation of natriuretic peptides. Previous studies have demonstrated that ARNI therapy promotes reverse ventricular remodelling, improves LV systolic function, increases left ventricular ejection fraction (LVEF), and reduces ventricular dimensions^[7, 8]. Several studies have also reported improvements in conventional echocardiographic indices of LA structure and function following ARNI therapy, including maximal and minimal LA volume (LAVmax and LAVmin), LA volume index (LAVI), and peak atrial longitudinal strain (PALS)^[9, 10]. Beyond neurohormonal modulation, ARNIs may further improve LA function by attenuating oxidative stress, a key contributor to endothelial dysfunction and adverse cardiac remodelling^[11]. However, to our knowledge, no previous study has comprehensively evaluated the effects of ARNI therapy on the three phasic components of LA strain, including LASr, LAScd, and LASct, in patients with HFrEF.

2. Methods

2.1 Study Cohort

This single-centre retrospective observational study consecutively enrolled patients with HFrEF who were hospitalized for decompensated HF at the Affiliated Taicang Hospital of Soochow University between January 1, 2021, and December 31, 2024. Decompensated HF was defined as an unplanned hospitalization lasting ≥ 24 hours for new or worsening dyspnoea, orthopnoea, or peripheral oedema accompanied by signs of congestion, including pulmonary rales, jugular venous distension, or radiographic pulmonary oedema, requiring intravenous diuretic therapy.

Eligible patients had a baseline LVEF $\leq 40\%$ and New York Heart Association (NYHA) functional class II–IV. Additional inclusion criteria were age between 18 and 80 years, a history of decompensated HF of at least one year, and continuous treatment with either an ARNI or perindopril for at least six months. Patients with severe renal or hepatic disease, atrial fibrillation, previous cardiac transplantation, severe valvular heart disease, or inadequate echocardiographic image quality were excluded.

All echocardiographic examinations were performed using equipment from a single manufacturer (Canon Medical Systems, Tokyo, Japan). Written informed consent was obtained from all participants, and the study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki (No. 2022-ky-022).

2.2 Clinical Data and Standard Echocardiography

Baseline clinical assessments included blood pressure, heart rate, HF duration, NYHA functional class, QRS duration, demographic characteristics, comorbidities, circulating biomarkers, pharmacological therapies, insurance status, and cardiovascular risk factors. Standard echocardiographic

measurements included LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and LVEF. Doppler-derived indices of LV filling pressure were also recorded, including the ratio of early transmitral inflow velocity (E wave) to early diastolic mitral annular velocity (e' wave) (E/e').

2.3 Three-Dimensional Speckle-Tracking Echocardiography

Three-dimensional speckle-tracking echocardiography (3D-STE) was performed using a commercially available ultrasound system (Canon Medical Systems, Tokyo, Japan) equipped with a PSI-30VX (1.8–5.2 MHz) phased-array transducer. Images were acquired at a frame rate of 25–40 frames/s. During a breath hold, six consecutive subvolumes were obtained over six cardiac cycles and automatically reconstructed into a full-volume pyramidal 3D dataset. Offline analysis was performed using vendor-specific software (3D Wall Motion Tracking for Left Atrium Analysis, Version 2.0; Canon Medical Systems).

Each dataset was displayed in five standard views, including apical four-chamber and two-chamber views and three short-axis planes (basal, mid-atrial, and roof levels). Images were analysed using semiautomated software (Supplementary Fig. 1). All analyses were independently performed by two experienced echocardiographers blinded to treatment allocation. Interobserver and intraobserver reproducibility were evaluated in 20 randomly selected patients using intraclass correlation coefficients (ICCs) and Bland–Altman analysis.

A three-dimensional LA model was generated by manually identifying reference points along the mitral annulus in the apical four-chamber and two-chamber views. The LA appendage and pulmonary veins were excluded from the analysis. The following volumetric parameters were measured:

- maximal LA volume (LAVmax) and maximal LA volume index (LAVImax), immediately before mitral valve opening;
- minimal LA volume (LAVmin) and minimal LA volume index (LAVImin), at mitral valve closure;
- pre-atrial contraction LA volume (LAVpreA) and pre-atrial contraction LA volume index (LAVIpreA), measured at the onset of the P wave on electrocardiography.

LA phasic function was assessed using the following indices:

- LA expansion fraction = $(\text{LAVmax} - \text{LAVmin}) / \text{LAVmax} \times 100\%$;
- LA passive emptying fraction = $(\text{LAVmax} - \text{LAVpreA}) / \text{LAVmax} \times 100\%$;
- LA active emptying fraction = $(\text{LAVpreA} - \text{LAVmin}) / \text{LAVpreA} \times 100\%$.

LA strain was quantified using an endocardial point-and-click tracking method. Eighteen myocardial segments were analysed (six segments per view). Three phasic LA strain parameters were derived: LASr, defined as the peak atrial longitudinal strain at ventricular end-systole before mitral valve opening; LAScd, defined as the strain difference between mitral valve opening and the onset of the P wave; and LASct, calculated as LASr minus LAScd (Supplementary Fig. 2).

2.4 Follow-up and Study Endpoints

Patients were routinely followed in the outpatient clinic after hospital discharge. Those unable to attend scheduled visits were contacted by telephone every month. At the 6-month follow-up, all participants underwent repeat clinical assessment, including biomarker testing, electrocardiography, and echocardiography.

The primary endpoint was the adjusted change in LA strain at 6 months. The secondary endpoint was the time to the first MACE, defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as the mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]), whereas categorical variables are expressed as counts and percentages. Between-group comparisons were performed using the independent-samples *t* test, Mann–Whitney *U* test, or χ^2 test, as appropriate.

For the primary endpoint, analysis of covariance (ANCOVA) was performed with the 6-month LA strain as the dependent variable, treatment group as the fixed factor, and baseline LA strain, age, sex, NYHA functional class, baseline LVEF, blood pressure, HF duration, insurance type, treating clinical team, and baseline guideline-directed medical therapy (beta-blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors, and vericiguat) as covariates. Adjusted means with 95% confidence intervals (CIs) are reported.

Prespecified subgroup analyses according to baseline LVEF ($\leq 30\%$ vs. $30\text{--}40\%$) were conducted using interaction testing. Time-to-event outcomes were analysed using Kaplan–Meier curves with log-rank tests. Reproducibility was assessed using ICCs with 95% CIs and Bland–Altman analysis. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant, except for subgroup interaction analyses, for which $P < 0.10$ was considered suggestive of interaction.

3. Results

3.1 Patient Characteristics

Between January 1, 2021, and December 31, 2024, a total of 1,247 patients with HF were admitted to our cardiology ward. Among them, 246 (19.7%) had an LVEF $\leq 40\%$, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels > 100 pg/mL, and NYHA functional class II–IV. Of these patients, 159 met the inclusion criteria and received either ARNI therapy ($n = 99$) or perindopril ($n = 60$). The study flowchart is presented in Fig. 1.

Baseline characteristics are summarized in Table 1. The mean age of the study population was 64.1 ± 12.9 years, and 113 patients (71.1%) were male. Body surface area (BSA), body mass index (BMI), heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were comparable between the two groups. The median duration of HF was 2.04 years (IQR, 1.17–3.83 years), with no significant between-group difference.

Table 1
Baseline characteristics of the patients

Age(years)	ARNI(n = 99)	Perindopril(n = 60)	P value
	61.74 ± 11.00	64.23 ± 8.24	0.108
Female (n,%)	25(25.3%)	21(35.0%)	0.189
BMI	24.81 ± 3.97	24.20 ± 2.90	0.299
BSA(kg/m ²)	1.83 ± 0.23	1.80 ± 0.15	0.314
Systolic blood pressure (mmHg)	136.57 ± 23.79	131.65 ± 21.58	0.210
Diastolic blood pressure (mmHg)	87.11 ± 15.63	83.45 ± 12.00	0.111
Heart rate (b.p.m.)	89.39 ± 19.06	94.90 ± 19.25	0.071
QRS duration (ms)	106.00(96.25,125.50)	119.00(100.00,138.00)	0.057
HF duration(years)	2.04(1.17, 3.83)	1.00(1.00, 2.00)	0.119
Coronary heart disease (n,%)	63(63.6%)	42(70.0%)	0.411
hypertension (n,%)	54(54.5%)	34(56.7%)	0.794
diabetes (n,%)	76(76.8%)	41(68.3%)	0.242
renal dysfunction (n,%)	16(16.2%)	6(10.0%)	0.275
cardiomyopathy (n,%)	67(67.7%)	34(56.7%)	0.162
cancer (n,%)	9(9.1%)	5(8.3%)	0.870
Laboratory values			
leukocyte(*10 ⁹ /L)	7.40(5.90–8.75)	6.60(5.80–8.45)	0.400
hemoglobin(g/L)	135.95 ± 17.72	130.95 ± 17.64	0.093
hs-CRP(mg/L)	5.38(2.00-12.98)	5.73(2.00-12.75)	0.825
glutamic-pyruvic transaminase(U/L)	26.25(17.00-49.73)	23.50(17.38–45.52)	0.676
urea(mmol/L)	7.10(5.90–8.75)	7.25(5.86–8.25)	0.748
eGFR(ml/min)	77.71(60.95-100.53)	77.90(54.27–90.08)	0.911
Potassium(mmol/L)	3.98 ± 0.51	3.94 ± 0.49	0.633
Uric acid (mmol/L)	430.20 ± 134.31	442.34 ± 174.50	0.675
hs-TnI(ng/L)	0.022(0.012–0.067)	0.031(0.012–0.132)	0.457
NT-proBNP (pg/ml)	3620(1320,7360)	4215(1702.25,8647.50)	0.375
Triglyceride(mmol/L)	1.20(0.94–1.67)	1.01(0.69–1.52)	0.465
Cholesterol(mmol/L)	4.32(3.46–5.20)	3.89(2.89–4.74)	<0.05
LDL-C(mmol/L)	2.85(1.91–3.49)	2.20(1.59–2.90)	<0.05
D-dimer(mg/L)	0.63(0.40–1.15)	0.86(0.50–1.74)	0.138
NYHA class			0.673
II(n,%)	21(21.2%)	10(16.7%)	
III(n,%)	27(27.3%)	18(30.0%)	
IV(n,%)	51(51.5%)	32(53.3%)	
Treatments			
Beta-blockers (n,%)	71(71.7%)	41(68.3%)	0.650
Spironolactone (n,%)	96(97.0%)	58(96.7%)	0.915
Antiplatelet(n,%)	52(52.5%)	34(56.7%)	0.611
Data are presented as the mean ± SD for normally distributed data and median and interquartile range for nonnormally distributed data, or n (%).			
Abbreviations: ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BSA, body surface area; HF, heart failure; hs-CRP, LVEF; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2			

Age(years)	ARNI(n = 99)	Perindopril(n = 60)	P value
	61.74 ± 11.00	64.23 ± 8.24	0.108
Statin(n,%)	60(60.6%)	40(66.7%)	0.443
Anticoagulant(n,%)	15(15.2%)	10(16.07%)	0.799
SGLT-2 inhibitor(n,%)	50(50.5%)	26(43.3%)	0.380
Viloxazine(n,%)	10(10.1%)	6(10.0%)	0.984
Data are presented as the mean ± SD for normally distributed data and median and interquartile range for nonnormally distributed data, or n (%).			
Abbreviations: ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BSA, body surface area; HF, heart failure; hs-CRP, LVEF; eGFR, estimated glomerular filtration rate; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2			

Coronary artery disease was present in 105 patients (66.0%), diabetes mellitus in 117 (73.6%), and hypertension in 88 (55.3%). Regarding NYHA functional class, 83 patients (52.3%) were classified as class IV, 45 (28.3%) as class III, and 31 (19.4%) as class II.

The proportions of patients prescribed ARNI by the three clinical teams were 62.2%, 59.4%, and 66.7%, respectively, which were comparable with the overall prescription rate of 62.3%, indicating no evidence of physician-level prescribing preference (Supplementary Table 1). Likewise, insurance status was well balanced between the treatment groups ($P = 0.55$), suggesting that treatment allocation was unlikely to have been substantially influenced by socioeconomic factors (Supplementary Table 2).

All enrolled patients had impaired LV systolic function, with a mean LVEF of $32.29 \pm 6.09\%$. Severe LV systolic dysfunction ($\text{LVEF} \leq 30\%$) was present in 58 patients (36.5%). After excluding patients who were lost to follow-up or discontinued treatment, 135 patients remained for the primary endpoint analysis, including 80 in the ARNI group and 55 in the perindopril group. Detailed information regarding medication titration and baseline cardiometabolic therapies is provided in Table 1.

3.2 Effects of Treatment on Cardiac Structure

Detailed echocardiographic findings are presented in Table 2. Reductions in LAVImin and LAVI_{max} were significantly greater in the ARNI group than in the perindopril group (-15.52 ± 9.15 vs. -7.73 ± 5.69 mL/m² and -14.60 ± 10.13 vs. -6.49 ± 8.17 mL/m², respectively; both $P < 0.05$). Likewise, patients receiving ARNI exhibited greater reductions in LVESD and LVEDD than those receiving perindopril (-4.80 ± 10.70 vs. 0.15 ± 9.24 mm and -4.53 ± 10.64 vs. 1.00 ± 8.66 mm, respectively; both $P < 0.05$).

Table 2
Changes in clinical, laboratory, and echocardiographic details with ARNI or perindopril f

characteristic	baseline		Pvalue	6months	
	ARNI	perindopril		ARNI	perindopril
BMI	24.81 ± 3.97	24.20 ± 2.90	0.299	24.74 ± 3.75	24.09 ± 2.44
BSA	1.83 ± 0.23	1.80 ± 0.15	0.314	1.83 ± 0.33	1.78 ± 0.12
Mean arterial pressure, mmhg	103.37 ± 16.73	99.52 ± 12.07	0.095	85.64 ± 12.23	90.30 ± 10.95
Heart rate, bpm	89.39 ± 19.06	94.90 ± 19.25	0.071	77.23 ± 9.15	85.95 ± 13.77
QRS duration, ms	106.00(96.25,125.50)	119.00(100.00,138.00)	0.057	101.00(92.00, 118.75)	114.00(100.00, 14
Laboratory values					
hemoglobin,g/L	136.89 ± 18.90	132.33 ± 17.18	0.129	137.45 ± 18.01	128.95 ± 16.83
eGFR,mL/min/1.72 m2	81.06(61.14,101.29)	77.42(55.90,89.16)	0.328	100.69(80.46,115.55)	88.08(72.59,102.5
Serum potassium (mmol/L)	4.01(3.54,4.32)	4.03(3.60,4.32)	0.600	4.09(3.83,4.38)	4.01(3.72,4.39)
NT-proBNP, pg/mL	3665.00(1707.50,7595.00)	4340.00(1647.00,8800.00)	0.433	1101.00(849.50,4727.50)	2200.00(1200.00,
hs-TnI (ng/L)	0.024(0.012,0.063)	0.025(0.012,0.086)	0.582	0.012(0.012,0.020)	0.013(0.012,0.035
Echocardiography					
LAVmax, mL	108.83 ± 38.87	111.21 ± 29.95	0.850	80.82 ± 25.76	100.28 ± 25.31
LAVImax,mL/m2	60.22 ± 21.43	70.91 ± 21.82	0.152	44.69 ± 14.80	63.18 ± 18.05
LAVmin, mL	83.10 ± 31.61	84.08 ± 33.42	0.929	56.91 ± 23.24	75.13 ± 25.25
LAVImin,mL/m2	46.11 ± 17.94	53.86 ± 23.60	0.252	31.51 ± 13.03	47.37 ± 17.11
LAVpreA, mL	100.84 ± 37.93	96.74 ± 31.82	0.742	68.62 ± 24.37	86.60 ± 21.05
LAVIpreA,mL/m2	55.88 ± 20.98	61.79 ± 22.91	0.423	37.96 ± 13.98	54.46 ± 14.70
LA expansion fraction, %	24.68 ± 9.50	26.33 ± 12.03	0.637	31.03 ± 12.79	26.25 ± 10.86
LA passive emptying fraction,%	7.71 ± 6.52	13.67 ± 7.83	<0.05	15.68 ± 8.21	13.50 ± 5.27
LA active emptying fraction,%	18.10 ± 10.15	14.75 ± 9.78	0.333	18.55 ± 10.70	14.92 ± 10.76
E/e'	12.19 ± 3.74	13.85 ± 4.94	0.334	9.49 ± 3.01	12.66 ± 7.45
LVESD,mm	52.68 ± 8.77	51.95 ± 8.54	0.610	48.20 ± 11.52	52.02 ± 8.34
LVEDD,mm	63.53 ± 9.11	62.45 ± 7.85	0.449	59.55 ± 10.15	63.09 ± 8.45
LVEF, %	32.32 ± 6.01	32.23 ± 6.26	0.928	39.61 ± 11.90	33.38 ± 6.62
LASr,%	10.40 ± 2.74	10.12 ± 2.28	0.504	17.97 ± 6.46	12.82 ± 3.23
LAScd,%	3.96 ± 2.51	3.74 ± 1.63	0.490	8.77 ± 4.72	5.12 ± 2.05
LASct,%	6.44 ± 2.36	6.42 ± 2.11	0.955	9.20 ± 3.21	7.70 ± 2.71
Δ = 6-month value – baseline value					
Abbreviations: ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; NT-maximal left atrial volume; LAVImax, maximal left atrial volume index; LAVmin, minimal left atrial volume; LAVImin, minimal left atrial volume index; LAVpreA/contraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LASr, left a					

Table 3
Adjusted 6-month LA strain by treatment group (ANCOVA)[†]

Adjusted 6-month LA strain by treatment group (ANCOVA)†						
parameter	Group	Adjusted mean (SE)	95% CI	Adjusted mean difference (ARNI vs perindopril)	P value*	partial η²
LASr	ARNI	14.82 ± 1.12	(12.62, 17.03)	4.31 (95% CI:3.02 – 5.60)	< 0.05	0.278
	Perindopril	10.52 ± 1.13	(8.28, 12.75)			
LAScd	ARNI	6.51 ± 0.96	(4.61, 8.40)	3.13 (95% CI: 2.02–4.23)	< 0.05	0.217
	Perindopril	3.38 ± 0.97	(1.46, 5.29)			
LASct	ARNI	7.91 ± 0.86	(6.20, 9.62)	1.43 (95% CI: – 0.43 to 2.43)	< 0.05	0.066
	Perindopril	6.48 ± 0.87	(4.75, 8.21)			
Abbreviations: ARNI, angiotensin receptor–neprilysin inhibitor; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial booster strain; CI, confidence interval						
†Adjusted for baseline LA strain (same parameter), age, sex, NYHA class, baseline LVEF, systolic/diastolic/mean arterial pressure, HF duration, insurance type, clinical team, and baseline use of beta-blockers, MRAs, SGLT2 inhibitors, and vericiguat.						
*p-value for between-group difference from ANCOVA.						

3.3 Effects of Treatment on Cardiac Function

The reduction in LAVIpreA was significantly greater in the ARNI group than in the perindopril group (-17.91 ± 9.88 vs. -7.33 ± 10.69 mL/m²; $P < 0.05$). Improvements in LA expansion fraction (LAEF), LA passive emptying fraction (LAPEF), and LVEF were also significantly greater in patients receiving ARNI than in those receiving perindopril (6.32 ± 13.19 vs. $0.00 \pm 5.19\%$, 7.94 ± 10.21 vs. $-0.17 \pm 8.21\%$, and 7.71 ± 10.22 vs. $1.45 \pm 8.31\%$, respectively; all $P < 0.05$). In contrast, the change in LA active emptying fraction (LAAEF) did not differ significantly between the two groups. The Doppler-derived E/e' ratio decreased significantly from baseline in both treatment groups, with no significant between-group difference at follow-up (Table 2).

3.4 Effects of Treatment on LA Strain

The reproducibility of LA strain measurements was evaluated in 20 randomly selected patients. The intraobserver and interobserver ICCs ranged from 0.95 to 0.96 and from 0.94 to 0.95, respectively (Supplementary Table 3). Bland–Altman analysis demonstrated no systematic bias, indicating excellent reproducibility for all LA strain parameters (Supplementary Fig. 3).

3D-STE demonstrated that the increase in LASr was significantly greater in the ARNI group than in the perindopril group ($7.58 \pm 4.60\%$ vs. $2.73 \pm 2.55\%$; $P < 0.05$). Similarly, increases in LAScd and LASct were significantly greater in patients receiving ARNI than in those receiving perindopril ($4.73 \pm 3.79\%$ vs. $1.34 \pm 1.39\%$ and $2.85 \pm 3.03\%$ vs. $1.35 \pm 2.87\%$, respectively; both $P < 0.05$). Among the three phasic LA strain parameters, the greatest improvement was observed for LASr (Table 2 and Fig. 2).

After adjustment for baseline LA strain, age, sex, NYHA functional class, baseline LVEF, blood pressure, HF duration, insurance status, clinical team, and background guideline-directed medical therapy (beta-blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 inhibitors, and vericiguat), ANCOVA showed that patients receiving ARNI had significantly higher 6-month LA strain values than those receiving perindopril across all three strain parameters (Table 4).

For LASr, the adjusted mean $\pm$ standard error (SE) was 14.82 ± 1.12 in the ARNI group and 10.52 ± 1.13 in the perindopril group, corresponding to an adjusted mean difference of 4.31 (95% CI, 3.02–5.60; $P < 0.05$; partial $\eta^2 = 0.28$). The model explained 70.1% of the variance (adjusted $R^2 = 0.65$).

For LAScd, the adjusted mean $\pm$ SE was 6.51 ± 0.96 in the ARNI group and 3.38 ± 0.97 in the perindopril group, with an adjusted mean difference of 3.13 (95% CI, 2.02–4.23; $P < 0.05$; partial $\eta^2 = 0.22$). The model explained 57.0% of the variance (adjusted $R^2 = 0.50$).

For LASct, the adjusted mean $\pm$ SE was 7.91 ± 0.86 in the ARNI group and 6.48 ± 0.87 in the perindopril group, yielding an adjusted mean difference of 1.43 (95% CI, 0.43–2.43; $P < 0.05$; partial $\eta^2 = 0.07$). The model explained 33.7% of the variance (adjusted $R^2 = 0.22$).

In exploratory post hoc analyses stratified by baseline LVEF ($\leq 30\%$ vs. $30\text{--}40\%$), patients receiving ARNI with a baseline LVEF of $30\text{--}40\%$ showed a significantly greater improvement in LASr than those with a baseline LVEF $\leq 30\%$ ($8.41 \pm 4.71\%$ vs. $6.32 \pm 4.20\%$; $P < 0.05$). For LAScd and LASct, the point estimates also favored the LVEF $30\text{--}40\%$ subgroup; however, the interaction tests were not statistically significant (both $P > 0.1$). Given the exploratory nature of these analyses and the limited sample size within each subgroup, these findings should be interpreted with caution.

3.5 Effects of Treatment on Mean Arterial Pressure, Renal Function, and NT-proBNP

At the 6-month follow-up, patients in the ARNI group exhibited greater reductions in mean arterial pressure and heart rate than those in the perindopril group (-18.26 ± 9.94 vs. -9.05 ± 3.96 mmHg and -13.91 ± 17.51 vs. -9.20 ± 21.87 beats/min, respectively; both $P < 0.05$). In contrast, changes in BSA and BMI were comparable between the two groups.

Renal function improved to a greater extent in the ARNI group, with a significantly larger increase in estimated glomerular filtration rate (eGFR) than in the perindopril group (median [IQR], 13.57 [12.53–17.85] vs. 7.04 [4.50–12.28] mL/min/1.73 m²; $P < 0.05$). Likewise, the reduction in NT-proBNP was significantly

greater in the ARNI group than in the perindopril group (median [IQR], -1330.00 [-3290.00 to 116.25] vs. -150.00 [-3500.00 to 5890.00] pg/mL; $P < 0.05$) (Table 2).

3.6 Major Adverse Cardiovascular Events

During the 6-month follow-up, one cardiovascular death (sudden cardiac death) occurred in the ARNI group, whereas three cardiovascular deaths occurred in the perindopril group, including one sudden cardiac death and two deaths due to acute decompensated HF. No non-cardiovascular deaths were observed.

MACEs, including cardiovascular death, occurred in six patients (6.1%) in the ARNI group and seventeen patients (28.3%) in the perindopril group. The most common MACE was hospitalization for HF, which occurred in five patients receiving ARNI and twelve patients receiving perindopril. In addition, two patients in the perindopril group experienced non-fatal stroke during follow-up.

Kaplan–Meier analysis demonstrated a significantly lower cumulative incidence of MACEs in the ARNI group than in the perindopril group (log-rank $P < 0.05$) (Fig. 3). Because of the limited number of events, multivariable adjustment was not performed. Therefore, these findings should be interpreted as exploratory.

4. Discussion

This study provides novel evidence regarding the association between ARNI therapy and improvements in LA mechanical function in patients with advanced decompensated HFrEF. The principal findings are as follows. First, after adjustment for potential confounders, ARNI therapy was associated with significantly greater improvements in LASr, LAScd, and LASct at 6 months than perindopril. The greatest treatment effect was observed for LASr (adjusted mean difference, 4.31; 95% CI, 3.02–5.60; $P < 0.05$), suggesting that LASr may be the most sensitive marker of ARNI-associated improvement in LA function. This observation is consistent with the physiological role of reservoir strain, which reflects global LA compliance and is generally less load-dependent than conduit or booster strain. Second, the beneficial association between ARNI therapy and LASr appeared to be greater in patients with a baseline LVEF of 30–40% than in those with an LVEF $\leq 30\%$.

The LA is not merely a passive conduit for LV filling but performs three distinct phasic functions during the cardiac cycle, namely reservoir, conduit, and booster pump function, which together contribute to maintaining cardiac performance^[12, 13]. LA and LV mechanics are closely coupled throughout the progression of HF. According to the Frank–Starling mechanism, early LV dysfunction leads to compensatory LA dilatation and enhanced booster pump function, thereby maintaining LV filling despite increased filling pressure. As LV dysfunction progresses, persistent pressure and volume overload promote adverse LA remodelling, resulting in increased LA pressure, elevated pulmonary capillary wedge pressure, and eventually atrial failure^[14]. Once atrial myocardial fibres exceed their optimal operating length, LA contractile function progressively deteriorates. Although LA strain has emerged as an important marker of LA mechanical function in HFrEF, relatively few studies have evaluated the effects of pharmacological therapy on LA mechanics in this population.

The PARABLE-HF trial^[9] showed that ARNI therapy, compared with valsartan, was associated with a greater increase in LAVI. The authors proposed that enhanced cyclic guanosine monophosphate signalling mediated by natriuretic peptides, together with reversal of cardiomyocyte stiffness through titin hypophosphorylation, contributed to these structural changes. However, LA remodelling is a multilevel process involving molecular, cellular, tissue, and chamber-level alterations^[15]. Therefore, assessment of LA volume alone may not fully characterize the complexity of LA remodelling. Advances in speckle-tracking echocardiography have enabled direct assessment of LA myocardial deformation. Rossi et al^[16] demonstrated that LASr was an independent predictor of adverse outcomes in patients with HFrEF, even in the absence of LA enlargement.

Beyond haemodynamic unloading, ARNI therapy may improve LA function through metabolic mechanisms. Akhan and Ardahanli^[17] reported that hypoglycaemia was associated with impaired endothelial function and LV diastolic dysfunction, as reflected by abnormal E/A and E/e' ratios. Insulin resistance is considered a key contributor to these abnormalities. Previous studies have shown that ARNI therapy significantly reduces insulin resistance in patients with chronic HF, with the homeostasis model assessment of insulin resistance (HOMA-IR) decreasing from 3.10 to 1.96 after 3 months of treatment ($P < 0.05$)^[18]. This effect has been attributed to neprilysin inhibition, which preserves endogenous glucagon-like peptide-1 and other incretins, thereby improving insulin secretion and insulin sensitivity^[19]. In the present study, ARNI therapy was directly compared with perindopril rather than valsartan. The greater improvement in LASr observed in the ARNI group may therefore reflect not only haemodynamic unloading but also favourable metabolic effects. Nevertheless, these mechanistic hypotheses require confirmation in prospective mechanistic studies.

Similarly, Sun et al^[10] reported that ARNI therapy produced greater improvement in LASr than angiotensin receptor blockers and was associated with better clinical outcomes in patients with HFrEF. However, their study did not evaluate the effects of ARNI therapy on LAScd or LASct. Deferm et al^[20] investigated serial changes in LA mechanics in a small cohort of patients hospitalized with acute HFrEF (mean LVEF, 20%). Reservoir strain increased after decongestive therapy and continued to improve during the subsequent 6-week follow-up, whereas booster strain improved primarily during follow-up. Consistent with these findings, both treatment groups in our study demonstrated improvements in LA strain after 6 months of therapy. However, improvements in reservoir, conduit, and booster strain were significantly greater in patients receiving ARNI than in those receiving perindopril. Furthermore, patients with a baseline LVEF of 30–40% experienced greater improvement in LASr than those with an LVEF $\leq 30\%$. Extensive atrial fibrosis in advanced HFrEF may limit the reversibility of LA dysfunction in patients with more severe LV systolic impairment. The absence of significant subgroup interactions for LAScd and LASct may also reflect the limited sample size and greater variability within the LVEF $\leq 30\%$ subgroup.

The PARADIGM-HF trial demonstrated that ARNI therapy was superior to enalapril in reducing mortality and HF hospitalization in patients with HFrEF^[21]. Using perindopril as the comparator in the present study, our study showed that ARNI therapy was also associated with a lower incidence of MACEs than

perindopril. However, because only 23 MACEs occurred during follow-up, these findings should be considered exploratory and require confirmation in larger prospective studies.

LA dysfunction is common in patients with HFrEF, particularly impairment of reservoir function. Our findings suggest that ARNI therapy is associated with significant improvement in LA mechanical function, especially LASr, which may contribute to favourable atrial remodelling. Whether these improvements translate into a reduced risk of atrial arrhythmias requires further investigation, although our findings are consistent with previous reports suggesting a lower incidence of atrial fibrillation among patients receiving ARNI therapy^[22].

5. Limitations

This study has several limitations. First, this was a single-center retrospective study with a relatively small sample size, which may limit the generalizability of the findings. Second, the follow-up period was limited to 6 months and overlapped with the COVID-19 pandemic, which may have contributed to an increased loss to follow-up, particularly in the ARNI group. Pandemic-related restrictions, including limited hospital access and patients' concerns regarding in-person visits, may have affected scheduled echocardiographic examinations, medication adherence, and attendance at outpatient follow-up visits. When in-person follow-up was not feasible, patients were contacted by telephone according to the study protocol. Nevertheless, all patients included in the final analysis completed the planned 6-month follow-up assessments. Notably, 13 patients in the ARNI group were lost to follow-up during the study, resulting in a relatively high attrition rate. Third, we used perindopril rather than enalapril as the comparator, reflecting real-world prescribing patterns in our center (> 90% of ACEI prescriptions). Fourth, assessment of LA strain by 3D-STE requires adequate image quality to reliably track the thin-walled left atrium and therefore was not feasible in all initially screened patients. In addition, most patients received ARNI at a dose of 50 mg twice daily, whereas only a small proportion received 100 mg twice daily and none received doses exceeding 100 mg twice daily. This dosing pattern reflects routine clinical practice in Asian populations, in which relatively few patients achieve the recommended target dose of 200 mg twice daily. Finally, the exclusion criteria and the relatively homogeneous ethnic background of the study population may further limit the external validity of our findings.

6. Conclusions

In patients with HFrEF, ARNI therapy was associated with greater improvement in LA strain and a lower incidence of MACEs than perindopril. The greatest improvement was observed in LASr, suggesting that this parameter may be the most sensitive marker of ARNI-associated improvement in LA mechanical function. In exploratory subgroup analyses, the beneficial association between ARNI therapy and LASr appeared to be greater in patients with a baseline LVEF of 30–40% than in those with an LVEF $\leq$ 30%, indicating that patients with less advanced systolic dysfunction may derive greater improvement in LA function. Because this was a single-center retrospective study with a relatively short follow-up period, these findings should be considered hypothesis-generating and require confirmation in larger prospective studies with longer follow-up.

Abbreviations

ARNI, angiotensin receptor–neprilysin inhibitor;

ANCOVA, analysis of covariance

BMI, body mass index;

BSA, body surface area;

CIs, confidence intervals;

eGFR, estimated glomerular filtration rate;

HF, heart failure;

HFrEF, heart failure with reduced ejection fraction;

HFpEF, heart failure with preserved ejection fraction;

hs-TnI, high-sensitivity troponin I;

hs-CRP, high-sensitivity C-reactive protein

HOMA-IR, homeostasis model assessment of insulin resistance;

ICCs, intraclass correlation coefficients;

IQR, interquartile range;

LA, left atrial;

LAScd, left atrial conduit strain;

LASct, left atrial booster strain;

LASr, left atrial reservoir strain;

LV, left ventricular;

LVEF, left ventricular ejection fraction;

LAVmax, left atrial maximal volume;

LAVImax, left atrial maximal volume index;

LAVmin, left atrial minimal volume;

LAVImin, left atrial minimal volume index;

LAVpreA, pre-atrial contraction left atrial volume;

LAVIpreA, pre-atrial contraction left atrial volume index;

LVEDD, left ventricular end-diastolic diameter;

LVESD, left ventricular end-systolic diameter

LDL-C, low-density lipoprotein cholesterol;

LAEF, left atrial expansion fraction;

LAAEF, left atrial active expansion fraction;

LAPEF, left atrial passive expansion fraction;

MACE, major adverse cardiovascular event;

NT-proBNP, N-terminal pro-B-type natriuretic peptide

NYHA, New York Heart Association;

PALS, peak atrial longitudinal strain;

RAAS, renin–angiotensin–aldosterone system;

SE, standard error;

SD, standard deviation;

SGLT2, sodium-glucose cotransporter 2;

3D-STE, three-dimensional speckle-tracking echocardiography;

Declarations

Ethics approval and consent to participate

All procedures were performed in compliance with relevant laws and institutional guidelines and were approved by the Institutional Review Board (IRB) of the First Peoples' Hospital of Taicang, The Affiliated Taicang Hospital of Soochow University (No. 2022-ky-022).

Consent for publication

None

Competing interests

None

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Author Contribution

Y.M. Zhu and S.M.Zhao conceived and designed the study. Y.M.Zhu performed the experiments, collected the data, and wrote the main manuscript text. S.M.Zhao provided supervision and critically revised the manuscript. Y.H.Zhang performed echocardiographic examinations and analyzed the data.Q.M.Zong collected the data.Y.J.Tang analyzed the data.Both authors read and approved the final manuscript.

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None

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request

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Figures

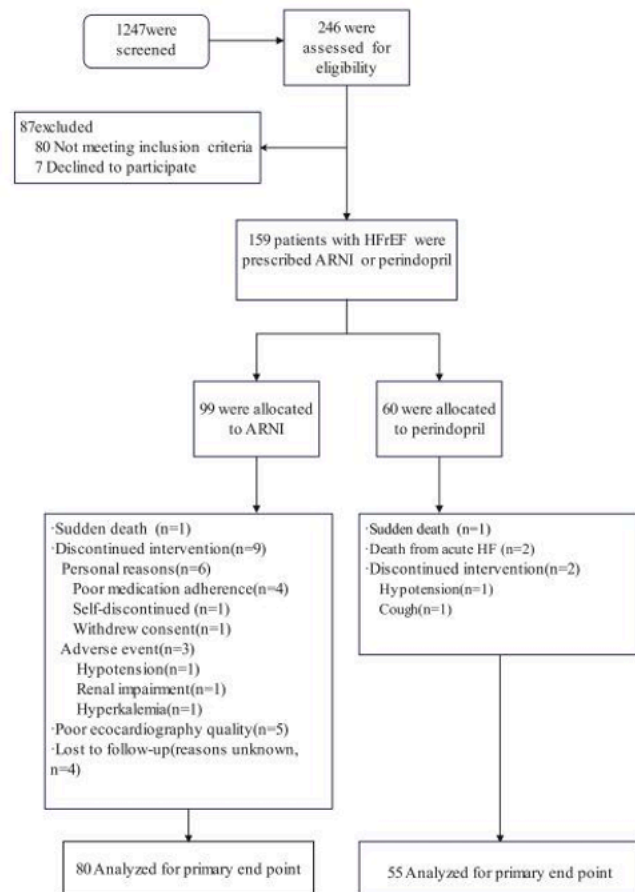


Figure 1

Flowchart of the study protocol.

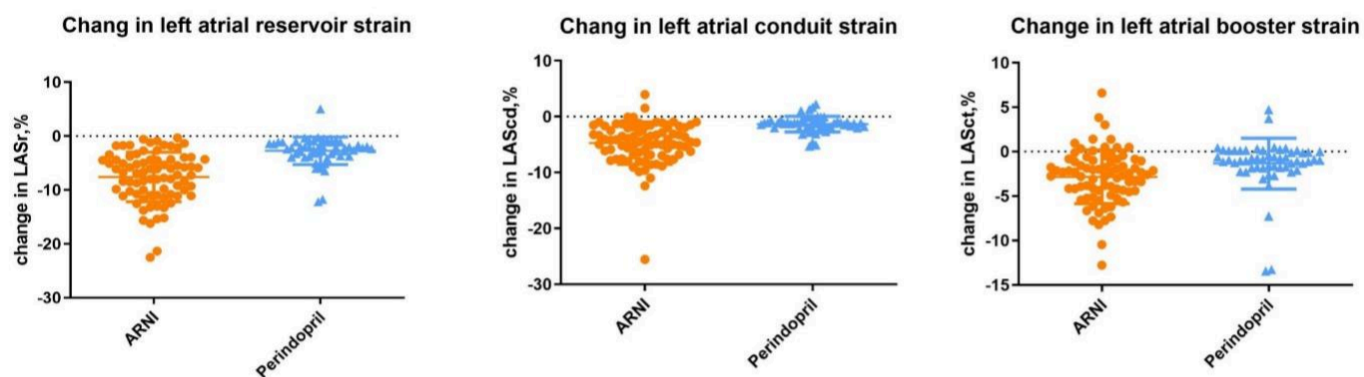
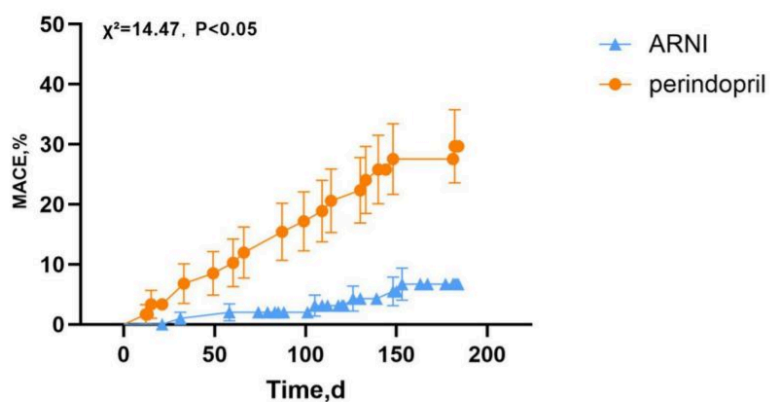


Figure 2

Changes in left atrial reservoir strain (LASr), left atrial conduit strain (LAScd), and left atrial booster strain (LASct). (A) Improvements in LASr were greater in patients treated with ARNIs compared with those receiving perindopril ($7.58 \pm 4.60\%$ vs $2.73 \pm 2.55\%$; $P < 0.05$). (B) Improvements in LAScd were greater in patients treated with ARNIs compared with those receiving perindopril ($4.73 \pm 3.79\%$ vs $1.34 \pm 1.39\%$; $P < 0.05$). (C) Improvements in LASct were greater in patients treated with ARNIs compared with those receiving perindopril (2.85 ± 3.03 vs $1.35 \pm 2.87\%$; $P < 0.05$).



NO.at risk					
	0	50	100	150	200
ARNI	99	97	91	79	74
Perindopril	60	53	49	43	42

Figure 3

Time to Cardiovascular Death and First Major Adverse Cardiovascular Event (MACE).

Kaplan–Meier curves for major adverse cardiovascular events (MACEs) in the ARNI group versus the perindopril group. Log-rank testing showed a significant between-group difference ($P < 0.05$)

Supplementary Files

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- [SupplementaryTablesFigs.docx](#)