



TITLE:

Prognostic value of reduction in left atrial size during a follow-up of heart failure: an observational study

AUTHOR(S):

Shiba, Masayuki; Kato, Takao; Morimoto, Takeshi; Yaku, Hidenori; Inuzuka, Yasutaka; Tamaki, Yodo; Ozasa, Neiko; ...
Sato, Yukihiro; Kuwahara, Koichiro; Kimura, Takeshi

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BMJ Open Prognostic value of reduction in left atrial size during a follow-up of heart failure: an observational study

Masayuki Shiba,¹ Takao Kato ,¹ Takeshi Morimoto ,² Hidenori Yaku,³ Yasutaka Inuzuka,⁴ Yodo Tamaki,⁵ Neiko Ozasa,¹ Yuta Seko,¹ Erika Yamamoto,¹ Yusuke Yoshikawa,¹ Takeshi Kitai,⁶ Yugo Yamashita,¹ Moritake Iguchi ,⁷ Kazuya Nagao ,⁸ Yuichi Kawase,⁹ Takashi Morinaga,¹⁰ Mamoru Toyofuku,¹¹ Yutaka Furukawa,⁶ Kenji Ando,¹⁰ Kazushige Kadota,⁹ Yukihito Sato,¹² Koichiro Kuwahara,¹³ Takeshi Kimura ,¹ On behalf of KCHF Study Investigators

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For numbered affiliations see end of article.

Correspondence to

Dr Takao Kato;
tkato75@kuhp.kyoto-u.ac.jp

ABSTRACT

Objective The association between sequential changes in left atrial diameter (LAD) and prognosis in heart failure (HF) remains to be elucidated. The present study aimed to investigate the link between reduction in LAD and clinical outcomes in patients with HF.

Design A multicentre prospective cohort study.

Setting This study was nested from the Kyoto Congestive Heart Failure registry including consecutive patients admitted for acute decompensated heart failure (ADHF) in 19 hospitals throughout Japan.

Participants The current study population included 673 patients with HF who underwent both baseline and 6-month follow-up echocardiography with available paired LAD data. We divided them into two groups: the reduction in the LAD group (change <0 mm) (n=398) and the no-reduction in the LAD group (change ≥0 mm) (n=275).

Primary and secondary outcomes The primary outcome measure was a composite of all-cause death or hospitalisation for HF during 180 days after 6-month follow-up echocardiography. The secondary outcome measures were defined as the individual components of the primary composite outcome measure and a composite of cardiovascular death or hospitalisation for HF.

Results The cumulative 180-day incidence of the primary outcome measure was significantly lower in the reduction in the LAD group than in the no-reduction in the LAD group (13.3% vs 22.2%, p=0.002). Even after adjusting 15 confounders, the lower risk of reduction in LAD relative to no-reduction in LAD for the primary outcome measure remained significant (HR 0.59, 95% CI 0.36 to 0.97 p=0.04).

Conclusion Patients with reduction in LAD during follow-up after ADHF hospitalisation had a lower risk for a composite endpoint of all-cause death or HF hospitalisation, suggesting that the change of LAD might be a simple and useful echocardiographic marker during follow-up.

INTRODUCTION

The prevalence of heart failure (HF) and the number of HF hospitalisations have been increasing worldwide with an ageing

Strengths and limitations of this study

- This study is a multicentre prospective observational study reporting the association between sequential changes in left atrial diameter (LAD) and prognosis in heart failure (HF).
- We calculated changes in LAD from the echocardiography during index hospitalisation to 6-month follow-up echocardiography.
- A link between reduction in LAD and favourable clinical outcomes was demonstrated even after adjusting for left atrial enlargement.
- The study results were derived from very selected patients from the Kyoto Congestive Heart Failure registry participants.
- Further studies are needed to generalise our study results.

population.¹ Further, the health expenditure for HF is progressively increasing, and HF is a crucial global health problem.² HF hospitalisations are often repeated,³ and quality of life and outcomes in HF progressively deteriorate with HF finally leading to death.⁴ Thus, the outpatient management of HF is critically important. However, there are very limited data on the association between longitudinal echocardiographic changes over time and clinical outcomes in patients with HF.⁵ Left atrial enlargement is an established prognostic predictor of HF⁶ and is related to mortality in heart diseases.^{7,8} Besides, left atrial enlargement was independently associated with cardiovascular events and death in the general population.⁹ Despite the prognostic importance of left atrial size, the relation between sequential change in left atrial size and the prognosis in HF has not been evaluated.

In this study, we evaluated left atrial diameter (LAD) during 6 months after hospitalisation for acute decompensated heart failure (ADHF) and investigated the effect of the reduction in LAD on clinical outcomes in patients who were discharged from ADHF hospitalisation.

METHODS

Patient population

In the Kyoto Congestive Heart Failure (KCHF) registry, we enrolled consecutive 4056 hospitalised patients who were diagnosed as ADHF by the modified Framingham criteria and were treated with HF-specific management involving intravenous drugs within 24 hours after hospital admittance between 1 October 2014 and 31 March 2016. The rationale, design and enrolment of the KCHF registry have been previously published in detail.¹⁰⁻¹² In parallel with the main KCHF study, we designed a prospective longitudinal follow-up study enrolling patients who were to have a visit and echocardiography at 6±1 months.¹⁰ At the 6-month visit, we collected data on physical findings, echocardiography, laboratory tests and medications. Exclusion criteria for the prospective longitudinal follow-up study included the following: no consent given for the longitudinal study (n=238), age <20 years (n=1), fever or infectious diseases at admission (n=297), acute coronary syndrome at admission (n=157), end-stage renal failure (n=218), severe comorbidity which limits the life expectancy

within 1 year assessed by attending physicians at each participating centre, such as end-stage cancer, severe cognitive dysfunction, and end-stage liver dysfunction (n=112), or ineligible for the protocol mandated follow-up by attending physicians' judgement (n=1516). The prospective longitudinal follow-up cohort included 1246 patients after excluding 2539 patients who had exclusion criteria, and 271 patients who died during index hospitalisation. Follow-up echocardiography at the 6-month visit was performed in 748 patients, and after excluding those patients with missing LAD data, the current study population consisted of 673 patients who underwent both baseline and follow-up echocardiography with available paired LAD data (figure 1A,B). We calculated changes in LAD from the echocardiography during index hospitalisation to 6-month follow-up echocardiography and divided the study population into two groups: the reduction in the LAD group (n=398) and the no-reduction in the LAD group (n=275).

Data on clinical characteristics and echocardiography were collected from hospital medical records. Clinical follow-up information was obtained from hospital medical records and/or from letters or telephone call to patients, their relatives or their referring physicians by the attending physicians or research assistants at each participating institution. Identifiable patient data were anonymised before analysis.

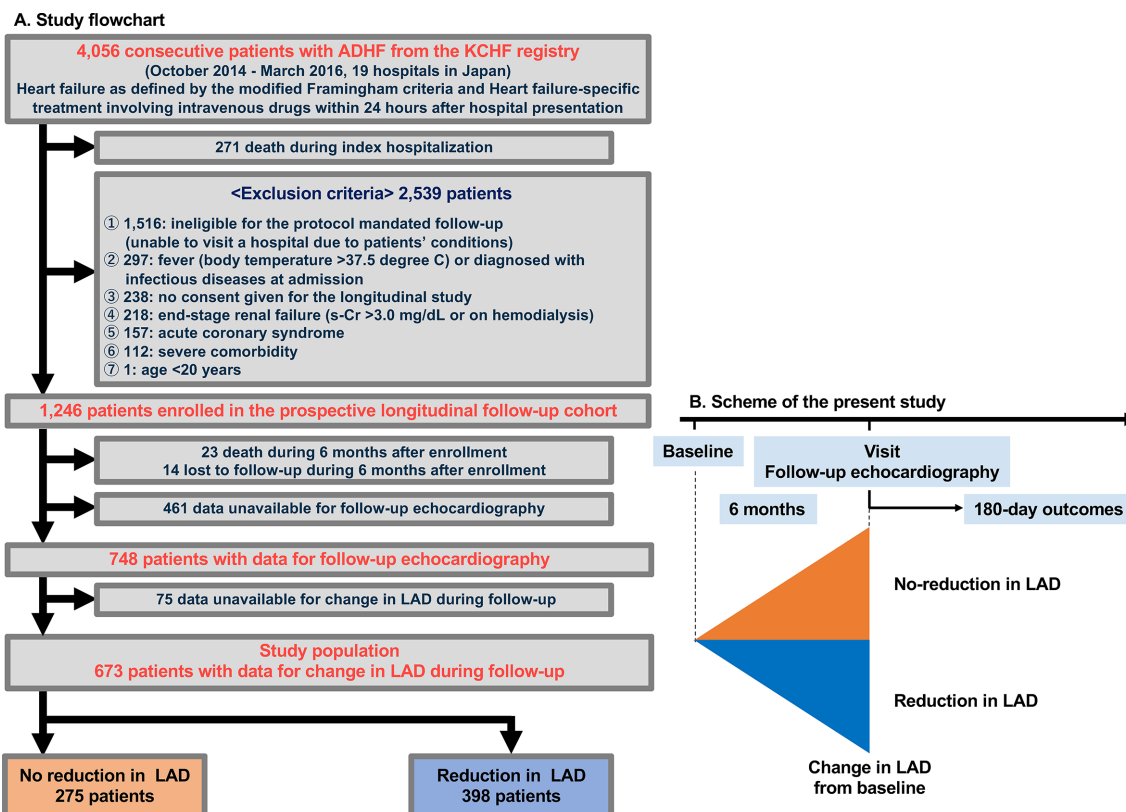


Figure 1 (A) Study flowchart. (B) A scheme of the present analysis. ADHF, acute decompensated heart failure; KCHF, Kyoto Congestive Heart Failure; LAD, left atrial diameter; s-Cr, serum creatinine.

Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from patients enrolled in the longitudinal prospective cohort study.

Outcomes

Clinical follow-up was performed at 1 year±1 month after enrolment; thus, the data were censored at 210 days after the follow-up echocardiography at 6 months after index hospitalisation and we performed time-to-event analyses. The date of follow-up echocardiography was regarded as time zero (figure 1B). The primary outcome measure in the present study was defined as a composite of all-cause death or hospitalisation for HF. The secondary outcome measures were defined as the individual components of the primary composite outcome measure and a composite of cardiovascular death or hospitalisation for HF. Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified.^{10 11} Cardiovascular death included death related to HF, sudden death, death related to stroke and death from other cardiovascular causes. Sudden death was an unexplained death in a previously stable patient.^{10 11}

Definitions

LAD was measured as anteroposterior diameter of left atrium during systolic phase in parasternal long-axis view by echocardiography. We did not adopt the data for LA measurement in other views. We defined a reduction in LAD from baseline to 6-month follow-up echocardiography as LAD change <0 mm and a no-reduction in LAD as LAD change ≥0 mm.

The detailed definitions of baseline patient characteristics were previously described.^{10–15} Anaemia was defined using the WHO criteria (haemoglobin <120 g/L in women and <130 g/L in men). End-stage renal disease was defined as estimated glomerular filtration rate <30 mL/min/1.73 m² based on the chronic kidney disease grades. HF was classified according to left ventricular ejection fraction (LVEF) at 6-month follow-up as HF with reduced LVEF (<40%) (HFrEF) and non-HF with reduced LVEF (≥40%) (non-HFrEF). In addition, we classified HF according to LVEF≥50% (HF with preserved EF), 40%–49% (HF with mid-range EF) and <40% (HFrEF). Left atrial enlargement was defined as LAD ≥40 mm.⁷ LV dilation was defined as left ventricular end-diastolic dimension (LVDd) >55 mm.¹⁶ High tricuspid regurgitation pressure gradient (TRPG) was defined as TRPG >31.4 mm Hg.¹⁷

Statistical analysis

Categorical variables were expressed as counts and percentages, and continuous variables were expressed as means with SD, or medians with IQR. A χ^2 test was used for categorical variables. An unpaired, two-tailed t-test was used for normally distributed continuous variables or the Wilcoxon rank-sum test was used for non-normally

distributed continuous variables. Baseline patient characteristics and clinical outcomes were compared between the two groups based on LAD change patterns. A paired t-test was used for continuous variables and sign test was used for binary variables to compare them between baseline and follow-up. Cumulative incidences were estimated by Kaplan-Meier analysis and the between-groups differences were assessed by log-rank test. We used the Cox proportional hazards regression model to estimate the effect of reduction in LAD relative to no-reduction in LAD for the primary and secondary outcome measures incorporating 15 clinically relevant risk-adjusting variables including age ≥80 years, sex, atrial fibrillation/flutter, renal failure, anaemia, LVEF <40%, moderate/severe mitral regurgitation (MR), LAD ≥40 mm, TRPG >31.4 mm Hg, change in TRPG >0 mm Hg, LVDd >55 mm, change in LVDd >0 mm, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker, β -blockers and mineralocorticoid receptor antagonist. The results were presented as the HRs and their 95% CIs. The subgroup analyses were performed in the 10 clinically relevant subgroups such as age equal to or greater than 80 years, sex, atrial fibrillation/flutter, moderate/severe MR, LVEF less than 40%, and LAD equal to or greater than 40 mm, TRPG higher than 31.4 mm Hg, change in TRPG higher than 0 mm Hg, LVDd >55 mm and change in LVDd >0 mm. We also used the Cox proportional hazards regression model to estimate the interactions between the subgroup factors and the effect of LAD change patterns on clinical outcomes. Additionally, factors associated with reduction in LAD were analysed using univariate and multivariate logistic regression models, adjusting for 17 clinically relevant variables. The 17 adjusting variables consisted of change in LVDd >0 mm, change in LVEF >0%, change in TRPG >0 mm Hg, data at discharge from index hospitalisation which correspond to the risk-adjusting variables of the main analysis and diuretics at discharge. Statistical analyses were performed using JMP pro software, V.14 (SAS). A two-tailed p value <0.05 was considered as statistically significant in all analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

RESULTS

Clinical characteristics, laboratory test results and medications at the 6-month visit

The clinical characteristics at the 6-month visit were well balanced between the two groups, except for the lower prevalence of patients with age ≥80 years in the reduction in the LAD group than in the no-reduction in the LAD group (table 1). The laboratory test results and medications were also well balanced between the two groups, except for the higher haemoglobin level and lower B-type natriuretic polypeptide level in the reduction in the

Table 1 Patient characteristics at 6-month echocardiographic follow-up

Variable	No reduction in LAD (n=275)	Reduction in LAD (n=398)	P value	Number of patients analysed
Clinical characteristics				
Age (years)	76.1±11.6	74.2±12.6	0.07	673
Age≥80 years*	130 (47%)	154 (39%)	0.03	673
Women*	130 (47%)	165 (41%)	0.14	673
BMI (kg/m ²)	23.0±5.1	22.5±4.4	0.64	506
BMI≤22 kg/m ²	107 (50%)	144 (49%)	0.81	506
Medical history				
Atrial fibrillation or flutter*	156 (57%)	222 (56%)	0.81	673
Hypertension	212 (77%)	287 (72%)	0.15	673
Diabetes	115 (42%)	141 (35%)	0.09	673
Previous myocardial infarction	69 (25%)	79 (20%)	0.11	673
Tests at 6-month follow-up				
BNP (pg/mL)	224.1 (114.4–435.5)	153.9 (63.3–312.0)	0.0002	507
eGFR (mL/min/1.73 m ²)	43.4±19.4	46.5±20.8	0.06	642
eGFR <30 mL/min/1.73 m ² *	71 (27%)	86 (23%)	0.23	642
Albumin (g/dL)	3.9±0.46	3.9±0.57	0.24	608
Albumin <3 g/dL	7 (2.8%)	16 (4.5%)	0.26	608
Haemoglobin (g/L)	118±22	121±23	0.03	638
Anaemia *	169 (64%)	208 (56%)	0.03	638
Medications at 6-month follow-up				
ACE-I or ARB*	139 (60%)	194 (62%)	0.70	545
β-blocker*	181 (78%)	249 (79%)	0.79	545
MRA*	104 (45%)	142 (45%)	1.0	544
Diuretic	198 (85%)	259 (82%)	0.33	547

Diuretics included loop diuretic, thiazide and tolvaptan.

*Risk-adjusting variables selected for the Cox proportional hazards regression model.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; MRA, mineralocorticoid receptor antagonist.

LAD group than in the no-reduction in the LAD group (table 1).

Echocardiographic findings

The reduction in the LAD group had a larger LAD, larger LVDD and higher TRPG at baseline echocardiography than the no-reduction in the LAD group. At 6-month follow-up echocardiography, TRPG was smaller in the reduction in the LAD group than in the no-reduction in the LAD group (table 2). Between baseline and 6-month follow-up echocardiography, decrease in TRPG and decrease in the prevalence of moderate/severe MR and tricuspid regurgitation were observed only in the reduction in the LAD group. The magnitudes of the decrease in LVDD, the decrease in TRPG and the increase of LVEF were greater in the reduction in the LAD group than in the no-reduction in the LAD group (table 2).

Clinical outcomes: the reduction in the LAD group versus the no-reduction in the LAD group

The follow-up rate at 180 days after 6-month follow-up echocardiography was 96.3%. The cumulative 180-day incidence of the primary outcome measure (a composite endpoint of all-cause death or hospitalisation for HF) was significantly lower in the reduction in the LAD group than in the no-reduction in the LAD group (13.3% vs 22.2%, p=0.002) (figure 2A). After adjusting for confounders, the lower risk of the reduction in the LAD group relative to the no-reduction in the LAD group for the primary outcome measure remained significant (HR 0.59, 95% CI 0.36 to 0.97 p=0.04) (table 3). Regarding the secondary outcome measures, the cumulative 180-day incidence of all-cause death was also significantly lower in the reduction in the LAD group than in the no-reduction in the LAD group (4.6% vs 8.6%, p=0.01) (figure 2B). After adjusting for confounders, the lower risk of the reduction in the LAD group relative to the no-reduction in the

Table 2 Changes in echocardiographic parameters from baseline to 6-month visit

Variable	No reduction in LAD (n=275)			Reduction in LAD (n=398)			Between-groups comparison				
	Baseline	Follow-up	Delta*	P value (paired)	Baseline	Follow-up	Delta*	P value (paired)	P value (baseline)	P value (follow-up)	P value (delta)
LAD (mm)	43.0±8.9	46.9±8.8	4.0±4.1	<0.0001	46.7±8.0	40.8±8.4	-5.8±4.5	<0.0001	<0.0001	<0.0001	<0.0001
LAD ≥40 mm†	172/275 (63%)	227/275 (83%)	55 (20%)	<0.0001	333/398 (84%)	225/398 (57%)	-108 (-27%)	<0.0001	<0.0001	<0.0001	<0.0001
LVDD (mm)	51.8±9.2	51.1±9.3	-0.7±5.0	0.02	53.7±9.6	50.2±9.5	-3.6±6.0	<0.0001	0.008	0.16	<0.0001
LVDD >55 mm†	91/275 (33%)	83/275 (30%)	-8 (-2.9%)	0.24	152/397 (38%)	95/397 (24%)	-57 (-14%)	<0.0001	0.17	0.07	0.0004
Change in LVDD >0 mm†	n/a	100/275 (36%)	n/a	n/a	n/a	105/397 (26%)	n/a	n/a	n/a	0.006	n/a
LVEF (%)	46.0±15.7	49.5±15.8	3.5±11.4	<0.0001	44.6±17.3	51.1±15.7	6.6±13.3	<0.0001	0.18	0.11	0.004
LVEF <40%†	96/274 (35%)	76/274 (28%)	-20 (-7.3%)	0.006	173/398 (44%)	109/398 (27%)	-64 (-16%)	<0.0001	0.03	0.92	0.06
Moderate/Severe MRT	90/270 (33%)	94/270 (35%)	3 (1.5%)	0.58	152/395 (38%)	114/395 (29%)	-38 (-9.6%)	<0.0001	0.17	0.10	0.004
Moderate/Severe TR	73/275 (27%)	82/275 (30%)	9 (3.3%)	0.21	119/398 (30%)	97/398 (24%)	-22 (-5.5%)	0.020	0.34	0.12	0.02
TRPG (mm Hg)	31.5±12.3	30.3±14.0	0.37±13.3	0.69	34.2±13.2	27.5±12.2	-6.0±14.1	<0.0001	0.02	0.008	<0.0001
TRPG >31.4 mm Hgt	77/194 (40%)	87/194 (45%)	10 (5.2%)	0.18	157/303 (52%)	95/303 (31%)	-62 (-20%)	<0.0001	0.008	0.002	<0.0001
Change in TRPG >0 mm Hgt	n/a	94/194 (48%)	n/a	n/a	n/a	98/303 (32%)	n/a	n/a	n/a	0.0003	n/a

Changes in LVDD and TRPG were calculated according to the following equation: (the value at 6-month visit) – (the value at baseline).

*Delta were calculated for continuous variables according to the following equation: (the value at 6-month visit) – (the value at baseline) and for binary variables according to the following equation: (the numbers at 6-month visit) – (the numbers at baseline).

†Risk-adjusting variables selected for the Cox proportional hazards regression model.

LAD, left atrial diameter; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; n/a, not available; TR, tricuspid regurgitation; TRPG, tricuspid regurgitant pressure gradient.

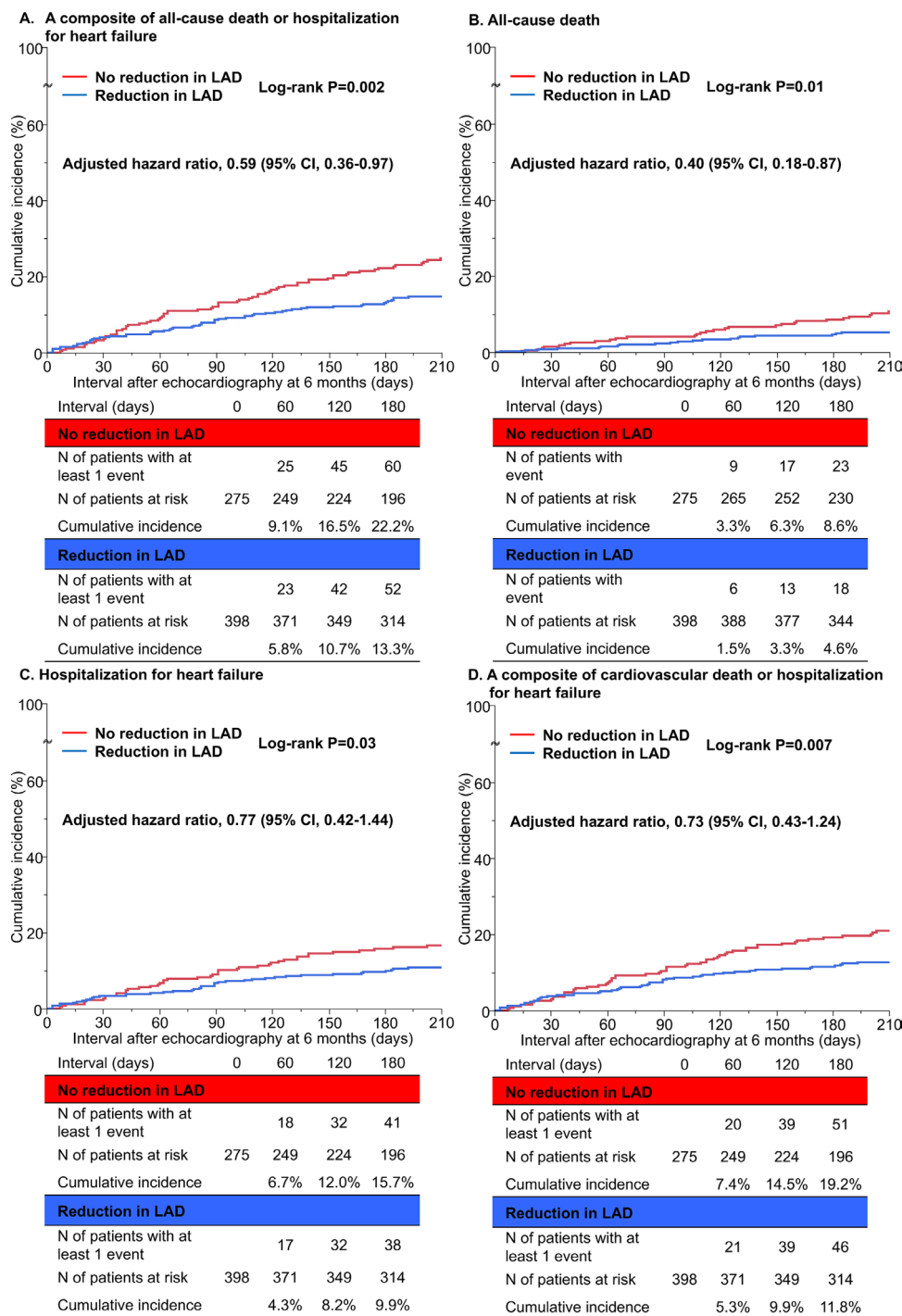


Figure 2 Kaplan-Meier curves for (A) the primary outcome measure, (B) all-cause death, (C) hospitalisation for heart failure and (D) a composite of cardiovascular death or hospitalisation for heart failure. LAD, left atrial diameter.

LAD group for all-cause death remained significant (HR 0.40, 95% CI 0.18 to 0.87, $p=0.02$) (table 3). The cumulative 180-day incidences of hospitalisation for HF and a composite of cardiovascular death or hospitalisation for HF were also significantly lower in the reduction in the LAD group than in the no-reduction in the LAD group (9.9% vs 15.7%, $p=0.03$, figure 2C and 11.8% vs 19.2%, $p=0.007$, figure 2D, respectively). However, after adjusting for confounders, the lower risk of the reduction in the LAD group relative to the no-reduction in the LAD group

for hospitalisation for HF and a composite of cardiovascular death or hospitalisation for HF were no longer significant (HR 0.77, 95% CI 0.42 to 1.44, $p=0.42$ and HR 0.73, 95% CI 0.43 to 1.24, $p=0.24$, respectively) (table 3).

Subgroup analyses

When we stratified patients according to the subgrouping factors, the reduction in LAD was greater in patients aged below 80 years, men, and patients without MR, LAD >40 mm, or an increase in TRPG and LVDD (online

Table 3 Clinical outcomes at 180 days after follow-up echocardiography

Clinical outcome measures	Number of patients with event/Number of patients at risk (cumulative 180-day incidence)		HR (95% CI)			
	Reduction in LAD (n=398)	No reduction in LAD (n=275)	Crude	P value	Adjusted	P value
All-cause death or hospitalisation for heart failure	52/314 (13.3%)	60/196 (22.2%)	0.57 (0.40 to 0.81)	0.002	0.59 (0.36 to 0.97)	0.04
All-cause death	18/344 (4.6%)	23/230 (8.6%)	0.48 (0.27 to 0.85)	0.01	0.40 (0.18 to 0.87)	0.02
Hospitalisation for heart failure	38/314 (9.9%)	41/196 (15.7%)	0.63 (0.41 to 0.97)	0.04	0.77 (0.42 to 1.44)	0.42
Cardiovascular death or hospitalisation for heart failure	46/314 (11.8%)	51/196 (19.2%)	0.59 (0.40 to 0.87)	0.007	0.73 (0.43 to 1.24)	0.24

The Cox proportional hazards regression model was constructed adjusting for 15 clinically relevant risk-adjusting variables: age ≥ 80 years, sex, atrial fibrillation/flutter, renal failure, anaemia, LVEF $< 40\%$, moderate/severe MR, LAD ≥ 40 mm, TRPG > 31.4 mm Hg, change in TRPG > 0 mm Hg, LVDd > 55 mm, change in LVDd > 0 mm, ACE-I or ARB, β -blockers and MRA. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; TRPG, tricuspid regurgitation pressure gradient.

supplemental table 1). In the subgroup analyses, there were no significant interactions between all the subgroup factors (age, sex, atrial arrhythmias, moderate/severe MR, reduced LVEF, LAD enlargement, high TRPG and its change, LV dilation and its change) and the effects of reduction in LAD relative to no-reduction in LAD on the primary outcome measure (online supplemental figure 1). When stratified by LVEF $\geq 50\%$, $40\%–49\%$ and $< 40\%$, there was no interaction between the LVEF status and the effect in reduction in LAD (online supplemental table 2).

Factors associated with the reduction in LAD

Among the variables listed in online supplemental table 3, the following variables were significantly associated with reduction in LAD in univariate logistic regression analysis: age ≥ 80 years, LAD ≥ 40 mm, change in LVDd > 0 mm, LVEF $< 40\%$, change in LVEF $> 0\%$, TRPG > 31.4 mm Hg and change in TRPG > 0 mm Hg (online supplemental table 4). In multivariate logistic regression analysis, LAD ≥ 40 mm, TRPG > 31.4 mm Hg and change in TRPG > 0 mm Hg were significantly associated with the reduction in LAD (online supplemental table 4).

DISCUSSION

The main findings of the present study are as follows: (1) a reduction in LAD during 6-month follow-up after ADHF hospitalisation was associated with echocardiographic parameters such as large LA at baseline, an increase in LVEF and a decrease in both LVDd and TRPG; and (2) a reduction in LAD during 6-month follow-up was associated with a lower risk for a composite of all-cause death or hospitalisation for HF.

Many studies reported that left atrial enlargement was a very useful prognostic marker in patients with heart disease including HF.^{7 8 18–20} However, they assessed

left atrial size at a single time point, not serially. Meris *et al*²¹ investigated the association of the change of left atrial volume indexed to body surface area with clinical outcomes in patients with acute myocardial infarction. However, no previous study researched the association between sequential change in left atrial size and clinical outcomes in patients with HF. In clinical settings, we serially assess the cardiac structure and function by echocardiography during follow-up. In addition, LAD is a fundamental measurement of echocardiogram^{22 23}; thus, changes of LAD can be easily evaluated. In the present study, we showed that the change of left atrial size was associated with the prognosis in patients with HF regardless of the presence of left atrial enlargement.

The differences between the reduction and no-reduction in the LAD groups in echocardiographic findings might indicate that more LV reverse remodelling occurred in the reduction in the LAD group. Functionally, LA modulates LV filling and cardiovascular performance as a reservoir for pulmonary venous inflow during LV systole, a conduit for pulmonary venous flow during early ventricular diastole and an active pump to aid LV filling during late ventricular diastole.¹⁸ LA is structurally and functionally correlated with LV function.^{24 25} In particular, LA size is closely linked to LV filling pressure, indicating the change in LA size would be correlated to the change in LV filling pressure.^{24–26} In our study, the increase of LVEF was greater in the reduction in the LAD group than in the no-reduction in the LAD group. Thus, the improved LV systolic function in the reduction in the LAD group might be attributed to decrease in LV volume and LV filling pressure. In addition, a reduction in LA size and a decrease in the prevalence of moderate/severe MR and TRPG in the reduction in the LAD group might be related to

improvement of LV diastolic dysfunction. Altogether, a reduction in LAD suggestive of LA reverse remodelling might be an indicator of the recovery from diastolic and systolic LV dysfunction.

In our study, patients with a reduction in LAD during 6-month follow-up after ADHF hospitalisation showed a better outcome than those with no-reduction in LAD. After adjusting for confounders including medications for HF, LA reverse remodelling was independently associated with a lower risk for a composite of all-cause death or hospitalisation for HF. LV dilation/remodelling is the conventional risk factor for HF and mortality.^{27 28} LVEF was correlated to mortality in patients with chronic HF.²⁹ Echocardiographic findings in index hospitalisation suggested a worse condition in the reduction in the LAD group with larger LA, larger LV, higher TRPG and higher prevalence of reduced LVEF. Although remodelling may not be similar in different types of HF aetiologies, improved outcome associated with reduction in LAD was consistently observed regardless of the presence of LV systolic dysfunction. LV reverse remodelling with increase of LVEF and decrease of LVDD was more frequently observed in the reduction in the LAD group than in the no-reduction in the LAD group. A definitive conclusion could not be drawn because of the limited number of patients analysed in subgroup; however, LV reverse remodelling might have contributed to improved outcome in the reduction in the LAD group.

Several studies on the change in LA volume index were derived from the data of patients with myocardial infarction or those with a risk factor of HF.^{21 30} The present study population consisted of patients who experienced hospitalisation(s) for ADHF. Thus, more elderly patients with more chronic comorbidities such as chronic kidney disease, chronic lung disease and atrial fibrillation were included.^{21 30} Despite the presence of many poor prognostic factors for HF, our study showed that reduction in LAD was independently associated with a significant reduction in the primary composite outcome measure, and all-cause death, as well as a trend for reduction in HF hospitalisation and a composite of cardiovascular death or hospitalisation for HF. Further studies are needed to combine the changes in various chamber sizes and other echocardiographic parameters together in one model and see which is the most important predictor of better clinical outcomes in these patients.

Limitations

Several limitations of the present study should be noted. First, two most recent chamber quantification guidelines recommend the use of left atrial volume assessment to quantify left atrial size instead of antero-posterior diameter, although we did not collect the left atrial volume.^{22 23} LAD is not enough to measure left atrial size in patients with HF. This is a strong limitation of the present study. In addition, the echocardiographic data were not analysed by an echocardiography core

laboratory, but by each participating institution. There might be interobserver and intraobserver differences in the measurement of LAD, although it is easy and fundamental in echocardiography. Diagnostic accuracy of LA measurement by echocardiography was validated when compared with that of CT or cardiac MRI.^{22 23} Second, we did not collect the echocardiographic data on cardiac output and diastolic function. We collected the peak early (E) and late (A) diastolic transmitral flow velocity and E/A ratio in patients with sinus rhythm, while Doppler early diastolic mitral annular velocity (e') and other surrogate markers of diastolic dysfunction were not collected in the present study.¹⁷ Furthermore, although LA and LV global longitudinal strain are useful for evaluating patients with HF,^{31 32} speckled tracking was not performed in this study. Third, it is possible that absent data can alter the study results (ie, selection bias); many patients ineligible for the protocol mandated follow-up were excluded from KCHF registry participants (N=4056). The participating physicians judged that it was difficult for the patients to visit 19 participating hospitals and undergo laboratory tests and echocardiography at 6±1 months because of poor compliance with follow-up and HF management, cognitive dysfunction, frailty or functional disability or because they were discharged to and were mainly followed by primary-level hospitals and clinics, nursing care facilities and facilities offering long-term medical care or treatment unconnected with the participating hospitals or moved to a distant area, respectively. The mortality during 6 months after index hospitalisation (1.8%) (figure 1) and in the ensuing 180 days after 6-month follow-up echocardiography (4.6%–8.6%) (table 3) was much lower than the 180-day mortality of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) and trial-eligible GWG-HF (Get With The Guidelines–Heart Failure) cohorts (18.6% and 21.2%).³³ Indeed, the 180-day mortality of the 1516 patients ineligible for the protocol mandated follow-up (15.0%) (data not shown) was comparable to that of the previous trials. In addition, many other patients were excluded at each stage (see figure 1). This study population only comprised 673 patients of the 4056 patients enrolled in the KCHF registry or of the 1246 patients scheduled for a 6-month echocardiography. This very significant selection of patients remains a major limitation to the present study. Further studies are needed to generalise our study results. Finally, there may be residual and unmeasured confounding factors related to outcomes, although we adjusted for 15 variables relevant to HF outcomes.

CONCLUSION

Patients with reduction in LAD during follow-up after ADHF hospitalisation had a lower risk for a composite of all-cause death or HF hospitalisation, suggesting that the

change of LAD might be a simple and useful echocardiographic marker during follow-up.

Author affiliations

- ¹Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
²Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan
³Department of Cardiology, Mitsubishi Kyoto Hospital, Kyoto, Japan
⁴Cardiovascular Medicine, Shiga General Hospital, Moriyama, Japan
⁵Division of Cardiology, Tenri Hospital, Tenri, Japan
⁶Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
⁷Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
⁸Department of Cardiology, Osaka Red Cross Hospital, Osaka, Japan
⁹Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan
¹⁰Department of Cardiology, Kokura Memorial Hospital, Kokura, Japan
¹¹Department of Cardiology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan
¹²Department of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
¹³Department of Cardiovascular Medicine, Shinshu University Graduate School of Medicine, Nagano, Japan

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Contributors Conceived the design: MS and TK. Collected data: HY, YI, YT, NO, YSe, EY, YYo, TK, YYa, MI, KN, YK, TM, MT, YF, KA, KKa, YSa and Kku. Performed statistical analysis: MS, TK, TM. Wrote the manuscript: MS and TK. Made critical revision: HY, YI, YT, NO, YSe, EY, YYo, TK, YYa, MI, KN, YK, TM, MT, YF, KA, KKa, YSa, Kku, TM and TK. Supervised: TM and TK.

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ORCID iDs

Takao Kato <http://orcid.org/0000-0001-8213-7999>
 Takeshi Morimoto <http://orcid.org/0000-0002-6844-739X>
 Moritake Iguchi <http://orcid.org/0000-0001-5029-1203>
 Kazuya Nagao <http://orcid.org/0000-0002-5043-8778>
 Takeshi Kimura <http://orcid.org/0000-0002-5665-4076>

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Supplementary Table 1. Change of left atrial diameter from baseline to 6-month follow-up based on the subgroup factors in the subgroup analyses

Subgroup	N of patients	Change of LAD (mm)	P value
Age ≥80 years			
Yes	284	-1.14 ± 6.70	0.02
No	389	-2.35 ± 6.30	
Women			
Yes	295	-1.36 ± 6.59	0.02
No	378	-2.21 ± 6.40	
AF or AFL			
Yes	378	-1.38 ± 6.41	0.10
No	295	-2.43 ± 6.57	
Moderate/Severe MR			
Yes	208	-1.09 ± 6.48	0.02
No	457	-2.18 ± 6.51	
LVEF <40 %			
Yes	185	-1.58 ± 6.40	0.71
No	487	-1.94 ± 6.54	

LAD \geq 40 mm				
Yes	452	-0.23 \pm 5.85		<0.0001
No	221	-5.12 \pm 6.52		
TRPG >31.4 mmHg				
Yes	201	-0.48 \pm 6.69		0.001
No	396	-2.35 \pm 6.17		
Change in TRPG >0 mmHg				
Yes	192	-0.53 \pm 6.46		<0.0001
No	305	-2.96 \pm 6.25		
LVDd >55 mm				
Yes	178	-1.31 \pm 6.93		0.20
No	495	-2.03 \pm 6.32		
Change in LVDd >0 mm				
Yes	205	-0.43 \pm 5.92		<0.0001
No	467	-2.46 \pm 6.65		

Continuous variables were presented as mean \pm SD.

LAD, left atrial diameter; AF, atrial fibrillation; AFL, atrial flutter; MR, mitral regurgitation; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitant

pressure gradient; LVDd, left ventricular end-diastolic dimension; SD, standard deviation.

Supplementary Table 2. Subgroup analysis for the primary endpoint according to left ventricular ejection fraction

Subgroup	N of patients with at least 1 event/N of patients at risk (Cumulative 180-day incidence)		Crude HR (95% CI)	P interaction	Adjusted HR (95% CI)	P interaction
	Reduction in LAD (N=398)	No reduction in LAD (N=275)				
	LVEF					
≥50 %	23/231 (10.1 %)	31/150 (21.0 %)	0.45 (0.27-0.74)		0.50 (0.30-0.84)	
40-49 %	8/58 (14.0 %)	7/48 (14.6 %)	1.00 (0.36-2.85)	0.33	1.17 (0.35-3.80)	0.35
<40 %	21/109 (19.7 %)	22/76 (29.9 %)	0.64 (0.36-1.16)		0.67 (0.37-1.23)	

Adjusting variables: age ≥80 years, sex and LAD ≥40 mm.

LAD, left ventricular diameter; LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

Supplementary Table 3. Details of factors for the association with the reduction in left atrial diameter

Variable	No reduction in	Reduction in	P value	N of patients analyzed
	LAD (N=275)	LAD (N=398)		
Age ≥80 years	130 (47%)	154 (39%)	0.03	673
Women	130 (47%)	165 (41%)	0.14	673
History of Atrial fibrillation or flutter at discharge	151 (55%)	217 (55%)	0.92	673
eGFR at discharge <30 mL/min/1.73m ²	56 (21%)	71 (18%)	0.41	668
Anemia at discharge	163 (61%)	221 (57%)	0.39	655
ACE-I or ARB at discharge	191 (69%)	281 (71%)	0.75	673
β-blocker at discharge	210 (76%)	312 (78%)	0.54	673
MRA at discharge	140 (51%)	209 (53%)	0.68	673
Diuretic at discharge	242 (88%)	346 (87%)	0.68	673
LAD ≥40 mm (baseline)	172/275	333/398	<0.0001	673

	(63%)	(84%)		
LVDd >55 mm (baseline)	91/275	152/397	0.17	672
	(33%)	(38%)		
LVEF <40% (baseline)	96/274	173/398	0.03	672
	(35%)	(44%)		
Moderate/Severe MR (baseline)	90/270	152/395	0.17	665
	(33%)	(38%)		
TRPG >31.4 mmHg (baseline)	77/194	157/303	<0.0001	497
	(40%)	(52%)		
Change in LVDd >0 mm (from baseline to follow-up)	100/275	105/397	0.006	672
	(36%)	(26%)		
Change in LVEF >0% (from baseline to follow-up)	158/274	261/398	0.04	672
	(58%)	(66%)		
Change in TRPG >0 mmHg (from baseline to follow-up)	94/194	98/303	0.0003	497
	(48%)	(32%)		

Diuretics included loop diuretic, thiazide and tolvaptan.

LAD, left atrial diameter; eGFR, estimated glomerular filtration rate; ACE-I,

angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; MRA,

mineralocorticoid receptor antagonist; LVDd, left ventricular end-diastolic dimension;

LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TRPG, tricuspid

regurgitant pressure gradient.

Supplementary Table 4. Factors associated with reduction in left atrial diameter

Variables	Reduction in LAD			
	Crude OR		Adjusted OR	
	(95% CI)	P value	(95% CI)	P value
Age ≥80 years	0.70 (0.52-0.96)	0.03	0.67 (0.44-1.02)	0.06
Women	0.79 (0.58-1.08)	0.14	0.90 (0.59-1.38)	0.64
History of Atrial fibrillation or flutter at discharge	0.98 (0.72-1.34)	0.92	0.82 (0.53-1.28)	0.82
eGFR at discharge <30 mL/min/1.73m ²	0.85 (0.57-1.25)	0.41	0.93 (0.56-1.54)	0.77
Anemia at discharge	0.87 (0.63-1.20)	0.39	1.25 (0.81-1.91)	0.31
ACE-I or ARB at discharge	1.06 (0.76-1.48)	0.75	1.03 (0.67-1.58)	0.89
β-blocker at discharge	1.12 (0.78-1.62)	0.54	1.22 (0.75-1.97)	0.43

MRA at discharge	1.07 (0.78-1.45)	0.68	0.81 (0.53-1.24)	0.81
Diuretic at discharge	0.91 (0.57-1.45)	0.68	0.83 (0.44-1.54)	0.55
LAD \geq 40 mm (baseline)	3.07 (2.14-4.40)	<0.0001	3.49 (2.10-5.80)	<0.0001
LVDd >55 mm (baseline)	1.25 (0.91-1.73)	0.17	0.79 (0.47-1.33)	0.38
LVEF <40% (baseline)	1.43 (1.04-1.97)	0.03	1.45 (0.89-2.36)	0.13
Moderate/Severe MR (baseline)	1.25 (0.90-1.72)	0.18	0.96 (0.63-1.46)	0.86
TRPG >31.4 mmHg (baseline)	1.56 (1.10-2.22)	0.01	1.55 (1.02-2.37)	0.04
Change in LVDd >0 mm (from baseline to follow-up)	0.63 (0.45-0.88)	0.006	0.74 (0.49-1.14)	0.17
Change in LVEF >0% (from baseline to follow-up)	1.40 (1.02-1.92)	0.04	1.07 (0.71-1.63)	0.74

Change in TRPG >0 mmHg	0.51	0.003	0.62	0.03
(from baseline to follow-up)	(0.35-0.74)		(0.41-0.95)	

Diuretics included loop diuretic, thiazide and tolvaptan.

eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme

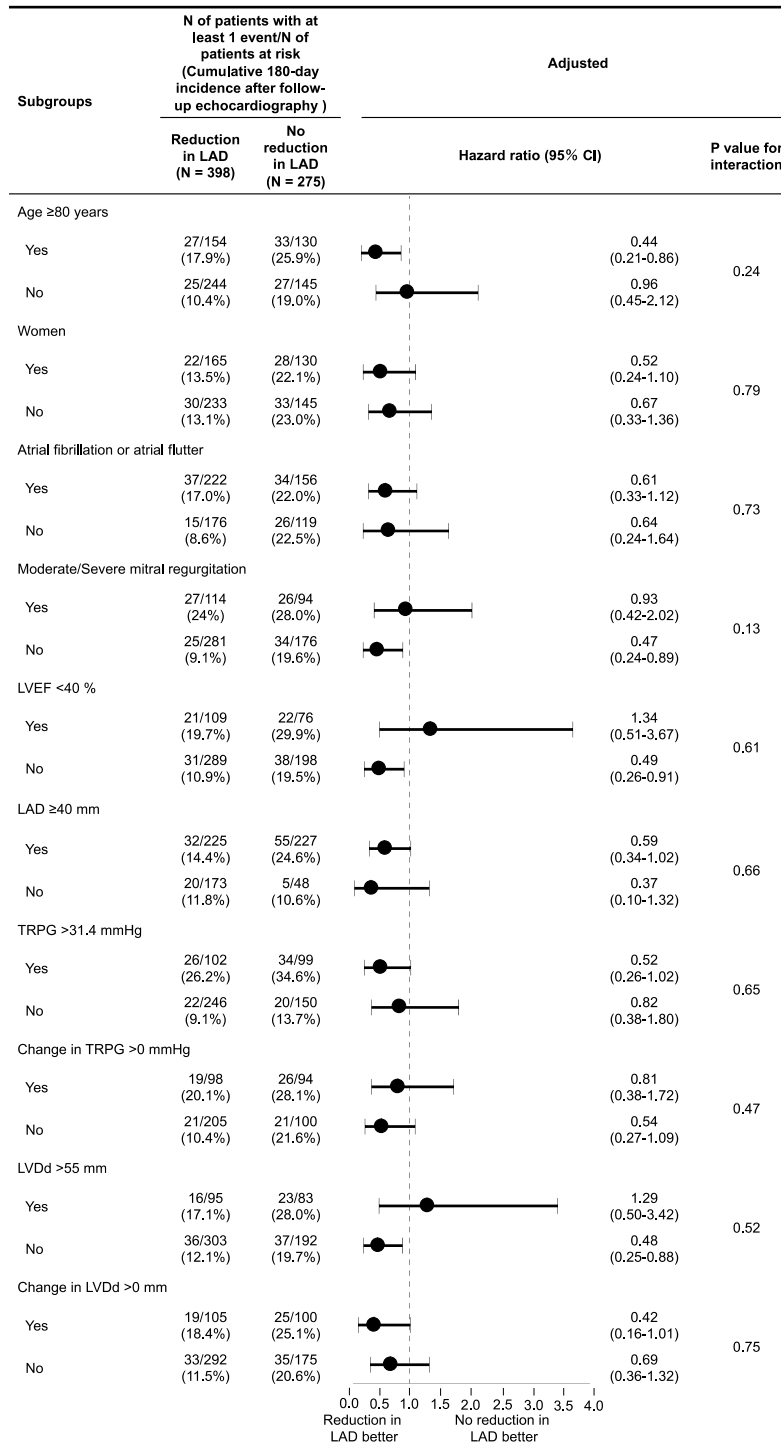
inhibitor; ARB, angiotensin-receptor blocker; MRA, mineralocorticoid receptor

antagonist; LAD, left atrial diameter; LVDD, left ventricular end-diastolic dimension;

LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TRPG, tricuspid

regurgitant pressure gradient; OR, odds ratio; CI, confidence interval.

Supplementary Figure 1



Supplementary Figure legends

Supplementary Figure 1. Subgroup analysis for the primary endpoint according to left atrial diameter change patterns.

LVEF, left ventricular ejection fraction; LAD, left atrial diameter; TRPG, tricuspid regurgitation peak gradient; LVDd, left ventricular end-diastolic dimension; CI, confidence interval.