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(Citation)
Echocardiography,40(9):976-982

(Issue Date)
2023-09

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100483106

Identification of Factors Associated with Progression of Left Atrial Enlargement in Patients with Atrial Fibrillation

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Running head: Progressive LA enlargement in AF

Abstract

Objectives: Left atrial (LA) enlargement frequently occurs in atrial fibrillation (AF) patients, and this enlargement is associated with the development of heart failure, thromboembolism or atrial functional mitral regurgitation (AFMR). AF patients can develop LA enlargement over time, but its progression depends on the individual. So far, the factors that cause progressive LA enlargement in AF patients have thus not been elucidated, so that the aim of this study was to identify the factors associated with the progression of LA enlargement in AF patients.

Methods: We studied 100 patients with persistent or permanent AF (aged: 67±2 years, 40 females). Echocardiography was performed at baseline and 12 (5-30) months after follow-up. LA size was evaluated as the LA volume index which was calculated with the biplane modified Simpson's method from apical four-and two-chamber views, and then normalized to the body surface area (LAVI). The deterioration of AFMR after follow-up was defined as a deterioration in severity of mitral regurgitation (MR) by a grade of 1 or more.

Results: Multivariate regression analysis demonstrated that hypertension (P=0.03) was an independently associated parameter of progressive LA enlargement, as was baseline LAVI. In addition, the Kaplan-Meier curve indicated that patients with hypertension tended to show greater deterioration of AFMR after follow-up than those without hypertension (log-rank P = 0.08).

Conclusions: Hypertension proved to be strongly associated with progression of LA enlargement over time in patients with AF. Our findings provide new insights for better management of patients with AF to prevent the development of AFMR.

Key words: atrial fibrillation, left atrial enlargement, hypertension, atrial functional mitral regurgitation

Introduction

Atrial fibrillation (AF) is the most common form of sustained arrhythmia seen in clinical practice and is associated with serious clinical consequences such as heart failure (HF), stroke, and increased mortality [1, 2]. Left atrial (LA) enlargement frequently occurs in AF patients [3] and has been found to be related to the duration of AF [4]. In addition, LA enlargement in AF patients is associated with the development of HF or thromboembolism [5-10]. Mitral regurgitation, and a recently recognized disease entity known as atrial functional mitral regurgitation (AFMR), occurs due to mitral annular dilatation with LA enlargement in AF patients and is closely related to prognosis [7-10]. Catheter ablation is a currently well-established treatment for AF patients to prevent adverse events such as the development of HF or stroke [11, 12]. However, not all AF patients are candidates for catheter ablation, and a significant number of AF patients remain in AF during follow-up. AF patients can develop LA enlargement over time, but the development of LA enlargement depends on the individual. So far, the factors that cause progressive LA enlargement in AF patients have thus not been elucidated, so that the aim of this study was to identify the factors associated with the progression of LA enlargement in AF patients.

Methods

Study population

A total of 233 patients with persistent, long-standing persistent, or permanent AF, who underwent multiple echocardiographic studies at Kobe University Hospital between January 2014 and December 2021 were retrospectively enrolled in this study. We excluded 48 patients who underwent therapeutic intervention for cardiovascular disease within the follow-up period, 40 patients with insufficient echocardiographic image quality for measuring LA volume using the biplane modified Simpson's method, 34 patients with too short a follow-up period of less than one month, 7 patients with previous history of therapeutic intervention for mitral valve disease, and 4

patients with significant organic mitral valve disease including mitral valve prolapse and degeneration. The remaining 100 AF patients were then enrolled in this study. Hypertension was defined as ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure or being treated with anti-hypertensive drugs based on the 2021 World Health Organization guideline[13]. This study was approved by the local ethics committee of our institution in conformity with the Declaration of Helsinki (No. B220167).

Echocardiography

All echocardiographic studies were performed at baseline and during a follow-up of 12 months (range: 5-30 months) with a commercially available echocardiography system (Aplio Artida, Aplio 400, Canon Medical Systems, Tochigi, Japan; Vivid 7 and E9, GE-Vingmed, Horten, Norway; iE33 and EPIQ CVx, Philips Medical Systems, Andover, MA). Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography [14]. Specifically, LA size was evaluated as the LA volume index (LAVI), which was calculated with the biplane modified Simpson's method from apical four-and two-chamber views, and then normalized to the body surface area. AFMR was defined as MR primarily due to LA enlargement and mitral annular dilatation[15].

Definition of endpoint

The primary endpoint was defined as progression of LAVI enlargement during follow-up, which was defined as larger follow-up LAVI than baseline LAVI. The secondary endpoint was defined as worsening of AFMR during follow-up. The severity of MR was assessed as quantitative or semi-quantitative assessment based on the current guideline [16] and the worsening of AFMR was determined as an increase in severity of MR by a grade of 1 or more.

Statistical analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data.

Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared by using the Student *t* test or Mann-Whitney U test as appropriate. Proportional differences were evaluated with Fisher's exact test or the χ^2 test as appropriate. Independent associations of progression of LA enlargement with clinical and echocardiographic parameters, evaluated by means of the univariate regression analysis, was followed up by means of a multivariate regression model using stepwise selection. The entry criterion for an individual item into the multivariate regression model was $P < 0.05$, and candidate predictors for LA enlargement were the use of angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor blocker (ARB)s / angiotensin receptor/neprilysin inhibitor (ARNI), the use of β-blockers, the use of mineralocorticoid receptor antagonists, the use of diuretics, hypertension, diabetes mellitus, dyslipidemia, estimated glomerular filtration rate, hemoglobin, left ventricular (LV) end-diastolic volume, LV ejection fraction (LVEF), LAVI, LV mass index (LVMI), age and gender. Event-free curves showing no further worsening of AFMR were determined with the Kaplan-Meier method and cumulative event rates were compared by using the log-rank test. The intraclass correlation coefficient was used to determine inter- and intra-observer reproducibility for LAVI from 20 randomly selected patients using an identical cine-loop for each view. For all steps, a p value of < 0.05 was considered statistically significant. All the analyses were performed with the commercially available software MedCalc, version 20.106; MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the 100 AF patients are summarized in Table 1. Their mean age was 67.4±2.2 years old and 40% were female. The intraclass correlation coefficient for inter- and intra-observer reproducibility of LAVI were 0.980 (95 % confidence interval 0.948 - 0.992) and 0.971 (95 % confidence interval 0.927 - 0.989), respectively.

Factors Associated with Enlargement of LAVI

During the follow-up period of 12 (range: 5-30) months, 58 (58%) patients reached the primary endpoint with progression of LAVI enlargement. The change of LAVI was 5.5 (-9.4 – 17.1) mL/m^2. The comparison of baseline characteristics of the patients with and without progression of LAVI enlargement are shown in Table 2. The baseline characteristics were similar between two groups. The results of multivariate regression analysis for independent associations of LA enlargement with clinical and echocardiographic parameters are shown in Table 3. An important finding of this analysis was that hypertension, as well as baseline LAVI, was independently associated with progression of LAVI enlargement.

Figure 1 shows representative cases of the apical four-chamber view at baseline and follow-up for patients with and without hypertension.

Association of Hypertension with worsening AFMR

Twenty-two (22%) patients reached the secondary endpoint with worsening AFMR. The Kaplan-Meier curve indicated that AFMR of patients with hypertension tended to worsen compared to that of patients without hypertension (log-rank P=0.083, Figure 2).

Discussion

The findings of our study demonstrate that hypertension is associated with progression of enlargement of LAVI in patients with persistent or permanent AF. Furthermore, our AF patients with hypertension tended to show worsening AFMR compared to those without hypertension.

Adverse effect of LA enlargement on AF patients

LA enlargement refers to adaptive or maladaptive changes in the atrial architecture in response to external stressors; these changes occur at both macroscopic and microscopic levels. The cells may undergo ultrastructural changes, such as atrial myocyte lysis, morphological hypertrophy, atrial connexin, and homozygous distribution of nuclear staining during LA enlargement [17, 18]. This

structural LA enlargement is mainly characterized by atrial contraction, atrial myocyte ultrastructural changes and atrial fibrosis, with atrial fibrosis being the most prominent manifestation of arrhythmogenic structural remodeling by AF. LA enlargement is also related to complex alterations in response to pressure or volume overload. Atrial myocyte hypertrophy seen in LA remodeling is likely induced by factors such as mechanical stretch, growth factors, and cytokines, for example, angiotensin II, endothelin-1, insulin growth factor-1, and interleukin-6. Furthermore, an increase in collagen turnover has been associated with LA enlargement.

It is also noteworthy that LA enlargement in AF patients is reportedly closely associated with the development of HF and thromboembolism. Taniguchi et al found that LAVI was a significant predictor for HF development in a multivariable analysis of 562 AF patients without significant valvular heart disease, congenital heart disease, and with reduced LVEF [5]. They also showed that there were stepwise increases in risk of new HF events with each increment in indexed LAVI, and that the estimated 5-year HF event-free survival rate was 95% for patients with LAVI < 40 mL/m^2, 89% for those with LAVI: 40-60 mL/m^2, and 86% for those with LAVI > 60 mL/m^2. In addition, Shiraki et al showed that LAVI was an independent predictor of LAA thrombus formation as well as LAA flow for 737 non-valvular AF patients treated with appropriate oral anticoagulation therapy [6]. Another of their findings was that the prevalence of LA appendage thrombus formation in non-valvular AF patients without LA enlargement (LAVI ≤ 34 mL/m^2) was extremely rare (0.4%), as well as in those with a mild LA enlargement (LAVI: 34 to 49.9 mL/m^2) and paroxysmal AF was also extremely rare (0.0%). However, the prevalence of LA appendage thrombus formation in non-valvular AF patients with severe LA enlargement (LAVI ≥50 mL/m^2) was as high as 8.7%.

Recent findings related to LA enlargement in AF patients mention occurrence of AFMR caused by mitral annular dilatation without LV systolic dysfunction [7-10]. Abe et al showed that more than moderate AFMR was more frequently seen in AF patients with AF duration >10 years, and that more than moderate AFMR was independently associated with poor outcomes [7]. In addition, Gertz et

al revealed that AFMR improved if sinus rhythm is restored, as seen in 828 AF patients undergoing first AF ablation [9].

Hypertension as a risk factor for the development of LA enlargement in AF patients

Elevated blood pressure is a major risk factor for the development of various types of HF, a risk that extends across all age ranges [19]. Furthermore, in a population with incident HF, higher blood pressures were associated with a higher rate of adverse cardiovascular events, which further supports the importance of optimizing blood pressure control for patients with hypertension [20]. Although the impact of hypertension on the progressive enlargement of LAVI was not clarified, hypertension was found to be independently associated with progressive enlargement of LAVI during a follow-up of this study. In their previously mentioned study, Gertz et al showed that AF patients with more than moderate AFMR were more likely to have hypertension compared to those without it [9].

Clinical implications

LA enlargement in AF patients is closely associated with various adverse events, especially the development of HF, AFMR and thromboembolism, and catheter ablation is a currently well-established treatment for AF patients to prevent such adverse events [11, 12]. The CASTLE-AF trial showed that catheter ablation for AF patients with HF and reduced LVEF ≤ 35% was associated with a significantly lower rate of a composite end point of death from any cause or hospitalization for worsening HF than was medical therapy [21]. LA size has also been reported to decrease with catheter ablation for maintaining sinus rhythm in chronic AF patients [22]. The current guideline, based on a class IIa recommendation and evidence level B, states that catheter ablation is recommended to improve survival and reduce HF hospitalization of selected AF patients with HF with reduced ejection fraction (HFrEF) [12]. However, not all AF patients are candidates for catheter ablation, and a significant number of AF patients therefore remain in AF during follow-up.

On the other hand, novel cardioprotective drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and ARNI are reportedly effective for reducing LA size. Soga et al reported that LAVI

significantly decreased 6 months after administration of SGLT2 inhibitors of dapagliflozin in a prospective multicenter study using 58 T2DM patients with stable HF [23]. Furthermore, the Empire HF trial showed that SGLT2 inhibitors of empagliflozin significantly reduced LAVI compared with results for a placebo during a 12-week follow-up without any change in LVEF for stable HFrEF patients [24]. The PROVE-HF study, which was a prospective study of 794 HFrEF patients for whom ARNI therapy was initiated, showed that LAVI significantly decreased 12 months after administration of ARNI [25]. In addition, the use of ARNI showed greater reduction of LAVI and was associated with a better prognosis compared with the use of ACE inhibitors / ARBs for 274 patients with HFrEF [26]. Finally, we showed that hypertension for AF patients was associated with progressive enlargement of LAVI and tended to worsen AFMR. In accordance with our findings, watchful observation may be necessary for AF patients with hypertension such as performing repeated echocardiography or periodical monitoring using cardiac biomarkers. Early use of novel cardioprotective drugs, such as ARNI, or SGLT2 inhibitors for complications caused by diabetes mellitus or HF may be a potential preventive strategy against the development of the enlargement of LAVi or worsening AFMR for such patients.

Study limitations

This study with a short follow-up period comprised a small number of patients and was a single-center retrospective study, so that future prospective studies with larger patient populations and longer follow-up periods will be needed to validate our findings. In addition, the progression of LA enlargement may be associated with the follow-up duration, however, the duration between baseline and follow-up echocardiography for each patient had a very wide range in this study.

Conclusion

Hypertension proved to be strongly associated with progression of LA enlargement over time in patients with AF. Our findings provide new insights for better management of patients with AF to prevent the development of AFMR or HF.

Acknowledgments:

We are grateful for the support of the echocardiography laboratory of the Kobe University Hospital

Disclosures:

We have no disclosures.

Conflict of interest:

None

Data availability statement:

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions:

Koya Uemura: Concept/design, data analysis/interpretation, drafting article, statistics, data collection

Makoto Nishimori: Concept/design, data analysis/interpretation, approval of article

Shun Nagai: Concept/design, data analysis/interpretation, approval of article

Mariko Takeuchi: Concept/design, data analysis/interpretation, approval of article

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Eriko Hisamatsu: Concept/design, data analysis/interpretation, approval of article

Ken-ichi Hirata: Concept/design, data analysis/interpretation, approval of article

Hidekazu Tanaka: Concept/design, data analysis/interpretation, drafting article, statistics, data collection

Figure Legends

Figure 1: Representative cases of apical four-chamber view baseline and follow-up for patients with and without hypertension.

LAVI, left atrial volume index

Figure 2: Kaplan-Meier curve representing the secondary endpoint with worsening AFMR, showing that patients with hypertension tended to show worsening of atrial functional mitral regurgitation (AFMR) compared to those without hypertension.

References

1. McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. *Circulation*. 2012; 126: e143-146.

2. Tsang TS, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol*. 2006; 47: 1018-1023.

3. Dittrich HC, Pearce LA, Asinger RW, et al. Left atrial diameter in nonvalvular atrial fibrillation: An echocardiographic study. Stroke Prevention in Atrial Fibrillation Investigators. *Am Heart J*. 1999; 137: 494-499.

4. Petersen P, Kastrup J, Brinch K, et al. Relation between left atrial dimension and duration of atrial fibrillation. *Am J Cardiol*. 1987; 60: 382-384.

5. Taniguchi N, Miyasaka Y, Suwa Y, et al. Usefulness of Left Atrial Volume as an Independent Predictor of Development of Heart Failure in Patients With Atrial Fibrillation. *Am J Cardiol*. 2019; 124: 1430-1435.

6. Shiraki H, Tanaka H, Yamauchi Y, et al. Characteristics of non-valvular atrial fbrillation with left atrial appendage thrombus who are undergoing appropriate oral anticoagulation therapy. *Int J Cardiovasc Imaging*. 2022; 38: 941-951.

7. Abe Y, Akamatsu K, Ito K, et al. Prevalence and Prognostic Significance of Functional Mitral and Tricuspid Regurgitation Despite Preserved Left Ventricular Ejection Fraction in Atrial Fibrillation Patients. *Circ J*. 2018; 82: 1451-1458.

8. Izumi C, Eishi K, Ashihara K, et al. JCS/JSCS/JATS/JSVS 2020 Guidelines on the Management of Valvular Heart Disease. *Circ J*. 2020; 84: 2037-2119.

9. Gertz ZM, Raina A, Saghy L, et al. Evidence of atrial functional mitral regurgitation due to atrial fibrillation: reversal with arrhythmia control. *J Am Coll Cardiol*. 2011; 58: 1474-1481.

10. Saito C, Minami Y, Arai K, et al. Prevalence, clinical characteristics, and outcome of atrial functional mitral regurgitation in hospitalized heart failure patients with atrial fibrillation. *J Cardiol*. 2018; 72: 292-299.

11. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Europace*. 2018; 20: 157-208.

12. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021; 42: 373-498.

13. Campbell NRC, Paccot Burnens M, Whelton PK, et al. 2021 World Health Organization guideline on pharmacological treatment of hypertension: Policy implications for the region of the Americas. *Lancet Reg Health Am*. 2022; 9: 1-10.

14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015; 28: 1-39 e14.

15. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022; 43: 561-632.

16. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129: e521-643.

17. Oliver W, Matthews G, Ayers CR, et al. Factors Associated With Left Atrial Remodeling in the General Population. *Circ Cardiovasc Imaging*. 2017; 10:

18. Platonov PG, Mitrofanova LB, Orshanskaya V, et al. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol*. 2011; 58: 2225-2232.

19. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet*. 2003; 361: 1843-1848.

20. Lip GY, Skjoth F, Overvad K, et al. Blood pressure and prognosis in patients with incident heart failure: the Diet, Cancer and Health (DCH) cohort study. *Clin Res Cardiol*. 2015; 104: 1088-1096.

21. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med*. 2018; 378: 417-427.

22. Oral H, Pappone C, Chugh A, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006; 354: 934-941.

23. Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018; 17: 132.

24. Omar M, Jensen J, Ali M, et al. Associations of Empagliflozin With Left Ventricular Volumes, Mass, and Function in Patients With Heart Failure and Reduced Ejection Fraction: A Substudy of the Empire HF Randomized Clinical Trial. *JAMA Cardiol*. 2021; 6: 836-840.

25. Januzzi JL, Jr., Prescott MF, Butler J, et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA*. 2019; 322: 1085-1095.

26. Sun Y, Song S, Zhang Y, et al. Effect of angiotensin receptor neprilysin inhibitors on left atrial remodeling and prognosis in heart failure. *ESC Heart Fail*. 2022; 9: 667-675.

Table 1

Baseline characteristics of the patients

Variables	
Clinical Data	
Age, year	67.4 ± 2.2
Gender (female), n (%)	40 (40)
Body surface area, m^2	1.63 ± 0.04
Systolic blood pressure, mmHg	121.0 (105.5-136.0)
Diastolic blood pressure, mmHg	69.5 (60.5-79.5)
Comorbidities, n (%)	
Hypertension	64 (64.0)
Diabetes mellitus	35 (35.0)
Dyslipidemia	46 (46.0)
Blood examination	
Serum BNP concentration, pg/mL	243 (131-422)
eGFR, mL/min/1.73m^2	53.0 (39.6-65.2)
Hemoglobin, g/dL	12.9(11.3-14.2)
Echocardiography	
LV end-diastolic volume, mL	80.8 (58.0-102.7)
LV end-systolic volume, mL	33.0 (22.9-51.6)
LV ejection fraction, %	57.0 (46.4-63.6)
Interventricular septal thickness, mm	10.2 (8.7-11.4)
LV posterior wall thickness, mm	10.2 (9.2-11.8)
LV mass index, g/m^2	96.6 (79.8-117.6)
LA volume index, mL/m^2	66.6 (54.0-84.3)
MR (≥ moderate)	31 (31%)
TR (≥ moderate)	36 (36%)
AR (≥ moderate)	13 (13%)
Medications, n (%)	
ACE inhibitors / ARBs / ARNI	51 (51.0)
β-blockers	74 (74.0)
MRAs	52 (52.0)
Diuretics	73 (73.0)

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left ventricular; LA, left atrial; MR, mitral regurgitation; TR, tricuspid regurgitation; AR, aortic regurgitation; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; βblocker, beta-blocker; MRA, mineralocorticoid receptor antagonist;

Table 2

Comparison of baseline characteristics of the patients with and without progression of LAVI enlargement

Variables	Patients **with** progression of LAVI enlargement (n=58)	Patients **without** progression of LAVI enlargement (n=42)	P Value
Clinical Data			
Age, year	67.1±3.0	67.8±3.2	0.754
Gender (female), n (%)	24 (41)	16 (38)	0.462
Body surface area, m^2	1.63 ± 0.06	1.64 ± 0.06	0.731
Systolic blood pressure, mmHg	127 ± 6	120 ± 7	0.172
Diastolic blood pressure, mmHg	71± 3	70± 5	0.684
Comorbidities, n (%)			
Diabetes mellitus	22(38)	13(31)	0.485
Dyslipidemia	27 (47)	19 (45)	0.898
Blood examination			
Serum BNP concentration, pg/mL	299 ± 62	15.0 ± 5.6	0.058
eGFR, mL/min/1.73m^2	51.9 ± 3.8	54.5 ± 7.0	0.483
Hemoglobin, g/dL	12.8 ± 0.6	12.8 ± 0.6	0.948
Echocardiography			
LV end-diastolic volume, mL	86.0 ± 11.2	92.4 ± 13.5	0.461
LV end-systolic volume, mL	39.6 ± 8.0	49.8 ± 11.9	0.138
LV ejection fraction, %	56.5± 3.2	51.1± 4.5	0.051
Interventricular septal thickness, mm	10.5±0.6	9.6±0.7	0.062
LV posterior wall thickness, mm	10.7±0.9	10.3±0.6	0.341
LV mass index, g/m^2	102.3 ± 8.7	101.1 ± 9.7	0.845

LA volume index, mL/m^2	70.1 ± 9.2	77.0 ± 6.9	0.265
MR (≥ moderate)	16(28)	15(36)	0.391
TR (≥ moderate)	17(29)	19(45)	0.150
AR (≥ moderate)	8(14)	5(12)	0.784
Medications, n (%)			
ACE inhibitors / ARBs / ARNI	36(62)	28 (67)	0.823
β-blockers	42 (72)	32 (76)	0.675
MRAs	29 (50)	23 (23)	0.642
Diuretics	43(74)	30 (71)	0.488

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).
All abbreviations as in Table 1.

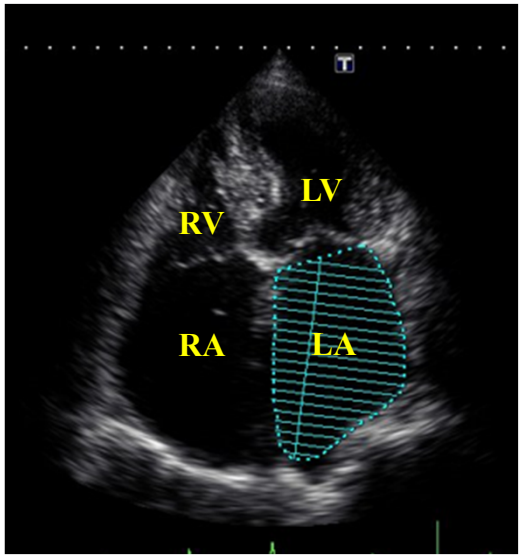
Table 3
Multiple regression analysis for predicting LA enlargement

	Standardizing coefficient	t value	p value
Female	-8.594	-1.353	0.179
Hypertension	13.73	1.873	0.031
LA volume index	0.251	2.515	0.014
LV ejection fraction	0.441	1.873	0.064

All abbreviations as in Table 1.

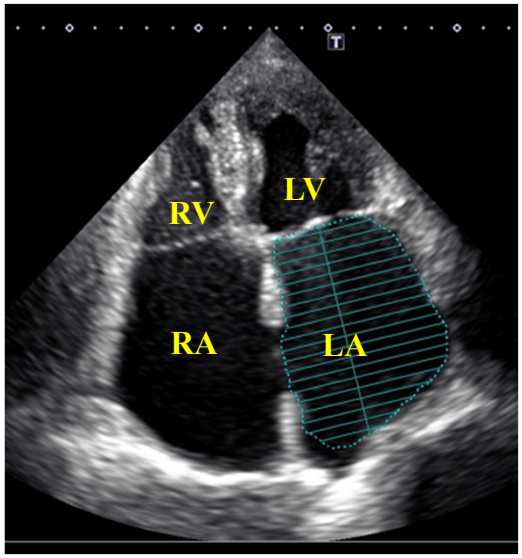
A 76-year-old male **with** hypertension

Baseline



LAVI =83.0 mL/m^2

35 months follow-up

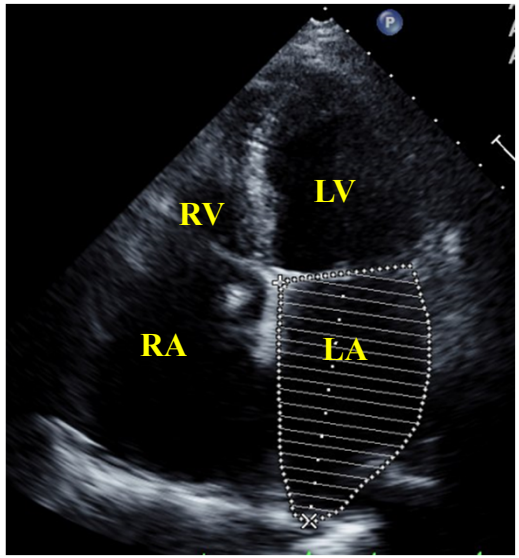


LAVI = 101.4 mL/m^2

ΔLAVI= 18.4 mL/m^2

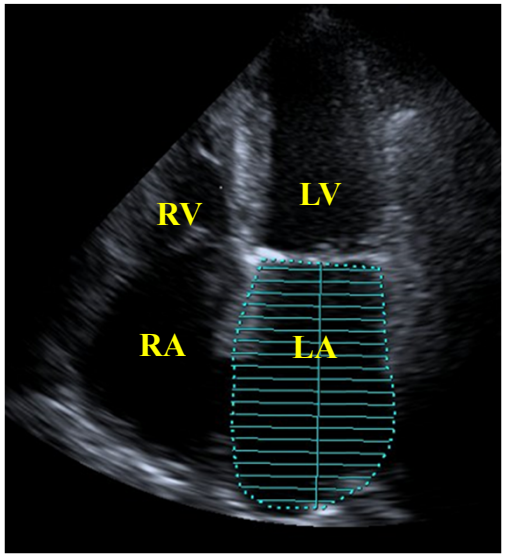
A 72-year-old female **without** hypertension

Baseline



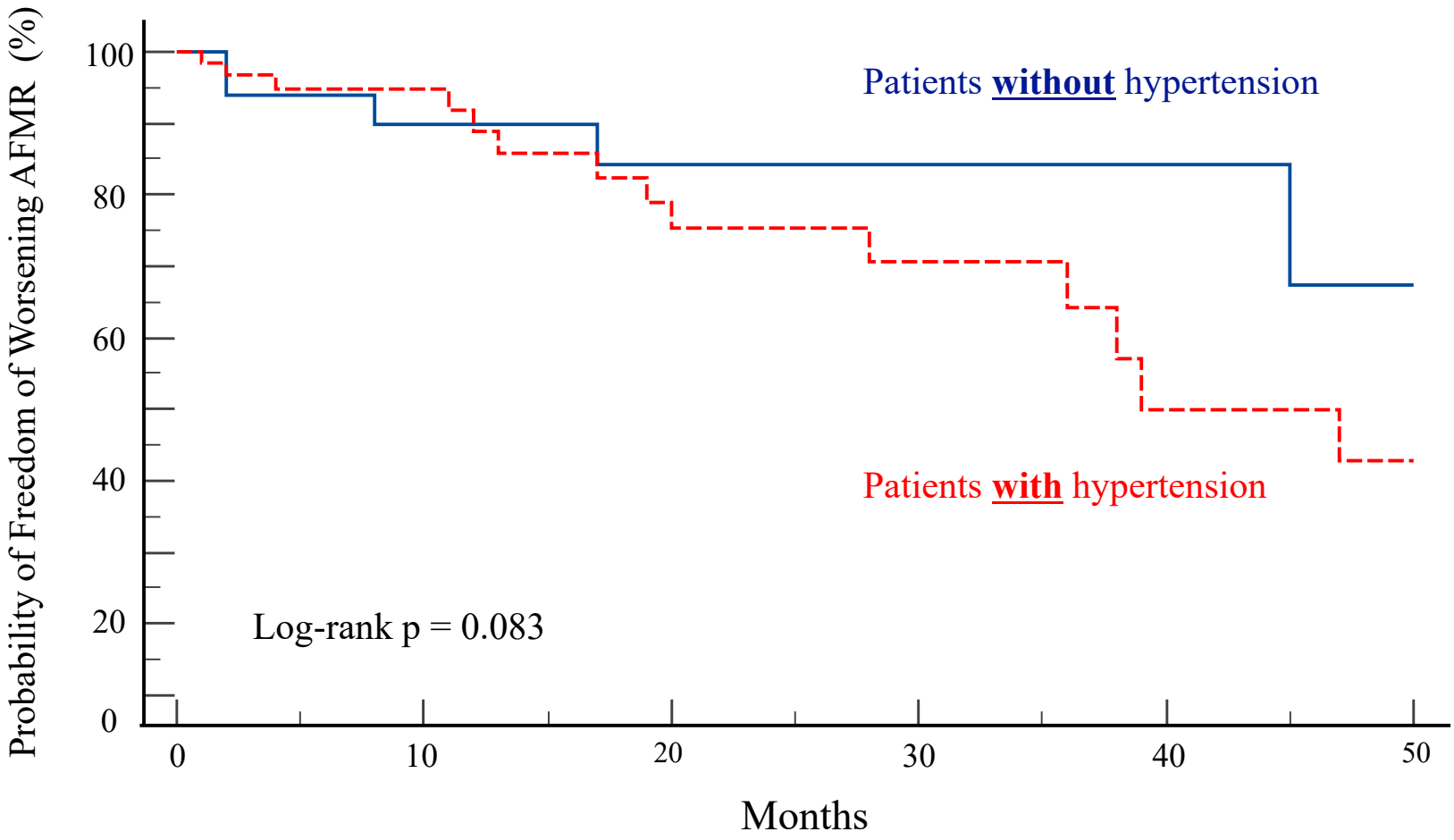
LAVI=79.5 mL/m^2

38 months follow-up



LAVI = 77.8 mL/m^2

ΔLAVI = - 1.7 mL/m^2



Number at risk

Patients **without** hypertension	36	20	13	11	5	4
Patients **with** hypertension	64	36	19	13	7	5