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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Novel Method for Risk Stratification of Major Adverse Clinical Events Using Pre- and Post-Ablation Left Atrial Volume Index in Patients With Persistent Atrial Fibrillation

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Background: The relationship between changes in the left atrial volume index (LAVI) post-catheter ablation (CA) and long-term prognostic events in patients with persistent atrial fibrillation (AF) remains unclear. We evaluated the incidence of major adverse clinical events (MACE), including all-cause death, unplanned heart failure hospitalization, and unplanned cardiovascular hospitalization using pre- and post-CA LAVI.

Methods and Results: We collected data retrospectively from 150 patients with persistent AF who underwent their first CA. LAVI was calculated during preprocedural echocardiography under AF rhythm (pre-CA LAVI) and 3 months post-CA under sinus rhythm (post-CA LAVI). The cumulative incidence of MACE was compared among 3 subgroups based on the cutoff values of pre-CA (45.5 mL/m^2) and post-CA (46.5 mL/m^2; both determined using the c-statistic) LAVI. The subgroup of a pre-CA LAVI >45.5 mL/m^2 with a post-CA LAVI >46.5 mL/m^2 (n=45) had a significantly higher MACE incidence compared with other subgroups (P=0.002). Multivariate analysis identified this subgroup as independently at higher risk for MACE. The subgroup of a pre-CA LAVI >45.5 mL/m^2 with a post-CA LAVI ≤46.5 mL/m^2 (n=49) had an incidence comparable with those with pre-CA LAVI ≤45.5 mL/m^2 (n=56) and exhibited a significantly greater reduction in LAVI than other subgroups did (P<0.001).

Conclusions: Combining pre-CA and post-CA LAVIs is valuable in stratifying long-term MACE development risk following CA.

Key Words: Atrial fibrillation; Catheter ablation; Heart failure; Left atrial volume index; Major adverse clinical events

Left atrial (LA) enlargement, a hallmark of maladaptive deterioration in patients with atrial fibrillation (AF), is commonly referred to as "LA remodeling".[1–3] This change is frequently observed with the progression of AF, particularly in the transition from paroxysmal to persistent AF, characterized by LA volume expansion.[3] LA remodeling is closely linked to an elevated risk of critical events such as worsening heart failure (HF) and stroke.[4] Hence, it is rational to explore therapies aimed at mitigating this remodeling with the expectation of improving the long-term prognosis.[1,4]

Catheter ablation (CA) for AF has emerged as a primary therapeutic option because of its superior ability to restore sinus rhythm with a high safety profile compared with pharmacological therapy.[5] Additionally, CA has been reported to be effective in reversing LA remodeling and impeding AF progression.[5–7] Although previous studies have suggested a potential association between reverse LA remodeling and a reduced risk of arrhythmic recurrence, there remains a paucity of information regarding the prognostic events following CA.[6–8] Previously we reported a strong association between atrial tachyarrhythmia recurrence and the

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incidence of prognostic events, especially heart failure hospitalization (HFH), in patients undergoing CA for AF.[9–11]

Considering that patients who experience reverse LA remodeling after CA for AF tend to demonstrate lower risks of arrhythmic recurrence, it is conceivable that they may also encounter fewer clinical events, particularly HFH. In addition, investigations focusing on the LA volume before and after the restoration of sinus rhythm by CA could provide better selection for stratifying long-term prognostic risks.

To comprehensively address this clinical inquiry, we assessed the association between LA volume before/after CA and the incidence of major adverse clinical events (MACE) during a long-term follow-up period in patients with persistent AF who underwent CA at Yamaguchi University Hospital. The present study aimed to explore the clinical utility of LA volume pre- and post-CA in stratifying the risk of long-term MACE.

Methods

Study Outline

This was a single-center historical cohort study. The study was approved by the ethics committee of Yamaguchi University Hospital. The requirement for informed consent was waived because an opt-out system was used. The study followed the principles outlined in the Declaration of Helsinki and the ethical standards established by the Committee on Human Experimentation.

We collected retrospective data on patients with persistent AF who underwent CA between January 2010 and December 2020 at Yamaguchi University Hospital. Among these patients, we assessed those who maintained AF rhythm at preoperative echocardiography and restored sinus rhythm at echocardiography 3 months after CA. Persistent AF was defined as episodes that lasted longer than 7 days.[2,12]

Patients for whom echocardiography information, particularly the left atrial volume index (LAVI; with LA volume corrected for body surface area), was unavailable were excluded. In addition, those who only had echocardiography data with a mismatched rhythm (e.g., sinus rhythm at pre-CA or AF rhythm at post-CA) were also excluded.

Study Design

We divided the entire cohort of patients who achieved restoration of sinus rhythm into subgroups based on 3 different cutoff criteria for LAVI values: 1 using solely pre-CA LAVI values (2 subgroups); 1 using solely post-CA LAVI values (2 subgroups); and 1 using both pre-CA and post-CA LAVI values (3 subgroups). The incidences of endpoints among these subgroups were then compared.

Study Endpoints

The primary endpoint was the MACE incidence following CA. As mentioned in our previous studies,[9,11] MACE represents a composite endpoint, including all-cause death (ACD), HFH, and cardiovascular hospitalization (CVH). HFH refers to an unplanned hospitalization for the treatment of decompensated HF, whereas CVH refers to an unexpected hospitalization for the treatment of cardiovascular diseases other than HF. Events that occurred during the blanking period (within 3 months of the initial procedure) were excluded.

In terms of the secondary endpoint, we compared the extent of reduction in LAVI between pre- and post-CA, and other demographic parameters among the subgroups. We also compared the cumulative incidence of arrhythmic recurrence among the subgroups. In addition, we assessed the utility of the combination of cutoff values of LAVI for discriminating the risk of MACE incidence, using multivariate analysis to adjust for confounding factors.

CA Procedure and Follow up

During the study period, our procedural strategy for persistent AF focused on treating the triggers for AF (i.e., pulmonary vein isolation and superior vena cava isolation using radiofrequency energy or second-generation cryoballoon energy), as described in our previous studies.[11] Patients with clinically diagnosed or induced atrial flutters/tachycardias underwent additional ablation to specifically target those arrhythmias.

After the procedure, all patients underwent ambulatory follow up. Echocardiography was performed mandatorily 3 months after the procedure. Arrhythmic recurrence was defined as atrial tachyarrhythmia lasting longer than 30 s after the blanking period. The success rate was defined as the proportion of patients free from arrhythmic recurrence at a specified time. If patients experienced a recurrence of atrial tachyarrhythmia, a repeat procedure was scheduled unless the patient refused. Data regarding clinical events were obtained by asking the primary care physician about each patient in December 2021.

Echocardiography Evaluation

Our echocardiography protocol was performed in accordance with the American Society of Echocardiography's guidelines.[13] The LAVI was calculated by combining images obtained from the apical 2- and 4-chamber views. Patients with poor images were substituted using only an apical 4-chamber view. The definition of "severely dilated" LA was set as >40 mL/m^2, as per guidelines.[13] The AF rhythm was calculated from the index beat. The extent of reduction in LAVI was calculated as follows: ([Post-CA LAVI − Pre-CA LAVI]/Pre-CA LAVI * 100).

Cutoff Values for LAVI

We determined the cutoff values for both pre-CA and post-CA LAVI using the c-statistic. The value with the maximum area under the curve (AUC) in the receiver operating characteristic curve was set as the cutoff value.

Statistical Analysis

Normally and non-normally distributed variables were expressed as mean±SD and medians with interquartile ranges (first and third quartiles), respectively.

Differences in continuous variables between pre- and post-CA state were evaluated using the Wilcoxon signed-rank test. Differences in categorical variables were evaluated using the McNemar test. Differences in the reduction of LAVI among the 2 and 3 subgroups were evaluated using the Wilcoxon rank-sum test, and an analysis of variance, respectively.

Differences in demographic parameters among the subgroups were compared using analysis of variance. When conducting post-hoc pairwise comparisons between 2 of the 3 groups, a t-test was used for normally distributed data, a Wilcoxon test for non-normally distributed data, and a chi-square test for categorical data, with Bonferroni correction applied.

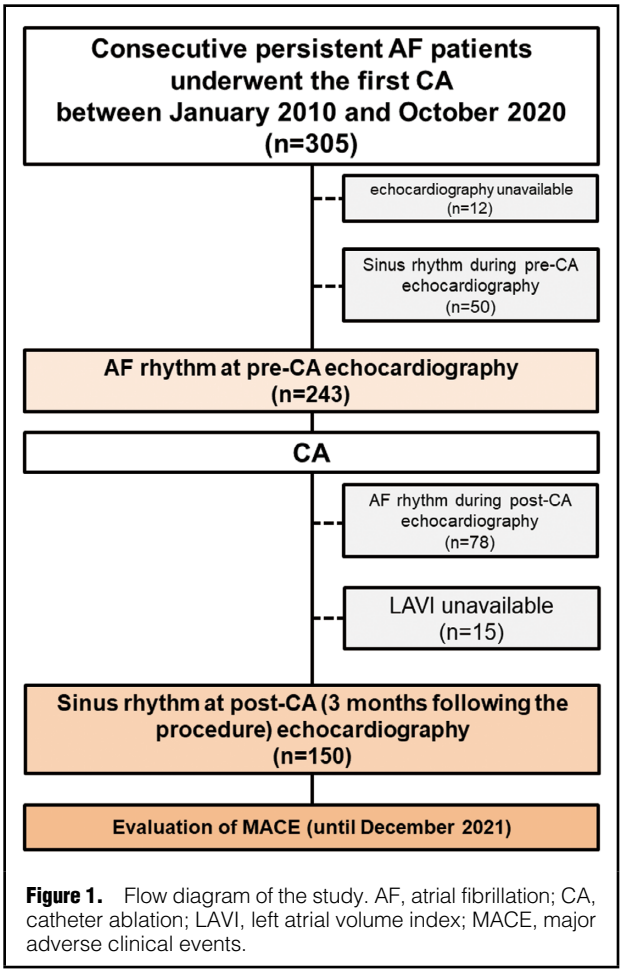

Figure 1. Flow diagram of the study. AF, atrial fibrillation; CA, catheter ablation; LAVI, left atrial volume index; MACE, major adverse clinical events.

Table 1. Patient Characteristics

	Total (n=150)
Age (years)	65±10
Female sex	34 (23)
History of AF (months)	7 (3, 13)
BMI (kg/m²)	25±4
Prior HFH	29 (19)
CTR	51±5
Pacemaker	3 (2)
ICD/CRT	5 (3)
$CHADS_2$	1.45±1.27
CHA_2DS_2-VASc	2.19±1.64
Hypertension	87 (58)
DM	28 (19)
CAD	11 (7)
HCM	11 (7)
DCM/DHCM	4 (3)
VHD	2 (1)
Ablation-related parameter	
Radiofrequency-PVI	149 (99.5)
Cryo-PVI	1 (0.5)
CTI-ablation	21 (14)
Posterior wall isolation	0
LA-linear ablation	0
SVC isolation	113 (75)
Therapeutic agent	
ACEI/ARB	78 (52)
β-blocker	103 (69)
MRA	25 (17)
Diuretics	44 (29)
Digitalis	6 (4)
CCB	64 (43)
AADs	15 (10)
Amiodarone	10 (7)
Laboratory data	
eGFR (mL/min/1.73 m²)	61±17
BNP level (pg/mL)	160 (95, 229)

Numerical data are expressed as mean ± SD or median (interquartile range [IQR]; first quartile–third quartile). Categorical data are expressed as n (%). AADs, antiarrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CCB, calcium channel blocker; CRT, cardiac resynchronisation therapy; CTI, cavotricuspid isthmus; CTR, cardiothoracic ratio; DCM, dilated cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; LA, left atrium; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation; SD, standard deviation; SVC, superior vena cava; VHD, valvular heart disease.

The incidence of each event and arrhythmic recurrence was expressed as the cumulative incidence with a 95% confidence interval (CI) calculated at the median follow up. The log-rank test was used to compare the cumulative incidence among the subgroups. A c-statistic was performed to compare the discrimination ability for the development of MACE between using solely pre-CA LAVI and the combination of pre- and post-CA LAVI. The difference was compared using the DeLong test.

For the univariate and multivariate analysis, factors associated with the development of long-term adverse events in HF patients were selected as variable.[9–11,14] We applied a stepwise approach in the multivariate analysis, imputing variables with a P value <0.05 from the univariate analysis. The continuous variables used in the analysis were dichotomized according to conventional cutoff points. The findings are presented as hazard ratios and 95% CIs. Statistical analyses were conducted using R version 4.3.2, and the results were considered statistically significant at a P value <0.05, except for post-hoc pairwise comparisons with Bonferroni correction, where a significance level of 0.017 was used.

Results

Study Population

A flow diagram of the study protocol is illustrated in **Figure 1**. Among the 305 patients with persistent AF who underwent CA, 243 underwent pre-CA echocardiography for AF rhythm. All patients underwent CA successfully. Of these, 150 patients were included in the present study. Patient demographics are presented in **Table 1**. The success rates were 87% and 79% at 6 months and 1 year after the first procedure, respectively. Among patients who experienced atrial tachyarrhythmia recurrence, a median of 1.0 (0.5, 1.0) additional procedure was performed. The success

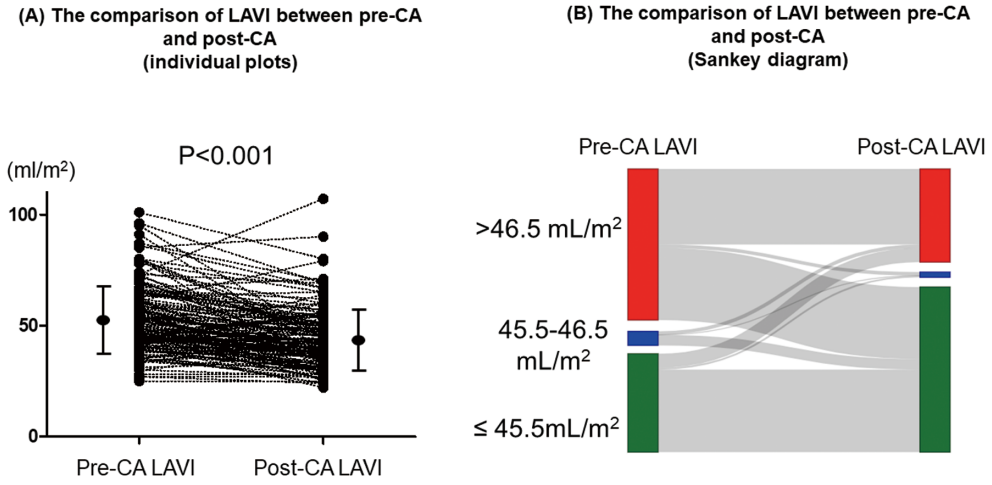

Figure 2. Comparison of the left atrial volume index (LAVI) between pre- and post-catheter ablation (CA) LAVI. (**A**) Individual plots illustrating the transition of the actual value of LAVI from pre-CA to post-CA periods. (**B**) Sankey diagram showing the transition of LAVI range from the pre-CA to post-CA periods (red: LAVI >46.5 mL/m²; blue: LAVI 45.5–46.5 mL/m²; green: LAVI ≤45.5 mL/m²).

rates following the last procedure were 92% (6 months) and 88% (1 year), and 90% (6 months) and 82% (1 year) were no longer taking antiarrhythmic drugs.

Change of Echocardiography and Associated Parameters Between Pre- and Post-CA Periods

Supplementary Table 1 presents a comparison of the echocardiography and associated parameters between the pre- and post-CA periods. In general, systolic blood pressure increased significantly, with a significant reduction in heart rate following CA. The left ventricular ejection fraction also increased significantly. The LAVI reduced significantly after the procedure (53±15 mL/m² vs. 44±14 mL/m²; P<0.0001; **Figure 2A**).

Figure 2B illustrates the changes in LAVI between the pre- and post-CA periods. Although most patients had a severely dilated LA (LAVI >40 mL/m²) in the pre-CA period, the proportion was significantly decreased in the post-CA period (121/150 [81%] vs. 78/150 [52%] patients; P<0.0001).

MACE Incidence and the Cutoff Value for Pre- and Post-CA LAVI

During the entire follow-up period (median 4.1 [2.8, 5.7] years), 16 patients developed at least 1 MACE. Of those events, HFH accounted for the majority (18/28 [64%] events), followed by ACD (6/28 [21%] events) and CVH (4/28 [14%] events). A list of patient demographics is presented in **Supplementary Table 2**. Moreover, HFH was the first major adverse clinical event in 10 of 16 (63%) events. The c-statistic for discriminating MACE provided a cutoff value of 45.5 mL/m² with the highest AUC (0.66 [95% CI 0.53, 0.79]) for pre-CA LAVI, and 46.5 mL/m² (0.64 [95% CI 0.48, 0.78]) for post-CA LAVI.

Cumulative MACE Incidence Among the Subgroups

Figure 3 and **Table 2** compare the cumulative incidence of MACE among the subgroups based on the pre- and post-CA LAVIs. In the sugroup using solely pre-CA LAVI values, the group with a pre-CA LAVI ≤45.5 mL/m² (n=56) had a significantly lower MACE incidence than did those with a pre-CA LAVI >45.5 mL/m² (n=94; 1.85% [0, 5.38] vs. 13.13% [6.00, 20.54]; P=0.007; **Figure 3A**; **Table 2A**). The subgroup using solely post-CA LAVI values also followed the same trend: the group with a post-CA LAVI ≤46.5 mL/m² (n=53) had a significantly lower MACE incidence than did those with a post-CA LAVI >46.5 mL/m² (n=97; **Figure 3B**; **Table 2B**).

In contrast, the subgroups using both pre-CA and post-CA LAVI values showed a difference in MACE incidence among patients with a pre-CA LAVI of >45.5 mL/m². The group of pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m² (n=45) had a significantly higher incidence of MACE than did the other subgroups (22.01% [7.00, 34.79]; P=0.002; **Figure 4**; **Table 2C**). The incidence of HFH also followed a similar trend (P=0.003). The subgroup of pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m² (n=70) had an incidence of MACE comparable with that in the subgroup with a pre-CA LAVI ≤45.5 mL/m² (4.96% [0, 11.53]; **Table 2C**).

The c-statistic for the development of MACE indicated a higher tendency for discrimination ability when combining pre- and post-CA LAVI (AUC [95% CI] 0.71 [0.59, 0.83] for pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²) compared with using solely pre-CA LAVI (LAVI >45.5 mL/m²; P=0.440) and solely post-CA LAVI (LAVI >46.5 mL/m²; P=0.003).

Extent of Reduction in LAVI Among the Subgroups

Supplementary Figure 1 compares the reduction in LAVI among subgroups. The subgroup with a pre-CA LAVI >45.5 mL/m² showed a significantly greater reduction in LAVI compared with those with LAVI ≤45.5 mL/m² (pre-CA LAVI >45.5 mL/m²: −20.70% [−33.30, −10.50] vs. pre-CA LAVI ≤45.5 mL/m²: −8.20% [−19.00, 6.37]; P<0.001; **Supplementary Figure 1A**). The subgroup based on a post-CA LAVI also followed the same trend (post-CA LAVI >46.5 mL/m²: −23.10% [−33.30, −10.00] vs. post-CA

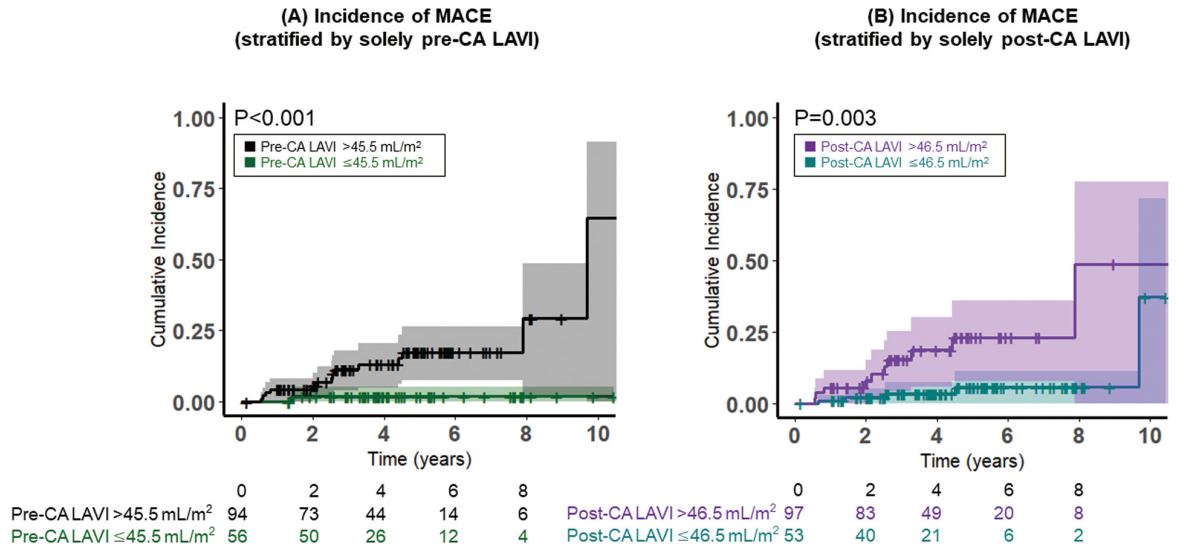

Figure 3. Cumulative incidence of major adverse clinical events (MACE) stratified by the cutoff values for the left atrial volume index (LAVI). (**A**) Kaplan-Meier curve illustrating the cumulative incidence stratified solely by pre-catheter ablation (CA) LAVI (black: pre-CA LAVI >45.5 mL/m^2; green: pre-CA LAVI ≤45.5 mL/m^2). (**B**) Kaplan-Meier curve illustrating the cumulative incidence stratified solely by post-CA LAVI (turquoise: post-CA LAVI >46.5 mL/m^2; purple: post-CA LAVI ≤46.5 mL/m^2).

Table 2. Cumulative Incidence of Each Event

A. Stratified by Pre-CA LAVI

	Cumulative incidence at median follow-up period (4.1 years), % (95% CI)		P value
	Pre-CA LAVI ≤45.5 mL/m²	Pre-CA LAVI >45.5 mL/m²	
MACE*	1.85 (0, 5.38)	13.13 (6.00, 50.54)	0.007
ACD	0	3.08 (0, 7.21)	0.050
HFH*	0	8.86 (2.20, 15.07)	0.02
CVH	1.85 (0, 5.38)	2.63 (0, 6.17)	0.600

B. Stratified by Post-CA LAVI

	Cumulative incidence at median follow-up period (4.1 years), % (95% CI)		P value
	Post-CA LAVI ≤46.5 mL/m²	Post-CA LAVI >46.5 mL/m²	
MACE*	3.48 (0, 7.30)	18.80 (5.74, 30.04)	0.003
ACD	1.45 (0, 4.23)	2.44 (0, 7.05)	0.400
HFH*	2.32 (0, 5.46)	11.55 (1.06, 20.92)	0.004
CVH	1.12 (0, 3.29)	4.71 (0, 10.87)	0.080

C. Stratified by Pre- and Post-CA LAVI

	Cumulative incidence at median follow-up period (4.1 years), % (95% CI)			P value
	Pre-CA LAVI ≤45.5 mL/m²	Pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m²	Pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²	
MACE*	1.85 (0, 5.38)	4.96 (0, 11.53)	22.01 (6.72, 34.79)	0.002
ACD	0	3.12 (0, 8.97)	2.78 (0, 8.00)	0.200
HFH*	0	4.84 (0, 11.25)	13.61 (1.19, 24.47)	0.003
CVH	1.85 (0, 5.38)	0	5.48 (0, 12.59)	0.100

*Statistical significance (P<0.05). ACD, all-cause death; CA, catheter ablation; CI, confidence interval; CVH, cardiovascular hospitalization; HFH, heart failure hospitalization; LAVI, left atrial volume index; MACE, major adverse clinical events.

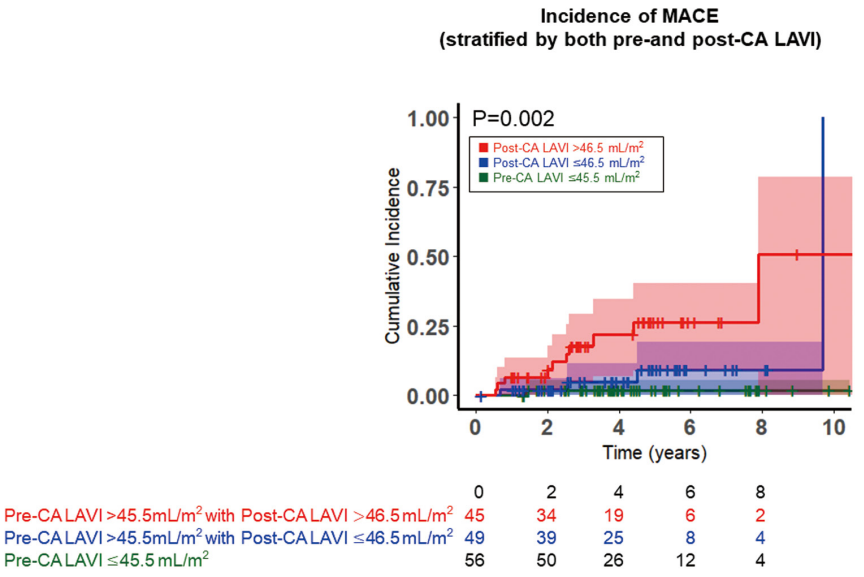

Figure 4. Comparison of the reduction of the left atrial volume index (LAVI) among subgroups. Kaplan-Meier curve illustrating the cumulative incidence stratified by both pre-catheter ablation (CA) and post-CA LAVIs (red: pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²; blue: pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m²; green: pre-CA LAVI ≤45.5 mL/m²). MACE, major adverse clinical events.

Table 3. Comparison Between Subgroups

	Pre-CA LAVI ≤45.5 mL/m² (n=56)	Pre-CA LAVI >45.5 mL/m² with Post-CA LAVI ≤46.5 mL/m² (n=49)	Pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m² (n=45)	P value (ANOVA)	P value (post-hoc pairwise comparison)†
Fundamental information					
Age (years)	62±10 [0]	64±11 [0]	70±8 [0]	0.001*	0.031
Female sex	10 (18) [0]	9 (18) [0]	15 (33) [0]	<0.001*	0.002*
History of AF (months)	8 (4, 13) [0]	7 (4, 12) [0]	6 (3, 13) [0]	0.808	0.505
Prior HFH	4 (7) [0]	10 (20) [0]	15 (33) [0]	0.003*	0.236
Structural heart diseases§	5 (9) [0]	7 (14) [0]	16 (36) [0]	0.001*	0.031
eGFR (mL/min/1.73 m²)	66±18 [0]	60±14 [0]	57±17 [0]	0.022	0.400
BNP level (pg/mL)	126 (78, 176) [0]	134 (89, 198) [0]	229 (163, 358) [0]	<0.001*	0.001*
Echocardiography parameters (pre-CA)					
LVEF (%)	60±10 [0]	59±13 [0]	57±15 [0]	0.374	0.541
LAVI (mL/m²)	39±5 [0]	57±12 [0]	65±13 [0]	<0.001*	<0.001*
E/e′ ratio	8.26±2.42 [0]	9.43±3.65 [2]	10.80±3.42 [5]	<0.001*	0.070
ePASP (mmHg)	24±4 [2]	25±6 [0]	29±6 [2]	<0.001*	0.005*
Echocardiography parameters (post-CA)					
LVEF (%)	62±9 [0]	61±9 [0]	59±13 [0]	0.227	0.332
LAVI (mL/m²)	37±10 [0]	38±6 [0]	58±12 [0]	<0.001*	<0.001*
E/e′ ratio	9.23±5.78 [1]	8.42±2.40 [1]	11.40±4.38 [3]	0.005*	<0.001*
ePASP (mmHg)	26±5 [7]	25±5 [8]	30±9 [3]	0.003*	0.004*
TMF-E/A ratio	1.16±0.43 [3]	0.87±0.27 [2]	1.16±0.65 [2]	0.003*	0.009*

Numerical data are expressed as mean ± SD or median (interquartile range [IQR]; first quartile–third quartile). [] indicates a missing number. *Statistical significance (P<0.05 for ANOVA, P<0.0167 for post hoc pairwise comparison). †The post hoc pair-wise comparison was performed between the subgroup of pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m² and post-CA LAVI >46.5 mL/m². §Structural heart diseases refers to the proportion of patients who had any of CAD, HCM, DCM/DHCM, or VHD. ANOVA, analysis of variance; ePASP, estimated pulmonary artery systolic pressure; LVEF, left ventricular ejection fraction; TMF, trans-mitral flow. Other abbreviations as in Tables 1,2.

LAVI ≤46.5 mL/m²: −7.69% [−17.70, 6.52]; P<0.001; **Supplementary Figure 1B**).

In a scenario of stratyfying by pre- and post-CA LAVI, the subgroup of a pre-CA LAVI >45.5 mL/m² with a post-CA LAVI ≤46.5 mL/m² experienced significantly greater reductions than did the other subgroups (pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m²: −31.40% [−43.00, −21.10]; pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²: −11.30% [−18.90, 1.89]; P<0.001; **Supplementary Figure 2**).

Comparison of Demographic Parameters Among the Subgroups

Table 3 presents the comparison of demographic parameters

Table 4. Uni- and Multivariate Analysis for Factors Associated With MACE

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²*	5.27	1.80, 15.46	0.002	3.84	1.24, 11.87	0.019
Age >75 years	2.73	0.90, 8.25	0.073			
Female sex	1.01	0.28, 3.61	0.990			
Prior HFH	3.36	1.18, 9.56	0.023	2.25	0.76, 6.58	0.138
eGFR <45 mL/min/1.73 m² (at 3 months after CA)	2.50	0.68, 9.10	0.163			
Arrhythemic recurrence (at 1 year after CA)	2.48	0.88, 6.95	0.084			
BNP >200 pg/mL (at 3 months after CA)	5.74	1.56, 21.12	0.008	2.65	0.69, 10.24	0.155

*Statistical significance after adjustment in the multivariate analysis (P<0.05). HR, hazard ratio. Other abbreviations as in Tables 1,2.

among the 3 subgroups. The subgroup with pre-LAVI ≤45.5 mL/m² demonstrated a lower proportion of prior HFH and structural heart diseases, a higher estimated glomerular filtration rate, and lower levels of B-type natriuretic peptide compared with the other subgroups.

Within the subgroups with pre-CA LAVI >45.5 mL/m², the subgroup with post-CA LAVI ≤46.5 mL/m² exhibited a significantly lower proportion of females, lower levels of B-type natriuretic peptide, and lower pre-CA estimated pulmonary artery systolic pressure compared with the subgroup with post-CA LAVI >46.5 mL/m².

Regarding post-CA echocardiography parameters, the subgroup with post-CA LAVI ≤46.5 mL/m² showed a significantly lower E/e′ ratio, lower estimated pulmonary artery systolic pressure, and a lower E/A ratio of transmitral flow compared with the subgroup with post-CA LAVI >46.5 mL/m². Interestingly, the post-CA LAVI and other echocardiography parameters in the subgroup were comparable with that in the subgroup with pre-CA LAVI ≤45.5 mL/m².

Difference of Arrhythmic Recurrence Among the Subgroups

We compared the cumulative incidence of atrial tachyarrhythmia among the 3 subgroups. At 1 year follow up after the first session, the incidence in the subgroup with a pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m² was significantly higher than other subgroups (pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²: 35.56% [19.94, 48.13]; pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m²: 16.33% [5.31, 26.06]; pre-CA LAVI ≤45.5 mL/m²: 16.07% [5.88, 25.16]; P=0.030).

The difference was consistent following the last session (pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m²: 46.93% [24.71, 62.60]; pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m²: 15.80% [4.15, 26.04]; pre-CA LAVI ≤45.5 mL/m²: 16.31% [4.11, 26.96]; P<0.001).

Univariate and Multivariate Analysis for the Risk of Developing MACE

Table 4 presents the results of the univariate and multivariate analyses for the risk of developing MACE. The univariate analysis showed that a pre-CA LAVI >45.5 mL/m² with a post-CA LAVI >46.5 mL/m², prior HFH, and a B-type natriuretic peptide level >200 pg/mL (3 months after CA) were identified as the significant factors. The multivariate analysis identified a pre-CA LAVI >45.5 mL/m² with a post-CA LAVI >46.5 mL/m² as the only independent factor associated with MACE development risk (adjusted hazard ratio [95% CI] 3.84 [1.24, 11.87]; P=0.019).

Discussion

Main Findings

The important findings of the present study are as follows (**Supplementary Figure: Graphical Abstract**). First, after the restoration of sinus rhythm due to CA, the reduction in LAVI after the procedure (53±15 mL/m² vs. 44±14 mL/m²) resulted in a marked decrease in the proportion of patients with severely dilated LA (LAVI >40 mL/m²) from 81% to 52% (121/150 vs. 78/150 patients; P<0.001). Second, the subgroup of a pre-CA LAVI >45.5 mL/m² with a post-CA LAVI >46.5 mL/m² had a significantly higher incidence of MACE than did the other subgroups; however, the subgroup of pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m² had a risk comparable with those with pre-CA LAVI ≤45.5 mL/m². Third, the extent of reduction in LAVI was significantly greater in the subgroup of pre-CA LAVI >45.5 mL/m² with post-CA LAVI ≤46.5 mL/m² (−31.40% [−43.00, −21.10]; P<0.001). Fourth, pre-CA LAVI >45.5 mL/m² with post-CA LAVI >46.5 mL/m² remained an independent factor associated with the risk of MACE development after multivariate adjustment.

Reverse LA Remodeling Following CA

Various stressors, such as deleterious hemodynamics, electrical abnormalities, and metabolic disorders, are believed to contribute to the mechanism of LA remodeling.[1,4,15] Chronic exposure to these stressors may impair atrial compliance and foster a vicious cycle of LA remodeling. The LA remodeling can be characterized by the progression of late gadolinium enhancement, as demonstrated by a previous study using cardiac magnetic resonance imaging.[16] Histologically, even patients with long-standing persistent AF exhibited degenerative changes such as fibrosis, increased intercellular space, and decreased myocardial nuclear density, representing LA remodeling.[17] Furthermore, those findings showed a significant correlation with electrical changes, such as low-voltage areas and fractionated electrograms obtained from electroanatomic mapping.[17]

Although the progression of LA remodeling represents histological and electrical alterations, studies have suggested that reverse LA remodeling, characterized by a recovery in LA functions and a reduction in LA volume, can be observed following CA for AF in a certain proportion of

patients.[7,8,18] Consistent with these findings, we novelly demonstrated that patients with pre-CA LAVI >45.5 mL/m^2 and post-CA LAVI ≤46.5 mL/m^2 exhibited a greater extent of LA volume reversal and had a significantly lower incidence of long-term MACE than did those with pre-CA LAVI >45.5 mL/m^2 and post-CA LAVI >46.5 mL/m^2, even though both subgroups suggested a poor long-term MACE incidence based on criteria solely using preoperative LAVI. This finding is further supported by a recent study, which reported that patients with enlarged LAVI post-CA for AF faced a heightened risk of adverse events such as HFH, regardless of arrhythmic recurrence.[19] Our result, indicating that post-CA LAVI is crucial for the risk of clinical events, aligns with the literature.

The mechanism behind the variation in the extent of reverse LA remodeling can be postulated to the difference in the underlying myocardial condition. In both the atria and ventricles, reverse remodeling can be expected in milder myocardial degeneration.[20] In cases of AF, findings suggestive of limited progression, such as a shorter history of AF, fewer symptoms, and a lack of myocardial fibrosis, have been reported as predictors of favorable remodeling after ablation.[21] Furthermore, cases that exhibit favorable reverse LA remodeling can tend to involve the etiology where AF acts as a primary cause of the remodeling, similar to "arrhythmia-induced cardiomyopathy".[22,23] Conversely, cases with poor reverse LA remodeling may reflect an underlying myocardial dysfunction where AF is an epiphenomenon.[22] In such scenarios, the benefit of the restoration of sinus rhythm would be limited, as AF represents a consequence of a progressive myocardial condition, such as atrial cardiomyopathy.[24] Our results may reflect the difference. Of note, the subgroup with poor reverse LA remodeling (post-CA LAVI >46.5 mL/m^2) still demonstrated findings suggestive of increased left atrial pressure (higher E/e′, higher estimated pulmonary artery systolic pressure, and higher E/A ratio of trans-mitral flow) regardless of the restoration of sinus rhythm. Conversely, the subgroup with fair reverse LA remodeling (post-CA LAVI ≤46.5 mL/m^2) showed that these parameters were comparable with those in the subgroup without dilated LA, further supporting our inference.

Our population would contain patients with heterogeneous backgrounds as it consists of cases derived from clinical practice, making it difficult to thoroughly assess the differences in underlying myocardial conditions among subgroups based solely on LAVI in this study. However, the LAVI-related indicators obtained in this study would be considered useful for stratification in estimating prognostic events following CA. For a better understanding of the underlying mechanisms, qualitative evaluation of the altered atrial myocardial substrate using advanced modalities such as cardiac magnetic resonance and LA strain echocardiography is deemed useful. Although our results provide risk stratification information post-procedure only, further investigations using these modalities may offer valuable information pre-procedure.

Clinical Implications

Our investigation highlights the novel potential significance of integrating pre-CA and post-CA LAVI measurements to identify long-term MACE after CA in patients with persistent AF. Notably, patients exhibiting pre-CA LAVI >45.5 mL/m^2 with post-CA LAVI >46.5 mL/m^2 demonstrated a higher risk of developing long-term MACE. In contrast, those with pre-CA LAVI >45.5 mL/m^2 and post-CA LAVI ≤46.5 mL/m^2 had a level of risk comparable with those who suggested a fair prognosis based solely on the cutoff of pre-CA LAVI (≤45.5 mL/m^2) and experienced a greater extent of reverse LA remodeling.

Generally, a dilated LA in patients is considered to impair the success rate for CA, which often leads to hesitation in choosing this treatment option.[2,21] Despite having a dilated LA, patients who achive greater reverse LA remodeling are likely to benefit from sinus rhythm restoration through CA greatly and thus represent ideal candidates for this procedure. We believe that the use of pre-CA and post-CA LAVI measurements can provide clinically useful insights regarding the effectiveness of CA in patients with persistent AF.

Study Limitations

Our study has some limitations. First, the retrospective collection of data solely from our institution, as part of a single-center historical cohort design, raises questions regarding the generalizability of the obtained cutoff values to other populations. Thus, validation at different institutions is essential. Second, our study design included only patients who achieved the restoration of sinus rhythm 3 months after CA. Considering the challenging success rate of CA for persistent AF in a single procedure, several patients were excluded due to recurrence, which potentially introduced selection bias into our study. Third, the process of reverse LA remodeling involves various factors beyond the restoration of sinus rhythm. For instance, medications for heart failure may be associated with LA reverse remodeling.[25,26] Therefore, factors other than the restoration of sinus rhythm could have influenced the reverse remodeling observed in our study. Last, in the present study, we did not focus on the extent of reverse LA remodeling for risk stratification, but rather on pre-CA and post-CA LAVI. The combination of the extent of LA remodeling and post-CA LAVI may enable more practical stratification, and further research is needed.

Conclusions

Our findings showed that combining pre- and post-CA LAVI could facilitate the risk stratification of long-term MACE development following CA in patients with persistent AF.

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IRB Information

This manuscript followed the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation.

The Institutional Review Boards of Yamaguchi University Hospital (H2019-044-2) approved this study.

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Supplementary Files

Please find supplementary file(s);
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