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Prognostic impact of increase in left atrial volume following left atrial appendage closure: Insights from the OCEAN-LAAC registry

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ABSTRACT

Background: Percutaneous left atrial appendage closure (LAAC) is an effective therapy to prevent thromboembolic events among patients with atrial fibrillation (AF). However, since the left atrial appendage (LAA) contributes to left atrial volume and serves as a buffer for increasing left atrial pressure, this procedure may impair left atrium (LA) compliance, enlarge LA, and deteriorate diastolic function. In this study, we sought to investigate the change in left atrial volume index (LAVI) following LAAC and its effect on prognosis.

Methods and Results: We analyzed 225 patients from the OCEAN-LAAC registry, an ongoing, multicenter Japanese study. Comparing LAVI measurements at baseline and 6 months after LAAC, no significant increase was observed (55.0 [44.0, 70.0] ml/m^2 vs. 55.0 [42.0, 75.6] ml/m^2; P = 0.31). However, some patients underwent LAVI increase. Particularly, a smaller LAVI (odds ratio [OR]: 0.98 [95 % confidence interval (CI): 0.97–0.996]) and elevated tricuspid regurgitation pressure (TRPG) at baseline (OR: 1.04 [95 % CI: 1.00 – 1.08]) were significantly related to the increase in LAVI at 6-month follow-up. In addition, a 5 ml/m^2 increase in LAVI was significantly associated with subsequent heart failure hospitalization (HFH) (hazard ratio: 3.37 [95 % CI: 1.18–9.65]). This association, however, was not observed in patients with lower baseline LAVI (≤55 ml/m^2) but was only seen in those with a baseline LAVI over 55 ml/m^2.

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Conclusion: Our study demonstrated an increase in LAVI after LAAC was related to smaller LAVI or elevated TRPG at baseline. The LAVI increase was significantly associated with subsequent HFH.

1. Introduction

Transcatheter left atrial appendage closure (LAAC) is a promising approach to prevent thromboembolic events for patients with atrial fibrillation (AF). The left atrial appendage (LAA), where blood clots are prone to form, is occluded, consequently leading to a reduction in thrombotic events. This less-invasive therapy has demonstrated clinical efficacy and safety in large-scale studies [1,2].

However, an LAA is not a completely vestigial structure that should be removed. The LAA contributes to the left atrial volume, is a reservoir in terms of diastolic function, and possibly plays a important hemodynamic role in the left atrium (LA) by buffering the increase in LA pressure [3,4]. Given these other roles of LAA, LAAC may impair LA compliance and a preclinical study has demonstrated this potential negative impact [5]. The impaired compliance causes elevated intra-atrial pressure and LA dilation, leading to pulmonary edema and resulting in heart failure (HF).

In clinical data, a small-scale study has shown that transcatheter LAAC increases left atrial volume index (LAVI) at 12 months after the procedure, compared to not undergoing LAAC [5]. Another study consistently reported progressive LA enlargement following LAAC [6]. However, no large-scale study has verified this effect of LAAC.

In this study, we sought to investigate the impact of LAAC on LA among patients in a multicenter LAAC registry. Impaired LA compliance is critical for patients with AF because it is a substantial factor causing HF. Elucidating this potential negative effect will aid in selecting appropriate patients for LAAC and optimizing patient follow-up, eventually improving their outcomes.

2. Methods

2.1. Study design and description of participants

We conducted this study on patients in the OCEAN-LAAC (Optimized Catheter Valvular Intervention-Left Atrial Appendage Closure) registry, which is an ongoing, prospective, multicenter observational registry including patients with non-valvular AF (NVAF) who underwent LAAC at 20 sites across Japan from September 2019. The detailed protocol for this registry is described in a previous report [7]. This project has been registered in the University Hospital Medical Information Network (UMIN000038498) and has been conducted in accordance with the Helsinki Declaration.

The study flow chart for this analysis is described in Supplementary File 1. In the current analysis, we selected patients registered from September 2019 to October 2023. Among them, we analyzed 225 cases whose echocardiographic data at baseline and 6 months after LAAC were available and who did not develop adverse events in 6 months. Of these patients, we evaluated LAVI as a parameter of the impact of LAAC on the LA. LAVI obtained from transthoracic echocardiography (TTE) at baseline and 6-month follow-up after LAAC was assessed based on previous studies [5,6]. LAVI increase was defined as a rise of 5 ml/m^2 between baseline and at 6 months [8,9]. Furthermore, tricuspid regurgitation pressure gradient (TRPG) was also analyzed as a parameter of increase in LA pressure, and an elevation of 5 mmHg between baseline and at 6 months was identified as TRPG increase [9,10]. An analysis similar to that conducted on LAVI was also performed on TRPG and is documented in the supplementary files.

2.2. LAAC procedure

In the OCEAN-LAAC registry, LAAC was performed according to standard techniques, as previously described [11,12]. All patients enrolled in this analysis underwent transcatheter LAAC using WATCHMAN 2.5 (Boston Scientific, Maple Grove, MN, USA) or WATCHMAN FLX (Boston Scientific, Maple Grove, MN, USA). Prosthesis type and size, and other procedure strategies were determined by the local brain–heart team based on findings on preprocedural echocardiography or computed tomography.

2.3. Echocardiographic assessment

In the OCEAN-LAAC registry, TTE and transesophageal echocardiography (TEE) were conducted in all patients before LAAC as baseline assessments to determine eligibility and procedural strategy. Based on the current guidelines by the American Society of Echocardiography, over three consecutive heartbeats were recorded for the measurements to be averaged, and two-dimensional (2D) and three-dimensional (3D) echocardiographic assessments were performed [13]. For the measurement of LA volume, we incorporated biplanar TTE using the sum of disks and the operators in charge of LA volume assessment are not same between baseline and 6 month follow-up according to the sites. As for the LAA evaluation at baseline, ostium diameter and vertical depth were recorded at 0°, 45°, 90°, and 135° by TEE, and LAA morphology was assessed [14]. At 6 months after the procedure, an echocardiographic assessment of LA function was conducted by TTE with the same approach.

2.4. Endpoints

In our initial analysis, we investigated the associations between baseline data, including patient characteristics and procedural factors, and the increases in LAVI. Multivariable analyses were conducted, with the objective variable being an elevation in LAVI. Subsequently, we evaluated the predictive value of an increase in LAVI at a 6-month follow-up, concerning the incidence and time to cardiocerebrovascular events (heart failure hospitalization, acute coronary syndrome, hospitalization for percutaneous coronary intervention, and hemorrhagic and ischemic stroke), complications (device embolization, device-related thrombosis), and all-cause death from 6 months to 2 years following LAAC. As an indicator of intra-atrial pressure, TRPG at baseline and the 6-month follow-up was similarly analyzed, which was described in supplementary files.

2.5. Statistical analysis

Continuous variables were described as mean ± SD or median (IQR). Categorical variables were expressed as frequency and percentage, which were compared using Student's t-test or the Mann-Whitney U test based on the variable's distribution. Analysis of variance or the Kruskal-Wallis test was used to compare three or four groups for normally distributed and skewed variables, respectively. Categorical variables were compared using the chi-square or Fisher exact test. The change in LAVI and TRPG over the 6-month follow-up period was illustrated with boxplots and the Wilcoxon signed-rank test was used for comparison. Furthermore, we employed a histogram and alluvial plot to see the details of the change in LAVI and TRPG from baseline to 6 months after LAAC.

To identify the baseline clinical, echocardiographic, and procedural

factors significantly associated with a 5 ml/m^2 increase in LAVI at 6 months, logistic regression analyses were conducted. In the multivariable analysis, we used three models with different covariates: "Model 1" includes baseline and procedural factors altogether, "Model 2" only includes baseline factors, and "Model 3" includes factors related to the procedure. The covariates included in the multivariable analysis were those that showed significance in univariate analysis or that were previously reported to have an association with LA enlargement. We assessed multicollinearity using the variance inflation factor; all variables in the multivariable models had low variance inflation factors (<2). Since LAA ostium diameter and depth had multicollinearity variance inflation factors between 4 and 5, we only included LAA diameter for multivariable analysis as a parameter of ostium size.

Clinical outcomes from 6 months to 2 years after LAAC was initially evaluated using the chi-square or Fisher exact test, followed by multivariable Cox proportional analysis adjusted by age. Hazard ratios (HR) and 95 % confidence intervals (CI) were presented for assessment of the predictive value of LAVI and TRPG increase. Counts, incidence rates, and time to clinical outcomes in the 2-year follow-up were described using the Kaplan-Meier curve, in which differences between the groups were compared using the log-rank test. Additionally, the predictive value of LAVI increase was compared to other covariates by age-adjusted multivariable Cox proportional analysis, presented using a forest plot. The predictive value of LAVI increase was further assessed using stratified analysis, in which age-adjusted multivariable Cox proportional analysis and P for interaction were employed.

P values described in the results were 2-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed with R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

In the analysis of all the included patients (n = 225), no significant change was observed in LAVI at baseline, 6 months, and 1 year after LAAC (Graphical Abstract A). Graphical Abstract B is a histogram of the difference value of LAVI from baseline to 6 months after LAAC, exhibiting a parametric distribution with some suspected outliers. Graphical Abstract C is an alluvial plot of changes in the number of patients divided by quartiles of LAVI from baseline to 6-month follow-up. Specific patients experienced an elevation in LAVI, yet no obvious changes in the proportion of the whole were seen in each LAVI quartile. We conducted further analyses, dividing the subjects into paroxysmal AF (n = 92), persistent AF (n = 39), and long-standing persistent AF (n = 94) groups, since the pace of LA enlargement differs, depending on the type of AF [15]. However, no significant changes were observed in the subgroup analysis (Supplementary File 2).

We conducted the same analysis on TRPG as a surrogate of LA pressure and documented them in supplementary files. Similar to LAVI, no significant change in TRPG was observed between baseline and at 6 months (Supplementary File 3A). TRPG at 1 year was not compared due to missing values. The histogram of the difference in TRPG likewise showed parametric distribution (Supplementary File 3B) and an alluvial plot revealed no obvious changes in the proportion of each TRPG quartile from baseline to 6-month follow-up (Supplementary File 4).

Table 1 shows the baseline characteristics of the study participants. Patients were divided into two groups based on whether LAVI increased by 5 ml/m^2 at 6-month follow-up (n = 85) or not (n = 140). Comparing patients with and without LAVI increase, patients with an increase in LAVI were more frequently male and had lower left ventricular ejection fraction (LVEF) and higher TRPG. Additionally, the group with LAVI increased more frequently and had chronic HF. In terms of AF types, the percentage of paroxysmal AF was slightly higher in patients with LAVI increase, but no significant difference was observed. Baseline LAVI and valvular diseases of moderate or greater severity were not significantly different between the two groups.

Table 1
Baseline Characteristics.

	Overall	LAVI increase (−)	LAVI increase (+)	P value
N	225	140	85	
Age (mean (SD))	78.20 (7.87)	78.31 (7.94)	78.02 (7.79)	0.79
Gender = Female/Male (%)	76/149 (33.8/66.2)	55/85 (39.3/60.7)	21/64 (24.7/75.3)	0.04
BMI (mean (SD))	23.07 (3.59)	23.05 (3.58)	23.11 (3.63)	0.90
BNP (median [IQR])	162.60 [88.37, 268.35]	165.55 [92.23, 264.18]	160.15 [85.70, 276.42]	0.89
CHA_2DS_2-VASc score (mean (SD))	4.90 (1.49)	4.88 (1.50)	5.03 (1.47)	0.61
HAS-BLED score (mean (SD))	3.26 (0.92)	3.27 (0.89)	3.20 (1.10)	0.70
AF type (%)				0.40
Paroxysmal AF	92 (40.9)	61 (43.6)	31 (36.5)	
Persistent AF	39 (17.3)	21 (15.0)	18 (21.2)	
Long-standing persistent AF	94 (41.8)	58 (41.4)	36 (42.4)	
Medical history				
HTN (%)	195 (86.7)	123 (87.9)	72 (84.7)	0.64
DM (%)	76 (33.8)	43 (30.7)	33 (38.8)	0.27
CHF (%)	136 (60.4)	80 (57.1)	56 (65.9)	0.25
IHD (%)	114 (50.7)	69 (49.3)	45 (52.9)	0.69
PMI (%)	39 (17.3)	21 (15.0)	18 (21.2)	0.32
Valve surgery (%)	14 (6.2)	9 (6.4)	5 (5.9)	1.00
TAVI (%)	21 (9.3)	13 (9.3)	8 (9.4)	1.00
TEER (%)	14 (6.2)	9 (6.4)	5 (5.9)	1.00
Ischemic stroke (%)	86 (38.2)	60 (42.9)	26 (30.6)	0.09
Hemorrhagic stroke (%)	24 (10.7)	16 (11.4)	8 (9.4)	0.80
Thromboembolic event (%)	55 (24.4)	34 (24.3)	21 (24.7)	1.00
Echocardiographic findings				
LVEF (median [IQR])	60.00 [52.00, 65.00]	61.00 [53.75, 66.00]	59.00 [47.00, 63.00]	0.02
LVEF (%)				0.10
≤ 40 %	13 (10.2)	13 (9.3)	10 (11.8)	
40–50 %	25 (11.1)	11 (7.9)	14 (16.5)	
50 % <	177 (78.7)	116 (82.9)	61 (71.8)	
LAVI (%) (median [IQR])	55.00 [44.00, 70.00]	56.00 [46.75, 69.25]	55.00 [40.00, 72.00]	0.24
LAVI ≥ 34 ml/m^2 (%)	203 (90.2)	130 (92.9)	73 (85.9)	0.14
AR (moderate, severe) (%)	9 (4.0)	3 (2.1)	6 (7.1)	0.09
AS (moderate, severe) (%)	11 (4.9)	6 (4.3)	5 (5.9)	0.751
MR (moderate, severe) (%)	38 (16.9)	21 (15.0)	17 (20.0)	0.43
TRPG (median [IQR])	25.00 [20.25, 32.00]	24.00 [19.00, 31.00]	25.50 [22.00, 34.00]	0.03
TEE measurements of LAA				
Mean ostium diameter (median [IQR])	21.50 [19.00, 23.81]	21.42 [18.83, 23.69]	21.73 [19.26, 23.91]	0.74
Mean depth (median [IQR])	26.80 [22.30, 30.75]	26.40 [22.45, 29.70]	27.85 [22.00, 32.30]	0.32

Values are described as mean (standard deviation [SD]), n (%), or median (interquartile range [IQR]). "Valve surgery" includes mitral valve repair, replacement, and aortic valve replacement. LAVI, left atrial volume index; BMI, body mass index; BNP, brain natriuretic peptide; AF, atrial fibrillation; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; IHD, ischemic heart disease; PMI, pacemaker implantation; TAVI, transcatheter aortic valve implantation; TEER, transcatheter mitral valve edge-to-edge repair; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; AS, aortic stenosis;

MR, mitral regurgitation; TRPG, tricuspid regurgitation pressure gradient; TEE, transesophageal echocardiography; LAA, left atrial appendage.

The table on TRPG increase is attached as Supplementary File 5. Patients with TRPG increase had higher brain natriuretic peptide (BNP) levels and more frequently had hypertension (HTN) and aortic regurgitation. Other than these variables, there were no significant differences between the two groups.

Procedural findings are shown in Table 2 (LAVI increase (−) vs. (+)) and Supplementary File 6 (TRPG increase (−) vs. (+)). Procedural variables were comparable between groups, and no statistically significant findings were identified.

Two-year clinical follow-up was completed for 33 patients and the median follow-up period was 375 days. Clinical events at 2-year follow-up are presented in Supplementary File 7. From 6 months to 2 years after LAAC, 11 patients died. Compared to patients without an increase in LAVI, those with LAVI increase had a significantly higher incidence of heart failure hospitalization (HFH; 3.6 % vs. 14.1 %; P < 0.01). Age-adjusted Cox proportional hazards model of increase in LAVI for hard outcomes is presented in Supplementary File 8. A 5 ml/m^2 increase in LAVI demonstrated significant predictive value for HFH hospitalization (Adjusted HR: 3.03; 95 % CI: 1.03–8.89; P = 0.04), and the Kaplan-Meier curve is depicted in Graphical Abstract D (log-rank test: P = 0.04).

With regard to TRPG increase, no obvious difference in the incidence of adverse events between groups was detected and TRPG increase had no statistically significant predictive value in our analysis (Supplementary Files 9 and 10).

In the Cox proportional hazards model of each variant (baseline LVEF, baseline TRPG, valvular heart disease of moderate or greater severity, LAVI increase, LAVI at 6 months, and TRPG at 6 months) and age for HFH, valvular heart disease of moderate or greater severity, LAVI increase, LAVI at 6 months, and TRPG at 6 months, were significant predictors of post-LAAC HFH (Supplementary File 11). Due to the rare incidence of HFH (n = 17), we only added age and each variant to the model. Notably, the LAVI increase demonstrated a significant HR of 3.37 (95 % CI: 1.18–9.65).

Table 2
Procedural Findings.

	Overall	LAVI increase (−)	LAVI increase (+)	P value
n	225	140	85	
Procedural time (min) (mean (SD))	63.33 (28.03)	60.86 (26.02)	67.40 (30.80)	0.09
Pre-procedural mean LAP (mmHg) (mean (SD))	12.53 (3.83)	12.37 (3.55)	12.81 (4.27)	0.43
Device size (%)				0.18
20, 21, 24 mm	33 (14.9)	25 (18.1)	8 (9.6)	
27, 30, 31 mm	121 (54.8)	75 (54.3)	46 (55.4)	
33, 35 mm	67 (30.3)	38 (27.5)	29 (34.9)	
Recapture (%)	101 (46.8)	63 (47.4)	38 (45.8)	0.93
Compression rate (%) (mean (SD))	18.71 (8.41)	19.19 (8.07)	17.94 (8.93)	0.28
Leakage (≥3 mm) (%)	13 (5.8)	8 (5.7)	5 (5.9)	1.00
Protrusion (%)	148 (65.8)	94 (67.1)	54 (63.5)	0.68
IASD (%)				0.62
R → L shunt	13 (7.1)	9 (7.9)	4 (5.7)	
Bidirectional shunt	1 (0.5)	1 (0.9)	0 (0.0)	
L → R shunt	170 (92.4)	104 (91.2)	66 (94.3)	
Residual trabeculation (%)	10 (4.7)	8 (6.0)	2 (2.5)	0.33

Values are described as mean (standard deviation [SD]), n (%), or median (interquartile range [IQR]). LAVI, left atrial volume index; LAP, left atrial pressure; IASD, iatrogenic atrial septal defect; R, right; L, left.

Univariable and multivariable logistic regression analysis for LAVI increase are presented in Table 3. In a multivariable analysis adjusted for baseline and procedural factors (Model 1), LAVI at baseline (odds ratio [OR]: 0.98; 95 % CI: 0.97–0.996; P = 0.01) and TRPG at baseline (OR: 1.04; 95 % CI: 1.00–1.08; P = 0.03) were significant predictors of a subsequent increase in LAVI. Since the HR of LAVI at baseline was under 1.0, we additionally depicted boxplots on the change in LAVI, categorized by LAVI quartiles at baseline (Supplementary File 12). This analysis revealed that a significant increase in LAVI was exclusively observed in patients whose baseline LAVI was less than 44 ml/m^2 (Supplementary File 12). In the same manner, the predictors of TRPG increase after LAAC were also investigated (Supplementary File 13). Due to the low incidence of TRPG increase, we solely conducted two models for multivariable analysis. BNP at baseline and HTN were significantly associated with TRPG increase in model 2, but procedural variables did not show any significant difference in terms of post-LAAC TRPG increase, similar to the analysis for LAVI elevation.

To further confirm the predictive value of a LAVI increase, we additionally performed a stratified analysis of the LAVI increase, as presented in Supplementary File 14. The results indicated LAVI increase could still predict HFH following LAAC in subgroups divided by age, gender, diabetes, AF type, baseline BNP levels, ischemic heart disease, baseline LVEF, baseline LAVI (divided by the median value of 55 ml/m^2), valvular heart disease of moderate or greater severity, and baseline TRPG. No significant interaction was found between LAVI increase and other confounding variables. Furthermore, HRs generally exceeded 1.0 in groups except for patients with valvular heart disease of moderate or greater severity.

We lastly analyzed the predictive value of LAVI increase in patients with smaller baseline LAVI and those with larger baseline LAVI, because LAVI increase itself was frequently observed in patients with smaller baseline LAVI. As shown in the Kaplan-Meier curve in Fig. 1, LAVI increase in those with smaller LAVI at baseline (≤55 ml/ m^2, the median value) did not have a significant predictive value for HFH; only in patients with LAVI over 55 ml/m^2 did LAVI increase have a statistically significant predictive value for HFH (adjusted HR: 1.64; 95 % CI: 1.02–2.64; P = 0.04).

4. Discussion

Our research has revealed several findings as follows: 1) No significant increase in LAVI from baseline to 6 months after LAAC was observed in overall population; 2) Specific patients experienced an increase in LAVI, and smaller LAVI and elevated TRPG at baseline were predictors of a subsequent increase, whereas any procedural factors did not demonstrate significant association with it; 3) An increase in LAVI of 5 ml/m^2 at 6 months following LAAC was significantly related to the incidence of HFH from 6 months to 2 years after LAAC; 4) Smaller LAVI at baseline was a predictor of post-LAAC LAVI increase, but the increase in patients with a smaller LAVI (≤55 ml/m^2) at baseline was not associated with subsequent HFH, while the increase observed in those with higher LAVI at baseline (over 55 ml/m^2) was significantly linked to subsequent HFH; 5) TRPG, investigated as a surrogate of LA pressure in this study, did not change significantly at 6-month follow-up and the 5 mmHg increase in TRPG has no prognostic value.

Although we initially hypothesized that LAAC could impair LA compliance, increase LAVI and deteriorate diastolic function, no significant increase was observed in the overall population (n = 225). This was not consistent with previous small-scale studies (5, 6). However, a single center study published in China (n = 282) has reported no significant change in LAVI over 1 year following LAAC in their subanalysis, similar to our study findings [16]. We propose that the reason for this inconsistency is that the impact on the LA is minimal, and proper detection can be challenging. Given that the reported incidence of cardiac adverse events following LAAC is not frequent, the impact of LAAC may not have clinical significance [16,17]. Currently, LA strain

Table 3
Logistic Regression Analysis for 5 ml/m^2 Increase in LAVI at 6-month Follow-Up.

	Univariable		Multivariable: Model1		Multivariable: Model2		Multivariable: Model3	
	OR [95 % CI]	P value	OR [95 % CI]	P value	OR [95 % CI]	P value	OR [95 % CI]	P value
Patient backgrounds								
Age	1.00 [0.96 1.03]	0.79	1.00 [0.96 1.04]	0.96	1.00 [0.96 1.04]	0.95	0.99 [0.95 1.03]	0.72
Male	1.97 [1.08 3.59]	0.03	1.59 [0.82 3.09]	0.17	1.78 [0.90 3.50]	0.09	1.46 [0.74 2.88]	0.27
DM	1.43 [0.81 2.52]	0.21						
HTN	0.77 [0.35 1.67]	0.50						
CHF	1.27 [0.83 1.94]	0.27			1.09 [0.57 2.09]	0.79		
AF type	1.10 [0.82 1.48]	0.52			1.04 [0.74 1.47]	0.80		
IHD	1.16 [0.67 1.99]	0.60			0.88 [0.47 1.63]	0.68		
Baseline echocardiographic parameters								
LVEF	0.97 [0.95 0.998]	0.03	0.98 [0.95 1.01]	0.17	0.98 [0.95 1.01]	0.11		
LAVI	0.99 [0.98 1.005]	0.34	0.98 [0.97 0.996]	0.01	0.98 [0.97 0.999]	0.03		
Valvular disease (moderate or greater)	1.57 [0.84 2.95]	0.16	1.63 [0.78 3.40]	0.19	1.48 [0.71 3.12]	0.29		
TRPG	1.03 [1.00 1.06]	0.04	1.04 [1.00 1.08]	0.03	1.04 [1.01 1.08]	0.02		
LAA major ostium diameter (TEE)	1.02 [0.99 1.05]	0.30	1.02 [0.98 1.05]	0.27			0.02 [0.98 1.05]	0.34
LAA mean ostium diameter (TEE)	1.00 [0.92 1.09]	0.98						
Procedural factors								
Devise size (mm)	1.04 [0.97 1.12]	0.30	1.02 [0.93 1.11]	0.70			1.03 [0.94 1.13]	0.56
Iatrogenic ASD	1.46 [0.95 2.23]	0.51					1.27 [0.67 2.42]	0.46

Univariable and multivariable logistic regression analyses were conducted. Models 1, 2, and 3 include both preprocedural and procedural factors, preprocedural factors only, and procedural factors, respectively. "Valvular disease" includes aortic stenosis (n = 9), regurgitation (n = 11), and mitral regurgitation (n = 38) of moderate or greater severity. Since LAA ostium diameter and depth had multicollinearity with variance inflation factors between 4 and 5, we only included LAA diameter for multivariable analysis as a parameter of ostium size. OR, odds ratio; CI, confidence interval; LAVI, left atrial volume index; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; AF, atrial fibrillation; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; LAA, left atrial appendage; ASD, atrial septal defect.

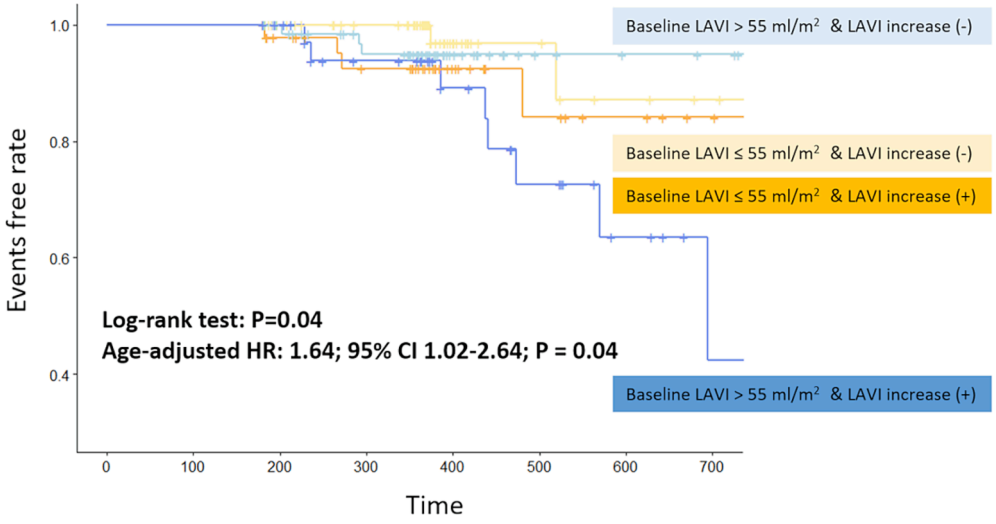

Fig. 1. Kaplan-Meier Curve for HFH from 6-Month to 2-Year Follow-Up According to 4 Groups Based on Baseline LAVI and Increase in LAVI at 6-Month Follow-Up. The group with baseline LAVI over 55 ml/m^2 (median value of LAVI in the included patients) who experienced an increase in LAVI at 6-month follow-up had the worst clinical course among the four groups, whereas the group with smaller baseline LAVI (≤55 ml/m^2) who experience an increase in LAVI did not accumulate much adverse events. HR were adjusted by age. HFH, heart failure hospitalization; LAVI, left atrial volume index; HR, hazard ratio; CI, confidence interval.

and 3D LA analysis can evaluate LA conditions more precisely than the parameters we used in the present study. In fact, one of the previous studies which showed a significant LAVI increase after LAAC employed 3D evaluation [6]. Therefore, further accurate follow-ups would be beneficial for drawing definitive conclusions on this topic.

On the flip side, particular patients experienced LA dilatation after LAAC, as illustrated in Graphical Abstract A and B. According to our analysis, a smaller LAVI and higher TRPG at baseline were significantly associated with LA enlargement after LAAC. Elevated baseline TRPG signifies decompensation at baseline, which is a plausible cause for a subsequent increase in LAVI. Meanwhile, the subsequent increase in patients with smaller baseline LA sizes may be because a smaller LA has the capacity and available intrapericardial space to dilate further. Since baseline LAVI in the overall population in this study was higher compared to other studies, a larger LA size in our cohort might not have sufficient capacity or space for further enlargement. As this phenomenon has not been reported in other studies, further investigation is required.

With regard to the analysis of the predictive value for hard outcomes, LA dilatation was substantially associated with HFH after the procedure.

The predictive value of an increase in LAVI was also reported in patients with heart failure with preserved ejection fraction (HFpEF) [18]. Although our analysis demonstrated that the increase in LAVI was more frequently observed in patients with a smaller LA size at baseline, previous studies reported that patients with a smaller LA size experienced better clinical outcomes [3,16]. Therefore, we additionally analyzed the clinical significance of LAVI increase in patients with smaller LA at baseline, which was not consequently related to worse clinical outcomes.

Aside from LA dilatation, ostium diameter at baseline was also reported to have significant predictive value for adverse cardiac events after LAAC [16]. Occlusion of a large ostium can cause substantial impairment in LA compliance and exert significant hemodynamic loads on the LA, potentially leading to adverse cardiac events. We assessed the relation between baseline ostium size and the change in LAVI, but none was identified. As mentioned previously, the effect of LAAC on the LA might be slight and challenging to detect by current parameters. More advanced evaluation might be able to reveal the impact of occluding a larger ostium on the LA.

Percutaneous LAAC creates an iatrogenic atrial septal defect (IASD), which imposes a volume overload after the procedure, thus potentially exerting additional stress on the LA. Our study did not reveal any significant relationship between LA size and IASD, possibly because the IASD resulting from LAAC is generally small and closes spontaneously, or it may take time before an apparent effect appears [19].

We selected patients from the OCEAN-LAAC registry, and the final population had a few characteristics that could have potentially influenced the results. First of all, the enrolled patients had large LA sizes. In our study, the median LAVI at baseline was 55 ml/m^2, which was higher than that reported in previous studies [6,16]. This is directly linked to baseline LA conditions and may affect the subsequent change in LAVI and TRPG. As for the proportion of AF types, which may influence the subsequent alteration in LAVI and TRPG, as well, the percentage was almost the same as that in previous reports [6,16,19]. Lastly, adverse cardiac events following LAAC occurred less frequently compared to those reported in other studies [16,20]. This could be due to the follow-up conditions at the institutions where the studies were conducted or to insufficient follow-up rates.

4.1. Limitations

Our study has several limitations. Firstly, a large number of patients were initially excluded due to the lack of LAVI measurements.

Secondly, this study model cannot eliminate the effects of AF itself, and other heart diseases (valvular heart disease, HFpEF, etc.) on LAVI. This means that other cardiac diseases can cause LA enlargement, and the intrinsic effect of LAAC alone cannot be analyzed. Theoretically, a comparison between patients undergoing LAAC and those with AF but not undergoing LAAC with the patients' baseline matched is ideal.

Third, since the present study was conducted in Japan and most of the study participants were Japanese, results should not be generalized to other population groups.

Lastly, the follow-up rate was insufficient. The registry itself is still ongoing and the number of events is low. This limitation is crucial for the assessment of predictive value. Following further collection of clinical data, additional analysis and verification in a large population is warranted.

4.2. Implications for future research

Since research papers related to LAAC generally focus on procedural strategy, safety, and thromboembolic events after the procedure, the data on subsequent HF and LA compliance and size are scarce. More rigorous studies comparing patients with AF undergoing LAAC to those who are not subjected to the procedure, and precise assessment of LA conditions with advanced techniques, such as strain and 3D, will potentially be effective in elucidating the intrinsic impact of LAAC on the LA. Determination of specific risk factors, such as larger ostium diameter, can lead to a more appropriate selection of candidates and intensive follow-up, eventually enhancing clinical outcomes following the procedure.

5. Conclusion

To the best of our knowledge, this was the first multicenter study to verify the impact of LAAC on the LA volume. Our analysis did not demonstrate any significant negative effects, yet we demonstrated that an increase in LAVI following LAAC had significant predictive value for subsequent HFH. On multivariable analysis, a smaller LA and elevated TRPG at baseline were predictors for subsequent LAVI increase; however, such an increase in LAVI among patients with a smaller baseline LA was not associated with subsequent HFH. Conversely, an increase in LAVI in patients with a larger LA at baseline was significantly associated with HFH following LAAC. Further investigations are warranted, particularly via advanced approaches in assessing LA function (strain, 3D), and in comparison with patients who have AF but do not undergo LAAC over the same periods.

CRediT authorship contribution statement

Hideaki Nonaka: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Masahiko Asami:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Yu Horiuchi:** Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Jun Tanaka:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision. **Daiki Yoshiura:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Kota Komiyama:** Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation. **Hitomi Yuzawa:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Kengo Tanabe:** Formal analysis, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Mitsuru Sago:** Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Shuhei Tanaka:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Ryuki Chatani:** Software, Supervision, Writing – review & editing. **Daisuke Hachinohe:** Resources, Supervision, Writing – review & editing. **Toru Naganuma:** Supervision, Writing – review & editing. **Yohei Ohno:** Conceptualization, Data curation, Supervision. **Tomoyuki Tani:** Conceptualization, Data curation, Supervision. **Hideharu Okamatsu:** Conceptualization, Data curation, Supervision. **Kazuki Mizutani:** Conceptualization, Data curation, Supervision. **Yusuke Watanabe:** Conceptualization, Data curation, Supervision. **Masaki Izumo:** Conceptualization, Data curation, Supervision. **Mike Saji:** Conceptualization, Data curation, Supervision. **Shingo Mizuno:** Conceptualization, Data curation, Supervision. **Hiroshi Ueno:** Conceptualization, Data curation, Supervision. **Shunsuke Kubo:** Conceptualization, Data curation, Supervision. **Shinichi Shirai:** Conceptualization, Data curation, Resources, Supervision. **Masaki Nakashima:** Conceptualization, Data curation, Supervision. **Masanori Yamamoto:** Conceptualization, Data curation, Resources, Supervision. **Kentaro Hayashida:** Conceptualization, Data curation, Resources, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The OCEAN-LAAC registry, which is part of OCEAN-SHD registry, is supported by Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Medical, and Daiichi Sankyo Company. Drs Asami, Hachinohe, Ueno, Kubo, Nakashima, and Yamamoto are clinical proctors for Boston Scientific. Dr Asami has received speaker fees from Daiichi Sankyo Company, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Abbott medical, Edwards Lifesciences, Medtronic, Canon Medical, and Boston Scientific. Dr. Tanabe receives remuneration from Medtronic, Edwards Lifesciences, Boston Scientific, and Abbott Medical. Dr Naganuma has received speaker fees from Daiichi Sankyo Company. Dr Ohno has received lecture fees from Daiichi Sankyo Company, Bristol Myers Squibb, and Boston Scientific. Dr Izumo has received speaker fees from Daiichi Sankyo Company, Bayer, and Bristol Myers Squibb. Dr Saji has received speaker fees from Abbott Medical. Dr Ueno has received speaker fees from Daiichi Sankyo Company, Bayer, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Boston Scientific. Dr Kubo has received speaker fees from Daiichi Sankyo Company and Boehringer Ingelheim. Dr Nakashima has received speaker fees from Daiichi Sankyo Company, Bristol Myers Squibb, and Boston Scientific. Dr Yamamoto has received speaker fees from Daiichi Sankyo Company, Bayer, Bristol Myers Squibb, and Pfizer. Dr Hayashida has received speaker fees from Daiichi Sankyo Company, Bayer, Bristol Myers Squibb, and Pfizer. The remaining authors have reported that they have no relationships relevant to the contents of this paper to disclose].

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Appendix A. Supplementary data

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