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Left Atrial Volume Index as a Predictor for Left Atrial Appendage Thrombus in Patients with Non-Valvular Atrial Fibrillation Receiving Appropriate Oral Anticoagulation Therapy: A Prospective Multi-Center Study

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Running head: LAVI for AF Patients

Abstract

Objectives: We previously reported a higher left atrial volume index (LAVI) was independently associated with left atrial (LA) appendage (LAA) thrombus formation in 737 patients with non-valvular atrial fibrillation (NVAF) receiving appropriate oral anticoagulation therapy. Since our previous study was a retrospective single-center study, we designed and conducted a prospective multi-center study to verify our findings for LAVI as a predictor of LAA thrombus in patients with NVAF receiving appropriate oral anticoagulation therapy.

Methods: This prospective multi-center study comprised 746 consecutive patients with NVAF recruited between December 2021 and March 2023 from eight institutions in Japan, who were receiving appropriate oral anticoagulation therapy, had undergone transthoracic echocardiography and transesophageal echocardiography (TEE).

Results: LAA thrombi were observed in 21 patients (2.8%). The prevalence of LAA thrombus formation in patients with paroxysmal AF (PAF) was significantly lower than that in patients with non-PAF (0.7% vs. 4.1%, P=0.006). LAA thrombus formation was detected in none (0/171) of the patients with normal size LA (LAVI ≤ 34mL/m^2). The prevalence of LAA thrombus formation in patients with mildly dilated LA (LAVI: 34-49.9 mL/m^2) was 2.1% (6/283), but that in PAF patients was low at 1.0% (1/104). Furthermore, this prevalence in patients with severely dilated LA (LAVI ≥ 50mL/m^2) was high at 5.1% (15/292).

Conclusions: The findings of this prospective multi-center study are consistent with those of our previous study. Thus, the need for TEE prior to catheter ablation or electrical cardioversion can be determined by the level of LAVI.

Keywords; non-valvular atrial fibrillation; thrombus; transesophageal echocardiography, anticoagulants, left atrium, left atrial appendage

Introduction

The left atrial (LA) appendage (LAA) is well known to be a major source of cardiac thrombus for all types of atrial fibrillation (AF)[1]. Transesophageal echocardiography (TEE) is currently considered the gold standard for identification of LAA thrombus and is widely used in clinical practice for screening of all types of AF patients. However, TEE is a somewhat invasive examination and is not routinely performed. On the other hand, non-invasively obtained parameters such as enlarged LA size, especially an enlarged LA volume index (LAVI), which is easily assessed by means of transthoracic echocardiography, has been shown to be a powerful marker for the occurrence of stroke in patients with AF [2-6]. LAA thrombus formation can reportedly occur in small number of patients with AF, even when oral anticoagulation therapy has been administered, irrespective of the appropriateness of the dose[7]. Thus, there may be no small amount of risk of stroke from catheter ablation or electrical cardioversion even in patients with AF receiving appropriate oral anticoagulation therapy is on appropriate anticoagulation therapy. With that background, we previously investigated whether the prevalence of LAA thrombus formation was directly related to LA size in 737 patients with non-valvular AF (NVAF) receiving appropriate oral anticoagulation therapy who were scheduled for catheter ablation or electrical cardioversion [5]. We found that the prevalence of LAA thrombus formation in patients with a normal LA size of LAVI $\leq$ 34 mL/m^2 was low at 0.4%, and that in patients with a severely dilated LA size of LAVI $\geq$ 50 mL/m^2 was high at 8.7%. In addition, the prevalence of LAA thrombus formation in patients with mildly dilated LA size of LAVI (34-49.9 mL/m^2) was 1.5%, but in PAF patients it was 0. However, our previous study was a retrospective single-center study so that a prospective multi-center study was needed to validate our findings. We therefore designed and conducted a prospective multi-center study to validate our findings that LAVI is a predictor for LAA thrombus in patients with NVAF receiving appropriate oral anticoagulation therapy.

Methods

This prospective multi-center study comprised 746 consecutive patients with NVAF, recruited between December 2021 and March 2023 from eight institutions in Japan, who were receiving appropriate oral anticoagulation therapy, had undergone transthoracic echocardiography and transesophageal echocardiography (TEE) and were scheduled for catheter ablation or electrical cardioversion for NVAF. TEE was performed in all patients 3 weeks or later after completion of appropriate oral anticoagulation therapy, in accordance with current guidelines. The median delay between transthoracic echocardiography and TEE was 36 days (8-95). The type of AF, such as paroxysmal AF (PAF), was determined by using the current guidelines of the American Heart Association (AHA) / American College of Cardiology (ACC)[8]. This study was approved by the local ethics committee of our institution (No. B210226) and was conducted in accordance with the Declaration of Helsinki.

Appropriate oral anticoagulation therapy

For patients on warfarin, the target prothrombin time/international normalized ratio (PT-INR) range was set at 2.0-3.0 for patients < 70 years old and at 1.6-2.6 for patients ≥ 70 years old, based on the guidelines of the Japanese Circulation Society/Japanese Heart Rhythm Society. The time in therapeutic range (TTR) at the time of the TEE was calculated as the percentage of the period spent in the appropriate therapeutic range with the PT-INR for the total duration of warfarin therapy. We used TTR data assessed within 4 weeks of TEE. For patients on direct oral anticoagulant (DOAC)s, the prescribed dose was compared to the recommended dose to identify patients who were receiving less than the recommended dosage. In Japan, the recommended dosage of DOACs is 2-tiered, and depends on the patient's renal function, body weight, age, and concomitant drugs. The following dosages were used: dabigatran, 150 or 110 mg twice daily; rivaroxaban, 15 or 10 mg once daily; apixaban, 5 or 2.5 mg twice daily; edoxaban, 60 or 30 mg once daily. Insufficient anticoagulation therapy was defined as TTR < 60% or prescription of less than the recommended DOAC dose based on the Japanese Circulation Society/Japanese Heart Rhythm Society Guidelines.

Echocardiographic examination

All patients underwent a standard echocardiographic examination using commercially available echocardiography systems. Standard transthoracic echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography [9]. Specifically, the LAVI was calculated using the biplane modified Simpson's method from apical four-and two-chamber views and then normalized to the body surface area. Normal LA size was defined as ~~a~~an LAVI of < 34 mL/m^2 based on the current guidelines [9], and severely dilated LA size was defined as a LAVI of ≥ 50 mL/m^2 based on findings from a previous study of ours [5]. The presence or absence of an LA thrombus by means of transthoracic echocardiography was determined by sonographers. For TEE, written informed consent was obtained from all patients prior to the examination. The presence or absence of an LAA thrombus was determined by physicians at each of the participating institutes who were board certified fellows of the Japan Society of Ultrasonics in Medicine (HT, JM, HS, HM, FS, JI, SY, HS, TO).

Statistical analysis

Continuous variables were expressed as mean values with standard deviations for normally distributed data, and as medians with interquartile ranges for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared using Student's t-test or the Mann-Whitney *U* test, depending on data distribution. Proportional differences were evaluated using Fisher's exact test. For all steps, a p-value of <0.05 was considered statistically significant. All analyses were performed using commercially available software (MedCalc software version 19.0.7., Mariakerke, Belgium).

Results

Patient characteristics

The baseline clinical and echocardiographic characteristics of the 746 patients with NVAF

are summarized in Table 1. The mean age of the patients was 69.7 ± 10.3 years, 205 patients (27.5%) were female, and 284 (38.0%) were suffering from paroxysmal AF. LAA thrombus formation was observed in 21 of the 746 patients with NVAF receiving appropriate oral anticoagulation therapy (2.8%). Figure 1 shows a comparison between patients with PAF and non-PAF receiving appropriate oral anticoagulation therapy for the prevalence of LAA thrombus formation in patients with NVAF. LAA thrombus formation in patients with PAF was significantly less prevalent than in patients with non-PAF (0.7% vs. 4.1%, P=0.006).

Prevalence of LAA thrombus in patients with NVAF receiving appropriate oral anticoagulation therapy in relation to LA size

Figure 2 shows the prevalence of LAA thrombus formation in patients with NVAF receiving appropriate oral anticoagulation therapy in relation to LA size. LAA thrombus formation was detected in none (0/171) of the patients with normal LA size (LAVI ≤ 34mL/m^2). The prevalence of LAA thrombus formation in patients with mildly dilated LA size (LAVI: 34-49.9 mL/m^2) was 2.1% (6/283), while that in PAF patients was low at 1.0% (1/104), relatively high at 2.8% (5/179) in non-PAF patients (Figure 3), and high at 5.1% (15/292) in patients with severely dilated LA (LAVI ≥ 50mL/m^2).

Discussion

The findings of this study indicates that 2.8% of the 746 patients with NVAF receiving appropriate oral anticoagulation therapy had nevertheless developed an LAA thrombus. This prospective multi-center study produced results consistent with those of our previous retrospective single-center study, in which the prevalence of LAA thrombus formation in patients with NVAF receiving appropriate oral anticoagulation therapy was directly related to LA size.

Findings from our previous retrospective study for LAA thrombus formation in patients with NVAF treated with appropriate oral anticoagulation therapy

Our previous retrospective single-center study showed that LAA thrombus was observed in

22 (3.0%) of the 737 patients with NVAF treated with appropriate oral anticoagulation therapy. and it tended to increase in line with the $CHADS_2$ score. Moreover, the multivariate logistic regression analysis showed that LAVI, as well as LAA flow, was an independent predictor of LAA thrombus formation, and receiver operating characteristic curve analysis identified the optimal cutoff value of LAVI for predicting LAA thrombus as ≥ 50 mL/m^2, with a sensitivity of 77.3%, specificity of 73.8%, and area under the curve of 0.787 ($p < 0.01$). The main finding of our previous study showed that the prevalence of LAA thrombus formation in patients with NVAF receiving appropriate oral anticoagulation therapy was directly related to LA size. Specifically, the prevalence of LAA thrombus formation in patients with an LA of normal size of LAVI ≤ 34 mL/m^2 was low at 0.4% (1/238). The prevalence of LAA thrombus formation in patients with mildly dilated LA (LAVI 34-49.9 mL/m^2) was 1.5% (4/268), but that of PAF patients was 0 (0/159), while it was high at 8.7% for patients with severely dilated LA size of LAVI ≥ 50 mL/m^2. Furthermore, the prevalence of patients with an LA volume index of > 34 mL/m^2 without LAA thrombus formation was 99.1% (216/218) for PAF and 92.2% (226/245) for non-PAF patients, and that of patients with an LA volume index of < 50 mL/m^2 without LAA thrombus formation was 100% (345/345) for PAF and 96.9% (156/161) for non-PAF patients.

Association of LA Size with LAA Thrombus Formation in Patients with NVAF

Clinical risk scores such as the $CHADS_2$ or CHA_2DS_2-VASc have often been used to predict the development of thromboembolism following development of an LAA thrombus as well as to provide a guide for anticoagulation therapy strategies for patients with NVAF. In addition, LAA is believed to be the cause of approximately 90% of AF-related thromboembolisms [10], and the presence of an LAA thrombus is thought to substantially increase the risk of stroke and transient ischemic attack [11]. TEE is currently considered the gold standard for identification of LAA thrombus and is widely used in clinical practice to screen all types of AF patients [12]. It is therefore advisable to perform TEE before cardioversion and proceed with cardioversion if no LAA thrombus is identified in patients with

AF or atrial flutter of 48 hours' or longer duration or of unknown duration who have not been anticoagulated for the preceding 3 weeks and for those patients to be classified as class IIa of recommendation and level B of evidence in accordance with the recent AHA/ACC guideline[8]. However, TEE is an invasive procedure and is therefore not routinely performed. On the other hand, an increase in LA size, especially enlargement of LAVI is easily and routinely evaluated by means of transthoracic echocardiography. As mentioned above, we previously found that LAVI as a parameter of transthoracic echocardiography for multivariate logistic regression analysis was the only independent predictor of LAA thrombus formation for 737 patients with NVAF who had received appropriate oral anticoagulation therapy [5]. A possible mechanism of this strong association of the enlargement of LAVI with LAA thrombus formation is that various parameters for AF-related thromboembolisms or LAA thrombus formation, such as spontaneous echocardiographic contrast, low LAA flow, LAA morphology, left ventricular dysfunction, metabolic syndrome, chronic kidney disease, hypertension, diabetes mellitus, aging, and high $CHADS_2$ and CHA_2DS_2-VASc scores [1, 13] can be eventually associated with an increase in LA size. Thus, watchful observation should be required even for AF patients who have an enlarged LAVI because LAVI is important for the prediction of AF-related thromboembolisms.

Association of LAA Thrombus with Duration of Oral Anticoagulation Therapy

LAA thrombus are basically nonspecific from a histopathological point of view. In fact, recent atrial mural thrombus consists of a complex network of fibrin where platelets and blood cells are entrapped. With passage of time, the thrombus body may undergo organization, usually starting from its base. Thus, their structure is highly dependent on the time of the thrombus formation, and a fully organized thrombus is much less prone to embolization. However, the duration of AF may not correlate with the duration of thrombus, making it difficult to discuss embolic risk.

Clinical implications

In this study, the prevalence of LAA thrombus formation in all patients with NVAF receiving

appropriate oral anticoagulation therapy with LAVI of normal size, < 34 mL/m^2, was not observed (0.0%) and was rare in PAF patients with a slightly dilated LA (LAVI: 34-49.9 mL/m^2) (1.0%). On the other hand, the prevalence of LAA thrombus formation in all patients with NVAF receiving appropriate oral anticoagulation therapy but with a severely dilated LA (LAVI ≥ 50 mL/m^2) was high (5.1%), and was relatively high in non-PAF patients with NVAF receiving appropriate oral anticoagulation therapy with a slightly dilated LA (LAVI: 34-49.9 mL/m^2) (2.8%). Thus, our data provide an algorithm for patients with NVAF receiving appropriate oral anticoagulation therapy to undergo catheter ablation or electrical cardioversion but without TEE (Figure 4). This algorithm is simple, highly feasible and not time-consuming, and may have important clinical implications for patients with NVAF receiving appropriate oral anticoagulation therapy who are scheduled for catheter ablation or electrical cardioversion though a small risk of stroke.

Study limitations

This study was a prospective multi-center study but comprised a relatively small number of patients, so that further studies with larger patient populations are needed to validate our findings. Assessment of LAA morphology using cardiac computed tomography was not performed in this study. Patients with AF with non-chicken wing-type LAA had a higher prevalence of stroke events[14-16], and non-chicken wing-type LAA was associated with low LAA flow in patients with AF[16]. Furthermore, the assessment of LA function by means of computed tomography or magnetic resonance image or LA strain by means of speckle-tracking strain was not part of this study. Finally, this study was conducted based on Japanese guidelines, but should also be validated based on Western guidelines. Specifically, not only $CHADS_2$ score recommended in Japanese guidelines, but also $CHA2DS_2$-VASc score recommended in the Western guidelines should be validated.

Conclusions

The prevalence of LAA thrombus formation in patients with NVAF receiving appropriate oral

anticoagulation therapy is associated with LA size. Thus, the need for TEE prior to catheter ablation or electrical cardioversion can be determined with a simple assessment of LAVI by means of transthoracic echocardiography.

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Author Contributions:

Hiroaki Shiraki: Concept/design, data analysis/interpretation, drafting article, statistics, data collection

Hiroshi Tsunamoto: Concept/design, data analysis/interpretation, approval of article

Tetsuari Onishi: Concept/design, data analysis/interpretation, approval of article

Jun Muka: Concept/design, data analysis/interpretation, approval of article

Hiroyuki Simoura: Concept/design, data analysis/interpretation, approval of article

Hiroki Matsuzoe: Concept/design, data analysis/interpretation, approval of article

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Hiroyuki Sano: Concept/design, data analysis/interpretation, approval of article

Yusuke Tanaka: 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

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Figure Legends

Figure 1: The prevalence of LAA thrombus formation in PAF and non-PAF patients with NVAF receiving appropriate oral anticoagulation therapy.

Figure 2: The prevalence of LAA thrombus formation in patients with NVAF receiving appropriate oral anticoagulation therapy based on LA size.

Figure 3: The prevalence of LAA thrombus formation in PAF and non-PAF patients with mildly dilated LA (LA volume index: 34-49.9 mL/m^2).

Figure 4: Algorithm for identify determining whether TEE is necessary to identify LAA the presence of thrombus in patients with NVAF patients receiving appropriate oral anticoagulation therapy who are scheduled for catheter ablation or electrical cardioversion.

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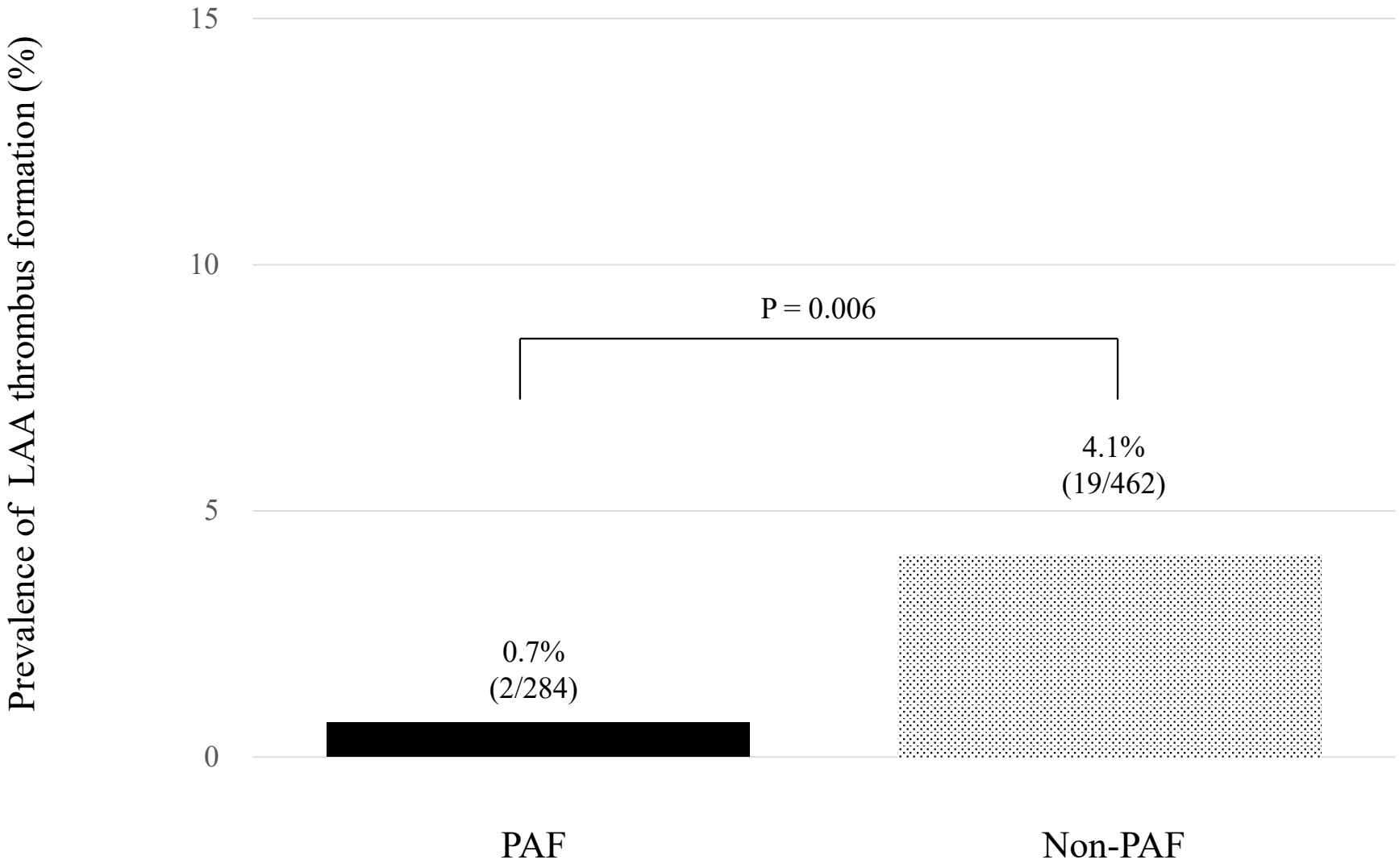
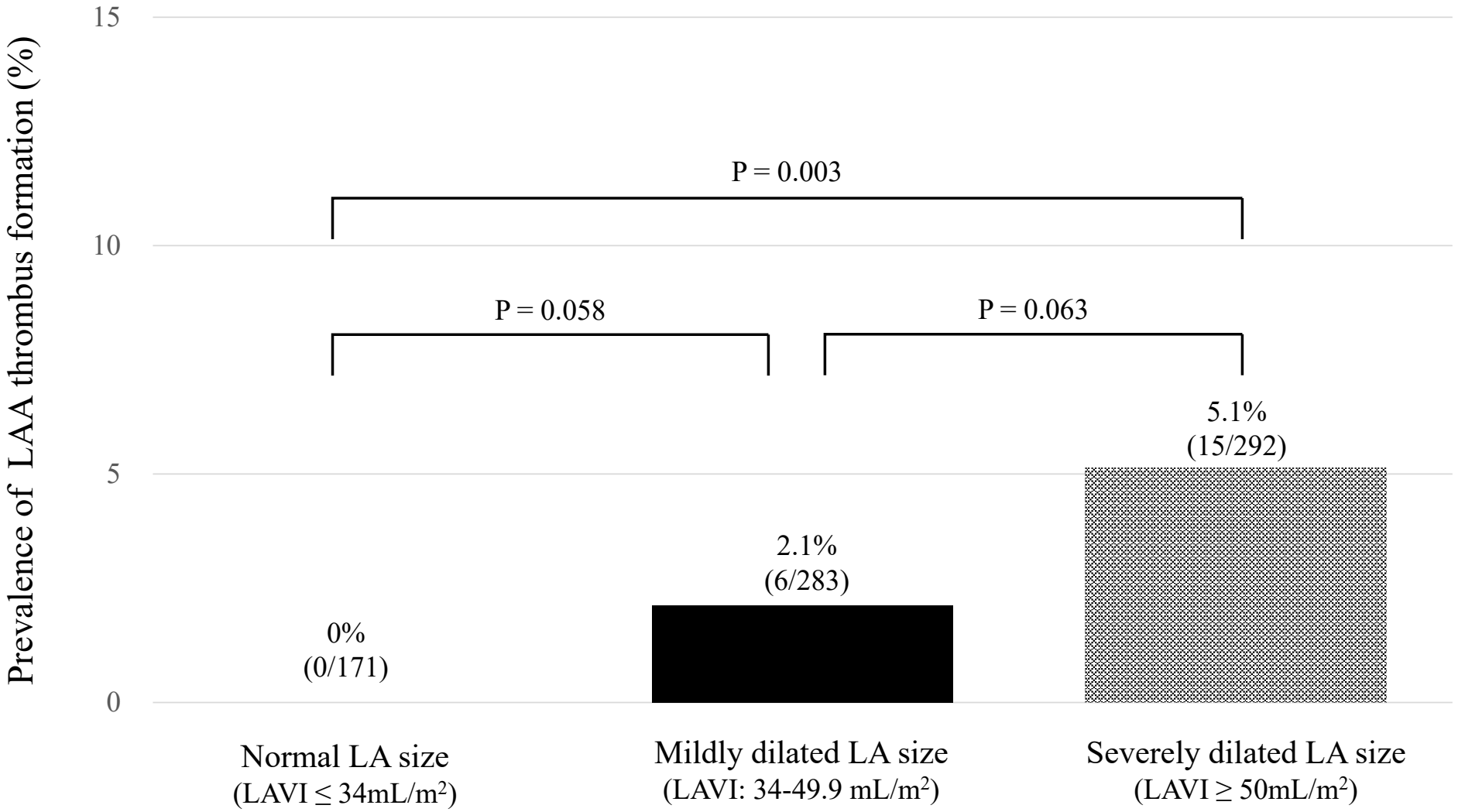
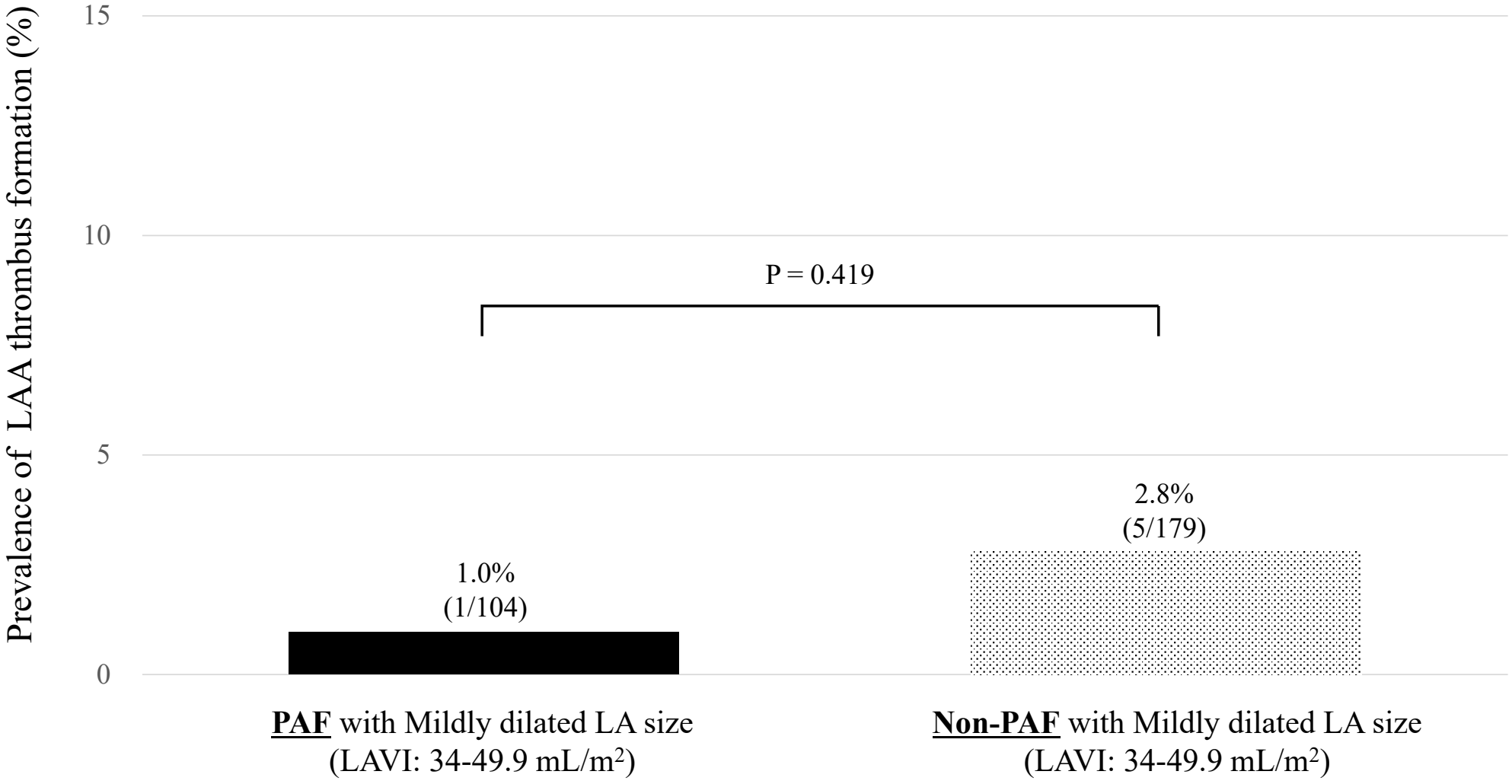

Prevalence of LAA thrombus formation (%)
15
10
5
0
P = 0.006
4.1%
(19/462)
0.7%
(2/284)
PAF
Non-PAF


Prevalence of LAA thrombus formation (%)
15
10
5
0
P = 0.003
P = 0.058
P = 0.063
0%
(0/171)
2.1%
(6/283)
5.1%
(15/292)
Normal LA size
(LAVI ≤ 34mL/m2)
Mildly dilated LA size
(LAVI: 34-49.9 mL/m2)
Severely dilated LA size
(LAVI ≥ 50mL/m2)


Prevalence of LAA thrombus formation (%)
15
10
5
0
P = 0.419
1.0%
(1/104)
2.8%
(5/179)
PAF with Mildly dilated LA size
(LAVI: 34-49.9 mL/m2)
Non-PAF with Mildly dilated LA size
(LAVI: 34-49.9 mL/m2)

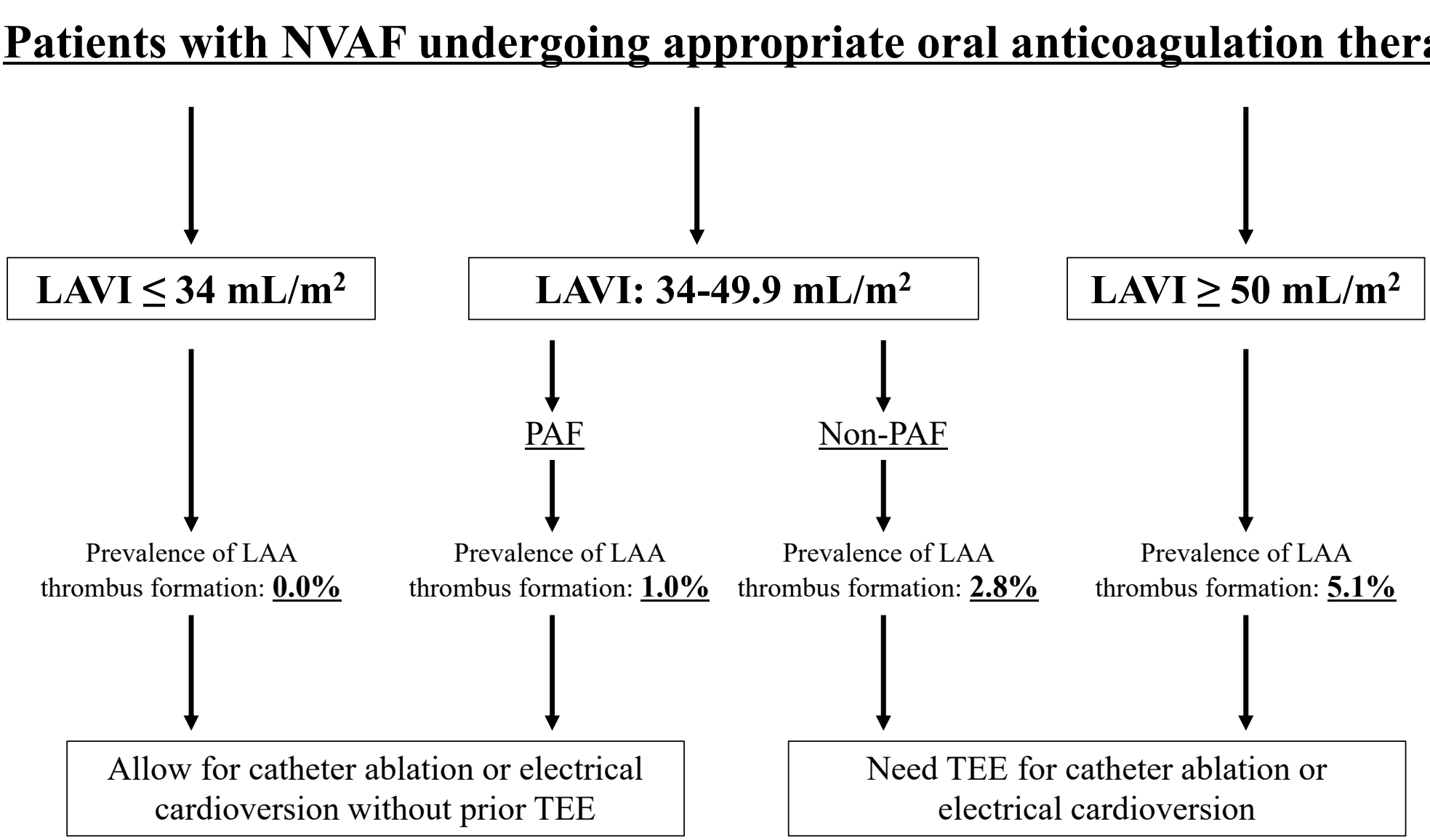

Patients with NVAF undergoing appropriate oral anticoagulation therapy
LAVI ≤ 34 mL/m²
LAVI: 34-49.9 mL/m²
LAVI ≥ 50 mL/m²
PAF
Non-PAF
Prevalence of LAA thrombus formation: 0.0%
Prevalence of LAA thrombus formation: 1.0%
Prevalence of LAA thrombus formation: 2.8%
Prevalence of LAA thrombus formation: 5.1%
Allow for catheter ablation or electrical cardioversion without prior TEE
Need TEE for catheter ablation or electrical cardioversion

Table 1
Baseline clinical and echocardiographic data of patients

	All Patients (n=746)	LAVI ≤ 34mL/m^2 (n=171)	LAVI: 34-49.9 mL/m^2 (n=283)	LAVI > 50 mL/m^2 (n=292)
Clinical data				
Age, years	69.7 ± 10.3	65.9 ± 9.9	69.3 ± 10.1	72.4 ± 9.9
Gender (male), n (%)	541 (72.5%)	129 (75.4%)	232 (82.0%)	180 (61.4%)
Body surface area, kg/m^2	1.68 ± 0.22	1.76 ± 0.21	1.72 ± 0.21	1.61 ± 0.20
Type of AF, n (%)				
Paroxysmal AF	284 (38.1%)	101 (59.1%)	104 (36.8%)	79 (27.0%)
Non-Paroxysmal AF	462 (61.9%)	70 (40.9%)	179 (63.3%)	213 (72.7%)
$CHADS_2$ score, n (%)				
0	111 (14.9%)	38 (22.2%)	52 (18.4%)	21 (7.2%)
1	212 (28.4%)	61 (35.7%)	82 (29.0%)	69 (23.6%)
2	206 (27.6%)	46 (26.9%)	83 (29.3%)	77 (26.3%)
≥3	217 (29.1%)	26 (15.2%)	66 (23.3%)	125 (42.7%)
Oral anticoagulation therapy, n (%)				
Warfarin	41 (5.5%)	2 (1.2%)	12 (4.2%)	27 (9.2%)
DOAC	701 (94.2%)	169 (98.8%)	269 (95.1%)	263 (89.8%)
Dabigatran	39 (5.2%)	11 (6.4%)	14 (5.0%)	14 (4.8%)
Rivaroxaban	194 (26.0%)	54 (31.6%)	77 (27.2%)	63 (21.5%)

Apixaban	156 (20.9%)	36 (21.1%)	64 (22.6%)	56 (19.1%)
Edoxaban	312 (41.8%)	68 (39.8%)	114 (40.3%)	130 (44.4%)
Comorbidities, n (%)				
Congestive heart failure	301 (40.3%)	32 (18.7%)	91 (32.2%)	178 (61.0%)
Hypertension	491 (65.8%)	107 (62.6%)	187 (66.1%)	197 (67.2%)
Diabetes	185 (24.8%)	38 (22.2%)	64 (22.6%)	83 (28.3%)
Stroke/Transient ischemic attack	61 (8.2%)	11 (6.4%)	19 (6.7%)	31 (10.6%)
Blood examination				
Creatinine, mg/dL	1.10 ± 0.85	0.92 ± 0.28	1.07 ± 0.80	1.22 ± 1.07
eGFR, mL/min/1.73m^2	57.2 ± 17.7	63.3 ± 16.1	58.0 ± 15.9	52.9 ± 19.0
BNP, pg/mL	138.2 (60.8-260.1)	59.8 (26.9-134.0)	131.5 (57.0-210.2)	209.3 (122.0-430.5)
Echocardiographic parameters				
LV end-diastolic volume index, mL/m^2	52.4 ± 19.7	45.8 ± 13.7	50.8 ± 17.4	57.9 ± 23.0
LV end-systolic volume index, mL/m^2	24.1 ± 14.9	18.9 ± 7.9	22.8 ± 12.0	28.6 ± 18.9
LV ejection fraction	56.0 ± 11.5	59.7 ± 8.2	56.6 ± 10.7	53.4 ± 13.2
LV mass index, mg/m^2	123.6 ± 36.2	109.7 ± 25.8	120.1 ± 33.3	218.5 ± 73.2
LAVI, mL/m^2	48.3 ± 19.8	26.8 ± 5.3	42.1 ± 4.6	66.9 ± 17.7
E/e' septal	12.7 ± 7.7	9.8 ± 2.8	12.6 ± 9.8	14.4 ± 6.9
LAA flow, cm/s	38.8 ± 21.6	53.3 ± 24.3	38.8 ± 19.3	30.1 ± 17.0

Values are mean ± standard deviation for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).
AF=atrial fibrillation; DOAC=direct oral anticoagulant; eGFR=estimated glomerular filtration rate; BNP=B-type natriuretic peptide; LV=left ventricular; LA=left atrial; E=peak early diastolic mitral flow velocity; e'=spectral pulsed-wave Doppler-derived early diastolic velocity from the septal mitral annulus; LAA=left atrial appendage