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ORIGINAL RESEARCH

Patients With Larger Left Atrial Appendage Orifice Presented Worse Prognosis Contributed by Acute Heart Failure After Left Atrial Appendage Closure

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BACKGROUND: Left atrial appendage (LAA) closure (LAAC) could prevent stroke in patients with atrial fibrillation. However, LAAC may impair the compliance of the left atrium and result in poor prognosis. This study aimed to comparatively evaluate the prognosis of LAAC among patients with different sizes of LAA orifice.

METHODS AND RESULTS: Three hundred two consecutive patients who underwent successful LAAC were included and divided into 4 groups based on LAA orifice size that was measured using transesophageal echocardiography. Clinical outcomes including thromboembolic events, major cardiocerebrovascular adverse events, and acute heart failure (AHF) were compared among 4 quartile groups and between propensity-score matched groups of large and small LAAs. Through follow-up of 39.6±8.4 months, survival of thromboembolic events was similar. Survival of major cardiocerebrovascular adverse events was significantly lower in the group with the largest LAA orifice (log-rank P<0.001), including a higher incidence of AHF with New York Heart Association class III to IV (21.4%, log-rank P=0.009). A large LAA orifice (by cutoff) could predict major cardiocerebrovascular adverse events (hazard ratio, 3.749 [95% CI, 2.074–6.779]) in most patients, except for subgroups of those aged <65 years, with paroxysmal atrial fibrillation, and/or with failed rhythm/rate control. Further compared with a propensity-score matched small-LAA group, the large-LAA orifice group still presented worse survival of AHF with New York Heart Association class III to IV (log-rank P=0.010).

CONCLUSIONS: Patients with a larger LAA orifice presented a worse prognosis after LAAC, including a higher incidence of AHF. A large LAA orifice could predict a post-LAAC AHF event in most patients, except for young patients, patients with paroxysmal atrial fibrillation, and/or with failed rhythm/rate control.

REGISTRATION: URL: clinicaltrials.gov; Unique identifier: NCT04185142.

Key Words: heart failure ■ left atrial appendage ■ left atrial appendage closure ■ major adverse cardiocerebrovascular events ■ prognosis

The left atrial appendage (LAA) is a finger-like structure originating from the embryonic left atrium (LA). As a structure rich in pectinate muscle, with a volume of ≈10 mL,[1] it serves as an essential reservoir that compensates for pressure and/or volume overload. Moreover, it has an endocrine function that regulates hemodynamics through secretion of natriuretic peptides.[2]

In recent years, transcatheter LAA closure (LAAC) has been recognized as an effective method for stroke prevention.[3] However, closure of the LAA can cause

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CLINICAL PERSPECTIVE

What Is New?

- Based on our cohort that underwent successful left atrial appendage closure (LAAC), we observed an incidence of acute heart failure (AHF) following LAAC of 18.8%.
- Compared with patients with a small left atrial appendage (LAA) orifice, although patients with larger LAA orifice had similar survival of thromboembolic events, a worse survival rate of major adverse cardiocerebrovascular events was observed, contributed by a high incidence of AHF with New York Heart Association class III to IV of 21.4%.
- Survival analysis adjusting confounding factors showed that a large LAA orifice could be an independent risk factor for post-LAAC AHF events in most patients, except for young patients, patients with paroxysmal atrial fibrillation, and/or patients with failed rhythm/rate control.

What Are the Clinical Implications?

- AHF after LAAC is not an uncommon adverse event. Risk of AHF after LAAC and monitoring AHF during follow-up should be taken into consideration for management of atrial fibrillation.
- The closure of a large LAA could provide stroke prophylaxis, but could pose a risk of AHF following LAAC except for those young patients, patients with paroxysmal atrial fibrillation, and/or patients with failed rhythm/rate control.
- Because LAA size and morphology could lead to a worse prognosis, LAA dimensional features should be thoroughly evaluated before LAAC.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
LAA	left atrial appendage
LAAC	left atrial appendage closure
LAVI	left atrial volume index
MACCE	major adverse cardiocerebrovascular events
NYHA	New York Heart Association
PVI	pulmonary vein isolation
TEE	transesophageal echocardiography

an acute volume reduction of the total LA chamber leading to increased LA pressure.[4] Moreover, closure inhibits the active emptying of the LAA and interferes with its secretory function, eventually decreasing the overall compliance of the LA.[5]

Concerns have been raised that LAAC might disturb hemodynamics and lead to the development of heart failure (HF). Nevertheless, the occurrence of acute HF (AHF) has not been evaluated in current, well-designed LAAC trials, with only limited, small-sized studies having reported that the incidence of AHF ranged from 16.0% to 23.9%, which was attributed mostly to preexisting HF.[6–8] More importantly, the dimensions of the LAA reflect its reservoir function, but the value of these dimensional features for predicting HF after LAAC has not yet been investigated.

In the present study, we enrolled patients who had undergone successful LAAC and stratified them according to their LAA dimensions by orifice diameter from 2-dimensional transesophageal echocardiography (TEE). We then explored the correlation of orifice diameter and other clinical features, and further evaluated the predictive value of orifice diameter for periprocedural complications and follow-up prognosis including thromboembolic events and development of AHF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Enrollment

From May 2017 to December 2019, patients with atrial fibrillation (AF) who underwent LAAC were consecutively enrolled in the study. Patients who had undergone pulmonary vein isolation combined with LAAC were from the registered CLACBAC (Combining Left Atrial Appendage Closure With Cryoballoon Ablation in the Chinese Population; number NCT04185142) study. Inclusion criteria were (1) patients diagnosed with AF and (2) patients having undergone a percutaneous LAAC procedure. Exclusion criteria were (1) patients with history of valvular heart disease, (2) patients with concomitant arrhythmia except AF who required extrapulmonary vein ablation, (3) patients who underwent other concomitant procedures except pulmonary vein isolation, (4) patients with failed occluder implantation because of any reason, (5) patients whose echocardiographic data could not be retraced, and (6) patients enrolled in other clinical trials. Detailed inclusion and exclusion criteria are described in Data S1.[9–12] A study flowchart is displayed in Figure 1. This study complies with the Declaration of Helsinki, and was approved by the local ethic committee of Shanghai Tenth People's Hospital (approval number SHSY-IEC-4.1/21/231/01). Written informed consent was given by every patient included.

Data Collection

For TEE measurement, 2-dimensional TEE (GE Vivid E9 or Philips EPIQ 7C) was performed according to guidelines.[11] Under at least 3 different degrees, namely 45°, 90°, and 135°, LAA orifice diameter was measured from

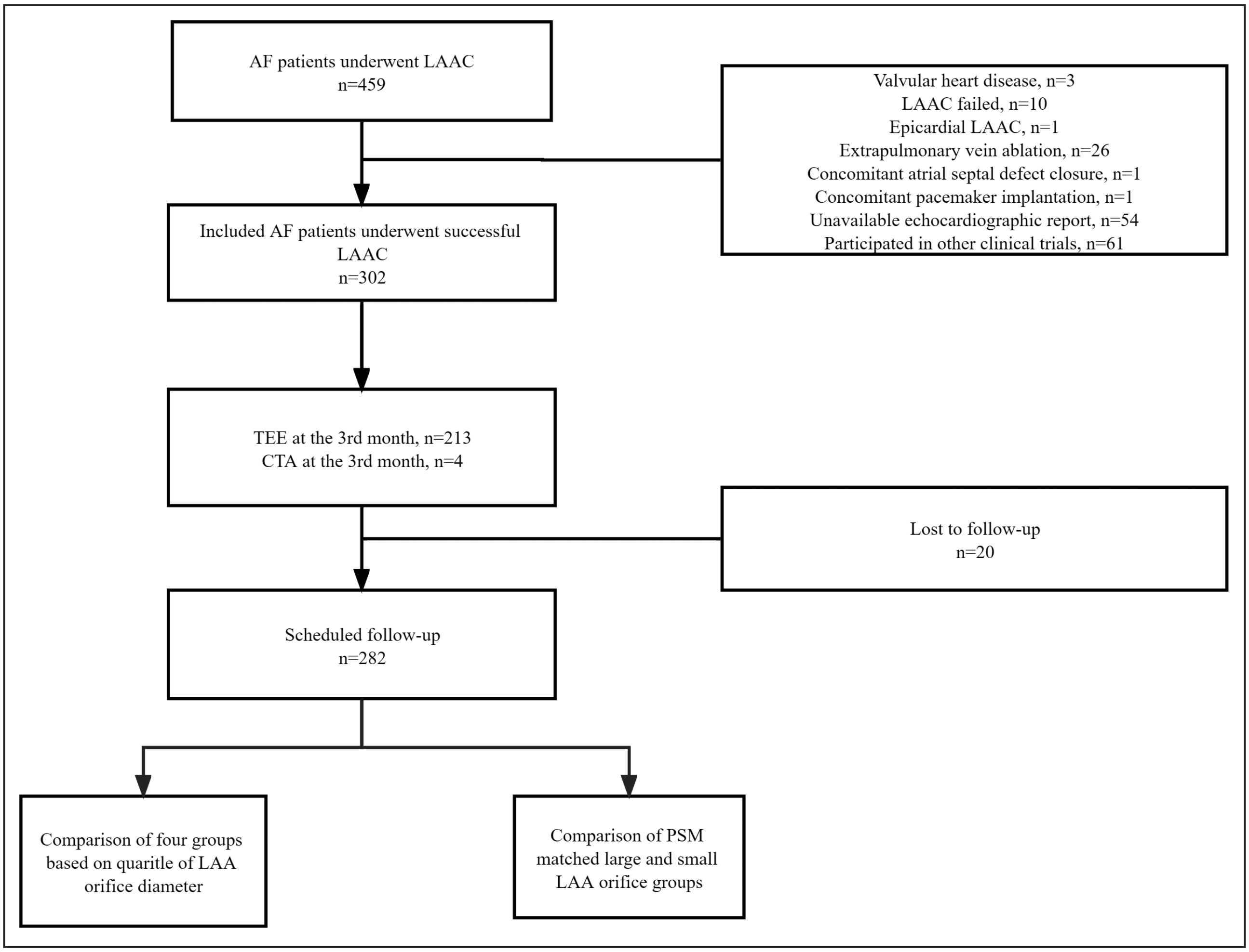

Figure 1. The study flowchart.
AF indicates atrial fibrillation; CTA, computed tomography angiography; LAA, left atrial appendage; LAAC, left atrial appendage closure; PSM, propensity-score matching; and TEE, transesophageal echocardiography.

the circumflex artery to a point 1 to 2 cm superior within the LA ridge. Concurrently, LAA depth was measured as the length from the middle of the LAA orifice perpendicular to the inner border of the LAA. The maximum depth was acquired if LAA was lobulated. Detailed information of other data collected is described in Data S1.

Percutaneous LAAC

All patients included underwent standard cryoballoon ablation for only pulmonary vein isolation (PVI). Details of cryoballoon ablation was as previously published[13] and described in Data S1.[14] LAAC was performed under local anesthesia and as previously described.[13] Both plug occluders (WATCHMAN; Boston Scientific) and pacifier occluders (Lifetech Scientific, Shenzhen, China) were used. Under guidance of fluoroscopy and TEE, the occluder was delivered through a 14 F delivery sheath. For the plug occluder, the size was 4 to 6 mm larger than the measured diameter of the landing zone to ensure an optimal compression ratio from 10% to 20%. For the pacifier occluder, the size of the outer plate should be 2 to 3 mm larger than the measured orifice diameter to ensure complete sealing. After angiography confirmed complete sealing and tug tests confirmed stability, the occluder was deployed, and angiography and TEE were checked again to evaluate occluder positioning and possible periprocedural complications.

After LAAC, 3-month oral anticoagulation therapy (dabigatrian, rivaroxaban, or warfarin) was prescribed. Once follow-up TEE or computed tomography angiography in the third month showed satisfactory sealing (residual flow <3 mm), an antithrombotic regimen was recommended with 3-month double antiplatelet therapy and ensuing 6-month single antiplatelet therapy. For patients who underwent ablation, class I/III antiarrhythmic drugs were prescribed for 3 months after the procedure.

Follow-Up Schedule

Patients were required to have outpatient follow-up in the third month, sixth month, and every year after the

Table 1. Baseline Characteristics of Patients Undergoing LAA Closure Divided by Mean LAA Orifice Diameter

Characteristic	Overall, n=302	Q1 OD≤18.0, n=78	Q2 18.0<OD≤20.7, n=83	Q3 20.7<OD≤23.3, n=66	Q4 OD>23.3, n=75	*P* for trend
Age, y	71.2±8.7	70.3±8.7	72.3±8.7	70.4±9.1	71.2±8.7	0.640
Men, n (%)	181 (59.9)	38 (48.7)	54 (65.1)	39 (59.1)	50 (66.7)	0.057
Body mass index, kg/m^2	25.6±3.5	26.4±3.7	25.6±3.3	24.7±3.5	25.7±3.4	0.144
AF type, n (%)						0.095
Paroxysmal AF	103 (34.1)	26 (33.3)	27 (32.5)	20 (30.3)	30 (40.0)	
Short-term persistent AF	69 (22.9)	21 (26.9)	19 (22.9)	9 (13.6)	20 (26.7)	
Long-term persistent AF	130 (43.1)	31 (39.7)	37 (44.6)	37 (56.1)	25 (33.3)	
CHA_2DS_2-VASc	4.0 [3.0–5.0]	4.0 [3.0–5.0]	4.0 [3.0–6.0]	3.0 [2.0–5.0]	4.0 [3.0–5.0]	0.796
HAS-BLED	2.0 [2.0–3.0]	3.0 [2.0–3.0]	3.0 [2.0–3.0]	2.0 [1.3–3.0]	2.0 [2.0–3.0]	0.437
NT-proBNP, pg/mL	800.1 [360.3–1419.0]	602.6 [229.6–1389.0]	779.4 [466.1–1563.8]	702.1 [376.3–1222.0]	849.6 [444.6–1686.5]	0.025*
NYHA functional class, n (%)						0.525
IV	13 (4.3)	4 (5.1)	3 (3.6)	4 (6.1)	2 (2.7)	
III	17 (5.6)	4 (5.1)	5 (6.0)	4 (6.1)	4 (5.3)	
II	50 (16.6)	10 (12.8)	14 (16.9)	14 (21.2)	12 (16.0)	
I	21 (7.0)	4 (5.1)	6 (7.2)	4 (6.1)	7 (9.3)	
Previous illness, n (%)						
Stroke	101 (33.4)	20 (25.6)	35 (42.2)	22 (33.3)	24 (32.0)	0.676
Cerebral infarction	98 (32.5)	19 (24.4)	35 (42.2)	21 (31.8)	23 (30.7)	0.725
Intracranial hemorrhage	10 (3.3)	2 (2.6)	5 (6.0)	1 (1.5)	2 (2.7)	0.654
Heart failure	60 (19.9)	12 (15.4)	12 (14.5)	15 (22.7)	21 (28.0)	0.557
Hypertension	222 (73.5)	62 (79.5)	60 (72.3)	46 (69.7)	54 (72.0)	0.274
Diabetes	78 (25.8)	19 (24.4)	18 (21.7)	15 (22.7)	26 (34.7)	0.074
Perivascular disease	17 (5.6)	4 (5.1)	5 (6.0)	3 (4.5)	5 (6.7)	0.784
Coronary heart disease	93 (30.8)	19 (24.4)	30 (36.1)	19 (28.8)	25 (33.3)	0.405
Echocardiographic measurement						
LAVI, mL/m^2	25.3 [20.3–31.4]	24.2 [17.4–29.7]	25.0 [19.6–29.5]	24.4 [20.1–31.4]	25.3 [20.3–31.4]	0.002*
LVEF, %	58.0 [55.0–63.9]	59.1 [55.0–64.0]	58.0 [55.0–63.0]	62.0 [57.8–64.5]	56.4 [52.9–62.5]	0.013*
LVEF group, n (%)						0.052
>50%	269 (89.1)	72 (92.3)	76 (91.6)	59 (89.4)	62 (82.7)	
40%–50%	13 (4.3)	2 (2.6)	4 (4.8)	2 (3.0)	5 (6.7)	
≤40%	20 (6.6)	4 (5.1)	3 (3.6)	5 (7.6)	8 (10.7)	
LVMI, g/m^2	96.4 [85.1–108.8]	94.7 [86.2–107.5]	93.9 [81.1–101.5]	98.5 [89.6–109.2]	96.4 [85.1–108.8]	0.122
LV hypertrophy, n (%)	47 (15.6)	14 (17.9)	8 (9.6)	9 (13.6)	16 (21.3)	0.436
E/e′	13.2 [10.4–17.1]	11.3 [9.2–15.1]	12.5 [10.8–18.5]	13.2 [9.7–18.8]	15.4 [11.2–17.5]	0.046 *

(*Continued*)

Table 1. (Continued)

Characteristic	Overall, n=302	Q1 OD≤18.0, n=78	Q2 18.0<OD≤20.7, n=83	Q3 20.7<OD≤23.3, n=66	Q4 OD>23.3, n=75	*P* for trend
E/e′group, n (%)						0.016*
≥14	110 (36.4)	23 (29.5)	26 (31.3)	22 (33.3)	39 (52.0)	
7–14	172 (57.0)	50 (64.1)	53 (63.9)	38 (57.7)	31 (41.3)	
<7	20 (6.6)	5 (6.4)	4 (4.8)	6 (9.0)	5 (6.7)	
LAA measurement						
Mean LAA orifice diameter, mm	20.7 [18.0–23.3]	16.7 [15.7–17.3]	20.0 [19.3–20.3]	22.0 [21.7–22.7]	26.0 [24.7–27.8]	<0.001*
Mean LAA depth, mm	21.0 [18.7–23.7]	18.3 [16.0–20.0]	20.7 [19.2–22.0]	22.8 [20.2–24.3]	24.0 [21.3–26.3]	<0.001*
Spontaneous echo contrast, n (%)	68 (22.5)	8 (10.3)	20 (24.1)	14 (21.2)	26 (34.7)	0.001*

HAS-BLED a score to evaluate major bleeding risk for atrial fibrillation population incoporating hypertension, abnormal liver/kidney function, stroke history, bleeding history, labile international normalized ratio, elder age, and drug predisposing bleeding/alcohol abuse.

Continuous variables are presented as mean±SD or as median with interquartile range; categorical variables are presented as percentage. AF indicates atrial fibrillation; E/e′, ratio of mitral inflow velocity (E) and average mitral valve velocity (e′); LA, left atrium; LAA, left atrial appendage; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OD, orifice diameter; and Q, quartile.[1]

*Significant *P* value.

procedure. Additionally, TEE examination in the third month from the procedure was required. Composite primary end points included thromboembolic events and major hemorrhagic events. Thromboembolic events comprised cerebral infarction, transient ischemic attack, and perivascular thrombosis confirmed via imaging examination. Secondary end points were (1) major adverse cardiocerebrovascular events (MACCE) including ischemic or hemorrhagic stroke, AHF with New York Heart Association (NYHA) functional class grading III to IV, acute myocardial infarction, malignant arrhythmia, cardiac tamponade, and all-cause mortality; (2) rehospitalization because of cardiovascular diseases; (3) rehospitalization because of AHF; (4) rehospitalization because of atrial tachycardia; and (5) other cardiovascular events including bradycardia requiring pacemaker implantation and AF recurrence for patients who underwent concomitant PVI.

AHF was confirmed when at least 2 of the following conditions were met[15]: (1) severe chest distress with dyspnea and/or edema of bilateral lower limbs excluding acute onset of pulmonary or renal diseases, (2) level of NT-proBNP (N-terminal pro-B-type natriuretic peptide) at admission >300 pg/mL at sinus rhythm, level of NT-proBNP >800 pg/mL at AF rhythm, and (3) echocardiography showing left ventricular ejection fraction (LVEF) <40% and structural change (left atrial volume index [LAVI] ≥34 mL/m^2 and/or left ventricular mass index ≥115 g/m^2 for men or ≥95 g/m^2 for women). NYHA functional class grading was defined by severity of symptoms according to guideline.[15] Specifically, grade IV was defined as when patients were unable to carry on physical activity because of discomfort and discomfort persisted at rest, and grade III was defined as markedly limited physical activity because of discomfort. Detailed definitions of other follow-up events are described in Data S1.[16]

Statistical Analysis

Patients were divided into 4 groups based on quartile (Q) of LAA orifice diameter. Continuous variables were described as mean±standard deviation if they conformed to normal distribution, or median with interquartile range if they had a skewed distribution. Categorical variables were described as numbers with percentages. The comparison of baseline characteristics was done by ANOVA and sign-rank test for continuous variables or Cochran-Mantel-Haenszel test for categorical variables. A *P* value for trend was generated by linear, logistic, or Cox regression with quartiles of LAA orifice diameter. For continuous variables that did not conform normal distribution even after transformation, a Wilcoxon-type test for trend was applied, and the comparison of baseline and follow-up information was done by repeated-measures ANOVA.

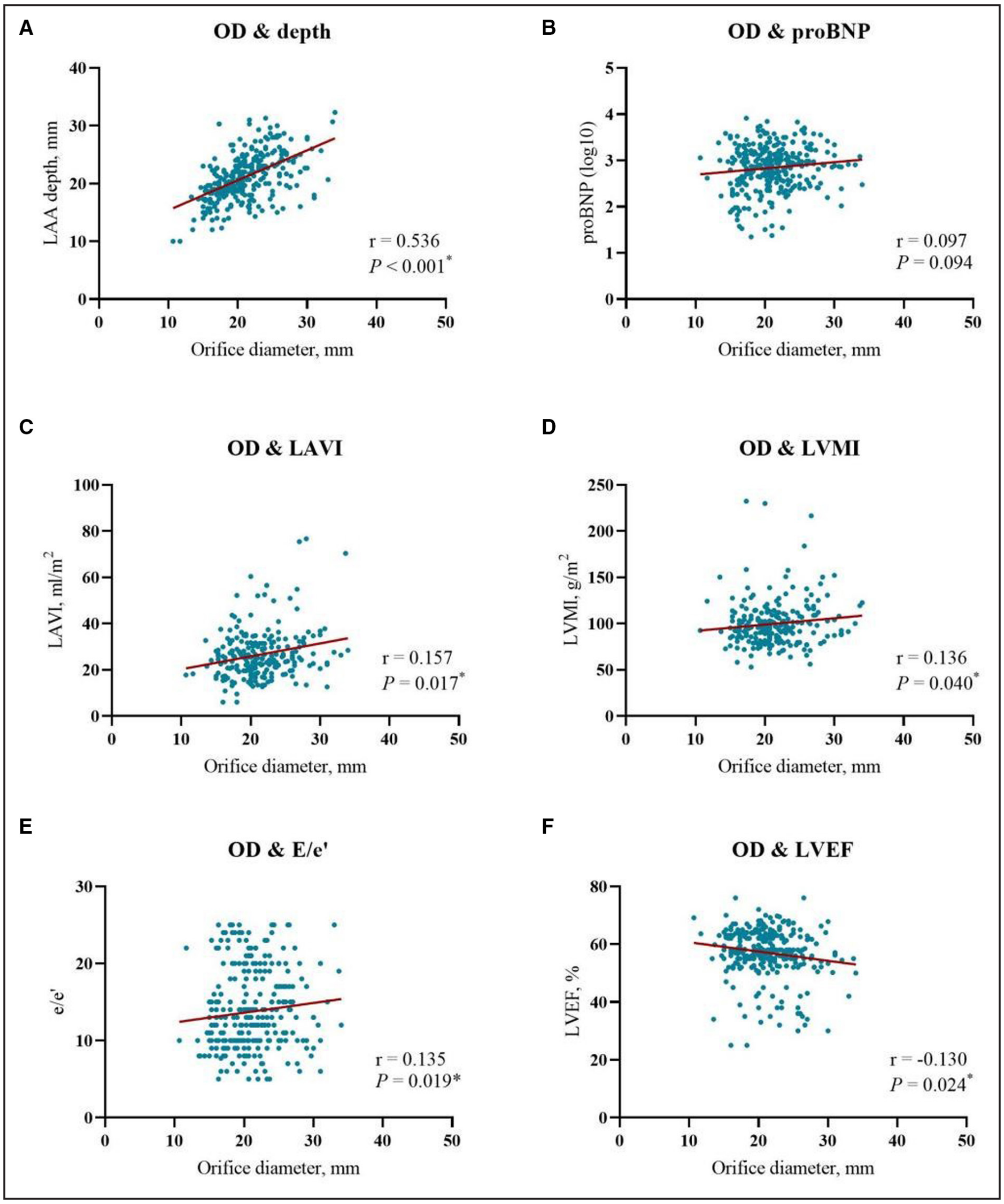

Figure 2. Correlation of left atrial appendage (LAA) orifice diameter (OD) with other clinical variables.

A, OD was strongly correlated with LAA depth. **B**, OD was not associated with baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) level. **C** through **F**, Displayed correlation with echocardiographic measurements, showing that OD was weakly correlated with left atrial volume index (LAVI), left ventricular mass index (LVMI), ratio of mitral inflow velocity (E) and average mitral valve velocity (e′) (E/e′), and negatively correlated with left ventricular ejection fraction (LVEF).

The association between 2 variables was analyzed by Spearman correlation analysis.

A receiver operator characteristics analysis of LAA orifice diameter for MACCE was performed, and a cutoff value was determined by the largest Yoden index. Based on cutoff value, patients were divided into groups of large LAA and small LAA for further analysis. For survival data, a Kaplan-Meier estimate was used with a log-rank test to detect the difference between patients with different LAA orifice diameters. A Cox proportional hazard model was applied to further evaluate the prognostic value of LAA orifice diameter. Time-dependent Cox model, log(–log[survival]) plot and Schoenfeld residual plot were used to validate the proportional hazards assumption. If any variable could not satisfy the assumption, a time-dependent Cox regression analysis was performed. The multivariable models for overall population and for subgroup analysis were adjusted for age and sex.

Table 2. LAAC Procedure Detail of Patients With Different LAA Orifice Diameter

Detail	Overall, n=302	Q1 OD≤18.0, n=78	Q2 18.0<OD≤20.7, n=83	Q3 20.7<OD≤23.3, n=66	Q4 OD>23.3, n=75	*P* for trend
LAAC procedure time, min	47.8±16.2	48.1±15.4	46.9±17.3	49.2±14.6	47.4±13.8	0.476
Concomitant PVI, n (%)	177 (58.6)	46 (59.0)	51 (61.4)	42 (63.6)	38 (50.7)	0.356
Plug occluder, n (%)	225 (74.5)	65 (83.3)	63 (75.9)	54 (81.8)	43 (57.3)	0.001*
Disc size (pacifier), mm	34.0 [30.0–36.0]	30.0 [26.0–32.0]	32.0 [30.0–34.0]	34.0 [31.0–36.0]	36.0 [34.0–38.0]	<0.001*
Compression ratio (plug), %	20.9 [17.0–25.0]	20.0 [17.0–25.0]	21.0 [17.5–26.0]	20.0 [17.0–23.2]	20.9 [17.0–25.0]	0.588
Recapture, n (%)	58 (19.2)	7 (9.0)	20 (24.0)	14 (21.2)	17 (22.7)	0.061
Resize, n (%)	27 (8.9)	7 (9.0)	7 (8.4)	7 (10.6)	6 (8.0)	0.080
Postprocedural residual flow, n (%)	14 (4.6)	2 (2.6)	4 (4.8)	4 (6.1)	4 (4.6)	0.383
Remnant LAA, n (%)	2 (0.7)	1 (1.3)	0	1 (1.5)	0	0.572
Protruded occluder, n (%)	3 (1.0)	1 (1.3)	0	2 (3.0)	0	0.848
Periprocedural complication, n (%)	11 (3.6)	3 (3.8)	2 (2.4)	5 (7.6)	1 (1.3)	0.779
Pericardial effusion	5 (1.7)	2 (2.6)	0	3 (4.5)	0	0.608
Cardiac tamponade	1 (0.3)	1 (1.3)	0	0	0	0.594
Occluder detached from LAA	1 (0.3)	0	0	1 (1.5)	0	0.689
Circumflex artery compressed	1 (0.3)	0	0	1 (1.5)	0	0.689
TEE follow-up at the third month, patients (%)	220 (72.8)	60 (76.9)	58 (69.9)	47 (71.2)	55 (73.3)	0.684
Residual flow, n (%)	14 (6.4)	4 (6.7)	3 (5.2)	3 (6.4)	4 (7.3)	0.841
≥3 mm, n (%)	6 (2.7)	1 (1.7)	1 (1.7)	1 (2.1)	3 (5.5)	0.290
<3 mm, n (%)	8 (3.6)	3 (5.0)	2 (3.4)	2 (4.2)	1 (1.8)	0.428
Device related thrombosis, n (%)	2 (0.9)	0	1 (1.7)	0	1 (1.8)	0.498

LAA indicates left atrial appendage; LAAC, left atrial appendage closure; OD, orifice diameter; PVI, pulmonary vein isolation; Q, quartile; and TEE, transesophageal echocardiography.
*Significant *P* value.

Table 3. Primary Follow-Up Events After LAA Closure Procedure

Event	Events (rate*)					LAA OD, quartile		LAA OD, cutoff	
	Overall, n=282	Q1, n=72	Q2, n=79	Q3, n=61	Q4, n=70	HR (95% CI)	*P* value	HR (95% CI)	*P* value
MACCE	45/850.1 (5.3%)	10/226.5 (4.4%)	9/247.2 (3.6%)	5/197.8 (2.5%)	21/178.5 (11.8%)	1.407 (1.072, 7.847)†	0.014†‡	3.580 (1.989, 6.445)†	<0.001†‡
AHF, NYHA III–IV	32/840.6 (3.8%)	7/226.8 (3.1%)	6/244.0 (2.5%)	4/195.1 (2.1%)	15/174.7 (8.6%)	2.111 (1.444, 3.088)	<0.001‡	8.253 (3.687, 18.476)	<0.001‡
AHF	53/826 (6.4%)	14/216.6 (6.5%)	10/240.1 (4.2%)	7/194.6 (3.6%)	22/174.6 (12.6%)	1.267 (0.992, 1.618)	0.058	3.743 (2.158, 6.493)	<0.001‡
Thromboembolic event	29/875.5 (3.3%)	7/231.5 (3.0%)	6/243.7 (2.5%)	3/204.7 (1.5%)	13/195.6 (6.6%)	1.289 (0.923, 1.801)	0.136	3.765 (1.796, 7.894)	<0.001‡
Stroke	12/840.7 (1.4%)	4/224.2 (1.8%)	2/244.0 (0.8%)	0/195.1 (0%)	6/177.5 (3.4%)	0.985 (0.642, 1.511)	0.946	7.995 (2.332, 27.413)	<0.001‡
Ischemic	9/899.5 (1.0%)	4/237.1 (1.7%)	1/249.5 (0.4%)	0/209 (0%)	4/204 (2.0%)	0.929 (0.501, 1.721)	0.815	2.962 (0.791, 11.093)†	0.107†
Hemorrhagic	4/899.5 (0.4%)	1/237.1 (0.4%)	1/249.5 (0.4%)	0/209 (0%)	2/204 (1.0%)	1.276 (0.525, 3.102)	0.591	3.904 (0.494, 30.830)	0.197
Major hemorrhage	5/919.1 (0.5%)	1/245.0 (0.4%)	1/257.5 (0.4%)	0/208.4 (0%)	3/208.3 (1.4%)	1.134 (0.448, 2.871)	0.791	4.885 (0.717, 32.299)	0.105

AHF indicates acute heart failure; HR, hazard ratio; LAA, left atrial appendage; MACCE, major adverse cardiocerebrovascular events; NYHA, New York Heart Association; OD, orifice diameter; and Q, quartile.

*Incidence rate was calculated as event per 100 patient-years.

†HR (95% CI) and *P* value were generated by time-fixed Cox proportional hazard model because they satisfy the proportional hazard assumption. HR (95% CI) and *P* value of other variables were calculated by time-dependent Cox proportional hazard model.

‡Significant *P* value.

To reduce bias of baseline characteristics between large-LAA and small-LAA groups, 1:1 greedy propensity-score matching was performed. Significantly different baseline variables including age, sex, body mass index, AF type, occluder type, concomitant PVI, previous history of HF, LAVI, left ventricular mass index, ratio of mitral inflow velocity and average mitral valve velocity, and LVEF were incorporated in a multivariable logistic regression model to generate propensity scores and matched by greedy algorithm.

A 2-sided $P<0.05$ was considered statistically significant. SAS 9.4 software (SAS Institute, Cary, NC) was used to conduct the analysis.

RESULTS

To reveal the correlation of LAA orifice diameter with other clinical parameters, 302 patients were included. Based on quartiles of LAA orifice diameter, the cohort was divided into 4 groups, Q1 (≤18.0 mm), Q2 (18.0–20.7 mm), Q3 (20.7–23.3 mm), and Q4 (>23.3 mm). The average ages were similar, whereas Q4 had a nonsignificant higher proportion of men (66.7%, *P*=0.092). Patients in Q4 had a worse condition, including a higher proportion of persistent AF (77.3%, *P*=0.076), greater extent of diastolic dysfunction (ratio of mitral inflow velocity and average mitral valve velocity=15.4 [11.2–17.5], *P*=0.046), and lower LVEF (56.4% [52.9%–62.5%], *P*=0.013). A higher prevalence of spontaneous echo contrast was observed in Q4 (34.7%, *P*=0.004). Detailed baseline information is listed in Table 1. Correlation analysis showed that LAA orifice diameter had a weak positive correlation with LAVI (*r*=0.157, *P*=0.017), left ventricular mass index (*r*=0.136, *P*=0.040), ratio of mitral inflow velocity and average mitral valve velocity (*r*=0.135, *P*=0.019), and a weak negative correlation with LVEF (*r*=−0.130, *P*=0.024) (Figure 2).

With regard to LAAC procedural information, a pacifier occluder was preferable for closing a large LAA (42.7%, *P*=0.001). Meanwhile, the incidence of periprocedural complications and postprocedural residual flow were comparable among the 4 quartile groups. Among 220 (72.8%) patients undergoing TEE examination at the third month, no difference was found in residual flow, device-related thrombosis, or other complications. Detailed information is listed in Table 2. AF ablation parameters were similar among the groups, as displayed in Table S1.

Postprocedural medication and management are displayed in Table S2. The antithromboembolic regimen was comparable among the 4 groups. For AF rhythm and rate management, 202 (66.9%) patients had either PVI or antiarrhythmic drugs for rhythm

Table 4. Detailed Follow-Up Outcome After Left Atrial Appendage Closure

Outcome	Overall, n=282	Q1 OD ≤18.0, n=72	Q2 18.0<OD≤20.7, n=79	Q3 20.7<OD≤23.3, n=61	Q4 OD>23.3, n=70	*P* for trend
Thromboembolic event	29 (10.3)	7 (9.7)	6 (7.6)	7 (11.5)	9 (12.9)	0.073
Ischemic/hemorrhagic stroke/transient ischemic attack	19 (6.7)	4 (5.6)	5 (6.3)	4 (6.6)	6 (8.6)	0.850
Pulmonary embolism	1 (0.4)	0	0	1 (1.6)	0	1.000
Perivascular thrombosis	9 (3.2)	3 (4.2)	1 (1.3)	3 (4.9)	2 (2.9)	0.278
Major hemorrhagic event	5 (1.8)	1 (1.4)	1 (1.3)	0	3 (4.3)	0.290
MACCE	45 (16.0)	10 (13.9)	9 (11.4)	5 (8.2)	21 (30.0)	0.014*
All-cause mortality	4 (1.4)	0	3 (3.8)	0	1 (1.4)	0.886
Ischemic/hemorrhagic stroke	12 (4.3)	4 (5.6)	2 (2.5)	0	6 (8.6)	0.423
AHF, NYHA III–IV	32 (11.3)	7 (9.7)	6 (7.6)	4 (6.6)	15 (21.4)	0.027*
Cardiac tamponade	2 (0.7)	0	1 (1.3)	1 (1.6)	0	0.242
Malignant arrhythmia	0	0	0	0	0	1.000
Acute myocardial infarction	1 (0.4)	1 (1.4)	0	0	0	1.000
Rehospitalization						
CVD admission	98 (34.8)	24 (33.3)	24 (30.4)	16 (26.2)	34 (48.6)	0.005*
AHF admission	53 (18.8)	14 (19.4)	10 (12.7)	7 (11.5)	22 (31.4)	0.070
AF/atrial flutter admission	53 (18.8)	12 (16.7)	9 (11.4)	10 (16.4)	22 (31.4)	<0.001*
Rhythm/rate control outcome						
AF recurrence	76 (27.0)	17 (23.6)	18 (22.8)	14 (23.0)	27 (38.6)	0.052
AF recurrence after ablation	42/166 (25.3)	9/43 (20.9)	10/48 (20.8)	8/39 (20.5)	15/36 (41.7)	0.054
AF recurrence after AADs	4/23 (17.4)	1/6 (16.7)	1/4 (25.0)	1/4 (25.0)	1/9 (11.1)	0.727
Uncontrolled rate	2/101 (2.0)	0	0	1 (5.3)	1 (3.2)	0.242

AADs indicates antiarrhythmic drugs; AF, atrial fibrillation; AHF, acute heart failure; CVD, cardiovascular disease; MACCE, major adverse cardiocerebrovascular events; NYHA, New York Heart Association; OD, orifice diameter; and Q, quartile.

*Significant *P* value.

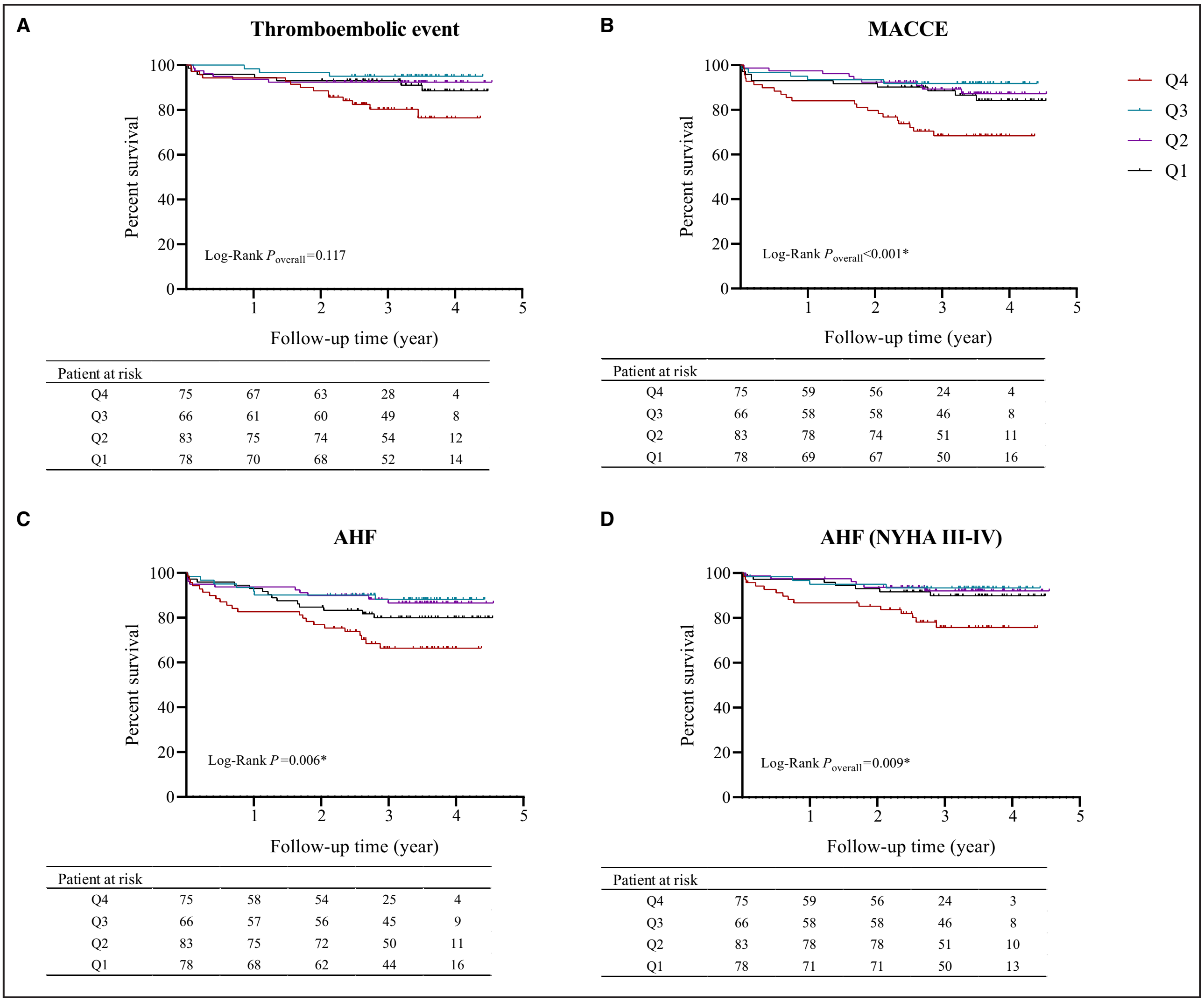

Figure 3. Survival of thromboembolic events, MACCE, AHF, and AHF with NYHA III–IV among 4 quartile groups divided by LAA orifice diameter.

A, Survival curve for thromboembolic events; no significant difference was observed among groups. **B**, Survival curve for MACCE showed survival rate in quartile (Q) 4 was significantly lower than other groups. **C** and **D**, Survival curves for AHF showed survival rates of overall AHF and AHF with NYHA III to IV were significantly lower in Q4. AHF indicates acute heart failure; LAA, left atrial appendage; MACCE, major adverse cerebrocardiovascular events; and NYHA, New York Heart Association. *significant *P* value.

control, 109 (36.1%) had rate control, and 38 (12.6%) patients had neither rhythm nor rate control. Of note, there was a nonsignificant higher proportion of antiarrhythmic drugs and correspondingly lower proportion of ablation for rhythm control in Q4.

Over the course of 39.6±8.4 months, 20 (6.6%) patients were lost to follow-up. Incidence of primary follow-up events are listed in Table 3, and detailed follow-up results are listed in Table 4. For stroke prevention, overall stroke incidence was 1.4% per 100 patient-years, with the highest incidence in Q4 of 3.4% per 100 patient-years. There was no significant difference among the 4 groups (Table 3). In terms of AF management outcome, higher AF recurrence in Q4 was observed in the overall population (38.6%, P=0.052) and in patients who underwent PVI (41.7%, P=0.054) (Table 4).

When comparing the survival of MACCE (Figure 3), Q4 presented the worst survival rate among the 4 quartiles (log-rank $P_{overall}$<0.001), contributed to by a significant higher incidence of AHF with NYHA III to IV (30.0%, log-rank $P_{overall}$=0.009). In addition, survival of overall AHF, cardiovascular disease, and atrial tachycardia rehospitalization were also significantly lower in Q4, and AF recurrence was higher in Q4 (Figure 4). Using receiver operating characteristic analysis for MACCE (Figure S1), an LAA orifice diameter cutoff value of 23.6 mm was chosen (sensitivity of 46.7% and specificity of 80.2%), and patients with a large LAA (orifice diameter ≥23.6 mm) had significantly worse

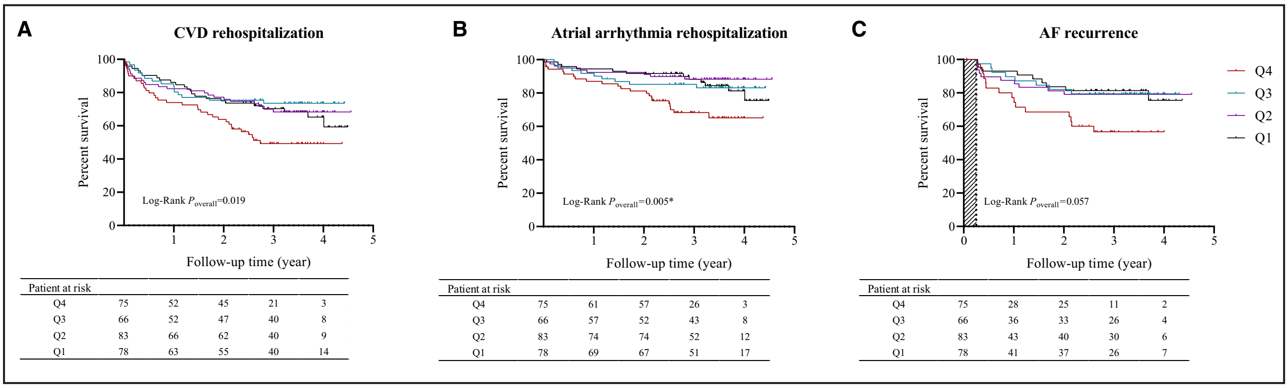

Figure 4. Survival of rehospitalization because of CVD (A), atrial arrhythmia (B), and AF recurrence for patients who underwent concomitant AF ablation (C).

Shadowed area in (**C**) indicates 3-month blank period. AF indicates atrial fibrillation; and CVD, cardiovascular diseases. *significant *P* value.

survival rate of MACCE, AHF with NYHA III to IV, and overall AHF events (Figure 5).

To investigate the contribution of potential confounding factors to post-LAAC AHF, we first compared survival curves of AHF NHA III to IV for patient groups divided by those factors, indicating that a previous history of HF, diabetes, occlude type, and rhythm/rate control outcome contributed significantly to AHF NHA III to IV occurrence. Results are shown in Figure S2. An age- and sex-adjusted multivariable Cox model for MACCE showed that age, occulder type, previous history of diabetes, LAVI, LAA depth, and orifice diameter were predictors for post-LAAC AHF. Notably, LAA orifice diameter showed a significant hazard ratio of 3.749 (95% CI, 2.074–6.779) (Figure 6). To confirm large LAA orifice diameter per se rather than other confounding factors that could result in higher incidence of post-LAAC AHF, we performed subgroup analysis of LAA orifice cutoff groups, as shown in Figure 7. The results indicated that a large LAA orifice could still predict MACCE after LAAC in subgroups divided by previous history of HF and diabetes, occluder type, and procedure type (concomitant PVI), except in patients aged <65 years, patients with paroxysmal AF, and patients with failed rhythm/rate control outcome. No significant interaction was found in LAA orifice diameter with other confounding variables for MACCE occurrence.

Moreover, we matched patients with a small LAA to patients with a large LAA using propensity-score matching that rendered baseline and procedure information comparable (Table 5). Further survival analysis showed that the incidence of AHF with NYHA III to IV of the large-LAA group remained significantly higher than the matched small-LAA group (Figure 5).

In addition, comparing the change of NT-proBNP level and echocardiographic indexes during follow-up between matched groups, only the level of NT-proBNP at the third month of the large-LAA group was significantly higher than baseline level, whereas the change of LAVI and LVEF were nonsignificant (Figure 8).

DISCUSSION

In the present study, we explored the correlation of LAA orifice diameter with other clinical variables, and we comparatively evaluated the outcomes of patients with different LAA sizes after LAAC. Our major findings are as follows: (1) Patients with a larger LAA orifice had a worse condition. (2) Patients with a larger LAA orifice presented worse survival for MACCE, resulting from a higher incidence of AHF, although no difference in periprocedural complication and thromboembolic events. (3) A comparison of propensity-score matched groups showed that a large LAA orifice could be an independent risk factor for post-LAAC AHF events.

Although successive clinical trials like PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy),[17] EWOLUTION (Registry on WATCHMAN Outcomes in Real-Life Utilization),[18] and PRAGUE-17 (Left Atrial Appendage Closure versus Novel Anticoagulation Agents in Atrial Fibrillation)[19] have provided promising evidence toward the safety and efficacy of LAAC for preventing thromboembolic events and reducing the risk of bleeding, studies reported that some patients presented poor prognosis after LAAC. In 2019, Schneider et al reported an onset of acute decompensated HF after LAAC in a 79-year-old woman, stressing their concern of developing HF after LAAC.[20] More recently, 3 small-sized studies reported significant occurrence of post-LAAC HF ranging from 16% (16/106) to 23.9% (16/67).[6–8] In line with previous findings, we also observed an incidence of post-LAAC HF of 17.5%, including 10.6% with NYHA class III to IV. It

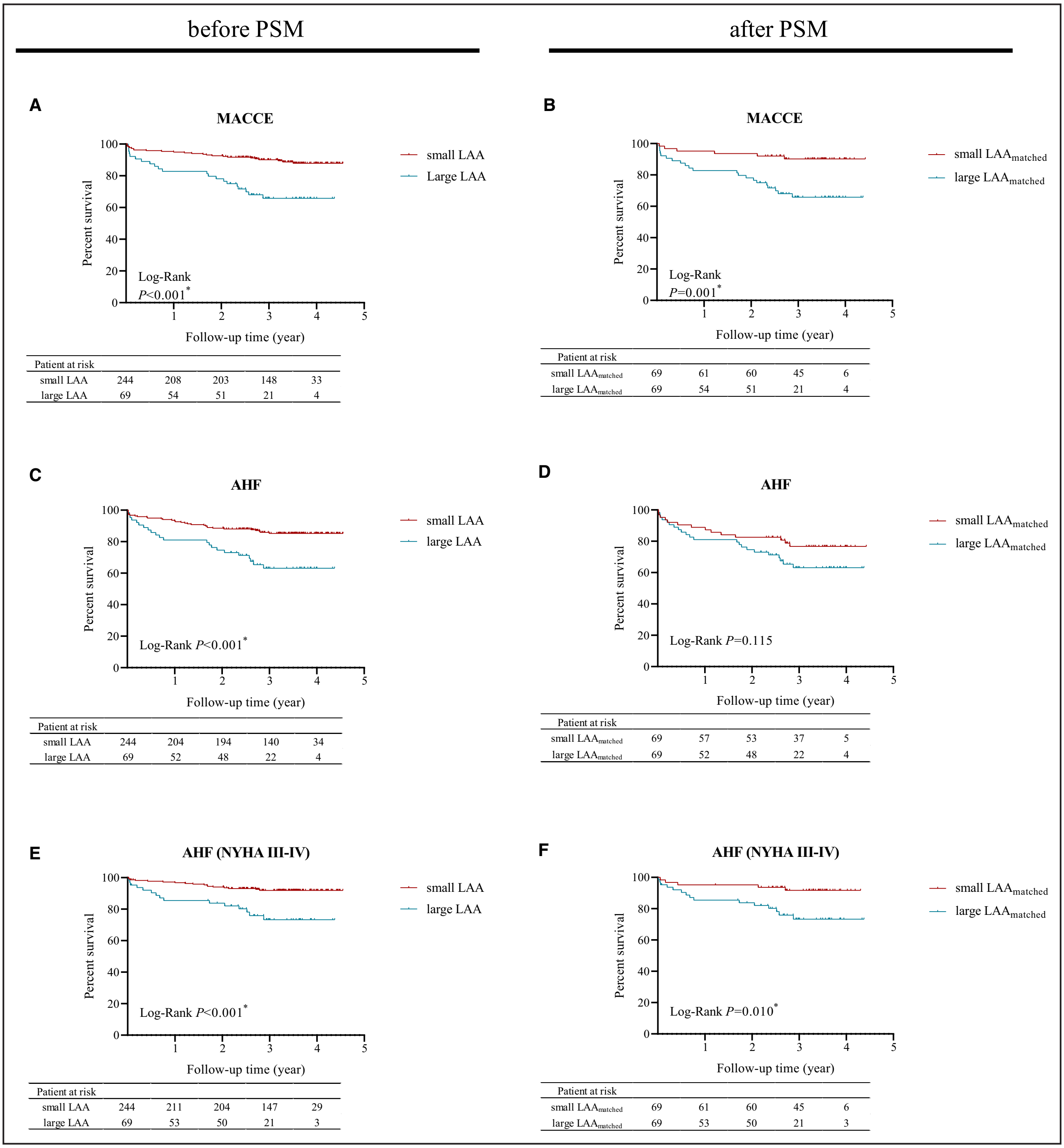

Figure 5. Survival curves of patients grouped by cutoff value of LAA orifice diameter before (left) and after PSM (right).
A and **B**, After PSM-adjusted baseline characteristics, survival rates of MACCE were still significantly lower in the large-LAA group. **C** and **D**, survival rates of overall AHF became nonsignificant after PSM. **E** and **F**, Survival rates of AHF with NYHA III to IV remained significantly lower in the large-LAA group. AHF indicates acute heart failure; LAA, left atrial appendage; MACCE, major adverse cardiocerebrovascular events; NYHA, New York Heart Association; and PSM, propensity-score matching. *significant *P* value.

should be noted that HF after LAAC is not uncommon and warrants further investigation.

Currently, the role of LAA dimensions in predicting a post-LAAC HF event has not yet been assessed. As mentioned, occlusion of the LAA would impair the total reservoir capacity of LA and increase the volume load of the remaining LA chamber,[4] whereas the outcome of such volume reduction depends on both the contribution of LAA as a volume reservoir before occlusion and the adaptive capacity of the remaining LA and left ventricle. On one hand, an LAA with larger volumes receives more blood, and by occluding large a LAA, the

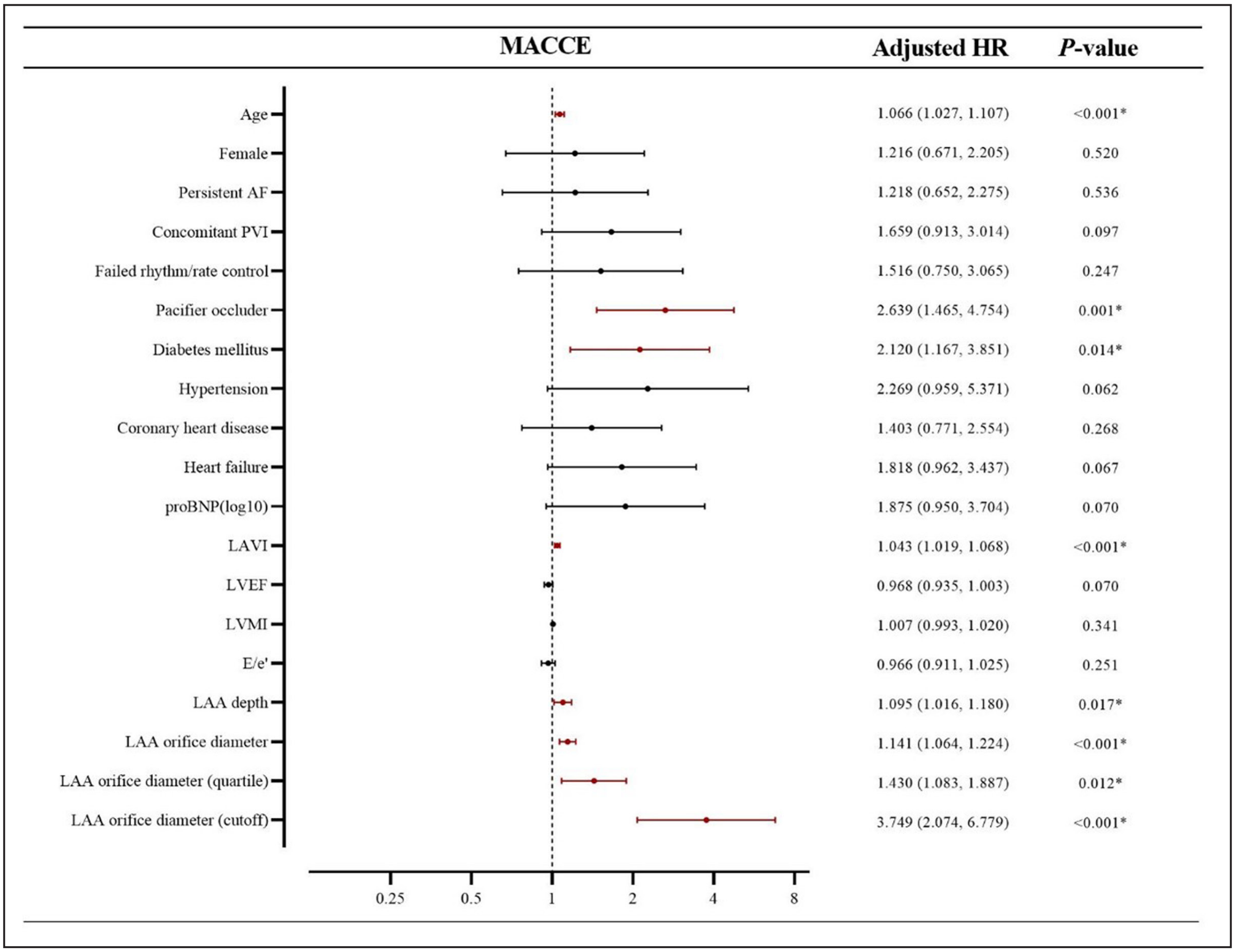

Figure 6. Forest plot of age- and sex-adjusted hazard ratio for MACCE by multivariable Cox proportional hazard model.
Red bar indicates significant hazard ratio >1. AF indicates atrial fibrillation; E/e′, ratio of mitral inflow velocity (E) and average mitral valve velocity (e′); HR, hazard ratio; LAA, left atrial appendage; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MACCE, major adverse cardiocerebrovascular events; proBNP, pro-B-type natriuretic peptide; and PVI, pulmonary vein isolation. *significant *P* value.

heart is rendered more vulnerable to excessive volume load. Although a large LAA could be inborn, an LAA could also become maladaptively enlarged under concurrent cardiac abnormalities such as persistent AF,[21] which might further worsen the outcomes of LAAC. On the other hand, for patients with a larger LAA, we also found worse baseline conditions. Greater LA and left ventricular remodeling would further weaken the adaptive capacity in response to volume overload. As the results show in our study, a large LAA orifice per se could be an independent risk factor for post-LAAC, AHF, NYHA III to IV event in most patients, providing clinical support that LAAC might impair the LA and cause worsened outcome. However, we found that LAA orifice diameter could not predict MACCE in subgroups of those aged <65 years with paroxysmal AF and failed rhythm/rate control outcome before AHF. Because the development of post-LAAC AHF is multifactorial, we think such results are reasonable because (1) younger patients and patients with paroxysmal AF had better atrial function, and volume reduction by LAAC might be well compensated; (2) failed rhythm/rate control adds insult to injury that uncontrolled rhythm/rate becomes a dominant contributor for post-LAAC AHF. Limited to the sample size and design of this study, we were unable to further confirm the contribution of LAA orifice for AHF in those subgroups. Future studies are warranted to investigate the role of LAA dimensions in those subgroups. Collectively, patients with larger LAA dimensions are under a high risk of developing AHF after LAAC, and the decision to perform LAAC should be taken with caution.

Notably, for patients with a large LAA who are eligible for LAAC, their situation presents a dilemma, namely that a large LAA poses a high risk of thromboembolism[22] but also a higher risk of developing

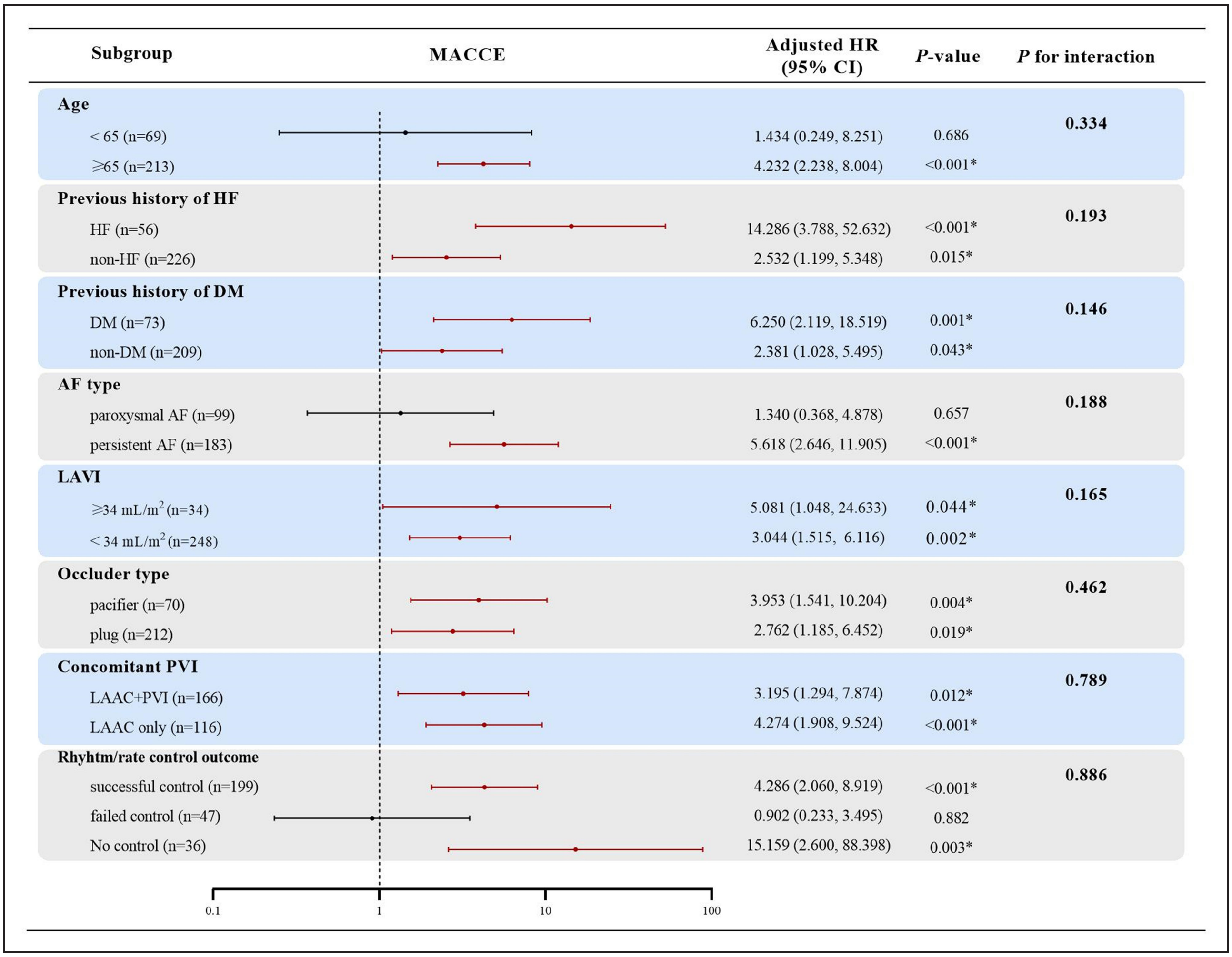

Figure 7. Subgroup analysis of LAA orifice diameter cutoff groups for MACCE by multivariable Cox proportional hazard model.

Hazard ratio of LAA orifice cutoff groups was adjusted for age and sex. Red bar indicates significant hazard ratio >1. AF indicates atrial fibrillation; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; LAA, left atrial appendage; LAAC, left atrial appendage closure; LAVI, left atrial volume index; MACCE, major adverse cardiocerebrovascular events; and PVI, pulmonary vein isolation.

HF after LAAC. Previous studies have found that a bulged LAA not only correlates with reduced blood flow velocity, but also promotes platelet activation,[23] eventually resulting in a hypercoagulable state. In the present study, we also observed a higher prevalence of spontaneous echo contrast and a higher incidence of stroke after LAAC in patients with a large LAA. Therefore, patients with a large LAA are under a higher risk for stroke, and more intense stroke prevention management should be implemented. However, for patients with a large LAA, not only the benefit of stroke prevention by LAAC, but the development of post-LAAC AHF should be considered. The decision of LAAC in patients with high risk of HF (large LAA, prior HF, lower LVEF) should be taken with caution. If LAAC is decided for those patients, more intense monitoring of HF should be as important as stroke prevention for follow-up management. As the LAA exerts a secretory function, closure of the LAA could alter the expression pattern of brain type natriuretic peptide,[24] and routine measurement of brain type natriuretic peptide might not reflect the patient's real condition. Results from PRAGUE-17 trial showed no difference in several HF biomarkers including both brain and atrial-type natriuretic peptide.[25] Further investigation is required into the valuable biomarkers for monitoring following LAAC HF events. Moreover, AF ablation for rhythm control should be carefully considered for patients with a large LAA. Large LAA volume poses a higher risk for recurrence after AF ablation.[26] Similarly, we found that patients with a large LAA had a higher recurrence after concomitant cryoballoon ablation. Although the association between ablation and recurrence rates has not yet been elucidated, these higher recurrence rates should be considered when making the decision.

Table 5. The Comparison Between Groups With Large and Small LAA Before and After Propensity-Score Matching

	Large LAA, OD ≥23.6 mm, n=69	Small LAA, OD <23.6 mm, n=233	*P* value	Small $LAA_{matched}$, OD<23.6 mm, n=69	*P* value
Age, y	71.8±8.3	71±8.8	0.516	70.9±8.9	0.540
Men, n (%)	47 (68.1)	134 (54.9)	0.114	48 (69.6)	0.854
Body mass index, kg/m^2	25.7±3.2	25.6±3.6	0.843	25.6±3.0	0.918
Persistent AF, n (%)	55 (79.7)	155 (63.5)	0.006*	58 (84.1)	0.507
CHA_2DS_2-VASc	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	0.425	4.0 [3.0, 5.0]	0.462
HAS-BLED	2.0 [2.0, 3.0]	2.0 [2.0, 3.0]	0.959	2.0 [2.0, 3.0]	0.873
NT-proBNP, pg/mL	935.1 [462.5–1769.0]	722.3 [332.6–1389.3]	0.020*	1009.5 [457.4–1570.3]	0.880
Previous illness, n (%)					
Stroke	22 (31.9)	79 (32.4)	0.755	25 (36.2)	0.590
Cerebral infarction	21 (30.4)	77 (31.6)	0.684	23 (33.3)	0.715
Intracranial hemorrhage	1 (1.4)	9 (3.7)	0.325	2 (2.9)	0.556
Heart failure	19 (19.9)	22 (27.5)	0.069	41 (16.8)	0.576
Hypertension	51 (73.5)	171 (73.9)	0.931	56 (70.1)	0.308
Diabetes	28 (25.8)	50 (40.6)	0.001*	28 (20.5)	1.000
Perivascular disease	4 (5.6)	13 (5.8)	0.945	3 (5.3)	0.698
Coronary heart disease	23 (30.8)	70 (33.3)	0.603	27 (28.7)	0.479
Echocardiographic measurement					
LAVI, mL/m^2	27.0 [22.9–33.9]	24.5 [19.0–29.8]	0.007*	27.1 [24.4–32.7]	0.645
LVEF, %	56.0 [51.8–62.5]	59.2 [55.0–63.8]	0.003*	58.0 [52.5–62.4]	0.432
LVEF group, n (%)			0.056		0.759
>50%	56 (81.2)	213 (91.4)		57 (82.6)	
40%–50%	5 (7.2)	8 (3.4)		3 (4.3)	
≤40%	8 (11.6)	12 (5.2)		9 (13.0)	
LVMI, g/m^2	101.7 [88.6–119.0]	95.0 [84.7–105.5]	0.021*	100.7 [90.7–111.0]	0.608
LV hypertrophy, n (%)	16 (23.2)	31 (13.3)	0.047*	13 (18.8)	0.531
E/e′	15.0 [11.0–17.0]	12.0 [10.0–17.0]	0.008*	13.0 [10.0–18.0]	0.287
E/e′ group, n (%)			0.003*		0.055
≥14	37 (53.6)	73 (31.3)		25 (36.2)	
7–14, n (%)	28 (40.6)	144 (61.8)		42 (60.9)	
<7, n (%)	4 (5.8)	16 (6.9)		2 (2.9)	
LAA measurement					
Mean LAA orifice diameter, mm	26.3 [25.0–28.0]	20.0 [17.3–21.5]	<0.001*	20.0 [17.3–21.3]	<0.001*
Mean LAA depth, mm	24.0 [21.3–26.7]	20.3 [18.0–22.7]	<0.001*	21.0 [19.0–23.0]	<0.001*
Spontaneous echo contrast, n (%)	25 (36.2)	43 (18.5)	0.002*	22 (31.9)	0.590
Treatment, n (%)					
Rhythm/rate control	61 (88.4)	203 (87.1)	0.778	57 (82.6)	0.333
Rhythm control	42 (60.9)	160 (68.7)	0.227	39 (56.5)	0.604
Concomitant PVI	33 (47.8)	144 (59.0)	0.038*	33 (47.8)	1.000
I/III AADs	9 (13.0)	16 (6.9)	0.102	6 (8.7)	0.412
Rate control	34 (49.3)	75 (32.2)	0.009*	29 (42.0)	0.393
Plug occluder	38 (55.1)	187 (80.3)	<0.001*	42 (60.9)	0.490
Rhythm/rate control outcome					
AF recurrence	25/64 (39.1)	51/218 (23.4)	0.013*	19/63 (30.2)	0.292
AF recurrence after ablation	13/31 (41.9)	29/135 (21.5)	0.018*	10/30 (33.3)	0.488
AF recurrence after AADs	1/8 (34.8)	3/15 (20.0)	1.000	1/5 (20.0)	1.000
Uncontrolled rate	1/31 (3.2)	1/70 (1.4)	1.000	1/27 (3.7)	1.000

HAS-BLED a score to evaluate major bleeding risk for atrial fibrillation population incoporating hypertension, abnormal liver/kidney function, stroke history, bleeding history, labile international normalized ratio, elder age, and drug predisposing bleeding/alcohol abuse.

AADs indicates antiarrhythmic drugs; AF, atrial fibrillation; E/e′, ratio of mitral inflow velocity (E) and average mitral valve velocity (e′); LAA, left atrial appendage; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OD, orifice diameter; and PVI, pulmonary vein isolation.[2]

*Significant *P* value.

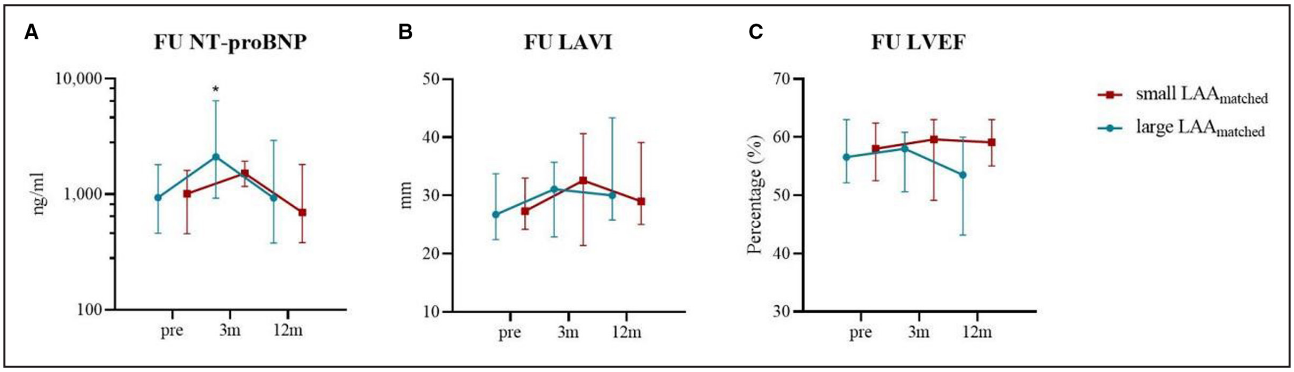

Figure 8. Change of NT-proBNP and echocardiographic measurements of matched groups during follow-up.
A, Level of NT-proBNP was increased at the third month and fell back to baseline level, whereas only the increased level of NT-proBNP of the large-LAA group at the third month was statistically significant. Neither the change of LAVI (**B**) nor LVEF (**C**) showed significance at the third month and 1 year. Asterisk (*) indicates $P<0.05$. FU indicates follow-up; LAA indicates left atrial appendage; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Limitations

The results of this study should be interpreted with caution. First, the sample size of our study is limited. Hence, the incidence rate of the 4 quartile groups might be biased, and only age and sex were adjusted considering overfitting in the multivariable Cox model. The occurrence of AHF is multifactorial, and ablation strategy, rhythm/rate control outcome, and occlude choice could confound the results. The present study included patients who underwent only PVI, and efficacy might be compromised for patients with long-term persistent AF. The predictive value of LAA orifice diameter was not significant in patients with failed rhythm/rate control. In addition, a different occluder type is also an important confounding factor, because a pacifier device (LAmbre) could possibly cause more volume reduction compared with a plug device. Though we attempted to minimize confounding by subgroup analysis and propensity-score matching, our study showed no significant interference with our primary conclusion, and we are unable to verify whether factors other than LAA orifice, different ablation strategy, rhythm/rate control outcome, and occluder type could lead to a worse atrial function and subsequently worse prognosis. Future well-designed randomized studies are needed to address these important issues.

Second, our results were based on a comparison of 1:1 matched small-LAA groups to large-LAA groups with comparable baseline characteristics, whereas future well-designed trials are needed to provide stronger evidence. In addition, because this studied cohort was not designed to monitor the progression of HF, follow-up echocardiography and HF biomarker examination were not routinely performed. Therefore, follow-up change of echocardiographic and NT-proBNP measurement could be biased. Orifice diameter cannot comprehensively reflect the dimensional feature of LAA, because the LAA varies in shape and depth. Moreover, LAA dimension depends on volume load, because the LAA orifice and depth would enlarge following fluid infusion.[27] Further studies using imaging modalities like computed tomography and magnetic resonance imaging are warranted to precisely investigate the importance of LAA dimensional features. Last, we lack a control group without LAAC, which could further strengthen the conclusion of the study. Future well-designed controlled studies with comprehensive echocardiographic evaluation are needed to illustrate the impact of LAAC on atrial function and prognosis.

CONCLUSIONS

Patients with a larger LAA orifice had worse conditions, and presented worse prognoses after the LAAC procedure, primarily arising from a high incidence of AHF. A large LAA orifice could be an independent risk factor for developing post-LAAC AHF in most patients, except for patients aged <65 years, patients with paroxysmal AF, and/or patients with failed rhythm/rate control.

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Patient enrollment

patients with AF who underwent LAAC were consecutively enrolled on the study. Patients who had undergone pulmonary vein isolation combined with LAAC were from the registered study, Combining Left Atrial Appendage Closure With Cryoballoon Ablation in the Chinese Population (CLACBAC, No.NCT04185142). The diagnosis of AF was referred to 2016 ESC guideline of AF management [9]: irregular RR intervals and no discernible, distinct P waves lasting longer than 30 seconds recorded by electrocardiogram. Paroxysmal AF was defined as self-terminating AF within 48 hours or AF cardioverted within 7 days, while persistent AF was defined as AF that last longer than 7 days. Patients who were eligible for LAAC procedure must fulfill at least one of the following conditions [10]:

a. High stroke risk (CHA_2DS_2-VASc score ≥ 2) and/or high bleeding risk (HAS-BLED score ≥ 3) ;

b. Contraindications to long-term oral anti-coagulants (OACs) (active major hemorrhagic diseases, inherited hemorrhagic disorders, or severe side effects under OAC therapy)

c. Refusal of OACs according to personal willingness despite comprehensive explanation.

Inclusion criteria of this study were:

a. patients diagnosed with AF;

b. patients having undergone successful percutaneous LAAC procedure.

Exclusion criteria were:

a. patients with history of valvular heart disease;

b. patients with concomitant arrhythmia except AF required extrapulmonary vein ablation (concomitant LA posterior wall ablation, mitral isthmus ablation, cavo-tricuspid isthmus ablation);

c. patients underwent other concomitant procedures except pulmonary vein isolation (pacemaker implantation, atrial septal defect closure, percutaneous coronary intervention);

d. failed occluder implantation due to any reason (oversized LAA, severe adverse event during transseptal puncture, prior ablation or before occluder implanted);

e. patients whose echocardiographic data cannot be retraced;

f. patients enrolled in other clinical trials.

Data collection

Demographic information, history of illness, medications, laboratory results, and echocardiographic data were retraced from medical records. Baseline level of NT-proBNP was measured from peripheral blood sample that collected before any treatment. Transthoracic echocardiography was done within 24 hours after admission.

Transthoracic echocardiography (GE Vivid E9 or Philips EPIQ 7C) was performed and indexes were measured according to JASE consensus [12]. LV diastolic and systolic volume was measured by biplane disc summation method and left ventricle (LV) ejection fraction (LVEF) was calculated as:

$$\text{LVEF} = \frac{\text{LV end diastolic volume} - \text{LV end systolic volume}}{\text{LV end diastolic volume}}\ \%$$

Maximum LA volume and LA volume index (LAVI) was measured by biplane summation method excluding pulmonary veins and LAA. Left ventricle mass and LVM index (LVMI) was calculated using cube formula as:

$$\text{LV mass} = 0.8 \times 1.4 \times [(\text{IVS} + \text{LV diastolic diameter} + \text{posterior wall thickness})^3 - (\text{LV diasolic diameter})^3] + 0.6 \text{ g},$$

$$\text{LVMI} = \frac{\text{LV mass}}{\text{body surface area}} \text{ g/m}^2.$$

LV hypertrophy was defined as LVMI $\geqslant$ 115 g/m^2 in male or LVMI $\geqslant$ 95 g/m^2 in female. Mitral inflow velocity (E) and lateral and septal mitral valve velocity (e') were obtained and E/e' was calculated.

Pulmonary vein isolation

Pulmonary vein isolation performed for the included patients of the study was accomplished using cryoballoon. Detailed procedure could be found in previously published results [14]. briefly, under local anesthesia with sedation, a transseptal puncture was performed and second generation cryoballoon (Arctic Front; Medtronic, MN) was advanced through a steerable sheath (FlexCath, Medtronic, MN) into the LA. After balloon inflated and complete pulmonary vein occlusion confirmed by angiography, cryo ablation was performed. Ablation followed the sequence from left superior pulmonary vein, left inferior pulmonary vein, right superior pulmonary vein to right inferior pulmonary vein. The freezing duration for each pulmonary vein was based on time to isolation (TTI): 150-180 s when TTI $\leq$ 30 s; 180 s When 30 s < TTI < 60 s; 180 s + 120 s when TTI >60 s or TTI was not recorded. During the freezing of the right superior and right inferior pulmonary veins, continuous phrenic pacing (8 - 10 V, pace interval 2000 ms) was applied to prevent phrenic palsy. During procedure, freezing was instantly halted once the patient complained severe discomfort including chest pain and vomiting. activated clotting time > 300 s was maintained during the procedure.

Definition of follow-up adverse event

Composite primary endpoints included thromboembolic events and major hemorrhagic events.

1. Thromboembolic events comprised cerebral infarction, transient ischemic attack and perivascular thrombosis confirmed by computed tomography or magnetic resonance imaging.

2. A major hemorrhagic event was defined as a drop of hemoglobin ≥ 2.0 g/dl within 24 hours, transfusion of ≥ 2 units of packed red cells, hemorrhage at a critical site, or lethal hemorrhage [16].

Secondary endpoints included 1. major adverse cardiocerebrovascular events (MACCE) including ischemic or hemorrhagic stroke, acute HF with New York Heart Association (NYHA) functional class grading III-IV, acute myocardial infarction, malignant arrhythmia, cardiac tamponade and all-cause mortality. Ischemic or hemorrhagic stroke was confirmed with imaging examination. 2. rehospitalization due to cardiovascular diseases (CVD), including clinically diagnosed coronary artery diseases, arrhythmia, HF and structrual heart diseases; 3. rehospitalization due to AHF; 4. rehospitalization due to atrial arrhythmia, including frequent premature atrial contraction, atrial tachycardia, atrial flutter and AF; 5. other cardiovascular events including bradycardia requiring pacemaker implantation and AF recurrence for patients who underwent concomitant pulmonary vein isolation (PVI). AF recurrence was defined as recorded atrial tachycardia, atrial flutter and/or AF lasting longer than 30 seconds after a 3-month blank period.

Table S1. Detailed parameters of pulmonary vein isolation by cryoballoon ablation.

	Overall (n=177)	Q1 OD≤18.0 (n=46)	Q2 18.0＜OD ≤ 20.7 (n=51)	Q3 20.7＜OD ≤ 23.3 (n=42)	Q4 OD＞23.3 (n=38)	*P*-value for trend
Procedure time, min	38.5±8.7	37.2±9.7	37.5±8.4	39.1±9.2	38.9±6.4	0.361
Pulmonary vein isolation rate, n (%)	177 (100)	46 (100)	51 (100)	42 (100)	38 (100)	1.000
Left superior pulmonary vein	177 (100)	46 (100)	51 (100)	42 (100)	38 (100)	1.000
Left inferior pulmonary vein	176 (99.4)	45 (97.8)	51 (100)	42 (100)	38 (100)	0.283
Right superior pulmonary vein	177 (100)	46 (100)	51 (100)	42 (100)	38 (100)	1.000
Right inferior pulmonary vein	176 (99.4)	45 (97.8)	51 (100)	42 (100)	38 (100)	0.283
Nadir temperature, °C						
Left superior pulmonary vein	-51.0 [-55.0, -	-52.0 [-55.0,	-52.0 [-55.0, -	-49.0 [-54.0, -	-51.0 [-54.5, -	0.249

	47.0]	47.0]	47.0]	46.0]	46.0]	
Left inferior pulmonary vein	-45.0 [-48.0, -43.0]	-46.0 [-51.0, -43.0]	-45.0 [-48.5, -43.0]	-45.0 [-47.0, -43.0]	-44.0 [-47.0, -42.0]	0.147
Right superior pulmonary vein	-53.0 [-56.0, -49.0]	-54.0 [-56.0, -51.0]	-53.0 [-56.0, -48.0]	-54.0 [-56.0, -49.0]	-52.0 [-56.0, -49.0]	0.368
Right inferior pulmonary vein	-48.0 [-53.0, -44.0]	-47.0 [-52.0, -43.0]	-49.0 [-54.0, -44.0]	-48.0 [-53.0, -44.0]	-48.0 [-52.0, -43.5]	0.482
Freezing duration, sec						
Left superior pulmonary vein	180.0 [180.0, 287.0]	180.0 [180.0, 240.0]	210.0 [180.0, 300.0]	180.0 [180.0, 281.0]	180.0 [180.0, 296.5]	0.371
Left inferior pulmonary vein	180.0 [180.0, 205.0]	180.0 [180.0, 220.0]	180.0 [180.0, 205.0]	180.0 [180.0, 180.0]	180.0 [180.0, 230.0]	0.524
Right superior pulmonary vein	180.0 [150.0, 180.0]	150.0 [120.0, 180.0]	180.0 [150.0, 180.0]	180.0 [120.0, 180.0]	180.0 [150.0, 180.0]	0.116

Right inferior pulmonary vein	180.0 [150.0, 180.0]	180.0 [150.0, 180.0]	180.0 [150.0, 233.0]	180.0 [150.0, 180.0]	180.0 [154.5, 180.0]	0.723
TTI, sec						
Left superior pulmonary vein	40.5 [30.0, 55.0]	42.0 [30.0, 55.0]	43.0 [34.0, 55.0]	39.0 [30.0, 45.0]	44.5 [35.0, 55.0]	0.084
Left inferior pulmonary vein	30.0 [24.5, 42.0]	30.0 [18.0, 42.0]	29.0 [25.0, 42.0]	30.0 [25.0, 45.0]	34.5 [30.0, 40.0]	0.182
Right superior pulmonary vein	28.0 [20.0, 40.0]	25.0 [22.0, 39.0]	30.0 [20.0, 42.0]	26.0 [20.0, 35.0]	27.0 [20.0, 45.0]	0.542
Right inferior pulmonary vein	39.5 [25.0, 52.0]	35.0 [20.0, 52.0]	35.0 [23.0, 50.0]	39.0 [26.0, 55.0]	40.0 [30.0, 56.0]	0.341

TTI denotes time to isolation.

Table S2. AF management strategy before discharge.

	Overall (n=302)	Q1 OD ≤ 18.0 (n=78)	Q2 18.0 < OD ≤ 20.7 (n=83)	Q3 20.7 < OD ≤ 23.3 (n=66)	Q4 OD > 23.3 (n=75)	*P* for trend
Rhythm control	202 (66.9)	52 (66.7)	56 (67.5)	46 (69.7)	48 (64.0)	0.802
Ablation	177 (58.6)	46 (59.0)	51 (61.5)	42 (63.6)	38 (50.7)	0.356
Anti-arrhythmic drugs *	25 (8.3)	6 (7.7)	5 (6.0)	4 (6.1)	10 (13.3)	0.221
Rate control	109 (36.1)	31 (39.7)	23 (27.7)	21 (31.8)	34 (45.3)	0.382
No rhythm/rate control	38 (12.6)	9 (11.5)	12 (14.5)	9 (13.6)	8 (10.7)	0.833
Anti-arrhythmic drugs*	240 (79.5)	61 (78.2)	60 (72.3)	55 (83.3)	64 (85.3)	0.118
Class I/III	154 (51.0)	36 (46.2)	44 (53.0)	37 (56.1)	37 (49.3)	0.635
Class II/IV	109 (36.1)	31 (39.7)	23 (27.7)	21 (31.8)	34 (45.3)	0.382
Anti-thromboembotic drugs						

New oral anticoagulants †	261 (86.4)	67 (85.9)	70 (84.3)	57 (86.4)	67 (89.3)	0.479
Warfarin	14 (4.6)	3 (3.9)	4 (4.8)	3 (4.6)	4 (5.3)	0.696
Dual anti-platelet therapy	27 (8.9)	8 (10.3)	9 (10.8)	6 (9.1)	4 (5.3)	0.255

* AAD class I-IV were classified according to Vaughan Williams Classification.

† NOAC includes dabigatrian and rivaroxaban.

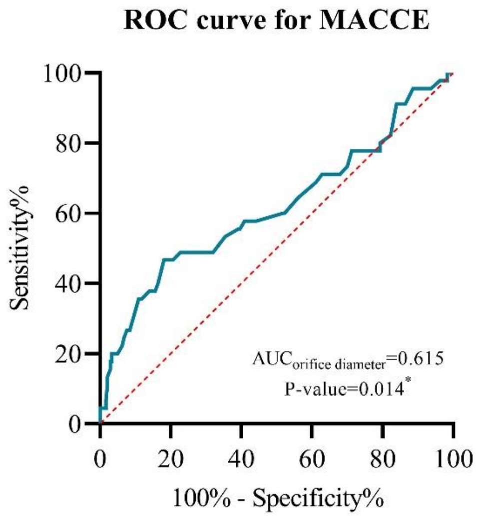

Figure S1. Receiver operator characteristics curve of LAA orifice diameter for predicting MACCE. Asterisk (*) indicate significant P value. AUC denotes area under curve, MACCE major adverse cerebrocardiovascular event.

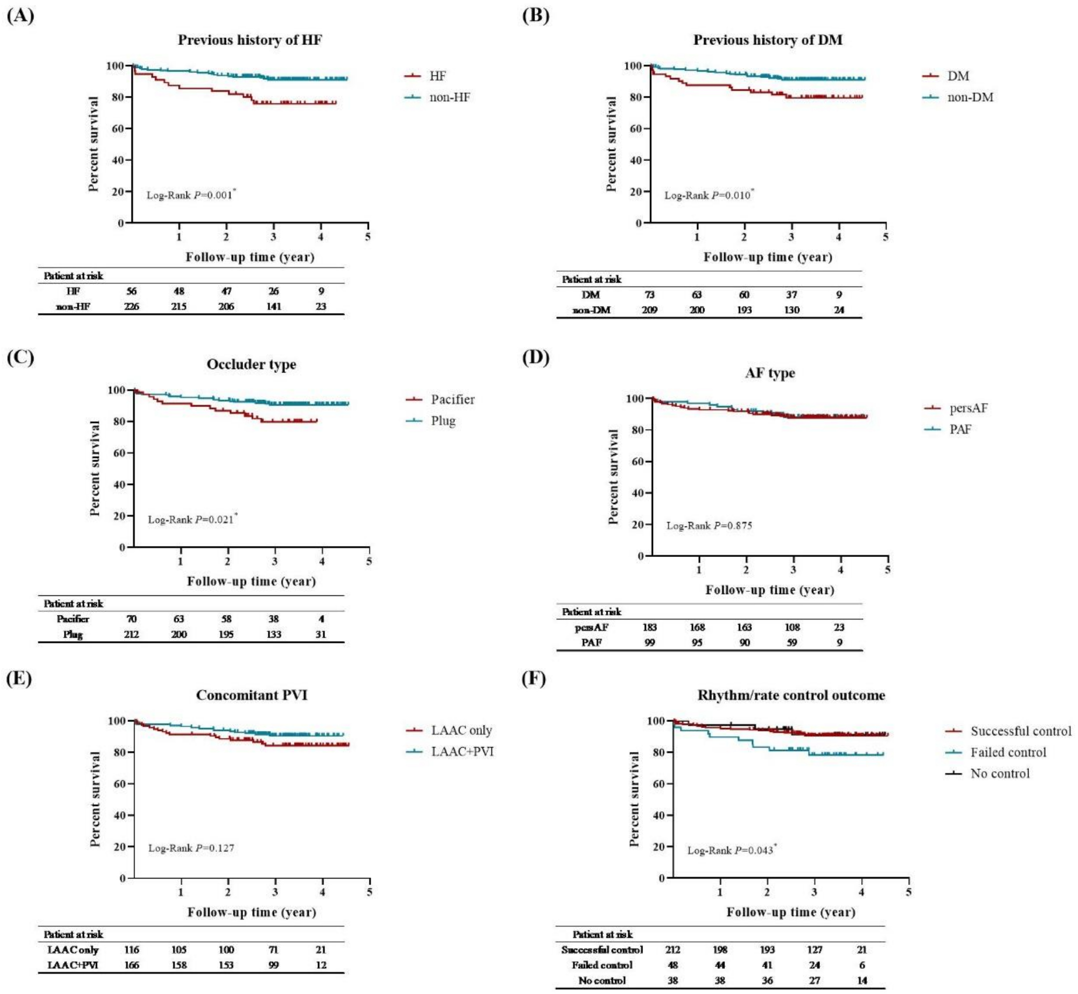

Figure S2. Comparison of survival curves of AHF NYHA III-IV for patients divided by potential confounding factors. Asterisk (*) indicates significant *P*-value. For rhythm/rate control outcome, successful or fail was defined according to control results before occurrence of AHF NYHA III-IV. AF denotes atrial fibrillation, DM diabetes mellitus, HF heart failure, LAAC left atrial appendage closure, PAF paroxysmal atrial fibrillation, persAF persistent atrial fibrillation, PVI pulmonary vein isolation.