Prevalence, predictors and management of left atrial appendage thrombogenic milieu in atrial fibrillation with low thromboembolic risk

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Abstract

Background The present study aimed to investigate the prevalence, predictors, and management of left atrial appendage (LAA) thrombogenic milieu (TM) identified with transesophageal echocardiography (TEE) in non-valvular atrial fibrillation (NVAF) patients with low to moderate thromboembolic (TE) risk.

Methods We retrospectively analyzed the baseline clinical data and TEE findings in 391 NVAF patients (54.7±8.9 years, 69.1% male) with low to moderate TE risk according to the CHA_2DS_2-VASc score. LAA TM was defined as LAA thrombus (LAAT), sludge or spontaneous echo contrast (SEC). Management of LAA TM was at the discretion of the treating physician.

Results A total of 43 patients (11.0%) were detected with LAA TM, including 5 with LAAT (11.6%), 4 with LAAT + Sect. (9.3%), 3 with sludge (7.0%), and 31 with Sect. (72.1%). In multivariate model, non-paroxysmal AF (OR 3.121; 95% CI 1.205–8.083, p = 0.019), and a larger left atrial diameter (LAD) (OR 1.134; 95% CI 1.060–1.213, p < 0.001) were significantly associated with the presence of LAA TM. All LAATs or sludges effectively resolved after mean duration of 117.5±20.0 days for oral anticoagulant (OAC) medication. TE events occurred in 3 patients (18.8%) among those discontinuing OAC over a mean follow-up of 26.2±8.8 months, while no TE events occurred in patients with continuous OAC.

Conclusions LAA TM could be identified in 11.0% in NVAF patients with low to moderate TE risk, especially in those with non-paroxysmal AF and enlarged LAD. Short-term OAC medication could effectively resolve the LAAT or sludge.

Keywords Atrial fibrillation, Left atrial appendage, Transesophageal echocardiography, Thromboembolism, Anticoagulation

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Introduction

Atrial fibrillation (AF) is associated with increased risk of death and cardiovascular events, especially thromboembolic (TE) events [1, 2]. Left atrial appendage (LAA) is shown to play a major role in atrial thrombosis and subsequent TE events in non-valvular AF (NVAF) [3–5]. According to current guidelines, the CHA_2DS_2-VASc scoring system (congestive heart failure, hypertension, age≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, female sex) is recommended in NVAF patients to identify those with high TE risk (≥2 points in male or ≥3 points in female), who could largely benefit from anticoagulation [6]. However, the real-world TE risk of patients with low to moderate TE risk determined by CHA_2DS_2-VASc score has not been completely investigated. Consequently, the indication for long-term anticoagulation in patients with low to moderate TE risk has not been well-established.

Transesophageal echocardiography (TEE) has been widely used to detect the LAA thrombus (LAAT) formation [7]. Recent studies have shown that the presence of LAA thrombogenic milieu (TM), including LAAT, sludge and spontaneous echo contrast (SEC), could serve as a high risk marker for TE events [8–10]. Therefore, the present study aimed to investigate the prevalence, risk factors, and management of LAA TM identified with TEE in NVAF patients with low to moderate TE risk according to CHA_2DS_2-VASc score.

Methods

Study population

In the present retrospective single-center observational study, we screened all in-hospital patients who were diagnosed with AF in our institution between September 2017 and June 2021, among whom, TEE data were available in 1,209 patients. The exclusion criteria were: (1) TEE not relevant to LAA; (2) history of LAA occlusion or ligation; (3) valvular heart disease. After the screening process, the demographic and medical data of the remaining 812 patients were collected. According to CHA_2DS_2-VASc score, the patients were further stratified into low (CHA_2DS_2-VASc=0 in male or CHA_2DS_2-VASc=1 in female), moderate (CHA_2DS_2-VASc=1 in male or CHA_2DS_2-VASc=2 in female) and high (CHA_2DS_2-VASc≥2 in male or CHA_2DS_2-VASc≥3 in female) TE risk groups. Finally, a total of 391 patients with low to moderate TE risk were included in the present study. (Fig. 1) The study protocol was reviewed and approved by the institutional review board. The study complies with the Declaration of Helsinki.
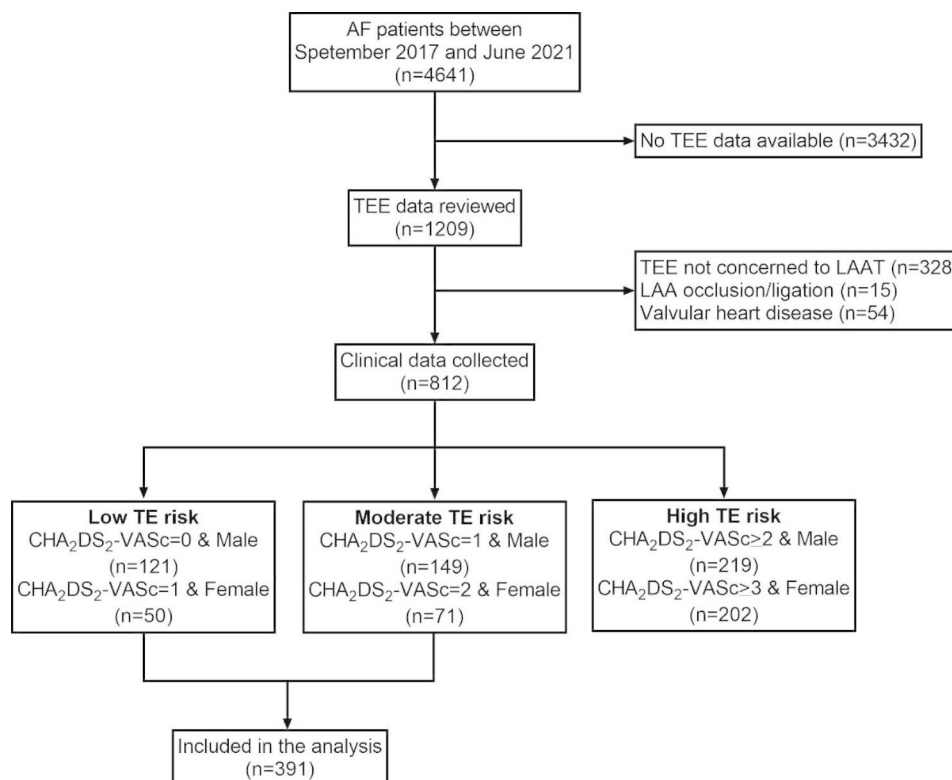

Fig. 1 Flow chart of the study design. AF, atrial fibrillation; TEE, transthoracic echocardiography; LAA, left atrial appendage; LAAT, left atrial appendage thrombosis; TE, thromboembolism
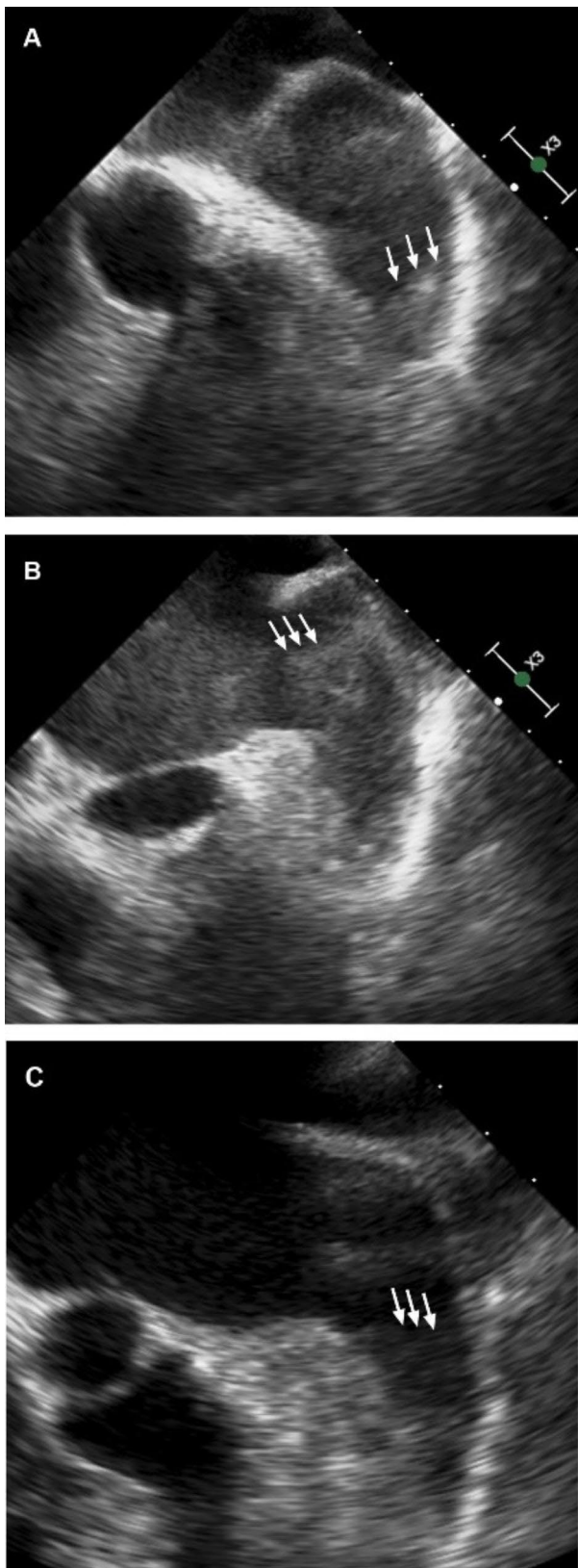
Fig. 2 The example of left atrial appendage thrombosis (A), left atrial appendage sludge (B), and left atrial appendage spontaneous echo contrast (C)

Echocardiographic studies

Transthoracic echocardiography (TTE) data using a standard two-dimensional and Doppler echocardiography with color flow mapping were reviewed. In case of patients with multiple TTEs, the study from the same hospitalization with TEE was used for data collection and subsequent analysis. Left ventricular ejection fraction (LVEF) was calculated according to the Simpson's biplane method. Mitral regurgitation (MR) was evaluated according to current recommendations using an integrative approach that includes qualitative, semiquantitative, and quantitative data and classified into four grades: none, mild, moderate and severe.

TEE was performed after standard clinical preparation with a 5.0-mHZ, 128-element, multiplane probe (Phillips) by experienced echocardiographers who were blinded to the clinical histories of the patients. LAA was scanned in multiple mid-esophageal imaging planes from 0° to 180° to optimize the visualization of the entire LAA. LAAT was defined as a localized echo-dense intracardiac mass distinct to the LAA endocardium and pectinate muscles, which was present in >1 imaging plane [11] (Fig. 2A). LAA sludge was defined as a viscid gelatinous, precipitous echodensity within the LAA, which could be continuously seen throughout the cardiac cycle without a discrete organized mass [9] (Fig. 2B). LAA SEC was defined as characteristic dynamic swirling echoes within the LAA cavity with optimal gain setting [10] (Fig. 2C).

To evaluate the inter- and intra-observer concordance in assessing LAA TM, a randomly selected group of 20 patients from our database, including LAAT (5), sludge (5), Sect. (5), and normal control (5), was and analyzed by the 2 same observers in a blinded manner at different occasions and time (4 weeks apart), as previously reported [12].

Management of LAA TM

All patients with LAAT or sludge received oral anticoagulant (OAC) for at least 3 months. The type of OAC was at the discretion of the treating physician. For anticoagulation with a Vitamin K antagonist (VKA), the target international normalized ratio (INR) was 2.0 to 3.0, and time in therapeutic range (TTR) was calculated. A staged TEE was performed 3–4 months after discharge to demonstrate if LAAT or sludge resolved. The treatment of patients with LAA SEC was left to the physician's discretion and patient's choice. The clinical data of follow-up period were retrospectively collected in the medical system or through telephone visit.

Statistical analysis

Continuous variables were described as the mean±standard deviation for normally distributed data and median (25–75% quartile) for non-normally distributed data.

Comparisons between groups were performed with Student t test (normally distributed data) or Kruskal–Wallis test (non‑normally distributed data). Categorical variables were described as counts (percentage) and compared by chi‑square analysis. Kappa statistics were calculated to evaluate the inter- and intra-observer concordance in identification of LAA TM. Binominal logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the presence of LAA TM. Variables selected for testing in the multivariate analysis were those with P<0.05 in the univariate model. A receiver operating characteristic (ROC) analysis was used to determine the cut-off value of left atrial diameter (LAD) for predicting the presence of LAA TM. All tests were two-tailed, and a statistical significance was established at P<0.05. All analyses were performed using SPSS software (version 22.0; SPSS, Inc.).

Results
Baseline characteristics of the study population
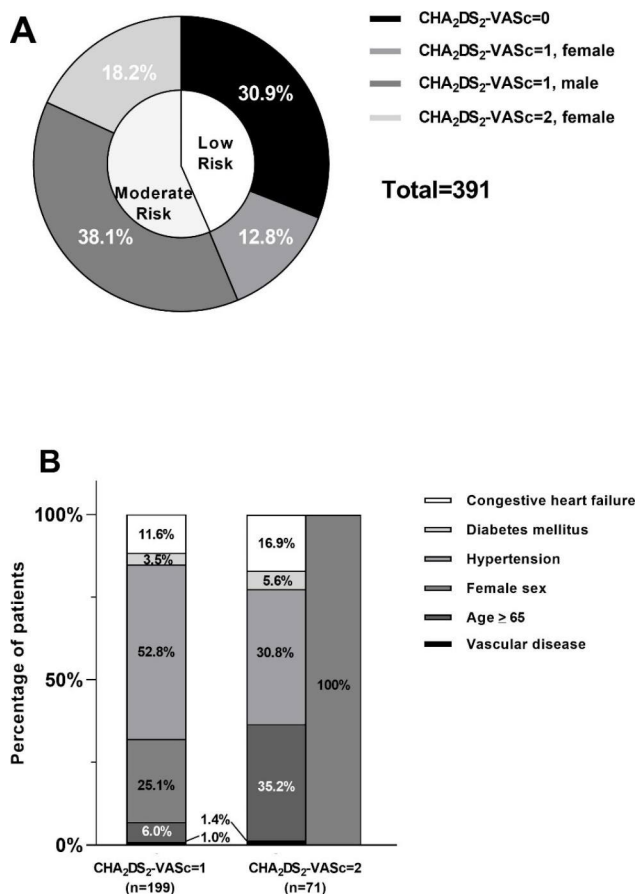A total of 391 patients with NVAF were included in the study. Mean age was 54.7±8.9 years, and 270 (69.1%)

Fig. 3 The thromboembolic (TE) risk of the study population. A, TE risk stratification according to the CHA_2DS_2-VASc score; B, prevalence of different risk factors in patients with CHA_2DS_2-VASc score of 1 and 2

were male. The medium CHA_2DS_2-VASc score was 1.0 (0–1.0). The number of patients with CHA_2DS_2-VASc score of 0, 1, 2 was 121 (30.9%), 199 (50.9%), and 71 (18.2%), respectively.

Figure 3 shows the TE risk of the whole study population. According to the CHA_2DS_2-VASc score, 171 (43.7%) patients were stratified to low TE risk group, while the remaining 220 (56.3%) patients were at moderate TE risk.

Inter- and intra-observer concordance
The inter- and intra-observer concordance in identification of different status of LAA TM was both very high, with the overall kappa of 0.92 and 1.00, respectively.

Prevalence and characteristics of patients with LAA TM
During TEE examination, 199 patients were in normal sinus rhythm. LAA TM was detected in 43 patients (11.0%) in TEE. The baseline characteristics of the patients with and without LAA TM are shown in Table 1. Patients with LAA TM were older (p=0.025), had a higher prevalence of non-paroxysmal AF (p<0.001), congestive heart failure (p<0.001), and had higher CHA_2DS_2-VASc scores (p=0.022), fibrinogen (p=0.042), N-terminal pro-B type natriuretic peptide (NT-ProBNP) (p<0.001), and serum uric acid levels (p=0.033). In transthoracic echocardiography (TTE), patients with LAA TM had significantly larger LAD (p<0.001), LVEDD (p<0.001), lower LVEF (p<0.001) and a higher prevalence of MR (p<0.001).

More details on patients with LAA TM are shown in Table 2. The number of patients who were detected with LAAT, LAA sludge, LAA SEC was 9, 3, 35, respectively. Notably, 4 patients showed both LAAT and SEC in TEE.

Predictors of patients with LAA TM
In univariate analysis, factors significantly associated with an increased risk for the presence of LAA TM were higher age (OR 1.046; 95% CI 1.005–1.089, p=0.026), non-paroxysmal AF (OR 9.341; 95% CI 4.195–20.799, p<0.001), congestive heart failure (OR 5.470; 95% CI 2.484–12.043, p<0.001), a higher CHA_2DS_2-VASc score (OR 1.684; 95% CI 1.060–2.677, p=0.027), a larger LAD (OR 1.202; 95% CI 1.135–1.273, p<0.001), and MR (OR 4.087; 95% CI 2.064–8.091, p<0.001). After combining these individual risk factors in a multivariate regression model, only non-paroxysmal AF (OR 3.121; 95% CI 1.205–8.083, p=0.019), and a larger LAD (OR 1.134; 95% CI 1.060–1.213, p<0.001) remained significantly associated with the presence of LAA TM. (Table 3)

As was shown in the ROC curve, the optimal cut-off value for LAD displaying the best predictive value was 40.5 mm (sensitivity=69.8% and specificity=79.9%; area under the curve=0.829; Fig. 4). In addition,

Table 1 Baseline characteristics of the study population

Variables	LAA TM		Total	P
	Absent n=348	Present n=43	n=391	value
Demographic characteristics				
Age, years old	54.4±9.0	57.6±6.9	54.7±8.9	0.025
Male sex, n (%)	241 (69.3)	29 (67.4)	270 (69.1)	0.809
BMI, kg/m^2	24.4±3.2	24.8±3.5	24.5±3.3	0.517
Clinical characteristics				
Non-paroxysmal AF, n (%)	111 (31.9)	35 (81.4)	146 (37.3)	<0.001
Hypertension, n (%)	119 (34.2)	15 (34.9)	134 (34.3)	0.929
Diabetes mellitus, n (%)	8 (2.3)	3 (7.0)	11 (2.8)	0.207
Congestive heart failure, n (%)	23 (6.6)	12 (27.9)	35 (9.0)	<0.001
Coronary artery disease, n (%)	22 (6.3)	4 (9.3)	26 (6.6)	0.678
CHA$_2$DS$_2$-VASc score	1.0 (0, 1.0)	1.0 (1.0, 2.0)	1.0 (0, 1.0)	0.022
Laboratory findings				
Hematocrit, %	48.4±8.4	51.1±9.1	48.7±8.5	0.066
Platelet, 10^9/L	184.5±46.7	179.0±48.7	183.9±46.9	0.484
D-dimer	0.06 (0.03, 0.1)	0.06 (0.04, 0.12)	0.06 (0.03, 0.1)	0.358
Fibrinogen,	2.7±0.5	2.9±0.5	2.7±0.5	0.042
NT-ProBNP, pg/ml	168.7 (62.1, 436.0)	843.0 (445.5, 1265.8)	227.8 (72.3, 572.0)	<0.001
Serum uric acid, umol/L	387.6±99.3	422.3±96.1	391.4±99.5	0.033
Creatinine, umol/L	85.4±68.1	83.2±20.0	85.1±64.7	0.839
eGFR, ml/min/1.73m^2	86.5±26.3	85.1±30.1	86.3±26.7	0.757
Medications				
Antiplatelet, n (%)	26 (7.5)	3 (7.0)	29 (7.4)	1.000
Anticoagulant, n (%)	27 (7.8)	3 (7.0)	30 (7.7)	1.000
beta-blocker, n (%)	166 (47.7)	20 (46.5)	186 (47.6)	0.883
ACEI/ARB/ARNI, n (%)	44 (10.0)	2 (4.7)	46 (11.8)	0.125
MRA, n (%)	17 (3.9)	8 (18.6)	25 (6.4)	0.002
AADs, n (%)	90 (25.9)	5 (11.6)	95 (24.3)	0.040
Statins, n (%)	62 (17.8)	7 (16.3)	69 (17.6)	0.803
Diuretics, n (%)	2 (0.6)	0 (0)	2 (0.5)	1.000
TTE				
LAD, mm	36.3±5.8	44.2±6.6	37.1±6.4	<0.001
LVEDD, mm	46.3±4.8	49.1±6.2	46.6±5.0	<0.001
LVEF, %	63.5±7.0	56.7±11.1	62.7±7.8	<0.001
MR	48 (13.8)	17 (39.5)	14 (35.5)	<0.001
Mild MR	27 (7.8)	10 (23.3)	7 (64.5)	0.003
Moderate MR	21 (6.0)	7 (16.3)	7 (64.5)	0.032

LAA, left atrial appendage; TM, thrombogenic milieu; BMI, body mass index; AF, atrial fibrillation; NT-ProBNP, N-terminal pro-B type natriuretic peptide; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; AADs, anti-arrhythmic drugs; TTE, transthoracic echocardiography; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

Table 2 Number of patients with LAAT, sludge, SEC, and TM

	LAAT	LAAT+SEC	LAA sludge	LAA SEC	LAA TM
Low TE risk, n (%)	2 (0.5)	2 (0.5)	0 (0)	6 (1.5)	10 (2.6)
Moderate TE risk, n (%)	3 (0.8)	2 (0.5)	3 (0.8)	25 (6.4)	33 (8.4)
Total, n (%)	5 (1.3)	4 (1.0)	3 (0.8)	31 (7.9)	43 (11.0)

LAA, left atrial appendage; LAAT, left atrial appendage thrombus; SEC, spontaneous echo contrast; TM, thrombogenic milieu; TE, thromboembolism.

non-paroxysmal AF increased more than twofold risk for the presence of LAA TM.

Management of patients with LAA TM

All patients with LAAT or sludge were prescribed with oral anticoagulant (OAC) at discharge, among whom, 7 patients received standard dose of non-Vitamin K antagonist oral anticoagulant (NOAC), 2 patients received reduced dose of NOAC, and 3 patients received Vitamin K antagonist (VKA) (target INR 2.0–3.0). After a mean duration of 117.5±20.0 days, all of the thrombi and

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Table 3 Univariate and multivariate analysis of LAA TM

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.046 (1.005–1.089)	0.026	1.048 (0.996–1.104)	0.071
Male sex	1.087 (0.552–2.140)	0.809		
BMI	1.032 (0.939–1.133)	0.516		
Non-paroxysmal AF	9.341 (4.195–20.799)	< 0.001	3.121 (1.205–8.083)	0.019
Hypertension	1.031 (0.530–2.005)	0.929		
Diabetes mellitus	3.187 (0.813–12.503)	0.096		
Congestive heart failure	5.470 (2.484–12.043)	< 0.001	1.894 (0.701–5.122)	0.208
Coronary artery disease	1.520 (0.498–4.639)	0.462		
CHA_2DS_2-VASc score	1.684 (1.060–2.677)	0.027	1.203 (0.663–2.180)	0.543
Antiplatelet	0.929 (0.269–3.208)	0.907		
Anticoagulant	0.892 (0.259–3.073)	0.856		
Hematocrit	1.035 (0.997–1.074)	0.072		
D-dimer	1.027 (0.039–26.875)	0.987		
fibrinogen	1.712 (0.968–3.027)	0.065		
LAD	1.202 (1.135–1.273)	< 0.001	1.134 (1.060–1.213)	< 0.001
MR	4.087 (2.064–8.091)	< 0.001	1.330 (0.596–2.970)	0.486

LAA, left atrial appendage; TM, thrombogenic milieu; OR, odds ratio; CI, confidence interval; BMI, body mass index; AF, atrial fibrillation; LAD, left atrial diameter; MR, mitral regurgitation.

sludges resolved with a detailed recheck of TEE (Table 4). In patients with solely SEC, 22 patients underwent catheter ablation and 1 patient underwent surgical LAA ligation. No peri-operational TE event occurred. The remaining 8 patients received medication of OAC.

Over a mean follow-up of 26.2±8.8 months, 27 patients (62.8%) were continuous on OAC therapy (14 patients with standard dose of NOAC, 11 patients with reduced dose of NOAC, and 2 patients with VKA). No TE events occurred in patients with continuous OAC, while 2 patients (12.5%) experienced ischemic stroke and 1 patient (6.3%) experienced peripheral artery embolism in patients discontinuing OAC. (Fig. 5)

Discussion

The major findings of our study are: (1) the prevalence of LAA TM was 11.0% in a hospital-based cohort with low to moderate TE risk; (2) non-paroxysmal AF and LAD were independently associated with the presence of LAA TM; (3) All of the LAATs or sludges could effectively resolve in 3–4 months; (4) in patients with LAA TM yet discontinuing OAC, 18.8% individuals experienced TE events. The implication is that the TE risk should not be overlooked despite a low CHA_2DS_2-VASc score, especially in patients with non-paroxysmal AF and enlarged LAD, and long-term OAC may be warranted to minimize the TE risk.

Evaluating TE risk of individual NVAF patients is of crucial value for decision making to long-term OAC treatment. Although the widely accepted $CHADS_2$ and CHA_2DS_2-VASc scoring system could provide predictive value in TE risk stratification, studies have shown that moderate to severe SEC and even LAAT were not uncommon in low risk patients who underwent TEE examination. However, the prevalence of LAA TM in these patients varied from 0.6 to 29.0% according to previous studies [8, 9, 12–14]. Puwanant S et al. [12] observed LAAT, sludge or SEC in 29.0% of pre-ablation patients with $CHADS_2$ score of 0 or 1. Kleemann T et al. [13] identified LAAT or dense SEC in 10.1% patients with $CHADS_2$ score of 0 or 1. Yarmohammadi H et al. [8] reported that 2.3% of patients with low TE risk were detected with LAAT or sludge in an adequate coagulated cohort who were scheduled for cardioversion. Whereas a recent study by Göldi T et al. [14] shown that the prevalence of LAA TM was only 0.6% in pre-ablation patients with CHA_2DS_2-VASc score of 0 or 1. In the present study, we found that LAA TM could be detected in 11.0% (LAAT 2.3%, LAA sludge 0.8%, solely LAA Sect. 7.9%) of NVAF patients with low to moderate TE risk, which is comparable to Kleemann T's finding. We believe that the variability among studies results from difference in definition of LAA TM, patient characteristics and sample size.

Several clinical features have been proposed to predict the presence of LAA TM. Studies showed that $CHADS_2$ or CHA_2DS_2-VASc scores correlated with the risk of LAA TM [8, 14, 15]. In addition, non-paroxysmal AF has been shown to be independently associated with the presence of LAA TM [14]. In concordance with that, non-paroxysmal AF independently increased more than twofold risk for LAA TM in our study. Furthermore, certain echocardiographic parameters, such as enlarged LAD, impaired LVEF and reduced LAA flow velocity, have been revealed to predict the presence of LAA TM by several studies [8, 12, 13, 16, 17]. The role left atrium (LA) enlargement playing in TE events has been controversial. Although previous studies showed that enlarged LAD in TTE was not predictive of stroke event in two large cohorts [18, 19], echocardiographic studies reproducibly demonstrated that LA enlargement was a strong predictor of LAA TM [9, 13, 17]. We found that LAD independently predicted the presence of LAA TM after
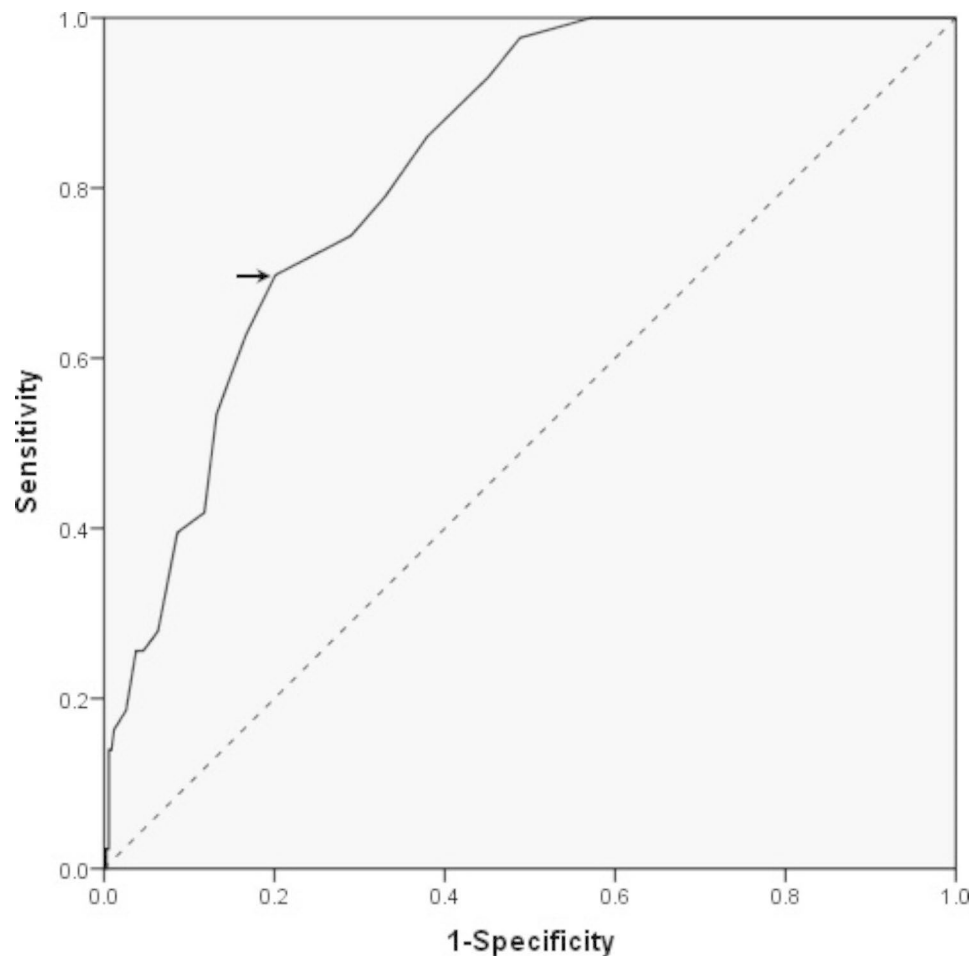
Fig. 4 Receiver operating characteristic curve of left atrial diameter (LAD) for predicting left atrial appendage thrombogenic milieu. Arrow shows the optimal cut-off value for LAD.

adjusting for potential confounders, with the best cut-off value of 40.5 mm. Interestingly, the medications of the present cohort differed between patients with and without LAA TM. More patients with LAA TM had medication of MRA, which might be due to a higher prevalence of congestive heart failure. In contrast, less patients with LAA TM had medication of AADs, which might be explained by a higher prevalence of non-paroxysmal AF who were more likely to accept the rate control strategy.

Short-term OAC, including NOACs and VKA, has long been used to resolve LAAT or sludge in patients with NVAF. Previous studies investigating the efficacy of NOACs or AVK showed conflicting results with the resolution rate of LAAT ranging from 41.5–85.7% [14, 20–24]. However, in the present study, all LAATs or sludges effectively resolved after OAC medication of 3–4 months, whether standard-dose NOAC, reduced-dose NOAC or VKA (TTR ranging from 60 to 75%). We believe the high resolution rate in our study may result from the Asian race and low CHA_2DS_2-VASc scores. Previous study demonstrated that the patients with LAAT

resolution had lower CHA_2DS_2-VASc scores [22]. In addition, the overall resolution rate is obviously higher in the Asian race [22–24]. The racial disparity of effectiveness and safety with OAC has been discussed in various studies. A recent meta-analysis showed that Asian race was associated with lower stroke and systematic embolism rate on standard-dose NOAC therapy [25]. On the other hand, Asians were reported to be more susceptible to OAC related bleeding events [26, 27]. This phenomenon was attributed to greater platelet reactivity and endogenous fibrinolysis in Asian population [28].

The presence of LAAT or SEC was demonstrated to be associated with increased long-term TE risk and even all-cause mortality [9, 10]. However, previous studies showed that long-term OAC may compensate these adverse effects [13, 29]. Vinereanu D et al. [29] investigated the relationship between echocardiographic risk factors and clinical outcomes in a sufficiently anticoagulated cohort and found that these factors could not predict the long-term TE events. Indeed, no patients receiving continuous OAC experienced TE events in the present study, which

Table 4 Management of patients with LAAT or sludge

Patient #	Age (y/o)	Sex	AF type	CHA$_2$DS$_2$-VASc score	LAD (mm)	MR	OAC before TEE	LAAT or sludge	LAA SEC	OAC after TEE	LAAT/sludge resolution	Time to resolution (day)
1	61	Male	PeAF	1	57	None	No	LAAT	No	Rivaroxaban 10 mg QD	Yes	141
2	55	Male	PeAF	0	48	None	No	LAAT	No	Rivaroxaban 20 mg QD	Yes	106
3	60	Female	PeAF	1	49	None	No	LAAT	Yes	Dabigatran 110 mg BID	Yes	94
4	48	Male	PeAF	1	48	Moderate	No	LAAT	Yes	VKA (TTR 75%)	Yes	168
5	59	Male	PeAF	1	45	None	No	LAAT	Yes	VKA (TTR 60%)	Yes	84
6	64	Female	PeAF	2	44	Mild	No	LAAT	No	Rivaroxaban 20 mg QD	Yes	140
7	63	Male	PAF	0	42	Mild	Yes	LAAT	No	Rivaroxaban 20 mg QD	Yes	135
8	59	Male	PAF	0	35	None	No	LAAT	Yes	Rivaroxaban 20 mg QD	Yes	102
9	45	Male	PeAF	1	45	None	No	LAAT	No	Rivaroxaban 20 mg QD	Yes	119
10	58	Male	PeAF	1	43	Mild	No	sludge	No	VKA (TTR 67%)	Yes	96
11	58	Male	PAF	1	38	None	No	sludge	No	Rivaroxaban 20 mg QD	Yes	121
12	55	Female	PeAF	2	45	Mild	No	sludge	No	Rivaroxaban 20 mg QD	Yes	104

LAAT, left atrial appendage thrombus; AF, atrial fibrillation; LAD, left atrial diameter; MR, mitral regurgitation; OAC, oral anticoagulant; TEE, transesophageal echocardiography; SEC, spontaneous echo contrast; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; VKA, Vitamin K antagonist; TTR, time in therapeutic range.
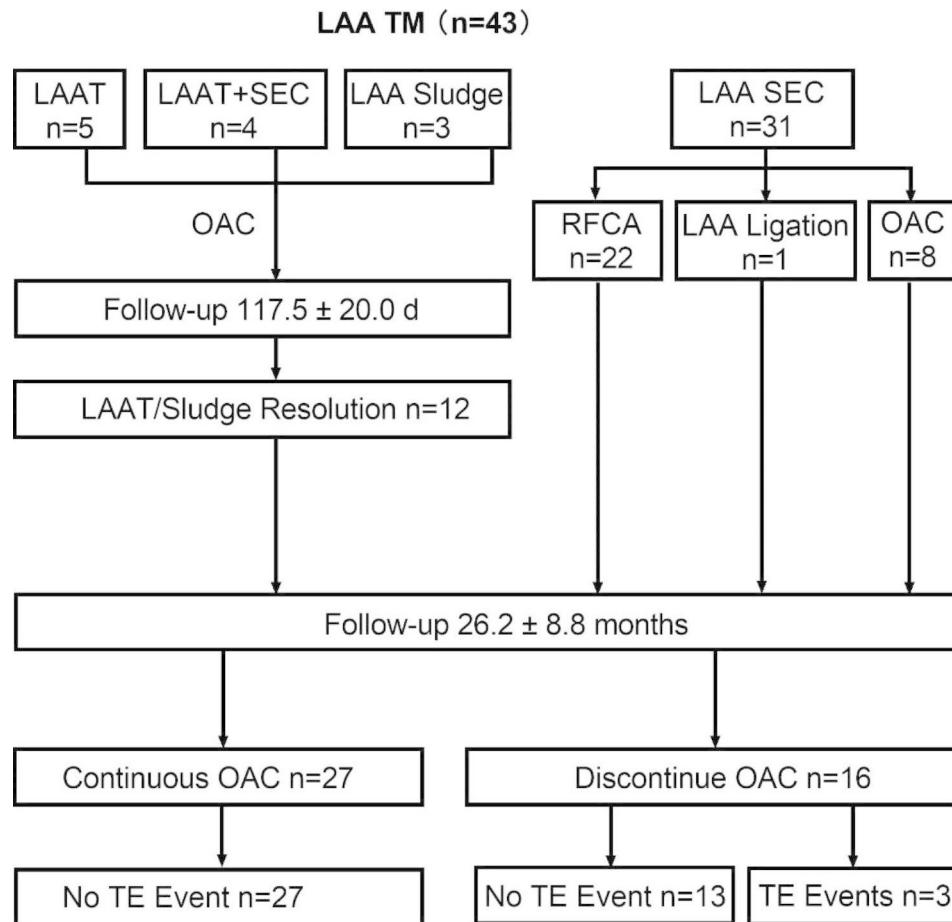
Fig. 5 The management of patients with left atrial appendage thrombogenic milieu. LAA, left atrial appendage; TM, thrombogenic milieu; LAAT, left atrial appendage thrombosis; SEC, spontaneous echo contrast; OAC, oral anticoagulant; RFCA, radiofrequency catheter ablation; TE, thromboembolism

implies the necessity of long-term coagulation in those with LAA TM, even with low CHA_2DS_2-VASc scores.

The present study has several limitations. Firstly, this study is a retrospective observational single-center in-hospital study with a limited sample size, which may limit the generalization of the results. Secondly, the anti-coagulation rate before TEE in the study is low. Thirdly, the LAA flow velocity and grade of SEC were not available in this study, which limits the quantitative and semi-quantitative analysis of LAA TM. However, the inter- and intra-observer variability of qualitative TEE data is very low. Fourthly, only 3 patients experienced TE events in the follow-up period, which limits the multivariate analysis to evaluate the hazard ratio of discontinuing OAC to long-term TE risk. Further research based on a larger sample size is needed to investigate this issue.

Conclusion

Although with low to moderate TE risk, the LAA TM could be identified in 11.0% in an in-hospital cohort, especially in those with non-paroxysmal AF and enlarged LAD. Short-term OAC medication could effectively resolve the LAAT or sludge. However, long-term OAC medication may still be needed to minimize the TE risk.

List of Abbreviations

AAD	Antiarrhythmic drug
ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
INR	International normalized ratio
LAA	Left atrial appendage
LAAT	Left atrial appendage thrombus
LAA TM	Left atrial appendage thrombogenic milieu
LAD	Left atrial diameter
LVEDD	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
NOAC	Non-Vitamin K antagonist oral anticoagulant
NT-ProBNP	N-terminal pro-B type natriuretic peptide
NVAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
OR	Odds ratio
PAF	Paroxysmal atrial fibrillation
PeAF	Persistent atrial fibrillation
RFCA	Radiofrequency catheter ablation

ROC	Receiver operating characteristic
SEC	Spontaneous echo contrast
TE	Thromboembolism
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

Author Contribution

YQ, GN conceptualized the idea. YQ, ZZ, and XC organized the database. YQ and XC performed the statistical analysis. YQ, ZZ and XC performed literature search and wrote the first draft of the manuscript. All authors critically reviewed the manuscript.

Data Availability

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

Declarations

Ethical approval

This retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All statistical analyses in our study were based on available summary data and therefore no ethical approval was required.

Competing interests

The authors declare that they have no competing interest.

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