Left Atrial or Left Atrial Appendage Thrombus Resolution After Adjustment of Oral Anticoagulant Treatment

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Background: There are few reports about non-vitamin K antagonist oral anticoagulant (NOAC) treatment for resolution of left atrium (LA) or left atrial appendage (LAA) thrombus. LAA thrombus is an important cause of cardiogenic cerebral thromboembolism, and the detection rate increases due to more and more patients receiving catheter ablation. However, the results from NOAC use for LA or LAA thrombus are still unknown in real-world practice. The aim of this study was to discover the resolution of LA or LAA thrombus after anticoagulant treatment in real-world practice. *Method*: From January 2013 to December 2016, a total 864 patients underwent transesophageal echocardiography (TEE), and 41 cases of LA or LAA thrombus were detected in our hospital. Among them, a total of 22 patients underwent follow-up TEE to detect the resolution of LA or LAA thrombus. *Result:* The average age of the study patients was 72.0 ± 11 years old, and 61% were male. The average CHA2DS2-VASc scores were 3.76 ± 2.01 points. A total of 22 patients underwent follow-up TEE, and 19 (86.4%) patients presented LA or LAA thrombus resolution. The average resolution duration was 258.47 ± 218.17 days. One-year all-cause mortality was 4.9%, and the incidence of ischemic stroke was 4.9%. Most physicians favored titration of the dosage of NOAC or warfarin in real-world practice. *Conclusion:* In real-world practice, most physicians favored titration of the dosage of NOAC or warfarin for LA or LAA thrombus. LA or LAA thrombus could exist if the patient received a reduced dose of NOAC. High frequency of LAA or LA thrombi could resolve, and a low incidence of ischemic stroke occurred after adjustment of oral anticoagulant treatment.

Key Words: Left atrium thrombus—left atrial appendage thrombus—transesophageal echocardiography—oral anticoagulant treatment—non-vitamin K antagonist oral anticoagulant

Introduction

Atrial fibrillation (AF) is the most frequently sustained cardiac arrhythmia, with a prevalence of about 2%-3% in the general population and 2.8%-15.8% in the community-based Asian population.[1,2] AF is associated with the development of left atrial (LA) and left atrial appendage (LAA) thrombi, which are the main source of stroke and systemic embolisms.[3] Approximately 90%

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of atrial thrombi in nonvalvular AF are found within the LAA.[3] In AF, ineffective irregular contraction, dilatation, and diminished blood-flow velocities result in significant blood stasis in the LAA and, coupled with abnormal blood constituents and atrial wall abnormalities, this leads to a prothrombotic or hypercoagulable state in LAA by fulfillment of Virchow's triad.[4] The prevalence of LAA thrombus in patients with nonvalvular AF varies between 0.6% and 7%, depending on anticoagulation status and thromboembolic risk that can be assessed clinically by using the CHA2DS2-VASc score.[5-7]

Transesophageal echocardiogram (TEE) is recognized as the gold standard for evaluating for the presence of LA thrombus and is routinely used before cardioversion and catheter ablation procedures to minimize the risk of periprocedural stroke.[8] TEE allows high-quality imaging of the LAA in nearly all patients owing to the proximity of the esophagus to LAA and provides the serial image at follow-up of LA and LAA thrombi.[9] If an LA or LAA thrombus is detected during TEE evaluation, current guidelines recommend treatment with vitamin K antagonist (VKA) therapy for 3 weeks, with an international normalized ratio (INR) range of 2.0-3.0.[1] A follow-up TEE assessment for 3-4 weeks is recommended to ensure thrombus resolution before the cardioversion procedure or catheter ablation procedure.[1]

Until recently, the only option for chronic oral anticoagulation was VKA therapy, warfarin being the most-used drug globally. When used as thromboprophylaxis for AF, VKA treatment results in a 64% reduction in stroke and 26% reduction in all-cause mortality when compared with placebo or control, as well as a 37% stroke risk reduction when compared with antiplatelet therapy.[10] When compared to VKA, several non-vitamin K antagonist oral anticoagulants (NOACs) have been shown in randomized studies to result in reduction in stroke and systemic embolism and more importantly, a significant reduction in hemorrhagic stroke.[11-14] In clinical practice, more experience was known about VKA use for LA or LAA thrombi. However, the results from NOAC use for LA or LAA thrombi are still unknown in the real-world practice. The aim of this study was to investigate the association of the status of VKA/NOAC use and the resolution of LA/LAA thrombus in the real-world practice.

Materials and Methods

Patients and Groups

From January 2013 to December 2016, a total of 864 patients underwent TEE for thrombus evaluation due to new onset of an ischemic stroke, valvular heart disease, or preablation or cardioversion.

The patients with severe valvular regurgitation, severe valvular stenosis, mechanic valve disease, prosthetic valve disease, or post percutaneous mitral valvuloplasty were excluded. A total of 41 nonvalvular AF cases with LA or LAA thrombus (4.7 %) were detected in our hospital. Among them, 22 patients underwent follow-up TEE to detect the status of resolution of LA or LAA thrombus and the other 19 patients did not undergo follow-up TEE due to the patient's refusal, inability to tolerate the procedure, or totally dependent status post cerebral infarction. If the patients received warfarin, INR followed per 1 month in out-patient department. The medical backgrounds of patients (in particular, the presence of structural heart disease or coronary artery disease) and CHA2DS2-VASc score of all subjects were evaluated.

The Institutional Review Committee on Human Research at our institution approved the study protocol.

Definitions

Typing of AF (paroxysmal, persistent, or long-standing) followed 2016 ESC Guidelines.[1] Cardiovascular mortality was defined as death related to a myocardial infarction, cardiac arrhythmia, or heart failure. All-cause mortality was defined as death from any cause. The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation established a definition and classification of chronic kidney disease in 2002 and defined chronic kidney disease as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73 m^2 for at least 3 months.[15]

Study Endpoints

The primary endpoints of our study were LA or LAA thrombus resolution and stroke (ischemic and hemorrhagic) during the 1-year follow-up period. The secondary endpoints were cardiovascular mortality and all-cause mortality during the follow-up period.

Statistical Analysis

Data are presented as mean ± standard deviation or percentages or median with interquartile range. The clinical characteristics between the study groups were compared by independent samples t test or Mann-Whitney U test for continuous variables or chi-square test or Fisher's exact test for categorical variables. All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY). A P value of less than .05 is considered statistically significant.

Results

Baseline Characteristics of Study Participants

Among 41 patients (4.7% of 864 patients), 12 (29.3%) patients had noted LA thrombus, and another 29 (70.7%) patients had noted LAA thrombus (Table 1). The average age of the study patients was 72.0 ± 11 years, and 61.0% were male. The most common comorbidity was hypertension (68.3%). Most patients presented with persistent or

Table 1. *Baseline characteristics of the study patients with LA or LAA thrombus*

	LA or LAA thrombus (N = 41)
The site of thrombus	
LA	12 (29.3)
LAA	29 (70.7)
General demographics	
Age (y)	72.0 ± 11
Male gender	25 (61.0)
Comorbidities	
CAD	7 (17.1)
Heart failure	12 (29.3)
Severe valvular heart disease	5 (12.2)
Hypertension	28 (68.3)
Diabetes	16 (39.0)
Prior stroke or TIA	15 (36.6)
PAOD	0 (0)
Thyroid disease	3 (3.7)
Chronic kidney disease > stage 3	6 (14.6)
Atrial fibrillation	
Paroxysmal	16 (39.0)
Persistent/long-standing	25 (61.0)
CAHDS2 score	2.85 ± 1.68
CHA2DS2-VASc score	3.76 ± 2.01
LVEF (%)	61.78 ± 15.05
LA diameter (mm)	46.51 ± 6.47
AF ablation (%)	5 (12.2)
F/U TEE (%)	22 (53.7)
Thrombus without resolution	3 (13.6)
Thrombus with resolution	19 (86.4)
The median of resolution days	165 (118-278)
F/U days	488.39 ± 378.12
Ischemic stroke event (%)	2 (4.9)
One-year cardiovascular mortality (%)	1 (2.4)
One-year all-cause mortality (%)	2 (4.9)

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; F/U, follow-up; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; PAOD, peripheral arterial occlusive disease; TIA, transient ischemic attack.

Data are expressed as mean ± SD or as number (percentage) or as median with interquartile range.

Table 2. *Medication use and strategies before and after LA or LAA thrombus found*

	LA or LAA thrombus	
Medication	Before	After
None	9	5
Aspirin	10	4
NOAC	13	18
Warfarin	9	14

Abbreviations: LA, left atrium; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant.

Data are expressed as number.

long-standing AF (61.0%). The average CHADS2 score was 2.85 ± 1.68 points and the average CHA2DS2-VASc score was 3.76 ± 2.01 points. The average diameter of LA was 46.51 ± 6.47 mm. At an average follow-up period of 488.39 ± 378.12 days, 2 patients experienced ischemic stroke, 1 patient died from myocardial infarction with cardiogenic shock, and another patient died from sepsis.

Medication Use and Strategies Before and After LA or LAA Thrombus Found

The frequency of the use of anticoagulation increased from 53.7% to 78.0% after LA/LAA thrombus was found (Table 2). The reasons for not using anticoagulation were hemorrhagic stroke and large stroke with hemorrhagic transformation and bedridden status. Among 22 patients with previous anticoagulation use and having follow-up TEE (Table 3), most physicians favored titration of the dose of NOAC from inappropriate reduced dosage to standard recommended dosage (n = 4) or increased the dosage of warfarin to a higher range of the INR (from 1.65 ± 0.59 to 2.23 ± 0.68) (n = 8).

The Comparison of the Patients With and Without Thrombus Resolution

At an average follow-up period of 575.2 ± 436.7 days, 22 patients underwent follow-up TEE to detect the status of LA or LAA thrombus and 19 patients (86.4%) experienced thrombus resolution (Table 4). The remaining 3 patients without LA or LAA thrombi resolution even with titration of oral anticoagulants or by switching anticoagulation medication had significantly higher prevalence of prior stroke and had higher CHADS2/CHA2DS2-VASc score and were all in persistent/long-standing AF. These 3 patients did not experience recurrent ischemic stroke during the follow-up period.

Among the 19 patients with LA/LAA thrombus resolution, 4 patients received titration of the dose of NOAC from inappropriate reduced dosage to standard recommended dosage, 4 patients received increased the dosage of warfarin to a higher range of the INR, 1 patient received switching from NOAC to warfarin, 1 patient received switching from warfarin to NOAC, 4 patients received the same dose of NOAC, and other 5 patients received switching from aspirin to NOAC or warfarin.

Discussion

In patients with AF, a poorly contractile LA and failure of atrial systole, causing stasis, are the major concerns about thrombus formation and promote the prothrombotic or hypercoagulable state.[4,16,17] LAA is the most common site of intra-atrial thrombus formation because the anatomy of LAA provides blood stasis environment.[18]

Table 3. *Strategies for the patients with LA or LAA thrombus who already used NOAC or warfarin*

	LA or LAA thrombus (N = 22)
Strategies	
Titrate NOAC dose or warfarin	12
Warfarin	8 (INR increased from 1.65 ± 0.59 to 2.23 ± 0.68)
NOAC	4 (from inappropriate low dose to standard dose)
Keep the same dose of NOAC	6
Switching from NOAC to warfarin	2
Switching from warfarin to NOAC	2

Abbreviations: INR, international normalized ratio; LA, left atrium; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant.

Data are expressed as number.

Increased fibrin turnovers has been reported in patients with acute onset or chronic AF, and fibrin D-dimer was an independent predictor of the presence of LAA thrombi on TEE.[19,20] Previous studies reported that history of heart failure, diabetes, previous stroke/transient ischemic attack, and LA dimension identified patients with LAA thrombus.[5,6,21,22] Furthermore, spontaneous echo contrast visualized on TEE, reflecting abnormal blood stasis in the LA and LAA, has been shown to be an independent risk factor for thromboembolism in AF patients.[23] In real-world practice, it is important for the physician to know the status of LA or LAA thrombus resolution after anticoagulation, especially in patients who need to receive electrical or pharmacological cardioversion, catheter ablation, or LAA occluder implantation.

The prevalence and incidence of AF increased gradually in Western countries and Asian countries due to the increasing elderly population.[24,25] In most countries, increasing numbers of patients received catheter ablation for AF, even in elderly patients and heart failure patients.[26,27] Therefore, more patients were diagnosed with LA or LAA thrombus due to increasing number of patients receiving catheter ablation. Even though anticoagulation was used for at least 3 weeks as recommended by guidelines, some patients still had LA or LAA thrombus, especially the patients with high CHA2DS2-VASc scores.[28] In several case reports and case series, most patients' LA or LAA thrombi disappeared after prolonged oral anticoagulation, but the duration of anticoagulation was longer than 3-4 weeks.[29-36] On the other hand, in

Table 4. *The comparison of baseline characteristics between with and without thrombus resolution*

	Thrombus resolution (N = 19)	No thrombus resolution (N = 3)	*P* value
The site of thrombus			.952
LA	6 (31.6)	1 (33.3)	
LAA	13 (68.4)	2 (66.7)	
General demographics			
Age (y)	72.0 ± 12	75.7 ± 10	.604
Male gender	14 (73.7)	1 (33.3)	.227
Comorbidities			
CAD	5 (26.3)	1 (33.3)	.800
Heart failure	9 (47.4)	1 (33.3)	.650
Hypertension	14 (73.7)	1 (33.3)	.163
Diabetes	10 (52.6)	0 (0)	.089
Prior stroke or TIA	4 (21.1)	3 (100)	.006
Thyroid disease	2 (10.5)	0 (0)	.556
Chronic kidney disease > stage 3	5 (26.3)	0 (0)	.312
Atrial fibrillation			.300
Paroxysmal	8 (42.1)	0	
Persistent/long-standing	11 (57.9)	3 (100)	
CAHDS2 score	2.84 ± 1.86	3.33 ± 1.53	.671
CHA2DS2-VASc score	3.74 ± 2.10	4.68 ± 2.08	.485
LVEF (%)	55.63 ± 15.44	60.00 ± 6.08	.639
LA diameter (mm)	48.32 ± 6.49	50.33 ± 1.53	.605
Ischemic stroke event (%)	0 (0)	0 (0)	-
One-year cardiovascular mortality (%)	1 (5.3)	0 (0)	.684
One-year all-cause mortality (%)	1 (5.3)	0 (0)	.684

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

Data are expressed as mean ± SD or as number (percentage).

previous TEE study or CLOT-AF study, not all patients experienced LA or LAA resolution.[37,38] In real-world practice, not all patients are willing to receive short-term follow-up TEE for status of LA or LAA thrombus, because this procedure causing discomfort. Although TEE is a relatively low-risk procedure, it may cause some complications such as dental trauma and some injury of the esophagus and upper gastrointestinal tract if the patient cannot cooperate.[39] Moreover, the use of anticoagulation also increased the possibility of bleeding during echoscope insertion. Therefore, in clinical scenario, we may prolong the follow-up period for LA or LAA thrombus after anticoagulation use, even if the guideline suggests the follow-up period of TEE is 3-4 weeks. The guidelines classify this recommendation of TEE follow-up of 3-4 weeks as class I recommendation, level of evidence C.[1] One meta-analysis study showed that computed tomography could be considered a noninvasive alternative to TEE for detecting LA/LAA thrombus,[40] but computed tomography could not detect spontaneous echo contrast. Therefore, TEE is still a necessary tool to evaluate intra-atrial thrombus and spontaneous echo contrast, but the duration of follow-up may be extended in real-world practice, especially for the patients with high CHA2DS2-VASc score, large LA, and long-standing AF.

In our study, most patients with LA/LAA thrombus had hypertension, persistent AF, or high CHA2DS2-VASc score. The resolution rate was 86.4% and the average resolution time was around 258.47 ± 218.17 days. During thrombus resolution with oral antithrombotic, a low ischemic stroke rate (4.9%) was noted. Four patients with inappropriate reduced dosage of NOAC had LA or LAA thrombus, which was resolved after titration to standard recommended dosage. Three patients' LAA thrombus could not be resolved even with a high INR and different NOAC use. In real-world practice, most physicians favored titration of the dosage of NOAC or warfarin for LA or LAA thrombi. However, some organized thrombus and spontaneous echo contrast still existed in the patients with high CHA2DS2-VASc scores, large LA, and long-standing AF even with adequate dosage of oral anticoagulants and prolonged duration of anticoagulation.

According to previous studies, including single case report, case series, cohort studies, and randomized studies (Table 5), the average times for LA or LAA thrombus resolution are listed. In the TEE study, the resolution rate was 81.8% in the patients with warfarin use for LAA thrombus during a 4-9-weeks follow-up period.[37] In the prospective X-TRA study and CLOT-AF registry, the resolution rates in patients with rivaroxaban for LA or LAA thrombus were 41.5% and 62.5%, respectively.[38] In several case reports, LA or LAA thrombi could be resolved regardless of the kind of NOAC prescribed.[29-36]

Limitations

This was a retrospective single center study about LA or LAA thrombus resolution and 46.3% (19/41) of patients were missed to carried out follow-up TEE. However, we still shared the precious view and results of the clinical outcomes about optimized anticoagulation for LA or LAA thrombus. Our research also provides strategies into possible improvements in treatment for LA or LAA thrombus resolution in real-world practice.

Conclusions

In real-world practice, most physicians favored titration of the dosage of NOAC or warfarin for LA or LAA thrombus. LA or LAA thrombus could exist if the patient received a reduced dose of NOAC. High frequency of LAA or LA thrombi could resolve, and a low incidence of ischemic stroke occurred after adjustment of oral anticoagulant treatment.

Table 5. *Published studies and case-report studies on LA or LAA thrombus resolution with warfarin or NOACs*

Study or case report	Anticoagulation	The site of thrombus	Duration (weeks)	The percentage of resolution
TEE study	Warfarin	LAA	4-9	81.8 (9/11)
Case series	Dabigatran 150 mg bid	LA	≧ 6	100 (3/3)
Case report	Dabigatran 150 mg bid	LAA	4	100 (1/1)
Case report	Dabigatran 150 mg bid	LA	12	100 (1/1)
X-TRA study	Rivaroxaban 20/15 mg qd	LA/LAA	6-8	41.5 (22/53)
CLOT-AF registry	Rivaroxaban 20/15 mg qd	LA/LAA	3-12	62.5 (60/96)
Case report	Rivaroxaban 15 mg qd	LAA	6	100 (1/1)
Case report	Rivaroxaban 10 mg qd	LAA	5	100 (1/1)
Case report	Apixaban 5mg bid	LAA	2	100 (1/1)
Case report	Apixaban 2.5 mg bid	LAA	11	100 (1/1)
Case report	Edoxaban 60/30 mg qd	LAA	2	100 (2/2)

Abbreviations: LA, left atrium; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant; TEE study, transesophageal echocardiography study.

X-TRA study, exploring the efficacy of once daily oral rivaroxaban for treatment of thrombus in left atrial/left atrial appendage in subjects with nonvalvular atrial fibrillation or atrial flutter study; CLOT-AF registry, retrospective registry providing baseline data on the outcome of left atrial or la appendage thrombus in patients with nonvalvular atrial fibrillation or atrial flutter after standard of care anticoagulant therapy.

Human Rights Statements and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

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