ORIGINAL ARTICLE

Left atrial appendage thrombus in patients referred for electrical cardioversion for atrial fibrillation: a prospective single-center study

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KEY WORDS

anticoagulation, atrial fibrillation, cardioversion, left atrial appendage, thrombus

ABSTRACT

INTRODUCTION Left atrial appendage thrombus (LAAT) is a risk factor for stroke; however, the actual health risk associated with LAAT in patients with atrial fibrillation (AF) on chronic anticoagulation is unknown.

OBJECTIVES We aimed to assess the prevalence and predictors of LAAT, and its predictive role in relation to mortality, stroke, and systemic thromboembolic events among consecutive AF patients on oral anticoagulation (OAC) admitted for electrical cardioversion.

PATIENTS AND METHODS This was a prospective, single-center cohort study. The participants underwent transesophageal echocardiography before electrical cardioversion. A total of 296 patients were enrolled. The primary outcome was the presence of LAAT. All participants were followed for 12 months to evaluate the incidence of systemic thromboembolic events, stroke, and death.

RESULTS Despite uninterrupted OAC in patients with AF of above 48-hour duration scheduled for cardioversion, we found a high prevalence of LAAT, reaching 14.5%. There was no difference in the prevalence of thrombi between different types of OAC ($P = 0.26$). The independent predictors of LAAT were chronic obstructive pulmonary disease, heart failure, prior myocardial infarction, greater left atrial diameter, lower left ventricular ejection fraction, higher CHA_2DS_2-VASc score, and reduced dabigatran dose. The optimal cutoff values for the prediction of LAAT were the age of at least 74 years, left atrial diameter equal or greater than 52 mm, left ventricular ejection fraction equal or lower than 40%, and CHA_2DS_2-VASc score equal or greater than 3. No strokes or systemic thromboembolic events occurred over the follow-up period.

CONCLUSIONS The presence of LAAT had no practical value for predicting stroke, thromboembolic events, or death in patients with AF and on chronic anticoagulation.

INTRODUCTION Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. The prevalence of AF is now estimated at 2%, which doubles that reported in the last decade.[1] Stroke is one of the main issues associated with AF.[2-4] Stroke risk stratification in AF patients represents an issue more complicated than a simple arrhythmia-related calculation.[4] Left atrial appendage thrombus (LAAT) is regarded as a risk factor for stroke in these patients[4-6]; however, the actual LAAT-related health risk in AF patients on chronic anticoagulation remains unknown.[7] The prevalence and risk factors of LAAT in AF patients on oral anticoagulation (OAC) (ie, vitamin K antagonists [VKAs] and non-VKA oral anticoagulants [NOACs]) have not yet been fully determined in a real-world setting. It seems that beyond the presence of LAAT, left atrial appendage morphology, thrombus age, and medical management and procedures (ie, cardioversion, conservative management) also contribute to the stroke risk in that group of patients.[4] Restoration of sinus rhythm in AF patients increases the stroke risk[8,9]; however, the stroke mechanism in these clinical conditions can be difficult to elucidate.[4] Appropriate anticoagulant therapy reduces the stroke risk in patients with AF undergoing

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WHAT'S NEW?

Patients with atrial fibrillation (AF) are at a risk of stroke. However, the risk stratification remains complicated. It is currently unknown whether left atrial appendage thrombus (LAAT) in patients with AF on chronic anticoagulation contributes significantly to that risk. In this study, during a 12-month follow-up, we investigated mortality, stroke, and systemic thromboembolic events in patients with AF on oral anticoagulation and transesophageal echocardiography–confirmed LAAT. No stroke or thromboembolic events were recorded, and deaths (1.01%) in the LAAT group were not considered LAAT-related. We speculate that the presence of LAAT might not serve as a real indicator of inadequacy of oral anticoagulation in patients with AF.

cardioversion.[4,10-12] Therefore, this study aimed to assess the prevalence and predictors of LAAT and to investigate the predictive role of LAAT in relation to mortality and the risk of stroke and systemic thromboembolic events among consecutive AF patients on OAC referred for cardioversion.

PATIENTS AND METHODS **Study group** Consecutive patients with AF on OAC were admitted to the cardiology department for transesophageal echocardiography (TEE)-guided direct current cardioversion (DCC). Of the 296 patients enrolled between December 2010 and June 2018, 226 (76.3%) underwent DCC. The inclusion criteria were the age of at least 18 years, arrhythmia duration longer than 48 hours, symptomatic or poorly tolerated arrhythmia, and OAC for longer than 3 weeks. The exclusion criteria were as follows: systolic blood pressure below 90 mm Hg, bradycardia below 60/bpm, signs of exacerbation of congestive heart failure (HF), symptoms of peripheral hypoperfusion, history of electrical cardioversion, history of ablation, any prosthetic heart valve, moderate to severe mitral stenosis defined as mitral orifice area equal to or lower than 1.5 cm^2 with mean pressure gradient of at least 5 mm Hg, and history of intracardiac thrombus. All patients were followed for 12 months from the day of TEE. The evaluation of clinical events included systemic thromboembolic events, stroke, and death.

Anticoagulation therapy All enrolled patients were on OAC therapy according to the current guidelines: VKA therapy with international normalized ratio (INR) equal to or above 2.0, or uninterrupted NOAC for at least 3 weeks before inclusion in the study.[13-16] For patients on a VKA regimen, INR was tested every week for 3 weeks, with all the outcomes expected to be in the therapeutic range. For patients on dabigatran, treatment with 150 mg twice daily was required, but 110 mg twice daily was also allowed for those fulfilling the following criteria: age at least 80 years and / or concomitant use of verapamil and / or estimated glomerular filtration rate 30–49 ml/min/1.73 m^2 and / or a HAS-BLED score equal to or above 3.[14] In the case of rivaroxaban, treatment with 20 mg once daily was required; however, 15 mg once daily was also allowed in patients fulfilling the following criteria: estimated glomerular filtration rate 15–49 ml/min/1.73 m^2 and / or HAS-BLED score equal to or above 3. In the case of apixaban, treatment with 5 mg twice daily was required, but 2.5 mg twice daily was also allowed in patients fulfilling at least 2 of the following criteria: age at least 80 years, body weight equal to or below 60 kg, and serum creatinine level at least 1.5 mg/dl. Glomerular filtration rate was assessed according to the MDRD formula.[17] The first patients treated with a VKA, dabigatran, rivaroxaban, and apixaban were enrolled on December 14, 2010, March 6, 2013, October 6, 2015, and November 7, 2016, respectively.

Echocardiographic examination All examinations were performed by 3 independent, certified echocardiographers using a Vivid E9 (GE Vingmed Ultrasound AS, Horten, Norway) ultrasound machine with a multiplanar transducer according to the approved protocol.[18] On TEE, the left atrial appendage was visualized in the mid-esophageal view with an appropriate total gain and depth. The imaging plane of the TEE transducer was axially rotated from 0° to 180° to better visualize the contours of the endocardium. The thrombus was defined as a uniformly echo-dense intracavitary mass with defined margins distinct from the endocardium and seen throughout systole and diastole, observed in more than one imaging plane, and not related to the pectinate muscles.[19,20] Left ventricular ejection fraction (LVEF) was calculated using the Simpson's biplane method and manual tracing on 2-dimensional apical 4- and 2-chamber view.[21] The anteroposterior diameter of the left atrium (LA) was assessed in end-systole in a plane perpendicular to the long axis of the ascending aorta in the parasternal long-axis view. All transthoracic echocardiogram and TEE examinations were recorded and stored, and were available for re-evaluation if needed.

Statistical analysis Quantitative data were presented as arithmetic mean and SD or median and interquartile ranges, when appropriate. The numbers and percentages were used to describe qualitative data. Group comparisons were conducted using the Fisher exact test or the χ^2 test for qualitative variables. Due to a violation of the assumption of normality (normality of the distribution was checked with the Shapiro–Wilk test), the distributions of quantitative variables were compared using the Mann–Whitney test (for 2 groups) or the Kruskal–Wallis test (for more than 2 groups). For the comparison of distributions of more than 2 groups, post-hoc tests were conducted to define differences in pairs when the global null hypothesis about identical compared distributions was rejected. The χ^2 test or the Fisher exact test was used to compare qualitative variables in post-hoc tests. The *P* value for these post-hoc tests was not corrected for

multiple comparisons. Crude and adjusted odds ratios (ORs) and 95% CIs were calculated to determine the predictors of LAAT on TEE. A multivariable logistic regression model was built using the variables from the age- (<75 or ≥75 years) and sex-adjusted univariable analyses. Receiver operating characteristic (ROC) analysis was performed to assess whether quantitative variables had a significant ability to distinguish between the group with LAAT and the group without LAAT. The ROC analysis included calculation of the area under the curve. Quantitative predictors of LAAT on TEE received from the ROC analysis were transformed into qualitative variables with 2 categories and treated as dichotomous prior to further analyses using a previously defined cutoff point (optimal decision threshold). The optimal cutoff point was determined as the point maximizing the Youden index. For all tests, the *P* value below 0.05 was considered significant (2-tailed). All statistical analyses were performed using the R software package version 3.6.2 (R: language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

The study protocol was approved by the local ethics committee (reg. no. 21/2010). All procedures performed in this study were in accordance with the ethical standards of the local bioethics committee and the Declaration of Helsinki. Written informed consent was obtained from all patients.

RESULTS The baseline characteristics according to the anticoagulant agent administered are provided in TABLE 1. LAAT was detected in 43 patients (14.5%). There was no difference in the occurrence rate of LAAT between the groups receiving different anticoagulant agents. Patients with LAAT were older and more frequently had chronic obstructive pulmonary disease (COPD), HF, implantable cardioverter-defibrillator (ICD), previous coronary artery bypass grafting (CABG), greater LA diameter, lower LVEF, higher CHA_2DS_2-VASc score, and a CHA_2DS_2-VASc score equal to or above 2 (TABLE 2). In the dabigatran group, the dose was reduced in 12 patients (9.4%) without LAAT and in 7 patients (41.2%) with LAAT ($P = 0.002$). In the rivaroxaban group, the dose was reduced in 10 patients (14.5%) without LAAT and in 3 patients (27.3%) with LAAT ($P = 0.37$). Multivariable analysis demonstrated that the presence of COPD, HF, ICD, prior myocardial infarction, previous CABG, greater LA diameter, lower LVEF, higher CHA_2DS_2-VASc score, and reduced dabigatran dose (110 mg twice daily) were independent risk factors for thrombus formation in patients with AF (TABLE 3). ROC analysis identified age, LA diameter, LVEF, and CHA_2DS_2-VASc score as predictors of LAAT presence. Optimal cutoff values based on the Youden index for these variables were age of at least 74 years, LA diameter equal to or above 52 mm, LVEF equal to or below 40%, and CHA_2DS_2-VASc score of at least 3. Univariable and multivariable analyses confirmed their ability to predict LAAT presence (TABLE 4).

Effectiveness of electrical cardioversion DCC was performed in 226 patients and sinus rhythm was restored in 197 individuals without further complications. Ten patients with LAAT were prepared for DCC over the next 4 weeks. Of these, 7 still had LAAT confirmed in the control TEE. Dissolution of the thrombus was observed in 3 patients after changes in therapy from rivaroxaban to VKA, dabigatran to rivaroxaban, and dabigatran to apixaban, respectively (TABLE 5). Other patients with LAAT did not consent to a repeated TEE and underwent the heart-rate control strategy.

Follow-up Follow-up was completed for all participants. No stroke or systemic thromboembolic events occurred during the 12 months following TEE but there were 3 deaths (1.01%). All deaths occurred in the heart-rate control group in patients with HF with reduced ejection fraction and LAAT; however, these deaths were not considered LAAT-related.

DISCUSSION We demonstrated an unexpectedly high rate of LAAT despite the anticoagulation managed according to the guidelines; however, the LAAT predictive value during 12 months of follow-up was not confirmed. Nevertheless, LAAT identification prior to DCC affects the decision-making process. We hypothesize that our results may suggest the need for a greater caution, watchfulness, and discretion in patients at high LAAT risk referred for DCC without TEE guidance. Interestingly, the reduced dabigatran dose was more frequently observed in the LAAT group, and it affected the LAAT presence in the logistic regression. Moreover, in the sex- and age- adjusted multivariable model, greater LA diameter, decreased LVEF, and CHA_2DS_2-VASc score were the predictors of the LAAT presence.

As per the European Society of Cardiology and American Heart Association's recommendations for AF,[2,3,22] the crucial aspect of the AF therapeutic strategy is the prevention of stroke and thromboembolic events. OACs reduce stroke risk but do not eliminate it and may be associated with serious side effects. In recent years, the widespread use of novel anticoagulants has been observed. Owing to the relatively short observation time, the effectiveness of individual NOACs has been intensively studied and compared to the effectiveness of VKAs in various clinical situations. The rules for DCC preparation in patients with persistent AF on VKAs were developed following small, nonrandomized trials.[8,23] Dabigatran was introduced after a post-hoc analysis of the randomized RE-LY study.[24] Rivaroxaban was included after a post-hoc analysis of the randomized ROCKET-AF study and considering the results of the X-VeRT study, which compared its effectiveness with that of VKAs.[25,26]

TABLE 1 Baseline characteristics according to the anticoagulant agent

Variable	VKA (n = 61)	Rivaroxaban (n = 80)	Dabigatran (n = 145)	Apixaban (n = 10)	*P* value
Age, y	67 (61–71)	66.5 (60.8–70.2)	64 (58–70)	67.5 (63.5–70.8)	0.33
Age range, y	27–87	31–87	32–82	42–75	N/A
Female sex	23 (37.7)	31 (38.8)	56 (38.6)	4 (40.0)	>0.99
BMI, kg/m^2	29 (26–32.2)	29.4 (27.2–32.8)	29.1 (27.2–32.6)	29.2 (26.4–31.3)	0.81
SBP, mm Hg	120 (120–130)	129 (120–130)	120 (120–130)	125 (120–130)	0.73
DBP, mm Hg	80 (70–80)	80 (70–80)	80 (70–80)	80 (72.5–80)	0.79
Heart rate, bpm	94 (85–110)	93 (83–110)	90 (80–110)	114 (98–117.2)	0.19
COPD	3 (4.9)	3 (3.8)	7 (4.8)	1 (10.0)	0.72
Arterial hypertension	48 (78.7)	62 (77.5)	108 (74.5)	8 (80.0)	0.93
Heart failure	27 (44.3)	25 (31.2)	44 (30.3)	6 (60.0)	0.08
Myocardial infarction	7 (11.5)	6 (7.5)	7 (4.8)	0	0.33
Peripheral artery disease	1 (1.6)	1 (1.2)	2 (1.4)	0	>0.99
CABG	3 (4.9)	2 (2.5)	2 (1.4)	0	0.46
Diabetes mellitus	8 (13.1)	21 (26.2)	25 (17.2)	1 (10.0)	0.2
Stroke/TIA/systemic thromboembolism	6 (9.8)	5 (6.2)	10 (6.9)	1 (10.0)	0.71
Current smoker	3 (4.9)	8 (10.0)	16 (11.0)	2 (20.0)	0.3
eGFR, ml/min/1.73 m^2	60.6 (52.5–68.1)	65.8 (55.7–74.7)	66.2 (58.3–76.2)	58.5 (45.9–69)	0.049
P values for eGFR	vs Rivaroxaban: 0.15 Dabigatran: 0.01 Apixaban: 0.75	vs Dabigatran: 0.3 Apixaban: 0.29	vs Apixaban: 0.13	–	N/A
eGFR ≥60 ml/min/1.73 m^2	33 (54.1)	51 (63.8)	97 (66.9)	5 (50.0)	0.26
eGFR 50.0–59.9 ml/min/1.73 m^2	18 (29.5)	15 (18.8)	32 (22.1)	2 (20.0)	
eGFR 30.0–49.9 ml/min/1.73 m^2	9 (14.8)	12 (15.0)	16 (11.0)	3 (30.0)	
eGFR <30 ml/min/1.73 m^2	1 (1.6)	2 (2.5)	0	0	
LA diameter, mm	46 (42–50)	44 (42–48)	45 (42–48)	46 (43.5–50)	0.52
LVEF, %	51 (45–60)	58.5 (48.8–61)	59 (51–60)	55 (38.5–60)	0.02
P values for LVEF	vs Rivaroxaban: 0.01 Dabigatran: 0.002 Apixaban: 0.44	vs Dabigatran: 0.68 Apixaban: 0.65	vs Apixaban: 0.52	–	N/A
LVEF ≥50%	38 (62.3)	59 (73.8)	121 (83.4)	6 (60.0)	0.01
LVEF 40%–49%	10 (16.4)	13 (16.2)	10 (6.9)	1 (10.0)	
LVEF <40%	13 (21.3)	8 (10.0)	14 (9.7)	3 (30.0)	
LVEF <50%	23 (37.7)	21 (26.2)	24 (16.6)	4 (40.0)	0.005
P values for LVEF <50%	vs Rivaroxaban: 0.14 Dabigatran: 0.001 Apixaban: 1	vs Dabigatran: 0.08 Apixaban: 0.45	vs Apixaban: 0.08	–	N/A
LVEF <40%	13 (21.3)	8 (10.0)	14 (9.7)	3 (30.0)	0.03
P values for LVEF <40%	vs Rivaroxaban: 0.06 Dabigatran: 0.02 Apixaban: 0.68	vs Dabigatran: 0.93 Apixaban: 0.1	vs Apixaban: 0.81	–	N/A
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)	2 (1–3)	3 (2.2–3.8)	0.17
CHA_2DS_2-VASc ≥2	52 (85.2)	68 (85.0)	102 (70.3)	8 (80.0)	0.03
P values for CHA_2DS_2-VASc score ≥2	vs Rivaroxaban: 0.97 Dabigatran: 0.02 Apixaban: 0.65	vs Dabigatran: 0.014 Apixaban: 0.65	vs Apixaban: 0.72	–	N/A
LAAT	13 (21.3)	11 (13.8)	17 (11.7)	2 (20.0)	0.26

Data are presented as number (percentage) or median (interquartile range) unless indicated otherwise.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CHA_2DS_2-VASc, scale for stroke and thromboembolic risk assessment; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implanted cardioverter--defibrillator; LA, left atrium; LAAT, left atrial appendage thrombus; LVEF, left ventricular ejection fraction; N/A, not applicable; SBP, systolic blood pressure; TIA, transient ischemic attack; VKA, vitamin K antagonists

TABLE 2 Clinical characteristics of patients with and without left atrial appendage thrombus

Variable	AF without thrombus (n = 253)	AF with thrombus (n = 43)	*P* value
Age, y	65 (59–70)	67 (62.5–75)	0.01
Age <65 y	120 (47.4)	15 (34.9)	0.003
Age 65–74 y	109 (43.1)	16 (37.2)	
Age ≥75 y	24 (9.5)	12 (27.9)	
Age ≥75 y	24 (9.5)	12 (27.9)	<0.001
Female sex	100 (39.5)	14 (32.6)	0.38
BMI, kg/m^2	29.3 (27–32.5)	27.9 (26.1–31.9)	0.16
SBP, mm Hg	120 (120–130)	125 (120–130)	0.76
DBP, mm Hg	80 (70–80)	80 (70–80.5)	0.41
Heart rate, bpm	92 (82–110)	96 (81–110)	0.78
COPD	9 (3.6)	5 (11.6)	0.04
Arterial hypertension	195 (77.1)	31 (72.1)	0.48
Heart failure	74 (29.2)	28 (65.1)	<0.001
Myocardial infarction	14 (5.5)	6 (14.0)	0.053
Peripheral artery disease	3 (1.2)	1 (2.3)	0.47
CABG	3 (1.2)	4 (9.3)	0.01
Diabetes mellitus	46 (18.2)	9 (20.9)	0.67
Stroke/TIA/systemic thromboembolism	19 (7.5)	3 (7.0)	>0.99
eGFR, ml/min/1.73 m^2	64.6 (55.6–74.8)	61.7 (51.7–74.7)	0.51
ICD	4 (1.6)	9 (20.9)	<0.001
Current smoker	24 (9.5)	5 (11.6)	0.59
LA diameter, mm	44 (42–48)	47 (45–54)	<0.001
LA diameter >40 mm	213 (84.2)	39 (90.7)	0.27
LVEF, %	59 (50–60)	45 (20.5–57)	<0.001
LVEF ≥50%	206 (81.4)	18 (41.9)	<0.001
LVEF 40%–49%	28 (11.1)	6 (14.0)	
LVEF <40%	19 (7.5)	19 (44.2)	
LVEF <40%	19 (7.5)	19 (44.2)	<0.001
CHA_2DS_2-VASc score	3 (1–3)	3 (3–4)	<0.001
CHA_2DS_2-VASc score 0	20 (7.9)	0 (0.0)	0.006
CHA_2DS_2-VASc score 1	44 (17.4)	2 (4.7)	
CHA_2DS_2-VASc score ≥2	189 (74.7)	41 (95.3)	
CHA_2DS_2-VASc score ≥2	189 (74.7)	41 (95.3)	0.003

Data are presented as number (percentage) or median (interquartile range).

Abbreviations: see **TABLE 1**

Apixaban was added after a post-hoc analysis of the randomized ARISTOTLE study and the results of the EMANATE study, which compared its effectiveness with VKAs.[27,28] Despite uninterrupted OAC therapy in patients with longer than 48-hour AF scheduled for DCC, we revealed an unexpectedly high prevalence of LAAT that reached 14.5%. There was no difference in the prevalence of thrombi between different types of OAC (*P* = 0.26). Previous reports also described the presence of thrombi in patients being prepared for DCC with VKAs and NOACs but this percentage was significantly lower. In a study by Schaeffer et al,[29] the overall prevalence of thrombus formation was 4.7%; patients without anticoagulation therapy showed the highest prevalence (9.5%), whereas patients receiving anticoagulation therapy had a lower but still remarkable rate of thrombus occurrence (4.1%). Moreover, the thrombi were diagnosed at a lower rate in the NOAC group than in the VKA group (2.5% vs 5.3%, *P* = 0.02).[29] A study of a Korean population of 424 patients showed the presence of thrombi in 2.2% of patients prepared for DCC with VKA, as compared with 4.3% of those receiving NOAC (*P* = 0.28).[30] An exceptionally low rate of thrombi was found in studies performed before DCC in a group of 510 Italian patients with persistent AF treated with a VKA (0.6%) and dabigatran (0.6%).[31] Frenkel et al[32] demonstrated that the prevalence of LA thrombus in patients prepared for catheter ablation of AF and atrial flutter (AFL) on NOACs was 4.4%, which was comparable to those on warfarin. Additionally, congestive HF was identified as a predictor of LA thrombus formation. Gorczyca et al[33] retrospectively evaluated 1256 AF patients on dabigatran or rivaroxaban and revealed a 4.1% TEE thrombus detection rate prior to DCC or catheter ablation, regardless of the anticoagulant agent used. However, the significant LAAT predictors in patients treated with dabigatran were nonparoxysmal AF (vs paroxysmal AF), HF, and eGFR below 60 ml/min/1.73 m^2; the predictors in patients treated with rivaroxaban were nonparoxysmal AF (vs paroxysmal AF) and HF. Jaroch et al[34] retrospectively evaluated 202 patients with persistent AF, who underwent TEE before electrical cardioversion, and revealed the presence of LAAT/sludge in 31 and a spontaneous echo contrast in 25 individuals. In addition, they reported the duration of AF exceeding 1 year, LA diameter exceeding 51 mm, left ventricular end-diastolic dimension exceeding 52 mm, and radiographic evidence of aortic plaque as the independent predictors of the presence of LAAT, sludge, and spontaneous echo contrast. Angelini et al[35] performed TEE in 352 consecutive patients with nonvalvular AF treated with NOACs. Left atrial thrombus (LAT) / LAAT was detected in 27 patients (7.7%). A CHA_2DS_2-VASc score above 3 and obesity were major thrombus predictors. In a review of 23 studies including patients with nonrheumatic AF and variable anticoagulation status, TEE, autopsy, or surgical evaluation identified thrombus in 17% of 1288 cases.[5] Overall, the prevalence of LAAT in AF patients on OAC seems to be lower than in those without OAC. However, direct prospective comparisons have never been reported.[7]

In our study, the LAAT resolution was evident in a repeated TEE in 3 cases (30%). In the X-TRA study[36], thrombus resolution or reduction was evident in 60.4% of patients; in the CLOT-AF study[36], thrombus resolution rate was 62.5%. The X-TRA was a multicenter study examining LAT/LAAT resolution with rivaroxaban in VKA/NOAC-naïve patients or in patients

TABLE 3 Uni- and multivariable logistic regression analyses for the prediction of left atrial appendage thrombus formation in patients with atrial fibrillation receiving chronic anticoagulation

Variable	Crude OR	*P* value	Sex- and age-adjusted OR	*P* value
Age, y	1.05 (1.01–1.1)	0.01	N/A	N/A
Age ≥65 (vs <65) y	1.68 (0.87–3.38)	0.13	N/A	N/A
Age ≥75 (vs <75) y	3.69 (1.64–8.03)	0.001	N/A	N/A
Female sex	0.74 (0.36–1.44)	0.39	N/A	N/A
BMI, kg/m^2	0.95 (0.88–1.03)	0.21	0.97 (0.89–1.05)	0.43
BMI ≥25 (vs <25) kg/m^2	1.12 (0.41–3.94)	0.84	1.35 (0.47–4.98)	0.61
SBP, mm Hg	0.99 (0.97–1.03)	0.73	1 (0.97–1.03)	0.78
DBP, mm Hg	1.02 (0.98–1.06)	0.37	1.02 (0.98–1.07)	0.34
Heart rate, bpm	1 (0.99–1.02)	0.78	1 (0.99–1.02)	0.63
COPD	3.57 (1.05–1.91)	0.03	3.52 (0.99–11.28)	0.04
Arterial hypertension	0.77 (0.38–1.64)	0.48	0.75 (0.36–1.62)	0.44
Heart failure	4.52 (2.31–9.14)	<0.001	4.36 (2.19–8.99)	<0.001
Myocardial infarction	2.77 (0.93–7.38)	0.049	2.96 (0.98–8.09)	0.04
Peripheral artery disease	1.98 (0.1–15.91)	0.56	1.39 (0.06–12.42)	0.79
CABG	8.55 (1.82–44.78)	0.006	9.95 (2.06–53.59)	0.004
Diabetes mellitus	1.19 (0.51–2.56)	0.67	1.15 (0.48–2.52)	0.74
Stroke/TIA/systemic thromboembolism	0.92 (0.21–2.87)	0.9	1.1 (0.25–3.52)	0.88
eGFR, ml/min/1.73 m^2	0.99 (0.97–1.01)	0.46	1 (0.97–1.02)	0.8
eGFR <60 (vs ≥60) ml/min/1.73 m^2	1.41 (0.73–2.71)	0.3	1.24 (0.57–2.61)	0.58
Severe mitral regurgitation	6.12 (0.72–52.18)	0.07	5.36 (0.57–49.18)	0.11
Hypertrophic cardiomyopathy	1.18 (0.06–7.56)	0.88	1.73 (0.09–11.58)	0.62
PFO	1.28 (0.29–4.14)	0.71	1.14 (0.25–3.91)	0.84
ICD	16.48 (5.08–63.6)	<0.001	15.48 (4.55–61.65)	<0.001
Current smoker	1.26 (0.4–3.25)	0.66	1.38 (0.43–3.73)	0.55
LA diameter, mm	1.14 (1.08–1.22)	<0.001	1.15 (1.08–1.23)	<0.001
LA diameter >40 (vs ≤40) mm	1.83 (0.69–6.35)	0.27	1.83 (0.67–6.49)	0.28
LVEF, %	0.93 (0.91–0.95)	<0.001	0.92 (0.9–0.95)	<0.001
LVEF <50 (vs ≥50)%	6.09 (3.09–12.22)	<0.001	6.35 (3.09–13.47)	<0.001
LVEF <40 (vs ≥40)%	9.75 (4.57–21.12)	<0.001	1.82 (4.72–25.67)	<0.001
CHA_2DS_2-VASc score per 1	1.46 (1.16–1.85)	0.002	1.5 (1.14–1.99)	0.004
CHA_2DS_2-VASc score ≥2 (vs <2)	6.94 (2.05–43.35)	0.009	7.16 (2.03–45.54)	0.009
Dabigatran 110 (vs 150) mg	6.77 (2.18–21.03)	0.001	6.92 (1.94–24.65)	0.003

Abbreviations: OR, odds ratio; PFO, patent foramen ovale; others, see **TABLE 1**

TABLE 4 Uni- and multivariable logistic regression analyses for the prediction of the left atrial appendage thrombus formation in patients with atrial fibrillation

Variable	Crude OR	*P* value	Sex-and age-adjusted OR	*P* value
Age ≥74 (vs <74) y	3.33 (1.57–6.91)	0.001	N/A	N/A
LA diameter ≥52 (vs <52) mm	8.54 (3.93–18.72)	<0.001	9.38 (4.05–22.17)	<0.001
LVEF ≤40 (vs >40)%	1.55 (5.03–22.52)	<0.001	1.75 (4.84–24.69)	<0.001
CHA_2DS_2-VASc score ≥3 (vs <3)	3.12 (1.53–6.93)	0.003	3.04 (1.36–7.21)	0.008

Abbreviations: see **TABLE 1**

with suboptimal VKA therapy with nonvalvular AF or AFL. The aim of the CLOT-AF[36] registry was to provide retrospective thrombus--related patient outcome data after standard--of-care anticoagulant therapy in individuals with AFL or nonvalvular AF who had documented LAT/LAAT on TEE.[36] In contrast, the RIVA--TWICE study[37] showed that the increased dose of rivaroxaban (15 mg twice daily in patients with AF and LAAT despite rivaroxaban 20 mg once a day) was associated with LAAT resolution in 46.7% of the participants. Unfortunately, the RE-LATED_AFNET7 trial[38] on the efficacy of dabigatran in LAAT resolution has not been published due to its premature termination.

TABLE 5 Management of patients with thrombus

No.	Primary treatment	Thrombus	Secondary treatment	Thrombus on control TEE	Postponed DCC
1	VKA	+	VKA	+	N
2	Rivaroxaban	+	VKA	+	N
3	VKA	+	Dabigatran	+	N
4	Rivaroxaban	+	VKA	–	Y
5	Dabigatran	+	VKA	+	N
6	Dabigatran	+	Apixaban	+	N
7	Rivaroxaban	+	Dabigatran	+	N
8	Dabigatran	+	Rivaroxaban	–	Y
9	Dabigatran	+	Apixaban	–	Y
10	Apixaban	+	Apixaban	+	N

Abbreviations: DCC, direct current cardioversion; TEE, transesophageal echocardiography; N, no; Y, yes; others, see **TABLE 1**

We speculate that the shorter period from the initial to final TEE, the unknown thrombus age (ie, acute vs organized), no application of nonstandard anticoagulation, and the smaller number of LAAT-positive participants may serve as the possible explanation for the relatively low thrombus resolution rate (30%) in our study.

Chronic kidney disease remains an important issue in NOAC dosing protocols. GFR estimation methods are currently being discussed.[39,40] The unequivocal superiority of the Cockcroft-Gault formula has not been proven, and the source of criticism is in the lack of standardization of creatinine assays used for the method development and differences between the estimated and measured creatinine clearance. A significant proportion of our patients had heart failure, and thus fluid retention, which might have increased the patients' body mass. Finally, the MDRD formula was considered more specific for detecting lower GFR values.[40]

An unexpectedly high thrombus identification rate was found in our study. Several confounders might have contributed to that finding. Unfortunately, we did not collect data on the total OAC duration and AF burden. In addition, we did not use any echocardiographic contrast agents to improve visualization and increase sensitivity of the LAAT detection. An alternative imaging modality (eg, computed tomography) would probably further decrease the false positive LAAT detection rate.

In view of the relatively high LAAT rate in the present study, we analyzed the potential risk factors for thrombus occurrence. Our findings are consistent with those of previous reports on the relationship between the prevalence of LAAT and clinical characteristics in patients with AF. These reports revealed that the occurrence of LAAT is associated with diabetes mellitus, hypertension, congestive HF, structural heart disease, cardiomyopathy, low flow rates in the LA appendage, spontaneous echocardiographic contrast in the LA appendage upon TEE, enlarged LA size, higher CHA_2DS_2-VASc score or $CHADS_2$ score, decreased LVEF, increased lobe number of the LA appendage, and previous thromboembolic events.[41-46]

LAAT is regarded as a stroke risk factor in patients with AF[4-6]; however, the predictive role of LAAT in relation to mortality and the risk of stroke and systemic thromboembolic events in AF patients on a chronic OAC regimen remains unknown. It might be speculated that the stratification of stroke risk also considers the LA appendage morphology, thrombus age, medication, and procedures (ie, conservative treatment, cardioversion, and ablation), in addition to the presence of LAAT. AF-related thrombogenesis is a complex process and is considered more severe in structurally abnormal hearts. It is known that the restoration of sinus rhythm in patients with AF increases stroke risk[8]; however, the stroke mechanism in patients with this clinical condition can be difficult to establish. Proper anticoagulation decreases stroke risk in AF patients undergoing cardioversion.[4,10-12] In a study of 2150 patients, Frederiksen et al[47] demonstrated a low thromboembolic complication rate for non-TEE–guided cardioversions in AF patients receiving OAC therapy; thromboembolism occurred in 1 of 684 patients (0.15%) receiving NOAC and 2 of 1466 patients (0.14%) receiving warfarin (risk ratio, 1.07; 95% CI, 0.10–11.81). In the ACUTE[10] study, among 1222 patients with AF longer than 2 days, there was no significant difference in the rate of embolic events between an early TEE-guided cardioversion and a conventional approach of 3 weeks of warfarin anticoagulation prior to cardioversion (0.8% vs 0.5%, respectively; $P = 0.5$). Moreover, at 8 weeks, there were no significant differences between these groups in the rates of death, maintenance of sinus rhythm, or functional status.[10] In the present study, cardioversion was not performed in patients with thrombi; there were no exceptions. Nevertheless, an extrapolation from the study by Frederiksen et al[47] and the ACUTE study[10] suggests that cardioversion after 3 weeks of effective OAC carries the same thromboembolic risk irrespective of whether the thrombus is present on TEE.

The long-term clinical consequences of LAAT in patients with AF under OAC are not well documented, and the actual risk of stroke, thromboembolic events, and deaths associated with these pathologies is unknown. A study of 424 AF patients on OAC with 12-month follow-up showed that ischemic strokes occurred significantly more often in the LAAT group than in the group without LAAT (7.1% vs 4.4%; $P = 0.001$).[48] In contrast, in a study of 55 AF patients over a 34-month follow-up, no significant effect of the presence of LAAT on the incidence of stroke and death was demonstrated,[49] which was consistent with the study by Nair et al[50] in which the stroke incidence in the AF patients in the groups with and without LAT/LAAT did not differ significantly. It should be noted, however, that not all patients in these 2 studies were treated with anticoagulants.

In the present study, during the 12-month follow-up, no stroke or thromboembolic events were recorded. We speculate that the uneventful follow-up rather than the absence of LAAT might be a real indicator of the adequacy of OAC therapy in patients with AF, and the predictive role of LAAT in relation to mortality, stroke, and systemic thromboembolic events among patients with AF and chronic OAC remains unclear.

Study limitations Our study has several limitations. First, although all consecutive patients were included, the sample size was relatively small. Second, we did not examine patients on edoxaban. Third, we did not use echocardiographic contrast agents for assessment of the endocardial borders, structural abnormalities, or left ventricular function. Therefore, some extent of hypersensitivity in the LAAT recognition cannot be excluded. Fourth, we used the MDRD formula to estimate the GFR, which was designed for individuals with a body surface area of 1.73 m^2, and we did not calculate the body surface area. Therefore, incorrect dosing of dabigatran and rivaroxaban may have occurred. Fifth, we did not examine the total duration of OAC intake prior to the study inclusion. Sixth, we did not examine the total duration of arrhythmia prior to the study inclusion. Seventh, we did not calculate the LA area and volume. Eighth, we did not examine the association between the morphology of the LAA and the emptying velocities of the LAA and LAAT. Ninth, we were not able to observe enough secondary outcomes as the study was not adequately powered due to the short follow-up and small sample size.

Conclusions Despite the unexpectedly high LAAT presence rate, these thrombi had no practical value in mortality, stroke, and systemic thromboembolic event prediction among patients with AF and chronic OAC.

ARTICLE INFORMATION

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