Prevalence and Resolution of Left Atrial Thrombus in Patients With Nonvalvular Atrial Fibrillation and Flutter With Oral Anticoagulation

Adam D. Niku, MD[a], Takahiro Shiota, MD[b], Robert J. Siegel, MD[b], and Florian Rader, MD, MSc[b,*]

Left atrial appendage (LAA) thrombus in nonvalvular atrial fibrillation or flutter (AF) is a major cause of stroke and presents a therapeutic dilemma in a rhythm-control strategy. The prevalence and resolution of LAA thrombus has not been studied well in the era of non−vitamin K antagonist oral anticoagulant use. This study sought to establish (1) the prevalence of LAA thrombus (2) the prevalence of LAA thrombus despite antithrombotic therapy, (3) the rate of persistence of LAA thrombus despite appropriate anticoagulant prescriptions, and (4) determinants of LAA thrombus persistence. Consecutive transesophageal echocardiograms (TEE) performed in patients with AF were reviewed to estimate the overall prevalence of LAA thrombus and the resolution rate in those with repeat studies. Multivariable logistic regression was used to identify clinical and echocardiographic predictors of thrombus resolution. Of 1,485 patients with AF, 117 (8%) had LAA thrombus. Of those, 62 had repeat TEE within 1 year and 58 (94%) were prescribed adequate anticoagulation in TEE studies (mean interval 96 ± 72 days). Thirty-seven patients (60%) had LAA thrombus resolution. Thrombus resolution rate was only 79% in patients considered on appropriate anticoagulation. Patients with persistent LAA thrombus were more likely to have diabetes; no other clinical or echocardiographic variable was independently associated with thrombus resolution. There was no significant difference in LAA thrombus resolution between non−vitamin K antagonist oral anticoagulants and warfarin. LAA thrombus persistence despite adequate anticoagulation is relatively common and difficult to predict clinically; TEE before electrical cardioversion should be considered regardless of anticoagulation status. **(Am J Cardiol 2019;123:63−68)**

Thromboembolic stroke due to left atrial appendage (LAA) thrombus is the most catastrophic complication of atrial fibrillation and atrial flutter (AF), and is a major risk in electrical cardioversion. Non−vitamin K antagonist oral anticoagulants (NOACs) are noninferior to warfarin before and after electrical cardioversion.[1−3] However, medication noncompliance is common,[4,5] and can lead to serious embolic complications after electrical cardioversion. This study aimed to establish (1) the prevalence of LAA thrombus, (2) the prevalence of LAA thrombus despite antithrombotic therapy, (3) the rate of LAA thrombus persistence on repeat transesophageal echocardiogram (TEE) despite appropriate anticoagulation, and (4) determinants of LAA thrombus persistence. Such real-world estimates will identify the risk associated with performing electrical cardioversion of AF without TEE in the NOAC era. In addition, our data may identify high-risk patients in whom TEE should be considered before cardioversion.

Methods

We reviewed 2,016 consecutive TEE studies performed in 1,485 individuals with AF between January 2013 and February 2017 in the Cedars-Sinai noninvasive laboratory. TEEs were identified by collecting a list of all studies performed with ICD coding for AF. For LAA thrombus prevalence estimates, we only considered a patient's first thrombus identification (1 study per individual patient). LAA sludge was treated as equivalent to thrombus because there is evidence that rates of thromboembolism are high in patients with LAA sludge[6] and cardioversion would be delayed in practice. Sludge (or prethrombus) was defined as a layered, viscid echodensity without a discrete mass, which was present throughout the cardiac cycle and not consistent with spontaneous echo-contrast.[6] Demographic and clinical characteristics were collected from electronic medical records. In addition, each chart was reviewed for documented antiplatelet and antithrombotic therapy. Echocardiographic variables were collected from our echocardiogram database. We identified patients with LAA thrombus or prethrombus who had a repeat TEE within 1 year to obtain estimates of thrombus persistence in all patients and in those prescribed appropriate antithrombotic medications. Finally, subsequent thromboembolic complications such as stroke, transient ischemic events, or peripheral thromboembolism in included patients were identified from chart review.

[a]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California; and [b]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California. Manuscript received July 9, 2018; revised manuscript received and accepted September 11, 2018.

See page 67 for disclosure information.

*Corresponding author: Tel: (310) 248-7641; fax: (310) 967-3805.
E-mail address: Florian.Rader@cshs.org (F. Rader).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.09.027

Patients with left atrial occluder devices and those with previous surgical LAA ligation were excluded. For prevalence estimates of LAA thrombus (but not rate of resolution) we included preoperative TEEs of patients who underwent LAA occluder device placement or orthotopic heart transplant (n = 4 and n = 1, respectively, with LAA thrombus). In patients with multiple TEEs performed for atrial fibrillation, we only considered the initial TEE for prevalence estimates. Many patients had multiple follow-up TEEs after LAA occluder device placement or heart transplant; these studies were excluded from analyses.

Descriptive statistics of patient characteristics are presented as mean and standard deviation for continuous variables and as percentages for categorical variables. Variables were compared with student *t* test and chi-square statistics, as appropriate. A logistic regression model with thrombus resolution as the dependent variable was created considering the following variables: age, ethnicity, gender, type of atrial fibrillation (paroxysmal vs chronic), history of diabetes, current smoking, history of hypertension, history of coronary artery disease, history of stroke or transient ischemic attack, history of heart failure, LV dysfunction, abnormal LAA emptying velocity, LAA configuration, severe mitral regurgitation, moderate or severe mitral stenosis, and CHA_2DS_2-VASC score. Paroxysmal atrial fibrillation was defined as a continuous episode of palpitations or documented atrial fibrillation lasting < 7 days with self-termination. We assessed colinearity of variables in the regression model with the variance inflation factor and considered values of > 4 suggestive of colinearity. Backward variable elimination of nonsignificant variables at an α-level ≥ 0.05 derived a parsimonious model for thrombus resolution. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) are reported. SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for statistical analyses. The Cedars-Sinai Institutional Review Board approved this retrospective study with the requirement for individual patient informed consent waived.

Results

Among 1,485 patients with AF underwent TEE, 117 patients (7.8%) were found to have LAA thrombus or prethrombus. Demographic and clinical characteristics of patients with LAA thrombus or prethrombus are shown in Table 1. Echocardiographic characteristics of patients with LAA thrombus are described in Table 2.

The antithrombotic regimens of patients with LAA thrombus or prethrombus are described in Table 3A. Among 117 patients with LAA thrombus, 61 were on an antiplatelet agent (including aspirin), and all but one of these was also on anticoagulation (warfarin, NOAC, or low molecular weight heparin [LMWH]). Among patients with repeat TEE, all were anticoagulated. Of 31 patients on warfarin, only 17 (59%) had international normalized ratio values ≥ 2.0 preceding the index TEE. Thirty-nine patients (33%) were prescribed a NOAC, with rivaroxaban being the most frequently prescribed (54%). Therefore, half of the patients (n = 56) who had LAA thrombus would be considered appropriately anticoagulated without the need for TEE before cardioversion per currently accepted standards.[10]

Of 117 patients with identified left atrial thrombus, 63 patients had a repeat TEE within 1 year (mean interval 96 $\pm$ 72 days) and documented continuous anticoagulant therapy. LAA thrombus resolution was seen in 37 (58.7%) of these patients (Figure 1). In total, 23 (20%) patients had electrical cardioversion within a year of the index TEE—3 after the index TEE and 20 after repeat (or third) TEE. There was no significant difference in resolution rates between those with true LAA thrombus and those with LAA sludge on initial TEE (62% and 55%, respectively). Among patients without thrombus resolution, 13 had true LAA thrombus on initial TEE. Of these, 11 (85%) had persistent thrombus on repeat TEE, while 2 (15%) had sludge. Further subgroup analysis was not performed due to low power and the fact that the presence of either finding would preclude cardioversion.

Anticoagulation regimen in TEEs is shown in Table 3B. Of the patients prescribed NOACs, 2 (7.1%) were prescribed dabigatran, 12 (43%) rivaroxaban, and 16 (50%) apixaban. Overall, 73% of patients were on appropriate anticoagulant medications before repeat TEE, but only 59% had thrombus resolution.

As shown in Table 1, patients without thrombus resolution in TEE studies were more likely to be diabetic and on antiplatelet therapy. A history of hypertension was numerically more frequent in those without thrombus resolution, while atrial flutter was numerically more frequent in patients with thrombus resolution. All other clinical and echocardiographic variables were similar in groups. LAA configurations were assessed for all patients. Fourty-nine (49%) had the "cauliflower" configuration, 48 (41%) had the "windsock" configuration, 12 (10%) had the "cactus" configuration, and only 6 (5%) had the "chickenwing" configuration. Two patients had unidentified LAA configurations due to incomplete long-axis imaging of the appendage. There were no significant differences in LAA thrombus resolution among different LAA configurations.

Limited by sample size, rates of resolution among different anticoagulation classes were statistically nonsignificant, although numerically more frequent with NOACs. Sixteen of 29 (55%) patients on warfarin had thrombus resolution on repeat TEE, while 21 of 32 (66%) patients on a NOAC had thrombus resolution (Figure 2). The fact that international normalized ratio levels in therapeutic range (> 2) in warfarin users was also not associated with LAA thrombus resolution suggests that lack of power for such comparisons may explain these results.

The only multivariable-adjusted determinant of thrombus persistence was a history of diabetes mellitus (OR 0.23, 95% CI 0.061 to 0.853, p = 0.028). Diabetes also remained the only significant predictor (OR 0.167, CI 0.029 to 0.965, p = 0.046) after exclusion of patients with severe mitral regurgitation, severe mitral stenosis, and low molecular weight heparin use. There was a trend for higher LV ejection fraction being associated with thrombus resolution, but this was not statistically significant (OR 1.42, 95% CI 0.91 to 2.21, p = 0.1). No other clinical or echocardiographic characteristic was predictive of thrombus persistence/

Table 1
Clinical characteristics

Variable	All subjects (n = 117)	Subjects with repeat TEE (n = 63)	Thrombus resolved (n = 37)	Thrombus not resolved (n = 26)	p Value resolved vs not resolved
Demographic Characteristics					
Age, (years)	73.6 (SD 12)	71.9 (SD 11.9)	72.5 (SD 13.4)	71 (SD 9.1)	0.6370
Men	52 (44%)	17 (27%)	10 (27%)	7 (27%)	0.9329
Non-Hispanic Black	18 (16%)	9 (14%)	5 (14%)	4 (15%)	1.000
Medical History					
Paroxysmal Atrial Fibrillation	21 (18%)	9 (14%)	5 (15%)	4 (14%)	0.2753
Atrial Flutter	10 (9%)	6 (10%)	6 (16%)	0 (0%)	0.0727
Smoker	5 (4%)	2 (3%)	2 (5%)	0 (0%)	0.5108
History of Heart Failure	73 (62%)	35 (56%)	22 (60%)	13 (50%)	0.5612
History of Hypertension	87 (74%)	42 (67%)	22 (60%)	20 (77%)	0.0897
Diabetes Mellitus	26 (22%)	13 (21%)	4 (11%)	9 (35%)	0.0257
Prior Stroke	21 (18%)	10 (16%)	3 (2%)	7 (27%)	0.0743
History of Peripheral Arterial Disease	8 (7%)	4 (6%)	0 (0%)	4 (15%)	1.0000
History of Coronary Artery Disease*	49 (42%)	25 (40%)	14 (38%)	11 (42%)	0.6275
CHA_2DS_2-VASC Score, mean (SD)	3.9 (2)	3.4 (2)	3.3 (1)	3.7 (2)	0.3167

* History of coronary artery disease was defined as the presence of atherosclerosis of the coronary arteries on cardiac angiography or any history of a positive stress test.

resolution in multivariable comparisons, although this was limited by our sample size.

Among patients with repeat TEE, 3 (4.8%) suffered a cardioembolic stroke within a year. The average age of these patients was 77 ± 3 years at the time of repeat TEE, and all 3 patients had a CHA_2DS_2-VASC score of 3 at presentation. In this group, all 3 had sludge on initial TEE; 1 had thrombus and 2 had sludge on repeat TEE. All 3 patients were placed on anticoagulation with a NOAC (2 with rivaroxaban, 1 with apixaban) after the initial diagnosis of LAA thrombus. Two patients had persistent thrombus or prethrombus on repeat TEE (mean interval in TEEs 54 ± 9.3 days), and had anticoagulation continued indefinitely thereafter. One patient was reported to be noncompliant with rivaroxaban in the weeks before CVA.

Of 54 patients without repeat TEE, 5 suffered cardioembolic complications (3 ischemic strokes, 1 transient ischemic attack, and 1 splenic infarction) in follow-up. The average age was 73 ± 13 years, and average CHA_2DS_2-VASC score was 4 at presentation. Among these, 2 had sludge on TEE and 3 had thrombus. Four patients were prescribed a NOAC (2 with rivaroxaban, 2 with apixaban) after diagnosis of LAA thrombus, and 1 was prescribed warfarin. One patient was documented to be noncompliant with rivaroxaban in follow-up.

Discussion

In our real-world observational study, we report the following major findings: (1) LAA thrombus or prethrombus (i.e., sludge) was found in 8% of patients with AF who underwent TEE, of whom half would be considered appropriately anticoagulated. Therefore, the rate of LAA thrombus despite apparently appropriate anticoagulation is 4%. (2) Among those patients with LAA thrombus with a follow-up TEE, 77% were prescribed an appropriate anticoagulant regimen, but only 60% (79% of appropriately anticoagulated patients) had thrombus resolution. There was no statistically significant difference in the rate of LAA thrombus resolution between oral anticoagulant classes, although this observation was limited by relatively small sample size. (3) The only multivariable-adjusted determinant of thrombus persistence was a clinical history of diabetes mellitus.

Table 2
Echocardiographic characteristics

Variable	All subjects (n = 117)	Subjects with repeat TEE (n = 63)	Thrombus resolved (n = 37)	Thrombus not resolved (n = 26)	p Value resolved vs not resolved
Initial TEE					
Left Ventricular Dysfunction	51 (44%)	24 (38%)	12 (32%)	12 (46%)	0.2170
Severe Left Ventricular Dysfunction	39 (33%)	20 (32%)	14 (38%)	6 (23%)	0.2529
Mitral Regurgitation, severe	8 (7%)	4 (6%)	4 (100%)	0 (0%)	0.1411
Mitral Stenosis, moderate to severe	6 (5%)	3 (5%)	2 (5%)	1 (4%)	1.000
Left Atrial Appendage Velocity Reduced	102 (87%)	58 (92%)	35 (97%)	23 (89%)	0.5624
Left Atrial Thrombus	62 (53%)	34 (54%)	21 (57%)	13 (50%)	0.6
Left Atrial Sludge	55 (47%)	29 (46%)	16 (43%)	13 (50%)	0.6

Table 3
Anticoagulation regimen

Variable	All subjects (n = 117)	Subjects with repeat TEE (n = 63)	Thrombus resolved (n = 37)	Thrombus not resolved (n = 26)	p Value resolved vs not resolved
A. Anticoagulation regimen at initial TEE					
Any antiplatelet medication	61 (52%)	31 (49%)	14 (38%)	17 (65%)	0.03
Vitamin K antagonist	31 (27%)	21 (33%)	13 (35%)	8 (31%)	0.7
INR therapeutic at time of scan	17 (55%)	17 (81%)	6 (46%)	3 (38%)	0.4
Non-Vitamin K antagonist Oral Anticoagulant	39 (33%)	20 (32%)	11 (30%)	9 (35%)	0.9
B. Interval Anticoagulation regimen					
Any antiplatelet medication	N/A	29 (46%)	17 (46%)	12 (46%)	1
Vitamin K antagonist	N/A	29 (46%)	16 (43%)	13 (50%)	0.6
INR therapeutic at Time of scan	N/A	12 (41%)	7 (44%)	5 (38%)	0.8
Non-Vitamin K antagonist Oral Anticoagulant	N/A	32 (51%)	21 (57%)	11 (42%)	0.3
Low Molecular Weight Heparin	N/A	2 (3.2%)	0 (0%)	2 (7.7%)	0.09

Previous studies have reported the prevalence of left atrial thrombi between 8% and 30%;[7–11] our study falls on the lower end of this range (8%). Although, it remains common practice to perform electrical cardioversion without TEE guidance after 3 weeks of therapeutic anticoagulation, our data suggests that there remains a small (at least 4%) risk of LAA thrombus, which may cause iatrogenic stroke. This risk must be weighed against the much smaller risk of performing a precardioversion TEE in an already sedated patient. Additionally, subclinical thromboembolism—as seen in most patients underwent transcatheter aortic valve replacement[12]—may occur after cardioversion without TEE guidance, an avoidable risk that may be greater than previously believed.

Several studies have reported the predictive value of various echocardiographic parameters, including LV

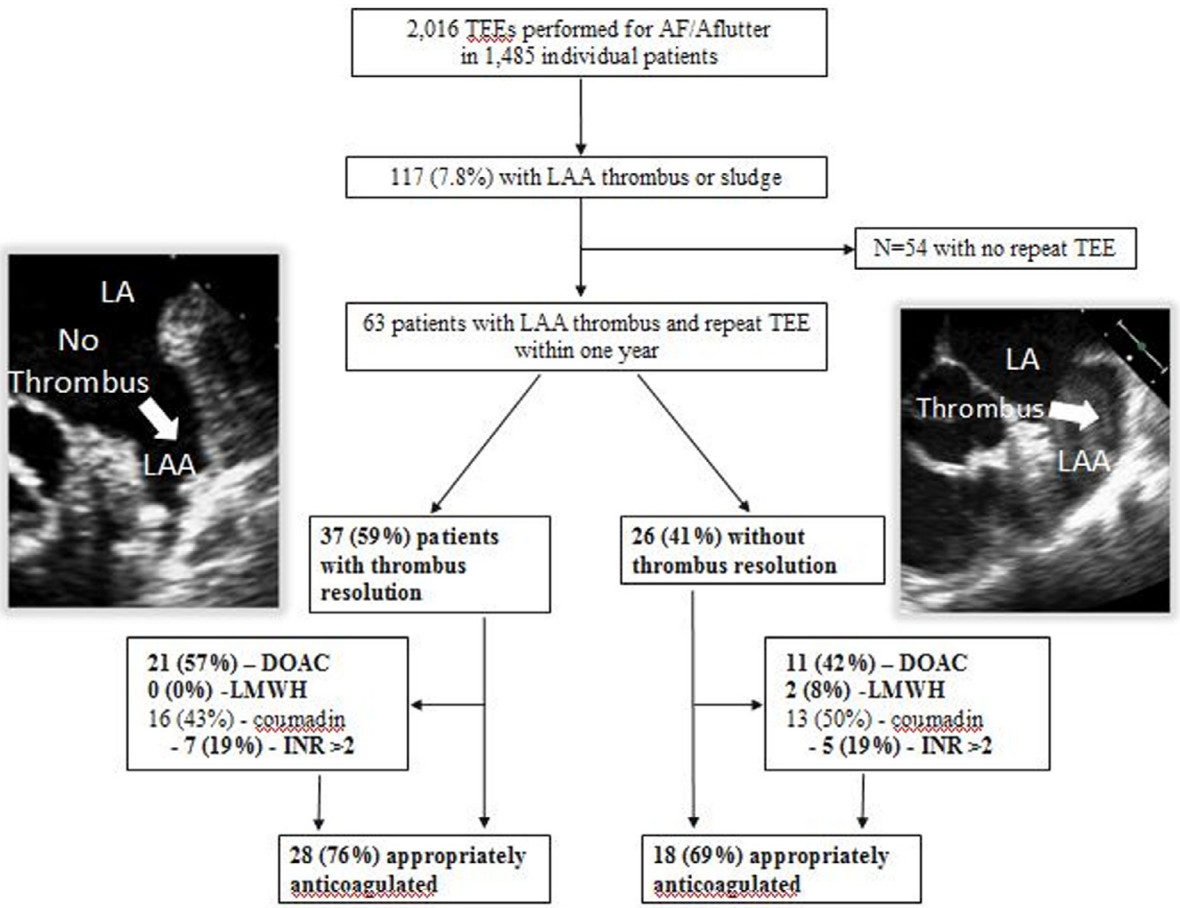

Figure 1. Patient flow chart including prevalence and resolution rate of LAA thrombus and prethrombus (sludge), prevalence of anticoagulation regimens, and prevalence of appropriate anticoagulation in each group. Abbreviations: AF = indicates atrial fibrillation; INR = international normalized ratio; LA = left atrium; LAA = left atrial appendage; LMWH = low molecular weight heparin; NOAC = direct-acting oral anticoagulant; TEE = transesophageal echocardiogram.

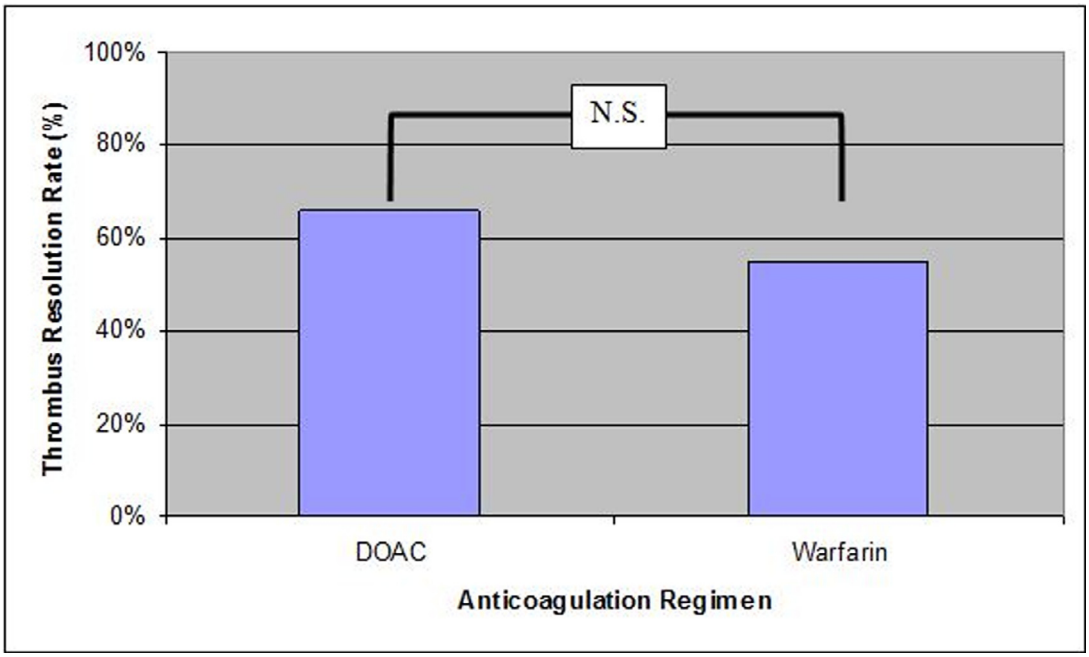

Figure 2. Resolution rates of LAA thrombus and pre-thrombus in patients on warfarin (55%) and patients on NOACs (66%, difference nonsignificant). Abbreviations: LAA indicates left atrial appendage; N.S., non-significant p value.

ejection fraction, LAA velocity, and LV volume.[13–27] Our data could not confirm these associations. Additionally, there is a growing interest in the relevance of LAA configuration in predicting the risk of thromboembolic stroke.[18,19] This study could not confirm an association of LAA configuration with presence or resolution of thrombus. Here, a history of diabetes mellitus was the only predictor of LAA thrombus persistence. This suggests that in heterogeneous populations, practitioners cannot reliably predict an individual's risk for thrombus persistence. This may be particularly relevant in patients prescribed NOACs, where medication compliance and adequacy of anticoagulation cannot be easily assessed.

Despite the efficacy of NOACs in prevention of thromboembolic complications of AF,[20–22] there have been few studies examining their efficacy in resolving known LAA thrombus. Previous studies with warfarin showed thrombus resolution rates from 50% to 90%.[23–25,26,27] The XTRA trial demonstrated comparable resolution of LAA thrombus with rivaroxaban and warfarin.[28] Our data suggest that left atrial thrombi resolve at similar rates with NOACs as with warfarin and although some prospective, controlled studies have reported higher rates of thrombus resolution,[23–25,27] our results may better represent the real-world effectiveness of these medications when nonadherence to anticoagulant therapy, which has been reported to be as high as 50%[5,29,30] plays a more important role. Thus, compliance should not be assumed, but the opposite considered when planning electrical cardioversion.

Our single-center, retrospective study of a heterogeneous (all-comer) population is limited by the potential for unmeasured confounders. Patients at high risk for thrombus persistence may have been more likely to undergo repeat TEE. However, given that currently no reliable clinical predictors of thrombus resolution exist, we believe our findings are still relevant in clinical practice. As done in practice, 3D imaging was not utilized in all patients and documentation of medication compliance was imperfect. As this was a retrospective study, we were unable to ensure standardization in timing and use of repeat TEE for assessment of thrombus resolution. We were also unable to specifically examine the rate of LAA thrombus in those patients with <48 hours of atrial fibrillation or those with exactly 3 to 4 weeks of anticoagulation, who are considered the best candidates for cardioversion without TEE. We were unable to collect information on the incidence of thromboembolism in patients without LAA thrombus on TEE. Most importantly, our results are limited by relatively low statistical power. Additional prospective and multicenter studies should be performed to confirm our findings and identify predictors of LAA thrombus incidence, resolution, and embolization while treated with different anticoagulant regimens.

In conclusion, in this observational study, 8% of patients with AF had LAA thrombus on TEE, while 4% of patients on adequate oral anticoagulants had LAA thrombus, supporting the clinical observation that some patients develop LAA thrombus despite seemingly appropriate anticoagulation. Follow-up studies are warranted to more reliably estimate the magnitude and implications of this finding. Furthermore, we found an imperfect thrombus resolution rate: 79% in patients considered on appropriate anticoagulation. Thus, performing low-risk TEE before electrical cardioversion should be considered in all patients.

Disclosures

There are no conflicts of interest of any of the authors.

1. Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, Zhu J, Mohan P, Garcia D, Bartunek J, Vinereanu D, Husted S, Harjola VP, Rosenqvist M, Alexander JH, Granger CB. ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial. *J Am Coll Cardiol* 2014;63:1082–1087.
2. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KA, Califf RM, Breithardt G. ROCKET AF Steering Committee & Investigators. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol* 2013;61:1998–2006.
3. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation* 2011;123:131–136.
4. Wasserfallen J-B, Bourgeois R, Bula C, Yersin B, Buclin T. Composition and cost of drugs stored at home by elderly patients. *Ann Pharmacother* 2003;37:731–737.
5. Borne RT, O'Donnell C, Turakhia MP, Varosy PD, Jackevicius CA, Marzec LN, Masoudi FA, Hess PL, Maddox TM, Ho PM. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. *BMC Cardiovasc Disord* 2017;17:236.
6. Lowe BS, Kusunose K, Motoki H, Varr B, Shrestha K, Whitman C, Tang WH, Thomas JD, Klein AL. Prognostic significance of left atrial appendage "sludge" in patients with atrial fibrillation: a new transesophageal echocardiographic thromboembolic risk factor. *J Am Soc Echocardiogr* 2014;27:1176–1183.
7. Brown J, Sadler DB. Left atrial thrombus in non-rheumatic atrial fibrillation: assessment of prevalence by transesophageal echocardiography. *Int J Cardiol Imaging* 1993;9:65–72.
8. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF. Assessment of cardioversion using transesophageal echocardiography investigators: use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;344:1411–1420.
9. Romero J, Husain SA, Kelesidis I, Sanz J, Medina HM, Garcia MJ. Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: a meta-analysis. *Circ Cardiovasc Imaging* 2013;6:185–194.
10. Stoddard MF, Dawkins PR, Prince CR, Ammash N. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic Study. *J Am Coll Cardiol* 1995;25:452–459.
11. Fukuda S, Watanabe H, Shimada K, Aikawa M, Kono Y, Jissho S, Taguchi H, Umemura J, Yoshiyama M, Shiota T, Sumiyoshi T, Yoshikawa J. Left atrial thrombus and prognosis after anticoagulation therapy in patients with atrial fibrillation. *J Cardiol* 2011;58:266–267.
12. Lansky AJ, Brown D, Pena C, Pietras CG, Parise H, Ng VG, Meller S, Abrams KJ, Cleman M, Margolis P, Petrossian G, Brickman AM, Voros S, Moses J, Forrest JK. Neurologic complications of unprotected transcatheter aortic valve implantation (from the Neuro-TAVI Trial). *Am J Cardiol* 2016;118:1519–1526.
13. Watanabe A, Yamashita N, Yamashita T. Blood stasis secondary to heart failure forms warfarin-resistant left atrial thrombus. *Int Heart J* 2014;55:506–511.
14. Watanabe A, Suzuki S, Kano H, Matsuno S, Takai H, Kato Y, Otsuka T, Uejima T, Oikawa Y, Nagashima K, Kirigaya H, Kunihara T, Sagara K, Yamashita N, Sawada H, Aizawa T, Yajima J, Yamashita T. Left atrial remodeling assessed by transthoracic echocardiography predicts left atrial appendage flow velocity in patients with paroxysmal atrial fibrillation. *Int Heart J* 2016;57:177–182.
15. Garcia-Sayan E, Patel M, Wassouf M, Pant R, D'Silva O, Kehoe RF, Doukky R. Derivation and validation of E/e' ratio as a parameter in the evaluation of left atrial appendage thrombus formation in patients with nonvalvular atrial fibrillation. *Int J Cardiovasc Imaging* 2016;32:1349–1356.
16. Boyd AC, McKay T, Nasibi S, Richards DA, Thomas L. Left ventricular mass predicts left atrial appendage thrombus in persistent atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2013;14:269–275.
17. Kupczynska K, Michalski BW, Miskowiec D, Kasprzak JD, Wejner-Mik P, Wdowiak-Okrojek K, Lipiec P. Association between left atrial function assessed by speckle-tracking echocardiography and the presence of left atrial appendage thrombus in patients with atrial fibrillation. *Anatol J Cardiol* 2017;18:15–22.
18. Bisbal F, Gomez-Pulido F, Cabanas-Grandio P, Akoum N, Calvo M, Andreu D, Prat-Gonzalez S, Perea RJ, Villuendas R, Berruezo A, Sitges M, Bayes-Genis A, Brugada J, Marrouche NF, Mont L. Left atrial geometry improves risk prediction of thromboembolic events in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2016;27:804–810.
19. Chen Z, Bain W, Li C, Wang H, Tang H, Qin Y, Rao L. Left atrial appendage parameters assessed by real-time three-dimensional transesophageal echocardiography predict thromboembolic risk in patients with nonvalvular atrial fibrillation. *J Ultrasound Med* 2017;36:1119–1128.
20. Connolly SJ, E M, Yusuf S, Eikelboom J, Oldgre J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
21. Patel MR, M K, Garg J, Pan G, Singer DE, Hacke WMD, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM. ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
22. Granger CB, A. J, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyin S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, LOpez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wellentin L. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
23. Collins LJ, Silverman DI, Douglas PS, Manning WJ. Cardioversion of nonrheumatic atrial fibrillation: reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. *Circulation* 1995;92:160–163.
24. Corrado G, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, Santarone M. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation: a transesophageal echocardiographic study. *CHEST* 1999;115:140–143.
25. Jaber WA, Prior DL, Thamilarasan M, Grimm RA, Thomas JD, Klein AL, Asher CR. Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: a transesophageal echocardiographic study. *Am Heart J* 2000;140:150–156.
26. Yaghi S, Chang D, Hung P, Mac Grory B, Collins S, Gupta A, Reynolds J, Finn CB, Hemedinger M, Cutting SM, McTaggart RA, Jayaraman M, Leasure A, Sansing L, Panda N, Song C, Chu A, Merkler A, Gialdini G, Sheth KN, Kamel H, Elkind MSV, Greer D, Furie K, Atalay M. Left atrial appendage morphology and embolic stroke of undetermined source: a cross-sectional multicenter pilot study. *J Stroke Cerebrovasc Dis* 2018;27:1497–1501.
27. Saeed M, Rahman A, Afzal A, Agoston I, Jammula P, Birnbaum Y, Ware DL, Uretsky BF, Schwarz ER, Rosanio S. Role of transesophageal echocardiography guided cardioversion in patients with atrial fibrillation, previous left atrial thrombus and effective anticoagulation. *Int J Cardiol* 2006;113:401–405.
28. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, van Eickels M, Cohen A. X-TRA study and CLOT-AF registry investigators. Left atrial thrombus resolution in atrial fibrillation or flutter: Results a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). *Am Heart J* 2016;178:126–134.
29. Stephenson JJ, Shinde MU, Kwong WJ, Fu AC, Tan H, Weintraub WS. Comparison of claims vs patient-reported adherence measures and associated outcomes among patients with nonvalvular atrial fibrillation using oral anticoagulant therapy. *Patient Prefer Adher* 2018;12:105–117.
30. Brown JD, Shewale AR, Talbert JC. Adherence to rivaroxaban, dabigatran, and apixaban for stroke prevention in incident, treatment-naïve nonvalvular atrial fibrillation. *J Manag Care Spec Pharm* 2016;22:1319–1329.