Received: 18 May 2022 | Accepted: 17 June 2022

DOI: 10.1111/anec.12989

ORIGINAL ARTICLE

WILEY

Incidence of left atrial appendage thrombus despite 3 weeks of anticoagulation and the need for precardioversion echocardiography

Marc Erickson MD[1] | Harika Yadav MD[2] | Eliea Sneij MD[2] | Jordan Austin DO[2] | Harish Manyam MD[1]

[1]Department of Cardiology, University of Tennessee College of Medicine, Chattanooga, Tennessee, USA

[2]Department of Internal Medicine, University of Tennessee College of Medicine, Chattanooga, Tennessee, USA

Correspondence
Harika Yadav, University of Tennessee College of Medicine, 960 E 3rd Street, Chattanooga, TN 37403, USA.
Email: harika.yadav94@gmail.com

Abstract

Background: One of the most catastrophic complications of Atrial fibrillation (AF) is thromboembolic stroke. Current guidelines recommend that 3 weeks of anticoagulation is adequate prior to direct current cardioversion (DCCV) to prevent thromboembolism. Here we present data regarding, which anticoagulant is most likely to show a presence of an Left atrial appendage thrombus (LAAT) on trans esophageal echocardiogram (TEE) for DCCV despite 3 weeks of anticoagulation.

Objective: To investigate the effectiveness of both vitamin k antagonist (VKA) and direct oral anticoagulants (DOAC) in patients with AF as an anticoagulant for LAAT after 3 weeks of medication.

Methods: This is a single-high volume tertiary center, where TEE precardioversion is the standard practice. We reviewed data over 10 months where DCCV was intended on individuals with AF who were fully anticoagulated for at least 3 weeks with either a VKA or taking a DOAC.

Results: The data showed a statistical difference between patients who were fully anticoagulated for at least 3 weeks with VKA in comparison to DOACs. Patients on DOACs are significantly less likely to have an LAAT after at least 3 weeks of anticoagulation. OR = 0.04 (CI 95% 0.005–0.42; p-value < .05). Despite anticoagulation for at least 3 weeks, 40% of our patients still had a LAAT.

Conclusion: Our data indicates that all patients should be required to undergo a TEE prior to DCCV. This data also adds to the current evidence and supports the use of DOAC in AF to prevent LAAT.

KEYWORDS
anticoagulation, atrial fibrillation, cardioversion, DOAC, stroke prevention, stroke prophylaxis

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias in the United States affecting approximately about 1% of the population (Ryder & Benjamin, 1999). AF is an independent risk factor for thromboembolism complications such as stroke often due to clot formation in the left atrium. Oral anticoagulation is known to reduce the incidence of stroke by over 60% in these patients (Airaksinen, 2015). Elective cardioversion is a well-established treatment for this potentially fatal arrhythmia (Soulat-Dufour et al., 2022). However, the electro cardioversion procedure itself poses a risk of clot dislodgement. Though the rate of embolic events after elective cardioversion is low at about 0.4%–1.8%, the global burden of AF and escalation of use of cardioversion, increases this risk (Gentile et al., 2002). Advances in trans esophageal echocardiogram (TEE) imaging have made it possible to fully visualize the left atrial appendage (LAA) and assess the presence of thrombus there. Although, TEE has been incorporated as part of the practice, it is not required in fully anticoagulated patients who have been anticoagulated for at least 3 weeks per 2019 AHA guidelines. (January, 2019). With the high risk of stroke in AF and varying anticoagulation regimens, TEE can be routinely done to rule out thrombi before elective cardioversion in patients.

2 | METHODOLOGY

We conducted a retrospective cohort study at a single teaching hospital, manually reviewing TEE records between November 2019 and September 2021. Inclusion criteria were: a patient had to have been on an anticoagulant, including warfarin, rivaroxaban, dabigatran, or apixaban for at least.

Three weeks, a TEE prior to DCCV, and age greater than 18. We collected data on the left atrial volume index, and absolute left atrial size, age, race, sex, presence of the clot on the TEE, and type of medication used for anticoagulation. We did not assess INR values for inclusion, as these were not always available for review prior to the procedure. Patients were asked if they had been taking their medications as directed, and if they had therapeutic INRs if they were on warfarin. Analysis of the data was performed with Microsoft Excel and RStudio.

3 | RESULTS

Between November 2019 and September 2021, 40 patients [22 men and 18 women] were identified who met our inclusion criteria of having Atrial fibrillation or atrial flutter and fully anticoagulated for at least 3 weeks. 25 patients [12 males, 13 females] were identified that met criteria to undergo TEE with DCCV as no left atrial appendage thrombus (LAAT) was identified while 15 patients [10 male, 5 female] were found to have a LAAT. The mean age of all the patients was 68.775 [36–94] years. The average age of those patients without a LAAT was 69.12 [36–91] while those with a LAAT had an average of 68.2 years [50–94]. 80% of the participants were taking a DOAC at the time of the study while the other 20% were taking Coumadin. Of the patients taking a DOAC, 25% (8 patients) were found to have a LAAT. Of the patients taking Coumadin, 88% (7 patients) were found to have a LAAT. Figure 1 graphically represents the percentage of LAAT identified on TTE while on each anticoagulant.

Patients included in this study underwent echocardiography and had left atrial volume index (LAVI) and left atrial size measured. The average LAVI of all participants was 43.46 ml/mA [two patients with a LAAT did not have documented LAVI]. The 25 patients without a LAAT had an average LAVI of 43.60 ml/mA while the patients with a LAAT had an average LAVI of 43.18 ml/mA. The average LA size of all participants was 4.36 cm [one patient with LAAT did not have documented LA Size]. The patients without an LAAT had an average LA size of 4.30 cm while the patients with a LAAT had an average LA size of 4.48 cm.

The data indicates that there is a clinically significant difference in the effectiveness of DOACs compared to Vit K antagonists in preventing LAAT in patients with atrial fibrillation or atrial flutter who have been anticoagulated for at least 3 weeks.

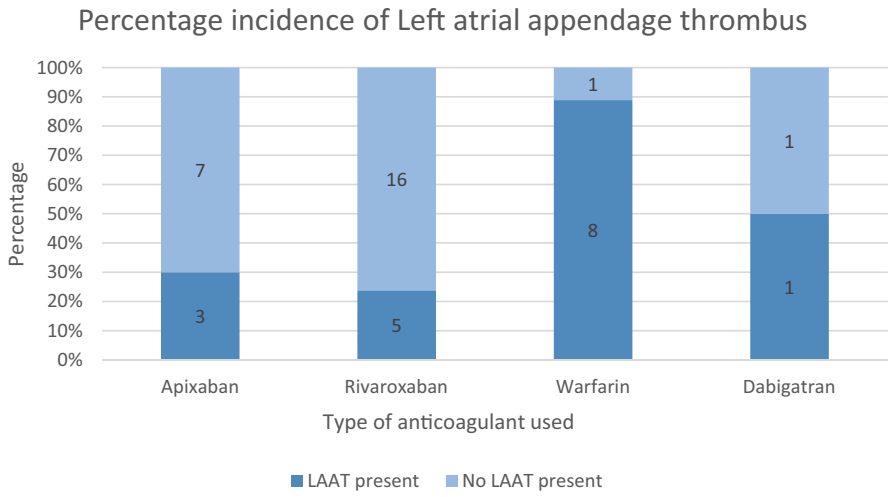

FIGURE 1 Percentage of left atrial appendage thrombus identified on TTE and anticoagulant used

4 | DISCUSSION

Intracardiac thrombosis can be identified in any of the four chambers of the heart, but it is most commonly found in the left ventricle and the left atrium, specifically the left atrial appendage. Like most thrombosis, its pathophysiology is associated with Virchow's Triad, that is, stasis, endothelial damage and hypercoagulable state. Risk factors for the development of intracardiac thrombus include atrial fibrillation, abnormal endocardium, left atrial dilatation related to valvular disease or heart failure, and post myocardial infarction (Al-Sadawi et al., 2020). Transesophageal echocardiogram (TEE) is considered the gold standard to detect left atrial appendage thrombi with a specificity of about 99% (Romero et al., 2013). Dating to an old study, before relying on TEE, (Aschenberg et al., 1987) described that they observed an enlargement in the left atrial appendage, which gave rise to thrombi in the LAA in valvular atrial fibrillation. In their study, seven out of the 24 patients developed a thrombus while being fully anticoagulated with a negative trans-thoracic echocardiogram (TTE). (Aschenberg) The most dangerous complication of an intracardiac thrombus is embolization and subsequent ischemic cerebrovascular event. Oral anticoagulant medications have long been used for treatment and prevention of LAA thrombi.

In the past, vitamin K antagonists (VKA) were considered standard of care. Vitamin K antagonists are a class of medications that disrupt the formation of factors II, VII, IX, Protein C and S. Warfarin is the most commonly used VKA and has a long half-life of 40 h and time to therapeutic range can be 3–5 days. VKAs have many complications including a very narrow therapeutic window and frequent lab monitoring of INR. Its dose–response curve varies extensively among patients and can be influenced by an array of factors including body weight, age, dietary ingestion of vitamin K, liver disease and genetic factors (Schulman, 2017). The requirement of frequent laboratory monitoring makes patient compliance with VKA very difficult. One study showed that in patients on warfarin for AF, patients were in therapeutic range approximately 50% of the time (Bertomeu-González et al., 2015). The intensity of periprocedural warfarin anticoagulation is inversely associated with a higher rate of thromboembolism during elective cardioversion (Hellman, 2017).

Due to the complications of VKA treatment, newer agents such as Direct oral anticoagulants (DOACs) are gaining favor. DOACs have become favored alternatives for the prevention of thrombosis in cardiovascular diseases such as AF. DOACs are classified as either oral direct factor Xa inhibitors, such as rivaroxaban and apixaban, and direct thrombin inhibitors, such as dabigatran. Since their release in 2010, DOACs have received FDA-approval for treatment and prevention of thrombosis in nonvalvular AF, deep vein thrombosis, and pulmonary embolism (Goldman, 2020). Comorbidities such as renal and hepatic impairment and obesity affect the pharmacokinetics of DOACs but dose adjusted regimens exist. Unlike VKAs, DOACs do not require monitoring, have fewer drug interactions and do not require dietary restrictions; likely increasing their compliance. They also have less risk of major bleeding and intracranial hemorrhage (Julia & James, 2017; Chen et al., 2020).

Cardioversion is a mainstay of treatment in specific patient populations for resolution of symptomatic AF. Large prospective randomized control trials such as ENSURE-AF, EMANATE and one from the European Heart Society support the safety and efficacy of DOACs over VKA for thromboembolism prevention with AF undergoing cardioversion (Cappato, 2014; Ezekowitz, 2018; Goette, 2016). Our study concurs with these studies in preferring a DOAC over VKA for prevention and treatment of LAA thrombus in patients with AF. This is likely due to the multiple complications with VKA and difficulty in maintaining therapeutic range.

Cardioversion provides a substantial risk of embolization with conversion to sinus rhythm in patients who have an underlying LAA thrombus. An initial TEE can be done to evaluate for thrombus, in the absence of a thrombus, cardioversion is performed. Current clinical guidelines from both the European Heart Rhythm Association and American Heart Association recommend that when cardioverting a patient with AF, they should be treated with at least 3 weeks of uninterrupted therapy. It is recommended but not required to perform a TEE after this period of treatment to evaluate for presence of LAA thrombus. The decision about anticoagulant therapy beyond 4 weeks prior to scheduled cardioversion is based on a bleeding risk evaluation and thromboembolic risk profile. One small study evaluated DOAC efficacy for resolution of left ventricular thrombus, they found that about 15 out of 16 patients had resolution on a follow up TEE, but only after a significantly large mean duration of therapy of 112 days (Fleddermann, 2019).

Left end diastolic volume index has been shown to be an independent risk factor for all composite cardiovascular mortality including strokes (Thadani et al., 2020). (Van Chien et al., 2019) studied that in new onset, nonvalvular AF, using CHADS-VASc scoring system along with LAVI and LA strain parameters could predict the possibility of thrombus formation in patients that were not anticoagulated. They found a positive correlation between LA size and the incidence of LAAT, although they excluded patients that were previously on anticoagulation (Van Chien et al., 2019). As described in the results, LA size greater than 4.48 cm was more likely to be associated with presence of LAAT.

Our study showed that despite anticoagulation for the recommended 3 weeks prior to cardioversion a significant number (40%) of patients were found to have a left atrial thrombus. We demonstrated that patients on warfarin had a much higher incidence of LAAT, as shown in previous studies. However, one-fourth of patients on DOACs were found to have a LAAT as well. We believe this suggests that TEE prior to cardioversion should be required despite anticoagulation therapy to prevent the risk of consequent thromboembolism. As more research continues to show the benefit of early rhythm control in patients with atrial fibrillation, we expect the number of cardioversions to increase over the next decade (Soulat-Dufour, 2022; Kirchhof, 2020). We hope to promote further research with large multicenter trials to change the existing guidelines for evaluation of LAAT prior to cardioversion.

4.1 | Limitations

As a single center trial, we are limited by a small study population. Larger trials are necessary to improve the power of the study. This study did not include factors to calculate a CHADS-VASc score on each patient. We did not isolate patients with a new diagnosis of atrial fibrillation, and look at time until sinus rhythm was achieved. This study did not account for patients who underwent ablation before cardioversion. We did not delineate between the different burdens of atrial fibrillation.

5 | CONCLUSION

This retrospective study shows the importance of using TEE to verify the absence of clot in the LAA, prior to DC cardioversion despite at least 3 weeks of anticoagulation. It also highlights how ineffective warfarin is compared to DOACs for our patient population. This research adds to the growing body of work that shows the superiority of DOACs compared to VKA.

AUTHOR CONTRIBUTIONS

All authors participated in the review. They were involved in data collection, data analysis, writing and revising the article prior to submission.

CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interest with respect to research, authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

Ethical approval was obtained from the Internal Review Board at Erlanger Hospital, Chattanooga, TN.

INFORMED CONSENT

This was a retrospective review and informed consent is not applicable.

ORCID

Harika Yadav https://orcid.org/0000-0003-0845-2047

REFERENCES

Airaksinen, K. J. (2015). Cardioversion of atrial fibrillation and oral anticoagulation. *Journal of Atrial Fibrillation*, *8*(3), 1260. https://doi.org/10.4022/jafib.1260

Al-Sadawi, M., Francois, J., Rodriguez Ortega, R., Capric, V., & Budzikowski, A. S. (2020). Novel oral anticoagulants in intracardiac thrombosis resolution: A case series. *European Heart Journal: Case Reports*, *4*(5), 1–6.

Aschenberg, W., Siglow, V., Kremer, P., Schlüter, M., & Bleifeld, W. (1987). Thromben im linken Herzohr bei Mitralvitien trotz adäquater Antikoagulation. Vorteile der transösophagealen Echokardiographie [thrombi in the left atrial appendage in mitral defects despite adequate anticoagulation. The advantages of transesophageal echocardiography]. *MW-Deutsche Medizinische Wochenschrift*, *112*(17), 663–668. https://doi.org/10.1055/s-2008-1068117

Bertomeu-González, V., Anguita, M., Moreno-Arribas, J., Cequier, Á., Muñiz, J., Castillo-Castillo, J., Sanchis, J., Roldán, I., Marin, F., & Bertomeu-Martínez, V. (2015). Quality of anticoagulation with vitamin K antagonists. *Clinical Cardiology*, *38*(6), 357–364.

Cappato, R., Ezekowitz, M. D., Klein, A. L., Camm, A. J., Ma, C. S., Le Heuzey, J. Y., Talajic, M., Scanavacca, M., Vardas, P. E., Kirchhof, P., Hemmrich, M., Lanius, V., Meng, I. L., Wildgoose, P., van Eickels, M., Hohnloser, S. H., & X-VeRT Investigators. (2014). Rivaroaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *European Heart Journal*, *35*, 3346–3355.

Chen, A., Stecker, E., Warden, B. A., & Bruce, A. (2020). Direct oral anticoagulant use: A practical guide to common clinical challenges. *Journal of the American Heart Association*, *9*(13), e017559. https://doi.org/10.1161/JAHA.120.017559#d2862441e1

Ezekowitz, M. D., Pollack, C. V. Jr, Halperin, J. L., England, R. D., Nguyen, S. V., Spahr, J., Sudworth, M., Cater, N. B., Breazna, A., Oldgren, J., & Kirchhof, P. (2018). Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *European Heart Journal*, *39*(32), 2959–2971. https://doi.org/10.1093/eurheartj/ehy148

Fleddermann, A., Eckert, R., Muskala, P., Hayes, C., Magalski, A., & Main, M. L. (2019). Efficacy of direct acting oral anticoagulant drugs in treatment of left atrial appendage thrombus in patients with atrial fibrillation. *The American Journal of Cardiology*, *123*(1), 57–62.

Gentile, F., Elhendy, A., Khandheria, B. K., Seward, J. B., Lohse, C. M., Shen, W. K., Bailey, K. R., Montgomery, S. C., Burger, K. N., & Tajik, A. J. (2002). Safety of electrical cardioversion in patients with atrial fibrillation. *Mayo Clinic Proceedings*, *77*(9), 897–904.

Goette, A., Merino, J. L., Ezekowitz, M. D., Zamoryakhin, D., Melino, M., Jin, J., Mercuri, M. F., Grosso, M. A., Fernandez, V., al-Saady, N., Pelekh, N., Merkely, B., Zenin, S., Kushnir, M., Spinar, J., Batushkin, V., de Groot, J. R., Lip, G. Y., & ENSURE-AF investigators. (2016). Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): A randomised, open-label, phase 3b trial. *Lancet*, *388*, 1995–2003.

Goldman, L., Schafer, A., & Cecil, R. (2020). Chapter 76: Antithrombotic and antiplatelet therapy. In L. Goldman, D. A. Ausiello, & A. I. Schafer (Eds.), *Goldman-Cecil medicine* (26th ed., pp. 495–501). Elsevier.

Hellman, T., Kiviniemi, T., Nuotio, I., Vasankari, T., Hartikainen, J., Lip, G. Y. H., & Airaksinen, K. E. J. (2017). Intensity of anticoagulation and risk of thromboembolism after elective cardioversion of atrial fibrillation. *Thrombosis Research*, *156*, 163–167.

Julia, S., & James, U. (2017). Direct Oral anticoagulants: A quick guide. *European Cardiology Review*, *12*(1), 40–45.

Kirchhof, P., Camm, A. J., Goette, A., Brandes, A., Eckardt, L., Elvan, A., Fetsch, T., van Gelder, I. C., Haase, D., Haegeli, L. M., Hamann, F., Heidbüchel, H., Hindricks, G., Kautzner, J., Kuck, K. H., Mont, L., Ng, G. A., Rekosz, J., Schoen, N., … Breithardt, G. (2020). Early rhythm-control therapy in patients with atrial fibrillation. *The New England Journal of Medicine*, *383*(14), 1305–1316. https://doi.org/10.1056/NEJMoa2019422

Romero, J., Husain, S. A., Kelesidis, I., Sanz, J., Medina, H. M., & Garcia, M. J. (2013). Detection of left atrial appendage thrombus by cardiac computed tomography in patients with atrial fibrillation: A meta-analysis. *Circulation. Cardiovascular Imaging*, *6*(2), 185–194.

Ryder, K. M., & Benjamin, E. J. (1999). Epidemiology and significance of atrial fibrillation. *The American Journal of Cardiology*, *84*(9A), 131R–138R. https://doi.org/10.1016/s0002-9149(99)00713-4

Schulman, S., Singer, D., Ageno, W., Casella, I. B., Desch, M., & Goldhaber, S. Z. (2017). NOACs for treatment of venous thromboembolism in clinical practice. *Thrombosis and Haemostasis*, *117*(7), 1317–1325. https://doi.org/10.1160/TH17-01-0065

Soulat-Dufour, L., Lang, S., Addetia, K., Ederhy, S., Adavane-Scheuble, S., Chauvet-Droit, M., Jean, M. L., Nhan, P., Ben Said, R., Kamami, I., Issaurat, P., Capderou, E., Arnaud, C., Boccara, F., Lang, R. M., & Cohen, A. (2022). Restoring sinus rhythm reverses cardiac remodeling and reduces valvular regurgitation in patients with atrial fibrillation. *Journal of the American College of Cardiology*, *79*(10), 951–961.

Thadani, S. R., Shaw, R. E., Fang, Q., Whooley, M. A., & Schiller, N. B. (2020). Left atrial end-diastolic volume index as a predictor of cardiovascular outcomes: The heart and soul study. *Circulation. Cardiovascular Imaging*, *13*(4), e009746.

Van Chien, D., Thai Giang, P., Son, P. T., Truong, L. V., & Nguyen, S. P. (2019). Novel models for the prediction of left atrial appendage thrombus in patients with chronic nonvalvular atrial fibrillation. *Cardiology Research and Practice*, *2019*, 1496535.

How to cite this article: Erickson, M., Yadav, H., Sneij, E., Austin, J., & Manyam, H. (2022). Incidence of left atrial appendage thrombus despite 3 weeks of anticoagulation and the need for precardioversion echocardiography. *Annals of Noninvasive Electrocardiology*, *27*, e12989. https://doi.org/10.1111/anec.12989