Ann Med Res 2020;27(7):1908-12

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.03.284

Original Article

Anticoagulants in left atrial thrombus resolution

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Abstract

Aim: Warfarin has been used for protection from peripheral embolism in patients with atrial fibrillation (AF) and it has been shown that the direct oral anticoagulants are effective in protection against stroke as much as warfarin and cause lower bleeding complications. Our aim is to compare the efficacies of different anticoagulants in resolution of left atrial appendage thrombi.

Materials and Methods: 264 patients were included in study. 39 patients had left atrial appendage thrombus; 17 patients underwent a repeat transesophageal echocardiography (TEE) after switching/administering an anticoagulant treatment regimen.

Results: Thrombus was detected in 3 patients using apixaban, who were switched to dabigatran. Those patients were found to have thrombus resolution by the repeat TEE procedures. Of 5 patients using warfarin, 3 were switched to dabigatran, in one of whom thrombus resolution was not achieved. One patient continued warfarin with a target INR of 2.5-3.5 and a repeat TEE showed complete thrombus resolution. The remainder patient using warfarin was swithed to rivaroxaban, with complete thrombus resolution having been achieved. Two patients using edoxaban had their thrombi resolved by dabigatran. Seven patients were not receiving any anticoagulant regimen. Among these, warfarin was administered to 4 patients and apixaban to 2; repeat TEEs showed no thrombus. The remainder patient was administered low molecular weight heparin, and repeat TEE showed persistence of LAA thrombus.

Conclusion: Irrespective of patients being anticoagulated, TEE should be planned before interventional procedures and cardioversion. If thrombus develops in a patient receiving anticoagulant treatment, switching to a different anticoagulant would be a logical option.

Keywords: Atrial fibrillation; echocardiography; transesophagealfactor; Xa inhibitors; thrombosis

INTRODUCTION

Atrial fibrillation (AF) causes left atrial stasis as a reason of thrombus formation especially in the left atrial appendage, leading to a stroke or systemic embolization. Warfarin has been used for protection from peripheral embolism in patients with AF for many years (1). However, in recent years, it has been shown that the direct oral anticoagulants (DOACs) are effective in protection against stroke as much as warfarin and cause lower bleeding complications (2). Although their efficacy has been proven in stroke prevention, there are no large-scale studies on the resolution of already formed thrombus. Our aim is to compare the efficacies of different anticoagulants in resolution of left atrial appendage thrombi.

MATERIAL and METHODS

This study enrolled a total of 350 patients who were admitted to our adult cardiology outpatient clinic and who underwent transesophageal echocardiography (TEE) procedure between June 2017 and June 2019. Patients' demographic data, transthoracic and transesophageal echocardiographic examinations, and laboratory test results were recorded retrospectively. Patients with missing medical data, cancer with ongoing treatment, hematological thrombotic disorders, and catheter thrombus surveilled by successive TEE examinations were excluded. As a result, 264 patients were included at the beginning of the study. Of these 264 patients, 39 patients had left atrial appendage thrombus; 17 patients underwent a repeat TEE after switching/administering an anticoagulant treatment regimen. Hence, we included the data of 17 patients in the final analysis. A repeat TEE was performed at least 3 weeks after effective anticoagulation with DAOCs, warfarin, or low molecular weight heparin. Atrial fibrillation was categorized by patient history and ESC atrial fibrillation guideline (3). Accordingly, paroxysmal atrial fibrillation was defined by symptoms lasting up to 7 days; persistent AF between 7 days to 1 year; long standing persistent AF more than 1 year; and permanent AF for an undetermined period of time. Newly diagnosed AF was diagnosed according to the onset of symptoms and the absence of any previous AF history.

For all patients, hemoglobin, white blood cell count, platelet count, creatinine, high density lipoprotein, triglyceride, and low-density lipoprotein levels were recorded. The study protocol was approved by the local ethics committee. A

Received: 31.03.2020 **Accepted:** 25.04.2020 **Available online:** 06.07.2020
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standardized questionnaire was used to collect clinical and demographic information, including medication history.

Medications, antiplatelet and anticoagulant agents used before and after TEE were also recorded.

Normally distributed continuous variables were expressed as the mean ± standard deviation; non-normally distributed continuous variables as median (min-max); and categorical variables as number (%). All statistical analyses were performed using the SPSS statistical software package (version 25; SPPS, Chicago, IL, USA).

RESULTS

The mean age of 17 patients was 61.5 ± 12.1 years. 52.9 % of the patients were male Table 1. All patients except one patient had AF. As for the AF types, 6 patients had paroxysmal AF; 9 patients had persistent AF; and 1 patient had long-standing persistent AF Table 2. The mean left atrial diameter was 44.4 ± 4.3 mm; and the mean ejection fraction was 52.8 ± 11.4% Table 3. The mean CHA2DS2VASc score was 2.76 ± 1.82. Ten of 17 patients were already receiving anticoagulant therapy Table 4. Four patients were using acetyl salicylic acid, but none was on an anticoagulant.

Table 1. Demograhic data and drug treatment of patients

Parameters	Thrombus + (n=17)
Age (years)	61.5 ± 12.1
Gender (male) (%)	9 (52.9)
Hypertension(%)	10 (58.8)
Diabetes mellitus (%)	5 (29.4)
Hyperlipidemia (%)	3 (17.6)
Smoking (%)	7 (41.2)
CAD history in family (%)	6 (35.3)
Presence of AF (%)	16 (94.1)
Presence of PFO (%)	2 (11.8)
Presence of prosthesis valves (%)	0
CAD (%)	7 (1.2)
Systolic dysfunction (%)	7 (41.2)
History of cerebrovascular disease (%)	2 (11.8)
Renal failure (%)	1 (5.9)
CHA2DS2VASc score	2.76 ± 1.82
Antiplatelet treatment	4 (23.5)
Anticoagulant treatment	10 (58.8)
ACEI/ARB	9 (52.9)
Beta-blocker	11 (64.7)
Calcium channel blocker	5 (29.4)
Statin	3 (17.6)
Spironolactone	2 (11.8)

CAD:Coronary Artery Disease; AF:Atrial Fibrillation; PFO:Patent Foramen Ovale;ACEI/ARB: Angiotensin Converting Enzyme Inhibitor/Angiotensinogen Receptor Blocker

Table 2. Atrial fibrillation types of patients

AF types	(n=17)
Paroxismal	6 (35.3)
Persistent	9 (52.9)
Long standing persistent	1 (5.9)
Chronic	-

Table 3. Echocardiographic and laboratory data of patients

Parameters	Thrombus + (n=17)
Ejection Fraction (%)	52.8 ± 11.4
EDV (ml)	94.1 ± 27.1
LA diameter (mm)	44.4 ±4.3
RA diameter (mm)	39.0 ± 3.2
LVH in echo	30 (76.9)
Diastolic Dysfunction	13 (33.3)
Creatinine (mg/dl)	1.38 ±0.99
Hemoglobine(g/dl)	12.6 ± 1.8
WBC	6.5 ± 1.8
Platelet	205.7 ± 47.0
LDL (mg/dl)	115.5 ± 30.7
HDL (mg/dl)	44.5 ±12.1
TG (mg/dl)	123.7 ± 52.9

EDV:End-Diastolic Volume; LA:Left Atrium; RA:Right Atrium; LVH:Left Ventricular Hypertrophy; WBC: White Blood Cell; LDL:Low Density Lipoprotein; HDL:High Density Lipoprotein; TG:Triglyceride

Table 5 shows the anticoagulant medications used before and after the TEE procedure. A left atrial appendage thrombus was detected in 3 patients using apixaban, who were switched to an effective dose of dabigatran. Those patients were found to have thrombus resolution by the repeat TEE procedures. Of 5 patients using warfarin, 3 were switched to dabigatran, in one of whom thrombus resolution was not achieved. One patient continued warfarin with a target INR of 2.5-3.5 and a repeat TEE showed complete thrombus resolution. The remainder patient using warfarin was switched to rivaroxaban, with complete thrombus resolution having been achieved. Two patients using edoxaban had their thrombi resolved by dabigatran. Seven patients were not receiving any anticoagulant regimen. Among these, warfarin was administered to 4 patients and apixaban to 2; the repeat TEEs showed complete thrombus resolution. The remainder patient who had no AF history was administered a low molecular weight heparin, and a repeat TEE showed persistence of LAA thrombus.

Table 4. Anticoagulant and antiplatelet treatments of patients	
Anticoagulant treatment	**n=17**
Warfarin	5 (29.4)
Apixaban	3 (17.6)
Edoxaban	2 (11.8)
None	7 (41.2)
Antiplatelet treatment	
ASA	4 (23.5)
None	13 (76.5)
ASA: Acetyl Salicylic Acid	

In our study, TEE was planned for patients screened generally due to AF. The only patient for whom dabigatran was not effective had long-term persistent AF. Nine patients had persistent; 6 had paroxysmal AF; 1 had no history of AF; and 1 had long-standing persistent AF, In the latter, thrombus was persisted despite switch was made from warfarin to dabigatran.

During this period, no bleeding or stroke was observed in any of the patients.

Table 5. Detailed charactestics of anticoagulant regimen and AF types of patients				
	AF type	**Previous anticoagulant**	**Switched Treament**	**Thrombus in control TEE**
Patient 1	Persistent	Apixaban	Dabigatran	-
Patient 2	Paroxismal	Apixaban	Dabigatran	-
Patient 3	Persistent	Apixaban	Dabigatran	-
Patient 4	Persistent	Warfarin	Dabigatran	-
Patient 5	Persistent	Warfarin	Dabigatran	-
Patient 6	**Long standing persistant**	**Warfarin**	**Dabigatran**	**+**
Patient 7	Persistent	Warfarin	Warfarin	-
Patient 8	Persistent	Warfarin	Rivaroxaban	-
Patient 9	Paroxismal	Edoxaban	Dabigatran	-
Patient 10	Paroxismal	Edoxaban	Dabigatran	-
Patient 11	Paroxismal	None	Warfarin	-
Patient 12	Persistent	None	Warfarin	-
Patient 13	Persistent	None	Apixaban	-
Patient 14	Paroxismal	None	Warfarin	-
Patient 15	Paroxismal	None	Warfarin	-
Patient 16	Persistent	None	Apixaban	-
Patient 17	**None**	**None**	**LMWH**	**+**
TOE:Transesophageal Echocardiography, LMWH:Low Molecule Weight Heparine				

DISCUSSION

Traditionally, warfarin has long been the primary drug preferred for protection against thromboembolic events in atrial fibrillation (1). However, in the RE-LY study published in 2009, it was shown that dabigatran 150 mg twice daily was better in terms of stroke prevention than warfarin, albeit with a higher risk of bleeding (4). In 2011, the ROCKET-AF study was published, which showed that rivaroxaban was non-inferior to warfarin for stroke prevention (5). ARISTOTLE study was published in 2011, where apixaban was found non-inferior to warfarin for stroke and thromboembolism prevention; furthermore, apixaban was associated with lower bleeding rates than warfarin (6,7). Currently, available AF guidelines recommend anti-FXa inhibitors and direct thrombin inhibitors be preferred over warfarin in non-valvular atrial fibrillation (3). However, the available data are more limited in the treatment of thrombus in the left atrial appendage (8,9).

In our study, only 2 of 17 patients did not have thrombus resolution. All TEE examinations were performed after at least 3 weeks of effective anticoagulation. One of the patients without thrombus resolution was receiving dabigatran and the other was taking low molecular weight heparin (LMWH). A total of 8 of 17 patients were administered dabigatran. It was observed that thrombus (87.5 %) resolution was seen in 7 of 8 patients. Dabigatran 150 mg twice daily was administered to all of these patients.

In another study (10) in which 16 patients was examined, it was found that thrombus did not resolve in one patient. In that study, thrombus persisted in the patients receiving rivaroxaban. Thrombus was not detected in 9 patients using apixaban and 4 patients using dabigatran. In that study, only DOACs were used as oral anticoagulant agents; moreover, those patients had not used any anticoagulant before. But in our study, warfarin was also preferred in addition to DOACs, and a patient who was on warfarin continued warfarin therapy aiming at higher INR levels. The repeat TEE in that patient showed thrombus resolution. This finding suggests that warfarin is still an important option for thrombus resolution. On the other hand, 5 of our patients with LAA thrombus were receiving warfarin. It is unclear if prothrombin times of these patients were at an effective range at long term follow-up. However, it is a well-known fact that an important limitation for warfarin usage is the need for indefinite INR monitoring.

No study has yet showed the superiority of a DOAC over another for thrombus resolution. Miwa et al. reported a patient who received both warfarin and dabigatran for left atrial appendage thrombus but the latter was not eliminated. After switching therapy to apixaban 10 mg once daily thrombus resolution was achieved (11). In a case report Bolayir et al. (12) used apixaban for left ventricular apical thrombus that they couldn't give warfarin. After one month anticoagulation, they observed complete disappearance of thrombus. In a trial by Hussain et al. (13) comparing warfarin and DOACs with respect to thrombus resolution in 45 patients, 23 patients received warfarin and 22 patients DOACs. After at least 3 weeks of anticoagulation, thrombus resolution rates were 76% for warfarin and 77% for DOACs. There was no significant difference between the two groups in this regard. However, similar to other studies, they included patients with newly detected thrombus, so they reported no data of patients who failed with any oral anticoagulant and were switched to other oral anticoagulants. In our study, dabigatran 150 mg twice daily was more commonly preferred and it provided a thrombus resolution rate of 87.5 % for recurrent thrombi. All of those patients had thrombus while using an oral anticoagulant. Thus, we showed for the first time that dabigatran 150 mg twice daily can be given patients having thrombus while receiving an oral anticoagulant. In our study, 7 patients were not using any oral anticoagulant. Warfarin was preferred in 4 of these 7 patients, apixaban in 2, and LMWH in 1. Thrombus was detected in the patient who used LMWH. We gave an appropriate dose of LMWH adjusted to a patient's weight although we did not use anti-FXa for testing effectiveness. We believe that anti-FXa level was not in range for anticoagulation.

Xing et al. (14) investigated dabigatran in 58 patients with left atrial thrombus for whom a repeat TEE was performed. Complete thrombus resolution was detected in 62.1 % of the patients. The authors listed the indicators of ineffective resolution as AF type, left atrial diameter, left atrial ejection fraction and left atrial appendage flow rate. In another study (15), 226 patients underwent TEE after 4 weeks of anticoagulation with apixaban; thrombus was detected 3.1 %.

CONCLUSION

In our study dabigatran was preferred more than the other oral anticoagulants, which may be related with dabigatran's trial results, which suggested that dabigatran 150 mg twice daily has been shown to be more effective than warfarin in preventing stroke.

As it can be seen from the above mentioned studies, none of the drugs developed to protect from embolism reduces the risk of intra-cardiac thrombus to zero. Therefore, irrespective of patients being anticoagulated, TEE should be planned before interventional procedures and cardioversion. If thrombus develops in a patient receiving anticoagulant treatment, switching to a different anticoagulant would be a logical option. In our study we used dabigatran 150 mg twice daily to achieve that goal. It should also not be forgotten that these drugs have to be given in recommended doses to observe an effective response.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Ethics approval was obtained from Baskent University Faculty of Medicine Ethics Committee with protocol number KA20 /149.

REFERENCES

1. European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med 1995;333:5-10.
2. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J Cardiovasc Pharmacother 2018;39:1330-93.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar A, Casadei D et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J Cardiovasc Pharmacother 2016;37:2893-962.
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
5. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. NEngl J Med 2011;365:883-91.
6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patientswith atrial fibrillation. N Engl J Med 2011;365:981-92.
7. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. Am J Emerg Med 2016;34:3-8.
8. Kawakami T, Kobayakawa H, Ohno H, et al. Resolution of left atrial appendage thrombus with apixaban. Thromb J 2013;11:26-9.

9. Lip GY, Hammerstingl C, Marin F, et al. Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). Am Heart J 2016;178:126-34.
10. leddermann A, Eckert R, Muskala P, et al. Efficacy of Direct Acting Oral Anticoagulant Drugs in Treatment of Left Atrial Appendage Thrombus in Patients with Atrial Fibrillation. Am J Cardiol 123;1:57-62.
11. Miwa Y, Minamishima T, Sato T, et al. Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban. J Arrhytmia 2016;32:233-5.
12. Bolayir HA, Gunes H, Sahin O, et l.Complete resoution of huge left ventricular thrombus with apixaban treatment. Int J Cardiovascular Academy 2016;2:160-1.
13. Hussain A, Katz WE, Genuardi MV, et al. Non-vitamin K oral anticoagulants versus warfarin for left atrial appendage thrombus resolution in nonvalvular atrial fibrillation or flutter. Pacing Clin Electrophysiol. 2019;1-8.
14. Xing FX, Liu NN, Han YL, et al. Anticoagulation efficacy of dabigatran etexilate for left atrial appendage thrombus in patients with atrial fibrillation by trasthoracic and transesophageal echocardiography. Medicine 2018;97:26
15. Whiteside HL, Nagabandi A, Brown K, et al. Prevalance and clinical characteristics associated with left atrial thrombus detection: Apixaban. World J Cardiol 2019: 11;84-93.