Efficiency of the Left Atrial Appendage Thrombus Dissolution in Patients with Persistent Nonvalvular Atrial Fibrillation with Warfarin or Direct Oral Anticoagulants Therapy

Mazur E.S.*, Mazur V.V., Bazhenov N.D., Yu.A. Orlov Yu.A.

Tver State Medical University, Tver, Russia

Aim. Compare the incidence of the left atrial appendage (LAA) thrombus dissolution in patients with persistent nonvalvular atrial fibrillation receiving warfarin and direct oral anticoagulants (DOAC).

Materials and methods. 68 patients with persistent nonvalvular atrial fibrillation were included in a retrospective study (age was 59.7±9.8 years, 60.3% men), in whom at least one repeated transesophageal echocardiographic examination was performed after detecting a thrombus. After detecting a thrombus in the LAA, 37 (54.4%) patients started or continued taking warfarin in doses that ensure the INR maintenance at the level of 2-3, 14 (20.6%) started or continued taking dabigatran at a dose of 150 mg 2 times/day, 14 (20.6%) started or continued taking rivaroxaban 20 mg 1 time/day and 3 (4.4%) started or continued taking apixaban 5 mg 2 times/day. Repeated transesophageal echocardiographic examination was performed on average 33.3±14.2 days after the first one.

Results. Dissolution of a previously identified thrombus was found in 26 (83.9%) of 31 patients receiving DOAC and in 19 (51.4%) of 37 patients receiving warfarin (p=0.011). The logistic regression analysis showed that the chances of a thrombus dissolution in LAA while taking DOAC are 14.8 times (95% confidence interval [CI] was 2.469-88.72) higher than while taking warfarin. The size and the rate at which blood is expelled from the LAA also have an independent influence on the chances of thrombus dissolution. An increase in the size of a thrombus by 1 mm reduces the chances of a thrombus dissolution by 1.136 (95% CI was 1.040-1.244) times, and an increase in the rate of blood expulsion from the LAA by 1 cm/sec increases these chances by 1.105 (95% CI was 1.003-1.219) times.

Conclusion. In the present study, the incidence of the LAA thrombus dissolution in patients with persistent nonvalvular atrial fibrillation while receiving DOAC was higher than while receiving warfarin.

Key words: atrial fibrillation, transesophageal echocardiography, left atrial appendage thrombosis, oral anticoagulants, warfarin.

For citation: Mazur E.S., Mazur V.V., Bazhenov N.D., Yu.A. Orlov Yu.A. Efficiency of the Left Atrial Appendage Thrombus Dissolution in Patients with Persistent Nonvalvular Atrial Fibrillation with Warfarin or Direct Oral Anticoagulants Therapy. *Rational Pharmacotherapy in Cardiology* 2021;17(5):724-728. DOI:10.20996/1819-6446-2021-10-08.

*Corresponding Author: mazur-tver@mail.ru

Received: 27.07.2021
Accepted: 14.09.2021

Introduction

Modern recommendations for the diagnosis and treatment of atrial fibrillation (AF) offer two options for preparing for cardioversion in patients with arrhythmia paroxysm persisting for more than 48 hours [1, 2]. The first option provides for anticoagulant therapy for at least 3 weeks, the second option provides for the implementation of anticoagulant therapy immediately before cardioversion of transesophageal echocardiography (TEE) to identify contraindications to the restoration of sinus rhythm. If a thrombus is detected in the left atrial appendage (LAA), the planned cardioversion is recommended to be postponed for at least 3 weeks, during which the patient should receive adequate anticoagulant therapy. The question of the preferred use of certain anticoagulants in patients with a diagnosed thrombus in the LAA is not considered in the recommendations [1, 2].

The data presented in the literature on the effectiveness of various anticoagulants for the treatment of patients with a thrombus detected in LAA are few and contradictory. For example, according to the X-TRA study and the CLOT-AF register, complete the thrombus dissolution is observed in 41.5% of cases after 6-8 weeks of taking rivaroxaban, and in 62.5% of cases after 3-12 weeks of treatment with vitamin K antagonists [3]. But in the study by A. Hussain et al [4], thrombus dissolution during repeated TEE, performed on average 67 days after the first study, was found in 77% of patients receiving direct oral anticoagulants (DOAC), and in 74% of patients receiving warfarin. No differences in the effectiveness of DOAC and warfarin were found in the A.D. Niku et al [5], in which the the thrombus dissolution was noted in 58.7% of cases with repeated TEE performed 96±72 days after the first study. The RE-LATED AF-AFNET 7 study, launched in 2016 and aimed at comparing the efficacy of dabigatran and warfarin in dissolving thrombus in LAA, was terminated early due to the inability to enroll the required number of patients [6,7]. A study comparing thrombolytic therapy with rivaroxaban and warfarin (NCT03792152) is currently ongoing but its results can be expected no earlier than 2022. Participants in the Delphic panel discussion discussed the effectiveness of anticoagulant therapy in patients with AF and concluded that information for making detailed recommendations for treatment there are still not enough patients with identified atrial thrombosis [8]. Therefore, we considered it expedient to analyze and present our own data on the frequency of thrombus dissolution in LAA by the time of repeated TEE in patients with persistent AF receiving warfarin and DOAC.

The aim of this work is to compare the frequency of the LAA thrombus dissolution in patients with persistent nonvalvular AF receiving warfarin or DOAC.

Materials and methods

The study was of a retrospective nature and was carried out in accordance with the standards of good clinical practice and the principles of the Declaration of Helsinki, approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education of the Tver State Medical University of the Ministry of Health of Russia and agreed with the administration of the medical institution on the basis of which it was conducted. Upon admission to the hospital, all patients gave written informed consent to use the results of their studies for scientific purposes.

The information source for this study was the TEE register performed before the planned cardioversion in patients with persistent AF in 2011-2018 by one of the authors of this article. The studies were carried out on Vivid E9 and Vivid S70 devices (GE, USA) and a 6VT-D transesophageal array multiplane phased transducer (2D/3D/4D). LAA scanning was performed from the mid-esophageal approach in sections from 0 to 180° with a stepwise interval of 10-30°. Thrombus in LAA was defined as discrete echo-positive masses, different in density from the endocardium and comb muscles. The entry of information into the register began after the operator performed 50 transesophageal studies, the results of which could formally be considered unreliable.

At the time of analysis, the registry contained information on 662 patients with persistent AF, 124 (16.5%) of whom had a thrombus in the LAA during the first TEE performed before the planned cardioversion. 68 patients (age was 59.7±9.8 years, 60.3% of men) were included in the study, in whom at least one repeated TEE was performed after a thrombus was detected.

At the time of a thrombus detection, all patients received anticoagulant therapy but its duration exceeded 3 weeks only in 30 (44.1%) of them (prepared patients). After detecting a thrombus in the LAA, 37 (54.4%) patients started or continued taking warfarin in doses that ensure the maintenance of INR at the level of 2-3 units, 14 (20.6%) started or continued taking dabigatran at a dose of 150 mg 2 times/days, 14 (20.6%) started or

continued taking rivaroxaban 20 mg 1 time/day and 3 (4.4%) started or continued taking apixaban 5 mg 2 times/day. Repeated TEE was performed on average 33.3±14.2 days after the first one. Also, the INR before both the first and the second TEE was within the target range in all warfarin-treated patients, but the total time to maintain optimal anticoagulation was unknown.

Statistical analysis was carried out using the SPSS Statistics 22 software (IBM, USA). In intergroup comparisons of mean values, the Student's t-test was used in the case of a normal distribution of the trait, and the Mann-Whitney's test was used otherwise. The $\chi 2$ test was used when comparing sample shares. The multivariate analysis of logistic regression by the method of stepwise inclusion according to the Wald's test was used to identify factors that influence the likelihood of thrombus dissolution in LAA. The results were considered statistically significant with an alpha-error probability of less than 5% ($p<0.05$).

Results

According to the data presented in Table 1, the groups of patients who received DOAC and warfarin were comparable in all characteristics taken into account in this study, with the exception of gender: the proportion of men in the first of these groups was significantly higher than in the second: 77.4% versus 45, 9% (p=0.017). At the same time, the number of thrombus dissolution cases by the time of repeated TEE in the group of patients receiving DOAC was greater than in the group of patients receiving warfarin: 83.9% versus 51.4% (p=0.011). The presented data allow us to consider gender and DOAC intake as potential predictors of successful LAA thrombus dissolution in patients with persistent nonvalvular AF.

Multivariate analysis of logistic regression didn't confirm the effect of the patient's gender on the likelihood of a thrombus dissolving in the LAA but showed that the DOAC use increased the chances of its dissolution by almost 15

Table 1. Characteristics of patients with persistent nonvalvular AF and the LAA thrombus who received warfarin and POAC

Parameter	DOAC group (n=31)	Warfarin group (n=37)	p
Age, years	60,9±10,2	58,7±9,5	0,363
Men, n (%)	24 (77,4)	17 (45,9)	0,017
Idiopathic AF, n (%)	7 (22,6)	6 (16,2)	0,723
Arterial hypertension, n (%)	22 (71,0)	24 (64,9)	0,783
Coronary heart disease, n (%)	5 (16,1)	4 (10,8)	0,776
History of myocardial infarction, n (%)	2 (6,5)	3 (8,1)	0,837
Dilated cardiomyopathy, n (%)	1 (3,2)	5 (13,5)	0,289
Heart failure, n (%)	12 (38,7)	10 (27,0)	0,445
Diabetes mellitus, n (%)	4 (12,9)	6 (16,2)	0,968
History of stroke, n (%)	2 (6,5)	3 (8,1)	0,837
CHA_2DS_2-VASc, points	2,26±1,53	2,19±1,31	0,841
High risk of stroke, n (%)	19 (61,3)	19 (51,4)	0,564
Adequate ACT, n (%)	15 (48,4)	15 (40,5)	0,687
Atrial flutter, n (%)	4 (12,9)	6 (16,2)	0,968
Paroxysm, days	54,7±35,7	52,4±45,4	0,815
Thrombus length, mm	20,4±9,09	19,5±9,28	0,681
Thrombus>18 mm, n (%)	17 (54,8)	17 (45,9)	0,627
Blood flow in LAA, cm/sec	13,1±6,32	12,9±7,39	0,918
LAA area, cm^2	5,53±1,02	5,74±1,61	0,523
Interval between studies, days	34,6±16,8	32,0±11,7	0,470
Thrombus lysis, n (%)	26 (83,9)	19 (51,4)	0,011

Data are presented as M±SD, unless otherwise indicated.

ACT – anticoagulant therapy, DOAC – direct oral anticoagulants, LAA – left atrial appendage, AF – atrial fibrillation, CHA_2DS_2-VASc — clinical scale for assessing the stroke risk

Table 2. Results of multivariate logistic regression analysis

Factor	OR	95% CI	p
Taking DOAC	14,800	2,469-88,72	0,003
Thrombus size, mm	0,880	0,804-0,962	0,005
Blood flow in LAA, cm/sec	1,105	1,003-1,219	0,044
Arterial hypertension	0,153	0,023-1,017	0,052

CI – confidence interval, OR – odds ratio, DOAC – direct oral anticoagulants, LAA – left atrial appendage

times (Table 2). In addition, it was shown that an increase in the thrombus size by 1 mm reduces the chances of its dissolution by 14%, and an increase in the blood flow velocity in the LAA by 1 cm/sec increases these chances by 11%. The effect of hypertension was also close to the level of statistical significance, the presence of which reduces the chances of a thrombus dissolution by 6.5 times.

Thus, the DOAC use turned out to be the most powerful of the factors identified in this study that increase the likelihood of a thrombus dissolving in LAA.

Discussion

The frequency of thrombus dissolution by the time of the second TEE in the patients included in the present study (66.1%) didn't differ significantly from the results of other nonrandomized studies: 58.7% according to the A.D. Niku et al. [5], and 74-77% according to the study by A. Hussain et al. [4]. The fundamental difference lies in the fact that in the present study, the frequency of thrombus dissolution while taking DOAC was higher than that while taking warfarin (83.9% versus 51.4%; p=0.011), while in the mentioned studies there were no such differences. Moreover, according to the X-TRA study and the CLOT-AF register [3], the rate of thrombus dissolution with rivaroxaban was lower than with vitamin K antagonists (41.5% versus 62.5%; p=0.008). But in some later studies, DOACs have shown significantly higher efficacy in the treatment of patients with a thrombus detected in LAA. For example, in the study by F.X. Xing et al. [9], the thrombus dissolution while taking dabigatran was found in 36 (62.1%) of 58 patients examined over time. According to M. Harada et al. [10], 13 (81.3%) of 16 patients who received dabigatran at a daily dose of 300 mg dissolved the thrombus in the LA. The study by K.C. Yilmaz et al. [11] showed the thrombus dissolution in the LAA in 10 (90.9%) of 11 patients examined in dynamics, receiving DOAC. Thus, the data obtained in this study on the frequency of thrombus dissolution in the presence of DOAC (83.9%) are quite comparable with the data presented in the literature. We can talk about relatively low effectiveness of warfarin in our study (51.4%) since all patients receiving warfarin in the last two of the studies mentioned above dissolved the thrombus. It's possible that the relatively low frequency of thrombus dissolution during treatment with warfarin is associated with the objective difficulties of careful monitoring of the INR level in real clinical practice [12,13].

The need to continue comparative studies of the DOAC and warfarin effectiveness in relation to thrombus lysis in LAA is beyond doubt since the choice of an anticoagulant is the only way to influence the results of treatment in such patients. However, several other factors also influence the likelihood of thrombus dissolution during anticoagulant therapy, in particular the AF type, left atrial diameter, and blood flow velocity in LAA [9]. The present study confirmed the independent influence of blood flow velocity in LAA on the chances of thrombus dissolution and showed that the initial size of a thrombus also affects the likelihood of thrombus dissolution. Similar data were previously obtained for left ventricular thrombus [14,15]. The study showed that an increase in the apical thrombus size by 1 mm reduces the chances of its dissolution against the background of anticoagulant therapy by 1.06 times (95% confidence interval was 0.99-1.14), that is, by 6.2% (p=0.053). According to the present study, an increase in the thrombus size in the LAA by 1 mm reduces the chances of its dissolution by 1.14 times (95% confidence interval was 1.04-1.24), that is, by 14% (p=0.005). Thus, the data obtained in this study on the effect of the LAA thrombus size on the probability of its dissolution are almost completely consistent with the data on the size and probability of the left ventricular thrombus dissolution presented in the literature.

We can assume that the pronounced differences in the

above data on the efficiency of thrombus dissolution are largely associated with the differences in the patients included in the study, in particular, with the differences in the thrombus initial size and the blood expulsion rate from the LAA. We can't exclude that such features have a different effect on the thrombus dissolution efficiency when using various anticoagulants. This issue deserves a separate study, as does the issue of the effect of the anticoagulant intake duration on the likelihood of thrombus dissolution. In the present study, no such effect was found, which may be due to the relatively short observation period.

Study limitations

The present study was non-randomized and included a relatively small number of patients, which must be taken into account when interpreting the results obtained.

Conclusion

Repeated TEE revealed the previously detected thrombus dissolution in 26 (83.9%) of 31 patients with persistent nonvalvular AF who received DOAC, and in 19 (51.4%) of 37 patients who received warfarin (p=0.011). Thus, the chances of thrombus dissolution in the LAA were higher with POAC than with warfarin. In addition, the size and the rate at which blood is expelled from the LAA have an independent influence on the chances of thrombus dissolution. Increasing the thrombus size decreases the chances of it dissolving, and an increase in the rate at which blood is expelled from the LAA increases these chances.

Relationships and Activities: none.

Funding: The study was performed with the support of the Tver State Medical University.

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About the Authors:

Evgeniy S. Mazur
eLibrary SPIN 3898-6719, ORCID 0000-0002-8879-3791
Vera V. Mazur
eLibrary SPIN 9798-0540, ORCID 0000-0003-4818-434X
Nikolay D. Bazhenov
eLibrary SPIN 1053-3892, ORCID 0000-0003-0511-7366
Yuriy A. Orlov
eLibrary SPIN 8518-2831, ORCID 0000-0001-9114-0436