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Risk of cardiovascular complications in patients with persistent atrial fibrillation after dissolution of a thrombus in the left atrial appendage

Aim	To compare the incidence of cardiovascular complications (CVC) in patients with persistent atrial fibrillation (AF) following thrombus dissolution in the left atrial appendage (LAA) and in patients with persistent AF without preceding LAA thrombosis.
Material and methods	The main group included 43 patients who had been diagnosed with LAA thrombosis on the first examination, transesophageal echocardiography, and who showed dissolution of the thrombus on a repeated study performed after 7.1+2.0 weeks of the anticoagulant treatment. The control group consisted of 123 patients with a risk score >0 for men without LAA thrombosis and score >1 for women without LAA thrombosis according to the CHA_2DS_2-VASc scale. The patients were followed up for 47.3±17.9 months. The following unfavorable outcomes were recorded: all-cause mortality, ischemic stroke or systemic thromboembolism, hemorrhagic stroke or severe bleeding, and myocardial infarction (MI).
Results	Unfavorable clinical outcomes were observed in 39.5% of patients in the main group and in 3.3% of patients in the control group (p<0.001). Furthermore, the incidence of ischemic stroke (relative risk (RR), 12.9; 95% confidence interval (CI), 2.89–57.2), and MI (RR, 5.72; 95% CI, 1.09–30.1) was higher in the main group. However, the number of MI cases in both groups and the number of stroke cases in the control group increased during the entire follow-up period, while the number of stroke cases rapidly increased only during the first year of follow-up.
Conclusion	In patients with persistent AF, the risk of CVC after LAA thrombus dissolution remains significantly higher than in patients with AF without LAA thrombosis.

Keywords	Atrial fibrillation; left atrial appendage thrombosis; oral anticoagulants; stroke
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Introduction

Atrial fibrillation (AF) is a common arrhythmia. Its clinical value is highly correlated with the risk of thromboembolic complications (TCs), mainly cardioembolic stroke [1]. The only effective way to prevent thromboembolism in AF is anticoagulant therapy (ACT), depending on the assessment of stroke risk using the CHA_2DS_2 VASc score [2-4]. Besides clinical predictors of stroke used in this score, a high risk of stroke is also evidenced by the presence of a left atrial appendage (LAA) thrombus as shown by transesophageal echocardiography (TEE) and/or high-intensity spontaneous echochardiographic contrast (SEC). Lowe et al. [5] showed that the odds ratio (OR) of TCs is 2.74 (95% confidence interval [CI]: 1.23–6.08) in AF patients and an LAA thrombus and 3.43 (95% CI: 1.56–7.42) in patients with high-intensity SEC. According to Melduni et al. [6], the OR of stroke in patients with an LAA thrombus as shown by TEE was equal to 3.21 (95% CI: 1.48–6.95). However, the current guidelines [2-4] do not regard LAA thrombi is as an independent risk factor that must be considered when ordering continuous ACT. It is only indicated that if there is a thrombus, the scheduled cardioversion procedure should be postponed, effective ACT should be administered for at least 3 weeks before cardioversion, repeat TEE conducted to make sure that the thrombus has dissolved [2]. There are no recommendations for patient management in case that the thrombus is preserved. The management of patients after successful thrombolysis is not considered. Patients with dissolved thrombus should be treated as patients with undiagnosed thrombosis—that is, depending on the assessment of stroke risk according to CHA_2DS_2 VASc. However, this approach is not entirely reasonable because of a history of stroke indirectly indicating the presence of an atrial thrombosis, which adds 2 more points to the risk score, and the direct detection of a thrombus is not considered in the TC risk assessment.

It seems relevant to answer the above questions, because detecting an LAA thrombus in AF patients is not casuistry. According to various studies [7], TEE reveals LAA thrombi in

AF patients receiving ACT in 0.5%–17.8% of cases [8, 9] and in 5.1%–20.8% of patients who do not receive such treatment [8, 10]. Thrombi are lyzed in 50%–95% of patients after 6–8 weeks of ACT [11-13]. In all such cases, a physician has to decide on patient management without relying on the basic clinical guidelines, which, according to experts, cannot be developed due to the lack of sufficient evidence [14]. In other words, there is a need for data on the frequency of complications after thrombus dissolution in AF patients.

Aim

Compare the incidence of cardiovascular events (CVEs) in patients with persistent AF after the dissolution of LAA thrombi in patients with persistent AF without a history of LAA thrombosis.

Materials and methods

This prospective observational study was carried out following Good Clinical Practice and the Declaration of Helsinki of the World Medical Association, and approved by the Ethics Committee of Tver State Medical University (Minutes no. 7 dated 3/26/2014). The study was conducted in the Tver Regional Clinical Hospital from September 2014 to September 2019.

The study included patients with persistent AF, who underwent TEE before cardioversion. Patients were examined on the day of the scheduled cardioversion using Vivid E9 and Vivid S70 devices (GE, USA). LAA was scanned via mid-esophagus access in sections from 0°–180° with 10°–30° intervals. LAA thrombi were defined as a discrete echo-positive mass with a density different from the endocardium and pectineal muscles, and spontaneous echo contrast was defined as contrast mobile, cloud-like echo-signals in the left atrium.

During the inclusion period, 312 patients with persistent AF underwent TEE: 237 (76.0%) patients had no contraindications to cardioversion—that is, they had no LAA thrombus and/or high-intensity SEC. A total of 97 male patients had stroke risk scores according to CHA_2DS_2 VASc equal to 0, and 66 female patients had a risk score of 1; 42 patients withdrew from the study. The remaining 123 patients signed the informed consent to participate in the study and were included in the control group.

An LAA thrombus was revealed by the first transesophageal examination in 59 (18.9%) patients, and high-intensity SEC without atrial thrombosis in 16 (5.12%) patients. The efficacy of the newly administered or adjusted ACT in 54 patients with LAA thrombi was evaluated by repeated TEE procedures. The thrombus dissolved after the mean duration of treatment of 7.1±2.0 weeks in 43 (79.6%) patients. All these patients signed the informed consent to participate in the study and were included in the main group.

The included patients were followed up until June 2020. The following adverse outcomes (endpoints) were assessed: all-cause death, ischemic stroke (IS) or systemic embolism, hemorrhagic stroke or major bleeding, myocardial infarction (MI). The mean follow-up period was 47.3±17.9 months.

Statistical analysis of the data obtained was performed using the SPSS Statistics 15.0 software suite. The quantitative characteristics with normal distribution were calculated as the mean and standard deviation (M±SD). The mean values were compared between the two groups using the Student's t-test for free variables. In non-normal distribution, the data were expressed as the median and interquartile range (Me [P25; P75]). In this case, the comparisons between groups were made using the Mann–Whitney U-test. The chi-square test was used for the frequency analysis of qualitative variables. Time to the occurrence of events was analyzed by constructing the Kaplan–Meier curves, which were compared using the log-rank test. The intergroup differences were statistically significant in all cases with $p<0.05$.

Results

The groups compared were similar in age, sex, and prevalence of concomitant diseases except for chronic heart failure, which was reported 1.5 times more often in the main group compared to the control group (Table 1). Concomitant coronary artery disease was more frequent in the main group, but the differences were not statistically significant.

The groups were comparable in the mean CHA_2DS_2 VASc scores of IS risk, which was caused by the exclusion of individuals with a score of 0 from the comparison group. In the main group, 2 (4.7%) patients had CHA_2 DS_2 VASc 0.

The duration of the last paroxysmal AF was virtually identical in the two groups. The median was 31 days, but the disease was of significantly longer duration in the control group than in the main group (24 vs. 4 months, respectively; $p<0.001$). It is likely that the differences in the disease duration are due to the fact that the proportion of patients receiving continuous ACT was almost twofold in the control group compared to the main group (69.1% vs. 39.5%, respectively; $p<0.005$). It should be noted that the majority of patients in the main group received warfarin, and warfarin and direct oral anticoagulants (DOACs) were used equally frequently in the control group. At the end of the study, all included patients received continuous ACT, and warfarin was administered in about 30% of patients in both groups.

During the follow-up, adverse clinical outcomes were reported in 21 (12.7%) of the 166 patients included in the study: IS in 11 (6.6%) patients, hemorrhagic stroke in 2 (1.2%) patients, major bleeding in 1 (0.6%) patient, and MI in 6 (3.6%) patients. Seven (4.2%) patients died. The cause of death was IS in 3 (42.9%) cases, hemorrhagic

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Table 1. Characteristics of the study and control groups

Parameter	Group		p
	Main group (n=43)	Control group (n=123)	
Age, years	63.6±8.7	62.2±9.2	0.373
Male	26 (60.5)	79 (64.2)	0.660
Arterial hypertension	32 (74.4)	103 (83.7)	0.177
Coronary artery disease	10 (23.3)	14 (11.4)	0.057
Congestive CHF	24 (55.8)	44 (35.8)	0.022
Dilated CMP	2 (4.7)	1 (0.8)	0.104
Hypertrophic CMP	1 (2.3)	0	0.582
Diabetes mellitus	7 (16.3)	21 (17.1)	0.905
History of thromboembolism	7 (16.3)	17 (13.8)	0.694
CHA_2DS_2 VASc, score	3.0±2.1	2.6±1.4	0.236
>1 in males, >2 in females	29 (67.4)	92 (74.8)	
1 in males, 2 in females	12 (27.9)	31 (25.2)	0.050
0 in males, 1 in females	2 (4.7)	0	
Duration of the disease, months	4.0 [1.0; 36.0]	24.0 [4.0; 60.0]	0.000
Duration of paroxysm, days	40.0 [14.0; 90.0]	30.0 [4.5; 91.0]	0.178
Continuous ACT			
• Before the beginning of the study	17 (39.5)	85 (69.1)	0.002
• Including warfarin	14 (82.4)	42 (49.4)	0.013
• At the time of completing the study	43 (100)	123 (100)	1.000
• Including warfarin	15 (34.9)	43 (35.0)	0.993
Total adverse outcomes	17 (39.5)	4 (3.3)	0.000
Ischemic stroke	9 (20.9)	2 (1.6)	0.000
Hemorrhagic complications	3 (7.0)	0	0.022
Myocardial infarction	4 (9.3)	2 (1.6)	0.021
All-cause death	6 (14.0)	1 (0.8)	0.002

The data are expressed as the mean and the standard deviation (M±SD), the median and the interquartile range (Me [P_{25}; P_{75}], the absolute and relative values (n (%)). CHF, chronic heart failure; CMP, cardiomyopathy; CHA_2DS_2 VASc, score for atrial fibrillation stroke risk; ACT, anticoagulant therapy.

complications in another 3 (42.9%) cases, and MI in 1 (14.3%) case. Thus, 66.7% of adverse outcomes and 85.7% of deaths were associated with TCs of AF and hemorrhagic complications of ACT.

Adverse outcomes were reported significantly more often in the main group: 39.5% vs. 3.3%, respectively (p<0.001). In the main group, SI (OR 12.9, 95% CI: 2.89–57.2) and MI (OR 5.72; 95% CI: 1.09–30.1) were equally more frequent. However, the number of MI cases in both groups and the number of strokes in the control group increased during the follow-up period, and the number of strokes in the main group increased rapidly only in the first year after the inclusion (Figure 1).

All adverse outcomes developed during ACT: DOACs in 108 (65.1%) patients and warfarin in 58 (34.9%) at the end of the study. In the control group, the numbers of outcomes occurring in patients receiving warfarin and DOACs did not differ. However, IS and hemorrhagic complications with warfarin were more frequent than with DOACs in the main group (Table 2). In the main group, OR of IS during warfarin therapy was 14.9 (95% CI: 2.05–108.4) compared with DOACs, and OR of hemorrhagic complications was 3.73 (95% CI: 0.36–37.9). At the same, OR of MI in patients taking warfarin lower than in those treated with DOACs in the main group–0.62 (95% CI: 0.07–5.48).

Thus, within a year after the dissolution of an LAA thrombus, the risk of IS is higher in patients with persistent AF than in patients without thrombi on TEE. The risk of IS after the thrombus dissolution is higher in patients receiving warfarin than in patients receiving DOACs.

Discussion

The study assessed the incidence of stroke in AF patients after the dissolution of an LAA thrombus. Based on the available literature, this is the first study of this kind, but the incidence of stroke in AF patients with LAA thrombi revealed by TEE has been studied repeatedly. For example, Bernhardt et al. [15] followed up 43 patients for 3 years, who had permanent or persistent AF and LAA thrombi detected be TEE. All patients received warfarin, and the target international normalized ratio (INR) was 2.5. IS occurred in 22 (51%) patients, 5 of whom died. Given the follow-up duration, the annual incidence of IS was 17% in this study. This is the highest incidence of stroke described in the literature in AF patients with LAA thrombi identified by TEE.

Dawn et al. [16] followed up 87 patients with persistent and permanent AF and LAA thrombi and high-intensity SEC, 67% of whom received warfarin. TECs occurred in 21 (24%) patients, which, given the follow-up time (28±19 months) was almost 10% per year. In a more recent study by Lowe et al. [5], IS was reported in patients with LAA thrombi much less frequently—20% in 6.4±3.6 years of follow-up, or 3.2% per year. Significant reduction in the incidence of stroke compared with previous studies may be explained by the fact that the approach to administering ACT in AF patients changed within the 10 years: antiplatelet drugs are now almost not used for the prevention TECs in AF.

In this study, the incidence of IS was 20.9% in the main group within 3.1±1.9 years of follow-up (6.81% per year)—it was higher than in the study by Lowe et al. [5]. The study by Lowe et al. [5] included patients with detected but not dissolved LAA thrombi, but this study included patients with the dissolved thrombi. Thus, the dissolution of a LAA thrombus in AF patients does not reduce the risk of IS.

The second, and even more important, difference between the findings of comparable studies is that all cases of stroke were reported in this study during the first year of follow-up,

Figure 1. Probability curves of ischemic stroke (A) and myocardial infarction (B) in the treatment and control groups

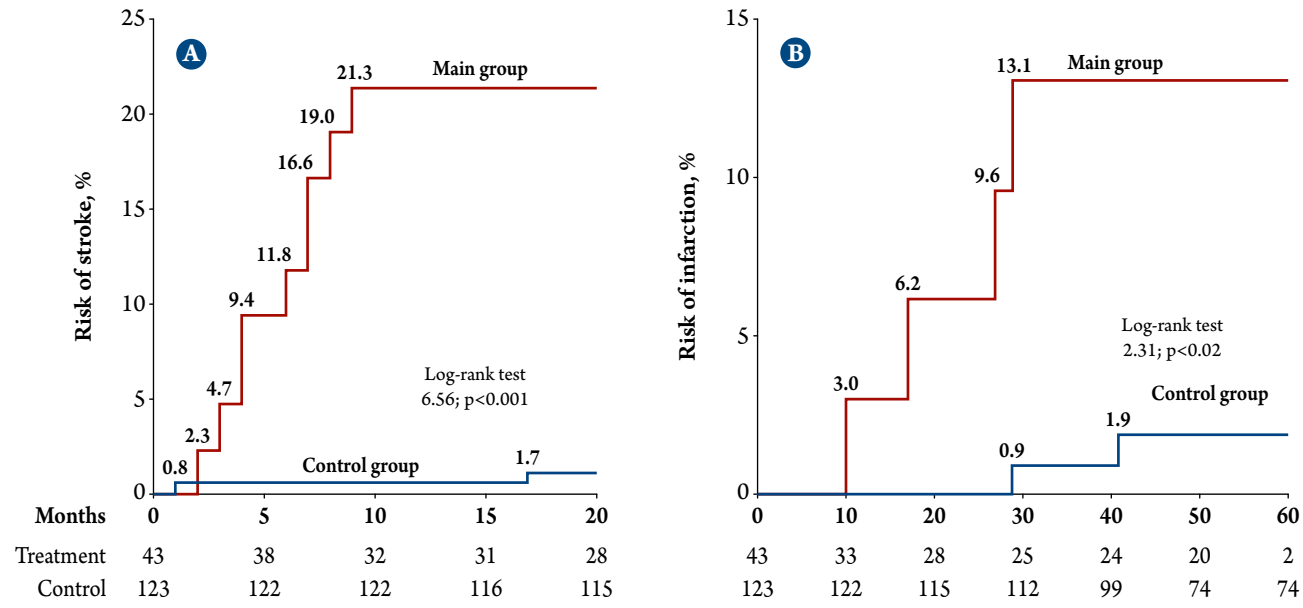

Table 2. Frequency of adverse outcomes in patients receiving warfarin and direct oral anticoagulants

Outcome	Treatment group			Control group		
	Warfarin (n=15)	DOACs (n=28)	p	Warfarin (n=43)	DOACs (n=80)	p
Ischemic stroke	8 (53,3)	1 (3,6)	0,000	0	2 (2,5)	0,296
Hemorrhagic complications	2 (13,3)	1 (3,6)	0,232	–	–	–
Myocardial infarction	1 (6,7)	3 (10,7)	0,664	0	2 (2,5)	0,296
All-cause death	4 (26,7)	2 (7,1)	0,079	0	1 (1,3)	0,462
All adverse outcomes	12 (80,0)	5 (17,9)	0,000	0	4 (5,0)	0,137

The data are expressed as the absolute and relative values (n (%)). DOACs, direct oral anticoagulants.

and Lowe et al. [5] reported the number of strokes increasing throughout the follow-up period. Survival curve analysis showed that the likelihood of stroke is 3.19% in 1 year after the detection, 4.86% in 2 years, 8.28% in 3 years, 14.0% in 4 years, and 20% in 5 years. Similar changes were observed by Melduni et al. [6]: the likelihood of stroke in patients with LAA thrombi during five years of follow-up was 2.4%, 5.1%, 7.7%, 11.2%, and 19.3%, respectively.

These differences suggest that thrombus dissolution not only reduces the stroke risk but increases the likelihood of its development during the first year after thrombolysis. From a pathophysiological point of view, this assumption seems quite plausible because TECs are not caused by an LAA thrombus, but thromboemboli not fixed to the atrial endocardium, which may appear as a thrombus dissolves or develops. For example, a thrombus and SEC are known to be predictors of IS of high risk; SEC develops in the sharp slowing of blood flow in the atrium and is, in fact, a manifestation of the blood "readiness" to form a thrombus. Lowe et al. [5] followed up 47 patients with SEC, 25% of whom had IS. OR of stroke in patients with contrast was higher than in patients with LAA thrombi: 3.43 (95% CI: 1.56–7.53) vs. 2.74 (95% CI: 1.23–6.08), respectively.

In this study, the correlation between the thrombus dissolution and the appearance of SEC was not studied. Thus, we can only speak about some kind of "hemocoagulation instability," which may occur when the thrombus dissolves and thromboembolism can develop. The appearance of such instability is associated mainly with the use of warfarin. Indeed, 8 out of 9 cases of stroke reported in the main group occurred in patients taking warfarin. In the control group, stroke developed in patients receiving DOACs in both cases.

The anticoagulant effect of warfarin is unstable due to the influence of various factors, from the administration of other drugs to the patient's diet [17]. The risk of IS is higher in patients receiving inadequate warfarin therapy than in patients not receiving ACT [4, 18, 19]. After thrombus dissolution, even the slightest fluctuations in the anticoagulant effect may provoke the repeated formation of a thrombus, which explains a higher incidence of stroke within the first year after the thrombus dissolution in patients receiving warfarin.

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Interestingly, a similar situation is observed in patients with mechanical prosthetic heart valves, for which warfarin is the only option for thrombosis prevention. Prosthetic valve thrombosis is known to develop in about 10% of patients in the first year after surgery, but later the frequency of thrombosis decreases sharply, to 0.3%–1.3% per year [20].

Thus, according to the findings of this study, the dissolution of an LAA thrombus detected by TEE does not reduce the risk of IS, especially in patients receiving warfarin. The results of this study seem unexpected and very important from a practical point of view, which is why it is necessary to confirm or disprove them in further studies.

Limitations

The study missed several factors that can influence the results. In particular, it did not consider the nature and efficacy of heart rhythm therapy: preventive use of antiarrhythmic drugs, the incidence of AF recurrences and repeated cardioversions, or catheter ablation.

The exclusion of patients with detected and not dissolved LAA thrombi is a disadvantage of the design. Despite a relatively small number of such patients, data on the incidence of stroke in this group could be very useful for evaluating and interpreting the study results.

Conclusion

After the dissolution of the left atrial appendage thrombus, the risk of ischemic stroke is significantly higher in patients with persistent atrial fibrillation than in patients with atrial fibrillation who had no thrombi according to transesophageal echocardiogram. The likelihood of ischemic stroke after dissolution of the left atrial appendage thrombus is significantly higher in patients receiving warfarin than in patients receiving direct oral anticoagulants.

No conflict of interest is reported.

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