Cardiology Journal

VIA MEDICA

ORIGINAL ARTICLE

DOI: 10.5603/CJ.a2022.0054
Copyright © 2022 Via Medica
ISSN 1897–5593
eISSN 1898–018X

# Left atrial appendage thrombus in patients with atrial fibrillation who underwent oral anticoagulation

Jarosław Karwowski[1], Jerzy Rekosz[2], Renata Mączyńska-Mazuruk[1], Anna Wiktorska[2], Karol Wrzosek[1], Wioletta Loska[2], Katarzyna Szmarowska[2], Mateusz Solecki[2], Joanna Sumińska-Syska[1], Mirosław Dłużniewski[1]

[1]Department of Heart Diseases, Medical Center of Postgraduate Education, Warsaw, Poland
[2]2nd Department of Cardiology, Masovian Brodnowski Hospital, Warsaw, Poland

## Abstract

**Background:** *Electric cardioversion of atrial fibrillation (AF) is associated with an increased risk of embolism, with embolic material existing in the heart cavities. The initiation of oral anticoagulation therapy reduces the risk of thromboembolic events. The aims of this study were to evaluate the prevalence of left atrial appendage (LAA) thrombi in non-valvular AF, to compare vitamin K antagonists (VKAs) and non-vitamin K oral anticoagulants (NOACs) with respect to thrombus prevalence, and to evaluate the rate of LAA thrombus persistence on repeat transesophageal echocardiography (TEE) after treatment change.*

**Methods:** *We enrolled 160 consecutive AF patients who presented with an AF duration > 48 h and had undergone TEE before cardioversion.*

**Results:** *Left atrial appendage thrombus was observed in 12 (7.5%) patients, and spontaneous echo contrast 4 was observed in 19 (11.8%) patients; the incidence was similar between the NOAC and VKA groups (8.9% vs. 3.6% and 12.4% vs. 18.5 %, respectively). Among patients on NOAC, thrombus prevalence was detected in 8.4% of users of rivaroxaban, 8% of users of dabigatran, and 12.5% of users of apixaban.*

**Conclusions:** *The LAA thrombus developed in 7.5% of patients despite anticoagulation therapy, demonstrating similar prevalence rates among patients either on NOAC or VKA. Lower mean LAA flow velocity and a history of vascular disease were independent predictors of embolic material in the LAA. It seems that in the case of embolic materials in LAA under NOAC treatment, switching to VKA provides additional clinical benefit to the patients.* (Cardiol J)

**Key words: electric cardioversion, atrial fibrillation, left atrial appendage thrombus, transesophageal echocardiography, non-vitamin K antagonist oral anticoagulants**

## Introduction

Atrial fibrillation (AF), the most common type of arrhythmia, occurs in approximately 3% of the population aged over 20 years and in approximately 9% of the population over 80 years old [1–3]. This arrhythmia is associated with a 1.5- to 1.9-fold increase in the risk of mortality and a 2- to 5-fold increase in the risk of thromboembolic events, including stroke, transient ischemic attack, and systemic embolism. Restoration of sinus rhythm remains an integral part of the treatment for this type of arrhythmia. Electric cardioversion is associated with an increased risk of embolism with embolic material existing in the heart cavities [4, 5]. The initiation of oral anticoagulation with a vita-

Address for correspondence: Jarosław Karwowski, PhD, Department of Heart Diseases, Postgraduate Medical School, ul. Poznańska 22, 00–685 Warszawa, Poland, tel: +48 22 5251276, e-mail: karwowski.jarek@gmail.com

Received: 1.02.2022 Accepted: 28.04.2022 Early publication date: 9.06.2022

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

min K antagonist (VKA) at least 3 weeks before cardioversion (and continuation of this treatment for a minimum of 4 weeks after the procedure) may reduce the risk of a thromboembolic event to less than 1% [6, 7]. Among patients permanently treated with an oral VKA, ad hoc restoration of sinus rhythm may be attempted if the efficacy of this treatment is proven by the therapeutic outcome of the international normalized ratio (INR) [2, 3]. However, in the group treated with non-vitamin K oral anticoagulants (NOACs) cardioversion can be performed when the patient confirms regular intake of these drugs. In the era of the increasingly common use of NOACs, the question remains whether they are an effective and safe alternative.

This study aimed to do the following: (1) establish the prevalence of left atrial appendage (LAA) thrombi in patients with AF; (2) compare VKA vs. NOACs with respect to thrombus prevalence; (3) evaluate the rate of LAA thrombus persistence on repeat transesophageal echocardiogram (TEE) despite appropriate anticoagulation; and (4) define predictors of LAA thrombus incidence.

## Methods

We retrospectively evaluated 211 consecutive patients who presented with an AF duration > 48 h and had undergone TEE at our hospital between January 2018 and December 2019. In the authors' center all patients on NOACs and patients on VKA without weekly INR control underwent TEE before electric cardioversion of AF. We excluded 47 patients who were not on anticoagulation therapy and 4 patients who were treated with subtherapeutic doses of NOACs. Finally, the study population consisted of 160 patients.

Baseline demographic and clinical data were collected, and $CHA_2DS_2VASc$ scores were calculated for each patient. Recorded data included age, sex, cardiovascular risk factors, history of heart failure, type and duration of AF, and type and total duration of continuous oral anticoagulant therapy. Conventional transthoracic echocardiography (TTE) was performed in each patient, and data were collected.

Transesophageal echocardiogram was performed in all study patients before planned electric cardioversion using General Electric Vivid 9. Standard TEE acquisition was performed with focused imaging of the LAA, including a continuous 0° to 180° arc at the mid-esophageal plane at 10° to 30° intervals. An LAA thrombus was defined as a discrete echo-dense mass in the LAA, distinct from the LA endocardium or pectinate muscles. The severity of spontaneous echo contrast (SEC) was estimated according to Fatkin's criteria: 0 = none (absence of echogenicity); 1+ = mild (minimal echogenicity located in the LAA or sparsely distributed in the main cavity of the left atrium [LA], may be detectable only transiently during the cardiac cycle, imperceptible at operating gain settings for two-dimensional echocardiographic analysis); 2+ = mild to moderate (more dense swirling pattern than 1+ but similar distribution, detectable without increased gain settings); 3+ = moderate (dense swirling pattern in the LAA, generally associated with somewhat lower intensity in the main cavity; may fluctuate in intensity but detectable constantly throughout the cardiac cycle); and 4+ = severe (intense echo density and very slow swirling patterns in the LAA, usually with similar density in the main cavity) [8].

Patients with thrombi in the LAA did not undergo cardioversion.

Patients with an LAA thrombus underwent at least one TEE to determine thrombus prognosis and the possibility of thrombus resolution. Changes in oral anticoagulation therapy were made at the cardiology meetings. Among patients whose therapy was changed on VKA, the treatment efficacy was monitored by weekly INR control.

Finally, in each patient with LAA thrombus, follow-up clinical data were collected for up to 2 years (after the first TEE, median 2.9 years). Using telephone contact, we obtained information about the incidence of cardiovascular death, thromboembolic events (stroke, transient ischemic attacks, or systemic embolism), and bleeding.

The study was approved by an Institutional Bioethical Committee. The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study.

### Statistical analysis

Continuous variables are presented as means ± standard deviation or as medians and interquartile ranges for normally and non-normally distributed data, respectively. The t-test, $\chi^2$ test, and Fisher exact test were used to evaluate differences between two groups. Comparisons between three groups were performed using one-way analysis of variance or Cochran–Mantel–Haenszel modified ridit scores (row mean scores statistic). Multivariable logistic regression analysis with a backward variable selection procedure was used to identify independent, significant thrombus predictors among all variables tested. A significance

**Table 1.** Baseline characteristics and comparison between patients with and without left atrial thrombus.

| | Total (n = 160) | Thrombus (–) (n = 148) | Thrombus (+) (n = 12) | P |
|---|---|---|---|---|
| Age [years], mean ± SD | 73.4 ± 10.3 | 73.1 ± 10.4 | 77.0 ± 8.7 | 0.212 |
| Female | 80 (50.0%) | 73 (49.3%) | 7 (58.3%) | 0.548 |
| Heart failure | 53 (33.1%) | 45 (30.4%) | 8 (66.7%) | 0.021 |
| Hypertension | 143 (89.4%) | 132 (89.2%) | 11 (91.7% ) | 1.00 |
| Renal failure, GFR < 60 mL/min/1.73 $m^2$ | 69 (43.1%) | 63 (42.6%) | 6 (50.0%) | 0.617 |
| Previous stroke | 14 (8.7%) | 13 (8.8%) | 1 (8,3%) | 1.00 |
| Diabetes mellitus | 60 (37.5%) | 58 (39.2%) | 2 (16.7%) | 0.213 |
| Vascular disease | 43 (26.9%) | 36 (24.3%) | 7 (58.3%) | 0.017 |
| $CHA_2DS_2$-VASc, mean ± SD | 3.83 ± 1.64 | 3.77 ± 1.67 | 4.58 ± 1.0 | 0.021 |
| $CHA_2DS_2$-VASc score 0–1 | 14 (8.8%) | 14 (9.5%) | 0 (0%) | 0.602 |
| $CHA_2DS_2$-VASc score 2–4 | 85 (53.1%) | 81 (54.7%) | 4 (33.3%) | 0.153 |
| $CHA_2DS_2$-VASc score ≥ 5 | 61 (38.1%) | 53 (35.8%) | 8 (66.7%) | 0.059 |
| AF duration < 7 days | 45(28.1%) | 44 (29,3%) | 1 (8.3%) | 0.183 |
| AF duration ≥ 30 days | 88 (55.0%) | 77 (52.0%) | 11 (91.7%) | 0.013 |
| LVEF [%], mean ± SD | 56.1 ± 9.2 | 56.7 ± 8.9 | 49.2 ± 10.5 | 0.007 |
| Left atrial area [$cm^2$], mean ± SD | 25.7 ± 4.6 | 25.6 ± 4.5 | 26.8 ± 4.9 | 0.379 |
| Mitral regurgitation mild or severe | 37 (25.0%) | 36 (26.3%) | 1 (9.1%) | 0.292 |
| LAA flow velocity [m/s], mean ± SD | 35.8 ± 15.0 | 37.0 ± 15.0 | 22.8 ± 6.4 | < 0.0001 |
| SEC 4* | 26 (16.2%) | 19 (12.8%) | 7 (58.3%) | < 0.0001 |
| Apixaban 2.5 mg bid | 5 (3.1%) | 4 (2.7%) | 1 (8.3%) | 0.326 |
| Apixaban 5 mg bid | 11 (6.9%) | 10 (6.8%) | 1 (8,3%) | 0.588 |
| Dabigatran 110 mg bid | 13 (8.1%) | 12 (8.1%) | 1 (8.3%) | 1.000 |
| Dabigatran 150 mg bid | 12 (7.5%) | 11 (7.4%) | 1 (8.3%) | 1.000 |
| Rivaroxaban 15 mg | 26 (16.2%) | 22 (14.9%) | 4 (33.3%) | 0.108 |
| Rivaroxaban 20 mg | 57 (35.6%) | 54 (36.5%) | 3 (25.0%) | 0.541 |
| Acenocoumarol | 22 (13.7%) | 21 (14.2%) | 1 (8.3%) | 1.00 |
| Warfarin | 6 (3.7%) | 6 (4.1%) | 0 (0%) | 1.00 |
| Enoxaparin | 8 (5.0%) | 8 (5.4%) | 0 (0%) | 1.00 |

Data are presented as number (percentage) of patients unless otherwise indicated; *According to Fatkin's criteria; AF — atrial fibrillation; GFR — glomerular filtration rate; LAA — left atrial appendage; LVEF — left ventricular ejection fraction; SEC — spontaneous echo contrast

level of 0.05 was required for a variable to remain in the final model. Two-sided p-values were considered statistically significant at a level of < 0.05. Statistical analyses were performed using SAS 9.4.

## Results

### Study group characteristics

A total of 160 patients were enrolled in this study. The mean age was 73.4 years, and half of the patients were female (Table 1). The mean $CHA_2DS_2VASc$ score was 3.83, and 8.7% of patients had a history of stroke or transient ischemic attack. Among the cohort, 88 (55%) were persistent AF patients with the duration of arrhythmia exceeding 1 month. All patients were on anticoagulation therapy, with 124 patients on NOAC (57 on rivaroxaban, 26 on dabigatran, 16 on apixaban), 28 on VKA, and 8 on enoxaparin. A series of INR data before admission to the hospital was not available among patients with VKA.

### Prevalence of LAA thrombus

A comparison of the clinical and echocardiographic characteristics of patients with and without LAA thrombus is summarized in Table 1. There were significantly more patients with a history of heart failure (66.7% vs. 30.4%, p = 0.02) and

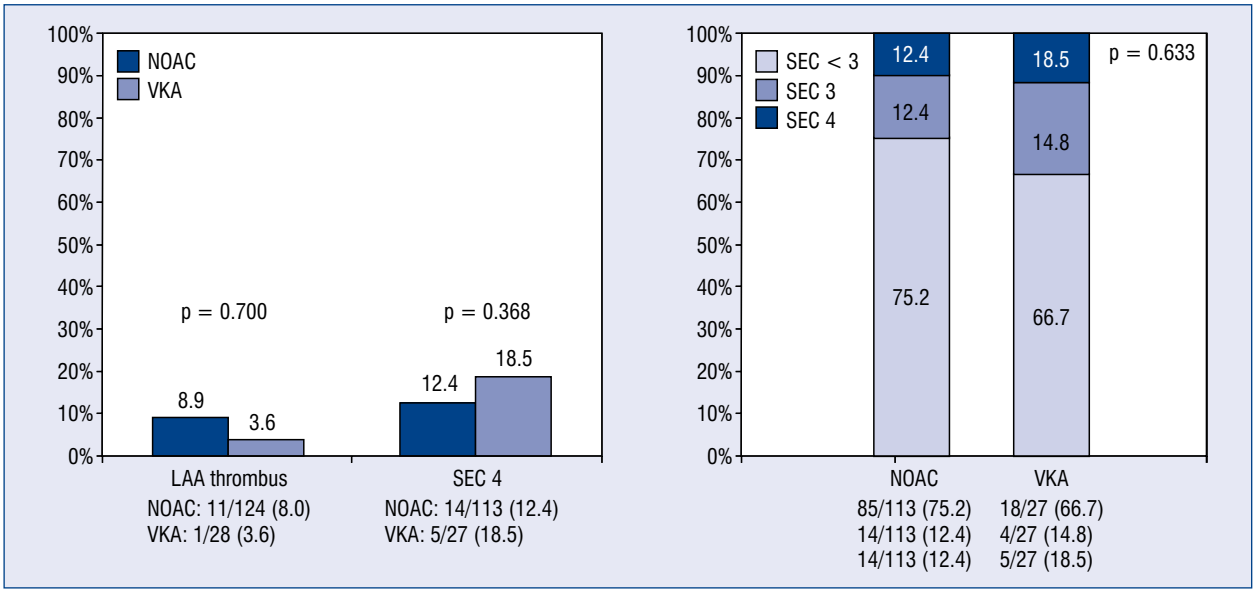


**Figure 1.** Comparison of rates of the left atrial thrombus and spontaneous echo contrast (SEC) among patients on non-vitamin K oral anticoagulant (NOACs) versus vitamin K antagonists (VKAs); data are presented as counts (percent) of patients; LAA — left atrial appendage.

vascular disease (58.3% vs. 24.3%, p = 0.02), and more patients with AF duration exceeding 1 month (91.7% vs. 52%, p = 0.01) in the LAA thrombi group. Patients with LAA thrombi had a significantly higher mean $CHA_2DS_2VASc$ score (4.58 vs. 3.77, p = 0.02). Among the echocardiographic findings, patients with LAA thrombi had significantly lower left ventricular ejection fraction (49.2% vs. 56.7%, p = 0.007), lower mean value LAA flow velocity (22.8 vs. 37 cm/s, p < 0.001), and higher incidence of SEC 4+ in LAA (58.3% vs. 12.8%, p < 0.0001) in comparison to patients without LAA thrombus.

## Comparison of NOAC and VKA therapy

Left atrial appendage thrombus was observed in 12 (7.5%) patients, and SEC 4 was observed in 19 (11.8%) patients; the incidence was similar between the NOAC and VKA groups (8.9% vs. 3.6% and 12.4% vs. 18.5 %, respectively) (Fig. 1). There were no differences in the clinical characteristics and echocardiographic findings between the NOAC and VKA patients (Table 2). Among patients on NOAC, the rates of thrombus detection were 8.4% for rivaroxaban, 8% for dabigatran, and 12.5% for apixaban (Fig. 2). The clinical characteristics of these patients are summarized in Table 3.

## Predictors of LAA thrombus

Multivariable analysis demonstrated that a history of vascular disease and LAA flow velocity were significant, independent predictors of developing an LAA thrombus (Table 4).

## Follow-up measures

The median follow-up with the interquartile range was 29.9 (24.0–34.6) months (Tables 5, 6). Patients with a thrombus in the LAA did not undergo cardioversion. Among the 12 patients with LAA thrombus, 11 were on NOACs and one was on acenocoumarol. Of the patients treated with NOACs, 7 had changed drugs on VKA and 4 stayed on NOACs. The patient was treated with VKA before thrombi material detection, after which he was treated with apixaban. Among the 12 patients with identified left atrial thrombus, 11 had at least one repeat imaging examination, 10 patients had a repeat TEE, one had computed tomography, and one patient had a systemic embolic event before repeat imaging. Among the 7 patients whose treatment changed from NOACs to VKA, LAA thrombus resolution was seen in 5. Patients on acenocoumarol before detection and with a changed anticoagulation regimen on apixaban also had LAA thrombus resolution. Patients with systemic embolic events had embolus in the left popliteal artery approximately 14 weeks after detection.

# Discussion

The main source of embolic material (approximately 90%) in non-valvular AF is the LAA [9].

**Table 2.** Characteristics of patients depending on anticoagulation regimen.

| | VKA (n = 28) | NOAC (n = 124) | P |
|---|---|---|---|
| Age [years], mean ± SD | 70.6 ± 11.0 | 74.3 ± 9.6 | 0.072 |
| Female | 15 (53.6%) | 62 (50%) | 0.723 |
| Heart failure | 9 (32.1%) | 42 (33.9%) | 0.861 |
| Hypertension | 26 (92.9%) | 110 (88.7%) | 0.738 |
| Renal failure, GFR < 60 mL/min/1.73 $m^2$ | 12 (42.9%) | 54 (43.5%) | 0.947 |
| Vascular disease | 8 (28.6%) | 34 (27.4%) | 0.902 |
| Previous stroke | 4 (14.3%) | 9 (7.3%) | 0.260 |
| Diabetes mellitus | 12 (42.9%) | 47 (37.9%) | 0.627 |
| $CHA_2DS_2$-VASc score, mean ± SD | 3.96 ± 1.69 | 3.87 ± 1.62 | 0.785 |
| AF duration < 7 days | 8 (28.6%) | 34 (27.4%) | 0.902 |
| AF duration ≥ 30 days | 14 (50%) | 69 (55.6%) | 0.588 |
| LVEF [%], mean ± SD | 54.5 ± 10.6 | 56.5 ± 8.4 | 0.293 |
| Left atrial area [$cm^2$], mean ± SD | 26.0 ± 5.1 | 25.7 ± 4.5 | 0.718 |
| Mitral regurgitation mild or severe | 7 (25.9%) | 29 (25.4%) | 0.958 |
| LAA flow velocity [m/s], mean ± SD | 0.34 ± 0.14 | 0.36 ± 0.15 | 0.584 |

Data are presented as number (percentage) of patients unless otherwise indicated; AF — atrial fibrillation; GFR — glomerular filtration rate; LAA — left atrial appendage; LVEF — left ventricular ejection fraction; NOAC — non-vitamin K oral anticoagulant; VKA — vitamin K antagonists

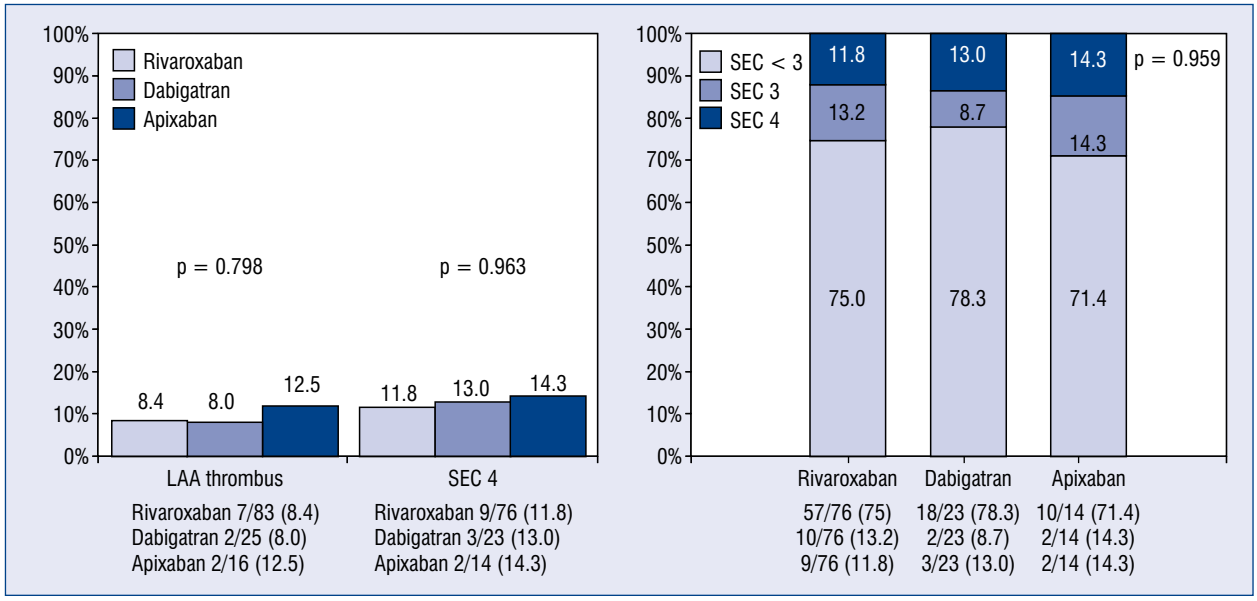


**Figure 2.** Comparison of rates of the left atrial thrombus and spontaneous echo contrast (SEC) among patients on specific non-vitamin K oral anticoagulant (NOACs); data are presented as counts (percent) of patients; LAA — left atrial appendage.

Based on current knowledge, it seems that the incidence of embolic material in the LAA is similar among patients treated with VKA and NOACs. In the ARISTOTLE study, the cardioversion was preceded by TEE in 86 patients treated with apixaban and 85 patients treated with warfarin; no LAA thrombus was detected in any of the groups [10]. In the RELY study, 1,983 cardioversions were performed in 1,270 patients [11]. A thrombus was found in 1.8% of patients treated with dabigatran 2 × 110 mg, 1.2% treated with dabigatran 2 × 150 mg, and 1.1% treated with

**Table 3.** Characteristics of patients depending on anticoagulation regimen.

| | Rivaroxaban (n = 83) | Dabigatran (n = 25) | Apixaban (n = 16) | P |
|---|---|---|---|---|
| Age [years], mean ± SD | 74.3 ± 9.9 | 73.3 ± 10.0 | 75.7 ± 7.3 | 0.787 |
| Female | 43 (51.8%) | 13 (52.0%) | 6 (37.5%) | 0.726 |
| Heart failure | 25 (30.1%) | 9 (36.0%) | 8 (50.0%) | 0.297 |
| Hypertension | 73 (87.9%) | 23 (92.0%) | 14 (87.5%) | 0.834 |
| Renal failure, GFR < 60 mL/min/1.73 $m^2$ | 32 (38.5%) | 13 (52.0%) | 9 (56.3%) | 0.270 |
| Vascular disease | 21 (25.3%) | 7 (28.0%) | 6 (37.5%) | 0.604 |
| Stroke | 5 (6.0%) | 0 (0%) | 4 (25.0%) | 0.016 |
| Diabetes mellitus | 33 (39.8%) | 7 (28.0%) | 7 (43.7%) | 0.498 |
| $CHA_2DS_2$-VASc score, mean ± SD | 3.81 ± 1.64 | 3.64 ± 1.47 | 4.56 ± 1.63 | 0.169 |
| AF duration < 7 days | 21 (25.3%) | 6 (24.0%) | 7 (43.7%) | 0.290 |
| AF duration ≥ 30 days | 47 (56.6%) | 16 (64.0%) | 6 (37.5%) | 0.238 |
| LVEF [%], mean ± SD | 56.1 ± 8.8 | 57.7 ± 7.2 | 56.5 ± 8.2 | 0.733 |
| Left atrial area [$cm^2$], mean ± SD | 25.9 ± 4.4 | 25.0 ± 5.4 | 25.1 ± 3.6 | 0.647 |
| Mitral regurgitation mild or severe | 22 (28.6%) | 6 (26.1%) | 1 (7.1%) | 0.238 |
| LAA flow velocity [m/s], mean ± SD | 34.7 ± 13.3 | 36.6 ± 18.2 | 41.3 ± 21.6 | 0.327 |

Data are presented as number (percentage) of patients unless otherwise indicated; AF — atrial fibrillation; GFR — glomerular filtration rate; LAA — left atrial appendage; LVEF - left ventricular ejection fraction; NOAC — non-vitamin K oral anticoagulant; VKA — vitamin K antagonists

**Table 4.** Independent predictors of left atrial appendage (LAA) thrombus. Results of multivariable logistic regression analysis.

| Predictors | Odds ratio [95% CI] | P |
|---|---|---|
| Vascular disease | 3.972 [1.026–15.379] | 0.046 |
| LAA flow velocity (↑ 1 m/s) | 0.874 [0.795–0.960] | 0.005 |

AUC [95% CI]: 0.831 [0.700–0.962]; AUC — area under curve; CI — confidence interval

warfarin, among these with performed TEE before cardioversions. An analysis of the randomized studies comparing NOAC and VKA in patients undergoing electrical cardioversion obtained the following results regarding the incidence of thrombus in the LAA: the ENSURE-AF study, 8.0% in the edoxaban group and 7.1% in the warfarin group; the XVeRT study, 5.1% in the rivaroxaban group and 4.6% in the VKA group; and the EMANATE study, 7.2% of patients in the apixaban group and 7.1% in the VKA group [12–14]. In the meta-analysis of 4 randomized controlled trials (ENSURE-AF, X-VeRT, ARISTOTLE, and RE-LY) comprising 2397 AF patients (NOACs: n = 1412, VKAs: n = 985), the incidence of thrombus in the LAA was estimated to be approximately 5% in both the VKA and NOAC groups [15]. A similar rate of thrombus occurrence was demonstrated by Frenkel et al. [16], who analyzed the results of TEE performed in 388 patients prior to AF/atrial flutter ablation. A thrombus was detected in 4.4% of 183 patients treated with NOACs and in 2.9% of 205 patients treated with warfarin. Furthermore, in a retrospective study of 559 patients in the Asian population undergoing anticoagulation treatment for ≥ 3 weeks, thrombi in the LAA were detected in 2.6% and 2.8% of patients treated with NOAC and VKA, respectively [17].

In our retrospective, real-world study, the rate of LAA thrombus detection was comparable between patients on NOAC and those on VKA, at 8.9% and 3.6%, respectively, despite a minimum of 4 weeks of anticoagulation therapy. In comparison to the aforementioned studies, in our study, the incidence of LAA thrombus was slightly higher. It is worth noting that our study group had a higher incidence of comorbidities and known predictors of embolic complications, such as mean age (73.4 years), a higher mean $CHA_2DS_2VASc$ score (3.83), and higher incidence of hypertension (89.4%), heart failure (33.1%), diabetes mellitus (37.5%), and vascular disease (26.9%), in comparison to previously published studies [12–14, 16, 18, 19].

In the present study, among individual NOAC agents, thrombi were observed in 8.4% for rivar-

**Table 5.** Characteristics and treatment of patients with left atrial thrombus.

| Patient no. | Age [years], gender | $CHA_2DS_2$-VASc score; LVEF [%] | Treatment before detection | Treatment after detection | Control TEE | Further anti-coagulation treatment; Status of KE | Last control and final treatment | Conclusion | Follow-up [days] |
|---|---|---|---|---|---|---|---|---|---|
| **NOAC-VKA** | | | | | | | | | |
| 1 | 84, F | 6; 68% | Rivaroxaban 20 mg, 4–8 w | Warfarin, 4–8 w TR | Thrombus resolution, incidence of SEC 4+* | Warfarin Withdrawn from KE | – | Thrombus resolution | 957 |
| 2 | 83, M | 4; 33% | Rivaroxaban 20 mg, 4–8 w | Acenocoumarol, 4–8 w TR | Thrombus resolution | Acenocoumarol Underwent KE | – | Thrombus resolution | 1215 |
| 3 | 61, F | 2; 48% | Rivaroxaban, ≥ 8 w | Warfarin, 4–8 w TR | Thrombus persistent | Warfarin > 12 w Withdrawn from KE | Thrombus resolution Warfarin Spontaneous recovery of sinus rhythm | Thrombus resolution | 915 |
| 4 | 85, F | 5; 48% | Rivaroxaban, ≥ 8 w | Acenocoumarol, 4–8 w TR | Thrombus resolution, incidence of SEC 4+* | Acenocoumarol Underwent KE | – | Thrombus resolution | 1173 |
| 5 | 85, F | 5; 62% | Rivaroxaban, ≥ 8 w | Acenocoumarol, ≥ 8 w TR | Thrombus resolution | Acenocoumarol Underwent KE | | Thrombus resolution | 949 |
| 6 | 79, M | 5; 40% | Dabigatran 110 mg bid, ≥ 8 w | Acenocoumarol, 4–8 w TR | Thrombus persistent, incidence of SEC 4+* | Acenocoumarol Withdrawn from KE | | Thrombus persistent | 937 |
| 7 | 80, M | 5; 39% | Rivaroxaban 20 mg, ≥ 8 w | Acenocoumarol, 4–8 w TR | Thrombus persistent | Acenocoumarol > 12 w Withdrawn from KE | Thrombus persistent Acenocou-marol | Thrombus persistent | 948 |
| **NOAC-NOAC** | | | | | | | | | |
| 8 | 71, F | 5; 35% | Dabigatran 150 mg, ≥ 8 w | Apixaban 5 mg bid, 4–8 w | Thrombus resolution, incidence of SEC4+* | Apixaban 5 mg bid Withdrawn from KE | | Thrombus resolution | 685 |
| 9 | 69, F | 5; 46% | Apixaban 5 mg bid, ≥ 8 w | Apixaban 5 mg bid, > 12 w | Embolus in left subfemoral artery | – | – | Systemic embolization | 1013 |
| 10 | 83, F | 4; 47% | Dabigatran 110 mg bid, 4–8 w | Apixaban 5 mg bid | No data | – | – | No data | 608 |

**Table 5 (cont.).** Characteristics and treatment of patients with left atrial thrombus.

| Patient no. | Age [years], gender | $CHA_2DS_2$-VASc score; LVEF [%] | Treatment before detection | Treatment after detection | Control TEE | Further anti-coagulation treatment; Status of KE | Last control and final treatment | Conclusion | Follow-up [days] |
|---|---|---|---|---|---|---|---|---|---|
| 11 | 74, M | 5; 20% | Apixaban 2.5 mg bid, 8 w | Apixaban > 12 w (allergy to VKAs) | Thrombus persistent | Apixaban Withdrawn from KE | Thrombus persistent | | 934 |
| **VKA-NOAC** | | | | | | | | | |
| 12 | 66, M | 4; 46% | Acenocou-marol, ≥ 8 w | Apixaban 5 mg bid, > 12 w | Thrombus resolution, incidence of intense echodensity, SEC 4+* | Apixaban 5 mg bid Underwent KE | – | Thrombus resolution | 1097 |

*According to Fatkin's criteria; F — female; KE — electric cardioversion; LAA — left atrial appendage; LVEF — left ventricular ejection fraction; M — male; NOAC — non-vitamin K oral anticoagulant; SEC — spontaneous echo contrast; TR — time range; VKA — vitamin K antagonists; w — weeks

**Table 6.** Clinical follow-up of patients with left atrial thrombus.

| Patient no. | Age [years], gender | $CHA_2DS_2$-VASc score; LVEF [%] | All-cause mortality | Cardiovascular death | Stroke or TIA | Systemic embolization | Myocardial infarction | Bleeding complication | Follow-up [days] |
|---|---|---|---|---|---|---|---|---|---|
| **NOAC-VKA** | | | | | | | | | |
| 1 | 84, F | 6; 68% | No | No | No | No | No | No | 957 |
| 2 | 83, M | 4; 33% | No | No | No | No | No | No | 1215 |
| 3 | 61, F | 2; 48% | No | No | No | No | No | No | 915 |
| 4 | 85, F | 5; 48% | No | No | No | No | No | No | 1173 |
| 5 | 85, F | 5; 62% | No | No | No | No | No | No | 949 |
| 6 | 79, M | 5; 40% | No | No | No | N0 | No | No | 937 |
| 7 | 80, M | 5; 39% | No | No | No | No | No | No | 948 |
| **NOAC-NOAC** | | | | | | | | | |
| 8 | 71, F | 5; 35% | No | No | No | No | No | No | 685 |
| 9 | 69, F | 5; 46% | No | No | No | Yes (105 day of follow up) | No | No | 1013 |
| 10 | 83, F | 4; 47% | No | No | No | No | No | No | 608 |
| 11 | 74, M | 5; 20% | Yes (924 day of follow up, hepatic cancer) | No | No | No | No | No | 934 |
| **VKA-NOAC** | | | | | | | | | |
| 12 | 66, M | 4; 46% | No | No | No | No | No | No | 1097 |

F — female; LVEF — left ventricular ejection fraction; M — male; NOAC — non-vitamin K oral anticoagulant; TIA — transient ischemic attack; VKA — vitamin K antagonists

oxaban, 8% for dabigatran, and 12.5% for apixaban. The highest rate of emboli material was observed in patients with LAA treated with apixaban. These findings may be explained by the higher incidence of high-risk patients in the apixaban group, with a higher prevalence of previous stroke (25% of patients) and higher but not statistically significant mean $CHA_2DS_2VASc$ score, in comparison to the rivaroxaban and dabigatran groups. In other real-world scenarios, the occurrence of LAA thrombi under specific NOAC agents is low and comparable between drugs. Kawabata et al. [17] showed that the rates of LAA thrombus detection were 2.06%, 3.3%, and 2.5% among patients on dabigatran, rivaroxaban, and apixaban, respectively. In a study by Frenkiel et al. [16], thrombus was found in 5.4% of patients treated with dabigatran, 4.8% treated with rivaroxaban, and 0% treated with apixaban. Also, Gorczyca et al. [18], showed that the incidence of LAA thrombus was comparable between dabigatran and rivaroxaban, at 5% and 3.2%, respectively.

## Predictors of LAA thrombus

It is known that the incidence of LAA thrombi increases with an increasing number of clinical risk factors. It has been reported that among patients treated with anticoagulants, separate clinical factors such as chronic heart failure, age, female sex, structural heart disease, other cardiomyopathy, use of antiarrhythmic drugs, and duration of arrhythmia may be helpful in identifying patients with a high probability of thrombus in the LAA [19–23]. In our study, patients with LAA thrombus had a higher prevalence of heart failure and vascular disease than those without thrombus. However, in the multivariable analysis, only a prior history of vascular disease was an independent, significant predictor of emboli in the LAA. This finding may partially explain the increased risk of thromboembolism in patients with AF and vascular disease reported in previous studies [24–26].

Furthermore, scales for the clinical risk of thromboembolic events in AF ($CHADS_2$ and $CHA_2DS_2$-VASc) have the potential to predict LAA thrombus occurrence. In studies by Uz et al. [27] and Tang et al. [28], which enrolled a total of 1100 patients, no thrombi were detected in patients with a score of 0–2 and 0, respectively, on the $CHA_2DS_2$-VASc scale. In our study population undergoing anticoagulation regimen, thrombi were seen only in those with a $CHA_2DS_2$-VASc score ≥ 2. These findings agree with the results of Kawabata et al. [17], in that LAA thrombi were not detected in those with a $CHA_2DS_2VASc$ score of 0–1. However, a low $CHADS_2$ score cannot reliably rule out embolic material in the LAA. In the ACUTE study, a thrombus was detected by TEE in 14 out of 138 patients without anticoagulant treatment, despite a $CHADS_2$ score of 0 [29]. Furthermore, we revealed that patients with LAA thrombus had significantly higher mean $CHA_2DS_2VASc$ scores than those without thrombus, but it was not an independent predictor of thrombus in our multivariable analysis.

Previous studies have reported echocardiographic predictors of thrombosis in the LAA. These include features and parameters assessing the structure and function of the heart, as a whole, as well as the atrium or its appendage separately. It has been shown that a reduced ejection fraction (EF < 50%), hypertrophy, increased left ventricular end-diastolic pressure, left atrial enlargement (LA > 50 mm, LA area > 30 $cm^2$, LA volume index > 28 $mL/m^2$), or degree of spontaneous blood contrasting in the LA cavity may indicate patients with a higher risk of LAA thrombus [19–22, 30–34]. In our study, multivariate analysis revealed that only a lower mean LAA flow velocity independently predicted emboli in the LAA.

## LAA thrombus resolution with treatment modification

Unfortunately, there is no consensus on the management of LAA thrombi. We showed that the thrombus resolved in most patients who underwent repeat imaging. It seems that NOAC switching to VKA in the case of embolic materials in the LAA was an appropriate modification and appeared to be effective after ≥ 4 weeks of treatment in 5 out of 7 patients. We also revealed thrombus resolution among the other 2 patients under anticoagulation therapy for a minimum of 8 weeks before the first TEE. In the first case, we changed dabigatran to apixaban. In the second case, we changed acenocoumarol to apixaban.

Studies with adequate power and endpoints that can determine the best management strategy are lacking. The use of NOACs creates new therapeutic possibilities in the presence of embolic material in the LAA; however, available data are limited to a small number of studies and case reports. To the best of our knowledge, only one prospective study has assessed the effect of rivaroxaban on a newly detected thrombus in the LAA, the X-TRA study [35]. Sixty patients were enrolled in the study. Three-quarters (76.7%) of the patients had not been treated with anticoagulants before, and the remainder were treated with suboptimal or

ineffective doses of VKA. Follow-up TEE showed that after 6 weeks of treatment with rivaroxaban, there was resolution in 41.5% of patients, reduction in thrombus size in 19%, no change in 17%, and an increase in size in 22.5% of patients.

### Thromboembolic events in patients with an LAA thrombus

It is known that embolic material in the LAA is associated with a high risk of thromboembolic events. Stoddard et al. [36] revealed that LAA thrombi significantly predicted transient ischemic attack in 261 patients with AF during a mean follow-up of 2.5 years. In another study [37] of 317 patients with recent stroke, a thrombus in the LA was detected in 20% of patients, all of which were in the LAA.

Among our 12 patients who developed an LAA thrombus and during the follow-up of 29.9 months (median), 1 patient suffered a thromboembolic complication in the form of a right popliteal artery embolism. This systemic embolic event occured before repeat TEE in patient with left prolonged treatment with an apixaban dosage of 5 mg twice a day.

### Limitations of the study

Our study has several limitations. The first is the retrospective nature of the analysis. There was no protocol for changing the type of oral anticoagulation or the timing of the second TEE after LAA thrombus detection. Secondly, among VKA patients, we could not report the percentage of time in the therapeutic range INR before the first TEE. Thirdly, the presence of a thrombus was not confirmed by an independent echocardiographer. Finally, our study had insufficient power to evaluate the differences in LAA thrombus and severe SEC detection between the individual NOAC agents.

## Conclusions

Left atrial appendage thrombus developed in 7.5% of patients despite anticoagulation therapy, and the prevalence was shown to be similar in patients either on NOAC or VKA. The incidence of severe SEC was also comparable between the groups. The presence of thrombi in this location is associated with an increased risk of peripheral embolism. There are known predictors of LAA thrombus occurrence, such as lower LAA flow velocity and vascular disease in the patient's history; however, it is still difficult to identify patients with LAA thrombus without imaging. It seems that in the case of embolic materials in LAA under NOAC treatment, switching to VKA was an appropriate modification. Therefore, further prospective research is needed to assess the best treatment strategy for thrombi despite anticoagulation therapy.

**Conflict of interest:** None declared

## References


1. Haim M, Hoshen M, Reges O, et al. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc. 2015; 4(1): e001486, doi: 10.1161/JAHA.114.001486, indexed in Pubmed: 25609415.
2. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995; 155(5): 469–473, indexed in Pubmed: 7864703.
3. Piwońska A, Piwoński J, Szcześniewska D, et al. Population prevalence of electrocardiographic abnormalities: results of the Polish WAWKARD study. Kardiol Pol. 2019; 77(9): 859–867, doi: 10.33963/KP.14911, indexed in Pubmed: 31354161.
4. Airaksinen K, Grönberg T, Nuotio I, et al. Thromboembolic complications after cardioversion of acute atrial fibrillation. J Am Coll Cardiol. 2013; 62(13): 1187–1192, doi: 10.1016/j.jacc.2013.04.089, indexed in Pubmed: 23850908.
5. Lip GY. Cardioversion of atrial fibrillation. Postgrad Med J. 1995; 71(838): 457–465, doi: 10.1136/pgmj.71.838.457, indexed in Pubmed: 7567751.
6. Arnold AZ, Mick MJ, Mazurek RP, et al. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol. 1992; 19(4): 851–855, doi: 10.1016/0735-1097(92)90530-z, indexed in Pubmed: 1545081.
7. Saeed M, Rahman A, Afzal A, et al. Role of transesophageal echocardiography guided cardioversion in patients with atrial fibrillation, previous left atrial thrombus and effective anticoagulation. Int J Cardiol. 2006; 113(3): 401–405, doi: 10.1016/j.ijcard.2006.03.036, indexed in Pubmed: 16822564.
8. Fatkin D, Kuchar DL, Thorburn CW, et al. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardiol. 1994; 23(2): 307–316, doi: 10.1016/0735-1097(94)90412-x, indexed in Pubmed: 8294679.
9. Andrade JG, Macle L, Nattel S, et al. Contemporary atrial fibrillation management: a comparison of the current AHA/ACC/HRS, CCS, and ESC Guidelines. Can J Cardiol. 2017; 33(8): 965–976, doi: 10.1016/j.cjca.2017.06.002, indexed in Pubmed: 28754397.
10. Flaker G, Lopes RD, Al-Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). J Am Coll Cardiol. 2014; 63(11): 1082–1087, doi: 10.1016/j.jacc.2013.09.062, indexed in Pubmed: 24211508.
11. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011; 123(2): 131–136, doi: 10.1161/CIRCULATIONAHA.110.977546, indexed in Pubmed: 21200007.

12. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014; 35(47): 3346–3355, doi: 10.1093/eurheartj/ehu367, indexed in Pubmed: 25182247.
13. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet. 2016; 388(10055): 1995–2003, doi: 10.1016/S0140-6736(16)31474-X, indexed in Pubmed: 27590218.
14. Ezekowitz MD, Pollack CV, Halperin JL, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. Eur Heart J. 2018; 39(32): 2959–2971, doi: 10.1093/eurheartj/ehy148, indexed in Pubmed: 29659797.
15. Reers S, Karanatsios G, Borowski M, et al. Frequency of atrial thrombus formation in patients with atrial fibrillation under treatment with non-vitamin K oral anticoagulants in comparison to vitamin K antagonists: a systematic review and meta-analysis. Eur J Med Res. 2018; 23(1): 49, doi: 10.1186/s40001-018-0350-9, indexed in Pubmed: 30352632.
16. Frenkel D, D'Amato SA, Al-Kazaz M, et al. Prevalence of left atrial thrombus detection by transesophageal echocardiography: a comparison of continuous non-vitamin k antagonist oral anticoagulant versus warfarin therapy in patients undergoing catheter ablation for atrial fibrillation. JACC Clin Electrophysiol. 2016; 2(3): 295–303, doi: 10.1016/j.jacep.2016.01.004, indexed in Pubmed: 29766887.
17. Kawabata M, Goya M, Sasaki T, et al. Left atrial appendage thrombi formation in japanese non-valvular atrial fibrillation patients during anticoagulation therapy — warfarin vs. direct oral anticoagulants. Circ J. 2017; 81(5): 645–651, doi: 10.1253/circj.CJ-16-1089, indexed in Pubmed: 28179613.
18. Gorczyca I, Chrapek M, Jelonek O, et al. Left atrial appendage thrombus formation despite continuous non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients undergoing electrical cardioversion or catheter ablation: a comparison of dabigatran and rivaroxaban. Cardiol Res Pract. 2020; 2020: 1206402, doi: 10.1155/2020/1206402, indexed in Pubmed: 33014453.
19. Scherr D, Dalal D, Chilukuri K, et al. Incidence and predictors of left atrial thrombus prior to catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2009; 20(4): 379–384, doi: 10.1111/j.1540-8167.2008.01336.x, indexed in Pubmed: 19017348.
20. Wallace TW, Atwater BD, Daubert JP, et al. Prevalence and clinical characteristics associated with left atrial appendage thrombus in fully anticoagulated patients undergoing catheter-directed atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2010; 21(8): 849–852, doi: 10.1111/j.1540-8167.2010.01729.x, indexed in Pubmed: 20158561.
21. Calvo N, Mont L, Vidal B, et al. Usefulness of transoesophageal echocardiography before circumferential pulmonary vein ablation in patients with atrial fibrillation: is it really mandatory? Europace. 2011; 13(4): 486–491, doi: 10.1093/europace/euq456, indexed in Pubmed: 21186230.
22. Zoppo F, Brandolino G, Berton A, et al. Predictors of left atrium appendage clot detection despite on-target warfarin prevention for atrial fibrillation. J Interv Card Electrophysiol. 2012; 35(2): 151–158, doi: 10.1007/s10840-012-9707-0, indexed in Pubmed: 22869388.
23. Budnik M, Gawałko M, Gorczyca I, et al. Risk of left atrial appendage thrombus in patients with atrial fibrillation and chronic kidney disease. Cardiol J. 2022; 29(2): 205–215, doi: 10.5603/CJ.a2020.0036, indexed in Pubmed: 32207840.
24. Conway DSG, Lip GYH. Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol. 2004; 93(11): 1422–5, A10, doi: 10.1016/j.amjcard.2004.02.047, indexed in Pubmed: 15165931.
25. Siu CW, Jim MH, Ho HH, et al. Transient atrial fibrillation complicating acute inferior myocardial infarction: implications for future risk of ischemic stroke. Chest. 2007; 132(1): 44–49, doi: 10.1378/chest.06-2733, indexed in Pubmed: 17400657.
26. Lip GYH. Coronary artery disease and ischemic stroke in atrial fibrillation. Chest. 2007; 132(1): 8–10, doi: 10.1378/chest.07-0500, indexed in Pubmed: 17625079.
27. Uz O, Atalay M, Doğan M, et al. The CHA2DS2-VASc score as a predictor of left atrial thrombus in patients with non-valvular atrial fibrillation. Med Princ Pract. 2014; 23(3): 234–238, doi: 10.1159/000361028, indexed in Pubmed: 24751402.
28. Tang RB, Dong JZ, Liu XP, et al. Is CHA2DS2-VASc score a predictor of left atrial thrombus in patients with paroxysmal atrial fibrillation? Thromb Haemost. 2011; 105(6): 1107–1109, doi: 10.1160/TH10-12-0800, indexed in Pubmed: 21544316.
29. Yarmohammadi H, Varr BC, Puwanant S, et al. Role of CHADS2 score in evaluation of thromboembolic risk and mortality in patients with atrial fibrillation undergoing direct current cardioversion (from the ACUTE Trial Substudy). Am J Cardiol. 2012; 110(2): 222–226, doi: 10.1016/j.amjcard.2012.03.017, indexed in Pubmed: 22503581.
30. Tsai LM, Lin LJ, Teng JK, et al. Prevalence and clinical significance of left atrial thrombus in nonrheumatic atrial fibrillation. Int J Cardiol. 1997; 58(2): 163–169, doi: 10.1016/s0167-5273(96)02862-8.
31. Kleemann T, Becker T, Strauss M, et al. Prevalence and clinical impact of left atrial thrombus and dense spontaneous echo contrast in patients with atrial fibrillation and low CHADS2 score. Eur J Echocardiogr. 2009; 10(3): 383–388, doi: 10.1093/ejechocard/jen256, indexed in Pubmed: 18835820.
32. Zhao Y, Ji L, Liu J, et al. Intensity of left atrial spontaneous echo contrast as a correlate for stroke risk stratification in patients with nonvalvular atrial fibrillation. Sci Rep. 2016; 6: 27650, doi: 10.1038/srep27650, indexed in Pubmed: 27277939.
33. Ayirala S, Kumar S, O'Sullivan DM, et al. Echocardiographic predictors of left atrial appendage thrombus formation. J Am Soc Echocardiogr. 2011; 24(5): 499–505, doi: 10.1016/j.echo.2011.02.010, indexed in Pubmed: 21440414.
34. Ozcan Cetin EH, Ozbay MB, Cetin MS, et al. A new risk model for the evaluation of the thromboembolic milieu in patients with atrial fibrillation: the PALSE score. Kardiol Pol. 2020; 78(7-8): 732–740, doi: 10.33963/KP.15402, indexed in Pubmed: 32483955.
35. Lip G, 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: 126–134, doi: 10.1016/j.ahj.2016.05.007, indexed in Pubmed: 27502860.
36. Stoddard MF, Singh P, Dawn B, et al. Left atrial thrombus predicts transient ischemic attack in patients with atrial fibrillation. Am Heart J. 2003; 145(4): 676–682, doi: 10.1067/mhj.2003.91, indexed in Pubmed: 12679765.
37. Stoddard MF, Dawkins PR, Prince CR, et al. 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(2): 452–459, doi: 10.1016/0735-1097(94)00396-8, indexed in Pubmed: 7829800.