Risk factors for thrombosis and spontaneous echocardiographic contrast with sludge in atrial fibrillation patients treated with oral anticoagulants before electrical cardioversion

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ABSTRACT

Background: Knowledge of thrombosis (T) risk predictors and transesophageal echocardiography (TEE) are important tools in appropriate qualification of patients for safe electrical cardioversion.

Aims: We aimed to investigate predictors of T and spontaneous echocardiographic contrast (SEC) with sludge in the left atrium (LA) and appendage (LAA) in atrial fibrillation (AF) patients on oral anticoagulation.

Methods: The study included 300 patients with AF lasting >48 hours. Two hundred and nineteen patients were treated with oral anticoagulants (OACs) (study group, rivaroxaban: 104 [47.5%], apixaban: 52 [23.7%], dabigatran: 23 [11.5%], VKAs: 40 [18.3%]). Eighty-one consecutive patients with AF lasting >48 hours and not treated with OACs constituted the control group. Before electrical cardioversion, all patients underwent transthoracic echocardiography and TEE.

Results: TEE revealed T in the LAA in 4.7% of cases. The number of patients with T or SEC4+ with sludge in the OAC and control groups was similar, 5.9% vs. 1.2% and 16.4% vs. 16.0%, respectively. The risk of SEC4+/T in patients treated with OACs was lowest in those taking rivaroxaban (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.21–0.87; $P = 0.027$) and highest in those receiving VKAs (OR, 2.49; 95% CI, 1.15–5.39; $P = 0.018$). Multivariable analysis showed independent prognostic factors for SEC 4+/T: female sex (OR, 3.800; 95% CI, 1.592–9.072; $P = 0.003$), left ventricular ejection fraction (OR, 0.932; 95% CI, 0.890–0.957; $P < 0.001$), and minimum LAA flow velocity (LAAfly min) (OR, 0.895; 95% CI, 0.841–0.954; $P < 0.001$).

Conclusions: Female sex, transthoracic echocardiography, and TEE results should be taken into account in assessing the risk of T/SEC with sludge in LA/LAA patients with AF.

Key words: atrial fibrillation, echocardiography, electrical cardioversion, oral anticoagulant therapy

INTRODUCTION

Atrial fibrillation (AF) is the most common cause of hospitalization in cardiology departments [1]. The incidence of the disease increases with age – it is <1% in the group of patients under 45 years of age and >10% in people over 80 years of age [2–4]. The results of epidemiological studies showed that, in 2010, the number of AF cases in the US was 5.2 million and this number will increase to 12.1 million by 2030. In Europe, in 2010, there were 8.8 million cases of the disease, and that number is expected to increase to 17.0 million in 2060 [5–7]. AF increases the risk of cardiovascular events, including ischemic stroke (IS) 5-fold [8–10]. Epidemiological data from the last two decades indicate that the proportion of AF-related IS cases has increased from

WHAT'S NEW?

In our analysis of cases of paroxysmal and persistent atrial fibrillation lasting >48 hours, we found that female sex is an independent risk factor for thrombosis and spontaneous echocardiographic contrast with sludge in the left atrium and its appendage. This result, along with knowledge of other predictors and echocardiography results, increases the chance of identifying atrial fibrillation patients with the highest risk of thromboembolic complications before planned restoration of sinus rhythm.

24.2% to 31.5%. Studies demonstrated that the course of IS in AF patients is more severe than in the case of other etiologies [11–12].

In everyday practice, the CHA_2DS_2-VASc score and echocardiography are the most useful methods for evaluating the risk of thromboembolic complications. These complications were observed even in the group of patients with a score of 0–1 [13].

This single-center retrospective study aimed to investigate predictors of thrombus (T) formation and spontaneous echocardiographic contrast (SEC) with sludge in the left atrium (LA) and its appendage (LAA) in AF patients on oral anticoagulation.

METHODS

We performed a retrospective analysis of the medical records of consecutive AF patients at the 2nd Department of Cardiology of the Masovian Brodnowski Hospital in Warsaw in the years 2017–2020. The patients with paroxysmal AF lasting >48 hours and with persistent AF were included in our study.

Data, including demographics, clinical characteristics, and laboratory and echocardiographic findings were collected. The degree of thromboembolic risk was assessed using the CHA_2DS_2-VASc score; the risk of hemorrhagic complications was also evaluated with the HAS-BLED score.

Patients with moderate/severe mitral stenosis, prosthetic mechanical valves, decompensated hyperthyroidism or hypothyroidism, liver dysfunction (aspartate aminotransferase [AST], alanine aminotransferase [ALT] >2 upper limit normal), chronic kidney disease stage 4 (glomerular filtration rate [GFR] <30 ml/min/1.73 m^2) or a diagnosed hemorrhagic and hypercoagulable disorders were excluded from the study.

The study group consisted of 219 patients treated with OACs. The patients were taking non-vitamin K antagonists (NOACs) or vitamin K antagonists (VKAs). In the study group, 104 (47.5%) patients were treated with rivaroxaban, 52 (23.7%) with apixaban, and 23 (11.5%) with dabigatran. Forty people (18.3%) were treated with VKAs (*acenocoumarol*/warfarin). The NOAC therapy was considered effective if the drug was taken regularly and in recommended doses at least 3 weeks before hospitalization, and, in the VKA group, if at least 3 therapeutic international normalized ratio (INR) results (INR >2) were achieved in the last 21 days. The control group consisted of 81 AF patients without anticoagulant treatment (non-OAC; nOAC).

The study was approved by the local bioethics committee.

Echocardiography

In all AF patients, electrical cardioversion (ECV) was preceded by transthoracic echocardiography (TTE). The indication for transesophageal echocardiography (TEE) was all AF cases lasting >48 hours, both treated and untreated with OACs.

TTE and TEE were performed using an Affiniti70C ultrasound device (Philips Healthcare, Andover, MA, US). The following parameters were assessed using the 2D method in the apical four-chamber view (4CH): dimensions of the LA, left atrium length (LAl), left atrium width (LAw), left atrium area (LAa, cm^2), left atrium volume (LAV, ml), and left atrium volume index (LAVI, ml/m^2). Left ventricular ejection fraction (LVEF, %) was assessed planimetrically using Simpson's method in the 4CH view.

In the TEE examination, the X7-2t53Hz probe was used to obtain images in the middle projection from the esophagus in the 0°–110° plane. The systolic dimension of the left atrial appendage ostium (LAAo, cm) and left atrial appendage length (LAAl; cm) were assessed, as well as the presence and intensity of SEC in the LA and LAA using the Fatkin score [14]. According to the score, the intensity of SEC is classified into grades from 0 to 4+. The group with SEC 0–3+ was described as nonSEC4+ (nSEC4+). The study identified cases with SAC4+ and sludge. The term sludge was used to describe dynamic, gelatinous echogenicity observed in each cardiac cycle, but without any clear features of a separated mass in the cardiac chambers [15, 16].

A thrombus (T) in the LA or LAA was diagnosed by echocardiography in more than one views. A mobile, round, oval, or irregularly shaped structure independent of the endocardium was found.

The minimum and maximum left atrium appendage flow velocity (min., max.; LAAflv, cm/sec) was evaluated using the pulsed wave Doppler imaging.

All examinations were performed and assessed by an experienced echocardiography specialist.

Statistical analysis

Depending on the distribution of variables assessed by the Kolmogorov–Smirnov test, the results were presented as

arithmetic means with standard deviations (SD) or as medians (interquartile range [IQR]: 25th and 75th percentiles). The significance of differences between mean values was assessed using Student's t-test. In cases of deviations from the normal distribution, the Wilcoxon test was used to estimate the distribution of continuous variables. Categorical variables were shown as frequencies and percentages and compared using the chi-squared test and Fisher's exact test. The Breslow-Day test or logistic regression were applied to verify the homogeneity of odds ratios. Optimal cut-off points of continuous echocardiographic parameters for predicting SEC4+/T were determined based on the receiver operating characteristic curve and the Youden index. Independent predictors of SEC 4+/T were identified using logistic regression. Odds ratios (OR) were given with a 95% confidence interval (CI). All variables were included in the initial multivariable regression model. A stepwise variable selection was used. Interactions revealed in univariate analyses were examined. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Inc, Durham, NC, US).

RESULTS

The study involved 300 patients. Among all patients, a thrombus was detected in 4.7% of cases, SEC4+ in 16.3%, and SEC4+/T in 18.7% of cases (Table 1). No differences were observed in the incidence of thrombi, SEC4+, and SEC4+/T between the OAC treated and control groups.

The patients in the study group were older than those in the control group ($P = 0.02$) (Table 1). Women accounted for 57.3% of all cases. In the control group, coronary artery disease (CAD) was diagnosed more often, while thyroid disease was found less frequently than in the OAC-treated group ($P = 0.04$ and $P = 0.005$), respectively. In the control group, acetylsalicylic acid (ASA) was taken more often than in the study group ($P < 0.001$), while beta blockers, thyroid hormones, and proton pump inhibitors were used less frequently ($P < 0.001$, $P = 0.04$, $P = 0.02$, respectively).

The analysis showed that females were older than males ($P < 0.001$, Supplementary material, *Table S1*). Both groups had similar mean *body mass index* values. Females had higher CHA_2DS_2-VASc scores and a higher number of cases of paroxysmal AF than males ($P < 0.001$ and $P = 0.004$, respectively). However, there were no differences in the

Table 1. Characteristics of the study group depending on the use of OACs

	All study group n = 300	OAC n = 219	nOAC n = 81	*P*-value
Age, years, mean (SD)	74.2 (9.2)	75.0 (8.8)	72.3 (10.1)	0.02
Female sex, n (%)	172 (57.3)	129 (58.9)	43 (53.1)	0.44
BMI, kg/m^2 mean (SD)	28.9 (25.8–32.9)	29.0 (26.2–31.6)	28.9 (25.7–33.0)	0.882
Comorbidities				
CAD, n (%)	76 (25.3)	48 (21.9)	28 (34.6)	0.04
MI, n (%)	30 (10)	20 (9.1)	10 (12.3)	0.54
AH, n (%)	232 (77.3)	169 (77.2)	63 (77.8)	>0.99
DM, n (%)	95 (31.8)	73 (33.5)	22 (27.2)	0.37
PE, n (%)	4 (1.3)	4 (1.8)	0 (0)	0.58
DVT, n (%)	6 (2.0)	6 (2.7)	0 (0)	0.19
History of stroke/TIA, n (%)	21 (7.0)	17 (7.8)	4 (4.9)	0.54
Thyroid disease, n (%)	59 (19.7)	52 (23.9)	7 (8.6)	0.005
CKD, n (%)	79 (26.5)	63 (29.0)	16 (19.7)	0.14
Pharmacotherapy				
ASA, n (%)	41 (13.7)	11 (5.0)	30 (37.0)	<0.001
Clopidogrel, n (%)	9 (3)	5 (2.3)	4 (4.9)	0.26
Ticagrelor, n (%)	1 (0.3)	0	1 (1.2)	0.27
BB, n (%)	231 (77)	180 (82.2)	51 (63.0)	<0.001
ACEI, n (%)	110 (36.7)	77 (35.2)	33 (40.7)	0.45
ARB-AT1, n (%)	86 (28.7)	67 (30.6)	19 (23.5)	0.28
Ca-blocker, n (%)	90 (30)	63 (28.8)	27 (33.3)	0.53
Thyroid hormone, n (%)	50 (16.7)	43 (19.6)	7 (8.6)	0.04
Anti-thyroid drugs n (%)	7 (2.3)	7 (3.2)	0	0.20
PPI, n (%)	75 (25.1)	63 (28.9)	12 (14.8)	0.02
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.99
SEC / Thrombus				
Thrombus, n (%)	14 (4.7)	13 (5.9)	1 (1.2)	0.12
SEC 4+, n (%)	49 (16.3)	36 (16.4)	13 (16.0)	1.00
SEC 4+/T, n (%)	63 (21.7)	42 (19.2)	14 (17.3)	0.84

Abbreviations: AH, arterial hypertension; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker — AT1; ASA, acetylsalicylic acid; BB, beta blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; DVT, deep venous thrombosis; IQR, interquartile range; MI, myocardial infarction; nOAC, non-oral anticoagulant; OAC, oral anticoagulant; PE, pulmonary embolism; PPI, proton-pump inhibitor; SEC, spontaneous echocardiographic contrast; T, thrombus; TIA, transient ischemic attack

number of patients with persistent AF between the two groups. Men were more likely than women to have coexisting CAD, myocardial infarction, and a history of stroke/ /transient ischemic attack (TIA) (P <0.001; P <0.001 and P = 0.04), while women were more likely to have thyroid disease and CKD (P <0.001 and P = 0.01, respectively). Platelet and white blood cell counts were higher in women than in men (P <0.001 and P = 0.03), while hemoglobin and GFR values were lower (P <0.001 and P <0.001) in the former group. Thyroid hormone and beta blockers were more commonly used in women than in men (P <0.001 and P = 0.05).

nSEC4+/T VS. SEC4+/T

Entire study population

In patients with SEC4+/T, the history of CAD and stroke/TIA was more frequent than in the nSEC4+ group. However, echocardiographic findings showed lower LVEF, higher LAa and LAVI, and lower LAAflv min. and LAAflv max. (Table 2 and 3).

Study group — treated with anticoagulants

The patients with SEC4+/T were older than those with nSEC4+ (77.3 vs. 74.4 years; P = 0.03); they had a higher CHA_2DS_2-VASc score and were more likely to have persistent AF (Table 2). Moreover, the patients with SEC4+/T had lower LVEF, higher LAVI, and lower LAAflv min. and LAAflv max. (Table 3).

Control group — without anticoagulant treatment

In patients with SEC4+/T, lower LVEF, higher LAa and LAVI, and lower LAAflv min. and LAAflv max. were observed compared to the nSEC4+ group (Table 3).

SEC4+/T STUDY GROUP VS. SEC 4+/T CONTROL GROUP

The patients with embolic material in the left atrial appendage in the study group were older and had a lower platelets count compared to the controls. However, they used ASA less often and proton pump inhibitors more frequently than the control group. Paroxysmal AF occurred more often in the study group (Table 2). There were no differences between the 2 groups in terms of echocardiographic findings (Table 3).

ANALYSIS OF OPTIMAL CUT-OFF POINTS

Table 4 shows the optimal cut-off points of echocardiographic parameters important for detecting SEC4+ and/or T in the entire study population. Except for LAVI, for which sensitivity and specificity are comparable, the remaining indices are characterized by high specificity, but low sensitivity. The highest sensitivity of 62.5% was demonstrated for LAVI. The results of univariate analyses indicated the optimal cut-off points for predicting SEC4+/T: LVEF 46.0%, LAa 26.1 cm^2, LAVI: 43.7 ml/m^2 and LAAflv min. 17.6 cm/sec.

SEC 4+/T RISK FACTORS

Multivariable logistic analysis, including only clinical data and patient characteristics, showed independent risk factors for SEC 4+/T such as persistent AF (OR, 3.161; 95% CI, 1.508–6.627; P = 0.002) and the use of rivaroxaban, which reduced the risk by half (OR, 0.438; 95% CI, 0.217–0.886; P = 0.02). The results are presented in Table 5.

Multivariable analysis extended with basic echocardiographic data showed independent prognostic factors for SEC4+/T such as female sex (OR, 2.584; 95% CI, 1.144–5.833; P = 0.02) — the risk of SEC4+/T in women was over 2.5-fold higher than in men, CHA_2DS_2-VASc score (OR, 1.278; 95% CI, 1.017–1.607; P = 0.03) and low LVEF (OR, 0.919; 95% CI, 0.888–0.951; P <0.001) — the lower its value, the higher the probability of SEC4+/T.

Adding additional data regarding the LAAflv value produced the final model with the best prediction (area under the curve [95% CI]: 0.835 [0.772–0.899]). This confirmed that the risk of SEC4+/T increased with decreasing LVEF. The risk was higher in women than in men. Additionally, the risk increased with decreasing LAAflv min. (OR, 0.895; 95% CI, 0.841–0.95; P < 0.001) (Table 5).

THE RISK OF SEC4+/T AND SEX

No differences were found in the incidence of thrombosis, SEC4+, and SEC4+/T between the female and male groups (Supplementary material, *Table S1*). The analysis of TTE results showed that the female group had higher LVEF values compared to the male group (P <0.001). Furthermore, women had lower LAI, LAa, and LAV values than men (P <0.001, P <0.001, and P <0.001, respectively; Supplementary material, *Table S1*).

THE RISK OF SEC 4+/T AND ANTICOAGULANTS

The odds ratio for SEC4+/T, depending on the type of anticoagulant in the study group, is shown in Figure 1. The probability of SEC4+/T was lower in patients taking rivaroxaban and higher in patients taking VKAs. LVEF of patients taking rivaroxaban was higher than those on other anticoagulants (57.9% vs. 54.2%; P <0.001).

DISCUSSION

In our retrospective study, the main findings were 1) the presence of T in the LA/LAA in 4.7% and SEC4+ with sludge in 16.3% of all patients; the incidence of both phenomena in the group treated and untreated with OACs was similar; 2) the predictors of T and SEC4+ with sludge in the LA/LAA are female sex, LVEF, and LAAflv min.; 3) rivaroxaban plays a role in the risk of T formation.

Several studies have shown that in AF patients treated with OACs, the incidence of T in the LA/LAA was within

Table 2. Characteristics of the study group depending on the presence of SEC and T, and the use of OACs

Variable	All study group			OAC			nOAC			SEC 4+ /T OAC vs. nOAC
	nSEC 4+ n = 244	SEC 4+/T n = 56	*P*-value	nSEC 4+ n = 177	SEC 4+/T n = 42	*P*-value	nSEC 4+ n = 67	SEC 4+/T n = 14	*P*-value	
Age, years, mean (SD)	74.1 (9.3)	75.0 (8.8)	0.50	74.4 (9.1)	77.3 (6.9)	0.03	73.1 (9.9)	68.1 (10.3)	0.09	<0.001
Female sex, n (%)	137 (56.1)	35 (62.5)	0.47	102 (57.6)	27 (64.3)	0.54	35 (52.2)	8 (57.1)	0.97	0.87
Comorbidites										
CAD, n (%)	55 (22.5)	21 (37.5)	0.03	34 (19.2)	14 (33.3)	0.07	21 (31.3)	7 (50.0)	0.22	0.43
MI, n (%)	21 (8.6)	9 (16.1)	0.15	14 (7.9)	6 (14.3)	0.23	7 (10.4)	3 (21.4)	0.36	0.68
AH, n (%)	188 (77.1)	44 (78.6)	0.95	135 (76.3)	34 (80.9)	0.66	53 (79.1)	10 (71.4)	0.50	0.47
DM, n (%)	79 (32.5)	16 (28.6)	0.68	60 (34.1)	13 (30.9)	0.84	19 (28.4)	3 (21.4)		0.73
PE, n (%)	4 (1.6)	0 (0.0)	>0.99	4 (2.3)	0 (0.0)	>0.99	0 (0)	0 (0)	>0.99	>0.99
DVT, n (%)	4 (1.6)	2 (3.6)	0.31	4 (2.3)	2 (4.8)	0.33	0 (0)	0 (0)	>0.99	>0.99
History of stroke/TIA, n (%)	13 (5.3)	8 (14.3)	0.04	11 (6.2)	6 (14.3)	0.10	2 (3.0)	2 (14.3)	0.14	>0.99
Thyroid disease, n (%)	47 (19.3)	12 (21.4)	0.87	41 (23.3)	11 (26.2)	0.85	6 (9.0)	1 (7.1)	>0.99	0.26
CKD, n (%)	62 (25.5)	17 (30.9)	0.52	48 (27.3)	15 (36.6)	0.32	14 (20.9)	2 (14.3)	0.72	0.18
Laboratory tests										
Hgb, g/dl, mean (SD)	13.9 ± 1.75	13.6 ± 1.53	0.32	13.9 ± 1.77	13.6 ± 1.46	0.417	13.9 ± 1.7	13.6 ± 1.8	0.56	0.98
WBC, K/ul, median (IQR)	7.3 (6.1–8.8)	7.2 (6.1–8.6)	0.73	7.2 (6.0–8.7)	7.2 (6.0–8.5)	0.899	7.60 (6.50–8.90)	7.25 (6.20–9.40)	0.76	0.82
PLT, K/ul, median (IQR)	212 (168–257)	199 (157–237)	0.27	212 (167–251)	189 (152–233)	0.09	215 (169–265)	225 (191–313)	0.41	0.048
GFR, ml/min/1.73 m^2, median (IQR)	60 (55–60)	60 (47.5–60)	0.20	60 (54–60)	60 (45.6–60)	0.063	60 (59–60)	60 (60–60)	0.38	0.06
LDL cholesterol, mg/dl, median (IQR)	77 (56–1062)	70 (59–96)	0.34	77 (56–102)	69 (59–92)	0.343	78 (60.5–106)	78.0 (55–115)	0.97	0.40
AST, U/l, median (IQR)	23 (18–32)	23 (19–34)	0.69	23 (18–32)	24 (19–37)	0.462	24.5 (16–36)	23 (16–28)	0.65	0.48
ALT, U/l, median (IQR)	24 (16–33.5)	24 (16–27)	0.56	23 (16–32)	24 (18–30)	0.681	26.5 (17.0–49.0)	26 (13–27)	0.06	0.56
TSH, uIU/ml, median (IQR)	1.64 (0.99–2.53)	1.28 (0.85–2.02)	0.11	1.86 (0.88–2.66)	1.35 (1.04–2.02)	0.197	1.41 (1.02–2.09)	0.86 (0.58–2.57)	0.21	0.22
Pharmacotherapy										
ASA, n (%)	34 (13.9)	7 (12.5)	0.94	9 (5.1)	2 (4.8)	1.00	25 (37.3)	5 (35.7)	>0.99	0.01
Clopidogrel, n (%)	7 (2.9)	2 (3.6)	0.68	4 (2.3)	1 (2.4)	1.00	3 (4.5)	1 (7.1)	0.54	0.44
Ticagrelor, n (%)	0 (0)	1 (1.8)	0.19	0 (0)	0 (0)		0 (0)	1 (7.1)	0.17	0.25
Thyroid hormone, n (%)	38 (15.6)	12 (21.4)	0.39	32 (18.1)	11 (26.2)	0.330	6 (9.0)	1 (7.1)	>0.99	0.25
Anti-thyroid drugs, n (%)	7 (2.9)	0 (0)	0.35	7 (3.9)	0 (0)	0.351	0 (0)	0 (0)	>0.99	>0.99
PPI, n (%)	63 (25.9)	12 (21.4)	0.60	51 (29.0)	12 (28.6)	1.000	12 (17.9)	0 (0)	0.11	0.03
CHA_2DS_2-VASc score, median (IQR)	4 [3–5]	4 [3–5]	0.03	4 [3–5]	4 [3–5]	0.02	4 [3–5]	4 [2–6]	0.75	0.57
Paroxysmal AF, n (%)	151 (61.9)	33 (58.9)	0.80	139 (78.5)	30 (71.4)	0.435	12 (17.9)	3 (21.4)	0.72	0.003
Persistent AF, n (%)	148 (60.7)	45 (80.4)	0.009	108 (61)	34 (81.0)	0.024	40 (59.7)	11 (78.6)	0.30	>0.99

Abbreviations: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; Hgb, hemoglobin; IQR, interquartile range; LDL, low-density lipoprotein; PLT, platelets; PPI, proton-pump inhibitor; WBC, white blood cells; other — see Table 1

Table 3. Echocardiographic findings depending on the presence of SEC and T, and the use of OACs

	All study group			OAC			nOAC			SEC 4+ /TOAC vs. nOAC
	nSEC 4+ n = 244	SEC 4+ /T n = 56	*P*-value	nSEC 4+ n = 67	SEC 4+ /T n = 14	*P*-value	nSEC 4+ n = 177	SEC 4+ /T n = 42	*P*-value	
TTE										
LVEF, %, mean (95% CI)	59.0 (52.7–62.0)	52.0 (40.0–57.0)	<0.001	60.0 (54.0–63.6)	54.3 (44.5–60.0)	0.002	55.8 (49.0–61.0)	46.0 (32.9–55.0)	0.01	0.10
LAl 4CH, cm, mean (95% CI)	5.4 (5.0–5.7)	5.4 (5.1–5.7)	0.72	5.4 (5.0–5.7)	5.4 (5.1–5.7)	0.92	5.4 (5.1–5.7)	5.4 (5.3–5.8)	0.60	0.41
LAw 4CH, cm, mean (95% CI)	4.5 (4.2–4.8)	4.4 (4.2–4.8)	0.77	4.5 (4.2–4.8)	4.4 (4.1–4.7)	0.30	4.5 (4.2–4.8)	4.7 (4.3–4.9)	0.19	0.06
LAa 4CH, cm², mean (95% CI)	24.9 (21.8–27.6)	26.4 (22.7–29.5)	0.03	24.3 (21.7–27.4)	26.0 (21.3–29.5)	0.28	25.4 (22.0–28.0)	27.6 (25.0–29.6)	0.03	0.11
LAV, ml, mean (95%CI)	77.1 (65.2–92.8)	82.1(70.0–102.5)	0.09	76.3 (65.5–92.4)	80.4 (62.4–102.0)	0.47	81.7 (64.8–93.1)	97.8 (78.9–109)	0.03	0.08
LAVI, ml/m², mean (95% CI)	40.4 (33.9–48.8)	46.1(39.1–56.1)	0.002	40.4 (33.5–48.5)	45.7 (36.2–57.8)	0.03	40.3 (35.1–49.1)	47.4 (43.0–55.3)	0.02	0.36
TEE										
LAAl, cm, mean (95% CI)	2.8 (2.4–3.4)	3.1 (2.7–3.5)	0.08	2.8 (2.5–3.4)	2.9 (2.6–3.5)	0.28	2.8 (2.4–3.2)	3.2 (3.0–3.4)	0.10	0.43
LAAo, cm, mean (95 % CI)	1.4 (1.2–1.7)	1.5(1.3–1.8)	0.16	1.4 (1.2–1.7)	1.5 (1.3–1.7)	0.24	1.5 (1.3–1.7)	1.6 (1.3–1.8)	0.39	0.59
LAAflv min, cm/sec, mean (95% CI)	24.5 (20.8–30.9)	19.4(16.2–24.2)	<0.001	24.5(20.8–30.9)	19.7 (17.0–26.1)	<0.001	25 (21.3–30.9)	17.0 (16.0–21.3)	<0.001	0.13
LAAflv max, cm/sec, mean (95% CI)	38.5 (30.9–53.9)	30.6(24.0–40.5)	<0.001	39.4 (30.9–55.4)	30.6 (24.0–40.5)	<0.001	37.8 (30.9–51.7)	26.6 (21.3–36.0)	0.002	0.14

Abbreviations: LAAflv max., left atrium appendage flow velocity max.; LAAflv min., left atrium appendage flow velocity min.; LAAl, left atrium appendage length; LAAo, left atrium appendage ostium; LAa 4CH, left atrium area from 4 chamber views; LAl 4CH, left atrium length from 4 chamber views; LAw 4CH, left atrium width from 4 chamber views; LAV, left atrium volume; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; other — see Table 1

wide limits <1.0%–>15% [16–19]. The correlation of this thrombogenic phenomenon with the CHA_2DS_2-VASc score is most often emphasized. The lower incidence of T in the LA/LAA particularly affects patients with CHA_2DS_2-VASc scores 0–1 [20, 21].

In contrast, patients with a CHA_2DS_2-VASc score ≥2.0 had a higher incidence of this complication [22, 23].

There are also reports showing a significant incidence of T in the LA/LAA; 11.0% of AF patients treated with OACs had a low or moderate risk of thromboembolic complications according to the CHA_2DS_2-VASc score [24]. In the present study, we assumed that these results may be due to the differential response of patients of Asian ethnicity to the NOACs used. Thus, the underlying thromboembolic risk may have other causes in addition to the known predictors.

The CHA_2DS_2-VASc score >3.0 found in our study, similar in the treated group compared to the group untreated with OACs, indicated that all patients had a high thromboembolic risk. At the same time, given that there were no differences in the analyzed echocardiographic parameters between the groups, it was assumed that the obtained numbers of T and SEC4+ sludge counts in the LA/LAA were a true reflection of the prevalence of a thrombogenic milieu in our study.

The older the age of patients in the OAC-treated group, the higher the number of cases with recurrent arrhythmia in this group compared to the control group; however, advanced age did not contribute to the difference in the incidence of T and SEC4+ with sludge in the LA/LAA between the groups.

Our analysis of the data from 300 AF patients was enriched by further experience from daily clinical practice. In some patients with persistent AF not treated with OACs, TEE showed insignificant SEC (0–3+ according to Fatkin) and no thrombus in the LA or LAA. There was one case of a 60-year-old man with AF persisting for 2 weeks without OAC treatment. The patient had comorbidities: hypertension, ischemic heart disease, and nephrotic syndrome. The presence of a thrombus and significant SEC were excluded by TEE (Figure 2). Subsequent observations included patients treated with the same NOAC drug. Patients did not differ in age, comorbidities, or echocardiographic findings, except for a different degree of SEC (Figure 3 A–B).

These cases suggest that among patients with AF, regardless of known thromboembolic risk factors, the coexistence of congenital or acquired coagulation abnormalities should also be considered. These anomalies may affect the effectiveness of appropriate anticoagulant therapy. The above observations, together with similar results in the incidence of T and SEC4+ with sludge in the group treated and untreated with OACs, may support our assumption about coagulation abnormalities. However, this would require specialized laboratory tests. Based on the results obtained and daily clinical observations, it seems reasonable to assume that TEE can act as a method for monitoring the effectiveness of anticoagulant therapy in

Table 4. The usefulness of echocardiography in detecting SEC 4+/T

Variable	Optimal cut–off point	Sensitivity, %	Specificity, %	Youden index	AUC (95% CI)	*P*-value
TTE						
LVEF, %[a]	≤46.0	40.0	89.4	0.294	0.678 (0.620–0.732)	<0.001
LAa 4CH, cm^{2a}	>26.1	53.4	64.5	0.180	0.591 (0.532–0.647)	0.04
LAVI, ml/m^{2a}	>43.7	62.5	61.7	0.242	0.632 (0.575–0.687)	0.002
TEE						
LAAflv min, cm/sec[a]	≤17.6	46.1	92.9	0.390	0.722 (0.667–0.773)	<0.001
LAAflv max, cm/sec[a]	≤27.2	45.4	90.2	0.356	0.717 (0.622–0.767)	<0.001

[a]A unit refers to the optimal cut-off point

Abbreviations: AUC, area under the curve; CI, confidence interval; other — Table 1 and 3

Table 5. Prediction of *SEC 4+/T* occurrence. Results of multivariable logistic regression analysis

	OR (95% CI)	*P*-value	AUC (95% CI)
Model I — medical data			
Rivaroxaban	0.438 (0.217–0.886)	0.02	0.653 (0.583–0.724)
Persistent AF	3.161 (1.508–6.627)	0.002	
Model II — medical data + TTE			
LVEF (%)	0.919 (0.888–0.951)	<0.001	0.756 (0.680–0.833)
Female	2.584 (1.144–5.833)	0.02	
CHA_2DS_2-VASc score	1.278 (1.017–1.607)	0.03	
Model III — medical data + TTE and TEE			
LVEF (%)	0.932 (0.890–0.957)	<0.001	0.800 (0.723–0.876)
LAAflv min. (cm/sec)	0.895 (0.841–0.954)	<0.001	
Female	3.800(1.592–9.072)	0.003	

Abbreviations: OR, odds ratio; other — see Table 2, 3 and 4

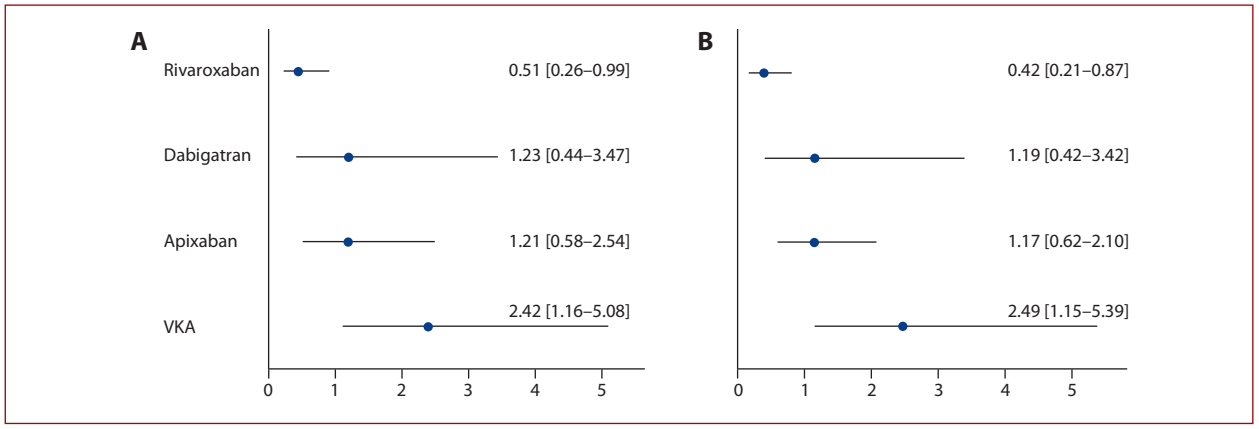

Figure 1. Odds ratio (95% CI) for the presence of SEC4+/T depending on the type of oral anticoagulant (OACs). **A**. In all patients (n = 300). **B**. In the group of patients taking OACs (n = 219)

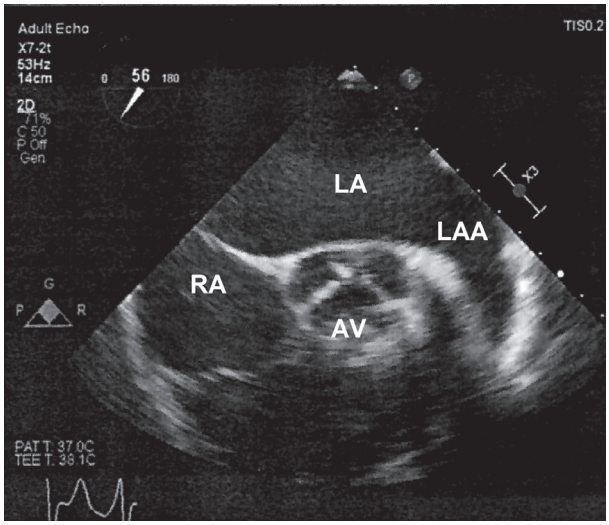

Figure 2. Multi-plane transesophageal echocardiography 56°: no thrombus or sludge detected in the LAA

Abbreviations: AV, aortic valve; LA, left atrium; LAA, left atrial appendage; RA, right atrium

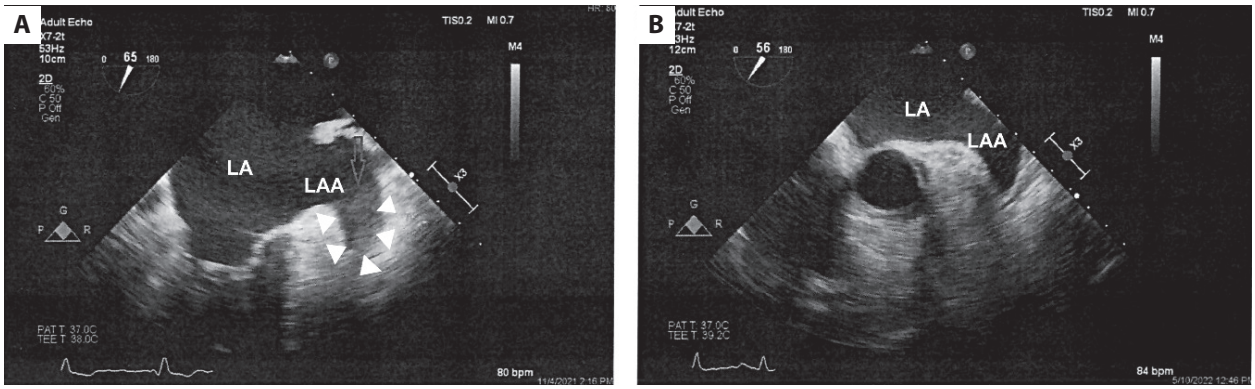

Figure 3. Multi-plane transesophageal echocardiography 65° and 56°. **A**. 86-year-old woman. The presence of sludge in the LAA (arrows). **B.** 83-year-old woman. No sludge was detected

Abbreviations: see Figure 2

a group of patients using NOACs. While in the case of VKA use, the effectiveness of therapy is assessed by successive INR values, there are no standards for such monitoring in the case of NOACs.

Multivariable logistic analysis of clinical data in our 300 patients showed that persistent AF is an independent risk factor for T and SEC4+ with sludge. Several publications indicate the formation of thrombotic material in the heart in both paroxysmal AF and non-paroxysmal AF [22, 23, 25–27]. Non-paroxysmal AF patients are a heterogeneous group (persistent and permanent AF), and different durations of arrhythmia may have different effects on thrombogenic material formation. Cases of T in the LA/LAA in patients with sinus rhythm have also been described [20, 28]. Among all our patients, there were no cases of permanent AF and no cases with sinus rhythm. Only patients with paroxysmal and persistent AF were evaluated in our study.

Many publications on AF patients demonstrate that men predominate in that patient population [18, 21, 26, 29]. Advanced age and male sex are the main risk factors for AF, and therefore the potential risk of thromboembolic complications. Predisposing factors for this form of arrhythmia include obesity, hypertension, and diabetes [30, 31]. While all 3 diseases favor the onset of AF and increase the incidence of recurrent arrhythmias, obese AF patients have been shown to have the so-called "obesity paradox" i.e., a lower risk of thromboembolic complications and lower mortality [30, 32, 33]. In contrast, Hansson et al. observed no significant relationship between a higher body mass index and IS and systemic embolism [34]. Among all patients in our cohort, women were a larger group. Multivariable logistic analysis showed that female sex is an independent predictor of thrombogenic milieu formation in the LA/LAA. A high CHA_2DS_2-VASc score, comorbidities including CKD, as well as higher platelet and white blood cell counts found in the female study group, are considered to be favorable factors for the formation of thrombogenic material [25, 26, 34–36].

Persistent and permanent AF, because of the longer duration of the arrhythmia, leads to LA remodeling and poses a higher risk of T formation, compared to paroxysmal AF. In contrast, in our study, a higher incidence of paroxysmal AF was found among women, and female sex was a predictor of T and SEC4+ with sludge.

The role of echocardiography in the diagnosis, treatment, and risk assessment of AF patients has been recognized [13, 28, 37–39]. Parameter analysis on our TTE showed higher LVEF values and lower LA values in the female group compared to men. These results suggest better cardiac function and lower risk of T formation and SEC with sludge in the LA/LAA among women in our study. Thus, it can be speculated that shorter arrhythmia duration and better echocardiographic parameters may reduce the risk of thrombotic material formation in females, an independent risk factor. The results provide further evidence of the validity of performing echocardiography in AF patients, including those treated with OACs, especially if the patient has not had it performed before.

Analysis of echocardiographic findings among 300 patients showed that predictors of T and SAC 4+ with sludge in the LA/LAA LVEF were assessed by TTE and LAAflv minimum by TEE. These variables have been presented in other publications but were mainly related to patients with LVEF <40% and LAAflv <28 cm/sec [13, 15–17]. In our study, we demonstrated that thromboembolic risk may apply to cases with EF values >40% and significantly smaller LAAflv compared to the previous publications.

Available meta-analyses and national registries show a lower risk of IS and systemic embolism in AF patients treated with NOACs, compared to those treated with VKAs [40, 41]. On the other hand, analyses comparing the efficacy of individual NOACs, in this group of patients, show that the risk of thrombotic complications is lower when using apixaban or dabigatran than in the group treated with rivaroxaban [41, 42].

Analysis of the anticoagulant therapy used in our patients showed that only rivaroxaban administration reduced thromboembolic risk by 50%. Gawałko et al. [43] showed that the number of T events in the LA/LAA in AF patients treated with VKAs and NOACs was similar and did

not differ between the groups treated with dabigatran and rivaroxaban. In our study, the only parameter that differed between patients taking rivaroxaban, compared to the group using other OACs, was higher LVEF. Therefore, it should be assumed that rivaroxaban given to AF patients with good cardiac function will be an effective drug in preventing T and SEC4+ formation with sludge.

Thromboembolic risk in AF patients is closely related to sinus rhythm restoration procedures: ECV and catheter ablation (CA). The European Society of Cardiology guidelines recommend appropriate management of these cases [44]. While the sinus rhythm restoration method is contraindicated in patients with T in the LA/LAA and therefore it should be deferred, there are no clear recommendations in cases with SEC. A retrospective study by Lowe et al. [15] showed, in patients treated with OACs, a similar high risk of thromboembolic complications and death in the group with SEC and sludge on TEE, compared to the group with thrombi. Contrast-enhanced echocardiography performed before ECV in patients with SEC and sludge increased the rate of T diagnosis in this group by up to >20% [45, 46]. Thus, SEC and sludge patients should be considered a high-risk group for IS and systemic embolism.

Based on these results, in our center, we performed TEE in all patients before planned ECV. We considered this procedure to be safer for the patient because it reduces the risk of thromboembolic complications. In cases where we found T and SEC with sludge, we started treatment with OACs if that therapy had not been used before. On the other hand, according to the recommendations, in patients who had been taking an anticoagulant, we changed it to another previously unused drug [47]. ECV was deferred for 4 weeks. We did not record a case of IS or TIA in any patient after ECV during the hospitalization period.

TEE plays an important role in the diagnosis and treatment of AF patients, especially in detecting the risk of thrombotic complications. However, a multicenter analysis by Farkowski et al. [48] showed that TEE is routinely performed before ECV or CA in only 12% of centers. Based on the results of our study and daily clinical practice, it seems reasonable to extend the indication for this test in AF patients before ECV or CA. The procedure may further reduce thromboembolic complications in this group of patients.

Limitations

The retrospective nature of our analyses is one of several limitations of this study. The study group may appear to be small, but it was a carefully selected population. We did not evaluate variables such as obesity or current smoking. In our study, we evaluated multiple laboratory results. N-terminal pro B-type natriuretic peptide results were not presented because at our center this test is not routinely performed in all AF patients. The duration of patient follow-up that included only the period of hospitalization can be considered another limitation of this study. For technical reasons, we were unable to extend echocardiographic diagnostics in the analyzed period with contrast examinations. However, it is worth emphasizing that our assessment reflects approaches and everyday practice developed in our center for patients with AF.

CONCLUSIONS

Knowledge about risk predictors of thrombotic material formation in patients with atrial fibrillation plays an important role in identifying cases with a high probability of IS or systemic thrombosis. Among these predictors, we can include female sex. TEE allows not only for confirming the presence of a thrombogenic milieu in the LA/LAA but also serves as a method for controlling the effectiveness of anticoagulant therapy, especially with NOACs. In cases of constant presence of T/SEC4+ with sludge in the LA/LAA, despite the change of OAC agents, it is reasonable to perform specialized coagulation investigations in such patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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