ORIGINAL ARTICLE

Predictors of left atrial appendage thrombogenic milieu in patients subjected to transesophageal echocardiography prior to cardioversion of persistent atrial fibrillation

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KEY WORDS

ABSTRACT

atrial fibrillation, cardioversion, left atrial appendage thrombus **INTRODUCTION** Evidence of left atrial appendage thrombogenic milieu (LAA TM) on transesophageal echocardiography (TEE) is recognized as a surrogate marker for an increased stroke risk. Although the CHA₂DS₂-VASc scale is commonly used as a measure of thromboembolic risk in patients with atrial fibrillation (AF), it was shown to have only low-to-moderate ability to predict the presence of LAA TM. The potential role of transthoracic echocardiography (TTE) in the refinement of clinical scales for the detection of LAA TM in patients with AF has been readdressed recently.

OBJECTIVES The aim of the study was to identify the predictors of LAA TM among the components of the CHA_2DS_2 -VASc scale and TTE parameters in patients scheduled for electrical cardioversion due to persistent AF.

PATIENTS AND METHODS We conducted a retrospective analysis of demographic, clinical, laboratory, echocardiographic, and medication data of 202 patients (123 men and 79 women; mean age, 65.6 years) with persistent AF, who underwent TEE before electrical cardioversion.

RESULTS Duration of AF exceeding 1 year (odds ratio [OR] = 13.9; P = 0.02), left atrial diameter exceeding 51 mm (OR = 3.98; P = 0.009), left ventricular end-diastolic dimension (LVEDd) exceeding 52 mm (OR = 2.42; P = 0.01), and radiographic evidence of aortic plaques (OR = 2.97; P = 0.007) were shown to be independent predictors of LAA TM in a multivariate regression analysis.

CONCLUSIONS The CHA₂DS₂-VASc scale did not predict the presence of LAA TM on TEE in patients scheduled for electrical cardioversion due to persistent AF. Of the CHA₂DS₂-VASc components, only radiographic evidence of aortic plaques, and of TTE parameters, only left atrial enlargement and LVEDd were independent predictors of LAA TM. A comprehensive clinical and echocardiographic assessment of individual risk is indicated in patients before electrical cardioversion due to persistent AF.

INTRODUCTION Echocardiography can provide information on thromboembolic risk in patients with atrial fibrillation (AF). Transesophageal echocardiography (TEE) is considered a procedure of choice for the detection of a left atrial appendage (LAA) thrombus in individuals with AF in whom adequate anticoagulation has not been

achieved prior to cardioversion.¹ Several TEE measures of LAA thrombotic milieu (LAA TM), including the presence of a thrombus, sludge, and spontaneous echo contrast (SEC), are recognized as surrogate markers of an increased risk of stroke.²

However, the question arises of whether LAA TM can be predicted if TEE is not performed,

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or whether one can identify patients at increased thromboembolic risk in whom TEE should be considered before cardioversion apart from adequate anticoagulant therapy.

Clinical risk stratification algorithms, such as the CHADS₂ or CHA₂DS₂-VASc scales, are commonly used in the assessment of thromboembolic risk; however, these scales were demonstrated to have only low-to-moderate ability to identify TEE surrogate markers of stroke.³⁻⁶ The potential role of transthoracic echocardiography (TTE) in the refinement of these scales for the detection of surrogate markers of stroke has been recently readdressed by researchers.^{4,7}

The aim of the study was to identify the predictors of LAA TM among the components of the CHA_2DS_2 -VASc scale and TTE parameters in patients with persistent AF prior to electrical cardioversion.

PATIENTS AND METHODS We conducted a retrospective analysis of the data from 202 patients (123 men and 79 women; mean age, 65.6 years) with persistent AF, who underwent TEE before direct-current cardioversion in the years from 2009 to 2013. Demographic, anthropometric, laboratory, clinical, and medication data were retrieved from medical records. Persistent AF was defined as AF that persisted longer than 7 days.8 Patients with significant (moderate or severe) valvular diseases and prosthetic heart valves were excluded from the analysis. TEE was performed with HITACHI ALOKA Alpha 10 echocardiographic equipment, with the use of harmonic imaging. A thrombus/sludge was defined as an echo-dense mass/gelatinous echo with a density different from that of the LAA endocardial wall.⁹ SEC was defined as smoke-like echoes, swirling pattern, detectable constantly throughout the cardiac cycle.9 Gain was adjusted for optimal analysis. In order to visualize the whole LAA, we used the following procedures: 1) to obtain 2 perpendicular views of the LAA, we acquired a regular LAA view at about 20° to 60°, then brought the LAA to the center of the image and turned the image plane by 90° for the second acquisition; 2) we swept around the left atrium, acquiring a long loop showing a slow sweep around the atrium from 0° to 180°; and 3) in additional imaging of a thrombus, after detecting the thrombus, we acquired 2 additional image planes from slightly different positions (higher/deeper), which showed the pathology.

TEE images were reviewed for the presence of LAA thrombus/sludge and SEC by 2 experienced observers blinded to clinical histories of the patients. An echocardiographic assessment of LAA TM variables may be difficult and is associated with high interobserver variability. Hence, patients with different types of LAA TM on echocardiography were excluded from the analysis in this study. From TTE, the left atrial anteroposterior diameter was measured by the M-mode from the parasternal view, and left ventricular dimensions and ejection fraction (EF) were evaluated by the Teichholtz method.¹⁰ Aortic plaque was detected on chest X-ray. CHA₂DS₂-VASc scores were calculated for each patient as described previously.⁵ All patients gave their written informed consent to undergo TEE, and the study protocol was approved by the Local Bioethics Committee at the Wroclaw Medical University, Wrocław, Poland.

Statistical analysis Statistical characteristics of quantitative variables were presented as arithmetic means and their standard deviations. The normality of the variable distribution was verified with the Lilliefors and Shapiro-Wilk tests. The t test for independent variables was used to compare the statistical characteristics of normally--distributed quantitative independent variables. The homogeneity of variance was examined with the Levene and Brown-Forsyth tests. The significance of differences in the mean values of variables with nonhomogeneous variances was verified using the *t* test with independent estimation of variance. Statistical characteristics of qualitative variables were expressed as percentages and compared with the maximum likelihood χ^2 test. Relationships between the analyzed variables were verified using correlation and regression analyses. Depending on the type of variable distribution, the Pearson's and Spearman's coefficients of correlation were calculated for the pairs of quantitative variables. Parameters of the model obtained during a progressive stepwise multivariate regression analysis were estimated using the least square method. The results of all the tests were considered significant at a P value of less than 0.05.

RESULTS Clinical characteristics and transesophageal echocardiography markers of left atrial appendage thrombogenic milieu LAA thrombus/sludge was found in 31 of 202 patients, and SEC-in 25 of 202 subjects (a total of 56 patients [27.7%] with the markers of LAA TM, group A). The remaining 146 subjects (72.3%) did not show the evidence of LAA TM on TEE (group B). Patients from groups A and B did not differ in terms of age, prevalence of hypertension, diabetes mellitus, cardiovascular diseases, history of stroke, glomerular filtration rate, CHA₂DS₂-VASc scores, and anticoagulant treatment. Heart failure was more prevalent in group A than in group B (P =0.01). Similarly, long-term AF (>1 year) was more frequent in group A than in group B (P = 0.002). Data are presented in TABLE 1.

Transthoracic echocardiography findings Low EF (<35%) was observed significantly more often in group A than in group B (P <0.001). Patients from group A presented with significantly higher mean left atrial diameters (LAD) than individuals from group B (47.9 ±4.5 mm vs 46.4 ±4.6 mm; P = 0.04), as well as with significantly higher values of left ventricular end-diastolic

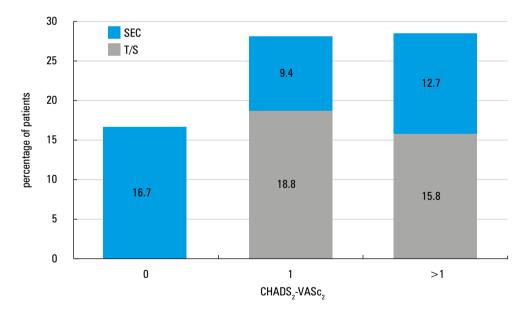
 TABLE 1
 Clinical and echocardiographic characteristics of patients with evidence of left atrial appendage thrombotic milieu (group A) and without such evidence (group B)

Variable	Group A	Group B	P value
	(n = 56)	(n = 146)	
age, y	65.1 ±10.5	66.7 ± 9.5	0.27ª
women	30.4	42.5	0.16
AF >1 year	20.1	1.4	0.002
hypertension	62.5	76.0	0.08
diabetes	26.8	19.2	0.32
heart failure	39.3	20.6	0.01
cardiovascular disease	25	26	0.98
history of stroke	12.5	9.6	0.73
CHA ₂ DS ₂ -VASc	3.1 ±1.7	3.0 ±1.7	0.66 ^b
aspirin	23.2	25.7	0.86
oral anticoagulants	51.8	64.6	0.13
INR within the therapeutic range	27.3	40.6	0.17
GFR, ml/min/m ²	91.9 ±29.1	96.7 ±29.8	0.32 ^b
LAD, mm	47.9 ±4.5	46.4 ±4.6	0.04ª
LVEDd, mm	56.4 ± 8.4	53.0 ±7.5	0.006ª
EF <35%	17.9	2.9	<0.001
aortic plaque	30.4	15.1	0.02

Data are presented as mean \pm standard deviation or percentage of patients.

a t test, b Mann–Whitney test

Abbreviations: AF, atrial fibrillation; EF, ejection fraction; GFR, glomerular filtration rate; INR, international normalized ratio; LAD, left atrial diameter; LVEDd, left ventricular end-diastolic dimension



diameter (LVEDd, 56.4 ±4.7 mm vs 53.0 ±7.5 mm; P = 0.006). Furthermore, patients from group A showed the radiographic evidence of aortic plaques significantly more often than those from group B (P = 0.02; TABLE 1).

Relationship between the presence of left atrial appendage thrombus/sludge or spontaneous echo contrast and CHA₂DS₂-VASc scores None of the 12 patients with CHA₂DS₂-VASc scores of 0 were diagnosed with LAA thrombus/sludge, and only 2 individuals from this subset (16%) showed the presence of SEC. The group of 32 participants with CHA₂DS₂-VASc scores of 1 included 6 patients (18.7%) with thrombus/sludge and 3 patients (9.3%) with SEC. Thrombus/sludge were found in 20 patients (12.6%) and SEC in 25 patients (15.8%) of the 158 patients with a CHA₂DS₂-VASc score of 2 or higher. Data are presented in FIGURE 1.

Predictors of left atrial appendage thrombogenic milieu A univariate logistic regression analysis

FIGURE 1 Relationship between the presence of left atrial appendage thrombus/sludge (T/S) or spontaneous echo (SEC) contrast and CHA₂DS₂--VASc scores TABLE 2 Predictors of left atrial appendage thrombogenic milieu in a univariate analysis

Variable	P value	OR (95% CI)
age ≥75 years	0.77	0.83 (0.40–1.75)
female sex	0.16	0.59 (0.31–1.14)
heart failure	0.01	2.50 (1.28–4.89)
hypertension	0.08	0.53 (0.27–1.02)
history of stroke	0.73	1.35 (0.51–3.53)
diabetes mellitus	0.32	1.54 (0.75–3.17)
cardiovascular disease	0.98	0.95 (0.47–1.92)
AF >1 year	0.008	8.64 (1.69–44.2)
aspirin	0.86	0.87 (0.42–1.80)
oral anticoagulants	0.13	0.59 (0.32–1.10)
INR within the therapeutic range	0.12	0.55 (0.28–1.09)
GFR ≤80 ml/min/m²	0.56	1.27 (0.67–2.40)
LAD >51 mm	0.002	4.53 (1.74–11.8)
LVEDd > 52 mm	0.002	2.84 (1.47–5.49)
aortic plaque	0.02	2.46 (1.19–5.09)
EF <35%	0.001	7.39 (2.21–24.7)
CHA_2DS_2 -VASc = 0	0.58	0.50 (0.11–2.37)
CHA_2DS_2 -VASc = 1	0.87	1.02 (0.44–2.37)
CHA₂DS₂-VASc ≥2	0.79	1.19 (0.56–2.57)
smoking	0.08	2.60 (0.99–6.80)

Abbreviations: CI, confidence interval; OR, odds ratio; others, see TABLE 1

	TABLE 3	Predictors of left atrial appendage thrombogenic milieu identified in a multivariate analysis
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Variable	b coefficient	Standard error	P value	OR	95% CI
Slope	-1.9244	-	-	-	-
AF >1 year	+2.6317	1.137	0.02	13.90	1.50-129.2
LAD >51 mm	+1.3809	0.530	0.009	3.98	1.41–11.2
LVEDd >52 mm	+0.8827	0.357	0.01	2.42	1.20-4.87
aortic plaque	+1.0902	0.405	0.007	2.97	1.35–6.58

Abbreviations: see TABLES 1 and 2

identified heart failure (odds ratio [OR] = 2.5; P = 0.01), EF <35% (OR = 7.39; P = 0.001), duration of AF exceeding 1 year (OR = 8.64; P = 0.008), LAD exceeding 51 mm (OR = 4.53; P = 0.002), LVEDd exceeding 52 mm (OR = 2.84; P = 0.002), and aortic plaques (OR = 2.46; P = 0.02) as predictors of LAA TM on TEE (TABLE 2). Duration of AF exceeding 1 year (OR = 13.9; P = 0.02), LAD exceeding 51 mm (OR = 3.98; P = 0.009), LVEDd exceeding 52 mm (OR = 2.42, P = 0.01), and aortic plaques (OR = 2.97, P = 0.007) were shown to be the independent predictors of LAA TM in the multivariate analysis (TABLE 3).

DISCUSSION Thrombus, sludge, or SEC in the LAA observed on TEE have been previously identified as independent risk factors for stroke and thromboembolism. However, the detection of LAA TM is challenging, unless TEE is performed in high-risk patients with persistent AF.

The aim of our retrospective analysis was to identify the predictors of LAA TM among the

components of the $\rm CHA_2\rm DS_2\text{-}VASc$ scale and TTE parameters in patients with persistent AF who underwent TEE before electric cardioversion.

Relationship between the presence of left atrial appendage thrombus/sludge or spontaneous echo contrast and CHA, DS,-VASc We did not find significant differences in the incidence of TEE markers of LAA TM in patients with various CHA₂DS₂-VASc scores. Moreover, individuals with and without LAA TM did not differ significantly in terms of their CHA₂DS₂-VASc scores. In contrast, previous studies of a multiethnic United States population and Portuguese patients reported significant associations between $\text{CHA}_{2}\text{DS}_{2}\text{-VASc}$ global scores and TEE markers of thromboembolism.^{3,4} Although Willens et al³ showed that the presence of TEE risk factors for thromboembolism was associated with higher CHA₂DS₂-VASc scores, the value of the CHA₂DS₂-VASc scale in predicting TEE risk factors in that study was controversial and lower than that of the CHADS₂ score. CHA₂DS₂-VASc scores (0, 1, or ≥ 2) did not discriminate between the presence or absence of a thrombus/sludge or SEC on precardioversion TEE in patients with persistent AF included in our series.

None of our subjects with a CHA_2DS_2 -VASc score of 0 had an LAA thrombus or sludge, and SEC was detected in only 2 individuals from this subset. Also Willens et al³ showed that patients classified as low-risk on the basis of their $CHADS_2$ and CHA_2DS_2 --VASc scores were virtually free from TEE risk factors for thromboembolism. Similarly, Providentia et al⁴ did not find any TEE markers of thromboembolism in low-risk patients. This evidence is consistent with the data on CHA_2DS_2 -VASc scores for subjects at a truly low risk of stroke.^{6,11}

CHA, DS,-VASc components as predictors of left atrial appendage thrombogenic milieu The available data on the value of CHA₂DS₂-VASc components as predictors of LAA thrombus are still inconclusive.¹² Also our study did not provide conclusive results with regards to the components of the CHA₂DS₂-VASc scale as predictors of LAA TM. Heart failure, EF of less than 35%, and aortic plaques were the only components of the CHA₂DS₂-VASc scale that predicted the presence of LAA TM in the univariate analysis, with aortic plaques being the only independent predictor identified in the multivariate analysis. To the best of our knowledge, this is the first study to show a relationship between the radiographic evidence of aortic plaques and the presence of LAA TM on TEE in patients with AF scheduled for cardioversion. In the Stroke Prevention in Atrial Fibrillation (SPAF) III Study, the presence of aortic plaques was shown to be associated with the TEE evidence of dense SEC.¹³ Aortic plaques may constitute a marker of atherothrombosis. In line with the Virchow's triad of thrombogenesis, AF may predispose to stroke as it satisfies the principal prerequisites of thrombus formation, namely, vessel wall abnormalities (structural heart disease or vascular disease), abnormal blood flow (stasis associated with arrhythmia), and abnormal blood constituents (abnormalities of clotting and platelets observed in the course of AF).¹⁴⁻¹⁶

Aside from aortic plaques, we did not identify any other components of the CHA₂DS₂-VASc scale to be independent predictors of LAA TM. This is consistent with the results of previous studies in which the CHA₂DS₂-VASc scale showed lowto-moderate ability to discriminate between the presence or absence of TEE risk factors for thromboembolism.³⁻⁶ Interestingly, while both heart failure and EF of less than 35% turned out to be the predictors of LAA TM in the univariate regression analysis, none of these variables proved to be the independent predictors in the multivariate analysis. In contrast, Puwanant et al¹⁷ showed that both the history of congestive heart failure and left ventricular EF were associated with the presence of a thrombus/sludge in patients with AF subjected to TEE before pulmonary vein isolation. Furthermore, normal EF was demonstrated to be associated with the absence of an LAA thrombus in AF patients subjected to TEE. $^{\rm 18}$

Transthoracic echocardiography parameters as predictors of left atrial appendage thrombogenic mi-Most previous studies on the role of TTE palieu rameters as the predictors of stroke or the markers of risk in patients with AF focused on reduced EF, and the value of EF is well established.¹⁹ Our findings regarding EF as a marker of the presence of LAA TM were discussed above since EF is also included in the CHA₂DS₂-VASc scale. Previous studies documented the potential use of other TTE parameters, including left atrial indices, in risk stratification for LLA TM. Also in our study, left atrial diameter exceeding 51 mm was identified as an independent predictor of LAA TM. Recently, Faustino et al²⁰ have shown that indexed measurements of the left atrial area and volume are independent determinants of TEE surrogate markers for stroke in patients with nonvalvular AF. Moreover, a normal left atrial volume index was shown to be associated with the absence of LAA thrombi in patients with AF.²¹ Also, an association between the markers of a compromised left atrium and left ventricular systolic dysfunction may be useful in discriminating TEE risk factors for stroke. Kleemann et al¹⁸ identified EF of less than 40% and LAD of 50 mm or lower as independent predictors of a thrombus and dense SEC. Also Ayirala et al¹² showed that higher CHADS, scores, increased left atrial volume indices, and lower EF may predict the presence of an LAA thrombus.

End-diastolic dimension of the left ventricle (LVEDd) exceeding 52 mm was another essential echocardiographic parameter that proved to be an independent predictor of LAA TM in our study. LVEDd was not previously considered as a predictor of LAA TM in patients with AF. However, a univariate analysis conducted within the framework of the SPAF I-III clinical trials showed that a LVEDd of 50 ±8 mm was strongly associated with the risk of stroke (P < 0.001).¹⁹ As the cut-off value identified in our study (LVEDd >52 mm) was too low to satisfy the criteria of left ventricular dilation, it should be considered a risk factor for thromboembolism only in patients with persistent AF who present with concomitant left atrial enlargement.

Not surprisingly, we identified a duration of AF of longer than 1 year as an independent predictor of LAA TM. Long-term AF is associated with mechanical and electrical remodeling which may result in an increased propensity for persistent or recurrent disease. Furthermore, a delay in the normalization of atrial function is associated with an increase in the risk of thrombus formation.²²

Conclusions CHA_2DS_2 -VASc scores did not discriminate between the presence or absence of TEE risk factors for thromboembolism in patients scheduled for cardioversion due to persistent AF. Radiographic evidence of aortic plaques was the

only component of the CHA₂DS₂-VASc scale that proved to be an independent predictor of LAA TM on TEE. Other independent predictors of LAA TM were TTE parameters: left atrial hypertrophy and LVEDd. Complex clinical and echocardiographic assessment of individual risk seems to be a valuable approach in subjects scheduled for cardioversion due to persistent AF.

Clinical implications TEE still constitutes the gold standard for the exclusion of LAA thrombus in patients scheduled for cardioversion. Consideration of conventional TTE parameters as a component of clinical risk assessment may define indications for precardioversion TEE in high-risk patients with AF. However, further follow-up studies including clinical endpoints are necessary to confirm this hypothesis.

Study limitations This was a retrospective, single--center study, which included a relatively small sample of patients, exclusively Caucasians. Although the definitions of sludge and SEC used in our study were relatively subjective, all TEEs were performed and interpreted by experienced echocardiographers, and patients with different types of LAA TM on echocardiography were excluded from the study. LAA TM variables are recognized as markers of an increased risk of stroke; however, only the presence of a thrombus is a contraindication to electrical cardioversion. We aimed to look for predictors of TM variables for an LAA thrombus only because some authors consider even SEC or low LAA velocities as equivalent to thrombus. TEE changes are part of a dynamic process and 1 TEE exam may not be fully representative of the past and future changes.^{7,23} Our analysis did not include some TTE parameters that might be associated with LAA TM, such as left ventricular hypertrophy and left ventricular mass. Moreover, it would be valuable to include other left atrial parameters as more accurate indices of left atrial enlargement. Unfortunately, owing to a retrospective character of the study, those parameters were unavailable in our data. On the other hand, left atrial diameter is the simplest left atrial parameter of significant clinical use in every patient. Some limitations inherent to echocardiography itself should be also considered. Finally, the duration of AF and adequacy of anticoagulation treatment might not be reliably retrieved from medical records.

Contribution statement KŁ-G and JJ conceived the idea for the study. KŁ-G, JJ, and AK-K contributed to the study design. All authors were involved in data collection. KŁ-G, JJ, and AK-K analyzed the data. KD performed the statistical analysis. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Predyktory występowania materiału zakrzepowego w uszku lewego przedsionka w echokardiograficznym badaniu przezprzełykowym u pacjentów przed kardiowersją elektryczną przetrwałego migotania przedsionków

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SŁOWA KLUCZOWE STRESZCZENIE

kardiowersja, migotanie przedsionków, zakrzep w uszku lewego przedsionka

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Pol Arch Med Wewn. 2016; 126 (1-2): 25-31 Copyright by Medycyna Praktyczna, Kraków 2016 **WPROWADZENIE** Obecność materiału zakrzepowego w uszku lewego przedsionka (*left atrial appendage thrombogenic milieu* – LAA TM) w echokardiograficznym badaniu przezprzełykowym (*transesophageal echocardiography* – TEE) jest uznanym markerem zwiększonego ryzyka udaru mózgu. Mimo że skalę CHA₂DS₂-VASc powszechnie stosuje się w stratyfikacji ryzyka zakrzepowo-zatorowego u chorych z migotaniem przedsionków (*atrial fibrillation* – AF), jej wartość w przewidywaniu obecności LAA TM określa się jako niską lub umiarkowaną. Ostatnio wraca się do potencjalnej roli echokardiografii przezklatkowej (*transthoracic echocardiography* – TTE) jako metody uzupełniającej skale kliniczne w predykcji LAA TM u chorych z AF.

CELE Celem pracy było określenie predyktorów LAA TM spośród komponentów skali CHA₂DS₂-VASc oraz parametrów TTE u chorych przed kardiowersją elektryczną przetrwałego AF.

PACJENCI I METODY Przeprowadzono analizę retrospektywną danych demograficznych, klinicznych, laboratoryjnych, echokardiograficznych oraz terapeutycznych 202 pacjentów (123 mężczyzn i 79 kobiet; średnia wieku 65,6 roku) z przetrwałym AF, których poddano badaniu TEE przed kardiowersją elektryczną.

WYNIKI Czas trwania AF >1 rok (iloraz szans [*odds ratio* - OR] = 13,9; p = 0,02), średnica lewego przedsionka >51 mm (OR = 3,98; p = 0,009), wymiar późnorozkurczowy lewej komory >52 mm (*left ventricular end-diastolic dimension* - LVEDd; OR = 2,42; p = 0,01) i obecność blaszek miażdżycowych aorty w RTG (OR = 2,97; p = 0,007) okazały się niezależnymi predyktorami LAA TM w analizie wielo-czynnikowej.

WNIOSKI Skala CHA₂DS₂-VASc nie przewidywała występowania LAA TM w TEE u chorych przed kardiowersją elektryczną przetrwałego AF. Niezależnym czynnikiem predykcyjnym LAA TMS spośród komponentów skali CHA₂DS₂-VASc była jedynie obecność blaszek miażdżycowych aorty w RTG, a z parametrów TTE – powiększenie lewego przedsionka i LVEDd. Wskazana jest kompleksowa, kliniczna i echokardiograficzna ocena indywidualnego ryzyka chorego przed kardiowersją elektryczną przetrwałego AF.