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Does the CHA_2DS_2-VASc scale sufficiently predict the risk of left atrial appendage thrombus in patients with diagnosed atrial fibrillation treated with non-vitamin K oral anticoagulants?

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Abstract

The CHA_2DS_2-VASc scale does not include potential risk factors for left atrial appendage thrombus (LAAT) formation such as a form of atrial fibrillation (AF) and impaired kidney function. The real risk of thromboembolic complications in AF patients is still unclear as well as an optimal anticoagulant treatment in males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.

The aim of this study was to compare the predictive value of the CHA_2DS_2-VASc scale and other scales to estimate the risk of LAAT formation in AF patients treated with non-vitamin K oral anticoagulants (NOACs) and to assess the prevalence of thrombi in patients at intermediate risk of stroke.

The observational study included consecutive patients with a diagnosis of non-valvular AF treated with NOACs, admitted to 3 high-reference institutions between 2013 and 2018. All individuals underwent transoesophageal echocardiography before cardioversion or ablation.

Out of 1163 enrolled AF patients (62.1% male, mean age 62 years) the LAAT had been detected in 50 individuals (4.3%). Among patients with LAAT, 1 patient (2.0%) was classified as a low-risk category, 9 (18.0%) were at intermediate-risk, and 40 (80.0%) were at high risk of thromboembolic complications according to CHA_2DS_2-VASc scale. All patients were treated with NOACs: 51.0% rivaroxaban, 47.1% dabigatran, and 1.9% apixaban.

Patients at intermediate stroke-risk with detected LAAT had higher R_2CHADS_2 score (2.1 ± 1.2 vs 1.2 ± 0.8, $P = .007$), higher CHA_2DS_2-VASc-RAF score (6.4 ± 4.4 vs 3.7 ± 2.6, $P = .027$) and more often had an estimated glomerular filtration rate below 56 mL/min/1.73 m^2 (44.4% vs 13.2%, $P = .026$) compared to patients without LAAT. The receiver operating characteristics revealed

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that the CHA_2DS_2-VASc-RAF scale had better predictive ability to distinguish between patients with and without LAAT in the study group than CHA_2DS_2-VASc ($P = .0006$), $CHADS_2$ ($P = .0006$) and R_2CHADS_2 scale ($P = .0140$).

The CHA_2DS_2-VASc scale should be supplemented with an assessment of renal function and form of AF to improve stroke risk estimation. The application of additional scales to estimate the risk of LAAT might be especially useful among males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.

Abbreviations: AF = atrial fibrillation, eGFR = estimated glomerular filtration rate, ESC = European Society of Cardiology, LAAT = left atrial appendage thrombus, NOAC = non-vitamin K oral anticoagulant, ROC = receiver operating characteristics, TOE = transesophageal echocardiography.

Keywords: anticoagulation, atrial fibrillation, intermediate risk, scales

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in clinical practice, affecting approximately 3% of the population.[1] AF is associated with a significantly increased risk of stroke and systemic embolism due to left atrial appendage thrombus (LAAT) formation.[2] Noteworthy, the risk of thromboembolic complications might differ among patients with a diagnosis of AF due to the presence of concomitant diseases, advanced age, and female gender.[3,4] A CHA_2DS_2-VASc score is currently a stratification tool used to estimate the risk of stroke in patients with non-valvular AF. However, other variables not included in the CHA_2DS_2-VASc scale such as the presence of chronic kidney disease also could increase the risk of thromboembolic complications.[5,6]

Thromboembolism prevention is recommended among AF patients with an increased risk of stroke and systemic embolism. At present Authors of the American Heart Association / American College of Cardiology / Heart Rhythm Society guidelines and The European Society of Cardiology (ESC) guidelines for the management of AF recommend thromboprophylaxis for females with CHA_2DS_2-VASc score ≥ 3 and males with a CHA_2DS_2-VASc score ≥ 2 points. According to the European and American guidelines, among AF patients with 1 additional non-sex risk factor administration of oral anticoagulants should be considered. Both the European and American guidelines do not recommend the use of anticoagulant prophylactic among patients with no risk factor of stroke in the CHA_2DS_2-VASc scale.[7,8]

The real risk of LAAT and thromboembolic complications in AF patients is still unclear as well as an optimal anticoagulant treatment in males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.[9]

2. Purpose

The aim of this study was to compare the predictive value of the CHA_2DS_2-VASc scale and other scales, which included a renal function to estimate the risk of the incidence of LAAT in AF patients treated with non-vitamin K oral anticoagulants (NOACs) and to assess the prevalence of thrombi in males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.

3. Methods

3.1. Study group

The presented multicenter study was an observational registry of consecutive patients aged ≥18 years with AF, who underwent transesophageal echocardiography (TOE) prior to electrical cardioversion or catheter ablation at 3 references Medical Center between January 1, 2013 and December 31, 2018. Exclusion criteria were moderate or severe mitral valve stenosis and mechanical heart valve.

Patients characteristics, echocardiographic and laboratory data were obtained retrospectively from in-hospital records. The study was approved by the Ethics Committees of each institution. All patients were selected depending on the AF type: paroxysmal, persistent, and "permanent" AF, based on careful data analysis form available medical documentation. Patients were classified as having "permanent" AF after unsuccessful cardioversion during the hospitalization index or if they had been previously diagnosed with permanent AF, and the diagnosis was subsequently changed to long-standing persistent AF before cardioversion or ablation. These patients were classified as "permanent" AF to distinguish them from persistent AF patients with presumably lower AF burden.

The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease equation. The $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, and CHA_2DS_2-VASc-RAF scales were used to estimate the risk of thromboembolic events in patients with AF.[10–13] All scales applied to estimate the risk of thromboembolic complications in AF patients are listed in Table 1. Twenty-two percent of patients in the study group were included in the validation cohort in the Kapłon–Cieślicka study, based on which the CHA_2DS_2-VASc-RAF scale was proposed.

3.2. Management of anticoagulation therapy

All patients received NOACs (apixaban, dabigatran, or rivaroxaban) at least 3 weeks prior to TOE. The reduced dose of NOACs was used according to registration recommendations for individual drugs.

3.3. Echocardiographic evaluation

TOE studies were executed by certified echocardiographers (second-degree accreditation in echocardiography of the Section of Echocardiography of the Polish Cardiac Society (PCS)). TOE examinations are conducted directly or a few hours before the scheduled procedure (usually at 48 hours prior to the procedure) in all engaged reference cardiology centers. To the examination was used the EPIQ 7 Ultrasound Machine (Philips Medical Systems, Andover, MA) or the iE33 ultrasound machine (Philips Medical Systems) with the X72t TOE ultrasound transducer (Philips Medical Systems). LAAT was defined as a well circumscribed echogenic mass with a unique echotexture contrasting with the surrounding endocardium or pectinate muscles and detected in more than 1 imaging plane. Spontaneous echocardiographic contrast, defined as a dynamic "smoke-like" signal with a distinctive swirling motion, occurs due to increased ultrasonic density without creating a discrete mass. In the case of

Table 1

Scales applied to estimate the risk of thromboembolic complications among patients with atrial fibrillation.

	Scales			
Risk factors	$CHADS_2$ (maximum score 6)	R_2CHADS_2 (maximum score 8)	CHA_2DS_2-VASc (maximum score 9)	CHA_2DS_2-VASc-RAF (maximum score 21)
Congestive heart failure	1	1	1	1
Hypertension	1	1	1	1
Diabetes mellitus	1	1	1	1
Vascular disease	-	-	1	1
Age 65–74 yr	-	-	1	1
Stroke or transient ischemic attack	2	2	2	2
Age ≥75 yr	1	1	2	2
Female sex	-	-	1	1
Creatinine clearance < 60 mL/min	-	2	-	-
eGFR < 56 mL/min/1.73 m^2	-	-	-	2
Persistent AF	-	-	-	4
Permanent AF	-	-	-	10
Risk categories				
Low	0	0	0 points in men, 1 point in women	0–4 points in men, 1–5 points in women
Intermediate	1	1	1 point in men, 2 points in women	-
High	2	2	≥2 points in men, ≥3 points in women	≥5 points in men, ≥6 points in women

AF = atrial fibrillation, $CHADS_2$ = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, CHA_2DS_2-VASc-RAF = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, renal dysfunction and AF type, eGFR = estimated glomerular filtration rate, R_2CHADS_2 = creatinine clearance below 60 mL/min, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack.

suspected LAAT occurrence, the examination was consulted with additional echocardiographer. In a doubtful event, 3 qualified echocardiographers evaluated the study to establish a correct diagnosis. Written informed consents for TOE examination were obtained from each engaged individual.

3.4. Study endpoint

The primary endpoint was the presence of LAAT on TOE.

4. Statistical analysis

Quantitative variables were presented as means and standard deviations as well as medians and interquartile ranges. Categorical data were expressed as numbers and percentages. For quantitative data, the differences between 2 groups were analyzed through *t*-test or Mann–Whitney *U* test according to normal or non-normal distributions. The normality assumption was verified by Shapiro–Wilk test. For quantitative data the differences between more than 2 groups were assessed by Kruskal–Wallis test. Proportions were compared with the chi-square test or Fisher exact test. Receiver operating characteristics (ROC) were evaluated to test the ability of analyzed scales (CHA_2DS_2-VASc and other scales) to distinguish between patients with and without LAAT. The area under the ROC curve with 95% confidence interval (95%CI) were estimated.

All *P*-values are 2-sided and statistical significance was set at *P*-values < .05. All statistical analysis were performed using the R software package version 3.6.1.

5. Results

5.1. Clinical characteristics of the study group

The study group consisted of 1163 consecutive patients with AF (722, 62.1% male, mean age 62 years) admitted to 3 high-reference cardiology departments for catheter ablation (51.4%) or electrical cardioversion (48.6%). Patients were divided into 5 groups based on CHA_2DS_2-VASc score: CHA_2DS_2-VASc = 0 (11.0%), female without additional factor (4.4%), male with CHA_2DS_2-VASc = 1 (18.3%), female with CHA_2DS_2-VASc = 2 (8.5%) and male with CHA_2DS_2-VASc ≥ 2 together with female with CHA_2DS_2-VASc ≥ 3 (57.8%) (Table 2). In the study population, patients with a CHA_2DS_2-VASc = 0 and CHA_2DS_2-VASc = 1 together with AF female patients with a CHA_2DS_2-VASc score = 2 accounted for 42.2% of the overall patients. The majority of patients remained at high risk of thromboembolic complications. Risk factors according to the CHA_2DS_2-VASc scale in AF patients are shown in Table 3.

5.2. Stroke prevention therapy

All patients were anticoagulated with NOACs: 51.0% with rivaroxaban, 47.1% with dabigatran and 1.9% with apixaban. In our study, 8.4% of patients received a reduced NOACs dose. No statistically significant differences in relation to the frequency of apixaban, dabigatran, rivaroxaban use were seen between selected groups of patients. The use of NOACs in reduced dose increased in parallel with increasing score in the CHA_2DS_2-VASc scale, as presented in Table 2.

5.3. Assessment of the predictive value of selected scales

In the study population, the LAAT had been detected in 4.3% of individuals (N = 50/1163). Table 4 shows the percentage of AF patients with detected LAAT in reference to the CHA_2DS_2-VASc score. ROC curves corresponding to the discriminant capacity of selected scales indicated that the CHA_2DS_2-VASc-RAF scale had better predictive ability to differentiate the thrombus and no-thrombus groups than any of the presented scales (Fig. 1). Table 5 presents AUC for the $CHADS_2$, the CHA_2DS_2-VASc, the R_2CHADS_2 and the CHA_2DS_2-VASc-RAF score in the study group.

Table 2

Clinical characteristics across CHA_2DS_2-VASc groups treated with non-vitamin K oral anticoagulants.

Variable	CHA_2DS_2-VASc = 0 n = 128	CHA_2DS_2-VASc = 1 (female without additional factor) n = 51	CHA_2DS_2-VASc = 1 (in male) n = 213	CHA_2DS_2-VASc = 2 (in female) n = 99	CHA_2DS_2-VASc≥2 (in male) CHA_2DS_2-VASc≥3 (in female) n = 672	*P*
Age, yr						< .001
Mean ± SD	49.8 ± 10.7	52.9 ± 12.5	54.8 ± 8.9	61.0 ± 6.3	67.9 ± 8.8	
Median (Q1–Q3)	53.0 (41.0–59.0)	58.0 (50.0–61.5)	57.0 (49.0–61.0)	62.0 (59.0–64.0)	68.0 (64.0–73.0)	
Stroke risk stratification						
CHADS2						<.001
Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 0.3	0.8 ± 0.4	2.0 ± 1.0	
Median (Q1–Q3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	2.0 (1.0–3.0)	
R2CHADS2						<.001
Mean ± SD	0.1 ± 0.5	0.4 ± 0.8	1.2 ± 0.8	1.4 ± 0.9	2.8 ± 1.5	
Median (Q1–Q3)	0.0 (0.0–0.0)	0.0 (0.0-0.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	3.0 (2.0–4.0)	
CHA2DS2-VASc-RAF						<.001
Mean ± SD	2.3 ± 2.7	2.8 ± 2.8	3.6 ± 2.7	3.9 ± 2.7	7.2 ± 3.2	
Median (Q1–Q3)	0.0 (0.0–4.0)	1.0 (1.0–5.0)	5.0 (1.0–5.0)	2.0 (2.0–6.0)	7.0 (5.0–9.0)	
Renal function						
eGFR, ml/min						<.001
Mean ± SD	82.1 ± 14.7	76.6 ± 19.0	77.7 ± 16.2	71.7 ± 17.9	68.9 ± 18.7	
Median (Q1-Q3)	81.7 (72.6–90.0)	79.0 (60.9–90.0)	80.3 (66.8–90.0)	70.0 (57.7–90.0)	67.5 (54.1–90.0)	
eGFR<30 mL/min, n (%)	0.0 (0.0)	0.0 (0.0)	1.0 (0.5)	0.0 (0.0)	9.0 (1.3)	.0004
eGFR 30–59 mL/min, n (%)	7.0 (5.5)	11.0 (21.6)	29.0 (13.6)	31.0 (31.3)	236.0 (35.1)	
eGFR > 59 mL/min, n (%)	121.0 (94.5)	40.0 (78.4)	183.0 (85.9)	68.0 (68.7)	427.0 (63.5)	
eGFR < 56 mL/min, n (%)	3.0 (2.3)	7.0 (13.7)	21.0 (9.9)	23.0 (23.2)	193.0 (28.7)	<.001
Form of atrial fibrillation, n (%)						
Non-paroxysmal	61.0 (47.7)	17.0 (33.3)	115.0 (54.0)	32.0 (32.3)	474.0 (70.5)	<.001
Paroxysmal	67.0 (52.3)	34.0 (66.7)	98.0 (46.0)	67.0 (67.7)	198.0 (29.5)	<.001
Persistent	54.0 (42.2)	15.0 (29.4)	105.0 (49.3)	29.0 (29.3)	436.0 (64.9)	
Permanent	7.0 (5.5)	2.0 (3.9)	10.0 (4.7)	3.0 (3.0)	38.0 (5.7)	
Non-permanent	121.0 (94.5)	49.0 (96.1)	203.0 (95.3)	96.0 (97.0)	634.0 (94.3)	.892
Echocardiography						
LA, mm	42.3 ± 4.8	40.8 ± 5.8	45.7 ± 5.3	40.9 ± 5.6	45.7 ± 6.5	<.001
Mean ± SD	42.0 (39.0–45.0)	41.0 (37.2–42.8)	45.5 (41.0–49.2)	40.0 (36.5–46.0)	45.0 (42.0–49.0)	
Median (Q1–Q3)	n = 49	n = 22	n = 84	n = 35	n = 287	
LVEF, %	58.0 ± 6.1	57.7 ± 8.4	55.4 ± 10.5	60.1 ± 5.2	53.1 ± 10.1	<.001
Mean ± SD	60.0 (55.0–62.0)	60.0 (57.5–64.0)	58.0 (51.5–60.0)	60.0 (59.5–64.5)	55.0 (49.0–60.0)	
Median (Q1–Q3)	n = 45	n = 19	n = 92	n = 47	n = 377	
LVDD, mm	52.1 ± 5.7	45.7 ± 13.4	52.8 ± 5.9	47.1 ± 4.2	51.7 ± 7.2	.003
Mean ± SD	52.0 (48.0–54.0)	50.0 (44.0–53.0)	53.0 (48.0–56.0)	48.0 (45.0–50.0)	51.0 (47.0–56.0)	
Median (Q1–Q3)	n = 28	n = 13	n = 59	n = 21	n = 253	
LAAT, n (%)	1.0 (0.8)	0.0 (0.0)	4.0 (1.9)	5.0 (5.1)	40.0 (6.0)	.005
SEC, n (%)	17.0 (13.3)	6.0 (11.8)	40.0 (18.8)	16.0 (16.2)	118.0 (17.6)	.570
LAAV, cm/s	0.6 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	0.5 ± 0.3	0.4 ± 0.2	<.001
Mean ± SD	0.6 (0.4–0.8)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.8)	0.4 (0.3–0.6)	
Median (Q1–Q3)	n = 93	n = 46	n = 153	n = 88	n = 392	
Anticoagulant treatment, n (%)						
Apixaban	1.0 (0.8)	0.0 (0.0)	4.0 (1.9)	0.0 (0.0)	17.0 (2.5)	.413
Dabigatran	68.0 (53.1)	23.0 (45.1)	90.0 (42.3)	41.0 (41.4)	326.0 (48.5)	.216
Rivaroxaban	59.0 (46.1)	28.0 (54.9)	119.0 (55.9)	58.0 (58.6)	329.0 (49.0)	.138
Apixaban or rivaroxaban group	60.0 (46.9)	28.0 (54.9)	123.0 (57.7)	58.0 (58.6)	346.0 (51.5)	.216
NOAC reduced dose	2.0 (1.6)	1.0 (2.0)	6.0 (2.8)	5.0 (5.1)	84.0 (12.5)	<.001

AF = atrial fibrillation, $CHADS_2$ = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category; CHA_2DS_2-VASc-RAF = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, renal dysfunction and AF type, eGFR = estimated glomerular filtration rate, LA = left atrial; LAAT = left atrial appendage thrombus, LAAV = left atrial appendage peak emptying velocity, LVDD = left ventricular diastolic diameter, LVEF = left ventricular ejection fraction, NOAC = non-vitamin K oral anticoagulant; R_2CHADS_2 = creatinine clearance below 60 mL/min, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, SEC = spontaneous echocardiographic contrast.

Table 3

Risk factors according to CHA_2DS_2-VASc scale in patients with atrial fibrillation.

Risk factors, n (%)	CHA_2DS_2-VASc = 1 (in male) n = 213	CHA_2DS_2-VASc = 2 (in female) n = 99	CHA_2DS_2-VASc ≥ 2 (in male) CHA_2DS_2-VASc ≥ 3 (in female) n = 672
Heart failure	18.0 (8.5)	2.0 (2.0)	230.0 (34.2)
Hypertension	166.0 (77.9)	72.0 (72.7)	597.0 (88.8)
Age ≥ 75 yr	0.0 (0.0)	0.0 (0.0)	139.0 (20.7)
Diabetes mellitus	2.0 (0.9)	2.0 (2.0)	212.0 (31.5)
Stroke, TIA, thromboembolism	0.0 (0.0)	0.0 (0.0)	85.0 (12.6)
Vascular disorders	8.0 (3.8)	1.0 (1.0)	232.0 (34.5)
Age 65–74 yr	19.0 (8.9)	22.0 (22.2)	350.0 (52.1)

CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, TIA = transient ischemic attack.

5.4. Comparison of AF patients with LAAT and without LAAT among males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2

The group of patients at intermediate risk of stroke according to CHA_2DS_2-VASc scale with detected LAAT consisted of 9 individuals (mean age 59.4 ± 6.1 years). In this population, AF was classified as paroxysmal in 33.3%, persistent in 44.4% and permanent in 22.2% of patients. The paroxysmal type of AF was the most common form of arrhythmia in the group of patients without LAAT (53.5%). Noteworthy, the largest percentage of individuals with moderate impaired renal function (55.6%) was in the group of patients with detected LAAT. Variables such as non-permanent AF type ($P = .049$) and renal dysfunction defined as eGFR < 56 mL/min/1.73 m^2 ($P = .026$) proved strong predictors of LAAT. The echocardiographic data were not significantly different between groups. The R_2CHADS_2 scale ($P = .007$) and the CHA_2DS_2-VASc-RAF scale ($P = .027$) have better predictive value than the $CHADS_2$ scale ($P < .608$) with regard to the incidence of LAAT in analyzed groups. Table 6 presents a comparison of the group with thrombus and without thrombus among males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.

5.5. Main findings

LAAT was detected in all analyzed groups (except females without additional risk factors) of AF patients treated with NOACs independently of risk categories calculated by the CHA_2DS_2-VASc scale.

Table 4

The frequency of left atrial appendage thrombus among the study population.

CHA_2DS_2-VASc Score	LAAT, no. (%)
0	1/128 (0.8)
1	4/264 (1.5)
2	8/272 (2.9)
3	16/214 (7.5)
4	10/138 (7.2)
5	5/88 (5.7)
6	4/43 (9.3)
7	1/7 (14.3)
8	1/8 (12.5)
9	0/1 (0.0)

CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, LAAT, left atrial appendage thrombus.

Decreased renal function and AF type in combination with the CHA_2DS_2-VASc score were additional predictors of LAAT.

The application of additional scales to estimate the risk of thromboembolic complications might be especially useful among males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2.

6. Discussion

6.1. The prevalence of thrombi among thromboembolic risk categories according to the CHA_2DS_2-VASc scale

The present study showed that LAAT occurred in anticoagulated patients at low- and intermediate-risk of thromboembolic

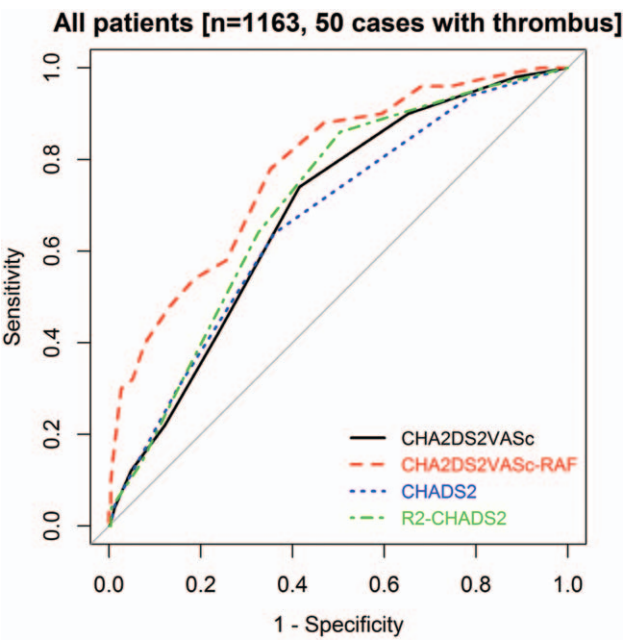

Figure 1. Receiver operating characteristic curves for the $CHADS_2$, the CHA_2DS_2-VASc, the R_2CHADS_2 and the CHA_2DS_2-VASc-RAF score in the study group. $CHADS_2$ = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, CHA_2DS_2-VASc-RAF = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, renal dysfunction and AF type, R_2CHADS_2 = creatinine clearance below 60 mL/min, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack.

Table 5

Area under the curve for the $CHADS_2$, the CHA_2DS_2-VASc, the R_2CHADS_2, and the CHA_2DS_2-VASc-RAF score in the study group.

	All patients	
	AUC*	95% CI AUC*
CHA_2DS_2-VASc	0.683	0.617–0.749
CHA_2DS_2-VASc-RAF	0.780	0.716–0.844
$CHADS_2$	0.666	0.596–0.736
R_2CHADS_2	0.703	0.639–0.767

$CHADS_2$ = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, CHA_2DS_2-VASc-RAF = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, renal dysfunction and AF type, R_2CHADS_2 = creatinine clearance below 60 mL/min, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack.

* Area under the receiver operating curve with 95% confidence interval.

complications, which have suggested the presence of additional stroke risk factors not including in the CHA_2DS_2-VASc scale (Table 4). Among patients with detected thrombus, 1 person (2%) was classified as a low-risk patient, 9 (18%) of individuals were at intermediate-risk, and 40 (80%) of patients were at high risk of thromboembolic events. The percentage of patients with LAAT increased with the risk of stroke calculated by the CHA_2DS_2-VASc scale. LAAT is a surrogate for ischemic stroke. Lip et al reported a slightly lower percentage of thromboembolic events (0.6%) among patients at intermediate risk of stroke according to the CHA_2DS_2-VASc score. The authors recommend that the use of OAC should be considered among patients at intermediate risk of stroke because of the potentially greater benefit of overtreatment than undertreatment.[14] In a study of the incidence and predictors of LAAT, Bertaglia et al confirmed the occurrence of LAAT in a group of patients treated with NOAC (N=15/414, 3.6%).[15] In real-world observation Niku et al, including 1485 patients with AF, LAAT was detected in 8% of patients, of which half (4% of patients) received adequate anticoagulation.[16] The incidence of thrombi in AF patients receiving apparently adequate anticoagulation justifies the consideration of TOE before electrical cardioversion or ablation regardless of the stroke risk categories.

6.2. Other potential risk factors for LAAT

In our study, renal dysfunction and non-paroxysmal AF were strong predictors of LAAT. Ganesan et al in a meta-analysis, including data of 99,996 patients, showed that non-paroxysmal AF was associated with increased risk of thromboembolism and mortality compared to the paroxysmal type of AF.[17] The study by Lopatowska et al,[18] including 1556 patients with AF, reported the highest thromboembolic risk among patients with the permanent type of AF ($P<.001$). Similarly, Vanassche et al presented a significantly higher risk of stroke among patients with permanent AF compared to patients with non-permanent AF, which was particularly evident in patients with CHA_2DS_2-VASc≥2 (increased risk of embolic events by 50%–100%).[19] In the study of 7329 anticoagulated AF patients, individuals with paroxysmal type AF had lower stroke rates compared with patients with persistent type AF, although both groups had broadly similar risk factors for stroke.[20] A decision regarding treatment low- and intermediate-risk patients with OACs should be based on the net clinical benefit of stroke risk reduction against an increase in bleeding risk. In case that the benefit-risk balance of anticoagulant therapy is inconclusive among this patient population, the form of AF may be useful to consider.

Table 6

Comparison of groups with thrombus and without thrombus in male patients (CHA_2DS_2-VASc score of 1) and female patients (CHA_2DS_2-VASc score of 2) with atrial fibrillation.

Variable	Patients with thrombus n=9	Patients without thrombus n=303	*P*
Age, yr			.506
Mean±SD	59.4±6.1	56.7±8.7	
Median (Q1–Q3)	60.0 (58.0–61.0)	58.0 (51.5–63.0)	
Risk factors according to CHA_2DS_2-VASc, n (%)			
Heart failure	2.0 (22.2)	18.0 (5.9)	.107
Hypertension	4.0 (44.4)	234.0 (77.2)	.037
Diabetes mellitus	1.0 (11.1)	3.0 (1.0)	.111
Vascular disorders	1.0 (11.1)	8.0 (2.6)	.234
Age 65–74 yr	1.0 (11.1)	40.0 (13.2)	1.000
Stroke risk stratification			
CHADS2			.608
Mean±SD	0.8±0.4	0.8±0.4	
Median (Q1–Q3)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	
R2CHADS2			.007
Mean±SD	2.1±1.2	1.2±0.8	
Median (Q1–Q3)	3.0 (1.0–3.0)	1.0 (1.0–1.0)	
CHA2DS2-VASc-RAF			.027
Mean±SD	6.4±4.4	3.7±2.6	
Median (Q1–Q3)	6.0 (4.0–7.0)	4.0 (1.0–5.0)	
Renal function			
eGFR, ml/min			.059
Mean±SD	64.1±20.1	76.2±16.8	
Median (Q1–Q3)	57.4 (48.0–90.0)	77.7 (63.4–90.0)	
eGFR<30 mL/min, n (%)	0.0 (0.0)	1.0 (0.3)	.044
eGFR 30–59 mL/min, n (%)	5.0 (55.6)	55.0 (18.2)	
eGFR>59 mL/min, n (%)	4.0 (44.4)	247.0 (81.5)	
eGFR<56 ml/min, n (%)	4.0 (44.4)	40.0 (13.2)	.026
Form of atrial fibrillation, n (%)			
Non-paroxysmal	6.0 (66.7)	141.0 (46.5)	.315
Paroxysmal	3.0 (33.3)	162.0 (53.5)	.051
Persistent	4.0 (44.4)	130.0 (42.9)	
Permanent	2.0 (22.2)	11.0 (3.6)	
Non-permanent	7.0 (77.8)	292.0 (96.4)	.049
Anticoagulant treatment, n (%)			
Apixaban	0.0 (0.0)	4.0 (1.3)	1.000
Dabigatran	6.0 (66.7)	125.0 (41.3)	.173
Rivaroxaban	3.0 (33.3)	174.0 (57.4)	.182
Apixaban or rivaroxaban	3.0 (33.3)	178.0 (58.7)	.173
NOAC reduced dose	0.0 (0.0)	11.0 (3.6)	1.000
Echocardiography			
SEC, n (%)	3.0 (33.3)	53.0 (17.5)	.207
LAAV, cm/s			.370
Mean±SD	0.5±0.4	0.5±0.3	
Median (Q1-Q3)	0.3 (0.2–0.8)	0.5 (0.3–0.7)	

AF = atrial fibrillation, $CHADS_2$ = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, CHA_2DS_2-VASc = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, CHA_2DS_2-VASc-RAF = congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular, age 65 to 74 years, sex category, renal dysfunction and AF type, eGFR = estimated glomerular filtration rate, LAAV = left atrial appendage peak emptying velocity; NOAC = non-vitamin K oral anticoagulant; R_2CHADS_2 = creatinine clearance below 60 mL/min, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, SEC = spontaneous echocardiographic contrast.

In our study, the type of NOAC did not differentiate patients with or without LAAT. Several studies have shown that renal dysfunction is associated with an increased risk of stroke, thromboembolism and major bleeding complication in patients with AF.[21–23] Our observations confirmed that renal dysfunction, defined as eGFR <56 mL/min/1.73 m^2, was able to distinguish individuals with and without LAAT ($P = .026$) among the group of AF patients at intermediate-risk of stroke, 44.4% vs 13.2%, respectively (Table 6). R_2CHADS_2 and ATRIA scales, which include the renal dysfunction in risk stratification improved the ability to predict thromboembolic events in the population of AF patients.[12,24] Kapłon-Cieślicka et al[13] proposed the CHA_2DS_2-VASc-RAF scale, which significantly improved thromboembolic risk stratification among AF patients by adding AF type and renal dysfunction to CHA_2DS_2-VASc scale. Our results confirmed the role of R_2CHADS_2 and CHA_2DS_2-VASc-RAF scales in thromboembolic risk stratification.

6.3. Should males with a CHA_2DS_2-VASc score of 1 and females with a CHA_2DS_2-VASc score of 2 be treated with anticoagulant?

The decision to treat the intermediate-risk patients is a challenge in everyday clinical practice. Available data about the treatment of males with CHA_2DS_2-VASc scores of 1 and females with CHA_2DS_2-VASc scores of 2 are inconclusive. Chao et al[25] reported that the administration of OAC therapy derived greater clinical benefits than withdrawal from this therapy (risk of stroke 1.96%–3.5% and risk of significant bleeding 0.25%–1.45% per year) among intermediate-risk AF patients. However, Fiberg et al[26] demonstrated that the clinical benefits of OAC use in this group of patients were ambiguous (risk of ischemic stroke 0.5%–0.7%). Jackson et al[27] showed that the American Heart Association / American College of Cardiology guidelines for the prevention of stroke in patients with AF at low- and intermediate-risk are not fully accomplished. In Jackson study, most patients with CHA_2DS_2-VASc = 0 to 1 received OAC therapy, and the absolute risk of death/stroke/TIA was relatively low for males with CHA_2DS_2-VASc = 0 to 1 and females with CHA_2DS_2-VASc = 1 to 2.

ESC Working Group on Cardiovascular Pharmacotherapy and ESC Council on Stroke created consensus about OAC in patients with AF and a CHA_2DS_2-VASc score of 1, which reported the therapeutic preference should be based on the individual balance between thromboembolic and bleeding risk and should not harm patients. Authors recommend individual assessment of AF patients at intermediate stroke risk to choose the best therapeutic option customized to the patient's clinical situation.[28] Unfortunately, no unambiguous parameters are providing the refinement thromboembolic risk assessment among males with CHA_2DS_2-VASc scores of 1 and females with CHA_2DS_2-VASc scores of 2.

Randomized controlled trials are needed to identify predictors of thromboembolic complications and to evaluate the effectiveness of therapy and to clarify the optimal anticoagulation strategy among patients at intermediate-risk of thromboembolic complications.

6.4. Limitations of the study

First, the presence LAAT was considered a surrogate for thromboembolic complications due to the significant prevalence thrombus across the left atrial appendage. Most frequently LAAT led to thromboembolic events in patients with AF. Secondly, the study is limited by the retrospective nature of the collected data. We were able to source these diagnoses, examinations, or obtain other crucial information which had been coded into binary ICD-10 codes. The percentage of patients treated with apixaban, dabigatran, rivaroxaban considerably differed in the analyzed population. Third, we could not determine the AF burden. This lack of sufficient data did not allow us to distinguish between persistent and long-standing persistent AF.

7. Conclusions

The prevalence of LAAT among AF patients treated with NOACs at high stroke risk is greater compared to patients at low stroke risk. With regard to LAAT CHA_2DS_2-VASc-RAF scale have better predictive value than currently used scales (CHA_2DS_2-VASc and $CHADS_2$). The extension of the CHA_2DS_2-VASc scale might be particularly useful in AF patients with a lower class of recommendations for anticoagulation.

Author contributions

All authors were responsible for the concept and the design of the study. AM, IG, MC, AKC, BUŻ and BWK contributed to the design of the research. AM, IG, KS, OJ, MB, MG, PK, AJ, PS, JK, MK were involved in the data collection. AM, IG, MC, AKC, BUŻ, KS, OJ, BWK analyzed the data. IG, MC was responsible for the statistical analysis. AM, IG, MC and BWK wrote the manuscript. All authors edited and approved the final version of the manuscript.

AM and IG contributed to the manuscript equally.

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