ORIGINAL ARTICLE

Differences in the predictors of left atrial appendage thrombus between men and women treated with dabigatran or rivaroxaban

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KEY WORDS

atrial fibrillation, non–vitamin K antagonist oral anticoagulant therapy, sex-related differences

ABSTRACT

INTRODUCTION Some patients with atrial fibrillation (AF) develop left atrial appendage thrombus (LAAT) despite receiving anticoagulant treatment. Different scores were proposed to evaluate thromboembolic risk in patients with AF. Risk stratification according to sex is common in clinical practice.

OBJECTIVES We aimed to identify predictors of LAAT separately in men and women treated with dabigatran or rivaroxaban.

PATIENTS AND METHODS This retrospective study included 1256 patients (479 women [38.1%]) with AF who underwent transesophageal echocardiography before electrical cardioversion or catheter ablation, between January 2013 and December 2019, and received dabigatran or rivaroxaban for at least 3 weeks.

RESULTS Multivariable logistic regression analysis revealed nonparoxysmal AF to predict LAAT in women (odds ratio [OR], 9.70; $P = 0.002$). In men, the predictors were heart failure (OR, 4.14; $P = 0.001$), diabetes (OR, 2.64; $P = 0.002$), nonparoxysmal AF (OR, 5.61; $P = 0.02$), and estimated glomerular filtration rate below 60 ml/min/1.73 m^2 (OR, 2.77; $P = 0.01$). In the receiver operating characteristic curve analysis, the CHA_2DS_2-VASc-RAF score had the highest value for predicting LAAT in women (area under the curve [AUC] = 0.786). In men, CHA_2DS_2-VASc-RAF, CHA_2DS_2, CHA_2DS_2-VASc, and R_2CHADS_2 had sufficient predictive value (AUC = 0.786, 0.726, 0.734, and 0.780, respectively).

CONCLUSIONS The predictors of LAAT differ between men and women treated with dabigatran or rivaroxaban. In women, the CHA_2DS_2-VASc-RAF score had the highest predictive value, while in men all the scores had equally sufficient predictive value.

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INTRODUCTION Atrial fibrillation (AF) is a common life-threatening arrhythmia affecting 1% to 2% of the general population. Thromboembolic complications constitute the most severe consequences of AF. They may be caused by a thrombus formation due to impaired blood flow in the left ventricle as a result of arrhythmia, most often in the left atrial appendage.[1] So far, numerous clinical and echocardiographic predictors of left atrial appendage thrombus (LAAT) have been identified in patients on anticoagulant treatment. The $CHADS_2$ and CHA_2DS_2-VASc scores are used for the assessment of thromboembolic risk in patients with nonvalvular AF. The CHA_2DS_2-VASc-RAF score additionally includes the type of AF and renal dysfunction as LAAT predictors, which appeared to improve the thromboembolic risk stratification.[2-4] Despite optimal treatment with

WHAT'S NEW?

Transesophageal echocardiography (TEE) is a gold standard for the exclusion of left atrial appendage thrombus (LAAT). There are no unequivocal data on whether patients awaiting ablation or electric cardioversion should routinely undergo TEE, which is an invasive procedure performed by trained and experienced personnel. Some patients with atrial fibrillation (AF) develop LAAT despite receiving anticoagulant treatment. The $CHADS_2$ and CHA_2DS_2-VASc scores are used to assess thromboembolic risk in patients with nonvalvular AF. The CHA_2DS_2-VASc-RAF score has been developed to improve thromboembolic risk stratification. In this study, we identified sex-related predictors of LAAT in patients treated with dabigatran or rivaroxaban. All the assessed scores had a similar predictive value in men, while the CHA_2DS_2-VASc-RAF score had the highest predictive value in women.

vitamin K antagonists and the currently preferred non–vitamin K oral antagonists (NOACs), LAAT still develops in 2% to 10% of patients on anticoagulant treatment.[5-8] The gold standard for the exclusion of LAAT is transesophageal echocardiography (TEE).[9,10] However, there are no unequivocal data on whether patients awaiting ablation or electric cardioversion should routinely undergo TEE, which is an invasive procedure that should be performed by trained and experienced personnel.[11-14] Risk stratification according to sex is common in clinical practice. Sex-related differences in myocardial anatomy as well as the epidemiology, pathophysiology, and risk factors of heart diseases, including genetic cardiomyopathies, have been well described. Moreover, differences in the risk of stroke according to sex were reported in clinical trials.[15-17] The aim of this study was to identify differences in the predictors of LAAT between men and women treated with NOACs (dabigatran or rivaroxaban).

PATIENTS AND METHODS

Study design and participants In this retrospective study, we evaluated 1312 patients with AF from 3 centers in Poland, who underwent TEE before electrical cardioversion or catheter ablation between January 2013 and December 2019 and received continuous therapy with NOACs for at least 3 weeks. Patients taking apixaban (n = 56) were excluded from the study due to a small sample size. The final study population included 1256 individuals treated with dabigatran or rivaroxaban. The patients with moderate or severe mitral valve stenosis and those with a mechanical heart valve were excluded. The research protocol was approved by the ethics committee of each institution (17/2016). As this was an observational retrospective study, the patients' written informed consent was not necessary.

Clinical, laboratory, and echocardiographic data were obtained retrospectively from medical records. The patients were divided into 3 groups (paroxysmal, persistent, or permanent AF) on the basis of a comprehensive analysis of the medical records. The patients were classified as having permanent AF after unsuccessful cardioversion during index hospitalization or if their original diagnosis of permanent AF was changed to long-standing persistent AF before electrical cardioversion or catheter ablation. These patients were classified as having permanent AF to distinguish them from those with persistent AF with a presumably lower AF burden. Vascular disease was defined as previous aortic plaque, myocardial infarction, or peripheral arterial disease. Kidney function was assessed using estimated glomerular filtration rate (eGFR) calculated with the Modification of Diet in Renal Disease Study formula.

Evaluation of thromboembolic risk Thromboembolic risk in patients with AF was assessed using the following scores: $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, and CHA_2DS_2-VASc-RAF. The CHA_2DS_2-VASc-RAF expands the risk assessment according to the CHA_2DS_2-VASc score by adding the type of AF and kidney function. The scoring systems used to estimate the risk of thromboembolic complications in patients with AF are described in detail in TABLE 1.

Anticoagulant therapy All patients received continuous therapy with dabigatran or rivaroxaban for at least 3 weeks before TEE, including the day TEE was performed. The drugs were administered according to the Summary of Product Characteristics.

Echocardiographic evaluation All TEE examinations were performed by certified echocardiographers (second-degree accreditation in echocardiography of the Section of Echocardiography of the Polish Cardiac Society) within 48 hours before the scheduled procedure (electrical cardioversion or catheter ablation). The examinations were done using General Electric Vivid 7 or E95 Ultrasound System (General Electric, Milwaukee, Wisconsin, United States), EPIQ 7 Ultrasound Machine (Philips Medical Systems, Andover, Massachusetts, United States), or iE33 Ultrasound Machine (Philips Medical Systems) with an X72t TEE ultrasound transducer (Philips Medical Systems).

LAAT was defined as an independently mobile echo-dense structure that was distinct from the surrounding pectinate muscles or endocardium and that was detected in more than 1 imaging plane. Dense spontaneous echo contrast was defined as a dynamic "smoke-like" signal with a characteristic swirling motion, or a dynamic, gelatinous, precipitous echo density without a discrete mass, present throughout the cardiac cycle.

If LAAT was suspected, the images were evaluated by 2 echocardiographers to establish a unanimous diagnosis and enable a safe referral of the patient for electrical cardioversion or catheter ablation. Written informed consent for TEE was obtained from all patients. In cases with confirmed LAAT, a decision against the reversal of

TABLE 1 Thromboembolic risk assessment scores in patients with atrial fibrillation

Parameter	Score			
	$CHADS_2$ (max. 6 points)	R_2CHADS_2 (max. 8 points)	CHA_2DS_2-VASc (max. 9 points)	CHA_2DS_2-VASc-RAF (max. 25 points)
Risk factors				
Heart failure	1	1	1	1
Hypertension	1	1	1	1
Diabetes mellitus	1	1	1	1
Vascular disease	–	–	1	1
Age 65–74 y	–	–	1	1
Stroke or transient ischemic attack	2	2	2	2
Age ≥75 y	1	1	2	2
Female sex	–	–	1	1
Creatinine clearance eGFR <60 ml/min/1.73 m^2	–	2	–	–
eGFR <56 ml/min/1.73 m^2	–	–	–	2
Persistent AF	–	–	–	4
Permanent AF	–	–	–	10
Risk categories				
Low	0	0	0 (men); 1 (women)	0–4 (men); 1–5 (women)
Medium	1	1	1 (men); 2 (women)	–
High	2	2	≥2 (men); ≥3 (women)	≥5 (men); ≥6 (women)

Abbreviations: 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 disease, age 65–74 years, sex category; CHA_2DS_2--VASc-RAF, congestive heart failure, hypertension, age over 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 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

sinus rhythm was made. Decisions on further procedures in these patients were made on individual basis. The study end point was the presence of LAAT on TEE.

Statistical analysis For qualitative variables, percentage values were calculated separately for each study group. The χ^2 test was used to compare the groups. For quantitative variables, means with SDs were calculated. The quantitative variables with non-normal distribution were presented as median (interquartile range). Normally distributed variables were compared with the *t* test. Non--normally distributed variables were compared with the Mann–Whitney test.

A univariable and a multivariable logistic regression analysis were performed separately in women and men to evaluate associations between age, heart failure (HF), diabetes mellitus (DM), stroke / transient ischemic attack / peripheral artery disease, vascular disease, nonparoxysmal AF, creatinine clearance (eGFR <60 ml/min/1.73 m^2), and LAAT. A stepwise forward regression was used. Odds ratios (ORs) and 95% CIs were calculated. For all qualitative predictors, the absence of an event was considered as a reference point (0 value). In the logistic regression analysis, age was presented as quantitative data.

Two criteria for entering the variables into the model were applied. The Pearson correlation analysis was used for normally distributed variables and the Spearman correlation analysis was employed for variables with a distribution deviating from normal. The analyses investigated the relationship between the dependent variables and the predictors. The predictors whose correlation value with the dependent variable was below 0.05 were included in the model. Additionally, the model included the variables associated with the outcome known from the research literature.

To assess the 4 variables of $CHADS_2$, CHA_2DS_2--VASc, CHA_2DS_2-VASc-RAF, and R_2CHADS_2 scores as well as to identify the optimal cutoffs for predicting LAAT, the receiver operating characteristic curve (ROC) analysis was used separately for women and men. The area under the curve (AUC) with 95% CI was the measure of each score. The optimal cutoff was the highest value of the Youden index (sensitivity + specificity – 1). For all calculations, a *P* value below 0.05 was considered significant. Statistical analysis was performed using the Statistica package (Tibco program, version 13.1, Warsaw, Poland).

RESULTS The study included 1256 patients (479 women [38.1%]) with AF hospitalized due

TABLE 2 Baseline characteristics of all patients and separately of men and women

Variable	All patients (n = 1256)	Women (n = 479)	Men (n = 777)	*P* value
Age, y, mean (SD)	62.5 (11.4)	66.6 (11.7)	60.0 (9.7)	<0.001[a]
Clinical characteristics, n (%)				
Heart failure	263 (20.9)	86 (18.4)	175 (22.5)	0.08[b]
Hypertension	911 (72.5)	379 (79.1)	532 (68.5)	<0.001[b]
Diabetes mellitus	231 (18.4)	91 (19)	140 (18)	0.66[b]
Stroke/TIA/embolism	93 (7.4)	41 (8.6)	52 (6.7)	0.14[b]
Vascular disease	34 (2.7)	13 (2.7)	21 (2.7)	0.99[b]
Type of AF				
Paroxysmal	517 (41.2)	227 (47.4)	290 (37.3)	<0.001[b]
Nonparoxysmal	739 (58.8)	252 (52.6)	487 (62.7)	
Permanent	65 (5.2)	19 (4)	46 (5.9)	0.13[b]
Persistent	674 (53.7)	233 (18.6)	441 (56.8)	0.005[b]
Treatment, n (%)				
Rivaroxaban	653 (52)	264 (55.1)	389 (50)	0.08[b]
Dabigatran	603 (48)	215 (44.9)	388 (49.9)	
Reduced dose	110 (8.8)	63 (13.2)	47 (6)	<0.001[b]
Thromboembolic risk				
$CHADS_2$, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.002[c]
$CHADS_2 = 0$, n (%)	248 (19.8)	80 (16.7)	168 (21.6)	0.03[b]
$CHADS_2 = 1$, n (%)	535 (42.6)	199 (41.5)	336 (43.2)	
$CHADS_2 \geq 2$, n (%)	473 (37.7)	200 (41.8)	273 (35.1)	
CHA_2DS_2-VASc, mean (SD)	3.30 (1.56)	3.32 (1.56)	1.89 (1.49)	<0.001[a]
CHA_2DS_2-VASc = 0, n (%)	135 (10.8)	0	135 (17.4)	<0.001[b]
CHA_2DS_2-VASc = 1, n (%)	280 (22.3)	53 (11.1)	227 (29.2)	
CHA_2DS_2-VASc ≥2, n (%)	841 (67)	426 (88.9)	415 (53.4)	
CHA_2DS_2-VASc-RAF, median (IQR)	5 (3–8)	6 (3–9)	5 (2–7)	<0.001[c]
R_2CHADS_2, median (IQR)	n = 1221; 2 (1–3)	n = 466; 2 (1–4)	n = 755; 1 (1–3)	<0.001[c]
HASBLED, median (IQR)	1 (1–2)	2 (1-2)	1 (1–2)	<0.001[c]
HASBLED <3, n (%)	1105 (88)	391 (81.6)	714 (91.9)	<0.001[b]
Laboratory data				
Hemoglobin, g/dl, median (IQR)	n = 1229; 14.2 (13.2–15.2)	n = 460; 13.4 (12.6–14.2)	n = 769; 14.7 (13.8–15.5)	<0.001[c]
Platelets, 10^9/l, median (IQR)	n = 1225; 217 (179–253)	n = 461; 230 (199–266)	n = 764; 208 (172–243)	<0.001[c]
Creatinine, mg/dl, median (IQR)	1.04 (0.9–1.2)	0.97 (0.83–1.1)	1 (0.97–1.24)	<0.001[c]
eGFR, ml/min/1.73 m^2, median (IQR)	72 (58.2–90)	62.6 (52.4–90)	76.7 (63.4–90)	<0.001[c]
eGFR <60 ml/min/1.73 m^2, n (%)	359 (28.6)	216 (54.9)	143 (18.4)	<0.001[b]
Echocardiographic data				
LA, mm, median (IQR)	n = 516; 45 (41–48)	n = 194; 43 (40–46)	n = 322; 46 (42–50)	<0.001[c]
LVDD, mm, median (IQR)	n = 412; 51 (47–55.25)	n = 150; 48 (45–52)	n = 262; 46 (42–50)	<0.001[c]
LVEF, %, median (IQR)	n = 616; 58 (50–60)	n = 241; 60 (55–60)	n = 375; 55 (45–55)	<0.001[c]
LAAV, cm/s, median (IQR)	n = 769; 0.45 (0.3–0.7)	n = 302; 0.41 (0.28–0.59)	n = 467; 0.47 (0.3–0.7)	0.007[c]
End point				
LAAT, n (%)	51 (4.1)	22 (4.6)	29 (3.7)	0.45[b]

a *t* test

b χ^2 test

c Mann–Whitney test

Si conversion factors: to convert Hb to mmol/l multiply by 0.6206, creatinine to μmol/l muliply by 88.40.

Abbreviations: IQR, interquartile range; LA, left atrium; LAAT, left atrial appendage thrombus; LAAV, left atrial appendage flow velocity; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; others, see **TABLE 1**

to ablation and electrical cardioversion and treated with dabigatran or rivaroxaban. The mean (SD) age of the women was 60 (11.7) years, and of the men 67 (9.7) years. The clinical characteristics of the women and men are compared in TABLE 2.

LAAT was diagnosed in 51 patients (4.1%), including 22 women (4.6%) and 29 men (3.7%) (P = 0.45). The women with LAAT were older, were more likely to have HF and nonparoxysmal AF, received a reduced dose of anticoagulants, had a higher CHA_2DS_2-VASc-RAF score and lower left ventricular ejection fraction (LVEF) than the women without LAAT.

The men with LAAT were older, were more likely to have HF, nonparoxysmal AF, and DM, had higher $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, and CHA_2DS_2-VASc-RAF scores, as well as lower eGFR and LVEF than the men without LAAT. A detailed comparison between the patients with and without LAAT is shown in TABLE 3.

The results of the univariable regression analysis in men and women are presented in TABLE 4. In the multivariable logistic regression analysis, only nonparoxysmal AF was a predictor of LAAT in women (OR, 9.70; 95% CI, 2.24–41.97; P = 0.002). In men, the predictors of LAAT included HF (OR, 4.14; 95% CI, 1.82–9.40; P = 0.001), DM (OR, 2.64; 95% CI, 1.19–5.88; P = 0.002), nonparoxysmal AF (OR, 5.61; 95% CI, 1.29–24.46; P = 0.02), and eGFR <60 ml/min/1.73 m^2 (OR, 2.77; 95% CI, 1.25–6.13; P = 0.01). The results of the multivariable regression analysis in men and women are presented in Supplementary material, *Tables S1* and *S2*.

Based on the receiver operating characteristic curve analysis, CHA_2DS_2-VASc-RAF had the highest diagnostic accuracy for predicting LAAT in women (FIGURE 1, TABLE 5). In men, all the scores had sufficient diagnostic power for predicting LAAT (FIGURE 2, TABLE 6).

DISCUSSION Our study yields several major findings. First, women and men are at a similar risk of LAAT. Second, the frequency of LAAT in women and men is independent of the NOAC dose. Third, men and women differed in terms of the LAAT predictors and the predictive value of the thromboembolic risk scores.

The prevalence of LAAT was similar in women and men treated with dabigatran and rivaroxaban. Risk stratification according to sex is a common approach in clinical practice. There have been numerous studies assessing the risk of stroke depending on sex. Girijala et al[15] analyzed sex-related differences in terms of the epidemiology of risk factors, symptoms, as well as methods and results of stroke treatment. Epidemiological data indicated a higher rate of stroke in older women, which raised the question of the neuroprotective role of sex hormones.[16] In a retrospective study on the frequency of ischemic stroke in women and men with AF, Yoshida et al[17] assessed sex-related differences in the risk factors for stroke as well as the anatomy and function of the left atrium. They concluded that for the same level of increase in the risk of stroke, worsening of left atrial function is greater in women than in men, which could explain a more frequent occurrence of ischemic stroke in women. In our study, women had a smaller left atrial size, smaller left ventricular diastolic diameter, and higher LVEF than men. Similarly, Shah et al[18] observed that left atrial dilation, absence of severe mitral regurgitation, and lower LVEF are associated with an increased risk of LAAT.

HF is a component of all thromboembolic risk scores.[19] In our study, the patients with LAAT significantly more often had HF. In the univariable logistic regression analysis, it was a strong predictor of LAAT both in men and women.

Di Mino et al[20] conducted a meta-analysis including 72 studies and a total of 20 516 patients, in which they investigated the frequency of LAAT in individuals undergoing electric cardioversion or ablation. A higher frequency of LAAT was observed in women than in men (OR, 1.35; 95% CI, 1.04–1.75). The frequency of LAAT in women and men was independent of NOAC dose. Rivaroxaban was used by 52% of the patients, of which 55.1% were women. Dabigatran was used by 48% of the patients, of which 44.9% were women. However, the differences were not significant. A reduced dose of dabigatran and rivaroxaban was used by 13.2% of women and 6% of men (P <0.001). The reduced dose was not a predictor of LAAT in either of the sexes. Similarly, Bertaglia et al[7] studied a group of 414 patients treated with NOACs for more than 3 months, who underwent TEE before cardioversion or ablation. The reduced dose was not a predictor of LAAT either in men or in women.

Renal impairment is a documented risk factor for cardiovascular disease and it is associated with hypertension and DM, which are included in the $CHADS_2$ and CHA_2DS_2-VASc scores. Arnson et al[21] conducted a retrospective analysis of 85 116 patients with AF and concluded that advanced kidney disease was associated with a higher risk of stroke, death, and bleeding. Some studies[2,3] identified renal dysfunction to be an important predictor of LAAT, enhancing the prognostic value of the CHA_2DS-VASc score. In our study, eGFR below 60 ml/min/1.73 m^2 was reported in 54.9% of the women and only 18.4% of the men. Impaired renal function was a predictor of LAAT only in men.

We found that the type of AF (ie, nonparoxysmal AF) was the strongest independent predictor of LAAT both in men and women. In men, additional independent predictors of LAAT were HF, DM, and impaired kidney function. In a retrospective study, Wei-dong et al[22] assessed 705 of the 1346 patients with a low CHA_2DS_2-VASc score in whom TEE was performed before ablation or cardioversion. Nonparoxysmal AF was the strongest independent risk factor of LAAT / spontaneous echo contrast (OR, 3.766; 95% CI, 1.282–11.061; P = 0.02).

TABLE 3 Baseline characteristics of the study groups according to sex and the presence of left atrial appendage thrombus

Variable	Women		*P* value	Men		*P* value
	Without LAAT (n = 457)	With LAAT (n = 22)		Without LAAT (n = 748)	With LAAT (n = 29)	
Age, y, mean (SD)	66.4 (9.7)	71.0 (8.9)	0.03[a]	59.7 (11.7)	65.9 (8.1)	0.002[a]
Clinical characteristics, n (%)						
Heart failure	80 (17.5)	8 (36.4)	0.03[b]	156 (20.9)	19 (65.5)	<0.001[b]
Hypertension	361 (79)	18 (81.8)	0.75[b]	510 (68.2)	22 (75.9)	0.38[b]
Diabetes mellitus	86 (18.8)	5 (22.7)	0.65[b]	127 (17)	13 (44.8)	<0.001[b]
Stroke/TIA/peripheral embolism	39 (8.5)	2 (9.1)	0.93[b]	49 (6.6)	3 (10.3)	0.42[b]
Vascular disease	12 (2.6)	1 (4.6)	0.59[b]	20 (2.7)	1 (3.5)	0.80[b]
Type of AF, n (%)						
Paroxysmal	225 (49.3)	2 (9.09)	<0.001[b]	288 (38.5)	2 (6.9)	<0.001[b]
Nonparoxysmal	232 (50.8)	20 (90.9)		460 (61.5)	27 (93.1)	
Permanent	12 (3.6)	7 (31.8)	<0.001[b]	38 (5.1)	8 (27.6)	<0.001[b]
Persistent	220 (48.1)	13 (60)	0.32[b]	422 (56.4)	19 (65.5)	0.33[b]
Treatment, n (%)						
Rivaroxaban	257 (56.2)	7 (31.8)	0.02[b]	375 (50.1)	14 (48.3)	0.84[b]
Dabigatran	200 (43.8)	15 (68.2)		373 (49.9)	15 (51.7)	
Reduced dose	57 (12.5)	6 (27.3)	0.04[b]	46 (6.2)	1 (3.4)	0.55[b]
Thromboembolic risk						
$CHADS_2$, median (IQR)	1 (1–2)	2 (1–2)	0.18[c]	1 (1–2)	2 (1–3)	<0.001[c]
$CHADS_2$ =0, n (%)	78 (17.1)	2 (9.1)	0.40[b]	167 (22.3)	1 (3.4)	<0.001[b]
$CHADS_2$ =1, n (%)	191 (41.8)	8 (36.4)		329 (44)	7 (24.1)	
$CHADS_2$ ≥2, n (%)	188 (41.1)	12 (54.6)		252 (33.7)	21 (72.4)	
CHA_2DS_2-VASc, median (IQR)	3 (2–4)	3.5 (3–5)	0.16[c]	2 (1–3)	3 (1–3)	<0.001[c]
CHA_2DS_2-VASc = 0, n (%)	0	0	0.24[b]	134 (17.9)	1 (3.4)	0.005[b]
CHA_2DS_2-VASc=1, n (%)	53 (11.6)	0		223 (29.8)	4 (13.8)	
CHA_2DS_2-VASc ≥2, n (%)	404 (88.4)	22 (100)		391 (52.3)	24 (82.8)	
CHA_2DS_2-VASc-RAF, median (IQR)	6 (3–9)	10 (7–14)	<0.001[c]	5 (2–7)	7 (7–13)	<0.001[c]
R_2CHADS_2, median (IQR)	n = 444; 2 (1–3)	3 (2–4)	0.14[c]	n = 726; 1 (1–2)	3 (2–4)	<0.001[c]
HASBLED, median (IQR)	2 (1–2)	2 (1–3)	0.11[c]	1 (1–2)	2 (1–2)	0.01[c]
HASBLED <3, n (%)	375 (82.1)	16 (72.7)	0.27[b]	689 (92.1)	25 (86.2)	0.25[b]
Laboratory results						
Hemoglobin, g/dl, median (IQR)	n = 439; 13.4 (12.6–14.2)	n = 21; 13.3 (12.6–14.3)	0.95[c]	n = 742; 14.7 (13.9–15.5)	n = 27; 14.3 (13.4–15.23)	0.08[c]
Platelets, 10^9/l, median (IQR)	n= 440; 230 (199–267)	n=21; 204 (195–258)	0.25[c]	n = 737; 208 (173–244)	n = 27; 172 (153–214)	0.008[c]
Creatinine, mg/dl, median (IQR)	0.96 (0.83–1.1)	1.05 (0.85–1.2)	0.47[c]	1.09 (0.97–1.23)	1.25 (0.99–1.36)	0.04[c]
eGFR, ml/min/1.73 m^2, median (IQR)	62.6 (52.4–90)	55.10 (49.7–84.53)	0.44[c]	76.95 (63.98–90)	60.95 (56.8–90)	0.02[c]
eGFR <60 ml/min/1.73 m^2, n (%)	204 (44.6)	12 (54.5)	0.36[b]	130 (17.4)	13 (44.8)	<0.001[b]
Echocardiographic data						
LA, mm, median (IQR)	n = 184; 43 (40–46)	n = 10; 46.5 (45–47)	0.03[c]	n = 312; 46 (42–50)	n = 10; 48 (42–57)	0.26[c]
LVDD, mm, median (IQR)	n = 142; 48 (45–52)	n = 8; 49 (44.5–54)	0.80[c]	n = 252; 53 (49–57)	n = 10; 54 (51–58)	0.61[c]
LVEF, %, median (IQR)	n = 228; 60 (55–60)	n = 13; 55 (55–58)	0.01[c]	n = 360; 55 (47–60)	n = 15; 47 (40–55)	0.006[c]
LAAV, cm/s, median (IQR)	n = 287; 0.42 (0.29–0.58)	n = 15; 0.3 (0.15–0.73)	0.07[c]	n = 449; 0.48 (0.3–0.7)	n = 18; 0.36 (0.21–0.85)	0.32[c]

Abbreviations: see TABLES 1 and 2

TABLE 4 Univariable regression analysis in women and men of risk factors for left atrial appendage thrombus occurrence

Variable	Women			Men		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Heart failure	2.69	1.09–6.63	0.03	7.21	3.29–15.82	<0.001
Hypertension	1.20	0.40–3.62	0.75	1.47	0.62–3.48	0.38
Age	1.06	1.01–1.12	0.02	1.05	1.02–1.09	0.005
Diabetes mellitus	1.27	0.46–3.53	0.65	3.97	1.87–8.84	<0.001
Stroke/TIA /peripheral embolism	1.17	0.26–5.20	0.84	1.80	0.53–6.18	0.35
Vascular disease	1.77	0.22–14.23	0.59	1.30	0.17–10.03	0.80
Nonparoxysmal AF	9.70	2.24–41.97	<0.001	8.45	1.20–35.81	0.004
eGFR <60 ml/min/1.73 m^2	1.49	0.63–3.51	0.36	3.86	1.81–8.23	0.001
Reduced NOAC dose	2.63	0.989–7.001	0.05	0.55	0.07–4.1	0.56

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulants; OR, odds ratio; others, see **TABLES 1** and **2**

TABLE 5 Receiver operating curve analysis for predicting left atrial appendage thrombus in women

Variable	AUC	95% CI	*P* value	Cutoff value	Youden index	True positives	False positives	False negatives	True negatives	Sensitivity	Specificity
$CHADS_2$	0.580	0.460–0.700	0.19	2	0.134	12	188	10	269	0.545	0.589
CHA_2DS_2VASc	0.586	0.462–0.700	0.14	2	0.116	22	404	0	53	1.00	0.116
CHA_2DS_2VASc–RAF	0.775	0.675–0.875	<0.001	10	0.394	13	90	9	367	0.591	0.803
R_2CHADS_2	0.592	0.476–0.708	0.12	2	0.144	17	279	5	165	0.773	0.372

Abbreviations: AUC, area under the curve; others, see **TABLE 1**

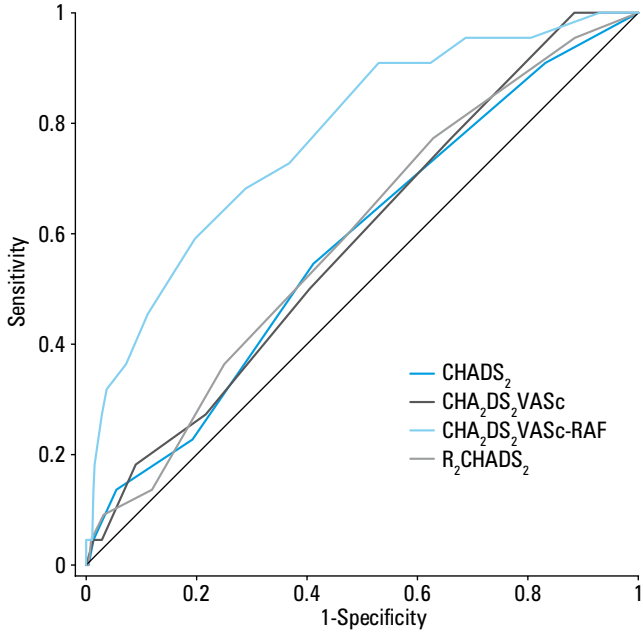

FIGURE 1 Receiver operating curves for predicting left atrial appendage thrombus in women according to different thromboembolic risk scores
Abbreviations: see **TABLE 1**

The guidelines of the European Society of Cardiology indicated that the type of AF does not affect the thromboembolic risk. However, some studies on this issue have been recently published. Dimitrova et al[23] conducted a systematic overview of epidemiological studies on thromboembolic risk depending on the duration of AF, which were published in the MEDLINE and PubMed in the years 2005–2019. The authors emphasized a relatively low number of relevant studies, which may be due to methodological reasons (difficulty in a reliable assessment of the incidence of paroxysmal AF, which may be asymptomatic and thus underestimated or, on the other hand, it may recur frequently, resulting in a relatively long duration of arrhythmia). Importantly, in a meta-analysis of 12 studies including a total of 99 996 patients, Ganesen et al[24] confirmed that the thromboembolic risk is higher in patients with nonparoxysmal than paroxysmal AF. Interesting conclusions were also reported in a retrospective study by Go et al.[25] They assessed the thromboembolic risk in patients with paroxysmal AF depending on the total arrhythmia time. The patients with a longer total time of AF episodes had a higher risk of nonischemic stroke.

Study limitations First, we could only indirectly identify the factors predisposing the patients with AF to thromboembolic complications by using LAAT as a surrogate end point. However, as the source of embolism in patients with AF is most often the LAA, the presence of LAAT can be considered a good surrogate for thromboembolic complications. A second limitation of the study is its restrictive nature. For example, detailed echocardiographic data (eg, LAAV, LVEF) were not available for all subjects, and hence, they could not be included in the multivariable analysis. Another limitation was the inability to determine the AF burden. In particular, the duration of arrhythmia in the patients was unknown, which

TABLE 6 Receiver operating curve analysis for predicting left atrial appendage thrombus in men

Variable	AUC	95% CI	*P* value	Cutoff value	Youden index	True positives	False positives	False negatives	True negatives	Sensitivity	Specificity
$CHADS_2$	0.726	0.639–0.812	<0.001	2	0.387	21	252	8	496	0.724	0.663
CHA_2DS_2VASc	0.734	0.644–0.823	<0.001	3	0.441	21	212	8	536	0.724	0.717
$CHA_2DS_2VASc–RAF$	0.786	0.707–0.865	<0.001	7	0.471	22	215	7	533	0.713	0.471
R_2CHADS_2	0.780	0.708–0.853	<0.001	2	0.507	27	308	2	418	0.931	0.576

Abbreviations: see **TABLES 1** and **5**

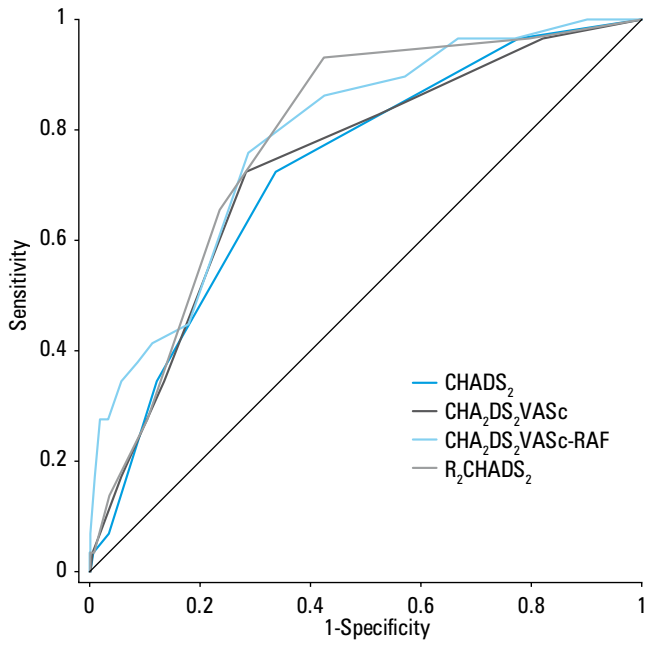

FIGURE 2 Receiver operating curves for predicting left atrial appendage thrombus in men according to different thromboembolic risk scores
Abbreviations: see **TABLE 1**

did not allow us to distinguish between persistent and long-standing persistent AF. The small number of patients with LAAT, the inability to evaluate the frequency of indications for NOAC dose reduction, and the risk of noncompliance were further limitations of the study.

Conclusions LAAT was present with a similar frequency in women and men despite using dabigatran and rivaroxaban. Nonparoxysmal AF was a strong predictor of LAAT in box sexes. Sex-related differences in the risk factors of LAAT and predictive value of thromboembolic risk scores were found. The predictors of LAAT in men were HF, DM, and eGFR below 60 ml/min/1.73 m^2. In women, the highest predictive value of LAAT risk was revealed for CHA_2DS_2-VASc-RAF score, while in men, all the scores had a similar predictive value.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT All authors had full access to all the data in the study and take responsibility for the data integrity and the accuracy of the analysis. ACS, IG, and AKC conceived the concept of the study. All other authors were responsible for the acquisition of data and were involved in the final manuscript preparation.

CONFLICT OF INTEREST IG-G received lecture honoraria from Bayer and Boehringer Ingelheim; AK-C and KJF received lecture honoraria from Bayer, Boehringer Ingelheim, MSD, and Pfizer; GO and BW-K received lecture honoraria from Bayer, Boehringer Ingelheim, and Pfizer. Other authors declare no conflict of interest.

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