Prevalence and predictors of left atrial thrombosis in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants

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ABSTRACT

Background. Few data are available regarding the prevalence of left atrium (LA) thrombi in atrial fibrillation (AF) patients treated with non-vitamin K antagonist oral anticoagulants (NOACs).

Methods. We evaluated the prevalence and predictors of LA/LA appendage (LAA) thrombi in non-valvular AF patients treated with NOACs referring to a single center for a scheduled electrical cardioversion (ECV) or catheter ablation (CA). Transesophageal echocardiography (TEE) was performed within 12 hours prior to the index procedure.

Results. 352 consecutive patients with non-valvular AF treated with NOACs were included in the present analysis (ECV group n = 176, CA group n = 176) between 2013 and 2018. 85 patients (24.2%) were on dabigatran, 150 (42.7%) on rivaroxaban, 104 (29.6%) on apixaban and 13 (3.7%) on edoxaban. A LA/LAA thrombus was detected by TEE in 27 (7.7%) patients, 18 in the ECV group and 9 in the ablation group; 18 (5.1%) patients presented dense LA/LAA spontaneous echo contrast (SEC). Predictors of LA/LAA thrombi were a CHA_2DS_2-VASc score > 3 (OR 4.54, 95% CI 1.50 – 13.70, p-value 0.007) and obesity (OR 6.01, 95% CI 1.95 – 18.50, p-value 0.001).

Conclusion. Among real-world patients with non-valvular AF treated with NOACs, we found a high incidence of LA/LAA thrombi compared to previous reports. The main predictors of LA/LAA thrombosis were a CHA_2DS_2-VASc score > 3 and obesity.

Keywords: atrial fibrillation, thrombi, NOAC, VKA.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and its prevalence in the general population is predicted to rise steeply in the coming years.[1,2] Oral anticoagulation with vitamin K antagonists (VKAs) was shown to reduce the incidence of AF-related stroke by 64% compared to control or placebo and proved to be superior to antiplatelet agents therapy regarding stroke prevention;[3] nonetheless, recent studies and randomized trials demonstrating a more favorable risk/benefit trade-off for non-vitamin K antagonist oral anticoagulants (NOACs) than VKAs laid the ground for NOACs' widespread use.[4]

Besides antithrombotic therapy, restoring and maintaining sinus rhythm remains crucial in AF management and synchronized electrical cardioversion (ECV) represents an effective way to convert AF to sinus rhythm.[5] An alternative treatment aimed at maintaining SR in AF patients is the invasive isolation of the pulmonary veins by means of catheter ablation (CA), which is generally pursued after failure or intolerance to antiarrhythmic therapy. [6,7]. Both ECV and CA carry an inherent risk of stroke and systemic embolism in non-anticoagulated patients and current guidelines recommend routine effective anticoagulation before and after these procedures accordingly.[5,8,9]

Despite the considerable systemic embolism risk reduction provided by VKAs and NOACs in AF patients undergoing ECV or CA, the incidence of left atrial/left atrial appendage (LA/LAA) thrombi in patients on VKAs ranges between 0.6 and 7% [10] and is not negligible in patients on NOACs as well. [11,12] Nevertheless, the rate of clinically significant thromboembolic events is low, standing at 0.5%-1% for patients treated with either VKAs or NOACs.[13]

The aim of the present study was to assess the prevalence and patients' characteristics associated with the detection of LA/LAA thrombi at the transesophageal echocardiography (TEE) performed before scheduled ECV or CA for AF in NOACs-treated patients.

METHODS

This was a monocentric, retrospective study including consecutive adult patients (≥ 18 years old) treated with NOACs (apixaban, dabigatran, edoxaban or rivaroxaban) for non-valvular AF admitted to the Division of Cardiology of Città della Salute e della Scienza Hospital (Turin, Italy) for a scheduled ECV or CA from January 2013 to December 2018. Patients underwent TEE within 12 hours before the index procedure, according to the Center protocol.

Patients were excluded if at least one of the following criteria were met: AF due to a reversible cause (i.e. hyperthyroidism, infection, transient perioperative AF), mitral stenosis or mechanical prosthetic heart valve, need for aspirin > 100 mg/day or dual antiplatelet therapy, active liver disease, pregnancy, stroke within 14 days, evidence of LA/LAA thrombi in the prior 3 months, off-label NOAC dosages and non-compliance to NOAC therapy (Figure 1).

AF was categorized as paroxysmal (if self-terminating or cardioverted within 7 days), persistent (if lasting longer than 7 days) and long-standing persistent AF (continuous AF lasting ≥ 1 year when it is decided to adopt a rhythm control strategy) according to current AF guidelines.[5]

Baseline characteristics. Clinical characteristics of the included patients were retrospectively collected. The cardiovascular risk profile for each patient was evaluated based on the presence of hypertension, obesity (BMI ≥ 30 kg/m^2), smoking (within the last 20 years), family history of cardiovascular diseases, CHA_2DS_2-VASc score (2 points for history of stroke or age ≥ 75 years, 1 point each for age 65 to 74 years, history of hypertension, diabetes mellitus, heart failure, vascular disease and female sex) [14] and HAS-BLED score (1 point each for hypertension, abnormal renal

function, abnormal liver function, history of stroke, prior major bleeding or predisposition to bleeding, labile INR, elderly [>65 years], drugs predisposing to bleeding, alcohol use). [15]

Admission treatment. In accordance to current guidelines oral anticoagulation treatment with a NOAC [dabigatran (110 mg or 150 mg BID), rivaroxaban (15 mg or 20 mg OD), apixaban (2.5 mg or 5 mg BID), edoxaban (30 mg or 60 mg OD)] was started ≥ 3 weeks before the scheduled procedure.[5] In patients scheduled for CA, NOACs were last administered the day before the procedure, as per Center protocol. NOACs were regularly assumed after the procedure, at the scheduled time, after at least 3 hours from sheath removal and achievement of regular hemostasis.

Imaging. Transthoracic echocardiography was performed on admission in all patients to evaluate left ventricular ejection fraction (LVEF) and LA size [volume (ml/m^2)]; echocardiographic measurements were performed according to current recommendations.[16] Reduced LVEF was defined as LVEF < 50%; dilated LA was defined as LA volume > 34 ml/m^2. TEE was performed in all patients within 12 hours before the scheduled procedure to determine the presence of atrial thrombi in LA/LAA, spontaneous echo contrast (SEC), LAA flow velocity (cm/s) and LAA morphology (windsock, chicken wing, cauliflower, cactus). The cine loops of the LA and LAA were examined for the presence of thrombi or dense SEC, which was defined as SEC ≥ 3+ (“intense echo density and very slow swirling patterns in the LAA, usually with similar density in the main cavity”), according to the scoring system previously proposed by Fatkin et al.[17]

Follow-up. Patients with LA/LAA thrombi or dense SEC at TEE did not undergo the scheduled procedure and were switched to VKAs with a target INR of 2.0 to 3.0, as per Center protocol; after 30 days of VKAs therapy with INR in therapeutic range, all these patients underwent a second TEE procedure to assess the potential persistence of LA/LAA thrombi or dense SEC. Cerebral ischemic

events (strokes or transient ischemic attacks) occurrence during this 30-days period was recorded as well.

Statistical analysis

Continuous data were reported as mean and standard deviations (SD); categorical variables as absolute numbers and percentages. Baseline clinical and echocardiographic characteristics of patients with and without LA/LAA thrombi at TEE, both in the overall population and in the two individual ECV and CA groups, were compared by means of one-way ANOVA and chi-squared test for continuous and categorical variables, respectively. A multivariate logistic regression analysis was performed to determine independent predictors of LA/LAA thrombi in the overall population and in the two separate ECV and CA groups. Variables with a univariate p-value < 0.10 or presenting clinical relevance were entered into the model. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

As sensitivity analyses, baseline characteristics of patients with LA/LAA thrombi or dense SEC were compared to the remainder and independent predictors of LA/LAA thrombosis or dense SEC were determined by logistic regression; these analyses were performed addressing both the overall population and the ECV and CA groups separately.

A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Baseline features

Between January 2013 and December 2018, 1215 consecutive non-valvular AF patients were referred to our center for a scheduled ECV or CA. After patients' exclusion according to pre-specified criteria, a total of 352 patients on NOACs (ECV, n=176; CA, n = 176) were included in the present analysis. Table 1 reports clinical and echocardiographic characteristics of the study population. Mean age was 64.9 ± 9.9 years; 92 (26.1%) patients were female, 67 (19.0%) were obese. 85 (24.2%) patients were on dabigatran, 150 (42.7%) on rivaroxaban, 104 (29.6%) on apixaban, and 13 (3.7%) on edoxaban (Table 2). Overall, 58 patients (16.5%) were receiving a low dose of NOAC.

Prevalence and predictors of atrial thrombosis

LA/LAA thrombosis was found at pre-procedural TEE in 27 (7.7%) patients, 18 (10.2%) in the ECV subgroup and 9 (5.1%) in the CA subgroup; among these, 6 (22.2%) patients were anticoagulated with dabigatran 12 (44.4%) with rivaroxaban, 6 (22.2%) with apixaban and 3 (11.1%) with edoxaban (Table 2).

At univariate analysis, clinical characteristics associated to LA/LAA thrombosis (Table 1) were older age, obesity, a history of stroke/TIA, a higher CHA_2DS_2-VASc score and a lower LAA velocity. After adjustment by multivariate analysis (Table 3), significant predictors of LA/LAA thrombi were a CHA_2DS_2-VASc score > 3 (OR 4.54, 95% CI 1.50 – 13.70, p-value 0.007) and obesity (OR 6.01, 95% CI 1.95 – 18.50, p-value 0.001).

ECV group and CA group. Patients scheduled for ECV were on average older than patients referred for CA, more commonly had a history of HF and suffered from arterial hypertension, leading to an overall higher mean CHA_2DS_2-VASc score (Table S1). Moreover, at echocardiography, patients

referred for ECV presented lower LVEF, a higher LA volume and lower LAA velocity. Nevertheless, ECV and CA patients did not differ significantly in the incidence of LA/LAA thrombus finding at pre-procedural TEE. After adjustment by logistic regression, predictors for LA/LAA thrombosis in ECV subgroup were CHA_2DS_2-VASc score > 3, obesity and lower LAA velocity, while higher LA volume represented a predictor in CA subgroup (Table 3).

Sensitivity analysis

At pre-procedural TEE the composite of LA/LAA thrombosis or dense SEC was observed in 45 patients, with 18 (5.1%) patients presenting only dense SEC (6.8% in ECV group vs. 3.4% in CA group); the composite outcome was more common in patients scheduled for ECV.

Female sex, a history of HF, hypertension, a higher CHA_2DS_2-VASc score and AF/AFL at TEE were more frequent in patients with LA/LAA thrombosis or dense SEC. Moreover, at echocardiography ECV patients with LA/LAA thrombosis or dense SEC were more likely to have lower LVEF, a higher LA volume and lower LAA velocity. At logistic regression analysis significant predictors of LA/LAA thrombi or dense SEC were a CHA_2DS_2-VASc score > 3 (OR 5.27, 95% CI 2.01 – 13.84), obesity (OR 5.49, 95% CI 1.99 – 15.16) and lower LAA velocity (OR 1.03, 95% CI 1.01-1.08). At multivariate analysis predictors of LA/LAA thrombi and dense SEC stratified by scheduled procedure confirmed data from the main analysis. Full details regarding the sensitivity analysis are reported in Table S2.

As per Center protocol, all the 27 patients with LA/LAA thrombus and the 18 patients with dense SEC were switched to VKAs therapy; after 30-days of adequate anticoagulation (INR between 2.0 and 3.0) no patients presented LA/LAA thrombi or dense SEC and none of them suffered cerebral ischemic events during the 30 day-follow-up period.

DISCUSSION

The aim of the present study was to assess the prevalence and predictors of LA/LAA thrombi in non-valvular AF patients anticoagulated with NOACs.

A LA/LAA thrombus was detected in 7.7% of AF patients on NOACs in the present analysis; factors associated with LA/LAA thrombosis were CHA_2DS_2-VASc score > 3 and obesity in the overall population, CHA_2DS_2-VASc score > 3, obesity and lower LAA velocity in the ECV group and higher LA volume in the CA group.

VKAs have been the cornerstone of AF antithrombotic therapy for many years. Despite VKAs' efficacy in reducing stroke and systemic embolism risk down to 0.82-2.63% per 100 person-years, [18] the rate of LA/LAA thrombi detection before ECV or CA is not trivial in VKAs-treated patients. [13,19] Likewise, albeit the incidence of thromboembolic events is less than 1% in patients on NOACs undergoing ECV for AF,[20] the prevalence of LA/LAA thrombi ranges between 0.6% and 7% in these same patients cohorts.[10]

In our study the overall incidence of LA/LAA thrombi in NOAC-treated individuals was notable, standing at 7.7% in the overall population. The numerically higher incidence of LA/LAA thrombi found in the ECV group compared to the CA group (10.2% vs. 5.1%) might be predominantly due to the different thromboembolic risk profile (CHA_2DS_2-VASc 2.67 ± 1.5 vs. 1.99 ± 1.15) and baseline clinical features of these two populations, with patients scheduled for ECV being on average older and presenting a higher incidence of hypertension and heart failure.

A CHA_2DS_2-VASc score > 3 was associated with higher risk of LA/LAA thrombosis at multivariate analysis. While this result may appear obvious at first glance, it must be recalled that the CHA_2DS_2-VASc score was developed to predict the risk of stroke which does not invariably depend upon the presence of LA/LAA thrombi. The ability of the CHA_2DS_2-VASc score to predict LA/LAA thrombosis

in the present analysis provides indirect evidence regarding the link between LA/LAA thrombi and stroke in AF patients and further emphasizes the paramount role of the CHA_2DS_2-VASc score in stroke risk assessment as well as in the evaluation of the LA/LAA thrombi formation risk.

Alongside the CHA_2DS_2-VASc score, obesity was found to be an independent predictor of LA/LAA thrombosis. Obesity has become a worldwide pandemic and its importance as a risk factor for AF has been widely underscored in the recent 2020 AF European Society of Cardiology guidelines and weight loss in conjunction with healthy lifestyle modifications have become an integral part of the treatment of AF patients.[5] Besides, obesity has long been known to increase thrombosis risk due to several multifaceted mechanisms, including chronic inflammation, impaired fibrinolysis and altered expression of adipokines and microRNAs.[21] Conversely, the association between obesity and thromboembolic stroke in the AF population has been only marginally explored, with a previous study by Overvad et al. suggesting that obesity itself might be a risk factor for cerebrovascular events or death in AF patients even after adjustments for the CHA_2DS_2-VASc score. [22] Obesity was able to predict LA/LAA thrombosis in the present study, thus stressing the key role of overweight in thrombus formation risk and its potential association with thromboembolic events. As patients at the extremes of the weight spectrum were underrepresented in NOACs clinical trials [23] and may prove a challenge for NOACs' regular pharmacokinetics and efficacy, the result of the present study highlights the need for future studies specifically addressing this issue.

Interesting data were derived from the multivariate analyses according to the individual interventions. The key role of high CHA_2DS_2-VASc score and obesity in LA/LAA thrombosis was confirmed in the ECV population; also, low LAA velocity was associated with higher risk of LA/LAA thrombosis or dense SEC in this population, which can be easily explained based on the Virchow's triad, with blood slow flow being a major determinant of thrombi formation.[24] As for CA patients, dilated LA was associated with greater risk of LA/LAA thrombosis; albeit this result may

be explained by Virchow's triad as well, one could wonder why slow LAA velocity could not predict LA/LAA thrombosis in this population; however, the sample size of the CA population, mainly consisting of an overall healthier population with higher mean LAA velocities compared to the ECV population, might not be large enough to accurately describe such association. A recent study also reported that LA dilation and LVEF reduction synergically increase the risk of LA/LAA thrombosis, thus supporting the results of the present study.[25] Data from the sensitivity analyses considering the presence of both LA/LAA thrombi and dense SEC as the primary outcome were consistent with the results of the primary analyses.

It is noteworthy that all the 27 patients with LA/LAA thrombosis on NOACs at the TEE examination no longer presented LA/LAA thrombi after one month of VKAs therapy in therapeutic range. Indeed, albeit NOACs efficacy has been widely assessed in randomized trials,[4] their potency in populations excluded from validation studies is unknown; moreover, the administration of fixed doses of NOACs in all patients may be inadequate, as exemplified by the risk of potential underdosing in obese patients.[26] Could the greater effectiveness of VKAs in dissolving LA/LAA thrombi resistant to NOACs therapy be due to the possibility of assessing VKAs' efficacy by means of INR monitoring and consequent patient-tailored drug dosing? Plasma tests for NOACs' anticoagulation levels assessment are not uniformly standardized and are not routinely used in clinical practice. As for dabigatran, the activated partial thromboplastin time (aPTT) provides only a qualitative assessment of its anticoagulant activity, while the thrombin time (TT) is very sensitive and a normal TT excludes even very low dabigatran plasma concentrations; nevertheless, the TT is not suited for the quantitative assessment of dabigatran plasma concentrations expected in the clinical range. Anti-Factor-X-activated (FXa) chromogenic assays are available to measure plasma concentrations of the FXa inhibitors (Rivaroxaban, Apixaban and Edoxaban) using validated calibrators providing acceptable inter-laboratory precision for low and high plasma drug levels; the

absence of anti-FXa activity with these assays excludes clinically relevant plasma concentrations of FXa inhibitors.[27]

In view of the disproportion between the high rate of LA/LAA thrombosis and the rarer occurrence of thromboembolic events, the clinical impact of LA/LAA thrombi and dense SEC still remains to be defined. Notably, thromboembolic events may occur even in the absence of LA/LAA thrombi and the role of extra-cardiac sources of emboli such as the aortic arch and the carotid arteries, which are more difficult to evaluate by trans-thoracic and trans-oesophageal echocardiography, should be taken into account.[28]

LIMITATIONS

We must acknowledge several limitations. First, this was a single center observational study; however, our purpose was to provide data derived from a real-world experience and the observational nature of the study allowed for a better representation of real-life clinical setting. NOACs were used at the discretion of the treating physician; moreover, comparisons among NOACs should be interpreted with caution since they are also biased by small sample sizes, especially for edoxaban, and analyses were not stratified for different molecules. Data on oral anticoagulation duration treatment prior to the scheduled procedure were not available, and this might have affected the study results. Unmeasured confounding variables may have altered the study results, despite adjusted statistical models were used to reduce this risk; nevertheless, these results should be interpreted as descriptive and hypothesis-generating.

CONCLUSIONS

Among real-world patients with non-valvular AF treated with NOACs, we found a high incidence of LA/LAA thrombi compared to previous reports. The main predictors of LA/LAA thrombosis were CHA_2DS_2-VASc score > 3 and obesity.

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TABLES

Table 1. Clinical and echocardiographic characteristics of study patients and univariate analysis

	Overall (n = 352)	Non-thrombi group (n = 325)	Thrombi group (n = 27)	p-value
Age (years)	64.9 ± 9.9	64.6 ± 10.1	69.1 ± 7.3	**0.023**
Female sex	92 (26.1%)	83 (25.5%)	9 (33.3%)	0.376
BMI (kg/m^2)	27.1 ± 4.3	27.0 ± 4.2	28.0 ± 5.2	0.230
Obesity	67 (19.0%)	58 (17.8%)	9 (33.3%)	**0.049**
Hypertension	261 (74.1%)	237 (72.9%)	24 (88.9%)	0.069
Smoking history	101 (28.7%)	94 (28.9%)	7 (25.9%)	0.961
COPD	30 (8.5%)	28 (8.6%)	2 (7.4%)	0.980
Heart failure	44 (12.5%)	38 (11.7%)	6 (22.2%)	0.405
Diabetes mellitus	46 (13.1%)	41 (12.6%)	5 (18.5%)	0.328
Dyslipidemia	124 (35.2%)	111 (34.2%)	13 (48.1%)	0.990
Known PAD	26 (7.4%)	22 (6.8%)	4 (14.8%)	0.125
Previous stroke/TIA	38 (10.8%)	32 (9.8%)	6 (22.2%)	**0.046**
CHA_2DS_2-VASc	2.3 ± 1.4	2.26 ± 1.4	3.22 ± 1.4	**< 0.001**
CHA_2DS_2-VASc > 3	69 (19.6%)	57 (17.5%)	12 (44.4%)	**0.001**
Thyroid disease	60 (17.1%)	58 (17.9%)	2 (7.4%)	0.383
AF/AFl at TEE	275 (78.1%)	250 (76.9%)	25 (92.6%)	0.058
LVEF (%)	58.5 ± 8.8	58.8 ± 8.6	54.5 ± 10.5	**0.014**
LA volume (ml/m^2)	46.0 ± 14.6	45.6 ± 14.4	50.6 ± 15.9	0.111
LAA velocity (cm/s)	45.4 ± 21.5	46.7 ± 21.5	31.2 ± 14.8	**0.001**
Indication				0.071
ECV	176 (50.0%)	158 (89.8%)	18 (10.2%)	
CA	176 (50.0%)	167 (94.9%)	9 (5.1%)	

Legend: AF/AFl: atrial fibrillation/atrial flutter; BMI: body mass index; CA: catheter ablation; ECV: electrical cardioversion; LA: left atrium; LAA: left atrial appendage; LVEF: left ventricular ejection fraction; PAD: peripheral artery disease; SEC: spontaneous echo contrast; TIA: transient ischemic attack.

Table 2. Distribution of NOAC molecules and respective prevalence of LA/LAA thrombi

Type of NOAC	Overall (n = 352)	Non-thrombi (n = 325)	Thrombi (n = 27)
Dabigatran	85 (24.2%)	79 (24.3%)	6 (22.2%)
110 mg	39	36	3
150 mg	46	43	3
Rivaroxaban	150 (42.7%)	138 (42.5%)	12 (44.4%)
15 mg	9	8	1
20 mg	141	130	11
Apixaban	104 (29.6%)	98 (27.9%)	6 (22.2%)
2.5 mg	7	7	0
5 mg	97	91	6
Edoxaban	13 (3.7%)	10 (3.1%)	3 (11.1%)
30 mg	3	1	2
60 mg	10	9	1

Legend: LA/LAA: Left atrium/left atrium appendage; NOAC: Non-vitamin K antagonist Oral Anticoagulants

Table 3. Multivariate analysis for predictors of LA/LAA thrombi

	Overall		
	OR	95% CI	p-value
LVEF	0.97	0.93 – 1.02	0.245
LAA velocity (cm/s)	0.97	0.94 – 1.00	0.058
LA volume (ml/m2)	1.01	0.98 – 1.05	0.563
Obesity	6.01	1.95 – 18.50	**0.002**
CHA_2DS_2-VASc > 3	4.54	1.50 – 13.70	**0.007**
	ECV group		
LVEF	0.97	0.92 – 1.02	0.246
LAA velocity (cm/s)	0.95	0.90 – 0.99	**0.040**
Obesity	10.60	2.41 – 46.60	**0.002**
CHA_2DS_2-VASc > 3	10.75	2.60 – 44.37	**0.001**
	CA group		
LAA velocity (cm/s)	0.99	0.95 – 1.04	0.756
LA volume (ml/m2)	1.07	1.01 – 1.14	**0.025**
Obesity	0.86	0.07 – 10.58	0.908

Legend: ECV: electrical cardioversion; LA/LAA: Left atrium/left atrium appendage; LVEF: left ventricular ejection fraction; OR: odds ratio

FIGURES

Fig. 1 Flow diagram of the study design

Legend. AF: atrial fibrillation; ECV: electrical cardioversion; LA/LAA: Left atrium/left atrium appendage; NOAC: Non-vitamin K antagonist Oral Anticoagulants