Association of Left Atrial Appendage Morphology and Function With Stroke and Transient Ischemic Attack in Atrial Fibrillation Patients

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We aimed to correlate left atrial appendage (LAA) structure and function with the history of stroke/transient ischemic attack (TIA) in patients with atrial fibrillation (AF). We analyzed the data of 649 patients with AF who were scheduled for catheter ablation. Patients underwent cardiac computed tomography and transesophageal echocardiography before ablation. The LAA morphologies depicted by cardiac computed tomography were categorized into 4 groups: cauliflower, chicken wing, swan, and windsock shapes. The mean age was 61.3 ± 10.5 years, 33.9% were women. The prevalence of stroke/TIA was 7.1%. After adjustment for the main risk factors, the LAA flow velocity ≤35.3 cm/s (odds ratio [OR] 2.18, 95% confidence interval [CI] 1.09 to 4.61, p = 0.033) and the swan LAA shape (OR 2.69, 95% CI 0.96 to 6.86, p = 0.047) independently associated with a higher risk of stroke/TIA, whereas the windsock LAA morphology proved to be protective (OR 0.32, 95% CI 0.12 to 0.77, p = 0.017) compared with the cauliflower LAA shape. Comparing the differences between the LAA morphology groups, we measured a significantly smaller LAA orifice area (389.3 ± 137.7 mm^2 in windsock vs 428.3 ± 158.9 ml in cauliflower, p = 0.021) and LAA volume (7.4 ± 3.0 mm^2 in windsock vs 8.5 ± 4.8 mm^2 in cauliflower, p = 0.012) in patients with windsock LAA morphology, whereas the LAA flow velocity did not differ significantly. Reduced LAA function and swan LAA morphology were independently associated with a higher prevalence of stroke/TIA, whereas the windsock LAA shape proved to be protective. Comparing the differences between the various LAA morphology types, significantly lower LAA volume and LAA orifice area were measured in the windsock LAA shape than in the cauliflower LAA shape. **(Am J Cardiol 2024;221:37−43)**

Keywords: atrial fibrillation, cardiac computed tomography angiography, left atrium, stroke

Atrial fibrillation (AF) is the most prevalent type of sustained cardiac arrhythmia with clinical relevance, which affects 33.5 million patients worldwide.[1] Among many other factors, AF is an independent risk predictor of ischemic stroke and transient ischemic attack (TIA), with almost a 5-fold increase in stroke risk, as reported in the Framingham Study.[2] Moreover, 1/3 of the patients with ischemic stroke have been found to have either clinical or subclinical AF.[3] Previous studies reported that LAA morphology correlates with stroke/TIA in patients with AF.[4−6] Cardiac computed tomography (CT) is commonly used for the visualization of left atrial (LA) anatomy in patients who underwent catheter ablation.[7] Besides cardiac CT, transesophageal echocardiographic (TEE) examinations are routinely performed in patients with AF before catheter ablation for the exclusion of LAA thrombus. Moreover, TEE is the gold-standard method for the evaluation of LAA flow velocity, which is a surrogate of LAA function. In this study, we hypothesized that the type of LAA morphology and LAA function were related to the risk of previous stroke/TIA. Accordingly, we analyzed geometry, dimensions, and flow velocity values of the LAA using cardiac CT and TEE examinations in patients with AF.

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See page 42 for Declaration of Competing Interest.

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Methods

The study population consisted of 649 patients with drug-refractory AF who underwent cardiac CT before catheter ablation in the Heart and Vascular Center of Semmelweis University, Budapest, Hungary between 2014 and 2017. Exclusion criteria were age under 18 years, nondiagnostic image quality of CT, repeated ablation, and patients in whom the assessment of LAA flow velocity was not feasible. Those without data on the history of stroke/TIA were also excluded from the analysis. History of stroke/TIA was collected from the patients' chart reviews.

Cardiac CT examinations were performed with a 256-slice scanner (Brilliance Ict 256, Philips Healthcare, Best, The Netherlands) with prospective electrocardiogram-triggered axial acquisition mode. For cardiac CT, 100 to 120 Kv with 200 to 300 mAs tube current was used depending on patient anthropometrics. Image acquisition was performed with 128- × 0.625-mm detector collimation and 270-ms gantry rotation time. For heart rate control, a maximum of 50 to 100 mg metoprolol was given orally and 5 to 20 mg intravenously, if necessary. Iomoprol contrast material (Iomeron 400, Bracco Ltd, Milan, Italy) was used with 85 to 95 ml contrast agent at a flow rate of 4.5 to 5.5 ml/s through an antecubital vein by way of an 18-gauge catheter, using a 4-phasic protocol. Bolus tracking in the left atrium was used to obtain proper scan timing. A total of 0.8 mg sublingual nitroglycerin was given between the native and CT angiography acquisitions. CT data sets were reconstructed with 0.8-mm slice thickness and 0.4-mm increment.

After defining the LA and LAA borders with caution to the orifices of the pulmonary veins and the level of the mitral valve, we measured the LA and LAA volumes and determined the LAA morphologies based on 3-dimensional volume-rendered images using a semiautomated software package (EP Planning, Philips IntelliSpace Portal, Philips Healthcare). Because assessment of the LAA morphology can be highly subjective, the LAA morphologies were determined by consensus reading of 3 expert readers using rigorous definitions to minimize interobserver variability. The LAA morphologies were classified in 4 different types, as previously described: (1) cauliflower if the LAA has limited length and the distal width exceed the proximal width, (2) windsock if the primary structure is 1 dominant lobe with sufficient length, (3) chicken wing if the dominant lobe has an obvious bend in the proximal or middle part, and (4) swan if the LAA has a second sharp curve folding the dominant lobe back.[8] Representative examples are provided in Figure 1.

A maximum of 24 hours before ablation, all patients underwent TEE examination to exclude the presence of LAA thrombus. Ie33 and Epiq 7C (Philips Medical System, Andover, Massachusetts) systems equipped with S5-1 phased array and × 7 to 2-t matrix TEE transducers were used. TEE was performed during conscious awake sedation. The LAA was imaged from 0°, 45°, 90°, and 135° views to detect spontaneous echo contrast, sludge, or thrombus. Subsequently, a sample volume was placed at the middle portion of the LAA and the peak velocity of the outflow of the LAA was measured.

Categorical variables are expressed as frequencies (percentages), and continuous values are expressed as mean ± SD. The normality of continuous parameters was tested with Shapiro−Wilk test. Tests for significance were conducted using Mann−Whitney−Wilcoxon or Kruskal−Wallis tests for continuous variables and Pearson's chi-square or Fisher's exact tests (if 5 or less observations were included) for categorical variables. The odds ratio (OR) and 95% confidence interval (CI) values of stroke/TIA were computed using univariate and multivariate logistic regression analyses. In the multivariate model, adjustment was made for CHA_2DS_2-VASc score risk factors, such as, heart failure, left ventricular systolic dysfunction (defined as left ventricular ejection fraction <50%), blood pressure >140/90 mm Hg or antihypertensive therapy, age >65 years, diabetes mellitus, peripheral vasculopathy, obstructive coronary artery disease (defined as >50% luminal stenosis), and female gender. Moreover, obesity (defined as body mass

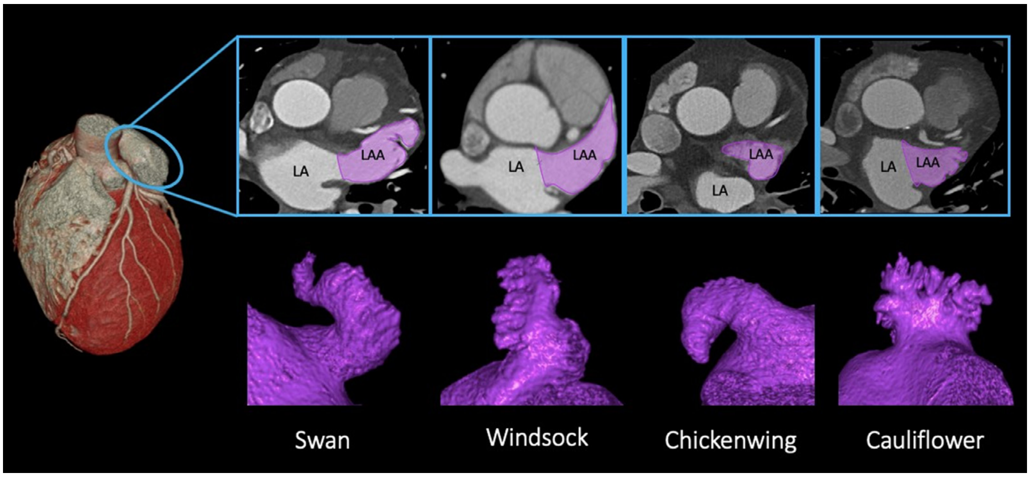

Figure 1. Representative examples of the various LAA morphology categories. LAA morphologies were classified in 4 different types, as previously described: swan if LAA has a second sharp curve folding the dominant lobe back, windsock if the primary structure is one dominant lobe with sufficient length, chicken wing if the dominant lobe has an obvious bend in the proximal or middle part, and cauliflower if the LAA has limited length and the distal width exceeds the proximal width. LA = left atrium.

index >30 kg/m^2), hyperlipidemia, and renal dysfunction (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2) were also included in the model beyond LA and LAA parameters. To avoid collinearity, CHA_2DS_2-VASc score was not included in the multivariate analysis. Receiver operating characteristic curve analysis was performed to determine optimal cut-off points of the LAA orifice area and flow velocity for stroke/TIA based on the Youden index. Differences between the various LAA morphology types were determined using analysis of variance and post hoc Tukey honest significant difference test. All tests were 2-sided and a p <0.05 was considered statistically significant. All analyses were performed using statistical software R (version 3.6.1) and its packages, namely, Proc (version 1.15.3), yarrr (version 0.1.5).

The data underlying this article will be shared upon reasonable request to the corresponding author.

Results

Altogether, 649 patients were included in this retrospective study. The mean age was 61.3 ± 10.5 years, 33.9% were women. Prevalence of previous stroke/TIA was 7.1% in the study population. Altogether, 15 patients (2.3%) had a TIA and 31 (4.8%) had ischemic stroke before the preablational cardiac CT. The prevalence of cauliflower, windsock, chicken wing, and swan morphologies were 50.2%, 32.5%, 12.4%, and 4.8% in patients without previous stroke/TIA versus 63.0%, 13.0%, 8.7%, and 15.2% in those with previous stroke/TIA, respectively (p = 0.002). Demographic and clinical characteristics and LA and LAA measurements of the patients are listed in Figure 2, Supplementary Table 1, and Table 1.

The optimal cut-off point of LAA orifice area was 561.5 mm^2 and 35.3 cm/s for LAA flow velocity (sensitivity,

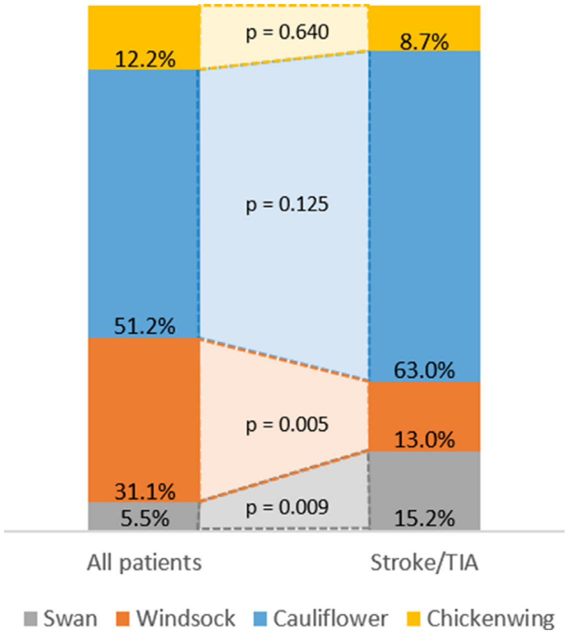

Figure 2. Comparison of LAA morphologies in the whole study group versus in those with previous stroke/TIA. Patients with previous stroke/TIA had significantly higher rate of swan and lower rate of windsock LAA morphology.

specificity, positive predictive value, negative predictive value, and accuracy were 21.7%, 87.3%, 11.5%, 93.6%, and 82.6% for LAA orifice area and 73.9%, 43.3%, 9.0%, 95.6%, and 45.5% for LAA flow velocity, respectively). Univariate and multivariate logistic regression analyses were performed to determine the significant associates of stroke/TIA. In the univariate analysis, hyperlipidemia (OR 2.01, 95% CI 1.07 to 3.72, p = 0.027), heart failure (OR 3.75, 95% CI 1.20 to 9.88, p = 0.012), left ventricular ejection fraction <50% (OR 2.26, 95% CI 1.02 to 4.61, p = 0.032), LAA flow velocity ≤35.3 cm/s (OR 2.16, 95% CI 1.13 to 4.43, p = 0.026), and swan LAA morphology (OR 2.52, 95% CI 0.95 to 6.00, p = 0.026) were significantly associated with increased risk of stroke/TIA, whereas windsock LAA morphology proved to be protective (OR 0.32, 95% CI 0.12 to 0.73, p = 0.013). After adjustment for the main risk factors, reduced LAA flow velocity (multivariate OR 2.18, 95% CI 1.09 to 4.61, p = 0.033) and swan LAA shape (multivariate OR 2.69, 95% CI 0.96 to 6.86, p = 0.047) were independent associates of stroke/TIA, whereas windsock LAA morphology proved to be protective (multivariate OR 0.32, 95% CI 0.12 to 0.77, p = 0.017). Detailed results of the logistic regression analyses are listed in Table 2.

Comparing the differences between LAA morphology groups, we measured significantly smaller LAA orifice area (389.3 ± 137.7 mm^2 in windsock type vs 428.3 ± 158.9 ml in cauliflower type, p = 0.021) and LAA volume (7.4 ± 3.0 mm^2 in windsock type vs 8.5 ± 4.8 mm^2 in cauliflower type, p = 0.012) in patients with windsock LAA morphology, whereas the LAA flow velocity did not differ significantly between the LAA shape groups. Violin plot diagrams of the differences in LAA parameters between the LAA morphology groups are shown in Figure 3.

Discussion

In our retrospective study of 649 patients with AF, decreased LAA flow velocity and swan LAA morphology were independently associated with an increased risk of stroke/TIA, whereas the windsock LAA shape proved to be protective. Comparing the differences between the various LAA morphologies, significantly lower LAA volume and LAA orifice area were measured with cardiac CT in the windsock LAA shape group than in the cauliflower morphology. The data are limited regarding the association between cardiac structural and functional characteristics and the risk of stroke/TIA in patients with AF. In our study, we investigated the association of cauliflower, chicken wing, swan, and windsock morphologies with cardiac structural and functional characteristics to explore the potential underlying mechanisms of stroke/TIA in patients with AF.

The LAA represents a frequent site of thrombus formation because this part of the heart is prone to dysfunction, structural changes of the endothelium, and abnormal blood stasis and homeostasis.[9] The anatomic morphology of the LAA is highly variable. Previous studies have reported contradictory results regarding the association between LAA morphology and the risk of ischemic stroke. Although Di Biase et al[4] suggested that nonchicken wing morphology might be associated with increased risk of stroke, other

Table 1
Patient characteristics

	All patients (n=649)	No stroke/TIA (n=603)	Stroke/TIA (n=46)	p
Age (years)	61.3±10.5	61.2±10.6	63.0±9.3	0.295
Female, n (%)	220 (33.9%)	208 (34.5%)	12 (26.1%)	0.263
BMI (kg/m^2)	28.8±4.6	28.8±4.6	29.0±4.5	0.722
Hypertension, n (%)	471 (72.6%)	432 (71.6%)	39 (84.8%)	0.059
Hyperlipidemia, n (%)	164 (25.3%)	146 (24.2%)	18 (39.1%)	**0.034**
Diabetes mellitus, n (%)	96 (14.8%)	88 (14.6%)	8 (17.4%)	0.665
Heart failure, n (%)	24 (3.7%)	19 (3.2%)	5 (10.9%)	**0.022**
Valvular disease, n (%)	23 (3.5%)	23 (3.8%)	0 (0.0%)	0.397
Peripheral vasculopathy, n (%)	19 (2.9%)	16 (2.7%)	3 (6.5%)	0.145
Obstructive CAD, n (%)	59 (9.1%)	53 (8.8%)	6 (13.0%)	0.295
eGFR <60 ml/min/1.73m^2	153 (23.6%)	144 (23.8%)	9 (19.6%)	0.592
CHA2DS$_2$-VASc-score >2	102 (15.7%)	67 (11.1%)	35 (76.1%)	**<0.001**
Anticoagulation therapy, n (%)*	430 (66.3%)	389 (64.5%)	41 (89.1%)	**0.001**
LVEF <50%	76 (11.7%)	66 (11.0%)	36 (21.7%)	**0.032**
LA volume (ml)	105.3±31.8	105.1±31.6	107.2±34.4	0.845
LAA volume (ml)	8.0±4.0	7.9±4.0	8.4±4.6	0.810
LAA orifice area (mm^2)	408.9±152.7	407.7±151.7	424.4±166.4	0.520
LAA flow velocity (cm/sec)	35.7±14.8	35.9±14.6	32.9±16.6	0.116
LAA morphology				
Cauliflower, n (%)	332 (51.2%)	303 (50.2%)	29 (63.0%)	**0.002**
Windsock, n (%)	202 (31.1%)	196 (32.5%)	6 (13.0%)	
Chicken wing, n (%)	79 (12.2%)	75 (12.4%)	4 (8.7%)	
Swan, n (%)	36 (5.5%)	29 (4.8%)	7 (15.2%)	

AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

* Anticoagulation status was defined by the use of a direct oral anticoagulant or vitamin K antagonist.

Continuous values are expressed as means±SD and categorical variables are expressed as frequencies.

authors reported that cauliflower morphology is more common in patients with ischemic stroke.[4,5,10] However, these studies categorized LAA morphologies into cauliflower, windsock, chicken wing, and cactus shapes, whereas we used another classification of cauliflower, windsock, chicken wing, and swan morphologies, as previously applied by other authors.[8,11] Our research group has previously investigated the association between LAA morphology and the risk of stroke/TIA in patients with and without AF, where swan LAA morphology was independently associated with previous stroke/TIA in both patient populations.[11] In line with this finding, in our study population of patients with AF, the swan morphology was associated with a more than 2.5-fold risk of stroke/TIA, whereas the windsock morphology decreased this risk by 68%. In this study, we aimed to explore the potential underlying mechanisms responsible for the association between LAA shape and the risk of stroke/TIA. Given the clinical availability of LAA functional data measured by TEE in patients with AF, we focused our study on investigating these associations within this specific patient population.

Although a previous autopsy study of 500 heart specimens has reported that LAA enlargement is an important contributor of stroke/TIA, imaging studies using cardiac CT and cardiovascular magnetic resonance could not confirm this correlation.[4,12] In this study, LAA volume was not directly associated with the risk of stroke/TIA; however, patients with windsock LAA morphology had significantly lower LAA volumes than patients with cauliflower morphology, suggesting that the protective role of windsock LAA shape can be partly explained by the significantly smaller size of this morphology.

LAA flow velocity indexes reflect global LA function.[13] Moreover, it has been reported as a quantitative surrogate parameter for thromboembolic risk because lower LAA flow velocity may cause blood stasis, which is a major cause of thrombus formation.[14] Previous studies concluded that peak LAA filling and emptying velocity differ significantly between patients with and without AF.[15,16] Through a series of studies, the peak LAA emptying velocity was used to measure LAA flow velocity, revealing a significant correlation between reduced peak LAA emptying velocity and an increased risk of stroke.[10,17−20] In line with this finding, LAA flow velocity ≤35.3 cm/s doubled the odds of stroke/TIA in our study population. Although some studies used the velocity of 20 cm/s, other studies applied higher cut-off values of 21.5 and 37 cm/s.[21−25] Because of the lack of a widely accepted threshold in previous studies for determining the stroke risk, in our study, the optimal cutoff for LAA flow velocity was determined using the Youden index to maximize the balance between sensitivity and specificity, providing the best overall diagnostic accuracy. Previous authors also suggested that the role of the various LAA morphologies in the occurrence of TIA/stroke might be because of the differences in LAA orifice sizes and flow velocity between the LAA categories.[17,26] However, when analyzing the mechanisms underlying the differences in stroke/TIA rates between the LAA morphology groups, we

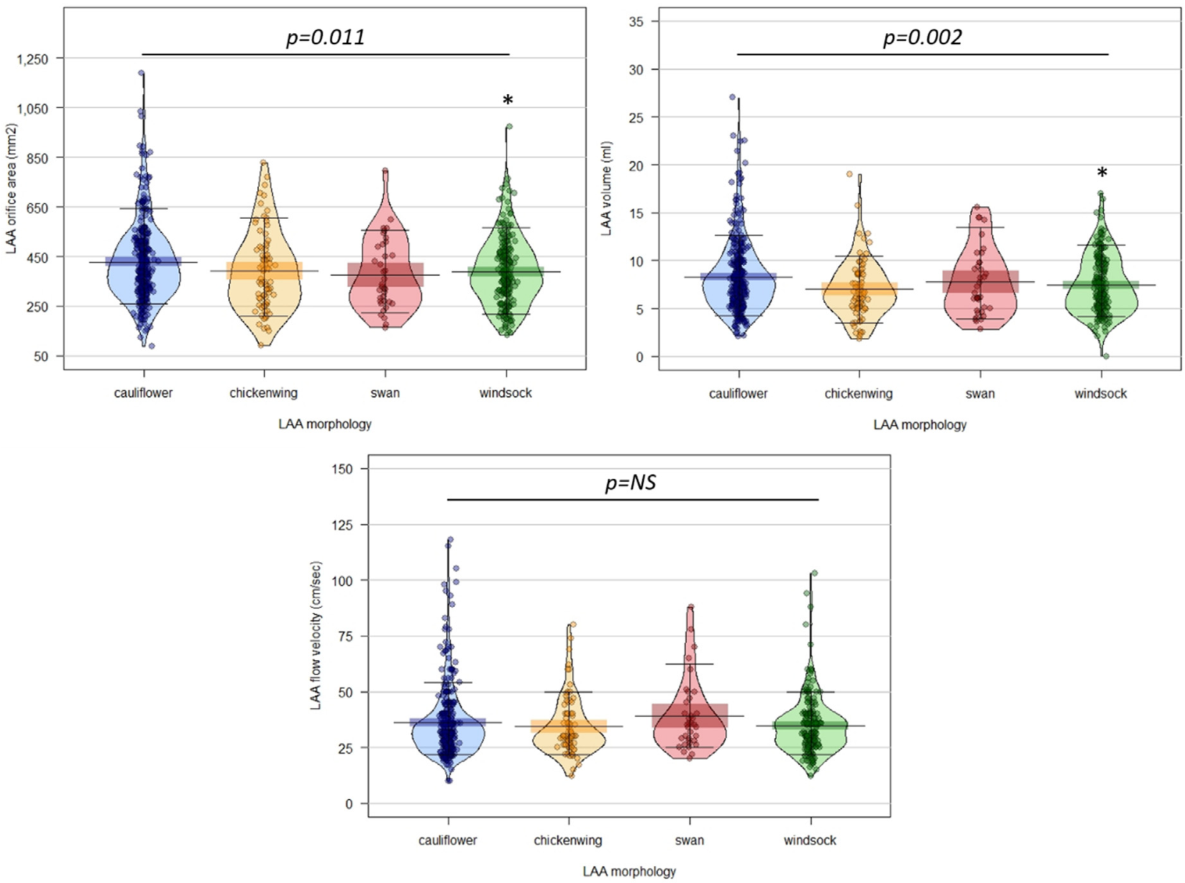

Figure 3. The relation between LAA shape and LAA orifice area, volume, and flow velocity. *p Value <0.05 versus cauliflower type. Violin plots show the probability density of the examined LAA parameters for each LAA morphology category. The line in the middle indicates median, box presents IQR, whiskers show 95% CI, and the shape of the violin displays frequencies of the values.

Table 2
Associates of stroke/TIA

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Age >65 years	1.29	0.71-2.36	0.400	1.30	0.65-2.59	0.456
Female	0.67	0.33-1.29	0.248	0.56	0.26-1.17	0.137
BMI >30 kg/m^2	0.71	0.34-1.36	0.315	0.71	0.33-1.44	0.358
Hypertension	2.21	1.03-5.47	0.060	1.96	0.83-5.26	0.148
Hyperlipidemia	**2.01**	**1.07-3.72**	**0.027**	1.54	0.76-3.04	0.225
Diabetes mellitus	1.23	0.52-2.60	0.607	0.88	0.35-2.01	0.780
Heart failure	**3.75**	**1.20-9.88**	**0.012**	3.11	0.76-11.16	0.093
Peripheral vasculopathy	2.56	0.58-8.06	0.147	2.15	0.45-7.66	0.278
eGFR <60 ml/min/1.73m^2	0.78	0.34-1.58	0.507	0.64	0.27-1.39	0.282
Obstructive CAD	1.56	0.57-3.59	0.337	1.01	0.34-2.60	0.988
LVEF <50%	**2.26**	**1.02-4.61**	**0.032**	2.05	0.78-4.97	0.125
LA volume	1.00	0.99-1.01	0.663	0.99	0.98-1.01	0.254
LAA volume	1.02	0.95-1.08	0.483	0.99	0.90-1.09	0.884
LAA orifice area >561.5 cm^2	1.90	0.86-3.85	0.090	1.90	0.74-4.58	0.163
LAA morphology						
Cauliflower	Reference		...	Reference		. . .
Windsock	**0.32**	**0.12-0.73**	**0.013**	**0.32**	**0.12-0.77**	**0.017**
Chicken wing	0.56	0.16-1.47	0.287	0.52	0.15-1.45	0.257
Swan	**2.52**	**0.95-6.00**	**0.046**	**2.69**	**0.96-6.86**	**0.047**
LAA flow velocity ≤35.3 cm/sec	**2.16**	**1.13-4.43**	**0.026**	**2.18**	**1.09-4.61**	**0.033**

AF = atrial fibrillation; BMI = body mass index; eGFR = estimated glomerular filtration rate; LA = left atrium; LAA = left atrial appendage; LVEF = left ventricular ejection fraction; OR = odds ratio; TIA = transient ischemic attack.

measured significantly lower LAA orifice area values in patients with a windsock LAA shape than in those with a cauliflower morphology. However, there was no difference in LAA function between the groups. Moreover, we did not find any significant differences in LAA orifice area, volume, and flow velocity in those with a swan LAA shape compared with those with a cauliflower LAA morphology. However, it could be hypothesized that because of its curved structure, the swan LAA morphology is prone to blood stasis, leading to thrombus formation and occurrence of stroke/TIA. This hypothesis is in line with previous studies suggesting that some LAA characteristics, such as the angle of the LAA bend, the depth, and the number of lobes, are associated with stroke risk because stroke risk increased with increasing complexity of the LAA morphology.[27−31]

Anticoagulation plays a crucial role in the prevention of stroke/TIA in patients with AF. In our study population, there were no difference in the distribution of anticoagulation therapy across the LAA morphology groups. Our results are in line with previous published data.[11] Nevertheless, the decision for anticoagulation therapy is made solely based on patient demographics and clinical data, neglecting to consider any morphologic or functional information regarding the left atrium and the LAA.[32] Our results suggest that incorporating some important LAA features might be essential for improved assessment of thromboembolic risk and the prevention of stroke/TIA in patients with AF.

This study has several limitations. First, it is a single-center, retrospective study, which needs confirmation in multicenter prospective studies. The type of stroke and medications taken at the time of stroke/TIA could not be recorded in all patients. Second, the stroke/TIA rates were small because our study is limited to patients with AF who underwent catheter ablation. Moreover, it is impossible to prove that all stroke/TIA events were of cardiac origin; however, this is inherent to all studies focusing on this topic.

In this retrospective study including 649 patients with AF, reduced LAA flow velocity and swan LAA morphology were independently associated with higher odds of stroke/TIA, whereas the windsock LAA morphology seemed to play a protective role. Comparing the differences between the various LAA morphology types, significantly lower LAA volume and LAA orifice area were measured in windsock LAA shape than in the cauliflower LAA morphology.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.03.025.

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