

Left Atrial Appendage Structural Characteristics Predict Thrombus Formation

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Abstract

Background: Non-valvular atrial fibrillation (NVAf) is a highly prevalent arrhythmia where loss of synchronized atrial contraction increases the risk of intracardiac thrombus particularly within the left atrial appendage (LAA). Anticoagulation is the mainstay of stroke prevention based on the CHA2DS2-VASc score; however, it does not account for LAA structural characteristics. **Methods:** The research comprises a retrospective matched case-control study of 196 subjects with NVAf who underwent transesophageal echo (TEE). The control group, without thrombus (n=117), was selected from two different groups, both pools had: NVAf and CHA2DS2-VASc score [?] 3. One group underwent screening TEE prior to Watchman closure device placement from January 2015 to December 2019 (n=74) the second underwent TEE prior to cardioversion from February to October 2014 (n=43). The study group, with thrombus (n=79), included patients with NVAf, TEE study performed between February 2014 and December 2020, and LAA thrombus. The propensity score method was utilized to determine the matched controls while accounting for confounding from prognostic variables resulting in 61 matched pairs included in the analysis data set. LAA ostial area (OA) (calculated from orthogonal measurements 0, 90° or 45, 135°), LAA maximal depth, and peak LAA outflow velocity were measured. **Results:** Patient characteristics and TEE data were collected (Table [I](#tbl-cap-0001)) and compared using the t-test or chi-square analysis. We observed a lower LAA peak exit velocity in the thrombus group as compared to the control group. Additionally, we found that patients in the thrombus group had smaller LAA OA at 0 and 90 degrees, at 45 and 135 degrees, using largest diameter, as well as using aggregate OA, and smaller maximum LAA depth compared to patients in the control group. Candidate conditional logistic regression models for the outcome of presence of thrombus were evaluated (Table [II](#tbl-cap-0002)). Statistical results from the best-fitting conditional regression model were calculated (Table [III](#tbl-cap-0003)) showing a significant association between aggregate OA and LAA exit velocity with presence of thrombus. **Conclusion:** Utilizing LAA structural characteristics to predict thrombus formation may help refine current cardioembolic stroke (CES) risk estimation.

Title:

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Short title :

LAA Characteristics Predict Thrombus Formation

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Abstract:

Background: Non-valvular atrial fibrillation (NVAf) is a highly prevalent arrhythmia where loss of synchronized atrial contraction increases the risk of intracardiac thrombus particularly within the left atrial appendage (LAA). Anticoagulation is the mainstay of stroke prevention based on the CHA2DS2-VASc score; however, it does not account for LAA structural characteristics.

Methods: The research comprises a retrospective matched case-control study of 196 subjects with NVAf who underwent transesophageal echo (TEE). The control group, without thrombus (n=117), was selected from two different groups, both pools had: NVAf and CHA2DS2-VASc score [?] 3. One group underwent screening TEE prior to Watchman closure device placement from January 2015 to December 2019 (n=74) the second underwent TEE prior to cardioversion from February to October 2014 (n=43). The study group, with thrombus (n=79), included patients with NVAf, TEE study performed between February 2014 and December 2020, and LAA thrombus. The propensity score method was utilized to determine the matched controls while accounting for confounding from prognostic variables resulting in 61 matched pairs included in the analysis data set. LAA ostial area (OA) (calculated from orthogonal measurements 0, 90° or 45, 135°), LAA maximal depth, and peak LAA outflow velocity were measured.

Results: Patient characteristics and TEE data were collected (Table I) and compared using the t-test or chi-square analysis. We observed a lower LAA peak exit velocity in the thrombus group as compared to the control group. Additionally, we found that patients in the thrombus group had smaller LAA OA at 0 and 90 degrees, at 45 and 135 degrees, using largest diameter, as well as using aggregate OA, and smaller maximum LAA depth compared to patients in the control group. Candidate conditional logistic regression models for the outcome of presence of thrombus were evaluated (Table II). Statistical results from the best-fitting conditional regression model were calculated (Table III) showing a significant association between aggregate OA and LAA exit velocity with presence of thrombus.

Conclusion: Utilizing LAA structural characteristics to predict thrombus formation may help refine current cardioembolic stroke (CES) risk estimation.

Background:

In atrial fibrillation (AF), thrombus formation typically occurs within the left atrial appendage (LAA) and is less common in the left atrial cavity (LAC)¹⁻³. Based on transesophageal echocardiography (TEE), the prevalence of LAA thrombus in AF patients in the absence of anticoagulation is 7.5%, with a 1.8% prevalence of LAC thrombus⁴, though extra-appendage thrombus appears to be a rare finding in non-valvular atrial fibrillation⁵. LAA/LAC thrombus may be associated with embolization to the brain, causing stroke. The LAA has distinct structural, anatomic, and physiologic properties that permit the structure to serve its role as a decompression chamber during periods of elevated left atrial pressure. The volume, orifice size, length, shape, and lobulation of the LAA may vary markedly between individual^{6, 7}.

The pathogenesis of thrombus formation in the LAA in the setting of non-valvular AF (NVAF) is not fully understood. Investigators have examined structural and functional characteristics of the LAA and how they contribute to LAA thrombus formation and cardioembolic stroke (CES) risk. Reduced blood inflow and outflow velocities at the LAA orifice based upon Doppler transesophageal echocardiography (TEE) measurements have predicted LAA thrombus risk⁸. More recent studies seeking to correlate descriptive LAA morphologies with thromboembolic risk have reported lower risks of embolic events with Chicken-Wing LAA morphology⁷⁻⁹.

The LAA anatomic determinants that predict thromboembolic risk in NVAF have not been completely elucidated. This study aimed to compare the LAA orifice size, maximal depth, and peak exit velocities between AF patients with LAA thrombus and high-risk AF patients without thrombus. Identifying novel LAA anatomic determinants of thrombus formation may help stratify AF thromboembolic risk in the future.

Methods:

Study design and patient population.

The study procedures were reviewed and approved by the Institutional Research Board (IRB) of Medical College of Wisconsin. In this single-center retrospective study, AF patients with LAA thrombus were identified through a query of ICD-10 codes within the electronic medical record system. This search identified patients with the diagnosis of non-valvular atrial fibrillation (NVAF), a TEE study performed between February 1, 2014, and December 31, 2020, and a diagnosis of intracardiac thrombus. In this manner 216 subjects were identified. Two study cardiologists (MB and AW) manually reviewed the TEE images and medical records for these subjects. Subjects with intracardiac thrombus not contained within the LAA or thrombus unconfirmed by the two study reviewers, and those for whom imaging did not permit orthogonal measurements of the left atrial appendage ostial diameters were excluded from the study. A total of 79 patients constituted the final thrombus cohort (Figure 1).

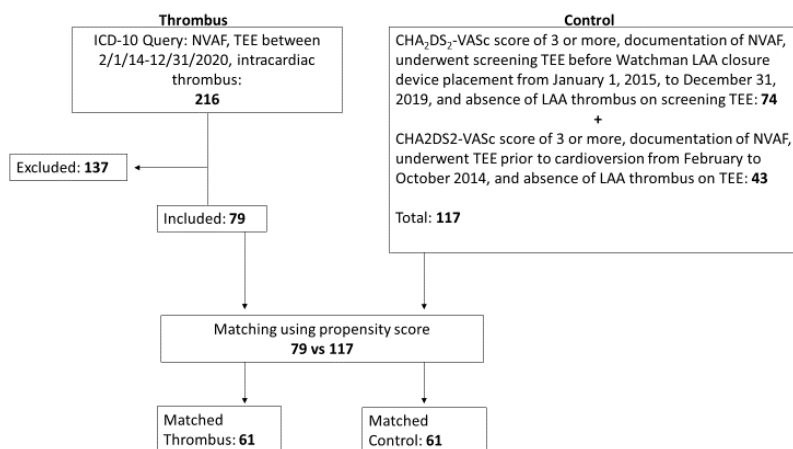


Figure 1. Flow chart depicting patient selection methodology.

The control cohort for this study was identified differently. The control group included consecutive patients identified with the following characteristics: a CHA₂DS₂-VASc score of 3 or more, documentation of NVAF, underwent screening TEE before Watchman LAA closure device (Boston Scientific Corporation, St Paul MN) placement from January 1, 2015, to December 31, 2019, and absence of LAA thrombus on screening TEE. A total of 74 subjects were thus identified and included in the control cohort. The control group was selected based on prior Watchman screening for their elevated risk for LAA thrombus based on an elevated CHA₂DS₂-VASc score, the presence of prior TEE imaging, confirmed absence of LAA thrombus on TEE,

and prior confirmed history of AF. Additional subjects were added to the control cohort with the following characteristics: CHA2DS2-VASc score of 3 or more, documentation of NVAF, underwent TEE prior to cardioversion from February to October 2014, and absence of LAA thrombus on TEE. A total of 43 subjects were thus identified and included in the control cohort resulting in 117 total subjects (Figure 1). For all 117 control subjects, imaging permitted orthogonal measurements of the LAA ostial diameters. Primary TEE imaging and electronic medical record data were confirmed by two study cardiologists (MB and AW).

Transesophageal echocardiography and measurement of clinical parameters .

2D multiplane TEE was performed and interpreted by experienced cardiologists using an EPIQ ultrasound system and X8-2t probe (Philips Medical Systems, Andover, MA). Studies were performed according to the American Society of Echocardiography guidelines. LAA peak exit velocities were measured approximately 1 cm below the outlet of the LAA cavity using pulse wave Doppler ultrasound in the 45° view. Peak exit velocities were measured as the average of three consecutive cardiac cycles in patients with normal sinus rhythm and five consecutive cardiac cycles in patients with AF at the time of examination. The LAA imaging was obtained at end-diastole when the LAA diameter and volume was maximal; and was evaluated in four different mid-esophageal planes: 0°, 45°, 90°, and 135°. In each of the four planes, LAA ostial diameters were measured from the inferior portion of the ostium at the level of the circumflex coronary artery up to the point 2 cm from the tip of the left superior pulmonary vein limbus. In each plane, LAA depth was measured from the ostial line orthogonal to the LAA neck axis to the LAA apex. Given the retrospective nature of the study, measurements at all four mid-esophageal planes were not uniformly available. All TEE studies were independently reviewed by two cardiologists. The final LAA ostial diameter and length measurements were derived from an average of the echocardiographers' measurements. The orifice area was calculated using two orthogonal measured ostial radiuses (a) and (b) using the formula πab . Orthogonal LAA radiuses were measured at TEE planes 0° and 90°, as well as 45° and 135°, provided all four planes were available for review. Aggregate OA was calculated as the average of the measured OAs for the subjects where all four mid-esophageal planes were available (0° and 90°, as well as 45° and 135°). In the case that only one pair of orthogonal measurements (0° and 90° or 45° and 135°) was available then this value alone was used in the calculation of aggregate OA. Similarly, regarding OA at the largest diameter, when all four mid-esophageal planes were available (0° and 90°, as well as 45° and 135°) the largest diameter and its orthogonal plane was selected. 42 of the 61 subjects in the thrombus group and 48 of the 61 subjects in the control group had all four mid-esophageal planes available. LAA thrombus was identified as independently mobile echo-densities that corresponded with contrast echocardiography filling defects.

Chart review was completed for each patient to determine anticoagulation status, underlying rhythm, and CHA2DS2-VASc score all at the time of TEE. Medical history was also reviewed for ischemic stroke or TIA history.

Statistical Analysis

In this matched case-control study, the exposures consist of two clusters of variables. The first cluster includes 4 variables associated with the ostial area: OA at 0 and 90 degrees, OA at 45 and 135 degrees, OA calculated using the largest radius in the 4 TEE planes and the orthogonal radius, and aggregate OA. The other cluster includes two variables: Maximum LAA depth and LAA Exit Velocity. The outcome is a binary variable called LAA thrombus (Yes vs. No). The patients with thrombus were identified as cases. The patients without thrombus were considered as the candidate controls. The propensity score method was utilized to determine the matched controls while accounting for confounding from prognostic variables. The matching variables included age, LVEF, and sinus rhythm at the time of TEE. The greedy nearest neighbor technique was used to achieve the 1:1 matched design to produce the slightest within-pair difference. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients were less than or equal to 0.5 times the pooled estimate of the standard deviation (see Figure 2). Another variable, therapeutic anticoagulation at the time of TEE, was exactly matched. Thus, the possibility of investigating the independent effects of those variables on the outcome can be effectively eliminated. 61 matched pairs were identified in the analysis data set (Figure 1).

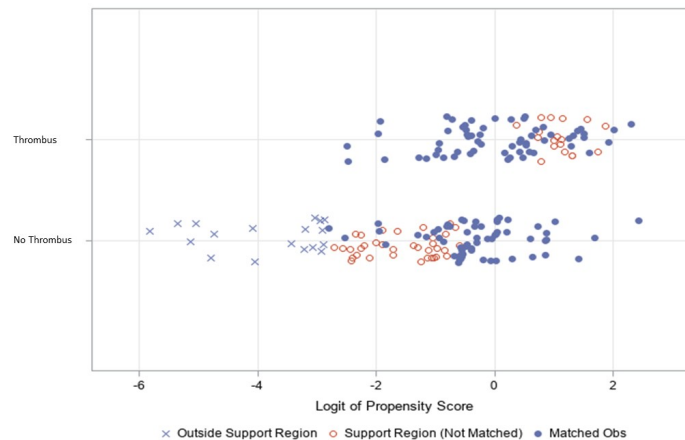


Figure 2. Propensity score matching plot.

Continuous variables were summarized using descriptive statistics such as mean and standard error. All categorical variables were summarized using frequencies and percentages. To further investigate the balance of prognostic variables between the case and control groups, univariate analyses were performed using the t-test or chi-square test upon specific requirements. All the variables associated with prognostic factors and disease history demonstrated no significant impact on the outcome, except one variable, LVEF (see Table I). The conditional logistic regressions (an extension of logistic regression which considers stratification and matching) were used to examine the potential association between the exposure(s) and the outcome while adjusting for the covariate LVEF. A unique matching ID for each pair was generated to indicate the stratum. Thus, the matched variables were controlled simultaneously because their combined information was already incorporated into the matched pairs by this ID. To identify the best-fitting model, we conducted a model selection process based on 6 candidate models whose exposure variables varied (see Table II). The goodness-of-fit measurement Akaike information criterion (AIC) was used to compare these candidates. The preferred model is the one with the minimum AIC value. Thus, Model 1 was the final model for our statistical results and inference. Odds ratios and 95% confidence intervals were reported in Table III and displayed in the forest plot (Figure 3). All analyses were performed at a two-sided 5% Type I error rate by SAS 9.4 (SAS Institute, Cary, NC).

Results:

Table I summarizes the patient characteristics and TEE data for the control cohort and the thrombus cohort for the 61 matched pairs. Univariate analysis showed a significant difference ($p = 0.0285$) between the cohorts in LVEF with the control group ($50.4\% \pm 1.5$) having greater left ventricular systolic function compared to the thrombus group ($45.1\% \pm 1.8$). There were no significant differences between the thrombus and control cohorts in age at TEE (69.1 ± 1.7 vs 71.0 ± 1.4 $p = 0.3885$), sex ($p = 0.2694$), BMI (30.2 ± 1.1 vs 32.9 ± 1.1 $p = 0.0784$), pulmonary artery systolic pressure (37.9 ± 1.7 vs 38.3 ± 1.7 $p = 0.8529$), CHA2DS2-VASc Score (4.5 ± 0.3 vs 4.1 ± 0.2 $p = 0.2485$), rates of hypertension (95.1% vs 91.8% $p = 0.4645$), diabetes (39.3% vs 27.9% $p = 0.1797$), stroke, TIA, or thromboembolism (26.2% vs 24.6% $p = 0.8353$), peripheral arterial disease (31.15% vs 44.3% $p = 0.1351$), myocardial infarction (24.6% vs 18.0% $p = 0.3765$), coronary artery disease (55.8% vs 41.0% $p = 0.1030$), LA volume index (50.9 ± 2.1 vs 48.9 ± 1.7 $p = 0.4685$), therapeutic anticoagulation status at TEE (98.4% vs 98.4% $p = 1.0000$), or sinus rhythm at TEE (8.20% vs 8.20% $p = 1.0000$). There were significant differences between the thrombus and control cohorts in ostial area at 0 and 90 degrees (231.7 ± 13.0 vs 328.6 ± 12.9 $p < 0.0001$), ostial area at 45 and 135 degrees (229.3 ± 12.6 vs 336.4 ± 14.1 $p < 0.0001$), ostial area at the largest diameter (239.0 ± 12.1 vs 356.3 ± 13.5 $p < 0.0001$), aggregate ostial area (223.3 ± 11.0 vs 334.2 ± 12.4 $p < 0.0001$), maximum LAA depth (26.7 ± 0.7 vs $29.4 \pm$

0.7 p = 0.0088), and LAA exit velocity (24.7 ± 1.6 vs 37.9 ± 2.6 p <0.0001).

Table I. Univariate Analysis of Patient Characteristics and TEE Data

	Thrombus (N=61)	No Thrombus (N=61)	P Value
Patient Characteristics			
Age at TEE (years)	69.1 ± 1.7	71.0 ± 1.4	0.3885
Sex (Male/Female)	39/22	33/28	0.2694
BMI (kg/m ²)	30.2 ± 1.1	32.9 ± 1.1	0.0784
Pulmonary systolic pressure (mmHg)	37.9 ± 1.7	38.3 ± 1.7	0.8529
LVEF (%)	45.1 ± 1.8	50.4 ± 1.5	0.0285
CHA2DS2-VASc Score	4.5 ± 0.3	4.1 ± 0.2	0.2485
Hypertension (total, %)	58 (95.1)	56 (91.8)	0.4645
Diabetes (total, %)	24 (39.3)	17 (27.9)	0.1797
Stroke, TIA, Thromboembolism (total, %)	16 (26.2)	15 (24.6)	0.8353
Peripheral Arterial Disease (total, %)	19 (31.15)	27 (44.3)	0.1351
Myocardial Infarction (total, %)	15 (24.6)	11 (18.0)	0.3765
Coronary artery disease (total, %)	34 (55.8)	25 (41.0)	0.1030
TEE Data			
LA Volume Index (mL/m ²)	50.9 ± 2.1	48.9 ± 1.7	0.4685
Anticoagulated at TEE (total, %)	60 (98.4)	60 (98.4)	1.0000
Sinus Rhythm at TEE (total, %)	5 (8.20)	5 (8.20)	1.0000
OA at 0 and 90 degrees (mm ²)	231.7 ± 13.0	328.6 ± 12.9	<0.0001
OA at 45 and 135 degrees (mm ²)	229.3 ± 12.6	336.4 ± 14.1	<0.0001
OA at the largest diameter (mm ²)	239.0 ± 12.1	356.3 ± 13.5	<0.0001
Aggregate OA* (mm ²)	223.3 ± 11.0	334.2 ± 12.4	<0.0001
Maximum LAA depth (mm)	26.7 ± 0.7	29.4 ± 0.7	0.0088
LAA Exit Velocity (cm/sec)	24.7 ± 1.6	37.9 ± 2.6	<0.0001

* Aggregate OA was calculated as the average of the measured OAs for the subjects where all four mid-esophageal planes were available (0° and 90°, as well as 45° and 135°). In the case that only one pair of orthogonal measurements (0° and 90° or 45° and 135°) then the available value was used. 42 of the 61 subjects in the thrombus group and 48 of the 61 subjects in the control group had all four mid-esophageal planes available.

+ TEE = transesophageal echo, BMI = body mass index, LVEF = left ventricular ejection fraction, TIA = transient ischemic attack, LA = left atrial, OA = ostial area, LAA = left atrial appendage

Table II summarizes candidate conditional logistical regression models for the outcome presence of LAA thrombus. Model 1 included aggregate OA, LAA exit velocity, and LVEF and was selected as the final model for statistical results and inference based on the lowest AIC (27.578) representing the best goodness-of-fit measurement among the candidate models. Table III summarizes results from the best-fitting conditional regression model (Model 1) examining the relationship of aggregate OA, LAA exit velocity, and LVEF to the primary outcome presence of thrombus. There was a significant association found between aggregate OA and presence of LAA thrombus ($p = 0.0038$) as well as LAA exit velocity and presence of LAA thrombus ($p=0.0107$) in the logistic regression model, supporting these two LAA characteristics as risk factors for presence of LAA thrombus. There was no association ($p = 0.2161$) between LVEF and presence of LAA thrombus in the logistic regression analysis, suggesting that LVEF does not represent an independent risk factor predictive of LAA thrombus. These results are depicted graphically in Figure 3, a Forest plot for the best-fitting conditional logistic regression.

Table II. Candidate Conditional Logistic Regression Models for the Outcome (Thrombus or not)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Strata identified by Matched ID	X	X	X	X	X	X
Exposure variables *						
Aggregate OA	X	X				
LAA Exit Velocity	X		X			
OA at the largest diameter				X		
OA at 45 and 135 degrees					X	
Maximum LAA depth						X
Prognostic factor						
LVEF	X	X	X	X	X	X
Modeling Fitting measurement						
AIC	27.578	43.303	50.859	44.868	45.197	66.146

* OA at 0 and 90 degrees were not considered due to more than 20% missing data (i.e., 26 patients out of 122).

+ OA = ostial area, LAA = left atrial appendage, LVEF = left ventricular ejection fraction, AIC = Akaike information criterion

Table III. Statistical results from the best-fitting conditional regression model (Model 1)

Predictor variables	Estimate (SE)	OR (95%CI)	P Value
Aggregate OA	-0.0208 (0.0072)	0.979 (0.966, 0.993)	0.0038
LAA exit velocity	-0.1065 (0.0417)	0.899 (0.828, 0.976)	0.0107
LVEF	-0.0763(0.0617)	0.927 (0.821, 1.046)	0.2161

*SE = standard error, OR = odds ratio, CI = confidence interval, OA = ostial area, LAA = left atrial appendage, LVEF = left ventricular ejection fraction

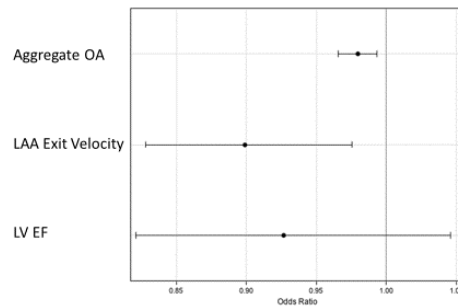


Figure 3. Forest plot for the best-fitting conditional logistic regression.

Discussion:

Widely used scores predicting CES risk in NVAf have emphasized clinical characteristics including age and comorbidities. Few studies have explored the contribution of LAA structural characteristics to thrombotic risk. Clarifying the relationships between LAA anatomy, physiology, and thrombotic risk may refine CES risk estimates and impact anticoagulation or other stroke mitigation procedure decisions for NVAf patients.

Previous examinations of LAA morphologic determinants of CES risk relied on qualitative classifications of LAA shape, distinguishing between appendages that resemble a Chicken-Wing, Windsock, Cactus, and Cauliflower⁷. Several studies have demonstrated a lower risk of stroke and transient ischemic attack, and a higher LAA emptying flow velocities with Chicken-Wing type LAAs compared to other LAA morphologic types⁷⁻⁹. The variable appearance of LAA morphology in different TEE imaging planes, as well as LAA anatomic complexity and heterogeneity, may limit the reproducibility and utility of such morphologic criteria. Wu et al. examined inter-observer agreements categorizing qualitative descriptions of LAA morphology by CT in 2264 AF patients and found that all 3 reviewers came to consensus in only 28.9% of scans¹⁰. Thus, LAA anatomic and physiologic measurements that are objective and reproducible could be valuable in predicting thrombus formation and thromboembolic risk in NVAf.

Lower LAA emptying velocities are known to confer higher risk of thrombogenesis⁸. The presence of AF during TEE and persistent AF has predicted lower maximal LAA emptying flow velocities. Petersen et al. observed higher flow velocities in patients with AF who had Chicken-Wing LAA morphology, but interestingly only when patients were in sinus rhythm at the time of TEE¹¹. After controlling for sinus rhythm at the time of TEE, we observed lower LAA exit velocities in the LAA thrombus cohort, consistent with prior publications.

The relationship between the LAA orifice area, a simple and reproducible measurement on TEE and cardiac CT, and thromboembolic risk in NVAf is unclear as previously published findings are conflicting. Khurram et al. studied 678 patients undergoing AF ablation with pre-procedure cardiac CT imaging, reporting an association of smaller LAA orifice size with thromboembolic events in univariate analyses¹². In contrast, Lee JM et al. found that NVAf patients with stroke had larger LAA orifice area and larger LA volume¹³. Similarly, Lee Y et al. demonstrated larger LAA orifice diameters in patients with CES¹⁴. These conflicting reports describing the relationship of LAA orifice size and CES risk highlight the importance of further investigation.

In contrast to prior work examining the relationship between LAA structural characteristics and clinical

thromboembolic event risk in AF, our study examines the structure and function of the LAA in AF patients with documented LAA thrombus. This difference in outcome of interest compared to previous studies that used clinical history of stroke and TIA as a surrogate for intracardiac thrombus formation represents a unique aspect of our study insulating our results from the variability associated with accurately diagnosing stroke or TIA. While most ischemic strokes in patients with NVAF are cardioembolic, at least 24% may have a non-cardioembolic etiology¹⁵. It may therefore be advantageous to directly study patients with documented LAA thrombus when characterizing LAA measurements that potentially predict thrombus formation in NVAF. We observed a lower LAA peak exit velocity in the thrombus group as compared to the control group (24.7 ± 1.6 cm/s vs. 37.9 ± 2.6 cm/s, $p < 0.0001$). Additionally, we found that patients in the thrombus group had smaller LAA OA at 0 and 90 degrees (231.7 ± 13.0 mm² vs. 328.6 ± 12.9 mm², $p < 0.001$), smaller LAA OA at 45 and 135 degrees (229.3 ± 12.6 mm² vs. 336.4 ± 14.1 mm², $p < 0.0001$), smaller OA at the largest diameter (239.0 ± 12.1 mm² vs. 356.3 ± 13.5 mm², $p < 0.0001$), smaller aggregate OA (223.3 ± 11.0 mm² vs. 334.2 ± 12.4 mm², $p < 0.0001$), and smaller maximum LAA depth (26.7 ± 0.7 mm vs. 29.4 ± 0.7 mm, $p = 0.0088$) as compared to patients in the control group. Our primary novel finding, smaller LAA ostial area as an independent risk factor for LAA thrombus in NVAF, may help refine current CES risk estimation models. In particular, incorporating physiologic and anatomic measurements in clinical thromboembolic risk models may be useful to identify truly low-risk AF patients.

There were several limitations to this study. In this case-control study, we identified patients with NVAF that were placed into the thrombus and control groups from different populations of NVAF patients undergoing TEE. This permitted identification of a larger number of patients for the thrombus group but introduced selection bias into the study. We undertook propensity matching in order to reduce the possibility of confounding from differences in baseline characteristics between the groups including age, LVEF, anticoagulation status at time of TEE, and sinus rhythm at time of TEE. Despite the propensity matching, a significant difference in the baseline characteristic of LVEF persisted with the thrombus group having a lower LVEF compared to the control group ($45.1 \pm 1.8\%$ vs. $50.4 \pm 1.5\%$, $p = 0.0285$). However, this association did not persist after best-fitting conditional regression model analysis was performed ($p = 0.2161$). Given the retrospective identification of patients, LAA ostial diameter measurements via TEE at all four mid-esophageal planes (0° and 90°, as well as 45° and 135°) were not universally available. Aggregate OA was calculated in order to incorporate maximal available measured LAA ostial data. Aggregate OA was found to be significantly smaller in the thrombus cohort as were all other OA evaluations including OA at 0° and 90°, OA at 45° and 135° and OA at largest diameter adding validity to these significant findings. Finally, the calculation of the OA used an ellipse formula that does not factor in the irregular shape of the LAA ostium. This limitation likely has less significance as both groups were evaluated with the same formulaic assumptions.

Conclusion:

Our study identified smaller LAA ostial cross-sectional area as a novel predictor of LAA thrombus risk, independent of LAA peak exit velocity. Incorporating structural and physiologic LAA measurements into clinical thromboembolic risk stratification may improve decisions regarding risk mitigation in NVAF.

Citations:

1. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. Feb 1996;61(2):755-9. doi:10.1016/0003-4975(95)00887-X
2. Cresti A, García-Fernández MA, Sievert H, et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroIntervention*. Jun 2019;15(3):e225-e230. doi:10.4244/EIJ-D-19-00128
3. Scherr D, Sharma K, Dalal D, et al. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. Dec 2009;20(12):1357-63. doi:10.1111/j.1540-8167.2009.01540.x
4. Noubiap JJ, Agbaedeng TA, Ndoadougue AL, et al. Atrial thrombus detection on transoesophageal

echocardiography in patients with atrial fibrillation undergoing cardioversion or catheter ablation: A pooled analysis of rates and predictors. *J Cardiovasc Electrophysiol*. 2021;32(8):2179-2188. doi:10.1111/jce.15082, 10.1111/jce.15082

5. Cresti A, Garcia-Fernandez MA, Sievert H, et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroIntervention*. 2019;15(3):e225-e230. doi:10.4244/EIJ-D-19-00128, 10.4244/EIJ-D-19-00128

6. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging*. Dec 2014;7(12):1251-65. doi:10.1016/j.jcmg.2014.08.009

7. Wang Y, Di Biase L, Horton RP, Nguyen T, Morhanty P, Natale A. Left atrial appendage studied by computed tomography to help planning for appendage closure device placement. *J Cardiovasc Electrophysiol*. Sep 2010;21(9):973-82. doi:10.1111/j.1540-8167.2010.01814.x

8. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol*. Aug 2012;60(6):531-8. doi:10.1016/j.jacc.2012.04.032

9. Basu-Ray I, Sudhakar D, Schwing G, et al. Complex Left Atrial Appendage Morphology Is an Independent Risk Factor for Cryptogenic Ischemic Stroke. *Front Cardiovasc Med*. 2018;5:131. doi:10.3389/fcvm.2018.00131

10. Wu L, Liang E, Fan S, et al. Relation of Left Atrial Appendage Morphology Determined by Computed Tomography to Prior Stroke or to Increased Risk of Stroke in Patients With Atrial Fibrillation. *Am J Cardiol*. 04 2019;123(8):1283-1286. doi:10.1016/j.amjcard.2019.01.024

11. Petersen M, Roehrich A, Balzer J, et al. Left atrial appendage morphology is closely associated with specific echocardiographic flow pattern in patients with atrial fibrillation. *Europace*. Apr 2015;17(4):539-45. doi:10.1093/europace/euu347

12. Khurram IM, Dewire J, Mager M, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. *Heart Rhythm*. Dec 2013;10(12):1843-9. doi:10.1016/j.hrthm.2013.09.065

13. Lee JM, Shim J, Uhm JS, et al. Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. *Am J Cardiol*. Mar 2014;113(6):963-9. doi:10.1016/j.amjcard.2013.11.058

14. Lee Y, Park HC, Kim SG. Comparison of Morphologic Features and Flow Velocity of the Left Atrial Appendage Among Patients With Atrial Fibrillation Alone, Transient Ischemic Attack, and Cardioembolic Stroke. *Am J Cardiol*. 05 2017;119(10):1596-1604. doi:10.1016/j.amjcard.2017.02.016

15. Freeman JV, Varosy P, Price MJ, et al. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol*. 04 2020;75(13):1503-1518. doi:10.1016/j.jacc.2019.12.

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