Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation

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BACKGROUND Atrial fibrillation (AF) is an important cause of stroke. Given the morbidity and mortality associated with stroke, the risk stratification of patients based on left atrial appendage (LAA) characteristics is of great interest.

OBJECTIVE To explore the association between LAA morphology and LAA characteristics including the extent of trabeculations, orifice diameter, and length with prevalent stroke in a large cohort of patients with drug refractory AF who underwent AF ablation to develop mechanistic insight regarding the risk of stroke.

METHODS An institutional cohort of 1063 patients referred for AF ablation from 2003 to 2012 was reviewed to identify patients that underwent preprocedural cardiac computed tomography (CT). LAA morphology was characterized as chicken wing, cactus, windsock, or cauliflower by using previously reported methodology. Left atrial size and LAA trabeculations, morphology, orifice diameter, and length were compared between patients with prevalent stroke and patients without prevalent stroke.

RESULTS Of 678 patients with CT images, 65 (10%) had prior stroke or transient ischemic attack. In univariate analyses, prevalent heart failure (7.7% in cases vs 2.8% in controls; \( P = .033 \)), smaller LAA orifice (2.26 ± 0.52 cm vs 2.78 ± 0.71 cm; \( P < .001 \)), shorter LAA length (5.06 ± 1.17 cm vs 5.61 ± 1.17 cm; \( P < .001 \)), and extensive LAA trabeculations (27.7% vs 14.4%; \( P = .019 \)) were associated with stroke. LAA morphologies were unassociated with stroke risk. In multivariable analysis, smaller LAA orifice diameter and extensive LAA trabeculations remained independently associated with thromboembolic events.

CONCLUSIONS The extent of LAA trabeculations and smaller LAA orifice diameter are associated with prevalent stroke and may mediate the previously described association of cauliflower LAA morphology with stroke.

KEYWORDS Atrial fibrillation; Thromboembolism; Stroke; Left atrial appendage morphology; Computed tomography; CT; Trabeculations

ABBREVIATIONS AF = atrial fibrillation; CI = confidence interval; CT = computed tomography; LA = left atrium; LAA = left atrial appendage; MPR = multiplanar reconstruction; OR = odds ratio; TIA = transient ischemic attack

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Methods
Study patients
The patient population was composed of the Johns Hopkins institutional cohort of 1063 consecutive patients with AF referred for catheter ablation from January 2001 to December 2012 who agreed to participate in the prospective registry. Of all patients, 678 (63.8%) had undergone pre-procedural contrast-enhanced electrocardiogram-gated multidetector CT imaging and were included in the study. A history of transient ischemic attack (TIA) or stroke documented at the time of enrollment into the cohort led to a “case” designation with the remaining patients as controls. The CHADSVASe score before stroke occurrence was calculated on the basis of patient comorbidities.

CT
Contrast-enhanced CT images were acquired by using 3 different scanners over the 11-year course of the study. Patients from 2003 to 2006 were scanned by using the 64-slice Sensation CT (Siemens Medical, Erlangen, Germany), from 2006 to 2007 by using the 256-slice Aquilion (Toshiba, Houston, TX), and from 2007 to 2012 by using the 320-slice Aquilion ONE (Toshiba). An image analysis of the 3-dimensional LA and LAA structures was performed by using multiplanar reconstruction (MPR) with UltraVisual software (Merge Healthcare, Chicago, IL). Three independent observers that were blinded to clinical data (including history of stroke/TIA) and were trained on an initial sample of 25 cases classified the extent of LAA trabeculations, orifice diameter, length, and morphologies. Figure 1 describes the process for the classification of LAA trabeculations into mild, moderate, and extensive categories. Mild trabeculations were defined by minimal or no indentations on the LAA wall; moderate trabeculations were defined by trabeculations on part of the LAA wall with portions of the LAA showing minimal or no indentations, while extensive trabeculations were defined by diffuse indentation throughout the LAA wall. Various LAA morphologies are shown in Figure 2, which were classified as chicken wing, cactus, windsock, and cauliflower as reported previously.7,8 The chicken wing morphology (Figure 2A) was identified as a dominant single lobe that has a clear single bend after the initial origin of the LAA with or without secondary lobes or twigs. The cactus morphology (Figure 2B) was identified as a dominant central lobe without any bend, with secondary lobes extending from it. The windsock (Figure 2C) was identified as a dominant central lobe of significant length with more than 1 bend or with long secondary lobes arising from it. The cauliflower morphology (Figure 2D) was classified as an irregularly shaped LAA with loss of the dominant lobe soon after the origin with multiple secondary lobes.7 The LAA orifice diameter was measured as the largest measurement of the LAA orifice at the insertion into the LA in any MPR plane. The LAA length was measured from the LAA ostial plane to the apex of the primary lobe along the central axis and followed along the bends, with the total LAA length as the summation of all individual length of primary lobe axis in different planes and curves by using MPR as described previously.9

Statistical analysis
Continuous data are expressed as mean ± SD and categorical data as numbers and percentages. LAA characteristics including morphologies, extent of trabeculations, orifice diameter, LAA length, and the ratio of LAA diameter to main LA anteroposterior diameter were compared between patients with a history of stroke/TIA and patients without a history of stroke/TIA. Univariate comparisons were made by using the unpaired Student t test, Pearson χ^2, Fisher’s exact, or analysis of variance where appropriate. Multivariable comparisons were made by using logistic regression. P values less than .05 were considered statistically significant. For the determination of interuser variability, 2 observers blinded to the initial review (by another reviewer) repeated the analysis for 100 patients and Cohen’s kappa was used to examine the reproducibility of data (adequate level of agreement at > 0.61).10 Analyses were performed by using Stata software (version 12, College Station, TX).

Results
Of 678 patients included in the study, 65 (9.6%) had a history of stroke/TIA. The mean age was 59.5 ± 9.7 years, 507 (74.8%) were men, the mean body mass index was 29.2 ± 7 kg/m^2, the mean left ventricular ejection fraction was

Figure 1  Computed tomography–based images of the left atrial appendage (LAA): (A) an LAA with mild trabeculations with chicken wing morphology; (B) an LAA with moderate trabeculations with cactus morphology; (C) an LAA with extensive trabeculations with cauliflower morphology.
56.7% ± 8.3%, and the mean CHADSVASc score (before stroke) was 1.38 ± 1.17.

CT characteristics
Complete CT characteristics for cases and controls are listed in Table 1. The mean LA anteroposterior diameter was 4.65 ± 0.68 cm. No difference in LA diameter was observed between case and control patients (4.64 ± 0.64 cm in cases and 4.65 ± 0.68 cm in controls; \( P = .905 \)). The mean LAA length was 5.56 ± 1.18 cm. The length of the LAA was shorter in case patients than in control patients (5.06 ± 1.17 cm vs 5.61 ± 1.17 cm; \( P < .001 \)). The mean LAA orifice diameter was 2.73 ± 0.71 cm. The diameter of the LAA orifice was shorter in cases than in controls (2.26 ± 0.52 cm vs 2.78 ± 0.71 cm; \( P < .001 \)). The extent of trabeculations was minimal in 176 (26.0%) patients from the overall cohort. Minimal trabeculations were seen in 15 (23.1%) case patients and 161 (26.3%) control patients. Extensive trabeculations were noted in 106 (15.6%) patients from the overall cohort. Extensive trabeculations were more frequently observed in case patients than in control patients (27.7% vs 14.4%; \( P = .019 \)).

In multivariable logistic regression analysis (Table 2), extensive trabeculations remained independently associated with case/control status (odds ratio [OR] 3.1; 95% confidence interval [CI] 1.28–7.38; \( P = .012 \)) after adjusting for baseline CHADSVASc, renal function, type of AF, LA size, and LAA length, and orifice diameter. The LAA orifice diameter also remained independently associated with case/control status (OR 0.33; 95% CI 0.19–0.58; \( P < .001 \)). In contrast, LAA length was no longer associated with case/control status (OR 0.88; 95% CI 0.7–1.2; \( P = .394 \)).

LAA morphology
The most common LAA morphology was chicken wing, which was present in 306 (45.1%) patients. The cactus morphology was noted in 125 (18.4%) patients. The windsock morphology was noted in 179 (26.4%) patients, and the cauliflower morphology was noted in 68 (10.3%) patients. LAA morphologies were unassociated with case/control status in univariate analyses. LAA morphologies were associated with LAA characteristics under study, as summarized in Table 3. The cactus morphology was associated with smaller LAA orifice diameter and shorter LAA length. The cauliflower morphology was associated with extensive trabeculations.

Interuser variability
The agreement for the determination of the extent of trabeculations was 78.4%, with a \( \kappa \) score of 0.62 (\( P < .001 \)).

![Figure 2](https://example.com/figure2.png) Various left atrial appendage (LAA) morphologies: (A) chicken wing; (B) cactus; (C) wind sock; (D) cauliflower.
The agreement for the determination of LAA morphology was 58.82% with a $\kappa$ score of 0.427. The agreement for the identification of extensive trabeculations was 85.3% ($\kappa$ score 0.64; $P < .001$).

### Discussion

The objective of this study was to evaluate the relationship between morphologic characteristics of the LAA and TIA/stroke risk. There are 2 main findings of this study. First, extensive LAA trabeculations and smaller LAA orifice size are independently associated with a history of TIA/stroke in patients with AF. Second, LAA morphologies were unassociated with stroke risk and were not reproducibly assessable by trained observers.

#### LAA and stroke

It is well established that the LAA is a common source of stroke in patients with AF. Manning et al reported that 97% of LA thrombi were confined to the LAA in patients with AF. In a meta-analysis of 23 studies with the visual inspection of the LAA of patients with nonrheumatic AF by autopsy, transesophageal echocardiography, or direct intraoperative visualization, 91% of thrombi were found in the LAA. These observations led to the multiple studies focusing on LAA closure as an alternate therapy to anticoagulation for protection against stroke.
We sought to examine the generalizability of these results to other centers and other trained image readers. The results of our study stand in stark contrast to the studies described above. Not only did we not observe a relationship between LAA morphology and stroke risk, we also found that the determination of LAA morphology was not reproducible between trained readers. The reason for these different findings is unclear. Considering the marked variability in LAA morphology identification among the observers, definite conclusions correlating LAA morphology and stroke risk cannot be made accurately in this study. However, given the subjectivity of the classification, it may not be generalizable to most centers. Table 4 list varying distributions of LAA morphologies in different studies, demonstrating the diversity in the prevalence of each morphology observed by different investigators. The cauliflower morphology indicates a high risk for stroke. However, the proportion of patients with AF to have this particular LAA morphology is quite variable in different studies. The initial study of Wang et al\(^7\) reported a prevalence of 29% for the cauliflower LAA morphology. Di Biase et al\(^7\) later reported a prevalence of 3% for the cauliflower morphology. Kimura et al\(^17\) later found a prevalence of 40% for the cauliflower morphology. In our study, the prevalence of the cauliflower morphology was 10%. Such diversity in measurements across similar populations suggests that the ascertainment of these subjective morphology measures is difficult and not reproducible. A poor reproducibility of morphology classifications despite extensive imaging experience and prior training was also noted in our study. We believe that the findings of Di Biase et al\(^7\) are important and have the potential to dramatically improve stroke risk stratification in patients with AF. However, we believe their findings will be more generalizable if the high-risk morphology characteristics are decomposed into more objective measures such as LAA orifice diameter and the extent of trabeculations. Importantly, Table 3 indicates that image features including the extent of trabeculations are associated with LAA morphologies and may therefore mediate the associations previously noted with the cauliflower morphology.

### Table 2  Multivariable logistic regression results to identify independent predictors of stroke in the AF population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% confidence interval for odds ratio</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate trabeculations</td>
<td>0.88</td>
<td>0.40–1.92</td>
<td>.744</td>
</tr>
<tr>
<td>Extensive trabeculations</td>
<td>3.1</td>
<td>1.28–7.38</td>
<td>.012</td>
</tr>
<tr>
<td>LAA orifice diameter</td>
<td>0.33</td>
<td>0.19–0.58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LAA length</td>
<td>0.88</td>
<td>0.67–1.17</td>
<td>.394</td>
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<tr>
<td>CHADS(V)ASC score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.25</td>
<td>0.50–3.15</td>
<td>.637</td>
</tr>
<tr>
<td>2</td>
<td>1.90</td>
<td>0.74–4.87</td>
<td>.18</td>
</tr>
<tr>
<td>3</td>
<td>1.36</td>
<td>0.40–4.62</td>
<td>.618</td>
</tr>
<tr>
<td>4</td>
<td>1.63</td>
<td>0.38–6.96</td>
<td>.506</td>
</tr>
<tr>
<td>5</td>
<td>7.63</td>
<td>0.58–101.28</td>
<td>.123</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>1.84</td>
<td>0.91–3.75</td>
<td>.091</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>2.82</td>
<td>1.07–7.46</td>
<td>.036</td>
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<tr>
<td>LA diameter</td>
<td>1.04</td>
<td>0.64–1.71</td>
<td>.866</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.25</td>
<td>0.05–1.30</td>
<td>.101</td>
</tr>
</tbody>
</table>

\(AF = \) atrial fibrillation; \(LA = \) left atrial; \(LAA = \) left atrial appendage.

### Table 3  Association of novel LAA variables measured in this study with different LAA morphologies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chicken wing</th>
<th>Cactus</th>
<th>Windsock</th>
<th>Cauliflower</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA orifice diameter (cm)</td>
<td>2.8 ± 0.7</td>
<td>2.4 ± 0.6</td>
<td>2.8 ± 0.7</td>
<td>2.8 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LAA length (cm)</td>
<td>5.8 ± 1.0</td>
<td>4.8 ± 1.0</td>
<td>5.9 ± 1.3</td>
<td>5.1 ± 1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trabeculations (%)</td>
<td>Mild</td>
<td>33.0</td>
<td>11.2</td>
<td>31.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>61.1</td>
<td>74.4</td>
<td>55.3</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>Extensive</td>
<td>5.9</td>
<td>24.4</td>
<td>13.4</td>
<td>67.7</td>
</tr>
</tbody>
</table>

LAA = left atrial appendage.
insights into the association between LAA anatomy and stroke risk. To our knowledge, no prior studies have performed this type of analysis. The results of our study reveal that patients with AF with a small LAA orifice and extensive trabeculations are at a higher risk of developing thromboembolic events. Three-dimensional CT imaging of the LA has been shown to accurately define anatomy, LAA thrombi, and the extent of trabeculations caused by pectinate muscles. \(^2\)\(^3\)\(^4\) LAA trabeculations, which can easily be visualized by CT, are a potential cause of stasis and of thrombus generation. \(^2\)\(^5\)\(^6\) In addition, smaller LAA orifice size may lead to greater stasis and thrombus generation. Therefore, these results are biologically plausible and readily applicable to patients with AF referred for ablation with preprocedural CT imaging.

### Other stroke risk scoring systems

The CHADS risk score is the most commonly used scoring system for the evaluation of stroke risk. \(^2\)\(^2\) Most of our patients (a total of 564 [83.3%], with 55 [84.6%] patients with stroke [score determined before their stroke] and 509 [83.2%] controls) had a CHADS2 score less than 2 and would therefore have been deemed low risk. Other scoring systems such as the CHADSVaS score \(^2\)\(^3\)\(^4\) and the addition of renal function to the scoring systems have been shown to improve stroke risk stratification in patients with AF. \(^2\)\(^5\) Based on our data, anatomical features such as a narrow LAA orifice (<2.3 cm) and extensive LAA trabeculations may improve the diagnostic performance of future risk stratification schemes.

### Study limitations

There are several potential limitations to our study. This is a retrospective study of an AF ablation cohort with case/control status determined by prevalent stroke/TIA. Therefore, the population is selected for individuals referred for catheter ablation to a tertiary center and the results are not generalizable to all patients with AF. Different CT scanners were used during the study. However, prior studies have shown similar diagnostic performance for different generator scanners and the use of multiple scanners increases the generalizability of our results. \(^2\)\(^6\)\(^7\) The sample size of patients with stroke/TIA was relatively small, thus limiting the power for multivariable analyses. In addition, we did not collect data regarding some stroke risk factors such as dyslipidemia, LAA velocities, and left atrial volume. Therefore, some unmeasured confounding may exist. Similar to prior studies, we were unable to reliably determine anticoagulation status at the time of stroke. However, the associations between the risk of prior stroke and LAA characteristics were independent of the CHADSVaS score, which likely formulated the anticoagulation strategy in each participant. The results, therefore, are likely accurate, but warrant validation in a prospective study. Finally, it is important to note that the associations uncovered in this study are not necessarily causal and may simply imply that an unknown variable that has a causal association with stroke is also associated with the LAA characteristics under study.

### Conclusions

The findings of this study reveal that anatomical LAA features including orifice diameter and extent of trabeculations are independently associated with prevalent stroke in a population of patients with AF referred for ablation.

### References

6. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation: developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm 2012;9:632–696, e621.

### Table 4

Prevalence of various LAA morphologies across different cohorts of patients with AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Modality</th>
<th>Sample size</th>
<th>Chicken wing</th>
<th>Cactus</th>
<th>Windsock</th>
<th>Cauliflower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang (2010)(^1)</td>
<td>CT</td>
<td>612</td>
<td>18</td>
<td>6</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>DeBiase (2012)(^7)</td>
<td>CT</td>
<td>433</td>
<td>50</td>
<td>30</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Kimura (2013)(^17)</td>
<td>CT</td>
<td>80</td>
<td>18</td>
<td>5</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Current study</td>
<td>CT</td>
<td>678</td>
<td>45</td>
<td>18</td>
<td>26</td>
<td>10</td>
</tr>
</tbody>
</table>

\(CT =\) computed tomography; \(MRI =\) magnetic resonance imaging.


