External validation of a novel transthoracic echocardiographic tool in predicting left atrial appendage thrombus formation in patients with nonvalvular atrial fibrillation

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Background
A recent study demonstrated that in patients with nonvalvular atrial fibrillation (AF), a ratio of left ventricular ejection fraction (LVEF) to the left atrial volume index (LAVI) of ≤1.5 has 100% sensitivity for detecting left atrial appendage (LAA) thrombus. We sought to validate this prediction tool in an external cohort.

Methods
We conducted a cohort study of consecutive AF patients who underwent transoesophageal echocardiogram (TEE) to ‘rule-out’ LAA thrombus and had a prior transthoracic echocardiogram (TTE). The LAVI and LVEF were measured to calculate LVEF/LAVI ratio. The sensitivity and specificity of LVEF/LAVI ≤1.5 were calculated.

Results
Among 215 subjects, 19 (8.8%) had LAA thrombus and also had a higher mean CHADS2 score (2.5 vs. 1.9, \(P = 0.04\)), lower mean LVEF (24 vs. 44%, \(P < 0.001\)), higher mean LAVI (44 mL/m² vs. 30 mL/m², \(P < 0.001\)), and higher prevalence of cardiac failure (79 vs. 52%, \(P = 0.02\)). The LVEF and LAVI were found to be independent predictors of LAA thrombus (\(P < 0.05\)). The LVEF/LAVI ratio diagnosed LAA thrombus with an area under the curve = 0.83 by the receiver operator characteristics curve analysis (\(P < 0.001\)). All 19 (100%) subjects with LAA thrombus had LVEF/LAVI ≤1.5 vs. 87 (44%) among those without LAA thrombus (\(P < 0.001\)). The sensitivity and specificity of LVEF/LAVI ≤1.5 were 100 and 55.6%, respectively.

Conclusion
This investigation validates a simple TTE prediction rule to exclude the diagnosis of LAA thrombus, which may obviate the need for pre-cardioversion TEE in selected patients with nonvalvular AF.

Keywords
Left atrial appendage thrombus • Atrial fibrillation • Left atrial volume • Ejection fraction • Transoesophageal echocardiogram (TEE) • Transthoracic echocardiogram (TTE)

Introduction
Nonvalvular atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence approaches 10% in the elderly population. Its most dreaded complication involves an increased risk of thromboembolic events, including stroke.1,2 Presence of left atrial appendage (LAA) thrombus or spontaneous echo contrast has been known to be a strong indicator for increased risk of stroke.3–8 Although transthoracic echocardiography (TTE) plays an essential role in the initial assessment of all patients with newly diagnosed AF, transoesophageal echocardiography (TEE) remains the gold standard for identifying LAA thrombus due to its superior sensitivity and specificity approaching 100 and 91%, respectively.9,10 Therefore, TEE is commonly used to exclude the presence of LAA thrombus in patients with AF prior to restoration of sinus rhythm with electrical or chemical cardioversion, radiofrequency ablation procedures, and testing of implantable cardioverter-defibrillator (ICD).11,12 However, data from several studies demonstrate that LAA is free of thrombi in ~86% of AF patients who underwent a TEE prior to cardioversion.11,12

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The cost implications of this practice are particularly important because TEE is an increasingly utilized procedure, let alone the small associated risk of complications such as oral and oesophageal trauma, in addition to the risks of conscious sedation. Therefore, there may be a role for risk stratification in patients with AF to determine the need for a TEE to exclude the presence of LAA thrombus prior to restoration of sinus rhythm.

Several studies have attempted to establish a tool to predict the presence or absence of LAA thrombus using clinical and/or TTE parameters. Aiyarla et al. identified left ventricular ejection fraction (LVEF) and the left atrial (LA) volume to be independent predictors of LAA thrombus diagnosed by TEE. These authors developed a simple echocardiographic tool utilizing the ratio of the LVEF to LA volume indexed (LAVI) to the body surface area as a predictor of LAA thrombus and identified LVEF/LAVI ratio <1.5 to have 100% sensitivity in diagnosing LAA thrombus. Therefore, this simple indicator, derived from standard TTE, could potentially obviate the need for TEE in many low-risk individuals prior to undergoing electrophysiology procedures or cardioversion. The LVEF/LAVI cut-off of <1.5 was retrospectively optimized in a single-centre study cohort to achieve 100% sensitivity and, thus, may not be applicable to other patient populations. Therefore, it is imperative to validate this prediction tool in an external patient cohort prior to applying it in the clinical setting.

Methods

Patient population

We compiled a cohort of all consecutive patients with nonvalvular AF who underwent TTE to ‘rule-out’ LAA thrombus prior to cardioversion or electrophysiology procedures (cardioversion, AF ablation, and ICD implantation and testing) at Rush University Medical Center (Chicago, IL, USA) in the period from 1 January 2005 until 31 December 2009 and had had a prior TTE (performed within 1 year). Exclusion criteria included: mitral valve surgery, mitral stenosis, mitral regurgitation of >2+ in severity (on a scale of 0–4), mitral prosthesis, and status post-orthotopic heart transplantation. Patients with aortic valvular disease and right-sided valvular heart disease were not excluded.

Echocardiographic and clinical data collection

An expert National Board of Echocardiography-certified echocardiographer, who was blinded to TTE findings, reviewed all TTEs offline to ascertain the presence of LAA thrombus. LAA thrombus was defined as a fixed or mobile echogenic mass within the LAA. The TTEs of all subjects were reviewed prospectively for the purpose of this investigation by a different board-certified echocardiographer who was blinded to LAA thrombus status. The left ventricular (LV) septal and infarolateral wall thicknesses, LV end diastolic, and end systolic internal dimensions were measured from the parasternal M-mode or 2D images. Additionally, LA anteroposterior dimension was measured from the parasternal long axis view, whereas the LA mediolateral and inferosuperior dimensions were measured from the apical four-chamber view. All measurements were performed in adherence with the American Society of Echocardiography Guidelines. The LV mass was calculated in accordance with the recommendations from the American Society of Echocardiography: LV mass = (0.8 × \[1.04 \times \left[\frac{LVIDd + ILWTd + SWTd}{2}\right] - \text{LVIDd}^2\] + 0.6 g), where LVIDd is LV internal diastolic dimension, ILWTd is infarolateral wall thickness in diastole, and SWTd is septal wall thickness in diastole. The LA volume was calculated as \[4/3 \times \left(D1/2\right) \times \left(D2/2\right)\]. The LV mass and the LA volume were indexed to the body surface area. Additionally, LV volumes and ejection fraction (LVEF) were calculated using the biplane Simpson’s method or the Teichholz formula, when the former was not feasible.

Furthermore, the ratio of LVEF to LAVI was calculated, based on which the patient cohort was categorized into LVEF/LAVI <1.5 (test positive) and ≥1.5 (test negative) as initially described by Aiyarla et al. The subjects were then arranged in a 2 × 2 table based on LVEF/LAVI ratio (<1.5 (test positive) vs. ≥1.5 (test negative)) and LAA thrombus status (present vs. absent). The sensitivity (true positives/true positives + false negatives), specificity (true negatives/true negatives + false positives), likelihood ratio (LR) of a positive test [LR+ = sensitivity/(1–specificity)], LR of a negative test [LR− = (1–sensitivity)/specificity], negative predictive value (NPV = true negatives/all negatives), and positive predictive value (PPV = true positives/all positives) were calculated.

Statistical analysis

The dichotomous and continuous variables were expressed as frequency (%) and mean ± standard deviation, respectively. The χ² test was used to compare dichotomous variables. Fisher’s exact test was used to compare dichotomous variables when the frequency of the observed events is <5. The independent samples Student’s t-test was used to compare continuous normally distributed variables, whereas the Mann–Whitney–Wilcoxon test was used to compare those not adhering to normal distribution. Multivariate logistic regression analysis models were used to identify independent predictors of LAA thrombus. In these models, the LAA thrombus was the dependent (outcome) variable, whereas predictors of LAA thrombus of interest were the independent variables. The risk of LAA thrombus was expressed as odds ratios (OR) with 95% confidence intervals (CI). The receiver operator characteristics (ROC) curve analysis was used to evaluate the discriminatory capacity of LVEF/LAVI ratio in predicting LAA thrombus, which was expressed as area under the curve (AUC) and CI. A two-tailed P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 18.0 software (SPSS, Chicago, IL, USA). The study was approved by the institutional review board of Rush University Medical Center.

Results

We identified 215 patients who met the inclusion and exclusion criteria. The electrophysiological procedures that prompted the TEE were cardioversion in 91 (42.3%), AF ablation in 64 (29.8%), ICD implantation in 42 (19.5%), and ICD revision or testing in 18 (8.4%) subjects. All patients in the cohort were euthyroid. The median time interval between the TTE and TEE in the cohort was 7 days, and 75% of subjects had both studies performed within 80 days. LAA thrombus was detected by TEE in 19 patients (8.8%). The baseline characteristics of patients
with vs. without LAA thrombus are detailed in Table 1. Most notably, patients with LAA thrombus had a higher CHADS2 score, a greater prevalence of cardiac failure, and were more likely to receive oral anticoagulation therapy (Table 1). Multivariate logistic regression analysis demonstrated that the CHADS2 score was an independent predictor of LAA thrombus \( \text{OR} 1.38 \ (\text{CI} \ 1.13–1.68), \ P = 0.001 \), and warfarin anticoagulant was protective of LAA thrombus \( \text{OR} 0.44 \ (\text{CI} \ 0.27–0.75), \ P = 0.002 \), whereas the use of antiplatelet agents was not an independent predictor \( \text{OR} 0.92 \ (\text{CI} \ 0.55–1.55), \ P = 0.77 \).

Furthermore, patients with LAA thrombus were found to have lower mean LVEF and larger mean LAVI than those without LAA thrombus and, thus, significantly smaller mean LVEF/LAVI ratio (Table 2, Figure 1). Multivariate logistic regression analysis determined that LAVI and LVEF predicts LAA thrombus independent of the CHADS2 score [LAVI: \( \text{OR} 1.05 \ (\text{CI} \ 1.02–1.09), \ P = 0.005 \); LVEF: \( \text{OR} 0.95 \ (\text{CI} \ 0.92–0.98), \ P = 0.004 \)]. However, the CHADS2 score was no longer independently predictive of LAA thrombus when tested with LVEF and LAVI in the same regression model \( \text{OR} 0.95 \ (\text{CI} \ 0.62–1.45), \ P = 0.82 \). The latter finding is likely related to multiple co-linearities between the clinical and echocardiographic covariates within the regression model.

When the LVEF/LAVI ratio was dichotomized at a threshold of 1.5, all 19 patients (100%) with LAA thrombus had a LVEF/LAVI \( \leq 1.5 \) vs. 87 (44.4%) among those without LAA thrombus \( (P < 0.001) \), as shown in Table 3. Furthermore, we plotted the study patients in a standard 2 x 2 table based on test status (LVEF/LAVI \( \geq 1.5 \) vs. \( < 1.5 \)) and the LAA thrombus status as shown in Table 3. Based on these data, the sensitivity and the NPV of LVEF/LAVI \( \leq 1.5 \) to detect LAA thrombus were 100%; whereas the specificity and the PPV were 55.6 and 17.9%, respectively. The LR for LVEF/LAVI \( < 1.5 \) (LR+) was 2.25 and for LVEF/LAVI \( \geq 1.5 \) (LR−) was zero.

The ROC curve analysis demonstrated that the LVEF/LAVI ratio has an excellent discriminatory capacity in predicting LAA thrombus.

### Table 1. Baseline characteristics of the validation cohort

<table>
<thead>
<tr>
<th>LAA thrombus present ( (n = 19) )</th>
<th>LAA thrombus absent ( (n = 196) )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) 65.5 ± 12.5</td>
<td>62.5 ± 14.1</td>
<td>0.38</td>
</tr>
<tr>
<td>Age ( \geq 75 ) (%) 5 (26.3)</td>
<td>42 (21.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Female gender (%) 5 (26.3)</td>
<td>68 (34.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Diabetes mellitus (%) 8 (42.1)</td>
<td>54 (27.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension (%) 16 (84.2)</td>
<td>129 (65.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiac failure (%) 15 (78.9)</td>
<td>101 (51.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke (%) 2 (10.5)</td>
<td>22 (11.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>CHADS2 score 2.5 ± 1.3</td>
<td>1.9 ± 1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine (mg/dL) 1.6 ± 0.67</td>
<td>1.3 ± 0.69</td>
<td>0.05</td>
</tr>
<tr>
<td>Warfarin (%) 15 (83.3)</td>
<td>109 (56.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Antiplatelet agents (%) 10 (52.6)</td>
<td>90 (46.2)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data are expressed as frequency (%) or as mean ± standard deviation.

### Table 2. Results: univariate analysis

<table>
<thead>
<tr>
<th>LAA thrombus present ( (n = 19) )</th>
<th>LAA thrombus absent ( (n = 196) )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%) 23.5 ± 13.2</td>
<td>43.8 ± 19.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA volume index (mL/m²) 44.2 ± 13.1</td>
<td>30.4 ± 13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF/LAVI ratio 0.6 ± 0.3</td>
<td>1.8 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF/LAVI ( &lt; 1.5 ) 19 (100%)</td>
<td>87 (44.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass index (g/m²) 124.0 ± 44.8</td>
<td>124.5 ± 43.5</td>
<td>0.96</td>
</tr>
<tr>
<td>LV volume index (mL/m²) 95.6 ± 38.2</td>
<td>74.2 ± 34.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are expressed as frequency (%) or as mean ± standard deviation.

### Table 3. Validation of LVEF/LAVI ratio prediction rule

<table>
<thead>
<tr>
<th>LAA thrombus present ( n = 19 ) (8.8%)</th>
<th>LAA thrombus absent ( n = 196 ) (91.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF/LAVI ( &lt; 1.5 ) 106 (49%)</td>
<td>19 (100%)</td>
</tr>
<tr>
<td>LVEF/LAVI ( \geq 1.5 ) 109 (51%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Figure 1. Box plots of LVEF/LAVI ratio based on the presence or absence of LAA thrombus.
Transthoracic echocardiographic tool predicts left atrial thrombus

Thrombus with an AUC of 0.83 (CI 0.76–0.90, P < 0.001), as shown in Figure 2. The ROC curve coordinates demonstrated that in our particular cohort, none of the patients with LVEF/LAVI ratio ≥1.12 had LAA thrombus.

Discussion

This is the first investigation to validate a prediction tool using TTE parameters to exclude the diagnosis of LAA thrombus in an external patient cohort with nonvalvular AF prior to undergoing a cardioversion or electrophysiology procedure. The ROC curve analysis demonstrates that the LVEF/LAVI ratio has an excellent discriminatory capacity in predicting LAA thrombus with an AUC of 0.83, which is similar to the originally reported 0.88 value.15 We reproduced the findings of Ayirala et al. demonstrating that the LVEF/LAVI ratio of <1.5 has a 100% sensitivity and NPV in detecting LAA thrombus with specificity and PPV of 55.6 and 17.8%, respectively. The diagnostic performance values of the LVEF/LAVI prediction rule identified in this validation cohort were nearly identical to those reported by Ayirala et al. who identified a sensitivity and NPV of 100%; whereas the specificity and PPV were 56 and 16%, respectively.15 The low PPV is primarily related to the low prevalence of LAA thrombus in the validation cohort (8.8%). However, the greatest value of this tool lays in its very high sensitivity and NPV, which can accurately identify patients with nonvalvular AF who are at a very low risk to have LAA thrombus, obviating the need to perform a TEE procedure prior to cardioversion or electrophysiology procedure. Such a practice would add efficiency to patient care and eliminate the small risks associated with TEE in patients at low risk to form an LAA thrombus. Furthermore, in the current climate of escalating costs of medical care, it is crucial to eliminate unneeded testing. Having applied this prediction rule could have avoided TEE in more than one-half of the patients without adding any incremental cost because it utilizes readily available data from TTE that should be obtained in all patients with AF based on the current practice guidelines regardless of whether cardioversion is contemplated or not.1 Moreover, the rate of utilizing TEE has risen from 3.4 per thousand Medicare claims to 5.5 per thousand in 2008.15 Much of this increase is likely related to the increased use of advanced interventions such as ablation and electrical or chemical cardioversion in patients with nonvalvular AF. This utilization is likely to escalate further, given the increasing prevalence of AF due to ageing population and the heart failure epidemic.10 Given that the current Medicare reimbursement for a TEE is ≈$317, in addition to the cost of administering moderate sedation, the potential cost savings from implementing this prediction rule are significant.

The fact that LVEF/LAVI is highly predictive of LAA thrombus is not particularly surprising. It is physiologically plausible that impaired LVEF and the consequent elevation in the LV filling pressure lead to LA enlargement and blood stasis that result in LAA thrombus formation.21 It is also plausible that chronic elevation in LA pressure and the consequent LA volume and pressure overload lead to deterioration of LAA contractility, leading to additional LA blood stasis and consequent thrombus formation.22 Furthermore, LA enlargement often confounds permanent AF; a known independent predictor of LAA thrombus formation.23 Therefore, a ratio of LVEF to LAVI encompasses multiple robust physiological predictors for LAA thrombus formation.

Furthermore, because LAA thrombus is the source of the majority of systemic thromboembolic events in AF, predicting LAA thrombus is a clinical challenge of utmost importance.3–8 The CHADS2 and CHADS-VASc scores are well validated and widely used clinical risk prediction tools in nonvalvular AF.2,24,25 We propose that applying additional TTE prediction rules such as LVEF/LAVI ratio may help to further risk stratify patients. Its particularly high sensitivity can potentially identify patients at low stroke risk and, thus, avoid the significant morbidity associated with oral anticoagulants. This hypothesis needs to be tested in an outcome study looking at systemic thromboembolism, including stroke, as a main endpoint, rather than LAA thrombus.

One of the inherent features of an external validation is that the patient population in which the tool was developed is different than the one it is applied to, or validated against. Our cohort had some differences from the one reported by Ayirala et al., including a higher mean CHADS2 score (2.53 vs. 2.3 and 1.87 vs. 1.7 in the patients with and without LAA thrombus, respectively) and a higher proportion of patients on anticoagulation (83.3 vs. 44 and 56.5 vs. 21% in the patients with and without LAA thrombus, respectively). Moreover, the proportion of patients with LAA thrombus was lower in our study (8.8 vs. 15.6%), which can be at least partially explained by higher utilization of oral anticoagulants. Despite these differences, our results did not deviate significantly from the original description of this tool by Ayirala et al. Furthermore, in our cohort, the LA volume was calculated using three linear dimensions [4πr3 (L/2) (D1/2) (D2/2)], whereas Ayirala et al. implemented the area-length method.16 Both of these methods are endorsed by the American Society of Echocardiography guidelines.15 Although the difference in methodology may yield slight differences in LA volume calculations, it would not take away from the excellent reproducibility of the diagnostic
performance of the prediction rule. In fact, our study suggests that the prediction rule performs well irrespective of the method used to calculate the LA volume.

The clinical data of the study subjects were collected retrospectively, which limited our ability to discern the chronicity of AF in many subjects. Echocardiographic parameters, however, were prospectively measured offline for the purpose of compiling this cohort. The retrospective nature of clinical data collection does not impact the conclusion of this study because it is primarily based on objective echocardiographic measurements. Additionally, it would have been ideal, if the TTE and TEE of the study subjects were performed on the same day. However, in the majority of the subjects, these studies were separated only by a few days. Furthermore, this limitation is expected to bias the study towards the null because the TEE and TTE may have been performed under different haemodynamic and anticoagulation statuses and, thus, rendering TTE less effective in predicting LAA thrombus. Moreover, it is plausible that the TTE findings such as depressed LVEF and LA enlargement could have biased the treating physician in favour of utilizing oral anticoagulants to prevent LAA thrombus and stroke, thus reducing the likelihood of diagnosing LAA thrombus by TEE a few weeks later. Nonetheless, such a bias would not affect the sensitivity or the NPV of the LVEF/LAVI prediction rule. On the contrary, it may have reduced the likelihood of LAA thrombus and, thus, decreased the specificity and PPV of the prediction rule.

We also acknowledge that this study is limited by small sample size and, more importantly, by the low number of LAA thrombus events, which limited our ability to study multiple covariates within a single logistic regression model. This problem was compounded by multiple co-linearities between the major clinical and echocardiographic predictors (CHADS2, LVEF, and LAVI). Despite this limitation, the current sample size and event rate were sufficient to demonstrate the main study objective of validating the LVEF/LAVI ratio as a predictor of LAA thrombus.

Conclusion

This investigation validates the use of LVEF/LAVI ratio <1.5 as a prediction rule for LAA thrombus with an excellent sensitivity and NPV. Thus, a ratio ≥1.5 virtually ‘rules-out’ LAA thrombus, obviating the need for TEE. Although these results are very promising, a prospective validation of this tool in a large cohort will be needed before its wide implementation in clinical practice.

Acknowledgements

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Funding

Internal.

Conflicts of interest: None declared.

References


18. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the
A 43-year-old man with repaired tetralogy of Fallot presented with chest pain. His electrocardiogram revealed sinus rhythm with non-specific ST-T wave changes, and a nuclear stress test was negative for ischaemia. Transthoracic echocardiography in the parasternal short-axis view at the level of the aortic cusp (AC) revealed that the left main coronary artery (LMCA) and right coronary artery (RCA) shared a single ostium (Panel A).

Cardiac computed tomographic angiography (CTA) confirmed the diagnosis and further delineated the course of the coronary branches (Panels B–D). In the short-axis view at the level of the AC, a solitary coronary artery gave rise to the RCA, a diminutive middle branch, and a long LMCA (Panel B). Volume-rendered three-dimensional reconstruction of the heart and great vessels demonstrated a single coronary ostium branching off the RCA (Panel C) as well as the LMCA, which coursed anterior to the right ventricular outflow tract and gave rise to the left anterior descending (LAD) artery and left circumflex coronary (LCX) artery (Panel D).

Coronary anomalies occur in 10% of patients with tetralogy of Fallot. The anomaly of a single coronary from the right cusp giving rise to the RCA and LMCA has only been reported in two previous cases. This case highlights the importance of echocardiography and cardiac CTA as powerful diagnostic tools in this highly complicated population with adult congenital heart disease. *Single common trunk.

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