Relation of Left Atrial Enlargement to Subsequent Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients With Low to Borderline Embolic Risk

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The current thromboembolic risk stratification of non-valvular atrial fibrillation (NVAF) does not include parameters from transthoracic echocardiography (TTE). We hypothesized that left atrial enlargement (LAE) on TTE could discriminate who require anticoagulation therapy among NVAF patients with low/borderline clinical embolic risk. This single-center cohort study included 6,602 patients with NVAF (median age, 56 years, 70.0% male) with a low to borderline clinical embolic risk (CHA_2DS_2-VASc score: 0 to 1 in males, 1 to 2 in females). LAE was classified as mild (≥41 mm in males; ≥39 mm in females) or moderate-severe (≥47 mm in males; ≥43 mm in females). The main study outcome was thromboembolic event (ischemic stroke and systemic embolism). Mild and moderate-severe LAE was diagnosed in 26.1% and 32.9% of the cohort, respectively. The patients with moderate-severe LAE showed a higher prevalence of baseline comorbidities and valvular heart disease and had a higher incidence of thromboembolic events than patients with mild or no LAE at 2 years of follow-up (2.5% vs 1.3% vs 1.1%, respectively, $p < 0.001$). After multivariable adjustment, patients with moderate-severe LAE were at a higher risk of thromboembolic event (hazard ratio, 2.54; 95% CI, 1.65 to 3.90; $p < 0.001$) compared to those with no LAE. This result persisted in a subgroup analysis of anticoagulant-naÿve patients. The rate of thromboembolic events in patients with low clinical embolic risk and moderate-severe LAE was not different to those with high clinical embolic risk without LAE. In conclusion, Moderate-severe LAE on TTE was a significant predictor of thromboembolic events in NVAF patients at low/borderline clinical embolic risk. **(Am J Cardiol 2021;143:67−73)**

The burden of atrial fibrillation (AF) is continuously growing with the global aging population.[1] Prevention of thromboembolic events is a fundamental component of managing AF.[2] Currently, the decision to prescribe anticoagulation in AF patients is made using the CHA_2DS_2-VASc score which mainly comprises clinical risk factors.[3,4] Although this well-designed scoring system is useful in clinical practice, its overall performance to discriminate at-risk patients is not strong enough.[5] To ensure these potentially high-risk patients who require standard anticoagulation are not missed by the scoring system, additional parameters are required. Left atrial enlargement (LAE) identified by transthoracic echocardiography (TTE) is a useful index which reflects the degree of left atrial (LA) remodeling associated with AF.[6] This simple indicator is easy to measure, highly reproducible, and known to be associated with the risk of incident AF or ischemic stroke.[7−10] However, the clinical usefulness of LAE to guide anticoagulation in a specific population has not been sufficiently evaluated. In this study, we hypothesized that LAE on TTE could identify patients who require anticoagulation within a group classed as low embolic risk using a clinical risk stratification scheme. We evaluated the data from a large single-center registry to find the clinical effectiveness of LAE to predict future thromboembolic risks in AF patients.

Methods

This is a retrospective observational review of consecutive non-valvular AF patients in our center. A total of 20,889 patients were diagnosed with AF between 2006 and 2016 in Asan Medical Center, Seoul, Korea. Patients were excluded from the study if they met the following criteria: (1) had valvular AF (mitral stenosis or prosthetic valve), (2) were lost to follow-up after the initial presentation, (3) had no baseline echocardiography available, or (4) were at high embolic risk (CHA_2DS_2-VASc score >1 in males and >2 in females). The outcome data of patients with a CHA_2DS_2-VASc score of 2 in males and 3 in females (or a CHA_2DS_2-VA score of 2 of both gender, n = 3,281) was excluded from the main analysis but used as control in the subgroup analysis. The patients were divided into 3 groups in accordance with the findings of the baseline TTE: (1) those without LAE, (2) those with mild LAE, and (3) those with moderate-to-severe LAE. This study was approved by the Institutional Review

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See page 72 for disclosure information.

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Board of Asan Medical Center (IRB No. 2020-0696). Informed consent was waived by the board due to the retrospective nature of the study.

Data of the study subjects were extracted from the Asan Biomedical Research Environment system, which is a big-data solution in our center incorporating all the demographic, imaging, and follow-up data in an anonymized form.[11] The baseline characteristics, imaging findings, and medications for all patients were acquired from the medical records at the time nearest to each patient's AF diagnosis. The baseline thromboembolic risk was calculated using the CHA_2DS_2-VASc scoring system. CHA_2DS_2-VA score was also calculated in which the sex category of CHA_2DS_2-VASc score was omitted. Patients at low/borderline embolic risk were defined as having a CHA_2DS_2-VASc score of 0 to 1 in males and 1 to 2 in females (or a CHA_2DS_2-VA score of 0 to 1 in both genders) because female gender is not an independent risk factor for thromboembolic events in a low/borderline embolic risk in the Asian population.[12,13] The groups with LAE were defined according to the findings of the baseline TTE and based on the anterior-posterior dimensions in a parasternal long-axis view: mild (≥41 mm in males; ≥39 mm in females) and moderate-to-severe (≥47 mm in males; ≥43 mm in females).[7,14]

The primary outcome was the incidence of new-onset ischemic stroke or systemic embolism during follow-up. The data on the primary outcomes were gathered from reviews of all available medical records, imaging findings, and disease-specific codes. From these data, ischemic stroke was diagnosed primarily based on the imaging findings and clinical presentation[15] which was confirmed by the individual neurologist who was blinded to the clinical outcomes. Systemic embolism was defined as a sudden loss of perfusion in a limb or organ based on clinical manifestations, imaging, and functional studies.

The categorical variables were presented as frequency with percentage and continuous variables as median and interquartile range or mean and standard deviation. The results between the groups were compared using the chi-square test for categorical variables and using analysis of variance with post hoc analysis with Tukey's method or Wilcoxon rank-sum test as appropriate for continuous variables. The Kaplan-Meier method was used to calculate the unadjusted event rates, and the groups were compared using a log-rank test. The Cox proportional hazards model was used to assess the relative risk of each variable to affect the study outcomes. The log [−log survival)] curves and partial (Schoenfeld) residuals were tested using the proportional hazard assumption. Moreover, a 3-step Cox proportional hazards model was made: Model 1, unadjusted; Model 2, adjusted for components of the CHA_2DS_2-VASc score; and Model 3, adjusted for CHA_2DS_2-VASc score, body mass index, persistent AF, chronic kidney disease, pervious cardiac surgery, and moderate-to-severe valve disease (other than mitral stenosis). This analysis was repeated in those whom naïve to the anticoagulation treatment for sensitivity analysis (n = 5513). In this subgroup, the subjects were censored when the study outcome occurred, anticoagulants were prescribed, or the follow-up period ended, whichever came first. All statistical analyses were performed using R software version 3.3.1 and 2-sided p values <0.05 were considered statistically significant.

Results

Of the 20,889 AF patients treated at our center, 6,602 patients met the inclusion and exclusion criteria (Figure 1). In those patients with low/borderline thromboembolic risk, 26.1% (n = 1,726) of them were diagnosed with mild LAE

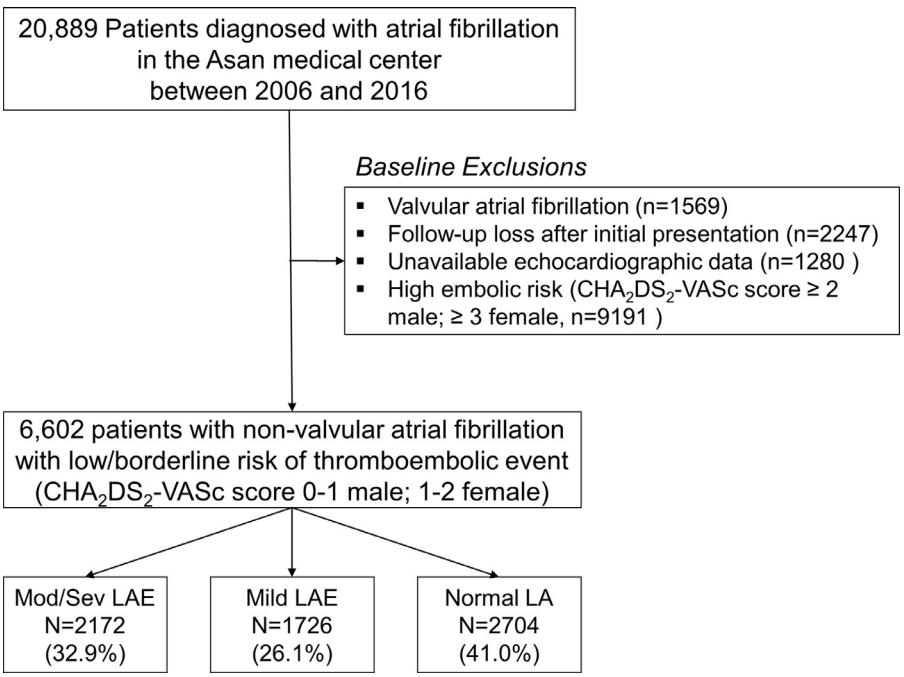


Figure 1. Study design.

Table 1
Baseline characteristics of patients with atrial fibrillation classed as low/borderline thromboembolic risk

Variable	Overall (n = 6602)	None (n = 2704)	Left atrial enlargement		p value
			Mild (n = 1726)	Moderate/severe (n = 2172)	
Age (years)	55.9 ± 10.3	54.1 ± 11.5	56.8 ± 9.2	57.5 ± 9.1	<0.001
Men	4620 (70.0%)	2016 (74.6%)	1385 (80.2%)	1219 (56.1%)	<0.001
Body mass index (Kg/m^2)	24.4 ± 3.4	23.4 ± 3.2	25.0 ± 2.9	25.1 ± 3.6	<0.001
Persistent atrial fibrillation	2775 (42.0%)	678 (25.1%)	730 (42.3%)	1367 (62.9%)	<0.001
Hypertension	2292 (34.7%)	695 (25.7%)	666 (38.6%)	931 (42.9%)	<0.001
Diabetes mellitus	213 (3.2%)	88 (3.3%)	64 (3.7%)	61 (2.8%)	0.286
Vascular disease*	58 (0.9%)	29 (1.1%)	12 (0.7%)	17 (0.8%)	0.356
Congestive heart failure	170 (2.6%)	45 (1.7%)	33 (1.9%)	92 (4.2%)	<0.001
Chronic lung disease	156 (2.4%)	89 (3.3%)	34 (2.0%)	33 (1.5%)	<0.001
Chronic kidney disease	811 (12.3%)	311 (11.5%)	175 (10.1%)	325 (15.0%)	<0.001
CHA_2DS_2-VA score†					<0.001
0	2758 (41.8%)	1431 (52.9%)	657 (38.1%)	670 (30.8%)	
1	3844 (58.2%)	1273 (47.1%)	1069 (61.9%)	1502 (69.2%)	
CHA_2DS_2-VASc score					<0.001
0	1947 (29.5%)	1064 (39.3%)	533 (30.9%)	350 (16.1%)	
1	3484 (52.8%)	1319 (48.8%)	976 (56.5%)	1189 (54.7%)	
2	1171 (17.7%)	321 (11.9%)	217 (12.6%)	633 (29.1%)	
Echocardiography					
Left atrial diameter (mm)	42.6 ± 8.5	35.2 ± 3.8	42.8 ± 1.9	51.7 ± 7.0	<0.001
LV ejection fraction (%)	58.4 ± 8.2	60.0 ± 7.0	58.4 ± 7.9	56.5 ± 9.3	<0.001
LV end-diastolic diameter (mm)	50.0 ± 6.4	48.0 ± 5.4	50.1 ± 5.4	52.3 ± 7.4	<0.001
Previous cardiac operation	288 (4.4%)	80 (3.0%)	50 (2.9%)	158 (7.3%)	<0.001
Mod/Sev Left sided Valvular disease‡	688 (10.4%)	47 (1.7%)	78 (4.5%)	563 (25.9)	<0.001
Mod/Sev MR	556 (8.4%)	18 (0.7%)	51 (3.0%)	487 (22.4%)	<0.001
Mod/Sev AS	73 (1.1%)	14 (0.5%)	10 (0.6%)	49 (2.3%)	<0.001
Mod/Sev AR	139 (2.1%)	21 (0.8%)	22 (1.3%)	96 (4.4%)	<0.001
Mod/Sev TR	607 (9.2%)	68 (2.5%)	83 (4.8%)	456 (21.0%)	<0.001
RV-RA PG (mmHg)	24.8 ± 9.4	22.9 ± 8.0	23.3 ± 6.8	28.4 ± 11.6	<0.001
E/E' > 15	1064 (16.1%)	167 (6.2%)	188 (10.9%)	709 (32.6%)	<0.001
Medications on atrial fibrillation diagnosis					
Anticoagulants	1087 (16.5%)	297 (11.0%)	291 (16.9%)	499 (23.0%)	<0.001
Aspirin	2063 (31.2%)	828 (30.6%)	645 (37.4%)	590 (27.2%)	<0.001
Clopidogrel	736 (11.1%)	305 (11.3%)	222 (12.9%)	209 (9.6%)	0.006
Beta-blocker	407 (6.2%)	159 (5.9%)	124 (7.2%)	124 (5.7%)	0.119
Calcium channel blocker	1862 (28.2%)	685 (25.3%)	498 (28.9%)	679 (31.3%)	<0.001
Digoxin	1363 (20.6%)	525 (19.4%)	390 (22.6%)	448 (20.6%)	0.039
Amiodarone	992 (15.0%)	167 (6.2%)	201 (11.6%)	624 (28.7%)	<0.001
Class 1 anti-arrhythmics	383 (5.8%)	91 (3.4%)	105 (6.1%)	187 (8.6%)	<0.001

AS = aortic stenosis; AR = aortic regurgitation; LV = left ventricle; Mod/Sev = Moderate to severe; MR = mitral regurgitation; RA = right atrium; RV = right ventricle; TR = tricuspid regurgitation.

* Previous myocardial infarction, peripheral artery disease, and aortic plaque.

† CHA_2DS_2-VASc score without sex category.

‡ Moderate-severe mitral regurgitation, aortic stenosis, and aortic regurgitation.

and 32.9% (n = 2,172) moderate-to-severe LAE. Table 1 shows the summary of the baseline characteristics of the patients. Compared to those without LAE, patients with moderate-to-severe LAE were characterized by a higher age and higher prevalence of comorbidities such as hypertension, congestive heart failure, or chronic kidney disease. The CHA_2DS_2-VA and CHA_2DS_2-VASc scores of the patients with moderate-to-severe LAE were significantly higher than those of patients without LAE. The proportion of patients with persistent/permanent AF was higher in those with moderate-to-severe LAE than in those without LAE. Based on the results of the baseline echocardiography, moderate-to-severe valvular disease (other than mitral stenosis) was more prevalent in those with moderate-to-severe LAE. LAE patients were also characterized by lower left ventricular (LV) ejection fraction and larger LV dimension. Standard anticoagulation was more frequently used in moderate and/or severe LAE.

During the follow-up period (median 2.9 years, interquartile range 1.1 to 5.1 years), the primary outcome occurred in 163 patients (2.5%). Figure 2 shows the crude incidence of the primary outcome. Patients with moderate-to-severe LAE had a significantly higher rate of primary outcome compared to those with mild LAE or without LAE (moderate-to-severe LAE, 2.5%; mild LAE, 1.3%; and without LAE, 1.1%, $p < 0.001$). This finding persisted when the analysis was confined to the anticoagulation-naïve population (moderate-to-severe LAE, 3.4%; mild LAE,

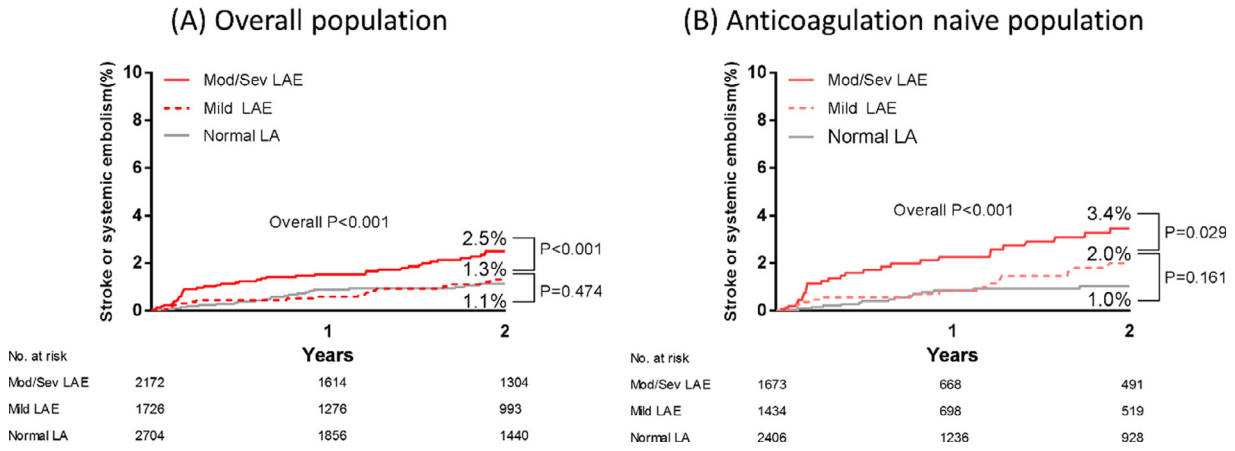


Figure 2. Incidence of ischemic stroke or systemic embolism in patients with low/borderline thromboembolic risk with atrial fibrillation grouped by left atrial enlargement.

2.0%; and without LAE, 1.0%, $p < 0.001$). In the Cox proportional hazards model (Table 2, Supplementary Table 1), patients with moderate-to-severe LAE were at a higher risk of thromboembolic event in the unadjusted model (Model 1, hazard ratio [HR] 2.38, 95% confidence interval [CI] 1.64 to 3.46, $p < 0.001$), the model adjusted for CHA_2DS_2-VASc score (Model 2, HR 2.14, 95% CI 1.46 to 3.15, $p < 0.001$), and the model adjusted for CHA_2DS_2-VASc score and other independent predictors (Model 3, HR 2.54, 95% CI 1.65 to 3.90, $p < 0.001$). The same trend was noted in the subgroup of anticoagulation-naïve patients. The risk of thromboembolic events in patients with mild LAE was not significantly higher than that in those without LAE in any of the models. These results were consistent when the analysis was confined to those patients without significant valvular disease or baseline anticoagulation (n = 5035) (moderate-to-severe LAE 3.4%; mild LAE, 1.4%; and without LAE, 1.1%, $p < 0.001$). LA diameter was a statistically significant predictor when it was entered as a continuous variable in the models.

Figure 3 shows the subgroup analysis according to the presence of moderate-to-severe LAE and CHA_2DS_2-VA score. The higher incidence of the primary outcome in the group with moderate-to-severe LAE compared to the groups with mild LAE or without LAE was consistent in each of the CHA_2DS_2-VA score groups. Importantly, those patients with moderate-to-severe LAE with a $CHADS_2$-VA score of 0 or 1 were at a similar thromboembolic risk as those patients without LAE or mild LAE with a CHA_2DS-VA score of 2, in whom standard anticoagulation was clearly indicated.

The CHA_2DS_2-VA or CHA_2DS_2-VASc scores and the presence of LAE were only modest discriminators for the primary outcome in these patients with low thromboembolic risk (Table 3). However, their discriminating performance was improved significantly when the presence of LAE was added to the clinical risk scores.

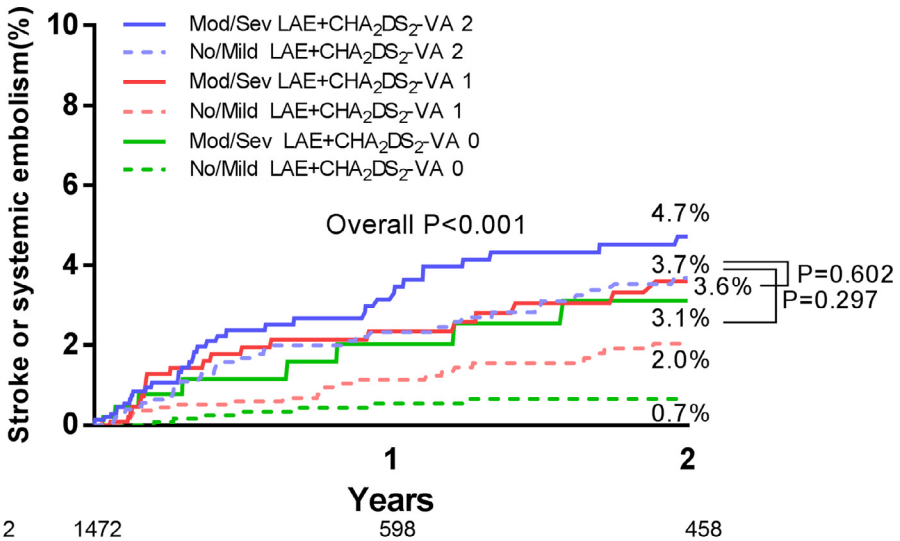
Discussion

The major findings of the current study were as follows: (1) moderate-to-severe LAE on TTE was a common finding in NVAF patients with low and/or borderline embolic risk; (2) moderate-to-severe LAE was a significant predictor of thromboembolic events; (3) the embolic risk of patients with moderate-to-severe LAE at low/borderline embolic risk was comparable to those without moderate-to-severe LAE at high embolic risk; and (4) the presence of LAE on TTE enhanced the

Table 2
Implication of left atrial enlargement (LAE) on future thromboembolic events in patients with atrial fibrillation

	Model 1: Unadjusted		Model 2: Adjusted for components of the CHA2DS2-VASc score*		Model 3: Adjusted for model 2 and other relevant factors†	
Variable	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Overall population (n = 6602)						
Mild LAE (vs. normal LA)	1.18 (0.75−1.87)	0.473	1.09 (0.68−1.72)	0.730	1.23 (0.77−1.97)	0.380
Moderate to severe LAE (vs. normal LA)	2.38 (1.64−3.46)	<0.001	2.14 (1.46−3.15)	<0.001	2.54 (1.65−3.90)	<0.001
LA diameter (per 5 mm)	1.15 (1.06−1.24)	<0.001	1.13 (1.04−1.23)	0.004	1.17 (10.6−1.29)	0.002
Anticoagulation-naïve population (n = 5513)						
Mild LAE (vs. normal LA)	1.25 (0.77−2.03)	0.363	1.09 (0.67−1.77)	0.743	1.52 (0.85−2.72)	0.154
Moderate to severe LAE (vs. normal LA)	2.41 (1.61−3.60)	<0.001	2.18 (1.44−3.30)	<0.001	2.96 (1.68−5.22)	<0.001
LA diameter (per 5 mm)	1.15 (1.06−1.26)	0.001	1.14 (1.04−1.26)	0.006	1.32 (1.13−1.54)	<0.001

* Adjusted for age, sex, hypertension, diabetes, congestive heart failure, and vascular disease.
† Adjusted for age, sex, body mass index, persistent atrial fibrillation, hypertension, diabetes, congestive heart failure, vascular disease, chronic kidney disease, previous cardiac surgery, and moderate to severe valve disease.



No. at risk			
Mod/Sev LAE + CHA_2DS_2-VA 2	1472	598	458
No/Mild LAE + CHA_2DS_2-VA 2	1809	838	623
Mod/Sev LAE + CHA_2DS_2-VA 1	1157	462	339
No/Mild LAE + CHA_2DS_2-VA 1	2013	1017	769
Mod/Sev LAE + CHA_2DS_2-VA 0	516	208	153
No/Mild LAE + CHA_2DS_2-VA 0	1827	918	682

Figure 3. Incidence of thromboembolic events according to left atrial enlargement and clinical embolic risk.

discriminating performance of the CHA_2DS_2-VASc risk stratification scheme.

The CHA_2DS_2-VASc system used for risk stratification in major cardiovascular guidelines incorporates only clinical risk parameters without sufficient discriminating performance, as shown in our data as well as in its original description.[5] As TTE is recommended in the initial phase of AF diagnosis to differentiate between valvular AF and the presence of structural heart disease, it is available in a large proportion of NVAF patients.[16] The degree of LAE is already known to be associated with the degree of LA structural remodeling,[17] and the LA anterior-posterior diameter used in our analysis is a standardized parameter of LAE with excellent reproducibility.[7] Therefore, LAE at initial TTE has the potential to be a universal and clinically useful marker to guide anticoagulation in NVAF patients with a low thromboembolic risk.

The present study demonstrated that the addition of LAE as a parameter enabled the identification of high-risk patients who were classified as clinically low-risk patients using the CHA_2DS_2-VASc scheme. An overall relationship between LAE and subsequent thromboembolic events has been documented in other recent registry studies.[9,10] Furthermore, the present study demonstrated an additive prognostic implication of moderate-to-severe LAE in this specific population of patients with a low/borderline clinical risk profile (CHA_2DS_2-VA score 0 to 1). As presented in Table 3, CHA_2DS_2-VA score alone is not sufficient for discriminating patients who require anticoagulation. In particular, anticoagulation should be considered in patients with a CHA_2DS_2-VASc score of 1 according to most of the guidelines, but it is not based on firm clinical evidence.[3,4] With the recent introduction of non-vitamin K antagonist oral anticoagulation lowering the threshold for anticoagulation, some advocate standard anticoagulation in this low or borderline risk population.[18] We agree with this, but defining a group at higher risk within these patients would maximize the risk-benefit ratio of anticoagulation. In this regard, one of the interesting findings of our study is that in patients with moderate-to-severe LAE, not only those with a CHA_2DS_2-VA score of 1 but also those with a score of 0 had a risk comparable to the patients without LAE with a CHA_2DS_2-VA score of 2, which were clearly subject to standard anticoagulation. Therefore, our study suggested that patients with moderate-to-severe LAE should be treated with standard anticoagulation, even when the patient is at a low or borderline risk according to the CHA_2DS_2-VASc or CHA_2DS_2-VA scheme. We believe our findings are of clinical importance to avoid missing anticoagulation therapy in potentially high-risk patients. The effectiveness of anticoagulation in this group should be evaluated in large and prospective studies.

The mechanism by which LAE is associated with thromboembolic risk is beyond the scope of the current study but may be partly explained in the following ways. LAE is significantly associated with the structural remodeling of the LA, which is important for triggering and perpetuating

Table 3
Additive predictive performance of left atrial enlargement (LAE) for risk of ischemic stroke or systemic embolism

Variable	C-static	95% CI
CHA_2DS_2-VA score	0.572	0.529–0.615
CHA_2DS_2-VASc score	0.573	0.527–0.620
LAE	0.604	0.552–0.656
CHA_2DS_2-VA score + LAE*	0.636	0.589–0.683
CHA_2DS_2-VASc score + LAE†	0.628	0.578–0.678

* $p < 0.001$ for pairwise comparison with the CHA_2DS_2-VA score.
† $p = 0.001$ for pairwise comparison with the CHA_2DS_2-VASc score.

AF.[17,19] The enlargement of the chamber, decreased contractility, and reservoir functions in AF patients are also associated with increased blood stasis.[20] Either way, this could mechanistically link LAE with the risk of thromboembolism. The detailed parameters of LA function such as LA strain for LA contractile dysfunction may more directly represent the underlying mechanism, but their clinical relevance should still be evaluated. Based on current evidence, we believe that LAE itself is also clinically useful, especially considering its popularity, ease of measurement, and reproducibility.

However, our study has several limitations. Inherent selection bias cannot be avoided in a retrospective observational study. In the same context, study outcomes could be underestimated as only consecutive patients were included. The definition of low to borderline embolic risk is not based on standard CHA_2DS_2-VASc score as we omitted the sex category study population based on observational findings from the Korean NHIS data. Therefore, the generalization of our findings should be done carefully as it has not been sufficiently evaluated in the clinical data of other populations. The LA anterior-posterior diameter is fundamentally a 1-dimensional measurement of LAE and possibly less accurate than the LA area or volume, despite its excellent reproducibility. It could also be dynamically changed for the persistence of AF as well as volume status of patient in some degree. The indications for anticoagulation would not be consistent for its long enrollment period. Finally, novel parameters with better discriminating performance, such as LA strain or LA volume index, cannot be acquired in all patients.

In conclusion, moderate-to-severe LAE on TTE is a clinically useful predictor of thromboembolic events in NVAF patients with a low clinical embolic risk. Standard anticoagulation should be considered in these patients.

Authors' Contributions

Conceptualization and Methodology: Min Soo Cho, Jun Kim, Gi-Byoung Nam, Kee-Joon Choi; Resources: Min Soo Cho, Minsoo Kim, and Ungjeong Do; Formal analysis and data curation: Min Soo Cho; Writing − original draft, review, and editing: Min Soo Cho and Kee-Joon Choi; Supervision: Kee-Joon Choi; Manuscript approval: All authors

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.034.

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