Left Atrial Diameter and Atrial Ectopic Burden in Patients with Embolic Stroke of Undetermined Source: Risk Stratification of Atrial Fibrillation with Insertable Cardiac Monitor Analysis

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Background and Purpose An insertable cardiac monitor (ICM) has been demonstrated to be a useful tool for detecting subclinical atrial fibrillation (AF) in patients with embolic stroke of undetermined source (ESUS). This study aimed to identify the clinical predictors of AF in ESUS patients with ICMs.

Methods We retrospectively selected consecutive patients with an ICM implanted for AF detection following ESUS. The primary endpoint was defined as any AF episode lasting for longer than 5 min. The atrial ectopic burden (AEB) was calculated as the percentage of the number of conducted QRS from atrial ectopy on Holter monitoring.

Results This study included 136 patients. AF lasting $\geq$5 min was detected in 20 patients (14.7%) during a median follow-up period of 6.6 months (interquartile range, 3.3−10.8 months). AF patients had a higher AEB (0.20% vs. 0.02%, $p<0.001$) and a larger left atrial diameter (LAD, 41.0 mm vs. 35.3 mm, $p<0.001$) than those without AF. The areas under the receiver operating characteristic curves were 0.795 and 0.816 for the LAD and log-transformed AEB, respectively, for the best cutoff values of 38.5 mm for LAD and 0.050% for AEB. AF lasting $\geq$5 min was detected in 34.6% (9/26) of patients with LAD $\geq$38.5 mm and AEB $\geq$0.050%, and in 0% (0/65) of those with LAD <38.5 mm and AEB <0.050%.

Conclusions AF was detected in a significant proportion of ESUS patients during a 6.6-month follow-up. The LAD and AEB are good predictors of AF and might be useful for AF risk stratification in ESUS patients.

Key Words stroke; atrial fibrillation; electrocardiography; monitoring, ambulatory.

INTRODUCTION

Despite ongoing technical advancements in imaging methods and improved pathophysiological understanding, the definitive cause of ischemic stroke remains inconclusive in 20−40% of cases.[1,2] There is a large amount of evidence that thromboembolism accounts for most of these so-called cryptogenic strokes.[2] This has led to the pragmatic clinical construct of embolic stroke of undetermined source (ESUS) being proposed, which is currently being used preferentially.[2]

Atrial fibrillation (AF) is the most common cause of cardioembolism and is therefore a potential cause of ESUS.[3] Considering that oral anticoagulant (OAC) therapy substantially reduces the risk of recurrent stroke compared with aspirin and no treatment,[4] identifying hidden AF is of paramount importance for the secondary prevention of stroke. However,

given that AF is often asymptomatic and occurs sporadically, it might not be identified in the prolonged electrocardiography (ECG) monitoring performed during hospitalization for acute stroke.

An insertable cardiac monitor (ICM) is a small device that is implanted in the subcutaneous layer of the anterior chest wall that allows continuous ambulatory ECG monitoring.[5] An ICM has a sensitivity and negative predictive value of >95% in detecting AF, with AF episodes detected in approximately 20% of ESUS patients who were followed up for 2 years.[6] Despite the good performance in detecting AF in patients with ESUS, the cost of ICM insertion remains high (approximately USD 10,000 in the USA).[7] The cost-effectiveness of an ICM could be substantially improved if low-risk patients were excluded, because most of them do not benefit from the ICM. However, data regarding predictors of AF in this population are rare, and so the present study aimed to identify the predictors of AF in ESUS patients with an ICM.

METHODS

Study population and design
We retrospectively selected all consecutive ESUS patients who underwent ICM insertion for AF detection from March 1, 2016 to July 31, 2020 at our institution. The diagnosis of ESUS was established by neurologists when the patients satisfied the following criteria: nonlacunar brain infarction, open arteries (<50% stenosis) proximal to the infarct, and no major risk of cardioembolic source (AF or severe left ventricular dysfunction).[2] The diagnostic assessment included brain computed tomography or magnetic resonance imaging showing a nonlacunar infarct, transthoracic echocardiography, 12-leads ECG and Holter monitoring for ≥24 h, and imaging of the extracranial and intracranial arteries supplying the area of the brain infarct.[2] Demographic, clinical, laboratory, Holter, and echocardiographic data were obtained from a prospective stroke registry database or by reviewing electronic medical records.[8] Patients who were lost to follow-up immediately after ICM implantation (e.g., due to transfer to another hospital) were excluded.

The primary endpoint was the detection of any AF episode lasting ≥5 min by ICM during follow-up. The period of 5 min is reportedly the shortest duration of AF that potentially increases the risk of stroke.[5,9] The secondary endpoint was the longest duration of an AF episode per subject. The study patients were followed from the date of ICM implantation to the date of death or until July 31, 2020, whichever came first.

This study was approved by the Institutional Review Board (Approval number: B-2005/613-111) and conducted according to the principles of the Declaration of Helsinki. The need to obtain informed consent was waived due to the retrospective nature of the study and the minimal risk to the participants.

Insertable cardiac monitor
All study participants were implanted with a Reveal XT/LIN-Q™ (Medtronic, Minneapolis, MN, USA) ICM device. It was reported previously that this device had a sensitivity, specificity, positive predictive value, and negative predictive value for the detection of AF of 98.1%, 98.5%, 91.9%, and 99.7%, respectively.[5] All AF episodes recorded by the ICM device were reviewed by two electrophysiologists. There were no disagreements in the diagnosis of AF.

Calculation of CHA_2DS_2-VASc score
The CHA_2DS_2-VASc score is one of several risk stratification systems for ischemia that can help determine the 1-year risk of a thromboembolic event in a nonanticoagulated patient with nonvalvular AF. The CHA_2DS_2-VASc score for stroke prediction was calculated as the summed score for the following medical conditions: 1 point each for congestive heart failure ("C"), hypertension ("H"), age ("A") between 65 and 74 years, diabetes mellitus ("D"), female sex ("Sc"), and vascular disease ("V"; prior myocardial infarction or peripheral artery disease), and 2 points each for a history of stroke/transient ischemic attack/thromboembolism ("S_2") or age ≥75 years ("A_2").[4] Since the study participants had ESUS, all received a CHA_2DS_2-VASc score of at least 2 points.

Echocardiographic measurement
Echocardiography was performed during hospitalization for acute stroke. The left atrial diameter (LAD) was measured from the anterior to the posterior wall of the left atrium (LA) in a parasternal long-axis view at ventricular end-systole. The LA volume was measured using the Simpson method in apical four-chamber and apical two-chamber views at ventricular end-systole.[10] The LA volume index (LAVI) was calculated as the LA volume in milliliters divided by the body surface area in square meters.

Calculation of the atrial ectopic burden
The atrial ectopic burden (AEB) was calculated as follows based on the data from Holter monitoring (Pathfinder SL/Impresario Holter System, Spacelabs Healthcare, Snoqualmie, WA, USA) performed closest to the date of acute stroke (mostly during hospitalization):

$$AEB\ (\%)= \frac{\text{Number of conducted QRS complexes from atrial ectopy}}{\text{Total number of QRS complexes}} \times 100.$$

All arrhythmic episodes in Holter monitoring were reviewed independently by two electrophysiologists.

Statistical analysis

Categorical variables are presented as numbers and frequencies, while continuous variables are presented as mean±standard deviation values or median and interquartile range (IQR) values. Student's *t*-test and the Kruskal-Wallis test were used to compare continuous variables according to whether or not they conformed to a normal distribution, while the chi-square test was used to compare categorical variables.

Kaplan-Meier curves were plotted to analyze the cumulative incidence of AF, and Cox proportional-hazards regression models were used to predict AF detection. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive accuracy of a variable in AF detection. If data did not conform to a normal distribution and were highly skewed (e.g., AEB), the values were log-transformed for Cox regression and ROC analysis. Statistical tests were performed using SPSS (version 22, IBM Corp., Armonk, NY, USA).

RESULTS

This study finally analyzed 136 patients after excluding 5 patients who were lost to follow-up or transferred to other hospitals. The median period between ESUS diagnosis and ICM implantation was 2.1 months (IQR, 0.3−8.9 months). During the median follow-up period of 6.6 months (IQR, 3.3−10.8

months) after ICM insertion, AF was detected in 25 patients (18.4%), among which 20 had an AF episode lasting ≥5 min (Fig. 1). The median period for detecting AF lasting ≥5 min was 15 days (IQR, 3−32 days). The Kaplan-Meier curve for the detection of AF lasting ≥5 min is shown in Fig. 2A. The median maximum duration of episodes lasting AF ≥5 min was 24.1 h (IQR, 15.4−33.8 h) (Fig. 2B). In contrast, the total duration of AF episodes in the five patients who had AF lasting <5 min was 2.5±1.0 min during the 10.4-month follow-up (data not shown).

Patients in whom AF lasted ≥5 min were older (70.4 years vs. 62.9 years, *p*=0.004) and had a higher AEB (0.20% vs. 0.02%, *p*<0.001), larger LAD (41.0 mm vs. 35.3 mm, *p*<0.001), and higher LAVI (46.5 mL/m^2 vs. 32.7 mL/m^2, *p*=0.004) than those
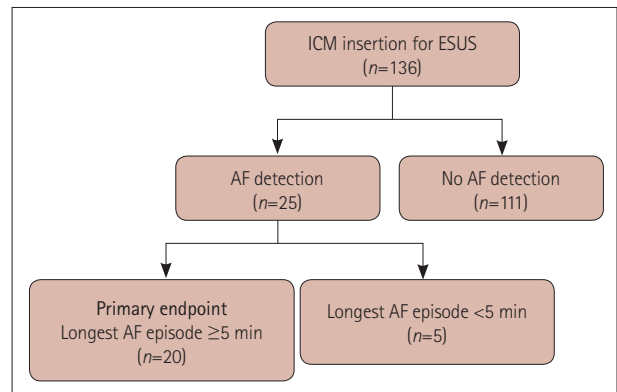
Fig. 1. Flow chart of AF detection after implanting an ICM. AF: atrial fibrillation, ESUS: embolic stroke of undetermined source, ICM: insertable cardiac monitor.
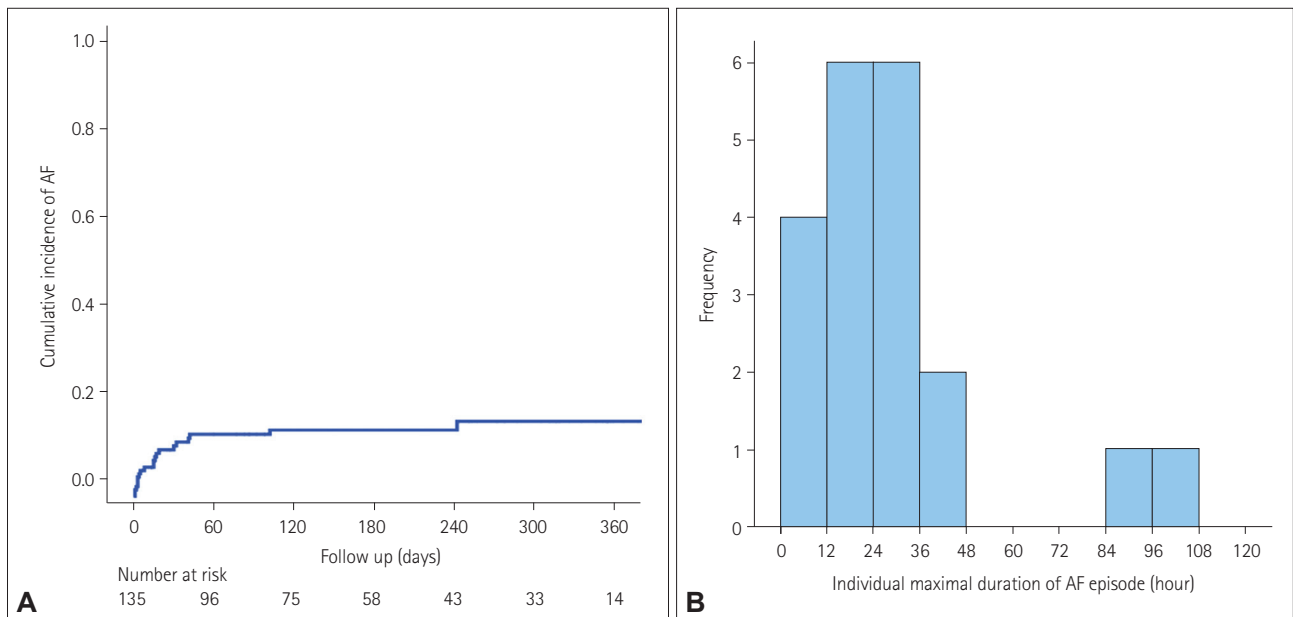
Fig. 2. Incidence and distribution of maximal duration of AF. Kaplan-Meier curve for AF detection in patients with embolic stroke of undetermined source (A) and maximum duration of AF episodes in individual patients (B). AF: atrial fibrillation.

without AF lasting ≥5 min (Table 1). The mean CHA$_2$DS$_2$-VASc score did not differ significantly between these two groups (4.5 vs. 4.0, p=0.101). OACs had been prescribed more frequently at discharge in patients who had AF lasting ≥5 min

Table 1. Baseline characteristics of the study population

	AF not detected (n=116)	AF detected (n=20)	p
Age, years	62.9±14.0	70.4±9.3	0.004
Female	41 (35.3)	5 (25.0)	0.366
Height, cm	164.0±9.5	163.2±9.6	0.711
Weight, kg	66.0±11.0	65.1±11.8	0.751
Body mass index, kg/m^2	24.4±2.9	24.3±2.4	0.827
Past history			
Hypertension	60 (51.7)	13 (65.0)	0.335
Diabetes mellitus	31 (26.7)	7 (35.0)	0.446
Myocardial infarction	0 (0.0)	1 (5.0)	0.147
Hypertrophic CMP	1 (0.9)	0 (0.0)	>0.999
CHA$_2$DS$_2$-VASc score	4.0±1.4	4.5±1.5	0.101
ECG PR interval, ms	177.1±27.3	186.3±49.5	0.230
Holter monitoring			
Number of APCs	18 (6–67)	168 (37–1,326)	<0.001
AEB, %	0.021 (0.007–0.068)	0.199 (0.040–1.602)	<0.001
Echocardiography			
LVEF, %	63.3±4.6	62.7±5.8	0.608
LAD, mm	35.3±5.2	41.0±4.8	<0.001
LAVI, mL/m^2	32.7±8.5	46.5±18.9	0.004
Patent foramen ovale	26 (22.4)	5 (25.0)	0.799
Discharge medication			
Aspirin	94 (81.0)	15 (75.0)	0.532
Clopidogrel	59 (50.9)	7 (35.0)	0.190
OAC	2 (1.7)	2 (10.0)	0.043
Statin	103 (88.8)	16 (80.0)	0.278

Data are n (%), mean±standard-deviation, or median (interquartile range) values.
AEB: atrial ectopic burden, AF: atrial fibrillation, APCs: atrial premature complexes, CMP: cardiomyopathy, ECG: electrocardiography, LAD: left atrial diameter, LAVI: left atrium volume index, LVEF: left ventricular ejection fraction, OAC: oral anticoagulant.

than in those with no AF lasting ≥5 min (10.0% vs. 1.7%, p= 0.043). The detailed baseline characteristics are presented in Table 1.

Atrial fibrillation prediction

In the univariable Cox proportion-hazards regression models, age [hazard ratio (HR), 1.043; 95% confidence interval (CI), 1.005–1.083], log-transformed AEB (HR, 2.724; 95% CI, 1.843–4.028), LAD (HR, 1.244; 95% CI, 1.137–1.362), and LAVI (HR, 1.040; 95% CI, 1.022–1.058) were significantly associated with AF lasting ≥5 min (Table 2). In the multivariable analysis, the log-transformed AEB (HR, 2.311; 95% CI, 1.463–3.649) and LAD (HR, 1.198; 95% CI, 1.085–1.323) were significantly associated with AF lasting ≥5 min.

The areas under the ROC curves for age, LAD, LAVI, and log-transformed AEB were 0.653, 0.795, 0.771, and 0.816, respectively (Fig. 3). The best cutoff values of LAD and AEB for detecting AF ≥5 min were 38.5 mm (sensitivity and specificity of 0.700 and 0.707, respectively) and 0.050% (0.725 and 0.691), respectively. When the AEB and LAD were plotted, no patient with LAD <38.5 mm and AEB <0.050% showed AF lasting ≥5 min during follow-up, whereas those with LAD ≥38.5 mm and AEB ≥0.050% showed an incidence of AF lasting ≥5 min of 34.6% (Fig. 4).

DISCUSSION

This study assessed the incidence of AF in East Asian patients with ESUS, and tested the predictive accuracy of the AEB and LAD in detecting AF. The main findings can be summarized as follows: 1) during the median follow-up period of 6.6 months, significant AF (lasting ≥5 min) was detected in 14.7% of all ESUS patients with an ICM; 2) the AEB and LAD showed good predictive accuracy for AF; and 3) the AEB and LAD seem to improve the ability to determine the risk of hidden AF in ESUS.

The AF incidence in our study (14.7%) over a shorter follow-up is consistent with those found in previous studies (21.5–41% for 2–3 years of follow-up).[3,6,11] Echocardiography and Holter

Table 2. Cox proportional-hazards regression analysis of atrial fibrillation detection

	Univariable		Multivariable*	
	HR (95% CI)	p	HR (95% CI)	p
Age, years	1.043 (1.005–1.083)	0.026	1.001 (0.959–1.044)	0.977
Log(AEB)	2.724 (1.843–4.028)	<0.001	2.311 (1.463–3.649)	<0.001
LAD, mm	1.244 (1.137–1.362)	<0.001	1.198 (1.085–1.323)	<0.001
LAVI, mL/m^2	1.040 (1.022–1.058)	<0.001		
CHA$_2$DS$_2$-VASc score	1.261 (0.934–1.702)	0.130		

*Adjusted variables are age, log-transformed AEB, and LAD. LAVI exhibited collinearity with LAD. LAD was selected in the multivariable model due to its better prediction accuracy in the receiver operating characteristic analysis.
AEB: atrial ectopic burden, HR: hazard ratio, LAD: left atrial diameter, LAVI: left atrium volume index.
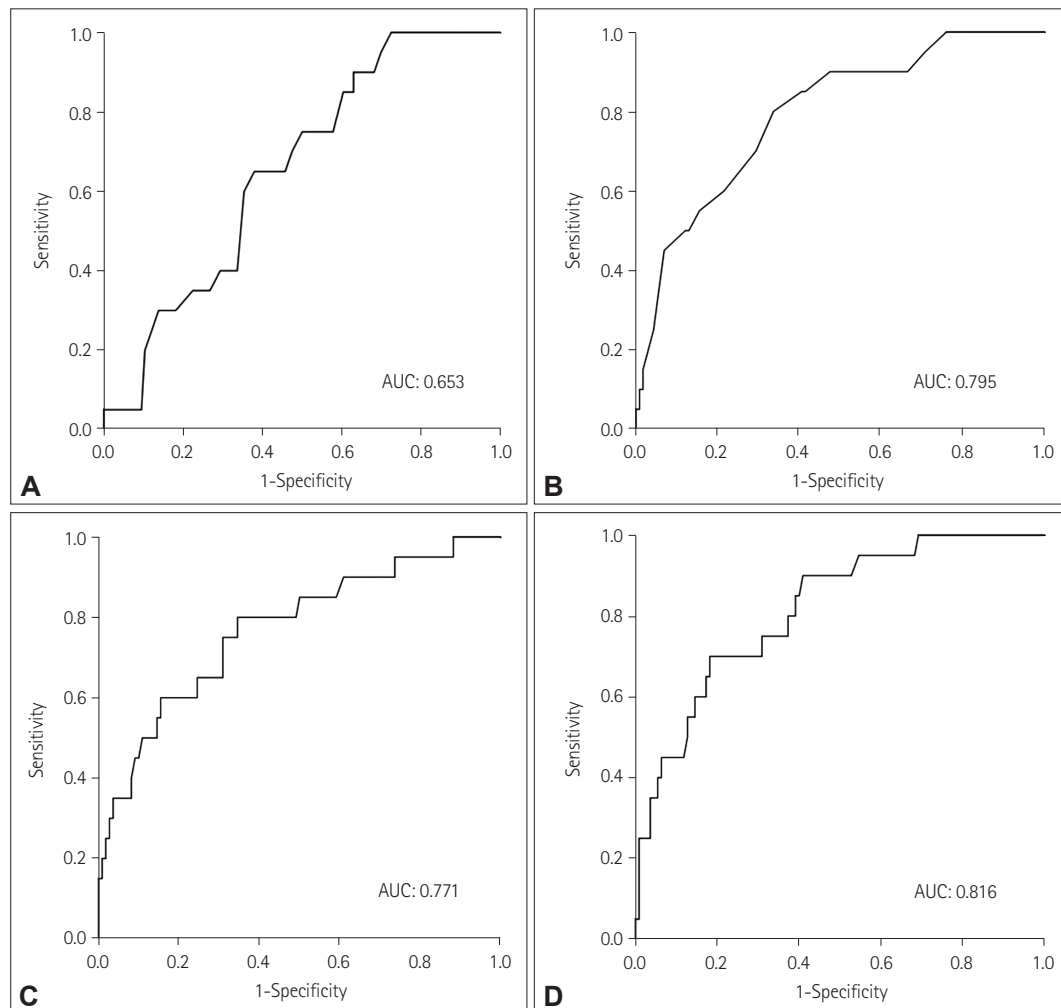
Fig. 3. ROC curve analysis of age (A), LAD (B), LAVI (C), and log-transformed AEB (D) for atrial fibrillation detection. The LAD, LAVI, and log-transformed AEB showed a good predictive accuracy, with areas under the ROC curves of 0.795, 0.771, and 0.816, respectively. Log-transformed due to skewness of the data. AEB: atrial ectopic burden, LAD: left atrial diameter, LAVI: left atrium volume index, ROC: receiver operating characteristic.

monitoring are essential screening examinations for assessing the cause of stroke, and the LAD and AEB can be easily obtained from these examinations. We consider our results to be valuable since they have yielded a novel risk prediction model that combines two variables known to be strongly associated with AF without requiring any additional costs or examinations.[12-15]

The cost-effectiveness of the ICM for the prevention of recurrent stroke in ESUS patients has been evaluated in several European countries and the USA,[7,16] and is expected to vary with the socioeconomic status of different countries. In this study, the incidence of AF was 0% in patients with a LAD <38.5 mm and AEB <0.050%, who accounted for almost half (48%, 65/136) of the study participants. Theoretically, if these patients are excluded, the cost-effectiveness of an ICM would improve significantly. However, it is not possible to assess the AF risk precisely based on the present small-

scale study, and so further large-scale studies are required to identify patients at a low risk of developing AF.

The prevalence of stroke increases with age, affecting 11.5% of males and 13.4% of females aged >80 years, and stroke mortality shows a similar trend with age.[17] In addition, stroke sequelae significantly reduce the quality of life. No apparent cause was found in up to 40% of patients with ischemic stroke even after a proper workup.[18] The rate of recurrent stroke was also high in this population, reaching 5.6% within 3 months[19] and 14−20% within 2 years.[20] Therefore, identifying AF is very important for the secondary prevention of stroke. A large randomized controlled trial including ESUS patients found that the AF detection rate was 12.4% in the ICM group and 2.0% in the control group.[21] The current global guidelines include a Class IIa recommendation to use an ICM to document silent AF in patients with stroke, and state that OAC therapy should be implemented after AF is detected.[4]
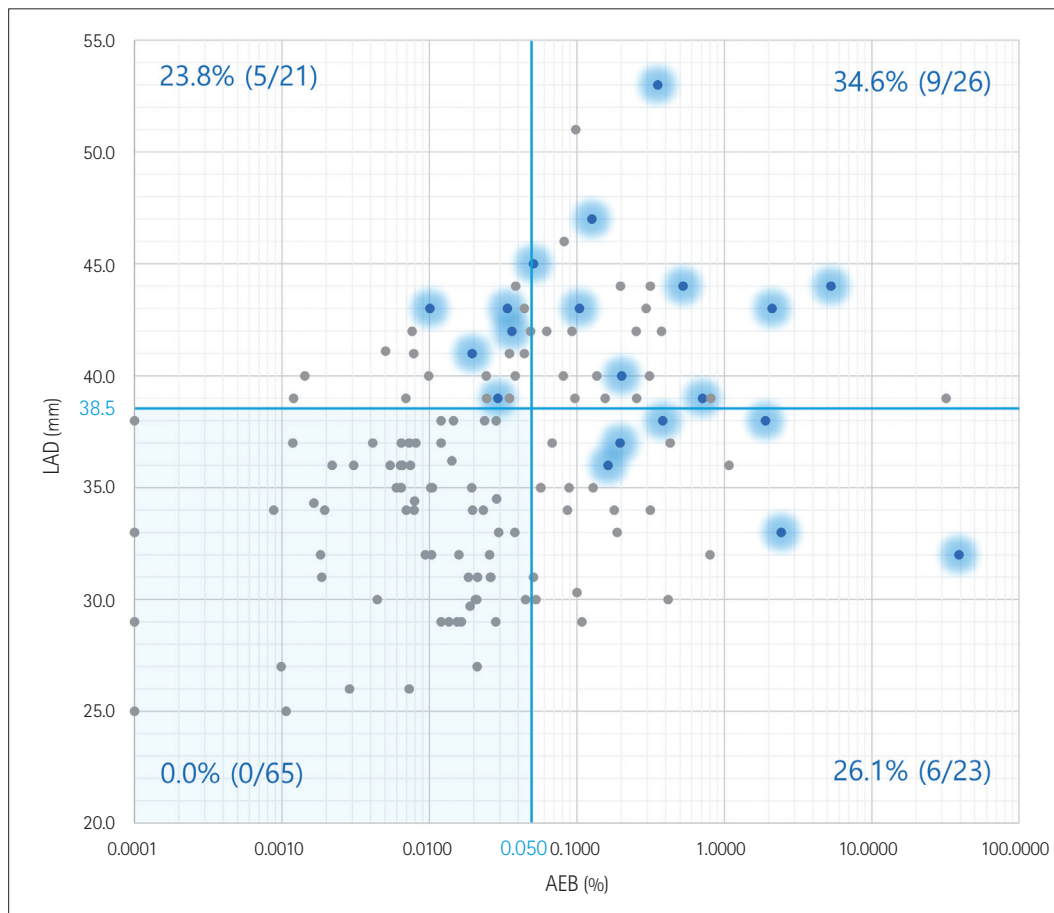
Fig. 4. Scatter plot of the LAD and AEB according to AF detection. No AF was detected in patients with LAD <38.5 mm and AEB <0.050%. Patient with missing information on the AEB (*n*=1) was excluded. AEB: atrial ectopic burden, AF: atrial fibrillation, LAD: left atrial diameter.

There is no general agreement or established data on the causal relationship between AF duration and stroke. Short-lasting AF is unlikely to cause stroke.[22] In a subgroup analysis of the Atrial Diagnostics Ancillary Study of the Mode Selection trial, patients with subclinical AF lasting ≥5 min had a 2.8-fold higher risk of the composite endpoint including stroke and death.[10] In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial, subclinical AF episodes lasting at least ≥24 h were associated with an increased risk of stroke.[23] Another prospective observational study found that AF or an atrial tachycardia burden of ≥5.5 h/day (on any day) appeared to double the risk of thromboembolism.[24] Based on these findings, current guidelines recommend initiating OAC therapy when subclinical AF lasts longer than 5 min after reviewing electrograms in patients with cardiac implantable electronic devices.[4] However, previous studies involved patients with a pacemaker or implantable cardiac defibrillator, and so the obtained cutoff values for AF duration might not apply to ESUS patients. In the present study, among the 20 patients in whom AF was detected, 10 (50%) had

AF episodes lasting ≥24 h and 17 (85%) had an AF episodes lasting ≥5 h (data not shown). We speculate that these proportions would have increased if the patients had been followed up for longer.

This study had some limitations. First, it included a small population and was conducted at a single center. However, the median follow-up period of 6.6 months might have been sufficient to detect significant AF, because 18 of the 20 AF episodes were detected within 2 months. The optimal cutoff values of AEB and LAD for AF prediction may be different in studies with larger samples or longer follow-up durations. Second, a selection bias might have occurred because only those who agreed to undergo ICM insertion could be enrolled in the study. From January 1, 2019 to July 31, 2020, only 21.2% of patients with ESUS agreed to undergo ICM insertion in our institute, and those who refused may have had relatively unfavorable clinical characteristics such as older age and a higher comorbidity load. Third, the prediction model was based on data obtained from East Asians (e.g., LAD), and so it might not be applicable to other races with different anthropometric characteristics. Finally, the small number of events

(*n*=20) restricted the number of variables that could be included in the multivariable model.

In conclusion, this retrospective study detected AF in a significant proportion of ESUS patients with an ICM. The LAD and AEB had good predictive accuracy in detecting AF in ESUS patients. These parameters might be valuable for risk stratification prior to AF detection and for improving the cost-effectiveness of ICM utilization by excluding patients with a low probability of developing AF.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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