# RESEARCH



# Factors associated with the detection of atrial fibrillation in patients with embolic stroke of undetermined source

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# Abstract

**Background** Detection of atrial fibrillation (AF) in patients with embolic stroke of undetermined source (ESUS) is important for the secondary prevention of stroke. We investigated the factors associated with the detection of newly diagnosed AF in ESUS patients during follow-up.

**Methods** Patients with acute ischemic stroke classified as ESUS were included. All patients underwent transthoracic echocardiography and Holter to detect the source of embolism. Structural, electrophysiological markers of left atrial cardiopathy (i.e., left atrial enlargement [LAE], non-sustained tachycardia [NSAT]) as well as lesion patterns of ischemic stroke were examined. Implantable loop recorder (ILR) was implanted in selective patients. Sensitivity and positive predictive value analysis was used to assess the predictive value for AF detection.

**Results** Among 312 patients with ESUS, AF was detected in 24 (7.7%) patients during follow-up. Patients with AF had a higher prevalence of LAE, NSAT, and the imaging pattern of confluent plus additional lesions in a single vascular territory. Multivariable analysis showed that ILR implantation (hazards ratio 11.497 [95% confidence interval 3.795–34.818]), LAE (3.204 [1.096–9.370]), NSAT (4.070 [1.378–12.018]), and confluent plus additional lesions (4.977 [1.649–15.019]) were independent predictors of AF detection. The sensitivity of detecting AF in those with LAE, NSAT, or confluent plus additional lesions pattern was 91.7%. The positive predictive value of detecting AF in those with LAE, NSAT and confluent plus additional lesions pattern was 40.0%.

**Conclusion** In conclusion, patients with LAE, NSAT, or confluent plus additional lesions may benefit from ILR monitoring detecting new AF.

Keywords ESUS, Implantable loop recorder, Atrial cardiopathy, Left atrial enlargement

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## Introduction

In a considerable portion of patients with ischemic stroke, the embolic source is not determined after routine evaluation, and is thus referred to embolic stroke of undetermined source (ESUS) [1]. Efforts have been made to determine the efficacy of non-vitamin K dependent oral anticoagulants for the prevention of stroke in these patients, but failed mainly due to the heterogeneous nature of ESUS. Therefore, the detection of covert atrial fibrillation (AF) is critical for secondary stroke prevention in ESUS patients.

Implantable loop recorder (ILR) is now widely used for the detection of AF in patients with ESUS. While ILR can significantly improves the detection of covert AF in ESUS patients, less than one-third of ESUS patients show AF during follow-up [2–4]. Moreover, insertion of ILR is invasive and can cause adverse effects such as pain, bleeding, and infection, the use of ILR is limited due to limitations in resources and patient refusal [5]. Therefore, identifying those who may benefit from ILR monitoring is important and the strategy for selecting ESUS patients who truly need ILR monitoring must be established.

Previous randomized trials have shown that prolonged cardiac monitoring increases the detection of AF, but the effect on reducing recurrent stroke is unknown [6, 7]. The ongoing randomized trial to evaluate intensified heart rhythm monitoring leads to a reduction of recurrent cardioembolism is Find-AF 2 study [8]. Recently, many studies have focused on the clinical implications of left atrial cardiopathy, in ESUS patients and reported the use of various echocardiographic, electrophysiologic, and serologic markers of left atrial cardiopathy for predicting the detection of AF after stroke [9–13]. Also, ischemic lesion patterns shown in diffusion-weighted images (DWIs) are different according to the potential embolic source from the heart [14].

Here, we comprehensively evaluated the cardiac and neuroimaging factors associated with newly diagnosed AF in ESUS patients. We also compared the sensitivity of these factors and their combinations is detecting AF in order to determine which subgroup of ESUS patients may benefit from long-term rhythm monitoring using ILR.

# Materials and methods

# Patient selection

We retrospectively screened patients with acute ischemic stroke who were admitted to the stroke center at Asan Medical Center between January 2017 and May 2021. Of them, patients classified as having ESUS according to the Cryptogenic stroke/ESUS International Working Group criteria were included [15]. Briefly, those who were nonlacunar stroke patients without (1) a major-risk cardioembolic source, (2) significant artery stenosis (>50%) at the corresponding artery proximal to the ischemic lesion, or (3) any known embolic source (e.g., dissection, cancerassociated stroke) were enrolled. Patients without a visible lesion on DWI were excluded.

The study patients had undergone neuroimaging at the emergency center for the diagnosis of ESUS. For those who were suspected of embolic stroke but without a known cause, extensive work was done to determine the embolic source including cardiac work-up (described below). The final decision for ESUS was made after all the evaluations. Newly diagnosed AF was obtained from the follow-up data of outpatient visits. Data was accessed during the study period of January 1, 2022 to December 31, 2022. The Asan Medical Center ethics committee approved this study, and patient informed consent was not obtained because of the retrospective nature of the study. The data that support the findings of this study are available from the Asan Medical Center Stroke Registry upon reasonable request.

## **Cardiac evaluation**

All patients underwent electrocardiogram, cardiac telemetry, 24-hour Holter monitoring, and transthoracic echocardiography during admission. The presence and burden of atrial premature complex (APC) and non-sustained atrial tachycardia (NSAT) were determined using the results of Holter monitoring. NSAT was diagnosed if the rhythm occurred in three or more consecutive beats at a rate of greater than 100 beats per minute. The number of APCs was regarded as significant if it exceeded 100 per 24 h [16]. Left atrial diameter (LAD) was measured at the greatest dimension in the long axis view from transthoracic echocardiography. Left atrial enlargement (LAE) was defined as LAD of > 38 mm in females and >40 mm in males [17].

Brain natriuretic peptide (BNP) was measured on the day of admission, and levels higher than 100 pg/ml were considered significant [13]. Transesophageal echocardiography or chest computed tomography (CT) was additionally used to evaluate patent foramen ovale (PFO) or aorta disease in selected patients [18, 19]. High-risk PFO was defined as PFO with atrial septal aneurysm (protrusion of septum of at least 15 mm), hypermobile septum (septal excursion more than 10 mm), or large-sized PFO (maximum separation during Valsalva maneuver of more than 2 mm) [18]. Complex aortic atheroma was defined as protruding (4 mm thick), ulcerated, or with a mobile component in transesophageal echocardiography or CT [20]. ILR was additionally performed at the discretion of the attending physician and in patients who agreed to its insertion during admission.

#### Neuroimaging and lesion pattern

Magnetic resonance image including DWI was performed at the emergency medical center on the day of admission. The number, location and size of ischemic lesions were determined from the DWI.

The number of ischemic lesion on DWI was counted and was dichotomized to single and multiple. The location of lesions was classified according to the vascular territory. Confluent lesion was defined as a lesion with a maximum diameter of more than 20 mm from the axial image. Based on these factors, the lesion pattern was classified into (1) single small lesion, (2) single large lesion, (3) multiple small lesions in a single vascular territory, (4) a confluent plus additional lesions in a single vascular territory, and (5) multi-territory lesions [14]. Lesion patterns were analyzed and categorized by two experienced stroke neurologists who were blinded to all clinical data. If case of discrepancy, the lesion pattern was determined in a consensus meeting.

## **Detection of AF**

Detection of AF was determined from the medical records and evaluation results obtained at regular outpatient visits. ILR was implanted during admission for acute ischemic stroke based on the decision from the multidisciplinary approach of neurologists and cardiologists. The Reveal LINQ intracardiac monitoring system (Medtronic, Minneapolis, MN, USA) was implanted in the subcutaneous tissue of the 4th -intercostal space on the left hemithorax. According to our center protocol, stroke patients were instructed to visit to the outpatient clinic at 1 month after discharge and then every 3 to 6 months. In those who received ILR, monitoring for newly detected AF was performed at each visit.

In those who did not receive ILR implantation, EKG, cardiac telemetry, or Holter monitoring was repeated at each visit at the discretion of the attending stroke neurologist. Any AF detected in routine electrocardiogram at follow-up or those lasting more than 30 s in follow-up Holter monitoring or ILR monitoring was regarded as newly diagnosed AF. Newly diagnosed AF was confirmed by an experienced cardiologist.

### Statistical analysis

The characteristics of those with newly diagnosed AF and those without were compared. Student's *t*-test and chi-squared test were used appropriately. We also performed univariable and multivariable analyses to identify the predictors of newly diagnosed AF in patients with ESUS. Factors with potential association (P < 0.10) were entered into the multivariable analysis.

Sensitivity analysis was used to assess the predictive value of various factors that were independently associated newly diagnosed AF in the multivariable analysis and their combinations. Kaplan-Meier analysis and logrank tests were performed to compare the time from stroke to new AF diagnosis between ESUS patients with at least one of the factors associated with newly diagnosed AF and those without. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) and *P*values < 0.05 were considered statistically significant.

# Results

Of the 3866 patients with acute ischemic stroke who were admitted to our center during the study period, 312 (8.1%) had ESUS. The mean age of ESUS patients was 67.5±13.5 years and 188 (60.3%) were male. Fortytwo (13.5%) patients underwent ILR insertion. Regarding the markers of left atrial cardiopathy, LAE was present in 89 (28.5%) patients, NSAT in 107 (34.3%) patients, and BNP>100 pg/ml in 50 (16.0%) patients. The most common lesion pattern in ESUS patients were multiple small lesions in a single vascular territory (26.3%), followed by confluent plus additional lesions (20.2%) and a single large lesion (19.6%). During follow-up, AF was detected in 24 (7.7%) patients at a median of 235.5 days; AF was detected in 12 patients (28.6%) who received ILR and 12 patients (4.4%) who did not. Among the patients with AF detection who did not undergo ILR, 11 patients was detected by EKG and 1 patient was detected by cardiac telemetry during follow up.

#### Characteristics of patients with new incident AF

The characteristics of patients according to the presence of newly diagnosed AF during follow-up are presented in Table 1. There was no significant difference in terms of demographics including age or vascular risk factors. Patients with newly diagnosed AF had a higher prevalence of abnormal findings of left atrial cardiopathy markers including larger LAD (41.1 mm vs. 36.8 mm, P < 0.001), more LAE (54.2% vs. 26.4%, P = 0.004), NSAT (62.5% vs. 32.1%, P = 0.003), APC > 100/24 hr (50.0% vs. 26.7%, P = 0.015), and BNP > 100 pg/ml (45.0% vs. 19.2%, P = 0.007).

In terms of lesion patterns, confluent plus additional lesions at a single vascular territory (41.7%) was the most prevalent lesion pattern in those with newly diagnosed AF, followed by multiple small lesions in a single vascular territory (29.2%) and a single large lesion (25.0%); none of the patients with newly diagnosed AF showed the multi-territory lesion pattern. In contrast, among those without newly diagnosed AF, the most prevalent pattern was multiple small lesions in a single vascular territory (26%) and the multi territory lesion pattern was present in 20.1%.

#### Table 1 Baseline characteristics of the study population

	AF detected (n=24)	AF not detected (n=288)	Pvalue	
Age (years)	69.2±11.4	67.3±13.6	0.524	
Age≥75 years	9 (37.5)	95 (33.0)	0.652	
Male sex	17 (70.8)	171 (59.4)	0.270	
Hypertension	13 (59.1)	174 (60.4)	0.902	
Diabetes mellitus	7 (31.8)	95 (33.0)	0.911	
Hyperlipidemia	12 (54.5)	132 (45.8)	0.430	
CAD	6 (27.3)	52 (18.1)	0.285	
History of stroke	6 (27.3)	79 (27.4)	0.987	
Current smoker	11 (50.0)	112 (38.9)	0.305	
Left atrial cardiopathy markers				
LAD (mm)	41.1±6.8	36.8±5.6	< 0.001	
LAE	13 (54.2)	76 (26.4)	0.004	
NSAT	15 (62.5)	92 (32.1)	0.003	
APC (n)	373.4±602.9	543.5±2238.3	0.711	
APC>100/24hr	12 (50.0)	77 (26.7)	0.015	
APC≥720/24hr	2 (8.3)	21 (7.3)	0.851	
BNP (pg/mL)	224.7±310.7	113.1±319.4	0.127	
BNP > 100	9 (45.0)	41 (19.2)	0.007	
Insular lesion	5 (20.8)	41 (14.2)	0.381	
Neuroimaging markers				
Single small lesion	1 (4.2)	46 (16.0)	0.010	
Single large lesion	6 (25.0)	56 (19.4)		
Multiple small lesions	7 (29.2)	75 (26.0)		
Confluent + additional lesions	10 (41.7)	53 (18.4)		
Multi-territory lesions	0 (0.0)	58 (20.1)		
High risk PFO	4 (17.4)	43 (18.7)	0.878	
Complex AAA	4 (18.2)	73 (32.3)	0.172	
ILR monitoring	12 (50.0)	30 (10.4)	< 0.001	
Duration until AF detection (days)	235.5 (58.8–578.5)	N/A		
Follow-up (days)	764.0 (394.0-1173.5)	577.0 (294.0–1076.0)	0.214	

Values are presented as n (%), median (interquartile range), or mean  $\pm$  standard deviation

AF indicates atrial fibrillation; CAD, coronary artery disease; LAD, left atrial diameter; LAE, left atrial enlargement; NSAT, non-sustained atrial tachycardia; APC, atrial premature complex, BNP, brain natriuretic peptide; PFO, patent foramen ovale; AAA, aortic arch atherosclerosis; ILR, implantable loop recorder; Confluent + additional lesions, confluent plus additional lesions in a single vascular territory

# Factors associated with AF detection

The presence of ILR implantation was associated with the detection of AF at follow-up. Furthermore, all parameters associated with left atrial cardiopathy — LAD, LAE, NSAT, APC > 100/24 hr and BNP > 100 pg/ml were associated with the detection of newly diagnosed AF (Table 2). After dichotomizing the lesion pattern into confluent plus additional lesions and others, the pattern of confluent plus additional lesions in a single vascular territory was significantly associated with AF detection.

Multivariable analysis showed that ILR implantation (hazards ratio [HR]11.497, 95% confidence interval [CI] 3.795–34.818; P<0.001) was the strongest predictor for detecting AF. Additionally, the presence of LAE (HR 3.204, 95% CI 1.096–9.370; P=0.033), NSAT (HR 4.070, 95% CI 1.378–12.018; P=0.011), and confluent plus additional lesions in a single vascular territory (HR 4.977, 95%

CI 1.649–15.019; P = 0.004) were independent predictors of AF detection at follow-up.

# Predictive value for AF detection

Among factors independently associated with newly diagnosed AF, presence of NSAT was most sensitive for detecting AF (62.5%), followed by LAE (54.0%) and confluent plus additional small lesion pattern (41.7%). Among the two-factor combinations, the combination of the presence of LAE or NSAT showed the highest sensitivity (83.3%) for detecting AF. Finally, the combination of the presence of LAE, NSAT, or confluent plus additional lesions had a sensitivity of 91.7% in predicting newly diagnosed AF. The combination of the presence of LAE, NSAT, and confluent plus additional lesions in a single vascular territory showed a positive predictive value of 40.0% in predicting newly diagnosed AF (Table 3).

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lable 2	Univariable and	multivariable i	oaistic rea	aression anai	vsis tor	Tactors a	associated wi	th atrial '	norillation	detection

	Univariable		Multivariable	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age	1.011 (0.978–1.044)	0.523		
Male sex	1.662 (0.242-1.497)	0.275		
Hypertension	0.946 (0.392-2.286)	0.903		
Diabetes mellitus	0.948 (0.374-2.403)	0.911		
Hyperlipidemia	1.418 (0.594–3.387)	0.432		
CAD	1.702 (0.635–4.558)	0.290		
History of stroke	0.992 (0.375–2.626)	0.987		
Current smoker	1.571 (0.659–3.746)	0.308		
LAD	1.136 (1.055–1.224)	0.001		
LAE	3.297 (1.417–7.672)	0.006	3.204 (1.096-9.370)	0.033
NSAT	3.551 (1.498–8.414)	0.004	4.070 (1.378-12.018)	0.011
APC	1.000 (1.000-1.000)	0.714		
APC > 100/24 hr	2.740 (1.181–6.358)	0.019		
BNP	1.001 (1.000-1.002)	0.175		
BNP > 100	3.432 (1.335–8.826)	0.010	-	-
Insular lesion	0.631 (0.223-1.783)	0.385		
Lesion pattern				
Others (reference)	1		1	
Confluent + additional lesions	3.167 (1.334–7.518)	0.009	4.977 (1.649–15.019))	0.004
High-risk PFO	0.916 (0.296–2.829)	0.878		
Complex AAA	0.466 (0.152-1.426)	0.181		
ILR monitoring	8.600 (3.549–20.837)	< 0.001	11.497 (3.795–34.818)	< 0.001

Values are presented as n (%), median (interquartile range), or mean ( $\pm$  SD)

AF indicates atrial fibrillation; CAD, coronary artery disease; LAD, left atrial diameter; LAE, left atrial enlargement; NSAT, non-sustained atrial tachycardia; APC, atrial premature complex; BNP, brain natriuretic peptide; PFO, patent foramen ovale; AAA, aortic arch atherosclerosis; ILR, implantable loop recorder; Confluent + additional lesions, confluent plus additional lesions in a single vascular territory

Table 3	Predictive values of	parameters rela	ated to atrial	cardiopathy	for the det	tection of n	iewly diagno	osed AF

	Sensitivity	Specificity	PPV	NPV
LAE	54.0%	71.5%	14.6%	95.1%
NSAT	62.5%	67.9%	14.0%	95.6%
Confluent + additional lesions	41.70%	81.60%	15.90%	94.40%
LAE or NSAT	83.3%	52.1%	12.7%	97.4%
LAE or confluent + additional lesion	59.70%	75.00%	13.40%	96.60%
NSAT or confluent + additional lesions	55.20%	75.00%	12.20%	96.40%
LAE or NSAT or confluent + additional lesions	91.70%	41.70%	11.60%	98.40%
LAE and NSAT and Confluent + additional lesions	16.70%	97.90%	40.00%	93.40%

AF indicates atrial fibrillation; APC, atrial premature complex; BNP, brain natriuretic peptide; LAE, left atrial enlargement; NPV, negative predictive value; NSAT, nonsustained atrial tachycardia; Confluent + additional lesions, confluent plus additional lesions in a single vascular territory; PPV, positive predictive value

The Kaplan-Meier analysis showed that the detection rate of newly diagnosed AF was higher in patients with LAE, NSAT, or confluent plus additional lesions compared with those who did not have any of these factors (log-rank test, P = 0.004; Fig. 1).

## Subgroup analysis of ILR inserted patients

The characteristics of patients who received ILR according to the presence of newly diagnosed AF during follow-up are described in supplementary Table 1. In terms of demographics including age, vascular risk factors between the two groups, there was no significant difference. Patients with newly diagnosed AF showed trend of a higher prevalence of confluent plus additional lesions at a single vascular territory (41.7% vs. 16.7%, P = 0.086). The subgroup analysis on those who received ILR showed a similar result that among factors independently associated with newly diagnosed AF. The presence of LAE, NSAT, or confluent plus additional lesions had a sensitivity of 91.7% (Supplementary Table 2).

# Discussion

In the present study, 7.6% patients with ESUS were diagnosed to have AF during follow-up. Implanting ILR increased the detection rate of AF by 6.5 times compared with routine follow-up of EKG or Holter monitoring. The



Fig. 1 Kaplan-Meier analysis for the detection of newly diagnosed AF in patients with ESUS. AF indicates atrial fibrillation; LAE, left atrial enlargement; NSAT, non-sustained atrial tachycardia

prevalence of new AF detection after ILR was similar to that reported in previous studies [21, 22]. The lesion pattern of a confluent plus additional lesions in a single vascular territory and biomarkers of left atrial cardiopathy including LAE and NSAT were independently associated with newly diagnosed AF in ESUS patients. The sensitivity of diagnosing new AF in ESUS patients with LAE, NSAT, or a confluent plus additional lesions pattern was 91.7%, suggesting that such patients may be the potential target for ILR implantation. The positive predictive value of diagnosing new AF in ESUS patients with LAE, NSAT, and a confluent plus additional lesions pattern was 40.0%. These patients might particularly benefit from ILR implantation. Most of the existing scoring systems for identifying potential ILR recipients focused on conventional risk factors or cardiac markers [23–25]. However, a more comprehensive approach regarding the culprit (i.e., markers of left atrial cardiopathy) and its result (i.e., ischemic lesions in the brain) may be needed. Ischemic lesion patterns well represent the stroke mechanism, and a recent study showed that a large territorial infarction in a single vascular territory pattern was associated with AF detection in ESUS patients receiving ILR [26]. Paroxysmal AF related-strokes showed larger lesions and higher NIHSS scores than aortic arch atheroma or PFO related strokes, explained by the large fibrin containing clot formed from the left atrium [27]. In comparison to stoke related to PFO, strokes related to AF showed confluent lesion with additional small lesions, as PFOs may work as filters, allowing only smaller emboli to pass through the shunt [14]. Previous study reported that aortic arch atheroma related-stroke group had smaller lesions in multiple vascular territories than AF related stroke group [27]. An autopsy study revealed that emboli containing cholesterol crystals such as emboli from aortic arch or large artery atherosclerosis frequently result in small borderzone infarction [28]. In line with these findings, we found that the sensitivity and positive predictive value of detecting AF among ESUS patients was maximized when the imaging pattern of a confluent plus additional lesions in a single vascular territory was used together with left atrial cardiopathy markers (i.e., LAE and NSAT).

Enlarged left atrium, a structural marker of left atrial cardiopathy, is associated with the risk of stroke [29]. It is possible that, LAE itself promotes blood stasis, thereby leading to the risk of stroke [30]. On the other hand, LAE may increase the risk of the development of AF, considering that LAE was associated with AF detection in patients with ESUS [10, 31]. Structural changes in the left atrium may have led to electrophysiological abnormalities such as AF. While the detection of NSAT from Holter monitoring is a potentially useful electrophysiological biomarker for left atrial cardiopathy, there are controversies on whether NSAT itself can cause stroke or increase the risk of stroke by reflecting the presence of hidden paroxysmal AF. While the previous studies mostly focused on the structural changes of the left atrium or their functions, electrophysiological changes with frequent APCs or NSAT may more directly reflect the risk of paroxysmal AF [32]. Accordingly, ischemic stroke patients with NSAT show similar characteristics to those with cardioembolic stroke [33].

Studies have shown that the left atrial appendage (LAA) accounts for over 90% of thrombi in patients with atrial fibrillation. A greater lobe number, a less bent LAA ostium, and a greater left atrial wall thickness are associated with an increased risk of cryptogenic stroke [34]. Additionally, the progression of AF has been linked to a 2–3 mm enlargement of the left ostial diameter [35]. However, due to the retrospective nature of our study and the absence of cardiac computed tomography angiography or transesophageal echocardiography in a significant proportion of patients, we were unable to assess Left Atrial Appendage morphology.

Though the use of ILR increased the detection of AF, it failed to translate to a significant reduction in recurrent stroke [6, 7]. This may be explained by the poor correlation between newly detected AF and recurrent stroke. However, the effect of anticoagulation may be more efficient in patients with markers of left atrial cardiopathy and a newly diagnosed AF. A subgroup analysis of the NAVIGATE ESUS trial showed that the use of NOAC

reduced the risk of recurrent stroke in those with LAE [36]. In another observation study, ESUS patients with severe LAE showed benefit from anticoagulation treatment [37]. The results of ongoing trials focusing on the effect of anticoagulation in ESUS patients with left atrial cardiopathy may therefore be of interest [8]. In addition, specific lesion patterns may also be considered in future clinical trials.

Our study has several limitations. First, as this study was performed at a single center, its results have limitations regarding generalizability. However, as all patients received cardiac evaluation under a standardized center protocol, the heterogeneity could be minimized. Second, the data were collected retrospectively and ILR was performed only in selected patients. A well-designed prospective study focusing on the efficacy of long-term monitoring in those with left atrial cardiopathy or specific imaging patterns may be helpful. Third, there was no association between age and the detection of AF in our cohort. This lack of association may be due to the small sample size. However, based on our findings, the decision for long-term monitoring should not be based solely on the patient's age. Lastly, we did not compare our results with the previous scoring systems as the purpose of our study was not to develop or validate a new scoring system. Rather, we tried to identify ESUS patients who may particularly benefit from ILR implantation, and the factors identified in our multivariable analysis had acceptable sensitivity and positive predictive value for detecting AF.

Despite these limitations, our study showed that the chance of missing hidden AF during follow-up was particularly low in ESUS patients with LAE, NSAT, or the imaging pattern of confluent plus additional lesions in a single vascular territory. In ESUS patients with LAE, NSAT, or the imaging pattern of confluent plus additional lesions in a single vascular territory, the chance of detecting newly diagnosed AF during follow-up was particularly high. Implanting ILR in this population may maximize the sensitivity and positive predictive value for AF detection.

Abbrevia	ations
AF	Atrial fibrillation
APC	Atrial premature complex
BNP	Brain natriuretic peptide
CT	Computed tomography
DWIs	Diffusion-weighted images
EKG	Electrocardiography
ESUS	Ambolic stroke of undetermined source
ILR	Inplantable loop recorder
LAD	Left atrial diameter
LAE	Left atrial enlargement.
NIHSS	National institutes of health stroke scale
NOAC	Non-vitamin K antagonist oral anticoagulants
NSAT	Non-sustained tachycardia

PFO Patent foramen ovale

# **Supplementary Information**

The online version contains supplementary material available at https://doi.or g/10.1186/s12883-024-04008-0.

Supplementary Material 1

#### Author contributions

KBJ were responsible for the study design and drafting of the article. JHB performed statistical analysis and wrote the manuscript. JYC, DWK, SUK, and JSK were responsible for design of the study and critically revising the draft. JCR and SHH gathered the data for the analysis. MSC and MJC advised on study design. All authors read and approved the manuscript.

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#### Data availability

The data that support the findings of this study are available from the Asan Medical Center Stroke Registry upon reasonable request.

#### Declarations

#### Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. Approval with a waiver for informed consent was granted by the local ethics committee (Asan Medical Center, Seoul, Korea, IRB number : S2021-1925-0001).

#### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare no competing interests.

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#### References

- Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke. 2017;48:867–72. https://doi.org/10.1161/STROKEAHA.116.016414
- Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467–77. https://doi.org/10.1056/NEJ Moa1311376
- Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–86. https://doi.org/10.1056/NEJMoa 1313600
- Ntaios G. Embolic stroke of undetermined source: JACC Review Topic of the Week. J Am Coll Cardiol. 2020;75:333–40. https://doi.org/10.1016/j.jacc.2019.1 1.024
- Diederichsen SZ, Haugan KJ, Hojberg S, Holst AG, Kober L, Pedersen KB, Graff C, Krieger D, Brandes A, Svendsen JH. Complications after implantation of a new-generation insertable cardiac monitor: results from the LOOP study. Int J Cardiol. 2017;241:229–34. https://doi.org/10.1016/j.ijcard.2017.03.144
- Kamel H, Longstreth WT Jr., Tirschwell DL, Kronmal RA, Marshall RS, Broderick JP, Aragon Garcia R, Plummer P, Sabagha N, Pauls Q, et al. Apixaban to prevent recurrence after cryptogenic stroke in patients with Atrial Cardiopathy: the ARCADIA Randomized Clinical Trial. JAMA. 2024;331:573–81. https://doi.org/1 0.1001/jama.2023.27188
- Huang WY, Ovbiagele B, Hsieh CY, Lee M. Association between implantable loop recorder use and secondary stroke prevention: a meta-analysis. Open Heart. 2022;9:e002034.

- Uhe T, Wasser K, Weber-Kruger M, Schabitz WR, Kohrmann M, Brachmann J, Laufs U, Dichgans M, Gelbrich G, Petroff D, et al. Intensive heart rhythm monitoring to decrease ischemic stroke and systemic embolism-the Find-AF 2 study-rationale and design. Am Heart J. 2023;265:66–76. https://doi.org/10. 1016/j.ahj.2023.06.016
- Perlepe K, Sirimarco G, Strambo D, Eskandari A, Karagkiozi E, Vemmou A, Koroboki E, Manios E, Makaritsis K, Vemmos K, et al. Left atrial diameter thresholds and new incident atrial fibrillation in embolic stroke of undetermined source. Eur J Intern Med. 2020;75:30–4. https://doi.org/10.1016/j.ejim.2 020.01.002
- Jordan K, Yaghi S, Poppas A, Chang AD, Mac Grory B, Cutting S, Burton T, Jayaraman M, Tsivgoulis G, Sabeh MK, et al. Left atrial volume index is Associated with Cardioembolic Stroke and Atrial Fibrillation Detection after Embolic Stroke of undetermined source. Stroke. 2019;50:1997–2001. https://doi.org/1 0.1161/STROKEAHA.119.025384
- Hamer ME, Wilkinson WE, Clair WK, Page RL, McCarthy EA, Pritchett ELC. Incidence of symptomatic atrial fibrillation in patients with paroxysmal supraventricular tachycardia. J Am Coll Cardiol. 1995;25:984–8. https://doi.org /10.1016/0735-1097(94)00512-0
- Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010;121:1904–11. https://doi.org/10.1161/CIRCULATIONAHA.109.87498 2
- Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, Brandes A, Bustamante A, Casadei B, Crijns H, et al. Searching for Atrial Fibrillation Poststroke: a White Paper of the AF-SCREEN International collaboration. Circulation. 2019;140:1834–50. https://doi.org/10.1161/CIRCULATIONAHA.11 9.040267
- Kim BJ, Sohn H, Sun BJ, Song JK, Kang DW, Kim JS, Kwon SU. Imaging characteristics of ischemic strokes related to patent foramen ovale. Stroke. 2013;44:3350–6. https://doi.org/10.1161/STROKEAHA.113.002459
- Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke EIWG. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429–38. https://doi.org/10.1016/S1474-4422(13)70310-7
- Himmelreich JCL, Lucassen WAM, Heugen M, Bossuyt PMM, Tan HL, Harskamp RE, van Etten-Jamaludin FS, van Weert H. Frequent premature atrial contractions are associated with atrial fibrillation, brain ischaemia, and mortality: a systematic review and meta-analysis. Europace: Eur Pacing Arrhythm Cardiac Electrophysiol : J Working Groups Cardiac Pacing Arrhythm Cardiac Cell Electrophysiol Eur Soc Cardiol. 2019;21:698–707. https://doi.org/10.1093/ europace/euy276
- Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, Homma S, Kamel H, Sacco RL, Elkind MS. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke. 2015;46:1488–93. https://doi.org/10.1161/STROKEAHA.115.008711
- Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, Song JM, Kang DH, Kwon SU, Kang DW, et al. Cryptogenic stroke and high-risk patent Foramen Ovale: the DEFENSE-PFO trial. J Am Coll Cardiol. 2018;71:2335–42. https://doi.org/10.101 6/j.jacc.2018.02.046
- Ntaios G, Pearce LA, Meseguer E, Endres M, Amarenco P, Ozturk S, Lang W, Bornstein NM, Molina CA, Pagola J, et al. Aortic Arch atherosclerosis in patients with embolic stroke of undetermined source: an exploratory analysis of the NAVIGATE ESUS Trial. Stroke. 2019;50:3184–90. https://doi.org/10.1161/ STROKEAHA.119.025813
- Katsanos AH, Giannopoulos S, Kosmidou M, Voumvourakis K, Parissis JT, Kyritsis AP, Tsivgoulis G. Complex atheromatous plaques in the descending aorta and the risk of stroke: a systematic review and meta-analysis. Stroke. 2014;45:1764–70. https://doi.org/10.1161/STROKEAHA.114.005190
- Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, Hagemeister C, Minnerup J, Schabitz WR. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thromb Haemost. 2017;117:1962–9. https://doi.o rg/10.1160/TH17-02-0072
- 22. Bertaglia E, Blank B, Blomstrom-Lundqvist C, Brandes A, Cabanelas N, Dan GA, Dichtl W, Goette A, de Groot JR, Lubinski A et al. Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence. Europace: European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2019;21:1459–1467. https://doi.org/10.1093/europace/euz172

- Bugnicourt JM, Flament M, Guillaumont MP, Chillon JM, Leclercq C, Canaple S, Lamy C, Godefroy O. Predictors of newly diagnosed atrial fibrillation in cryptogenic stroke: a cohort study. Eur J Neurol. 2013;20:1352–9. https://doi.o rg/10.1111/ene.12017
- Kneihsl M, Bisping E, Scherr D, Mangge H, Fandler-Hofler S, Colonna I, Haidegger M, Eppinger S, Hofer E, Fazekas F, et al. Predicting atrial fibrillation after cryptogenic stroke via a clinical risk score-a prospective observational study. Eur J Neurol. 2022;29:149–57. https://doi.org/10.1111/ene.15102
- Kim JG, Boo K, Kang CH, Kim HJ, Choi JC. Impact of neuroimaging patterns for the detection of Atrial Fibrillation by Implantable Loop Recorders in patients with embolic stroke of undetermined source. Front Neurol. 2022;13:905998. https://doi.org/10.3389/fneur.2022.905998
- Ryoo S, Chung JW, Lee MJ, Kim SJ, Lee JS, Kim GM, Chung CS, Lee KH, Hong JM, Bang OY. An Approach to working up cases of Embolic Stroke of undetermined source. J Am Heart Association. 2016;5:e002975. https://doi.org/10.11 61/JAHA.115.002975
- Masuda J, Yutani C, Ogata J, Kuriyama Y, Yamaguchi T. Atheromatous embolism in the brain. Neurology. 1994;44:1231–7.
- Xu Y, Zhao L, Zhang L, Han Y, Wang P, Yu S. Left atrial enlargement and the risk of stroke: a Meta-analysis of prospective cohort studies. Front Neurol. 2020;11:26. https://doi.org/10.3389/fneur.2020.00026
- Hamatani Y, Ogawa H, Takabayashi K, Yamashita Y, Takagi D, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, et al. Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Sci Rep. 2016;6:31042. https://doi.org/10.1038/srep31042
- 31. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. Circulation. 1994;89:724–30.

- Sagris D, Harrison SL, Buckley BJR, Ntaios G, Lip GYH. Long-term Cardiac Monitoring after Embolic Stroke of undetermined source: search longer, look Harder. Am J Med. 2022;135:e311–7. https://doi.org/10.1016/j.amjmed.2022.0 4.030
- Ok T, Lee SH, Kim JY, Lee KY, Jung YH. Nonsustained atrial tachycardia in 24-hour Holter monitoring: a potential cardiac source of embolism in acute ischemic stroke. Ann Transl Med. 2022;10:433. https://doi.org/10.21037/atm-2 1-5245
- Adukauskaite A, Barbieri F, Senoner T, Plank F, Beyer C, Knoflach M, Boehme C, Hintringer F, Mueller S, Cartes-Zumelzu F, et al. Left atrial appendage morphology is Associated with Cryptogenic Stroke: a CTA study. JACC Cardiovasc Imaging. 2019;12:2079–81. https://doi.org/10.1016/j.jcmg.2019.04.015
- Takaya Y, Nakayama R, Yokohama F, Toh N, Nakagawa K, Miyamoto M, Ito H. Left atrial appendage morphology with the progression of atrial fibrillation. PLoS ONE. 2022;17:e0278172. https://doi.org/10.1371/journal.pone.0278172
- Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, Haeusler KG, Mikulik R, Kasner SE, Toni D, et al. Recurrent stroke with Rivaroxaban compared with aspirin according to predictors of Atrial Fibrillation: secondary analysis of the NAVIGATE ESUS Randomized Clinical Trial. JAMA Neurol. 2019;76:764–73. https://doi.org/10.1001/jamaneurol.2019.0617
- Patel K, Mikhael E, Liu M, Rangaraju S, Ellis D, Duncan A, Belagaje S, Belair T, Henriquez L, Nahab F. Anticoagulation Therapy Reduces Recurrent Stroke in Embolic Stroke of Undetermined Source Patients With Elevated Coagulation Markers or Severe Left Atrial Enlargement. Front NEurol. 2021;12. https://doi.org/10.3389/fneur.2021.695378. eCollection 2021.

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