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Atrial Fibrillation After Ischemic Stroke Detected by Chest Strap-Style 7-Day Holter Monitoring and the Risk Predictors: EDUCATE-ESUS

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Aim: This study aimed to investigate the diagnostic yield of 7-day Holter monitoring for detecting covert atrial fibrillation (AF) in patients with recent embolic stroke of undetermined source (ESUS) and to identify the pre-entry screening biomarkers that had significant associations with later detection of AF (clinicaltrials.gov. NCT02801708).

Methods: A total of 206 patients who have recent ESUS without previously documented AF underwent Holter electrocardiography using a chest strap-style monitor. External validation of biomarkers predictive of AF was performed using 83 patients with ESUS who were implanted with insertable cardiac monitors.

Results: The 7-day Holter monitoring started at a median of 13 days after the onset of stroke. AF was detected in 14 patients, and three of these showed a single AF episode lasting <2 min. The median time delay to the first documented AF was 50 h. Each of serum brain natriuretic peptide ≥ 66.0 pg/mL (adjusted odds ratio 5.23), atrial premature contractions (APCs) ≥ 345 beats (3.80), and APC short runs ≥ 13 (5.74) on 24-h Holter prior to the 7-day Holter showed a significant association with detection of AF, independent of age and physiological findings in this derivation cohort, and all of these showed a significant association in the validation cohort (adjusted odds ratio 6.59, 7.87, and 6.16, respectively).

Conclusions: In recent ESUS patients, the detection rate of AF using the 7-day Holter monitoring was 6.8% (95% CI 4.1%–11.1%). Brain natriuretic peptide, APC count, and APC short runs in the standard clinical workup seemed to be predictors of covert AF.

Key words: Acute stroke, Atrial premature contraction, Brain natriuretic peptide, Cardioembolism, Insertable cardiac monitors

Introduction

Recent advances in diagnostic techniques have shown that most "cryptogenic strokes," i.e., ischemic stroke of uncertain cause, are embolic[1-3]. Thus, the term "embolic stroke of undetermined source (ESUS)" has been proposed as a new clinical entity to refine its definition,. Covert atrial fibrillation (AF) is thought to be relatively common among potential embolic sources of ESUS.

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AF is a leading cause of cardioembolic stroke[4]. The efficacy of anticoagulant therapy, including vitamin K antagonists and direct oral anticoagulants (DOACs), has been established in stroke prevention for patients with non-valvular AF[5, 6]. Thus, the same therapeutic regimen would also be efficacious for ESUS patients[1-3, 7]. However, two randomized controlled trials failed to demonstrate that DOACs were superior to aspirin for the secondary prevention of ESUS[8, 9]. Oral anticoagulants cannot be recommended on the basis of current evidence; therefore, detecting covert AF has important therapeutic implications in patients with ESUS.

However, being often paroxysmal and asymptomatic, AF can be missed with the conventional workup after stroke, such as electrocardiography (ECG) monitoring for 24 h, which was recommended in the current guidelines[10, 11]. Randomized controlled trials have proven that cardiac monitoring that last longer than 24 h clearly increases the probability of AF detection after ischemic stroke or transient ischemic attack[12-14], with the best results obtained by 3-year insertable cardiac monitoring devices[13]. However, considering their noninvasiveness and low cost, wearable devices for several-day monitoring would also be useful in practical clinical settings[15].

Aim

This present study aimed to investigate the diagnostic yield of a recently developed chest strap-style, ambulatory, 7-day Holter monitor for detecting covert AF in patients with recent ESUS and to determine the pre-entry screening biomarkers with significant associations with later detection of AF.

Methods

The enhanced detection of underlying covert atrial fibrillation using 7-day Holter electrocardiogram in patients with embolic stroke of undetermined source (EDUCATE-ESUS) was a multicenter (five stroke centers), prospective observational study. The prespecified inclusion criteria were patients aged ≥ 20 years without previously documented AF who were admitted within 3 months from stroke onset and who were diagnosed with ESUS. ESUS was defined using the following criteria, which were essentially identical with those of the Cryptogenic Stroke/ESUS International Working Group:[1] (1) ischemic stroke or transient ischemic attack with positive neuroimaging that is not lacunar, (2) absence of ≥ 50% stenosis or occlusion in cervical and intracranial arteries supplying the ischemic area, (3) no documentation of AF on 24-h Holter ECG, (4) no intracardiac thrombi on transthoracic echocardiography, (5) no other major cardioembolic sources, and (6) no other specific cause of stroke (e.g., arteritis, dissection, and vasospasm). The study was approved by each institutional review board (M29-030 in the National Cerebral and Cardiovascular Center), and informed consent was collected from all patients. The study was registered with the ClinicalTrials.gov identifier NCT02801708.

Fig. 1. The chest strap-style monitor for 7-day Holter ECG monitoring

[EV-201 (Parama-Tech, Fukuoka, Japan)]

All patients underwent 7-day Holter ECG monitoring using the EV-201 (Parama-Tech, Fukuoka, Japan), a chest strap-style monitor that is capable of 168 h of continuous single-lead ECG recording on a micro secure digital card **(Fig. 1)**. Patients could easily attach the recorder by themselves, could remove them before bathing or showering, and could then attach it again later with ease. Monitoring was performed within 3 months of stroke onset. The ECG recordings were analyzed by specially trained persons and were reviewed by another cardiac electrophysiology specialist. AF was defined as an ECG showing absolutely irregular R–R intervals without detectable P waves. If AF was detected, the details of the AF episodes were analyzed, including their duration, burden (defined as the proportion of time when AF episodes were recorded during a monitoring period), and time from the start of the examination to the first AF.

Baseline characteristics, including patient demographics, medical history, physiological data on admission, and stroke characteristics, were reviewed. In

addition, blood testing was done on admission, and transthoracic echocardiography and 24-h Holter monitoring were performed early in the hospitalization. Variables obtained from these three examinations were used to determine the predictors for detection of AF with the 7-day Holter monitoring. All data were recorded online with electronic data capture system.

The outcome measures were detection of AF of any duration using the 7-day Holter monitor, duration of the longest AF episode, AF burden, the time from the start of the monitoring to the first AF detection.

External validation of biomarkers predictive of AF was performed using an ongoing prospective single-center database (the National Cerebral and Cardiovascular Center Stroke Registry, ClinicalTrials.gov Identifier: NCT02251665). Consecutive patients who were admitted after the onset of acute ESUS and who started monitoring with insertable cardiac monitors (Reveal LINQ, Medtronic, Minneapolis, MN) were studied. Indications for the monitors were judged based on unique diagnostic criteria for ESUS, in accordance with current medical practice in Japan, such as mandatory screening with brain magnetic resonance imaging[2].

Statistical Analysis

Data are presented as median [interquartile range (IQR)] or numbers (%). Baseline characteristics and the 7-day Holter findings were compared between patients with AF and those without. Continuous variables were compared using the Wilcoxon rank-sum test. Comparisons of categorical variables were performed using the chi-squared test or Fisher's exact test, as applicable. Multivariate logistic regression analysis was performed to identify pre-entry screening biomarkers associated with detection of AF using the variables showing $P<0.05$ on univariate analysis. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff level of each biomarker. Statistical analysis was performed using Stata/SE 15.1 (StataCorp, College Station, TX, USA) with two-tailed p values <0.05 considered significant.

Results

A total of 206 patients (median age 71 years, 75 women) were enrolled in the present study between September 2014 and December 2017. **Table 1** presents the baseline clinical characteristics of the study population.

Detection of Atrial Fibrillation using the 7-Day Holter Monitoring

The 7-day Holter monitoring started at a median of 13 days (IQR 9–19 days) after stroke onset in the inpatient setting for 121 patients (59%) and in the outpatient setting for the remaining 85 patients. The median time of total ECG recording was 168.3 h (IQR 167.0–172.4 h), and the time did not reach 100 h in 11 patients (5%, 40.6–98.0 h). No technical problems were encountered by the patients in handling the device themselves. Any non-mild adverse events related to the examination were documented. The only mild adverse event was a transient skin rash related to wearing the device in 16 patients (8%).

AF with any duration was detected in 14 patients [6.8%, 95% confidence interval (CI) 4.1%–11.1%]. The median longest duration of AF was 50 min (IQR 25–236 min, **Fig. 2A**). It lasted >30 min in 11 patients (#1–13) and 67, 46, and 15 s in the remaining 3 patients (#12–14, respectively). Thirteen patients (6.3%, except for #14) met the definition of paroxysmal AF in the current guidelines (≥ 30 s)[16]. The median AF burden during the monitoring period amounted to 4.9% (IQR 0.9%–10.6%, **Fig. 2B**). AF was detected only once in the three patients with the longest duration of AF <2 min (#12–14). The median interval between the start of monitoring and the first documentation of AF was 50 h (IQR 25–236 h, **Fig. 2C**). The median interval between stroke onset and the initiation of monitoring was 10.5 days for these 14 patients versus 13 days for the remaining patients without documentation of AF ($P=0.69$, **Table 1**). The detection rates of AF during the quartile periods between stroke onset and the start of monitoring were 8.2% (4/49) in the first quartile (≤ 8 days), 7.0% (4/53) in the second (9–13 days), 2.1% (1/47) in the third (14–18 days), and 9.6% (5/47) in the fourth (≥ 19 days, $P=0.39$).

Association of Baseline Characteristics with Detection of Atrial Fibrillation

Patients with AF identified on the 7-day Holter monitoring were found to be older than the remaining patients without documentation of AF ($P=0.010$). Diabetes mellitus was less common ($P=0.013$), coronary artery disease was more common ($P=0.049$), systolic blood pressure (SBP, $P=0.020$) and diastolic blood pressure (DBP, $P=0.019$) were lower, heart rate was slower ($P=0.015$), serum brain natriuretic peptide (BNP) was higher ($P<0.001$), and both the atrial premature contraction (APC) count ($P=0.002$) and short runs of APCs ($P<0.001$), meaning triplets or more multiple runs, on the 24-h Holter ECG were more common in those with AF than in those without

Table 1. Baseline characteristics of the patients

	Total, $n=206$	AF (+), $n=14$	AF (−), $n=192$	P
Demographics				
Age, y	71 (61−78.3)	75.5 (73.3−83.5)	69.5 (61−78)	0.010
Female sex	75 (36.4)	4 (28.6)	71 (37.0)	0.52
Comorbidities / medical history				
Hypertension	139 (67.5)	11 (78.6)	128 (66.7)	0.34
Diabetes mellitus	39 (18.9)	0 (0)	39 (20.3)	0.013
Dyslipidemia	103 (50.0)	5 (35.7)	98 (51.0)	0.27
Heart failure	2 (1.0)	1 (7.1)	1 (0.5)	0.09
Chronic kidney disease	10 (4.9)	1 (7.1)	9 (4.7)	0.70
Coronary artery disease	13 (6.3)	3 (21.4)	10 (5.2)	0.049
Peripheral artery disease	0 (0)	0 (0)	0 (0)	−
Previous ischemic stroke except for the index one	35 (17.0)	2 (14.3)	33 (17.2)	0.76
CHADS2 score*	1 (1−2)	1.5 (1−2)	1 (1−2)	0.56
CHA2DS2-VASc score*	3 (2−4)	3 (2−4)	3 (1−4)	0.28
Physiological data on admission				
Body mass index, kg/m^2	22.9 (20.8−25.4)	21.7 (19.6−24.8)	22.9 (20.9−25.4)	0.23
Systolic blood pressure, mmHg	160 (139−179)	147 (130−158.5)	160.5 (139−180.8)	0.020
Diastolic blood pressure, mmHg	87 (76−100)	76 (71.5−83.8)	88 (78−100)	0.019
Heart rate, /min	78 (67−88.3)	68.5 (63.3−74.3)	78 (68−89.8)	0.015
Features of stroke				
National Institutes of Health Stroke Scale score	2 (1−5)	2.5 (0−4)	2 (1−5)	0.98
Infarct diameter < 1.5 cm	73 (36.4%)	5 (35.7)	68 (35.4)	0.98
Location of infarcts				0.12
Anterior circulation alone	128 (62.1)	10 (71.4)	118 (61.4)	
Posterior circulation alone	50 (24.3)	4 (28.6)	46 (24.0)	
Both	28 (13.6)	0	28 (14.6)	
Blood test				
Serum creatinine, mg/dL	0.76 (0.65−0.89)	0.78 (0.72−0.93)	0.75 (0.65−0.89)	0.31
Brain natriuretic peptide (BNP), pg/mL	32.1 (13.4−83.0)	114.8 (40.1−198.8)	28.4 (12.5−67.1)	<0.001
BNP ≥ 66 pg/mL†	58 (28.2)	10 (71.4)	48 (25.0)	<0.001
D-dimer, μg/mL	0.7 (0.5−1.2)	0.7 (0.7−4.2)	0.7 (0.5−1.1)	0.074
Transthoracic echocardiography				
Left atrial dimeter, mm	35 (31−39)	37.5 (32.6−42)	35 (31−39)	0.13
Left atrial dimeter ≥ 36.0 mm†	82 (39.8)	10 (71.4)	74 (38.5)	0.067
Left ventricular ejection fraction, %	64.1 (61−70)	62.3 (54.8−69.8)	64.3 (61−70)	0.22
24-hour Holter electrocardiography				
Atrial premature contractions (APCs), /24 h	80 (22−383)	391 (152−946)	64 (19−312)	0.002
APCs ≥ 345 beats /24h†	55 (26.7)	9 (64.3)	46 (24.0)	0.002
APC short runs, /24 h	1 (0−3)	8.5 (1−22)	1 (0−3)	<0.001
APC short runs ≥ 13 /24 h†	25 (12.1)	7 (50.0)	18 (9.4)	<0.001
7-day Holter monitoring				
Day after stroke onset, d	13 (9−19)	10.5 (7.8−24.3)	13 (9−18)	0.69

N (%) or median (IQR),
*Scores prior to the index stroke
†Each cutoff value was determined by receiver operatorating characteristic curve analysis.

(Table 1).

Baseline characteristics that were independently associated with AF detection were determined by multivariate analysis with the variables showing $P<0.05$ on univariate analysis (SBP was excluded from the variables due to its strong interaction with DBP, and diabetes was excluded due to no positive patients in the AF group) plus left atrial diameter (LAD) as a representative biomarker of echocardiography. BNP level was positively associated with AF, independent of

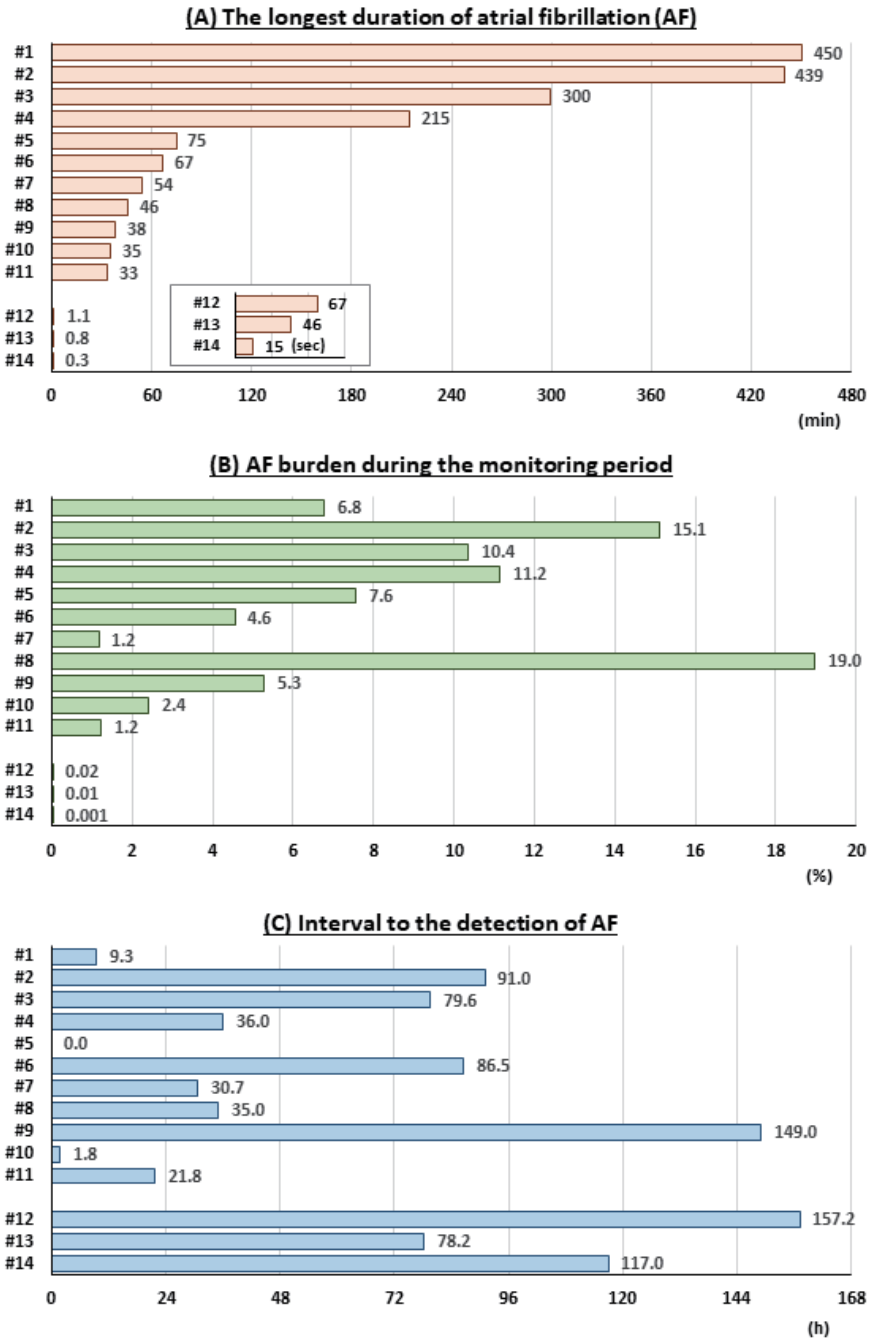

Fig. 2. Findings of atrial fibrillation detected by 7-day Holter monitoring

other variables **(Table 2)**.

Cutoff Levels of Pre-Entry Biomarkers for Predicting AF

The optimal cutoff levels of the biomarkers obtained by blood testing, transthoracic echocardiography, and 24-h Holter ECG prior to 7-day Holter monitoring that were predictive of AF detection were investigated. As the most powerful candidates of each examination, BNP was chosen among blood test findings, LAD was chosen among echocardiography findings, and the total counts of APCs and the short runs of APCs were chosen among the 24-h Holter ECG findings. **Fig. 3** shows the distribution of these four components for patients with and without AF detection. **Fig. 4** shows the associations of pairs of the four components.

The cutoff level of BNP based on the ROC curve

Table 2. Associations of baseline characteristics (continuous variables) with detection of atrial fibrillation

	Odds ratio (95% CI)	*P*
Age, per 10-year	1.78 (0.91−3.51)	0.093
Coronary artery disease	2.09 (0.38−11.47)	0.394
Diastolic blood pressure, per 10-mmHg	0.73 (0.45−1.19)	0.209
Heart rate, per 10-beat/min	0.61 (0.36−1.03)	0.063
Brain natriuretic peptide, per 10-pg/mL	1.09 (1.03−1.17)	0.007
Left atrial dimeter, per 1-mm	1.07 (0.99−1.17)	0.084
Atrial premature contraction (APC), per 100-beats/24 h	0.99 (0.97−1.01)	0.502
APC short runs, per 1-/24 h*	1.00 (1.00−1.00)	0.999

*Adjusted by age, diastolic blood pressure, heart rate, brain natriuretic peptide and left atrial dimeter
CI: confidence interval

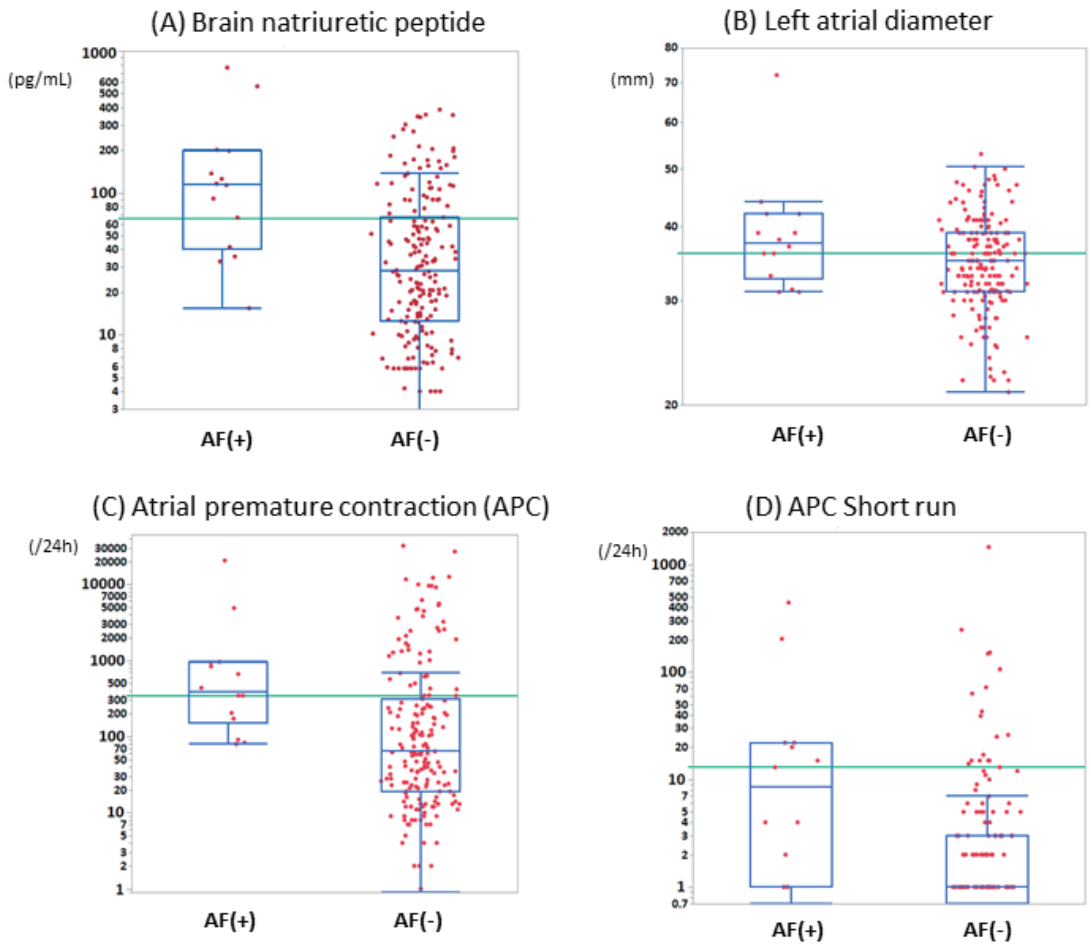

Fig. 3. Distribution of data from the pre-entry screening examinations

Horizontal lines show cutoff levels for predicting detection of atrial fibrillation by ROC curve analysis.
Box and whisker plots show 10th, 25th, 50th, 75th, and 90th percentile values.
AF: atrial fibrillation

analysis was 66.0 pg/mL with area under the curve (AUC) of 0.77, that of LAD was 36.0 mm with AUC of 0.62, that of APCs was 345 beats/24h with AUC of 0.75, and that of short runs of APCs was 13 beats/24h with AUC of 0.75. Sensitivity varied between 0.50 and 0.71, with the highest level for BNP (**Table 3**). Specificity varied between 0.53 and 0.90, with the highest level for short runs of APCs. Positive predictive values did not reach 0.3, and negative predictive values were 0.96 or 0.97 for all.

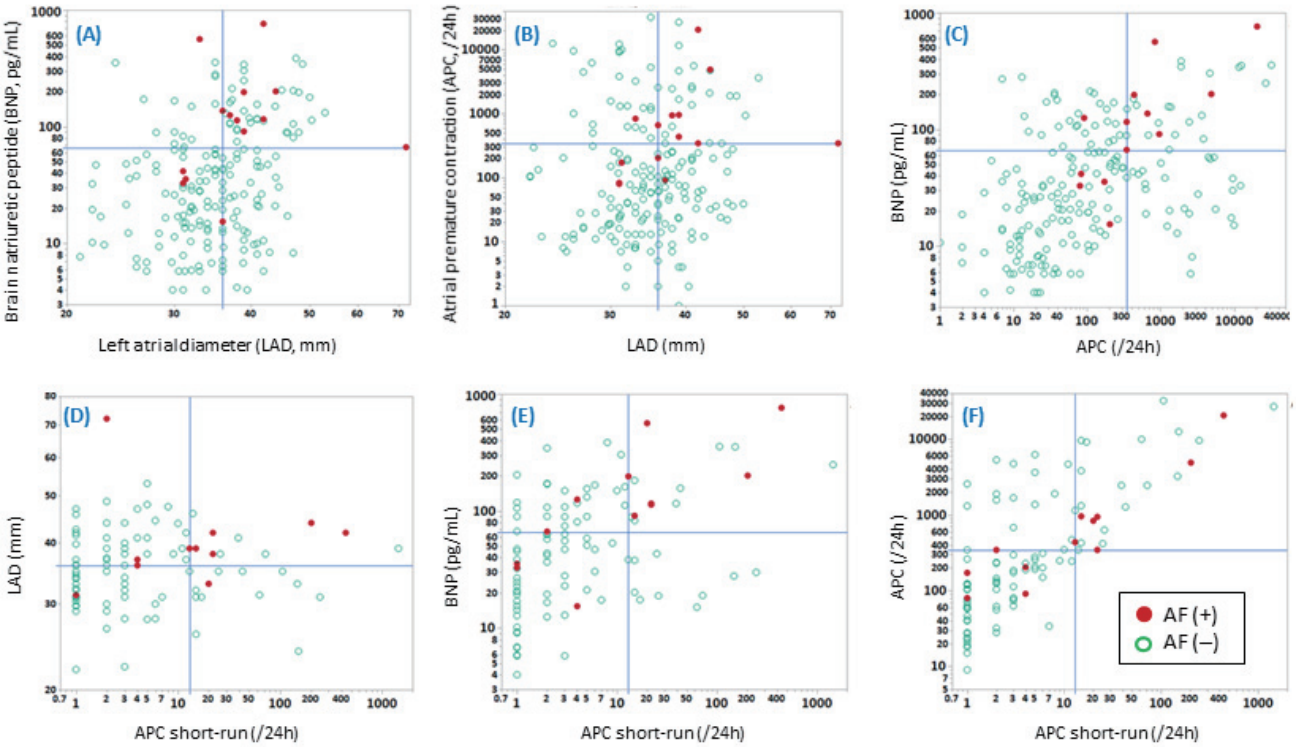

Fig. 4. Distribution of bivariate data from the pre-entry screening examinations

Lines show cutoff levels for predicting detection of atrial fibrillation by ROC curve analysis.
AF: atrial fibrillation

Table 3. Association of pre-entry screening data (dichotomized) with detection of atrial fibrillation

	Odds ratio (95% CI)	*P*	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Brain natriuretic peptide (BNP) ≥ 66 pg/mL	5.23 (1.47–18.67)	0.011	0.71	0.75	0.17	0.97
Left atrial dimeter (LAD) ≥ 36.0 mm	3.19 (0.89–11.50)	0.076	0.71	0.53	0.10	0.96
Atrial premature contractions (APC) ≥ 345/24h	3.80 (1.07–13.50)	0.039	0.64	0.76	0.16	0.97
APC short runs ≥ 13/24 h	5.74 (1.58–20.81)	0.008	0.50	0.90	0.28	0.96
BNP ≥ 66 pg/mL and LAD ≥ 36.0 mm	7.17 (2.05–25.08)	0.002	0.64	0.83	0.21	0.97
APC ≥ 345/24h and BNP ≥ 66 pg/mL	11.85 (3.03–46.25)	< 0.001	0.64	0.90	0.32	0.97
APC short runs ≥ 13/24 h and BNP ≥ 66 pg/mL	16.68 (3.98–69.85)	< 0.001	0.50	0.96	0.47	0.96
APC ≥ 345/24h and LAD ≥ 36.0 mm	8.23 (2.31–29.38)	0.001	0.50	0.90	0.26	0.96
APC short runs ≥ 13/24 h and LAD ≥ 36.0 mm	19.56 (4.18–91.66)	< 0.001	0.43	0.97	0.55	0.96

All variables are adjusted by age, coronary artery disease, diastolic blood pressure, and heart rate.

Exceeding each of these four cutoff levels was associated with AF detection independent of age, coronary artery disease, DBP, and HR, with adjusted odds ratios between 3.19 (for LAD) and 7.17 (for short runs of APCs, Table 3). Simultaneously exceeding any two of these four cutoff levels was also independently associated with AF detection, with the adjusted odds ratios between 7.17 and 19.56.

Validation

A total of 83 patients (median age 74 years, 36 women) were enrolled in the validation cohort between October 2016 and April 2020. Table 4 summarizes the baseline clinical characteristics of the cohort. The device identified AF in 24 patients (29%, 95% CI 20.3%–39.4%), the detection rate being 37% (11/30) in patients initiating monitoring within 30 days after onset of stroke, 35% (6/17) in those within

Table 4. Baseline characteristics of the validation cohort

	Total, $n=83$	AF (+), $n=24$	AF (−), $n=59$	P
Age, y	74 (62−79)	77.5 (70.8−80.8)	70 (60−77)	0.010
Female sex	36 (43)	10 (42)	26 (44)	0.84
National Institutes of Health Stroke Scale score	2 (0−6)	3 (1−9.25)	1 (0−4)	0.026
Day of implantation after stroke onset, d	48 (19−107)	31 (15.5−62.8)	59 (21−115)	0.045
Day of follow-up after implantation*, d	205 (68−548)	71 (14.5−138.5)	318 (142−628)	<0.001
Brain natriuretic peptide (BNP), pg/mL	42.2 (13.9−100.7)	112.2 (46.8−199.9)	24.9 (10.9−55.4)	<0.001
Left atrial dimeter on echocardiography, mm	35 (32−39)	38 (33−42)	34 (31−38)	0.030
Atrial premature contractions (APCs) on 24-hour Holter electrocardiography, /24 h	97 (19−352)	684.5 (125−3395)	53 (15−180)	<0.001
APC short runs, /24 h	2 (0−7)	9 (1−19.5)	1 (0−4)	<0.001

N (%) or median (IQR)
*Follow-up completed when atrial fibrillation was detected.

60 days, 29% (4/14) in those within 90 days, and 14% (3/22) in those later than 90 days ($P=0.26$). Age-adjusted odds ratios of predicting AF detection were 6.59 (95% CI 1.91–22.69) for BNP ≥ 66 pg/mL, 2.21 (0.80–6.11) for LAD ≥ 36.0 mm, 7.87 (2.45–25.31) for APCs ≥ 345 beats/24h, and 6.16 (1.60–23.74) for short runs of APCs ≥ 13 beats/24h.

Discussion

First, the ambulatory 7-day Holter monitoring detected previously unidentified AF in 6.8% (95% CI: 4.1%–11.1%) of the patients with recently diagnosed ESUS after completion of the standard clinical workup including 24-h Holter ECG. Second, the median time delay from starting the 7-day Holter monitoring to the first AF documentation was 50 h. Third, the serum BNP level and the APC count and short runs of APCs on 24-h Holter ECG in the standard workup seemed to be predictors of covert AF.

The rate of newly detected AF after ischemic stroke varies widely depending on its definition (minimal duration, etc.), study population, duration of cardiac monitoring, monitoring devices (e.g.., Holter ECG, external loop recorders, or implantable loop recorders), and interval from stroke onset to the start of monitoring[17]. Meta-analyses revealed that the detection rate of AF in patients with ischemic stroke using ambulatory Holter monitoring for 1 to 7 days was 10.7% (95% CI: 5.6%–17.2%) and that using monitoring for ≥ 7 days was 15% (11%–19%)[18, 19]. The present rate of AF detection was low compared to previous reports. A possible reason was that continuous cardiac monitoring during patients' stay in stroke care units for several days was often performed in addition to the 24-h Holter ECG as the standard clinical workup in the participating institutes. Moreover, this process might decrease the chance to register patients with covert AF, which could relatively easily appear into the 7-day Holter monitoring. Additionally, the detection rate of AF reportedly declines with the lapse of time after onset of stroke as was also shown in the present validation cohort[20]. In the derivation cohort, the first three quartile groups by the delay of initiation of the 7-day Holter showed the similar tendency, but the last quartile group did not, which was presumably partly due to the statistical error with the small patient number of each quartile group.

The rate of AF detection using insertable monitors was generally higher than that by the 7-day monitoring, being 8.9% at 6 months and 30.0% at 36 months in patients with cryptogenic stroke in the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial[13]. A high rate of 26% for a median follow-up of 7 months was reported in a multicenter registry in Japan, including one of the present participating institutes[21], in which the abovementioned diagnostic criteria for ESUS in accordance with current medical practice in Japan were used[2]. Despite its weaker detection power, the 7-day Holter monitoring seemed to have some features, making it superior to insertable monitors, such as noninvasiveness and low cost. Additionally, the present device can identify a transient AF episode lasting seconds, although regular insertable monitors have a 2-min time window to recognize AF[22]. Very short paroxysmal AF was relatively common. In a systematic review and meta-analysis, 56.3% of poststroke patients who had newly diagnosed AF had AF lasting <30 s[23]. In the present study, three patients showed AF lasting <2 min as the only AF episode. However, the prognostic significance of such a single transient episode of AF still remains uncertain. Current definitions of paroxysmal AF (≥ 30 seconds) were determined by an arbitrary consensus[17] and might have been related to the minimum required

duration of algorithms for automated detection of AF rather than on scientific grounds.

All of serum BNP, LAD, and APC counts are promising predictors for covert AF that later appeared in long-term monitoring with reported optimal cutoff levels of >70–100 pg/mL, >45 mm, and >222 beats/24 h, respectively[24-27]. Of several blood biomarkers, elevated BNP, high levels of N-terminal prohormone of BNP, midregional pro-atrial natriuretic peptide, fibroblast growth factor-23, and Galectin three were reportedly associated with AF[28-32]. Compared to these blood biomarkers, d-dimer and other known coagulation markers might be less predictive of AF detection[28]. BNP and LAD, along with P-wave terminal force in lead V1 on ECG, seem to also be associated with atrial cardiopathy, a potential emboligenic pathology to the brain[4, 33]. Of these, P-wave terminal force in lead V1 seemed to have a problem of interobserver variability; thus, we accordingly planned to analyze the marker with central reading in a future study separate from the other handy markers. The significance of short runs of APCs has remained unclear. Any episode of runs of ≥ 20 APCs in the 48-h Holter monitoring was reported to be predictive of AF development in the healthy cohort[34], and >5-beat/24-h APC runs in the 7-day Holter monitoring were reported to be predictive of AF in the stroke patients[35]. LAD did not show a significant difference between patients with and without AF detection in the present univariate analysis, and its cutoff value of 36.0 mm had relatively low specificity (0.53) compared to the others (0.75–0.90). Since the present cutoff of LAD was smaller compared with the reported value, and old Japanese patients often have a small stature, correction of LAD by body surface area would be better. BNP and APCs might accordingly be more promising biomarkers for choosing candidates with ESUS requiring somewhat invasive long-term cardiac monitoring. The superiority of BNP and APCs as predictors of AF to LAD was shown in the present validation cohort.

The limitations of the present study included the small number of patients with AF detection, limiting statistical power for some comparisons. In addition, the validation analysis was performed using different diagnostic tools (insertable cardiac monitors) from 7-day Holter monitoring; these two tools have different power to detect covert AF.

Conclusion

With ambulatory 7-day Holter monitoring, AF was newly detected in ≈7% of patients recently diagnosed with ESUS. Several serological, imaging, and electrocardiographic markers obtained at pre-entry screening seem promising as predictors of covert AF.

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Disclosures

No authors disclose conflict of interest related to the manuscript.

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