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ORIGINAL RESEARCH

Atrial Fibrillation Detection and Ischemic Stroke Recurrence in Cryptogenic Stroke: A Retrospective, Multicenter, Observational Study

Kenichi Todo, MD; Shuhei Okazaki, MD; Ryosuke Doijiri, MD; Hidekazu Yamazaki, MD; Kazutaka Sonoda, MD; Junpei Koge, MD; Tomonori Iwata, MD; Yuji Ueno, MD; Hiroshi Yamagami, MD; Naoto Kimura, MD; Masafumi Morimoto, MD; Daisuke Kondo, MD; Masatoshi Koga, MD; Eiichiro Nagata, MD; Nobukazu Miyamoto, MD; Yoko Kimura, MD; Yasufumi Gon, MD; Tsutomu Sasaki, MD; Hideki Mochizuki, MD; for the CRYPTON-ICM Registry Investigators*

BACKGROUND: Atrial fibrillation (AF) is known to be a strong risk factor for stroke. However, the risk of stroke recurrence in patients with cryptogenic stroke with AF detected after stroke by an insertable cardiac monitor (ICM) is not well known. We sought to evaluate the risk of ischemic stroke recurrence in patients with cryptogenic stroke with and without ICM-detected AF.

METHODS AND RESULTS: We retrospectively reviewed patients with cryptogenic stroke who underwent ICM implantation at 8 stroke centers in Japan. Cox regression models were developed using landmark analysis and time-dependent analysis. We set the target sample size at 300 patients based on our estimate of the annualized incidence of ischemic stroke recurrence to be 3% in patients without AF detection and 9% in patients with AF detection. Of the 370 patients, 121 were found to have AF, and 110 received anticoagulation therapy after AF detection. The incidence of ischemic stroke recurrence was 4.0% in 249 patients without AF detection and 5.8% in 121 patients with AF detection (P=0.45). In a landmark analysis, the risk of ischemic stroke recurrence was not higher in patients with AF detected ≤90 days than in those without (hazard ratio, 1.47 [95% CI, 0.41–5.28]). In a time-dependent analysis, the risk of ischemic stroke recurrence did not increase after AF detection (hazard ratio, 1.77 [95% CI, 0.70–4.47]).

CONCLUSIONS: The risk of ischemic stroke recurrence in patients with cryptogenic stroke with ICM-detected AF, 90% of whom were subsequently anticoagulated, was not higher than in those without ICM-detected AF.

Key Words: atrial fibrillation ■ cryptogenic stroke ■ ischemic stroke

See Editorial by Rosso and Cucchiara.

The cause of ischemic stroke remains uncertain in 9% to 25% of patients with ischemic stroke even after a thorough diagnostic workup, resulting in cryptogenic stroke or embolic stroke of undetermined source (ESUS).[1] Covert paroxysmal atrial fibrillation (AF) is recognized as 1 of the latent causes of

Correspondence to: Kenichi Todo, MD, PhD, Department of Neurology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita City, Osaka 565-0871, Japan. Email: ktodo@neurol.med.osaka-u.ac.jp

*A complete list of the CRYPTON-ICM Registry Investigators can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- Although overt atrial fibrillation (AF) is known to be associated with a robustly high risk of stroke, our study showed that the risk of stroke recurrence in patients with cryptogenic stroke with AF detected after stroke by insertable cardiac monitor (ICM) was not higher than that in patients with cryptogenic stroke without AF detected after stroke by ICM.
- The relatively small burden of AF detected after stroke by ICM, and appropriate initiation of anticoagulation therapy after AF detection may explain these results.

What Are the Clinical Implications?

- AF detected after stroke by ICM in patients with cryptogenic stroke may not carry as high a risk of stroke as conventional overt AF.
- Rather than empirically starting anticoagulation therapy before AF is detected in patients with cryptogenic stroke, it is reasonable to switch from antiplatelet therapy to anticoagulation therapy after AF is detected by ICM.
- Attention still needs to be paid to the other causative factors of ischemic stroke, especially in patients in whom AF has not been detected.

Nonstandard Abbreviations and Acronyms

ESUS	embolic stroke of undetermined source
ICM	insertable cardiac monitor
LAVI	left atrial volume index

cryptogenic stroke.[2] Overt AF is associated with a 5-fold increased risk of stroke and stroke severity.[3–5] In comparison to antiplatelet therapy, anticoagulation therapy can significantly reduce the incidence of stroke in patients with overt AF.[6,7] Therefore, the identification of covert AF in patients with cryptogenic stroke and subsequent anticoagulation is considered crucial to prevent ischemic stroke recurrence. Long-term recording with an insertable cardiac monitor (ICM), or an implantable loop recorder, has been used in patients with cryptogenic stroke and found to be useful for AF detection.[8,9] However, the superiority of long-term monitoring with external cardiac monitor or ICM over conventional monitoring for the prevention of stroke recurrence has not been demonstrated.[10–12] One of the explanations for this may be the lower cardiovascular burden and lower risk of stroke recurrence in patients with AF detected after stroke compared with patients with known AF before stroke.[11]

In this study, we aimed to assess the long-term risk of ischemic stroke recurrence in patients with cryptogenic stroke with AF detected by ICM compared with that in patients with cryptogenic stroke without AF detection. In addition, we investigated the risk of ischemic stroke recurrence in patients with cryptogenic stroke with a high-burden AF, in comparison to that in patients with cryptogenic stroke without a high-burden AF, based on a recent report indicating a higher stroke risk associated with high-burden AF in individuals with paroxysmal AF.[13]

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Ethical Approval

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan and complied with the Declaration of Helsinki guidelines for investigations involving humans. The institutional review boards of all 8 institutes approved this study. The requirement for written informed consent for this study was waived due to the retrospective nature of the study. Consent for participation and publication was obtained using an opt-out method.

Study Population

The current study was a retrospective, multicenter, observational study that enrolled consecutive patients who underwent ICM implantation for cryptogenic stroke between October 2016 and September 2020 from 8 stroke centers in Japan: CRYPTOgenic stroke evaluation in Nippon using Insertable Cardiac Monitor (CRYPTON-ICM) registry. This study was registered at http://www.umin.ac.jp/ctr/ (UMIN000044366). The inclusion criteria for this study were as follows: (1) patients diagnosed with cryptogenic stroke according to the Trial of Org 10172 in Acute Stroke Treatment criteria[14] and (2) patients who underwent ICM implantation for AF detection between October 2016 and September 2020. Given the retrospective nature of this study, the indications for ICM implantation were not standardized in this registry. All investigators followed the Japanese proposal for clinical indications of ICM, which strongly recommends magnetic resonance imaging, transthoracic echocardiography, cardiac monitoring for 24 hours or more with automated rhythm detection,

and imaging of both the extracranial and intracranial arteries supplying the area of brain ischemia (catheter, magnetic resonance, or computed tomography angiography, or cervical duplex ultrasonography); and additionally recommends transesophageal echocardiography, ultrasonic examination for right-to-left shunt, venous duplex ultrasonography, and special blood tests on thrombosis-hemostasis and other parameters for stroke.[15] Patients without ≥90 days of clinical follow-up and those without ≥90 days of ICM follow-up were excluded. Among the participants in this registry, 84 patients were included in a previous registry that we reported in 3 articles, in which we showed the detection rate of AF by ICM, the associations of AF detected by ICM with premature atrial contractions (PACs), and with major vessel occlusion.[9,16,17]

Baseline Clinical Variables

The following clinical information was obtained from the medical records: age at the time of ICM implantation, sex, the presence of hypertension, the presence of diabetes, past history of congestive heart failure, $CHADS_2$ score[18] after the index stroke, plasma B-type natriuretic peptide level or serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) level, parameters of 12-lead ECG (P-wave terminal force on lead V_1 and PR interval), parameters of 24-hour Holter ECG monitoring (number of PACs and the presence of atrial runs ≥10 beats), parameters of transthoracic echocardiography (left atrial diameter and left atrial volume index [LAVI]), findings of transesophageal echocardiography (left atrial appendage flow velocity, the presence of aortic complicated lesion, and the presence of patent foramen ovale), imaging findings of the index stroke (number of lesions and the maximum lesion size on diffusion-weighted imaging and the presence of major vessel occlusion), and the type of antithrombotic therapy. These data were obtained before ICM implantation, if not available, after ICM implantation and before AF detection.

High B-type natriuretic peptide and NT-proBNP levels were defined as >100 pg/mL and >300 pg/mL, respectively.[19] The P-wave terminal force on lead V_1 and PR interval were measured manually by local investigators blinded to the outcome measurements. The P-wave terminal force on lead V_1 was calculated as the duration of the negative terminal deflection of the P-wave multiplied by the absolute value of its amplitude at each hospital.[20] The left atrial appendage flow velocity was defined as the emptying flow velocity, and if the filling flow velocity was higher, we used it for the analysis. An aortic complicated lesion was defined as a localized raised lesion with a maximal intimal-medial thickness >4.0 mm and a markedly irregular surface. Major vessel occlusion was defined as an occlusion of the internal carotid artery, middle cerebral artery (M1, M2, or M3), basilar artery, and other vessels (vertebral artery, posterior inferior cerebellar artery, anterior cerebral artery, and posterior cerebral artery).

Because of the retrospective nature of this study, the selection of antithrombotic therapy and the switch to anticoagulation therapy after AF detection were determined by the attending physician. We obtained information on antithrombotic therapy at the time of ICM implantation, at the time of stroke recurrence, and at the end of clinical follow-up. Antithrombotic therapy was divided into 2 categories: with and without anticoagulation therapy. Patients with anticoagulation therapy included those receiving anticoagulation therapy alone and those receiving both anticoagulation and antiplatelet therapy. Patients without anticoagulation therapy included those receiving antiplatelet therapy alone and those receiving no antithrombotic therapy.

ICM Implantation, Follow-Up, and Data Collection

ICMs (Reveal LINQ; Medtronic, Minneapolis, MN), Confirm Rx;Abbott Laboratories, Lake Bluff, IL), or BioMonitor 2-AF; Biotronik SE & Co. KG, Berlin, Germany) were implanted in patients under local anesthesia in the left parasternal position. The choice of device was made by the attending physician. All the devices were programmed to detect AF using a unique algorithm. Device data were transmitted remotely to company servers, and study physicians received alerts when the devices detected AF. The waveforms of the first detected AF episodes lasting 2 minutes or more were adjudicated by the study physicians using the remote monitoring system. AF burden was defined as the percentage of the cumulative duration of AF episodes that were automatically detected during the entire follow-up period. We defined a high AF burden as being higher than the median of the patients with AF detection. The last ICM data were obtained remotely by March 2021.

Clinical Follow-Up and Outcome

Clinical information was obtained from the medical records of outpatient clinics. The outcome measure was ischemic stroke recurrence, defined as a new neurological deficit with corresponding evidence of acute ischemia on brain imaging (computed tomography and/or magnetic resonance imaging). Final clinical information was collected by March 2021. We evaluated the cumulative incidence of ischemic stroke recurrence after ICM implantation.

Sample Size Calculation

Overt AF is associated with a 5-fold higher incidence of stroke in patients without anticoagulation therapy.[3]

Anticoagulation therapy can reduce the incidence of stroke in patients with overt AF by one-half to two-thirds compared with antiplatelet therapy.[6,7] In our cohort, assuming that some participants would have received anticoagulation therapy before or after AF detection, we estimated less than a 5-fold increased risk and more than a 2-fold increased risk in patients with AF detection. In previous large randomized trials, the annualized rate of ischemic stroke recurrence in patients with ESUS receiving either anticoagulation or antiplatelet therapy was 4.0% to 4.7%, and up to 8.3% in the Japanese population.[21–23] Among patients with ESUS with 3 years of ICM recordings, AF was detected in one-third.[8,9] Taken together, we estimated that the annualized incidence of stroke would be 3% in patients without AF detection and 9% in patients with AF detection. Based on a 2-sided alpha level of 0.05 and a power of 0.8, we estimated that at least 300 patients (200 without AF detection and 100 with AF detection) would need to be enrolled to detect a higher incidence of ischemic stroke recurrence in patients with AF detection than in patients without AF detection.

Statistical Analysis

Continuous variables were expressed as the median values and interquartile range. Categorical data were expressed as numbers and percentages. Time-to-event analyses were performed using the Kaplan–Meier method. The starting point for the clinical follow-up was the time of ICM implantation. Patients were censored at the time of ischemic stroke recurrence or at the last follow-up date confirmed by outpatient medical records. To analyze the association between clinical characteristics and ischemic stroke recurrence, we used a mixed-effects Cox regression model to assess the hazard ratio (HR) of ischemic stroke recurrence, in which the site was modeled as a random effect. Cases with missing data were excluded from the univariate analysis. We developed logistic regression models to analyze the association of AF detection and a high AF burden with ischemic stroke recurrence. To analyze the risk of ischemic stroke recurrence after AF detection, first, we developed Cox regression models using a landmark analysis, in which the landmark time was set at 90 days from the date of ICM implantation, and analyzed the association between AF detection up to the landmark time and ischemic stroke recurrence after the landmark time. Second, we developed a time-dependent Cox regression model using AF detection as a time-dependent covariate. Subgroup analysis was performed based on baseline characteristics in which continuous variables were dichotomized at the median. The proportional hazards assumption was tested using Schoenfeld residuals, Martingale residuals, and Deviance residuals. Statistical significance was set at P values <0.05. All analyses were conducted with R software version 4.1.2 using the rms, survival, coxme, and pwr packages (https://cran.r-project.org/). We showed the R code in Data S1.

RESULTS

Study Population and Follow-Up Period

Among the 417 consecutive patients who underwent ICM implantation, we excluded 29 patients without clinical follow-up for 90 days or more and 18 patients without ICM follow-up for 90 days or more. Therefore, 370 patients were included in the analysis (Figure 1). The median (interquartile range) time from index stroke to ICM implantation was 22 (13–61) days. The time from ICM implantation to last visit and last ICM data collection was 578 (354–813) and 637 (433–861) days, respectively. During this period, AF was detected in 121 patients at 76 (15–263) days after ICM implantation, and ischemic stroke recurrence was observed in 17 patients at 399 (96–471) days after ICM implantation (Figure S1).

Background Characteristics and Ischemic Stroke Recurrence

A summary of the clinical characteristics is shown in the Table. Among the baseline characteristics, the presence of atrial runs (HR, 3.27 [95% CI, 1.09–9.81]; P=0.035) and the LAVI (HR [per 1-mL/m^2 increase], 1.06 [95% CI, 1.00–1.11]; P=0.037) were marginally associated with ischemic stroke recurrence. The proportional hazards assumption was satisfied (all were P>0.05) (Figure S2).

Anticoagulant therapy at the time of ICM implantation was not associated with subsequent ischemic stroke recurrence (HR, 1.93 [95% CI, 0.72–5.17]; P=0.19) (Table). In 121 patients with AF detection, excluding 1 patient with insufficient data, 110 patients (92%) received anticoagulation therapy after AF detection. Ischemic stroke recurrence was observed in 6 of 110 patients receiving anticoagulation therapy and in 1 of 10 patients not receiving anticoagulation therapy (5.5% versus 10.0%, P=0.33).

AF and Ischemic Stroke Recurrence

The incidence of ischemic stroke recurrence was 4.0% (95% CI, 1.9%–7.3%) in 249 patients without AF detection and 5.8% (95% CI, 2.4%–11.2%) in 121 patients with AF detection (odds ratio [OR] 1.47 [95% CI, 0.54–3.95], P=0.45) (Figure 2A). The median AF burden was 0.1%; thus, a high AF burden was defined as ≥0.1%. The incidence of ischemic stroke recurrence was 3.9% (95% CI, 2.0%–6.7%) in 307 patients without a high AF burden and 7.9% (95% CI, 2.6%–17.6%) in 63 patients

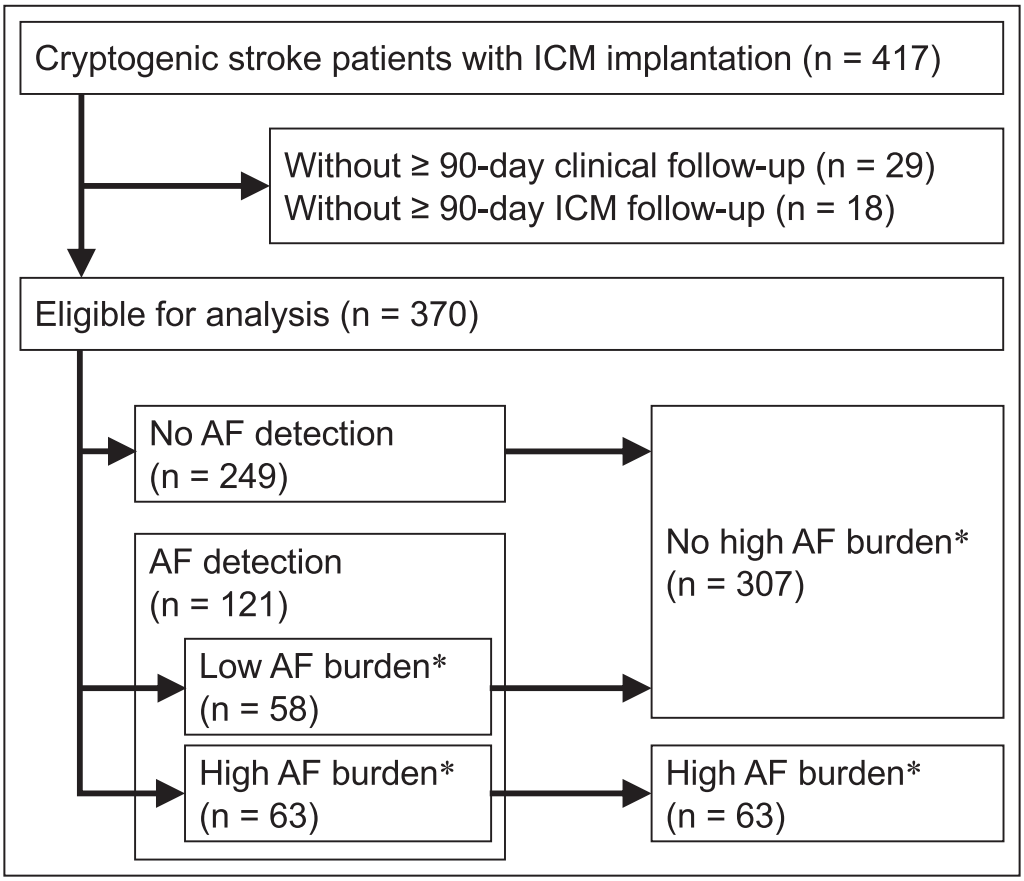

Figure 1. Flow diagram of the study population.
*AF burden was defined as the percentage of the cumulative duration of AF episodes automatically detected during the entire follow-up period. A high AF burden was defined as above the median among the patients with AF detection. The median AF burden was 0.1%; thus, a high AF burden was defined as ≥0.1%. AF indicates atrial fibrillation; ICM, insertable cardiac monitor.

with a high AF burden (OR, 2.12 [95% CI, 0.72–6.25]; *P*=0.17) (Figure 2B). Due to the small number of patients with ischemic stroke recurrence, we did not develop a multivariate logistic regression model.

Of the 370 patients, AF was detected within 90 days in 66 patients. In a landmark analysis, the risk of ischemic stroke recurrence beyond 90 days after ICM implantation was not higher in patients with AF detected in the first 90 days than in those without (HR, 1.47 [95% CI, 0.41–5.28]; *P*=0.57) (Figure 3A), in which the proportional hazards assumption was satisfied (*P*>0.05) (Figure S2).

AF was detected in 121 of 370 patients, in 118 of whom AF was detected before the last visit and in 3 of whom AF was detected after the last visit. When a univariate Cox regression model was developed using AF detection as a time-dependent covariate, the risk of ischemic stroke recurrence did not increase after AF detection (HR, 1.77 [95% CI, 0.70–4.47]; *P*=0.23) (Figure 3B), in which the proportional hazards assumption was satisfied (*P*>0.05) (Figure S2). A similar result was obtained when this analysis was restricted to patients with AF detection (HR, 1.81 [95% CI, 0.66–4.95]; *P*=0.25) (Figure S3). The individual days from ICM implantation to ischemic stroke recurrence are shown in Figure S4. Of the 17 patients with stroke recurrence, AF was detected before stroke recurrence in 6 patients and after stroke recurrence in 1 patient. Due to the small number of patients with ischemic stroke recurrence, we did not develop a multivariate Cox regression model.

The results of the subgroup analysis based on the baseline characteristics are shown in Table S1, in which the proportional hazards assumption was not satisfied in patients without patent foramen ovale (*P*=0.047) (Figures S5 and S6). AF detection was associated with ischemic stroke recurrence in male patients (OR, 6.76 [95% CI, 1.33–34.32]) but not in female patients (OR, 0.23 [95% CI, 0.028–1.90]) (*P* for interaction=0.013). A high AF burden was associated with ischemic stroke recurrence in patients with the number of PACs ≤ median (OR, 11.92 [95% CI, 1.55–91.67]) but not in

Table. Baseline Clinical Characteristics and Hazard Ratios of Ischemic Stroke Recurrence

	n		Hazard ratio* (95% CI)	*P* values
Age, median (IQR), y	370	71 (60–77)	1.03 (0.98–1.07)*	0.27
Male sex, n (%)	370	239 (65%)	0.43 (0.17–1.13)	0.086
$CHADS_2$ score after the index stroke	370			
2, n (%)		101 (27%)	1 [reference]	
3, n (%)		146 (39%)	7.89 (1.00–62.08)	0.050
4, n (%)		93 (25%)	5.58 (0.65–48.21)	0.12
≥5, n (%)		30 (8%)	3.21 (0.20–52.16)	0.41
Hypertension, n (%)	370	219 (59%)	3.18 (0.91–11.07)	0.069
Diabetes, n (%)	370	78 (21%)	0.79 (0.23–2.76)	0.71
Chronic heart failure, n (%)	370	14 (4%)	NA†	
High BNP or NT-proBNP‡, n (%)	352	66 (19%)	1.06 (0.30–3.71)	0.93
$PTFV_1$, median (IQR), mVmS	296	1.64 (0.63–3.09)	1.08 (0.86–1.36)*	0.52
PR interval, median (IQR), mS	366	170 (156–188)	0.99 (0.98–1.01)*	0.39
PACs, median (IQR), beats/d	344	60 (14–222)	1.00 (1.00–1.00)*	0.30
Atrial runs ≥10 beats, n (%)	342	54 (16%)	3.27 (1.09–9.81)	0.035
LAD, median (IQR), mm	366	35.3 (31.2–39)	1.01 (0.93–1.09)*	0.79
LAVI, median (IQR), mL/m^2	155	31.7 (25.4–38.3)	1.06 (1.00–1.11)*	0.037
LAAFV, median (IQR), cm/s	273	58 (45–77)	1.01 (0.99–1.04)*	0.36
Aortic complicated lesion, n. (%)	269	55 (20%)	2.69 (0.74–9.83)	0.13
Patent foramen ovale, n (%)	278	49 (18%)	1.98 (0.45–8.64)	0.36
Imaging findings of the index stroke				
Multiple stroke lesions, n (%)	370	175 (47%)	1.70 (0.64–4.49)	0.28
Lesion size in maximum ≥2 cm, n (%)	370	184 (50%)	1.02 (0.39–2.65)	0.97
Major vessel occlusion, n (%)	370	97 (26%)	1.54 (0.56–4.23)	0.40
Anticoagulation therapy at the time of ICM implantation, n (%)	370	117 (32%)	1.93 (0.72–5.17)	0.19

BNP indicates B-type natriuretic peptide; ICM, insertable cardiac monitor; IQR, interquartile range; LAAFV, left atrial appendage flow velocity; LAD, left atrial diameter; LAVI, left atrial volume index; mS, millisecond; mVmS, millivolt millisecond; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PACs, premature atrial contractions; and $PTFV_1$, P-wave terminal force on lead V_1.

*Hazard ratios per 1-unit increase.

†Ischemic stroke recurrence was not observed in patients with chronic heart failure.

‡High BNP or NT-proBNP levels were defined as >100 pg/mL or >300 pg/mL, respectively.

patients with the number of PACs >median (OR, 1.00 [95% CI, 0.25–3.93]) (*P* for interaction=0.048).

DISCUSSION

Although overt AF is known to be associated with a robustly high risk of stroke,[3] the risk of ischemic stroke recurrence in patients with cryptogenic stroke with AF detected after stroke with ICM and subsequent anticoagulation therapy was not higher than that in patients with cryptogenic stroke without AF. Two possible factors could explain the low incidence of ischemic stroke recurrence in patients with AF detection: a relatively small burden of AF and appropriate initiation of anticoagulation therapy.

The severity of the AF burden has been reported to be associated with the risk of subsequent ischemic stroke. In the Kaiser Permanente Real-World Heart Monitoring Strategy Evaluation, Treatment Patterns, and Health Metrics in Atrial Fibrillation (KP-RHYTHM) study, an observational study that enrolled 1965 adults with paroxysmal AF, the highest tertile of total AF burden during 14 days of continuous monitoring with a patch-style device (total AF burden of ≥11.4% during 14 days) was associated with a higher rate of thromboembolism compared with the combined lower 2 tertiles of AF burden.[13] In observational studies of patients with a pacemaker or defibrillator, an AF duration of >5.5 hours on any single day during 30 days or any single AF episode of >24 hours during 2.5 years was associated with an increased risk of subsequent stroke.[24,25] In the current study, the median burden of AF was a cumulative duration of 0.1% of the whole ICM recording period, or a total of ≈15 hours during 637 days, which might not be high enough to increase the risk of ischemic stroke recurrence, although a previous report showed that burdens >0.1% with ICM were associated with increased rates of health care utilization following

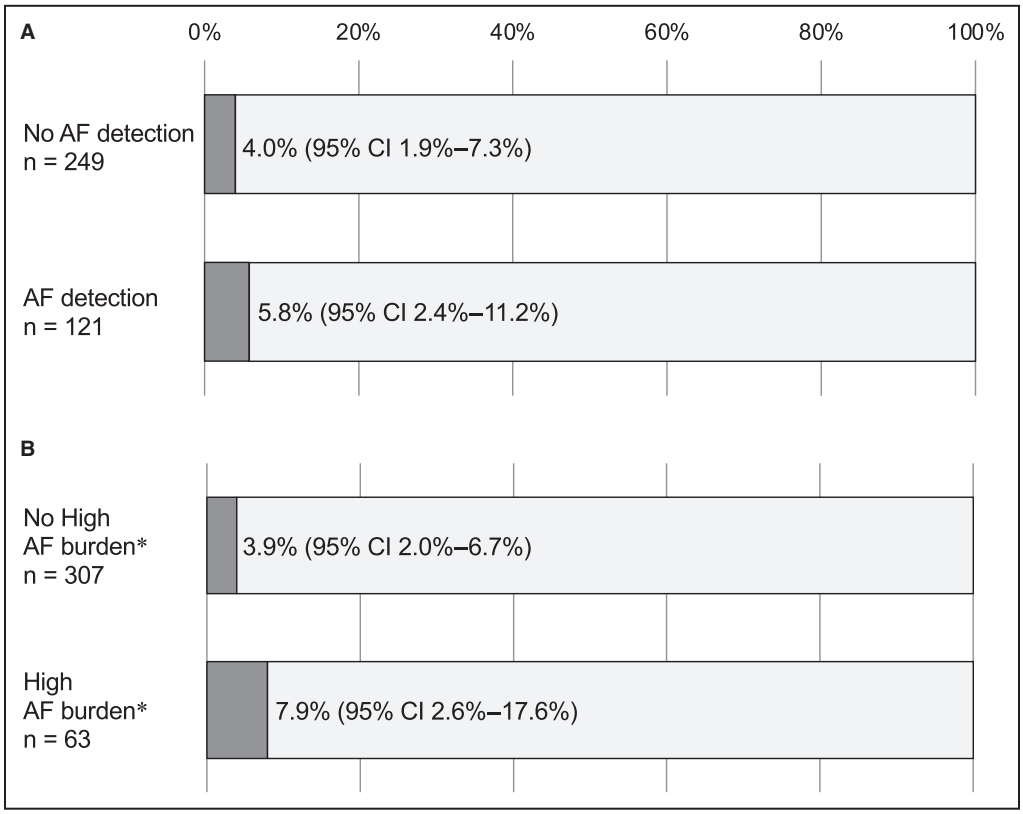

Figure 2. Incidences of ischemic stroke recurrence.
A, The incidence of ischemic stroke recurrence in patients with AF detection was not different from those without. **B**, The incidence of ischemic stroke recurrence in patients with a high AF burden was not different from those without. *AF was defined as the percentage of the cumulative duration of AF episodes automatically detected burden during the entire follow-up period. A high AF burden was defined as above the median among the patients with AF detection. The median AF burden was 0.1%; thus, a high AF burden was defined as ≥0.1%. AF indicates atrial fibrillation.

ablation therapy.[26] While the burden of AF detected after stroke with ICM is relatively low, because AF is generally considered a progressive disease evolving from paroxysmal to permanent forms,[27] attention should be given to the longer-term risk beyond the ICM recording period of 2 or 3 years.

In patients with ESUS, the efficacy of anticoagulation therapy was found to be equivalent to that of antiplatelet therapy.[21,22] Even when focusing on patients with AF detected by ICM, our results did not show the superiority of anticoagulation therapy over antiplatelet therapy. Because of the small proportion of patients without anticoagulation therapy after AF detection in our observational study, it was difficult to clarify the effect of anticoagulation therapy after AF detection. However, a recent report from a single-center cohort of patients with cryptogenic stroke indicated that the incidence of recurrent stroke or transient ischemic attack was lower in patients with ICM-detected AF who received anticoagulation therapy (3.23% [4/77]) than in patients with ICM-detected AF who did not receive anticoagulation therapy (26.20% [6/14]).[28] Returning to the comparison between patients with and without AF detection, this high proportion of patients with appropriate initiation of anticoagulation therapy after AF detection may be another reason for the low incidence of ischemic stroke recurrence in patients with AF detection. We suggest that it is not necessary to start anticoagulation therapy empirically before AF is detected; instead, it is reasonable to switch from antiplatelet therapy to anticoagulation therapy after AF is detected by ICM.

Attention must be given to the other causative factors of ischemic stroke. Atrial cardiomyopathy, or atrial cardiopathy, is an attractive model to address this issue; however, it has yet to be clearly defined. Several biomarkers reflecting atrial function have been reported to be associated with ischemic stroke independent of AF.[29] In the New Approach riVaroxaban Inhibition of Factor Xa in a Global trial versus ASA to prevenT Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial cohort, rivaroxaban reduced the risk of recurrent stroke in patients with severe left atrial enlargement of >4.6 cm in

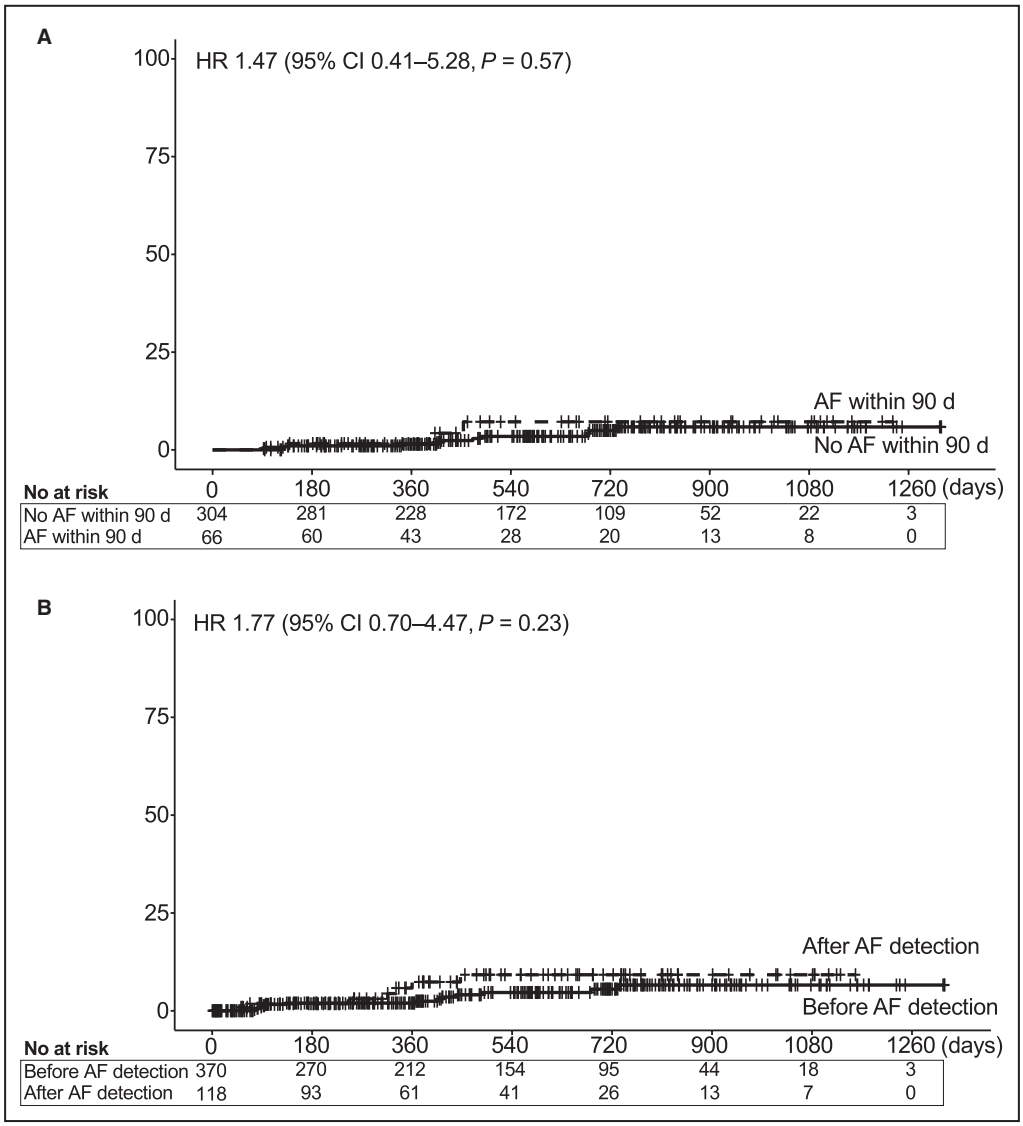

Figure 3. Kaplan–Meier estimates from insertable cardiac monitor implantation to recurrent ischemic stroke.
A, In a landmark analysis using the Cox regression model, AF detection within the first 90 days was not associated with ischemic stroke recurrence. **B**, In a Cox regression model using AF detection as a time-dependent covariate, the hazard of ischemic stroke recurrence did not increase after AF detection. AF indicates atrial fibrillation; and HR, hazard ratio.

the left atrial diameter.[30] The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) trial investigating the efficacy of apixaban in patients with cryptogenic stroke and atrial cardiopathy enrolled patients who meet at least 1 of the following criteria: P-wave terminal force on lead V_1 >5000 μVms, serum NT-proBNP >250 pg/mL, or left atrial diameter index ≥3 cm/m^2[31]; however, the trial was stopped after randomizing over 1000 patients because it did not show either benefit or harm. In the present study, atrial run and LAVI were marginally associated with ischemic stroke recurrence. Rather than concluding from these results that only atrial run and LAVI are specific markers of stroke recurrence, we have to comprehensively explore atrial dysfunction in patients with cryptogenic stroke.

In the subgroup analysis of the current study, a partial association between AF and ischemic stroke recurrence was observed in male patients and in patients with infrequent PACs. A previous report showed that female sex was a risk factor for ischemic stroke in patients with AF.[32] Patients with frequent PACs were shown to be associated with AF in patients with cryptogenic stroke.[15] However, these reports cannot explain the results of the subgroup analysis. We should not draw any conclusion from this exploratory subgroup

analysis; however, these results may support some association between ICM-detected AF and ischemic stroke recurrence.

Several limitations should be considered. First, owing to the smaller effect size than expected, the sample size of this study was not large enough to show the potential association between AF and stroke recurrence. Therefore, our findings cannot lead to a firm conclusion. Second, the marginal association of atrial run and LAVI with stroke recurrence could only be due to type I error. The partial association in subgroup analysis could only be owing to type I error as well. Third, because of the missing data, the analysis of the association of atrial run and LAVI with ischemic stroke recurrence could be biased. Fourth, given the retrospective design, a lack of standardized workup and antithrombotic therapy may lead to major selection bias, although we developed a mixed-effects Cox regression model in which the site was modeled as a random effect. Therefore, the results of our study cannot be applied to cryptogenic stroke in general. Fifth, the AF burden calculated from the automated analysis of the ICM may not be a good reflection of the actual AF burden due to false positives. Sixth, almost 32% of the population was treated with anticoagulation therapy at the time of ICM implantation, which may have influenced the results. One reason for this is the Japanese guideline, which states that warfarin may be considered for cryptogenic stroke.[33]

CONCLUSIONS

Despite the known high risk of stroke in patients with overt AF, our study showed that the risk of recurrent stroke in patients with cryptogenic stroke with AF detected by ICM was not higher than that in patients with cryptogenic stroke without AF, possibly because of a relatively small burden of AF and appropriate initiation of anticoagulation therapy after AF detection with >90% anticoagulation rate. We confirmed that it is reasonable to switch from antiplatelet therapy to anticoagulation therapy after detection of AF by ICM instead of empirically initiating anticoagulation therapy before AF detection in cryptogenic stroke.

ARTICLE INFORMATION

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Affiliations

Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan (K.T., S.O., Y.G., T.S., H.M.); Department of Neurology, Iwate Prefectural Central Hospital, Iwate, Japan (R.D.); Department of Neurology, Yokohama Shintoshi Neurosurgical Hospital, Yokohama, Kanagawa, Japan (H.Yamazaki); Department of Neurology, Saiseikai Fukuoka General Hospital, Fukuoka, Japan (K.S., D.K.); Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan (J.K., M.K.); Department of Neurology, Tokai University, Hiratsuka, Kanagawa, Japan (T.I., E.N.); Department of Neurology, Juntendo University Faculty of Medicine, Tokyo, Japan (Y.U., N.M.); Department of Stroke Neurology, National Hospital Organization Osaka National Hospital, Osaka, Japan (H.Yamagami, Y.K.); Department of Neurosurgery, Iwate Prefectural Central Hospital, Iwate, Japan (N.K.); and Department of Neurosurgery, Yokohama Shintoshi Neurosurgical Hospital, Yokohama, Kanagawa, Japan (M.M.).

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Supplemental Material

Data S1
Table S1
Figures S1–S6.

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