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Original article

Impact of atrial high-rate episodes on the risk of future stroke

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common type of arrhythmia. The definition of AF in patients with cardiac implantable electronic devices (CIEDs) is not clear, and the appropriate treatment guideline for patients with episodes of AF has not been established yet. Additionally, little is known about the incidence of AF and embolic stroke events in Japanese patients with CIEDs. The purposes of this study were to identify the incidence of embolic stroke events in Japanese patients with and without AF events detected by CIEDs and to examine the risk factors of embolic stroke events.

Methods: We retrospectively analyzed the database of our CIED clinic. Every 6 months, episodes of AF were checked by CIEDs. Using univariate (Student's *t*-test and Fisher's exact test) and multivariate analyses, we examined the characteristics and incidence of embolic stroke events and investigated the relationship between episodes of AF and the incidence of embolic stroke events.

Results: In this study, we enrolled 348 consecutive patients who had no prior history of AF and were not administering anticoagulants (follow-up period, 65 ± 58 months; age, 70 ± 16 years; male sex, 64%; implantable cardioverter defibrillator, 55%). The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 1.7 ± 1.1 and 2.8 ± 1.5 points, respectively. Fifty-five patients (16%) had AF events detected by CIEDs that lasted for ≥30 s, and 23 patients (6.6%) had embolic stroke during the follow-up period. Multivariate analysis demonstrated that independent predictors for embolic stroke were a left atrial diameter ≥40 mm [odds ratio (OR) 3.1, 95% confidence interval (CI) 1.2–7.9, $p = 0.016$] and episodes of AF (OR 5.3, 95% CI 2.2–13, $p = 0.0003$).

Conclusions: Embolic stroke events are common in Japanese patients with CIEDs. AF events lasting ≥30 s and an enlarged left atrium are the risk factors of embolic stroke in this population.

Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia; its incidence increases with age, and it manifests with a wide spectrum of symptoms and severity [1,2]. Paroxysmal, persistent, and permanent forms of AF require individualized approaches to management. AF-related embolic stroke tends to be more severe, and its mortality rate is higher than that of stroke without AF [3]. The definition of AF in patients with cardiac implantable electronic devices (CIEDs) is not clear, and the appropriate treatment guideline in patients with AF episodes has not been established. Recent CIEDs have led to an improvement in the early detection of atrial arrhythmic episodes, especially in patients who are asymptomatic [4]. Previous studies showed that atrial high-rate episodes (AHREs) detected by CIEDs are associated with embolic stroke events [5–12]. The relationship between AHREs and embolic stroke events has been recently described in the Japanese population too [8]. However, little is known about the incidence of AF and embolic stroke events in Japanese patients with CIEDs who have no prior AF and take no anticoagulant. Therefore, this study was designed to identify the incidence of embolic stroke events in Japanese patients with CIEDs who had no history of AF and had not received anticoagulant therapy, and to examine the risk factors of embolic stroke events.

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Methods

Study design and patient population

We retrospectively analyzed the database of the CIED clinic of Chiba University Hospital. We enrolled the patients receiving pacemakers and implantable cardioverter defibrillators (ICDs) between May 1980 and May 2016. Every 6 months, AHREs were checked by the CIEDs after implantation. Intracardiac electrograms captured by the CIEDs were reviewed by at least 2 experienced electrophysiologists, and we respectively confirmed episodes of AF detected by the CIEDs. Patients who had a history of AF or received anticoagulant therapies were excluded. History of AF was defined as AF documented by 12-lead electrocardiography (ECG) or Holter ECG monitoring. If the pacing mode of VVI or AAI was set in patients with CIEDs, we excluded these patients.

We examined the characteristics and incidence of embolic stroke events and investigated the relationship between AF episodes and the incidence of embolic stroke events. We measured the echocardiogram before implanting the CIEDs. Patients with AHRE should have further electrocardiogram monitoring to document overt AF before initiating oral anticoagulation therapy. Clinical data were obtained from patients' medical records and by interview with the patient when needed. The hospital's ethics committee approved this study.

Statistical analysis

The longer duration of an AHRE contributes to the higher risk of embolic stroke; thus, we drew a receiver operating characteristics (ROC) curve using this factor. We confirmed the cut-off duration that had the best sensitivity and specificity to predict the onset of embolic stroke. After dividing patients with or without AHREs based on the cut-off duration, we compared the clinical information including age, follow-up period, sex, complications of congestive heart failure, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, sick sinus syndrome and atrioventricular block, left atrial dilatation, left ventricular ejection fraction (LVEF), the proportion of ICDs, $CHADS_2$ score, CHA_2DS_2-VASc score, and HAS-BLED score between the2 groups. In addition, we compared these characteristics between patients with and without embolic stroke events using the Student's *t*-test and Fisher's exact test in univariate analysis. Multivariate analysis with logistic regression analysis was performed to identify risk factors of embolic stroke, and the characteristics with a *p*-value <0.10 in the univariate analysis were used. We defined the statistical threshold as $p < 0.05$. SPSS Statistics 25.0 software (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses.

Results

We enrolled 620 consecutive patients who were followed up at our CIED clinic. Fig. 1 shows the flow diagram of this study. Fifty-five patients were excluded because their pacing mode was set to VVI or AAI, and 205 patients who had a history of AF or had received anticoagulant therapies were excluded. Among 360patients, 12 patients were excluded because of lack of details on the device data due to terminal illness limiting survival, lead failure, or extraction. Therefore, 348 patients were included in this study (follow-up period, 65 ± 58 months; age, 70 ± 16 years; male sex, 64%; ICD, 55%). Fig. 2 demonstrates the underlying disease for ICD implantation. The mean $CHADS_2$ score and CHA_2DS_2-VASc score were 1.7 ± 1.1 points and 2.8 ± 1.5 points, respectively.

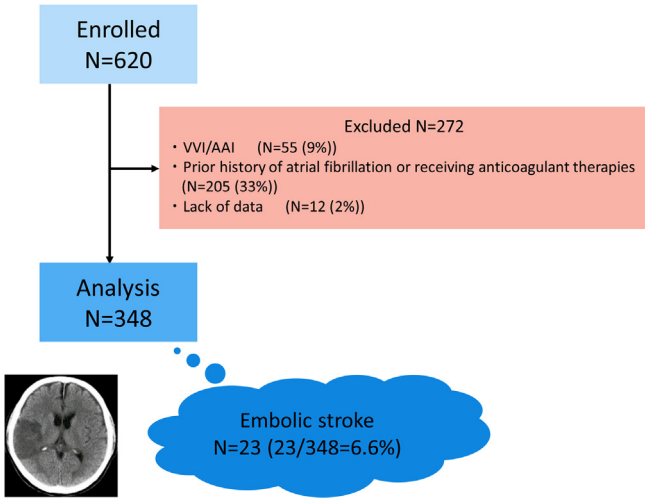

Fig. 1. Study flow chart.

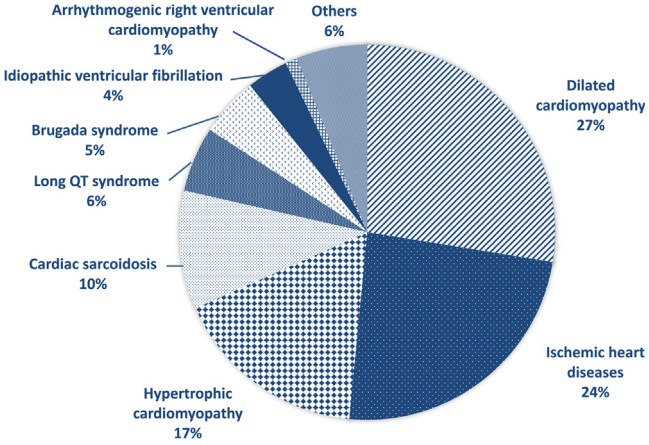

Fig. 2. The underlying disease for implantable cardioverter defibrillator implantation.

Implanted devices and detection of atrial high-rate episodes

All patients received dual-chamber CIEDs from Medtronic (Minneapolis, MN, USA), Abbott (St. Paul, MN, USA, now Abbot), and Biotronik (Berlin, Germany) based on a class I or IIa indication according to the Japanese Circulation Society [13]. The devices were programmed to the nominal setting of each device, and AHRE was detected when the atrial rate reached 175, 190, and 200 beats/min according to the Medtronic, Abbott, and Biotronik devices, respectively. The atrial sensitivity was also programmed as the nominal setting of each device. The atrial sensitivity of the pacemaker is 0.5 mV or less, and ICD is controlled automatically to adjust for the atrial sensing thresholds.

ROC curve analysis was performed, and the area under the curve (AUC) was calculated to determine the best duration of AHREs for predicting the risk of embolic stroke onset. ROC curve analysis confirmed that 30 s was the best cut-off time of AHREs detected by CIEDs for an embolic stroke event (AUC = 0.67) (Fig. 3). During the follow-up (median 84 months), 75 of 348 patients (22%) had AHREs detected by CIEDs. Of those, 55 patients (16%) had an AF episode lasting for ≥30 s, and 14 patients (4.0%) had an AHRE lasting for <30 s, as detected by CIEDs. Additionally, 6 patients

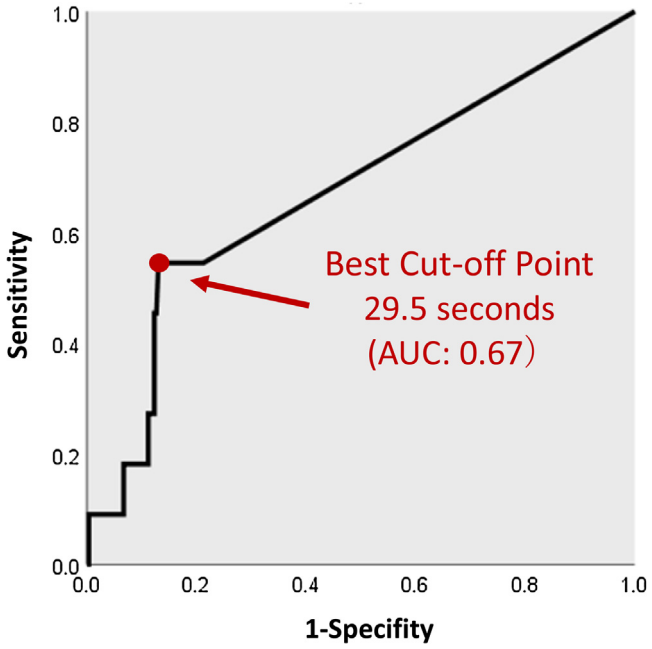

Fig. 3. Receiver-operating characteristic (ROC) curve for predicting embolic stroke onset. The area under the curve (AUC) was calculated to determine the best duration of atrial high-rate episodes (AHREs) for predicting the risk of embolic stroke onset. ROC curve analysis confirmed that 30 s is the best cut-off time of AHREs detected by cardiac implantable electronic devices for predicting the risk of embolic stroke events (AUC = 0.67).

(0.57%) had regular supraventricular tachycardia (including atrial flutter and atrial tachycardia) lasting for ≥30 s. Fig. 4 demonstrates the distribution of the duration of AHREs and AF detected by CIEDs.

Table 1 shows baseline characteristics of the 2 groups (patients with and without episodes of AF). Table 1 also demonstrates that there was no significant difference in the ICD and LVEF between patients with and without episodes of AF. Sick sinus syndrome was more prevalent in patients with AF episodes than in those without AF episodes (44% vs. 24%, $p < 0.0028$). On the contrary, atrioventricular block was more prevalent in patients without episodes of AF than in those with episodes of AF (66% vs. 20%, $p < 0.001$). Additionally, patients with episodes of AF had significantly higher $CHADS_2$ and CHA_2DS_2-VASc scores than those without episodes of AF (2.0 ± 1.5 vs. 1.6 ± 1.0, $p < 0.001$ and 3.3 ± 1.9 vs. 2.7 ± 1.4, $p < 0.001$).

Stroke events

In this study, embolic stroke, including transient ischemic attack and cerebral bleeding, was diagnosed by an experienced neurologist based on the patient's history, symptoms, and imaging findings. During the follow-up, 23 of 348 patients (6.6%) had embolic stroke. Thirteen patients (4.1%/year) and 10 patients (0.7%/year) had embolic stroke events with and without episodes of AF, respectively. Therefore, the incidence of embolic stroke events was 6.0 times higher in patients with episodes of AF than in those without episodes of AF (Table 2). Additionally, 5 of 348 patients (1.4%) had cerebral bleeding. Two patients (0.63%/year) and 3 patients (0.2%/year) had cerebral bleeding events with and without episodes of AF, respectively, and the incidence of cerebral bleeding events was 3.0 times higher in patients with episodes of AF than in those without episodes of AF (Table 2).

Relationship between episodes of AF and the incidence of embolic stroke events

The comparison of characteristics among patients with and without embolic stroke is shown in Table 3 (embolic stroke group vs. non-embolic group). The proportion of patients with new-onset AF episode and left atrial diameter was significantly higher in the embolic stroke group than in the non-embolic stroke group. We assessed the cut-off value of age ≥70 years, left atrial diameter≥40 mm, $CHADS_2$ score ≥2, and CHA_2DS_2-VASc score ≥4 using ROC curve analysis. In multivariate logistic regression analysis (Table 3), independent predictors for embolic stroke were new-onset episode of AF [odds ratio (OR) 5.3, 95% confidence interval (CI) 2.2–13, $p = 0.0003$), and an enlarged left atrium ≥40 mm (OR 3.1, 95% CI 1.2–7.9, $p = 0.095$). In multivariate analysis, ICD and LVEF were not independent predictors for embolic stroke in this population.

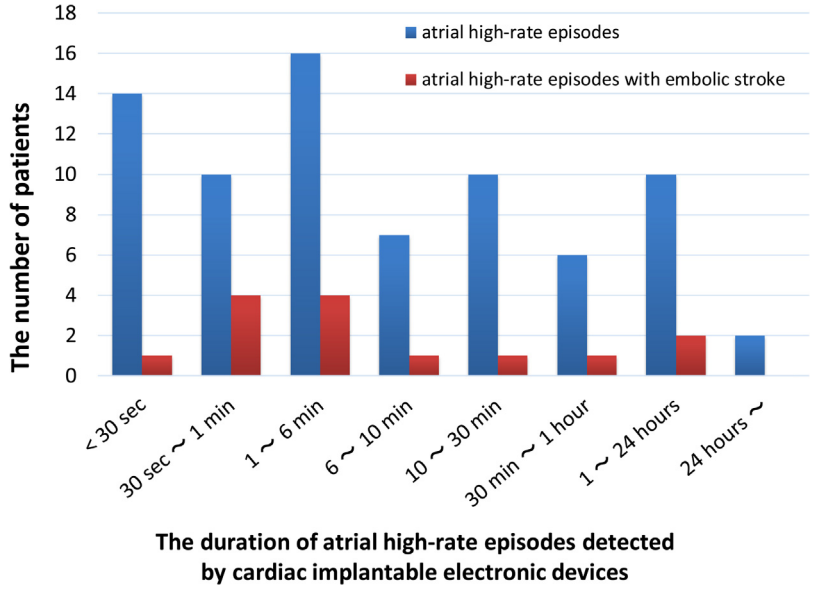

Fig. 4. The distribution of the duration of atrial high-rate episodes detected by cardiac implantable electronic devices.

Table 1
Baseline characteristics of study patients.

	All ($N=348$)	Patients with AF episode ($N=55$)	Patients without AF episode ($N=293$)	p-Value
Age	70 ± 16	73 ± 14	69 ± 15	0.19
Follow-up period (months)	65 ± 58	69 ± 42	60 ± 36	0.29
Sex (male, %)	224 (64)	40 (72)	184 (62)	0.17
Congestive heart failure, *n* (%)	171 (49)	28 (51)	143 (48)	0.30
Hypertension, *n* (%)	162 (46)	22 (40)	154 (40)	1.00
DM, *n* (%)	63 (18)	13 (24)	50 (17)	0.25
COPD, *n* (%)	18 (5.2)	3 (5.4)	15 (5.1)	1.0
Coronary artery disease, *n* (%)	81 (23)	13 (24)	68 (23)	1.0
eGFR ≤65, *n* (%)	125 (36)	23 (42)	102 (34)	0.35
BNP (pg/ml)	70 ± 58	82 ± 35	68 ± 56	0.47
TSH (μIU/ml)	1.7 ± 1.0	1.4 ± 0.8	1.8 ± 1.2	0.38
FT4 (ng/ml)	1.2 ± 0.1	1.16 ± 0.2	1.20 ± 0.2	0.82
LAD (mm)	41 ± 6.8	42 ± 7	41 ± 7	0.16
Left ventricular ejection fraction (%)	53 ± 17	53 ± 18	53 ± 17	0.98
ICD, *n* (%)	193 (55)	28 (51)	165 (56)	0.46
Atrial pacing rate (%)	25 ± 31	24 ± 30	25 ± 32	0.79
Ventricular pacing rate (%)	48 ± 47	51 ± 46	47 ± 48	0.45
Sick sinus syndrome, *n* (%)	97 (27)	25 (44)	72 (24)	0.0028
Atrioventricular block, *n* (%)	203 (58)	11 (20)	192 (66)	<0.001
Antiplatelet agent, *n* (%)	78 (22)	14 (25)	64 (22)	0.59
$CHADS_2$ score	1.7 ± 1.1	2.0 ± 1.5	1.6 ± 1.0	<0.001
CHA_2DS_2-VASc score	2.8 ± 1.5	3.3 ± 1.9	2.7 ± 1.4	<0.001
HAS-BLED score	1.7 ± 1.2	1.9 ± 1.3	1.6 ± 1.2	0.14

AF, atrial fibrillation; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; TSH, thyroid stimulating hormone; FT4, free thyroxine 4; LAD, left atrial diameter; ICD, implantable cardioverter defibrillator.

Table 2
Incidence of major stroke events.

	All ($N=348$)	Patients with AF episode ($N=55$)	Patients without AF episode ($N=293$)	p-Value
Embolic stroke, *n* (%)	23 (6.6)	13 (24)	10 (3.4)	<0.001
Cerebral bleeding, *n* (%)	5 (1.4)	2 (3.6)	3 (1.0)	0.18

AF, atrial fibrillation.

Discussion

CIEDs are increasingly being used, and they have rapidly evolved from simple pacing devices to ones that include several diagnostic functions. However, these functions are not adequately used in current clinical practice, and several redundant diagnostic tests, such as24-h electrocardiogram monitoring, are still prescribed to patients with CIEDs, which leads to an increase in costs and a delay in the final diagnosis.

The main finding of this study was that AF detected by CIEDs that lasted for ≥30 s was associated with embolic stroke events in a Japanese population that had no history of AF. In previous studies regarding AHREs, patients with a history of AF were also included and their proportions ranged from 20% of the patients in TRENDS to 100% of the patients in the Italian AT500 Registry [10,14]. Therefore, the solo effect of AHREs on the risk of embolic stroke cannot be reliably evaluated based on these studies. The ASSERT study is the only large, prospective trial to assess the relationship between AHREs and thromboembolism in patients without a history of clinical AF [11]. In the ASSERT study, an AHRE was defined as an atrial rate of at least 190 beats/min lasting for at least 6 min. During the follow-up period, a stroke or systemic embolism occurred in 4.2% (1.7%/year) of patients in whom AHREs had been detected compared to 1.7% (0.7%/year) of patients in whom AHREs had not been detected.

In the TRENDS trial, AHRE was defined as an atrial rate >175 beats/min, lasting ≥5.5 h [10]. In an analysis of the MOde Selection Trial, AHRE was defined as an atrial rate >220 beats/min lasting ≥5 min [12]. In our study, the ROC curve showed that the best cut-off duration time of AHREs for predicting the risk of embolic stroke was 30 s (Fig. 3). All cardiac electrograms obtained from CIEDs should be reviewed to exclude artifacts, and AF should be reviewed by qualified clinicians to verify diagnostic accuracy. Retrospective review of device-derived data has confirmed that most atrial tachyarrhythmias represent paroxysmal AF. However, false detection may occur due to far-field R-wave oversensing by the atrial lead or runs of premature atrial complexes. In addition, device-stored data based solely on marker channels, without electrocardiograms, cannot be used to verify AF because of the potential for diagnostic errors caused by oversensing or undersensing by the atrial lead. Therefore, we should focus on AFs confirmed by experienced electrophysiologists that last for ≥30 s in order to prevent patients without AF from developing embolic stroke.

During the follow-up (median 84 months), 75 of 348 patients (22%) had AHREs detected by CIEDs in this study. Of those, 55 patients (16%) had an AF episode lasting for ≥30 s. Early detection of asymptomatic episodes of AF is important for several clinical reasons. AHREs are correlated with a 5-fold to 6-fold increased risk of the development of clinical AF, as evidenced in the MOde Selection Trial and ASSERT study [11,12]. Additionally, several studies in the literature have shown an updated model for embolic stroke in AF/AHRE [15–17], and in this model, atrial cardiomyopathy plays a key role and can result in both AHRE and AF. Atrial cardiomyopathy can be characterized by atrial dilatation, mechanical dysfunction, fibrosis, and/or endothelial dysfunction, and cause hypercoagulability, i.e. the increased potential of blood or plasma to generate thrombin and fibrin. The updated model shows that atrial cardiomyopathy can lead to embolic stroke through hypercoagulability and that hypercoagulability can lead to

Table 3
Risk factors of embolic stroke.

	Embolic stroke group ($n=23$)	Non-embolic stroke group ($n=325$)	p-Value
(i) Univariate analysis (unpaired t-test or Fisher's exact test)			
Age $\geq$ 70 years, n (%)	14 (63)	176 (54)	0.35
Follow-up period (months)	88 $\pm$ 64	67 $\pm$ 67	0.28
Male, n (%)	19 (82)	205 (63)	0.33
Congestive heart failure, n (%)	15 (64)	156 (48)	0.37
Hypertension, n (%)	12 (54)	150 (49)	0.54
DM, n (%)	4 (18)	59 (18)	1.00
COPD, n (%)	2 (9)	16 (5)	0.39
New-onset AF episode, n (%)	13 (56)	42 (13)	0.0012
Coronary artery disease, n (%)	6 (26)	75 (23)	0.74
LAD $\geq$ 40 mm, n (%)	15 (64)	123 (38)	0.035
Left ventricular ejection fraction $\leq$ 60%, n (%)	15 (64)	221 (68)	0.72
ICD, n (%)	11 (48)	182 (56)	0.22
Sick sinus syndrome, n (%)	9 (39)	88 (27)	0.68
Atrioventricular block, n (%)	8 (35)	195 (60)	0.23
Antiplatelet agent, n (%)	6 (26)	72 (22)	0.61
$CHADS_2$ score $\geq$ 2, n (%)	10 (43)	92 (28)	0.15
CHA_2DS_2-VASc score $\geq$ 4, n (%)	6 (26)	40 (12)	0.10
	Odds ratio	95% confidence interval	p-Value
(ii) Multivariate analysis (logistic regression)			
New-onset AF episode	5.3	2.2–13	0.0003
LAD $\geq$ 40 mm	3.1	1.2–7.9	0.016
CHA_2DS_2-VASc score $\geq$ 4	2.5	0.85–7.2	0.095

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; LAD, left atrial diameter; ICD, implantable cardioverter defibrillator.

AF/AHRE through atrial cardiomyopathy [15–17]. Our data suggest that 13 patients (4.1%/year) and 10 patients (0.7%/year) had embolic stroke events with and without episodes of AF, respectively. Therefore, the incidence of embolic stroke events was 6.0 times higher in patients with episodes of AF than in those without episodes of AF. Episodes of AF lasting for $\geq$30 s may cause atrial cardiomyopathy and put Japanese patients with a CIED at risk of embolic stroke.

Independent predictors for embolic stroke were not only new-onset AF episode but also an enlarged left atrium $\geq$40 mm. Previous studies have shown that the duration of AF, left atrial appendage (LAA) emptying velocity, and left atrial diameter are significant predictors of long-term sinus rhythm maintenance [18]. Some degenerative changes can develop in both the left atrium and LAA due to structural or electrical remodeling in patients with AF. The changes that have been suggested may cause heterogeneous atrial conduction and slow or anisotropic conduction in atrium, and they are considered significant factors in the pathogenesis of AF. Furthermore, P-wave dispersion has been reported to be a simple, useful electrocardiographic marker for reflecting atrial inhomogeneous and anisotropic conduction.

In a previous study of 187 patients with acute ischemic stroke, AHREs for $\geq$5.5 h within 30 days before stroke were recorded in only 15% of patients [19]. In this small subgroup, a 5-day interval analysis revealed a transient effect of AHREs on stroke risk; the highest risk was within the first 5 days of the AHRE episode (OR 17.4, 95% CI 5.4–73.1), and the lowest risk was at $\geq$30 days later [19]. It is important to note that some strokes might not be of cardioembolic origin in patients with AF. The inconsistent temporal relationship between a high AHRE burden and stroke occurrence, despite a clear association between AHREs and an increased risk of stroke, suggests that the relationship between the two is complex. In addition to causing left atrial thrombi, AF and AHREs could be markers of underlying atrial disease, which might also contribute to thrombogenesis.

Anticoagulation may be based on a comprehensive assessment of the risk and benefit. Regarding the timing of starting anticoagulant therapy in patients with AHRE without a history of AF, there is no guideline because of a lack of evidence in support of antithrombotic treatment [20]. The 2016 European Society of Cardiology guidelines indicate that it is uncertain whether AHRE (>5–6 min and >180 beats/min) requires the same therapeutic approach as clinically overt AF, and recommend that patients with AHRE should have further electrocardiogram monitoring to document overt AF before initiating oral anticoagulation therapy [21]. Although clinical AF, such as paroxysmal or persistent AF documented by electrocardiogram monitoring, plays a major role in the pathogenesis of cardioembolic stroke, covert AF including asymptomatic AF and AHRE are believed to contribute to the pathogenesis of embolic stroke events. However, a recent consensus document of the European Heart Rhythm Association regarding device-detected subclinical atrial tachyarrhythmias indicated that oral anticoagulation is recommended for patients with two additional CHA_2DS_2-VASc risk factors ($\geq$2 in men or $\geq$3 in women) with AF burden >5.5 h/day [22]. Two large-scale randomized clinical trials of anticoagulation for patients with device-detected AHRE are ongoing: the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation and the Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes [23,24]. We eagerly await the results of these trials.

Limitations

The present study has several limitations. First, this study had a single-center, retrospective, observational design with a relatively small number of patients with CIEDs. Second, we collected clinical data at the time of CIED implantation, so the data at follow-up were not considered. Third, this study did not consider the frequency of AF episodes, rhythm of onset of embolic stroke, and motion of LAA. Fourth, there is a possibility that patients had already developed asymptomatic AF before CIED implantation because asymptomatic AF is undiagnosed by the conventional method. Fifth, we measured the echocardiogram just before implanting the CIEDs and did not measure it after the onset of AF or embolism. Sixth, patients who started

anticoagulant therapy after AF was detected by the device were not excluded from this study. Finally, 193 patients with an implanted ICD were included in this study, and the impact of low left ventricular function on new-onset AF was not considered.

Many people have a CIED, and clarification of the relationship between AHREs and embolic stroke events in patients with CIEDs is challenging and clinically important. Therefore, a large multicenter, prospective study of patients with CIEDs is needed. Although we focused on patients with a CIED, our observations may not apply to the general population.

Conclusions

Embolic stroke events are common in Japanese patients with CIEDs. Episodes of new-onset AF lasting for ≥30 s and an enlarged left atrium are risk factors of embolic stroke in this population. Therefore, when physicians detect new-onset AF in patients with CIEDs, they should consider a comprehensive assessment of the risk and benefit of prescribing an anticoagulant.

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Conflict of interests

Dr Kondo received research grants from Abbott Japan, Biotronik Japan, and Boston Scientific. Dr Kobayashi received research grants from Abbott Japan, Biotronik Japan, Boston Scientific, and Medtronic Japan. The other authors declare no conflicts of interest.

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