High Detection Rate of Atrial Fibrillation With Insertable Cardiac Monitor Implantation in Patients With Cryptogenic Stroke Diagnosed by Magnetic Resonance Imaging

Tomonori Iwata, MD,* Kenichi Todo, MD, PhD,† Hiroshi Yamagami, MD, PhD,‡ Masafumi Morimoto, MD, PhD,§ Tetsuya Hashimoto, MD, PhD,‖ Ryosuke Doijiri, MD,¶ and Hiroyuki Furuya, MD, PhD**

Background: Detection and treatment of atrial fibrillation (AF) is a major goal in preventing secondary stroke. Insertable cardiac monitors (ICMs) are available for diagnosis of arrhythmia monitoring in patients with cryptogenic stroke. Magnetic resonance imaging (MRI)-based diagnostic evaluation for acute ischemic stroke subtype classification is common in Japan and can be useful for specific diagnosis of cryptogenic stroke. *Purpose:* We aimed to investigate the detection rate of AF with an ICM in patients with cryptogenic stroke who were diagnosed by MRI. *Methods:* We performed a retrospective, multicenter, observational study. AF monitoring data of an ICM (Reveal LINQ) in patients with cryptogenic stroke were registered from 5 stroke centers in Japan between October 2016 and March 2018. ICM candidates in cryptogenic stroke were diagnosed by MRI-based evaluation and selected according to the criteria proposed by the Japan Stroke Society. Detection of AF was defined as AF for longer than 120 seconds. *Results:* Eighty-four consecutive patients (64 men; aged 38-90 years) underwent ICM implantation after diagnosis of cryptogenic stroke. AF was detected in 22 of 84 (26.2%) patients with an ICM during a median follow-up of 221.5 days (range: 93-365 days). The detection rate of AF within 3 months after ICM implantation was 21.4%. *Conclusions:* The AF detection rate with an ICM is approximately one fifth within 3 months in patients with cryptogenic stroke as diagnosed by MRI. Our data suggest that the Japanese criteria based on MRI may be useful for selecting adequate candidates for ICM implantation.

Key Words: Insertable cardiac monitor—atrial fibrillation—embolic stroke of undetermined source—cryptogenic stroke

Introduction

Ischemic stroke associated with atrial fibrillation (AF) is nearly twice as likely to be fatal as non-AF stroke. Furthermore, patients with stroke and AF have a poorer neurological outcome than patients with stroke without AF.[1] Recently, insertable cardiac monitors (ICMs) have become commercially available. Implantation of an ICM is a simple and minimally invasive procedure. There have

Abbreviations: (AF), atrial fibrillation; (CT), computed tomography; (DWI), diffusion-weighted imaging; (DOAC), direct oral anticoagulant; (ECG), electrocardiogram; (ESUS), embolic stroke of undetermined source; (ICM), insertable cardiac monitor; (IQR), interquartile range; (LA), left atrium; (MRI), magnetic resonance imaging

From the *Department of Neurology, Tokai University, Isehara, Japan; †Department of Neurology, Osaka University, Suita, Japan; ‡Department of Neurology, National Cardiovascular and Cerebral Center, Suita, Japan; §Department of Neurosurgery, Yokohama Shintoshi Neurosurgical Hospital, Yokohama, Japan; ‖Department of Neurology, Saiseikai Fukuoka General Hospital, Fukuoka, Japan; ¶Department of Neurology, Iwate Prefectural Central Hospital, Morioka, Japan; and **Basic Clinical Science and Public Health, Tokai University School of Medicine, Isehara, Japan.

Received April 9, 2019; revision received May 12, 2019; accepted May 21, 2019.

Address correspondence to Tomonori Iwata, MD, Department of Neurology, Tokai University, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. E-mail: toiwata-ths@tsc.u-tokai.ac.jp.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.023

been few reports of real-world data of an ICM for detecting AF in patients with cryptogenic stroke by MRI-based diagnostic evaluation.

Cryptogenic mechanisms account for 10%-40% of ischemic strokes.[2] The cause of stroke remains unidentified by routine diagnostic testing in approximately 40% of patients. Cryptogenic stroke generally refers to ischemic stroke of undetermined etiology. Cryptogenic stroke also refers to a nonlacunar infarction occurring in the absence of a specific identifiable high-risk source of cardioembolic sources or large-vessel stenosis. However, most cryptogenic mechanisms can be ascribed to embolic mechanisms. Embolic stroke of undetermined source (ESUS) was proposed for unifying embolic stroke of undetermined sources by Hart et al in 2014.[3,4] The causes of cryptogenic ischemic strokes are minor-risk potential thromboembolic sources, such as minor-risk potential cardioembolic sources, conversion of paroxysmal AF, cancer-associated causes, arteriogenic emboli, and paradoxical embolism. AF is one of the most frequent causes of ESUS. Advances in ICMs and electrocardiographic (ECG) monitoring techniques are used to determine the causes of cryptogenic strokes. These techniques can detect abnormal heart rhythms between 1 week and 3 years. The Reveal LINQ is a novel miniaturized ICM with improved algorithms. In a previous randomized, controlled trial, the AF detection ratio was approximately 10% and 30% per 1 year and 3 years, respectively.[5]

There are differences in criteria for diagnosis and proposed diagnostic assessment for ESUS between Japan and Western countries.[3,6] The definition of cryptogenic ischemic stroke is important for comparison and discussion in clinical research. However, the definition of cryptogenic stroke is not standardized. To discuss the detection rate of the causes of cryptogenic stroke, the extent of diagnostic criteria and evaluation need to be taken into account. The definition of ESUS is a distinct and a therapeutically relevant entity compared with cryptogenic stroke. In Japan, magnetic resonance imaging (MRI) is widely used in diagnosis of ischemic strokes and recommended for diagnosis of ICM candidates in cryptogenic stroke. A complex definition of cryptogenic stroke in Japan is ruling out lacunar infarction by diffusion-weighted imaging (DWI) compared with a simple definition of ESUS by computed tomography (CT) or MRI (mainly CT). Ruling out of small-vessel disease is not easy when only using CT images. Additionally, to rule out AF, the duration of cardiac monitoring varies among research protocols.[4] Cardiac monitoring for 24 hours or longer with automated rhythm detection is strongly recommended in Japan. A longer duration of ECG monitoring after ischemic stroke is useful for detecting previously unrecognized AF. Further, to rule out paradoxical embolism and aortogenic embolism, transesophageal echocardiography, and venous duplex ultrasonography are recommended in Japan. Therefore, the Japanese proposal for clinical indications of ICMs is strict compared with that in the US or Europe.

The detection rate of AF with an ICM in patients with cryptogenic stroke who are diagnosed by MRI-based evaluation has not been investigated. Previous studies have reported that there is a high incidence of previously unrecognized AF in patients at high risk for AF.[7] However, AF risk stratification has not been established.[8-10] Risk factors of AF were present in some reports, but additional research is required. MRI-based selection of ICM candidates might enhance the rate of AF detection. Therefore, this study aimed to investigate the incidence of AF using an ICM in patients with cryptogenic stroke by MRI-based diagnostic evaluation.

Methods

We conducted a retrospective, multicenter, observational registry study of consecutive ICM implantation for cryptogenic stroke in 5 stroke centers in Japan. Inclusion criteria in this study were patients (1) who had cryptogenic stroke, (2) who had Reveal LINQ implantation from October 2016 to March 2018, and (3) who were followed up for longer than 3 months. Patients were eligible for enrollment if they were 20 years or older, did not have known AF, and had an ischemic stroke of undetermined cause (according to Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria) diagnosed by a vascular neurologist. Moreover, MRI-based diagnostic evaluation for acute ischemic stroke subtype classification was recommended according to Japanese standard workup, including 12-lead ECG, ambulatory ECG monitoring using a monitor for at least 24 hours, and echocardiography. We applied the proposed diagnostic criteria in Japan by a detailed examination, including head MRI.[6] Patients were excluded if the most likely etiological diagnosis had already been determined (large-vessel or small-vessel disease or other known cause). We retrospectively identified consecutive patients who were hospitalized for acute ischemic stroke who met the ESUS diagnostic criteria. The patients' demographic information included age and sex. Baseline and diagnostic work-up findings were investigated.

Japanese Proposal for Clinical Indications

According to the Japanese diagnostic criteria, all of the patients were evaluated by MRI, by transthoracic echocardiography, cardiac monitoring for 24 hours or longer with automated rhythm detection, and any angiography of carotid/intracranial arteries.[6] Additionally, transesophageal echocardiography, CT aortography, an ultrasonic examination for right-to-left shunt, and venous duplex ultrasonography were performed in most of the study patients. Further, 7-day cardiac monitoring was performed in all patients in this study.

Monitoring Strategies

ICMs (Reveal LINQ; Medtronic, Minneapolis, MN) were implanted under local anesthesia in the left parasternal position where sufficient R-wave detection was obtained without detection of myopotentials. All devices were programmed to detect AF with the company's unique AF detection algorithm. These algorithms operate through continuous assessment of the regularity of RR intervals within a 2-minute time window to recognize AF. The AF detection algorithm of the Reveal LINQ also incorporates p-wave information. Monitoring type, duration, and all results were recorded. The ICM that was used automatically detects and records AF, irrespective of heart rate or symptoms. Patients were additionally provided a hand-held tool ("Patient Assistant"), which could be activated by the patient to instantaneously assess when the patient felt pain or discomfort in the chest. The Medtronic CareLink Network was used to remotely transmit the device data. If patients reported an episode of AF since the previous visit, information was collected and source documentation was acquired for adjudication.

Statistical Analysis

We analyzed the proportion of patients with AF detected by means of the study monitors among those who underwent any monitoring. Differences between the presence of AF and absence of AF were compared using Fisher's exact test for categorical variables and the Mann−Whitney *U* test for numerical variables. A *P* value of less than .05 was considered significant. Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc., version 17.0 for Windows, Chicago, IL).

Results

During the study period, 3348 patients with acute ischemic stroke were admitted in the participating stroke centers. On the basis of Japanese criteria, 626 patients were diagnosed with cryptogenic stroke. Among them, 84 consecutive patients (64 men; aged 38-90 years) underwent ICM implantation. All patients were followed for longer than 3 months. No patients were lost to follow-up or died. Baseline characteristics of the patients are shown in Table 1. The median age was 70 years and 23.8% of the patients were women. AF that lasted 120 seconds or longer was detected in 22 of 84 (26.2%) patients with ICM implantation during a median follow-up period of 221.5 days (range: 93-365 days). Complete atrioventricular block was detected in 1 patient. The rate of detecting AF at 3 months was 21.4% (Fig 1). The median time from implantation to detection of AF was 31.5 days (range: 1-318 days). AF was asymptomatic in all 21 first episodes and only 1 patient presented with complaints of palpitation. A total of 84 patients consecutively underwent ICM implantation without any short-term or long-term complications. The patients' characteristics according to AF detection are shown in Table 2. There were no significant differences in clinical characteristics and the follow-up period between patients with and without AF detection.

Table 1. *Clinical and radiological variables of the 84 patients*

Age [years], median (IQR)	70.0 (63.25-76.0)
Sex, male, no. (%)	64 (76.2%)
CHADS2 score, median (IQR)	3 (3-4)
Onset to implantation [days], median (IQR)	20.5 (14.0-37.75)
Follow up [days], median (IQR)	221.5 (161.25-341.0)

Abbreviation: IQR, interquartile range.

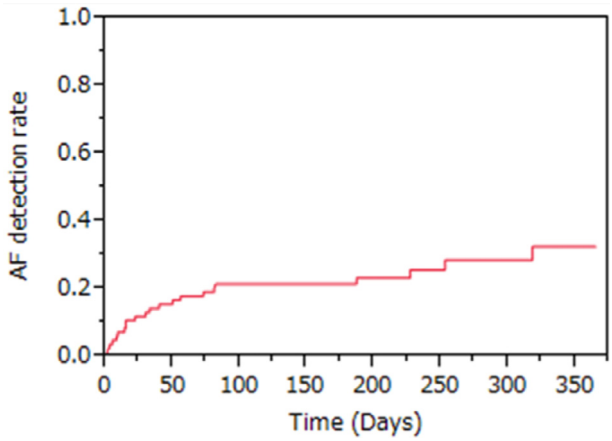

Figure 1. *Kaplan−Meier curve showing the time to first detection of AF by an ICM in patients with cryptogenic stroke who were diagnosed by MRI. Abbreviation: AF, atrial fibrillation; ICM, insertable cardiac monitors; MRI, magnetic resonance imaging.*

Discussion

Our study showed that the detection rate of AF was more than one fifth within 3 months after implantation of an ICM in patients with cryptogenic stroke. These patients were selected by the Japanese proposal for clinical indications of an ICM using MRI.

Ischemic stroke is one of the most common causes of morbidity and mortality worldwide.[11] AF is one of the most frequent causes of ischemic stroke and the most common arrhythmia affecting older patients.[12] The prevalence of AF is less than 1% in the general population, but it is approximately 2%-3% in people aged 80 years or older in Japan.[13] AF increases the risk and severity of stroke, and is associated with substantial morbidity and mortality.[14] AF is associated with a 3- to 5-fold increased risk of ischemic stroke.[15] Moreover, previous studies have reported that AF is associated with cognitive decline.[16] Early detection of AF is important to define proper medical treatment. In the Fushimi AF Registry, which is a community-based survey of patients with AF in Japan, the mean age of enrolled patients was 74.2 ± 11.0 years and 2323 (37.8%) patients were aged 75 years or older.[17]

Table 2. *Comparison of patients with and without AF*

	Patients without AF (N = 62)	Patients with AF (N = 22)	*P* value
Age [years], median (IQR)	70.0 (59.25-77.5)	70.0 (63.25-76.0)	.859
Sex, male, no [%]	46 [74.2%]	18 [81.8%]	.572
CHADS2 score, median (IQR)	3 (3-4)	3 (3-4)	.864
Onset to implantation [days], median (IQR)	21.5 (14.0-40.75)	20.0 (14.0-29.75)	.654
Follow up [days], median (IQR)	205 (162.75-356.57)	255.5 (153.0-333.75)	.907

Abbreviations: AF, atrial fibrillation; IQR, interquartile range.

Differences between absence of AF and presence of AF were compared using Fisher's exact test for categorical variables and the Mann−Whitney *U* test for numerical variables.

Patients aged 75 or older generally had higher CHADS2 scores. The AF detection rate in our study was higher compared with that in the CRYSTAL AF trial,[8] in which AF was detected in 10% of all patients after 12 months. In the CRYSTAL AF trial, AF detection rates were 8.9% at 6 months, 12.4% at 12 months, and 30% at 3 years.[8] A previous report showed that the AF detection ratio was high compared with the CRYSTAL AF trial. Seventy-five patients with cryptogenic stroke or transient ischemic attack were consecutively enrolled if at least one of the following AF risk factors was present: a CHA2DS2-VASc score greater than equal to 4, atrial runs, left atrial (LA) size more than 45 mm, left atrial appendage flow greater than 0.2 m/s, or spontaneous echo contrast in the LA appendage. Seventy-four patients underwent implantation of an ICM. After 6 months, AF was detected in 21 of 75 (28%) patients, and after 12 months it was detected in 25 of 75 (33.3%) patients. A total of 92% of AF episodes were asymptomatic. The detection rate of AF is approximately one third after 1 year if candidates for an ICM after cryptogenic stroke or transient ischemic attack are selected by AF risk factors. LA dilation and atrial runs independently predict AF.[18] In the REVEAL AF study, patients with a CHADS2 score of 3 or greater (or 2 with at least 1 additional risk factor) were enrolled.[7] Approximately 90% had nonspecific symptoms that were potentially compatible with AF, such as fatigue, dyspnea, and/or palpitations. The incidence of previously undiagnosed AF may be substantial in patients with risk factors for AF and stroke.[7] According to the REVEAL AF study, AF detection rates at 30 days and 6, 12, 24, and 30 months were 6.2%, 20.4%, 27.1%, 33.6%, and 40.0%, respectively. In our study, the AF detection rate was 21% at 3 months, which is similar to that at 2 years in the CRYSTAL AF trial.[5] It is not necessary to make a deep study of the most of potential thromboembolic sources according to the Cryptogenic Stroke/ESUS International Working Group.[3] We performed ICM (Reveal LINQ) implantation for patients who met the Japanese proposal for choosing candidates for ICMs. To rule out other embolic sources, the Japanese proposal for ICM implantation recommends performing transesophageal echocardiography, an ultrasonic examination for right-to-left shunt (transesophageal or transcranial), and venous duplex ultrasonography. Generally, DWI detects ischemic lesions significantly more frequently than does CT in the acute stroke setting. A magnetic resonance study with combined DWI and magnetic resonance angiography can provide accurate information. Routine examinations, including DWI, to rule out occlusion of small penetrating arteries are important and required for accurate diagnosis of ESUS. The Japanese proposal for clinical indications for ICM implantation, including MRI-based diagnosis, might have contributed to the high AF detection rate in cryptogenic patients.

The cost-effectiveness of an ICM for AF fibrillation in patients with cryptogenic stroke was reported in a previous study.[19] With long-term continuous monitoring with an ICM, preventing recurrent stroke in patients with cryptogenic stroke is expected to enable cost-effectiveness. In this previous study, ICM monitoring resulted in cost savings by reducing recurrent arrhythmias and in quality-adjusted life years gains.[19] ICM-based screening for AF was beneficial for economic reasons. ICM is a cost-effective diagnostic tool for the prevention of recurrent stroke in patients with cryptogenic stroke. ICM implantation was more cost-effectiveness than usual care regarding the potential clinical benefit and cost-utility.

ESUS is a therapeutically relevant entity. Some randomized, controlled trials have investigated aspirin versus direct oral anticoagulants (DOACs). Recently, superiority of DOACs was not demonstrated in NAVIGATE ESUS or RE-SPECT ESUS.[20,21] Therefore, DOACs are not superior to antiplatelet drugs, such as aspirin, in secondary prevention of stroke. Another randomized, controlled trial on DOACs, called the ATTICUS trial for secondary prevention of ESUS, is currently ongoing.[22] In patients with ESUS, recommendation of medical treatment has not been established and developed. If AF is detected in patients with ESUS, anticoagulation therapy is recommended. Therefore, identifying the occurrence of AF conversion after cryptogenic ischemic stroke is important. Patients who are appropriate for use of antithrombotic treatment should be selected on the basis of a detailed examination, including head MRI, in accordance with the current situation of medical practice. The ATTICUS randomized trial was designed to determine whether administration of the

factor Xa inhibitor apixaban within 7 days after ESUS is superior to acetylsalicylic acid for preventing new ischemic lesions as documented by brain MRI within 12 months after stroke.[22] The trial design was a prospective, randomized, blinded, parallel-group, open-label, German, multicenter phase III trial of approximately 500 patients with ESUS. A key inclusion criterion was the presence or planned implantation of an ICM. Therefore, indication of ICM implantation is important for daily medical practice.

There are some limitations in our research. First, our study involved a relatively small number of patients. Second, our study suffered from the limitations of a retrospective audit of patients. Finally, the follow-up was not long. Because of the small number of cases in the present study, a larger number of cases will be required to confirm our results.

Conlcusions

The AF detection rate with an ICM is approximately one fifth after 3 months in patients with cryptogenic stroke diagnosed by MRI. Our data suggest that the Japanese criteria based on MRI may be useful for selecting adequate candidates for ICM implantation.

Conflict of Interest

All authors declare no conflict of interest.

References

1. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996;27:1760-1764.
2. Saver JL. Cryptogenic stroke. N Engl J Med 2016;375:e26.
3. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-438.
4. Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke 2017;48:867-872.
5. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-2486.
6. Toyoda K, Okumura K, Hashimoto Y, et al. Identification of covert atrial fibrillation in cryptogenic ischemic stroke: current clinical practice in Japan. J Stroke Cerebrovasc Dis 2016;25:1829-1837.
7. Reiffel JA, Verma A, Kowey PR, et al. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. JAMA Cardiol 2017;2:1120-1127.
8. Thijs VN, Brachmann J, Morillo CA, et al. Predictors for atrial fibrillation detection after cryptogenic stroke: Results from CRYSTAL AF. Neurology 2016;86:261-269.
9. Makimoto H, Kurt M, Gliem M, et al. High incidence of atrial fibrillation after embolic stroke of undetermined source in posterior cerebral artery territory. J Am Heart Assoc 2017;6:e007448.
10. Fonseca AC, Brito D, Pinho e Melo T, et al. N-terminal pro-brain natriuretic peptide shows diagnostic accuracy for detecting atrial fibrillation in cryptogenic stroke patients. Int J Stroke 2014;9:419-425.
11. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-1757.
12. Franken RA, Rosa RF, Santos SC. Atrial fibrillation in the elderly. J Geriatri Cardiol 2012;9:91-100.
13. Yang PS, Ryu S, Kim D, et al. Variations of prevalence and incidence of atrial fibrillation and oral anticoagulation rate according to different analysis approaches. Sci Rep 2018;8:6856.
14. Lip GY, Potpara T, Boriani G, et al. A tailored treatment strategy: a modern approach for stroke prevention in patients with atrial fibrillation. J Intern Med 2016;279:467-476.
15. Saposnik G, Gladstone D, Raptis R, et al. Atrial fibrillation in ischemic stroke: predicting response to thrombolysis and clinical outcomes. Stroke 2013;44:99-104.
16. Chen LY, Norby FL, Gottesman RF, et al. Association of atrial fibrillation with cognitive decline and dementia over 20 years: the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). J Am Heart Assoc 2018;7:e007301.
17. Akao M, Chun YH, Wada H, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. J Cardiol 2013;61:260-266.
18. Poli S, Diedler J, Hartig F, et al. Insertable cardiac monitors after cryptogenic stroke—a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. Eur J Neurol 2016;23:375-381.
19. Diamantopoulos A, Sawyer LM, Lip GY, et al. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. Int J of Stroke 2016;11:302-312.
20. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191-2201.
21. Diener HC, Easton JD, Granger CB, et al. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). Int J of Stroke 2015;10:1309-1312.
22. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. Int J of Stroke 2017;12:985-990.