High Incidence of Occult Atrial Fibrillation in Asian Patients with Cryptogenic Stroke

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Background: Occult atrial fibrillation (AF) is not uncommon in patients with stroke. In western cohorts, insertable loop recorders (ILRs) have been shown to be the gold-standard and are cost-effective for AF detection. Anticoagulation for secondary stroke prevention is indicated if AF is detected. The incidence of occult AF among Asian patients with cryptogenic stroke is unclear. *Methods:* Patients with cryptogenic stroke referred between August 2014 and February 2017 had ILRs implanted. Episodes of AF >2 minutes duration were recorded using proprietary algorithms within the ILRs, whereupon clinicians and patients were alerted via remote monitoring. All AF episodes were adjudicated using recorded electrograms. Once AF was detected, patients were counseled for anticoagulation. *Results:* Seventy-one patients with cryptogenic stroke, (age 61.9 ± 13.5 years, 77.5% male, mean CHA_2DS_2VASc score of 4.2 ± 1.3) had ILRs implanted. Time from stroke to the ILR implant was a median of 66 days. Duration of ILR monitoring was 345 ± 229 days. The primary endpoint of AF detection at 6 months was 12.9%; and at 12 months it was 15.2%. Median time to detection of AF was 50 days. The AF episodes were all asymptomatic and lasted a mean of 77 minutes (± 118.9). Anticoagulation was initiated in all but 1 patient found to have AF. *Conclusions:* The incidence of occult AF is high in Asian patients with cryptogenic stroke and comparable to western cohorts. The combination of ILR and remote monitoring is a highly automated, technologically driven, and clinically effective technique to screen for AF. **Key Words:** Cryptogenic stroke—atrial fibrillation—Asian—occult—loop recorder.
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Introduction

Stroke is a leading cause of morbidity and mortality.[1] Despite extensive investigations, no known cause is found in up to 40% of strokes[2-4] ("cryptogenic stroke").

Since occult atrial fibrillation (AF) can result in embolic stroke, rhythm monitoring methods such as in-hospital telemetry, serial electrocardiograms (ECGs) and continuous ambulatory ECG monitoring (Holter), external loop recorders or implanted cardiac devices such as insertable loop recorders (ILRs) and pacemakers have been used to detect AF. The detection of AF ranges from 2.7% to 28% after up to 2.5 years of monitoring and depends on the duration of monitoring.[5-12]

"Intermittent" methods of ECG monitoring like the ambulatory Holter suffer from lack of sensitivity compared with implanted cardiac devices like ILRs which are capable of literally continuous ECG monitoring. More recently, the use of ILRs has demonstrated an AF detection rate of 8.9% at 6 months and 12.4% at 12 months[13] in patients with cryptogenic stroke in the Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial study. The diagnosis of occult AF in the setting of stroke is of paramount importance as it mandates anticoagulation, which reduces the risk of recurrent stroke. In contrast, initiating anticoagulation empirically on suspicion of, but without confirmation of AF exposes patients to the risks of bleeding without definite protection from recurrent stroke.[14,15]

The incidence of AF has been reported to be lower in the Asian population (about 1%) compared with the Western population (2%)[16-18] However, the risk of stroke for any CHA_2DS_2VASc score appears to be higher in Asians with AF. For instance, the annual rate of ischemic stroke in East Asian patients with AF and a CHA_2DS_2VASc score of 1 was 1.66%[19,20] compared with 1.3% in the West.[21]

Given the different demographics of AF and stroke in Asia, the applicability of an ILR-based strategy to detect occult AF in Asia is uncertain. This study aims to determine the value of ILR and remote monitoring to detect occult AF and examine the consequent changes in clinical management in a cohort of Asian patients with cryptogenic stroke.

Methods

Between August 2014 and February 2017, patients with a diagnosis of cryptogenic acute ischemic stroke (AIS) or transient ischemic attack (TIA) referred for ILR implantation in an academic medical center in Singapore were recruited. This is a single-center, observational study. The diagnosis of AIS/TIA was based on clinical presentation as well as consistent findings on magnetic resonance imaging or computed tomography scan. All patients had a normal transthoracic echocardiogram, duplex ultrasound of the carotid arteries, transcranial Doppler ultrasound of the intracranial vessels, inpatient continuous ECG monitoring for at least 24 hours, and outpatient ambulatory 24-hour Holter. Patients who had pre-existing AF, existing indications for anticoagulation, contraindication to anticoagulation or indication for a cardiac implantable electronic device were excluded.

All patients had a Medtronic Reveal LINQ (Medtronic Inc, Minneapolis, MN) ILR implanted subcutaneously and were placed on remote monitoring using the Medtronic CareLink system. Informed consent was obtained from the patients for the implant procedure, remote monitoring and follow-up, as well as review of the collected data. The ILR device was programmed to detect episodes of AF lasting a minimum of 2 minutes. An inbuilt proprietary algorithm which uses a Lorenz scatter plot of R-R

intervals was used to make the diagnosis of AF. Electrograms of any detected AF episode were recorded and flagged as an "event", triggering a physician alert notification via the remote monitoring system. All AF episodes were adjudicated by qualified cardiac electrophysiologists.

Subjects were monitored via the CareLink remote monitoring system without any scheduled in-person clinic visits until the battery of the ILR expires in 3 years. The primary end-point was the detection of an AF episode, whether symptomatic or asymptomatic. Patients and referring neurologists were contacted once AF episodes were detected, to initiate discussion regarding anticoagulation.

As this was a purely observational study on a currently accepted clinical practice, ethics approval was waived. Statistical analysis was performed using Stata MP version 14 (Stata Corporation, College Station, TX). Kaplan-Meier failure curve was generated for the time to detection of AF.

Results

Over a period of 30 months, 71 patients (age 61.9 ± 13.5 years, 77.5% male, mean CHA_2DS_2VASc score of 4.2 ± 1.3) were included in the study. The majority had hypertension (74.7%), while diabetes and vascular diseases were observed in more than 30% of the patients.

Median time from stroke event to the implant of the ILR was 66 days. The mean duration of ILR monitoring was 345 ± 229 days. Out of 71 patients, 11 patients were found to have AF detected during the period of observation. Except for gender, there was no significant difference in age, CHA_2DS_2VASc, and comorbid conditions identified between those with AF detected and those without. Baseline characteristics are shown in Table 1.

The primary outcome of detection of AF at 6 months was 12.9% and the secondary outcome of detection of AF at 12 months was 15.2% (Fig 1).

The median time to first AF detection was 50 days.

All the episodes of AF were asymptomatic. The mean duration of AF recorded was 77 ± 118.9 minutes, with mean of 15.5 ± 22.9 AF episodes detected in these 11 patients.

Of these patients with AF, 54.6% of episodes lasted <6 minutes, 18.2% between 6 minutes and 1 hour, 18.2% between 1 hour and 6 hours, and 9.1% lasted longer than 6 hours . Oral anticoagulation was started in 10 of 11 patients (90.9%) within 14.6 ± 14.2 days of diagnosis. Anticoagulation was deferred in 1 patient due to high fall risk.

Discussion

It is well established that most episodes of atrial fibrillation are asymptomatic,[22,23] underscoring the unreliability of using symptoms to guide timing of ECG recordings for the diagnosis of AF. In this study, all the episodes of AF were asymptomatic, consistent with the