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ORIGINAL COMMUNICATION

Occult paroxysmal atrial fibrillation in non-cryptogenic ischemic stroke

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Abstract

Objective To determine the prevalence and risk factors for paroxysmal atrial fibrillation (PAF) diagnosis in non- cryptogenic ischemic stroke (CIS) patients.

Methods In this pilot-prospective cohort study of non-CIS patients from September 2014 to September 2017, 53 patients were enrolled. 51/53 patients were implanted within 10 days of stroke onset with the Reveal LINQ insertable cardiac monitor and monitored until PAF detection or a minimum of 12 months. Inclusion required diagnosis of a non-AF stroke etiology, age ≥ 40, and either a virtual $CHADS_2$ score ≥ 3 or ≥ 2 PAF-related comorbidities.

Results Over a median monitoring period of 398 days, PAF was detected in 6/51 (11.8%) patients and anticoagulation was initiated in 5/6 (83.3%). Median time to PAF detection was 87 days (range 0–356 days). Median longest PAF episode was 96 min (range 1 to 1122 min), and 4/6 had multiple PAF recordings. Mean left atrial volume index was significantly higher in PAF patients (31.0 vs. 23.2 cc/m^2; $p = 0.04$).

Conclusion Long-term monitoring of non-CIS patients detected PAF in a clinically relevant proportion of patients, resulting in stroke prevention therapy optimization. Further study to confirm these findings and refine the subset that would benefit from long-term cardiac monitoring is warranted.

Keywords Ischemic stroke · Atrial fibrillation · Risk factors · Insertable cardiac monitor

Introduction

Atrial fibrillation and atrial flutter (AF) are well-known sources of embolic ischemic stroke worldwide [1, 2] and are the etiology of 10–20% of ischemic strokes in the United States [3–5]. As anticoagulation can significantly reduce the risk of ischemic stroke in high-risk patients [6], AF is a major modifiable stroke risk factor that is often undiagnosed [7, 8]. AF may be continuous or intermittent (paroxysmal), and is often asymptomatic [9]. Paroxysmal AF (PAF) is more common [10], and carries a similar stroke risk [11, 12].

AF is often diagnosed during the diagnostic evaluation following a first ischemic stroke or transient ischemic attack (TIA) [13]. Electrocardiography (ECG) reliably detects continuous AF. Short-term cardiac telemetry, or Holter monitoring, may detect episodes of PAF, however, longer monitoring periods improve detection [14]. In the last several years, use of insertable cardiac monitors (ICM), capable of detecting occult PAF episodes as brief as 2 min, and even shorter durations of symptomatic atrial flutter, has become common practice in the subsequent evaluation of cryptogenic ischemic stroke (CIS) patients following the initial diagnostic evaluation. About 25% of ischemic strokes are cryptogenic [15], and occult PAF may be detected in up to 31% of this population [16]. In the randomized CRYSTAL AF Trial, an AF detection rate of 12.4% was observed in CIS patients implanted with an ICM over the 12-month study

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period, compared to 2.0% in the standard monitoring (control) group, and treatment was changed from antiplatelet to anticoagulation therapy in 97% of those with AF detected [17].

Aims

No study to date has used ICMs to comprehensively examine the prevalence of occult PAF in non-cryptogenic ischemic stroke (non-CIS) patients; those with a diagnosed stroke etiology other than AF, such as small-vessel disease, arterial dissection, or an atheroembolic source. Since previous stroke or TIA are significant risk factors for recurrent stroke in the setting of AF, the diagnosis of PAF in this population has major implications for secondary stroke prevention. Whether all or some non-CIS patients would benefit from long-term cardiac monitoring with ICM is unknown. To address this, we performed a pilot-prospective-, single-center, non-blinded, cohort study to assess the prevalence and risk factors for PAF detection in ischemic stroke patients who have a presumed known stroke etiology other than AF.

Methods

Patients and procedures

All ischemic stroke patients admitted to the stroke service of a comprehensive stroke center were screened for study enrollment between September 2014 and September 2016. Patients were evaluated for underlying stroke mechanism according to standard institutional and national guidelines [2, 18]. Stroke etiology was determined by the treating stroke neurologist based on a complete stroke evaluation that included brain MRI, 12-lead ECG, a minimum of 24-h cardiac telemetry monitoring, transthoracic (TTE) and/or transesophageal (TEE) echocardiography, and CT and/or MR angiography of the head and neck.

Inclusion criteria include (1) presumed known stroke etiology other than AF; (2) age ≥ 40 years old; and either (3) a virtual $CHADS_2$ score ≥ 3 (2 points for index stroke plus at least one additional $CHADS_2$ risk factor: congestive heart failure, hypertension, age ≥ 75, or diabetes mellitus) or (4) two or more of the following AF-associated comorbidities: obstructive sleep apnea, coronary artery disease, chronic obstructive pulmonary disease, hyperthyroidism, body mass index > 30, prior myocardial infarction, PR interval > 175 ms, or renal impairment (glomerular filtration rate 30–60).

Patients were excluded if any of the following criteria were met: (1) history of AF or atrial flutter; (2) evidence of high-risk cardiac source of embolism (such as left ventricular or left atrial thrombus or "smoke", emboligenic valvular lesion, or tumor); (3) untreated hyperthyroidism; (4) myocardial infarction or coronary bypass grafting (CABG) within 1 month of index stroke; (5) valvular disease requiring surgical intervention; (6) permanent anticoagulation indication or contraindication; (7) commitment to another clinical trial; (8) life expectancy < 1 year; (9) pregnancy; (10) indication for implant with a pacemaker or implantable cardioverter defibrillator; or (11) inability to follow the procedures of the clinical investigation plan.

Potential study participants who met criteria were approached for informed consent if ICM implantation could be completed within 10 days of qualifying stroke onset. Once written informed consent was obtained, a Reveal LINQ ICM (Medtronic, Inc., Minneapolis, MN) was implanted by a trained study electrophysiology cardiologist. The indications for Reveal LINQ ICM implantation were per the study protocol only. Study subjects were not selected based on any other risk constellation. ICM signal quality was confirmed after insertion. Protocol and research personnel were approved by the local Institutional Review Board. Research conduct was consistent with the Declaration of Helsinki. This study was registered with http://www.clinicaltrials.gov NCT02232022.

Data collection and clinical evaluation

Clinical and diagnostic testing data were collected on a standardized case report form. Admission blood work, ECG, and echocardiographic (TTE and/or TEE) results were recorded. Brain and angiographic CT and MRI were evaluated for infarct location and pattern, and the presence of symptomatic intracranial or extracranial atherosclerotic stenosis or dissection. Stroke pathogenesis was classified by TOAST criteria [19].

The study cardiologist received an alert within 24–48 h if the device detected an AF episode. Participants were requested to perform a full manual device interrogation monthly. The study cardiologist manually reviewed the full summaries of device transmissions every 3 months. All adjudicated PAF detections were discussed with the participant's vascular neurologist and cardiologist, and decisions regarding anticoagulation therapy were made.

Study participants were scheduled for in-person study visits at 1 month, 6 months, and 12 months following study enrollment. Visits occurred by telephone if subjects were unable to attend in person. During follow-up visits, participants were assessed for any recurrent stroke or TIA, intracranial hemorrhage, interval medical history, device-related complications, or other adverse events.

Definitions and statistical analysis

PAF was defined as any period of 2 min or greater duration of atrial fibrillation, or any recorded atrial flutter, detected via irregularities in *R–R* interval and *P*-wave formation [20]. Our primary outcome measure was the detection of PAF. Secondary outcome measures included recurrent stroke or TIA, rate of device-related complications or other adverse events, and initiation of anticoagulation therapy in patients diagnosed with PAF. The level of statistical significance was set at <0.05. Each variable was compared between the PAF and non-PAF groups by one-sided non-paired *t* tests for continuous variables. Adjusted odds ratios were compared between the two groups by calculating 95% confidence intervals for binary variables.

Results

A total of 53 patients with mean age 64.8 years (range 40 to 88 years) were enrolled over the 2-year enrollment period. About one-third (17/53, 32.1%) of the subjects were female, and the majority (32/53, 60.4%) was Caucasian. All patients had ischemic stroke as the index event, with each infarction evident on brain MRI, except for one patient with an MRI-negative brainstem stroke. The mean admission NIHSS was 3.5 (range 0–11) and the mean discharge mRS was 1.9 (range 0–4). The mean virtual $CHADS_2$ score was 3.5 (range 3–5), the mean CHA_2DS_2-VASc score was 4.5 (range 3–8), and 12/53 (22.6%) had ≥ 2 PAF comorbidities. By TOAST criteria, there were 37 small vessel, 13 large vessel, and 3 cardioembolic (non-AF) strokes. Lacunar stroke etiology predominated ($n=33$), followed by extracranial atherosclerotic stenosis ($n=4$), intracranial atherosclerotic stenosis ($n=3$), extracranial dissection ($n=3$), cardioembolic ($n=3$; patent foramen ovale with deep vein thrombosis), and aortic arch atheroembolic ($n=2$). Five patients had multiple potential sources. More than half, 28/53 (52.8%) had posterior circulation strokes, 23 had MCA territory infarcts, one had unilateral multi-vascular territory infarction, and one had bilateral multifocal infarction. Baseline ECG demonstrated normal sinus rhythm in most ($n=44$), while six patients had sinus bradycardia, and three had sinus tachycardia. Mean duration of inpatient cardiac telemetry was 3.7 days (range 0.5 [single outlier] to 12 days).

Of 53 enrolled subjects, two withdrew consent prior to ICM implantation, leaving 51 participants for analysis. PAF was detected in 6/51 patients (11.8%) over a median monitoring period of 398 days (mean 405 days; range 13–1064 days). Characteristics of the patients diagnosed with PAF are detailed in Table 1. Excluding one patient who did not transmit following LINQ insertion, the minimum monitoring duration for patients not diagnosed with PAF was 34 days. The median time until PAF detection was 87 days (range 0–356 days), with 4/6 being diagnosed by 6 months (Figure 1). Mean and median duration of longest PAF episode was 237 and 96 min, respectively, with a range 1–1122 min. Two patients had 1 episode of PAF (including 1 min of atrial flutter and 196 min of atrial fibrillation), and four patients had multiple instances of atrial fibrillation (2, 3, 5 and 40 episodes per subject). All PAF episodes were asymptomatic, and 5/6 (83.3%) patients (all 5 with atrial fibrillation) were prescribed anticoagulation.

Almost all patients (50/51; 98.0%) either reached the study endpoint within 1 month ($n=1$) or completed at least 1 month of clinical follow-up ($n=49$). Three patients dropped out during the 12-month study period and one patient died from metastatic lung carcinoma. Of the remaining non-PAF patients, 35/41 (85.4%) completed 6 months of follow-up, and 32/41 (78.0%) completed 12 months of follow-up. One device-related complication (pending device erosion through the skin) was reported, requiring device removal.

Comparing PAF ($n=6$) and non-PAF ($n=45$) groups showed significantly higher mean LA volume index (cc/m^2)

Table 1 Description of atrial fibrillation and flutter patients

Case	Age (yr)	Sex	Race/ethnicity	NIHSS score	Stroke risk factors	$CHADS_2$ score	TOAST subtype	Vascular territory	Recorded episodes (*n*)	Episode duration[a] (min)
Case 1	69	F	H	3	HTN, DM	4	Small vessel	MCA	1[b]	1
Case 2	87	M	C	3	HTN, HLD, CS	4	Small vessel	Brainstem	1	196
Case 3	88	F	C	1	VHD	3	Small vessel	MCA	40	18
Case 4	55	M	C	4	HTN, HLD, PS	3	Small vessel	Brainstem	5	1122
Case 5	72	F	C	1	HLD, PS, TS	2	Large artery	MCA	2	8
Case 6	60	M	C	2	HTN	3	Small vessel	MCA	3	174

C Caucasian, *CS* carotid stenosis, *DM* diabetes mellitus, *F* female, *H* Hispanic, *HLD* hyperlipidemia, *HTN* hypertension, *M* male, *PS* past stroke, *TS* tobacco smoking, *VHD* valvular heart disease

[a]Denotes duration of the longest episode in those with more than one episode

[b]Episode of atrial flutter; all other episodes are atrial fibrillation

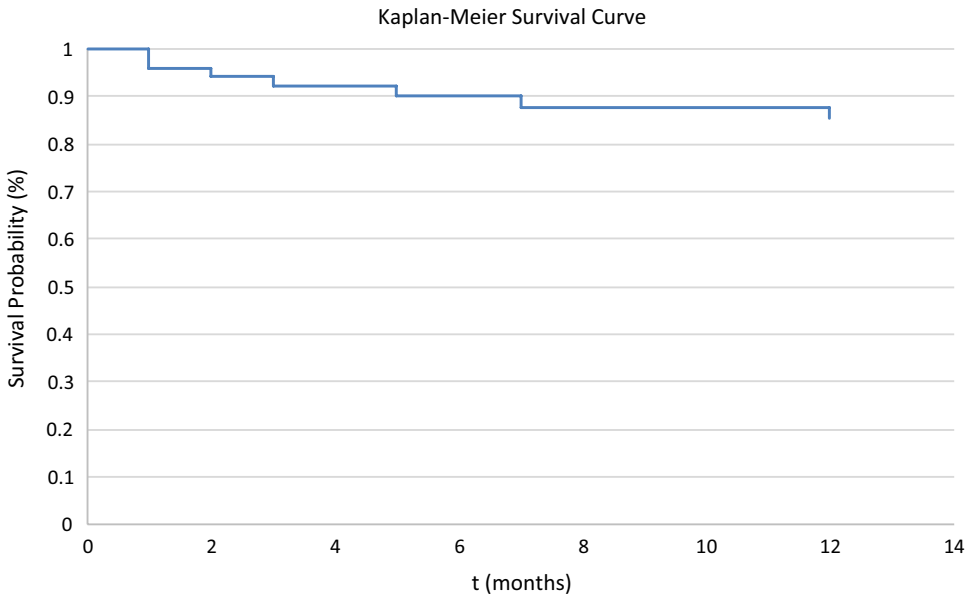

Fig. 1 Kaplan–Meier curve depicting time to paroxysmal atrial fibrillation and flutter detection

(31.0 vs. 23.2; $p = 0.04$) in patients diagnosed with PAF. While the PAF group was older (mean age (yrs) 71.8 vs. 62.6; $p = 0.08$), with a higher frequency of obesity (66.7% vs. 33.3%; $p = 0.13$), these and all other tested variables were not significantly different between groups.

Discussion

To our knowledge, this study is the first to estimate the frequency of occult PAF using ICM in patients with ischemic stroke of presumed known cause other than AF. Over a 12-month follow-up period, 11.8% of patients were diagnosed with PAF following early LINQ ICM insertion for prolonged, post-stroke cardiac rhythm monitoring. This is similar to the 12.4% detection rate for CIS patients found by the CRYSTAL AF Trial over a comparable monitoring period, but lower than the 31% in our recently reported retrospective series of CIS patients monitored post stroke after early ICM implantation [16]. The rate of 11.8% is also higher than the baseline prevalence of AF in the general, non-stroke population, which is estimated to be 1–2% [21, 22]. In patients older than 65 years, the prevalence increases to about 6%, and is highest at 9% in 80–89 year olds, but these are still lower than the rate found in the current study of non-CIS patients who were at least 40 years old at the time of the index stroke. As our cohort was selected based on the presence of $CHADS_2$ risk factors and/or AF-related medical comorbidities, our results cannot be generalized to the entire non-CIS population.

While it is not possible to demonstrate whether PAF was the cause of, or present prior to, the index stroke, certainly the diagnosis of PAF in this population has significant implications for clinical management in terms of secondary stroke prevention. All participants diagnosed with paroxysmal atrial fibrillation were switched from antiplatelet to anticoagulation therapy soon after PAF diagnosis. The one patient not switched to anticoagulation had a brief, one-minute, single episode of atrial flutter, in the setting of major interval cardiac disease.

Our data show a significant association between LA enlargement, as defined by a greater LA volume index, and the probability of detecting PAF in this non-CIS population. This is not unexpected, as an enlarged LA is the major cardiac structural abnormality associated with AF diagnosis in the general population [23, 24]. Older age and obesity trended towards, but did not reach, statistical significance. These associations with PAF propensity have been reported by others [14, 25–27]. We recently reported several risk factors associated with PAF detection in a retrospective series of CIS patients similarly implanted with a LINQ ICM during, or soon after, the index stroke admission. In this CIS population, older age, Caucasian race, prolonged PR interval (> 175 ms), larger LA diameter and LA volume index, and lower hemoglobin A1c levels were significantly associated with PAF detection [16]. Controlling for age, only obesity was a significant independent risk factor. Others have found that for CIS patients over 60 years old, PAF is associated with prior cortical or cerebellar infarcts [28], and the presence of cardiovascular risk factors [23]. Insular cortex involvement may also be associated with new onset PAF [29]. In the current study, stroke location by vascular territory or cortical vs. subcortical locations was not associated with PAF risk.

Our study has several limitations. While our prospective design enabled complete collection of baseline data from all

patients, the relatively small sample size limits our study's power to detect and confirm all factors associated with PAF detection. A larger prospective study, or similar analysis of data from the ongoing STROKE AF trial [30], may further refine these results. Evaluating factors associated with PAF detection in this population is important because likely not all non-CIS patients warrant long-term cardiac monitoring with an ICM, and proper selection of high-yield candidates would decrease the burden of unnecessary procedures and lower the cost of care. The number of non-PAF patients lost to follow-up by 6 and 12 months is a second limitation that may have resulted in an underestimation of PAF burden. While our study offers insight into the prevalence of PAF in patients with a presumed known, non-AF, stroke etiology, we are unable to determine the odds of AF detection in this population using the LINQ ICM for long-term cardiac monitoring, because we did not have a control group of patients who did not have an ICM. Further study is needed to establish whether detecting PAF in this population provides cost-effective clinical benefit in terms of stroke risk, quality of life, and mortality reduction.

A clinically significant number of non-CIS patients were found to have PAF by long-term post-stroke cardiac monitoring using the LINQ ICM. The diagnosis of PAF in follow-up led to a high likelihood of antithrombotic therapy change to anticoagulation. As might be expected, LA enlargement is a significant predictor of PAF detection in this population. Elucidation of the odds of PAF diagnosis in non-CIS patients and the risk factors associated with this diagnosis warrants further investigation with larger prospective studies.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The local Institutional Review Board (Northwell IRB) approved the study protocol, all study procedures were performed in accordance with the 1964 Declaration of Helsinki ethical standards, and all participants signed written informed consent prior to study activities.

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