Prevalence and Risk Factors for Paroxysmal Atrial Fibrillation and Flutter Detection after Cryptogenic Ischemic Stroke

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Introduction: Long-term cardiac monitoring with implantable loop recorders (ILRs) has revealed occult paroxysmal atrial fibrillation and flutter (PAF) in a substantial minority of cryptogenic ischemic stroke (CIS) patients. Herein, we aim to define the prevalence, clinical relevance, and risk factors for PAF detection following early poststroke ILR implantation. *Materials and methods:* A retrospective study of CIS patients (n = 100, mean age 65.8 years; 52.5% female) who underwent ILR insertion during, or soon after, index stroke admission. Patients were prospectively followed by the study cardiac electrophysiologist who confirmed the PAF diagnosis. Univariate and multivariate analyses compared clinical, laboratory, cardiac, and imaging variables between PAF patients and non-PAF patients. *Results:* PAF was detected in 31 of 100 (31%) CIS patients, and anticoagulation was initiated in almost all (30 of 31, 96.8%). Factors associated with PAF detection include older age (mean [year] 72.9 versus 62.9; $P = .003$), white race (odds ratio [OR], 4.5; confidence interval [CI], 1.8-10.8; $P = .001$), prolonged PR interval (PR > 175 ms; OR, 3.3; CI, 1.2-9.4; $P = .022$), larger left atrial (LA) diameter (mean [cm] 3.7 versus 3.5; $P = .044$) and LA volume index (mean [cc/m^2]; 30.6 versus 24.2; $P = .014$), and lower hemoglobin (Hb)A1c (mean [%] 6.0 versus 6.4; $P = .036$). Controlling for age, obesity (body mass index > 30 kg/m^2; OR, 1.2; CI, 1.1-1.4; $P = .033$) was independently associated with PAF detection. *Discussion:* PAF was detected with high prevalence following early postcryptogenic stroke ILR implantation and resulted in significant management changes. Older age, increased PR interval, LA enlargement, and lower HbA1c are significantly associated with PAF detection. Controlling for age, obesity is an independent risk factor. A larger prospective study is warranted to confirm these findings. **Key Words:** Stroke—atrial fibrillation—risk factors—Loop recorder—Implantable cardiac monitor—Cryptogenic stroke.

Stroke presents a significant public health and economic burden for the United States, where an estimated 692,000 new ischemic strokes occur annually.[1] When a stroke etiology is not identified during a comprehensive inpatient diagnostic evaluation, it is labeled a cryptogenic ischemic stroke (CIS).[2] An estimated 30% of ischemic stroke patients fall into this category.[3] While a small percentage of ischemic stroke patients are diagnosed with paroxysmal atrial fibrillation or atrial flutter (PAF) during their hospitalization, many remain unidentified due to the often asymptomatic and paroxysmal nature of these supraventricular arrhythmias.[2] Consensus is lacking within the vascular neurology and cardiology communities regarding the appropriate duration and mechanism of long-term poststroke cardiac monitoring. Both implantable and external long-term monitoring devices are available, and these are identifying a greater percentage of occult arrhythmias in the CIS population when compared with conventional methods such as Holter monitoring, intermittent electrocardiography (ECG), and

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outpatient physician visits.[4-9] In the randomized controlled CRYSTAL-AF trial, an implantable loop recorder (ILR) outperformed these conventional methods.[10] Prior studies have also shown that long-term monitoring for PAF is more cost-effective compared with previous methods.[11,12] Nonetheless, most of these studies did not require early poststroke device implantation, causing potential delays in diagnosis and possibly underestimating the degree of PAF burden in the CIS population. For instance, the CRYSTAL-AF trial enrolled patients up to 90 days after stroke onset, while the EMBRACE Trial, using a noninvasive event monitor, randomized patients who had CIS or transient ischemic attack in the previous 6 months.[6,10] The purposes of this study are to determine the yield of long-term cardiac monitoring in CIS patients who underwent early ILR insertion soon after their index stroke and to identify risk factors predictive of poststroke PAF diagnosis.

Materials and Methods

We conducted a retrospective review of a consecutive cohort of CIS patients (n = 100; mean age 65.8 years [range 28-93] and 52.5% female) admitted to the stroke service of a comprehensive stroke center who were implanted with the Reveal Insertable Cardiac Monitor (ICM; Medtronic, Inc.) between September 2013 and September 2015. During the study period, a total of 1286 ischemic stroke patients were seen at our hospital. Fifteen left against medical advice, 99 expired, and 494 had a modified Rankin score of 5. At our institution, 30% of ischemic strokes are cryptogenic, and only about half of all ischemic stroke patients are admitted to the stroke service. Of the estimated 204 CIS patients admitted to the hospital, approximately 100 were discharged from the stroke service and were potentially eligible for ILR placement during the study period. Patients admitted after February 2014 (n = 90) were implanted with the current Reveal LINQ ICM (Medtronic Inc, Minneapolis, MN), while the first 10 patients in the series were monitored with the older-generation Reveal XT device (Medtronic Inc, Minneapolis, MN). The Reveal LINQ ICM (Medtronic Inc, Minneapolis, MN) is a smaller device, approximately one third the volume of a AAA battery. Both devices detect PAF based on an algorithm that assesses R-R interval irregularities. The ILR also registers tachycardia events (defined as heart rate greater than 230 beats per minute minus age) of 16 or more beats, and any other incidents triggered by the Patient Activator, a companion device that enables patients to record their rhythm if they experience any symptoms.

Patients were diagnosed with CIS by fellowship-trained vascular neurologists based on a thorough inpatient diagnostic evaluation that included brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]), cervical and cerebral vascular imaging (magnetic resonance angiography or computed tomography angiography), echocardiography (transthoracic and/or transesophageal), a minimum of 24 hours of cardiac telemetry monitoring, ECG, and standard poststroke blood work. Patients with nonlacunar strokes and no identifiable stroke source were diagnosed with CIS. All patients underwent early ILR placement during or immediately after inpatient hospitalization for the index stroke. The mean time ± standard deviation (SD) from stroke admission date to ILR insertion was 4.2 ± 2.6 days (range 0-16 days). Cardiac monitoring data were prospectively followed until study completion in May 2016, ensuring a minimum of 8 months of potential monitoring for all patients in whom PAF was not detected. Patients with severe disabling stroke, defined as a modified Rankin Scale score >4, discharge to hospice, or death, and patients who refused implantation, did not undergo ILR placement and are therefore not included in this study.

The study cardiac electrophysiologist (D.G.) confirmed the diagnosis of PAF in all ILR-identified events of at least 2 minutes' duration, and briefer episodes of atrial flutter by review of tachycardia- or patient-triggered recordings. All events were defined as atrial fibrillation, atrial flutter, or both. Time to PAF detection was calculated in days between the date of ILR insertion and first PAF episode, and PAF arrhythmias were characterized by episode duration. In addition, other potentially relevant cardiac arrhythmias, such as bradycardia and sinus pauses, were recorded, as were changes in management, including the initiation of anticoagulation as a consequence of the PAF diagnosis.

Following local institutional review board approval, a retrospective chart review to extract demographic, clinical, laboratory, and cardiac variables was undertaken. Demographic and clinical variables include age, sex, admission National Institutes of Health Stroke Scale (NIHSS), blood pressure and heart rate, body mass index (BMI), discharge modified Rankin Scale score, discharge disposition, the presence of classic vascular risk factors (prior stroke, hypertension, hyperlipidemia, diabetes mellitus, and tobacco smoking), and other potentially relevant historical risk factors (hyperthyroidism, prior myocardial infarction, congestive heart failure, valvular heart disease, obstructive sleep apnea, and chronic obstructive pulmonary disease). Laboratory variables include admission white blood cell count, blood glucose, low-density lipoprotein cholesterol, and hemoglobin A1c. Cardiac variables include ECG findings (PR interval and baseline cardiac rhythm) and transthoracic and/or transesophageal findings (left atrial [LA] diameter, LA volume index, LA dilatation, left ventricular (LV) ejection fraction, mitral valve (MV) regurgitation, MV stenosis, aortic valve regurgitation, aortic valve stenosis, aortic root dilatation, concentric LV hypertrophy, LV diastolic dysfunction, patent foramen ovale, or atrial septal defect, atrial septal aneurysm, aortic arch plaque, and pulmonary hypertension). For the purpose of analysis, PR interval prolongation was defined as >175 ms, and the presence of cardiac valve disease was dichotomized as none to minimal versus mild to severe.