

TITLE

Occult Paroxysmal Atrial Fibrillation in Non-Cryptogenic Ischemic Stroke

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INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

Atrial Fibrillation (AF) is an independent risk factor for stroke.¹ Between 50 and 59 years of age, 1.5% of strokes are attributed to AF, but between 80 and 89 years of age the proportion increases to 23.5%. There are 15 strokes every hour from AF.

Paroxysmal AF (PAF) is sporadic, asymptomatic and has similar risk of stroke when compared to continuous AF.^{2,3} It is not clearly defined in the literature and is more prevalent than persistent AF in patients with ischemic stroke and TIA.⁴ The incidence of paroxysmal AF in cryptogenic stroke is 1 in 6 for age > 55 and 1 in 5 for age > 75.⁵ Most studies based on the prevalence of stroke in the US would suggest that approximately 200,000 individuals may have ischemic stroke associated with PAF. We suspect this number to be higher since long-term monitoring has been restricted only to the cryptogenic stroke population. The risk of stroke recurrence is four times greater among stroke patients with newly detected AF (15.5%) compared to those with either known AF or no AF (3.9%).⁶ Some studies have shown that 5% to 30% of cryptogenic strokes may be due to undetected AF.^{7,8}

The standard Holter monitor has a low sensitivity for detecting paroxysmal AF following an ischemic stroke (approximately 5%). In the recent Crystal AF study, 30% of cryptogenic stroke patients randomized to the Reveal Insertable Cardiac Monitor were found to have PAF compared to 3% of controls over a 3 year monitoring period.^{8,9} There are numerous observational studies that support greater detection of AF with longer monitoring. (Table 1)^{10,11} Median time to AF episode detection was 84 days. Prior studies have shown that long term monitoring for detection of PAF is cost effective.¹² While the relatively high incidence of silent PAF in cryptogenic stroke patients is just now being elucidated, there is no understanding of the frequency of silent PAF in patients with a “known” or presumed etiology for their ischemic stroke other than AF. If this incidence were also found to be significant, a dramatic change in stroke evaluation and management would likely occur.

Anticoagulation is the treatment of choice for AF and paroxysmal AF.¹³ Anticoagulation in patients with paroxysmal or chronic AF reduces the risk of stroke by 64% and death by 25%.⁵ The identification of paroxysmal AF in EMBRACE (30 day) and SURPRISE (mean 133 days) led to a change in management to full anticoagulation in 13% and 18% of patients, respectively. In the Crystal AF study, 97% of patients who were diagnosed with AF were changed to oral anticoagulants.⁸ It is postulated that in the era of the novel oral anticoagulants, the detection of AF and the appropriate initiation of anticoagulation as secondary stroke prevention will reduce the risk of recurrent ischemic stroke without increasing the rates of symptomatic intracerebral hemorrhage or systemic hemorrhage. For patients with a presumed stroke mechanism other than AF who are found to have silent PAF, a change in management to full anticoagulation could have similar effects.

OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

Primary Objective:

To determine the incidence of paroxysmal atrial fibrillation (AF) in ischemic stroke patients who have a presumed known stroke etiology other than atrial fibrillation.

Secondary Objectives:

- 1. Percentage of patients who are diagnosed with AF who are changed to anticoagulant therapy.**
- 2. Duration and frequency of AF episodes.**
- 3. Percentage of asymptomatic AF episodes.**
- 4. Incidence of recurrent ischemic stroke.**

SUBJECT SELECTION – ELIGIBILITY CRITERIA

The subject population will include patients with a diagnosis of Ischemic stroke. A total of 75 patients will be enrolled over a **2-year period**.

Inclusion Criteria:

Patients with a recent ischemic stroke or TIA with brain infarction on brain imaging.

1. No history of atrial fibrillation or finding of atrial fibrillation on standard inpatient monitoring (ECG, telemetry, 24-hour Holter monitor)
2. Have a presumed stroke etiology: Lacunar or small vessel thrombosis, extra-cranial or intracranial atherosclerotic stenosis or dissection, arteriopathy or vasculitis, hypercoagulable state, aortic arch plaque with or without mobile elements, or evidence of a low-risk cardiac source (e.g., PFO with or without atrial septal aneurysm and with or without evidence of venous thromboembolic source).

The following diagnostic tests are minimally required to determine the stroke etiology:

- Brain MRI
- 12-lead ECG for AF detection

- 24-h ECG monitoring for AF detection (eg, Holter monitor or cardiac telemetry)
- TTE and/or TEE
- CTA or MRA of head and neck
- Hypercoagulable blood panel for patients less than 55 years-old
 - Preliminary hypercoagulable work-up within 7 days will include the antiphospholipid antibody syndrome results, which will be needed to determine stroke management. All other results, which could take longer to return, including genetic tests of hypercoagulability, rarely change stroke management.

1. Have virtual CHADS2 score ≥ 3 , or
2. Have 2 or more of the following co-morbidities: obstructive sleep apnea, coronary artery disease, (Chronic Pulmonary Obstructive Disease (COPD), hyperthyroidism, BMI > 30, prior MI, prolonged PR interval (>175 ms) or renal impairment (GFR 30-60).
3. Patient or legally authorized representative who is willing to sign written consent form.
4. Patient is ≥ 40 years old (patients younger than 40 years old have a very low likelihood of having atrial fibrillation and are therefore excluded from the study).
5. Patient can have the device implanted within 10 days of the incident ischemic event

Exclusion Criteria:

1. Documented history of AF or atrial flutter.
2. Evidence of a high-risk cardiac source of embolism (LV or LA thrombus or “smoke,” emboligenic valvular lesion or tumor)
3. Untreated hyperthyroidism.
4. Myocardial infarction or coronary bypass grafting within 1 month prior to the stroke/TIA.
5. Valvular disease requiring immediate surgical intervention.
6. Permanent indication for anticoagulation at enrollment.
7. Permanent oral anticoagulation contraindication.
8. Already included in another clinical trial that will affect the objectives of this study.
9. Life expectancy is less than 1 year.
10. Pregnancy. Urine or serum pregnancy test is required for women of child bearing potential to exclude pregnancy.
11. Patient is indicated for implant with a pacemaker, ICD, CRT device, or an implantable hemodynamic monitoring system
12. Patient is not fit, or is unable or unwilling to follow the required procedures of the Clinical Investigation Plan.
13. Cryptogenic Stroke: A stroke/TIA will be considered cryptogenic if no cause is determined despite extensive inpatient workup (see Inclusion criteria) according to the standard diagnostic protocol at North Shore University Hospital

DESIGN:

This is a single center prospective, non-blinded, cohort study that will be conducted over a period of 3 years (2 year patient enrollment and a minimum of 12 months of ICM monitoring). Patients will be evaluated according to standard institutional stroke/TIA clinical guidelines. Participants will be recruited within 7 days after the diagnosis of a stroke once diagnostic tests have been completed and a presumed stroke etiology has been identified.

All eligible patients will be approached for an informed consent to participate in the study. The primary goal of the study is to detect paroxysmal atrial fibrillation (AF) in ischemic stroke patients who have a presumed or known stroke etiology other than AF. The detection of paroxysmal AF will very likely lead to a change in their secondary stroke prevention strategy.

Stroke or TIA is considered to be cryptogenic if no stroke mechanism can be determined after an evaluation according to the standards of American and European Guidelines. Such patients will be excluded from the study.

Reveal LINQ Insertable Cardiac Monitor:

The LINQ ICM (Medtronic, Inc.; See photo in Appendix B) is a small cardiac monitor implanted in the subcutaneous tissue of the chest wall that is designed to continuously record a single-lead ECG, monitoring the cardiac rhythm for up to three years. A previous study of a similar device (Reveal XT ICM; Medtronic, Inc.) has demonstrated the technology’s ability to correctly identify AF in 96.1% of patients and to correctly exclude AF in 97.4% of patients. The LINQ ICM (or future iterations) will be utilized in this study to detect occult paroxysmal AF in our study population. The LINQ ICM is approved by the FDA for use in patients where there is a suspicion of occult cardiac arrhythmias and is therefore being utilized in this study in accordance with the FDA labeling.

The LINQ device is 87 % smaller than the Reveal device. It is pre-loaded in the insertion tool. The size of the device is 1.2 cc and it is interrogated using external equipment. It is able to store 4 separate patient activated events in the electrogram.

EP Cardiology, directed by Dr. Jadonath, will be implanting the device and have been trained by the manufacturer of the device. The cardiologists have been implanting similar devices for several years and have been trained on this specific device since February 2014. The insertion procedure involves draping the patient followed by local anesthesia at the site of implant. This is done under sterile precautions. A small incision is made under local anesthesia. Electrocautery to achieve hemostatis is rarely required. The device is then inserted using the insertion tool provided in the device kit. There is a risk of local site bleeding, infection, device migration, allergy to the device component, cosmetic complications from incision and inability of the device to capture some particular arrhythmias.

The best location of insertion of the device is 45 degrees relative to sternum over the 4th intercostals space (V2-V3) electrode orientation. This assures good signal quality. The second best option is 4th intercostals space approximately 2 cm parallel to the edge of sternum. If the above-recommended locations are not suitable, optional locations must be considered. The device is compatible with mammography and MRI (1.5T and 3T magnets). For precautions related to these procedures please refer to Reveal LINQ ICM Medical Procedure Manual (to be attached to this document.)

LINQ settings for high sensitivity and specificity will be set to:

o AF only – All Episodes

-The device will store all AF episodes that are irregular. Capture of these episodes is not based on the ventricular rate, it is based on irregularity.

- Stored episodes are representative of the first two minutes of each episodes

- Device will store approximately 13 episodes of 2 minutes duration (max 27 minutes)

o Balanced Sensitivity

o Ectopic Rejection: Aggressive

Follow Up:

Device recording of an AF episode of at least 2 minute duration will be required to diagnose a patient with AF. A partial device transmission (summary of potential AF episodes) will be automatically downloaded daily via the Medtronic MyCareLink patient monitor and the study cardiologist will receive an alert within 24-48 hours if the computer monitoring system confirms an episode to be probable AF. Participants may also use the Reveal Patient Assistant to activate recording of cardiac information in the Reveal LINQ ICM while experiencing or immediately after a symptomatic event. Participants will be required to perform a manual device interrogation on a monthly basis. All downloaded rhythms will be manually reviewed every month for each enrolled patient by the study cardiologist. Each AF episode will also be independently adjudicated by a cardiologist blinded to the study protocol.

A total of 75 patients will be enrolled in the study. After enrollment, patients will have study visits at 1, 6, and 12 months. Six and 12 month follow-up visits will be conducted at these time intervals plus or minus 30 days. If the patient cannot come in for a follow-up visit, then the follow-up may be performed as a telephone interview. During the study visits, patients will be assessed for any interval stroke or TIA-like events, intracerebral hemorrhages, interval medical history, device related complications or other adverse events. At the 1-month visit, a NIH stroke scale score will be obtained. At each study visit, a modified Rankin score will be recorded. There will not be any research labs conducted at these study visits and only blood work associated with routine care may be obtained.

Patients will also have one EP cardiology clinical follow-up visit 10 days (plus or minus 4 days) after device implantation to ensure proper healing of the surgical site and functioning of the device.

At the completion of the study, if there is no clinical reason not to remove the device, then the device will be removed at 1 year from implantation. If there is a clinical indication for longer monitoring, then the device will be kept in longer for a maximum of 3 years. However, if clinical monitoring is required beyond the study period, then monitoring will be performed outside of the

study, and the patient or the patient's insurance will be responsible for any clinical fees associated with this post study monitoring.

At the conclusion of the study, Drs. Jadonath or Garlitzki will be primarily responsible for removing the device; however, they may appoint one of their colleagues as designee to remove the device if they are unavailable.

INFORMED CONSENT

Subjects meeting the above inclusion/exclusion criteria will be approached by a study physician investigator and invited to participate in the study. If the patient agrees the study investigator will guide the patient through the informed consent process. All enrollees will undergo a detailed informed consent process during which risks, benefits and alternatives of participation will be discussed.

In the case of diminished or altered capacity, the assessment of the subject's decision making capacity will be made by the treating Stroke Neurologist. If the subject is deemed incapable of making his or her own health-care decision, a legally authorized representative (LAR) may be assigned. If the patient is awake, alert, and oriented and demonstrates appropriate cognitive and communicative abilities as determined by the interviewing/treating physician, the patient will be deemed to have the appropriate capacity to consent, as defined in the North Shore University Hospital Policies and Procedures Manual, Informed Consent, Policy No. 100.23, Pg 3.

If the patient is deemed not to have the appropriate capacity to consent at the time of interview and a next of kin (NOK; spouse, adult child, parent, adult sibling, other relative) is available, that individual will be deemed the LAR (see North Shore University Hospital Policies and Procedures Manual, Informed Consent, Policy No. 100.23, Pg 4). Deeming a NOK as the LAR is necessary since stroke patients frequently lack capacity immediately following a stroke and because these patients are at high risk of recurrent stroke. This risk is especially high and relevant for patients who have undiagnosed atrial fibrillation, and who, therefore, would not be on appropriate antithrombotic therapy for secondary stroke prevention.

If the patient's decisional capacity is impaired, but the treating Stroke Neurologist deems the patient capable of assenting to study participation, then the patient and their LAR will be included in the informed consent process. In this case, enrollment will proceed only if the patient assents and the LAR gives consent to study enrollment. In the event that the participant is decisionally impaired to the point where both consent and assent cannot be obtained for the study, consent will be obtained from the LAR. In any other situation where the patient is deemed not to have the capacity to consent, the decision will be made not to enroll the patient in the study. All clarifications will be handled directly by the principal investigator.

The use of an LAR will be documented on the data collection form. Enrollment into the study after the informed consent process is completed will be documented in the medical record. In the event that an LAR consents on behalf of a patient lacking capacity, continuing informed consent will be obtained if the treating physician or study physician determines that the patient regains the capacity to consent during the course of the protocol. Assessment for regaining capacity to participate in the informed consent process will be performed at each study visit.

STATISTICAL ANALYSIS

Descriptive statistics (mean \pm standard deviation and median for continuous data such as age; frequencies and percentages for categorical data such as gender, medical history, etc) will be calculated for baseline patient characteristics.

The incidence of AF will be calculated as the total number of patients with AF in 12 months divided by the total number of patients studied, along with the corresponding 95% confidence interval.

The analysis of “time-to-first-documented-AF” will be accomplished by applying standard methods of survival analysis, i.e., computing the Kaplan-Meier¹ product limit curves. In cases where the endpoint event, “AF”, had not yet occurred, 12 months will be used and considered ‘censored’. The median rate will be obtained from the Kaplan-Meier/Product-Limit Estimates and its corresponding 95% confidence interval will be computed, using Greenwood’s formula² to calculate the standard error.

Univariate analyses will be performed to screen for potential predictors of AF. The chi-square test or Fisher’s exact test, as deemed appropriate, will be used to compare AF patients with non-AF patients for categorical variables and the two-sample t-test or Mann-Whitney test for continuous data.

As a possible secondary analysis, those factors that appear to be associated with AF in the univariate analysis ($p < 0.25$) will be included in a logistic regression model. Backwards selection will be used to remove variables that do not significantly contribute information to the model, given other factors included in the model. A receiver operating characteristic (ROC) curve will be constructed to look at the final model’s ability to predict AF. A numerical measure of the accuracy of the model will be obtained from the area under the curve (AUC), where an area of 1.0 signifies near perfect accuracy, while an area of less than 0.5 indicates that the model is worse than just flipping a coin. The following will be used as a guide for AUC:

0.9-1.0	Excellent
0.8-0.9	Very good
0.7-0.8	Good
0.6-0.7	Average
0.5-0.6	Poor

The Hosmer and Lemeshow Goodness-of-Fit test will also be used to test how well the model fits the data.

Unless otherwise specified, a result will be considered statistically significant at the $p < 0.05$ level of significance. All analyses will be performed using SAS (SAS Institute, Cary, NC).

DISCOMFORTS AND RISKS

The risks to the subjects are low in relation to the anticipated benefits of detecting paroxysmal AF, which will change the strategy of secondary stroke prevention from antiplatelet to anticoagulation

¹ Lee, E. T. (1992), *Statistical Methods for Survival Data Analysis*, Second Edition, New York: John Wiley & Sons.

² Greenwood M. (1926), *The Errors of Sampling of the Survivorship Table*, Vol. 33 of Reports on Public Health and Medical Subjects. London: Her Majesty’s Stationery Office

therapy and reduce the annual risk of recurrent stroke by allowing earlier treatment once AF is detected. The procedural risks have been reviewed under the section (“Design: Reveal LINQ Insertable Cardiac Monitor)

Potential risks and discomforts associated with receiving a Reveal LINQ ICM device include:

- Local site bleeding
- Temporary discomfort at the implant site.
- Rejection of the device by the body, which may have symptoms such as swelling, redness, or other irritation at or near the implant site
- Movement of the device from its original implant location
- Allergy reactions to the device
- Infection at the site of the implant
- Cosmetic complications at the site of device placement
- Inability of the device to capture some particular arrhythmias
- Risks associated with local anesthesia, including hypersensitivity and allergic reactions to the anesthetic agent, injection site bleeding or infection

POTENTIAL BENEFITS

The presence of paroxysmal AF in non-cryptogenic stroke patients, who have a presumed stroke etiology other than AF, will help in identifying a stroke etiology that carries a high risk for recurrent stroke and will most likely result in a significant management adjustment in terms of long-term anticoagulation for secondary stroke prevention. It is well accepted that long-term anticoagulation of ischemic stroke and TIA patients with paroxysmal AF decreases the incidence of recurrent stroke.

DISCONTINUATION OF STUDY/SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time without prejudice. The site investigator may withdraw the subject from the study and remove the implantable device in the event of intercurrent illness, adverse events, other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, protocol violation or other administrative reasons. Participants who regain decisional capacity and do not want the device in their body will also be withdrawn from the study and the implantable device will be removed. This will be discussed in detail during the enrollment and consenting process.

DATA AND SAFETY MONITORING

The Principal Investigator will be tasked with ensuring the data and safety of the study. This review will occur every 6 months after the first subject is enrolled. The PI, along designated co-investigators, will review the incoming data to determine if aspects of the study need to be changed or stopped. In addition, they will review any and all deviations, adverse events and unanticipated problems that may occur to determine their relatedness to the study, their severity, and whether they require study changes. Adverse events include any device related complications or interval new medical conditions. Adverse events will be considered severe if they require hospitalization or are life threatening, or result from a malfunctioning of the study device. In addition, any unanticipated problems will be reported to the IRB and the LINQ manufacturer as per their specific reporting requirements.

CONFIDENTIALITY

The data will be collected and stored on the “shared drive” that can be accessed by the investigators and research coordinators through a login and password on the NSLIJHS server. All PHI will be de-identified in the data set and will not be shared with any outside facility.

FUNDING

Funding for this research study is provided by Medtronic, Inc. The funding is used to support the activities of the Departments of Neurology and Cardiology to pay back the Departments for the costs of the study personnel. Medtronic may potentially donate up to 10 Reveal LINQ devices if the patient need arises. However, Medtronic is not donating all of the devices for this study. As the Reveal LINQ device is being used within its FDA indications, the charge for the device will be billed to the patient’s insurance carrier.

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APPENDICES:

Table 1. Recent Studies Comparing Different Methods of Evaluation for Detection of Silent Atrial Fibrillation in Patients After Cerebrovascular Event Sorted in Ascending Order According to Duration of Recording

Authors	Publication Year	Method of Recording	Sample Size	Characteristics	Approximate Recording Duration (hour)	AF Detection Rate (%) and 95% CI
Barthélémy et al ²⁷	2003	Holter	60	s/p	24	10 (4–21)‡
Jabaudon et al ²⁹	2004	Holter	169	s/p	24	5 (2–10)
Koudstaal et al ³⁰	1986	Holter	100	s/p	24	5 (2–11)‡
Hornig et al ³⁸	1996	Holter	300	s/p	24	3 (2–6)‡
Schuchert et al ³⁹	1999	Holter	82	s/p	24	1 (0–7)‡
Schaer et al ⁴⁰	2009	Holter	241	s/p	24	0 (0–2)‡
Schaer et al ⁴¹	2004	Holter	425	s/p	24	2 (1–4)‡
Shafiqat et al ⁴²	2004	Holter	465	s/p	24	2 (1–5)‡
Lazzaro et al ⁴³	2010	Holter	133	s/p	30	6 (3–12)
Eljowich et al ⁹	2009	CICT	218	s/p	48	1 (0–4)‡
Rizos et al ³⁵	2012	CEM	496	s/p	64	8 (6–11)‡
Barthélémy et al ²⁷	2003	ELR	60	s/p	70	15 (7–27)‡
Rem et al ⁴⁴	1985	CICT	184	s/p	72	3 (1–7)‡
Schuchert et al ³⁹	1999	Holter	82	s/p	72	6 (2–14)‡
Kallmünzer et al ⁴⁵	2012	CEM	501	s/p	73	16 (13–20)‡
Lazzaro et al ⁴³	2010	CICT	133	s/p	74	0 (0–3)
Stahrenberg et al ⁴⁶	2010	Holter	224	s/p	168	13 (8–18)‡
Ritter et al ⁴⁷	2013	Holter	60	s/p	168	2 (0–9)‡
Higgins et al ⁴⁸	2013	Holter	50	m/p	336	8 (2–19)
Sposato et al ⁴⁹	2012	CICT	155	s/p	480	14 (9–20)‡
Wallmann et al ⁵⁰	2007	ELR	127	s/p	504	14 (9–21)‡
Tayal et al ⁵¹	2008	MCOT	56	s/r	504	23 (13–36)‡
Kamel et al ⁵²	2013	MCOT	50	s/p	504	0 (0–17)
Eljowich et al ⁹	2009	MCOT	20	s/r	720	20 (6–44)‡
Flint et al ⁵³	2012	MCOT	239	m/p	720	12 (9–17)
Cotter et al ⁵⁴	2013	ILR	54	s/p	1152*	26 (13–38)
Jabaudon et al ²⁹	2004	ELR	88	s/p	1320	6 (2–13)
Ritter et al ⁴⁷	2013	ILR	60	s/p	1536	17 (7–26)
Etgen et al ⁵⁵	2013	ILR	393	s/p	8760	27 (11–50)
Ziegler et al ¹⁰	2010	ILR (ICD)	163	m/r†	9360	28 (21–35)‡
Dion et al ¹¹	2010	ILR	24	s/p	10440	0 (0–14)‡

