Stroke is a leading cause of long-term severe disability among adults and the fifth leading cause of death in the United States. Approximately 6.6 million Americans 20 years of age or older experience a stroke, affecting approximately 795,000 people each year. It is estimated that 87 percent of strokes are ischemic, and 25 to 40 percent of these occurrences are deemed cryptogenic, or a stroke of unknown cause. A large portion of these cryptogenic patients may have asymptomatic or undiagnosed atrial fibrillation (AF), and yet many patients do not receive additional cardiac monitoring following their initial stroke hospitalization. It is important to determine stroke etiology so that these patients are not at risk for additional strokes or even death.

At Cone Health Stroke Center in Greensboro, NC we developed a Cryptogenic Stroke Pathway that brings together an interdisciplinary team of neurologists, electrophysiologists, cardiologists, and stroke care health professionals to help provide more rigorous and integrated care with consistent follow-up and treatment so that every stroke patient receives the best possible outcome.

Implementing a Cryptogenic Stroke Pathway may help reduce recurrent strokes and improve outcomes for stroke patients.

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Atrial Fibrillation, Cryptogenic Stroke, and Long-Term Cardiac Monitoring

Atrial fibrillation is one of the most common and under-treated heart rhythm disorders in America and a major risk factor for stroke. It is important to determine if AF causes the stroke because oral anticoagulant treatment can help reduce or eliminate the condition, offering a 65 percent relative risk reduction for stroke.

The likelihood of developing AF increases with age and with additional risk factors, including hypertension, diabetes, cardiac disease, sleep apnea, and alcohol abuse. Once diagnosed with AF, a patient is three to five times more likely to have a stroke. An AF-related ischemic stroke is two times more likely to be fatal than a non-AF stroke.

Diagnosing AF can be challenging because episodes can be asymptomatic and intermittent. Historically, holter monitors and short-term event monitors (worn for less than 30 days) have been the only way to monitor patients for AF after discharge following a cryptogenic stroke. In these cases, patients would be admitted with stroke symptoms, and then would be diagnosed with an acute ischemic stroke. There would be suspicion of an embolic source based on stroke location.

PRACTICAL POINTERS

- Atrial fibrillation detection in cryptogenic stroke patients increases over time with prolonged monitoring.
- An atrial fibrillation diagnosis can alter treatment and will prevent recurrent stroke.
- Electrophysiology, cardiology, and neurology involvement in process development ensures a high rate of atrial fibrillation detection.
- A Cryptogenic Stroke Pathway leads to provision of exemplary stroke care.
or history, and an exhaustive workup would be completed, including a transesophageal echocardiogram (TEE) to look for the cardioembolic source. At discharge, the patient would be scheduled to receive a cardiac monitor with the option to receive it in the mail or during a subsequent in-office visit for placement and instruction. In these instances, a high percentage of patients would refuse monitoring due to a high copay or would not show for their follow-up appointment because they were feeling better. As a result, further cardiac evaluation for AF as the etiology of the stroke was often lost. For patients who used a short-term monitor as instructed, AF would still not have been detected in many patients as the median time to AF detection in cryptogenic stroke patients is 84 days.

As evidenced in CRYSTAL AF trial, continuous monitoring beyond 30 days with the Reveal Insertable Cardiac Monitor is superior to standard medical care for AF detection in patients with cryptogenic stroke. Key findings included:

- 7.3 percent more patients with AF detected at one year than standard medical care
- 30 percent more AF detected at three years versus three percent for standard medical care
- 97 percent of patients with AF were prescribed oral anticoagulants.

The clinical impact of these findings is that short-term monitoring is not sufficient for AF detection in cryptogenic stroke patients; however, AF detection increased overtime with long-term cardiac monitoring. Thus, to increase the chance of detecting AF, it is recommended that an insertable cardiac monitor be implanted to continuously monitor the heart's rhythm for up to three years.

**Cone Health Experience**

The stroke neurology and electrophysiology departments worked together to create a Cryptogenic Stroke Protocol in which the Reveal LINQ Insertable Cardiac Monitor was implanted in 95 patients from March 2014 through February 2015. Of the patients observed, there was a significant increase in AF detection beyond 30 days of monitoring, which led to a change from antiplatelet therapy to anticoagulation in most patients, thereby increasing secondary stroke prevention and decreasing stroke recurrence:

- Average age was 68.3 years with 57 percent of patients female and an average CHA2DS2-VASc score of 4.
- 18 patients (18.9 percent) were diagnosed with AF, and antiplatelet treatment was changed to anticoagulation in 17 of 18 patients within 3.8 +/- 2.9 days.
- Of the patients with an AF detection, all experienced episodes that lasted six minutes or more on one day.
- Median time from index event to device insertion was six days, with a mean time from implantation to AF detection of 50.875 days.
- Comparing CRYSTAL AF results with our facility results, we found more AF during the same period of time.

**Why Establish a Cryptogenic Stroke Pathway?**

Survivors of transient ischemic attack (TIA) or stroke are at an increased risk for another stroke. As caregivers, our goal is to reduce the risk of recurrent stroke. Establishing a Cryptogenic Stroke Pathway can help to detect and treat AF in order to significantly reduce a patient’s risk for another stroke, and also bring together all healthcare professionals involved to ensure a thorough standard of care.

Through a Cryptogenic Stroke Pathway, hospitals can provide an underserved patient population a better risk reduction strategy to prevent a secondary stroke, establish cross-functional healthcare professional relationships to ensure integrated care delivery, ensure multidisciplinary stroke care involving both neurological and cardiovascular care, and enhance a hospital’s reputation in providing exemplary stroke care.

To define our cryptogenic stroke patients, we used criteria similar to those used for the clinical definition in the RESPECT-ESUS Study. Inclusion Criteria include:

- 60 years or 50-59 plus at least one additional risk factor for stroke
- Acute ischemic non-lacunar stroke seen on MRI or CT.
- Lacunar stroke > 1.5 cm
- Arterial or cervical imaging extra-cranial or intracranial atherosclerosis without luminal stenosis greater than 50 percent
- AF not seen on telemetry.
Exclusion Criteria include:
- mRS > 4 at time of stroke or inability to swallow medications
- Major risk cardioembolic source of embolism
- Other indication for anticoagulation
- History of AF
- Other specific stroke etiology
- Primary intracerebral hemorrhage
- Other conditions associated with increased risk of bleeding
- History of symptomatic nontraumatic intracranial hemorrhage
- Renal impairment with CrCl < 30
- Hypersensitivity or known contraindication to aspirin or anticoagulants.

Once the Stroke Team ensures the stroke work-up is complete and deems the patient to have had a cryptogenic stroke, the following processes occur:
- Cardiology performs the TEE
- Electrophysiology is consulted for patient assessment prior to Reveal LINQ insertion
- If the TEE is unrevealing for embolic source, electrophysiology then inserts the Reveal LINQ and instructs the patient and family with educational follow up by a registered nurse and device representative
- The patient is discharged home with a patient monitor, and a planned wound follow-up in the device clinic is scheduled 10 days after inpatient implantation
- During follow-up, device transmissions are verified. Daily monitoring is performed by the device clinic
- The physician is notified within four hours of AF detection. The stroke neurology team advises on the preferred oral anticoagulant prior to discharge; and anticoagulation is prescribed and monitored by the cardiology team
- The cryptogenic stroke care team convenes on a regular basis to assess processes, and revises as indicated.

Putting a Cryptogenic Stroke Pathway into Practice

Prior to developing a Cryptogenic Stroke Pathway, one important step to take is to determine how cryptogenic stroke is defined in your hospital; then, consider these key insights to help ensure success in your pathway program:

- Identify Key Players in the Care Continuum—Determine the stroke champions and align on the multidisciplinary team. Your stroke team or the primary service caring for stroke patients is the first place to start.
- Protocol Alignment—Make sure all key stakeholders agree on a pathway and education plan. Key questions to align on can include: If there is a stroke protocol, do you currently have a Cryptogenic Stroke Pathway/protocol? What do you do if stroke etiology is not found? Is it included in your treatment algorithm? Then, what is the next step: Do you pursue a further work-up in the hospital or in the outpatient setting?

- Establish a plan for transition of care and long-term follow-up—This can be achieved by: determining who will own and drive the process (e.g., stroke team, neurology, cardiology); assessing if your hospital has the infrastructure and staff to support the program, and other development needs or logistics to support your plan; then, identify if this could be a quality improvement project or a process improvement project.

- Measuring Success—Align on key metrics to measure success and improvement in your pathway. For example, are there any data you would like to collect? What is your definition of success? Once a patient is deemed cryptogenic, what is the multi-disciplinary pathway, transition of care and follow-up plan in place for that patient?

It is vital that neurologists, electrophysiologists, and cardiologists work together in managing, diagnosing, and treating cryptogenic stroke patients. A vascular trained neurology staff helps to ensure appropriate patient selection for insertable cardiac monitors in high-risk patients. Based on our findings, we recommend clinicians implement a Cryptogenic Stroke Pathway at their hospital to help reduce recurrent strokes and improve outcomes for their stroke patients.

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