THE LINQ BETWEEN CRYPTOGENIC STROKE AND AF

Atrial fibrillation detection and treatment matters for improved stroke outcomes
CRYPTOGENIC STROKE IS A CHALLENGE

691,650
Americans experience ischemic strokes every year.¹

25%
Despite a comprehensive diagnostic workup, about 25% of ischemic stroke patients remain cryptogenic.²

Up to 30% of patients with cryptogenic stroke may have previously undetected paroxysmal AF.³

1 in 4
Stroke survivors will experience another stroke within 5 years.⁴
AF Detection and Treatment Matters

Detection of AF in Cryptogenic Stroke Patients Changes Treatment

- **Cryptogenic stroke**
  - Atrial Fibrillation
  - Anticoagulation*5-7 or other management
  - No Atrial Fibrillation
  - Antiplatelet until AF is identified*5-7

*If the patient is an appropriate candidate.

RE-SPECT ESUS and NAVIGATE ESUS trial results highlight the importance of detecting AF and tailoring treatment for cryptogenic stroke or ESUS patients.

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAVIGATE ESUS</td>
<td>NEGATIVE*&lt;sup&gt;8&lt;/sup&gt; Increase in bleeding in the rivaroxaban arm</td>
</tr>
<tr>
<td>RE-SPECT ESUS</td>
<td>FAILED PRIMARY OUTCOME*&lt;sup&gt;9&lt;/sup&gt; Dabigatran was not superior to ASA</td>
</tr>
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</table>

5x
There is a 5-fold increase in ischemic stroke risk for AF patients.<sup>10</sup>

2x
more likely for AF-related ischemic stroke to be fatal than non-AF stroke.<sup>11</sup>

79%
of first AF episodes are asymptomatic at 12 months.<sup>3</sup>
Atrial fibrillation after cryptogenic stroke was most often asymptomatic and paroxysmal and thus unlikely to be detected by strategies based on symptom-driven monitoring or intermittent short-term recordings.


**THE CRYSTAL-AF STUDY DEMONSTRATES THE SUPERIORITY OF ICM FOR AF DETECTION**

As published in the *New England Journal of Medicine*³

**CRYSTAL-AF study results**

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Atrial Fibrillation Detected (% of patients)</th>
<th>Hazard ratio, 8.8 (95% CI, 3.5–22.2)</th>
<th>P &lt; 0.001 by log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reveal™ ICM</td>
<td>8.9%</td>
<td>6.4X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.4%</td>
<td>7.3X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- **30%** AF detected at 3 years vs. 3% for SOC.
- Multiple studies show that short-term monitoring is NOT sufficient for AF detection in cryptogenic stroke.¹²,¹³

“"Atrial fibrillation after cryptogenic stroke was most often asymptomatic and paroxysmal and thus unlikely to be detected by strategies based on symptom-driven monitoring or intermittent short-term recordings.”

30-DAY CARDIAC MONITORING IS NOT ENOUGH

Short-term and intermediate-term cardiac monitoring may miss many patients with paroxysmal AF³

Considerations for monitoring of cryptogenic stroke patients:

Yield

88%
of patients who had AF would have been missed if only monitored for 30 days.*³,14

Patient Outcomes

55%
lower stroke recurrence for cryptogenic stroke/TIA patients when AF is detected by an ICM and treated.¹⁵

Patient Experience

< 5%
of ischemic stroke patients who initially receive short-term external cardiac monitoring (up to 30 days) go on to receive an ICM.¹⁶

*Based on Kaplan-Meier estimates.
Study objective: Evaluate the impact of prolonged cardiac rhythm monitoring (PCM) on secondary stroke prevention using data from available to date randomized clinical trials (RCTs) and observational studies.

The above forest plot represents the differences between prolonged (favors PCM) and conventional (favors non-PCM) cardiac rhythm monitoring in the risk of recurrent stroke.

### The meta-analysis included 4 studies for a total of 1,102 patients:

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Type</th>
<th>Conventional Cardiac Monitor Method</th>
<th>Total Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown ESUS-AF</td>
<td>OS</td>
<td>30-day noninvasive ambulatory ECG monitoring</td>
<td>117</td>
</tr>
<tr>
<td>CRYSTAL-AF</td>
<td>RCT</td>
<td>ECG monitoring at scheduled and unscheduled visits at the discretion of the site investigator</td>
<td>441</td>
</tr>
<tr>
<td>FIND-AF</td>
<td>RCT</td>
<td>At least 2 hours ECG monitoring</td>
<td>398</td>
</tr>
<tr>
<td>Rodriguez-Campello, et al.</td>
<td>OS</td>
<td>24–36 hours ECG monitoring</td>
<td>146</td>
</tr>
</tbody>
</table>
Patients who underwent PCM compared to conventional cardiac monitoring show:

- **2.5x** Increased incidence of AF detection.\(^{15}\)
- **2.1x** Increased incidence of anticoagulant initiation.\(^{15}\)
- **55%** Decreased risk of recurrent stroke.\(^{15}\)

The use of prolonged cardiac monitoring has a potential impact on secondary stroke prevention, as patients with cryptogenic IS/TIA undergoing PCM had higher rates of AF detection and anticoagulant initiation and lower stroke recurrence.\(^{15}\)
INFORM YOUR CLINICAL DECISIONS WITH THE REVEAL LINQ™ ICM SYSTEM

Up to 3 YEARS of continuous cardiac monitoring

The Reveal LINQ insertable cardiac monitoring system transforms your ability to diagnose atrial fibrillation with its proven AF detection algorithm.

The world’s smallest, most accurate insertable cardiac monitor17,18

1.5T & 3T MRI CONDITIONAL

No post-insertion wait time or patient positioning restrictions*

99.7% AF episode detection accuracy

Industry’s highest AF episode detection accuracy rate.19,20

*Reveal LINQ has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use. Please see the Reveal ICM clinician manual or MRI technical manual for more details.
Patients are more satisfied with ICMs than external wearable monitors\textsuperscript{21}

Percentage of patients “very satisfied” with monitoring strategy was higher in ILR vs. ELR arm (21% vs. 10%)\textsuperscript{21}

- The Reveal LINQ ICM is inserted just under the skin of the patient’s chest in a short and simple procedure.
- The heart monitor is one-third the size of a AAA battery (1.2 cc) and is not visible in most patients.
- Use of the Reveal LINQ system doesn’t require a change in daily activities.
2019 AHA/ACC/HRS Atrial Fibrillation Guidelines

Recommends use of implantable loop recorder (ILR) in patients with cryptogenic stroke (Class IIa, LOE B-R)\(^5\)

<table>
<thead>
<tr>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF.</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>COR</th>
<th>LOE</th>
</tr>
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<tr>
<td>IIa*</td>
<td>B-R</td>
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2016 ESC AF Guidelines

ICM recommendation for cryptogenic stroke (Class IIa, LOE B\(^1\))\(^6\)

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<td>In stroke patients, additional ECG monitoring by long-term, noninvasive ECG monitors or implanted loop recorders should be considered to document silent AF.</td>
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\(^5\)Class IIa is Benefit >> Risk and LOE B-R is moderate quality of evidence from 1 or more RCTs or meta-analysis of moderate-quality RCTs.

\(^6\)Endorsed by the European Stroke Organization (ESO), Class IIa is weight of evidence/opinion is in favor of usefulness/efficacy. LOE B is data derived from a single randomized clinical trial or large nonrandomized studies.
WHEN TO CONSIDER LOOKING FOR AF IN CRYPTOGENIC STROKE PATIENTS

Reveal LINQ ICM Indications*

▪ Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
▪ Patients who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain, that may suggest a cardiac arrhythmia

Appropriate

▪ Stroke detected by CT or MRI that is not lacunar
▪ Absence of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis in arteries supplying the area of ischaemia
▪ No major-risk cardioembolic source of embolism
▪ No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug misuse)
▪ First event — stroke or high-risk TIA
▪ CHADS\textsubscript{2} score ≥ 2 (minimal risk factors)

Not Appropriate

▪ Indication for chronic anticoagulation or already on anticoagulation
▪ Patients with a relative contraindication for long-term anticoagulation and not appropriate for LAA closure device

*See full brief statement for complete indications for use.
\textsuperscript{1}ABCD\textsubscript{2} Score > 5.

Pathway based on the consensus of the Cryptogenic Stroke Pathway steering committee. February 2016.
Many cryptogenic stroke patients are lost to follow-up. Pathways for transition of care and follow-up help to ensure these patients receive better care.
Why establish a cryptogenic stroke pathway?

Establishing a monitoring pathway to detect and treat AF can significantly reduce a patient’s risk for another stroke. When developing a cryptogenic stroke pathway, it is important to include all stakeholders involved in the care of the patient.

PATHWAY TIPS

- Less than 5% of ischemic stroke patients who initially receive short-term external cardiac monitoring (up to 30 days) go on to receive an ICM.\textsuperscript{16}

- Ischemic stroke patients seen by an electrophysiologist are 4x more likely to receive an ICM than a patient seen by a practitioner from a different specialty.\textsuperscript{16}

- The diagnostic yield of 30 days of monitoring is likely to be limited. Data suggest a rationale for proceeding directly to ILR prior to hospital discharge in cryptogenic stroke patients.\textsuperscript{23}
References


Brief Statement

Indications

Reveal LINQ™ LNQ11 Insertable Cardiac Monitor and Patient Assistant

The Reveal LINQ insertable cardiac monitor is an implantable patient-activated and automatically activated monitoring system that records subcutaneous ECG and is indicated in the following cases:

- Patients with clinical syndromes or situations at increased risk of cardiac arrhythmias
- Patients who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain, that may suggest a cardiac arrhythmia

This device has not specifically been tested for pediatric use.

Patient Assistant

The Patient Assistant is intended for unsupervised patient use away from a hospital or clinic. The Patient Assistant activates the data management feature in the Reveal™ insertable cardiac monitor to initiate recording of cardiac event data in the implanted device memory.

Contraindications

There are no known contraindications for the implant of the Reveal LINQ insertable cardiac monitor. However, the patient's particular medical condition may dictate whether or not a subcutaneous, chronically implanted device can be tolerated.

Warnings/Precautions

Reveal LINQ LNQ11 Insertable Cardiac Monitor

Patients with the Reveal LINQ insertable cardiac monitor should avoid sources of diathermy, high sources of radiation, electrosurgical cautery, external defibrillation, lithotripsy, therapeutic ultrasound, and radiofrequency ablation to avoid electrical reset of the device, and/or inappropriate sensing as described in the medical procedure and EMI precautions manual. MRI scans should be performed only in a specified MR environment under specified conditions as described in the Reveal LINQ MRI Technical Manual.

Patient Assistant

Operation of the Patient Assistant near sources of electromagnetic interference, such as cellular phones, computer monitors, etc., may adversely affect the performance of this device.

Potential Complications

Potential complications include, but are not limited to, device rejection phenomena (including local tissue reaction), device migration, infection, and erosion through the skin.

Medtronic MyCareLink™ Patient Monitor, Medtronic CareLink™ Network, and CareLink™ Mobile Application

Intended Use

The Medtronic MyCareLink patient monitor and CareLink network are indicated for use in the transfer of patient data from some Medtronic implantable cardiac devices based on physician instructions and as described in the product manual. The CareLink mobile application is intended to provide current CareLink network customers access to CareLink network data via a mobile device for their convenience. The CareLink mobile application is not replacing the full workstation, but can be used to review patient data when a physician does not have access to a workstation. These products are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. CareLink network availability and mobile device accessibility may be unavailable at times due to maintenance or updates, or due to coverage being unavailable in your area. Mobile device access to the internet is required and subject to coverage availability. Standard text message rates apply.

Contraindications

There are no known contraindications.

Warnings and Precautions

The MyCareLink patient monitor must only be used for interrogating compatible Medtronic implantable devices.

See the device manual for detailed information regarding the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1-800-328-2518 and/or consult the Medtronic website at medtronic.com.

Caution: Federal law (USA) restricts these devices to sale by or on the order of a physician.
CRYSTAL-AF study found that continuous monitoring with Reveal LINQ ICM is superior to standard monitoring for the detection of AF in cryptogenic stroke patients.³

55% Lower stroke recurrence in patients with cryptogenic stroke/TIA undergoing prolonged vs. conventional cardiac monitoring.¹⁶

30% AF DETECTED AT 3 YEARS WITH ICM vs. 3% for SOC³

**SHORT-TERM MONITORING IS NOT ENOUGH**

88% of patients who had AF would have been missed if only monitored for 30 days*³

**PROLONGED CARDIAC MONITORING AND SECONDARY STROKE PREVENTION**

SUPERIOR ACCURACY

Industry’s highest AF episode detection accuracy rate.¹⁹,²⁰