STROKE AS A HEALTHCARE ISSUE

- Each year, approximately 800,000 Americans experience a new or recurrent stroke.¹
- Ischemic stroke accounts for 87% of strokes overall, with the remaining 13% classified as hemorrhagic in origin.¹
- Stroke is the 5th most common cause of death in the United States; higher than Alzheimer’s and approximately twice the size of diabetes.²
- On average, in 2015, every 3 minutes, 45 seconds, someone died of a stroke.³
- Direct medical expenses average $44,752 per stroke in the 90-day period after the event.⁴ Long-term annual costs average $24,000-$102,000 (mean $64,629), depending on stroke severity.⁵

Despite a comprehensive diagnostic workup, about 30% of stroke patients remain cryptogenic.1-6

Most cryptogenic stroke patients receive antiplatelet for secondary prevention.7

Long-term monitoring reveals AF in ~ 30% of cryptogenic stroke patients.8

This enables treatment change from antiplatelet to oral anticoagulation.

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## CRYPTOGENIC STROKE DIAGNOSIS

### Cryptogenic Stroke

#### Cryptogenic stroke possible etiologies
- Substenotic atherosclerosis
- Aortic arch disease
- Paradoxical embolism through a PFO
- Paroxysmal occult atrial fibrillation
- Atrial cardiopathy and LAA dysfunction

#### Cryptogenic stroke includes
- Incomplete evaluation
- No cause found from assessment
- Multiple possible etiologies

#### ESUS is a subgroup of cryptogenic stroke
- Non-lacunar ischemic stroke detected by CT or MRI
- Absence of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis in areas supplying the area of ischemia
- No major-risk cardioembolic source of embolism
- No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug abuse)

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SECONDARY STROKE PREVENTION
AF DETECTION AND TREATMENT MATTERS

- There is a 5-fold increase in ischemic stroke risk for AF patients.¹
- Ischemic stroke associated with AF is twice as likely to be fatal as non-AF stroke.²
- There is a 67% decrease in AF stroke risk with oral anticoagulants.³
- 1 in 4 stroke survivors will experience another stroke within 5 years.⁴

CURRENT MEDICAL PARADIGM

The detection of AF in this patient population changes the medical management for secondary stroke prevention.

*If the patient is an appropriate candidate.

1 January CT, et al. Heart Rhythm. Published online January 28, 2019.
## ESUS OUTCOMES

<table>
<thead>
<tr>
<th>Study Drugs</th>
<th>Number of Required Outcomes</th>
<th>Sample Size</th>
<th>Trial Duration (months)</th>
<th>Primary Efficacy Outcome</th>
<th>Outcome</th>
<th>Messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAVIGATE ESUS¹</td>
<td>Rivaroxaban 15 OD vs. ASA 100 mg</td>
<td>555</td>
<td>7,121</td>
<td>24 Stopped early due to futility</td>
<td>Stroke and systemic embolism</td>
<td>Increase in bleeding in the rivaroxaban arm NEGATIVE¹</td>
</tr>
<tr>
<td>Bayer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-SPECT ESUS²</td>
<td>Dabigatran 150/110 BID vs. ASA 100 mg</td>
<td>353</td>
<td>5,390</td>
<td>36</td>
<td>Stroke</td>
<td>Dabigatran was not superior to ASA FAILED PRIMARY OUTCOME²</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


In ESUS patients, dabigatran was not superior to aspirin for prevention of recurrent stroke.²

There is no proven clinical benefit of giving oral anticoagulation therapy to all ESUS patients. No evidence of clinical benefit in changing current practice for treatment for ESUS¹.² (antiplatelet therapy).
There is no proven clinical benefit of giving oral anticoagulation therapy to all ESUS patients or in changing current practice for treatment of ESUS\(^1,2\) (antiplatelet therapy).

## CONVENTIONAL MONITORING STRATEGIES

<table>
<thead>
<tr>
<th>Bedside Monitoring</th>
<th>Holter Monitor</th>
<th>Event Recorder</th>
<th>Mobile Cardiac Telemetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>During stroke unit or intensive care unit stay</td>
<td>24 hours — 2 weeks of monitoring</td>
<td>Up to 30 days of monitoring</td>
<td>Up to 30 days of monitoring</td>
</tr>
<tr>
<td>Event-triggered recording available</td>
<td>External recorder</td>
<td>Event-triggered loop recorder</td>
<td>Ambulatory event monitor</td>
</tr>
<tr>
<td>Optional storage of cardiac rhythm data</td>
<td>Saves all cardiac rhythm data</td>
<td>Relies on patient to record symptoms; not appropriate for an asymptomatic patient</td>
<td>Saves all cardiac rhythm data</td>
</tr>
<tr>
<td>High false-positive rate&lt;sup&gt;1&lt;/sup&gt;</td>
<td>73-82% patient compliance&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>42-64% patient compliance&lt;sup&gt;4,5&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Dependent on type of MCT.
ICM DEFINITION

- An insertable cardiac monitor (ICM) is a small device that is inserted subcutaneously in the left pre-pectoral region to continuously monitor a patient’s ECG and other physiological parameters.¹

- The device records cardiac information in response to automatically detected arrhythmias and patient activation.¹

- Multiple studies have evaluated the ability of ICMs to detect AF in cryptogenic stroke.²⁻¹¹

- The CRYSTAL AF randomized study showed that an insertable cardiac monitor is more effective than conventional follow-up for detecting AF in patients with cryptogenic stroke.²

¹ Reference the Reveal LINQ ICM Clinician Manual for usage parameters.
CONTINUOUS MONITORING IS SUPERIOR TO INTERMITTENT CRYSTAL AF SUB-ANALYSIS: CHOE, AM J CARDIOL 2015¹

“Intermittent rhythm monitoring would have failed to identify previously undiagnosed AF in the vast majority of CS patients.”

Simulated intermittent monitoring was compared to continuous rhythm monitoring in 168 ICM patients

Short-term Monitoring
- 24-hour
- 48-hour
- 7-day Holter
- 21-day event recorder
- 30-day event recorder

Periodic Monitoring
- Quarterly 24-hour Holter
- Quarterly 48-hour Holter
- Quarterly 7-day Holter
- Monthly 24-hour Holter

Sensitivity was low: 1.3-22.8%
Negative predictive value: 82.3-85.6%

# SUMMARY OF ICM STUDIES IN CRYPTOGENIC STROKE

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of monitoring (months)</th>
<th>Definition of AF</th>
<th>Time to Diagnosis (days)</th>
<th>AF detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritter(^1)</td>
<td>10</td>
<td>&gt; 30 seconds</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>Etgen(^2)</td>
<td>12</td>
<td>&gt; 6 minutes</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>Cotter(^3)</td>
<td>8</td>
<td>2 minutes</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>SURPRISE(^4)</td>
<td>19</td>
<td>&gt; 2 minutes</td>
<td>109</td>
<td>16</td>
</tr>
<tr>
<td>Rojo-Martinez(^5)</td>
<td>9</td>
<td>2 minutes</td>
<td>102</td>
<td>33</td>
</tr>
<tr>
<td>Ziegler(^6)</td>
<td>6</td>
<td>2 minutes</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Poli(^7)</td>
<td>12</td>
<td>≥ 2 minutes</td>
<td>105</td>
<td>33</td>
</tr>
<tr>
<td>Jorfida(^8)</td>
<td>14.5</td>
<td>&gt; 5 minutes</td>
<td>162</td>
<td>46</td>
</tr>
<tr>
<td>CRYSTAL AF(^9) (ICM arm)</td>
<td>6, 12, 36</td>
<td>&gt; 30 seconds</td>
<td>41, 84, 252</td>
<td>9, 12, 30</td>
</tr>
</tbody>
</table>

CONTENTS

STROKE FACTS

CURRENT PRACTICE FOR MONITORING & TREATMENT

EVIDENCE

REVEAL LINQ™ ICM

CONCLUSIONS

PATHWAY DEVELOPMENT

CASE STUDY
CRYSTAL AF — JUNE 2014
STUDY DESIGN AND END POINTS

- Randomized, multicenter, controlled clinical trial with 441 patients
- Compared continuous, long-term monitoring with Reveal™ XT ICM vs. conventional
- Assessment at scheduled and unscheduled visits
- ECG monitoring performed at the discretion of the site investigator

**PRIMARY END POINT**
- Time to first detection of AF at 6 months of follow-up

**SECONDARY END POINT**
- Time to first detection of AF at 12 months
- Recurrent stroke or TIA
- Change in use of oral anticoagulation therapy

CRYSTAL AF: STUDY POPULATION

Patients were enrolled 447  Underwent randomization 441

Excluded 6
- 4 did not meet eligibility criteria
- 2 withdrew consent

Assigned to ICM 221
- 208 had ICM inserted
- 13 did not have ICM inserted

Crossed over to control 12

Exited the study 12
- 3 died
- 1 lost to follow-up
- 5 withdrew
- 3 withdrawn by investigator

Included in the intention-to-treat analysis 221

Assigned to control 220
- 220 received standard of care

Crossed over to ICM 6

Exited the study 13
- 2 died
- 1 lost to follow-up
- 7 withdrew
- 3 withdrawn by investigator

Included in the intention-to-treat analysis 220

CRYSTAL AF: RIGOROUS INCLUSION CRITERIA
PATIENTS WERE ONLY CATEGORIZED WITH CRYPTOGENIC STROKE AFTER EXTENSIVE DIAGNOSTIC TESTING

<table>
<thead>
<tr>
<th>Age 40-55 years</th>
<th>Age ≥ 55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diagnosis of stroke or TIA occurring within previous 90 days</td>
<td>• Ultrasonography of cervical arteries or transcranial Doppler ultrasonography of intracranial arteries allowed in place of MRA or CTA for patients aged ≥ 55 years</td>
</tr>
<tr>
<td>• Stroke was classified as cryptogenic after extensive testing:</td>
<td>• Magnetic resonance angiography, computerized tomography angiography, or catheter angiography of head and neck</td>
</tr>
<tr>
<td>• 12-lead ECG</td>
<td></td>
</tr>
<tr>
<td>• ≥ 24 hours of ECG monitoring</td>
<td></td>
</tr>
<tr>
<td>• TEE</td>
<td></td>
</tr>
<tr>
<td>• Screening for thrombophilic states</td>
<td></td>
</tr>
</tbody>
</table>

CRYS TAL AF: BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Male</th>
<th>White</th>
<th>Patent Foramen Ovale</th>
<th>Index Event STROKE</th>
<th>Index Event TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICM N = 221</td>
<td>61.6 ± 11.4</td>
<td>64.3%</td>
<td>87.8%</td>
<td>23.5%</td>
<td>90.5%</td>
<td>9.5%</td>
</tr>
<tr>
<td>CONTROL N = 220</td>
<td>61.4 ± 11.3</td>
<td>62.7%</td>
<td>86.8%</td>
<td>20.9%</td>
<td>91.4%</td>
<td>8.6%</td>
</tr>
<tr>
<td>P</td>
<td>0.84</td>
<td>0.77</td>
<td>0.60</td>
<td>0.57</td>
<td>0.87</td>
<td></td>
</tr>
</tbody>
</table>

ICM and control group have similar characteristics (including PFO).

CRYSTAL AF: MONITORING WITH ICM SUPERIOR TO SOC DETECTION OF AF

Primary End Point

- Time to first detection of AF at 6 months of follow-up
  - Continuous monitoring with Reveal™ ICM is superior to SoC for the detection of AF in cryptogenic stroke patients

Secondary End Point

- Time to first detection of AF at 12 months, recurrent stroke or TIA, and the change in use of oral anticoagulant drugs
  - At 12 months, 97% of patients in whom AF was detected received oral anticoagulant.1
  - 88% of patients who had AF would have been missed if only monitored for 30 days.*1

*Based on Kaplan-Meier estimates.
PREDICTORS OF AF OFFER ONLY POOR PREDICTIVE ABILITY
CRYSTAL AF SUB-ANALYSIS: THIJS, NEUROLOGY 2016¹

Increasing age and a prolonged PR-interval were independently associated with AF, but the predictive ability of these parameters was only moderate.

Parameters tested:
- Age, sex, race
- Body mass index
- Type and severity of index event
- CHADS² score
- PR-interval
- Diabetes, hypertension
- Congestive heart failure
- Patent foramen ovale
- Premature atrial contractions

REAL-WORLD VALIDATION OF CRYSTAL AF RESULTS

- 1,247 real-world cryptogenic stroke patients monitored by Reveal LINQ™ ICM
- Cryptogenic stroke diagnosis: physician’s discretion
- Follow-up: 12 months
- Diagnostic yield at 12 months: 16.3% (n = 147)
- 72% of AF patients would be missed if monitoring stopped at 30 days
- Analysis supports results of CRYSTAL AF
- Continuous monitoring for periods longer 30 days may be warranted in CS patients

DISCOVERYLINK – CRYPTOGENIC STROKE AT 2 YEARS
ZIEGLER, INT J CARDIOL. 2017

- De-identified Medtronic device database analysis at 2 years
- Follow-up: 579 ± 222 days
- AF ≥ 2 min was detected in 16.3% at 1 year and in 21.5% at 2 years (vs. 4.6% at 30 days)
- Median time to detection: 112 days
- In 74% of patients, the longest episode was > 1 hr
- In most patients with multiple AF episodes, durations increased following initial episode
- 79% of AF patients would have been missed with 30 days of monitoring

After 2 years of ICM monitoring, AF was diagnosed in 1/5 cryptogenic stroke patients (similar to CRYSTAL AF at 2 years: 21.1%).

EMBRACE & CRYSTAL AF: DIFFERENT STUDIES, DIFFERENT RESULTS

**EMBRACE**¹

**Study characteristics**
- 16 centers in Canada
- N = 575

**Two arms**
- 30-day recorder
- Standard care (24-hour Holter)

**Results:**
16.1% AF detection rate

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 55 years</td>
</tr>
<tr>
<td>Ischemic stroke or TIA within previous 6 months</td>
</tr>
<tr>
<td>Stroke classified as cryptogenic after standard workup</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of ≥ 1 episode of ECG-documented AF within 90 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of AF episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF lasting &gt; 30 seconds</td>
</tr>
</tbody>
</table>

**CRYSTAL AF**²

**Inclusion Criteria**
- Age ≥ 40 years
- Ischemic stroke or TIA within previous 90 days
- Stroke classified as cryptogenic after extensive workup

<table>
<thead>
<tr>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first detection of AF at 6 months follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of AF episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF lasting &gt; 30 seconds</td>
</tr>
</tbody>
</table>

**DIFFERENT STUDIES, DIFFERENT RESULTS**

When comparing the EMBRACE and CRYSTAL AF studies, there are notable differences in the criteria for inclusion and outcomes. Higher AF detection rates were observed in the EMBRACE study compared to CRYSTAL AF, but the reasons behind these differences are not explicitly explained in the text provided.

**Higher AF detection rates than CRYSTAL AF … why?**

**Stroke workup in EMBRACE was not as rigorous**
- TEE or intracranial vascular imaging not required
- Less ECG monitoring prior to study enrollment

**Average age was significantly different**
- 73 years in EMBRACE vs. 61 years in CRYSTAL AF

**AF duration criteria were different in intervention arm**
- 30 seconds in EMBRACE vs. 2 minutes in CRYSTAL AF

---

WHY EXTENDED MONITORING?
SHORT- AND INTERMEDIATE-TERM MONITORING MAY MISS MANY PATIENTS WITH PAROXYSMAL AF

79% of first AF episodes were asymptomatic at 12 months

88% of patients who had AF would have been missed if only monitored for 30 days*1

*Based on Kaplan-Meier estimates.
IMPACT OF PROLONGED CARDIAC MONITORING ON SECONDARY STROKE PREVENTION
TSIVGOULIS, STROKE 2019

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCM</th>
<th>Non-PCM</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.9.1 Randomized Clinical Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRYSTAL AF</td>
<td>4</td>
<td>221</td>
<td>4</td>
<td>220</td>
</tr>
<tr>
<td>FIND AF</td>
<td>5</td>
<td>220</td>
<td>9</td>
<td>198</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>421</td>
<td>418</td>
<td>64.3%</td>
<td>0.69 [0.30, 1.61]</td>
</tr>
<tr>
<td>Total Events</td>
<td>9</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.50); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.86 (P = 0.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9.2 Observational Studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown ESUS-AF</td>
<td>1</td>
<td>47</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>Rodríguez-Campello, et al.</td>
<td>2</td>
<td>65</td>
<td>9</td>
<td>81</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>112</td>
<td>151</td>
<td>35.7%</td>
<td>0.21 [0.06, 0.69]</td>
</tr>
<tr>
<td>Total Events</td>
<td>3</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.57 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>533</td>
<td>569</td>
<td>100.0%</td>
<td>0.45 [0.21, 0.97]</td>
</tr>
<tr>
<td>Total Events</td>
<td>12</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.10; Chi² = 3.55, df = 3 (P = 0.31); I² = 16%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.04 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.56, df = 1 (P = 0.11); I² = 60.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Meta-analysis: 2 RCTs and 2 observational studies reporting stroke recurrence in patients with cryptogenic stroke/TIA
- N = 1,102 monitored by ICM or 10-day ambulatory ECG
- Follow-up: 8-30 months
- Prolonged cardiac monitoring (PCM) vs. conventional monitoring showed:
  - 2.5x increased incidence of AF detection (RR = 2.46, 95% CI: 1.61-3.76 and P < 0.0001)
  - 2.1x increase incidence of OAC initiation (RR = 2.07, 95% CI: 1.36-3.17 and P = 0.0008)
  - 55% decreased risk of recurrent stroke (RR = 0.45, 95% CI: 0.21-0.97 and P = 0.04)
- 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.

---

# IMPACT OF PROLONGED CARDIAC MONITORING ON SECONDARY STROKE PREVENTION

The meta-analysis included 2 RCTs and 2 observational studies

Overview on the characteristics of included studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study type</th>
<th>Population</th>
<th>PM method</th>
<th>Reference method</th>
<th>Time from index event to enrollment</th>
<th>Follow-up time</th>
<th>AF definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown ESUS-AF&lt;sup&gt;1&lt;/sup&gt;</td>
<td>OS</td>
<td>ESUS</td>
<td>ICM</td>
<td>30-day noninvasive ambulatory ECG monitoring</td>
<td>N/A</td>
<td>259 days</td>
<td>&gt; 30 sec</td>
</tr>
<tr>
<td>CRYSTAL AF&lt;sup&gt;2&lt;/sup&gt;</td>
<td>RCT</td>
<td>CS</td>
<td>ICM</td>
<td>ECG monitoring at scheduled and unscheduled visits at the discretion of the site investigator</td>
<td>≤ 3 months</td>
<td>6 months</td>
<td>&gt; 30 sec</td>
</tr>
<tr>
<td>FIND-AF&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RCT</td>
<td>Selected IS*</td>
<td>ICM</td>
<td>10-day noninvasive ambulatory ECG monitoring at baseline, 3, &amp; 6 months</td>
<td>≤ 7 days</td>
<td>12 months</td>
<td>&gt; 30 sec</td>
</tr>
<tr>
<td>Rodríguez-Campello, et al.&lt;sup&gt;4&lt;/sup&gt;</td>
<td>OS</td>
<td>CS</td>
<td>ICM</td>
<td>24-36 hours ECG monitoring</td>
<td>5-7 days</td>
<td>30 months</td>
<td>&gt; 30 sec</td>
</tr>
</tbody>
</table>

*Excluding patients with significant extracranial or intracranial vessel stenoses and history of atrial fibrillation or detection of atrial fibrillation during the baseline diagnostic workup. RCT: randomized clinical trial, OS: observational study, CS: cryptogenic stroke, ESUS: embolic stroke of undetermined source, ICM: implantable cardiac monitor, ECG: electrocardiogram, AF: atrial fibrillation, IS: ischemic stroke N/A: not available.

---

AF INCIDENCE IN THE FIRST MONTH AFTER A CRYPTOGENIC STROKE IS DETECTED WITH AN ICM
AHA POSTER: MILSTEIN, CIRCULATION 2018¹

Design and Objectives

- To determine the incidence of ICM detected AF in the first 20 days following a cryptogenic stroke
- Patients included consecutive patients admitted for stroke or TIA with cryptogenic stroke classification despite cardiac/neural evaluation
- Patients had no arrhythmia > 30 seconds during in-hospital telemetry monitoring
- Patients had Reveal LINQ™ ICM inserted prior to hospital discharge

Results

- N = 343 (55% male)
- Patient characteristics: Age: 68 ± 11, CHA2DS2-VASc: 3.5 ± 1.7.
  - Time from TIA/stroke to implant: 3.7 ± 1.5 days
  - 18 patients had AF detected in first 30 days
  - First AF episodes by Week 1: 2 patients; Week 2: 4 patients; Week 3: 6 patients; Week 4: 6 patients
  - Most patients with AF in first month had episodes shorter than 24 hours

30 days of cardiac monitoring has a low diagnostic yield (5%), majority of cryptogenic stroke patients require extended cardiac monitoring to detect AF.

2019 AHA/ACC/HRS ATRIAL FIBRILLATION GUIDELINES
RECOMMEND USE OF ILR FOR CRYPTOGENIC STROKE

7.12. Device Detection of AF and Atrial Flutter (New)

Recommendations for Device Detection of AF and Atrial Flutter
Referenced studies that support new recommendations are summarized in Online Data Supplement 9.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>1. In patients with cardiac implantable electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant AF to guide treatment decisions (S7.12-1-S7.12-5)</td>
</tr>
<tr>
<td>IIA</td>
<td>B-R</td>
<td>2. 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 (S7.12-6).</td>
</tr>
</tbody>
</table>

2. The cause of ischemic stroke remains unknown in 20% to 40% of patients, leading to a diagnosis of cryptogenic stroke. Prolonged electrocardiogram monitoring with an implantable cardiac monitor in these patients (age > 40 years) has the advantage of increasing the likelihood of detecting silent AF that would escape detection with short-term monitoring. A recent RCT established the superiority of an implantable cardiac monitor over conventional monitoring for detecting silent AF, a finding with major clinical ramifications for these patients (S7.12-6). A role in screening for silent AF may also exist for remote electrocardiographic acquisition and transmission with a "smart" worn or handheld WiFi-enabled device with remote interpretation (S7.12-7,S7.12-8).

**RECOMMENDATION**

In stroke patients, additional ECG monitoring by long-term noninvasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.

**LEVEL OF EVIDENCE**

Data derived from a single randomized clinical trial or large non-randomized studies.

**CLASS**

IIa

DEFINITION

Weight of evidence/opinion is in favor of usefulness/efficacy

SUGGESTED WORDING TO USE

Should be considered

*Endorsed by the European Stroke Organization (ESO).

THE REVEAL LINQ™ ADVANTAGE
AN ADVANCED MONITORING SOLUTION

Reveal LINQ™ ICM
MyCareLink™ Patient Monitor
CareLink™ Network and Reports

SOLUTION ENABLERS

Insertion Tools
Minimally invasive procedure

Patient Assistant
One-button symptom marking
THE REVEAL LINQ™ ADVANTAGE
SIMPLE INSERTION PROCEDURE

Best Location
45 degrees to sternum over 4th intercostal space,
2 cm from left edge of sternum

97% of physicians found the insertion tool simple
and intuitive

Requires minimal procedure time and clinical resources

THE REVEAL LINQ™ ICM ADVANTAGE
SUPERIOR EVIDENCE

MOST STUDIED

Evidence portfolio that includes 700+ published clinical articles and abstracts on Reveal™ ICMs

MOST VALIDATED

Clinical validation across cryptogenic stroke, syncope, and atrial fibrillation patients

MOST UTILIZED

Data leveraged by clinical societies to develop treatment guidelines across conditions

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CONCLUSIONS

Stroke facts
- 30% of ischemic strokes are cryptogenic (unexplained).1-6
- Cryptogenic stroke patients have the highest mortality risk among all stroke types.7
- 1 in 4 survivors will experience another stroke within five years.8
- 5-fold increase risk for stroke in patients with atrial fibrillation (AF).9

Current practice for monitoring & treatment
- The detection of AF in this patient population changes the medical management for secondary stroke prevention.
- There is no proven clinical benefit in giving oral anticoagulation therapy to all ESUS patients.
- Short- and intermediate-term monitoring may miss many patients with paroxysmal AF.

Clinical evidence
- CRYS'TAL AF compared continuous, long-term monitoring with Reveal™ ICM vs. conventional.
- At 12 months 97% of patients in whom AF was detected received oral anticoagulant.
- 88% of patients who had AF would have been missed if only monitored for 30 days.*
- Continuous monitoring with ICM is guideline recommended in cryptogenic stroke patients.
  - 2016 ESC guidelines for AF screening
  - 2018 AHA/ACC/HRS AF guidelines

*Based on Kaplan Meier estimates.

WHY DO YOU NEED A CRYPTOGENIC STROKE PATHWAY?
BETTER MULTIDISCIPLINARY STROKE CARE

For your patients
- Better risk reduction strategy to prevent a secondary stroke
- Ensures quality post-stroke care
- Care focused on patient needs: Find an answer

For your hospitals
- Better risk reduction strategy to prevent secondary strokes
- Coordinated and integrated care
- Consistent and reproducible approach
- Enhanced hospital reputation in providing exemplary care
MULTIDISCIPLINARY CARE PATHWAY FOR CRYPTOGENIC STROKE
WHO ARE THE KEY STAKEHOLDERS?

ADMINISTRATION
NEUROLOGY
HOSPITALISTS
STROKE COORDINATORS
CRYPTOGENIC STROKE PATHWAY
NURSES
ELECTROPHYSIOLOGY
CARDIOLOGY
CRYPTOGENIC STROKE PATHWAY

Pathway based on the consensus of the Cryptogenic Stroke Pathway steering committee. February 2016.

Medtronic Disclosure Statement: This pathway is provided for educational purposes and should not be considered the exclusive source for this type of information. It is the responsibility of the practitioner to exercise independent clinical judgment.

Refer to the brief statement for indications, warnings/precautions, and complications for the Reveal LINQ™ ICM.
CONTENTS

STROKE FACTS

CURRENT PRACTICE FOR MONITORING & TREATMENT

EVIDENCE

REVEAL LINQ™ ICM

CONCLUSIONS

PATHWAY DEVELOPMENT

CASE STUDY
Scott’s story

Reveal LINQ ICM used to discover AF in 22-year-old stroke patient

On his way to a soccer game, 22-year-old Scott suddenly began wobbling. His head started throbbing. What he thought was dehydration turned out to be much worse. The college student had suffered a stroke. Surgeons removed a blood clot in his brain, but a looming question remained: What caused the stroke in this seemingly healthy young man?

Scott’s doctors suspected it was the result of atrial fibrillation (AF). So Scott’s doctors turned to the Reveal LINQ ICM, which, within a few months, confirmed he had AF.

The diagnosis not only gave Scott’s doctors the information they needed to prescribe stroke-preventive blood thinners; it gave Scott the peace of mind to live life fully again.

This story reflects one person’s experience. Not every person will receive the same results.
BRIEF STATEMENT

Reveal LINQ™ LNQ11 Insertable Cardiac Monitor and Patient Assistant

Indications

Reveal LINQ™ LNQ11 Insertable Cardiac Monitor

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 been specifically 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, electrocautery, 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.

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 this device to sale by or on the order of a physician.

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.

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