Cryptogenic Stroke

Curtis Given, MD
Why Talk About Cryptogenic Stroke?

- 678,000 ischemic strokes every year in the US\(^1\)
  - Leading cause of disability in the US and worldwide
- ~200,000 cryptogenic strokes yearly\(^1\)
- Most cryptogenic stroke patients receive anti-platelet for secondary prevention\(^2\)
- Long-term monitoring reveals AF in ~30% of cryptogenic stroke patients\(^3-9\)
  - These patients benefit from anticoagulant therapy

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Risk for Stroke in Patients With AF

- 5-FOLD increase in ischemic stroke risk for AF patients.¹
- 2X more likely for AF-related ischemic stroke to be fatal as non-AF stroke.²
- 67% decrease in AF patient stroke risk with oral anticoagulants.³

## Stroke as a Healthcare Issue

<table>
<thead>
<tr>
<th>~800,000</th>
<th>87%</th>
<th>5th</th>
<th>LEADING CAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>new or recurrent strokes yearly</td>
<td>ischemic; 13% hemorrhagic</td>
<td>leading cause of death</td>
<td>of serious long-term disability in the US</td>
</tr>
</tbody>
</table>

Cryptogenic Stroke is a Diagnosis of Exclusion

- **Atherosclerotic**
  - Small arterial occlusion
- **Cardioembolic**
  - Other causes
  - Cryptogenic

- **Arteroembolic**
  - Branch occlusive disease

- **Aortoembolic**

- **Other causes**
  - Paroxysmal atrial fibrillation
  - Paradoxical embolism
  - Cancer-related coagulopathy
  - Cryptogenic

## Conventional Monitoring Strategies

<table>
<thead>
<tr>
<th>Method</th>
<th>Duration</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>External loop recorder</td>
<td>24-48 hours</td>
<td>62% patient compliance¹</td>
</tr>
<tr>
<td>Event-triggered loop recorder</td>
<td>Up to 30 days</td>
<td>53-90% patient compliance²⁻⁵</td>
</tr>
<tr>
<td>Holter Monitor</td>
<td>Up to 30 days</td>
<td></td>
</tr>
<tr>
<td>Mobile Cardiac Telemetry</td>
<td>Up to 30 days</td>
<td></td>
</tr>
</tbody>
</table>

¹ Dependent on type of MCT.
## Studies of Outpatient Monitoring in Cryptogenic Stroke Patients

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>AF Definition</th>
<th>Monitoring Duration</th>
<th>AF Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tayal (2006)</td>
<td>56</td>
<td>Any duration</td>
<td>MCOT 21 Days</td>
<td>Overall 23%&lt;br&gt;AF &lt; 30 sec 18%&lt;br&gt;AF &gt; 30 sec 5%&lt;br&gt;AF &gt; 5 min 9%</td>
</tr>
<tr>
<td>Gaillard (2010)</td>
<td>98</td>
<td>32 seconds</td>
<td>TTM 30 days</td>
<td>9%</td>
</tr>
<tr>
<td>Bhatt (2011)</td>
<td>62</td>
<td>30 seconds</td>
<td>MCOT 28 days</td>
<td>Overall 11%&lt;br&gt;AF &lt; 30 sec 4%&lt;br&gt;AF &gt; 30 sec 7%</td>
</tr>
<tr>
<td>Flint (2012)</td>
<td>236</td>
<td>5 seconds</td>
<td>MCOT 30 days</td>
<td>0%</td>
</tr>
<tr>
<td>Kamel (2013)</td>
<td>20</td>
<td>30 seconds</td>
<td>MCOT 21 days</td>
<td>Overall 17%&lt;br&gt;AF &lt; 30 sec 12%&lt;br&gt;AF &gt; 30 sec 4%</td>
</tr>
<tr>
<td>Miller (2013)</td>
<td>156</td>
<td>30 seconds</td>
<td>MCOT 30 days</td>
<td></td>
</tr>
<tr>
<td>Gladstone (2014)</td>
<td>572</td>
<td>30 seconds</td>
<td>Event Monitor 30 days vs 24 Holter</td>
<td>16.1% in event monitor vs. 3.2% Holter</td>
</tr>
</tbody>
</table>

Studies of Insertable Cardiac Monitors (ICMs)

• Multiple studies have assessed the ability of ICMs to detect AF in patients with cryptogenic stroke
  – Cotter study
  – Ritter study
  – Etgen study
  – Rojo-Martinez study
  – SURPRISE
  – CRYSTAL AF

<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</td>
<td>10</td>
<td>&gt;30 seconds</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>Etgen</td>
<td>12</td>
<td>&gt;6 minutes</td>
<td>152</td>
<td>27</td>
</tr>
<tr>
<td>Cotter</td>
<td>8</td>
<td>2 minutes</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>SURPRISE</td>
<td>19</td>
<td>&gt;2 minutes</td>
<td>109</td>
<td>16</td>
</tr>
<tr>
<td>Rojo-Martinez</td>
<td>9</td>
<td>2 minutes</td>
<td>102</td>
<td>33</td>
</tr>
<tr>
<td>Ziegler</td>
<td>6</td>
<td>2 minutes</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Poli</td>
<td>12</td>
<td>≥ 2 minutes</td>
<td>105</td>
<td>33</td>
</tr>
<tr>
<td>Jorfida</td>
<td>14.5</td>
<td>&gt; 5 minutes</td>
<td>162</td>
<td>46</td>
</tr>
<tr>
<td>CRYSTAL AF (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>

CRYSTAL AF:

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

<table>
<thead>
<tr>
<th>End Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Time to first detection of AF at 6 months of follow-up</td>
</tr>
<tr>
<td>Secondary</td>
<td>Time to first detection of AF at 12 months</td>
</tr>
<tr>
<td></td>
<td>Recurrent stroke or TIA</td>
</tr>
<tr>
<td></td>
<td>Change in use of oral anticoagulant drugs</td>
</tr>
</tbody>
</table>

CRYSTAL AF:

Study Population

447 patients were enrolled

6 were excluded
- 4 did not meet eligibility criteria
- 2 withdrew consent

441 underwent randomization

221 were assigned to ICM
- 208 had ICM inserted
- 13 did not have ICM inserted

12 crossed over to control
12 exited the study
- 3 died
- 1 was lost to follow-up
- 5 withdrew
- 3 were withdrawn by investigator

221 were included in intention-to-treat analysis

220 were assigned to control
- 220 received standard of care

6 crossed over to ICM
13 exited the study
- 2 died
- 1 was lost to follow-up
- 7 withdrew
- 3 were withdrawn by investigator

220 were included in intention-to-treat analysis

CRYSTAL AF:

• Age ≥ 40 years

• Diagnosis of stroke or TIA occurring within previous 90 days

• Stroke was classified as cryptogenic after extensive testing:
  • 12-lead ECG
  • ≥ 24 hours of ECG monitoring
  • TEE

• Screening for thrombophilic states (in patients < 55 years of age)

• Magnetic resonance angiography, computerized tomography angiography, or catheter angiography of head and neck

• Ultrasonography of cervical arteries or transcranial Doppler ultrasonography of intracranial arteries allowed in place of MRA or CTA for patients aged ≥ 55 years

Patients were only categorized with cryptogenic stroke after extensive diagnostic testing.

# CRYSTAL AF: Selected Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICM (n = 221)</th>
<th>Control (n = 220)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6 ± 11.4</td>
<td>61.4 ± 11.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Male</td>
<td>64.3%</td>
<td>62.7%</td>
<td>0.77</td>
</tr>
<tr>
<td>White</td>
<td>87.8%</td>
<td>86.8%</td>
<td>0.60</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>23.5%</td>
<td>20.9%</td>
<td>0.57</td>
</tr>
<tr>
<td>Index event</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Stroke</td>
<td>90.5%</td>
<td>91.4%</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>9.5%</td>
<td>8.6%</td>
<td></td>
</tr>
</tbody>
</table>

CRYSTAL AF: monitoring with ICM superior to SOC for the DETECTION of AF

Detection of Atrial Fibrillation by 36 months

Hazard ratio, 8.8 (95% CI, 3.5 - 22.2)
P < 0.001 by log-rank test

CRYSTAL AF:

12 months

97% of patients in whom AF was detected received oral anticoagulants

CRYSTAL AF: Median Time to Detection of AF

84 Days in the ICM group (range 18 to 265 days)

53 Days in control group (range 17 to 212 days)

1247 real-world cryptogenic stroke patients monitored by Reveal LINQ™

Cryptogenic stroke diagnosis: physician’s discretion

Follow-up: 6 months

Diagnostic yield at 6 months: 12.2% (n=147)

Median time to detection: 58 days

- Analysis supports results of CRYSTAL AF
- Continuous monitoring for periods longer 30 days may be warranted in CS patients

• **Reveal LINQ recommendation for cryptogenic stroke**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be <strong>considered</strong> to document silent atrial fibrillation.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

* Endorsed by the European Stroke Organisation (ESO)

What is The Reveal LINQ SYSTEM?

- The smallest, most powerful insertable cardiac monitor. One-third the size of a AAA battery (1.2 cc)
- Up to a 3-year longevity for long-term monitoring
- MR Conditional at 1.5 and 3.0 Tesla
- Minimally invasive, simplified insertion procedure
- 96.7% of patients very satisfied or satisfied with Reveal LINQ ICM after insertion
Best location: 45 degrees to sternum over 4th intercostal space, 2 cm from left edge of sternum

Requires minimal procedure time and clinical resources
Reveal LINQ ICM SYSTEM

Solution Enablers

Insertion Tools
Patient Assistant
NEW app-based Reveal LINQ™ Mobile Manager
NEW Monitoring Service Solutions*
ischemic stroke work-up

Lacunar infraction: small vessel disease
- Standard stroke work-up
  - Antiplatelet agent

Embolic appearing stroke with no history of AF:
- Multiple foci of infarction
- Cortical watershed distribution
- Cerebellar
- Standard stroke work-up

History of AF?
- Standard stroke work-up
  - Anticoagulation

MRA or CTA of intracranial vessels
- Transesophageal Echocardiogram (TEE)

Symptomatic carotid stenosis greater than 50%
- CEA or stent
  - Monofocal
    - Medical management
    - Antiplatelet agents
  - Multifocal

Intracranial stenosis
- Positive TEE
  - Anticoagulant

Cryptogenic Stroke/ TIA

All testing negative?

CEA or stent
- Angiogram
- Lumbar puncture
- Vasculitis work-up
Cryptogenic Stroke Pathway

PATIENT DIAGNOSED WITH CRYPTOGENIC STROKE/TIA

Could detection of suspected AF impact patient management?

YES

Refer to cardiology to insert Reveal LINQ ICM

Inpatient

If unable to insert prior to discharge, potential external monitor bridge and schedule Reveal LINQ ICM

Insert Reveal LINQ ICM prior to discharge

Schedule clinical follow-up with treating physician and ensure long-term adherence to monitoring

NO

Not a candidate

Inpatient/outpatient insertion

Outpatient

Insert expeditiously

Bridge with external monitor

AF not detected

Insert Reveal LINQ ICM

AF detected

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.
CONCLUSIONS

• Approximately one-third of ischemic strokes are classified as cryptogenic, and up to 30% many have previously undiagnosed AF

• The more you look, the more you find
  – Short- to intermediate-term cardiac rhythm monitoring may not be enough to detect paroxysmal AF in your cryptogenic stroke patients
  – CRYSTAL AF demonstrates superiority of continuous, long-term monitoring of cryptogenic stroke patients with an ICM
  – 2016 ESC guidelines recommend monitoring with Reveal LINQ in cryptogenic stroke patients

• Reveal LINQ™ ICM
  – Up to 3 years of continuous cardiac monitoring with the world’s smallest ICM
  – Proven AF detection algorithm with industry leading accuracy
  – Safe for use in MRI setting same day at 1.5 and 3.0 Tesla*

*Reveal LINQ ICM has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use. Please see the Reveal LINQ ICM clinician manual or MRI technical manual for more details.
ICMs for AF DETECTION IN CRYPTOGENIC STROKE

- ICM detects low burden/asymptomatic AF in cryptogenic stroke patients. 
  Etgen’13, Cotter’13, Rojo-Martinez’13, SURPRISE’14

- ICM offers higher diagnostic yield than 7-day Holter, standard monitoring Ritter’13, CRYSTAL-AF’14 and intermittent monitoring Choe’15

- Continuous monitoring with ICM is guideline recommended in cryptogenic stroke patients - 2016 ESC guidelines for AF screening

- ICM is a cost-effective diagnostic tool for the prevention of recurrent stroke in cryptogenic stroke patients Diamantopoulos