Long Term Monitoring for Atrial Fibrillation in Cryptogenic Stroke

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Disclosures

Medtronic Honorarium
Objectives

01 Stroke Epidemiology
02 Diagnosis of Cryptogenic Stroke (CS)
03 What about PFO’s?
04 Long Term Cardiac Monitoring (LTM) for CS Patients
05 Case Example
06 Conclusion
Every 40 seconds someone suffers a stroke
Every 4 minutes someone dies.

5th Leading cause of death in the US

7,000,000 stroke survivors in the US

795,000 strokes/year

85% Ischemic
15% ICH

In 2015, direct and indirect cost of stroke was $95 billion

#1 cause of adult disability
Approximately 10% of all deaths worldwide

More than 15 million people worldwide suffer a stroke each year.

1 in 3 stroke patients die.

The World Health Organization (WHO) estimates that a stroke occurs every 5 seconds.

2nd leading cause of death globally.

1 in 3 patients will be permanently disabled.
Disability Associated With Stroke

- Remaining hemiparesis: 50%
- Unable to walk without assistance: 30%
- Cognitive deficits: 46%
- Depressive symptoms: 35%
- Aphasia: 19%
- Dependent on others: 26%
- Institutionalized: 26%

Recurrent Stroke

Recurrent Stroke Rate among Patients Discharged with a Primary Diagnosis of Stroke, South Carolina, 2002 \(^1\) (\(N = 10,399\))

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Recurrent Stroke Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>1.8</td>
</tr>
<tr>
<td>6 months</td>
<td>5</td>
</tr>
<tr>
<td>1 year</td>
<td>8</td>
</tr>
<tr>
<td>4 years</td>
<td>18.1</td>
</tr>
</tbody>
</table>

Stroke Subtypes

Ischemic Stroke:
Neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Pathological, imaging, or other objective evidence in a defined vascular distribution. 85% of Strokes are Ischemic

Hemorrhagic Stroke:
Rupture of a blood vessel with bleeding into the brain parenchyma (ICH). 15% are Hemorrhagic

Focal Brain Dysfunction
- Ischemic Stroke
- Intracerebral Hemorrhage
- Subarachnoid Hemorrhage

Diffuse Brain Dysfunction
- Clot occluding artery
- Bleeding into brain
- Bleeding around brain
Stroke Etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic</td>
<td>25-30</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>20</td>
</tr>
<tr>
<td>Lacunar/Small Vessel</td>
<td>15-20</td>
</tr>
<tr>
<td>Other/Uncommon</td>
<td>5-10</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>25-30</td>
</tr>
</tbody>
</table>

Foulkes MA, et al, *Stroke*, 1988;19;547-554. [34]
Cryptogenic Stroke

- 678,000 ischemic strokes/year in the US\(^1\)
- ~200,000 cryptogenic strokes yearly\(^1\)

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# Definitions Of Cryptogenic Stroke

## Classification Scheme

<table>
<thead>
<tr>
<th>TOAST&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Causative Classification of Stroke (CCS)&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Embolic strokes of undetermined source&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ASCO(D) phenotyping&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

## Required Work-up

<table>
<thead>
<tr>
<th>Not Specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging</td>
</tr>
<tr>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥ 24 hours</td>
</tr>
<tr>
<td>Does not include a cryptogenic stroke category</td>
</tr>
</tbody>
</table>

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ESUS
Embolic Stroke of Undetermined Source

Definition:
Non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources implies that a full standard evaluation was done, whereas traditional definitions of cryptogenic stroke did not require a full evaluation.

Criteria:
- Identified CT or MRI, not lacunar (subcortical infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension is ≤1.5 cm on CT or ≤2.0 cm on MRI DWI)
- Absence of extracranial or intracranial atherosclerosis causing ≥50 percent luminal stenosis of the artery supplying the area of ischemia
- No major-risk cardioembolic source of embolism (i.e., no permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (within four weeks) myocardial infarction, left ventricular ejection fraction <30 percent, valvular vegetations, or infective endocarditis)
- No other specific cause of stroke identified (e.g., arteritis, dissection, migraine, vasospasm, drug abuse)
- ESUS represents a subset of cryptogenic stroke and emphasizes the likelihood that most strokes of unexplained etiology are probably embolic from an unestablished source
Suggested approach for further evaluation of cryptogenic stroke

Connection between the left and right atria at the fossa ovale in fetal circulation remains open.

- 20-25% of the adult population
- Implicated in etiology of cryptogenic stroke
- 40% of adults with cryptogenic stroke
- Prevalence: greater in those <30 years old and less in those >80 years old.

Decades of observational data up to 2012 suggested benefit of PFO closure in secondary stroke prevention of cryptogenic stroke compared with medical therapy arm but these observational studies were likely biased by patient selection, differential ascertainment of recurrent events and publication bias.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furlan et al. (2012)^4</td>
<td>PFO with recent (&lt;6 months) cryptogenic stroke or TIA (18–60 years old)</td>
<td>PFO closure with the STARFlex Septal Closure System™, clopidogrel for 6 months &amp; aspirin indefinitely (n=447)</td>
<td>Warfarin or aspirin or both (n=462)</td>
<td>A composite of stroke/TIA, death</td>
<td>Lower rate of composite end point in closure group (5.5% vs. 6.8%) but statistically not significant (2-year mean follow-up)</td>
</tr>
<tr>
<td>Meier et al. (2013)^5</td>
<td>PFO with cryptogenic stroke, TIA, or a peripheral thrombo-embolic event (&lt;60 years old)</td>
<td>PFO closure with AM-PLATZER PFO Occluder™, ticlopidine/clopidogrel for 1–6 months &amp; aspirin for ≥5 months (n=204)</td>
<td>Antiplatelet therapy or oral anticoagulation (n=210)</td>
<td>A composite of death, nonfatal stroke, TIA, or peripheral embolism</td>
<td>Lower rate of composite end point in closure group (3.4% vs. 5.2%) but statistically not significant (4-year mean follow-up)</td>
</tr>
<tr>
<td>Mas et al. (2017)^6</td>
<td>PFO with recent (&lt;6 months) stroke attributed to PFO, and atrial septal aneurysm or large interatrial or large interatrial shunt (16–60 years old)</td>
<td>PFO closure, DAPT for 3 months followed by antiplatelet therapy indefinitely (n=238)</td>
<td>Antiplatelet therapy only arm (n=235) &amp; oral anticoagulation arm (n=187)</td>
<td>Occurrence of fatal or nonfatal stroke</td>
<td>Significantly lower stroke risk in closure group compared to antiplatelet arm (0% vs. 6%) but an increased risk of atrial fibrillation after closure (4.6% vs. 0.9%). Stroke rate 1.5% in anticoagulation group vs. 3.8% in the matched antiplatelet-only subcohort (5-year mean follow-up)</td>
</tr>
<tr>
<td>Saver et al. (2017)^5</td>
<td>PFO with cryptogenic ischemic stroke (&lt;270 days) (18–60 years old)</td>
<td>PFO closure with the AMPLATZER PFO Occluder™, DAPT for 1 month followed by aspirin only for 5 months, then antithrombotic use per treating physician (n=499)</td>
<td>Any antiplatelet therapy or oral anticoagulation (n=481)</td>
<td>A composite of recurrent nonfatal or fatal ischemic stroke, or early death after randomization</td>
<td>Significantly lower rate of recurrent ischemic strokes (3.6% vs. 5.8%) but higher venous thromboembolism in the closure arm (3.4% vs. 0.8%) (5.9-year median follow-up)</td>
</tr>
<tr>
<td>Søndergaard et al. (2017)^6</td>
<td>PFO with cryptogenic stroke (&lt;180 days), 81% with moderate/large interatrial shunts (18–59 years old)</td>
<td>PFO closure with the Helix Septal Occluder™ or the Cardioform Septal Occluder™, 300 mg clopidogrel load then antiplatelet monotherapy (n=441)</td>
<td>Any antiplatelet monotherapy (n=223)</td>
<td>Co-primary end points: (1) Clinical ischemic stroke, (2) composite of clinical ischemic stroke or silent brain infarction detected on imaging</td>
<td>Significantly lower clinical ischemic stroke (1.4% vs. 5.4%) but higher rates of device complications (1.4%) and atrial fibrillation (6.6% vs. 0.4%) in the closure arm (3.2-year median follow-up)</td>
</tr>
</tbody>
</table>
Trials did not require prolonged cardiac monitoring to rule out AF as a stroke etiology to consider inclusion into the ‘cryptogenic stroke’ category.

Cryptogenic population was not selective enough. ESUS subset of cryptogenic stroke is radiographically selective and requires thorough diagnostic testing to ensure truly no underlying explanation for stroke. The ESUS definition does not exclude presence of PFO, and so limiting inclusion to ESUS would assess the most appropriate patient population.

All primary outcomes from the clinical trials included recurrent strokes of all causes and not just cryptogenic stroke.
What have we learned?

<table>
<thead>
<tr>
<th>TABLE 1. UNIQUE LESSONS LEARNED FROM INDIVIDUAL TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPECT (long term)</strong></td>
</tr>
<tr>
<td>- Long-term follow-up is critical with low event rates to prove a treatment effect. US-based trials have a problem with retention in long-term trials.</td>
</tr>
<tr>
<td>- Atrial septal aneurysm and large shunts predict a greater treatment effect.</td>
</tr>
<tr>
<td>- Greater treatment effect for PFO closure was also suggested when compared with antiplatelet therapy, not anticoagulation treatment.</td>
</tr>
<tr>
<td>- Deep venous thrombosis and pulmonary embolism were more frequent in the device arm but appeared related to a history of deep vein thrombosis and the medical arm having 20% of patients treated with anticoagulation, which was allowed.</td>
</tr>
<tr>
<td>- Patients had a higher burden of cardiovascular risk factors and a significant proportion of recurrent strokes had a defined mechanism, especially when patients crossed the 60 years of age threshold.</td>
</tr>
<tr>
<td><strong>REDUCE</strong></td>
</tr>
<tr>
<td>- Overall successful primary outcomes, the clear benefit in reducing recurrent strokes, and the good safety profile will likely lead to approval of the Cardioform Septal Occluder.</td>
</tr>
<tr>
<td>- The number needed to treat at only 2 years was approximately 28.</td>
</tr>
<tr>
<td>- Despite its conformable nature, atrial fibrillation was still more frequent in the device arm.</td>
</tr>
<tr>
<td>- Brain imaging detected additional recurrent strokes not detected clinically.</td>
</tr>
<tr>
<td><strong>CLOSE</strong></td>
</tr>
<tr>
<td>- The dramatic results appeared linked to study design with inclusion of only patients with atrial septal aneurysm or large shunts, patients with a low burden of traditional vascular risk factors, comparison of PFO closure plus antiplatelet therapy to antiplatelet therapy only, and excellent trial conduct with minimal missing data.</td>
</tr>
<tr>
<td>- A trend showed reduced recurrent stroke rates in patients treated with anticoagulants versus antiplatelet agents.</td>
</tr>
<tr>
<td>- Atrial fibrillation was more common in the device arm at 4.6%.</td>
</tr>
<tr>
<td>- There is a suggestion that treatment benefit is a class effect.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Society of Cardiology</td>
<td>2010</td>
<td>In the case of documented systemic embolism probably caused by paradoxical embolism, isolated device closure of ASD/PFO should be considered (Class III; Level of Evidence C)</td>
</tr>
<tr>
<td>American College of Chest Physicians (ACC)/AATS</td>
<td>2012</td>
<td>In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR 2.5; range 2.0–3.0) and consideration of device closure over aspirin therapy (Grade 2C)</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE)</td>
<td>2013</td>
<td>Evidence on the safety of percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events shows serious but infrequent complications. Evidence on its efficacy is adequate. Therefore this procedure may be used with normal arrangements for clinical governance, consent, and audit.</td>
</tr>
<tr>
<td>American Heart Association/ American Stroke Association (AHA/ASA)</td>
<td>2014</td>
<td>For patients with a cryptogenic ischaemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A). In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C).</td>
</tr>
<tr>
<td>American Academy of Neurology (AAN)</td>
<td>2016</td>
<td>Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischaemic stroke outside of a research setting (Level IIb). For recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C)</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; INR, international normalized ratio; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
CENTRAL ILLUSTRATION: Evidence-Based Algorithm for PFO Closure in Ischemic Stroke Patients for Highest Clinical Yield, Based on Randomized Trials

Biological age ≤60 years
Ischemic stroke, and PFO

- Large artery atherosclerosis
- Cardioembolic source
- Small vessel disease
- Arterial dissection
- Hypercoagulable disorder

- Uncontrolled hypertension
- Uncontrolled diabetes
- Autoimmune disease
- Drug or alcohol abuse

- Atrial fibrillation or flutter (ideally ≥30-day cardiac monitoring)

- <1 year of life expectancy
- End-stage heart, liver, lung, or kidney disease
- Cardiac tumor
- Endocarditis or septicemia
- Severe valvular pathology

Medical therapy

Percutaneous PFO closure

Enhanced reasons for PFO closure:
- Prior venous thromboembolism
- Multifocal cerebral defects
- Large PFO
- Atrial septal aneurysm
- Eustachian valve or Chiari network

RoPE SCORE
(Risk of Paradoxical Embolism)

Table 4 RoPE score calculator

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total score (sum of individual points) 10

Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)

Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct) 0

Abbreviation: RoPE = Risk of Paradoxical Embolism.

European Position Paper on Management of PFO

- Risk of recurrence: low based on observational/randomized studies.
- Recurrent stroke risk on medical therapy of 4.6% over 3.8 years of follow-up.
- NNT to prevent 1 stroke:
  - All patients: 37 (95% CI, 26-68)
  - Patients with high-risk PFO: 21 (95% CI, 16-61)
- ASA, moderate-to-severe shunt, atrial septal hypermobility: strongly associated with causal role of PFO.
- ASA: convey a higher risk of recurrence.
- RoPE score: should only be used as part of comprehensive evaluation.
- Interdisciplinary collaboration (interventional cardiologist, neurologist) and active collaboration with patient are key.

General Approach and Left Circulation Thromboembolism. Eur Heart J 2018;Oct 25
European Position Paper on Management of PFO
## PFO Case Examples

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yo female with no PMH, L MCA stroke.</td>
<td>55 yo male with multifocal strokes, HTN, DM, HLD</td>
<td>70 yo female with HTN/HLD, R PCA stroke, small-moderate PFO, no high risk features.</td>
</tr>
<tr>
<td>2decho with + bubble, TEE with large PFO + ASA.</td>
<td>2decho w/o moderate sized PFO. TEE w/ moderate sized PFO without high risk features.</td>
<td>&gt;65yo</td>
</tr>
<tr>
<td>High Risk PFO: large, ASA</td>
<td>&lt;55-64 years old</td>
<td>No high risk PFO features</td>
</tr>
<tr>
<td>High RoPE Score</td>
<td>Moderate risk PFO</td>
<td>Traditional risk factors</td>
</tr>
<tr>
<td>No risk factors</td>
<td>Traditional risk factors</td>
<td></td>
</tr>
<tr>
<td>30 days of monitoring was negative, PFO closed.</td>
<td>Refer for ILR. If no AFIB &gt; 6 months, closure considered, patient deferred.</td>
<td>Refer for ILR. Reasonable to discuss closure if 6-12 months no AFIB.</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>
PFO closure is of moderate benefit compared to antiplatelet therapy alone in the prevention of recurrent ischemic stroke in adults up to 60 years of age. Patient selection should be limited to patients who meet strict criteria and based on shared decision making with a cardiologist, neurologist, and patient. LTM should be considered.
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 Atrial Fibrillation

AF is the most common cause of embolic stroke

15% of all strokes in the US can be attributed to AF

AF is associated with an increase in mortality, from 1.3-2 times

1 Nattel. Lancet 2006;367:262-272
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 stroke risk with oral anticoagulants.³

How Can We Find It??
Cardiac Monitoring
Conventional Monitoring Strategies

**Holter Monitor**
- 24-48 hours of monitoring
- External loop recorder
- Saves all cardiac rhythm data

**Event Recorder**
- Up to 30 days of monitoring
- Event-triggered loop recorder
- Saves events only
- 62% patient compliance\(^1\)

**Mobile Cardiac Telemetry**
- Up to 30 days of monitoring
- Ambulatory event monitor
- Saves all cardiac rhythm data
- 53-90% patient compliance\(^2-5\)

\(^1\) Dependent on type of MCT.

Insertable Cardiac Monitors (ICM)

Multiple studies have assessed the ability of ICMs to detect AF in patients with cryptogenic stroke.

- Cotter study
- CRYSTAL AF
- Ritter study
- Etgen study
- SURPRISE
- Rojo-Martinez study
Summary:
Days To Detection of AF in Clinical Studies Of ICMs$^1$-$^7$

![Bar chart showing days to detection of AF in clinical studies of ICMs](chart.png)

Summary:
AF Detection Yield in Clinical Studies of ICMs

<table>
<thead>
<tr>
<th>Study</th>
<th>AF Detection Yield (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotter PE et al. Neurology</td>
<td>25.5</td>
<td>51</td>
</tr>
<tr>
<td>Etgen T et al. Stroke</td>
<td>27.3</td>
<td>22</td>
</tr>
<tr>
<td>Ritter MA et al. Stroke</td>
<td>16.7</td>
<td>60</td>
</tr>
<tr>
<td>Rojo-Martinez E et al. Rev Neurol</td>
<td>33.7</td>
<td>101</td>
</tr>
<tr>
<td>SURPRISE</td>
<td>16.1</td>
<td>85</td>
</tr>
<tr>
<td>CRYSTAL AF*</td>
<td>30.0</td>
<td>441</td>
</tr>
<tr>
<td>Real-World</td>
<td>16.8</td>
<td>1247</td>
</tr>
</tbody>
</table>

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, MD, Ph.D.,
Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, MD,
Richard A. Bernstein, MD, Ph.D., Carlos A. Morillo, M.D.,
Marilyn Mollman Rymer, M.D., Vincent Thijs, MD, Ph.D.,
Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D.,
and Johannes Brachmann, M.D., For the CRYSTAL AF Investigators‘k
Crystal AF₁: Study Design and End Points

Randomized, controlled clinical trial with 441 patients

Compared continuous, long-term monitoring with Reveal™ ICM vs conventional monitoring for AFIB detection in CS patients

Assessment at scheduled (1 mo, 6 mo, 12 mo, q 6 months) and unscheduled visits

ECG monitoring performed at the discretion of the site investigator

End Point

Primary
- Time to first detection of AF (>30 secs) at 6 months of follow-up

Secondary
- Time to first detection of AF at 12 months
- Recurrent stroke or TIA
- Change in use of oral anticoagulant drugs

Crystal AF\textsubscript{1} : Study Population

447 patients were enrolled

441 underwent randomization

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

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

220 were assigned to control
- 220 received standard of care

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

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

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

### Crystal AF<sub>1</sub>: 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

### 6 Month Endpoints

<table>
<thead>
<tr>
<th></th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time from Randomization to AF Detection</td>
<td>41 days</td>
<td>32 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>74%</td>
<td>33%</td>
</tr>
<tr>
<td>Oral Anticoagulation Usage, overall</td>
<td>10.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>OAC use in patients with detected AF</td>
<td>94.7%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Testing required to detect AF</td>
<td>Automatic AF detection</td>
<td>88 ECGs 20 24-hour Holters 1 event recorder</td>
</tr>
</tbody>
</table>

### 12 Month endpoints

<table>
<thead>
<tr>
<th>Metric</th>
<th>ICM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time from Randomization to AF Detection</td>
<td>84 days</td>
<td>52.5 days</td>
</tr>
<tr>
<td>Patients found to have AF</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>% Asymptomatic Episodes</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>Oral Anticoagulation Usage, overall</td>
<td>14.7%</td>
<td>6.0%</td>
</tr>
<tr>
<td>OAC use in AF patients</td>
<td>96.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Testing required to detect AF</td>
<td>Automatic AF detection</td>
<td>121 ECGs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 - 24-hour Holters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 event recorder</td>
</tr>
<tr>
<td>Complications</td>
<td>5 (2.4%) ICMs removed due to insertion site infection or pocket erosion</td>
<td>NONE</td>
</tr>
</tbody>
</table>

Crystal AF<sub>1</sub>: Key Secondary Endpoint

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

Crystal AF_1: Median Time To Detection of AF

- in the ICM group (range 18 to 265 days)
- in control group (range 17 to 212 days)

Real World Validation of Crystal AF Results
Rogers, AAN, 2016

- 1247 real-world cryptogenic stroke patients monitored by Reveal LINQ™
- Cryptogenic stroke diagnosis: physician’s discretion
- Follow-up: 12 months
- Diagnostic yield at 12 months: 16.3% (n=147)
- Median time to detection: 86 days
  - Analysis supports results of CRYSTAL AF
  - Continuous monitoring for periods longer 30 days may be warranted in CS patients

72% of AF patients would be missed if monitoring stopped at 30 days
Predictors Of AF Offer Only Poor Predictive Ability

CRystal AF sub-analysis: Thijs, *Neurology*

**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

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

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

<table>
<thead>
<tr>
<th>Short – term monitoring</th>
<th>Periodic Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 - Hour</td>
<td>Quarterly 24 – hour holters</td>
</tr>
<tr>
<td>48 - Hour</td>
<td>Quarterly 48 – hour holters</td>
</tr>
<tr>
<td>7 – Day Holter</td>
<td>Quarterly 7 – day holters</td>
</tr>
<tr>
<td>21 – Day Event Recorder</td>
<td>Monthly 24 – Hour holters</td>
</tr>
<tr>
<td>30 – Day Event Recorder</td>
<td>Monthly 24 – Hour holters</td>
</tr>
</tbody>
</table>

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

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\(^1\)

ICM IIa Recommendation For Cryptogenic Stroke

2016 ESC GUIDELINES FOR THE MANAGEMENT OF AF

<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 considered to document silent atrial fibrillation.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack.

*Class of recommendation. Level of evidence.*
ICM IIa Recommendation For Cryptogenic Stroke

2019 AHA/ACC/HRS Focused Update for the Management of Patients With Atrial Fibrillation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</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>
<td>IIa</td>
<td>B-R</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack.

Class of recommendation. Level of evidence.
PROLONGED CARDIAC MONITORING IN SECONDARY STROKE PREVENTION

Objectives
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.

Methods
- A comprehensive literature search of MEDLINE, SCOPUS, CENTRAL, and conference proceedings was conducted to identify studies reporting stroke recurrence rates in patients with a history of cryptogenic stroke or TIA receiving PCM as compared to patients receiving conventional (non-PCM) cardiac monitoring.
- Literature search was performed on October 14, 2018.
- Quality control and bias identification were performed by two independent reviewers with the Cochrane risk-of-bias tool and all emerging conflicts were resolved with consensus.
- Small-study effect (i.e., publication bias) across individual studies was graphically evaluated for the primary outcome of interest (recurrent stroke/TIA) with funnel plot inspection and assessed with the Egger’s test.

Conclusion
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.

RESULTS

Patients who underwent PCM compared to conventional cardiac monitoring show:

- **2.5x increased incidence of AF detection** (n = 1,102, RR = 2.46, 95% CI: 1.61-3.76, and P < 0.0001)
- **2.1x increased incidence of anticoagulant initiation** (n = 956, RR = 2.07, 95% CI: 1.36-3.17, and P = 0.0008)
- **55% decreased risk of recurrent stroke** (n = 1,102, RR = 0.45, 95% CI: 0.21-0.97, and P = 0.04)

---

PATIENT DIAGNOSED WITH CRYPTOGENIC STROKE/TIA

Could detection of suspected AF impact patient management?

Not a candidate

Refer to cardiology to insert Reveal LINQ ICM

Inpatient

Inpatient/outpatient insertion

Outpatient

AF not Detected

AF not Detected

Bridge with external monitor

Insert expeditiously

AF not Detected

Insert Reveal UNQ ICM

Enroll in CareLink™ Network & perform remote monitoring

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

Inpatient if unable to insert prior to discharge. Potential external monitor bridge and schedule Reveal LINQ ICM

Insert Reveal LINQ ICM prior to discharge

Enroll in CareLink™ Network & perform remote monitoring

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

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.
Insertion

**Best location:** 45 degrees to sternum over 4th intercostal space, 2 cm from left edge of sternum.
The Complete Monitoring Solution

ICM
Wireless
MyCareLink™ Patient Monitor
Cellular
CareLink™ User Interface
Simplified Insertion Procedure
Patient Assistant
Mobile Alerts
Streamlined Reports
Case Study

62 y/o man who presented with aphasia and R sided hemiparesis s/p TPA. MRI demonstrated a left MCA stroke.

Workup
Vessel imaging, TTE/TEE, hypercoag panel, inpatient telemetry, 14 day event monitor did not reveal etiology of stroke.

Referral to EP
ILR implantation

Treatment
Neurology placed patient on Plavix 75 mg daily
Immediately started on oral anticoagulation with Eliquis.

Lives in an RV.

Following on Carelink with bedside monitor.

Moved to Tucson, Arizona— in his RV.

Continued remote monitoring with our office until his monitor was transferred to his new EP in Arizona.
Epidemiology:
- Stroke is the leading cause of disability and 5th leading cause of death.
- Secondary prevention is key, especially in patients with atrial fibrillation.

Cryptogenic stroke:
- 30% of these patients have atrial fibrillation.
- ESUS is a more selective appropriate term for this population.
- In order to be deemed this, an extensive workup is required.

PFOs:
- Within the cryptogenic stroke population, many will have PFOs. It is our job as neurologists to be the gatekeeper for closure as this will only benefit a select portion of these patients.
- Long term monitoring should still be considered.

Conclusions
- Stroke is the leading cause of disability and 5th leading cause of death.
- Secondary prevention is key, especially in patients with atrial fibrillation.

Long Term Monitoring:
- Short- to intermediate-term cardiac rhythm monitoring may not be enough to detect paroxysmal AF in your cryptogenic stroke patients.
- CRYS'TAL AF demonstrates superiority of continuous, long-term monitoring of cryptogenic stroke patients with an ICM.
- LTM leads to a change in treatment which decreases the risk of recurrent disabling stroke.
Thank You!

Questions!!