Occult Atrial Fibrillation and Cryptogenic Stroke

Neurology Perspective
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Disclosures
- Research funding, consultant, speakers bureau:
  - Medtronic, Lifewatch, Pfizer, Bristol Myers, Sanofi, Boehringer-Ingelheim, Janssen

The Era of Continuous Monitoring for AF
How much stroke of unknown cause is really due to atrial fibrillation?
- I don’t know.
- By the end of this lecture…
- You also won’t know
- We will all know within a year.

Occult Atrial Fibrillation
- Occult AF=AF that eluded detection during the initial stroke evaluation
- Paroxysmal AF that is “difficult” to detect and is only detectable with moderate or long term continuous monitoring
- Episodes may be extremely brief—how brief an episode counts as “ATRIAL FIBRILLATION” is not clear
- AF=atrial fibrillation that requires anticoagulation in a high risk patient
- af= atrial fibrillation that is of uncertain clinical significance

Cryptogenic Stroke
- Ischemic stroke of unknown cause
- Generally treated with anti-platelet agents
- Finding ATRIAL FIBRILLATION in these patients changes treatment and possibly clarify mechanism
- By definition: finding af: might clarify mechanism, might change treatment
**Cryptogenic Stroke: Diagnosis of exclusion**

- Patients may have stroke risk factors, but…
- No plausible mechanism identified after
  - TTE, TEE, Cardiac MRI
  - CTA, MRA, catheter angiogram of head and neck arteries
  - Coagulation testing
  - ECG monitoring
  - Other testing as appropriate

- **Anti-platelet agents**

**Continuous monitoring allows detection of otherwise un-findable AF (=Occult AF, af)**

**Newly Detected AF in Patients with Prior Thromboembolic Events**

- TRENDS study
- 1600 patients with pacemaker or AICD that can detect AF
- No known AF
- No anticoagulation
- No anti-arrhythmic

Ziegler et al. Stroke (online) Dec 31, 2009
Stroke Prevention in Afib: A Neurologist’s Perspective

Richard Bernstein, MD, PhD

High incidence of Occult AF

After 1 year, 30% of these patients had atrial fibrillation!

AF only occurred one day out of 10 or less in most patients

Most of the af occurred AFTER one month of monitoring

Ziegler P. et al. Stroke. 2010;41

<table>
<thead>
<tr>
<th>Time from Device Implant (months)</th>
<th>Freedom from AT/AF</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>163</td>
<td>89%</td>
</tr>
<tr>
<td>3 mo.</td>
<td>127</td>
<td>89%</td>
</tr>
<tr>
<td>6 mo.</td>
<td>111</td>
<td>89%</td>
</tr>
<tr>
<td>9 mo.</td>
<td>106</td>
<td>89%</td>
</tr>
<tr>
<td>12 mo.</td>
<td>67</td>
<td>89%</td>
</tr>
</tbody>
</table>

89% 89% 89% 89% of NDAF patients identified beyond 1 day

78% 78% 78% 78% of NDAF patients identified beyond 7 days

60% 60% 60% 60% of NDAF patients identified beyond 30 days
Does af=AF?

- ASSERT trial: patients with pacemakers or AICD
- 3 months of monitoring for occult AF
- Occult, brief subclinical af (really “atrial tachycardia”) increased risk at 2 years of
  - ATRIAL FIBRILLATION
  - STROKE
- This suggests that af=AF and raises risk of stroke

How Much AF Do You Need To Have A Stroke?

<table>
<thead>
<tr>
<th>Author</th>
<th>Duration</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capucci; JACC 2005;46:1913</td>
<td>24 Hrs</td>
<td>3.1</td>
</tr>
<tr>
<td>Glotzer; Circ Arrhythmia 2009; (5) 474</td>
<td>5 Hrs</td>
<td>2.2</td>
</tr>
<tr>
<td>MOST; Glotzer; Circ 2003;107:1614</td>
<td>5 minutes</td>
<td>2.0</td>
</tr>
</tbody>
</table>

AF and Stroke: It’s more than just duration

- Analysis of 568 patients with a pacemaker and a history of AF, with patients broken into three groups
- In some patients, any amount of atrial fibrillation is safe.
- In some patients, no atrial fibrillation is safe.
Stroke Prevention in Afib: A Neurologist’s Perspective

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Continuous monitoring: uncovering AF in cryptogenic stroke

- 56 year old female, no risk factors
- Left thalamic infarct with thrombus in PCA
- Negative work-up
  - Normal TTE and TEE
  - Normal cMRA h/n
  - No AF on several days of telemetry
- Implanted with Reveal XT

Small stroke, but thrombus suggested embolism

- Image with MRI scans indicating a small stroke with suggested embolism
- Continuous monitoring: uncovering AF in cryptogenic stroke
AF Burden In Cryptogenic Stroke

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>Duration</th>
<th>Definition of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shafqat</td>
<td>210</td>
<td>24 Hour</td>
<td>?</td>
</tr>
<tr>
<td>Schuchert</td>
<td>82</td>
<td>72 Hours</td>
<td>&gt; 60 seconds</td>
</tr>
<tr>
<td>Jabaudon</td>
<td>88</td>
<td>7 days</td>
<td>?</td>
</tr>
<tr>
<td>Tayal</td>
<td>56</td>
<td>21 days</td>
<td>Any</td>
</tr>
</tbody>
</table>

Cryptogenic Stroke Patients with AF Detected by Various Monitoring Methods

<table>
<thead>
<tr>
<th>Incidence of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Hour</td>
</tr>
<tr>
<td>72 Hours</td>
</tr>
<tr>
<td>7 days</td>
</tr>
<tr>
<td>Continuous</td>
</tr>
</tbody>
</table>

CRYpogenic STroke and underlying Atrial Fibrillation ("CRYSTAL AF")

**Purpose**
- To compare the continuous monitoring by Reveal XT to standard of care (SOC) in subjects after diagnosis of cryptogenic stroke/TIA.
- Assess the incidence of AF in these subjects and aims to demonstrate the benefit of timely AF detection for patient care.

**Scope**
- Prospective, randomized, multi-center, global, post-market study
- Approximately 450 subjects in Europe, US, & Canada
CRYSTAL AF

Study Overview

- Cryptogenic stroke/TIA subjects without a history of AF
- Randomized to standard of care monitoring or continuous monitoring with Reveal XT
- Endpoints are evaluated through 12 months (primary endpoint is detection of AF at 6 months)

Sinah et al. Amer Heart Journal 2010;160, 36-41

CRYSTAL AF

Key Inclusion Criteria

- Subjects must have had a cryptogenic stroke or TIA* within the previous 90 days
- As minimally defined by the American and European Stroke Guidelines and in conjunction with site-specific requirements a diagnosis of 'cryptogenic' must be established.
  - At a minimum the following tests are required by the protocol:
    - MRI or CT
    - 12-lead ECG
    - 24-hour ECG monitoring (e.g. Holter)
    - Transesophageal echocardiography (TEE)
    - CTA or MRA of head and neck to rule out arterial pathologies
    - (A few older patients were screened with CUS and TCD in Europe)
  
* Inclusion of TIA's are limited to those with a visible lesion (MRI or CT) that fits the symptoms of the TIA with one of the following: Speech problems, Weakness of arm or leg, or Hemianopsia

CRYSTAL AF

Key Exclusion Criteria

1. Known etiology of the stroke or TIA
   - Large artery atherosclerosis,
   - acute small artery occlusion with lesion <1cm,
   - High risk cardiac or aortic arch source of embolism,
   - History of DVT
2. Untreated hyperthyroidism
3. Myocardial infarction <1 month prior to stroke/TIA
4. Coronary bypass grafting <1 month prior to stroke/TIA
5. Valvular disease requiring immediate surgical intervention
6. History of AF or atrial flutter
7. Permanent indication for or contraindication for OAC at enrollment
8. Life expectancy less than 1 year
9. Indicated for implant with a pacemaker, ICD, CRT-device or an implantable hemodynamic monitoring system
CRYSTAL-AF

- Determine the incidence of Occult AF in cryptogenic stroke
- Determine if continuous monitoring is better than standard monitoring for detecting Occult AF.
- By looking at stroke recurrence: Is af = AF?
- Clinical, radiographic, and echocardiographic predictors of Occult AF.
- Medical economics and modeling of strokes prevented [based on assumptions about the relationship of af to AF]

SURPRISE study

- 43 patients with “Cryptogenic stroke” (non-standard definition, incomplete unspecified evaluation)
- REVEAL-XT implanted
- 8 patients (18.7%) had AF, all were anticoagulated
- AF patients were older, higher vCHADS2 score
- Mean time to AF detection: 133 days!!

Christensen, Krieger et al; Presented, International Stroke Conference 2012

Occult AF: in non-cryptogenic stroke

Finding AF in non-cryptogenic stroke has the same treatment implications as in cryptogenic stroke
For example: Stroke from carotid stenosis + occult AF = CEA + long term anticoagulation

Long term monitoring in non-cryptogenic stroke may be as important (and as high yield) as in cryptogenic stroke…next study.
Open questions: Occult AF and Stroke

- Is there a threshold of AF below which anticoagulation is not needed?
- How much ecg-AF is “Atrial Fibrillation” in the classic sense?
- Does minimal occult AF matter require anticoagulation?
- Does the burden or the length of AF episodes matter, if so which matters more?
- ……etc

CRYSTAL-AF

- Results expected in mid-2013

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