Cryptogenic Stroke: Searching for a Cause Using Implantable Loop Recorders

Neil K. Sanghvi, M.D., F.A.C.C., F.H.R.S.
I currently have a pen from Medtronic.

Scrap paper for notes donated by St. Jude.

The rep from Boston Scientific gave me a protein bar the other day after a long case.

In all seriousness, I have received honoraria and travel expenses from Boehringer Ingelheim, Medtronic, Boston Scientific, St. Jude Medical. I have also consulted for St. Jude Medical.
Discussion Goals

- Clinical prevalence and societal impact of cryptogenic stroke
- AF’s role in ischemic strokes
- Traditional workup
- Effectiveness of implantable loop recorders in complimenting workup
US Stroke Statistics

- Kills ~130,000 people annually – 1 out of every 19 deaths!
- On average, 1 person dies from a stroke every 4 minutes
- > 795,000 people suffer a stroke
  - ~610,000 are first or new strokes
  - ~185,000 (nearly 1:4) are recurrent
- Leading cause of long-term disability

http://www.cdc.gov/stroke/facts.htm
Direct and indirect costs (in billions of dollars) of major cardiovascular diseases and stroke (United States: 2010)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Billions of Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>204.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>36.5</td>
</tr>
<tr>
<td>Other CVD</td>
<td>28.0</td>
</tr>
</tbody>
</table>

Source: National Heart, Lung, and Blood Institute.

©2013 American Heart Association, Inc. All rights reserved.
Go AS et al. Published online in Circulation Dec. 18, 2013
Projected Total Costs of CVD, 2015–2030 (in Billions 2012$) in the United States

- All CVD: 1208 (2015), 1208 (2020), 1208 (2025), 1208 (2030)
- CHD: 656 (2015), 150 (2020), 184 (2025), 225 (2030)
- Other CVDs: 204 (2015), 251 (2020), 310 (2025), 380 (2030)

Stroke Etiologies

Subtypes of Ischemic Stroke

- **Large artery atherosclerosis** (15-20%)
- **Cardioembolic** (20-25%)
- **Small artery occlusion** (20-25%)
- **Other/Uncommon** (2-4%)
- **Cryptogenic** (30-40%)

Adams HP et al. Stroke 1993; 24; 35-41
Grau AJ et al. Stroke 2001; 32:2559-2566
Cryptogenic Stroke

An ischemic stroke that cannot be attributed to large vessel atherosclerosis, small artery occlusion, cardioembolic origin, or other/uncommon causes despite an extensive evaluation.

Adams HP et al. Stroke 1993; 24; 35-41
## Typical Workup

<table>
<thead>
<tr>
<th>Large Vessel Atheroma</th>
<th>Small Vessel Disease</th>
<th>Cardioembolic</th>
<th>Other/ Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-angiogram MRA</td>
<td>CT-angiogram MRA</td>
<td>TTE TEE</td>
<td>Hypercoagulable workup including blood work and genetic testing</td>
</tr>
<tr>
<td>Transcranial Doppler Carotid duplex</td>
<td></td>
<td>EKG Holter MCOT ZioPatch</td>
<td>Basic blood work ESR Syphilis (RPR)</td>
</tr>
</tbody>
</table>
ATRIAL FIBRILLATION AS A SOURCE FOR STROKE
Risk of Stroke with AF

Framingham Study (N= 5070)

Two-year Age-adjusted Incidence of Stroke / 1000*

Nearly 5-fold increased risk of stroke ($p<0.001$)

Without NVAF  

With NVAF

AF Classification - Stroke Risk

- Paroxysmal NVAF (N=460): 3.2%
- Sustained NVAF (N=1552): 3.3%

Hart RG. JACC 2000;35:183-7
AF burden ≥ 5.5hrs of AF on any day in the last 30 days was associated with a doubling of risk for a thromboembolic event.

ASSERT Trial

- 2580 pts recently implanted with a pacemaker or ICD and no prior h/o AF
- All patients > 65yo and h/o HTN
- Monitored for occurrence of AT or AF >190 bpm and > 6 min in the first 3 months after implantation
- Followed patients for 2.5yrs for ischemic stroke or embolism

Healy JS. NEJM 2012;366:120-129.
### Assert Trial

**Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline CHADS$_2$ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.**

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>No. of Patients</th>
<th>Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>no. of patients</td>
<td>no. of events</td>
</tr>
<tr>
<td>1</td>
<td>600</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>1129</td>
<td>119</td>
</tr>
<tr>
<td>&gt;2</td>
<td>848</td>
<td>72</td>
</tr>
</tbody>
</table>

*The P value for trend is 0.35.*

Risk of stroke ~4%/yr if CHADS$_2$ > 2

Healy JS. NEJM 2012;366:120-129.
AF Morbidity & Mortality

**Morbidity:**
- Increases risk of embolic CVA 3-5X;
- Constitutes 1/3 of all embolic strokes > 60 yr (15% of all strokes nationally)\(^1\)

**Mortality:**
- Increases mortality independent of preexisting risk factors:
  - Odds ratio: 1.5 in men and 1.9-2.1 in women\(^2, 3\)

---

ROLE FOR IMPLANTABLE LOOP RECORDERS
• N = 149
• Acute stroke or TIA and no history of AF
• ECG monitoring in Hospital
• 24-hour Holter recording if normal ECG
• 7-day event monitor if normal Holter

Incremental % AF Detection

Commercially Available ILRs
Basic Implantation of ILR

- Minimally invasive
- No leads or fluoroscopy required
- Well-tolerated
- Monitoring can last up to 3 years
- Now with wireless transmission of data
Cardiac Compass® Report
Trended Diagnostics

- Daily AF Burden
- Ventricular Rate During AF
- Day/Night HR
- Patient Activity
- Heart Rate Variability
Crystal AF – ISC 2014
Late Breaking Abstract

- 441 patients randomized
- Primary Endpoint – AF detection @ 6 months
- Follow-up 1, 6, 12, and every 6 months thereafter till study end
- AF defined as any episode lasting > 30 seconds
Crystal AF – ISC 2014
Late Breaking Abstract

ILR superior to standard monitoring in detecting AF

6 mo

36 mo

12 mo
## Monitoring to Detect AF

<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>

6 months

<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>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>Tests required to find AF</td>
<td>Automatic AF detection</td>
<td>121 ECGs 32 24-hour Holters 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>

12 months

Crystal AF – late breaking abstract; ISC 2014
Summary

- Cryptogenic stroke accounts for 30-40% of all ischemic strokes
- Asymptomatic AF may be detected in up to 25-30% of patients with cryptogenic stroke
- Thoroughly investigating for AF is paramount since detection will impact treatment and potentially prevent recurrent stroke
- Implantable loop recorders offer a powerful solution for long term monitoring