Cryptogenic Stroke: What Don’t We Know

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Financial Disclosures

• None
Objectives

• Principles of diagnostic evaluation and management of a patient with a cryptogenic stroke.
• Discuss evidence based management of intracranial atherosclerosis
• Current status of management of patients with an ischemic stroke and PFO.
• Discuss the role of long-term cardiac rhythm monitoring in the evaluation of cryptogenic stroke.
<table>
<thead>
<tr>
<th>Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis (embolus/thrombosis)*</td>
</tr>
<tr>
<td>Cardioembolism (high-risk/medium-risk)*</td>
</tr>
<tr>
<td>Small-vessel occlusion (lacune)*</td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
</tr>
<tr>
<td>a. Two or more causes identified</td>
</tr>
<tr>
<td>b. Negative evaluation</td>
</tr>
<tr>
<td>c. Incomplete evaluation</td>
</tr>
</tbody>
</table>
Diagnostic Evaluation

- Axial Imaging: Head CT, MRI
- Vascular Imaging
- Cardiac Imaging
- Laboratory
Case-1

- 60 years old male with left sided weakness
- CT shows subacute right frontal infarct
- Sinus rhythm on ECG/telemetry
- Carotid Duplex: normal
- TTE: normal
- LDL: 130 mg/dl
Intracranial Arterial Stenosis

• Missed if no intracranial vascular imaging performed
  • TCD
  • MRA
  • CTA
  • Angiography
Intracranial Arterial Stenosis

- WASID trial
  - Recent ischemic stroke/TIA with 50-99% stenosis of an intracranial artery
  - *Aspirin (1300 mg/d) vs. Warfarin*
  - Warfarin: significantly higher major hemorrhage and death rate
  - No difference in primary endpoint

*Chimowitz MI, N Engl J Med. 2005*
Intracranial Arterial Stenosis

• SAMMPRIS trial
  • Recent ischemic stroke with 70-99% stenosis of an intracranial artery
  • AMM vs. PTAS+AMM
  • 30 day stroke/death rate
    • 14.7% in PTAS group
    • 5.3% in AMM group

Aggressive medical management for intracranial arterial stenosis

- ASA 325mg/d
- Clopidogrel 75mg/d for 90 days
- LDL goal, 70mg/dl
- SBP goal < 140 mm Hg
  - < 130 mm Hg if diabetic
- Lifestyle coach
Patent Foramen Ovale

- **TTE**
  - With agitated saline
- **TEE**
- **TCD**
  - High sensitivity for detecting R→L shunt.
**PFO in Cryptogenic Stroke: PICSS**

- No difference between aspirin and Warfarin treatment subgroups
- Risk of recurrent stroke not dependent on size of PFO
- No effect of presence of ASA

*Shunichi Homma, Circulation. 2002*
PFO Closure Trials

- CLOSURE I (N=909)
  - STARFlex septal closure device
  - Medical therapy-6.8%
  - Device-5.5%

- RESPECT (N=980)
  - Amplatzer Occluder device
  - Intention to treat analysis: No difference

- PC (N=414)
  - Amplatzer
  - No difference in the primary end points
Brief History of Patent Foramen Ovale and Stroke

Anthony J. Furlan, MD

Lechat is usually credited with first calling attention to patent foramen ovale (PFO) and stroke in 1988.1 Previous studies of the role of echocardiography in stroke rarely, if ever, mentioned PFO and focused on now-almost-forgotten disorders, such as mitral valve prolapse.2

Interest in PFO has emerged for 3 main reasons: (1) renewed interest in cryptogenic stroke especially in younger patients; (2) technical advances, including bubble contrast transthoracic echocardiography, transesophageal echocardiography, and saline contrast transcranial doppler; and (3) perhaps most importantly, the emergence of endovascular device closure as a treatment option.

All 3 trials began >10 years ago. Before October 2006, PFO device closure for stroke prevention was approved under a Humanitarian Device Exemption (HDE) by the Food and Drug Administration (FDA). The HDE was predicated on <4000 procedures performed annually and required a recurrent stroke (not first stroke and not transient ischemic attack [TIA]) while on warfarin (not aspirin) for which no other explanation was apparent (phanerogenic stroke in arcane FDA language). However, it was likely that many >4000 patients were being closed annually in the United States alone using devices which were approved for ventricular septal defect or atrial septal defect off label. The exact numbers were never...
PFO Trials: What Went Wrong

- **High Prevalence**
  - 10-25% prevalence in non stroke population
  - ~40% prevalence in Cryptogenic stroke population

- **Cryptogenic Stroke +PFO ≠ Paradoxical embolism**
  - PFO may be incidental
<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>
<tr>
<td>Total score (sum of individual points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum score (a patient &lt;30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RoPE = Risk of Paradoxical Embolism.
The RoPE Score

- **High RoPE score**
  - Higher prevalence of PFO
  - PFO more likely to be pathogenic
  - Lower stroke recurrence risk
- **Highest stroke recurrence rate**
  - Low RoPE score
  - Least likely to have a PFO attributable CS
- **CLOSURE data**
  - $\leq 5$: 14.5% recurrence rate
  - $>5$: 4.2%, $p<0.0001$
Ongoing trials

- REDUCE: www.clinical.goremedical.com/REDUCE

- Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)
Occult Atrial Fibrillation

- 10-20% CS have PAF
- American Heart Association guidelines
  - Atleast 24 hours of cardiac rhythm monitoring
  - Most effective duration is unknown
- No significant difference in stroke risk between chronic and paroxysmal atrial fibrillation
  - Anticoagulation
Patients with Atrial Fibrillation Detected (%)

Duration of ECG Monitoring

24 Hr: 2.2
1 Wk: 7.4
2 Wk: 11.6
3 Wk: 12.3
4 Wk: 14.8
CRYSTAL-AF

- Implantable loop recorder compared to conventional monitoring
  - 8.9% vs. 1.4% at 6 months
  - 12.4% vs. 2.0% at 12 months
  - Median time-41 days
  - >70% episodes were asymptomatic

Limitations

• Patient selection
• Does not prove a causal relationship
  • Intracranial vascular imaging or TEE not mandatory in EMBRACE
• How long is enough?
• What about the duration?
  • “AF burden”
• Less than 1/3 CS had documented AF after 3 years
Conclusions

• **Intracranial stenosis**
  • High recurrence rate
  • Aggressive medical management

• **PFO**
  • Often incidental
  • Amplatzer device in young patients with pathogenic PFO

• **Occult AF**
  • Long term cardiac rhythm monitoring
  • Look hard and keep looking