Cryptogenic Stroke: A logical approach to a common clinical problem

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Disclosures

• Speakers Bureau
  • Boston Scientific
  • Medtronics Vascular
  • Philips/Volcano Corp
  • Novartis
Objectives

• Review common causes for cryptogenic stroke
• Review cardiovascular work up for stroke
• Review CHADS2Vasc score and the associated risk for stroke with atrial fibrillation
• Review the ROPE score and use in stroke associated with PFO
• Review interventionalal treatments to reduce risk of stroke
Importance of Stroke

• 795,000 strokes per year with 140,000 deaths
• 87% are of strokes are ischemic
• $34 billion yearly cost in US
• Leading cause of disability in the US
• 5th leading cause of death
Causes of stroke

- Most common is carotid artery disease or “large vessel atheroembolism
- Hypertension/lacunar strokes
- Atrial fibrillation: cardioembolic
- Aneurysm rupture
- Rare/look alikes: tumors/endocarditis/seizures/migraine
Patient Example

- 47 y.o. female presents to the ER with sudden speech difficulty associated with mild headache
- PMHx: migraines, no HTN, DM, HLP
- Medication: Imitrex prn
- VS: BP 138/86, HR 88, afebrile, sat 97% on RA
- Exam: normal except mild right sided weakness and slurred speech
- CT in ER, normal without bleed
- ECG: sinus rhythm without ST changes
- ER Labs: normal
Patient Example

- Patient seen by neurology and given TPA with resolution of symptoms in 2 hours
- Admitted to floor
- MRI shows left MCA stroke
- Carotid doppler study without plaque
- EEG negative
- MRA shows normal intracranial vessels
- Cardiology consulted: Dx Cryptogenic stroke
Cryptogenic Stroke

- 20-30% of strokes are classified as cryptogenic
- Stroke with no identifiable cause after initial work up
- Most common causes:
  - Paroxysmal atrial fibrillation
  - PFO
  - Aortic atheroma
Patient Example

- Cardiology recommended:
  - Telemetry monitoring for 48 hours
    - Initial assessment for AF
  - Bubble study
    - Initial assessment for PFO
  - TEE
    - Assessment for PFO and aortic atheroma
Paroxysmal Atrial fibrillation

- stroke risk same as permanent af
- stroke risk dependent on multiple risk factors
- highest incidence with conversion of atrial fibrillation to sinus rhythm
- Patient often in NSR on arrival
Why we worry about atrial fibrillation.
CHADS2Vasc Score

- Age >65
- Age >75
- Female
- Hypertension
- Diabetes
- Previous TIA/Stroke
- Vascular disease (coronary, carotid or PAD)
## KNOW YOUR STROKE RISK

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
<th>CHA2DS2-VASc Score</th>
<th>Adjusted stroke rate (% / year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF &lt;40%</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>2</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Stroke / TIA / Thromboembolism</td>
<td>2</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

*CHF = congestive heart failure; TIA - transient ischemic attack; LVEF = left ventricular ejection fraction.*
Detecting Atrial Fibrillation

- Rare during hospitalization
- 2 week event monitor as outpatient
- Implantable loop recorder more frequently used
  - Patients over age 60
  - Multiple atrial fibrillation “risk factors”
  - Symptoms of palpitations
Implantable loop recorders
Treatment

• Oral Anticoagulation
  • Warfarin
  • Novel oral anticoagulants: Pradaxa, Xarelto, Eliquis, Savaysa
• Left atrial appendage ligation/exclusion
  • Surgical
  • Endovascular
    • Lariat
    • Watchman
    • Amulet
Oral Anticoagulation

- Rely on Coumadin
- Pradaxa
dabigatran etexilate
    - Capsules
- Xarelto
  - rivaroxaban
- Eliquis
  - (apixaban) tablets
- Savaysa
  - (edoxaban) tablets
  - 60mg/30mg

CVAM
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Oral Anticoagulation is Standard of Care, but Not Ideal for All

Warfarin
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

Novel Oral Anticoagulants
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost

Anticoagulation Use Declines with Increased Stroke Risk

\( p < 0.001 \) (n=27,164)
Stroke Treatment Option: warfarin (Coumadin®)

Warfarin is an effective means of stroke reduction in patients with AF but can present challenges

- Many patients spend a significant amount of time outside of the therapeutic range.

- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans\(^2\)

44% of bleeding events occur in patients above

48% of thromboembolic events occur in patients

INR

Over-anti-

Under-anti-
Stroke Treatment Option: Novel Oral Anticoagulants (NOACs)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban(^1)</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban(^2)</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran(^3)   (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban(^4)     (60 mg / 30 mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin(^1-4)</td>
<td>17 – 28%</td>
<td>3.1 – 3.6%</td>
</tr>
</tbody>
</table>
Surgical left atrial appendage ligation.
Lariat
WATCHMAN™ LAAC Closure Device

Minimally Invasive, Local Solution
• Available sizes: 21, 24, 27, 30, 33 mm diameter

Intra-LAA design
• Avoids contact with left atrial wall to help prevent complications

Nitinol Frame
• Conforms to unique anatomy of the LAA to reduce embolization risk
• 10 active fixation anchors - designed to engage tissue for stability

Proximal Face
• Minimizes surface area facing the left atrium to reduce post-implant thrombus formation
• 160 micron membrane PET cap designed to block emboli and promote healing

Warfarin Cessation
• 92% after 45 days, >99% after 12 months\(^1\)
• 95% implant success rate\(^1\)
Watchman

- Performed in a cardiac cath lab/EP suite, performed by a Heart Team
  - IC/EP or IC&EP, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein
- 1 hour procedure and 1-2 day hospital stay
WATCHMAN™ Device Outcomes

Events in PROTECT AF trial at 2,621 patient years

- **Primary Efficacy**
  - 40% lower
  - Watchman Group: 2.3
  - Warfarin Group: 3.8

- **CV or Unexplained Death**
  - 60% lower
  - Watchman Group: 1
  - Warfarin Group: 2.4

- **All-Cause Death**
  - 34% lower
  - Watchman Group: 3.2
  - Warfarin Group: 4.8

All three endpoints met statistical superiority
PFO

- Common in general population: 10-25% of the population based on autopsy studies
- Dynamic structure
- 50% will be seen on trans thoracic echo with bubble study
- 90% will be seen on trans esophageal echo with bubble study
- Transcranial doppler, more sensitive but less specific
PFO Embryology

A
Right Left

B
Primary Foramen
Fenestrations

C
Secondary Foramen

D
PFO
Fossa Ovalis

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Association between PFO and Stroke

- Lechat in 1988 credited with first paper to describe the association between PFO and stroke in NEJM.
- Multiple studies have had different results
- Controversy has existed since the first FDA HDE for PFO closure before 2006, when it was removed to promote enrollment in trials
- CLOSURE, PC, RESPECT and REDUCE all took longer than expected to enroll patients
Are PFO’s associated with stroke?
## Risk Of Paradoxical Embolus

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hypertension</td>
<td>1</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1</td>
</tr>
<tr>
<td>No stroke/TIA</td>
<td>1</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>1</td>
</tr>
<tr>
<td>Age &lt;30</td>
<td>5</td>
</tr>
<tr>
<td>Age 30-39</td>
<td>4</td>
</tr>
<tr>
<td>Age 40-49</td>
<td>3</td>
</tr>
<tr>
<td>Age 50-59</td>
<td>2</td>
</tr>
<tr>
<td>Age 60-69</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;70</td>
<td>0</td>
</tr>
</tbody>
</table>

### Score vs. PFO % & 2yr TIA/CVA Recurrence

<table>
<thead>
<tr>
<th>Score</th>
<th>PFO %</th>
<th>2yr TIA/CVA recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>38%</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>34%</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>62%</td>
<td>8%</td>
</tr>
<tr>
<td>7</td>
<td>72%</td>
<td>6%</td>
</tr>
<tr>
<td>8</td>
<td>84%</td>
<td>6%</td>
</tr>
<tr>
<td>9-10</td>
<td>88%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Kent, D, MD., et al
Neurology 2013:81:619-625

UCVAM
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Treatment

• Medical Therapy
  • Aspirin
  • Aspirin plus dipyridamole
  • Aspirin plus clopidogrel
  • Warfarin

• Device Closure
Medical Therapy

- PICCS trial showed no difference between aspirin and warfarin and no association between size of PFO and ASA and stroke risk
- Controversy has existed because of FDA guidelines for closure for “recurrent stroke or TIA on medical therapy”
Device Closure

- One FDA approved device
  - Amplatzer PFO occluder
- One FDA reviewing device
  - Gore Cardioform
Amplatzer Device

AMPLATZER PFO Occluder

- Percutaneous, transcatheter device
- Self-expanding, double-disc design
- Nitinol wire mesh with polyester fabric/thread
- Radiopaque marker bands
- Sizes: 18, 25, 35 mm
- Recapturable and repositionable

*CAUTION: Investigational device in the United States. Limited by Federal (or U.S.) law to investigational use. Not available for sale in the U.S.*
RESPECT Trial

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)

- Event-free Probability
- Time from Randomization (Years)
  - AMPLATZER PFO Occluder (# strokes = 10)
  - Medical Management (# strokes = 23)
  - Risk Reduction: 62%
  - HR: 0.38 (95% CI: 0.18, 0.79)
  - Log-rank 2-sided p-value = 0.007

# at Risk (KM Estimates)
- AMPLATZER: 499 (0%) 476 (1.2%) 464 (1.2%) 447 (1.2%) 421 (1.5%) 362 (2.0%) 262 (2.0%) 197 (2.3%) 128 (2.3%) 77 (2.3%) 41 (2.3%)
- MM: 481 (0%) 433 (1.3%) 394 (2.7%) 360 (3.5%) 354 (4.0%) 262 (4.0%) 218 (4.0%) 150 (5.1%) 104 (5.0%) 59 (7.0%) 31 (11.1%)
The device delivery sheath is advanced via the inferior vena cava into the right atrium and through the patent foramen ovale. The left atrial disk is then expanded.

The left atrial disk is retracted against the septal wall, and the delivery sheath is pulled back into the right atrium, where the right atrial disk is deployed.

The device is fully expanded, closing the patent foramen ovale. The delivery sheath is removed.
Cardioform Device

Figure 3. The Gore Helex septal occluder.
REDUCE Study: Recurrent clinical ischemic stroke
Primary endpoint result: New brain infarct

- 49 percent relative risk reduction for PFO closure on new brain infarct at 2 years
- Difference in incidence of new brain infarct of 5.6 percent

The REDUCE Study is the first to assess the relationship between PFO closure and the reduction of new brain infarct.

Relative risk: 0.51
95% CI: 0.29 to 0.91
One-sided P = 0.024
Adjusted for multiple testing
Summary

- Cryptogenic stroke: 20-30% of stroke
- Atrial fibrillation and PFO most common
- AF requires long monitoring to exclude
- PFO requires bubble and TEE (age <60)
- Devices for monitoring and treatment of both readily available, safe and effective
- CHADS2Vasc and ROPE scores helpful in assessing individual patient risk