New Frontiers in AF Stroke Prevention

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Disclosures: none
Citations in slide notes
Objectives

• Defining risk of AF-related stroke
• Defining risks/benefits of anticoagulation
• Historical alternatives to oral anticoagulation
• New therapies to prevent AF-related stroke

• **These data are only applicable to *non-valvular AF*
Defining the risks

- 20-30% of all strokes are directly related to AF
- >90% of intracardiac thrombi are located in the LAA
- Anticoagulation generally reduces stroke risk by 1/2
- The only proven method to reduce mortality related to AF!

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF or LVEF ≤ 40%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 - 74</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
</tbody>
</table>
Options for anticoagulation

• Historically, coumadin was the only option
• Since 2009, NOACs have been an alternative (superior?) option
• >71,000 patients studied!
Balancing risks and benefits

- Oral anticoagulation is associated with a risk of bleeding
- For *most* patients, the benefits of OAC outweigh the risks
- Generally, bleeding can be addressed directly (endoscopy, cystoscopy, etc)
Historical alternatives to anticoagulation

- Since the LAA is the major source of AF-related emboli, LAA ligation/excision has been an attractive therapeutic option
  - Surgical approach (limited utility as a stand-alone procedure)
  - Widely variable success
    - 0% for stapler exclusion
    - 22% for suture ligation
    - Up to 73% for surgical excision (primarily smooth-walled stump; no residual trabeculations)
New approaches to LAA exclusion

• Device-based LAA ligation/exclusion has the advantage of producing more consistent LAA closure
  • AtriClip (AtriCure)
    • >90% closure efficacy
    • Surgical (less invasive) approach
  • LARIAT (SentreHeart)
    • Percutaneous approach, but requires epicardial access

• Extrinsic LAA ligation/exclusion also has the benefit of "silencing" the LAA
  • One of the focal "triggers" for atrial fibrillation

• Downsides of epicardial approach to LAA?
  • Pericarditis
  • Limited access in patients with prior surgery
What about totally percutaneous options for LAA occlusion?

• Watchman (Boston Scientific) LAA occlusion device
  • Entirely percutaneous – femoral venous access, transseptal puncture into LA
  • Deployment guided by fluoroscopy and TEE
  • Simple “plug” mechanism
  • Endovascular deployment – requires anticoagulation in the early post-closure period!
  • Followup TEE to ensure LAA closure (6 weeks)
Watchman experience

- PROTECT-AF trial (enrolled 2005-2008, followup through 2012)
  - 2:1 randomization to Watchman vs coumadin
  - 1 of more CHADS2-VASc risk factors
    - Mean 2.2
  - Eligibility for *long-term coumadin*
  - 88% acute deployment success
    - 92% LAA closure at 6 months
    - 87% discontinued coumadin at 45 days

<table>
<thead>
<tr>
<th>Device Group, No. (%) (n = 463)</th>
<th>Total Events</th>
<th>Early Events(^a)</th>
<th>Late Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious pericardial effusion</td>
<td>22 (4.8)</td>
<td>22 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>22 (4.8)</td>
<td>3 (0.6)</td>
<td>19 (4.1)</td>
</tr>
<tr>
<td>Procedure-related ischemic stroke</td>
<td>6 (1.3)</td>
<td>5 (1.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Device embolization</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3 (0.6)</td>
<td>0</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (0.9)</td>
<td>4 (0.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Early Events: Events occurring within the first 30 days of device deployment or 6 months of enrollment, whichever occurred later.
Watchman experience

• PREVAIL trial (enrolled through 6/2012)
  • 2:1 randomization to Watchman vs coumadin
  • CHADS2-VASc 2 or greater
    • Mean 3.8
  • Eligibility for *long-term coumadin*
  • 95% deployment success
    • 92% discontinued coumadin at 45 days
  • “Overperforming” control group
    • Non-inferiority NOT met

| Table 5 Safety Coprimary Endpoint Results and Events by Type |
|----------------------------------------|--------------|
| Intention-to-Treat: Device Group Only |
| Safety primary endpoint results        | % (n/N)      | 95% Crl |
|                                       | 2.2% (6/269) | 2.652%  |

<table>
<thead>
<tr>
<th>Safety events by type</th>
<th>No. of Events</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device embolization</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Pericardial effusion with cardiac tamponade</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Major bleed requiring transfusion</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Figures 4 and 5*
Watchman candidacy

• Non-valvular AF
• CHADS2-VASc =/> 3
• Ability to tolerate short-term OAC, with a reason to avoid long-term OAC
  • Recurrent GI bleeds/epistaxis/hematuria/intracranial lesions at risk but not actively bleeding
  • FALLS!!!
  • Lifestyle

• Exclusion:
  • Valvular AF
  • Alternative reason for long-term OAC
  • Documented LAA thrombus
  • Unfavorable LAA anatomy
  • Prior ASD/PFO closure with percutaneous device
Summary

- Stroke prevention is the only proven therapy to reduce AF-related mortality
- NOACs have proven themselves a suitable alternative to coumadin
  - Apparent superiority in followup analyses
- In patients who are not candidates for OAC, LAA closure is a viable therapeutic option
  - Extrinsic: clip/ligation/excision – more invasive, able to “silence” the LAA
  - Intrinsic: occlusion – entirely percutaneous

- Thank you! Questions/comments?

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Bonus: a few words on OAC reversal

- Vitamin K and FFP have traditionally been used for coumadin “reversal”
  - Supratherapeutic INRs
  - Acute bleeding
- With the exception of Praxbind (idarucizumab), there are no approved reversal agents for NOACs
  - Because they are a clotting factor *inhibitor*, the use of donor blood products is limited
- The data behind NOACs show non-inferiority (post-hoc superiority?) vs coumadin in bleeding events, and in all-cause mortality!
  - Less bleeding due to time spent “out-of-range”?
  - Less serious bleeding?
  - Overestimation of the utility of “reversal” agents?