Etiology of Stroke and the Pros and Cons of Device-Based LAA Closure

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Disclosures

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• I will be discussing the use of non-FDA approved or off-label use of investigational catheter-based devices.
AF-Related Stroke

- 500,000 strokes per year
- 15 – 20% of strokes/year are related to AF
- Functional Impact of AF-Related Stroke:
  - Transient: 11%
  - Moderately Disabling: 11%
  - Non-Disabling: 17%
  - Severe Neurological Deficit: 28%
  - Fatal: 31%
  - Unknown: 2%

## Efficacy of Warfarin

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Events</th>
<th>Patient-years</th>
<th>Risk Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>27</td>
<td>811</td>
<td></td>
</tr>
<tr>
<td>BAATAF</td>
<td>15</td>
<td>922</td>
<td></td>
</tr>
<tr>
<td>CAFA</td>
<td>14</td>
<td>478</td>
<td></td>
</tr>
<tr>
<td>SPAF</td>
<td>23</td>
<td>508</td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td>29</td>
<td>972</td>
<td></td>
</tr>
<tr>
<td>Combined*</td>
<td>108</td>
<td>3691</td>
<td></td>
</tr>
</tbody>
</table>

*Total risk reduction for all 5 studies combined is 69%
Difficulties with Warfarin Use

- Narrow therapeutic profile
  - Frequent blood draws

- Bleeding risk
  - Intracranial Hemorrhage

- Drug/Diet Interactions

- Physician Reluctance to prescribe to elderly patients
  - Risk of falling
  - Compliance issues
Warfarin Use in AF Patients

- Only 55% of AF patients with no contraindications to warfarin had evidence of warfarin use in previous 3 months
- Other studies site warfarin use among AF patients from 17% - 50%
- Elderly patients with an increased absolute risk of stroke were least likely to be taking warfarin

*Annals of Internal Medicine*, 1999; 131(12): 927-934
Warfarin Net Clinical Benefit: Impact of Age

Net Clinical Benefit, Events Prevented per 100 Person-Years

Warfarin Efficacy: Trial vs Practice

Stroke Risk Reductions

Effect of multiple antithrombotics on serious bleeding rates

A cohort study using Danish Registry of >100,000 AF patients

<table>
<thead>
<tr>
<th>Therapy</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin monotherapy</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td>0.93 (0.88-0.98)</td>
</tr>
<tr>
<td>Clopidogrel monotherapy</td>
<td>1.06 (0.87-1.29)</td>
</tr>
<tr>
<td>Aspirin + clopidogrel</td>
<td>1.66 (1.34-2.04)</td>
</tr>
<tr>
<td>Warfarin + aspirin</td>
<td>1.83 (1.72-1.96)</td>
</tr>
<tr>
<td>Warfarin + clopidogrel</td>
<td>3.08 (2.32-3.91)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>3.70 (2.89-4.76)</td>
</tr>
</tbody>
</table>

Novel Anticoagulant Strategies

- Novel Anticoagulants
  - Anti-Platelet Agents
  - Thrombin Inhibitors
    - Dabigatran (RELY)
  - Factor Xa Inhibitors
    - Apixaban (AVERROES)
    - Rivaroxaban (ROCKET AF)

- LA Appendage Closure
  - Surgical
  - Vascular
    - PLAATO
    - Amplatzer Cardiac Plug
    - WATCHMAN
  - Epicardial

**RELY**: Dabigatran vs Warfarin

RR = 0.66
95% CI = 0.53 – 0.82)
P < 0.001

**AVERROES**: Apixaban/ASA vs ASA

Dabigatran: Musings on Cost

• Costs in Ireland:
  – Warfarin (at 5 mg / day) = $3.55 / month
  – Dabigatran (110 mg BID) = $239.55 / month
  – Currently, > 32,500 patients in Ireland take the medication
  – If 50% switched, $45 million / year
    → Equivalent to 10% of total cost of CV drugs in Ireland

• Estimates for the US:
  – Dabigatran (150 mg BID) = $339 / month
    – Is 10 x cost of Warfarin (including INR monitoring)
  – In RELY, NNT to prevent 1 stroke w/ Dabigatran-150 is 357
  – Translates to $1.3 million to prevent 1 stroke (vs Warfarin)
  – If double the risk (eg, CHADS₂ = 3-4), cost halved
  – [Not take into account cost of care of a stroke patient … estimated at $28,500 over 1st year]

Stroke Prophylaxis: Alternatives to Drugs

- Novel Anticoagulants
  - Anti-Platelet Agents
  - Thrombin Inhibitors
    - Dabigatran
  - Factor Xa Inhibitors
    - Rivaroxaban

- LA Appendage Closure
  - Surgical
  - Epicardial
  - Vascular
    - PLAATO
    - Amplatzer Cardiac Plug
    - WATCHMAN

Blackshear and Odell, Ann Thoracic Surgery 1996
Stroke Prophylaxis: Alternatives to Drugs

- **Novel Anticoagulants**
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  - Thrombin Inhibitors
    - Dabigatran
  - Factor Xa Inhibitors
    - Rivaroxaban

- **LA Appendage Closure**
  - Surgical
  - Epicardial
  - Vascular
    - PLAATO
    - Amplatzer Cardiac Plug
    - WATCHMAN

(Modified from slide from: E Sosa, M Scanavacca, A d’Avila)
Stroke Prophylaxis: Alternatives to Drugs

- Novel Anticoagulants
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  - Thrombin Inhibitors
    - Dabigatran
    - Factor Xa Inhibitors
      - Rivaroxaban

- LA Appendage Closure
  - Surgical
  - Epicardial
  - Vascular
    - PLAATO
    - WATCHMAN
    - Amplatzer Cardiac Plug
PROTECT-AF: Overview

• Randomized FDA-IDE Trial
  – Can the WATCHMAN device *replace* Warfarin?

• Inclusion / Exclusion Criteria

• Efficacy Endpoint:
  – Stroke
  – CV death (& Unknown)
  – Systemic embolism

• Safety Endpoint

• Non-inferiority Study
  – Bayesian Sequential Design
  – Analysis at 600 pt-yrs & every 150 pt-yrs thereafter \( \rightarrow \) to 1500 pt-yr

<table>
<thead>
<tr>
<th>Cohort</th>
<th>WATCHMAN</th>
<th>Control</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1050 Pt-Yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rate (Events/100 Pt-Yrs)</td>
<td>Rate (Events/100 Pt-Yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-To-Treat</td>
<td>3.0</td>
<td>4.9</td>
<td>0.62</td>
<td>0.33, 1.17*</td>
</tr>
<tr>
<td>Post-Procedure</td>
<td>2.2</td>
<td>4.9</td>
<td>0.45</td>
<td>0.23, 0.90</td>
</tr>
</tbody>
</table>

* Using Cox Proportional Model

**Intention-To-Treat**

**Post-Procedure**

**Procedure-Related Stroke**

0%
### Primary Safety Results: Intent-To-Treat

<table>
<thead>
<tr>
<th>Cohort</th>
<th>WATCHMAN Rate (Events/100 Pt-Yrs)</th>
<th>Control Rate (Events/100 Pt-Yrs)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1050 Pt-Yrs</td>
<td>7.4</td>
<td>4.4</td>
<td><strong>1.69</strong></td>
<td><strong>0.96, 2.97</strong></td>
</tr>
</tbody>
</table>

#### Primary Safety

- **Pericardial Effusion / Tamponade**
  - 22 requiring Tx (4.8% of patients)
    - 15 treated percutaneously
    - 7 underwent surgical intervention
  - Extended hospitalization
  - No Death or Long-term Disability

- **Effect of operator experience**
  - < 2% (CAP Registry)

➡️ ➡️ How do we interpret this safety data?
Safety Data Interpretation

• As with any Device vs Drug comparison, must balance the:
  – Higher up-front, acute risk of complications with a procedure
  – Numerically-lower, but continual, risk of drug therapy

• Since complications different in each group, how to compare?
  – Composite event rates of each group
  – Time course of the events
  – Is there evidence for experience – related improvements?
  – What is the functional impact of this heterogeneous group of events?

## Intent-to-Treat: All-Cause Mortality

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device rate (95% CI)</th>
<th>Control rate (95% CI)</th>
<th>Rel. Risk (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 pt-yrs</td>
<td>2.9 (1.7, 4.4)</td>
<td>4.7 (2.5, 7.1)</td>
<td>0.61 (0.32, 1.32)</td>
<td>99.9%</td>
<td>88.9%</td>
</tr>
<tr>
<td>1050 pt-yrs</td>
<td>3.0 (1.9, 4.5)</td>
<td>4.8 (2.5, 7.1)</td>
<td>0.62 (0.34, 1.24)</td>
<td>99.9%</td>
<td>90.7%</td>
</tr>
</tbody>
</table>

**Event Free Probability over Time**

- **Watchman**
- **Control / Warfarin**

900 patient-year Analysis
## Significant Disability or Death (1350 pt-yrs)

<table>
<thead>
<tr>
<th></th>
<th>Watchman Rate Events (per 100 Pt-Yrs)</th>
<th>Control Rate Events (per 100 Pt-Yrs)</th>
<th>Relative Risk (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS Increase ≥ 1 Or Death</td>
<td>1.6 (14 / 902.6)</td>
<td>4.5 (21 / 468.4)</td>
<td>0.35 (0.18, 0.73)</td>
</tr>
<tr>
<td>MRS Increase ≥ 2 Or Death</td>
<td>1.2 (11 / 908.8)</td>
<td>3.8 (18 / 471.9)</td>
<td>0.32 (0.15, 0.72)</td>
</tr>
<tr>
<td>MRS Increase ≥ 3 Or Death</td>
<td>1.1 (10 / 910.3)</td>
<td>3.6 (17 / 475.0)</td>
<td>0.31 (0.14, 0.71)</td>
</tr>
</tbody>
</table>

Next Generation Watchman

- 18 Splines
- Bumper / Stabilizer
- Completely Re-Capturable
Next Generation Watchman
Next Generation Watchman
Next Generation Watchman
Final Thoughts

• Despite higher bleeding risk, the net benefit of Warfarin is even greater in the Elderly

• LAA Occlusion/Exclusion is an appropriate avenue of investigation for the prevention of stroke in patients with non-valvular AF

• LAA Closure with Implant
  – Watchman is a reasonable alternative to Warfarin
  – Safety issues related to experience
  – Need data w/ other devices