Percutaneous Left Atrial Appendage Occlusion - Watchman

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Disclosures

• None

Stroke Risk in Atrial Fibrillation

• AF afflicts 5-7 million individuals in the U.S.
• Incidence of AF is increasing
• AF increases the risk of stroke by 6-fold

Determining Stroke Risk

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
</tbody>
</table>

PK Mason Am J Medicine (2012)
Anticoagulants Decrease Risk for Stroke in AF
But how often are they used?

Anticoagulation Use Declines with Increased Stroke Risk

<table>
<thead>
<tr>
<th>CHADS₂ Score</th>
<th>AF Patients Using Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>40%</td>
</tr>
</tbody>
</table>

p < 0.001 (n=27,164)

Piccini, et al., Heart Rhythm, 2012; 9:1403-1408

Stroke Prophylaxis in AF

• Difficulties with Warfarin use
  – Frequent Monitoring
  – Difficulty in Compliance (TTR 48-63%)
  – Drug / Diet Interactions
  – Bleeding Risk (ICH)
  – Risks in Elderly (Falls, Poly-pharmacy)
• (NOACs also have issues)
• Autopsy & TEE data implicate LAA
• LAA Closure Devices

Left Atrial Appendage Closure
Important Issues To Consider

1. Can a thrombus originate from outside the LAA?
2. Were the patients enrolled in the trials of sufficient risk?
3. How safe is the Watchman implantation procedure?
4. PROTECT AF/PREVAIL were randomized against Warfarin … But now that we have NOACs …
5. How cost-effective is LAAC?
6. What if there is a strong contraindication to warfarin?
PROTECT-AF & PREVAIL
Design & Overview

- Randomized FDA-IDE Trials
  - Can the WATCHMAN device replace Warfarin?
  - PREVAIL: At least 25% new operators

- Efficacy Endpoints:
  - 1st Endpoint: Stroke / Systemic embolism / CV death (unknown)
  - 2nd endpoint: Thromboembolic Stroke / Systemic embolism (Post 7 days)

- Bayesian Statistical Plan
  - Non-inferiority & Superiority
  - Informative Prior?
    - PROTECT-AF: None
    - PREVAIL: Discounted data from PROTECT-AF

PROTECT AF
Superiority of Watchman over Warfarin

Primary Endpoint
- Stroke / SE / CV Death

CV Death
- Stroke / SE / CV Death

All-Cause Mortality vs Warfarin
Is a 34% Mortality Benefit by LAAC Plausible?

PROTECT-AF & PREVAIL
Combined Analysis

Table 1: PROTECT AF and CAP: Largest Data Sets to Evaluate Totality of Data

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>PREVAIL</th>
<th>CAP</th>
<th>CAP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>2000</td>
<td>400</td>
<td>566</td>
<td>579</td>
</tr>
<tr>
<td>Rando A</td>
<td>707</td>
<td>407</td>
<td>240</td>
<td>320</td>
</tr>
<tr>
<td>Watchman/warfarin</td>
<td>0.2</td>
<td>0.244</td>
<td>0.36</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean follow-up, y</td>
<td>4.0</td>
<td>2.2</td>
<td>3.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2,717</td>
<td>860</td>
<td>2,032</td>
<td>332</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3,373</td>
<td>1,530</td>
</tr>
</tbody>
</table>

CAP = Combined Access to PROTECT AF registry; CAP2 = Combined Access to PREVAIL registry; N/A = not applicable; PREVAIL = Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation vs Long-Term Warfarin Therapy; PROTECT AF = Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation.

Ruff et al., Lancet, 383:955 (2014)
## PROTECT-AF & PREVAIL Combined Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>1.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48</td>
<td>0.006</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.75</td>
<td>0.07</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.30</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleed, non procedure-related</td>
<td>0.51</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Favors WATCHMAN → Favors warfarin

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
</tr>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

## Impact of Strokes

**Disabling vs Non-Disabling**

<table>
<thead>
<tr>
<th>Category</th>
<th>Event Rate (per 100 pt-yrs)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>2.2</td>
<td>0.68 (0.42, 1.37)</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.5</td>
<td>1.2</td>
<td>0.37 (0.15, 1.00)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>1.0</td>
<td>1.0</td>
<td>1.05 (0.54, 2.80)</td>
</tr>
</tbody>
</table>

- PROTECT AF: 2621 pt-yrs
- Proportional Hazards Model
- Disabling stroke defined as MRS change of 2 or more or death
- Similar results if defined as absolute MRS > 2

## Left Atrial Appendage Closure

**Important Issues To Consider**

1. Can a thrombus originate from outside the LAA?
2. Were the patients enrolled in the trials of sufficient risk?
3. How safe is the Watchman implantation procedure?
4. Are there important workflow issues?
5. PROTECT AF/PREVAIL were randomized against Warfarin … But now that we have NOACs …
6. How cost-effective is LAAC?
7. What if there is a strong contraindication to warfarin?
Watchman Clinical Trials

Patients were at High Risk

CHA\(_{2}\)DS\(_{2}\)-VASc Score

- PROTECT AF
- CAP
- PREVAIL
- CAP2

- 93%
- 96%
- 100%
- 100%

Determine Bleeding Risk

HAS-BLED Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver and renal function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

(Modiﬁed) HAS-BLED Score

> 80% Patients at Moderate/High Bleeding Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Low Risk (%)</th>
<th>Moderate Risk (1-2)</th>
<th>High Risk (3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORTIF (Ximelegatran)</td>
<td>24.0</td>
<td>61.0</td>
<td>15.1</td>
</tr>
<tr>
<td>PROTECT AF (N=787)</td>
<td>6.4</td>
<td>73.1</td>
<td>19.9</td>
</tr>
<tr>
<td>PREVAIL (N=480)</td>
<td>4.1</td>
<td>88.9</td>
<td>7.9</td>
</tr>
<tr>
<td>CAP (N=505)</td>
<td>2.8</td>
<td>92.1</td>
<td>5.1</td>
</tr>
<tr>
<td>CAP2 (N=579)</td>
<td>2.8</td>
<td>69.9</td>
<td>28.3</td>
</tr>
</tbody>
</table>

Estimated – HAS-BLED Score retrospectively calculated. Labile INR and Abnormal LFT were not prospectively collected. Therefore, maximum score that WATCHMAN clinical trial patients could attain was 9.

Left Atrial Appendage Closure

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PROTECT AF
Primary Safety Endpoint

Follow-up Rate Ratio 95% CrI
2621 pt-ys 1.21 0.78, 1.94

Pericardial Effusion / Tamponade
22 requiring Tx (4.8% of patients)
10 treated percutaneously
1 underwent surgical Intervention
No Death or Long-term Disability

Effect of operator experience?

Key Procedural Safety Events
PROTECT AF vs CAP/PREVAIL

No Procedure-Related Deaths in the Clinical Trials (includes 1,877 patients receiving the device)

Safety Events Across Trials
PROTECT AF, CAP, PREVAIL & CAP-1

Patients with Safety Event (%)

PROTECT AF
1st Half 2nd Half
N=232 N=231 N=566 N=269 N=579

Pericardial Effusion / Tamponade
22 requiring Tx (4.8% of patients)
10 treated percutaneously
1 underwent surgical Intervention
No Death or Long-term Disability

Effect of operator experience?

PROTECT-AF & PREVAIL Combined Analysis
Less Bleeding after 6-mo Post-Implant

Free of Major Bleeding Event (%)

HR = 0.29 p<0.001

Warfarin+Aspirin Warfarin+Aspirin Clopidogrel Aspirin

V.Reddy et al., FDA Panel Presentation, October 2014.
Left Atrial Appendage Closure
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Drug Use Since the Introduction of NOACs
Warfarin is Still the Most Commonly Used Drug

Anticoagulant Use in Patients with NVAF and CHADS2 ≥ 2

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Total on Oral Anticoagulation

Warfarin

NOACs

Drug Use Since the Introduction of NOACs
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Total on Oral Anticoagulation

Warfarin

NOACs

Warfarin Use in General Practice
Non-Compliance is a Major Issue!


Preventing Stroke in Non-Valvular AF
Imputed Benefit of Different Strategies (vs Control)

% Reached statistical superiority relative to warfarin.
NOACs are Excellent Medications
But Not for Everyone…

2-yr Drug Cessation

RELY: Major Bleeding

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Economic Analysis: Cost Effectiveness
Watchman vs NOACs vs Warfarin

- Patient level Markov micro-simulation decision analytic model
- Assess Time-to-Cost Effectiveness (not just lifetime horizon – 20 yrs)
- Economic costs from the U.S. perspective, and costs in 2015 US$ 
  - For LAAC procedure, we used the new DRG 273/274 (US average: $16,109)
  - Latest PROTECT AF data (4 yrs f/u)
  - NOAC meta-analysis of all 4 NOACs (Ruff et al, Lancet 383:955, 2014)
  - Incorporated costs based on the level of disability resulting from strokes


Left Atrial Appendage Closure
Important Issues To Consider

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Watchman is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are:
1. At increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores
2. Are suitable for warfarin
3. And have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

Left Atrial Appendage Closure Important Issues To Consider
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The LAA is critical to the pathogenesis of stroke

- "Local" therapy with LAA closure is comparable to Warfarin
  - LAAC less effective in preventing Ischemic Strokes, but balanced by fewer Hemorrhagic Strokes
  - Over 50% reduction in Disabling Strokes
  - Over 50% reduction in Cardiovascular Mortality

- Overall safety event rate similar, but up-front risk
  - Cardiac Tamponade Rate decreases with operator experience

- 5% [PROTECT AF] → 1-2% [CAP/PREVAIL/CAP-2]

- Many evidence gaps:
  - Contraindicated Trial: ASAP-TOO will start in 2016
  - LAAC vs NOACs trial??!
  - How to integrate catheter ablation with LAAC in clinical practice?