PROTECT AF Trial:
Randomized Prospective Trial of Percutaneous LAA Closure vs Warfarin for Stroke Prevention in AF

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Relevant Financial Relationship(s)
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Facts about Atrial Fibrillation (AF)

- AF is the most common cardiac arrhythmia
  - Affects more than 3 million individuals in the US
  - Projected to increase to 16 million by 2050
- Patients with AF have a 5-fold higher risk of stroke
  - Over 87% of strokes are thromboembolic
  - Greater than 90% of thrombus accumulation originates in the Left Atrial Appendage (LAA)
- Stroke is the number one cause of long-term disability and the third leading cause of death in patients with AF
Non-Valvular Atrial Fibrillation Stroke Prevention

Medical Rx

- Warfarin cornerstone of therapy
- Assuming 51 ischemic strokes/1000 pt-yr
  - Adjusted standard dose warfarin prevented 28 strokes at expense of 11 fatal bleeds
  - Aspirin prevented 16 strokes at expense of 6 fatal bleeds
- Warfarin
  - 60-70% risk reduction vs no treatment
  - 30-40% risk reduction vs aspirin

Cooper: Arch Int Med 166, 2006
Challenges in Treating AF

- However warfarin is not always well-tolerated
  - Narrow therapeutic range (INR between 2.0 – 3.0)
  - Effectiveness is impacted by interactions with some foods and medications
  - Requires frequent monitoring and dose adjustments
- Published reports indicate that less than 50% of patients eligible are being treated with warfarin due to tolerance or non-compliance issues
- SPORTIF trials suggest only 60% of patients treated are within a therapeutic INR range, while 29% have INR levels below 2.0 and 15% have levels above 3.0
The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA.

The WATCHMAN® Left Atrial Appendage Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation.
WATCHMAN LAA Closure Device in situ

Plane of maximum diameter distal to ostium

Fixation barbs engage LAA wall
PROTECT AF Clinical Trial Design

• Prospective, randomized study of WATCHMAN LAA Device vs. Long-term Warfarin Therapy
• 2:1 allocation ratio device to control
• 800 Patients enrolled from Feb 2005 to Jun 2008
  • Device Group (463)
  • Control Group (244)
  • Roll-in Group (93)
• 59 Enrolling Centers (U.S. & Europe)
• Follow-up Requirements
  • TEE follow-up at 45 days, 6 months and 1 year
  • Clinical follow-up biannually up to 5 years
  • Regular INR monitoring while taking warfarin
• Enrollment continues in Continued Access Registry
Patient Study Timeline

- **Device**
  - Day 0: Preimplant interval
  - Day 2-14: Device subject takes warfarin
  - Day 45 postimplant: Device subject has ceased warfarin
  - Ongoing to 5 years: Device

- **Control**
  - Randomize
  - Day 0: Control subject takes warfarin
  - Ongoing to 5 years: Control

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**Ongoing to 5 years**
87% of implanted subjects were able to cease warfarin at 45 days and the rate further increased at later time points.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Watchman N/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 day</td>
<td>349/401 (87.0)</td>
</tr>
<tr>
<td>6 month</td>
<td>347/375 (92.5)</td>
</tr>
<tr>
<td>12 month</td>
<td>261/280 (93.2)</td>
</tr>
<tr>
<td>24 month</td>
<td>95/101 (94.1)</td>
</tr>
</tbody>
</table>

- Reasons for remaining on warfarin therapy after 45-days:
  - Observation of flow in the LAA (n = 30)
  - Physician Order (n = 13)
  - Other (n = 9)
PROTECT AF Trial Endpoints

• **Primary Efficacy Endpoint**
  - All stroke: ischemic or hemorrhagic
    - deficit with symptoms persisting more than 24 hours or
    - symptoms less than 24 hours confirmed by CT or MRI
  - Cardiovascular and unexplained death: includes sudden death, MI, CVA, cardiac arrhythmia and heart failure
  - Systemic embolization

• **Primary Safety Endpoint**
  - Device embolization requiring retrieval
  - Pericardial effusion requiring intervention
  - Cranial bleeds and gastrointestinal bleeds
  - Any bleed that requires $\geq 2$uPRBC

• NB: Primary effectiveness endpoint contains safety events
PROTECT AF Bayesian sequential design

- Accrue patient-yr up to possible maximum of 1,500
- Analyze at specific time points; 600 patient-yr, then every 150 pt-yr thereafter
- Successful non-inferiority based on first time success criterion met
- Success criterion defined on probability scale
  - >97.5% probability that primary efficacy event rate for WATCHMAN is less than two times control
  - >5% probability that primary efficacy event rate for WATCHMAN is less than control
### Key Participation Criteria

#### Key Inclusion Criteria
- **Age 18 years or older**
- **Documented non-valvular AF**
- **Eligible for long-term warfarin therapy, and no other conditions that would require long-term warfarin therapy**
- **Calculated CHADS2 score > 1**

#### Key Exclusion Criteria
- **NYHA Class IV Congestive Heart Failure**
- **ASD and/or atrial septal repair or closure device**
- **Planned ablation procedure within 30 days of potential WATCHMAN Device implant**
- **Symptomatic carotid disease**
- **LVEF < 30%**
- **TEE Criteria: Suspected or known intracardiac thrombus (dense spontaneous echo contract)**
## Patient Demographics

### Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WATCHMAN N= 463</th>
<th>Control N= 244</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.7 ± 8.8</td>
<td>72.7 ± 9.2</td>
<td>0.1800</td>
</tr>
<tr>
<td></td>
<td>463 (46.0, 95.0)</td>
<td>244 (41.0, 95.0)</td>
<td></td>
</tr>
<tr>
<td>Height (inches)</td>
<td>68.2 ± 4.2</td>
<td>68.4 ± 4.2</td>
<td>0.6067</td>
</tr>
<tr>
<td></td>
<td>462 (54.0, 82.0)</td>
<td>244 (59.0, 78.0)</td>
<td></td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>195.3 ± 44.4</td>
<td>194.6 ± 43.1</td>
<td>0.8339</td>
</tr>
<tr>
<td></td>
<td>463 (85.0, 376.0)</td>
<td>244 (105.0, 312.0)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>137/463 (29.6)</td>
<td>73/244 (29.9)</td>
<td>0.9276</td>
</tr>
<tr>
<td>Male</td>
<td>326/463 (70.4)</td>
<td>171/244 (70.1)</td>
<td></td>
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</tbody>
</table>
## Patient Demographics

### Baseline Risk Factors

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>WATCHMAN N= 463</th>
<th>Control N= 244</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>158/463 (34.1)</td>
<td>66/244 (27.0)</td>
<td>0.3662</td>
</tr>
<tr>
<td>2</td>
<td>157/463 (33.9)</td>
<td>88/244 (36.1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>88/463 (19.0)</td>
<td>51/244 (20.9)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37/463 (8.0)</td>
<td>24/244 (9.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19/463 (4.1)</td>
<td>10/244 (4.1)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4/463 (0.9)</td>
<td>5/244 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AF Pattern</th>
<th>WATCHMAN N= 463</th>
<th>Control N= 244</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>200/463 (43.2)</td>
<td>99/244 (40.6)</td>
<td>0.7623</td>
</tr>
<tr>
<td>Persistent</td>
<td>97/463 (21.0)</td>
<td>50/244 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>160/463 (34.6)</td>
<td>93/244 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6/463 (1.3)</td>
<td>2/244 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LVEF %</th>
<th>WATCHMAN N= 463</th>
<th>Control N= 244</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.3 ± 9.7</td>
<td>460 (30.0, 82.0)</td>
<td>56.7 ± 10.1</td>
<td>239 (30.0, 86.0)</td>
</tr>
</tbody>
</table>
### Intent-to-Treat

#### Primary Safety Results

**Randomization allocation (2 device : 1 control)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device Events (no.)</th>
<th>Device Total pt-yr</th>
<th>Device Rate (95% CI)</th>
<th>Control Events (no.)</th>
<th>Control Total pt-yr</th>
<th>Control Rate (95% CI)</th>
<th>Rel. Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 pt-yr</td>
<td>48</td>
<td>554.2</td>
<td>8.7 (6.4, 11.3)</td>
<td>13</td>
<td>312.0</td>
<td>4.2 (2.2, 6.7)</td>
<td>2.08 (1.18, 4.13)</td>
</tr>
</tbody>
</table>

**Event-free probability**

- **Device**: WATCHMAN
- **Control**

**Days**

<table>
<thead>
<tr>
<th>Days</th>
<th>Device</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>244</td>
<td>166</td>
</tr>
<tr>
<td>365</td>
<td>143</td>
<td>1</td>
</tr>
<tr>
<td>730</td>
<td>51</td>
<td>11</td>
</tr>
<tr>
<td>1,095</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

**Randomization allocation** (2 device : 1 control)
Intent-to-Treat
Primary Efficacy Results

Randomization allocation (2 device : 1 control)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Control</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Rel. Risk (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 pt-yr</td>
<td></td>
<td>20</td>
<td>582.3</td>
<td>3.4 (2.1, 5.2)</td>
<td></td>
<td>16</td>
<td>318.0</td>
<td>5.0 (2.8, 7.6)</td>
<td>0.68 (0.37, 1.41)</td>
<td>0.998</td>
<td>0.837</td>
</tr>
</tbody>
</table>

Event-free probability

Days

ITT Cohort: Non-inferiority criteria met

Randomization allocation (2 device : 1 control)
# PROTECT AF Trial

## What are the Analysis Issues

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>How do you deal with safety endpoints which are also primary efficacy endpoints?</td>
</tr>
<tr>
<td>2.</td>
<td>How do you deal with early procedural safety risks (seen with all invasive interventional procedures) vs late primary efficacy endpoints?</td>
</tr>
<tr>
<td>3.</td>
<td>How do you deal with a strategy of warfarin started immediately and indefinitely versus an invasive approach that also requires 45 days of warfarin (?double jeopardy)</td>
</tr>
<tr>
<td>4.</td>
<td>How do you factor in procedural learning curve?</td>
</tr>
</tbody>
</table>
Potential Safety Endpoints
Device

- Procedural complications
  - Pericardial effusion
  - Stroke – ischemic
- Bleeding during 45 days of Warfarin
## Intent-to-Treat
### Primary Safety Results

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (no.)</td>
<td>Total pt-yr</td>
</tr>
<tr>
<td>600 pt-yr</td>
<td>45</td>
<td>386.4</td>
</tr>
<tr>
<td>900 pt-yr</td>
<td>48</td>
<td>554.2</td>
</tr>
</tbody>
</table>

- **Pericardial effusions** – largest fraction of safety events in device group
- **Stroke events** – most serious fraction of safety events in control group
- **Bleeding events** were also frequent
Pericardial Effusions by Experience

- Pericardial effusions – most common safety issue
- Throughout PROTECT AF Trial, procedural modifications and training enhancements were implemented
- Procedural events would be expected to decrease over time

<table>
<thead>
<tr>
<th>Site implant group</th>
<th>Any</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Early patients (1-3)</td>
<td>13</td>
<td>8.4</td>
</tr>
<tr>
<td>Late patients (≥4)</td>
<td>27</td>
<td>7.0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>7.2</td>
</tr>
</tbody>
</table>

- Continued ACCESS Registry

<table>
<thead>
<tr>
<th>Any</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1/88</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Safety stroke events

- Also counted as efficacy events in efficacy analyses
- 5 events in device group classified as “ischemic stroke”
  - All periprocedural: extended hospitalization by 7 days
  - 3 were related to air embolism
- 1 hemorrhagic stroke in device group vs 6 in control group
  - Device event occurred 15 days post implant while patient was on warfarin
  - 4/6 stroke events in control group patients resulted in death
## Intent-to-Treat

### All Stroke

#### Event-free probability

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Device Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Control Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>RR (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 pt-yr</td>
<td>14</td>
<td>409.3</td>
<td>3.4 (1.9, 5.5)</td>
<td>8</td>
<td>223.6</td>
<td>3.6 (1.5, 6.3)</td>
<td>0.96 (0.43, 2.57)</td>
<td>0.927</td>
<td>0.488</td>
</tr>
<tr>
<td>900 pt-yr</td>
<td>15</td>
<td>582.9</td>
<td>2.6 (1.5, 4.1)</td>
<td>11</td>
<td>318.1</td>
<td>3.5 (1.7, 5.7)</td>
<td>0.74 (0.36, 1.76)</td>
<td>0.998</td>
<td>0.731</td>
</tr>
</tbody>
</table>

**Randomization allocation**

(2 device:1 control)

**ITT cohort: Non-inferiority criteria met**

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**900 patient-year analysis**

**Event-free probability**

**Days**

- 0: 244
- 365: 147
- 730: 52
- 1095: 12

- 0: 463
- 365: 270
- 730: 92
- 1095: 22
## Intent-to-Treat Hemorrhagic Stroke

### Device

<table>
<thead>
<tr>
<th>Cohort (pt-yr)</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>Events (no.)</th>
<th>Total pt-yr</th>
<th>Rate (95% CI)</th>
<th>RR (95% CI)</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>1</td>
<td>416.7</td>
<td>0.2 (0.0, 0.9)</td>
<td>4</td>
<td>224.7</td>
<td>1.8 (0.5, 3.9)</td>
<td>0.13 (0.00, 0.80)</td>
<td>0.998</td>
<td>0.986</td>
</tr>
<tr>
<td>900</td>
<td>1</td>
<td>593.6</td>
<td>0.2 (0.0, 0.6)</td>
<td>6</td>
<td>319.4</td>
<td>1.9 (0.7, 3.7)</td>
<td>0.09 (0.00, 0.45)</td>
<td>&gt;0.999</td>
<td>0.998</td>
</tr>
</tbody>
</table>

### Control

### Posterior probabilities

### Event-free probability

- **Watchman**
- **Control**

### Randomization allocation
(2 device:1 control)

### ITT cohort: Superiority criteria met

### 900 patient-year analysis

### Days

- **Device**: 244 (463)
- **Control**: 147, 53, 12

### Event-free probability

- 0.7, 0.8, 0.9, 1.0
Risk/Benefit Analysis

- Intent-to-treat analysis
- Primary endpoint (intent to treat) achieved
- Other statistically significant endpoint findings
  - Noninferiority for the primary efficacy event rate – 32% lower in device group
  - Noninferiority for all strokes – 26% lower in device group
  - Superiority for hemorrhagic stroke – 91% lower in device group
  - Noninferiority for mortality rate – 39% lower rate in device group
- Increased rate of primary safety events for the device group relative to the control group
  - Most events in the device group were procedural effusions that decreased over the course of the study
- 87% of patients were able to discontinue warfarin at 45 days
Summary

• Long-term warfarin treatment of patients with AF has been found effective, but presents difficulties and risk.

• PROTECT AF trial was a randomized, controlled, statistically valid study to evaluate the WATCHMAN device compared to warfarin.

• In PROTECT AF, hemorrhagic stroke risk is significantly lower with the device.
  • When hemorrhagic stroke occurred, risk of death was markedly increased.

• In PROTECT AF, all cause stroke and all cause mortality risk are non-inferior to warfarin.

• In PROTECT AF, there are early safety events, specifically pericardial effusion; these events have decreased over time.
The WATCHMAN LAA Technology offers a safe and effective alternative to warfarin in patients with non-valvular atrial fibrillation at risk for stroke and who are eligible for warfarin therapy.