Atrial Fibrillation: Preventing Stroke with LA Appendage Closure

Does It Improve Mortality Too?

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Disclosures

- **Grant support and/or Consultant:**
  - Boston Scientific Inc, Coherex Inc, St Jude Medical Inc

- I will be discussing non-approved catheter devices.
Overview

• The Watchman Trials
  – Introduction
  – Safety of LAA Closure
  – Efficacy of LAA Closure
    • PROTECT-AF
    • Combined Analysis of All Randomized Data
  – LAA Closure in Contraindicated Patients

• Context
Overview

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• Context
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)

- Autopsy & TEE data implicate LAA

- LAA Closure Devices

**Watchman**

- Cardiac Plug
- Wavecrest
- Lariat

In the US, WATCHMAN is an investigational device, limited by applicable law to investigational use only and not available for sale. CE Mark 2005
## LAA Closure Clinical Trials

### PROTECT AF / PREVAIL / CAP / CAP-2 / ASAP

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
<th>CAP-2</th>
<th>ASAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Warfarin-Eligible</td>
<td>Warfarin-Eligible</td>
<td>Warfarin-Eligible</td>
<td>Warfarin-Eligible</td>
<td>Warfarin-In Eligible</td>
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<tr>
<td><strong>Enrolled</strong></td>
<td>800</td>
<td>566</td>
<td>461</td>
<td>579</td>
<td>150</td>
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<tr>
<td><strong>Roll-in</strong></td>
<td>93</td>
<td>--</td>
<td>54</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
<td>707</td>
<td>--</td>
<td>407</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Watchman</strong></td>
<td>463</td>
<td>(566)</td>
<td>269</td>
<td>(579)</td>
<td>(150)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>244</td>
<td>--</td>
<td>138</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>New Operators / Sites</strong></td>
<td>--</td>
<td>--</td>
<td><strong>39.1% / 38.8%</strong></td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Follow-Up Pt-Yrs (Yrs)</strong></td>
<td><strong>2717 (4.0 y)</strong></td>
<td><strong>2022 (3.6 y)</strong></td>
<td><strong>860 (1.9 y)</strong></td>
<td><strong>332 (0.6 y)</strong></td>
<td><strong>206 (1.4 y)</strong></td>
</tr>
</tbody>
</table>
Watchman Clinical Trials
Patients were at High Risk

PROTECT-AF & PREVAIL
Design & Overview

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

• Efficacy Endpoints:
  – 1st Endpoint: Stroke / Systemic embolism / CV death (& Unknown)
  – 2nd Endpoint: Ischemic Stroke / Systemic embolism (Post 7 days)

• Bayesian Statistical Plan
  – Non-inferiority & Superiority
  – Informative Prior?
    • PROTECT-AF: (None)
    • PREVAIL: Discounted PROTECT-AF

Non-Valvular AF Risk Factors
Randomization (1:2)

Anticoagulation Regimen
• Implant to 6 weeks
  – Warfarin
  – Aspirin
• 6 weeks to 6 months
  – Clopidogrel
  – Aspirin
• After 6 months
  – Aspirin
### Warfarin Compliance in Control Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin Control Group: Mean TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>70%</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>68%</td>
</tr>
<tr>
<td>RE-LY&lt;sup&gt;1&lt;/sup&gt;</td>
<td>64%</td>
</tr>
<tr>
<td>ARISTOTLE&lt;sup&gt;2&lt;/sup&gt;</td>
<td>62%</td>
</tr>
<tr>
<td>ROCKET AF&lt;sup&gt;3&lt;/sup&gt;</td>
<td>55%</td>
</tr>
<tr>
<td>ENGAGE&lt;sup&gt;4&lt;/sup&gt;</td>
<td>68%</td>
</tr>
</tbody>
</table>

Overview

• The Watchman Trials
  – Introduction
  – Safety of LAA Closure
  – Efficacy of LAA Closure
    • PROTECT-AF
    • Combined Analysis of All Randomized Data
  – LAA Closure in Contraindicated Patients
• Context
Safety Events Across Trials
PROTECT AF, CAP, PREVAIL & CAP-2

V.Reddy et al, FDA Panel Presentation, October 2014.
Overview

• The Watchman Trials
  – Introduction
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  – Efficacy of LAA Closure
    • PROTECT-AF
      • Combined Analysis of All Randomized Data
    – LAA Closure in Contraindicated Patients

• Context
PROTECT AF  
Primary Efficacy Endpoint

HR (95% CI), 0.61 (0.38-0.97)
P = .04

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Device</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>463</td>
<td>398</td>
<td>382</td>
</tr>
<tr>
<td>370</td>
<td>360</td>
<td>345</td>
</tr>
<tr>
<td>337</td>
<td>327</td>
<td>317</td>
</tr>
<tr>
<td>285</td>
<td>257</td>
<td>217</td>
</tr>
<tr>
<td>196</td>
<td>141</td>
<td>121</td>
</tr>
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</table>

## Components of Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th>Event Rate (per 100 pt-yrs)</th>
<th>Rate Ratio (95% CrI)</th>
<th>Posterior Probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-inferiority</td>
</tr>
<tr>
<td><strong>WATCHMAN</strong> (N=463)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Systemic Embolization</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Death (CV &amp; Unexplained)</td>
<td>1.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

## Impact of Strokes
### Disabling vs Non-Disabling

<table>
<thead>
<tr>
<th>PROTECT AF</th>
<th>Event Rate (per 100 pt-yrs)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WATCHMAN N=463</td>
<td>Warfarin N=244</td>
<td></td>
</tr>
<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

## Components of Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th>Event Rate (per 100 pt-yrs)</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Non-inferiority</td>
</tr>
<tr>
<td><strong>WATCHMAN (N=463)</strong></td>
<td><strong>Control (N=244)</strong></td>
<td><strong>Non-inferiority</strong></td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Stroke (all)</td>
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</tr>
<tr>
<td>Ischemic</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Systemic Embolization</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Death (CV &amp; Unexplained)</td>
<td>1.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Intention-To-Treat Mortality

B  Cardiovascular mortality

C  All-cause mortality

### All-Cause Mortality

**Causes by Treatment Group**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Device Group, No. (%)</th>
<th>Warfarin Group, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>17 (3.7)</td>
<td>22 (9.0)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (0.6)</td>
<td>2 (0.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>2 (0.4)</td>
<td>8 (3.3)</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.4)</td>
<td>2 (0.8)</td>
<td>.61</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>4 (0.9)</td>
<td>4 (1.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Unexplained/other</td>
<td>5 (1.0)</td>
<td>5 (2.0)</td>
<td>.33</td>
</tr>
<tr>
<td>Cancer</td>
<td>10 (2.2)</td>
<td>3 (1.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>9 (1.9)</td>
<td>9 (3.7)</td>
<td>.21</td>
</tr>
<tr>
<td>Neurologic</td>
<td>2 (0.4)</td>
<td>1 (0.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Multisystem organ failure</td>
<td>6 (1.3)</td>
<td>1 (0.4)</td>
<td>.43</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.9)</td>
<td>5 (2.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3 (0.6)</td>
<td>3 (1.2)</td>
<td>.42</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (0.4)</td>
<td>1 (0.4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Unexplained/other</td>
<td>4 (0.9)</td>
<td>1 (0.4)</td>
<td>.66</td>
</tr>
</tbody>
</table>
Long-Term PROTECT AF
Differential Attrition

<table>
<thead>
<tr>
<th></th>
<th>Lost to Follow-Up</th>
<th>Other</th>
<th>Withdrawal of Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Group</td>
<td>4.5%</td>
<td>4.1%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Watchman Group</td>
<td>2.8%</td>
<td>2.4%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

- Long-term follow-up: 2621 pt-yrs
- Possible reasons for withdrawal in control group
  - Perception of little benefit from continued participation
  - Desire for alternate treatment

Updated Vital Status in PROTECT AF
More Strongly Favors Watchman

- Investigators / Centers contacted to obtain vital status
- *Ad Hoc* Vital Status gathered in 40% of withdrawals
  - 24 died (11 in Control & 13 in Watchman)
  - [Rem 1:2 Randomization]

<table>
<thead>
<tr>
<th>PROTECT AF (N=463)</th>
<th>WATCHMAN</th>
<th>Control (N=244)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value (Superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>[2621 pt-year]</td>
<td>57</td>
<td>12</td>
<td>44</td>
<td>18</td>
</tr>
</tbody>
</table>

Based on updated vital status

Is a Mortality Benefit Plausible?

**NOACs vs Warfarin**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>665/29292</td>
<td>724/29221</td>
<td>0.92 (0.83-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29292</td>
<td>432/29221</td>
<td>0.97 (0.78-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>2245/29221</td>
<td>0.90 (0.85-0.95)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

| Safety                    |                      |                          |                 |        |
| Intracranial haemorrhage  | 204/29287            | 425/29211                | 0.48 (0.39-0.59) | <0.0001|
| Gastrointestinal bleeding | 751/29287            | 591/29211                | 1.25 (1.01-1.55) | 0.043  |

Primary Efficacy Endpoint
Relative Risks According to Subgroups

<table>
<thead>
<tr>
<th>Source</th>
<th>Device Group</th>
<th>Warfarin Group</th>
<th>HR (95% CI)</th>
<th>Favors Device</th>
<th>Favors Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>No. of Patients</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>137</td>
<td>10</td>
<td>73</td>
<td>1.03 (0.48-2.23)</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>326</td>
<td>24</td>
<td>171</td>
<td>0.45 (0.25-0.81)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 75 y</td>
<td>22</td>
<td>190</td>
<td>22</td>
<td>115</td>
<td>0.63 (0.35-1.14)</td>
</tr>
<tr>
<td>&lt; 75 y</td>
<td>17</td>
<td>273</td>
<td>12</td>
<td>129</td>
<td>0.67 (0.32-1.41)</td>
</tr>
<tr>
<td>CHADS² score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.29 (0.08-1.03)</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.73 (0.44-1.20)</td>
</tr>
<tr>
<td>AF pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>18</td>
<td>200</td>
<td>14</td>
<td>99</td>
<td>0.62 (0.31-1.24)</td>
</tr>
<tr>
<td>Persistent</td>
<td>5</td>
<td>97</td>
<td>8</td>
<td>50</td>
<td>0.31 (0.10-0.95)</td>
</tr>
<tr>
<td>Permanent</td>
<td>16</td>
<td>160</td>
<td>12</td>
<td>93</td>
<td>0.84 (0.40-1.78)</td>
</tr>
<tr>
<td>History of TIA or stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>82</td>
<td>12</td>
<td>49</td>
<td>0.66 (0.30-1.45)</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>381</td>
<td>22</td>
<td>195</td>
<td>0.61 (0.35-1.08)</td>
</tr>
<tr>
<td>Prior years taking warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>25</td>
<td>226</td>
<td>19</td>
<td>125</td>
<td>0.72 (0.40-1.31)</td>
</tr>
<tr>
<td>≥1</td>
<td>14</td>
<td>230</td>
<td>14</td>
<td>116</td>
<td>0.52 (0.25-1.10)</td>
</tr>
<tr>
<td>LAA ostium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Median (21 mm)</td>
<td>18</td>
<td>249</td>
<td>18</td>
<td>128</td>
<td>0.52 (0.27-0.99)</td>
</tr>
<tr>
<td>&lt; Median</td>
<td>20</td>
<td>208</td>
<td>16</td>
<td>111</td>
<td>0.67 (0.35-1.29)</td>
</tr>
<tr>
<td>LAA length</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Median (30 mm)</td>
<td>16</td>
<td>235</td>
<td>16</td>
<td>124</td>
<td>0.49 (0.25-0.99)</td>
</tr>
<tr>
<td>&lt; Median</td>
<td>22</td>
<td>222</td>
<td>18</td>
<td>115</td>
<td>0.68 (0.36-1.27)</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Median (60%)</td>
<td>19</td>
<td>236</td>
<td>14</td>
<td>123</td>
<td>0.70 (0.35-1.41)</td>
</tr>
<tr>
<td>&lt; Median</td>
<td>20</td>
<td>224</td>
<td>19</td>
<td>116</td>
<td>0.56 (0.30-1.05)</td>
</tr>
<tr>
<td>All patients</td>
<td>0.61 (0.38-0.97)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Secondary Efficacy Endpoints

### Impact of Concomitant Medications

<table>
<thead>
<tr>
<th>Primary Efficacy Outcomes (2621 pt-yr)</th>
<th>WATCHMAN (N=463)</th>
<th>Control (N=244)</th>
<th>Rate Ratio (95% CrI)</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per-Protocol</strong></td>
<td>1.8</td>
<td>3.7</td>
<td>0.50</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td><strong>Late Therapy</strong></td>
<td>1.8</td>
<td>3.7</td>
<td>0.50</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

(Whole Study: 2621 pt-yrs)


- **Per-protocol Analysis (pre-specified):**
  - Includes Device patients who stopped **warfarin**

- **Late Therapy (post-hoc):**
  - Includes Device patients following discontinuation of **clopidogrel**
Overview

• The Watchman Trials
  – Introduction
  – Safety of LAA Closure
  – Efficacy of LAA Closure
    • PROTECT-AF
    • Combined Analysis of All Randomized Data
  – LAA Closure in Contraindicated Patients

• Context
PROTECT-AF & PREVAIL
Combined Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></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><strong>All-cause death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Hazard Ratio (95% CI)

## PROTECT-AF & PREVAIL

### Combined Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td>0.006</td>
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<tr>
<td><strong>All-cause death</strong></td>
<td>0.73</td>
<td>0.07</td>
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<td>Major bleed, all</td>
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<td>0.98</td>
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<td>0.002</td>
</tr>
</tbody>
</table>

**D.Holmes et al, TCT Presentation, September 2014.**
## PROTECT-AF & PREVAIL Combined Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
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Favors WATCHMAN ← 1 → Favors warfarin

The Big Picture
How Does Watchman Compare to Warfarin?

- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free

N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years

K.Huber et al, FDA Panel Presentation, October 2014.
The Big Picture
Cardiovascular Death Lower with Watchman

- **Cardiovascular / Unexplained Death** (includes CV deaths preceded by stroke)
- **Non-fatal Hemorrhagic Stroke**
- **Non-fatal Ischemic Stroke / Systemic Embolism**
- **Event-free**

Zoomed in to show N=500 of 1000 patients per arm. Each circle represents a single patient (N=1) with Watchman or warfarin followed through 5 years.

K.Huber et al, FDA Panel Presentation, October 2014.
The Big Picture

Hemorrhagic Stroke Lower with Watchman

Zoomed in to show N=500 of 1000 patients per arm. Each circle represents a single patient (N=1) with Watchman or warfarin followed through 5 years.

K.Huber et al, FDA Panel Presentation, October 2014.
The Big Picture

Add Ischemic Stroke/SE ➔ Watchman is an Alternative

- **Cardiovascular / Unexplained Death** (includes CV deaths preceded by stroke)
- **Non-fatal Hemorrhagic Stroke**
- **Non-fatal Ischemic Stroke / Systemic Embolism**
- **Event-free**

Zoomed in to show N=500 of 1000 patients per arm. Each circle represents a single patient (N=1) with Watchman or warfarin followed through 5 years.

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• Context
ASAP Registry

Contraindicated Pts (n=150): Watchman → ASA/Clop x 6 mo

➢ CHADS\textsubscript{2} = 2.8 ± 1.2
➢ Prior CVA/TIA in 41%
➢ Follow-up: 16.5 months

ASAP Registry

Contraindicated Pts (n=150): Watchman → ASA/Clop x 6 mo

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• Context
NOACs are Excellent Medications
But Not for Everyone…

FDA Slide Deck. Dabigatran FDA Review from Panel Meeting 2010
NOACs: Bleeding in the “Real World”

- Retrospective Cohort Study
- Pharmacy/Medical Claims (2010-2011) from a 5% random sample of Medicare beneficiaries
- Patients with newly-diagnosed AF who initiated Warfarin or Dabigatran

<table>
<thead>
<tr>
<th></th>
<th>Warfarin n=8102</th>
<th>Dabigatran n=1302</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>26.5%</td>
<td>32.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Major</td>
<td>5.9%</td>
<td>9.0%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minor</td>
<td>23.6%</td>
<td>28.6%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Preventing Stroke in Non-Valvular AF
Effectiveness of Different Strategies

* Reached statistical superiority relative to warfarin.
**Economic Analysis**

**Watchman vs Dabigatran vs Warfarin**

- **Assess:** Cost-effectiveness of LAAC & NOAC to warfarin
- **Methods:**
  - Patient level Markov micro-simulation decision analytic model
  - Lifetime horizon
  - From perspective of the Ontario Ministry of Health & Long Term Care

<table>
<thead>
<tr>
<th>Discounted</th>
<th>Cost (CAD 2012)</th>
<th>Incremental Cost (CAD 2012)</th>
<th>QALY$</th>
<th>Incremental QALY</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>$21,429</td>
<td>0</td>
<td>4.55</td>
<td>0</td>
<td>—</td>
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<tr>
<td>Dabigatran</td>
<td>$25,760</td>
<td>$4,331</td>
<td>4.64</td>
<td>0.09</td>
<td>$46,560*</td>
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<tr>
<td>LAA occlusion</td>
<td>$27,003</td>
<td>$1,243</td>
<td>4.68</td>
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<td>$30,256*</td>
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<tr>
<td>Warfarin</td>
<td>$21,429</td>
<td>0</td>
<td>4.55</td>
<td>0</td>
<td>—</td>
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<tr>
<td>LAA occlusion</td>
<td>$27,003</td>
<td>$5,574</td>
<td>4.68</td>
<td>0.13</td>
<td>$41,565**</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-years; ICER = incremental cost effectiveness ratio. *ICERs for Dabigatran and LAA occlusion are calculated compared to the next less inexpensive strategy. **ICER for LAA occlusion is calculated compared to warfarin.

Final Thoughts

• The LAA is critical to the pathogenesis of stroke

• “Local” therapy with LAA closure is comparable to Warfarin
  – Primary endpoint: stroke / systemic embolism / CV death
  – Increase in Ischemic Stroke balanced by a decrease in Hemorrhagic Stroke
  – 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) / 0% (Mount Sinai)

• Role of LAA Closure in setting of Novel OACs??
  – NOACs not tolerated in All / Double-Triple Tx increase bleeding (Elderly!)
  – LAA Closure is an option for pts who don’t tolerate OAC therapy