Left Atrial Appendage Closure: Neurological events

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Disclosures

- Speaker/Consultant/Board member
  - BSC
  - Abbott
  - Micardia
  - STENTYS
  - Endocross
  - Cardiodex
  - MValve
The PROTECT AF trial demonstrated the WATCHMAN Device’s non-inferiority to warfarin in 707 randomized patients

- PROTECT AF is the first prospective, randomized, multi-center trial comparing the WATCHMAN device to warfarin for thromboembolic prophylaxis

- 707 patients were randomized (2:1 device to medical therapy including warfarin)

- Primary efficacy endpoint (non-inferiority)
  - All stroke: ischemic or hemorrhagic
  - Systemic embolisms
  - Cardiovascular and unexplained death

- Patients who received the WATCHMAN device had 45 days of post operative warfarin therapy to ensure endothelialization

- Transesophageal echocardiography was performed at 45 days, 6 months and 1 year to verify device placement left atrial appendage flow and presence of thrombus.

### Baseline Risk Factors

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
<th>WATCHMAN</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.9%</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>34.1%</td>
<td>36.1%</td>
</tr>
<tr>
<td>3</td>
<td>19%</td>
<td>20.9%</td>
</tr>
<tr>
<td>4</td>
<td>8%</td>
<td>9.8%</td>
</tr>
<tr>
<td>5</td>
<td>4.1%</td>
<td>4.1%</td>
</tr>
<tr>
<td>6</td>
<td>0.9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Average age for WATCHMAN was 71.7 years +/- 8.8 years
At 1065 patient years, the WATCHMAN® Device was non-inferior to warfarin

- Following successful device implantation, rates of ischemic strokes with the WATCHMAN Device were 1.3 per 100 patient years vs. 1.6 with warfarin.

Rate of ischemic stroke is lower than warfarin following periprocedural period

Events in PROTECT AF trial at 1065 patient years

Holmes DR et al. Lancet 2009; 374: 534–42
After procedure, rates of ischemic and hemorrhagic stroke were lower with the WATCHMAN® Device.

After day 1, rates of hemorrhagic stroke increased sharply with warfarin, compared to a slight increase with the WATCHMAN Device.
In addition to efficacy, PROTECT AF demonstrated the long-term safety of the WATCHMAN® device

<table>
<thead>
<tr>
<th>Event Description</th>
<th>WATCHMAN (% of 463)</th>
<th>Warfarin (% of 244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>4.8%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>1.1%</td>
<td>NA</td>
</tr>
<tr>
<td>Device embolization</td>
<td>0.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.1%</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>0.4%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Subjects with Primary Safety Endpoints within 7 days of Procedure

- Both the WATCHMAN Device and warfarin patients experienced adverse events
- The WATCHMAN Device events were concentrated around procedure
- Warfarin events occurred at any time

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</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>0.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Device embolization</td>
<td>0.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.6%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.0%</td>
<td>5.3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4.1%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Subject with Primary Safety Endpoints >7 days after Procedure

Higher rates of adverse events seen post procedure with warfarin group
Procedure Related Stroke

- Stroke = 5 patients
- Air embolism during the procedure
- Outcomes:
  - Extended hospital stay by 9 days (5-9)
  - Three recovered with no long term effects
    - Two experienced significant/permanent neurological deficits
A continued access registry demonstrated ongoing improvement in the WATCHMAN® Device procedure safety.

- A continued access registry (CAP) implanted an additional 460 patients at 26 centers that participated in PROTECT AF.
- Primary safety endpoint:
  - Pericardial effusion/tamponade
  - Procedure related stroke
  - Device embolization and bleeding events

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>Mean CHADS₂</td>
<td>2.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Implantation Success

- 95% successfully implanted

Warfarin Discontinuation

- 95% discontinued warfarin at 45 days

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Foundation for Cardiovascular Medicine

Procedure related safety events declined as implant experience grew.

Rates of safety events within 7 days of procedure in PROTECT AF and CAP registry:

- **Pericardial effusion**
  - PROTECT AF: 5
  - CAP: 2.2

- **Procedure-related stroke**
  - PROTECT AF: 0.9
  - CAP: 0

- 56% reduction in pericardial effusion rates between studies
- Procedure-related stroke reduced to 0

Conclusion

- Rates of ischemic strokes with device in place are lower than with warfarin following peri procedural period.
  - 1.3 per 100 patient years.
- Peri procedural ischemic strokes were primarily caused by inadvertent introduction of air through large bore catheters leading to cerebral events.
- Risk of neurological adverse events with device implantation decreases dramatically with experience.
  - Procedure related strokes reduced to zero in CAP.