Randomized Trial of LAA Closure vs Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)

David R. Holmes, Jr., M.D.
Mayo Clinic, Rochester

ACC 2013
San Francisco, CA
Results of Randomized Trial of LAA Closure vs Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)

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¹Mayo Clinic, Rochester, MN, USA, ²Pacific Heart Institute / St. John’s Health Center, Santa Monica, CA, ³Cedars-Sinai Medical Center, Los Angeles, CA, ⁴Mercy Heart and Vascular, St. Louis, MO, ⁵Arizona Heart Rhythm Research Center, Phoenix, AZ, ⁶Intermountain Medical Center, Murray, UT, ⁷The Methodist Hospital Research Institute, Houston, TX, ⁸Cardiovascular Consultants, PC, Kansas City, MO, ⁹Fletcher Allen Health Care Inc., Burlington, VT, ¹⁰Mount Sinai School of Medicine, Cardiology, New York, NY

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Presenter Disclosure Information

David R. Holmes, Jr., M.D.

“Results of Randomized Trial of LAA Closure vs Warfarin for Stroke/Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)”

The following relationships exist related to this presentation:

Both Mayo Clinic and I have a financial interest in technology related to this research. That technology has been licensed to Atritech.
### PREVAIL

**Participating Centers**

<table>
<thead>
<tr>
<th>Swedish Cardiovascular Research</th>
<th>St. Thomas Research Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iowa Heart Center</td>
<td>Baptist Hospital of Miami</td>
</tr>
<tr>
<td>St. Lukes Hospital, Milwaukee</td>
<td>Cleveland Clinic</td>
</tr>
<tr>
<td>Minneapolis Heart Institute</td>
<td>Orange County Heart Institute and Research Center</td>
</tr>
<tr>
<td>Mt. Sinai School of Medicine</td>
<td>Pinnacle Health Cardiovascular Institute (MHVG)</td>
</tr>
<tr>
<td>Baylor Research Institute</td>
<td>ZASA Clinical Research</td>
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<td>Bryan LGH</td>
<td>William Beaumont</td>
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<tr>
<td>Cardiology Associates of N. Mississippi</td>
<td>Columbia University Medical Center</td>
</tr>
<tr>
<td>Emory University Hospital Midtown</td>
<td>Hospital of the University of Pennsylvania</td>
</tr>
<tr>
<td>Mercy Gilbert Medical Center</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>The Lindner Center</td>
<td>New York University School of Medicine</td>
</tr>
<tr>
<td>Lahey Clinic</td>
<td>NorthShore University Health System</td>
</tr>
<tr>
<td>Massachusetts General</td>
<td>Englewood Hospital and Medical Center</td>
</tr>
<tr>
<td>Texas Cardiac Arrhythmia Research Foundation</td>
<td>Florida Hospital Orlando</td>
</tr>
<tr>
<td>Carolinas Medical Center</td>
<td>University of Michigan</td>
</tr>
<tr>
<td>Foundation for Cardiovascular Medicine and Alvarado Hospital</td>
<td></td>
</tr>
</tbody>
</table>

Ten additional centers are listed on the next slide.
## PREVAIL
### Top 10 Participating Centers

<table>
<thead>
<tr>
<th>Investigational Center</th>
<th>Location</th>
<th>Principal Investigator</th>
<th>Total Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific Heart / St. Johns</td>
<td>Santa Monica, CA</td>
<td>Shephal Doshi, MD</td>
<td>45</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center</td>
<td>Los Angeles, CA</td>
<td>Saibal Kar, MD</td>
<td>32</td>
</tr>
<tr>
<td>Mercy Heart and Vascular</td>
<td>St. Louis, MO</td>
<td>J. Mauricio Sanchez, MD</td>
<td>32</td>
</tr>
<tr>
<td>Arizona Heart Rhythm Research Center</td>
<td>Phoenix, AZ</td>
<td>Vijay Swarup, MD</td>
<td>30</td>
</tr>
<tr>
<td>Intermountain Medical Center</td>
<td>Murray, UT</td>
<td>Brian Whisenant, MD</td>
<td>24</td>
</tr>
<tr>
<td>Methodist Hospital</td>
<td>Houston, TX</td>
<td>Miguel Valderrabano, MD</td>
<td>22</td>
</tr>
<tr>
<td>Scripps Green</td>
<td>La Jolla, CA</td>
<td>Matthew Price, MD</td>
<td>22</td>
</tr>
<tr>
<td>Central Baptist Hospital, Kentucky</td>
<td>Lexington, KY</td>
<td>Gery Tomassoni, MD</td>
<td>17</td>
</tr>
<tr>
<td>Fletcher Allen</td>
<td>Burlington, VT</td>
<td>Daniel Lustgarten, MD</td>
<td>17</td>
</tr>
<tr>
<td>St. Lukes Hospital, Kansas</td>
<td>Kansas City, MO</td>
<td>Kenneth Huber, MD</td>
<td>17</td>
</tr>
</tbody>
</table>

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Background

• People with AF have 5 times the risk of stroke compared to people without AF\(^1\)

• Stroke is more severe for patients with AF, as they have a 70% chance of death or permanent disability\(^1\)

• AF-associated ischemic strokes generally occlude large intracranial arteries depriving a more extensive region of the brain of blood flow\(^2\)

• Compared with non-AF patients, AF patients have poorer survival and more recurrences of stroke during the first year of follow-up\(^3\)

• Relative or absolute contraindications to long-term anticoagulation are present in up to 40% of AF patients, usually due to a history of bleeding or an elevated risk of falls and trauma. In fact, anticoagulation is not currently utilized in up to 50% of eligible AF patients\(^3\)

• The economic burden of stroke will continue to rise globally as the incidence of stroke increases\(^4\)

• 91% of stroke in AF is caused by thrombus formed in the LAA\(^5\)
The WATCHMAN® product is a device for percutaneous closure of the left atrial appendage

- WATCHMAN is a self-expanding nitinol frame with fixation anchors and a permeable fabric cover
- It is designed to be permanently implanted at or slightly distal to the opening of the LAA to trap potential emboli before they exit the LAA

- Five sizes of device (21, 24, 27, 30 and 33 mm) allow for precise fit within ostium
- It is implanted via a transseptal approach by use of a catheter-based delivery system
- The delivery catheter is capable of recapturing the device if necessary
-Received CE mark in 2005

WATCHMAN® LAA Closure Device
Images on file at Boston Scientific Corporation
WATCHMAN Clinical Program
History

- PROTECT AF was a randomized clinical trial which demonstrated WATCHMAN device is non-inferior to warfarin for stroke/thromboembolic protection in patients with non-valvular AF
  - 800 patients enrolled (463 randomized device patients) at 59 centers to be followed through 5 years
  - Reduction in pericardial effusions, procedure related stroke, and procedure time demonstrated from early to late enrolled patients

- Continued Access trial (CAP) demonstrated continued safety improvement with experience
  - Serious pericardial effusion rate was reduced to 2.2%
  - No procedure related strokes occurred
  - Relative risk reduction of 56% (p=0.002) in procedure or device related safety events
  - Relative risk reduction of 58% (p=0.014) in serious pericardial effusions

1 Holmes DR et al. Lancet. 2009;374:534–42

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## PROTECT AF
### Primary Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th>Device</th>
<th>Control</th>
<th>Rate Ratio</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed rate</strong></td>
<td>(events per 100 pt-yrs)</td>
<td>(events per 100 pt-yrs)</td>
<td>Intervention/Control</td>
<td>(95% CrI)</td>
<td>(95% CrI)</td>
</tr>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>(2.1, 4.3)</td>
<td>(2.6, 5.9)</td>
<td>0.71</td>
<td>(0.44, 1.30)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

### PROTECT AF
Primary Safety Results

<table>
<thead>
<tr>
<th></th>
<th>Device</th>
<th>Control</th>
<th>Rate Ratio (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed rate (events per 100 pt-yrs) (95% CrI)</td>
<td>Observed rate (events per 100 pt-yrs) (95% CrI)</td>
<td>Intervention/Control (95% CrI)</td>
</tr>
<tr>
<td>Primary Safety</td>
<td>5.5 (4.2, 7.1)</td>
<td>3.6 (2.2, 5.3)</td>
<td>1.53 (0.95, 2.70)</td>
</tr>
</tbody>
</table>

Rationale

- Concerns with early PROTECT AF safety results
  - High initial rate of pericardial effusions and procedure related strokes
  - Some WATCHMAN patients did not receive their assigned treatment (i.e., implant failures)
  - Safety outcome of procedures performed by new operators

- Second randomized trial to confirm late PROTECT AF and CAP safety results (PREVAIL)
Study Purpose

• PREVAIL: Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy

• Prospective, randomized, multicenter study to provide additional information on the safety and efficacy of the WATCHMAN LAA Closure Technology

• Confirmatory study conducted to provide additional information on the implant procedure and complication rates associated with the device
Study Goals and Design

- Similar design to PROTECT AF: prospective randomized 2:1 (device: control) trial
- 407 randomized patients from 41 US centers
- Confirm the results of PROTECT AF and demonstrate improved safety profile
- Inclusion of new centers and new operators to document that enhancements to the training program are effective
- Roll-in phase allowed new centers to implant 2 patients prior to randomization phase
## PROTECT AF vs PREVAIL
### Trial Design Differences (abbreviated)

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization</strong></td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td><strong>Time from randomization to implant</strong></td>
<td>7-14(^1) days</td>
<td>2 days</td>
</tr>
<tr>
<td><strong>Roll-in</strong></td>
<td>New implanter: 1st 3 patients(^2)</td>
<td>New implanter: 1st 2 patients Experienced: 1st patient</td>
</tr>
<tr>
<td><strong>Exclusion of clopidogrel</strong></td>
<td>No exclusion</td>
<td>Indication for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment</td>
</tr>
</tbody>
</table>
| **Inclusion differences** | CHADS\(_2\) > 1 | CHADS\(_2\) > 2 or CHADS\(_2\) = 1 if any of the following apply*:  
- Female age >75  
- Baseline LVEF > 30 and < 35%  
- Age 65-74 and has diabetes or coronary artery disease  
- Age 65 or greater and has documented congestive heart failure |

\(^1\) Original protocol allowed 14 days, but was reduced to 7 after a protocol revision  
\(^2\) After first 100 study patients, protocol was revised to include roll-in patients for new implanters  
*According to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation patients requiring warfarin therapy  
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Primary Endpoints

- **Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention**
  - Timepoint = 7 days post randomization

- **Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death**
  - Timepoint = 18 months

- **Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization**
  - Timepoint = 18 months
Bayesian Statistics
Overview

• Statistical technique that combines prior trial data with new trial data into the analysis of study results
  • Reduces trial size and duration
  • Exposes as few patients as possible to investigational therapies

• What is the likelihood of something happening based on our knowledge of past conditions and the context of them in the world

• The chance that a set of results reflects the larger reality and about making inference based on the limited data set
PREVAIL Enrollment

Total Enrolled 461

Roll-In Patients 54

Implant Attempt 54

Device Implanted 51

Unable to Implant 3

Randomized Patients 407

WATCHMAN (Device) 269

Warfarin (Control) 138

Implant Attempt 265

Device Implanted 252

Unable to Implant 13

No Implant Attempt 4

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### Demographics

#### Device Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROTECT AF N=463</th>
<th>CAP N=566</th>
<th>PREVAIL N=269</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>71.7 ± 8.8 (463)</td>
<td>74.0 ± 8.3 (566)</td>
<td>74.0 ± 7.4 (269)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(46.0, 95.0)</td>
<td>(44.0, 94.0)</td>
<td>(50.0, 94.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (Male)</strong></td>
<td>326/463 (70.4%)</td>
<td>371/566 (65.5%)</td>
<td>182/269 (67.7%)</td>
<td>0.252</td>
</tr>
<tr>
<td><strong>CHADS2 Score</strong></td>
<td>2.2 ± 1.2</td>
<td>2.5 ± 1.2</td>
<td>2.6 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Continuous)</td>
<td>(1.0, 6.0)</td>
<td>(1.0, 6.0)</td>
<td>(1.0, 6.0)</td>
<td></td>
</tr>
<tr>
<td><strong>CHADS2 Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>124/463 (26.8%)</td>
<td>108/566 (19.1%)</td>
<td>63/269 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>415/463 (89.6%)</td>
<td>503/566 (88.9%)</td>
<td>238/269 (88.5%)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>190/463 (41.0%)</td>
<td>293/566 (51.8%)</td>
<td>140/269 (52.0%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>113/463 (24.4%)</td>
<td>141/566 (24.9%)</td>
<td>91/269 (33.8%)</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>82/463 (17.7%)</td>
<td>172/566 (30.4%)</td>
<td>74/269 (27.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Most notable differences: Age, Diabetes, and Prior Stroke/TIA

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**Procedure Implant Success**

- **PROTECT AF**
  - Implant success: 90.9%
- **CAP**
  - Implant success: 94.3%
- **PREVAIL**
  - Implant success: 95.1%
  - p = 0.04

Implant success defined as deployment and release of the device into the left atrial appendage.
First Primary Endpoint

• Acute occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  • Timepoint = through 7 days post randomization or hospital discharge, whichever is later
  • Performance goal comparison
  • No comparison with prior studies required

• Additional safety analysis to compare event rates in PREVAIL to prior WATCHMAN studies and determine safety profile
First Primary Endpoint
Acute (7-day) Procedural Safety

- 6 events in device group = 2.2% (6/269)
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)
  - 95% CI = 2.618%

Results are preliminary; final validation not yet complete

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¹CI is one-sided
Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications¹

Vascular Complications

- 8.7% in PROTECT AF
- 4.1% in CAP
- 4.4% in PREVAIL

7 Day Serious Procedure/Device Related

No procedure-related deaths reported in any of the trials


¹Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

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Pericardial Effusions Requiring Intervention

**Cardiac perforation requiring surgical repair**
- **PROTECT AF**: 1.6%, n=7
- **CAP**: 0.2%, n=1
- **PREVAIL**: 0.4%, n=1

**Pericardial effusion with cardiac tamponade requiring pericardiocentesis or window**
- **PROTECT AF**: 2.4%, n=11
- **CAP**: 1.2%, n=7
- **PREVAIL**: 1.5%, n=4

*p = 0.027* for cardiac perforation
*p = 0.318* for pericardial effusion

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Stroke and Device Embolization

**Procedure/Device Related Strokes**
- **PROTECT AF**: 0.0% (n=5)
- **CAP**: 1.1% (n=1)
- **PREVAIL**: 0.4% (n=2)

**Device Embolizations**
- **PROTECT AF**: 0.2% (n=2)
- **CAP**: 0.4% (n=1)
- **PREVAIL**: 0.8% (n=2)

*p = 0.007
*p = 0.364

Procedure related strokes were reduced
Device embolizations remained low

*1 additional device embolization was reported at 45 days

PREVAIL Implant Success
New vs Experienced Operators

- Protocol required a minimum of 20% of subjects enrolled at new centers and 25% of subjects enrolled by new operators
- 18 out of 41 centers did not have prior WATCHMAN experience
- 40% of patients enrolled at new sites and by new operators

% of Successful Implants

<table>
<thead>
<tr>
<th></th>
<th>Study Implant Success</th>
<th>Experienced Operators</th>
<th>New Operators</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>% of Successful</td>
<td>95.1%</td>
<td>96.3%</td>
<td>93.2%</td>
</tr>
</tbody>
</table>

p = 0.256
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### PREVAIL Complications

#### New vs Experienced Operator

<table>
<thead>
<tr>
<th>Complication</th>
<th>Experienced</th>
<th>New</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Day Procedure/Device Related Vascular Complications</td>
<td>5.4%</td>
<td>2.9%</td>
<td>0.377</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>1.2%</td>
<td>0%</td>
<td>0.522</td>
</tr>
<tr>
<td>Vascular Complications</td>
<td>0.6%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiac Perforation</td>
<td>0.6%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>PE with Tamponade</td>
<td>1.8%</td>
<td>1.0%</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Second Primary Endpoint

- Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - Bayesian piecewise exponential technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  - Non-inferiority design with comparison of rate ratio of 18-month event rates
Second Primary Endpoint
Composite 18-month Efficacy

- Similar 18-month event rates in both control and device groups = 0.064
- Upper 95% CI bound slightly higher than allowed to meet success criterion (<1.75)
  - Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)

Results are preliminary; final validation not yet complete
PREVAIL
Control (Warfarin) Group Performance

- In spite of the high average CHADS$_2$ score of 2.6 in the control group, the observed rate of stroke in the PREVAIL Control group was lower than in other published warfarin studies.

- PREVAIL control group rate = 0.7 (95% CI 0.1, 5.1)
  - Wide confidence bounds due to small number of patients with 18-months of follow-up.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Control (Warfarin) Group Stroke, Systemic Embolism Rate (Per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF$^1$</td>
<td>1.6</td>
</tr>
<tr>
<td>RE-LY (Dabigatran)$^2$</td>
<td>1.7</td>
</tr>
<tr>
<td>ARISTOTLE (Apixaban)$^3$</td>
<td>1.6</td>
</tr>
<tr>
<td>ROCKET AF (Rivaroxaban)$^4$</td>
<td>2.2</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Results are preliminary; final validation not yet complete.

$^1$Ischemic stroke rate from Holmes et al. *Lancet* 2009; 374:534-42

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Third Primary Endpoint

- Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization
  - Bayesian piecewise exponential technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  - Non-inferiority based rate difference
Third Primary Endpoint
18-month Thrombolic Events

- Endpoint success in the presence of an over performing control group

<table>
<thead>
<tr>
<th>18-Month Rate Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
</tr>
</tbody>
</table>

0.0051
0.0191
0.0253
0.0268
0.0275

95% upper CI bound for non-inferiority

Device 18-Month Rate | Control 18-Month Rate
----------------------|------------------------
0.0253                | 0.0201

- Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)

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First Primary Endpoint
Summary

• Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  • Pre-specified criterion met for first primary endpoint (95% Upper confidence limit < 2.67%)

• The PREVAIL trial showed:
  • Improved procedural implant success p=0.04
  • Decreased composite vascular complications p=0.004
  • Decreased perforations requiring surgical repair p=0.027
  • Decreased procedural stroke rates p=0.007
  • Little difference in outcome of new versus experienced operators
Second Primary Endpoint
Summary

• Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  • Control group had lower than expected event rates (over performing)
  • Similar low event rates in both groups
  • Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)
  • Although event rates were similar, pre-specified non-inferiority criterion was not met (exceeded the upper 95% CI bound)
Third Primary Endpoint
Summary

• Comparison ischemic stroke or systemic embolism occurring >7 days post randomization
  • Bayesian technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  • Pre-specified non-inferiority criterion met (95% CI Upper Bound < 0.0275%)
Conclusions

- Despite implantation in higher risk patients the Watchman device can be safely implanted by new operators.
- 2 of 3 primary endpoints were met even in the presence of an over performing control group.
- The Watchman device is an alternative to oral anticoagulation therapy for thromboembolic prevention in patients with non valvular atrial fibrillation.