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

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

David R. Holmes¹, Shephal Doshi², Saibal Kar³, Jose Sanchez⁴, Vijay Swarup⁵, Brian Whisenant⁶, Miguel Valderrabano⁷, Kenneth Huber⁸, Daniel Lustgarten⁹, Vivek Reddy¹⁰ on behalf of the PREVAIL investigators

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
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.
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PREVAIL
Participating Centers

Swedish Cardiovascular Research
Iowa Heart Center
St. Lukes Hospital, Milwaukee
Minneapolis Heart Institute
Mt. Sinai School of Medicine
Baylor Research Institute
Bryan LGH
Cardiology Associates of N. Mississippi
Emory University Hospital Midtown
Mercy Gilbert Medical Center
The Lindner Center
Lahey Clinic
Massachusetts General
Texas Cardiac Arrhythmia Research Foundation
Carolinas Medical Center

St. Thomas Research Institute
Baptist Hospital of Miami
Cleveland Clinic
Orange County Heart Institute and Research Center
Pinnacle Health Cardiovascular Institute (MHVG)
ZASA Clinical Research
William Beaumont
Columbia University Medical Center
Hospital of the University of Pennsylvania
Mayo Clinic
New York University School of Medicine
NorthShore University Health System
Englewood Hospital and Medical Center
Florida Hospital Orlando
University of Michigan

Foundation for Cardiovascular Medicine and Alvarado Hospital

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\(^5\)

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1 Holmes DR. Seminars in Neurology. 2010;30:528–536
2 Tu HT et al, Cerebrovascular Disease. 2010;30(4):389-95
4 Klein A et al, Datamonitor. July 2011

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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

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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
**PROTECT AF**

**Primary Efficacy Results**

<table>
<thead>
<tr>
<th></th>
<th>Device</th>
<th>Control</th>
<th>Posterior Probabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(events per 100 pt-yrs)</td>
<td>3.0</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>(95% CrI)</td>
<td>(2.1, 4.3)</td>
<td>(2.6, 5.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Rate Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention/Control (95% CrI)</td>
<td>0.71</td>
<td>(0.44, 1.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-inferiority</strong></td>
<td>&gt;0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Superiority</strong></td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## PROTECT AF
### Primary Safety Results

<table>
<thead>
<tr>
<th></th>
<th>Device</th>
<th>Control</th>
<th>Rate Ratio Intervention/Control (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed rate</strong></td>
<td><strong>(events per 100 pt-yrs)</strong></td>
<td><strong>(events per 100 pt-yrs)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Safety</strong></td>
<td><strong>5.5 (4.2, 7.1)</strong></td>
<td><strong>3.6 (2.2, 5.3)</strong></td>
<td><strong>1.53 (0.95, 2.70)</strong></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>Randomization</td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Time from randomization to implant</td>
<td>7-14(^1) days</td>
<td>2 days</td>
</tr>
<tr>
<td>Roll-in</td>
<td>New implanter: 1st 3 patients(^2)</td>
<td>New implanter: 1(^{st}) 2 patients Experienced: 1(^{st}) patient</td>
</tr>
<tr>
<td>Exclusion of clopidogrel</td>
<td>No exclusion</td>
<td>Indication for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment</td>
</tr>
<tr>
<td>Inclusion differences</td>
<td>CHADS(_2) (\geq 1)</td>
<td>CHADS(_2) (\geq 2) and CHADS(_2)=1 patients not eligible for aspirin therapy alone</td>
</tr>
</tbody>
</table>

\(^1\) 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
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
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
  - No Implant Attempt 4
    - Device Implanted 252
    - Unable to Implant 13

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## Demographics
### Device Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=463</td>
<td>N=566</td>
<td>N=269</td>
<td></td>
</tr>
<tr>
<td>Age, years</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>Gender (Male)</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>CHADS$ _2$ Score</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></td>
<td>(1.0, 6.0)</td>
<td>(1.0, 6.0)</td>
<td>(1.0, 6.0)</td>
<td></td>
</tr>
</tbody>
</table>

### CHADS$ _2$ Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>124/463 (26.8%)</td>
<td>108/566 (19.1%)</td>
<td>63/269 (23.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>415/463 (89.6%)</td>
<td>503/566 (88.9%)</td>
<td>238/269 (88.5%)</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>
</tr>
<tr>
<td>Diabetes</td>
<td>113/463 (24.4%)</td>
<td>141/566 (24.9%)</td>
<td>91/269 (33.8%)</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>
</tr>
</tbody>
</table>

**Most notable differences:**

- Age
- Diabetes
- Prior Stroke/TIA

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Procedure Implant Success

Implant success defined as deployment and release of the device into the left atrial appendage

PROTECT AF
Implant success
90.9%

CAP
Implant success
94.3%

PREVAIL
Implant success
95.1%

p = 0.04

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

<table>
<thead>
<tr>
<th>N Subjects</th>
<th>% (n/N)</th>
<th>95% CI¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>269</td>
<td>2.2% (6/269)</td>
<td>2.618%</td>
</tr>
</tbody>
</table>

¹CI is one-sided

- 6 events in device group
- Success based on upper 95% CI bound for percentage of subjects with event
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)

Results are preliminary; final validation not yet complete
Vascular Complications

- Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>8.7%</td>
<td>4.1%</td>
<td>4.4%</td>
</tr>
<tr>
<td>n</td>
<td>39</td>
<td>23</td>
<td>12</td>
</tr>
</tbody>
</table>

\(p = 0.004\)

7 Day Serious Procedure/Device Related

No procedure-related deaths reported in any of the trials

\(^1\)Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding
Pericardial Effusions Requiring Intervention

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Pericardial effusion with cardiac tamponade requiring pericardiocentesis or window:
- PROTECT AF: 1.6% (n=11), p = 0.318
- CAP: 1.2% (n=7)
- PREVAIL: 1.5% (n=4)

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

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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>% of Successful Implants</th>
<th>90.0%</th>
<th>92.0%</th>
<th>94.0%</th>
<th>96.0%</th>
<th>98.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Implant Success</td>
<td></td>
<td></td>
<td>95.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced Operators</td>
<td></td>
<td></td>
<td></td>
<td>96.3%</td>
<td></td>
</tr>
<tr>
<td>N= 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Operators</td>
<td></td>
<td></td>
<td>93.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N= 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p = 0.256
PREVAIL Complications
New vs Experienced Operator

7 Day Procedure/Device Related Vascular Complications
- Experienced: 5.4% (n=9)
- New: 2.9% (n=3)
- p = 0.377

Device Embolization
- Experienced: 1.2% (n=2)
- New: 0% (n=1)
- p = 0.522

Cardiac Perforation
- Experienced: 0.6% (n=1)
- New: 0% (n=1)
- p = 1.00

PE with Tamponade
- Experienced: 1.8% (n=3)
- New: 1.0% (n=1)
- p = 1.00
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

<table>
<thead>
<tr>
<th></th>
<th>Device 18-Month Rate</th>
<th>Control 18-Month Rate</th>
<th>18-Month Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.064</td>
<td>0.064</td>
<td>1.07 (0.57, 1.88)</td>
</tr>
</tbody>
</table>

- Similar 18-month event rates in both groups
- 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

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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

<table>
<thead>
<tr>
<th>Device 18-Month Rate</th>
<th>Control 18-Month Rate</th>
<th>18-Month Rate Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0253</td>
<td>0.0201</td>
<td>0.0051 (-0.0191, 0.0268)</td>
</tr>
</tbody>
</table>

- Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)
- Endpoint success in the presence of an over-performing control group

Results are preliminary; final validation not yet complete
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 procedural stroke rates p=0.019
  - Decreased perforations requiring surgical repair p=0.027
  - 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