Left Atrial Appendage Closure for Stroke Prevention in Patients with Atrial Fibrillation

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Chair, Division of Cardiovascular Medicine
Mayo Clinic Florida
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Medtronic, Baxter</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
<td>None</td>
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<tr>
<td>Major Stock Shareholder/Equity</td>
<td>None</td>
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<td>Royalty Income</td>
<td>None</td>
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<tr>
<td>Ownership/Founder</td>
<td>None</td>
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<td>Intellectual Property Rights</td>
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<td>Other Financial Benefit</td>
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</tr>
</tbody>
</table>
Trans Catheter Left Atrial Appendage Closure

- Atrial fibrillation (AF) related stroke
- Benefits and risks of anticoagulation
- Left atrial appendage (LAA) anatomy and role in thrombus formation
- LAA closure:
  - Surgical methods
  - Catheter-based:
    - Techniques
    - The evidence-base.
Stroke in AF patients

- Patients with AF have 5 times the risk of stroke compared to those without AF\(^1\)

- Stroke is more severe for patients with AF (70% chance of death or permanent disability)\(^1\)

- AF patients have more recurrences of stroke during the first year of follow-up\(^2\)

- The economic burden of stroke will continue to rise globally as the incidence of stroke increases\(^3\)

Management of AF
Goals of Therapy

• Minimize symptoms
  – Conversion to sinus rhythm
  – Rate control

• Reduce thromboembolic risk
  – Pharmacologic: Anticoagulation
  – Mechanical: LAA closure

• Prolong life

Patients need to be well informed to participate in their treatment decisions
AF Treatment Options

AF

Ablation*

Pacing

Drugs for Rate Control

Embolic Management

Interventions

Surgical Ligation

LAA Clips

Endovascular LAA

Drugs (warfarin*)

Drugs (dabigatran, rivaroxaban)

*BSC currently has no ablation catheters FDA-approved for the treatment of AF.
Reduction of Stroke in A/Fib
Anticoagulation

• How do we decide who to treat?
• What is the bleeding risk?
Quantification of Stroke Risk in Afib
The CHADS$_2$ score

- CHADS$_2$ Score is a system for establishing the risk of stroke in patients with non-rheumatic atrial fibrillation (a-fib).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C  Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H  Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A  Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D  Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S$_2$ Previous stroke or TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

### Annual Risk of Stroke

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Aspirin</td>
</tr>
<tr>
<td>1</td>
<td>Aspirin or warfarin*</td>
</tr>
<tr>
<td>≥2</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

* Use of aspirin or warfarin is based on additional patient characteristics such as age, number of risk factors, etc.

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European Society of Cardiology Guidelines


Quantification of Stroke Risk in Afib

**CHA₂DS₂-VASc**

- **CHA₂DS₂-VASc** is a refinement of the CHADS₂ Score with addition of gender, vascular disease and greater emphasis on age.

### Condition/Risk Factor | Points
---|---
C | Congestive heart failure | 1
H | Hypertension | 1
A | Age ≥75 years | 2
D | Diabetes mellitus | 1
S₂ | Previous stroke or TIA | 2
V | Vascular disease | 1
A | Age 65-74 years | 1
Sₘ | Sex (female gender) | 1

### Annual Risk of Stroke

| CHA₂DS₂-VASc Score | Treatment |
---|---
0 | No treatment |
1 | Aspirin or warfarin or dabigatran |
≥2 | Warfarin or dabigatran |

- A high CHADS score often correlates with a high HAS-BLED score and these patients do not receive anticoagulation due to the high bleeding risk

### Quantification of Bleeding Risk

**HAS-BLED Score**

#### Quantification of Bleeding Risk

**HAS BLED**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Abnormal liver and renal function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E Elderly (age &gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

#### Risk of major bleeding in patients with AF in the Euro Heart Survey

<table>
<thead>
<tr>
<th>Score</th>
<th>Bleeds Per 100 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Pisters R et al. *Chest* 2010;138(5):1093-100
Warfarin, when taken appropriately and the INR is kept in the therapeutic range, is effective for stroke reduction in patients with atrial fibrillation.
Warfarin in A/Fib
Why Do Patients Need an Alternative

- Increased bleeding risk
- Requirement for lifetime monitoring
- Interaction with foods and medicines
- Complicates planning for surgery
- High rates of discontinuation and non-adherence to therapy

- tops the list for emergency hospitalizations for adverse drug events in older Americans

Warfarin Has a Narrow Range of Safety & Effectiveness

Over-anticoagulation

44% of bleeding events occur in patients above therapeutic range¹

Therapeutic Range

Under-anticoagulation

48% of thromboembolic events occur in patients below therapeutic range¹

Non-Adherence to Warfarin
The Elephant in the Room

% patients taking warfarin following a stroke\textsuperscript{1}

The rate of non adherence to coumadine is \textasciitilde{} 40\% \textsuperscript{2}

Patients who do not adhere to their warfarin regimen are at increased risk of ischemic and hemorrhagic stroke

# Warfarin Alternatives

The new oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>RE-LY(^1)</th>
<th>ROCKET-AF(^2)</th>
<th>ARISTOTLE(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Total Enrolled Subjects</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Randomized, controlled non-inferiority</td>
<td>Randomized, controlled, double-blind non-inferiority</td>
<td>Randomized, controlled, double-blind non-inferiority</td>
</tr>
<tr>
<td>Median Follow up</td>
<td>2 years</td>
<td>1.94 years</td>
<td>1.8 years</td>
</tr>
<tr>
<td>Average CHADS(_2) Score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Results (primary outcome = stroke or systemic embolism)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# The New Oral Anticoagulants

## Major bleeding rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Major Bleeding</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY¹</strong></td>
<td>Dabigatran (110 mg)</td>
<td>2.71%</td>
<td>0.12%</td>
</tr>
<tr>
<td></td>
<td>Dabigatran (150 mg)</td>
<td>3.11%</td>
<td>0.10%</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>3.36%</td>
<td>0.38%</td>
</tr>
<tr>
<td><strong>ROCKET-AF²</strong></td>
<td>Rivaroxaban</td>
<td>3.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>3.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>ARISTOTLE³</strong></td>
<td>Apixaban</td>
<td>2.13%</td>
<td>0.24%</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>3.09%</td>
<td>0.47%</td>
</tr>
</tbody>
</table>

Dabigatran vs. Warfarin
The RE-LY trial

Efficacy of dabigatran versus warfarin

- **Ischemic Stroke**: 1.34% (dabigatran 110mg), 0.92% (dabigatran 150mg), 1.20% (warfarin)
- **Hemorrhagic Stroke**: 0.12% (dabigatran 110mg), 0.10% (dabigatran 150mg), 0.38% (warfarin)
- **Major Bleeding**: 2.71% (dabigatran 110mg), 3.11% (dabigatran 150mg), 3.36% (warfarin)

0.76 relative risk compared to warfarin

Dabigatran

Rates of Non-Adherence to Therapy

- Dyspepsia, a frequent side effect, contributed to the high rates of discontinuation

\[\text{% patients discontinuing therapy}\]

![](chart.png)

1 Connolly S. *NEJM*. 2009;361:1139–51
**Rivaroxaban vs. Warfarin**

The ROCKET AF Trial

- **Major bleeding**
  - Rivaroxaban: 3.6
  - Warfarin: 3.4

- **Stroke or systemic embolism**
  - Rivaroxaban: 1.7
  - Warfarin: 2.2

- **Mortality**
  - Rivaroxaban: 1.9
  - Warfarin: 2.2

Rivaroxaban has similar rates of bleeding and adverse events compared to warfarin

Apixaban vs. Warfarin
The ARISTOTLE Study

Granger J et al, NEJM. 2011;365:981–92
Apixaban vs. Aspirin
The AVERROES Study

Patients with AF and elevated risk for stroke who were not suitable for warfarin therapy were randomized to apixaban 5 mg twice daily (n=2,808) vs. aspirin 81-324 mg daily (n=2,791).

- Clinically relevant nonmajor bleeding: 3.1%/year vs. 2.7%/year ($P=0.35$)
- Fatal bleeding: 0.1%/year vs. 0.2%/year ($P=0.53$)

Connolly SJ, et al. NEJM. 2011;364:806-17
The New Oral Anticoagulants

- The primary advantage of the new oral anticoagulants over warfarin is avoidance of regular INR monitoring, while the primary disadvantage is lack of reversibility.

- The bleeding risks and high rates of non-adherence with dabigatran and rivaroxaban are still a problem.

- The real-world and long-term efficacy and safety of Apixaban has yet to be determined.

- A need exists for an effective means of stroke reduction that does not expose patients to bleeding events or require lifetime pharmacologic therapy.
The Culprit of Stroke in Atrial Fibrillation
The Left Atrial Appenage (LAA)

- Forms during the 3rd week of gestation and serves as the left atrium in the fetus
- The LAA is about the size of a thumb and its ostium measures 10mm - 40mm
- The LAA has extremely variable morphology
91% of stroke in AF is caused by blood clots that form in the Left Atrial Appendage (LAA)

A/Fib causes blood stagnation in the LAA

LAA thrombus

Thrombus dislodgement to the arterial circulation

Ischemic stroke
Myocardial infarction
Acute limb ischemia etc..

Thrombus in the LAA

Images on file at Boston Scientific Corporation

Left Atrial Appendage (LAA) Closure

Surgical Technique
Surgical LAA Excision / Exclusion
Limited Efficacy in Stroke Prevention

137 pts underwent surgical LAA closure:

Pts with Successful closure – Stroke/TIA 11%

Pts with unsuccessful closure – Stroke/TAI 15%

Kanderian AS et al. JACC 2008;52:924–9.
Left Atrial Appendage (LAA) Closure

Transcatheter Technique
LAA Closure: The Watchman Device

A self-expanding nitinol frame with fixation anchors and a permeable fabric cover.

Device sizes (21, 24, 27, 30 and 34 mm)

It is implanted via a trans-septal approach by use of a catheter-based delivery system.

Received CE mark in 2005

Investigational device. Not for sale in the US.
LAA Closure: The Watchman Device
How is it done?
LAA Measurements

RAO caudal - 19 mm

RAO cranial - 18 mm

TEE 43° - 17 mm

TEE 93° - 17 mm
## WATCHMAN® LAA Closure
### Device Selection

<table>
<thead>
<tr>
<th>Max LAA Ostium (mm)</th>
<th>Device Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 – 19.9</td>
<td>21</td>
</tr>
<tr>
<td>20 – 22.9</td>
<td>24</td>
</tr>
<tr>
<td>23 – 25.9</td>
<td>27</td>
</tr>
<tr>
<td>26 – 28.9</td>
<td>30</td>
</tr>
<tr>
<td>29 – 31.9</td>
<td>33</td>
</tr>
</tbody>
</table>

**Diagram:**
- Nitinol Frame
- 160 µ PET fabric
- Barbs: 21, 24, 27, 30, 33 mm
LAA Closure: The Watchman Device

Device Deployment
WATCHMAN®: Device Implant Procedure

Transseptal puncture

Placement of WATCHMAN® in LAA

Human Pathology – 9 Months Post-implant (Non-device related death)

Images on file at Boston Scientific Corporation
## The Evidence Base for the WATCHMAN® Device

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>CAP&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ASAP&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>Warfarin</td>
<td></td>
<td>Warfarin contraindicated</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>All stroke, systemic embolism and CV death</td>
<td>All stroke, systemic embolism and CV death</td>
<td>All stroke, systemic embolism, and CV death</td>
<td>All stroke, systemic embolism and CV death</td>
</tr>
<tr>
<td><strong>Mean age /CHADS</strong></td>
<td>72/2.2</td>
<td>74/2.4</td>
<td>72.4/2.8</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total Enrolled Subjects</strong></td>
<td>707 randomized&lt;sup&gt;1&lt;/sup&gt;, 93 pts rolled in&lt;sup&gt;2&lt;/sup&gt;</td>
<td>460</td>
<td>150</td>
<td>461</td>
</tr>
<tr>
<td><strong>Implantation Success</strong></td>
<td>89.5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>95.0%</td>
<td>94.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Warfarin discontinuation at 45 days</strong></td>
<td>86.6%</td>
<td>94.9%</td>
<td>No warfarin used</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Rate ratio 0.71 (0.35–1.64) [Hemorrhagic Stroke: 0.09 (0.00–0.45)]</td>
<td>Reduction in procedure related stroke vs PROTECT AF (&lt;i&gt;P&lt;/i&gt;=0.04)</td>
<td>Decreased rate of stroke by 77% vs. expected rate per CHADS&lt;sub&gt;2&lt;/sub&gt; Score</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>HR 1.69 (1.01–3.19)</td>
<td>Reduction in pericardial effusions vs. PROTECT AF (&lt;i&gt;P&lt;/i&gt;=0.02)</td>
<td>Pericardial effusion with tamponade=2.0% Major bleeding=2.7%</td>
<td></td>
</tr>
</tbody>
</table>

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3. Sievert H. TCT 2011  
4. Reddy, ASAP WATCHMAN, HRS 2012
The PROTECT AF trial

- PROTECT AF was a prospective, randomized, multi-center trial which compared the WATCHMAN Device to warfarin for thromboembolic prophylaxis.
- 707 patients were randomized to either the WATCHMAN Device or warfarin in a 2:1 device to therapy ratio; 93 roll-in patients.

Baseline Risk Factors

<table>
<thead>
<tr>
<th>CHADS₂</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.

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 check for device placement, presence of thrombus and flow.

Patients received up to 5 years of biannual follow-up.

PROTECT AF
Primary efficacy & safety endpoints

- 91% of patients had successful implantation\(^1\)
- 87% of implanted patients discontinued warfarin at 45 days\(^2\)
- 92% of implanted patients had LAA closure at 6 months\(^1\)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Rate Ratio (Intervention/Control [95% CrI])</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patient-years</td>
<td>Events/patient-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population*</td>
<td>21/694.1</td>
<td>18/370.8</td>
<td>0.62 (0.35–1.25)</td>
<td>&gt;99.9%</td>
<td>90.0%</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>15/694.6</td>
<td>6/372.3</td>
<td>1.34 (0.60–4.29)</td>
<td>71.8%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Cardiovascular/unexplained death</td>
<td>5/708.4</td>
<td>10/374.9</td>
<td>0.26 (0.08–0.77)</td>
<td>&gt;99.9%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1/708.4</td>
<td>6/373.4</td>
<td>0.09 (0.00–0.45)</td>
<td>&gt;99.9%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>2/707.8</td>
<td>0/374.9</td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>All stroke</td>
<td>16/694.6</td>
<td>12/370.8</td>
<td>0.71 (0.35–1.64)</td>
<td>99.3%</td>
<td>76.9%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>21/708.4</td>
<td>18/374.9</td>
<td>0.62 (0.34–1.24)</td>
<td>&gt;99.9%</td>
<td>90.7%</td>
</tr>
</tbody>
</table>

\(^1\)Holmes DR et al. *Lancet* 2009;374:534–42
\(^2\)PROTECT-AF study data at 1500 patient years on file with Boston Scientific
Stroke was not significantly different between treatment arms.

Following the peri-procedural period, the rate of ischemic stroke with the WATCHMAN® Device was 1.3 per 100 patient years vs 1.6 with warfarin.
PROTECT AF
Ischemic and hemorrhagic stroke rates


Rate of ischemic stroke over time

Rate of hemorrhagic stroke over time
WATCHMAN®
Outcomes in patients with previous stroke

• 47% of AF patients experiencing a stroke will suffer a second stroke within 6 months¹

51% reduction in stroke, CV death and systemic embolism when used as secondary prevention

Primary efficacy in patients with previous stroke²

- 4.0
- 8.2

WATCHMAN  warfarin

2. Unpublished data on file
PROTECT AF
Older Patients

- Average length of follow-up was 27 months
- 190 patients randomized to the device group; implantation was attempted in 183 subjects
  - 164/183 (88%) were successfully implanted
- Mean CHADS\textsubscript{2} Score was 2.8 (compared to 2.2 in the Overall patient population)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Warfarin Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OVERALL</td>
</tr>
<tr>
<td></td>
<td>N/Total Implanted</td>
</tr>
<tr>
<td>45 day</td>
<td>348/401</td>
</tr>
<tr>
<td>6 month</td>
<td>355/385</td>
</tr>
<tr>
<td>12 month</td>
<td>345/370</td>
</tr>
</tbody>
</table>
PROTECT AF

Older Patients ITT Patient Population

95% of stroke were ischemic, non-inferiority P-values

<table>
<thead>
<tr>
<th></th>
<th>WATCHMAN®</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy</td>
<td>16/391.6</td>
<td>16/256.1</td>
</tr>
<tr>
<td>All Stroke</td>
<td>12/391.6</td>
<td>11/256.1</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>21/404.5</td>
<td>15/262.1</td>
</tr>
</tbody>
</table>

Kar, S. TCT 2012; PROTECT–AF: Watchman LAA Closure in AF Patients ≥ 75 Years
## PROTECT AF: Analysis of Older Patients

### Major Bleeding in Patients ≥75 Years

**ITT Patient Population**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Device (n=190)</th>
<th>Control (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (events/patient-years)</td>
<td>6.1 (23/374.8)</td>
<td>5.1 (13/252.8)</td>
</tr>
<tr>
<td><strong>Procedure related major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (events/patient-years)</td>
<td>2.9 (11/385.9)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(5.8% pts)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-procedure related major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate (events/patient-years)</td>
<td>3.3 (13/393.3)</td>
<td>5.1 (13/252.8)</td>
</tr>
</tbody>
</table>

Kar, S. TCT 2012; PROTECT-AF: Watchman LAA Closure in AF Patients ≥ 75 Years
**Study Objective:** Evaluate the PROTECT AF trial results using \( \text{CHA}_2\text{DS}_2\text{VASc} \) scores to better determine stroke risk

**Study Design:** PROTECT AF design used \( \text{CHADS}_2 \) scores. This analysis uses the same data replacing the \( \text{CHADS}_2 \) score with the \( \text{CHA}_2\text{DS}_2\text{VASc} \) score.

**Primary Endpoint:** Embolic stroke

**Patient Population:**
- \( n=463; \) Mean age=72;
- Mean \( \text{CHADS}_2 \) score=2.2, Mean \( \text{CHA}_2\text{DS}_2\text{VASc} = 3.5 \)

**Total Follow Up:** 1500 patient years

**Number of Sites:** 59 in the United States and Europe

**Presented by:** Sven Mobius–Winkler,; ESC 2012

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Mobius–Winkler, et al., WATCHMAN Pilot data; ESC 2012, Munich, Germany
• 93% had CHA$_2$DS$_2$VASc score >2
• Average CHA$_2$DS$_2$Vasc score: 3.5
• Expected risk of stroke: 3%
• Observed stroke rate: 2%
• 37.5 % reduction compared to expected
PROTECT AF
Health Economics Analysis

- **Analytic Perspective**
  - US healthcare provider perspective. 2009 US dollars

- **Approach**
  - Markov decision analytic model
  - Cohort of 65-year-old patients with NVAF
  - 6 stroke preventive strategies
  - 8 different health status in each 1 year Markov cycle
  - Time horizon = lifetime (85 years old)
## PROTECT AF

### Health Economics Analysis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total Costs (USD)</th>
<th>Total QALY gained</th>
<th>Cost per QALY gained (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>12,877</td>
<td>6.12</td>
<td>2,104</td>
</tr>
<tr>
<td>Warfarin</td>
<td>23,848</td>
<td>8.27</td>
<td>2,883</td>
</tr>
<tr>
<td>Clopidogrel &amp; aspirin</td>
<td>26,287</td>
<td>6.29</td>
<td>4,182</td>
</tr>
<tr>
<td>Dabigatran 110mg</td>
<td>42,540</td>
<td>8.77</td>
<td>4,850</td>
</tr>
<tr>
<td>Dabigatran 150mg</td>
<td>43,794</td>
<td>9.00</td>
<td>4,864</td>
</tr>
<tr>
<td>LAA closure</td>
<td>47,789</td>
<td>14.95</td>
<td>3,197</td>
</tr>
</tbody>
</table>

Cost per QALY = Lifetime incremental costs (USD) per quality-adjusted life year (QALY) gained for each strategy

Yan, B. TCT 2012; Cost Effectiveness of LAAO
PROTECT AF

Health Economics Analysis Monte Carlo Simulation

- LAAC was cost-effective >99% simulations using a cost-effectiveness threshold of US$50,000 per QALY gained

Yan, B. TCT 2012; Cost Effectiveness of LAAO
<table>
<thead>
<tr>
<th>LAA Closure</th>
<th>CHADS Score 0</th>
<th>CHADS Score 1</th>
<th>CHADS Score 2</th>
<th>CHADS Score 3</th>
<th>CHADS Score ≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cost</td>
<td>47,259</td>
<td>47,312</td>
<td>47,398</td>
<td>47,551</td>
<td>47,638</td>
</tr>
<tr>
<td>Total QALY Gained</td>
<td>14.95</td>
<td>14.95</td>
<td>14.95</td>
<td>14.95</td>
<td>14.95</td>
</tr>
<tr>
<td>Cost per QALY</td>
<td>3,161</td>
<td>3,165</td>
<td>3,171</td>
<td>3,181</td>
<td>3,187</td>
</tr>
<tr>
<td>ICER/QALY gained compared to next best alternative</td>
<td>4,323</td>
<td>4,022</td>
<td>3,587</td>
<td>2,952</td>
<td>2,659</td>
</tr>
<tr>
<td>ICER/QALY gained compared to warfarin</td>
<td>3,474</td>
<td>4,038</td>
<td>2,283</td>
<td>1,206</td>
<td>780</td>
</tr>
</tbody>
</table>

Analysis:
- Cost per QALY = Lifetime incremental costs (USD) per quality-adjusted life year (QALY) gained
- ICER/QALY = Lifetime incremental cost-effective ratio (ICER) per QALY gained between LAAC & other strategies

Yan, B. TCT 2012; Cost Effectiveness of LAAO
A continued access registry (CAP) enrolled an additional 460 patients at 26 centers which had also participated in PROTECT AF. Implantation success defined as device implantation followed by discontinuation of warfarin.

Pericardial Effusion Rates

**Pericardial effusion within 7 days of the procedure**

- **First 3 patients**: 6.5%
- **Subsequent patients**: 4.4%
- **CAP**: 2.2%

32% reduction in rates of pericardial effusion as experience increased

- **Pericardial effusion**:
  - 68% required pericardiocentesis
  - 32% required surgical intervention

Procedure related safety events

Safety events within 7 days of procedure

- Pericardial effusions in CAP:
  - 90% required pericardiocentesis
  - 10% required surgery

- Reduction of ~50% in pericardial effusion rates between studies
- Procedure-related stroke reduced to 0

The PREVAIL Study

- Prospective, multi-center, randomized (2:1) study comparing WATCHMAN to warfarin therapy (PREVAIL)
- Up to 50 sites in the US - 400 randomized
  - Minimum 20% of patients from new sites
  - Minimum 25% patients by new operators
- 1st Primary Endpoint (same as PROTECT AF)
  - Ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death
- 2nd Primary Endpoint
  - Ischemic stroke and systemic embolism >7 days post randomization
The ASAP registry, a non-randomized feasibility study, was designed to determine if the WATCHMAN® Device is a safe and effective treatment for people unable to take warfarin.

- AF patients who are contraindicated or intolerant of warfarin have few options for thromboembolic prophylaxis.
- Patients may be treated with aspirin and/or clopidogrel; this treatment paradigm has a higher stroke risk than warfarin.

ASAP Registry
150 AF patients with contraindication for warfarin therapy

- 4 European centers
- Average CHADS$_2$ = 2.8
- Post procedure anti-platelet regimen
  - Clopidogrel for 6 months
  - Aspirin indefinitely
- Followed up:
  - Clinical: Follow-up @ 3, 6, 12, 18 & 24 months
  - TEE: 3 and 12 months

94.7% successfully implanted

Reddy, ASAP WATCHMAN, HRS 2012, Boston, MA
ASAP Registry

Expected Stroke Rate

Mean CHADS\textsubscript{2} Score in ASAP = 2.8
ASAP Registry
Observed vs. Expected Efficacy Outcome

Ischemic Stroke

- Expected, based on CHADS₂ Score
- Observed rate in ASAP

77% Reduction
ASAP Registry
Observed vs. Expected Efficacy Outcome

Ischemic Stroke

- Expected, based on CHADS$_2$ Score: 7.3%
- 77% Reduction

- Expected, if Clopidogrel was used throughout follow-up: 5.1%
- 67% Reduction

- Observed rate in ASAP: 1.7%
ASAP Registry
Efficacy outcomes with devices

ASAP Registry

<table>
<thead>
<tr>
<th>Ischemic Stroke Rate (%/pt-yr)</th>
<th>Expected Rate (per CHADS₂)</th>
<th>Rate in Device Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.3%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

77% Reduction

Reddy, ASAP WATCHMAN, HRS 2012, Boston, MA

PLAATO

<table>
<thead>
<tr>
<th>Stroke/TIA Rate (%/pt-yr)</th>
<th>Expected Rate (per CHADS₂)</th>
<th>Rate in Device Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

59% Reduction


PLAATO is an investigational device and not FDA approved
Left Atrial Appendage (LAA) Ligation

Trans Catheter Technique (The LARIAT Device)
The LORIAT Device

Components

**LORIAT** suture delivery device

13F (4.3mm) Pericardial access Sheath

Remote suture delivery device compatible with access ≥4.3mm WITH open / close capabilities allow control & precise placement

40mm pre-tied, “0” polyester suture loop mounted on collapsible snare

Includes SofTIP & TenSURE accessories
The LORIAT Device
Components

EndoCATH Large Occlusion Balloon

15mm & 20mm compliant balloons, >8.5F introducer compatible

echogenic properties for identifying anatomic references

Angiography performed through side holes distal to balloon
The LORIAT Device
Components

**Accessories** for LARIAT

**SofTIP**
Guide Cannula
4.3mm cannula with compliant atraumatic tip

**TenSURE**
Suture Tightener
Reduces operator variability during suture tightening

**SureCUT**
Suture Cutter
Remote suture cutter used with LARIAT
LAA Closure: The LORIAT Device

How It Works

1. **Left atrial appendage**
2. **Inflated balloon**
3. **Catheter from leg**
4. **Magnet**
5. **Loop**
6. **Second magnet**
7. **Sheath**
8. **Loop is tightened**
9. **Tightened loop left in place**
LAA Closure: The LORIAT Device
Without Balloon Occlusion of the LAA
Residual Sac

LAA Closure: The LORIAT Device
With Balloon Occlusion of the LAA
No Residual Sac

Pre Procedure Imaging

Confirm position of target for best access approach

Confirm origin, shape, size & trajectory of target is compatible with LARIAT

Identify exclusions such as thrombus, adhesions or other anatomic factors
Identify approach to deliver LARIAT to apical aspect of exclusion target

Confirm absence of anatomical factors for delivery, e.g. adhesions
LAA Access

Femoral Vein Access  TEE Imaging  Placement of the EndoCATH & FindrWIRZ
Dilate access site to \( \geq 4.3 \text{mm} \)

Advance SofTIP guide cannula

Replace guide wire with .035” FindrWIRE
EndoCATH Positioning in the LAA

Left Atrium

EndoCATH

LAA
FindrWIRZ Attachment

EndoCATH

FindrWIRZ

SofTIP
LARIAT Delivery
Position snare at exclusion site using pre-determined reference

Retract snare actuator completely
Confirmation of LAA Capture

Exclusion location satisfactory?

No
Open snare and reposition

Yes
Move to “release of suture”

EndoCATH & 0.025” FindrWIRE removed
Suture Tightening
Suture Tightening

Snare opened

Complete exclusion with TenSURE Suture Tightener
Confirmation of LAA Closure

Before

After

LAA
Confirmation of LAA Closure

Before

After

Left Atrium

LAA

Pericardium
SureCUT

Remote suture cutter

Easy suture load method
Access catheters & SofTIP removed
Baseline

Post LARIAT exclusion

30 day TEE
### LAA Closure: The LORIAT Device Registry Data

<table>
<thead>
<tr>
<th></th>
<th>PLACE - PLACE II Study</th>
<th>ACP - Registry Data*</th>
<th>WATCHMAN - PROTECT AF Trial**</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pts</td>
<td>99</td>
<td>143</td>
<td>463</td>
</tr>
<tr>
<td>Intent-to-Treat</td>
<td>95/99 (96%)</td>
<td>132/143 (93%)</td>
<td>408/463 (88%)</td>
</tr>
<tr>
<td>Acute Closure</td>
<td>97/99 (98%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;30d Closure</td>
<td>82/85** (97%)</td>
<td>NA</td>
<td>346/408 (85%)**</td>
</tr>
<tr>
<td>LA Access Requirement</td>
<td>8.5F SL1</td>
<td>16F</td>
<td>14F</td>
</tr>
</tbody>
</table>

Complications: Pericardial Effusion 3%

---

*PLACE II Safety & Efficacy Study  
**Closure defined as “complete” would =71%, Closure 3mm +/- 2mm  
*Retrospective analysis of Registry data - No closure data included  
****Closure = ≤1mm
Trans Catheter LAA Closure

Conclusions

- Trans catheter closure of the LAA is a promising alternative to chronic anticoagulation in patients with non valvular atrial fibrillation.

- Patient’s access to this novel therapeutic modality, in the US, is based on their tolerance for chronic anticoagulation:
  - No contraindications to chronic anticoagulation
    - The Watchman device: CAP2
  - Contraindications to chronic anticoagulation
    - Trans catheter LAA closure (the LORIAT device)