Learning Objectives

1. Provide information on pathophysiology & prevalence for atrial fibrillation (AF)
2. Identify treatments for AF stroke risk reduction
3. Provide information on left atrial appendage closure (LAAC)
4. Identify potential patients for LAAC procedures

Agenda

• Atrial fibrillation (AF) & Stroke Risk Reduction
  – Pharmacologic Treatment Options
  – Non-pharmacologic Treatment Options
• Left Atrial Appendage Closure (LAAC)
  – Description
  – WATCHMAN™ Left Atrial Appendage Closure Device
  – Procedure
  – Patient Selection
  – Clinical Studies & Results
  – Patient Case Examples
Atrial Fibrillation (AF) & Stroke Risk Reduction

Many patients are unprotected

AF increases risk of stroke

Blood clots form in the left atrial appendage

>33M people worldwide have AF

>90% of stroke-causing clots that come from the left atrium in non-valvular AF are formed in the LAA

<90% Thrombus Originate LAA

15% Thrombus Originate LAA

15% Thrombus Originate Non-LAA

10% Thrombus Originate Non-LAA

70% Thrombus Originate Non-LAA

45% Treated with Warfarin

45% Contraindicated or Intolerant

~45% of patients eligible for warfarin are untreated (tolerance/adherence)


Patients With NAF Have Significantly Increased Risk of Stroke

*The risk of stroke is increased ~5-fold in NAF patients versus those without NAF.*

Incidence of Stroke According to Presence of NAF (Framingham Heart Study)
Pharmacologic Treatment for Stroke Risk Reduction

2014 AHA/ACC/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF

- Assess stroke risk with CHA₂DS₂-VASc score
  - Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  - Score 2: Annual stroke risk 2%-15%, oral anticoagulants are recommended
- Higher CHADS₂ score predicts worse outcomes (stroke, major bleeding & vascular mortality)³
- Balance benefit vs. bleeding risk
Warfarin is an effective means of stroke reduction in patients with AF but can present challenges.

- Many patients spend a significant amount of time outside of the therapeutic range.
- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans.

INR control is difficult with warfarin treatment & impacts stroke & bleeding risk.

- Only ~50% of patients on warfarin are at goal anticoagulation intensity.

Patients outside the therapeutic range are at an increased risk of ischemic and hemorrhagic stroke.

Warfarin use declines with increased stroke risk.

Medicare claims data, 2006-2007:
- Warfarin use less than 60% in high-risk patients.
Stroke Treatment Option: Novel Oral Anticoagulants (NOACs)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<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 (doses of dabigatran were blinded)</td>
<td>Randomized, controlled, double-blind, non-inferiority</td>
<td>Randomized, controlled, double-blind, non-inferiority</td>
</tr>
<tr>
<td>Median Duration of Follow-up</td>
<td>2 years</td>
<td>1.94 years</td>
<td>1.8 years</td>
</tr>
<tr>
<td>Average CHADS2 Score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Reduction in primary outcome compared to warfarin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduction in primary outcome compared to warfarin</td>
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<tr>
<td>Reduction in primary outcome compared to warfarin</td>
<td></td>
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</tr>
</tbody>
</table>

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs.

Non-Pharmacologic Treatment for Stroke Risk Reduction
Surgical approaches to thromboembolic prophylaxis have been explored since the 1940s. LAA closure or obliteration has most often been considered as an adjunct to other cardiac procedures such as mitral valvotomy or cardiac bypass surgery. Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events.

A review of the literature on LAA closure prior to 2010 found closure rates of 10%-73%.

### Stroke Treatment Option: LAA Ligation

- Surgical approaches to thromboembolic prophylaxis have been explored since the 1940s.
- LAA closure or obliteration has most often been considered as an adjunct to other cardiac procedures such as mitral valvotomy or cardiac bypass surgery.
- Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events.

### Stroke Treatment Options: LAA Ligation, LAA Clips and LAA Closure

#### LAA Closure (LAAC) Devices
- **PLAATO**
  - First LAAC device
  - Device no longer available

- **WATCHMAN™ Device**
  - Only LAAC device with 2 Randomized Controlled Trials
  - FDA approved with specific indication to reduce the risk of thromboembolism
  - NCT00550272 (PROTECT AF)
  - NCT01182441 (PREVAIL)

- **ACP**
  - US Trial halted in 2013
  - AtriClip™ Cardiac Plug Clinical Trial

#### LAA Clip
- **EXCLUDE Trial (completed)**
  - AHClip Device was FDA approved in 2010 for LAA closure
  - No specific indication for Stroke Reduction

### Surgical Ligation
- "Safety and Efficacy of Left Atrial Appendage Occlusion Devices" Observational Study (retrospective)
  - To compare LARIAT® vs. WATCHMAN™
  - LARIAT currently does not have a specific indication for LAA Closure or Stroke Reduction

### JACC Journals
- **From Percutaneous Left Atrial Appendage Closure: Procedural Techniques and Outcomes**
  - Table showing various devices and outcomes

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*SH-230506-AD June 2015*

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Left Atrial Appendage Closure (LAAC)

**Description**

- Device alternative to oral anticoagulation therapy in patients with non-valvular AF
- Designed to reduce the risk of thromboembolism by closing off the left atrial appendage (LAA), which is believed to be the source of a majority of stroke-causing blood clots in people with non-valvular AF
- Over time, patients may be able to stop taking oral anticoagulants

**Nitinol Frame**

- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention
- Features an intra-LAA design to avoid contact with Left Atrial wall

**160 Micron Membrane**

- Polyethylene teraphthalate (PET) cap
- Designed to block emboli from exiting the LAA

**WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview**
WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - EP/IC or EP&IC, TEE, General Anesthesia, Surgical Back-up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein
  (Does not require open heart surgery)
- General anesthesia (typical)
- 1 hour procedure (typical)
- 1-2 day hospital stay (typical)

WATCHMAN™ Device Patient Selection

Indications for Use

The WATCHMAN Device is intended to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

1. Are at an increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASC scores and are recommended for anticoagulation therapy;
2. Are deemed by their physicians to be suitable for warfarin, and
3. Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The WATCHMAN Access System is intended to provide vascular and transseptal access for all WATCHMAN Left Atrial Appendage Closure Devices with Delivery Systems.

Specific factors may include one or more of the following:

- History of major bleeding while taking anticoagulation therapy
- Patient’s prior experience with D/C (if applicable)
- Unwillingness to undergo required imaging
- Ability to undergo required imaging
- Unwillingness to comply with regular INR monitoring and unavailability of an approved alternative OAC
- History of major bleeding while taking anticoagulation therapy
- Medical condition, occupation, or lifestyle placing patient at high risk of major bleeding secondary to trauma
- Presence of indications for long-term warfarin use, other than non-valvular atrial fibrillation (e.g. mechanical heart valve, hypercoagulable states, recent deep venous thrombosis)

Specific factors that need to be considered for the WATCHMAN Device and Implantation procedure include:

- Overall medical status, including diagnosis which might preclude the safety of a percutaneous, transluminal procedure
- Suitability for percutaneous, transapical procedure, including considerations of:
  - medical anatomy relating to LAA size and shape
  - sinus rhythm
  - valve anatomy
  - valve function
  - atrial fibrillation duration
  - ability to undergo required imaging
  - ability to achieve stable INR while on warfarin and ability to maintain stable INR while on alternative OAC
  - successful deployment of the WATCHMAN Device implantation pharmacology regimen
  - successful deployment of the WATCHMAN Device implantation pharmacology regimen
  - ability to maintain stable INR while on alternative OAC
  - successful deployment of the WATCHMAN Device implantation pharmacology regimen

Specific factors that need to be considered for the WATCHMAN™ Device and Implantation procedure include:

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  - ability to maintain stable INR while on alternative OAC
  - successful deployment of the WATCHMAN Device implantation pharmacology regimen
WATCHMAN™ Device Clinical Studies & Results

**WATCHMAN™ Device Clinical Program**

- **Early feasibility with >6 years of follow-up**
- **WATCHMAN primary efficacy, CV death, and all-cause mortality superior to warfarin at 4 years**
- **Significantly improved safety results**
- **Expected rate of stroke reduced by 77% in patients contraindicated to warfarin**
- **Improved implant success; procedure safety confirmed with new and experienced operators**
- **Enrolled up to 1500 patients at ~60 sites**

**Favorable Procedural Safety Profile: 7-Day Safety Events**

- **PROTECT AF**
  - First Half: 9.9%
  - Second Half: 4.8%
- **CAP Registry**
  - 2nd Half: 4.3%
- **APRIL**
  - 2nd Half: 4.1%
- **CAP2**
  - 2nd Half: 3.8%

(1) Device and/or procedure-related serious adverse events within 7 days
Implant Success & Warfarin Cessation

Warfarin Cessation

<table>
<thead>
<tr>
<th>Study</th>
<th>45-day</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>87%</td>
<td>&gt;93%</td>
</tr>
<tr>
<td>CAP</td>
<td>96%</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>92%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

**PREVAIL Implant Success**

No difference between new and experienced operators

- Experienced Operators: n=26, 96%
- New Operators: n=24, 93%

**p = 0.28**

PREVAIL: Holmes, DR et al. JACC 2014; 64(1):1w12.

Most Studied LAAC Device. Only One with Long-Term Clinical Data

<table>
<thead>
<tr>
<th>PROTECT AF Registry</th>
<th>CAP Registry</th>
<th>PREVAIL Registry</th>
<th>CAP2 Registry</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>800</td>
<td>566</td>
<td>461</td>
<td>579</td>
</tr>
<tr>
<td>Randomized</td>
<td>707</td>
<td>---</td>
<td>407</td>
<td>---</td>
</tr>
<tr>
<td>WATCHMAN: warfarin (2:1)</td>
<td>463 : 244</td>
<td>566</td>
<td>269 : 138</td>
<td>579</td>
</tr>
<tr>
<td>Mean Follow-up (years)</td>
<td>4.0</td>
<td>3.7</td>
<td>2.2</td>
<td>0.58</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2717</td>
<td>2022</td>
<td>860</td>
<td>332</td>
</tr>
</tbody>
</table>

**SH-230506-AD June15**

Patient Risk Factors Across Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
<th>CAP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 Score</td>
<td>2.7±1.2</td>
<td>2.5±1.2</td>
<td>2.6±1.0</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CHADS2 Risk Factors (% of Patients)**

- CHF: 26.9%
- Hypertension: 89.8%
- Age ≥ 75: 43.4%
- Diabetes: 26.3%
- Stroke/TIA: 12.5%

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Score</th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>PREVAIL</th>
<th>CAP2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5±1.6</td>
<td>3.9±1.3</td>
<td>4.0±1.2</td>
<td>4.3±1.1</td>
<td>4.3±1.3</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Majority of Patients at High Stroke Risk, All Eligible for Anti-coagulation

Majority of Patients in the Trial were at Moderate to High Bleeding Risk

PROTECT AF 4-Year Results in JAMA

WATCHMAN™ Met Criteria for both Noninferiority and superiority for the Primary Composite Endpoint Compared to Warfarin

*Data from WATCHMAN Trial. WatchmanTM and WATCHMAN TM are trademarks of Boston Scientific Corporation or its affiliated or related companies. For professional use only. Always consult the product labeling before using any medical device. ©2013 Boston Scientific Corporation or its affiliates. All rights reserved.
**WATCHMAN™ PROTECT AF Study Overview**

**Long-Term, Final 5-Year Results**

**Study Design & Objectives**
Prospective, randomized (2:1), non-inferiority trial of LAA closure vs. warfarin in non-valvular AF patients for prevention of stroke

**Primary Endpoint**
- **Efficacy**: Composite end point of stroke, cardiovascular death or systemic embolization
- **Safety**: Major bleeding, device embolization or pericardial effusion

**Statistical Plan**
All analyses by intention-to-treat
Bayesian (stratified for CHADS2 score)
Primary Efficacy and Safety endpoints Cox Proportional All Secondary Analyses

**Patient Population**
- Mean CHADS2 = 2.2
- Mean CHADS2, VASC = 3.5

**Key Inclusion Criteria**
- Paroxysmal / Persistent / Permanent AF
- CHADS2 ≥ 1
- Eligible for long-term warfarin therapy
- Mean Follow-Up: 2,717 patient-years, 48 months
- Number of Sites: 59 in the United States and Europe

**Event Rate**
Event Rate
\[ \text{Per 100 Pt-Yrs} \]
\[ \text{Rate Ratio (95\% CrI)} \]
\[ \text{Posterior Probability} \]
**Posterior Probability**
**WANTHMAN**
**Warfarin**

- **Primary efficacy**
  - Rate Ratio: 0.61 (0.42, 1.07)
  - Posterior Probability: >99.9%

- **Stroke (all)**
  - Rate Ratio: 0.68 (0.42, 1.07)
  - Posterior Probability: 99.9%

- **Systemic embolism**
  - Rate Ratio: N/A
  - Posterior Probability: --

- **Death (Circulatory)**
  - Rate Ratio: 0.44 (0.06, 0.46)
  - Posterior Probability: 99.9%

**SH-230506-AD June15**

**PROTECT AF: Final, 5-Year Primary Efficacy Events Consistent with 4-Year Results**

<table>
<thead>
<tr>
<th>Event Rate (Per 100 Pt-Yrs)</th>
<th>Rate Ratio (95% CI)</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Death (Circulatory)</td>
<td>1.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.79</td>
<td>0.33</td>
</tr>
<tr>
<td>All stroke or SC</td>
<td>1.04</td>
<td>0.94</td>
</tr>
<tr>
<td>Total stroke or all</td>
<td>1.05</td>
<td>0.45</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.23</td>
<td>0.004</td>
</tr>
<tr>
<td>Total stroke or all, &lt;7 days</td>
<td>1.36</td>
<td>0.23</td>
</tr>
<tr>
<td>Cirrhosis-related death</td>
<td>0.48</td>
<td>0.10</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.47</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.20</td>
<td>0.68</td>
</tr>
<tr>
<td>Major bleeding, non-procedure-related</td>
<td>0.31</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Favor WATCHMAN \(\Phi\) \(\Phi\) Favor warfarin \(\Phi\) \(\Phi\)
**WATCHMAN™ Device Reduced Ischemic Stroke Over No Therapy**

![Graph showing ischemic stroke rate reduction](image)

- **Imputed Ischemic Stroke Rate**
- **Observed WATCHMAN Ischemic Stroke Rate**

---

**Clinical Trial Device Arm Drug Protocol**

![Protocol diagram](image)

---

**PROTECT AF/PREVAIL Pooled Analysis: Less Bleeding with WATCHMAN™ Device 6 Months Post-Implant**

![Bleeding event free rates](image)

- **Free of Major Bleeding Event (%)**
- **Time (days)**
- **Time (months)**

- **WATCHMAN**
- **Warfarin**
- **Aspirin**

**Definition of bleeding:** Serious bleeding event that required intervention or hospitalization according to adjudication committee.

**HR = 0.29, p<0.001**

*Reduced bleeding risk with WATCHMAN device compared to warfarin and aspirin.*
**Patient Case Examples**

- Mr. T.

---

**Case Study Slide**

- Mr. T is a 48 yo man with PAF, HOCM, HTN, and h/o syncope and NSVT
  - Sub Q ICD
  - Anticoagulation
- 1 month later… Sudden cardiac death with VT arrest and appropriate shock
  - Intracranial bleed
- High risk for CVA
- High risk for bleeding

---

**LAA on MRI**
3 Dimensional LAA depiction on CT

LAA on TEE
Fluoroscopy of LAA

TEE of Final Position

Outcomes At Bryan

• Procedural Success Rate: 22/23
• Warfarin Discontinuation Rate: >95%
• Hospital Length of Stay: Average 1.4 days
• Other Complications or Adverse Events:
  • Single patient required cardiac surgery
Conclusions

• Atrial Fibrillation is the most common cardiac arrhythmia
• AF places patients at high risk of stroke
• Anticoagulation has been the cornerstone of treatment
• Many patients cannot tolerate anticoagulation
• Left Atrial Appendage Closure devices represent a safe and effective alternative

ABBREVIATED STATEMENT

WATCHMAN™ Left Atrial Appendage Closure Device with Delivery System and WATCHMAN Access System

INDICATIONS FOR USE

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:
• Are at increased risk for stroke and systemic embolism based on CHADS² or CHA²DS²-VASc scores and are recommended for anticoagulation therapy;
• Are deemed by their physicians to be suitable for warfarin; and
• Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the WATCHMAN Device.

CONTRAINDICATIONS

Do not use the WATCHMAN Device if:
• Intracardiac thrombus is visualized by echocardiographic imaging.
• An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
• The LAA anatomy will not accommodate a device. See Table 46 in the DFU.
• Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
• There are contraindications to the use of warfarin, aspirin, or clopidogrel.
• The patient has a known hypersensitivity to any portion of the device material or the individual components (see Device Description section) such that the use of the WATCHMAN Device is contraindicated.

WARNINGS

• Device selection should be based on accurate LAA measurements obtained using fluoro and ultrasound guidance (TEE recommended) in multiple angles (e.g., 0º, 45º, 90º, 135º).
• Do not release the WATCHMAN Device from the core wire if the device does not meet all release criteria.
• If thrombus is observed on the device, warfarin therapy is recommended until resolution of thrombus is demonstrated by TEE.
• The potential for device embolization exists with cardioversion <30 days following device implantation. Verify device position post-cardioversion during this period.
• Administer appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

PRECAUTIONS

• The safety and effectiveness (and benefit-risk profile) of the WATCHMAN Device has not been established in patients for whom long-term anticoagulation is determined to be contraindicated.
• The LAA is a thin-walled structure. Use caution when accessing the LAA and deploying the device.
• Use caution when introducing the WATCHMAN Access System to prevent damage to cardiac structures.
• Use caution when introducing the Delivery System to prevent damage to cardiac structures.
• To prevent damage to the Delivery Catheter or device, do not allow the WATCHMAN Device to protrude beyond the distal tip of the Delivery Catheter when inserting the Delivery System into the Access Sheath.
• If using a power injector, the maximum pressure should not exceed 100 psi.
• In view of the concerns that were raised by the RE-ALIGN 1 study of dabigatran in the presence of prosthetic mechanical heart valves, caution should be used when prescribing oral anticoagulants in patients with mechanical heart valves and in patients who are at high risk of stroke with mechanical heart valves. The WATCHMAN Device has not been studied in patients with mechanical heart valves.

ADVERSE EVENTS

Potential adverse events (in alphabetical order) which may be associated with the use of a left atrial appendage closure device include:

• Death
• Embolism
• Endocarditis
• Hemorrhagic events
• Hemorrhagic stroke
• Hemorrhage
• Hemoptysis
• Hemopericardium
• Hemopneumothorax
• Hemorrhage from the puncture site(s)
• Hemorrhage from the transseptal access site
• Hemorrhage from the WATCHMAN Access System device
• Hemorrhage from the WATCHMAN Device
• Intraoperative death
• Myocardial ischemia
• Myocardial infarction
• Nervous system events
• Neurological deficit
• Nonsurgical stroke
• Pericardial effusion
• Pericardial tamponade
• Pulmonary edema
• Stroke
• Systemic embolism
• Thrombosis
• Thrombotic events
• Transient ischemic attack
• Trousseau’s syndrome
• Vascular access complications
• Vasovagal reactions

There may be other potential adverse events that are unforeseen at this time.