Transcatheter left atrial appendage occlusion for stroke prevention in atrial fibrillation

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Director, Interventional Echocardiography
Director, Heart Valve Clinic
AF is a Growing Problem Associated with Greater Morbidity and Mortality

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke
- High mortality and stroke recurrence rate

AF = most common cardiac arrhythmia, and growing

- 5x greater risk of stroke with AF

~5 M people with AF in U.S., expected to more than double by 2050

Connection Between AF-Related Stroke and the Left Atrial Appendage

23 studies of AF patients (n = 3,504)¹

- **Rheumatic AF**
  - Thrombi localized to LAA: 57% (N=222)

- **Non Rheumatic AF**
  - Thrombi localized to LAA: 91% (N=446)

P < .0001

Percutaneous LAA Occlusion Systems

WATCHMAN  Amulet  Lariat

Wavecrest  LAmbre  Occluetech
WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview

**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 terephthalate (PET) cap
- Designed to block emboli from exiting the LAA

*Designed specifically for the left atrial appendage*
WATCHMAN™ Device Clinical Program

Pilot
- Early feasibility with >6 years of follow-up

PROTECT-AF
- WATCHMAN primary efficacy, CV death, and all-cause mortality superior to warfarin at 4 years

CAP Registry
- Significantly improved safety results

ASAP
- Expected rate of stroke reduced by 77% in patients contraindicated to warfarin

PREVAIL
- Improved implant success; procedure safety confirmed with new and experienced operators

CAP2
- Enrolled up to 1500 patients at ~ 60 sites

Pilot Study

- 66 patients implanted at 8 sites in U.S. & Germany – out of 75 attempted
  - 2 procedural – scar in groin, wire malfunction
  - 7 unsuitable anatomy
- 93% complete closure at 45 days
- 333 patient years of follow-up
- Mean follow-up 58 ± 17 months

Courtesy of Dr. Turi
Stroke Rate

• Estimate risk based on CHADS$_2$ score of 1.9:
  – 4.0 %
• Actual Stroke Rate
  – 0.6 % (85% reduction compared to historical control)
Complications – Device Version 1.0

- 2 tamponades
- 3 effusions
- 1 air embolism - CPR
- 1 delivery wire fracture – surgical removal
- 2 device embolizations (retrieved)
- 4 thrombus layer at 6 months
  - Anticoagulation – resolved
  - Protocol added clopidogrel at 45 days
- 2 TIAs – 1 with thrombus
- 1 non-device related death at 9 months
WATCHMAN LAA Closure Device for Stroke Prophylaxis and Atrial Fibrillation

PROTECT-AF Trial

Multicenter, prospective, randomized, unblinded trial
Anticoagulation and Antiplatelet Therapy

- **Warfarin INR 2 - 3**
  - **Aspirin**
  - **Warfarin**
  - **Clopidogrel**
  - **Aspirin**

- Control
- Device

- **Aspirin**
- **Warfarin**
- **Clopidogrel**
- **Aspirin**

- 6 weeks
- 4.5 months
Primary Efficacy Endpoint:
Stroke,
Cardiovascular death,
Systemic embolism
Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation: A Randomized Clinical Trial

A. Ischemic stroke

<table>
<thead>
<tr>
<th>Ischemic Stroke, %</th>
<th>Time, mo</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.26</td>
</tr>
<tr>
<td>P</td>
<td>.49</td>
</tr>
</tbody>
</table>

B. Cardiovascular mortality

<table>
<thead>
<tr>
<th>Cardiovascular Mortality, %</th>
<th>Time, mo</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.40</td>
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<tr>
<td>P</td>
<td>.005</td>
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C. All-cause mortality

<table>
<thead>
<tr>
<th>All-Cause Mortality, %</th>
<th>Time, mo</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.66</td>
</tr>
<tr>
<td>P</td>
<td>.04</td>
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</table>

No. of patients

- Device: 463, 382, 360, 336, 314, 156
- Warfarin: 244, 220, 200, 172, 144, 64

Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation: A Randomized Clinical Trial

Primary Safety Endpoint:
Hemorrhage,
Hemorrhagic stroke,
Procedure related events

Primary safety end point

HR (95% CI), 1.21 (0.78-1.94)
P = .41
Procedural Complications: Substantial Learning Curve

- Pericardial effusion requiring drainage 5%
  - Rate 50% ↓ > 3 cases
- Periprocedure ischemic stroke 1.1%
  - Air or thromboemboli

Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy

The PREVAIL Trial

David R. Holmes Jr, MD,* Saibal Kar, MD,† Matthew J. Price, MD,‡ Brian Whisenant, MD,§ Horst Sievert, MD,|| Shephal K. Doshi, MD,¶ Kenneth Huber, MD,# Vivek Y. Reddy, MD**
Procedural Complications: Substantial Learning Curve

Patients with Safety Event (%)

- **PROTECT AF**
  - 1st Half: 9.9%
  - 2nd Half: 4.8%

- **CAP**
  - n=566: 4.1%

- **PREVAIL**
  - n=269: 4.1%

- **CAP2**
  - n=579: 3.8%

- ~50% New Operators in PREVAIL


All Device and/or procedure-related serious adverse events within 7 Days
Implant success defined as deployment and release of the device into the left atrial appendage.

### Warfarin Cessation

<table>
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<tr>
<th>Study</th>
<th>45-day</th>
<th>12-month</th>
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<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>
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**PREVAIL Implant Success**

No difference between new and experienced operators.

- Experienced Operators
  - n=26
  - 96%
- New Operators
  - n=24
  - 93%  
  \[ p = 0.28 \]

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 CHADS$_2$ or CHA$_2$DS$_2$-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 device compared to warfarin.
FDA Approval ≠ CMS Approval
FDA Approval

Device is “safe & effective”

CMS Approval

Device is “reasonable & necessary”

≠
CMS will cover percutaneous LAAC implants when specific criteria are met:

• Eligible patients must have a CHADS2 score of >2 or a CHA₂DS₂-VASc score >3

• Patients must be suitable for short-term warfarin, but deemed unable to take long-term oral anticoagulation

• Documented evidence of a formal shared decision interaction between the patient and an independent non-interventional physician

National Coverage Determination Effective Feb 2016
CMS will cover percutaneous LAAC implants when specific criteria are met:

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2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

• Assess stroke risk with CHA₂DS₂-VASc score
  – If CHA₂DS₂-VASc score ≥2: Annual stroke risk 2%-15%, oral anticoagulants are recommended
CMS will cover percutaneous LAAC implants when specific criteria are met:

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- Patients must be suitable for short-term warfarin, but deemed unable to take long-term oral anticoagulation

- Documented evidence of a formal shared decision interaction between the patient and an independent non-interventional physician
CMS will cover percutaneous LAAC implants when specific criteria are met:

- **Facility requirements**: the procedure must be furnished in a hospital with an established structural heart and/or EP program

- **Operator requirements**: Must be performed by an IC, EP, or cardiovascular surgeon who:
  - has received manufacturer prescribed training on safe and effective use of the device
  - has performed at least 25 TSP through intact septum
  - Must maintain at least 25 TSP over a two year period (at least 12 are LAAC)
CMS will cover percutaneous LAAC implants when specific criteria are met:

- **Registry**: Patients must be enrolled in a prospective national registry
  - NCDR LAAO Registry
Appropriate Patients?

- Poor long term candidates for anti-coagulation
  - History of major bleeding
  - Risk of major bleeding (high fall risk)
  - Poor tolerance of anti-coagulation

- Favorable anatomy for LAA closure

- Lifestyle

- Other factors:
  - noncompliance
  - those requiring dual anti-platelet therapy after stenting
PROTECT AF/PREVAIL Meta-Analysis (5 Years): WATCHMAN Efficacy Comparable to Warfarin

Hazard Ratio (95% CI) for various outcomes:

- **Efficacy**: 0.82 (0.3)
- **All stroke or SE**: 0.96 (0.9)
- **Ischemic stroke or SE**: 1.7 (0.08)
- **Hemorrhagic stroke**: 0.2 (0.0022)
- **Ischemic stroke or SE >7 days**: 1.4 (0.3)
- **CV/unexplained death**: 0.59 (0.03)
- **All-cause death**: 0.73 (0.04)
- **Major bleed, all**: 0.91 (0.6)
- **Major bleeding, non procedure-related**: 0.48 (0.0003)

Reddy VY, Holmes, DR et al. JACC 2017 in Press.
PROTECT AF/PREVAIL Meta-Analysis (5 Years):
WATCHMAN Stroke-Risk Reduction Comparable to Warfarin

Reddy VY, Holmes, DR et al. JACC 2017 in Press.
PROTECT AF/PREVAIL Meta-Analysis (5 Years):
WATCHMAN Significant Reduction in Disabling Strokes

Disabling Stroke defined as MRS ≥2
Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable

HR 0.45 (0.21 – 0.94)
P=0.03

55% Lower

Reddy VY, Holmes, DR et al. JACC 2017 in Press.
**PROTECT AF/PREVAIL Meta-Analysis (5 Years): WATCHMAN Mortality Reduction Significant When Compared to Warfarin**

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Reddy VY, Holmes, DR et al. JACC 2017 in Press.
PROTECT AF/PREVAIL Meta-Analysis (5 Years):
WATCHMAN Post-Procedure Bleeding Reduction Significant When Compared to Warfarin

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Favors WATCHMAN ➜ Favors warfarin

Reddy VY, Holmes, DR et al. JACC 2017 in Press.
WATCHMAN is the most studied LAAC Device with Long-term Clinical Data

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<th>Safety</th>
<th>WATCHMAN procedure is safe</th>
<th>95% implant success; ~4% complication rates¹</th>
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<td><strong>Primary Efficacy</strong></td>
<td>WATCHMAN comparable to warfarin</td>
<td>18% reduction in events (p=0.27)²</td>
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<td>Stroke</td>
<td>WATCHMAN comparable to warfarin</td>
<td>55% reduction in disabling/fatal stroke (p=0.03)*, largely driven by 80% reduction in hemorrhagic stroke (p=0.003)²</td>
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<td>Mortality</td>
<td>WATCHMAN statistically significant to warfarin</td>
<td>27% reduction in all-cause mortality (p=0.04)² 41% reduction in CV/unexplained mortality (p=0.03)²</td>
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<td>Major Bleeding</td>
<td>WATCHMAN statistically significant to warfarin post-procedure</td>
<td>72% reduction after 6-months (p=0.001)³</td>
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<td>Warfarin Cessation</td>
<td>WATCHMAN allows the majority of patients to discontinue warfarin</td>
<td>92% of patients discontinue after 45-days; 99% of patients discontinue after 1 year⁴</td>
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Percutaneous LAA Occlusion Systems

WATCHMAN  Amulet  Lariat

Wavecrest  LAmbre  Occluetech
Amulet LAAO

**Lobe**
- Positioned inside the LAA neck
- Designed to conform to different sizes and shapes of LAA anatomy

**Disc**
- Designed to completely seal the LAA at the orifice

**Waist**
- Maintains tension between lobe and disc
- Flexible connection allows device to self-orient

**Stabilizing Wires**
- Engage with the wall of the LAA
- Help hold the device in place

*Diagram showing the components of Amulet LAAO: Proximal End Screw, Disc, Waist, Lobe, Platinum Thread, Stabilizing Wires, Distal End Screw.*
Study Design

• A prospective, randomized, multicenter, active control worldwide trial to evaluate safety and effectiveness of the Amulet device

• Purpose: To evaluate the safety and effectiveness of the Amulet device by demonstrating that the device is non-inferior to the commercially available Boston Scientific LAA closure (LAAC) device (Control) in subjects with non-valvular atrial fibrillation

• Randomization will be 1:1 between Amulet (treatment) and the Boston Scientific LAA closure device (Control)
Study Design

AF Team selects study candidate

Subject signs consent

Baseline TEE (echo done within 90d prior to consent may be used)

Roll-in

Randomization 1:1

Amulet

Control

Amulet
Endpoints

Primary Endpoints

• **Safety**
  – A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months

• **Effectiveness**
  – A composite of ischemic stroke or systemic embolism through 18 months

• **Mechanism of Action**
  ▪ Device closure (defined as residual jet around the device ≤ 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow