Non-pharmacologic Methods Used to Reduce the Risk of Stroke from Atrial Fibrillation

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Director, Structural Heart Disease Program
Director, Interventional Echocardiography
Director, Heart Valve Clinic
Non-Valvular Atrial Fibrillation: An EPIDEMIC

Mayo Clinic data (assuming a continued increase in AF incidence)
Mayo Clinic data (assuming further increase in AF incidence)
ATRIA study data (50% >80 yo)

Patients with atrial fibrillation (millions)

Year


16 14 12 10 8 6 4 2 0

2.08 2.26 2.44 2.66 2.94 3.33 3.8 4.34 4.78 5.16 5.42 5.61 6.1 6.8 7.5 8.4 9.4 10.3 11.1 11.7 12.1 13.1 14.3 15.2 15.9
Prevalence of Atrial Fibrillation

The estimated number of US persons in 2005 with AF was 3.03 million

Naccarelli GV et al. Am J Cardiol 2009;104:1534–1539

The estimated prevalence of AF is 0.4% to 1% in the general population, increasing with age to 8% in those older than 80 yr
Figure 25. Population aged 80 or over: world, 1950-2050

- 2050: 379.0
- 2025: 153.4
- 2000: 69.2
- 1975: 31.4
- 1950: 13.8

UN population study
AF is a Growing Problem Associated with Greater Morbidity and Mortality

AF = most common cardiac arrhythmia, and growing

AF increases risk of stroke

• 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

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

5x greater risk of stroke with AF

Connection Between AF-Related Stroke and the Left Atrial Appendage

RESECTION OF THE LEFT AURICULAR APPENDIX

A Prophylaxis for Recurrent Arterial Emboli

JOHN L. MADDEN, M.D.
New York

A therapeutic problem which remains unsolved is the one pertaining to recurrent arterial emboli. Once a peripheral embolus has occurred there is a high incidence of recurrence. Unfortunately, all too frequently the recurrent embolus is fatal, commonly involving one of the cerebral arteries.¹ As Jefferson so aptly stated ²: “In the nature of things a very high percentage of successes is unlikely ever to be attained, for emboli are apt to be multiple and further infarction will sometimes carry off the patient in whom a local success has been won.”

Since a thrombus is the precursor of every arterial embolus, the ideal prophylaxis for recurrent arterial emboli should be the removal of the thrombus together with its site of origin. Rheumatic mitral stenosis is one of the commonest causes of a peripheral arterial embolus, an embolus occurring in approximately 45 per cent of the cases.¹ In this disease the embolus originates as a mural thrombus within the left auricle or its appendix, more commonly the latter.

Examination disclosed an embolic occlusion of the left common iliac artery. The heart was not decompensated. Approximately twenty hours after the onset of symptoms a transperitoneal embolectomy was performed successfully.

The patient was admitted to the hospital for the second time on Jan. 11, 1948 (fifteen month interval), complaining of numbness and tingling in the right leg of two hours’ duration. In the interval between admissions to the hospital manifestations of congestive heart failure occurred several times, but the symptoms abated after an increase in the maintenance dose of digitalis.

Examination showed an embolic occlusion of the right popliteal artery. About five hours after the onset of symptoms the embolus was removed successfully.

In view of the history of chronic rheumatic heart disease with mitral stenosis, auricular fibrillation and recurrent peripheral arterial emboli, a resection of the left auricular appendix was advised. On February 21, with intratracheal anesthesia (gas, oxygen and ether) a resection of the left auricular appendix was performed.

During the operation stoppage of the heart occurred. Immediate manual massage of the heart was begun concomitant with the maintenance of artificial respiration by a rhythmic compression of the breathing bag. The recovery of the patient was complete.

An examination immediately postoperative revealed a left hemiparesis, which was believed to be secondary to a right cerebral embolus. Subsequently, a decided personality change was observed, which persisted throughout the stay in the hospital.
Warfarin

- 1933 – Ed Carlson (farmer)
- 1941 – dicumerol
- 1948 – patented
- Wisconsin Alumi Research Foundation
  - WARFarin
Use in Humans

- 1951 – failed suicide by a navy recruit tx w/ Vit K
- Clinical studies in humans
- 1955 – President Eisenhower after his MI
Adjusted Dose Warfarin Compared with Placebo


Warfarin Better

Control Better

AFASAK
SPAF
BAATAF
CAFA
SPINAF
EAFT
All Trials

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

• Balance benefit vs. bleeding risk
Validated Scoring Systems to Assess Stroke Risks

**CHA\textsubscript{2}DS\textsubscript{2}VASc Score (Stroke Risk)\textsuperscript{3}**

<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 (SBP&gt;160)</td>
<td>1</td>
</tr>
<tr>
<td>A\textsubscript{2} Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S\textsubscript{2} Prior stroke, TIA or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease (PAD, MI)</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sex category (Female)</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL POINTS</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Yearly Stroke Risk (%)</th>
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<tbody>
<tr>
<td></td>
<td>No Warfarin</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
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2014 AHA/ACC/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF

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  – Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
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• Balance benefit vs. bleeding risk
• **Warfarin**
  
  – Effective treatment
  
  – Difficult to achieve therapeutic target
## Stroke Treatment Option: Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Dabigatran$^1$</th>
<th>Rivaroxaban$^2$</th>
<th>Apixaban$^3$</th>
<th>Edoxaban$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Enrolled Subjects</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</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>
<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>
<td>2.8 years</td>
</tr>
<tr>
<td>Average CHADS$_2$ Score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Results (primary outcome = stroke or systemic embolism)</td>
<td>Reduction in primary outcome compared to warfarin</td>
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<td>Reduction in primary outcome compared to warfarin</td>
</tr>
</tbody>
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1 Connelly SJ et al, *NEJM* 2009; 361:1139-51  
3 Granger, J MD. *NEJM* 2012;365:981-92  
4 Giugliano, R. *NEJM* 2013; 369(22): 2093-2104 – 2.8 yrs follow-up
Adherence to NOACs

- A retrospective study of 64,661 patients found that only 47.5% of patients on NOACs had >80% adherence during a median follow-up period of 1.1 years
  - Apixaban: 52.1%
  - Rivaroxaban: 47.6%
  - Dabigatran: 45.9%

- NOAC adherence was higher than warfarin
  - Warfarin: 38.7%

Yao X. J Am Heart Assoc. 2016;5:e003074
Despite Increasing NOAC Adoption, Overall Rate of Anticoagulation in High Risk NVAF Patients has Not Improved


Results from the NCDR PINNACLE Registry

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage or Death

Spontaneous intraparenchymal bleed

Hemorrhagic transformation
## Stroke Treatment Option: Novel Oral Anticoagulants

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<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;2&lt;/sup&gt;</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;3&lt;/sup&gt; (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;4&lt;/sup&gt; (60 mg / 30 mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>17 – 28%</td>
<td>3.1 – 3.6%</td>
</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.

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<sup>1</sup>Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs follow-up (Corrected)  
<sup>2</sup>Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT  
<sup>3</sup>Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up,  
<sup>4</sup>Giugliano, R. NEJM 2013; 369(22): 2093-2104 – 2.8 yrs follow-up.
Stroke and the Left Atrial Appendage

Thrombi localized to LAA

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

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<tr>
<th>Location</th>
<th>N</th>
<th>Percentage Population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>222</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>446</td>
<td>91%</td>
</tr>
</tbody>
</table>

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.

A review of the literature on LAA closure prior to 2010 found surgical closure rates of 17%-89.7%.

Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events.

A need exists for a less invasive approach that can consistently close the LAA.

References:
2. Kanderian et al. JACC 2008, 52:924–9
# Stroke Treatment Options: LAA Ligation, LAA Clips and LAA Closure

## LAA Closure (LAAC) Devices

<table>
<thead>
<tr>
<th>PLAATO</th>
<th>WATCHMAN™ Device</th>
<th>ACP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• First LAAC device (2001)</td>
<td>• Only LAAC device with 2 Randomized Controlled Trials</td>
<td>• US Trial halted in 2013</td>
</tr>
<tr>
<td>• Device no longer available</td>
<td>• FDA approved with specific indication to reduce the risk of thromboembolism</td>
<td>• AMPLATZER™ Cardiac Plug Clinical Trial</td>
</tr>
</tbody>
</table>

## LAA Clip

**EXCLUDE** Trial (completed)
- AtriClip 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
Percutaneous LAA Occlusion Systems

- WATCHMAN
- Amulet
- Lariat

Wavecrest
LAmbre
Occluetech
Medical Device Approval Process

1. Concept/Design
2. Pre-clinical development
3. Landmark Trials
4. FDA Review
5. Reimbursement Assignment
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

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1 Reddy, VY et al. HRS 2013.
4 Holmes, DR Jr et al., CIT 2013
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
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**

  - **CONTROL**
    - **DEVICE**
      - Aspirin
      - Warfarin
      - 6 weeks
      - Aspirin Clopidogrel
      - 4.5 months
      - Aspirin
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
- RR (95% CI), 1.26 (0.72-3.28)
- \( P = .49 \)

B. Cardiovascular mortality
- HR (95% CI), 0.40 (0.21-0.75)
- \( P = .005 \)

C. All-cause mortality
- HR (95% CI), 0.66 (0.45-0.98)
- \( P = .04 \)
Primary Safety Endpoint:
Hemorrhage,
Hemorrhagic stroke,
Procedure related events
Procedural Complications: Substantial Learning Curve

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

All Device and/or procedure-related serious adverse events within 7 Days
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

All Device and/or procedure-related serious adverse events within 7 Days

Implant Success & Warfarin Cessation

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

### 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%  
  \[ p = 0.28 \]
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 $\neq$ CMS Approval
FDA Approval

Device is “safe & effective”

CMS Approval

Device is “reasonable & necessary”
National Coverage Determination Effective Feb 2016

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

- Eligible patients must have a CHADS2 score of >2 or a CHA\textsubscript{2}DS\textsubscript{2}-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
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
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
- Assess stroke risk with CHA₂DS₂-VASc score
  - If CHA₂DS₂-VASc score ≥2: Annual stroke risk 2%-15%, oral anticoagulants are recommended
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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)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.82</td>
<td>0.3</td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.96</td>
<td>0.9</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.0022</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>0.91</td>
<td>0.6</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.48</td>
<td>0.0003</td>
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Reddy VY, Holmes, DR et al. JACC 2017 in Press.
PROTECT AF/PREVAIL Meta-Analysis (5 Years):
WATCHMAN Stroke-Risk Reduction Comparable to Warfarin

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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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
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</tbody>
</table>

Favors WATCHMAN   Favors warfarin ➔

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.82</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.96</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.59</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>0.91</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.48</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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
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 $\leq 5$ mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow
ASAP-TOO: The assessment of the Watchman device in patients unsuitable for oral anti-coagulation
PINNACLE FLX: Protection against Embolism for non-valvular AF
Subjects: Investigational Device Evaluation of the WATCHMAN FLX™ LAA Closure Technology
Non-pharmacologic Methods Used to Reduce the Risk of Stroke from Atrial Fibrillation

Sajjad A Sabir, MD
Director, Structural Heart Disease Program
Director, Interventional Echocardiography
Director, Heart Valve Clinic