Left Atrial Appendage (LAA) and Stroke

Kenneth C. Huber, MD, FACC
CEO, Saint Luke's Cardiovascular Consultants
Co-Executive Medical Director, Saint Luke's Mid America Heart Institute
Professor of Medicine, UMKC School of Medicine

Learning Objectives

• At the conclusion of this session, the learner should be able to:
  – Identify the role the Left Atrial Appendage (LAA) plays in stroke risk for patients with Atrial Fibrillation
  – Review data on LAA closure as an alternative to oral anticoagulants for stroke prevention in patients with Atrial Fibrillation
  – Develop strategies to incorporate LAA closure into contemporary clinical practice

Atrial Fibrillation → An Epidemic

Distribution of AF by Age

Over 50% of AF occurs in the 6% of the population ≥ 75 years of age

Savelieva, et al. Circ Cardiovasc 2008;31


LAA and Stroke

• Role of LAA in embolic stroke is in setting of patients with ATRIAL FIBRILLATION (AF)

WATCHMAN Advisory Board – Boston Scientific
WATCHMAN Professional Training Event - Proctor

Disclosure

Kenneth C. Huber, MD, FACC
**Atrial Fibrillation → Stroke Risk**

- AF increases the risk of stroke 5-fold (5-6% annual risk)
- AF is responsible for 15-20% of all strokes
- 800,000 strokes/yr in U.S. = 100,000 AF strokes/yr

**Functional Impact of AF-Related Stroke**

CATASTROPHIC

- 50% = Hemiparesis
- 19% = Aphasia
- 26% = Dependent ADL
- 26% = Nursing Homes

Generally occlude large intracranial arteries

**Atrial Fibrillation as a Systemic Vascular Disease**

- Hypertension
- Obesity
- Sleep Apnea
- Sedentary Lifestyle

**Thrombosis/Embolization**

- Electrical Fibrillation
- Insufficient contraction of LAA
- Stagnant blood flow
- Thrombosis / clot formation
- Thromboembolism
- Stroke

**Left Atrial Appendage Thrombosis**
LAA – Culprit
Location of Thrombi in Left Atrium

- LA: mostly smooth and “vein like” derived from sinus venosus
- LAA: derived from the embryonic/primordial muscular atrium

LAA Anatomy: Thrombi Haven

- LA: mostly smooth and “vein like” derived from sinus venosus
- LAA: derived from the embryonic/primordial muscular atrium

LAA Anatomy: Imaging Techniques

- TEE
- CT
- Angio

LAA : Highly Variable Structure


Atrial Fibrillation - Stroke
Risk Assessment
Comparing Risk Scores for the Prediction of Stroke in AF

Why CHA²DS²-VASc²?

- Patient:
  - Female
  - Age 72
  - Diabetes,
  - Vascular Disease
- CHADS² = 1
- CHA²DS²-VASc = 4
- Greater discriminatory ability

**Significant Limitations**

- c-statistic 0.65
- Incomplete clinical variables
- Biomarkers absent
- Anatomic factors not considered

CHA²DS²-VASc Score for Stroke Prediction in AF: Stroke Rates for All Patients

CHADS²-VASc-R Score

Relative Contribution of Each Risk Factor of CHA²DS²-VASc-R Score in Stroke Prevention

<table>
<thead>
<tr>
<th>Order of Importance</th>
<th>CHADS²-VASc-R Factor</th>
<th>CHI Square</th>
<th>Relative Hazard</th>
<th>CHI Square</th>
<th>Relative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>History of Stroke</td>
<td>1,959.99</td>
<td>1.42, p&lt;0.001</td>
<td>1,387.48</td>
<td>1.35, p&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Age ≥ 75 yrs</td>
<td>1,298.73</td>
<td>1.95, p&lt;0.001</td>
<td>906.27</td>
<td>1.77, p&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>27.34</td>
<td>1.50, p&lt;0.001</td>
<td>319.98</td>
<td>1.36, p&lt;0.001</td>
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<tr>
<td>4</td>
<td>African American</td>
<td>323.74</td>
<td>1.60, p&lt;0.001</td>
<td>197.18</td>
<td>1.45, p&lt;0.001</td>
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<tr>
<td>5</td>
<td>Hypertension</td>
<td>245.87</td>
<td>1.44, p&lt;0.001</td>
<td>23.80</td>
<td>1.13, p&lt;0.001</td>
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<tr>
<td>6</td>
<td>Heart Failure</td>
<td>227.37</td>
<td>1.27, p&lt;0.001</td>
<td>40.45</td>
<td>1.11, p&lt;0.001</td>
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<tr>
<td>7</td>
<td>Other vascular disease</td>
<td>173.28</td>
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<td>1.30</td>
<td>1.02, p&lt;0.001</td>
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<td>Diabetes</td>
<td>118.63</td>
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CHA²DS²-VASc-R = CHF, HTN, age≥75 yrs, CHA, prior stroke, vascular disease, age 65-74, female sex, and African American ethnicity

CV Biomarker Score and Clinical Outcomes in Patients with Afib:
Subanalysis of ENGAGE AF-TIMI 48 Clinical Trial

Biomarker Score: 0-4 5-7 8-11

Biomarkers:
- Troponin I
- NT-proBNP
- D-Dimer

Comparing Risk Scores for the Prediction of Stroke in AF

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Prognostic Value of Low LAA Wall Velocity in Patients with Ischemic Stroke and AF

![Prognostic Value of Low LAA Wall Velocity in Patients with Ischemic Stroke and AF](image)

DiBaise, L, et al. JACC 2012

Stroke Prevalence Based Upon Left Atrial Appendage Morphology

![Stroke Prevalence Based Upon Left Atrial Appendage Morphology](image)


Atrial Fibrillation - Stroke Therapies

![Atrial Fibrillation - Stroke Therapies](image)

Gold Standard Therapy

![Gold Standard Therapy](image)

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

- 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**
  - Threshold of Benefit > Risk
    - 1.7% / yr for warfarin
    - 0.9% / yr for NOAC

![2014 AHA/ACC/HRS Guidelines for the Management of Patients with AF](image)

Stroke Prevention: Medical Therapy: Oral Anticoagulants Cornerstone of Therapy: Warfarin

![Stroke Prevention: Medical Therapy: Oral Anticoagulants Cornerstone of Therapy: Warfarin](image)

2014 AHA/ACC/HRS Guidelines for the Management of Patients with AF

**Warfarin Problematic**

**Relative/Absolute contraindication in up to 40% of patients**

**WHY?**

- 25% anticoagulants
- 15% Contraindicated

**Bleeding**

- Cooper Meta-analysis
  - Given:
    - 51 ischemic strokes / 1000 pt-yr follow up
  - Warfarin Rx:
    - Prevents 28 ischemic strokes (55% RR ↓)
    - Expense 11 major/fatal bleeds (21% RR ↑)

**Bleeding Risk Assessment**

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>R</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g., age &gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum 9 points

**Bleeding**

- 10,000 A/C-related intracerebral hemorrhages annually in US
- 30-day mortality: 44%
- US Death Certificates 2003, 2006
  - A/C rated first in total mentions of death from drugs causing adverse effects in therapeutic use

**NVAF: Odds of Intracranial Hemorrhage & Age in 145 Case-patients (INR 2.0-3.0) and 870 Controls**
**Bleeding Risk Assessment**

- SPORTIF Cohort Bleeding Risk

<table>
<thead>
<tr>
<th>HAS-BLED Score (9)</th>
<th>Major Bleed Events</th>
<th>SPORTIF cohort (n=7,329) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4.1</td>
</tr>
<tr>
<td>High ≥ 3</td>
<td>3</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

- 20% at high risk of bleed ~ 7%/year

**“Real World” Bleeding**

- Real-life annual risk: 6-8%
- Age > 80: 13%
- OAC + DAPT: 15.7%
- OAC + Clopidogrel: 13.9%

**Outcomes According to Triple Therapy vs. DAPT**

Net Benefit: Risk / Reward

**Fundamental Treatment Dilemma**

- Balance difficult → specific patient

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>% Stroke</th>
<th>% Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Mod</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
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</tr>
<tr>
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<tr>
<td></td>
<td>4</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**Significant Undertreatment**

- Especially those at high risk

40 to 50% not treated

**Low Warfarin Use in High-risk Patients**

- Medicare claims data, 2006-2007
  - 27,174 patients
  - Warfarin use less than 60%
Net Clinical Benefit of Warfarin by Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Worse with Warfarin</th>
<th>Better with Warfarin</th>
<th>Events Prevented per 100 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65</td>
<td>-0.25</td>
<td>1.00</td>
<td>(0.43 - 0.40)</td>
</tr>
<tr>
<td>65-74</td>
<td>0.11</td>
<td>2.34</td>
<td>(1.29 - 3.30)</td>
</tr>
<tr>
<td>75-84</td>
<td>1.00</td>
<td>2.34</td>
<td>(1.29 - 3.30)</td>
</tr>
<tr>
<td>≥ 85</td>
<td>2.34</td>
<td>-0.25</td>
<td>(0.43 - 0.40)</td>
</tr>
</tbody>
</table>

Relative Prescription Rate of Aspirin (vs OAC) in Patients with CHA2DS2-VASc Score ≥ 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>1.19 (1.67 - 2.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAP</td>
<td>1.11 (1.61 - 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable angina</td>
<td>1.15 (1.11 - 1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD</td>
<td>1.08 (1.01 - 1.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.07 (1.01 - 1.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.07 (1.03 - 1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1.05 (1.00 - 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.05 (1.01 - 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.96 (0.92 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>0.94 (0.94 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.94 (0.93 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.93 (0.90 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>0.90 (0.86 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>0.81 (0.78 - 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.64 (0.60 - 0.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Antithrombotic Therapy in AF: ACTIVE-W Trial

Aspirin + Clopidogrel vs. Warfarin
Cumulative Risk of Stroke

Relative Prescription Rate of Aspirin vs OAC in Patients with CHA2DS2-VASc Score ≥ 2

Apixaban vs. ASA in NVAF: AVERROES

Primary Endpoint: Stroke or Systemic Embolism

New OAC Strategies

- Underused
- Suboptimally applied
- Difficult pharmacology
- Inappropriately discontinued
- Bleeding concerns

Game Changer?

Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Novel Anticoagulants: Overview

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Lixiana)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct thrombin inhibition</td>
<td>Factor Xa inhibition</td>
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<td>Direct thrombin inhibition</td>
</tr>
<tr>
<td>Dosing: Normal, Low</td>
<td>150mg, 75mg QD</td>
<td>20mg, 15mg QD</td>
<td>5mg, 2.5mg QD</td>
<td>60mg, 30mg QD</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>6.5%</td>
<td>80-100%</td>
<td>66%</td>
<td>62%</td>
</tr>
<tr>
<td>Half-Life (hours)</td>
<td>12-14</td>
<td>7-13</td>
<td>8-13</td>
<td>24</td>
</tr>
<tr>
<td>Involvement of CYP</td>
<td>No</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Potential Drug Interactions</td>
<td>p-Glycoprotein inhibitors</td>
<td>CYP3A4 and p-Glycoprotein inhibitors</td>
<td>CYP3A4 inhibitors</td>
<td>p-Glycoprotein inhibitors</td>
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Mechanism:
- Dabigatran (Pradaxa): Direct thrombin inhibition
- Rivaroxaban (Xarelto): Factor Xa inhibition
- Apixaban (Eliquis): Factor Xa inhibition
- Edoxaban (Lixiana): Direct thrombin inhibition

Dosing:
- Dabigatran: 150mg, 75mg BID
- Rivaroxaban: 20mg, 15mg QD
- Apixaban: 5mg, 2.5mg BID
- Edoxaban: 60mg, 30mg QD

Oral Bioavailability:
- Dabigatran: 6.5%
- Rivaroxaban: 80-100%
- Apixaban: 66%
- Edoxaban: 62%

Half-Life:
- Dabigatran: 12-14 hours
- Rivaroxaban: 7-13 hours
- Apixaban: 8-13 hours
- Edoxaban: 24 hours

Involvement of CYP:
- Dabigatran: No CYP involvement
- Rivaroxaban, Apixaban: CYP3A4 involvement
- Edoxaban: ~35% CYP3A4 involvement

Potential Drug Interactions:
- Dabigatran: p-Glycoprotein inhibitors
- Rivaroxaban: CYP3A4 and p-Glycoprotein inhibitors
- Apixaban: CYP3A4 inhibitors
- Edoxaban: p-Glycoprotein inhibitors

Novel Anticoagulants: Trial Comparison

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<td>RE-LY</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>20,500</td>
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<td>ROCKET-AF</td>
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<tr>
<td>ARISTOTLE</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ENGAGE-AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 48</td>
<td></td>
<td></td>
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</tr>
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No. of patients:
- Dabigatran: 18,113
- Rivaroxaban: 14,264
- Apixaban: 18,201
- Edoxaban: 20,500

Design:
- RE-LY, open label
- ROCKET-AF, double blind
- ARISTOTLE, double blind
- ENGAGE-AF, double blind
- TIMI 48, double blind

Inclusion criteria:
- Dabigatran: Non-valvular AF, 1 risk factor
- Rivaroxaban: Non-valvular AF, CHADS2 ≥ 2
- Apixaban: Non-valvular AF, 1 risk factor
- Edoxaban: Non-valvular AF, CHADS2 ≥ 2

Age, Female %:
- Dabigatran: 71, 36.4%
- Rivaroxaban: 73, 39.7%
- Apixaban: 70, 35.2%
- Edoxaban: 70, 35.2%

Previous VKA use:
- Dabigatran: 49.6%
- Rivaroxaban: 62.4%
- Apixaban: 57.2%
- Edoxaban: 57.2%

Avg. CHADS2 score:
- Dabigatran: 2.2
- Rivaroxaban: 3.5
- Apixaban: 2.1
- Edoxaban: 2.1

Persistent/Permanent AF:
- Dabigatran: 66.6%
- Rivaroxaban: 80.9%
- Apixaban: 84.7%
- Edoxaban: 84.7%

Follow-up:
- Dabigatran: Event driven, >12 months
- Rivaroxaban: Event driven, >14 months
- Apixaban: Event driven, >12 months
- Edoxaban: 24 months

Primary Outcome:
- Stroke/systemic embolism

Secondary outcomes:
- MI, PE, Mort (CV & Tot)
- MI, Vasc mort, TIA, Total mort
- Total mortality, major bleeding
- Total mortality, major bleeding

High Dose NOACs vs. Warfarin for AF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median F/U</th>
<th>Event Rate NOAC</th>
<th>Event Rate Warfarin</th>
<th>RR (95% CI)</th>
<th>ARR/ARI</th>
<th>NNT/NNH</th>
</tr>
</thead>
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<tr>
<td>Stroke/Systemic Embolism</td>
<td>2.2</td>
<td>3.11%</td>
<td>3.79%</td>
<td>0.81 (0.73-0.91)</td>
<td>0.68%</td>
<td>147</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>2.2</td>
<td>0.44%</td>
<td>0.90%</td>
<td>0.49 (0.38-0.64)</td>
<td>0.46%</td>
<td>210</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.2</td>
<td>5.26%</td>
<td>6.17%</td>
<td>0.86 (0.73-1.00)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>2.2</td>
<td>0.70%</td>
<td>1.45%</td>
<td>0.48 (0.39-0.59)</td>
<td>0.76%</td>
<td>132</td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>2.2</td>
<td>2.56%</td>
<td>2.02%</td>
<td>1.25 (1.01-1.55)</td>
<td>0.54%</td>
<td>-185</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>2.2</td>
<td>6.90%</td>
<td>7.68%</td>
<td>0.90 (0.81-0.95)</td>
<td>0.78%</td>
<td>128</td>
</tr>
</tbody>
</table>

Preventing Stroke in Non-Valvular AF

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median F/U</th>
<th>Event Rate NOAC</th>
<th>Event Rate Warfarin</th>
<th>RR (95% CI)</th>
<th>ARR/ARI</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/Systemic Embolism</td>
<td>2.2</td>
<td>3.11%</td>
<td>3.79%</td>
<td>0.81 (0.73-0.91)</td>
<td>0.68%</td>
<td>147</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>2.2</td>
<td>0.44%</td>
<td>0.90%</td>
<td>0.49 (0.38-0.64)</td>
<td>0.46%</td>
<td>210</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.2</td>
<td>5.26%</td>
<td>6.17%</td>
<td>0.86 (0.73-1.00)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>2.2</td>
<td>0.70%</td>
<td>1.45%</td>
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<td>0.90 (0.81-0.95)</td>
<td>0.78%</td>
<td>128</td>
</tr>
</tbody>
</table>

Advantages/Disadvantages of Novel Anticoagulants

Advantages
- No need for monitoring level of anticoagulation
- Fewer drug-drug interactions
- Decreased adverse outcomes compared to warfarin
- Short onset of action - no need for heparin bridging

Disadvantages
- Unable to verify compliance
- No specific approved antidote to reverse anticoagulation
- Cost
- Complex dosing schedule
- Unable to use in valvular AF, prosthetic valves, existing thrombus, dialysis patients

The Optimal OAC for Stroke Prevention in AF: Suggestions for Treatment Options
Atrial Fibrillation – Stroke
Non-Pharmacologic Treatment

NOAC Availability Increases Appropriate Use of Anticoagulants for Nonvalvular AF in Clinical Practice

Use of OACs in Patients with NVAF and CHADS₂ score ≥1

<table>
<thead>
<tr>
<th>Year</th>
<th>NOAC &amp; Warfarin</th>
<th>NOAC Only</th>
<th>Warfarin Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-2008</td>
<td>30%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>35%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>2011-2012</td>
<td>40%</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>2013-2014</td>
<td>45%</td>
<td>40%</td>
<td>35%</td>
</tr>
</tbody>
</table>

P<0.0001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban (60mg/30mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin</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

Strokes Treatment Option:
Novel Oral Anticoagulants (NOACs)

Non-pharmacologic Treatments

Transcatheter LAA Closure
- Watchman
- Amplatzer Plug
- Coherex WaveCrest

Ligation
- Surgical
  - Excision/suture
  - Suture
  - Staples/Clip
- Non-surgical
  - Lariat

LAA Ligation: Open Surgical Approach
- 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 valveotomy or CABG
- Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events — no definite data as standalone

Method of Successful LAA Closure

- Excision: 25%
- Ligation w/ Sutures: 33%
- Ligation w/ Staples: 10%

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

LAOS III target enrollment 4,700

LAA Closure Devices
Watchman® LAA Closure

Frame:
- Nitinol structure
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diam.)
  - 10 fixation anchors around device perimeter engage LAA tissue
  - Contour shape accommodates most LAA anatomy

Fabric Cap:
- PET Fabric
- Designed to prevent harmful emboli from exiting during the healing process
- 160 micron filter

WATCHMAN® LAA Closure System

WATCHMAN Access System

- Double or Single Curve styles
- 14F O.D. (4.7 mm), 12F I.D.
- 75 cm working length

Examples

WATCHMAN Implant:
Healing Process

- Canine Model – 45 days
- Human Pathology – 9 months

WATCHMAN LAA Closure System Implanted Device

Frame:
- Nitinol structure
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diam.)
  - 10 fixation anchors around device perimeter engage LAA tissue
  - Contour shape accommodates most LAA anatomy

Fabric Cap:
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WATCHMAN Access System

- Double or Single Curve styles
- 14F O.D. (4.7 mm), 12F I.D.
- 75 cm working length

Examples

WATCHMAN Implant:
Healing Process

- Canine Model – 45 days
- Human Pathology – 9 months
WATCHMAN: Clinical and Regulatory Timeline

- PROTECT AF 2005
- Registry CAP 2 2006
- PREVAIL 2008
- Registry CAP 2 2010
- FDA Approval 2015
- FDA PANEL 1 4/09
- FDA PANEL 2 12/13
- FDA PANEL 3 10/14
- CAP Registry 2008
- ASAP 2009
- CAP 2 Registry 2012
- CAP2 Registry 2015
- 21st Century Cures Act Approval 2016

WATCHMAN Clinical Studies

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>CAP Registry</th>
<th>PREVAIL</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>
<td>2406</td>
</tr>
<tr>
<td>Randomized</td>
<td>707</td>
<td>407</td>
<td>407</td>
<td></td>
<td>1114</td>
</tr>
<tr>
<td>WATCHMAN: Warfarin (2:1)</td>
<td>463 : 244</td>
<td>566</td>
<td>269:138</td>
<td>579</td>
<td>1877:382</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>
<td>N/A</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2717</td>
<td>2022</td>
<td>860</td>
<td>332</td>
<td>5931</td>
</tr>
</tbody>
</table>


Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROTECT AF (n=707)</th>
<th>CAP (n=556)</th>
<th>PREVAIL (n=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>72.0 ± 8.9</td>
<td>74.0 ± 8.3</td>
<td>74.3 ± 7.4</td>
</tr>
<tr>
<td>Age, range</td>
<td>41-95</td>
<td>44-94</td>
<td>50-94</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>70.3%</td>
<td>65.5%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Ethnicity/Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.7%</td>
<td>1.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Black</td>
<td>1.6%</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>91.5%</td>
<td>91.9%</td>
<td>94.4%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>5.7%</td>
<td>3.5%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Other</td>
<td>0.6%</td>
<td>1.1%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Majority of Patients at High Stroke Risk, All Eligible for Anti-coagulation

- Anticoagulation Eligible
- Majority of Patients at High Risk
- CHA₂DS₂-VASc Score ≥2
- 93% 96% 100%
Majority of Patients in the Trial were at Moderate to High Bleeding Risk

1. Estimated HAS BLED score. Labile INR and liver function were not included and given a score of zero.

Source: Holmes DR, et al. JACC 2015;

Warfarin Time in Therapeutic Range (TTR) for Control Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin Control Group Mean TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>70%</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>68%</td>
</tr>
<tr>
<td>RE-LY2 (Dabigatran)</td>
<td>64%</td>
</tr>
<tr>
<td>ARISTOTLE2 (Apixaban)</td>
<td>62%</td>
</tr>
<tr>
<td>ROCKET AF3 (Rivaroxaban)</td>
<td>55%</td>
</tr>
</tbody>
</table>

Endpoints

Efficacy Events
- Stroke (ischemic)
- Systemic Embolism
- CV / Unexplained Death

Safety Events
- Stroke (hemorrhagic)
- Stroke (procedure related)
- Both Efficacy & Safety
- Device Embolization
- Major Bleeding Events
- Pericardial Effusions

“Primary effectiveness endpoint captures the events that would also be considered significant safety events (i.e., stroke, death and systemic embolism)”

FDA Executive Summary

Favorable Procedural Safety Profile:

7-Day Safety Events

- Learning Curve: 9.9%
- 1st Half: 4.8%
- 2nd Half: 4.1%
- CAP: 4.1%
- PREVAIL: 4.1%
- CAP2: 3.8%

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

**Key Procedural Safety Events**

PROTECT AF vs. CAP/PREVAIL

- **Overall embolization rate across studies is 0.5%**

**WATCHMAN Clinical Trial**

**Efficacy**

PROTECT AF: Final Primary Efficacy Events Favor WATCHMAN

<table>
<thead>
<tr>
<th>Event Rate (per 100 pt-yrs)</th>
<th>Rate Ratio</th>
<th>Non-inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>2.3</td>
<td>3.7</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Stroke (all)</strong></td>
<td>1.5</td>
<td>2.2</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Ischemic</strong></td>
<td>1.3</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
<td>0.2</td>
<td>1.1</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Systemic Embolism</strong></td>
<td>0.2</td>
<td>0.0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Death (CV &amp; Unexplained)</strong></td>
<td>1.0</td>
<td>2.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**PROTECT AF: 5 Year Mortality**

WATCHMAN vs. Warfarin

- **Cardiovascular mortality**
  - HR 0.75% CI: 0.40 (0.21-0.75) *p=0.005
  - RRR 60%

- **All-cause mortality**
  - HR 75% CI: 0.66 (0.45-0.98) *p=0.04
  - RRR 34%

**All Cause Mortality Relative Reduction (vs warfarin) In Context**

- **RRR 14%**
- **RRR 34%**
Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke or SE</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.04</td>
<td>0.94</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.95</td>
<td>0.06</td>
</tr>
<tr>
<td>Ischemic stroke or &gt; 7 days</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>1.36</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Holmes, SR et al. JACC 2015

**Stroke Severity in PROTECT AF/PREVAIL**

Non-Disabling Stroke vs. Disabling/Fatal Stroke

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>WATCHMAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.73</td>
<td>0.73</td>
</tr>
<tr>
<td>p-value</td>
<td>0.73</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Holmes, SR et al. JACC 2015

**PROTECT AF & PREVAIL Meta-analysis:**

WATCHMAN Strokes Are Less Disabling

<table>
<thead>
<tr>
<th></th>
<th>WATCHMAN</th>
<th>Warfarin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Strokes</td>
<td>27%</td>
<td>61%</td>
<td>0.009</td>
</tr>
<tr>
<td>Ischemic Only Strokes</td>
<td>19%</td>
<td>33%</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Based on stroke with MRS change of 2 or more or cause of death related to stroke

**Stroke Severity in LAAC vs NOAC Trials**

Non-Disabling vs. Disabling Fatal Strokes

**PROTECT AF: Quality of Life**

Change in SF-12 Scale Scores (Baseline to 12 Months)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=186)</th>
<th>WATCHMAN (n=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.005

Price, MJ. Avoidance of Major Bleeding with WATCHMAN Left Atrial Appendage Closure Compared with Long-Term Oral Anticoagulation: Results from the PROTECT AF and PREVAIL RCTs. TCT 2014 (abstract)

V.Reddy et al, manuscript in preparation

V.Reddy et al, FDA Panel Presentation, October 2014
**Economic Analysis: Cost Effectiveness**

**WATCHMAN vs. NOACs vs Warfarin**

- Patient level Markov micro-simulation decision analytic model
- Assess Time-to-Cost Effectiveness (not just Lifetime horizon – 20 yrs)
- Economic costs from the US perspective, and costs in 2015, US$
  - For LAAC procedure, we used the newest DRG 273/274 (effective Oct 2015)
- Longest WATCHMAN follow up: PROTECT AF data (6 yrs f/u)
- NOAC meta-analysis of all 4 NOACs (Ruff et al. Lancet 2014;383:955)
- Incorporated costs based on the level of disability resulting from strokes

**Time to Cost Effectiveness (Cost/QALY)**

- Year 7 ($42,994/QALY)
- Year 10

**Time to Dominance (More Effective, Less Costly)**

- Year 5 (Dominant)

**Device-related Thrombus**

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF (n=408)</th>
<th>CAP (n=534)</th>
<th>PREVAIL (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus subjects</td>
<td>16 (3.9%)</td>
<td>13 (2.4%)</td>
<td>12 (4.8%)</td>
</tr>
<tr>
<td>Thrombus events</td>
<td>16</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Experienced ischemic stroke</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Experienced serious adverse event</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Annual Device thrombus related stroke rate (per 100 pt-yrs)</td>
<td>0.11</td>
<td>0.07</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**EWOLUTION WATCHMAN Registry**

- 1,025 patients
- CHD2DS2-VASc ≥ 5: 50%
- 72% “Unsuitable” for warfarin
- Procedural success 98.5%
  - Stroke: 0.4%
  - Embolization: 0.4%
  - Tamponade: 0.7%
- Post-implant anticoagulation regimen
  - DAPT 607; WAR 159; NOAC 113; Nothing 67
- 0.5% had device related serious adverse events not resolved at 3 months

**Saint Luke’s**

**MID AMERICA HEART INSTITUTE**
**ASAP Registry**

Contraindicated Pts (n=150): WATCHMAN → ASA/Clop x 6 mo

- CHADS2 = 2.8 ± 1.2
- Prior CVA/TIA in 41%
- Follow up: 16.5 months

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

\[ \text{CHADS2} = 2.8 \pm 1.2 \]

\[ \text{Prior CVA/TIA in 41\%} \]

\[ \text{Follow up: 16.5 months} \]

---

**WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy**

- PROTECT AF
- PREVAIL Only
- CAP

- Imputed Ischemic Stroke Rate* = 79%
- Observed WATCHMAN Ischemic Stroke Rate = 73%

\[ \text{Imputed Ischemic Stroke Rate}^* = 79\% \]

\[ \text{Observed WATCHMAN Ischemic Stroke Rate} = 73\% \]

---

**Preventing Stroke in Non-Valvular AF**

Imputed Benefit of Different Strategies (vs. Control)

- Warfarin
- Dabigatran-150
- Dabigatran-110
- Rivaroxaban
- Apixaban
- Edoxaban-40
- Edoxaban-30

- PROTECT/ PREVAIL

\[ \text{Imputed Benefit of Different Strategies (vs. Control)} \]

---

**Strategies to Incorporate LAA Closure into Clinical Practice**
**WATCHMAN Device Patient Selection**

**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:

* 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.

**NOT a broad replacement for oral anticoagulation**

**CMS “Conditions”**

- Eligible patients must have CHADS\(_2\) score ≥2 or CHA\(_2\)DS\(_2\)-VASC score ≥3
- There must be documented evidence of a formal shared decision interaction between patients and an independent, non-interventional physician
- Patients must be suitable for short-term warfarin, but deemed unable to take long-term OAC

**Frequently Asked Questions About CMS “Conditions”**

- Who is this “independent, non-interventional physician” involved in this shared decision process?
- What is this “evidence-based decision tool” that is to be used in the formal shared decision making interaction with the patient?
- What is the prospective national registry that we need to enroll our patients into?

**Clinical Scenarios: Potential Candidates**

- **CHA2DS2-VASC ≥ 3** AND Deemed unable to take long term OAC
- **History of Major Bleeding: on OAC**
  - GI/GU
  - Intracranial
  - ENT
- **High risk for major bleeding: Not on OAC**
  - HAS-BLED ≥ 3 (6% risk/yr)
  - Frailty/Fall Risk
  - CKD, Liver disease
  - Inflammatory Bowel Disease
  - Malignancy (Chemotherapy)
  - Seizure disorder
Clinical Scenarios: Potential Candidates

- Non-adherence/Non-compliance
  - Frailty/Dementia
  - Cost
  - Choice/Refusal
- Polypharmacy
  - Triple therapy – ACS/Vascular disease
- Occupation/Lifestyle
  - High risk of trauma

Clinical Scenarios: Not Candidates

- CHA2DS2-VASc 0, 1, or 2 (for Medicare pts)
- No issues with OAC
- Other reason to be on OAC
  - Valvular AF/Prosthetic valve
  - DVT
  - Hypercoagulable state
- LAA anatomy
  - Size/shape
  - Thrombus/sludge
- Vascular access issues
- Anesthesia risks

Clinical Scenarios: Contraindications

- **Absolute** contraindication to OAC or DAPT
  - Post Implant: 6 weeks OAC
    6 months DAPT
  - Time for endothelialization

  **ASAP TOO Trial**
  - WATCHMAN (DAPT x 3 mo, ASA x 12 mo)
  - Medical Therapy (no Tx, ASA alone, DAPT can be considered)
  - 2:1 randomization

MAHI Shared Clinical Decision Process

- **Goal:** Educate patient and family on the risks vs benefits of the three different scenarios

Shared Clinical Decision Process

1. Discuss personal risk of stroke
   - CHA2DS2-VASC score: % risk/year
2. Discuss benefits of 3 treatment options
   - RRR $\downarrow$60-70% (Class IA)
   - Non-inferior/imputed placebo ($\downarrow$70%)
3. Discuss Personalized relative risks of OAC; both warfarin & NOACS
   - Quantify if possible (HAS-BLED) variable threshold
   - Individual assessment of risk/benefit centered around pharmacotherapy issues
4. Discuss the risks of procedure
   - Risks (procedural/device embolization/device related thrombosis)
WATCHMAN Comparable to Warfarin for Primary Efficacy

- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free

WATCHMAN vs. Warfarin

N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years.

CV Death Lower with WATCHMAN vs. Warfarin

- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free

WATCHMAN and Warfarin Reduce Ischemic Stroke vs. No Therapy

- Ischemic Stroke / Systemic Embolism (includes fatal and non-fatal events)
- Free of Ischemic Stroke

Imputed Placebo* (OHADDB - VASc = 3.7)

67 events (75% relative reduction) - 45 events (83% relative reduction) - 270 events (reference)

* Imputed Placebo: Trillas, Eur Heart J (2013)

Hemorrhagic Stroke Lower with WATCHMAN vs. Warfarin

- Cardiovascular / Unexplained Death (includes CV deaths preceded by stroke)
- Non-fatal Ischemic Stroke / Systemic Embolism
- Non-fatal Hemorrhagic Stroke
- Event-free

Zoomed in to show N=500 of 1000 patients for each study arm; each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years.

Ischemic Stroke/SE Lower with Warfarin vs. WATCHMAN

N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years.

WATCHMAN Performs Better than Warfarin for Major Bleeding

- Major Bleed (related to procedure)
- Event-free
- Major Bleed (unrelated to procedure)

N=1000; Each circle represents a single patient (N=1) with WATCHMAN or warfarin followed through five years.
**Conclusions**

- The LAA plays a significant role in stroke risk in patients with AF.
- CHA2DS2-VASc score is current goal standard but has significant limitations:
  - Assessment of risk is key to understanding relative benefits of different treatment options.
- Oral anticoagulation is the primary therapy of choice and should be prescribed in virtually all patients:
  - Warfarin is cornerstone but problematic.
  - Is NOAC better but not perfect with major benefit due to decreased ICH; similar for non-cranial bleeding.

**Significant Under treatment**
- Unprotected 5,000,000 x 0.4 = 2,000,000 patients.

LAA closure with WATCHMAN has been well studied as currently the only device approved by FDA as an alternative to OAC:
- Overall efficacy non-inferior to warfarin, ischemic stroke ↑; hemorrhagic stroke ↓, mortality ↓.

Post FDA approval and CMS clarification on payment, appropriate case selection using a robust, shared, clinical decision making process should identify patients that will benefit.

**OAC Patient**

- **$$$$**
- **Did I take my medicine?**
- **Joints hurt! Need NSAID**
- **Out to dinner... what can I eat?**
- **Bronchitis... need antibiotic. Do I need to check INR?**
- **Did the cruise ship doctor know what Rivaroxaban is??**
- **What if I fall? If I fall, can the bleeding be stopped?**

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**LAA Closure**

**FREEDOM!!!!**