Left Atrial Appendage Closure – Identifying the Patients Who Will Benefit the Most

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Disclosure

SentreHeart, Inc
- Consultant
- Equity holder

Atrial Fibrillation

The most severe consequence of AF is potentially life threatening embolic events

Warfarin

It’s Not the Answer
- Too little = Stroke
- Too much = Hemorrhage
- Risks increase with age
- Low compliance
- Contraindications
Endocardial vs Pericardial

Ease of Use
No LA foreign body

Closure Efficacy
Complications

LAA Closure Devices Available in the US

Watchman Atriclip LARIAT

Watchman is FDA approved for stroke prevention Atriclip and LARIAT are FDA approved, but not for stroke prevention

WATCHMAN Clinical History

PROTECT-AF 800 pts, 59 sites
CAP Registry 566 pts, 26 sites
PREVAIL 400 pts, < 50 sites
PROTECT-AF Long-term F/U

Watchman device was non-inferior to warfarin in preventing strokes; FDA concerned with acute safety events
Significantly improved safety results
Improved success and procedural safety confirmed with new and experienced operators
Superior to warfarin for primary efficacy, CV death, and all-cause mortality at 4 years

PROTECT AF 4 Year: CV and All-Cause Mortality

Watchman FDA Approval

INDICATIONS FOR USE

This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) 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
- 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.

CONTRAINDICATIONS

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An ASD repair or closure device or a PFO repair or closure device is present.
- The LAA anatomy will not accommodate a device 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.

### Oral Anticoagulants

**DISCONTINUATION RATES**

**Mechanism**
- Dabigatran: Direct Thrombin Inhibitor
- Rivaroxaban: Factor Xa Inhibitor
- Apixaban: Factor Xa Inhibitor

**Dose**
- Dabigatran: 110 mg or 150 mg 2x/day, 20 mg/day
- Rivaroxaban: 5 mg 2x/day
- Apixaban: 2.5 mg 2x/day

**Efficacy in preventing embolic events**
- Superior (150 mg)
- Noninferior (150 mg)
- Superior

**Hemorrhagic stroke**
- Significantly less (110 mg)
- Identical (150 mg)
- Less

**GI bleeding**
- Not specified (110 mg)
- Major GI bleeding
- Less

**All bleeding events**
- Less (at 110 mg)
- Similar (at 100 mg)
- Less

*2.5 mg twice daily if two or more: age >80, weight <60 kg or Cr > 1.5 (25% renal excretion). Excluded if Cr > 2.5

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**Potential Incidence of Major Bleeding**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Annual Rate for Major Bleed</th>
<th>*Potential number of patients &lt;65 yo with major bleeding/year (x1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg 2x/day</td>
<td>3.32%</td>
<td>60.4</td>
</tr>
<tr>
<td>Rivaroxaban 15 – 20 mg/day</td>
<td>3.6%</td>
<td>65.6</td>
</tr>
<tr>
<td>Apixaban 5 mg 2x/day</td>
<td>2.13%</td>
<td>38.8</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3.09% - 3.57%</td>
<td>56.2 - 65.0</td>
</tr>
</tbody>
</table>

*Assumes 50% of AF patients treated with AF on OAC

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**Patients with Limited to NO options**

Patients with contraindications to OAC therapy

- 82 year old woman with paroxysmal AF
- History of both ICH and cardioembolic stroke, hypertension
- TEE reveals LAA thrombus

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**Stroke and Bleeding Risk in Patients with AF and OAC Contraindications**

Bjorn Redfors, MD, PhD, William A. Gray, MD, Randall J. Lee MD, Kenneth A. Ellenbogen MD, Machaon Bonafente PhD, PhD, Ori Ben-Yehuda, MD

Presented by Ben-Yehuda at TCT 2015
**Bleeding Rates by CHADS<sub>2</sub>**

Gastrointestinal, genitourinary, or respiratory tract bleeding that required transfusion or surgical intervention.

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>n=5,693</th>
<th>n=12,017</th>
<th>n=15,073</th>
<th>n=3,033</th>
<th>n=1,162</th>
<th>n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0%</td>
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<td></td>
</tr>
<tr>
<td>2.0%</td>
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<tr>
<td>4.0%</td>
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<tr>
<td>6.0%</td>
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<tr>
<td>8.0%</td>
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<tr>
<td>10.0%</td>
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<tr>
<td>12.0%</td>
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<tr>
<td>14.0%</td>
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<td></td>
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<tr>
<td>16.0%</td>
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</tr>
</tbody>
</table>

**Incidence and Outcomes of Patients with Atrial Fibrillation and Major Bleeding Complications: Findings from the TREAT-AF Study**

- In the mean follow-up of 4.2 years, 11.5% of patients had a major bleed.
- Patients with prior bleeding complications had greater risk of subsequent events including TIA, ischemic stroke, repeat bleeding events, and death.
- OAC started in 25% within 90 days of major bleeding event and was associated with a reduced stroke risk (HR 0.85), reduced risk of death (HR 0.88), and increased risk of major bleed (HR 1.49).

Presented by Kaiser at ACC 2015

**LAA Exclusion in OAC Contraindicated Patients**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>150</td>
<td>1,047</td>
</tr>
<tr>
<td>Age</td>
<td>72.5 7.4</td>
<td>75±8</td>
</tr>
<tr>
<td>Mean CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>2.8 1.2</td>
<td>4.43</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>14.4±8.6 months</td>
<td>13 months</td>
</tr>
<tr>
<td>Patient-years</td>
<td>176.9</td>
<td>1,349</td>
</tr>
<tr>
<td>Absolute # strokes/systemic embolism</td>
<td>4 (stroke)</td>
<td>9 (strokes), 9 (TIA)</td>
</tr>
<tr>
<td>Event rate (patient-years)</td>
<td>2.3%</td>
<td>0.7% stroke</td>
</tr>
</tbody>
</table>

**Watchman Safety Profile**

Acute & Long-term Outcomes of Percutaneous Left Atrial Appendage Suture Ligation: Results From A United States Multicenter Evaluation

- Multicenter registry. 18 US centers.
- Safety results of 424 consecutive LARIAT procedures.
- Micropuncture access technique utilized

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural-related mortality</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pts requiring surgery</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cardiac perfs (no surgery)</td>
<td>0.7%</td>
</tr>
<tr>
<td>Pts needing transfusion</td>
<td>0.5%</td>
</tr>
<tr>
<td>Peri-procedural stroke</td>
<td>0.5%</td>
</tr>
<tr>
<td>Structural injury</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other complications</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Lakkireddy et al. Heart Rhythm 2016

Merits of an Epicardial LAA Closure Approach

- Restore
- Maintain
- Protect
- Electrical Isolation
- LAA Exclusion

Thoracoscopic Appendage Exclusion With an Atriclip Device As a Solo Treatment for Focal Atrial Tachycardia

- Stefano Benussi, Patrizio Mazzone, Giuseppe Maccabelli, Pasquale Vergara, Filippo Grimaldi, Alberto Pozzoli, Pietro Spagnolo, Ottavio Alfieri, and Paolo Della Bella

Clinical success of various ablation techniques for persistent/long-standing persistent atrial fibrillation

Catheter Ablation of Long-Standing Persistent Atrial Fibrillation

After the first ablation procedure, sinus rhythm was documented in 41 of 202 (20.3%) patients.

After multiple procedures, sinus rhythm was maintained in 91 of 202 (45.1%) patients.

JACC 2012;60:1921–9.

Conversion of Persistent Atrial Fibrillation to Sinus Rhythm After LAA Ligation

- Multi-center, prospective randomized superiority trial
- Comparing LAA ligation and PVI versus PVI in patients with persistent and longstanding persistent AF
Case 1

- 72 yo woman with persistent AF.
- Intolerant to OAC due to fall risk and hx of traumatic injury
- Hx of prior cardioembolic stroke, DM, HTN and CABG

Case 1

- Recommend LAA occlusion device
- CABG is a contraindication to the LARIAT procedure
Case 2

- 68 yo man with PAF
- Hx of ICH, HTN, DM

Case 2

- Consider LARIAT or Atriclip
- Watchman requires at least 45 days of warfarin therapy post-implantation

Should We Recommend Oral Anticoagulation Therapy in Patients With Atrial Fibrillation Undergoing Coronary Artery Stenting

**Triple Therapy: Benefit vs Risks**

- Stent thrombosis: highest in the early phase after PCI
- Bleeding: risk of bleeding with triple therapy increases with duration of therapy

Case 3

- 65 yo man with persistent AF
- Hx of recent stent on ASA and plavix
- Hx of DM, HTN
Case 4
- 87 yo woman with PAF
- Hx of both ICH and cardioembolic stroke, HTN
- TEE reveals LAA thrombus

Case 5
- 63 yo man with PAF
- Hx HTN

Major Registry Studies Comparing Bleeding on Combinations of Antiplatelet and OAC Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-up, y</th>
<th>ASA</th>
<th>Clopidogrel</th>
<th>DAPT</th>
<th>OAC</th>
<th>OAC + ASA</th>
<th>OAC + Clopidogrel</th>
<th>TOAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buresly et al</td>
<td>21,443</td>
<td>1.8</td>
<td>3.2</td>
<td>NA</td>
<td>6.8</td>
<td>5.9</td>
<td>8.3</td>
<td>NA</td>
<td>8.5</td>
</tr>
<tr>
<td>Sørensen et al</td>
<td>40,812</td>
<td>1.3</td>
<td>2.6</td>
<td>4.6</td>
<td>3.7</td>
<td>4.3</td>
<td>5.1</td>
<td>12.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Lamberts et al</td>
<td>11,480</td>
<td>1.0</td>
<td>7.0</td>
<td>6.6</td>
<td>7.0</td>
<td>7.0</td>
<td>9.5</td>
<td>10.6</td>
<td>14.2</td>
</tr>
<tr>
<td>Hanson et al</td>
<td>118,60</td>
<td>3.3</td>
<td>3.7</td>
<td>5.6</td>
<td>7.4</td>
<td>3.9</td>
<td>6.9</td>
<td>13.9</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation after Electrical Isolation of the Left Atrial Appendage for Treatment of Atrial Tachyarrhythmias: An undescribed and under recognized complication of left atrial catheter ablation

Andreas Rillig, MD, Roland R. Titz, MD, Tina Lin, MD, Christian Heeger, MD, Anita Arya, PhD, Andreas Metzner, MD, Shibu Mathew, MD, Erik Wissner, MD, Hisaki Makimoto, MD, PhD, Peter Wohlmut, Karl-Heinz Huck, MD, Feifan Ouyang, MD

Clinical Cardiology 36: 585-594, 2013
AF Stroke Prevention and Coronary Events

Adapted from ACCP guidelines (You at al, Chest 2012)

Long term follow-up from the Prevail Trial

- The results of PROTECT AF and PREVAIL appear to be diverging, which introduces challenges in the interpretation of results of the pre-specified Bayesian analysis.
- PROTECT AF demonstrated a benefit of the WATCHMAN device driven by a reduction in hemorrhagic stroke rate; however, the Control group hemorrhagic stroke rate was substantially higher than observed in contemporary anticoagulation trials, and there are questions regarding the robustness of this potential benefit.

LAA ligation in patients with contraindications to OAC therapy

Kaplan-Meier Curves

Survival

Stroke
LARIAT device in AF patients with contraindications to OAC
Effectiveness in Stroke Reduction vs. Estimated

Tzikas et al EuroIntervention 2015

Watchman device in AF patients with contraindications to OAC

Reddy and Sievert et al., JACC 61: 2551–6, 2013

Warfarin use decreases with increasing age & stroke risk
UK General Practice database n= 41,910

Warfarin by CHADS2 score

Warfarin use decreases with increasing age & stroke risk
UK General Practice database n= 41,910

Event Rate (% per year)
Should we use LAA closure as an option to prevent stroke

- Medical rationale
- Efficacy
- Safety
- Reimbursement

Long term follow-up from the Prevail Trial

- Greater event rate of embolic stroke and systemic embolism in the Watchman arm compared to the control.
- The new ischemic strokes in the updated PREVAIL dataset occurred more than 1 year post-WATCHMAN implantation, raising questions about long-term device effectiveness.