LEFT ATRIAL APPENDAGE OCCLUDERS, AN ELECTROPHYSIOLOGISTS PERSPECTIVE

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Treating the Left Atrial Appendage: Can We Do It? Should We Do It?

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AHA Structural Heart Symposium
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I will be discussing devices not yet approved by FDA.
Disclosure:

Nothing relevant to disclosure
Overview of next 20 minutes

- Understand the modest data that implicates the left atrial appendage with stroke risk.

- Learn about how different LAA shapes may impact stroke risk.

- Discover the advantages and drawbacks associated with current LAA closure technologies.

- Tips from our experience with Lariat device.
AF/Stroke Epidemiology

- Each year, nearly 800,000 strokes in the U.S.
- 1 out of 19 deaths in the U.S. is due to a stroke
  - One new stroke every 40 seconds. One new stroke-related death every 4 minutes.
- Over 3 million Americans have AF
- AF quintuples the risk of ischemic stroke
- Strokes associated with AF are more lethal and disabling

AHA Heart Disease and Stroke Statistics — 2013 Update
Do people care about the LAA?

Growing interest in LAA ligation, largely driven by three developments:

1. Schuessler and Boineau developing the maze procedure (the first reliable operation for AF)

2. Advent of TEE, to document LAA thrombus and closure success

3. Development and marketing of percutaneous occlusion devices

Fig 1. Number of left atrial appendage publications in various periods from 1948 to 2011.
What is the LAA and why do we fear it?

- 2-4 cm long tubular structure
- Often uses a narrow junction
- Forms sharp angles
- In contrast, the RAA is broad based and triangular, forms a wide junction to the RA, gradually angles upward.
What is the LAA and why do we fear it?

• Review of operative/autopsy/TEE studies identified the LAA is as the source for 90% of left atrial thrombi in nonvalvular AF.

• LAA thrombus present in 64% of patients with rheumatic MV disease and systemic embolism.

• The LAA has been described in the literature as "our most lethal human attachment."

Blackshear JL. Ann Thorac Surg 1996
Johnson WJ. Eur J Cardothorac Surg 2000
What exactly does the LAA do?

• Endocrine organ: LAA contains stretch receptors that mediate thirst
  - 40 fold higher concentration of ANP in LAA than other areas in the heart
  - Water retention with bilateral atrial appendectomies

• Regulates the LA pressure-volume relationship

• Trigger for recurrent AF (up to 27% of redo AF ablation)

Does the Left Atrial Appendage Morphology Correlate With the Risk of Stroke in Patients With Atrial Fibrillation?

Results From a Multicenter Study

Luigi Di Biase, MD, PhD,‡‡ Pasquale Santangeli, MD,*‡ Matteo Anselmino, MD, PhD,§ Prasant Mohanty, MBBS, MPH,* Ilaria Salvetti, MD,§ Sebastiano Gili, MD,§ Rodney Horton, MD,* Javier E. Sanchez, MD,* Rong Bai, MD,* Sanghamitra Mohanty, MD,* Agnes Pump, MD,* Mauricio Cereceda Brantes, MD,* G. Joseph Gallinghouse, MD,* J. David Burkhardt, MD,* Federico Cesari, MD,|| Marco Marrouche, MD, ||

Austin, Texas, and Foggia, Turin.
Does LAA closure actually work?

Table 1. Comparison of Surgical Left Atrial Appendage Closure Techniques

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Country</th>
<th>No. Studied</th>
<th>Method of Closure</th>
<th>Closure Success Rate, a %</th>
<th>Effect of LAA Closure on Stroke Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson, 2000 [25]</td>
<td>USA</td>
<td>437</td>
<td>Excision</td>
<td>100</td>
<td>Positive</td>
</tr>
<tr>
<td>Katz, 2000 [30]</td>
<td>USA</td>
<td>50</td>
<td>Endocardial suture</td>
<td>64</td>
<td>None</td>
</tr>
<tr>
<td>Garcia-Fernandez, 2003 [31]</td>
<td>Spain</td>
<td>205</td>
<td>Endocardial suture</td>
<td>90</td>
<td>Positive</td>
</tr>
<tr>
<td>Bando, 2003 [38]</td>
<td>Japan</td>
<td>812</td>
<td>Endocardial suture</td>
<td>Not measured</td>
<td>Negative</td>
</tr>
<tr>
<td>Blackshear, 2003 [45]</td>
<td>USA</td>
<td>15</td>
<td>Thoracoscopic epicardial pursestring</td>
<td>93b</td>
<td>Positive</td>
</tr>
<tr>
<td>Pennec, 2003 [40]</td>
<td>France</td>
<td>30</td>
<td>Endocardial</td>
<td>70–80</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Excision</td>
<td>100</td>
<td>Positive</td>
</tr>
<tr>
<td>Schneider, 2005 [41]</td>
<td>Germany</td>
<td>6</td>
<td>Endocardial suture</td>
<td>17</td>
<td>Negative</td>
</tr>
<tr>
<td>Healey, 2005 [28]</td>
<td>Canada</td>
<td>77</td>
<td>Epicardial suture</td>
<td>45</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stapler</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Kanderian, 2008 [29]</td>
<td>USA</td>
<td>137</td>
<td>Excision</td>
<td>73 (20% stapler)</td>
<td>Positive trend</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Suture exclusion</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stapler</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bakhtiary, 2008 [33]</td>
<td>Germany</td>
<td>259</td>
<td>Clamp and epicardial suture</td>
<td>100b</td>
<td>Positive</td>
</tr>
</tbody>
</table>

a As assessed by transesophageal echocardiography.  b Remnant size not measured.

LAA = left atrial appendage.
Transcatheter Closure Devices

PLAATO

Watchman

Amplatzer Cardiac Plug

Lariat
PLAATO system (eV3)

- Self-expandable nitinol cage with a PTFE membrane.
- Largely positive results: compared 2.2% stroke rate to historical cohort (6.3% assumed rate) led to a 65% RRR in stroke.
PLAATO system (eV3)

PLAATO no longer available
(too many adverse events)
The AMPLATZER™ Cardiac Plug (ACP) is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in subjects who have nonvalvular atrial fibrillation.

CAUTION – Investigational device. Limited by Federal (or United States) law to investigative use.
Amplatzer Cardiac Plug
(AGA/St. Jude Medical)

Self-expanding nitinol mesh

Distal lobe with retaining hooks (anchor)

Proximal disk (cover, not permeable)

Device Description

The ACP device is delivered transseptally via delivery sheath into the left atrium (LA) and to the LAA
Amplatzer Cardiac Plug (AGA/St. Jude Medical)

- Amplatzer septal occluder has been used for 15+ years, extensive success in PFO/ASD closure

- Amplatzer cardiac plug (ACP) was specifically designed for LAA occlusion.

- Initial experience in EU: 143 pts; 96% successful implant; 7% SAE rate (5 tamponade, 2 embolization, 3 strokes).

- No warfarin. 1 month clopidogrel, 6 month ASA

- CE Mark 2008. 1,200+ procedures performed worldwide. Currently in phase 1 trial in US.
Watchman
(Atritech/Boston Scientific)

Caution: In the United States, WATCHMAN is an investigational device limited by Federal law and investigational use only. Not for sale in the US.
**Watchman Components**

**Frame:** Nitinol structure
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
  - 10 Fixation barbs around device perimeter engage LAA tissue
  - Contour shape accommodates most LAA anatomy

**Fabric Cap:** (PET) Fabric Polyethyl terephthalate
- Prevents harmful emboli from exiting during the healing process
- 160 micron filter

*9 months post implant*
Watchman Delivery System

Transseptal Access System
- Double or Single Curve styles
- 14F OD (4.7 mm), 12F ID
- 75 cm working length

Double Curve

Single Curve

Preformed curve shapes guide position in LAA
Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators

Lancet 2009; 374: 534-42

707 subjects

Occluder was noninferior to warfarin, but higher adverse event rate.

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=463)</th>
<th>Control (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious pericardial effusion*</td>
<td>22 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>16 (3.5%)</td>
<td>10 (4.1%)</td>
</tr>
<tr>
<td>Procedure-related ischaemic stroke</td>
<td>5 (1.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Device embolisation</td>
<td>3 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Haemorrhagic stroke‡</td>
<td>1 (0.2%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>Other§</td>
<td>2 (0.4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Defined as the need for percutaneous or surgical drainage. †Major bleeding is defined as a bleeding event that required at least 2 units of packed red blood cells or surgery to correct. ‡Of the seven haemorrhagic strokes, six resulted in death (intervention group, n=1; control group, n=5). §An oesophageal tear and a procedure-related arrhythmia.

Table 3: Adverse events
<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>CAP&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ASAP&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>PREVAIL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>Patients able to take warfarin</td>
<td></td>
<td>Warfarin contraindicated patients</td>
<td>Patients able to take warfarin</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>All stroke, systemic embolism and cardiovascular death</td>
<td>All stroke, systemic embolism and cardiovascular death</td>
<td>All stroke, systemic embolism, and cardiovascular death</td>
<td>All stroke, systemic embolism and cardiovascular death</td>
</tr>
<tr>
<td><strong>Mean age /CHADS</strong></td>
<td>72 years/2.2</td>
<td>74 years/2.4</td>
<td>72 years/2.8</td>
<td>74 years/2.6</td>
</tr>
<tr>
<td><strong>Total Enrolled Subjects</strong></td>
<td>707 randomized&lt;sup&gt;1&lt;/sup&gt;, 93 pts rolled in&lt;sup&gt;2&lt;/sup&gt;</td>
<td>460</td>
<td>150</td>
<td>461</td>
</tr>
<tr>
<td><strong>Total Patients Implanted</strong></td>
<td>542&lt;sup&gt;2&lt;/sup&gt;</td>
<td>437</td>
<td>142</td>
<td>303</td>
</tr>
<tr>
<td><strong>Implantation Success</strong></td>
<td>89.5%&lt;sup&gt;2&lt;/sup&gt;</td>
<td>95.0%</td>
<td>94.7%</td>
<td>95.1%</td>
</tr>
<tr>
<td><strong>Warfarin discontinuation at 45 days</strong></td>
<td>86.6%</td>
<td>94.9%</td>
<td>No warfarin used</td>
<td>Pending full results</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>Rate ratio 0.71 (0.35–1.64) [Hemorrhagic Stroke: 0.09 (0.00–0.45)]</td>
<td>Reduction in procedure related stroke vs PROTECT AF (&lt;i&gt;P&lt;/i&gt;=0.04)</td>
<td>Decreased rate of stroke by 77% vs. expected rate per CHADS&lt;sub&gt;2&lt;/sub&gt; Score</td>
<td>Pending full results</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>HR 1.69 (1.01–3.19)</td>
<td>Reduction in pericardial effusions vs PROTECT AF (&lt;i&gt;P&lt;/i&gt;=0.02)</td>
<td>Pericardial effusion with tamponade=2.0% Major bleeding=2.7%</td>
<td>Pending full results</td>
</tr>
</tbody>
</table>

1. Holmes DR, Lancet 2009  
2. Reddy VY, Circulation 2011  
3. Sievert H, TCT 2011  
4. Reddy VY, JACC 2013
Watchman
(Atritech/Boston Scientific)

• FDA denied approval in 2010 based on PROTECT-AF.

• CE Mark in 2005. It is approved in 50 countries.

• To date, over 5000 Watchmans (Watchmen?) implanted.

• PREVAIL study (using a "gentler" device) finished enrolling in July 2012. 6 month follow up at ACC 2013.
Safety Events Related to Implant

- **Total**
- **Effusion+drain**
- **Major bleeding**
- **Embolization**
- **Stroke**
- **Thrombus**

Legend:
- PROTECT AF
- CAP
- ASAP
- PREVAIL
In this study, "closure" was defined as "< 5mm jet"
1/3 of patients had residual flow.
Stroke risk increases with greater residual flow.

Impact of residual peridevice flow on the primary thromboembolic end point in PROTECT-AF, hazard ratio (HR, 95% CI)

<table>
<thead>
<tr>
<th>End point</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor peridevice vs no peridevice flow</td>
<td>0.85 (0.11-6.40)</td>
</tr>
<tr>
<td>Moderate peridevice vs no peridevice flow</td>
<td>0.83 (0.33-2.09)</td>
</tr>
<tr>
<td>Major peridevice vs no peridevice flow</td>
<td>0.48 (0.11-2.09)</td>
</tr>
<tr>
<td>Any peridevice flow and continued warfarin (vs no peridevice flow and discontinued warfarin)</td>
<td>0.63 (0.14-2.71)</td>
</tr>
</tbody>
</table>
Lariat LAA Excluder (SentreHEART)

Combination of epicardial and endocardial access

Magnet-tipped guidewires

40-mm pretied radioopaque suture loop to ligate the LAA from the epicardial surface
Lariat LAA Excluder
(SentreHEART)

• FDA Approved in 2009 to "facilitate soft tissue approximation"

• To date, over 2000 patients with LAA ligation

• Requires particular LAA anatomy, chest wall, no prior cardiac surgery
Tips from our experience with Lariat

• Choose appropriate patients and don’t minimize the potential risk

• Aim true: epicardial angle is important

• Use up-to-date imaging: atria (and appendages) can dilate over time

• Pericarditis: expect to manage pain afterward

• Anticipate fluid retention, faster AF, mild hypotension
Summary Slide: My Two Cents

• I wish we had more data.

• Is LAA closure worth doing? I think so, especially for patients at high risks for stroke.

• When safety profile improves, I suspect we’ll be offering this to an expanding population.

• Having options for LAA closure allows a personalized approach based on favorable anatomy or previous cardiac surgery.
Lariat LAA Excluder (SentreHEART)