Left Atrial Appendage Occlusion: Shutting Out Embolic Disease Without Anticoagulation

Zoltan G. Turi, M.D.
Rutgers Robert Wood Johnson Medical School
New Brunswick, NJ
There is no FDA approved technology for percutaneous LAA occlusion
All devices discussed are experimental in the United States or used off label.
LAA Occlusion: Why Is It Important?

1. Stroke in AF patients is particularly high risk
2. Oral anticoagulation remains the standard of care for embolic prevention
3. Oral anticoagulation is an iatrogenic disease
   1. High morbidity
   2. Poor compliance
4. 90% of emboli in AF originate from the LAA
5. LAA occlusion is technically achievable with relatively high efficacy and arguably reasonable risk
Current AF Treatment Options

AF

- Ablation
- Drugs for Rhythm Control
- Drugs for Rate Control
- Embolic Management
  - Anti-coagulation
LAA Occlusion: Why Is It Important?

2. Anticoagulation in AF is standard of care

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Warfarin Better</th>
<th>Control Better (placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAATAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Reduction of stroke: RRR 62%
- Reduction of all-cause mortality: RRR 26%

**Therapeutic Range is Narrow**

- **Odds Ratios**
  - < 1.5
  - 1.5-1.9
  - 2.0-2.5
  - 2.6-3.0
  - 3.1-3.5
  - ≥ 3.6

- **Thromboembolism**
- **Intracranial Hemorrhage**

- **Atria Study**
  - 48% of thromboembolic events occur in patients below therapeutic range*
  - 44% of bleeding events occur in patients above therapeutic range*

- **Odds Ratios**
  - 10.19
  - 11.12

*Courtesy Dr. Dan Singer MGH  Circ CV Qual and Outcomes 2009

3. Oral Anticoagulation is an Iatrogenic Disease

• Needs for extensive monitoring
• Food and medicine interactions
• Difficult to maintain therapeutic range
• Substantial morbidity
• Need to discontinue for surgery
• High rates of self-discontinuation and non-adherence
• Warfarin tops list of emergency hospitalizations for adverse drug events
Patients at Bleeding Risk are Also at High Stroke Risk

- High CHADS² or CHA²DS²VASc score correlates with high HAS-BLED score

**HAS-BLED**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H  Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A  Abnormal liver and renal function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S  Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B  Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L  Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E  Elderly (age &gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D  Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

**Risk of major bleeding in patients with AF in the Euro Heart Survey**

<table>
<thead>
<tr>
<th>Score</th>
<th>Bleeds Per 100 Patient Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
</tbody>
</table>
Warfarin Alternatives
(Factor II/XA inhibitors)

• Generally safe, effective, and do not require INR monitoring
  • → superior time in therapeutic range
• Warfarin remains the primary oral anticoagulant
• Core problems of anticoagulation remain:
  • Bleeding risks
  • High rates of non-adherence
• Antiplatelet agents – still bleeding risk, higher embolic risk
Current AF Treatment Options

AF
- Ablation
- Drugs for Rhythm Control
- Drugs for Rate Control

Embolic Management
- LAA Exclusion
  - Surgical Ligation
  - Surgical Clipping
- Anti-coagulation
- Percutaneous LAA Interventions
LAA Occlusion: Why Is It Important?

4. Emboli in Non-Valvular AF Originate in LAA

Insufficient or no contraction of LAA

- Stagnant blood flow

- Thrombosis / clot formation

- Thromboembolism

- Stroke

90% of thrombi are located in the LAA

Johnson. Eur J Cardiothoracic Surg 2000;17
5. Left atrial appendage occlusion is achievable with relatively high efficacy and arguably reasonable risk – the evidence base is incomplete on outcomes.
Surgical LAA Obliteration & Stroke Reduction

Ad hoc surgical adjunctive practice for > ½ century

Retrospective review of 205 patients with prior MV replacement

- 58/205 (28%) had LAA ligation
- 27 patients had embolic events
  - 1 of 58 ligated
  - 26 of 205 not ligated
- Absence of LAA ligation (Odds Ratio = 6.7:1)

Randomized Pilot Trial - LAAOS

- 77 CABG Patients at Risk – 52 to LAA occlusion
  - Suture – 55% failure by TEE at 8 weeks – residual flow across suture line
  - Staples – 28% failure – stump > 1 cm

Healey AHJ 2005 Toronto
Percutaneous LAA Occlusion
Feasibility Trial – First Generation LAA Occluder

- 111 patients – did not receive warfarin
- 97% deployment success
- Leak mild or less in 108
- 1° outcomes measure:

**Estimated** stroke risk based on CHADS$_2$
- 6.3%

**Actual** Observed Stroke Rate
- 2.2%

(65% reduction compared to historical control)

Ostermayer JACC 2005
• 9 procedure related SAEs
  • Pleural effusion, pericardial effusion (2), tamponade (2), hemothorax,
  • DVT, brachial plexus palsy, reintubation

• 7 MAEs
  • 4 cardiac or neurological deaths – non-device related
  • 2 strokes
  • 1 tamponade post transseptal, sternotomy, LAA ligation, DVT, cerebral hemorrhage, death

• 3 TIA's
Second Generation LAA Device

21 – 33 mm diameter

Permeable

160 µ Filter

Barbs
Fixation barbs engage LAA wall

Plane of maximum diameter distal to ostium
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
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
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*
The Only High Level Evidence Base

- Prospective randomized trial – device and proof of concept
  - 800 patients
  - Independent Data Analysis
    - Core Laboratories
    - Clinical Events Committee
    - Data Safety Monitoring Board
  - TEE baseline, 45 days, 6 months, 1 year
  - 5 year follow-up
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)

RR = 0.62 (95% CrI 0.35-1.25)
Primary Safety Endpoint
(Hemorrhage, hemorrhagic stroke, procedure related events)

RR = 1.17 (95% CrI 0.78-1.95)
Procedural Complications

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

![Chart showing procedure time and implant success percentages.]

![Chart showing primary safety event on day of procedure percentages.]

![Chart showing serious pericardial effusion within 7 days of implant percentages.]
PROTECT AF Redux

- Sample size – too small
- Enrollment criteria – too low risk
- Control group anticoagulation – not enough
- Device group anticoagulation – too much
- Duration of follow-up – too short
- Learning curve – too long
- Complication rate – too high
PROTECT AF Redux

- PREVAIL – 453 patients; 407 randomized 2:1
- Same design – higher risk population
- Three endpoints
  - Safety
  - Efficacy – same criteria as PROTECT AF
  - Ischemic stroke/systemic embolism after 7 days
## PREVAIL Met
### Safety Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>WATCHMAN (N=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>6</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>2.23%</td>
</tr>
<tr>
<td>95% Credible Interval (Crl)</td>
<td>2.65%</td>
</tr>
<tr>
<td>Performance Goal (1-sided 95% Crl)</td>
<td>&lt; 2.67%</td>
</tr>
</tbody>
</table>

Performance Goal

- Event Rate (95% Crl): 2.23%
PREVAIL: Efficacy Primary Endpoint (2013 and 2014)

Bayesian model results; Ad hoc analysis
PREVAIL Ad hoc Analysis: Second Primary Endpoint (2013 vs 2014)

Bayesian model results

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate Difference</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>0.0053</td>
<td>97.6%</td>
</tr>
<tr>
<td>2014</td>
<td>0.0163</td>
<td>89.2%</td>
</tr>
</tbody>
</table>
PREVAIL
Control (Warfarin) Group Performance

- High average CHADS\(_2\) score of 2.6 in the control group
- PREVAIL control group event rate = 0.7 events per patient year

<table>
<thead>
<tr>
<th>Trial</th>
<th>Control (Warfarin) Group Stroke, Systemic Embolism Rate (Per 100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF(^1)</td>
<td>1.6</td>
</tr>
<tr>
<td>RE-LY (Dabigatran)(^2)</td>
<td>1.7</td>
</tr>
<tr>
<td>ARISTOTLE (Apixaban)(^3)</td>
<td>1.6</td>
</tr>
<tr>
<td>ROCKET AF (Rivaroxaban)(^4)</td>
<td>2.2</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Results are preliminary; final validation not yet complete

Ischemic stroke rate from Holmes et al., Lancet 2009; 374:534-42
PREVAIL Ischemic Stroke Rate Aligns with Expected Rate

Friberg. Eur Heart J (2012); NICE UK (2014)
Safety = 12-0
Efficacy = 6-7
Benefit>risk = 6-5-1 *

GAITHERSBURG, Md. -- An FDA advisory committee struggling with limits of the regulatory process delivered a split vote Wednesday along with a nuanced recommendation – once again leaving the Watchman left atrial appendage closure device’s future in serious doubt.

The Circulatory System Devices Advisory Panel convened to deliberate the
The Assault on the Left Atrial Appendage in Perspective*

Zoltan G. Turi, MD
Camden, New Jersey

available stapler/cutter. That we have 3 such papers in 1 issue of the Journal (2–4) underscores the extent to which LAA interventions have benefited from a decade of technology development. However, despite substantial enthusiasm on the part of the interventional cardiology and electrophysiology communities, the evidence base for percutaneous approaches has been largely wanting as well, with only 1 high-level randomized controlled trial (5). Although the WATCHMAN and ACP are commercially available and widely distributed outside the United States, access in the United States is limited to investigational sites under rigidly controlled enrollment criteria that largely exclude patients who need the technology most; those with a high or
Amplatzer Cardiac Plug Registry

- Sites
- Patients
- Follow-up
- Success
- Embolization
- Procedural stroke
- Pericardial Effusion
- Tamponade
- Major complications

Cardiac Plug Registry

- 9
- 143
- 24 hours
- 96.4%
- 1.4%
- 2.1%
- 2.8%
- 3.5%
- 7%

Cardiac Plug Data from Park JW CCI 2011
Problems with Plugs

- Paradevice leak
- Metal left in heart
  - Anticoagulation
  - Antiplatelet Rx
- Pericardial effusions/tamponade
- Device embolization
Garrotting

SECTION 4 - 510(K) SUMMARY

This summary of 510(k)-safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

Intended Use:
The LARIAT II Suture Delivery Device facilitates suture placement and knot tying for use in surgical applications where soft tissue are being approximated and/or ligated with a pre-tied polyester suture.

Intended Use:
The FindrWIRZ System is intended for use in the cardiovascular system for introduction and positioning of over-the-wire catheters and therapeutic devices during interventional procedures. A FindrWIRZ may also be used to manipulate and or reposition another FindrWIRZ.
LARIAT

• CHADS2 scores:
  ▪ 45% = 1; 4.5% > 3

• Complete closure in 85 of 89

• 95% < 1 mm leak at 90 days

• Single site registry

• > ½ anticoagulated at one year
Our Rump Criteria for Lariat

- Contraindication, very high risk or refuses anticoagulation
- Compelling clinical picture/high CHADS$_2$ score
  - E.g. prior embolic event
### Recommendations for LAA closure/occlusion/excision

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.</td>
<td>IIb</td>
<td>B</td>
<td>115, 118</td>
</tr>
<tr>
<td>Surgical excision of the LAA may be considered in patients undergoing open heart surgery.</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
Left Atrial Appendage Occlusion — Closure or Just the Beginning?