Percutaneous LAA Closure: A Future Management Alternative for Stroke Prevention in AF Patients

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Atrial fibrillation is one of the most important causes of stroke
Especially in elder patients

% of strokes which are caused by AF

Framingham Study, Wolf, 1991
What is the Annual Risk of Stroke?
Nat. Registry of AF: CHAD\(S_2\)

<table>
<thead>
<tr>
<th>CHADS Score</th>
<th># Pts n=1773</th>
<th># Strokes n=94</th>
<th>NRAF adjusted Stroke Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>
"Let's take Coumadin!"
Randomized Clinical Trials of Coumadin in Atrial Fibrillation

-71%* -86%* -69%* -52% -79%* -66%*

* p<0.05
Warfarin Net Clinical Benefit: Impact of Age

Net Clinical Benefit, Events Prevented per 100 Person – Years

Coumadin is a good idea,...

... if you can take it
- Any localized or general physical condition in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Any personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Pregnancy
- Hemorrhagic tendencies
- Blood dyscrasias.
- Recent or contemplated surgery of central nervous system
- Recent or contemplated surgery of the eye
- Recent or contemplated traumatic surgery resulting in large open surfaces
- Gastrointestinal bleeding
- Genitourinary tract bleeding
- Respiratory tract bleeding
- Cerebrovascular hemorrhage
- Cerebral aneurysms
- Dissecting aorta
- Pericarditis
- Pericardial effusions
- Bacterial endocarditis
- Threatened abortion
- Eclampsia
- Preeclampsia
- Inadequate laboratory facilities
- Unsupervised patients
- Senility
- Alcoholism
- Psychosis
- Lack of patient cooperation
- Spinal puncture
- Other diagnostic procedures with potential for uncontrollable bleeding
- Therapeutic procedures with potential for uncontrollable bleeding
- Major regional anesthesia
- Lumbar block anesthesia
- Malignant hypertension
Anticoagulation Underuse

Only about 1/3 of all eligible patients are taking Coumadin

Stafford and Singer, Arch Int Med, 1996
Anticoagulation Use in General Practice

Discontinuation

Other drugs?
All Anticoagulants

- Per definition
  - have to be given lifelong
  - have a bleeding risk
- Bleeding risk increases with age
- At some point Anticoagulants have to be stopped
- You should avoid anticoagulants in elderly patients because of higher bleeding risk
- You should avoid anticoagulants in younger patients because they would have to take it for a longer time period
Where do the thrombi arise?
Thrombus in the LAA
90 % of all thrombi in non-rheumatic atrial fibrillation originate in the LAA

<table>
<thead>
<tr>
<th>Setting</th>
<th>N</th>
<th>Appendage (%)</th>
<th>LA Body (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>317</td>
<td>66 (21%)</td>
<td>1 (0.3%)</td>
<td>Stoddard; JACC ’95</td>
</tr>
<tr>
<td>TEE</td>
<td>233</td>
<td>34 (15%)</td>
<td>1 (0.4%)</td>
<td>Manning; Circ ’94</td>
</tr>
<tr>
<td>Autopsy</td>
<td>506</td>
<td>35 (7%)</td>
<td>12 (2.4%)</td>
<td>Aberg; Acta Med Scan ’69</td>
</tr>
<tr>
<td>TEE</td>
<td>52</td>
<td>2 (4%)</td>
<td>2 (3.8%)</td>
<td>Tsai; JFMA ’90</td>
</tr>
<tr>
<td>TEE</td>
<td>48</td>
<td>12 (25%)</td>
<td>1 (2.1%)</td>
<td>Klein; Int J Card Imag ’93</td>
</tr>
<tr>
<td>TEE &amp; Operation</td>
<td>171</td>
<td>8 (5%)</td>
<td>3 (1.8%)</td>
<td>Manning; Circ ’94</td>
</tr>
<tr>
<td>SPAF III TEE</td>
<td>359</td>
<td>19 (5%)</td>
<td>1 (0.3%)</td>
<td>Klein; Circ ’94</td>
</tr>
<tr>
<td>TEE</td>
<td>272</td>
<td>19 (7%)</td>
<td>0 (0.0%)</td>
<td>Leung; JACC ’94</td>
</tr>
<tr>
<td>TEE</td>
<td>60</td>
<td>6 (10%)</td>
<td>0 (0.0%)</td>
<td>Hart; Stroke ‘94</td>
</tr>
<tr>
<td>Total</td>
<td>2018</td>
<td>201 (10%)</td>
<td>21 (1.0%)</td>
<td></td>
</tr>
</tbody>
</table>

From: Blackshear & Odell; 1996
PLAATO™ Device

ePTFE membrane

anchors

LA

LAA

Nitinol Cage
The first patient who underwent successful closure of the LAA

- Aug 30, 2001
- A.S., 72 y/o, male
- AF since 2 years
- Multiple contraindications for coumadin
- Very unstable INR
- CHADS score 3
First successful attempt of LAA closure

- Procedure time 85 min
- Complete seal
- No complications
- Coumadin off since 2001
- No neurological events
- Participated in other FIM trials
- Had his 80th birthday in Jan 2009
Watchman Device

- Nitinol frame
- PET membrane
- row of fixation barbs around the mid perimeter
- 21, 24, 27, 30, 33 mm

CE mark
WATCHMAN Device

Canine Model

30 days

45 days
Watchman Implantation

- LAA diameter in TEE 19 mm

- anatomy of LAA in TEE and fluoro
**Watchman Implantation**

<table>
<thead>
<tr>
<th>Maximum measured LAA ostium (mm)</th>
<th>Implant diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 - 19.5</td>
<td>21</td>
</tr>
<tr>
<td>20 - 22.9</td>
<td>24</td>
</tr>
<tr>
<td>23 - 25.9</td>
<td>27</td>
</tr>
<tr>
<td>26 – 28.9</td>
<td>30</td>
</tr>
<tr>
<td>29 – 31.9</td>
<td>33</td>
</tr>
</tbody>
</table>

- device selection according to measurements
- Implantation of 21mm Watchman Occluder

![Ultrasound image showing the heart with the Watchman Implantation device]
Watchman Implantation

- Check position
- Check device compression
- Check residual flow
- Tug test
- Release
Protect AF
(System for Embolic PROTECTion in Patients with Atrial Fibrillation)

- Multicenter
- Prospective randomized
- WATCHMAN vs coumadin 2:1
- Non-inferiority trial
- 800 pts (enrollment closed June 2008)
- > 900 patient-years
In- & Exclusion

Major inclusion criteria

- Non valvular AF with Chads2 score ≥ 1
- No contraindications to coumadin
- No co-morbidities mandating chronic warfarin use other than AF

Major exclusion criteria

- LAA thrombus
- Large PFO with significant atrial septal aneurysm
- Mobile aortic atheroma
- Symptomatic carotid artery disease
PROTECT AF Trial Endpoints

• Primary Efficacy Endpoint
  • All stroke
  • Cardiovascular and unexplained death
  • Systemic embolization

• Primary Safety Endpoint
  • Device embolization requiring retrieval
  • Pericardial effusion requiring intervention
  • Cranial bleeds and gastrointestinal bleeds
  • Any bleed that requires ≥ 2uPRBC
Primary Efficacy Endpoint
Freedom from Stroke, Death, Systemic Embolization

LAA closure not inferior to anticoagulation
All Stroke

Events/100 patient years

Warfarin: 3.2
LAA Closure: 2.3

P<0.05

28%
Hemorrhagic Stroke

P < 0.05

Events/100 patient years

Warfarin: 1.6
LAA Closure: 0.1

94%
Mortality

- Events/100 patient years
- P<0.05

Warfarin: 4.8
LAA Closure: 3

38% reduction
Safety

Freedom from device embolization, pericardial effusion, Severe bleeding

Mostly stroke and bleeding

Mostly pericardial effusion without sequelae

Event-free probability

Days

0  365  730  1,095
PROTECT AF

- ... was the "Proof of concept":
  - Left atrial appendage closure prevents stroke
  - It is as effective as anticoagulation
- As expected there are more early safety events after LAA closure due to pericardial effusions
- Under anticoagulation therapy there are more late safety events due to stroke and bleeding
## Performance Metrics

### PROTECT AF vs CAP

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF</th>
<th>PROTECT AF</th>
<th>CAP</th>
<th>p-value*</th>
<th>p-value±</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure Time</td>
<td>62 ± 34</td>
<td>67 ± 36</td>
<td>58 ± 33</td>
<td>50 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Implant Success</td>
<td>485/542</td>
<td>239/271</td>
<td>246/271</td>
<td>437/460</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(89.5%)</td>
<td>(88.2%)</td>
<td>(90.8%)</td>
<td>(95.0%)</td>
<td></td>
</tr>
<tr>
<td>45-day Warfarin</td>
<td>414/478</td>
<td>194/235</td>
<td>220/243</td>
<td>352/371</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation Among Implant</td>
<td>(86.6%)</td>
<td>(82.6%)</td>
<td>(90.5%)</td>
<td>(94.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*From tests comparing the PROTECT AF cohort with CAP
±From tests for differences across three groups (early PROTECT AF, late PROTECT AF, and CAP)

- Improvements seen over time in PROTECT AF
  - Shorter implant time, higher implant success rate, higher warfarin discontinuation rate
- Trends confirmed in CAP
### Safety Event Rates

**PROTECT AF vs CAP**

<table>
<thead>
<tr>
<th>Event</th>
<th>PROTECT AF Early</th>
<th>PROTECT AF Late</th>
<th>CAP</th>
<th>p-value*</th>
<th>p-value±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure/Device Related Safety Adverse Events within 7 Days</td>
<td>27/271 (10.0%)</td>
<td>15/271 (5.5%)</td>
<td>17/460 (3.7%)</td>
<td>0.007</td>
<td>0.006</td>
</tr>
<tr>
<td>Serious Pericardial Effusions within 7 Days</td>
<td>17/271 (6.3%)</td>
<td>10/271 (3.7%)</td>
<td>10/460 (2.2%)</td>
<td>0.019</td>
<td>0.018</td>
</tr>
<tr>
<td>Procedure Related Stroke</td>
<td>3/271 (1.1%)</td>
<td>2/271 (0.7%)</td>
<td>0/460 (0.0%)</td>
<td>0.039</td>
<td>0.039</td>
</tr>
</tbody>
</table>

**Improvements seen over time for acute safety events**

**Fewer total procedure/device related events**

Kar et al. TCT 2010
Concept of PLAATO and Watchman

- To close the LAA like with a ball
Amplatzer Cardiac Plug ACP
Concept of Amplatzer Cardiac Plug ACP
M.I., female, 66 years
Assessment before release

- Tug test
M.I., female, 66 years
Final position

• 3D TEE: LA en-face view of the occluder

• 2D TEE 93°
<table>
<thead>
<tr>
<th></th>
<th>FIM Registry</th>
<th>CVC Frankfurt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>143</td>
<td>67</td>
</tr>
<tr>
<td><strong>Technical success rate</strong></td>
<td>96.4%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>MAE &lt; 24 hours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tamponade</td>
<td>3.5%</td>
<td>0</td>
</tr>
<tr>
<td>- Device embolisation</td>
<td>1.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>- Stroke</td>
<td>2.1%</td>
<td>0</td>
</tr>
</tbody>
</table>
New Approaches

• Endocardial
  - Occlutech
  - Coherex
  - Gore

• Epicardial
  - Epitec
  - AtriCure
  - SentreHeart
  - Aegis Medical
June 23 – 25, 2011 | Frankfurt, Germany

CSI 2011 – Catheter Interventions in Congenital & Structural Heart Disease

www.csi-congress.org

LIVE CASES
Take Home Messages

- Atrial fibrillation is a frequent cause of stroke
- Thrombi originate in the left atrial appendage
- Catheter closure of the atrial appendage is feasible and relatively safe
- The randomized trial with the Watchman device showed that the procedure is safe and effective in stroke reduction and not inferior compared to anticoagulation
- Currently two devices are available for LAA closure
- Many others are under development
Thank You