Left Atrial Appendage Occlusion

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Σύγκρουση Συμφερόντων: Όχι
Atrial fibrillation (AF) is the most common type of cardiac arrhythmia.¹

Atrial fibrillation
and the stroke connection

Patients with AF are
5x MORE LIKELY
To have a stroke.¹

AF is associated with a
3x HIGHER RISK
of heart failure.¹

AF related strokes tend to be more severe,
CAUSE GREATER DISABILITY
And have a worse outcome than non-AF-related strokes.²

AF AND MORTALITY³

<table>
<thead>
<tr>
<th>50%</th>
<th>27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood of death for AF-related strokes within 1 year after a stroke.</td>
<td>Likelihood of death for non-AF-related strokes within 1 year after a stroke.</td>
</tr>
</tbody>
</table>

(N) OAC Medications
Left atrial appendage
Thrombus

Thrombus shown within the left atrial appendage and pectinate muscle bundles

Images courtesy of Dr Andrew Cook, UCL, London
Watchman

Amplatzer
Major LAA Types

The **Wind Sock Type** LAA is an anatomy in which one dominant lobe of sufficient length is the primary structure.

The **Chicken Wing Type** LAA is an anatomy whose main feature is a sharp bend in the dominant lobe of the LAA anatomy at some distance from the perceived LAA.

The **Broccoli Type** LAA is an anatomy whose main feature is an LAA that has limited overall length with more complex internal characteristics.
WATCHMAN™ - Most Studied LAAC Device
Only one proven with long-term data from randomized trials and multi-center registries

<table>
<thead>
<tr>
<th>Key Trials</th>
<th>N</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF&lt;sup&gt;1&lt;/sup&gt; (2005-2008)</td>
<td>707</td>
<td>Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.</td>
</tr>
<tr>
<td>CAP&lt;sup&gt;2&lt;/sup&gt; (2008-2010)</td>
<td>566</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to PMA approval.</td>
</tr>
<tr>
<td>PREVAIL&lt;sup&gt;3&lt;/sup&gt; (2010-2012)</td>
<td>407</td>
<td>Prospective, randomized 2:1, non-inferiority trial to collect additional information on the WATCHMAN Device.</td>
</tr>
<tr>
<td>CAP2 (2012-2014)</td>
<td>579</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device prior to PMA approval.</td>
</tr>
<tr>
<td>EWOLUTION&lt;sup&gt;4&lt;/sup&gt; (2013-2015)*</td>
<td>1025</td>
<td>Prospective registry allowing all patients receiving a WATCHMAN Device at participating centers in Europe, Middle East and Russia</td>
</tr>
<tr>
<td>Total patients</td>
<td>&gt;3,000</td>
<td>~7,000 Patient-Years of Follow-up</td>
</tr>
</tbody>
</table>

* Majority of patients enrolled could not take anticoagulation and therefore contraindicated in the US per current labeling.
Favorable Procedural Safety Profile:
All Device and/or Procedure-related Serious Adverse Events within 7 Days

- PROTECT AF 1st Half N=232: 9.9%
- PROTECT AF 2nd Half N=231: 4.8%
- CAP N=566: 4.1%
- PREVAIL N=269: 4.1%
- CAP2 N=579: 3.8%
- EWOLUTION* N=1019: 2.8%

~50% New Operators in PREVAIL
## WATCHMAN is the most studied LAAC Device with Long-term Clinical Data

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td>WATCHMAN procedure is safe</td>
<td>95% implant success; ~4% complication rates(^1)</td>
</tr>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>WATCHMAN comparable to warfarin</td>
<td>21% reduction in events (p=0.22)(^3)</td>
</tr>
<tr>
<td><strong>All-Stroke</strong></td>
<td>WATCHMAN comparable to warfarin</td>
<td>63% reduction in disabling strokes (Ps=&gt;99%)(^2); 78% reduction in hemorrhagic strokes (p=0.004)(^3)</td>
</tr>
<tr>
<td><strong>CV / Unexp death</strong></td>
<td>WATCHMAN superior to warfarin</td>
<td>52% reduction in events (p=0.006)(^3)</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>WATCHMAN comparable to warfarin; superior to warfarin post-procedure</td>
<td>52% reduction post-procedure (p=0.002); 72% reduction after 6-months (p=0.001)(^4)</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>WATCHMAN allows the majority of patients to discontinue warfarin</td>
<td>92% of patients discontinue after 45-days; 99% of patients discontinue after 1 year(^5)</td>
</tr>
</tbody>
</table>
The WATCHMAN Device is indicated:

§ to reduce the risk of thromboembolism from the LAA in patients with Non Valvular AF

Ø who are at increased risk for stroke and systemic embolism based on CHADS$_2$ or CHA$_2$DS$_2$-VASc scores

Ø are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin

Ø taking into account the safety and effectiveness of the device compared to warfarin.
### AMPLATZER™ LAAO Clinical Data

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Centres</th>
<th>Main Findings</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008/2009</td>
<td>Initial European Registry¹</td>
<td>10 EU centres</td>
<td>Initial technical and safety study</td>
<td>N = 137</td>
</tr>
<tr>
<td>2009-2011</td>
<td>EU Prospective Observational Study²</td>
<td>15 EU centres</td>
<td>Improved safety confirmed learning curve effect</td>
<td>N = 204</td>
</tr>
<tr>
<td>2008-2013</td>
<td>Multicenter Study Experience</td>
<td>22 EU &amp; Can centres</td>
<td>Stroke reduction comparable to OAC therapy studies</td>
<td>N = 1047</td>
</tr>
<tr>
<td>2015 - 2016</td>
<td>Global Observational Study</td>
<td>61 global centres</td>
<td>Confirm Amulet occluder as safe alternative for stroke prevention in patients with non-valvular AF</td>
<td>N = 1088</td>
</tr>
</tbody>
</table>

### Physician-Driven Real-World Data

More than 8000 patient cases with AMPLATZER™ LAA Occluders published in over 200 papers with majority of patients implanted according to European guidelines (Unable to tolerate OAC)
2016 ESC Guidelines for the management of Atrial Fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC), Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC, Endorsed by the European Stroke Organisation (ESO)

Access to all treatment options for AF

Structured support for lifestyle changes
Anticoagulation
Rate control
Antiarrhythmic drugs
Catheter and surgical interventions (ablation, LAA occluder, AF surgery, etc.)
Complex management decisions underpinned by an AF Heart Team

Recommendation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>After surgical occlusion or exclusion of the LAA, it is recommended to continue</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>anticoagulation in at-risk patients with AF for stroke prevention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAA occlusion may be considered for stroke prevention in patient with AF and</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>contraindications for long-term oral anticoagulation treatment (e.g. those</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with a previous life-threatening bleed without reversible cause)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical occlusion of exclusion of the LAA may be considered for stroke</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>prevention in patients with AF undergoing open cardiac surgery.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical occlusion or exclusion of the LAA may be considered for stroke</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>prevention in patients with AF undergoing thoracoscopic AF surgery.</td>
<td></td>
<td></td>
</tr>
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</table>

Percutaneous LAAO vs. OAC: A propensity score matched study of 1000 patients with atrial fibrillation

Predefined endpoints, intention to treat analysis:
- Primary safety endpoint: All major procedural adverse events and major or life-threatening bleeding
- Primary efficacy endpoint: Stroke, systemic embolism and cardiovascular/unexplained death.
- Combined hazard endpoint (net clinical benefit): Combination of all above mentioned hazards.

**PRIMARY ENDPOINT**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LAAC (n=500)</th>
<th>OAC (n=500)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Safety Endpoint</td>
<td>3.6</td>
<td>4.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>5.6</td>
<td>7.8</td>
<td>0.026</td>
</tr>
<tr>
<td>Combined Hazard endpoint</td>
<td>8.1</td>
<td>10.9</td>
<td>0.018</td>
</tr>
</tbody>
</table>

**MORTALITY**

<table>
<thead>
<tr>
<th>Cause</th>
<th>LAAC (n=500)</th>
<th>OAC (n=500)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>8.3</td>
<td>11.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Cardiovascular and unexplained death</td>
<td>4</td>
<td>6.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>4.3</td>
<td>5.1</td>
<td>0.032</td>
</tr>
</tbody>
</table>
72% Major Bleeding Reduction Long Term Post-Implant

**Post Procedure Therapy**
- Warfarin + ASA (81mg) daily
- Clopidogrel (75mg) + ASA (325 mg) daily

**Destination Therapy**
- ASA (325mg) daily

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Implant | 45 days* | 6 months
EWOLUTION – OAT at Follow-Up

Pts with known medication: N = 997

Pts without FU information: N = 52

Pts with first medication discontinuation info: N = 945

Post-implant

- sAPT: 27%
- DAPT: 60%
- none: 6%
- OAC: 7%

After first discontinuation

- sAPT: 9%
- DAPT: 8%
- none: 28%
- OAC: 55%

OAC drop within 3 mo
DAPT drop within 6 mo

These data are for the full cohort of patients, 73% of whom may be contraindicated in the US per current labeling.

Boersma LVA, et al. HR32017, Late Breaking Clinical Trials: Chicago, IL, USA.
post-procedural medication: approval status

- WATCHMAN
  - dual antiplatelet (outside US)
  - NOAC (outside US)
  - warfarin 45 days - DAPT
    6mo - ASA (worldwide)

- AMULET
  - dual antiplatelet (outside US)

prospective data on > 1000 patients
Left Atrial Appendage Occlusion – New Indications

✓ Recurrent ischemic stroke despite well-controlled OAC
✓ Previous intracranial hemorrhage
✓ Recurrent GI bleeding
✓ Intolerance to new OAC drugs
✓ Coagulopathies

Clinical experts opinion; Europace 2013
Percutaneous Left Atrial Appendage Occlusion

- Access transfemoral (no open heart surgery)

Permanent implant
Performed in a cardiac cath/EP lab
Performed by EP/IC
Performed under general anesthesia or sedation
Procedure lasts approx. 1 hour
Hospital stay 1–2 days
LAA Occlusion Onassis Center Experience

- 14 procedures of LAA occlusion
- Patients Mean Age: 73 years
- CHA2DS2-VASc score: 5,1
- HAS-BLED score: 4,3
Clinical Indications for LAA Occlusion

- 22%
- 14%
- 14%
- 50%

Medical Treatment after LAA Occlusion

- AF - ΑΕΕ ΥΠΟ ΑΝΤΙΠΗΚΤΙΚΗ ΑΓΩΓΗ
- AF - ΥΠΟ ΑΝΤΙΠΗΚΤΙΚΗ ΑΓΩΓΗ - ΑΙΜΟΡΡΑΓΙΑ ΠΕΠΤΙΚΟΥ
- AF - ΑΙΜΟΡΡΑΓΙΚΟ ΑΕΕ - ΥΠΟΣΚΛΗΡΙΔΙΟ ΑΙΜΑΤΩΜΑ
- AF - ΥΠΟ ΑΝΤΙΠΗΚΤΙΚΗ ΑΓΩΓΗ - ΔΥΣΑΝΕΞΙΑ ΣΤΑ ΑΝΤΙΠΗΚΤΙΚΑ

Graph:
- DAPT
- OAC
- OAC + APT
Conclusions

✓ LAA occlusion is a safe and effective procedure

✓ after appropriate operator training

✓ Long-term follow-up results showed lower rates

✓ of stroke

✓ significant bleedings
Thank You

AF - CVA

OAC treatment

LAA Occlusion