Left atrial appendage closure

P. Widimsky
P. Widimsky – Potential conflicts of interest

Occasional speakers honoraria / advisory boards:
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Daiichi Sankyo
- Novartis
- Pfizer
- Servier
**Left atrial appendage**

- Complex structure with effective contractions during sinus rhythm, contractions disappear during AF
- Variable shape and size (volume, length, width, orifice size)

- Neurohumoral activity: atrial natriuretic factor (ANF, ANP) secretion in response to ↑ atrial volume / pressure → vasodilator and diuretic activity → ↓ blood pressure.
  - (X brain natriuretic peptide – similar, produced by ventricles).

- LAA visualization: TEE, CT, MR
- 92% of LA thrombi are localized in the LAA!
Morphologies (Di Biase et al.):

- cactus (30%)
- chicken wing (48%)
- cauliflower (3%)
- windsock (19%)
Why LAA occlusion?

• LAA is frequent source of systemic emboli

• Occlusion or removal of LAA may decrease the risk of systemic embolization

• It may be an alternative to OAC in patients with high bleeding risk

• It may be an additional treatment on top of OAC to reduce the risk of stroke
Types of occluders
Watchman™, Boston Scientific
AtriClip® (AtriCure)

Surgical (epicardial) LAA ligation
Potential indications for LAA occlusion in patients with AF

Secondary stroke prevention:
- Failed OAC: ischemic stroke in patients using OAC
- Severe bleeding occurred during OAC treatment
- Alternative to OAC in patients with high bleeding risk
- On top of OAC to further decrease risk of stroke recurrence

Primary stroke prevention:
- High bleeding risk AND high risk of stroke
Case from our center
Male, 61 years with 3 small strokes while on 3 different antithrombotic drugs

- 3/2010 first AF paroxysm, CHA$_2$DS$_2$-VASc = 0, → ASA alone.
- 12/2010 TIA on aspirin → warfarin (INR 2.3 on 6.5 mg/d)
- 2/2012 TIA on warfarin → dabigatran 300 mg/d
- 1/2015 small ischemic stroke on dabigatran, TEE: spontaneous contrast in LAA
- 6/2015 LAA closure
Published evidence
Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: PROTECT AF trial.


- Nonvalvular AF + CHADS$_2$ $\geq 1$, f-u 4 yrs.
- LAA occluder (n = 463) or warfarin target INR 2-3 (n = 244).

![Graph showing comparison between Watchman and Warfarin for Stroke/ sys. embolism/ death and Mortality with RR 0.60; 95% CI 0.41-1.05 and HR 0.66; 95% CI 0.45-0.98; P = .04.]

**Watchman**

**Warfarin**
A = Watchman (n=269)
B = Warfarin (n=138).

Complications: 2.2% (Watchman arm)

Pericardial effusions requiring surgical repair 0.4% (those requiring pericardiocentesis 1.5%)

PREVAIL trial
CHADS2 ≥2 and CHADS2=1 patients not eligible for aspirin therapy alone
Composite of stroke, systemic embolism, and cardiovascular/ unexplained death
Holmes et al. JACC 2014 Jul 8;64(1):1-12

![Graph showing stroke/systemic embolism/death and stroke/systemic embolism >7 days post randomization](image)
LAA Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis.

*Holmes et al. JACC 2015; 65: 2614-23.*

- 2406 pts from the PROTECT AF and PREVAIL trials, and their registries. Mean follow-up 2.7 years.
- Watchman: fewer hemorrhagic strokes, but more ischemic strokes in the device group.
- Watchman: fewer cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; p = 0.006)
- Watchman: fewer nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin.
LAAO for stroke prevention in AF: a systematic review and network meta-analysis of randomized controlled trials

Hanif H et al., J Cardiovasc Surg (Torino) 2018

Network meta-analysis (NMA) of randomized trials evaluating the efficacy of LAA occlusion compared with oral anticoagulant, antiplatelet, and placebo for stroke prevention.

Impact of LAA occlusion on mortality, major bleeding, and operative time.

Trend towards reduction in stroke (OR 0.84, 95% CrI 0.47-1.55) and mortality (OR 0.69, 95% CrI 0.44-1.10) for LAA occlusion versus warfarin, but no statistically significant effect.

LAA occlusion appears to preserve the benefits of OAC therapy for stroke prevention in patients with AF, but the current evidence is of low quality.
Outcomes and costs of LAAO from randomized trial and real-world experience relative to oral anticoagulation.

_Panniker S et al., Eur Heart J 2016_

Registry of LAAO from two centres (n=110). Follow-up 2 years.
Pts suitable and unsuitable for long-term OAC, CHA₂DS₂VASc 4.5 ± 1.6, and HAS-BLED 3.8 ± 1.1

Procedural success rate 92%.
Annual rates: stroke 0.9%, major bleeding 0.9%, all-cause mortality 1.8%.
Anticoagulant therapy was successfully stopped in 91% of implanted patients by 12 months.

Registry study stroke and major bleeding rates were lower than PROTECT AF results

Left atrial appendage closure achieved cost parity between 4.9 years vs. dabigatran 110 mg and 8.4 years vs. warfarin. At 10 years, LAAC was cost-saving against all therapies.
Bleeding After LAAO Compared With Long-Term Warfarin: Analysis of the WATCHMAN Randomized Trials.

*Price MJ et al., JACC Cardiovasc Interv 2015*

1,114 patients, median follow-up of 3.1 years.

No difference in major bleeding rate from randomization to the end of follow-up: 3.5 events vs. 3.6 events per 100 patient-years.

LAA closure significantly reduced bleeding >7 days post-randomization (1.8 events vs. 3.6 events per 100 patient-years), with the difference emerging 6 months after randomization (1.0 events vs. 3.5 events per 100 patient-years), when patients assigned to LAA closure were able to discontinue adjunctive oral anticoagulation and antiplatelet therapy.
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)

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www.escardio.org/guidelines

European Heart Journal - doi:10.1093/eurheartj/ehw210
Stroke prevention in atrial fibrillation

Mechanical heart valves or moderate or severe mitral stenosis

Yes

No

Estimate stroke risk based on number of CHA2DS2-VASc risk factors

0a

No antiplatelet or anticoagulant treatment (IIbB)

1

OAC should be considered (IIaB)

≥ 2

Oral anticoagulation indicated
Assess for contra-indications
Correct reversible bleeding risk factors

LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)

NOAC (IA)b

VKA (IA)c

a Includes women without other stroke risk factors
b IIaB for women with only one additional stroke risk factor
c IB for patients with mechanical heart valves or mitral stenosis
Main characteristics and outcomes in the PROTECT-AF trial comparing LAAO and warfarin

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized, unblinded (2:1)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>707</td>
</tr>
<tr>
<td>Follow-up period, years</td>
<td>2.3</td>
</tr>
<tr>
<td>Randomized treatments</td>
<td>Dose-adjusted warfarin or Watchman® left atrial appendage occlusion device (LAAO)</td>
</tr>
</tbody>
</table>

| Baseline patient characteristics               |               |
| Age, years (mean ± SD)                         | Warfarin: 73 ± 9; LAAO: 72 ± 8 years |
| Male sex, %                                    | Warfarin: 70%; LAAO: 70 |
| CHADS2 (mean)                                  | Warfarin: 2.3; LAAO: 2.2 |

| Outcomes                                       |               |
| Events per 100 patient-years (rate ratio and 95% credible interval) | Warfarin (n = 244) | LAAO device (n = 463) |
| All stroke                                    | 2.7 (1.5–4.1) | 2.0 (1.3–3.1) |
| Ischaemic stroke                               | 1.4 (0.6–2.4) | 1.9 (1.1–2.9) |
| Haemorrhagic stroke                            | 1.2 (0.5–2.3) | 0.3 (0.1–0.7) |
| Mortality                                      | 4.5 (2.8–6.2) | 3.2 (2.3–4.5) |

CHADS2 = congestive heart failure, hypertension, age ≥75, diabetes, prior stroke or transient ischaemic attack (2 points); LAAO = left atrial appendage occlusion device; PROTECT-AF = System for Embolic PROTECTION in patients with Atrial Fibrillation; SD = standard deviation.
### Occlusion or exclusion of the left atrial appendage

<table>
<thead>
<tr>
<th>Recommendations</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 anticoagulation in at-risk patients with AF for stroke prevention.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
Initiation or resumption of anticoagulation in atrial fibrillation patients after an intracranial bleed

Patient with AF suffering from an intracranial bleed on OAC
If acute event: establish intensity of anticoagulation (see bleeding flow chart)

Contra-indication for OAC

Factors favouring withholding of OAC:
- Bleeding occurred on adequately dosed NOAC or in setting of treatment interruption or underdosing
- Older age
- Uncontrolled hypertension
- Cortical bleed
- Severe intracranial bleed
- Multiple microbleeds (e.g. >10)
- Cause of bleed cannot be removed or treated
- Chronic alcohol abuse
- Need for dual antiplatelet therapy after PCI

Factors supporting reinitiation of OAC:
- Bleeding occurred on VKA or in setting of overdose
- Traumatic or treatable cause
- Younger age
- Well controlled hypertension
- Basal ganglia bleed
- No or mild white matter lesions
- Surgical removal of subdural haematoma
- Subarachnoid bleed: aneurysm clipped or coiled
- High-risk of ischaemic stroke

Consider further information to allow informed judgement

Patient or next of kin choice informed by multidisciplinary team advice

Initiate or resume OAC, choosing an agent with low intracranial bleeding risk, after 4–8 weeks (IIbB)

This approach is based on consensus within the Task Force, not on evidence.

NOAC: non-vitamin K antagonist oral anticoagulants
VKA: vitamin K antagonist
OAC: oral anticoagulation
PCI: percutaneous coronary intervention
LAA: left atrial appendage
IIb: recommendation grade
IIc: recommendation grade
Perspectives

• Longer follow-up (>5 years) may favor LAA occlusion as its complications occur early after implantation, while bleeding complications after OAC occur constantly over time.

• Randomized comparisons device vs. NOAC needed

• Randomized comparisons device vs. endoscopic epicardial surgical LAA closure needed
Interventional left atrial appendage closure vs novel anticoagulation agents in patients with atrial fibrillation indicated for long-term anticoagulation (PRAGUE-17 study)

Pavel Osmancik, MD, PhD, a Petr Tousek, MD, PhD, a Dalibor Herman, MD, PhD, a Petr Neuzil, MD, CSc, b Pavel Hala, MD, b Josef Stasek, MD, PhD, c Ludek Haman, MD, PhD, c Petr Kala, MD, PhD, d Martin Poloczek, MD, a Marian Branny, MD, PhD, e Jan Chovanec, MD, c Pavel Cervinka, MD, PhD, f Jiri Holy, MD, f Vlastimil Vancura, MD, PhD, g Richard Rokya, MD, PhD, g Milos Taborsky, MD, CSc, h Tomas Kovarnik, MD, PhD, i David Zemanek, MD, PhD, i Petr Peichl, MD, PhD, i Sarka Haskova, Eng, k Jiri Jarvovsky, Eng, k and Petr Widimsky, MD, DrSc a, on behalf of the PRAGUE-17 Investigators Prague, Prague, Brno, Trinec, Usti nad Labem; Pilsen, University Hospital Olomouc, General Faculty Hospital, Prague, and Brno, Czech Republic

Background Atrial fibrillation (AF), with a prevalence of 1% to 2%, is the most common cardiac arrhythmia. Without antithrombotic treatment, the annual risk of a cardioembolic event is 5% to 6%. The source of a cardioembolic event is a thrombus, which is usually formed in the left atrial appendage (LAA). Prevention of cardioembolic events involves treatment with anticoagulant drugs: either vitamin K antagonists or, recently, novel oral anticoagulants (NOAC). The other (nonpharmacologic) option for the prevention of a cardioembolic event involves interventional occlusion of the LAA.

Objective To determine whether percutaneous LAA occlusion is noninferior to treatment with NOAC in AF patients indicated for long-term systemic anticoagulation.

Study design The trial will be a prospective, multicenter, randomized noninferiority trial comparing 2 treatment strategies in moderate to high-risk AF patients (ie, patients with history of significant bleeding, or history of cardiovascular event[s], or a with CHA2DS2-VASc ≥3 and HAS-BLED score ≥2). Patients will be randomized into a percutaneous LAA occlusion [group A] or a NOAC treatment [group B] in a 1:1 ratio; the randomization was done using Web-based randomization software. A total of 396 study participants (198 patients in each group) will be enrolled in the study. The primary end point will be the occurrence of any of the following events within 24 months after randomization: stroke or transient ischemic attack (any type), systemic cardioembolic event, clinically significant bleeding, cardiovascular death, or a significant periprocedural or device-related complications.

Conclusion The PRAGUE-17 trial will determine if LAA occlusion is noninferior to treatment with NOAC in moderate- to high-risk AF patients. [Am Heart J 2017;183:108-14.]