Symposium annuel
Centre cérébrovasculaire – CHUV

Fermeture du FOP et de l’auricule

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Service de cardiologie CHUV
PFO closure
RCTs PFO closure

- **Closure-1 (2002)**: 909 patients
- **PC Trial (2012)**: 414 patients
- **RESPECT (2013)**: 980 patients
- **RESPECT (2017)**: 980 patients
- **CLOSE (2017)**: 663 patients
- **REDUCE (2017)**: 664 patients
- **DEFENSE-PRO (2018)**: 120 patients

Timeline from 2000 to 2022.
Study design initial trials

Cryptogenic stroke with evidence of PFO

Exclusion criteria

Randomization

Percutaneous Closure

Medical Treatment

Stroke/TIA and death (all cause mortality) +/- embolism
Closure-1

Closure not superior to medical therapy

![Graph showing probability of primary end point over days since baseline.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days since Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closure</td>
<td>447 411 406 399 392 389 384 380 254</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>462 421 405 388 378 365 359 356 242</td>
</tr>
</tbody>
</table>

NS
PC trial

Closure not superior to medical therapy

Hazard ratio, 0.63 (95% CI, 0.24–1.62)
P = 0.34

No. at Risk
Medical therapy 210
PFO closure 204

Years since Randomization

Patients with Primary End Point (%)
RESPECT trial (FU 2.6 y)

Closure not superior to medical therapy

A Intention-to-Treat Cohort

Event-free Probability

Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test

Years to Event

Closure group (N=9)
Medical-therapy group (N=16)
NS
RCTs PFO closure

- 2012: Closure-1
  - 909 patients
  - Negative

- 2013: PC Trial
  - 414 patients
  - Negative

- 2013: RESPECT
  - 980 patients
  - Negative
Closure-1, PC and RESPECT

• High crossover between groups

• Failure to randomise those patients whose strokes were likely to have been caused by PFO

• Inconsistent use of anticoagulants in the medical therapy group

• STARFlex occluder concerns (residual defects and left-sided thrombus formation)
RESPECT trial extended FU (5.9 y)

Reduction in ischaemic stroke NNT = 45

Significant
RCTs PFO closure

- **Closure-1** (2012): 909 patients, Negative
- **PC Trial** (2013): 414 patients, Negative
- **RESPECT** (2013): 980 patients, Negative
- **RESPECT** (2017): 980 patients
- **CLOSE** (2017): 663 patients, Positive
- **REDUCE** (2017): 664 patients
- **DEFENSE-PRO** (2018): 120 patients
Study design: recent trials

Cryptogenic stroke with evidence of PFO, ASA, large PFO

Exclusion criteria: Lacunar stroke

Randomization

Percutaneous Closure

Medical Treatment

Stroke/TIA and death (all-cause mortality) +/- embolism
REDUCE trial

Reduction in ischaemic stroke NNT = 25

Hazard ratio for recurrent stroke, 0.23 (95% CI, 0.09–0.62)
P = 0.002 by log-rank test

Significant
CLOSE trial

Reduction in ischaemic stroke NNT = 17

Significant
Defense Pro Trial

Reduction in stroke, vascular death and major bleeding NNT=8
RCTs PFO closure

- **2012**: Closure-1 (909 patients) - Negative
- **2013**: PC Trial (414 patients) - Negative
- **2017**: RESPECT (980 patients) - Positive
- **2017**: CLOSE (663 patients) - Positive
- **2017**: REDUCE (664 patients) - Positive
- **2018**: DEFENSE-PRO (120 patients) - Positive
Pooled Individual Patient Data

Log-rank $P < .001$

Patients with recurrent ischemic stroke, %

- **Medical therapy**
- **Device**

No. at risk
- **Device**: 1889, 1771, 1338, 1245, 1155, 854, 365, 262
- **Medical therapy**: 1851, 1668, 1194, 1094, 971, 699, 390, 253

Kent, JAMA, 2021
**RoPE score** (Risk of Paradoxical Embolism)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Total score (sum of individual points)**

- Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct): 10
- Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct): 0

Kent, Neurology, 2013
Validation of RoPE score

AUC-ROC = 0.75

Probability of stroke caused by PFO

Observed frequency of PFO

PFO prevalence in the general population

RoPE score

0-3 4 5 6 7 8 9-10

PFO likely incidental

PFO likely pathogenic of stroke

Rate of new incident atrial fibrillation at 10-year follow-up

20%

3%

Strambo, Stroke, 2021
# PASCAL (PFO-Associated Stroke Causal Likelihood)

<table>
<thead>
<tr>
<th>Risk source</th>
<th>Features</th>
<th>RoPE Score</th>
<th>Low(^b) &lt; 7</th>
<th>High(^b) ≥ 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>A PFO and a straddling thrombus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>A small-shunt PFO without an atrial septal aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) RoPE score ranges can be adjusted based on clinical judgment.
Points still unclear

- Neurologist
- Brain 6 Neck Imaging
- Echo TT
- Holter
- Blood tests

Cardioembolic stroke associated with patent foramen ovale

- Transesophageal echocardiography?
Transesophageal echocardiography

- Atrial septal defect
- Atrial myxoma, Fibroelastoma
- Aortic arch atheroma,
- Small aortic or mitral valvular vegetations
Points still unclear

- Neurologist
- Brain 6 Neck Imaging
- Echo TT
- Holter
- Blood tests

Cardioembolic stroke associated with patent foramen ovale

Transesophageal echocardiography?

Long term cardiac monitoring?
Afib detection

CRYSTA – AF (6 M)

61 yo

EMBRACE (30 D)

73 yo

↑ 6 X Afib Detection

↑ 5 X Afib Detection
Conclusions: Benefit – risk of PFO closure

The Benefit
- Annualized incidence of stroke
  - Medical therapy: 1.09%
  - Device closure was 0.47% (- 60%)

The Risk
- Incidence of atrial fibrillation
  - Medical therapy: 0.8%
  - Device closure was 2.4% (x 3)

FU 57 months (> 45 days)
LAA Closure
Recommendations for occlusion or exclusion of the LAA

LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).  

Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.
Rational of LAA closure

• Studies have reported that the LAA is the source of thrombus in about 90% of nonvalvular AF and 57% of valvular AF
Atrial Fibrillation: OAC

- \( \text{CHA}_2 \text{DS}_2 \text{VAS}_c \geq 1 \text{(M)} > 1 \text{(F)} \)

- Calculate HAS-BLED score
  - HAS-BLED \( \geq 3 \)
    - Flag up
    - Regular review

- Modifiable bleeding risk factors
  - Modify risk factors

- DOAC
**Bleeding Score: HAS-BLED**

**Table 10: Clinical risk factors in the HAS-BLED score**

<table>
<thead>
<tr>
<th>Risk factors and definitions</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Uncontrolled hypertension</td>
<td>1</td>
</tr>
<tr>
<td>SBP &gt;160 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal and/or hepatic function</td>
<td>1</td>
</tr>
<tr>
<td>Dialysis, transplant, serum creatinine &gt;200 μmol/L, cirrhosis, bilirubin &gt; × 2 upper limit of normal, AST/ALT/ALP &gt;3 × upper limit of normal</td>
<td>1 point for each</td>
</tr>
<tr>
<td><strong>S</strong> Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Previous ischaemic or haemorrhagic⁸ stroke</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Previous major haemorrhage or anaemia or severe thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td><strong>L</strong> Labile INR⁹</td>
<td>1</td>
</tr>
<tr>
<td>TTR &lt;60% in patient receiving VKA</td>
<td></td>
</tr>
<tr>
<td><strong>E</strong> Elderly</td>
<td>1</td>
</tr>
<tr>
<td>Aged &gt;65 years or extreme frailty</td>
<td></td>
</tr>
<tr>
<td><strong>D</strong> Drugs or excessive alcohol drinking</td>
<td>1</td>
</tr>
<tr>
<td>Concomitant use of antiplatelet or NSAID; and/or excessive⁵ alcohol per week</td>
<td>1 point for each</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td>9</td>
</tr>
</tbody>
</table>
A high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients.
What is the indication for the left atrial appendage (LAAC) closure?
Anticoagulation in Atrial Fibrillation

DOAC

Apixaban (ARISTOTLE)
Edoxaban (ENGAGE AF TIMI 48)
Rivaroxaban (ROCKET-AF)
Dabigatran (RE-LY)

Vit K ant.

DAPT

Aspirine + clopidogrel (ACTIVE W + A)

Aspirin
PROTECT AF + PREVAIL

1114 patients

1 X Warfarin

0 D

45 D

6 M

2 X LAAC

Warfarin + Aspirine

Clopidogrel + Aspirine

Aspirine

PROTECT: CHADS2 ≥ 1
PREVAIL: CHADS2 ≥ 1 + 1 risk factor
PREVAIL: CHADS2 ≥ 2
HAS-BLED: 60-70% 1-2
PROTECT AF and PREVAIL

5 years follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.82</td>
<td>0.3</td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.96</td>
<td>0.9</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.0022</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Disabling/Fatal Stroke (MRS change of ≥2)</td>
<td>0.45</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-Disabling Stroke</td>
<td>1.37</td>
<td>0.35</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.59</td>
<td>0.03</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>0.91</td>
<td>0.6</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.48</td>
<td>0.0003</td>
</tr>
</tbody>
</table>
Net Clinical Benefit

Outcomes

- All death events irrespective of cause
- Ischemic stroke
- Intracranial hemorrhage
- Major extracranial bleeding and the
  major procedural complication
- Pericardial effusion
Anticoagulation in Atrial Fibrillation

DOAC > Vit K ant. > DAPT > Aspirin

Apixaban (ARISTOTLE)
Edoxaban (ENGAGE AF TIMI 48)
Rivaroxaban (ROCKET-AF)
Dabigatran (RE-LY)

Aspirine + clopidogrel (ACTIVE W + A)
415 patients

1 X DOAC

1 X LAAC

0 D

3 M

Clopidogrel + Aspirine

Aspirine
PRAGUE-17 results

- 402 High-Risk AF Pts → Randomized
  - CHA₂DS₂-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Follow-up: 20.8 ± 10.8 mo (695 pt-year)

Primary Endpoint
Stroke, TIA, SE, CV Death, Bleeding, or Complications

![Graph showing cumulative incidence over time for LAAC and DOAC]

Non-inferiority: \( p = 0.004 \)

CHAMPION-AF Clinical Trial

3000 Patients
150 Sites

Randomization 1:1

WATCHMAN FLX

5 Year Follow-Up

2025

NOAC
Anticoagulation in Atrial Fibrillation

DOAC > Vit K ant.  > DAPT  > Aspirin

Maybe

Should be considered
Absolute contraindications to oral anticoagulants

- Severe thrombocytopenia <50 platelets/μL,
- Recent high-risk bleeding event
  - Intracranial haemorrhage (ICH)
  - GI bleeding such angiodysplasia
- Iterative DAPT
- Renal failure with contraindication to DOAC