Clinical Insights

A PUBLICATION DELIVERING CONCISE CLINICAL DATA

AMPLATZER™ PFO OCCLUDER

EUROPEAN POSITION PAPER ON THE MANAGEMENT OF PATIENTS WITH PATENT FORAMEN OVALE (PFO) – OVERVIEW OF KEY POSITION STATEMENTS AND UNDERLYING CLINICAL EVIDENCE

SUMMARY AND POSITION STATEMENT ON PERCUTANEOUS PFO CLOSURE

The European position paper on the management of patients with a PFO is a publication from an international group of experts in various clinical disciplines and with involvement of 8 European scientific societies. The paper represents the first largely shared, rational position statements on the management of patients with PFO and left circulation thromboembolism, based on the best available evidence. Evidence-based key statements are provided regarding the types of patients in whom percutaneous PFO closure is expected to achieve superior outcomes over medical therapy.

Among the most common devices for PFO closure, the paper identifies the Amplatzer™ PFO Occluder as the device achieving the highest rate of complete closure and associated with the lowest rate of post-procedural new-onset atrial fibrillation (AF), similar to medical therapy. The choice of device should take into consideration that most available evidence has been obtained with the Amplatzer PFO Occluder and GORE® HELEX® Septal Occluder (not available anymore) or the GORE® CARDIOFORM Septal Occluder. The use of the latter should be balanced against a lower complete closure rate and a higher risk of AF as compared to medical therapy.

SUMMARY OF POSITION STATEMENT ON PERCUTANEOUS PFO CLOSURE FOR SECONDARY STROKE PREVENTION	
Patients	Perform percutaneous PFO closure in carefully selected patients between 18 to 65 years of age, with confirmed cryptogenic stroke, TIA, or systemic embolism and an estimated high probability of a causal role of the PFO.
	Consider percutaneous PFO closure in patients >65 years or <18 years, taking into account on a case-by-case basis, the lack of evidence, age-related confounders and additional risks of interventional and drug therapies.
	Consider percutaneous PFO closure in patients with a cryptogenic stroke, TIA, or systemic embolism that occurred while on oral anticoagulants (OAC) or antiplatelet therapy.
Devices	Currently available devices with which most of the available evidence has been obtained: - Amplatzer PFO Occluder - GORE CARDIOFORM‡ septal occluder
	Amplatzer™ PFO Occluder: - May have lower residual shunt rates than other devices - Low rate of new-onset AF, similar to medical therapy
	Other devices, including their inherent risks, should be part of shared decision making with patients, considering technical, anatomical and clinical features.
Evidence	Statements are supported by the evidence presented in this summary, specifically: - Superiority of PFO closure over medical therapy for stroke prevention in the first 5 years after the procedure. - Anticipated increasing benefit of PFO closure over medical therapy at longer follow-up periods. - Compared to medical therapy, percutaneous PFO closure does not imply higher complication rates, except more frequent new-onset AF. The risk of new-onset AF was similar with the Amplatzer PFO Occluder and medical therapy while it was higher for the GORE CARDIOFORM‡ device when compared with medical therapy. - PFO closure and medical therapy have similar bleeding risk in the short term. Bleeding risk of medical therapy is likely to increase over long-term follow-up in patients growing older while on lifelong medical treatment.
	Outcomes from patients with high-risk PFO features (ASA, moderate-to-severe shunt, large PFO size) are the main drivers of the evidence. Risk assessment (i.e. is the patient at relatively low or high risk of PFO-mediated stroke recurrence) should be part of carefully informed choices which must be shared with patients and tailored to their personal values and preferences.
	Consistent results of all meta-analyses performed so far were confirmed when considering odds ratios, relative risks and attributable risks and sensitivity analysis, and also when including results from CLOSURE I, which is the most outdated trial. The certainty of the evidence is higher in patients with high-risk PFO features. Future studies are not likely to impact on the certainty of the evidence, at least not in high-risk populations.

UNDERLYING CLINICAL EVIDENCE

To evaluate the available evidence, scientific literature was reviewed and meta-analyses were performed regarding specific research questions. Statements were developed following a strict evidence-based process using GRADE[1] methodology and answering PICO[2] and non-PICO questions. The strength of the position statements was labeled as either 'strong' (printed in blue in this summary) or 'conditional' (printed in green), based on the consistency of the evidence supporting the statement.

DEFINITIONS	
Cryptogenic ischemic left circulation embolism	Any definite (symptomatic or asymptomatic) ischemia occurring in an arterial bed which lacks a known cause despite investigation.
PFO-related embolism	Embolism for which a PFO is thought likely to be implicated (only an event without clear PFO involvement should be labeled cryptogenic embolism).

ASPECTS GUIDING CLINICAL MANAGEMENT

To guide assessment and treatment of a PFO, aspects to be assessed include:

- The probability of a causative role of the PFO in the observed clinical picture.

- The probability of recurrence of the observed clinical event.

Probability of causative role of PFO

There are no single clinical, anatomical or imaging characteristics allowing a quantitative estimation of the role of PFO in left circulation thromboembolism. Instead, critical interdisciplinary clinical judgement of these characteristics should assess the role of PFO on an individual patient basis. The presence of other risk factors does not exclude the role of PFO. Aspects listed below are linked to a causative role of PFO in left circulation embolism.

ASPECTS LINKED TO A CAUSATIVE ROLE OF PFO IN LEFT CIRCULATION EMBOLISM	
Cortical infarcts are commonly embolic.	White matter infarcts can also, less frequently, be embolic.
Atrial septal aneurysm, shunt severity and atrial septal hypermobility.	Simultaneous pulmonary embolism and/or deep vein thrombosis.

The risk of paradoxical embolism (RoPE) score may be helpful to guide management decisions, but this score should always be used in conjunction with other evaluations, given the limited evidence for validation of the RoPE score.

Probability of recurrence

Observational and randomized studies suggest a recurrence rate after a PFO-associated stroke ranging from 0% to 5.8%, including PFO-mediated and non-PFO-mediated recurrences. The risk of recurrence should be estimated based on variables shown in the table below. Of these aspects, especially the presence of an atrial septal aneurysm and coagulation disorders are conditional indicators of an increased recurrence risk.

VARIABLES LINKED TO HIGHER RECURRENCE RATES IN PATIENTS WITH PFO
Presence of atrial septal aneurysm and/or PFO size
Older age
Coagulation disorders
Stroke at index
D-dimer >1,000 at admission
Use of aspirin vs. oral anticoagulation (OAC)

[1]GRADE: grading of recommendations assessment, development and evaluation
[2]PICO: population, intervention, comparator, outcome

DIAGNOSTIC WORKUP

If the probabilities of a causative role of PFO and of recurrence are both high, PFO closure should be advised. Low probabilities indicate consideration of medical therapy. Intermediate probabilities require further clinical judgement. As part of a diagnostic workup to support the choice of PFO closure versus permanent OAC, it is recommended to rule-out AF and consider concomitant diseases.

Ruling-out AF

Given the fact that recurrences of left circulation embolism are predominantly due to left atrial appendage thrombosis, rather than to paradoxical embolism, maximum diagnostic efforts should be undertaken to rule-out AF as a risk factor and/or to weigh embolic risks related to AF versus those related to PFO. Therefore, it is strongly recommended to obtain a 12-lead ECG and perform either in-patient cardiac telemetry or 24-hour Holter monitoring. The use of an insertable cardiac monitor (ICM) should be considered to increase the chance of detecting AF (see recommendations below).

RECOMMENDATIONS REGARDING THE USE OF AN ICM TO DETECT AF BEFORE DECIDING ON PFO CLOSURE
For patients with negative routine monitoring, ICM should be considered in the following situations: - Patients >65 years old - Patients 55 to 64 years old at risk for AF - Patients <55 years old with ≥2 high-risk factors for AF
ICM can be withheld for patients with clear evidence of causal PFO, such as simultaneous pulmonary embolism.
The ICM evaluation period should be at least 6 months.
Medical therapy should be maintained during ICM.
ICM should be extended for the full duration of the device life, regardless of the choice of therapy after 6 months.

Concomitant diseases

In the case of concomitant diseases, the decision to close the PFO should include weighing the PFO embolic risk against embolic risks associated with other diseases (see table below).

MANAGEMENT OF PFO IN THE PRESENCE OF CONCOMITANT DISEASES
PFO assessment for possible closure is recommended for patients: - on temporary OAC - on OAC for pulmonary embolism - for those with high recurrence risk despite OAC
Current AF guidelines recommend OAC in case of paroxysmal AF episodes: - >30 second on intermittent recordings - ≥5 minutes during ICM
ICM results should be interpreted with other clinical characteristics.
Routine thrombophilia testing is not warranted to indicate permanent OAC.

MEDICAL TREATMENT

- Effectiveness:
  - By meta-analysis of randomized controlled trial data, the stroke recurrence rate on medical therapy was 4.6% at 3.8 years of follow-up.
  - A meta-analysis of observational studies showed a stroke recurrence rate on medical therapy of 5% per year.
- Safety:
  - A recent meta-analysis of observational studies showed a bleeding complication rate of 1.1%. This surprisingly low rate must be interpreted with caution. Follow-up was limited and patients were relatively young, while most of them will undergo lifelong medical therapy with the risk of bleeding increasing with age.
  - By meta-analysis of data from PFO patients, OAC was associated with a more than 4 times higher risk of major bleeding than antiplatelet therapy.
  - The potential benefit of OAC might be outweighed by the risk of intracranial and major extracranial hemorrhage.

PERCUTANEOUS PFO CLOSURE

Clinical data with regard to PFO closure shows the following:

- Effectiveness:
  - Primary technical success approaches 100%
  - Complete closure is observed in 93 to 96% at 1 year
  - Larger devices are associated with higher risk of residual shunts; the Amplatzer™ PFO Occluder may have lower residual shunt rates than other devices.
  - Randomized study data show a relative risk reduction for stroke recurrence of up to 80%.
  - By meta-analysis, PFO closure was associated with a recurrence rate of 2% at 3.8 years of follow-up.
  - The number needed to treat to prevent 1 stroke is 37 for any PFO patient, and 21 for patients with high-risk PFO features.
  - Relative risk reduction for transient ischemic attack (TIA) recurrence and death are similar between PFO closure and medical therapy.
  - An increase in treatment effects with longer follow-up periods can be expected.

- Safety:
  - In randomized controlled trials, the incidence of procedural complications was 2.6%.
  - Most frequent complications include residual shunt (10-15%), atrial arrhythmias (0.5 – 15%), device thrombosis (1 – 2%), pericardial effusion / tamponade (0.5 – 1%) and early device embolization (0.9 – 1.3%).
  - The risk of long-term mortality or the need for cardiac surgery is < 0.1%.
  - AF is the most frequent adverse event after percutaneous PFO closure:
    - In a meta-analysis of randomized controlled trials, the incidence of AF was 4.6% after 3.8 years of follow-up.
    - By meta-analysis for incident AF, the overall number needed to harm was 25.
    - Beyond 45 days after implantation, PFO closure was not associated with an increased risk for AF.
    - The incidence of AF was lowest with the Amplatzer™ PFO Occluder.

MANAGEMENT AFTER PERCUTANEOUS PFO CLOSURE

Consensus on management of patients after percutaneous PFO closure is summarized below.

MANAGEMENT AFTER PFO CLOSURE
Dual antiplatelet therapy for 1 – 6 months after PFO closure
Single antiplatelet therapy to be continued for at least 5 years
Single antiplatelet therapy to be continued beyond 5 years by considering the patient's overall stroke risk for other causes versus hemorrhagic risk
Choice and type of antiplatelet medication is currently empiric
Currently, there is no data indicating the value of residual shunt after PFO closure

REFERENCE

Pristipino C et al. European position paper on the management of patients with patent foramen ovale. EuroIntervention 2018; August 25, doi: 10.4244/EIJ-D-18-00622 [Epub ahead of print]

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