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.

SUMMARY OF POSITION STATEMENT ON PERCUTANEOUS PFO CLOSURE FOR SECONDARY STROKE PREVENTION

<table>
<thead>
<tr>
<th>Patients</th>
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<tbody>
<tr>
<td>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.</td>
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<td>Consider percutaneous PFO closure in patients &gt;65 years or &lt;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.</td>
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<tr>
<td>Consider percutaneous PFO closure in patients with a cryptogenic stroke, TIA, or systemic embolism that occurred while on oral anticoagulants (OAC) or antiplatelet therapy.</td>
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<tr>
<th>Devices</th>
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<tr>
<td>Currently available devices with which most of the available evidence has been obtained:</td>
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<tr>
<td>- Amplatzer PFO Occluder</td>
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<td>- GORE CARDIOFORM Septal Occluder</td>
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<tr>
<td>Amplatzer™ PFO Occluder:</td>
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<tr>
<td>- May have lower residual shunt rates than other devices</td>
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<tr>
<td>- Low rate of new-onset AF, similar to medical therapy</td>
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<td>Other devices, including their inherent risks, should be part of shared decision making with patients, considering technical, anatomical and clinical features.</td>
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<tr>
<th>Evidence</th>
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<td>Statements are supported by the evidence presented in this summary, specifically:</td>
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<tr>
<td>- Superiority of PFO closure over medical therapy for stroke prevention in the first 5 years after the procedure.</td>
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<td>- Anticipated increasing benefit of PFO closure over medical therapy at longer follow-up periods.</td>
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<tr>
<td>- 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.</td>
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<tr>
<td>- 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.</td>
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<td>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.</td>
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<tr>
<td>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.</td>
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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.

The Amplatzer™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

See Important Safety Information referenced within.
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 methodology and answering PICO 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.

<table>
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<tr>
<th>DEFINITIONS</th>
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<tr>
<td>Cryptogenic ischemic left circulation embolism</td>
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<tr>
<td>PFO-related embolism</td>
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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.

<table>
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<tr>
<th>ASPECTS LINKED TO A CAUSATIVE ROLE OF PFO IN LEFT CIRCULATION EMBOLISM</th>
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<tbody>
<tr>
<td>Cortical infarcts are commonly embolic.</td>
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<tr>
<td>Atrial septal aneurysm, shunt severity and atrial septal hypermobility.</td>
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</table>

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.

<table>
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<tr>
<th>VARIABLES LINKED TO HIGHER RECURRENCE RATES IN PATIENTS WITH PFO</th>
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<tr>
<td>Presence of atrial septal aneurysm and/or PFO size</td>
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<td>Older age</td>
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<td>Coagulation disorders</td>
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<tr>
<td>Stroke at index</td>
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<tr>
<td>D-dimer &gt;1,000 at admission</td>
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<tr>
<td>Use of aspirin vs. oral anticoagulation (OAC)</td>
</tr>
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See Important Safety Information referenced within.
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.

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

REFERENCE

IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

The AMPLATZER™ PFO Occluder device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

CONTRAINDICATIONS

- Patients with intra-cardiac mass, vegetation, tumor or thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the PFO is gained.
- Patients whose vasculature, through which access to the PFO is gained, is inadequate to accommodate the appropriate sheath size.
- Patients with anatomy in which the AMPLATZER™ PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.
- Patients with other source of right-to-left shunts, including an atrial septal defect and/or fenestrated septum.
- Patients with active endocarditis or other untreated infections.

WARNINGS

- Patients who are at increased risk for venous thromboembolic events should be managed with thromboembolic risk reduction regimen after the PFO Closure following standard of care.
- Do not use this device if the sterile package is open or damaged.
- Prepare for situations that require percutaneous or surgical removal of this device. This includes availability of a surgeon.
- Embolized devices must be removed as they may disrupt critical cardiac functions. Do not remove an embolized occluder through intracardiac structures unless the occluder is fully recaptured inside a catheter or sheath.
- Patients who are allergic to nickel can have an allergic reaction to this device.
- This device should be used only by physicians who are trained in standard transcatheter techniques.
- Transient hemodynamic compromise may be encountered during device placement, which may require fluid replacement or other medications as determined by the physician.
- Do not release the device from the delivery cable if the device does not conform to its original configuration, or if the device position is unstable or if the device interferes with any adjacent cardiac structure (such as Superior Vena Cava (SVC), Pulmonary Vein (PV), Mitral Valve (MV), Coronary Sinus (CS), aorta (AO)). If the device interferes with an adjacent cardiac structure, recapture the device and redeploy. If still unsatisfactory, recapture the device and either replace with a new device or refer the patient for alternative treatment.
- Ensure there is sufficient distance from the PFO to the aortic root or SVC (typically defined as 9 mm or greater as measured by echo).

PRECAUTIONS

- The safety and effectiveness of the AMPLATZER™ PFO Occluder has not been established in patients (with):
  - Age less than 18 years or greater than 60 years because enrollment in the pivotal study (the RESPECT trial) was limited to patients 18 to 60 years old.
  - A hypercoagulable state including those with a positive test for a anticardiolipin antibody (IgG or IgM), Lupus anticoagulant, beta-2 glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy.
  - Unable to take antikoagulant therapy.
  - Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels associated with a ≥50% luminal stenosis.
  - Acute or recent (within 6 months) myocardial infarction or unstable angina.
  - Left ventricular aneurysm or akinesis.
  - Mitral valve stenosis or severe mitral regurgitation irrespective of etiology.
  - Aortic valve stenosis (mean gradient greater than 40 mmHg) or severe aortic valve regurgitation.
  - Mitral or aortic valve vegetation or prosthesis.
  - Aortic arch plaques protruding greater than 4 mm into the aortic lumen.
  - A left ventricular dilated cardiomyopathy with left ventricular ejection fraction (LVEF) less than 35%.
  - Chronic, persistent, or paroxysmal atrial fibrillation or atrial flutter.
  - Uncontrolled hypertension or uncontrolled diabetes mellitus.
  - Diagnosis of lacunar infarct probably due to intrinsic small vessel as qualifying stroke event.
  - Arterial dissection as cause of stroke.
  - Index stroke of poor outcome (modified Rankin score greater than 3).
  - Pregnancy at the time of implant.
  - Multi-organ failure.
- Use on or before the last day of the expiration month that is printed on the product packaging label.
- This device was sterilized with ethylene oxide and is for single use only. Do not reuse or re-sterilize this device. Attempts to re-sterilize this device can cause a malfunction, insufficient sterilization, or harm to the patient.
- The AMPLATZER™ PFO Occluder device consists of a nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device for a minimum of 60 days. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. Certain allergic reactions can be serious; patients should be instructed to notify their physicians immediately if they suspect they are experiencing an allergic reaction such as difficulty breathing or inflammation of the face or throat. Some patients may also develop an allergy to nickel if this device is implanted.
- Store in a dry place.
- Pregnancy – Minimize radiation exposure to the fetus and the mother.
- Nursing mothers – There has been no quantitative assessment for the presence of leachables in breast milk.

ADVERSE EVENTS

Potential adverse events that may occur during or after a procedure using this device may include, but are not limited to: Air embolus; Allergic drug reaction; Allergic dye reaction; Allergic metal reaction; Nitinol (nickel, titanium), platinum/iridium, stainless steel (chromium, iron, manganese, molybdenum, nickel); Anesthesia reactions; Apnea; Arrhythmia; Bacterial endocarditis; Bleeding; Brachial plexus injury; Cardiac perforation; Cardiac tamponade; Cardiac thrombus; Chest pain; Device embolization; Device erosion; Deep vein thrombosis; Death; Endocarditis; Esophageal injury; Fever; Headache/migraine; Hypertension/hypotension; Myocardial infarction; Pacemaker placement secondary to PFO device closure; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Peripheral embolism; Pleural effusion; Pulmonary embolism; Reintervention for residual shunt/device removal; Sepsis; Stroke; Transient ischemic attack; Thrombus; Valvular regurgitation; Vascular access site injury; Vessel perforation.