Patient foramen ovale (PFO) is the most common congenital heart abnormality. PFO develops after birth when physiologic breathing reduces the pulmonary vascular resistance and inverts blood flow through both the foramen ovale and the ductus arteriosus. The foramen ovale closes within a few years after birth in approximately 75% of people, which means it remains open in the remaining 25%. The prevalence of PFO in the adult population is 15% to 25% via echocardiography and 15% to 35% in autopsy studies. The prevalence of detected PFO is lower in older patients and tends to reduce with age. There are no sex- or race-related predominance of PFO. PFO size in adults ranges from 1 to 19 mm (mean, 4.9 mm) in autopsy studies. These measurements represent the maximal diameter of the opening between the septum secundum and primum. Observational studies have shown that the average size increases with each decade of life.

**SYMPTOMS AND SYNDROMES RELATED TO PFO**

PFO will remain undetected in most people who develop it for their entire life or will only appear as an incidental finding in asymptomatic patients. However, sometimes thrombi, air, or vasoactive peptides may cross a PFO from the venous to the arterial circulation, known as paradoxical embolism. Paradoxical embolism is associated with cryptogenic stroke, systemic embolus, decompression sickness, platypnea-orthodeoxia syndrome, and migraine with aura. Cryptogenic stroke is a cerebral ischemic event without a known cause despite extensive investigation, and only diagnosed once the known causes of stroke (eg, atrial fibrillation, atherosclerotic disease, carotid dissection, or intracerebral pathologies such as hemorrhage or space-occupying lesions) are excluded. Cryptogenic stroke represents 40% of stroke diagnoses. The suspected role of PFO in cryptogenic stroke is the translocation of the venous thrombus to the arterial circulation. When the right atrial pressure exceeds the left atrial pressure, the right-to-left shunt is facilitated and a thrombus can transit. Studies have demonstrated the strict association between PFO and cryptogenic stroke both in younger (< 55 years old) and older (> 55 years old) patients, although the risk of cryptogenic stroke is lower in the older population. The SPARC and NOMAS trials showed that the risk of ischemic stroke related to PFO in the general population is very low. For this reason, other existing stroke risk factor should be considered. These factors include:

- Anatomic features of PFO such as (1) size, which is observed more frequently in patients with cryptogenic stroke compared with those without a history of transient ischemic attack/stroke; (2) atrial septal aneurysm (ASA) defined as excursion of atrial septum > 10 mm from the plane of the atrial septum into the right or left atrium or a combined total excursion of 15 mm (the ASA prevalence is 2% to 3% of the population, while 60% of ASAs are associated with a PFO); additionally, larger PFOs are more frequently associated with ASA; and (3) the role of Eustachian valve is still controversial, although the presence of the Chiari network is commonly associated with ASA and PFO; a tunnel-like PFO could be associated to an increased risk of paradoxical emboli.

- Deep vein thrombosis, pelvic vein thrombosis, or conditions predisposing to thrombosis formation might facilitate paradoxical embolization; prothrombin G20210A and factor V Leiden thrombophilia are the more frequent mutations detected in patients with cryptogenic stroke and PFO.

- Common risk factors for venous thromboses, such as recent surgery, trauma, or use of oral contraceptives, may also increase the risk of paradoxical embolization through a PFO.

- Systemic embolization to the gut, limbs, and myocardium has been described, however, there is no evidence from randomized controlled trials that PFO closure is protective in these cases. Thus, PFO closure should be performed in selected cases of paradoxical embolism after a proper interdisciplinary evaluation.
TABLE 1. PFO CLOSURE DEVICES WITH CE MARK AND THEIR MAIN FEATURES

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Device Name</th>
<th>Size (right/left disk)</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Vascular</td>
<td>Amplatzer PFO occluder</td>
<td>18 mm (18/18 mm)/8 F; 25 mm (25/25 mm)/8 F; 30 mm (30/30 mm)/9 F; 35 mm (35/25 mm)/9 F</td>
<td>Nitinol and polyester construction, recapturable and repositionable, self-centering</td>
</tr>
<tr>
<td></td>
<td>Amplatzer multifenestrated septal occluder–Cribriform</td>
<td>18 mm (18/18 mm)/8 F; 25 mm (25/25 mm)/8 F; 30 mm (30/30 mm)/8 F; 35 mm (35/25 mm)/9 F; 40 mm (40/40 mm)/10 F</td>
<td>Nitinol and polyester construction; thin waist offers optimal fit and occlusion of the multifenestrated atrial septal defect</td>
</tr>
<tr>
<td>Cardia, Inc.</td>
<td>Ultrasept PFO occlude</td>
<td>20 mm/10 F; 25 mm/10 F; 30 mm/11 F; 35 mm/11 F</td>
<td>Two ivalon (polyvinyl alcohol) discs supported by nitinol struts</td>
</tr>
<tr>
<td>Comed BV</td>
<td>Hyperion PFO occlude</td>
<td>18-18 mm/10 F; 24-18 mm/10 F; 28-22 mm/12 F; 34-25 mm/12 F</td>
<td>Self-expandable PFO double occluder device made of 72 preoxidized nitinol wires. Available with and without hub using an asymmetric and symmetric design</td>
</tr>
<tr>
<td>Gore &amp; Associates</td>
<td>Cardioform septal occluder</td>
<td>20 mm (20/20 mm)/10 F; 25 mm (25/25 mm)/10 F; 30 mm (30/30 mm)/10 F</td>
<td>Minimal wire nitinol frame; thromboresistant ePTFE membrane allows tissue ingrowth; soft, conformable design to reduce wall injury; fully retrievable even after tension-free assessment</td>
</tr>
<tr>
<td>Kewei Rising</td>
<td>Amender PFO occluder</td>
<td>18-18, 25-18, 30-30 mm/8 F; 35-25 mm/9 F</td>
<td>Nitinol wire polyester fabrics</td>
</tr>
<tr>
<td>Lepu Medical</td>
<td>MemoPart PFO occluder</td>
<td>18-18, 18-24 mm/10 F; 22-22, 25-34 mm/12 F</td>
<td>Self-expanding nitinol mesh double disc device</td>
</tr>
<tr>
<td>Lifetech Scientific</td>
<td>CeraFlex PFO occluder</td>
<td>18-18 mm/9 F; 25-18 mm/10 F; 25-25 mm/10 F; 30-25 mm/12 F; 30-30 mm/12 F; 35-25 mm/14 F</td>
<td>Self-expandable PFO occluder device; all metallic structures are plated with titanium nitride</td>
</tr>
<tr>
<td>Nobles Medical Technologies II, Inc.</td>
<td>Noblestitch EL P, EL S, KwiKnot</td>
<td>1 size/12 F</td>
<td>Three devices provided in a single sterile kit for the release and attachment of suture in polypropylene 4-0 nonabsorbable</td>
</tr>
<tr>
<td>Occlutech International AB</td>
<td>Figulla Flex II</td>
<td>16/18 mm/7 F; 23/25 mm/9 F; 27/30 mm/9 F; 31/35 mm/11 F</td>
<td>Double disc made of self-expandable nitinol wire covered by a ceramic titanium oxide surface</td>
</tr>
<tr>
<td>PFM Medical Inc.</td>
<td>Nit-Occlud PDA</td>
<td>20/26 mm/9 F; 30 mm/10 F</td>
<td>Consists of a single nitinol wire with a double-layer right atrial disc and a single-layer left atrial disc</td>
</tr>
</tbody>
</table>
Decompression illness, typically related to divers and high-altitude pilots, is the result of a sudden change in pressure and may cause the formation of nitrogen bubbles in the body that enter the systemic arterial circulation, which provokes tissue trauma and vessel occlusion. Symptoms include muscle and joint pain, headache, dizziness, fatigue, rash, paresthesia, breathing difficulties, confusion, motor incoordination, and paralysis.16 The presence of a PFO facilitates nitrogen bubbles to bypass the pulmonary filter.17 Some research suggests PFO closure reduces symptomatic neurologic events in divers compared with those who continue to dive without closure.5

Platypnea-orthodeoxia syndrome is a condition characterized by positional oxygen desaturation and dyspnea (oxygen desaturation when seated, while normal oxygen saturations levels are reached in supine position) in individuals with a PFO. An altered geometry of the atrial septum allows the passage of deoxygenated blood into the left blood circulation from the inferior vena cava across the PFO (in cases of chest surgery, aortic dilatation, and aortic surgery or a tricuspid regurgitant jet). PFO closure should be considered for the resolution of this syndrome.5

For migraine with aura, the PFO-related migraine is most likely caused by vasoactive substances. However, at present, there is not enough evidence supporting PFO closure in this setting to offer a routine recommendation for therapy.5,18,19

DEVICE OVERVIEW
Various devices are currently available in Europe for PFO closure (Table 1). A direct PFO suture device (Noblestitch EL, Nobles Medical Technologies II, Inc.) has also been introduced in clinical practice. The most adopted PFO closure devices in randomized controlled trials are the Amplatzer PFO occluder (Abbott Vascular) and the Cardioform septal occluder (Gore & Associates). These devices are the only FDA-approved devices for PFO closure in the United States. In Europe, different PFO occluder devices are used for the percutaneous closure of PFO.20,21

Patient factors that may guide device choice include nickel allergy, contraindications to the use of antiplatelet drugs, high risk of endocarditis, and the need of future transeptal puncture.20 Anatomic features of PFO and the presence of a tunnel-like PFO, hypertrophic septum secundum, ASA, presence of Eustachian valve and Chiari network, multifenestrated PFO, or dilated aortic root, may also impact device choice.

CURRENT EVIDENCE
The first PFO trials (CLOSURE I, PC-Trial, and RESPECT) did not demonstrate superiority for closure compared with medical therapy in patients with PFO and a previous episode of clinically overt cerebral paradoxical embolism. On the contrary, the most recently published randomized controlled trials (RESPECT Long Term, REDUCE, and CLOSE) showed the superiority of PFO closure over medical therapy (Figure 1).4

The RESPECT trial compared the Amplatzer PFO Occluder with four pharmacologic treatment strategies: monotherapy with warfarin, with acetylsalicylic acid, or with clopidogrel, or a combination of acetylsalicylic acid with extended-release dipyridamole. A total of 980 patients aged 18 to 60 years with a cryptogenic stroke and PFO were randomized 1:1 (499 to PFO closure and 481 to medical therapy). The primary efficacy endpoint was a composite of recurrent nonfatal ischemic stroke,
fatal ischemic stroke, or early death after randomization in the time necessary for 25 events to occur. The primary analysis showed similar results in the prevention of stroke in the two arms (1.33% vs 1.73% at 1 year; 1.6% vs 3.02% at 2 years; and 2.21% vs 6.4% at 3 years; HR, 0.492; 95% CI, 0.217–1.114; \( P = .083 \)). Atrial fibrillation occurred in 0.6% of patients in both groups. There were no cases of device thrombus or embolization.

In 2017, after a 10-year follow-up period, an intention-to-treat analysis of the RESPECT Long Term trial reported how PFO closure using the Amplatzer PFO occluder resulted in a 62% relative risk reduction for recurrent ischemic stroke compared with medical management (HR, 0.38; 95% CI, 0.18–0.79; 10-year event rate, 2.3% vs 11.1%; \( P = .007 \)). The rates of atrial fibrillation, major bleeding, and death from any cause were comparable or lower in the device study arm.

The REDUCE trial investigated PFO closure with the Helex (Gore & Associates) or Cardioform septal occluders plus antiplatelet therapy versus antiplatelet treatment alone. Antiplatelet therapy included acetylsalicylic acid, a combination of acetylsalicylic acid and dipyridamole, or clopidogrel. A total of 664 patients aged 18 to 59 years with a cryptogenic ischemic stroke and PFO were randomized 2:1 (441 to PFO closure and 223 to medical therapy alone). The first coprimary endpoint was freedom from clinical evidence of an ischemic stroke at 24 months. The second coprimary endpoint was the incidence of new brain infarction (clinical ischemic stroke or silent brain infarction detected by MRI). The incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group (5.7% vs 11.3%; \( P = .04 \)), but the incidence of silent brain infarction did not differ significantly between the study groups (\( P = .97 \)). Atrial fibrillation occurred in 6.6% of patients after PFO closure versus 0.4% in the medical therapy arm (\( P < .001 \)).

The CLOSE trial compared (1) antiplatelet therapy plus transcatheter PFO closure using any PFO closure device; (2) antiplatelet therapy alone; and (3) anticoagulant therapy alone (with oral anticoagulant or direct oral anticoagulant). The study included 663 patients aged 16 to 60 years with a cryptogenic ischemic stroke and a PFO with an associated ASA or large interatrial shunt. Patients were randomized 1:1:1 (235 to antiplatelet only, 238 to PFO closure, and 190 to anticoagulant therapy alone). The primary endpoint was the occurrence of a fatal or nonfatal stroke at 3 years. The risk of recurrent stroke was significantly reduced in the PFO closure group as compared with the antiplatelet therapy alone group (97% relative risk; HR, 0.03; 95% CI, 0–0.26; \( P < .001 \)). A significantly higher rate of new-onset paroxysmal atrial fibrillation in the PFO closure group compared with the antiplatelet only group was also reported (4.6% vs 0.9%; \( P < .02 \)).

**RISK ASSESSMENT OF CRYPTOGENIC STROKE RELATED TO PFO AND DIFFERENTIAL DIAGNOSIS OF ISCHEMIC STROKE**

The two main principles that influence the assessment and treatment of PFO are (1) the probability that PFO is related to the stroke episode and (2) the risk of event recurrence. When the probability of both factors is high, PFO closure should be performed. When the probability of both factors is low, medical therapy should be considered. For patients with intermediate-risk, decision-making should include interdisciplinary involvement with a cardiologist and other specialists (eg, neurologist and internist).

Some centers use the Risk of Paradoxical Embolism (RoPE) score to classify the relationship between the cryptogenic stroke and PFO, but more research is needed for external validation. Furthermore, some anatomic factors of PFO (eg, ASA, shunt severity and an atrial septal hypermobility, PFO size, presence of Chiari network or Eustachian valve) seem to increase the risk of cryptogenic stroke. Some variables linked to a higher recurrence rate in PFO patients also include ASA and/or PFO diameter, older age, coagulation disorders, stroke at index, D–dimer > 1 at admission, and use of acetylsalicylic acid versus oral anticoagulant.

It is also important to focus on potential causes of stroke to exclude or assess the PFO-related nature of the ischemic event. Brain imaging (MRI, CT) is useful to detect signals of embolic stroke. Cortical and cerebellar strokes are most likely to be of embolic nature, which is not the case for lacunar strokes. Carotid imaging should be undertaken to exclude significant plaque disease. Investigation of thrombophilia pathway could be considered. Immobilization, recent major surgery, and an extended car or airplane journey can be related to the venous clot development. Presence of atrial fibrillation should also be considered.

Studies suggest that 13% of patients with atrial fibrillation have cardiac thrombus (located in left atrial appendage in 90% of cases). The presence of atrial fibrillation in the context of stroke is an indicator for anticoagulation; PFO closure is not indicated. Electrocardiography (ECG) monitoring using either a routine 12-lead ECG, in-hospital cardiac telemetry, or 24-hour Holter monitoring is sufficient to detect a permanent and/or long transient atrial fibrillation episode. Observational studies showed that insertable cardiac monitors are associated with increased evidence of paroxysmal atrial fibrillation. Younger patients (< 55 years old) with no risk factors for atrial fibrillation should be considered for a minimum of 72-hour ambulatory surface ECG to investigate the presence of paroxysmal atrial fibrillation. In older patients (> 65 years old), implantable cardiac monitoring extending to a minimum of 6 months (ie, duration of the battery) could be considered. In younger patients (< 55 years old) with at least two major risk factors for
atrial fibrillation (eg, uncontrolled hypertension, diabetes, structural heart alterations, or congestive heart failure) and patients aged 55 to 64 years old with major and minor risk factors for atrial fibrillation (eg, obesity, atrial runs, pulmonary disease, thyroid disease), an implantable cardiac monitor should be considered as well.4,5

THErapy

Once stroke-related PFO risk is assessed, the most suitable therapy can be chosen. For patients in whom medical therapy is chosen, the European position paper suggests choosing the specific anticoagulant drugs, weighing the individual risk of bleeding against the risk of PFO-related stroke recurrence.4 Long-term oral anticoagulant with vitamin K antagonists may be preferred to antiplatelet agents if the patient has a low hemorrhagic risk, good therapeutic compliance, and proper anticoagulant monitoring can be guaranteed. If these conditions cannot be satisfied or the risk of stroke recurrence is low, antiplatelet therapy should be prescribed. At present, no position can be expressed for direct oral anticoagulants.5 Meta-analyses and studies have consistently found a statistically significant advantage of oral anticoagulants over antiplatelet therapy in terms of recurrent stroke prevention and/or transient ischemic attack, although an increase in major bleeding has been reported.26-30 In the case of hypercoagulability, deep vein thrombosis, and pulmonary embolism, PFO closure may be considered when there is only a need for temporary oral anticoagulants or a high risk of recurrence despite permanent oral anticoagulants.4,5

CONCLUSION

The main indication for percutaneous PFO closure is 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 a cardiologist after an evaluation to exclude known causes of ischemic stroke or, in case of high risk, of paradoxical embolism due to predisposing factor or clinical conditions (deep vein thrombosis) after a proper interdisciplinary evaluation.21

The optimal regimen of antithrombotic therapy after device deployment remains uncertain. Aspirin and clopidogrel are usually given for 6 months in our practice, followed by a period of single antiplatelet therapy (in some studies extended to 2–5 years).4,5 An antibiotic prophylaxis may be done in the following 12 months after PFO closure.4,5