REVIEW ARTICLE

Long-term benefits and risks in patients after persistent foramen ovale closure: a contemporary approach to guide clinical decision making

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ABSTRACT
Persistent foramen ovale (PFO) is a congenital heart disease which represents 80% of atrial septal defects. It is a remnant of fetal circulation that functions in postnatal conditions as a transient interatrial right-to--left shunt of variable magnitude. Persistent foramen ovale may be implicated in the pathogenesis of several medical conditions, such as cryptogenic stroke, cryptogenic left circulation thromboembolism, migraine syndromes, and decompression sickness. The most frequent indication for PFO closure remains PFO-associated left circulation thromboembolism. In select patients, PFO closure reduces stroke recurrence in comparison with medical therapy after more than 3 years of follow-up on average, especially in patients with a high risk of recurrence. While in PFO-associated left circulation embolism, there is now conclusive evidence on the growing benefit of PFO closure in long-term follow-up, in many other clinical conditions, the degree of certainty of the results is deceiving. In this paper, we will review the benefits and risks that one can expect in the long term after percutaneous PFO closure in various clinical scenarios in order to facilitate therapeutic decision making.

Introduction Persistent (or patent) foramen ovale (PFO) is a congenital anomaly which represents 80% of atrial septal defects (ASDs).[1] It is a remnant of fetal circulation that functions in postnatal conditions as a transient interatrial right-to-left shunt of variable magnitude. The vast majority of individuals with PFO do not develop PFO-associated diseases. However, PFO may be implicated in the pathogenesis of several medical conditions, such as cryptogenic stroke, cryptogenic left circulation thromboembolism, migraine syndromes, and decompression sickness (DCS).[2]

The most frequent indication for PFO closure remains PFO-associated left circulation thromboembolism. The association between PFO and cryptogenic left circulation thromboembolism has mainly been addressed in studies performed in patients with cryptogenic stroke and is strongly supported by epidemiological data, clinical observational studies, and randomized clinical trials (RCTs). Particularly, RCTs conclusively showed that, in select patients, PFO closure reduces stroke recurrence in comparison with medical therapy after more than 3 years of follow-up on average. Since then, transcatheter percutaneous closure has become the therapy of choice for PFO-associated stroke in patients at high risk of recurrence.[2] It was suggested that percutaneous closure could be indicated also in other associated diseases, such as DCS, migraine, or desaturation syndromes, but conclusive data are still lacking.[3]

After more than 20 years of experience with dedicated PFO closure devices,[4] primary technical success approaches 100% and complete closure is seen in 93% to 96% of cases at 1 year with the most effective devices.[5] In this paper, we will review the benefits and risks that one can expect in the long term from percutaneous PFO closure in various clinical scenarios in order to facilitate therapeutic decision making.

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TABLE 1 Characteristics from early randomized clinical trials on persistent foramen ovale closure for secondary prevention of thromboembolic stroke compared with medical therapy

Study, year	Patients, n	Inclusion criteria	Device	Follow-up, y	Antithrombotic therapy	Primary endpoint	Result
CLOSURE I, 2012[6]	909	Patients aged 16–60 y with cryptogenic stroke/TIA and PFO	STARFlex septal closure system	2	Device arm: aspirin and warfarin (1 mo) followed by aspirin (2 y) Medical treatment arm: aspirin or warfarin or aspirin and warfarin	Early all-cause death, late death due to neurologic cause, stroke, TIA	Percutaneous PFO closure did not significantly reduce recurrent stroke/TIA compared with medical treatment alone.
RESPECT, 2013[7]	980	Patients aged 18–60 y with cryptogenic stroke and PFO	Amplatzer PFO occluder	5.9	Device arm: aspirin plus clopidogrel (1 mo), followed by aspirin (5 mo) Medical treatment arm: aspirin or warfarin or clopidogrel or aspirin and extended-release dipyridamole	Recurrent fatal and nonfatal stroke and early death	Similar results in the prevention of stroke in the 2 arms
PC, 2013[4]	414	Patients aged <60 y with cryptogenic stroke, TIA, or systemic embolism and PFO	Amplatzer PFO occluder	4	Device arm: aspirin (5–6 mo) and ticlopidine or clopidogrel (1–6 mo) Medical treatment arm: antiplatelet therapy or anticoagulation therapy	Death, nonfatal stroke, TIA, or peripheral embolism	Percutaneous PFO closure did not significantly reduce death or recurrent embolism compared with medical therapy alone.

Abbreviations: PFO, persistent foramen ovale; TIA, transient ischemic attack

Cryptogenic stroke: left-circulation thromboembolism An updated meta-analysis has served as the basis for the 2019 joint European position statement developed by 8 scientific societies on this topic.[2] The meta-analysis performed for the document showed that, after an average of 3.8 years of follow-up, the number needed to treat with PFO closure to prevent 1 stroke overall was 37 (95% CI, 26–68), and 21 in patients with high-risk PFO features (95% CI, 16–61), as compared with medical therapy.[2] Individual randomized studies showed a relative risk reduction of up to 80% for recurrent strokes after PFO closure. Studies including higher-risk PFO patients showed enhanced outcomes with percutaneous closure compared with those on unselected patients with prior cryptogenic cerebral events, emphasizing the heterogeneity of this population and the need for personalized assessment of risk before deciding on a therapy.

The first 3 RCTs (CLOSURE I,[6] RESPECT,[7] PC[4]) compared the efficacy and safety of percutaneous PFO closure with medical therapy for secondary stroke prevention in patients with previous cryptogenic stroke (the main characteristics of these trials are summarized in TABLE 1). Their results individually failed to show any superiority of PFO closure to reduce recurrent stroke compared with medical therapy alone. However, at that time already, a patient-level meta-analysis[8] pooled the individual data of 2303 patients from the 3 RCTs and suggested that PFO closure was superior to medical therapy for the secondary prevention of stroke (hazard ratio, 0.58; 95% CI, 0.34–0.98; $P = 0.043$).

Nonetheless, between 2017 and 2018, 3 new RCTs (CLOSE,[9] REDUCE,[10] DEFENCE-PFO;[11] the main characteristics are summarized in TABLE 2) and 10-years follow-up of the RESPECT trial[12] assessed the efficacy and safety of percutaneous PFO closure compared with medical therapy for the secondary prevention of cryptogenic ischemic stroke.

The RESPECT trial[7] is one of the first trials to compare transcatheter percutaneous closure with 4 treatment regimens (only warfarin, acetylsalicylic acid or clopidogrel, or a combination of acetylsalicylic acid with extended-release dipyridamole). Procedural success was 96.1% for implantation and 93.5% for effective closure at 6 months of follow-up. The primary publication in 2013 reported 25 (of 980) primary endpoint events (a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization in the time span necessary for 25 events to occur): 9 in the closure group, 16 in the medical group, all of which were recurrent nonfatal strokes. The primary analysis showed similar results in the prevention of stroke in the 2 arms ($P = 0.083$). However, the per-protocol analysis of 20 events suggested benefit from PFO closure. Subgroup analyses suggested a benefit

TABLE 2 Characteristics of recent randomized clinical trials on persistent foramen ovale closure for secondary prevention of thromboembolic stroke compared with medical therapy

Study, year	Patients, n	Inclusion criteria	Device	Follow-up, y	Antithrombotic therapy	Primary endpoint	Result
CLOSE, 2017[9]	663	Patients aged 16–60 y with cryptogenic stroke and PFO associated with atrial septal aneurysm or large interatrial shunt	Amplatzer, STARFlex, CardioSEAL, Intrasept, PFO-Star, HELEX, Premere, Occlutech, Cardioform	5.3	Device arm: aspirin and clopidogrel (3 mo), followed by single antiplatelet therapy Medical treatment arm: aspirin or clopidogrel or aspirin combined with extended-release dipyridamole or warfarin or NOAC	Recurrent stroke	Percutaneous PFO closure significantly reduced recurrent strokes compared with medical treatment alone.
REDUCE, 2017[10]	664	Patients aged 18–59 y with cryptogenic stroke and PFO	Helex septal occluder, Cardioform septal occluder	3.2	Device arm: clopidogrel (first 3 d) followed by the chosen antiplatelet therapy for the medical treatment arm Medical treatment arm: aspirin or aspirin and dipyridamole or clopidogrel	Freedom from clinical evidence of ischemic stroke and incidence of new brain infarction (clinically evident ischemic stroke and silent brain infarction detected on MRI)	Percutaneous PFO closure significantly reduced recurrent strokes and new brain infarcts compared with medical treatment alone.
DEFENSE--PFO, 2018[11]	120	Patients with ischemic stroke and no identifiable cause other than a high--risk PFO	Amplatzer PFO Occluder	2	Device arm: DAPT (6 mo), followed by single antiplatelet, DAPT or anticoagulant Medical treatment arm: aspirin, aspirin and clopidogrel, aspirin and cilostazol or warfarin	Stroke, vascular death, TIMI--defined major bleeding	Percutaneous PFO closure significantly reduced recurrent stroke compared with medical treatment alone, in patients with high-risk PFO.

Abbreviations: DAPT, dual antiplatelet therapy; MRI, magnetic resonance imaging; NOAC, non–vitamin K oral anticoagulant; TIMI, Thrombolysis in Myocardial Infarction; others, see TABLE 1

in the presence of a substantial shunt or atrial septal aneurysm. In the second publication in 2017,[12] the investigators reported that after 10 years, in an intention-to-treat analysis, PFO closure resulted in a 62% relative risk reduction for recurrent ischemic stroke compared with medical management (P = 0.007). The rates of atrial fibrillation, major bleeding, and death from any causes were comparable or lower in the device study arm.

The CLOSE trial[9] presented similar results. The study included patient aged 16 to 60 years with cryptogenic stroke and PFO with an associated atrial septal aneurysm (ASA) or large interatrial shunt. The 3 arms of the study were: 1) antiplatelet therapy (acetylsalicylic acid, clopidogrel, or acetylsalicylic acid combined with extended release dipyridamole) plus transcatheter PFO closure; 2) antiplatelet therapy alone; 3) anticoagulant therapy alone. The closure procedure was successful in 98.6% of patients and the rate of effective PFO closure was 93%. Recurrent fatal or nonfatal stroke occurred in 14 patients (of 663), but none in the PFO-closure group. Therefore, the risk of recurrent stroke was significantly reduced in the PFO closure group as compared with the antiplatelet-only group (P <0.001), at the expense of higher rate of new--onset paroxysmal atrial fibrillation in the PFO closure group (P <0.02).

The REDUCE trial[10] evaluated PFO closure plus antiplatelet therapy (acetylsalicylic acid, a combination of acetylsalicylic acid and dipyridamole or clopidogrel) compared with antiplatelet therapy alone. The implantation was successful in 98.8% of patients and effective at 12 months in 75.6% of those. Atrial septal aneurysm was present in 20% of patients undergoing closure and a moderate-to-large shunt was present in 80% of patients in both arms. The primary endpoint of clinically evident ischemic stroke occurred in 18 patients (of 664). The incidence of new brain infarction was significantly lower in the PFO closure group than in the antiplatelet-only group (5.7% vs 11.3%; P = 0.04), but the incidence of silent brain infarction did not differ significantly between the study groups (P = 0.97). Serious adverse events were similar in the 2 groups. Atrial fibrillation occurred in 6.6% of patients after PFO closure as compared with 0.4% (P <0.001).

The DEFENCE-PFO trial[11] enrolled patients with cryptogenic stroke and high-risk PFO (ASA, moderate-to-large shunt) compared PFO closure or medical therapy alone as chosen by the attending physician. Atrial septal aneurysm was present in 10% of both arms, atrial septal hypermobility in 45%, and a large shunt in 80% of patients. The primary endpoint (a composite of stroke, vascular death, or the Thrombolysis in Myocardial Infarction–defined major bleeding during 2-year follow-up) occurred in 6 patients undergoing medical therapy only and in none undergoing PFO closure (P = 0.013). The study reported 2 cases of atrial fibrillation (AF) in the group undergoing PFO closure and none in the medical therapy alone group.

In the meta-analysis of these 6 RCTs published in the European position paper,[2] a statistically significant improvement in stroke recurrence with percutaneous closure was observed only when compared with antiplatelet therapy (odds ratio [OR], 0.38; 95% CI, 0.17–0.84; P = 0.02), whereas oral anticoagulation yielded a similar risk of recurrence (OR, 1.19; 95% CI, 0.43–3.26; P = 0.74). Moreover, a subgroup analysis of the first 5 RCTs showed that patients with moderate-to-severe shunt size experienced enhanced outcomes with percutaneous closure relative to medical therapy. Furthermore, patients with high-risk PFO features (ASA, hypermobility of the atrial septum, moderate-to-severe shunt or large PFO size) reported enhanced outcomes with percutaneous closure compared with medical therapy (unselected PFO features: OR, 0.67; 95% CI, 0.42–1.09; P = 0.39; high-risk PFO features: OR, 0.18; 95% CI, 0.07–0.45; P = 0.0003), whereas in patients with low-risk PFO, there was no additional benefit from PFO closure as compared with medical therapy (low-risk PFO features: OR, 0.8; 95% CI, 0.54–1.18; P = 0.26; high-risk PFO features: OR, 0.34; 95% CI, 0.15–0.76; P = 0.008).

One exploratory analysis of the RESPECT trial[7] extended to a longer follow-up supports a growing benefit from percutaneous closure over medical therapy after that time limit. After 10 years, in an intention-to-treat analysis, PFO closure resulted in a 62% relative risk reduction for recurrent ischemic stroke compared with medical management (OR, 0.38; 95% CI, 0.18–0.79; 10-year event rates, 2.3% vs 11.1%; P = 0.007). Moreover, in 2019, an observational study[13] showed very low stroke rates (<1%), even up to 12 years after PFO closure.

Based on United States estimates, the cost-effectiveness analysis over 15 years favors percutaneous closure over medical therapy in patients with high-risk PFO features and with the use of an AMPLATZER PFO Occluder.[14]

Other conditions As mentioned above, PFO is also implicated in the pathogenesis of a number of medical conditions, such as decompression disease, migraine, and desaturation syndromes.[3] However, the high prevalence of PFO in the healthy population implies that PFO can be an incidental finding rather than a causative one especially in these uncommon syndromes. In these illnesses, PFO closure can be proposed in select cases, after a thorough and careful evaluation at the individual level to assess the role of PFO.

Decompression sickness Decompression sickness is a complex condition that occurs when a person moves from a higher-pressure to a lower-pressure environment. It is caused by generation of gas emboli which are subsequently trapped locally or remotely, after embolization, in vessels and tissues. It can result in a wide range of acute clinical scenarios, from transient to persistent, and from mild to severe disability or death.

In divers, the association between PFO and DCS is supported by retrospective case-controlled epidemiological studies, mechanistic studies, and association studies. Under some circumstances (a rise in right heart pressures and/or a spontaneous right-to-left shunt), a PFO can allow paradoxical embolization of venous gaseous emboli (VGE) into the left circulation.[15] Therefore, PFO-related DCS can produce earlier and more abundant VGE arterialization but its role should be weighed against other individual factors that affect VGE production and trapping. Several clinical features can be used to assess the role of PFO in a specific DCS and a multi-disciplinary evaluation is mandatory with a hyperbaric or aerospace medicine physician.[16] When the PFO role is deemed crucial in the pathophysiology of DCS which occurred without a high risk activity, it is rational to suggest to close it, with active involvement of patients in shared decision-making.[17]

Regarding PFO closure, one prospective study in 104 divers with previous DCS showed a statistically significant reduction in DCS recurrence over 5 years in patients who chose to have their PFO closed, compared with those who did not (risk of major DCS of 0.5/10 000 vs 35.8/10 000 dives, respectively).[17] However, the number of individuals was low and there was significant dropout.

Moreover, some case reports showed recurrent DCS after PFO closure.[18-20] Although a residual shunt was detected in some of these patients, it is possible that, in others, a provocative dive profile caused high VGE loads, resulting in recurrent DCS even with a successfully closed PFO. This underscores that, irrespective of PFO, secondary prevention should always be aimed primarily at suppressing VGE production, with specific behavioral measures up to possible permanent cessation of the activity. Therefore, strong evidence supporting benefit from

PFO closure in DCS is still lacking and PFO closure as secondary prevention should be restricted to particular cases on top of behavioral measures.[3] In particular when there is a high probability of causal PFO, cessation of diving / flying is not an option, and when it is not possible to achieve an effective behavioral change to prevent the production of venous gas emboli or when the risk of further DCS, despite conservative limitations, is deemed unacceptable by the patient after consultation with an experienced hyperbaric or aerospace medicine physician. No evidence is available on PFO closure as primary prevention of DCS.

Migraine Migraine is a common disorder, which affects approximately 12% of the general population and is often disabling.[21] The association between PFO and migraine has been suggested by a higher prevalence of PFO in those with migraine, especially among those with aura, than in the general population and by the findings of incidental improvement in migraine in patients who have undergone percutaneous closure of the PFO for other reasons.[22]

The first trial on this subject was the MIST, in 2008, comparing PFO closure with the STARFlex septal repair implant versus nonclosure in 147 patients with migraine.[23] The primary efficacy endpoint was cessation of migraine headache 91 to 180 days after the procedure. No significant difference was observed in the primary endpoint of migraine headache cessation between the implant and sham groups (3 of 74 versus 3 of 73, respectively; $P = 0.51$). Furthermore, considering the available data, the study had severe limitations, such as an undersized sample, use of a device which is now off the market, and less than optimal primary efficacy after implantation. Moreover, the study results were criticized by some of the investigators.

Eight years later, the PRISMA trial[24] compared PFO closure with AMPLATZER PFO Occluder against medical management. Nevertheless, the study was prematurely stopped because of the slow enrolment rate. The primary endpoint was a reduction in monthly migraine days during months 9 to 12 after randomization compared with the 3-month baseline period before randomization. At 6 months, 88% of patients in the device therapy arm had PFO successfully closed, as indicated by transesophageal echocardiography. At 1 year, a similar number of primary endpoint events was observed in the PFO closure group when compared with the control group (22.9 vs 21.7 days; $P = 0.17$). Post hoc analysis revealed a greater mean reduction in days with migraine with aura per month and in the number of migraine attacks with aura in the PFO closure group versus the control group (22.4 vs 20.6 days; $P = 0.0141$ and 22 vs 20.5; $P = 0.0003$, respectively).

The following years, the PREMIUM trial[25] compared PFO closure with the AMPLATZER PFO Occluder against medical management with a sham procedure (right heart catheterization). At 1 year, 78 primary efficacy events (a 50% reduction in migraine attacks) and 1 safety endpoint were adjudicated. The responder rate was similar in the 2 groups (45/117 in the device group and 33/103 in controls); however, device implantation significantly reduced the number of migraine with aura days ($P < 0.01$) and attacks ($P < 0.01$), and only after PFO closure did 8.5% of patients experience complete remission of migraine over a year.

Further RCTs are necessary to obtain satisfactory certitude of effects. Current data do not support interventional therapy as an alternative or as adjunct to medical therapy in patients with migraine. Based on these data, the European statement[3] suggested PFO closure only in clinical trials or for compassionate use in migraine with aura.

Arterial deoxygenation syndromes Arterial hypoxemia is a decrease in the content of oxygen in the blood (SaO_2 or SpO_2 <90% or PaO_2 <60 mm Hg), with or without cyanosis. Its main symptoms are exertional and / or resting dyspnea. Several case reports and some experimental and clinical studies have demonstrated that a shunt through a PFO has the potential to cause arterial deoxygenation by mixing venous and arterial blood. In most cases, PFO shunt only aggravates pre-existing causes of hypoxemia. In the infrequent case of platypnea-orthodeoxia syndrome (POS), the most common cause is PFO.[26] In obstructive sleep apnea syndrome, it is important to assess the number and severity of episodes of desaturation on therapy to evaluate the possible role of PFO in clinical findings.

No randomized trials have been performed addressing percutaneous closure of PFO in desaturation syndromes. Treatment is based on severity of symptoms and the pathogenic role of PFO in shunting. Patients with chronic severe pulmonary hypertension should be excluded from interventional treatment.

A meta-analysis of observational studies included in the European statement[3] compared SaO_2 or SpO_2 before and after PFO closure for POS and exertional desaturation, finding a statistically significant increase in SaO_2 or SpO_2 in both clinical conditions after the intervention. The studies on POS revealed stable relief of symptoms up to 5 years with improved standing arterial oxygen saturation in all patients who did not have other dominating causes of hypoxemia.[27] These data show that percutaneous closure of PFO has the potential to affect arterial oxygen saturation and improve symptoms in select patients with arterial hypoxemia

syndrome. The European position statement[3] suggests percutaneous closure of PFO in patients with any desaturation syndrome in which, despite best conventional treatment, the PFO has been demonstrated to unequivocally and critically contribute to the arterial desaturation and symptoms. More data are necessary to demonstrate effectiveness and safety in these contexts.

Risks **Late complications** Information regarding long-term risks after PFO closure are available only from observational data on PFO-associated left circulation thromboembolism.

Procedural complications have a 2.6% incidence in RCTs.[28] The most frequent late complication is device thrombosis, which is seen in 1% to 2% of cases. It involves thrombosis of device arms not covered by the endocardium. Sometimes it is asymptomatic, although the most common sign is systemic embolism. An early discontinuation of dual antiplatelet therapy (DAPT) after the procedure may explain this complication,[29] but more studies are needed.

Atrial fibrillation (AF), a common, mostly self-limiting, complication is observed mainly intra- or perioperatively with a 10% to 15% incidence. Consistently, the meta-analysis of the European position paper[2] found an increased risk of AF in the first 45 days after the closure procedure, whereas no increased risk was observed after 45 days. The risk of atrial arrhythmias seems to be higher in the elderly and in those with ASA. Possible mechanisms include a mechanical irritation and/or an electrophysiological interference due to the device. Given the low risk of AF in the long term, no routine heart rhythm monitoring strategy should be adopted in the long-term follow-up.

Residual shunt is seen in 10% to 15% of patients after PFO closure, but the incidence decreases in late follow-up because of the progressive endocardialization of the device and there is no consensus on the timing of follow-up to assess a PFO device.[2] Moreover, there are no data to determine its implication and further studies are also needed. At present, no relationship between PFO patency after closure and the incidence of recurrence has been found, but studies were small, often plagued by partially incomplete follow-up, and problematic regarding shunt detection accuracy.[30,31] In addition, a persistent shunt after closure may reveal other sources of paradoxical embolism, which were missed during the diagnostic phase.[32]

Device embolism is a serious early event, but at present, with a correct sizing of the device, it is very rare. In the early years after the PFO closure technique was initiated, it occurred at a rate of 0.9% to 1.3% intra- and perioperatively, but even then, it was rare later in the follow-up. In a late stage, it can be due to the erosion of the atrial septum or to device-PFO mismatch. The most frequent sign is pulmonary embolism, although sometimes it is asymptomatic.

Pericardial effusion and/or tamponade is seen in 0.5% to 1% of cases. In the late stages, it can be due to late erosion by an oversized device. More rarely, it is due to an allergic reaction. The most common signs are dyspnea and chest pain, but it could be asymptomatic.

Atrial wall erosions, atrio-aortic fistula, and endocarditis are serious events that have been reported anecdotally. The risk of long-term mortality or the need for cardiac surgery is less than 1 in 1000.

Prevention of complications after percutaneous closure No data on the best management after PFO closure are available to prevent long-term risks. While making the decision about post-procedural therapy, one should consider that:

- endothelialization of the device can continue up to 5 years postimplantation[33];
- one of the most frequent complication after PFO closure is device thrombosis;
- premature discontinuation of therapy may cause minor cerebrovascular events after PFO closure.[2]

A meta-regression of the PFO closure studies published in the European position paper for left circulation thromboembolism[2] suggests a trend towards an association between the duration of dual antiplatelet therapy after PFO closure and the incidence of transient ischemic attack in the follow-up. Therefore, it is reasonable to propose a prolonged dual antiplatelet therapy for 1 to 6 months after PFO closure, followed by a single antiplatelet therapy for at least 5 years. The extension of the therapy with a single antiplatelet agent beyond 5 years should be based on the balance between the patient's overall risk of stroke of other causes and hemorrhagic risk.

Moreover, it is also reasonable to suggest antibiotic prophylaxis for any invasive procedure performed in the first 6 months from PFO closure and beyond 6 months in patients with a residual shunt, therefore an assessment of the effectiveness of PFO sealing (by transcranial doppler and/or transesophageal echocardiography) at 6 months should be scheduled.

In case of closure of PFO after DCS, an unrestricted diving activity is possible only after a complete sealing of PFO without any persisting shunt.

Conclusions After more than 20 years of experience with dedicated PFO closure devices, the technique achieves high primary success and effective closure rates, with infrequent undesired effects in the short and long term. This offers an effective secondary prevention across a spectrum of associated diseases with an often satisfactory safety profile, when a casual link exists between a PFO and the considered condition.

While in PFO-associated left circulation embolism, there is now a conclusive body of evidence on the growing long-term benefit from PFO closure, in many other clinical scenarios, the degree of certainty of the results is deceiving. Therefore, a careful interdisciplinary assessment of the individual risk of patients is mandatory. While waiting for more conclusive evidence, the European position papers on the subject may serve as a guide to a rational approach in these situations.

Moreover, one should bear in mind that the high prevalence of PFO in the normal population implies that PFO can be an incidental finding rather than a causative one in the majority of cases. This is even more true when the associated diseases are infrequent. Unfortunately, to date, there are no studies performed to formally identify specific characteristics for a precise assessment of the role of PFO in these clinical conditions. For these reasons, a personalized medicine paradigm is necessary to precisely target the right treatment for the right person at the right time, increasing chances of appropriate treatment in these syndromes.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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