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Current status of transcatheter closure of patent foramen ovale

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SUMMARY

A patent foramen ovale (PFO) is a highly prevalent structure among the adult population. It allows the shunt of blood through the inter-atrial septum and has been associated with cryptogenic stroke, transient ischemic attack, significant right to left shunting resulting in resting and exercise-induced hypoxemia, platypnea orthodeoxia syndrome, and decompression sickness after scuba diving and migraines. Currently, transthoracic and transesophageal echocardiography and transcranial Doppler are the most important diagnostic tools, for the diagnosis of PFO. The sensitivity and specificity of the study depend on the modalities available: transthoracic (TTE), transesophageal (TEE), and transcranial Doppler (TCD), as well as the intravenous use of agitated saline and the site of injection.

Key words: *Transcatheter closure, Patent Foramen Ovale, cryptogenic stroke.*

RESUMEN

Un foramen oval permeable (FOP) es una estructura altamente prevalente entre la población adulta. Permite la derivación de sangre a través del tabique interauricular y se ha asociado con accidente cerebrovascular criptogénico, ataque isquémico transitorio, derivación significativa de derecha a izquierda que resulta en hipoxemia inducida por reposo e inducida por el ejercicio, síndrome de ortodeoxia por platipnea y enfermedad por descompresión después del buceo y las migrañas. Actualmente, la ecocardiografía transtorácica y transesofágica y el Doppler transcraneal son las herramientas de diagnóstico más importantes para el diagnóstico de FOP. La sensibilidad y la especificidad del estudio dependen de las modalidades disponibles: transtorácica (TTE), transesofágica (TEE) y Doppler transcraneal (TCD), así como el uso intravenoso de solución salina agitada y el sitio de inyección.

Palabras clave: *Cierre transcatéter, foramen oval permeable, accidente cerebrovascular criptogénico.*

INTRODUCTION

Transcatheter (TC) PFO closure has been shown in observational and prospective studies to be a safe and efficient therapy. The results of recent multiple randomized clinical trials (RCT) and meta-analysis of the combined studies showing positive results have finally demonstrated the beneficial impact of PFO catheter closure in this patient population. Thus

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nowadays, the best therapeutic option for the treatment of cryptogenic strokes in the presence of PFO is transcatheter closure of the PFO. In addition, encouraging results are reported for PFO catheter closure in patients with symptomatic hypoxemia, platypnea orthodeoxia syndrome, decompression sickness after scuba diving, and migraines.

Background

It has been over 140 years since the controversy regarding the potential cause-effect relationship between a PFO and cryptogenic strokes was originally proposed by Dr. Julius Cohnheim (1). Since then, multiple attempts have tried to prove that closure of PFO could be an effective therapy to prevent subsequent neurological events. The purpose of this chapter is to provide a review of different aspects regarding PFO and neurological syndromes, including anatomy, diagnosis, therapeutic, as well, as the data supporting different strategies. In addition, other potential indications for transcatheter PFO closure are also review.

Embryology and anatomy

The development of the foramen ovale is critical in the embryological development of the heart. Approximately at the 5th week of development, a very thin septum primum begins to migrate downwards towards the endocardial cushion. The hiatus in between both structures forms the foramen primum. As the migration of the septum primum continues, apoptotic changes within the septum will originate from the foramen secundum. On the right atrial surface of the foramen secundum a more muscular and thicker septum secundum migrates downwards covering the foramen secundum and leaving a small foramen on the bottom of the atrium, the foramen ovale. This structure will provide a right to left shunt necessary for fetal circulation. After birth, this communication will spontaneously close in approximately 75 % of the population (2). The anatomy of PFO is highly variable and may be associated with a long tunnel of >10 mm and atrial septal aneurysm which are redundancies of the atrial septum of over 15 mm.

Prevalence

In multiple autopsy reports, the prevalence of PFO in the adult population is approximately 26 % (3). The prevalence of PFO is similar to non-invasive methods with TEE (4). However, the incidence of PFO in young patients presenting with a cryptogenic stroke can reach up to 50 % (5).

Factors associated with paradoxical embolization

The PFO in Cryptogenic Stroke Study (PICSS) was a multicenter study that evaluated TEE findings in patients randomly assigned to warfarin or aspirin in the Warfarin-Aspirin Recurrent Stroke Study (WARSS). PICSS found that patients with cryptogenic stroke had a significantly higher incidence of large PFO when compared to those patients having a stroke of known cause (20 % vs. 9.7 % P<0.001) (6). Moreover, Steiner et al. performed TEE in 95 patients over 39 years of age with first ischemic stroke (7). The stroke subtype and MRI/CT imaging data were evaluated blindly to the presence of a PFO. These findings were compared between two groups: patients with a medium to large PFO (>2 mm) and small (<2 mm) or no PFO. Stroke patients with larger PFOs showed more brain imaging features of embolic infarcts than those with small PFOs.

The presence of a prominent Eustachian valve (EV) has been proposed as responsible for redirecting blood flow towards the septum, potentially allowing emboli to travel through the inter-atrial septum into the left atrium. This hypothesis was explored in a study by Schuchlenz et al by comparing patients that had cryptogenic strokes with healthy volunteers. The authors found a significantly higher incidence of PFO and EV by TEE in those patients with cryptogenic stroke (8).

The PFO and atrial septal aneurysm (ASA) study group followed 581 ischemic stroke patients under the age of 55 years of age. The patients were started on aspirin within 3 months of their neurological event and followed for 4 years. The patients were divided into groups depending on the characteristics of the inter-atrial septum. Mas et al found that the presence of both atrial septal abnormalities was a significant predictor

of increased risk of recurrent cerebrovascular events, whereas the presence of a PFO alone or an ASA alone was not (9). Moreover, their finding suggested that aspirin as secondary prevention for recurrent events may not be enough for his subgroup of patients. These findings are in agreement with the findings of other studies, especially in patients with a right-to-left shunt at rest (10). Stone et al, followed prospectively a group of stroke patients found to have a PFO during TEE and divided them into "large" degree shunt (≥20 micro bubbles) and "small" degree shunt (≥3 but<20 micro bubbles). Patients with "large" shun that a 31 % incidence of a recurrent event versus none in the "small" shunt group despite the use of antiplatelet therapy and/or anticoagulation. Therefore, patients with "large" shunts, should be considered at a significantly higher risk for subsequent adverse neurologic events (11).

It has also been proposed that "long-tunnel" PFO anatomy represents an environment fertile for clot formation, with subsequent embolization. However, there is no clear evidence supporting this hypothesis (12).

In a venography study, Stollberger et al presented evidence that patients with ischemic stroke due to suspected paradoxical embolization have a higher incidence of deep venous thrombosis (13). Therefore, conditions that facilitate the formation of deep venous thrombosis deserve special attention when evaluating patients with PFO and cryptogenic stroke. May-Thurner syndrome, in which the right common iliac artery compresses the underlying left common iliac vein, has a higher incidence in patients with PFO-related stroke (14-15). In a prospective study of patients with large pulmonary embolism (PE), it was found that those patients with PFO had a 6-fold higher risk of stroke when compared with those without PFO (16).

PFO diagnosis

It is very important to remember when evaluating a patient for the presence of a PFO, that one out of 4 normal subjects, approximately 25 % of the general healthy population will have a PFO (3). Thus, it is important to be mindful of the clinical presentation of every particular case. Moreover, the clinician should be able to identify particular "high risk" features that might make the presence of a PFO more relevant.

There are different modalities available for the diagnosis of PFO. The most commonly used are TTE, TEE, and TDC coupled with agitated saline injection in association with the Valsalva maneuver. The most common initial modality is TTE for the evaluation of cardiac sources of emboli. Agitated saline contrast increases the diagnostic sensitivity by enhancing echocardiographic detection of the trivial intermittent right-to-left shunt Ingacross the PFO. However, the sensitivity of TEE is higher than TTE despite the use of agitated saline (3). Hamman et al (17) demonstrated increased sensitivity when the injection of agitated saline was performed from the femoral vein versus the traditional antecubital vein probably because the bubbles ascending through the inferior vena cava will encounter the Eustachian valve and flow preferentially towards the septum. These findings were more evident when using TEE and TCD.

Medical therapy for secondary prevention of cryptogenic strokes

Medical therapy for secondary prevention of cryptogenic stroke continues to be the most common initial approach for patients after the initial neurological event. However, the definition of medical therapy has been loose in different studies and there is no consensus regarding the use of either antiplatelets or anticoagulation. Furthermore, there is no consensus regarding escalation in therapy in patients with "high risk" PFO anatomical features.

WARSS was the first randomized controlled study to compare the effect of warfarin and aspirin after prior non-cardio-embolic ischemic stroke. WARSS showed aspirin was as good as warfarin in the prevention of stroke recurrence, but the presence of a PFO was not specifically systematically evaluated (18). However, that same year in the same journal the report from the PFO and ASA study group (9), found in their prospective study of cryptogenic stroke patients treated with aspirin, that in patients with a PFO in association with an ASA, aspirin was not as effective for secondary prevention. A year later, a

sub-study of WARSS, the PICCS trial compared secondary prevention with aspirin versus warfarin in stroke patients with a PFO. In the cohort of patients with cryptogenic stroke, there was a trend towards less neurological events in the arm treated with warfarin when a PFO was present (6). The evidence seems to indicate that warfarin might be more appropriate for secondary prevention in patients with "highrisk" PFO; however, it was associated with an increase in bleeding complications.

New anticoagulation agents are now available, and it will be interesting to see how the use of this new medication class will impact the secondary prevention of cryptogenic strokes in patients with a PFO, especially those with "highrisk" features.

Surgical therapy for secondary prevention of cryptogenic strokes

Surgical closure of PFO has shown good results, with a low incidence of recurrent events (3). However, due to the invasive nature of the intervention surgery is not a commonly used therapy. Currently, it is reserved for cases that will require surgical intervention for other concomitant heart conditions.

Transcatheter therapy for secondary prevention of cryptogenic strokes

Over the past two decades, several observational studies and randomized trials have evaluated the efficacy and safety of transcatheter (TC) closure of PFO for the secondary prevention of recurrent neurological events in patients with cryptogenic stroke. Some reports have shown that TC-PFO closure is a safe intervention that is associated with favorable short- and intermediate-term outcomes (19). Moreover, there are reports of excellent long-term outcomes when used for secondary prevention in patients with cryptogenic stroke (20). A systematic review and meta-analysis of observational studies showed the annual rate of strokes after PFO-closure is approximately 0.3-0.8 %, lower than 1.98-5.0 % in the medical group translating into an 84 % reduction in the rate of recurrent neurological events when compared with medical management (3,21).

A prospective study with long term follow-up showed that the presence of substantial residual shunt after TC-PFO closure was an important predictor of recurrent neurological events with a relative risk of 4.2 % (22-23). Therefore, the use of a second device for the secondary prevention of recurrent neurological events has been an important clinical question. A retrospective study by Diaz et al. involving 424 patients with 5 % substantial residual shunt found that the placement of a second device was safe and efficient in treating the residual shunt. Moreover, there were no neurological events at a mean follow-up of 3 years. However, the clinical significance of treating residual shunts with a second device would be at least difficult to prove, since the event rate is low even with untreated PFOs (24).

In 2012-2013, results from three randomized controlled trials (RCTs) failed to show a significant benefit of TC PFO closure over medical therapy in patients with cryptogenic stroke (25-27). One trial studied the Cardioseal device (25), the other two studied the Amplatzer device (26-27). The main limitation of all three RCTs was the small number of events during the follow-up, raising the possibility of a "type 2 error" (failure to detect a true difference between treatments due to lack of power). This lack of power can be explained by the difficulties in enrolling patients in the trials while the study devices were available as an off-label therapy.

Another important observation about the three RCTs is the inclusion of relatively "low risk" PFOs into their analysis (25-27). The presence of an-ASA, a feature that has been associated with a higher incidence of recurrent neurological events, in patients that were included in the RCTs ranged from 23-26 %.

A meta-analysis of the three RCTs that sought to overcome the lack of power of the individual studies found that in the intention-to-treat analyses there was a statistically significant 41 % risk reduction in stroke and/or transient ischemic attack in the TC PFO closure group when compared to medical treatment (28). Device implantation was successful in 93.8 % on average, being lowest with the STARFlex device in the CLOSURE I trial (89.4 %). Moreover,

the meta-analysis showed that the development of new-onset atrial fibrillation was significantly higher in the TC PFO group when compared with medical therapy. However, when stratifying by type of device (excluding STARFlex device), the Amplatzer device had a non-significant increased risk for developing new-onset atrial fibrillation. This analysis is consistent with a meta-analysis of observational studies showing that STARFlex or CardiolSEAL, but not the Amplatzer device was associated with an increased risk of developing new-onset atrial fibrillation (29). Rengifo-Moreno et al. also showed that subjects with a significant shunt (substantial vs. trace, none, or moderate) tended to decreased vascular events when randomized to the TC PFO closure compared with medical therapy (28).

A subgroup analysis of the patients enrolled in the CLOSURE I trial, identified diabetes and atrial fibrillation as independent predictors of recurrent stroke. Therefore, a substantial proportion of recurrent events within the CLOSURE I trial were not due to paradoxical embolization but (29) were related to atrial fibrillation identified post-randomization and diabetes.

Recently, 3 RCTs and long-term follow-up of the RESPECT trial demonstrated that TC PFO closure was associated with a significant reduction in recurrent stroke compared with medical therapy alone (30-34) (Table 1). Unlike previous RCTs, the more recent trials (REDUCE, CLOSE, and DEFENSE-PFO) enrolled patients who had PFO with high-risk features, used a standardized evaluation to define previous cryptogenic stroke resulting in a lower likelihood of alternative causes of recurrent strokes, excluded patients with lacunar strokes, uncontrolled vascular risk factors, as well as with overt alternative causes of their index strokes, and used a reference treatment group that included patients who received antiplatelet therapy alone (as opposed to antiplatelet and/or anticoagulation in previous trials). A recent meta-analysis of 6 RCTs including 3,560 patients showed that TC PFO closure was associated with a lower risk of recurrent stroke compared with antithrombotic therapy (RR 0.36, 95 % CI 0.17-0.79). The beneficial effect of TC PFO closure was larger in patients with ASA or large shunt (RR 0.27, 95 % CI 0.11-0.70) compared with patients without these high-risk anatomical features (RR 0.80, 95 % CI 0.43-1.47). New-onset atrial fibrillation was more common in patients randomized to TC PFO closure vs. antithrombotic therapy alone (RR 4.33, 95 % CI 2.37-7.98). Based on data from extended follow-up of the RESPECT trial as well as that from the recent trials (30-34), the Food and Drug Administration approved the Amplatzer PFO Occluder (Abbott Vascular, Chicago, IL) in 2016 and the GORE Cardioform Septal Occluder (W.L. Gore and Associates, Newark, DE) in 2018 for TC PFO closure for secondary prevention of recurrent ischemic strokes in patients with cryptogenic stroke.

A multi-disciplinary approach with input from cardiologists, neurologists, hematologists, and interventional cardiologists provides the best therapeutic plan for each patient taking in to account the available data, but also, medical, social, and occupational considerations.

PFO Closure and symptomatic right to left shunting and hypoxemia

Pulmonary and critical care providers are often evaluating patients with hypoxemia and need to know when to consider assessment for PFO in their evaluation of refractory hypoxemia. No guidelines exist for PFO closure leading to hypoxemia; however, case series and anecdotal evidence suggest dramatic symptomatic relief post-closure (35). Closure should be avoided in patients with high right-sided pressures as this can lead to clinical decline. PFO-mediated hypoxemia occurs when deoxygenated venous blood from the right atrium enters and mixes with oxygenated arterial blood in the left atrium. Patients with an intracardiac right-to-left shunt may have profound hypoxemia out of proportion to underlying primary lung disease, even in the presence of normal right-sided pressures. The presence of right-to-left cardiac shunting can exacerbate the degree of hypoxemia in patients with underlying pulmonary disorders. In a subset of these patients, percutaneous PFO closure may result in a marked improvement in dyspnea and hypoxemia (35).

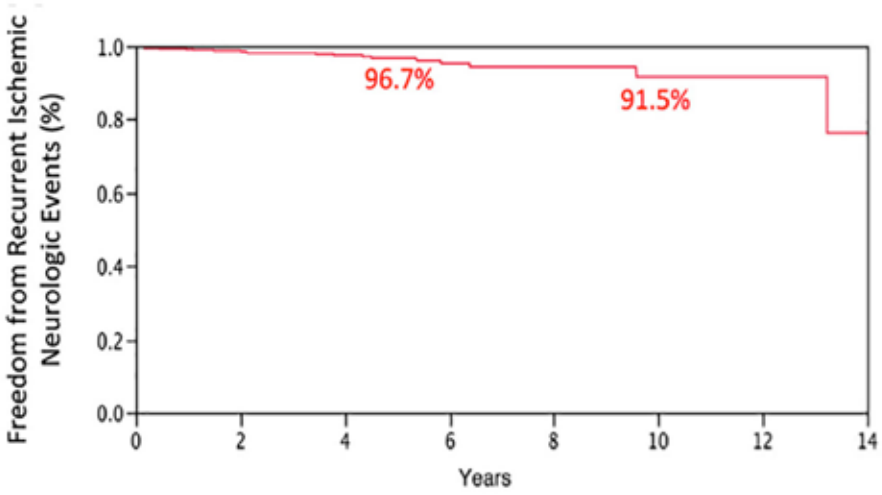

Figure 1. Kaplan-Meier curves depict the probability of freedom from recurrent ischemic neurologic events in subjects with previous cryptogenic stroke after successful PFO catheter closure. At 5- and 10-year follow-up, 96.7 % and 91.5 % of patients, respectively, were free of recurrent ischemic neurologic events. Modified from Inglessis I, Elmariah S, MD, Rengifo-Moreno P, MD, Margey R, O'Callaghan C, Cruz-Gonzalez I, Baron S, Mehrotra P, Tan TC, Hung J, MD, Demirjian Z, Buonanno F, Ning MM, Silverman SB, Cubeddu RJ, Pomerantsev E, Schainfeld RM, Dec GW, Palacios IF. Long-term experience and outcomes with transcatheter closure of patent foramen ovale. J Am Coll Cardiol Intv. 2013;6:1176-1183.

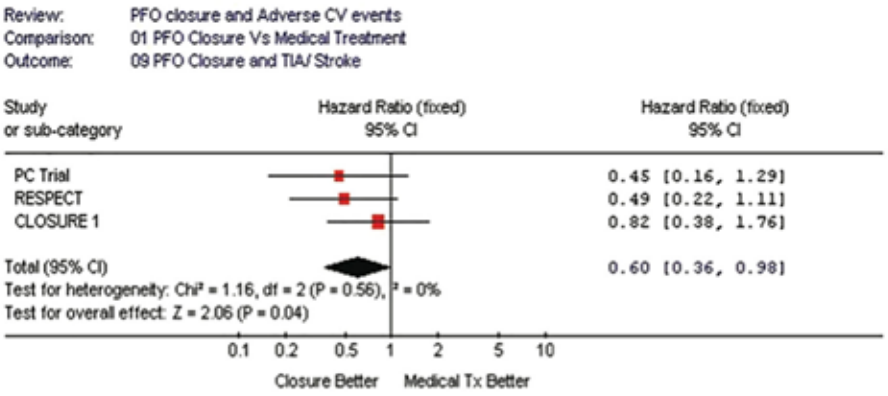

Figure 2. Meta analysis of comparison of PFO closure vs. medical treatment on adverse CV events and TIA/stroke. All three studies presented a composite outcome (death, recurrent neurological events, and peripheral embolism) based on intention-to-treat analyses showing a possible benefit of the TC PFO closure that was borderline statistically significant when compared with medical treatment, pooled HR = 0.67, 95 % CI (0.44–1.00), *P*-value = 0.05. Modified from Rengifo-Moreno P, Palacios IF, Junpaparp P, Witzke CF, Morris LD, Romero-Corral A. Patent foramen ovale transcatheter closure vs. medical treatment on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J. 2013;34(43):3342-3352.

Table 1

Characteristics of RCTs comparing transcatheter PFO closure versus medical therapy

	CLOSURE 1	PC Trial	RESPECT (Extended Follow-Up)	CLOSE	REDUCE	DEFENSE-PFO
Year of Publication	2012	2013	2017	2017	2017	2018
Design	Open-label, 2-arm, superiority	Open-label, parallel assignment	Open-label 499/481	Open-label, 3-group, superiority	Open-label 441/223	Open-label, superiority
N	447/462	204/210		238/235*		60/60
Inclusion Criteria	18 to 60 years of age; ischemic stroke or TIA within the previous 6 months; evidence of a PFO, as documented by TEE with a bubble study.	<60 years of age; PFO documented on TEE and no other identifiable cause of clinically and radiologically proven stroke, TIA or extra-cranial peripheral thromboembolism.	18 to 60 years of age; cryptogenic ischemic stroke (clinically and/ or radiologically proven) within previous 270 days; PFO identified on TEE	16 to 60 years of age; ischemic stroke within the previous 6 months with no identifiable cause other than a PFO with an associated ASA or large inter-atrial shunt detected on TEE	18 to 59 years of age; cryptogenic ischemic stroke (clinically and/or radiologically proven) within 180 days; PFO with a right-to-left shunt on TEE.	18 to 80 years of age; ischemic stroke within 6 months with no identifiable cause other than high-risk PFO (ASA with excursion ≥15 mm, hypermobile ≥10 mm, or large PFO ≥2 mm by TEE) with right-to-left shunt.
Exclusion Criteria	Any identified potential cause of ischemic stroke or TIA other than the PFO, such as clinically significant carotid artery stenosis, complex aortic-arch atheroma, clinically significant left ventricular dysfunction or left ventricular aneurysm or atrial fibrillation.	Any identifiable cause for the thromboembolic event other than PFO; contrain-dication/other indication for medical therapy; previous PFO closure; severe CNS disease.	Another identifiable mechanism of stroke; contra-indication to medical/device therapy; limited life expectancy.	Another cause of stroke associated with PFO; isolated ASD or ASD with PFO but with a hemodyna-mically significant left-to-right shunt requiring closure; previous PFOc closure; contraindication/ other indication for medical therapy	Another identifiable cause of stroke; uncontrolled diabetes mellitus; angina, uncontrolled hypertension; autoimmune disease; a recent history of alcohol or drug abuse; other specific indications for anticoagulation.	History of myocardial infarction, unstable intracranial bleeding, neurological disorders, left ventricular systolic dysfunction with aneurysm or akinesia, contraindications to antiplatelet therapy, oran underlying malignant disease.
Closure Device(s)	STARFlex (NMT Medical Inc., Boston, MA)	Amplatzer PFO Occluder Vascular, Chicago, IL)	Amplatzer PFO Occluder (Abbott Vascular, Chicago, IL)	Amplatzer PFO Occluder or Cribriform; STARFlex; CardioSeal; Intrasept PFO; PFOStar; HELEX; Premere; PFO occlude OCCLUTECH; GORE CARDIOFORM Occluder	HELEX or GORE CARDIOFORM Septal Occluder (W.L.Gore and Associates, Newark, DE)	Amplatzer PFO Occluder Vascular Chicago, IL)
Medical Therapy	Warfarin (INR 2-3), aspirin 325 mg/day, or both	Antiplatelet therapy or oral anticoagulation at the discretion of the treating physician	Aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole.	Aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole (Antiplatelet Group)	Aspirin alone (75 to 325 mg/day), a combinationof aspirin (50 to 100 mg/day) and dipyridamole (225 mg/day).or clopidogrel (75 mg/day).	Aspirin, aspirin + clopidogrel (75 mg/ day),aspirin + cilostazol (200mg/day,orwarfarin (INR 2-3)
Procedural Success	89.4%	95.9%	99.1%	99.6%	98.8%	100%
Follow-Up	2 years	Mean 4.1 years in the PFO closure group and 4.0 years in the medical therapy group.	Median (IQR) 5.9 (4.2-8.0) years.	Mean±SD 5.4±1.9 years in PFO closure group and 5.2±2.1 years in the antiplatelet-only group.	Median (IQR) 3.2 (2.2-4.8) years.	Median (IQR) 2.8 (0.9-4.1) years
Primary Endpoint	Composite of stroke or TIA during 2 years, all-cause death during the first 30 days, and neurological death between 31 days and 2 years	Composite of death, nonfatal stroke, TIA, or peripheral embolism.	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death from any cause (within 30 days after device implantation or 45 days after randomization, whichever occurred later).	Fatal or nonfatal stroke.	Two co-primary endpoints – clinical ischemic stroke and new brain infarction (composite of clinical ischemic stroke or silent brain infarction detected by the presence of at least one new hyperintense lesion of ≥3 mm in diameter on T2-weighted MRI)	Composite of stroke, vascular death, or Thrombolysis In Myocardial infarction–defined major bleeding.

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…continuación de Table 1.

	CLOSURE 1	PC Trial	RESPECT (Extended Follow-Up)	CLOSE	REDUCE	DEFENSE-PFO
Secondary Endpoints	Major bleeding, all-cause death, stroke, TIA, and transient neurologic events of uncertain cause.	Individual components of the primary endpoint, as well as cardiovascular death, new arrhythmias (particularly new-onset atrial fibrillation), myocardial infarction, hospitalization related to the PFO or its treatment, device problems, and bleeding.	Complete closure of the PFO on the 6-month follow-up TEE; absence of recurrent symptomatic nonfatal ischemic stroke or cardiovascular death; absence of a TIA.	Composite of ischemic stroke, TIA, or systemic embolism; disabling stroke; ischemic stroke; cerebral hemorrhage; TIA; systemic embolism; all-cause death; death from vascular-related causes; the success of device implantation; and success of PFO closure.	The success of PFO closure; adverse events.	Asymptomatic ischemic stroke on follow-up MRI at 6 months from randomization.

*in PFO closure vs. antiplatelet only groups
CLOSURE 1 = Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; PC Trial = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing; PFO Closure to Established Current Standard of Care Treatment; CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; REDUCE = GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale; DEFENSE-PFO = Device Closure Versus MedicalTherapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale; TIA = Transient ischemic attack; PFO = Patent foramen ovale; TEE = Transesophageal echocardiography; INR = Iinternational normalized ratio; CNS = Central nervous system; SD = Standard deviation; ASA = Atrial septal aneurysm; IQR = Interquartile range; MRI = Magnetic resonance imaging.

PFO Closure and platypnea/ortodeoxia syndrome

Platypnea-orthodeoxia syndrome (POS) is an uncommon condition of positional dyspnea (platypnea) and hypoxemia (orthodeoxia). The symptoms occur when the patient is upright and resolve quickly with recumbency. These findings are the opposite of those typically seen in cases of advanced heart failure and can pose a diagnostic dilemma. Causes can be broadly categorized into 4 groups: intracardiac shunting, pulmonary shunting, ventilation-perfusion mismatch, or a combination of these. Platypnea-orthodeoxia syndrome (POS) is an uncommon condition of positional dyspnea (platypnea) and hypoxemia (orthodeoxia). Platypnea-orthodeoxia syndrome should be suspected when normal arterial oxygen saturations are recorded while an individual is supine, followed by abrupt declines in those saturations when upright. Further investigations with the use of imaging and cardiac catheterization aid in the evaluation. When platypnea-orthodeoxia syndrome is due to intracardiac shunting without pulmonary hypertension, intracardiac shunt closure can be curative (35-36). We reported our experience with catheter closure of PFO in 18 patients presenting with platypnea orthorexia syndrome at the Massachusetts General Hospital. There were 8 females (44 %) and 10 males (56 %), mean age 65 ± 18 years. Mean supine oxygen saturation was 92.5 ± 6 %, mean upright oxygen saturation 82.6 ± 5.4 %. Associated conditions included ischemic CVA 1 (5 %), pulmonary embolism 1 (5 %). Pulmonary hypertension 1 (5 %), severe tricuspid regurgitation 1 (%%), obstructive sleep apnea 1 (5 %), and COPD 1 (5 %). A PFO was present in 16 (89 %) patients and an ASD in 2 (11 %) patients. A hypermobile atrial septum was present in 4 (22 %) patients. The mean right atrium was 9.6 ± 5.6 mm Hg and systolic right ventricular pressure were 13.9 ± 7.8 mm Hg. Catheter closure procedure was successful in 18 (100 %) of patients. Residual shunt was small in 8 (44 %), moderate 0 (0 %) and large in 0 (0 %) and non in 10 (55 %) of patients. A Sideris Buttoned device was used in 6 (33 %) of patients, a CardioSeal in 11 (61 %) of patients, and an Amplatzer atrial occluder in 1 (5 %) of patients. The average device size was 29.5 ± 7.7 mm, and the Device size/ASD or PFO size was 2.5 ± 0.7 mm. Mean arterial oxygen saturation increased from 83 % to 96 %. At long term follow-up, 2 patients had reintervention for significant recurrent shunt (11 %) for malalignment devices with a significant shunt, one patient had recurrent symptoms (1.9 %). Seventy-nine percent of the patients were free of recurrent symptoms at a long-term follow-up of 2.9 years (35).

PFO and migraines

The association between migraineurs with aura and the presence of a PFO remains controversial and small non-randomized studies assessing response to PFO closure have provided inconsistent results (37-51).

Two major mechanisms have been proposed to explain the putative association of PFO and migraine. First, vasoactive substances into the general circulation may bypass the metabolic filters of the lung thereby altering the natural equilibrium. Substance P and serotonin have been suggested as possible culprit agents. Furthermore, it has been suggested that patients with migraine have a high rate of abnormal pulmonary function that could result in decreased metabolism of vasoactive amines (47). Second, PFO may result in the passage of microemboli resulting in hypoxia and ischemia in the occipital cortex (45,51).

The MIST trial (52), studied the Starflex technology versus a sham procedure in a randomized fashion. The primary endpoint was the cessation of migraine headaches. The primary end-point was not significantly different between both arms. However, the exploratory analysis supported the further investigation.

The PRIMA trial was presented at TCT 2014 (53). In PRIMA in 107 migraineurs were randomized to either PFO closure or medical therapy were only 45 of 53 randomized to the device agreeing to undergo the procedure. Of these, only 41 underwent PFO closure. At one year, the primary end-point of mean reduction in headache days from baseline was 2.9 in the closure group and 1.7 in the medical-treatment group, a nonsignificant difference. However, for the secondary endpoint, reduction in migraine-with-aura days, closure patients saw reductions significantly greater than the control group. These results highlight the need for RCTs with enough power and appropriate primary end-point, to investigate the impact of TC PFO closure in migraineurs with aura.

Ben Assa et al evaluated the long-term effect of catheter closure of PFO on migraineurs with and without aura and examined the effect of residual right to left shunt. In this study we reported the impact of residual shunt post-PFO closure in a cohort of 110 migraineurs who underwent PFO closure; 77.0 % had an aura and 23.0 %were without aura, and 91.0 % had a cryptogenic stroke (54). During the long-term median follow-up of 3.2 (interquartile range: 2.1 to 4.9) years, there was a significant improvement in migraine symptoms in migraineurs with or without aura. Migraine burden was reduced by >50 % in 87.0 % of patients, and symptoms were completely abolished in 48 %. Presence of aura was associated with abolishment of migraine (odds ratio: 4.30; 95 % confidence interval: 1.50 to 12.30; p= 0.006). At 6 months after PFO closure, the residual right-to-left shunt was present in 26 % of patients. Absence of right-to-left shunt was associated with improvement in migraine burden by >50 % (odds ratio: 4.60; 95 % confidence interval: 1.30 to 16.10; p= 0.017). Long-term follow-up after transcatheter PFO closure was associated with significant improvement in migraine burden. Aura was a predictor of abolishing symptoms. The absence of residual right-to-left shunt was a predictor of a significant reduction in migraine burden (54).

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