Review of Data and Discussion – Who Should Undergo Patent Foramen Ovale Closure in 2014?

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Abstract

A patent foramen ovale is a relatively common finding in the general population and is associated with a number of conditions, including cryptogenic stroke. In 2014, percutaneous patent foramen ovale (PFO) closure is a frequently performed procedure; the bulk of these procedures being carried out for secondary prevention of cryptogenic stroke, along with other indications, such as prevention of decompression illness, platypnoea-orthodeoxia syndrome and migraine. Of these conditions the largest body of evidence available is for cryptogenic stroke and there is ongoing debate of the benefit of PFO closure over medical therapy. This article will review the available evidence of PFO closure in each of these contexts, with a particular focus on randomised controlled trials, and endeavour to outline in whom the evidence suggests closure should be considered.

Keywords

Stroke, cryptogenic embolism, patent foramen ovale, migraine, decompression illness, platypnoea-orthodeoxia syndrome

Disclosure: Brian Clapp has received consulting/speaking fees from St. Jude Medical, Boston Scientific, Medtronic and Abbott Medical.

Amit Bhan has no conflicts of interest to declare.

Received: 4 April 2014 **Accepted:** 26 April 2014 **Citation:** *Interventional Cardiology Review*, 2014;9(2):115–120

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The foramen ovale is an integral component of the fetal circulation, responsible for facilitating the flow of placental pre-oxygenated venous blood from the right atrium to the left, thereby circumventing the quiescent developing lungs. Physiological closure is usually achieved after birth when pulmonary vascular resistance and right heart pressures reduce, resulting in the left atrial pressure exceeding that of the right. The 'flap valve' is pressed up to the secundum septum and seals over; often in the early postnatal period, and this is usually completed within the first year of life. However, it has long been known that patency of the foramen ovale frequently persists into adulthood. Although not always shunting at rest, increases in right atrial pressure (as occurs during sneezing or a Valsalva manoeuvre) can cause short periods of significant passage of deoxygenated blood at the atrial level.

A patent foramen ovale (PFO) is usually asymptomatic; however, its presence has been implicated in a number of conditions including, but not limited to, paradoxical embolism (causing a stroke, peripheral arterial occlusion or myocardial infarction with normal coronary arteries), migraine (particularly those occurring with aura), decompression illness and the more rare and underdiagnosed platypnoea-orthodeoxia syndrome (POS). In addition, it may increase risk in large-scale orthopaedic surgery and neurosurgery performed in the seated position.

It is hypothesised that bloodborne material from the venous circulation, normally excluded from the systemic side during passage through lung vasculature, bypasses this through the PFO. Such materials could

include thrombus, air, vasoactive substances or even fragments of bone and fat in the context of fractures and surgery.

As a result, ever since the first report in 1988¹ of temporary closure of a PFO with a Swan-Ganz catheter to facilitate surgery, abolishing this shunt when found in specific circumstances has been attractive, particularly with modern day low-risk transcatheter techniques.

Prevalence of Patent Foramen Ovale in the General Population

A number of observational studies, both *in vivo* and pathological, have indicated a variable prevalence. In 1984 Hagen et al.² demonstrated from 965 autopsy specimens an overall prevalence of 27.3 %, which decreased with age; 34.3 % in the first three decades, 25.4 % during the 4th to 8th decades and 20.2 % during the 9th and 10th decades. The size ranged from 1 mm to 19 mm and was inversely related to age. Fifteen years later Meissner et al.³ found a similar rate of PFO *in vivo*. Using transoesophageal echocardiography (TOE) without contrast in 585 subjects over 45, they demonstrated a prevalence of 26 % of PFO. Furthermore, increased numbers within families has suggested a genetic basis for the failure of closure.⁴

Patent Foramen Ovale in Cryptogenic Stroke

A cryptogenic stroke (CS) occurs when no apparent cause can be found despite extensive investigation. The concept was initially developed for the stroke Data Bank by the US National Institute of Neurological and Communicative Disorders and Stroke⁵ and has been shown to account for up to 40 % of all strokes.⁶

Paradoxical embolism (PE) through a PFO has been implicated in such strokes since the 19th century, when the distinguished pathologist Julius Cohnheim performed an autopsy on a young lady who had succumbed to a large stroke.⁷ He noted venous thrombus and a large PFO, and hypothesised that a clot had formed in the lower limb veins and then traversed the PFO and onwards to the cerebral circulation.

In the 1950s case reports appeared in the medical literature of thrombus trapped in PFOs.^{8–10} However, it was not until the 1980s, with the advent of wider spread echocardiography, that researchers began searching for evidence to support a link between ischaemic strokes or transient ischaemic attacks and PFOs.

In 1988 two observational studies were published suggesting an association between PFO and cryptogenic stroke.^{11,12} At first, Lechat et al. demonstrated that those under 55 with CS had a 54 % prevalence of PFO, while Webster et al. found 50 % prevalence in their patients with ischaemic stroke or transient ischaemic attack (TIA). Both studies utilised contrast echocardiography to detect PFOs. A number of other studies have corroborated the link, even extrapolating to older patients with CS.^{13,14}

An associated atrial septal aneurysm (ASA), when the septum moves more than 1 cm during the cardiac cycle, has been shown to have a synergistic effect to increase risk.¹⁵ Mas et al.¹⁶ investigated the role of PFO and ASA in recurrent stroke. They followed 581 patients (under the age of 55) with a history of CS treated with aspirin – a TOE demonstrated an atrial septal abnormality in 48 %. After four years the rate of recurrent stroke was 6.2 % in those without an atrial septal abnormality, 5.6 % in the group with PFO alone and 19.2 % in the group with both PFO and ASA. A further meta-analysis of 15 case control studies¹⁷ revealed that stroke under the age of 55 was associated with either PFO or ASA alone or PFO and ASA together.

Not all studies found such a clear association. In the Patent Foramen Ovale in Cryptogenic Stroke study (PICCS),¹⁸ which was a TOE substudy of the Warfarin-Aspirin Recurrent Stroke study (WARSS), there was no relationship between recurrent stroke and PFO, regardless of size.

The first case series of catheter-based permanent PFO closure was published in 1992.¹⁹ Bridges et al. used a double umbrella device on 36 patients with presumed complications of PE (31 ischaemic strokes, 25 TIAs, four systemic arterial emboli and two brain abscesses). As well as a high rate of shunt closure and a very low rate of complication, they did not see any post-procedural events during a follow-up of 8.4 months.

Numerous small non-randomised series followed, brought together in a pooled analysis of 16 studies²⁰ (10 of transcatheter closure and six of medical therapy) that showed the one-year rate of recurrent stroke in medically treated patients was 3.8–12.0 % compared with 0.0–4.9 % in those who underwent device closure. On the basis of these observations it was predicted that a randomised trial would prove that PFO closure was preferable to medical therapy to prevent recurrent cryptogenic stroke.

Recently there have been three published randomised trials – 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 (CLOSURE I),²¹ the Randomized clinical trial comparing percutaneous closure of patent foramen ovale using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism (PC-Trial)²² and the Randomised Evaluation of recurrent Stroke comparing PFO closure to Established current standard of Care Treatment (RESPECT) trial²³ – with a further one currently recruiting (GORE HELEX™ Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale [REDUCE]), designed to determine the effectiveness of PFO closure as secondary prevention in cryptogenic stroke (see *Table 1*).

CLOSURE I

A multicentre, randomised, open-label trial of device closure with a STARFlex occluder (NMT Medical Inc., Boston, Massachusetts, US) versus medical therapy (aspirin and/or warfarin). The primary endpoint was a composite of stroke or TIA during two years of follow-up, death from any cause during the first 30 days, or death from neurological causes between 31 days and two years. The cumulative incidence (Kaplan–Meier estimate) of the primary endpoint was 5.5 % in the closure group (447 patients) as compared with 6.8 % in the medical therapy group (462 patients) (adjusted hazard ratio [HR], 0.78 95 % confidence interval [CI] 0.45–1.35 $p=0.37$). The respective rates were 2.9 % and 3.1 % for stroke ($p=0.79$), and 3.1 % and 4.1 % for TIA ($p=0.44$). Of concern, in the device arm there was a greater incidence of atrial fibrillation (5.7 versus 0.7 % $p<0.001$) and 1.1 % of patients had gross thrombus visible on the device by TOE at six months. Rates of successful device implantation were surprisingly low at only 89 % with a large number of residual shunts – effects that may be device attributable. In addition, a cause, other than paradoxical embolism, was usually apparent in patients with recurrent neurological events.

PC-Trial

A European study of 414 patients randomised to closure with the Amplatzer PFO occluder (St. Jude Medical, Saint Paul, MN, US) or to receive medical therapy (antiplatelet or anticoagulation at the discretion of the treating physician). The primary endpoint was a composite of death, non-fatal stroke, TIA or peripheral embolism. The primary endpoint occurred in 3.4 % (7) of the 204 device treated patients and 5.2 % (11) of the 210 medically treated group (HR 0.63 95 % CI 0.24–1.62 $p=0.34$). The power of the study was further reduced by a large number of patients (65) being lost to follow-up and 28 patients crossing from the medical to the device arm.

RESPECT Trial

This trial enrolled 980 patients in the US and Canada, and randomised in a 1:1 manner to receive either medical therapy (75 % with antiplatelet therapy and warfarin in the remainder) or the Amplatzer PFO occluder in addition to antiplatelet therapy. They were followed up for a maximum of seven years over a mean of 2.6 years. Raw data analysis was not possible due to a greater rate of drop-out in the medical arm producing a statistically lower total patient-years of follow-up. In the intention-to-treat analysis there was a very low rate of recurrent stroke with no statistical difference between the groups: 6 % (16) in the medical arm versus 2 % (9) in the device arm ($p=0.08$ HR 0.49 95 % CI 0.22–1.11). However, a number of events occurred prior to closure and analysis as treated found device treatment to be better than medicine with five and 16 events, respectively

Table 1: Summary of Randomised Controlled Trials Regarding Patent Foramen Ovale Closure in the Secondary Prevention of Cryptogenic Stroke

Trial	Design	Study Population	Best Medical Therapy	Device	Primary Endpoint	Outcomes	Comments
CLOSURE I (2012)	Randomised multicentre (87 sites in US and Canada)	18–60 with recent stroke 909 in total (447 in device arm and 462 in medical arm)	Aspirin +/-or warfarin	STARFlex (NMT)	Composite of stroke or TIA during 2 year follow-up, death from any cause during the first 30 days, or death from neurological causes between 31 days and 2 years	5.5 % in closure group versus 6.8 % (adjusted HR 0.78 95 % CI 0.45–1.35 p=0.37). The respective rates were 2.9 % and 3.1 % for stroke (p=0.79), and 3.1 % and 4.1 % for TIA (p=0.44)	High rates of residual shunts and complications attributed to device design
PC-Trial (2013)	Randomised multicentre (29 sites in Europe, Australia, Brazil and Canada)	<60 with recent stroke or TIA 414 patients (204 in device arm and 210 in medical arm)	Antiplatelet therapy or oral anticoagulation (at discretion of treating physician)	Amplatzer PFO occluder (St. Jude)	Composite of death from any cause, non-fatal stroke, TIA and peripheral embolism	3.4 % in the closure group versus 5.2 % (HR 0.63 95 % CI 0.24–1.62 p=0.34). Non-fatal stroke 0.5 % in the closure group versus 2.4 % (HR 0.20 95 % CI 0.02–1.72 p=0.14) and TIA occurred in 2.5 % and 3.3 %, respectively (HR 0.71 95 % CI 0.23–2.24 p=0.56)	Probably underpowered as low number of recurrent events
RESPECT (2013)	Randomised multicentre (69 sites in US and Canada)	Age 18–60 with recent stroke or TIA 980 patients (499 in closure arm and 481 in medical arm)	Aspirin or warfarin or clopidogrel or aspirin + dipyridamole or aspirin + clopidogrel	Amplatzer PFO occluder (St. Jude)	All-cause mortality recurrence of fatal or non-fatal ischaemic stroke	6 % in the closure group versus 2 % in the device arm (HR 0.49 95 % CI 0.22–1.11 p=0.08) Intention-to-treat	Subanalyses demonstrated greater risk reduction with closure in context of ASA or substantial shunt
REDUCE (2018)	Randomised multicentre (~80 sites in US, Canada and Europe)	Age 18–60 with recent presumed cryptogenic stroke or embolism. Estimated recruitment 664	Antiplatelet therapy only	Gore Septal Occluder (Gore)	Freedom from recurrent ischaemic stroke or imaging-confirmed TIA at least 24 months post-randomisation	Pending	Estimated primary completion date 2015

ASA = atrial septal aneurysm; CI = confidence interval; HR = hazard ratio; PFO = patent foramen ovale; TIA = transient ischaemic attack.

(HR 0.27 95 % CI 0.00–0.75 p=0.007). Analysis of the pre-specified per-protocol groups, which included the patients who received and adhered to the allotted therapy and had no major violation of inclusion or exclusion criteria, also showed a significant difference: six events in closure group versus 14 (HR 0.37 95 % CI 0.14–0.96 p=0.03). Furthermore, trends from subgroup analyses suggested that those with a substantial shunt (defined as patients with over 20 microbubbles on TOE) and those with associated ASAs had more benefit, and that recurrent events were anatomically more likely to be non-PFO related in the closure group.

REDUCE Trial

The REDUCE trial (ClinicalTrials.gov identifier: NCT00738894) is ongoing and currently enrolling. The aim is to enrol just under 700 patients in around 80 sites in the US, Canada and Europe, and compare the Gore® Septal Occluder (Gore) with antiplatelet medication only in those with recent presumed CS or embolism. Estimated primary completion date is 2015 and publication will probably be in 2018.

None of the published trials met their primary endpoints, although issues have been raised about them and their design. The relatively

low number of events in all the trials (vastly less than predicted when the trials were designed²⁴) meant that insufficient power is probable. Specifically in the PC-Trial, an intended power of 80 % was reduced to 40 % due to the overall lack of events.²⁵ This was compounded by slow recruitment, which in CLOSURE I trial led the investigators to reduce the target sample size by over 600 patients. Such recruitment problems may have indicated that clinicians excluded the patients perceived at highest risk, preferring to go directly to device closure, thus biasing the studies in favour of medical therapy – which itself was non-standardised. Additionally, the RESPECT trial suffered with a large number of dropouts from the medical arm, a significant proportion of who underwent off-label device closure. There was also variation in rigour with which PFO-probable strokes were enrolled between studies – a particular problem in the CLOSURE 1 study as the inclusion of TIAs increases uncertainty. A further criticism of the trials was length of follow-up. The relatively young population are clearly at risk for many decades, but importantly, along with ageing usually comes other risks for stroke, not related to PE – making simply extending the follow-up of current studies potentially flawed.

None of the trials incorporated any form of risk stratification within the device closure groups, meaning those with lower risk anatomy

Table 2: Summary of Randomised Trials Regarding Patent Foramen Ovale Closure in Migraine

Trial	Design	Study Population	Device	Primary Endpoint	Outcomes	Comments
MIST (2008)	Randomised multicentre sham controlled	18–60 years old with failed medical therapy for migraine 147 patients (74 in device arm and 73 in sham arm)	STARFlex (NMT)	Migraine cessation	No significant difference between the two groups at 6 months, 3 patients in each arm (p=0.51)	Short follow-up, potentially high rates of residual shunt (no echo core lab to assess shunts)
PREMIUM	Randomised multicentre (30 sites in US)	18–65 years of age migraine attacks (with and without aura). Device closure versus sham procedure. Estimated enrolment 230	Amplatzer PFO occluder (St. Jude)	Reduction in number of migraine attacks	Pending	Estimated primary completion date March 2014

PFO = patent foramen ovale.

may have obscured the benefit to those with higher risk anatomy (for example with concomitant ASA). There was an attempt to address this in the RESPECT trial with a subgroup analysis, and also in a recent meta-analysis performed on the three trials. A study by Rengifo-Moreno et al.²⁶ included 2,303 patients (1,150 undergoing device closure and 1,153 receiving medical therapy) with a mean follow-up of 3.5 years. There was a significant reduction in stroke and TIA in the device group compared with medical therapy (HR 0.59 95 % CI 0.36–0.97 p=0.04) and a suggestion, although not statistically significant, that patients with a substantial shunt benefitted the most (HR 0.35 95 % CI 0.12–1.03 p=0.06). A further paper by Khan et al.²⁷ also suggested a beneficial effect from device closure with hazard ratios of 0.67 (95 % CI 0.44–1.00) in the intention-to-treat cohort, 0.62 (95 % CI 0.40–0.95) in the per-protocol group and 0.61 (95 % CI 0.40–0.95) in the as-treated group.

These results must be interpreted with caution due to the heterogeneity in the trials; particularly concerning medical therapy and device employed. However, Khan et al. attempted to address this by also pooling only the results from the RESPECT trial and PC-Trial, as they both employed the Amplatzer device. This appeared to enhance the robustness of their findings with hazard ratios of 0.54 (95 % CI 0.29–1.01), 0.48 (95 % CI 0.24–0.94) and 0.42 (95 % CI 0.21–0.84) in the intention-to-treat, per-protocol and as-treated populations, respectively. In addition, a further meta-analysis published last year by Ntaios et al.²⁸ showed that risk of recurrent stroke was reduced in those closed with the Amplatzer device but not in those who had a STARFlex device.

The Risk of Paradoxical Embolism (RoPE) study,²⁹ has been used to develop and test risk models for application in selecting patients in the future most likely to benefit clinically and in designing ongoing trials of PFO closure for CS.

Overall these studies indicate that patients are at a lower risk of recurrent stroke than initially expected, PFO closure can be performed very safely with the Amplatzer device and that there is likely to be additional benefit of device closure above medical treatment in carefully selected patients, and in particular those with large shunts, ASAs or both.³⁰

Migraine

The link between PFO and migraine, particularly with aura, was initially suggested in the late 1990s,^{31–33} and in non-randomised

retrospective analyses up to 80 % of patients who underwent PFO closure for alternative indications reported an improvement or even cessation of migraine. Wilmshurst et al.³⁴ contacted 37 patients who had undergone closure of a right to left shunt of whom 21 (57 %) had a history of migraine before the procedure (with aura in 16, without in five). During long-term follow-up, ten patients reported no further migraine symptoms with a further eight others reporting improvement in frequency and severity of migraines. A single-centre, non-randomised trial of PFO closure in the context of migraine in patients with high-risk (for PE) anatomy found a significant reduction in migraine in the device closed patients.³⁵

MIST Trial

The Migraine Intervention with STARFlex Technology (MIST) trial³⁶ is the only published randomised trial addressing the question of PFO closure in the context of migraine, and did not meet its primary endpoint (complete freedom from headache) or significantly reduce headache burden. Follow-up was short (six months) and the inclusion criteria may have selected refractory headache patients. The lack of an independent core echocardiography laboratory has led to controversy about the effectiveness of closure, and procedural complications were high at 6.8 %, which may have influenced the outcome of the study.

The Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management (PREMIUM) trial with a primary endpoint of reduced migraine attacks has finished recruiting and expects to release results in the next 12 months, and although now terminated, data may be available from the international Percutaneous Closure of Patent Foramen Ovale In Migraine With Aura (PRIMA) trial in due course. Studies summarised in Table 2.

Platypnoea-orthodeoxia Syndrome

In patients with POS, significant right to left shunting occurs dependent upon position leading to desaturation on sitting or standing. In the context of PFO this can occur in any situation where atrial septal geometry is modified or heart-lung relationships are altered. Examples of such situations are kyphoscoliosis, post-pneumonectomy, diaphragm paralysis and dilatation of the ascending aorta.

The first reported case of PFO closure for POS, performed surgically in 1991, was in a patient with PFO and idiopathic hemidiaphragm

paralysis.³⁷ Subsequently device closure in similar patients has been shown to eliminate hypoxia³⁸ and although rare, this clearly should be considered in all patients with restricting symptoms.³⁹

Diving and Decompression Illness

PFO has been associated with specific presentations of decompression illness in divers;^{40,41} studies have been performed to identify those at higher risk⁴² and closure following neurological decompression illness has been reported.⁴³ PFO closure in continuing divers appears to prevent symptomatic neurological events and asymptomatic ischaemic brain lesions during long-term follow-up,⁴⁴ and has been shown to reduce arterial, although not venous, bubbles in simulated dives.⁴⁵

Neither recreational nor professional bodies recommend PFO screening in divers unless there has been an episode of a potentially PFO-attributable decompression illness. Given the complexity of assessing this, review by a physician with specific knowledge of diving medicine is mandatory. Recreational divers can be advised to restrict themselves to shallow depths (usually less than 15 m) and to adopt techniques to reduce nitrogen super-saturation including diving with nitrox using air tables and avoiding repetitive dives, or to consider PFO closure.⁴⁶ Professional divers will require sign-off by a diving specialist and this often includes removal of a shunt if clinically relevant to avoid disabling employment restrictions.³⁰

Surgery in the Seated Position

Some neurosurgery is preferably performed in the seated position and paradoxical air embolism is a well-recognised hazard. Perkins-Pearson et al.⁴⁷ demonstrated reversal of the normal inter-atrial pressure gradient making patients with an atrial communication at risk of PE, and

therefore the presence of a PFO is generally regarded as an absolute contraindication to surgery in the seated position. There are cases of PFO closure performed in this setting;⁴⁸ however, there are no large studies and there remain questions about the timing of surgery post-intervention, with regard to endothelialisation of the device and duration of antiplatelet therapy.

Conclusion

The results of data so far suggest that in patients with CS, PFO closure may be beneficial in reducing the risk of recurrent vascular events when compared with medical treatment. Furthermore, when using the Amplatzer device this can be performed with a very low-risk profile. The decision to proceed with PFO closure should be made on a case-by-case basis with the expertise of a multidisciplinary team and patient involvement. It is likely that in those with truly CS and a significant PFO device closure is appropriate; especially in those with high-risk anatomy.

In addition, closure for professional divers who have suffered an episode of PFO-attributable decompression illness, as well as amateur divers who are not willing to give up the sport and are able to accept the small risk of the procedure, is appropriate. As the data for migraine prevention is weaker it should be considered a last resort in those with severe refractory migraine.

In all these situations a combined decision should be made by expert physicians, mainly neurologists, and an experienced interventional cardiologist, alongside an open discussion with the patient. Further data is eagerly anticipated to increase clarity regarding those specific patients most likely to benefit from device closure. ■

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