Review

Patent foramen ovale and cryptogenic stroke: is there still a role for percutaneous closure?

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Practice points

- Patent foramen ovale (PFO) is more common in patients with stroke of unclear etiology or cryptogenic stroke. This association does not explain cause and effect.
- Treatment options include medical therapy with antiplatelets or anticoagulation, or percutaneous PFO closure.
- A large number of observational studies suggest superiority of PFO closure over medical management.
- Three randomized controlled trials have been presented and/or published comparing PFO closure with medical management in patients with presumed cryptogenic thromboembolic events.
- The CLOSURE 1 trial had several shortcomings, questioning the applicability of its neutral results.
- The RESPECT trial is a well-conducted trial that shows superiority of PFO closure compared with medical management if data are analyzed 'as treated', while intention-to-treat analysis fails to reach statistical significance.
- The PC-Trial documents a similar trend in treatment benefit with PFO closure, but owing to low event rates is underpowered and failed to show superiority of PFO closure.
- Considering data available to date, PFO closure can be considered in a subgroup of patients with perceived higher risk of stroke recurrence, such as patients with thrombophilias, recurrent stroke, and presence of atrial septal aneurysm, PFO with large shunt or intolerance to medical management.

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SUMMARY Ischemic strokes and patent foramen ovale (PFO) are two common conditions. PFO is more commonly found in patients with cryptogenic strokes, the largest subset of patients with ischemic stroke. Over the past 20 years, a large body of evidence (retrospective data) has been generated evaluating medical management and percutaneous PFO closure, which suggests PFO closure may be superior to medical management. To date, three randomized controlled trials have been completed, one of which has been published (CLOSURE 1) and two have been presented recently (RESPECT and PC-Trial). Overall, these studies did not demonstrate superiority of device closure over medical therapy. This article reviews the current data of percutaneous PFO closure and tries to identify a subgroup of patients in whom PFO closure may still be of benefit.

Stroke is the primary cause of disability and the third most common cause of death in the USA [1]. The vast majority of strokes are ischemic in etiology. The most common stroke subtype is cryptogenic or stroke of unclear etiology [2]. This subgroup makes up 25–50% of all patients with ischemic stroke [3,4]. The remainders are cardioembolic, lacunar or large vessel arterial in etiology. In the search for possible causes of cryptogenic strokes, patent foramen ovale (PFO) has been identified as a possible culprit. PFO is a tunnel-like structure formed by the septum primum and septum secundum resulting in a connection between the right and left atria. The foramen ovale is a normal part of the fetal circulation, bypassing 'unnecessary' blood flow through the nonfunctioning lungs *in utero*. After birth, the foramen ovale remains patent in approximately 10–25% of the population depending on the method of PFO detection [5,6]. The first description of a so-called paradoxical embolism, a thrombus originating in the venous system passing through the PFO into the systemic circulation, came from Cohnheim in the 19th century [7]. The first case–control studies reporting a greater prevalence of PFO in patients with cryptogenic stroke compared with age-matched patients without stroke were published in the late 1980s [8,9]. Over the years, several more published reports make it clear that PFOs is twice as common in patients suffering from a cryptogenic stroke, compared with normal controls [10,11]. Without knowing the cause-and-effect relationship between the two prevalent conditions, cryptogenic stroke and PFO, closure of the PFO was postulated to be an effective treatment strategy, potentially superior to medical therapies such as antiplatelets or anticoagulation. The first report of percutaneous PFO closure utilizing devices designed for closure of secundum atrial septal defects (ASD) was published in 1992 by Bridges *et al.* [12].

In the following years, additional devices have been developed specifically for percutaneous PFO closure and a large number of case series describing outcomes of this catheter-based procedure have been reported [13–18]. More recently, a single, randomized controlled trial (RCT; CLOSURE 1) comparing PFO closure with medical therapy has been published with disappointing neutral results [19]. Two other RCTs (RESPECT and PC) have been completed and were presented at the Transcatheter Cardiovascular Therapeutics 2012 conference (22–26 October 2012, Miami, FL, USA). Both trials technically failed to reach their primary end points. One trial (REDUCE) comparing medical therapy and device closure is still enrolling patients. To date, this trial has enrolled approximately 50% of its cohort and enrollment completion is expected in approximately 2 years. This article reviews the current data of percutaneous PFO closure and attempts to answer the question of whether device closure still has a role in treatment of cryptogenic stroke and PFO.

Medical management

Prior to the ability to close PFO percutaneously, the only realistic treatment option was antiplatelet therapy or anticoagulants. Although PFO closure can be accomplished surgically, given the invasiveness of the procedure this was not common practice. Several studies have evaluated the recurrence rates of stroke in patients with PFO. Most frequently quoted are the PCISS, a subanalysis of the WARSS, as well as the PFO and ASA landmark study by Mas *et al.* [20–22]. In the PCISS, the recurrence rate of ischemic

stroke was high, averaging approximately 15% at 2 years. Patients were treated with aspirin or warfarin, which resulted in statistically nonsignificant different stroke rates (9.5% warfarin group vs 17.9% aspirin group, hazard ratio [HR]: 0.52; 95% CI: 0.16–1.67; p = 0.28). Presence of a PFO or atrial septal aneurysm did not affect the recurrence rate. By contrast, the study by Mas *et al.* exclusively included patients with cryptogenic stroke under the age of 55 years who were all treated with aspirin for secondary prevention following the first cryptogenic stroke [22]. The study revealed a risk of recurrent stroke of only 2.3% at 4-years follow-up in patients with PFO. This recurrence rate was identical to patients without PFO. However, patients with a PFO and atrial septal aneurysm had a much higher recurrence rate of stroke (15.2%) at 4-years follow-up. Attempting to clarify the risk of recurrent events in patients with PFO and cryptogenic stroke, Almekhlafi *et al.* performed a meta-analysis of the available data [23]. This meta-analysis included 15 studies of medically treated patients with cryptogenic stroke and PFO. The absolute rate of recurrent stroke or transient ischemic attack (TIA) was four events per 100 person-years. Evaluating only patients with stroke, the recurrence rate was 1.6 events per 100 person-years. Four of those 15 studies compared patients with and without PFO. It was noted that the relative risk for recurrent TIA or stroke was 1.1 (95% CI: 0.8–1.5), indicating no increased risk of stroke in patients with PFO compared with those without. The authors concluded that in medically treated patients, available evidence does not support an increased risk of recurrent ischemic events in patients with ischemic stroke with or without PFO. Hence, PFO closure could not be recommended.

Nonrandomized data evaluating PFO closure

Since the first report of percutaneous PFO closure in 1992 by Bridges *et al.* [12], a large number of case series describing the results of a variety of different closure devices have been reported. There has been an evolution of device design over the years. The early, rather cumbersome devices, such as the Rashkind umbrella, Clamshell or ASDOS occluder, have been replaced by simpler and probably more effective occlusion devices, such as the Amplatzer® device (St Jude Medical, MN, USA), Helex® (WL Gore and Associates, NY, USA), Occlutech®-Figulla® Flex (Occlutech, Helsingborg, Sweden) and Premere™ (St Jude Medical) devices **(Figure 1)** [24–27]. Ease of use of the device and design affects short-term complication risk and long-term performance of PFO closure [28,29]. Hence, clustering all case reports of PFO closure into a single result with an 'average' complication rate and long-term performance is of questionable value. Results of more contemporary PFO occluders are probably comparable to each other [30,31]. The technical success rate for PFO closure should be 100% or very close to this, and complete closure rates should be well over 90% with these modern devices [29,32]. Major periprocedural complications, such as device embolization, tamponade or a need for emergent surgery are rare and should occur in less than 1% of cases [31,33,34]. Although device erosion during follow-up has been seen with some devices following closure

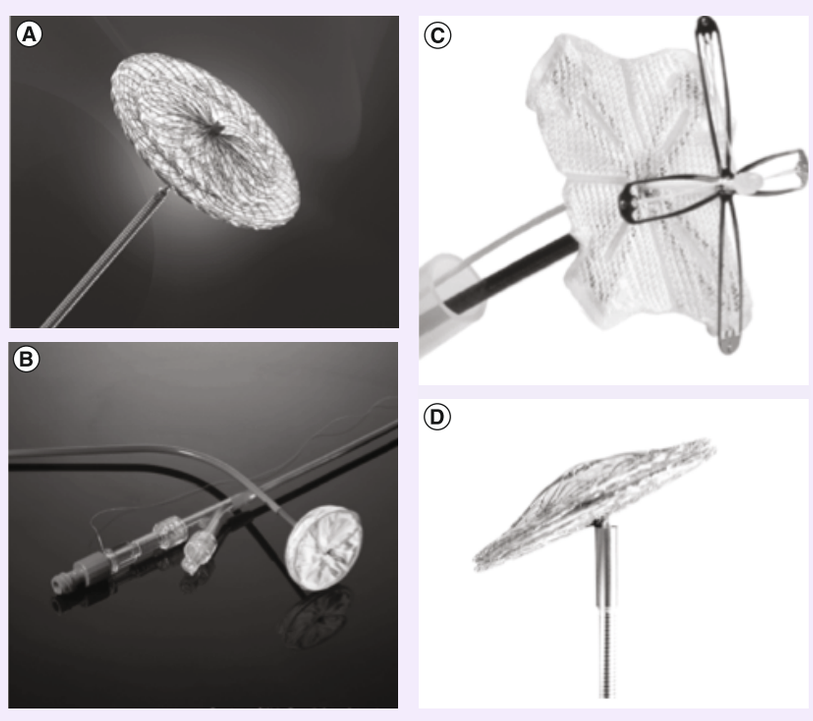

Figure 1. Devices commonly used for percutaneous patent foramen ovale closure. (A) Amplatzer® Multifenestrated Septal Occluder (St Jude Medical, MN, USA). Aside from the disc sizes, it is comparable to the Amplatzer Patent Foramen Ovale (PFO) Occluder, which is used outside the USA. **(B)** Gore® Helex® Septal Occluder (WL Gore and Associates, NY, USA). **(C)** Premere PFO Closure System, which is available outside the USA (St Jude Medical, MN, USA). **(D)** Occlutech® (Sweden) Figulla® Flex PFO Occluder.
Adapted with permission from [51].

of ASDs, this serious complication should be exceedingly rare with use of Amplatzer or Helex devices when closing PFOs [35–37]. Differences among occluders can be found, for example, in device-related thrombus formation, where the CardioSEAL®/STARFlex™ (WL Gore and Associates) device (now off the market) has a higher thrombus formation rate (6%) than the Helex or Amplatzer occluders (less than 1%) [27]. Other differences may be seen in the percentage of complete closure of the PFO and recurrence of atrial fibrillation, with both factors potentially affecting the long-term performance of the devices with regards to stroke recurrence [30,38,39]. Having all those limitations in mind, the first comprehensive review comparing percutaneous PFO closure with medical management for patients with PFO and presumed paradoxical embolism was published by Khairy *et al.* in 2003 [40]. The authors included ten case series of PFO closure including 1355 patients and six series of a total of 895 medically managed patients. Recurrent neurologic events were noted in 0–4.9% of patients undergoing PFO closure and 3.8–12% of medically managed patients [40]. Notably, there were significant differences in baseline characteristics between the two groups, with traditional cardiovascular factors for stroke being significantly more common in the medically managed patients. Furthermore, the nonstandardized definitions and uncontrolled data collection of the individual case series significantly limited the interpretation of those results. The most recent attempt of a systematic review of observational case series has been published in 2012 by Kitsios *et al.*, in which a meta-analysis of 66 studies was performed [41]. The vast majority of these 66 studies reported on results of PFO closure alone (n = 49), while only 17 studies also published results of a medical treatment arm [41]. In total, 52 studies were single arm and seven were comparative. All studies were nonrandomized and observational; three-quarters were prospective in design. In view of the baseline and study characteristics, it was noted that the studies evaluating medical treatment had a higher proportion of structured screening for recurrent stroke, compared with the percutaneous closure studies (88 vs 47%); similarly, recurrent events were more often ascertained by a neurologist in the medical treatment studies compared with the percutaneous closure studies (82 vs 55%) [41]. Patients in the PFO closure studies more often had an atrial septal aneurysm (31 vs 23%) and dyslipidemia (25 vs 18%), while patients in the medical treatment group were more commonly smokers (33 vs 22%) [41]. No difference in the prevalence of diabetes or hypertension was noted between the two study groups. The meta-analysis demonstrated that PFO closure resulted in an 81% reduction in the incidence rate of stroke compared with medical treatment: 0.36 (95% CI: 0.24–0.56) events per 100 person-years versus 2.53 (95% CI: 1.91–3.35) events per 100 person-years [41]. The difference in incidence rate of recurrent stroke in closure and medical treatment arms was not affected by the patients' age. Furthermore, meta-regression analysis of baseline characteristics revealed those not to be associated with heterogeneity of the incidence rate of either treatment modality. The meta-analysis also compared the incidence of recurrent stroke in patients treated with aspirin with those treated with warfarin. This analysis included nine studies and found that patients with anticoagulation had a statistically significant lower risk of recurrent stroke (1.27 events per 100 patient-years; 95% CI: 0.44–3.64) compared with patients treated with antiplatelets (3.17 events per 100 patient-years; 95% CI: 1.94–5.18) [41]. A second recent meta-analysis came to similar conclusions [42]. Overall, adjusted incidence rates were higher compared with the analysis by Kitsios *et al.* [41]. Recurrent neurologic events occurred at a rate of 0.8 (95% CI: 0.5–1.1) events per 100 person-years in the percutaneous closure group compared with 5.0 (95% CI: 3.6–6.9) events per 100 person-years in the medical management group [42].

One of the many shortcomings of comparative observational studies included in meta-analyses is the lack of adjustment for potential confounders. To overcome this limitation, a recent observational, nonrandomized comparison of medical management with percutaneous PFO closure used a propensity score-matched approach to account for differences in baseline characteristics [43]. A total of 103 propensity score-matched pairs of patients undergoing percutaneous closure or medical treatment were compared with each other. Patients were followed prospectively for a median follow-up of 10 years. It is important to note that in the medical group more than one-quarter of patients crossed over to subsequent percutaneous or surgical PFO closure. There was no difference in mortality between the two groups

(n = 6 [6%] for each group). For the composite outcome of recurrent stroke, TIA or peripheral embolism, PFO closure was superior to medical treatment (11 vs 21%, HR: 0.43 [95% CI: 0.20–0.94]; p = 0.033). The difference was caused by fewer TIAs in the PFO closure group as strokes occurred with the same frequency in both groups (PFO closure 6% vs medical management 8%; HR: 0.75 [95% CI: 0.26–2.16]; p = 0.59). Stratified analysis according to the presence of atrial septal aneurysm, shunt size, patients' age, gender or number of initial index events did not alter the treatment effect.

Randomized data evaluating PFO closure

The only published RCT comparing medical management with percutaneous PFO closure is the CLOSURE 1 study (evaluation of the STARFlex septal closure system in patients with stroke and/or transient ischemic attack owing to presumed paroxysmal embolism through the PFO). After much anticipation, the trial was first presented in the fall of 2010 during the annual scientific sessions of the American Heart Association in Chicago (IL, USA) with final results published in 2012 [19]. The trial enrolled 909 patients between the ages 18 and 60 years at 87 trial sites. Enrollment criteria were prior ischemic stroke or TIA within the previous 6 months and presence of a PFO on transesophageal echocardiography. With a 1:1 ratio, patients were either randomized to PFO closure and antiplatelet therapy or medical therapy alone. The primary end points were a composite stroke or TIA during 2 years of follow-up, as well as death. In total, 72% of patients had a cryptogenic stroke as the index event. Moderate or substantial shunt was seen in approximately half (50–56%) of the patients. An atrial septal aneurysm, defined as a septal excursion of over 10 mm, was present in 35–37% of patients. Of the 447 patients assigned to the closure group, 405 underwent the actual procedure. Of those, successful closure, defined as implantation of a STARFlex device with no procedural complications, was achieved in 362 participants (89.4% success rate). At 6-months follow-up, effective closure, defined as grade 0 or 1 residual shunt, was documented in 315 patients (86.1% closure rate). After 2-years follow-up, a statistically nonsignificant difference in the incidence of the primary end point was found (5.5 % closure group vs 6.2% medical therapy group [adjusted HR: 0.78; 95% CI: 0.45–1.35; p = 0.37]). The insignificant trend toward better outcome with PFO closure was driven by fewer TIAs in the closure group (3.1% closure group vs 4.1%; adjusted HR: 0.75, 95% CI: 0.36–1.55; p = 0.44). Stroke occurrence was identical among patients undergoing PFO closure compared with medically treated patients (2.9 vs 3.1%; adjusted HR: 0.90; 95% CI: 0.41–1.98; p = 0.79). Furthermore, no differences were found comparing the treatment modalities 'per protocol' compared with 'intention to treat'. Unexpectedly, potential alternative explanations for recurrent neurologic events (as opposed to PFO-mediated) were found in 80% of patients (87% of patients in the closure group and 76% of patients in the medical treatment group). These explanations included new atrial fibrillation, left atrial thrombus, lacunar strokes with other risk factors, such as aortic arch atheroma, among others. Three of the 12 strokes in the PFO closure group were thought to be due to atrial fibrillation. Two of those patients had device-related thrombus. It was further noted that no patients in the PFO closure group who suffered from recurrent neurologic events had residual shunt at the 6-month follow-up, again suggesting an alternate etiology for recurrent neurologic events aside from the PFO. Not unexpectedly, adverse events were more common in the PFO closure group. Vascular complication rate was 3.2% in the PFO closure group with none in the medical treatment arm. Incidence of atrial fibrillation was higher in the closure group compared with the medical treatment group (5.7 vs 0.7%; p < 0.001). Prespecified subgroup analysis did not demonstrate any increased benefit from closure in subgroups such as patients with atrial septal aneurysm or substantial right-to-left shunt.

The RESPECT trial (randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care) was presented as a late-breaking clinical trial at the TCT conference in October 2012 in Miami (FL, USA). Publication of the data are pending [44]. This was a multicenter trial randomizing PFO closure with the Amplatzer PFO occluder versus medical management, which could be either therapy with antiplatelets or anticoagulants. The trial enrolled 980 patients between the ages of 18 and 60 years with prior cryptogenic stroke and a PFO. Transient ischemia attacks

were not included. Primary end points were recurrence of stroke or death. In 464 patients, device implantation was attempted. Atrial septal aneurysms were present in one-third of patients. Procedural success was 96.1% and effective closure was achieved in 93.5% of patients. Procedural complications were rare with no device-related thrombus formation or device embolization. Major bleeding occurred in 1.6% and major vascular complications in 0.8% of cases. Median follow-up time was 2.2 years (range: 0–8.1 years). There were less patient dropouts in the device group (n = 48) as compared with the medical treatment group (n = 90). During follow-up, recurrent strokes occurred in nine patients in the PFO closure group compared with 16 events in the medical treatment group. Of the nine patients in the PFO closure group, three patients suffered a recurrent stroke following randomization, but prior to PFO closure. As a consequence, the primary end point was not reached in the intention-to-treat analysis (relative risk reduction: 46.6%; p = 0.157), while the as-treated analysis (classifying patients into treatment groups according to the treatment they actually received) was statistically significant (relative risk reduction: 72.7%; p = 0.007). Overall, recurrent event rate was low; at 5 years, recurrent strokes occurred in 2.21% of patients compared with 6.4% in medically treated patients. Two prespecified subgroups significantly benefited from PFO closure: patients with substantial shunt size (recurrent event rate: 0.8% [PFO closure] 4.3% [medical management]; HR: 0.178; 95% CI: 0.039–0.813), as well as patients with atrial septal aneurysm (recurrent event rate: 1.1% [PFO closure] vs 5.3% [medical management], HR: 0.187; 95% CI: 0.04–0.867).

The PC-Trial (percutaneous closure of PFO vs medical management in patients with cryptogenic stroke) was also presented at the TCT conference in October 2012 in Miami; the complete results have not yet been published [45]. This European trial randomized 414 patients to the two treatment strategies. Patients had to be less than 60 years of age and strokes and TIAs were allowed as index events. The primary end points were a composite of death, stroke, TIA or peripheral embolism. The trial documented no statistically significant benefit of PFO closure compared with medical management (HR: 0.63; 95% CI: 0.24–1.62; p = 0.34). Because of a low rate of recurrent events, the study was underpowered, questioning the validity of subgroup analysis. A little less than one-quarter of patients enrolled had an atrial septal aneurysm. Presence or absence of this septal abnormality did not influence treatment effect of PFO closure [45].

Conclusion

For the comparison of two different treatment modalities, RCTs are considered the gold standard. Hence, CLOSURE 1, RESPECT and the PC trial are the best data available to guide treatment recommendations for patients. To date, CLOSURE 1 is the only study of the three trials published. Preliminary RESPECT and PC-Trial data were presented, pending publication, limiting interpretation of the results. With regards to CLOSURE 1, several shortcomings and unexpected findings of this trial warrant mentioning prior to simply concluding that PFO closure is of no benefit to patients for secondary prevention of recurrent strokes.

First, patients with ischemic stroke and PFO were included in CLOSURE 1, not necessarily patients with cryptogenic stroke and PFO [46]. This is an important distinction as the diagnosis of cryptogenic stroke or stroke of unclear etiology depends on the extent of neurologic workup. The less thorough the workup is, the more likely the diagnosis of cryptogenic stroke. For example, patients with lacunar strokes, a distinctly different subtype of ischemic stroke (then cryptogenic strokes according to the TOAST classification), which is usually caused by small vessel cerebrovascular disease, would have been enrolled in CLOSURE 1 if a coexisting PFO was found on echocardiography [47]. A treatment benefit from PFO closure would not be expected in those patients. As further described below and in **Figure 2**, with PFO and ischemic stroke being two very prevalent conditions, treatment benefit of PFO closure in the majority of patients with any ischemic stroke and coexisting PFO is not expected. At the bare minimum, only patients with the diagnosis of cryptogenic stroke following a state-of-the-art neurological workup and PFO should be considered for closure. The problem of including an unselected ischemic stroke population with coexisting PFO in CLOSURE 1 contributed to the finding that 80% of recurrent neurological events were

explained by alternate mechanisms, aside from presumed paradoxical embolism via PFO.

Second, the ability to close PFOs in the USA using off-label devices (approved for ASD closure) likely resulted in the enrollment of lower-risk patients in CLOSURE 1. Patients at high risk for recurrence probably gain the greatest treatment benefit from PFO closure. Those patients would have probably undergone PFO closure outside of a trial, avoiding the risk of being randomized to medical therapy. Patients with recurrent stroke on medical therapy or patients with coexisting thrombophilias likely represent such a high-risk subset. It is important to note in this context that recurrent neurologic event rates following PFO closure in the CLOSURE 1 trial were more than three-times higher than those of observational studies (incidence rate per 100 person-years: 2.96 [PFO closure in CLOSURE 1] vs 0.8 [PFO closure in observational studies]) [48]. By contrast, event rates were no different in medically treated patients comparing CLOSURE 1 with observational data (incidence rate: 3.84 in CLOSURE 1 vs 4.73 in observational studies). This discrepancy between observational and randomized data points towards the shortcomings of observational studies, which commonly lack standardized follow-up with a stroke specialist, potentially resulting in under-reporting of recurrent events. However, this also suggests that the wrong patients were enrolled in CLOSURE 1 as it failed to enroll only patients with presumed PFO-related events.

Third, the STARFlex device used in CLOSURE 1 has been known to have inherent shortcomings compared with more commonly used devices, such as Helex and Amplatzer occluders. This was highlighted by the suboptimal procedural success of only 89.4% and effective closure rate at 6 months of only 86.1%. Furthermore, the high incidence of atrial fibrillation following PFO closure with the STARFlex device (5.7% in CLOSURE 1) was concerning and probably higher than with the use of the other, more contemporary devices [39].

The RESPECT trial provided valuable data to the field of PFO closure. Several limitations of CLOSURE 1 do not apply to this well-conducted study. Even though off-label PFO closure may have resulted in exclusion of the highest-risk patients, the trial, according to per protocol and 'as-treated' analysis, documented a statistically significant reduction in recurrent stroke in patients undergoing PFO closure. Of utmost importance is also the documented safety and rate of complete closure of percutaneous PFO closure. In this regard, the Amplatzer PFO occluder used in the RESPECT trial is clearly superior to the CLOSURE 1 data.

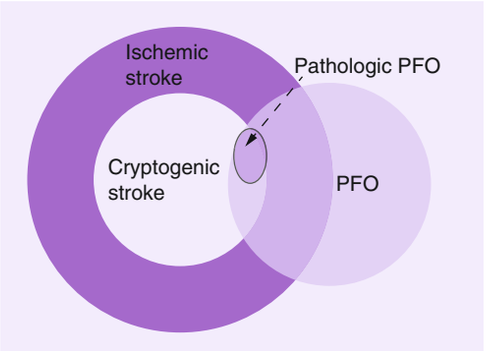

Figure 2. Relationship between ischemic stroke and patent foramen ovale population.
The majority of PFOs are likely innocent bystanders in patients suffering ischemic stroke. In a small percentage of patients a PFO is pathogenically related to the ischemic stroke. Mostly these are patients with cryptogenic strokes, although there likely is a small number of patients in whom a PFO can be 'pathologic' even though the etiology of the stroke is not deemed cryptogenic.
PFO: Patent foramen ovale.

Even though the intention-to-treat analysis of the RESPECT trial did not document a statistically significant superiority of PFO closure over medical management, it supports prior observational data in a consistent fashion. Several preliminary conclusions can be drawn that are also supported by the smaller PC trial, which too failed its primary end point, potentially because it was underpowered. First, recurrent event rates of stroke in patients with cryptogenic stroke and PFO are low. Second, the event rates seem to be lower following percutaneous PFO closure compared with medical management. Third, PFO closure with contemporary devices is very safe. Fourth, patients with atrial septal aneurysms coexisting with PFOs, identified as a high-risk subgroup in a prior landmark trial, have statistically significant fewer recurrent strokes when undergoing PFO closure.

Nevertheless, after decades of research and tens of thousands of PFO closure procedures

worldwide, it is still not known with certainty whether PFO closure is of benefit for the prevention of recurrent neurologic events in all patients with PFO and cryptogenic stroke, as even the individual RCTs were 'neutral' according to intention-to-treat analysis. We do know that PFO closure in patients with ischemic stroke, not necessarily cryptogenic stroke, is of no clinical benefit. On the other hand, there is likely to be a distinct patient population in which PFO closure seems to be of benefit in preventing recurrent ischemic strokes. This patient population is obviously much smaller than the large number of patients suffering from ischemic stroke who also happened to have a PFO. This population is perhaps composed of patients with PFO and associated atrial septal aneurysm and patients with large shunt size. The RoPE study is planning to develop mathematical methods and models identifying so-called 'PFO-related strokes' [49]. It is a sophisticated proposal to identify patients with PFOs that are pathogenically related to the initial stroke, as opposed to the larger number of 'innocent bystander PFOs'. Simply restricting PFO closure to only patients with the firm diagnosis of cryptogenic stroke would not be sufficient to prevent unnecessary PFO closure, as concurrent etiologies are found in more than one-third of patients with recurrent strokes with prior diagnosis of cryptogenic stroke [50].

With the RESPECT and PC trial not being published yet, we need to be highly selective in patient selection for PFO closure. Until we have a better idea of what exactly a pathologic PFO is and the complete results of the above trials become available, we need to use clinical judgment. We should base our current treatment recommendations on the totality of data, which includes all three RCTs. Most important in the context of PFO closure is a close cooperation between stroke neurologists and interventional cardiologists experienced in structural procedures. Patients need to be thoroughly educated on the controversy surrounding PFO closure, on treatment options, availability of trials and the off-label nature of the PFO closure procedure. Assuming a very low complication rate, which should run well below 1% with modern devices, PFO closure can be considered in a subset of patients **(Box 1)**. Inclusion of stroke type is of importance and lacunar strokes should not be counted as index events when considering PFO closure. Concerning the mechanism of paradoxical embolism, only patients with cortical infarcts confirmed on MRI should probably be considered for PFO closure. TIAs without radiographic confirmation of deficits should not qualify for PFO closure. Underlying thrombophilia may be another reason to consider PFO closure, especially if simultaneous deep venous thrombosis or pulmonary embolism has been documented. Furthermore, the clinical context of the stroke index event may be of importance, as strokes following Valsalva or Mueller maneuvers may increase the probability of the PFO being related to a patient's neurologic event. Patients who are intolerant to antiplatelet therapy or have encountered bleeding complications while using warfarin, aspirin or clopidogrel may further be considered for PFO closure. Patients with medical treatment failure presenting with recurrent stroke while taking antiplatelet or anticoagulation therapy may be candidates for PFO closure. Moreover, patients under the age of 60 years with atrial septal aneurysm and large shunt potentially represent a high-risk subset that may benefit from PFO closure. Overall, given this selected group of individuals, it is unlikely that RCTs can be carried out as it will be even more difficult to recruit such a high-risk group of individuals.

Future perspective

First, we need to wait for the publication of the RESPECT and PC trials to be able to fully interpret the results.

Box 1. Features and characteristics of patients in whom patent foramen ovale closure can be considered.

- Cortical infarcts
- Coexisting thrombophilia
- Deep venous thrombosis or pulmonary embolism documented at time of stroke
- Stroke occurring during Valsalva or Mueller maneuvers
- Intolerance to or major bleeding while on antiplatelet therapy or anticoagulation
- Medical treatment failure
- Atrial septal aneurysm and large shunt

Second, the REDUCE (Gore® Helex septal occluder for PFO closure in stroke patients) trial is still enrolling. The results of the REDUCE trial are expected in the next few years and will likely provide us with more important information on the use of a different device. Third, a meta-analysis of CLOSURE 1, RESPECT and the PC trials may be helpful by adding power, understanding inherent limitations of meta-analyses in general. Fourth, it is unlikely that another RCT will be started for this purpose, meaning that the aforementioned subgroup of individuals with most likely pathologic PFOs will remain unstudied in RCTs. For the time being, PFO closure for secondary prevention of ischemic stroke will remain controversial. As clinicians we need to continue to do what is right for our patients; weighing the risks and benefits of medical management and PFO closure for each individual. This discussion has to include an educated patient, stroke neurologist and interventional cardiologist proficient in PFO closure and, of course, insurance carriers, who ultimately will decide whether they will cover the cost of such procedures or not.

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