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Patent foramen ovale and atrial fibrillation as causes of cryptogenic stroke: is treatment with surgery superior to device closure and anticoagulation? A review of the literature

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Abstract

Closure of persistent foramen ovale (PFO) to avoid cryptogenic strokes is performed globally with enthusiasm but lacks prove of efficacy. We present a 79-year-old man who had had a PFO device introduced nine years previously because of cryptogenic strokes presenting as syncopes. The patient was referred from his general practitioner with two new syncopes. Transthoracic echocardiography revealed no cardiac causes of embolism. Transesophageal echocardiography (TEE) revealed a misplaced device like an umbrella in a storm, but no septum defects. Holter revealed seconds-long episodes of atrial fibrillation (AF). The patient was successfully treated with anticoagulation.

A literature review showed that: (i) the efficacy of PFO closure devices has not been proven in any trial, but was demonstrated in a meta-analysis comparing three different devices; (ii) PFO devices are rarely controlled by TEE during or after insertion; (iii) residual shunts are detected in up to 45% of cases; (iv) there is an increased rate of post-arrhythmic complications; (v) the risk of AF in congenital heart disease increases with increasing age, with a 13% risk of transient ischemic attacks and stroke; and (vi) surgical treatment of PFO was found to have a 4.1% risk of complications including stroke.

The question to be asked is whether device closure of PFO should be avoided, considering that PFO is a congenital heart defect with risks of AF and (cryptogenic) stroke? Heart surgery should be a treatment option for symptomatic PFO.

Keywords

Atrial septum defect, paradoxical embolism, cryptogenic stroke, stroke, transesophageal echocardiography, atrial fibrillation

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Introduction

To bypass the maternal oxygenated blood from fetal lung circulation, the blood passes through the foramen ovale. The onset of respiration after birth causes an increase in Q_p/Q_s, hence pulmonary vascular resistance decreases, leading to higher left atrial pressures and closure of the foramen ovale flap against the septum secundum. The contact between the septum primum flap and the septum secundum leads to fusion of these tissues and permanent closure of the foramen ovale (Fig. 1).

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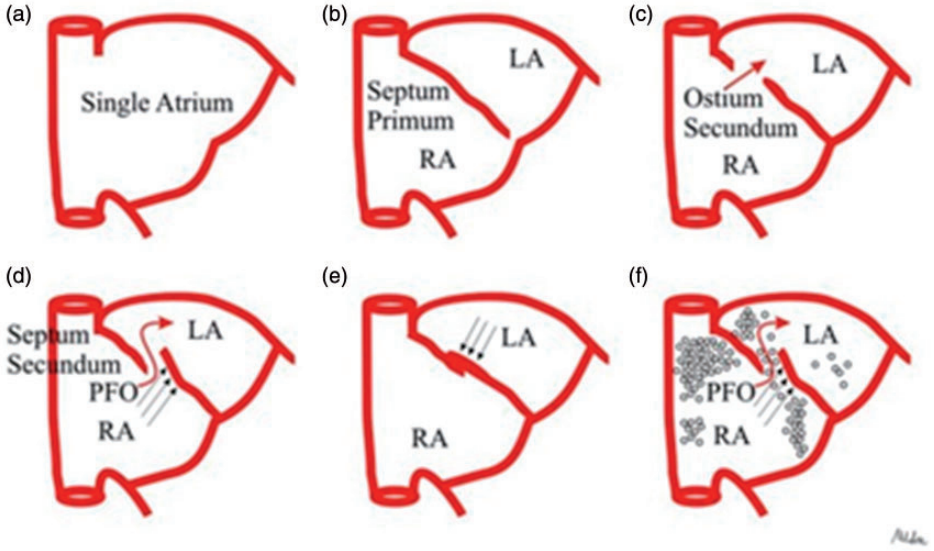


Fig. 1. Interatrial septal development. The primitive atrium is a single cavity (a) subsequently divided by the septum primum which grows down from the roof of the atrium, toward the developing endocardial cushions (b). Thus, small perforations begin to develop superiorly resulting in the ostium secundum (c). The atrial roof grows down along the right side of the septum primum, the septum secundum, which comes to lie over the ostium secundum; however, an opening remains between septa, the PFO (d). At birth, lung pressures drop and the blood pressure in the left atrium exceeds that of the right atrium, so that the septum primum is shoved against the septum secundum, obtaining septa fusion (e). If this final step does not occur, PFO results (f). With permission. Courtesy of Contaldi et al. Cardiovascular Ultrasound 2012;10:16.

Transesophageal studies (TEE) reveal that 9–12% of the general population have a persistent foramen ovale (PFO) (1), increasing to 29% with catheter probing during ablation for atrial fibrillation (AF) (2,3). Autopsy studies reveal that 27% of PFOs have diameters in the range of 1–10 mm and that size increases with age (4); the size of the PFO predicts the risk of paradoxical embolism (5).

PFO is reported to be the cause of cryptogenic stroke in 31–77% of cases, while atrial septal aneurysms are the cause in 4–25% of cases (6,7). Cryptogenic stroke through a PFO was first described in 1877 by Julius Cohnheim during an autopsy of a young woman with a fatal occlusion of a cerebral artery. He observed that the patient had a significant lower limb thrombus and a large PFO. He hypothesized that the latter served as a conduit for an arterial embolism that paradoxically started in the venous circulation. The Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study confirmed that patients with cryptogenic stroke have an increased prevalence (20%) of pelvic deep venous thrombosis (8). Cryptogenic stroke also seems to be associated with vigorous or strenuous exercise, decompression illness, sneezing, coughing, obstructive sleep apnea, and even migraine (9–17).

A transcatheter approach to close the most common congenital heart defect in adults, ostium secundum atrial septal defect (ASD), was successfully introduced in uncomplicated cases four decades ago due to its minimally invasive nature compared to open heart surgery (18,19). Inspired by the success in treating atrial septal secundum defects, closure of PFO to avoid cryptogenic stroke and hence transient ischemic attacks (TIA) (6,20) is performed globally with enthusiasm but lacks proof of efficacy (21–24).

This case drew our attention to find the best evidence documented treatment of PFO: a 79-year-old man who had had a PFO device introduced nine years previously, because of three cryptogenic strokes presenting as syncopes, was referred by his general practitioner to our department with two new syncopes. Initial Holter and biochemistry were normal (including screening for coagulopathies). Transthoracic echocardiography (TTE) did not reveal any cardiac causes of embolism. TEE revealed a misplaced device (Figs. 2–5) like an umbrella in a storm. Using the method described by Johansson et al. (25) with prerequisite Valsalva maneuvers before contrast injections, repeated five times, we found no septum defects (Figs. 6 and 7). A second Holter revealed paroxysmal episodes of AF lasting several seconds. The patient was treated with anticoagulation and has had no symptoms since. The patient gave verbal and written consent to the publication of this case report.

These questions were sought to be answered in the literature: (i) Is the position of atrial septum devices in PFO to avoid cryptogenic stroke monitored by TEE

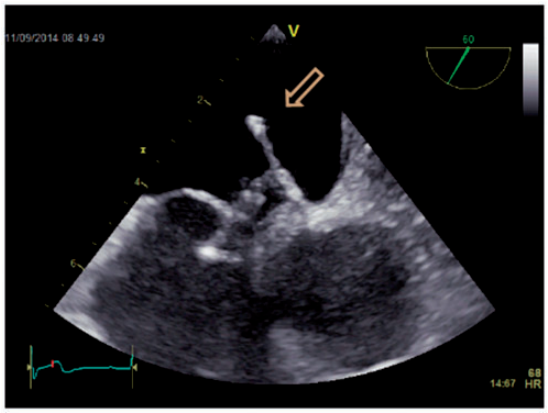


Fig. 2. 2D transesophageal echocardiography of a displaced atrial septal occluder (arrow).

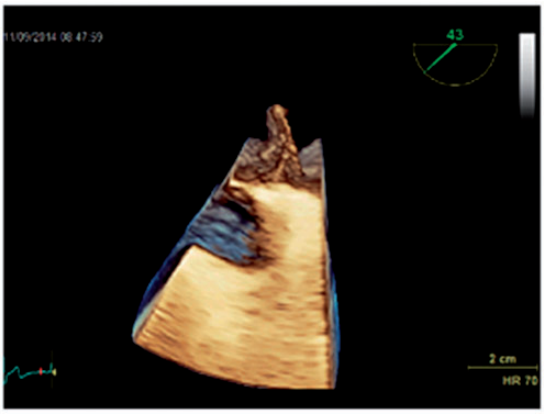


Fig. 4. 3D transesophageal echocardiography of a displaced atrial septal occluder (arrow).

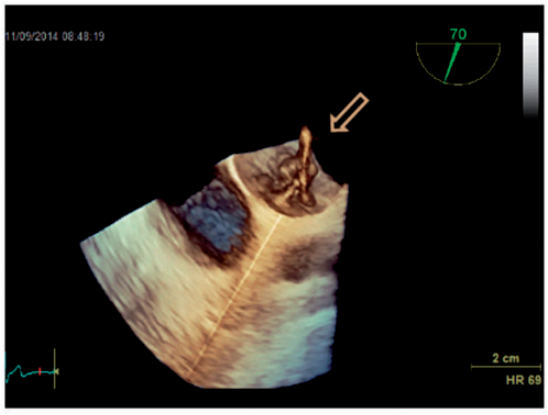


Fig. 3. 3D transesophageal echocardiography of a displaced atrial septal occluder.

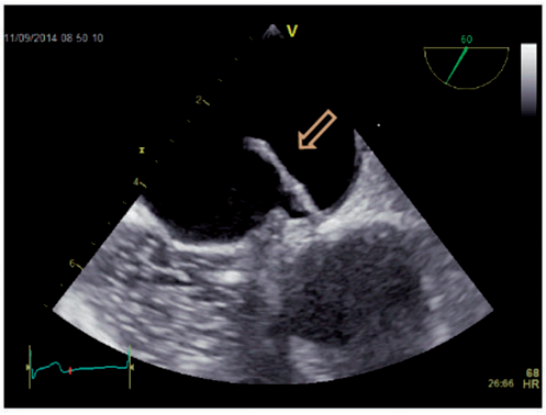


Fig. 5. 2D transesophageal echocardiography of a displaced atrial septal occluder (arrow). Test with isotonic solution of agitated saline water.

during or after insertion? (ii) What is the complication rate? (iii) Is insertion of atrial septum devices in PFO to avoid cryptogenic stroke beneficial compared with anticoagulation or open heart surgery? (iv) Is the rate of post-arrhythmic complications known? (v) Is there an increased risk of AF in patients with PFO?

Methods and Results

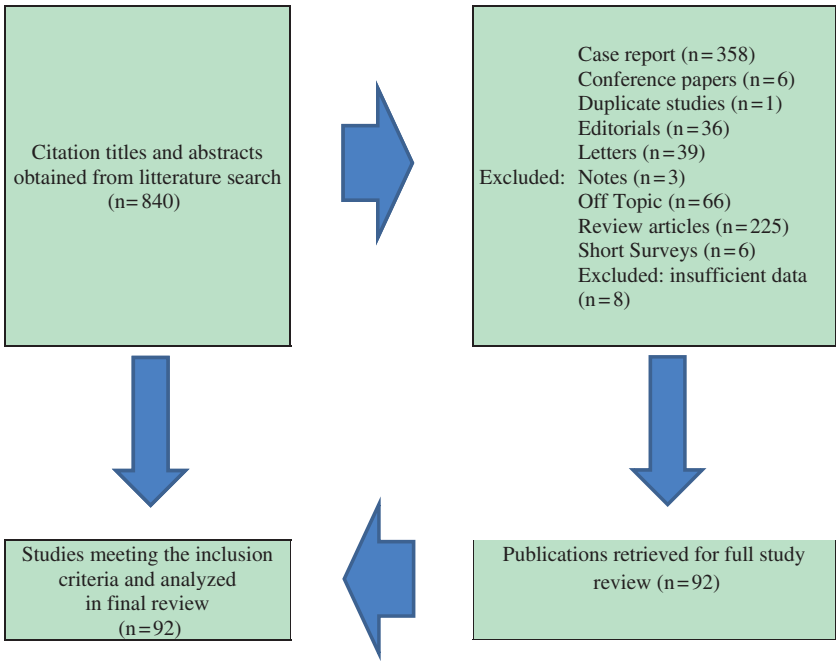
To answer the above questions, the following analysis and a review were performed in MEDLINE and the Cochrane Collaboration and Cochrane Register of Controlled Trials for relevant studies. The following search terms were used: "PFO" AND "cryptogenic stroke" resulted in 454 articles, while "PFO" AND "atrial fibrillation" resulted in 156 articles, and "PFO device" AND "heart surgery" resulted in 230 articles. Searches were not limited, but irrelevant articles and articles in languages other than English were excluded (Table 1). The main author performed the literature search. All studies that appeared to fit the inclusion criteria were identified for full review. The retrieved and selected articles were approved by all authors. Of those, 92 articles were selected as relevant for the review.

Discussion

Complication rate and control of the PFO device position

Atrial septum device misplacements are reported as rare, but the devices are rarely controlled by TEE post insertion (26–30). TTE may reveal transient changes in left atrial passive emptying and strain (31), while left ventricular function is not affected when assessed by magnetic resonance imaging (MRI) (32). However, as in our case, TTE may not reveal displaced devices or even remaining defects in the PFO.

Table 1. Literature search strategy.



Accordingly, a recent follow-up study concluded that devices evaluated > 5 years after closure with TTE were well placed (33), but two patients in this population had their devices surgically removed, and up to 45% had residual shunting when evaluated with contrast. While intracardiac ultrasound may be of help during the insertion of PFO devices (34–39), TEE remains the diagnostic ''gold standard'' for evaluating cardioembolic sources of stroke (40–44), and repeated prerequisite Valsalva maneuvers followed by contrast injections and careful evaluations are important to avoid misinterpretations and diagnostic failure (25).

PFO treatment: device closure versus medical therapy

Jean-Louis Mas et al. (45) reported that patients with both a patent foramen ovale and an atrial septal aneurysm who had had a cryptogenic stroke had a higher risk of recurrent stroke while taking aspirin than did patients with no septal abnormality or either septal abnormality alone. While overall causes for recurrent stroke (8%/year) seem equally protected by aspirin compared to warfarin (46), device closure of PFO has not yet been proven more effective than medical therapy in preventing recurrent cryptogenic stroke (47–49). The RESPECT trial, funded by St. Jude Medical, showed in the primary intention-to-treat analysis that there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic stroke, but in pre-specified per-protocol and as-treated analyses, device closure was superior to medical therapy, with a low rate of associated risks (50); these results from the RESPECT trial were later confirmed in a sub-analysis excluding patients (who actually had the device inserted) without indications for device closure and presented at a conference in Washington in November 2016, but have not yet been published. In the CLOSURE I trial, the first randomized clinical trial evaluating the effects of PFO closure on recurrent cryptogenic stroke and TIAs versus medical therapy (51), 909 patients were randomized to percutaneous PFO closure with a STARFlex® PFO device versus medical therapy with warfarin (target international normalized ratio of 2.0–3.0), aspirin 325 mg alone, or aspirin 81 mg plus warfarin. The results did not demonstrate a benefit of PFO closure with the STARFlex® device compared with medical therapy. Device closure was successful in only 87% of cases, which is similar to previous device closure studies with the STARFlex® device (52), but lower than that reported for other PFO closure devices (53–56). AF and major vascular complications were significantly higher in the device group, although the latter had no further implications for the patients, which was confirmed in other trials (57,58). The population in the CLOSURE I trial had several atherosclerotic risk factors, including increased body mass index, diabetes, hypertension, and

history of ischemic heart disease predicting recurrent ischemic neurologic events; however, a diagnosis of AF after trial enrollment portended the greatest risk of recurrent events (59).

Each trial on its own failed to significantly improve its primary endpoint in the intention-to-treat analyses. However, they all point in the same direction: all three trials were subjects of a recent meta-analysis showing a significant benefit of PFO closure with a > 40% relative risk reduction for recurrent stroke or TIAs and a 33% reduction of death or vascular events (60). The benefit of PFO closure over medical therapy was even more pronounced when only the trials using the Amplatzer® device were included in the analysis (61). Also, a single-center study (28) reporting on very long-term follow-up data on PFO closure or medical therapy showed significantly improved survival (the most compelling endpoint) in the PFO closure group, with a relative risk reduction for all-cause mortality of 60% ($P = 0.03$). Risks of thrombus formation at the devices seem comparable to other devices, decreasing to negligible after one year (62–64). However, concluding that device closure is safe by comparing different devices subject to different study designs and analyzing all data in one pool seems too ambitious, and as explained below, the complications following device closure point in another direction. Percutaneous closure of PFO with the indication obstructive sleep apnea or migraine also lacks proof of efficacy (65–68).

Post-arrhythmic complications after device closure

The incidence of AF following device closure is not reported by Inglessis et al. (69); it is excluded in all three trials with device closure (60). Interestingly, Rengifo-Moreno et al. reported a small, but statistically significant increased risk of developing new-onset AF with the transcatheter closure of PFO when compared with medical therapy alone (2.7% vs. 0.5%, odds ratio [OR] = 5.7, $P < 0.001$). In the CLOSURE I trial, it was associated with significantly higher rates of AF than was medical therapy (5.7% vs. 0.7%; $P < 0.001$) (51) and similar results were observed in trials with the Gore® septal occluder, the Intrasept® device, and the Spider® PFO occluder (70–72). By contrast, AF occurred at similar rates after PFO closure with Amplatzer® devices (St. Jude Medical, Plymouth, MN, USA) compared with medical therapy in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial (2.9% vs. 1.0%; $P = 0.16$) and in the PC trial (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) (3% vs. 1.5%; $P = 0.13$) (50,73). However, uniformly comparable heart rhythm monitoring before device closure was not available in any of the studies, and recent follow-up studies of "atrial septum defects closed with devices" demonstrate a high risk (6.6–17.9%) of AF in the first year after the procedure, decreasing to negligible (0–3.9%), but with only 76–82% of the original population included in one study (33,74,75).

The risk of AF in patients with PFO and other congenital heart diseases

AF, which occurs in 1–2% of the general population and is probably underestimated with an expected doubling in the coming decades, confers a fivefold risk of stroke and one in five of all strokes is attributed to this arrhythmia (76). The AF detection rate with 12-lead ECG or 24-h Holter is in the range of 2–6% after ischemic stroke or transient ischemic stroke (77,78). However, the CRYSTAL-AF (CRYptogenic STroke And underLying AF) trial conducted in Europe, Canada, and the United States used an insertable cardiac monitor (ICM) from Medtronic (REVEAL XT) and the EMBRACE study (30-Day Cardiac Event Monitor Belt for Recording AF After a Cerebral Ischemic Event) in Canada investigated a non-invasive, 30-day event-triggered loop recorder from Braemar (ER910AF Cardiac Event Monitor®) (79,80) to show that up to 36 months of heart rhythm monitoring increased the detection rate of AF from 8.9% after six months to 12.4% after 12 months and up to 30.0% after 36 months. The aforementioned results confirm the findings of observational studies that had demonstrated a high rate of undetected AF in patients after cryptogenic stroke (81).

PFO is considered to be a structural (congenital) heart disease (82) and as a result of structural heart disease, atrial arrhythmias increase with increasing age to up to 38% in 50-year-old patients. Yet, these numbers do not allow the exclusion of the risk associated with corrective or palliative surgical procedures (83,84). Catheter ablation for paroxysmal AF with coexisting PFO may increase procedure time, while success seems to be unaffected (2,3). Surgical correction of PFO, even with minimally invasive (robotic) surgery, is successful with a low risk of residual shunting or any other complications and with a lower recurrence of stroke compared with device closure and is considered to be the gold standard (85–90) in smaller studies: after a mean follow-up time of 24 months, only eight patients (all in one of the four studies) of a total of 194 were reported to have a TIA as a complication of the direct suture closure of PFO (Table 3). This is equivalent to

a total risk of 4.1% and hence considerably lower than with device closure of PFO.

A recent retrospective longitudinal multicenter study of 199 patients, ''DysrhythmiAs in patieNts with congenitAl heaRt diseAse'' (DaNaRA), demonstrated that patients with congenital heart disease, particularly patients with complex defects, develop AF at a young age and progress frequently from paroxysmal AF to (long-standing) persistent/permanent AF (91). Sixteen patients (8%) experienced a cerebrovascular event 14 (2–33) years before the first documented AF. The total incidence of TIA/stroke in the population was 13%. Coexistence of episodes of AF and regular atrial tachycardia occurred in a considerable number of patients in this study; most of them initially presented with regular atrial tachycardia, hence the authors suggest that aggressive therapy and close follow-up of congenital heart disease patients with atrial tachyarrhythmia is justified (91). A large retrospective study comparing the general Danish population to > 4400 patients (age range $=$ 1–49 years) with almost five decades of follow-up (92) demonstrated that: (i) AF is more prevalent in patients with ASD diagnosed and closed in childhood, with a cumulative incidence of 9.8% at the end of 50 years of follow-up; and (ii) the risk of arrhythmia is independent of whether the ASD was closed by catheter or surgery. Yet the authors of this important study ask: does closure of an ASD at a young age reduce AF later in life (92)?

In conclusion, PFO is a common heart defect associated with stroke that has been treated for decades with device closure, although the efficacy has never been proven. Device closure of PFO is associated with a high risk of remaining defects, including displacement, and an undetermined increased risk of AF; the latter may even be the natural cause of so-called cryptogenic strokes.

We interpret our review of the literature as follows (Table 2): (i) the efficacy of PFO closure devices has not been proven in any trial (however, efficacy was proven in a meta-analysis comparing three different devices); (ii) PFO device positions are rarely controlled by TEE during or after insertion; (iii) residual shunts can be demonstrated in up to 45% of cases; (iv) there is an increased rate of post-arrhythmic complications, especially AF, which was recently concluded to be an underdiagnosed and hence increasingly important cause of cryptogenic strokes; (v) the risk of AF in congenital heart disease (which PFO should be considered to be) increases with increasing age, with a 13% risk of TIAs and stroke; and (vi) surgery, both minimally invasive and open heart, is a proven treatment of congenital heart defects causing AF, with a 4.1% risk of complications.

The question to be asked is whether device closure of PFO should be avoided, considering that PFO is a congenital heart defect with the associated risks of AF and (cryptogenic) stroke? Heart surgery should be a treatment option for symptomatic PFO.

Table 2. Key points in the review.

Key point	Conclusion/review of literature	References
Is insertion of atrial septum devices in PFO to avoid cryptogenic stroke beneficial compared to anticoagulation or open heart surgery?	The efficacy of PFO closure devices has not been proven in any published trial	(21–24,26,36–49,73–78)
Is the position controlled with TEE before or after insertion?	The positions are rarely controlled with TEE before or after insertion	(26–27,30–33)
What is the complication rate?	Residual shunts can be demonstrated in up to 45% of cases	(30–33,41–44)
Is the rate of post-arrhythmic complications known?	The rate of post-arrhythmic complications increases, especially AF, recently concluded as an underdiagnosed and hence increasingly important cause of cryptogenic strokes	(30,40,41,58–60,62,63)
Is the risk of AF in patients with PFO increased?	(Considering PFO as a congenital heart disease) the risk of AF in congenital heart disease is increasing with increasing age, with a 13% risk of TIAs and stroke	(65–72)
How should we treat patients with cryptogenic stroke and PFO?	Literature points towards surgery as evident treatment of congenital heart defects including PFO causing AF	(2,3,36–49,73–80)

Table 3. Complication rate after surgical closure of PFO.

Reference	Patients (n)	Complications reported
Cujec B et al. Can J Cardiol 1999;15:57–64 (75)	14	No neurological recurrences during a mean follow-up of 43 months (crude incidence rate difference 12%/patient/year, 95% CI = 6.6–17.9, $P < 0.02$)
Dearani JA et al. Circulation 1999;100(19 Suppl):II171–II175 (74)	91	Follow-up totaled 176.3 patient-years and mean follow-up was 2.0 years. 8 had a TIA during follow-up. The overall freedom from TIA recurrence during follow-up was 92.5 ± 3.2% at 1 year and 83.4 ± 6.0% at 4 years
Devuyst G et al. Neurology 1996;47:1162–1166 (73)	30	After a mean follow-up of 2 years without antithrombotic treatment, no recurrent cerebrovascular event (stroke or TIA) and no new lesion on MRI had developed
Ruchat P et al. Eur J Cardiothorac Surg 1997;11:824–827 (76)	32	All patients were followed-up corresponding to a cumulative time of 601 patient-months. This revealed no recurrent vascular events nor silent new brain lesions on brain MRI
Sabata RA et al. World J Pediatr Congenit Heart Surg 2014;5:527–533 (77)	27	Follow-up: mean = 1.5 years, maximum = 4.2 years. No recurrence of neurological events

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Supplemental Material

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