Closure of patent foramen ovale for secondary prevention of cerebrovascular events

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ABSTRACT

Stroke is the most debilitating cardiovascular event. It has a variety of causes that may be present simultaneously. In young or otherwise healthy people a patent foramen ovale (PFO) is increasingly searched for. In stroke of the elderly atherosclerosis and atrial fibrillation are in the foreground but the PFO should not be ignored. The risk of a PFO related stroke over time is controversial and so is its prevention by PFO closure. Percutaneous PFO closure is a minimally invasive procedure which can be performed with high success and low morbidity. We review the rationale for PFO closure for secondary prevention of embolic events.

Stroke remains the third leading cause of mortality and the most important cause of serious, long-term disability. Most strokes are of ischaemic origin. Atherosclerosis plays a causative role as do other factors that vary among countries, genders, lifestyles, and a number of well documented risk factors. In the United States of America it is estimated that almost 90% of the roughly 800,000 strokes per year are ischaemic. Cardioembolic reasons account for 19% and carotid disease for 15% of them. A patent foramen ovale (PFO) is per se not yet considered a primary cause for stroke. It is subsumed under the 36% of strokes labelled cryptogenic. This article summarises the current evidence for percutaneous PFO closure for secondary prevention of cerebrovascular events.

PATENT FORAMEN OVALE

Autopsy studies revealed that the foramen ovale remains dynamically patent in approximately 1/4th of the general population. A PFO thus represents the most common cardiac congenital abnormality (Figure 1). It permits intracardiac shunting while right atrial pressure exceeds left atrial pressure (Figure 2). A PFO accounts for up to 95% of right-to-left shunts. Pulmonary shunts account for about 4% and atrial septal defects for less than 1%.

The prevalence of PFO declines from 34% during the first three decades of life, to 25% for the 4th to 8th decade, and to 20% beyond that. Spontaneous closure even late in life or selective mortality (reduced life expectancy of PFO carriers) has to be held accountable for that. In most individuals, a PFO will remain asymptomatic for life. However, since the initial blaming of a fatal stroke...
ASA is a congenital abnormality of the interatrial septum characterised by a redundant, central part of the septum primum (Figures 1 and 2). The prevalence of an ASA in the general population was about 1% in autopsy series and 2.2% in a population-based transoesophageal echocardiographic (TOE) study. ASA is associated with a PFO in 50% - 85% of cases and likely co-responsible for it. The constant motion of the ASA inhibits postnatal fusion and thus begets the PFO. The criteria for distinction between a floppy interatrial septum and ASA vary between autopsy, transthoracic echocardiography (TTE), and TOE. ASA is generally diagnosed if the diameter of the base of the flimsy portion of the interatrial septum exceeds 15 mm and the excursion of the aneurysmal membrane is ≥10 mm in either left or right atrium, or if the sum of the total excursion is ≥10 mm.

ASA has been associated with cerebral ischaemic events in numerous case-control studies. The combination of a PFO and ASA constitutes a particularly high risk situation with a relative risk of 16 (95% CI 3-86) comparing ischaemic stroke with non-stroke control subjects, and a relative risk of 17 (95% CI 2-134) comparing cryptogenic stroke with known stroke case control subjects (age <55 years).

The association of PFO with cryptogenic stroke, prominently documented in 1988, as well as numerous case reports depicting a thrombus straddling the PFO, establish paradoxical embolism as underlying mechanism. This is corroborated by an observational study of 139 patients suffering from major pulmonary embolism. Patients with PFO were more likely to die (44% vs. 13%, P=0.02) or to suffer a stroke (13% vs. 2%, P=0.02) or peripheral embolism (15% vs. 0%, P=0.01) in the presence of a PFO. The PFO constituted an independent predictor of mortality. The higher frequency of pelvic vein thrombosis at magnetic resonance (MR) venograms within 2 days of the onset of symptoms in stroke patients with PFO (20%) than with conventional stroke causes (4%) again points to paradoxical embolism via PFO. An observational study of 202 patients with transvenous pacing leads, in whom the presence of intracardiac shunts was associated with a >2-fold increased risk of systemic embolism during long-term follow-up, and a large Danish population based study on patients with deep venous thrombosis (n=25,199) or pulmonary embolism (n=16,925). Their relative risks of stroke during the first year after the thrombotic event were 2.2 (1.9-2.6) and 2.9 (2.3-3.7) fold increased compared with controls (n=163,566).

PFO AND FIRST ISCHAEMIC STROKE

In the European population, the annual incidence of a first ischaemic stroke is 139 per 100,000 inhabitants. Since around 60% of these events can be attributed to conventional causes, the annual risk attributed to paradoxical embolism has been estimated at 28 per 100,000 persons with a PFO per year. The association of PFO with cryptogenic stroke has been repeatedly confirmed.
2.9; 95% CI 1.7 to 5.0; p<0.001) as well as of PFO associated with ASA (15.2% vs. 4.4%; OR 3.9; 95% CI 1.8 to 8.5; p<0.001) among patients with cryptogenic stroke compared to those with conventional stroke causes.(28) A meta-analysis of 23 case-control studies, suggested that the odds of having a PFO were 2.9 times higher in patients with cryptogenic stroke when compared to controls (95% CI, 2.1 to 4.0).(29)

In contrast, 2 prospective population-based studies failed to confirm PFO as an independent risk factor for cryptogenic stroke,(30,31) with only a nonsignificant trend towards a higher incidence of stroke in persons with PFO. The Olmsted County study enrolled 588 randomly selected subjects.(30) PFO was identified using TTE in 24% and an ASA in 2%. During a mean follow-up of 5.1 years, cerebrovascular events (cerebrovascular death, ischaemic stroke, and TIA) had occurred in 41 subjects (7%). After adjustment for age and comorbidities, PFO was not an independent predictor of stroke (HR 1.46; 95% CI 0.74-2.88; p=0.28). The risk of stroke among subjects with ASA was almost four times greater than in those without, but proportional hazard regression analysis did not establish statistical significance (HR 3.72; 95% CI 0.88-15.71; p=0.074). The relatively small sample size and the advanced age (mean 67 years) of the study participants were criticised, in addition to the inadequate screening sensitivity resulting in a significant percentage of undetected PFOs.

Among the 1 100 participants of the Northern Manhattan study,(31) TTE detected a PFO in only 15% and an ASA in 3%. During 6.6 years of follow-up, 68 subjects suffered an ischaemic stroke (6%). After adjustment for demographic and risk factors, PFO was not significantly associated with stroke (HR 1.64; 95% CI 0.87-3.09). Isolated ASA was associated with an elevated stroke incidence (HR 3.66; 95% CI 0.88-15.30), but ASA associated with PFO was not (HR 1.25; 95% CI 0.17-9.24). The low prevalence of PFO as compared to autopsy studies confirms TTE as not sensitive enough to screen for a PFO.

**PFO AND RECURRENT CEREBROVASCULAR EVENTS**

The natural history after cerebrovascular events in patients with PFO remains insufficiently defined. This is problematic since the risk of recurrence determines the therapeutic value of interventions aimed at secondary prevention. Traditionally, most patients with presumed paradoxical embolism are treated with antithrombotic medications. Data are scarce concerning the efficacy of oral anticoagulation as opposed to antiplatelet agents, and the duration of treatment required. Observational studies on medical treatment in patients with PFO with either antiplatelet agents or coumarin reported a risk of recurrent stroke or TIA ranging from 3% - 12% during the first year.(10,11,27,32-34) Both larger PFO size,(15,17,15,36) and a greater degree of right-to-left shunt(15,22,15,37) signify a higher risk for paradoxical embolism. However, there are major differences in the baseline characteristics of the patient populations studied, which may account for the disparate recurrence rates reported. According to a meta-analysis of 15 studies of medical treatment in 2 548 patients with cryptogenic cerebrovascular events, the pooled rate of recurrent ischaemic stroke or TIA was 4.0 events per 100 patient-years (95% CI, 3.0-5.1) while the rate of recurrent ischaemic stroke was 1.6 events per 100 patient-years (95% CI, 1.1-2.1).(38) Of note, in trials with antiplatelet agents or oral anticoagulation, the risk of recurrence appeared lower with the latter. Although medical treatment lacks the risk of interventional procedures, it is associated with other adverse effects, most notably an increased risk of bleeding. Thus, major bleeding amounted to 1.5-2.2 per 100 patient years in the prospective PFO in cryptogenic stroke study (PICSS),(27) a subanalysis of the Warfarin-Aspirin Recurrent Stroke Study (WARSS), (39) with a marked but not significant difference showing poorer protection with acetylsalicylic acid than with oral anticoagulation. Treatment with acetylsalicylic acid has also been found suboptimal in patients with PFO and associated ASA.(8,11) Another important limitation of medical treatment is lack of compliance.

**PERCUTANEOUS PFO CLOSURE**

Percutaneous (device) closure of the PFO has supplanted surgical PFO closure and constitutes an alternative treatment. It eliminates the pathway for paradoxical embolism, and may thus circumvent the need for long-term blood thinners. However, it is associated with a small periprocedural risk and significant costs, both for the device (about 3 000 USD, according to regional markets) and the procedure.

Bridges, et al. introduced percutaneous PFO closure in 1992 to reduce the incidence of recurrent strokes.(40) Percutaneous PFO closure has been shown safe and feasible in numerous studies, using a variety of devices.(41-52) Figure 3 depicts the gold standard Amplatzer PFO Occluder with clinically approved offsprings. The reported success rates varied between 90 - 100%, with complication rates between 0 - 10%. Complete PFO closure was reported in
51 - 100% of patients, and yearly recurrence rates of ischaemic strokes and TIAs varied between 0 and 3.4%.

Patients typically undergo TOE prior to the intervention for initial diagnosis of PFO and detailed delineation of anatomy, i.e. associated ASA or Eustachian valve (Figure 4), as well as assessment of right-to-left shunt. The procedure can be performed on an outpatient basis under local anaesthesia and may take less than 30 minutes. Patients can be released to unrestricted physical activity as early as a few hours after the intervention. Antibiotics during the intervention are commonplace and prophylaxis against endocarditis is recommended for a few months until the device is completely covered by tissue. Failed implantation due to inability to canulate the PFO is extremely rare (<1%). Periprocedural complications have fallen below 1% in experienced centres, and complete closure rates of >90% can be expected. Follow-up treatment includes acetylsalicylic acid (80 - 300mg daily) for 1 - 6 months, with the addition of clopidogrel (75mg daily) for 1 - 6 months at some centres. At 3 - 6 months after percutaneous PFO closure, a contrast TOE should be repeated, to assess for residual shunt following endothelial overgrowth and exclude thrombosis of the device. Transcranial Doppler (TCD) constitutes an alternative. However, it cannot rule out a thrombus on the device. If the PFO proves completely closed, all medication can be discontinued, unless required for another indication, e.g. associated coronary artery disease. In case of persistence of a moderate or large residual shunt, implantation of a second device is recommended, which results in complete closure in approximately 90% of cases.

Complications consist mostly of rare arterio-venous fistulae at the groin and are device and technique related. The same holds true for residual shunts and thrombus formation. Erosions of the free atrial wall, more a threat with the larger devices used...
for atrial septal defect closure, device endocarditis, or need for surgical explantation are exceedingly rare. Long term safety is of the utmost importance for a preventive procedure against a low risk in natural history. Rarely, supraventricular arrhythmias can be induced or triggered by the device leading to the need for anticoagulation or left atrial ablation. Transseptal puncture (for later left atrial interventions) is not impeded after device implantation but rather optically facilitated (56) (Figure 5).

**COMPARISON OF MEDICAL TREATMENT WITH PFO CLOSURE**

Available evidence of studies assessing medical treatment and percutaneous PFO closure encompass multiple observational single arm studies, 2 comparative registries, a systematic review of case series, a propensity score matched study and 3 prospective, randomised clinical trials (CLOSURE I, PC, RESPECT). Wöhrle (60) and Agarwal, et al. (61) summarised clinical outcomes from 15 studies with medically treated patients and 12 studies with patients who underwent percutaneous PFO closure. The annual rate of stroke or TIA was significantly lower after percutaneous PFO closure compared with medical treatment and was comparable to event rates of patients without PFO.

In a study on long term follow up (median 9 years) in non-randomised, but propensity matched cohorts (closure vs. medical therapy), the primary composite outcome (stroke, TIA, or peripheral embolism) occurred in 11% of patients slated to PFO closure and 21% of patients slated to medical treatment (HR 0.43; 95% CI 0.20-0.94; P=0.033). The treatment effect was driven by a decrease in the risk of TIA of 5% versus 14%, respectively (HR 0.31; 95% CI 0.10-0.94; P=0.039). Mortality was significantly reduced when comparing the time periods after device closure to those before or without device closure.

The first randomised trial comparing the valve of PFO closure to medical therapy for stroke prevention, CLOSURE I (Prospective, Multicenter, Randomised Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best
Medical Therapy in Patients with a Stroke of Transient Ischaemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale), showed no significant benefit. It was limited to 2 years of follow-up and used the obsolete STARFlex device since withdrawn. Patients ≤60 years old with a PFO and cryptogenic stroke or TIA were randomly assigned either to device closure (n=447) or to medical therapy (n=462). Patients in the device group were treated with the STARFlex PFO closure device and received acetylsalicylic plus clopidogrel for 6 months followed by acetylsalicylic alone. Those in the medical therapy group were treated with acetylsalicylic, warfarin, or both. The primary endpoint was a composite of stroke or TIA at 2 years plus 30 day mortality and neurologic mortality beyond 30 days. By intention-to-treatment analysis, there was no significant difference between device closure and medical therapy in the rates of the primary endpoint (5.5% vs. 6.8%, HR 0.78, 95% CI 0.45-1.35), stroke (2.9% vs. 3.1%), or TIA (3.1% vs. 4.1%). Results were similar by per-protocol analysis. Major vascular complications were significantly more frequent with device closure (3.2% vs. 0%), as was atrial fibrillation (5.7% versus 0.7%, most of which was periprocedural or within the first 2 weeks). However, over a quarter of index events in CLOSURE I were TIA as were more than half of the outcome events. Fewer than two thirds of the baseline MR scans showed acute stroke. Without imaging confirmation, a trial of secondary stroke prevention becomes heavily dependent on the clinical judgment of individual investigators. Including patients with neurological symptoms that were not caused by ischaemia, cryptogenic or otherwise, would be a mistake. It would lower the outcome rate of recurrent stroke. But confusingly it may increase the rate of recurrent neurological events that are interpreted as TIA but which are actually due to migraine, seizure, or other mechanisms. Moreover, concerns about the performance of the STARFlex occluder were prominent enough in Bern that its use was abandoned a decade ago. Inferior device performance might explain why the incidence of the primary endpoint was barely different in the 2 treatment groups. Procedural success, defined by the protocol as “implantation of 1 or more devices during the index procedure with no procedural complications,” was achieved in 89%, i.e. failed in over 10% of procedures. Effective closure was assessed at 6 months with a surveillance TOE. This required procedural success and a residual shunt across the PFO of grade 0 or 1. This benchmark of effective closure was met in only 86%, representing a closure rate that is below what has been reported with contemporary devices such as the Amplatzer PFO Occluder. It should be noted that according to the CLOSURE I protocol, a shunt of grade 1 could be part of a successful procedural outcome and was also an inclusion criterion sufficient to be enrolled into the study. Indeed, of the 909 subjects in the study 428 (47%) had a trace shunt of 1 - 10 bubbles at baseline. Atrial fibrillation was seen during follow-up in 9 of the 362 subjects (2.4%) with a device implanted as compared to 3 of the 462 medically treated patients (0.6%). Atrial fibrillation represents a proven stroke aetiology. It would be unfortunate if PFO closure after successfully obliterating the conduit for paradoxical embolism introduced another important stroke mechanism. Some of these patients had probably already suffered from undetected paroxysmal atrial fibrillation at baseline but the difference between the groups strongly suggests a significant arrhythmogenic potential from the device, at least early on. Of considerable concern is the incidence of thrombus formation on the device. An earlier study reported a thrombus rate of 5% - 7% using the STARflex device, which is higher than the 1.1% reported during CLOSURE I. But 1.1% is still high when compared to other available devices (0% for the Amplatzer PFO Occluder and 0.5% with the Gore Helex Device). Since endothelialisation is not complete for several weeks, left-sided thrombus formation may explain recurrent events especially in the early period after device implantation. PFO-related events tend to occur over decades rather than over years, let alone months. Follow-up was stopped at 2 years in CLOSURE I which is vexing as longer follow-up could have been obtained in all patients. The first subject was enrolled on 23 June 2003 and the last one on 24 October 2008. Early procedural complications from PFO closure may be acceptable if there is a long-term reduction in recurrent stroke or drug-associated bleeds when compared with medical therapy alone.

The PC trial (Percutaneous Closure of the Patent Foramen Ovale using the Amplatzer PFO Occluder compared to Medical Treatment in Patients with Cryptogenic Embolism) randomly assigned 414 adults <60 years of age with PFO and ischaemic stroke, TIA, or a peripheral embolic event to treatment with the Amplatzer PFO Occluder or medical therapy. After a mean follow-up of 4 years, the composite primary endpoint of death, nonfatal stroke, TIA, or peripheral embolism for the intention-to-treat cohort occurred in 7 of 204 patients (3.4%) in the device closure group and 11 of 210 patients (5.2%) in the medical therapy group (HR 0.63, 95% CI 0.24-1.62, p=0.34). Similarly, results for the per-protocol cohort showed that the difference between the groups was not statistically significant (HR 0.7, 95% CI 0.27-1.85, p=0.48).
Nonfatal stroke occurred in 1 patient (0.5%) in the closure group and in 5 patients (2.4%) in the medical treatment group (HR 0.20, 95% CI 0.02-1.74, p=0.14), and TIA occurred in 5 patients (2.5%) and 7 patients (3.3%), respectively (HR 0.71; 95% CI 0.23-2.24, P=0.56). Adverse events were slightly more frequent in the device closure group, including a nonsignificantly higher rate of new-onset atrial fibrillation in the device closure group (2.9 vs. 1.0%).

In the RESPECT trial (Randomised Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment), 980 patients with a mean age of 46 years with a PFO and cryptogenic ischaemic stroke were randomly assigned to percutaneous closure using the Amplatzer PFO Occluder or medical therapy. The primary endpoint was a composite of recurrent nonfatal ischaemic stroke, fatal ischaemic stroke, or early death after randomisation. The trial results were analysed after reaching the preset target of 25 primary endpoint events, all of which nonfatal ischaemic strokes. Mean follow-up was 2.6 years. In the intention-to-treat cohort 9 of 499 patients (1.8%) in the closure group and 16 of 481 patients (3.3%) in the medical therapy group suffered a recurrent stroke. The difference was not statistically significant by time-to-event analysis (0.66 vs. 1.38 events per 100 patient-years, HR 0.49, 95% CI 0.22-1.11, p=0.08). However, in the prespecified per-protocol cohort (944 patients who received the assigned treatment, adhered to the mandated medical treatment, and did not have a major inclusion or exclusion violation), the event rate was significantly lower for device closure, with 6 vs. 14 strokes (0.46 versus 1.3 events per 100 patient-years, HR 0.37, 95% CI 0.14-0.96, p=0.03). Analysis for the prespecified as-treated cohort (958 patients who received a protocol-approved treatment, adhered to the mandated medical treatment, and classified according to the treatment actually received) also showed a significant benefit for device closure (5 vs. 16 strokes, 0.39 vs. 1.45 events per 100 patient-years, HR 0.27, 95% CI 0.10-0.75, p=0.007). Furthermore, percutaneous closure provided a significantly greater benefit in patients with severe right-to-left shunt at baseline (HR 0.18, 95% CI 0.04-0.81, p=0.01), in those with an associated ASA (HR 0.19, 95% CI 0.04-0.87, p=0.02), or when compared to those on antiplatelet agents (HR 0.34, 95% CI 0.12-0.94, p=0.03). Recurrent strokes were larger in the medical treatment group (moderate, large, or massive infarcts in 9 out of 13 (69%) vs. 1 out of 7 (14%, p=0.06). There was no significant difference between the device closure and medical treatment groups in the rate of TIAs (HR 0.89, 95% CI 0.31-2.54, p=0.83), serious adverse events (23% vs. 21.6%, p=0.65), or the total incidence of atrial fibrillation (3.0 vs. 1.5%, p=0.13).

Thus, with hazard ratios of 0.49 to 0.78, all 3 randomised trials suggested that PFO closure could be more effective than medical treatment alone for reducing event rates, but these results were not statistically significant by individual intention-to-treat analyses. An important shortcoming of all 3 trials is that the number of primary events was relatively low, with a total of 52 events in the CLOSURE I trial, 18 events in the PC trial, and 25 events in the RESPECT trial. Another issue concerns uneven dropout rates among both arms of these trials. Furthermore, follow-up in the CLOSURE I trial (2 years), the RESPECT trial (3 years), and even the PC trial (4 years) may not have been long enough to significantly demonstrate benefit of closure.

There was no significant benefit for stroke risk reduction in several meta-analyses of the intention-to-treat data. Wolfrum, et al. included a total of 14 studies (3 randomised controlled trials and 11 non-randomised observational studies) with a total of 4 335 patients. There was no significant treatment effect of PFO closure regarding stroke among the randomised controlled trials (HR 0.66, 95% CI 0.37-1.19, p=0.171). However, among non-randomised studies stroke was reduced (HR 0.37, 95% CI 0.20-0.67, p<0.001) after PFO closure. A time-to-event (stroke) analysis, combining all 3 randomised and the 2 non-randomised studies which applied strict multivariate adjustments, showed a borderline significant risk reduction after PFO closure (HR 0.58, 95% CI 0.33-0.99, p=0.047).

Neither risk of bleeding nor mortality differed significantly between the groups. However, there was a higher incidence of new onset atrial fibrillation in the closure group (HR 3.50, 95% CI 1.47-8.35, p=0.005). There were signals pointing towards a potential benefit if non-randomised data or only randomised controlled trials using the Amplatzer PFO Occluder are considered.

Along with other meta-analyses, Rengifo-Moreno, et al. analysed the 3 randomised studies including a total of 2 303 patients, with 1 150 patients randomised to PFO closure and 1 153 patients randomised to medical therapy. Mean follow-up was 3.5 years. Baseline characteristics (age, sex, and cardiovascular risk factors) were similar across studies. Intention-to-treat analyses showed a statistically significant risk reduction in stroke or TIA in the PCO closure group when compared to medical treatment (pooled HR 0.59, 95% CI 0.36-0.97, p=0.04). The combined outcome of death and vascular events showed a borderline significant benefit for PFO closure when compared to medical treatment (pooled HR 0.67, 95% CI 0.44-1.00, p=0.05). Patients with a substantial interatrial shunt seemed to benefit the
most from PFO closure (pooled HR 0.35, 95% CI 0.12–1.03, p=0.06). However, this did not reach statistical significance.

The Gore Helex Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (REDUCE, NCT00738894), the Patent Foramen Ovale Closure or Anti-coagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE, NCT00562289), and the Device Closure Versus Medical Therapy for Secondary Stroke Prevention in Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENCE-PFO, NCT01552588) trials are ongoing. However, due to the fact that lower than expected event rates have to be anticipated, the included patient numbers and follow-up durations will likely again be insufficient to achieve satisfactory power.

As per potential long-term hazards, device endocarditis represents a problem reported in a few case reports but not encountered in our experience. The device may embolise peri-procedurally but it should then be amenable to percutaneous retrieval in most cases. Late device embolisation is hardly possible. Arm fractures were reported for some obsolete devices, but not with Amplatzer occluders. Late atrial fibrillation may occur but a causal relationship to the device will be difficult to establish.

CONCLUSION

Despite the availability of the results of the long awaited first 3 randomised controlled trials, the optimal treatment strategy for patients with documented or suspected paradoxical embolism remains controversial. These results did not change many minds. The sceptics saw themselves confirmed by 3 negative randomised controlled studies. Those believing in the rationale for PFO closure were encouraged by the substantial albeit nonsignificant relative risk reduction of recurrent strokes (significant in the prespecified subgroups of patients with large shunts or ASA, or in all when compared to treatment with acetylsalicylic acid only), and the positive per-protocol and as-treated analyses of the RESPECT trial. It can be assumed that adding a couple more years to the protocol-based follow-up duration of the PC and the RESPECT trials will render them individually significant. Indeed, a non-randomised but propensity score matched analysis of a Bern cohort with long-term follow-up (median 9 years) showed a significant reduction of the primary composite outcome of stroke, TIA, or peripheral embolism and even a mortality benefit when analysed per treatment status.

Moreover, the PC and RESPECT trials promise an extended follow-up of their patients in addition to a continued analysis on patient-data basics. That might be quite compelling.

Percutaneous PFO closure is a minimally invasive procedure which can be performed with high success and low morbidity. With respect to secondary prevention of recurrent embolic events, percutaneous PFO closure appears to be clinically at least as effective as medical treatment without the risk of long term anticoagulation which should be with a vitamin K antagonist or perhaps a direct oral anticoagulant according to the RESPECT trial subanalysis. The overall safety profile of Amplatzer Occluders appears to be superior to that of other devices, especially the now defunct STARFlex occluder. While one can argue that closure cannot be presented as the recommended treatment, it should at least be mentioned as an attractive option. It has been referred to as a once-in-a-lifetime mechanical vaccination compared to lifelong medical treatment. However, one has to be reminded that the prevalence of PFO in the general population is high (~25%) and so discovering one, even in a patient with cryptogenic stroke, does not per se prove paradoxical embolism. The Risk of Paradoxic Embolism (RoPE) study has shown that there are baseline patient characteristics that can predict whether a discovered PFO is likely to be pathogenic or incidental. The scale unfortunately is built on the shaky ground that a PFO is the last of all stroke causes to be considered. Closing an incidental PFO is not going to prevent non-PFO-related stroke recurrence while exposing the patient to some, however small, procedural and device risks.

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