Review Article

Can We Close the Discussion on PFO-Closure?

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The development and availability of special closure devices for the treatment of patent *foramen ovale* (PFO) have facilitated an extended discussion on their use, especially in stroke patients or in those experiencing transient ischemic deficits. Many studies have reported both advantages and disadvantages of closure devices compared with medical therapy alone. Of late, the subject has been further elucidated by new investigations aimed at obtaining clearer insights into this clinical problem. In the present review, we address the most salient clinical questions in this context, taking into account the most prominent and recent clinical studies and their findings.

Introduction

Ischemic stroke or transient ischemic attacks (TIA) occur often, with an increase seen in their incidence over the last few decades.[1] The main underlying reasons are represented by micro- or macroangiopathy and cardiovascular thromboembolism. However, in a large number of cases, especially in young patients, the causes remain largely cryptic, with paradoxical embolism being the most likely factor responsible for such clinical findings.[2]

A PFO as a potential source of embolism can easily be diagnosed by transesophageal echocardiography (TEE), which indicates a prevalence of up to 20%.[3] The rate is even higher in autopsy studies.[4] The likelihood of PFO as the cause of cerebral embolism is underscored by a frequently coincidental atrial septal aneurysm or an interatrial septum pouch.[5,6] Interventional closure and medical anticoagulant treatment are most prominent among the therapies that exist in relation to the plausible causes of stroke.[7,8] If open heart surgery is performed for other reasons, simultaneous PFO closure should always be considered when practicable.

Over the past few decades, many studies have addressed the question as to whether PFO closure is superior to oral anticoagulation. However, prospectively collected (and hence resilient) data were lacking until quite recently.[9,10] The results of three prospective, randomized, multicenter trials from the United States and Europe were published in 2012 and 2013. The studies examined whether percutaneous closure was superior to medical therapy alone for patients with PFO suffering from ischemic events.[11-13] In this review, we seek to explore all clinical aspects of this complex cardiac/neurological interplay and evaluate the currently available literature.

Prevalence and pathological anatomy

A PFO is a special form of atrial septal defect; however, it is distinguished by the un-

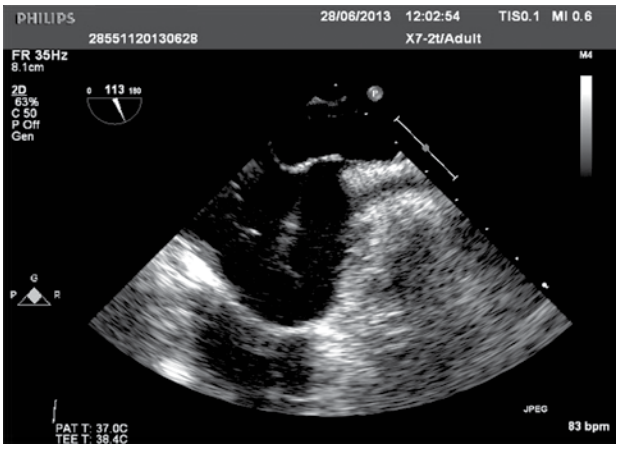

Figure 1. Typical atrial septum aneurysm with sagging of the *septum primum*.

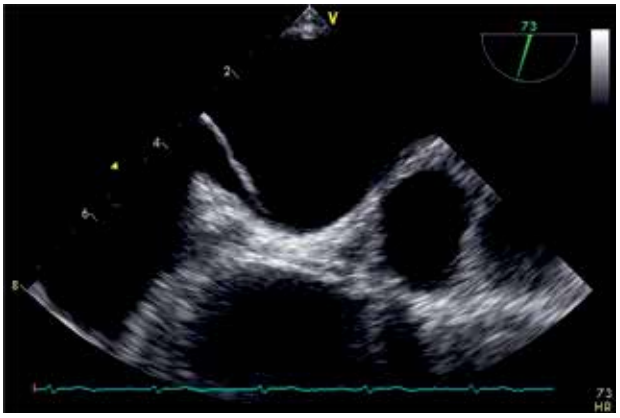

Figure 2. Atrial septal pouch with a broad interleave between *septum primum* and *secundum* as likely source of thromboembolism.

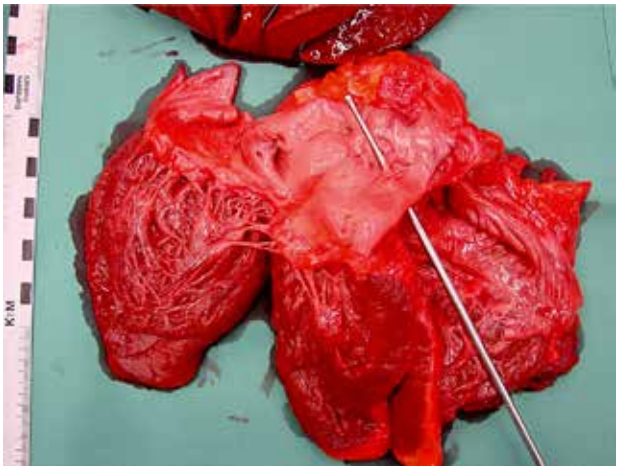

Figure 3. Cardiac autopsy with a probed patent *foramen ovale*.

derlying pathological mechanism of its development during the immediate newborn period. For instance, the actual pathology is a failed fusion of both the *septum primum* and *septum secundum*; thus, it does not necessarily involve a structural septal defect but in many cases a valve-like opening and closing that increases under Valsalva and Valsalva-release conditions. Other cases frequently show a hypermobile septum that excurses by more than 15 mm in total amplitude,[14] or even a septal aneurysm based on additional defects in the connective tissue of the *septum primum* (Figure 1). There are also instances involving a septal pouch, which may be the focus of thrombus formation (Figure 2).[15]

In echocardiographic examinations, the diagnosis of PFO is verified in up to 20% of cases using special methods of contrast echocardiography (i.e. agitated saline solution). Accurate diagnostic detection from autopsy studies, on the other hand, can be as high as 30% in a normal population (Figure 3). Three-dimensional anatomy helps distinguish between tubular and funnel-like defects (Figure 4). Reported in 1993, the results of an interesting investigation by the Mayo Clinic showed that a PFO may enlarge over time, increasing its diameter from 3.4 mm in the initial years up to 5.8 mm in the tenth decade of life. Kaplan and colleagues trace this finding back to an extension in the area of the *fossa ovalis* that takes place throughout the entire lifespan.[16] No differences were observed in terms of race or sex.

Clinical relevance in neurology

Apart from cardioembolic events triggered by known sources, micro- and macroangiopathy are the most prominent causes of both complete and transient stroke attacks. However, a considerable number of cases (up to 30%) remain cryptic.[2] In these cases, the incidence rate of PFO with or without an atrial septum aneurysm is doubled, and thus is significantly higher than in a population suffering from stroke based on unknown reasons. This is especially valid with regard to patients under 55 years of age, as reported by Handke et al in 2007.[17]

If it is likely to be of clinical relevance, the diagnosis of a PFO by echocardiography should initiate the search for a probable cavernous source of embolism, such as deep vein thrombosis (DVT).

In daily clinical routine, acute hemiplegia with or without aphasia is frequently diagnosed, with patients being put in intensive care with the option of

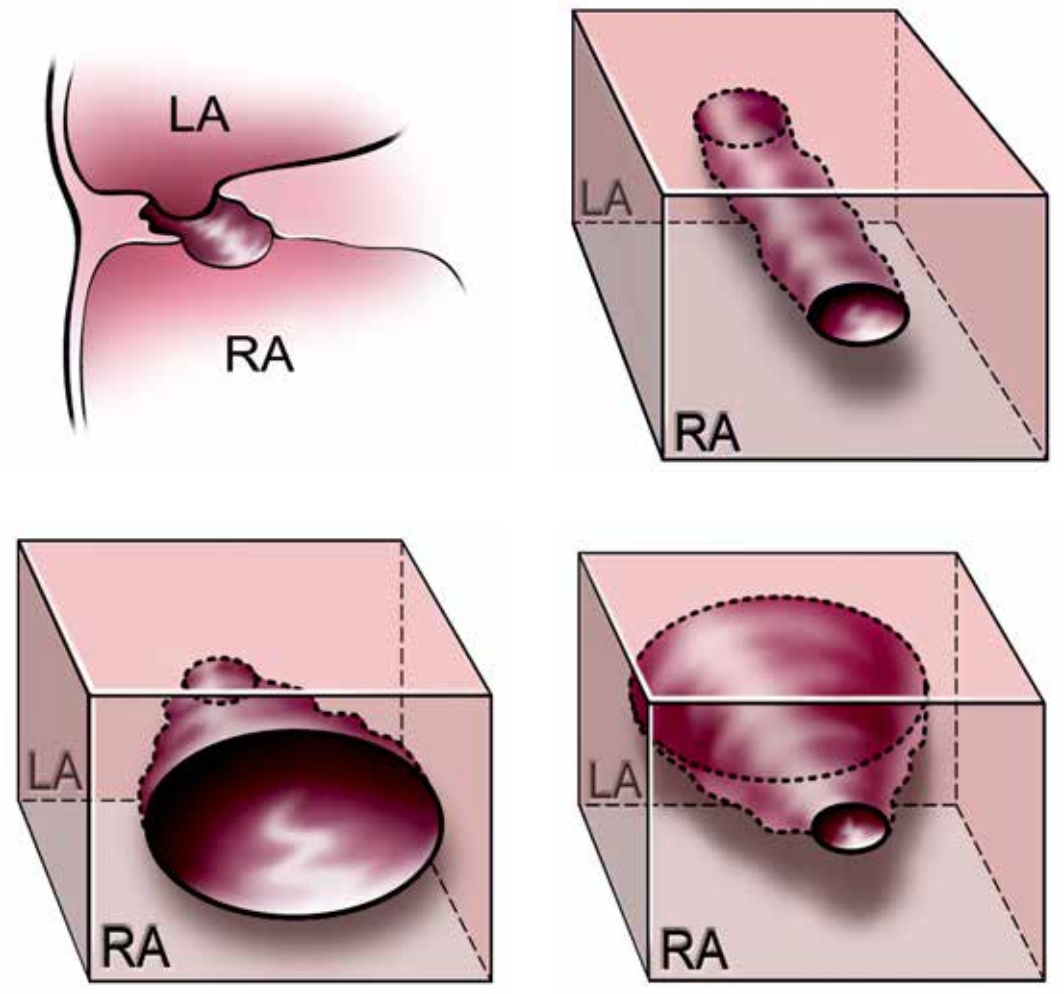

Figure 4. Different tubular and funnel-like types of patent *foramen ovale*. © St. Jude Medical, 2014. Reproduced with permission.

ventilation. Dysphagia in spontaneously breathing patients may complicate the situation and secondarily lead to mechanical ventilation due to aspiration pneumonia. Often, dilative tracheostomy is subsequently necessary for long-term ventilation. Specific anti-infective therapy based on the Tarragona strategy is one of our most prominent measures in this context.[18]

Apart from stroke, a link between PFO and migraine has also been reported,[20] which is likely to play a role in the transport of paradoxical emboli to the vertebro-basilar circuit and the release of vasoactive substances at this location. However, a definite recommendation for closure in such patients has yet to be validated.[21,22]

Furthermore, an increased prevalence of decompression sickness in divers has been reported, with the underlying mechanism of bypassing the pulmonary filters during emersion.[23] Personally referred data from the PRIMA study (patent *foramen ovale* in patients with migraine and aura) showed a slight clinical benefit to patients undergoing PFO closure who suffered from migraine with aura.

Diagnostics

Every patient with a transitory ischemic attack or a definite stroke will undergo a thorough screening for potential underlying causes of the local reduction of blood supply. This includes ultrasound, CT angiography or MR angiography of the carotids and all arteries that supply blood to the brain, 24 h Holter ECG, 24 h blood pressure measurements, and echocardiography. Echocardiography aims to iden-

tify sources of cardiac embolism. This includes the detection of a thrombus, valve abnormalities, vegetations, cardiomyopathy and endocarditis. Since auscultation findings in PFO are very infrequent, echocardiography is the gold standard in screening for PFO. In cases of satisfactory ultrasound conditions, the transthoracic apical four-chamber view may indicate a hypermobile septum. Contrast imaging is induced additionally by agitated saline solution and has to be applied using venous access in the right arm. In some instances, contrast passover flows from the right to the left atrium occur passively, although many cases require a Valsalva maneuver including a Valsalva release for such demonstration. Stroke imaging characteristics that suggest a cardiac source of a vessel-occluding embolus should initiate a TEE. The patency of the interatrial septum (IAS) can be examined here with high definition using a midesophageal view at 40º-50º (Figure 1). Contrast solution is used accordingly and Valsalva conditions can be induced in sedated patients by applying pressure to the epigastric angle. Color flow helps to indicate pathologic shunt flows. In addition, M-mode echocardiography allows the exact septum excursion to be verified once more. The threshold value of 15 mm indicates the quality of a hypermobile septum that is often combined with aneurysmatic sagging. In very rare cases, bubble filling of the left atrium is seen for other reasons, such as atrioventricular malformations adjacent to the atria. In this context, and if no structural defect is observed between the *septum primum* and *secundum*, a transcranial Doppler (TCD) with agitated saline solution may also be helpful for the detection of high-intensity transient signals.[24] In a recent study, Johansson and colleagues reported that the echocardiographic accuracy of diagnosis is notably higher in cases of a coincident septum aneurysm.[25]

In addition to echocardiography, taking a detailed history is the key to detecting a possible predisposition to thromboembolic events. A venous ultrasound examination for thrombosis of the deep lower legs is needed in most instances. Varicosis or immobilization for a long period of time may also predispose to thrombus generation. In addition, laboratory screenings should be conducted for thrombophilia, consisting of protein C and S concentration, Factor-V-Leiden mutation, prothrombin mutation, antithrombin III deficiency, the antiphospholipid-antibody syndrome on the venous side, and concentrations of homocysteine and lipoprotein, as well as the sticky-platelet syndrome, primarily on the arterial side.[26]

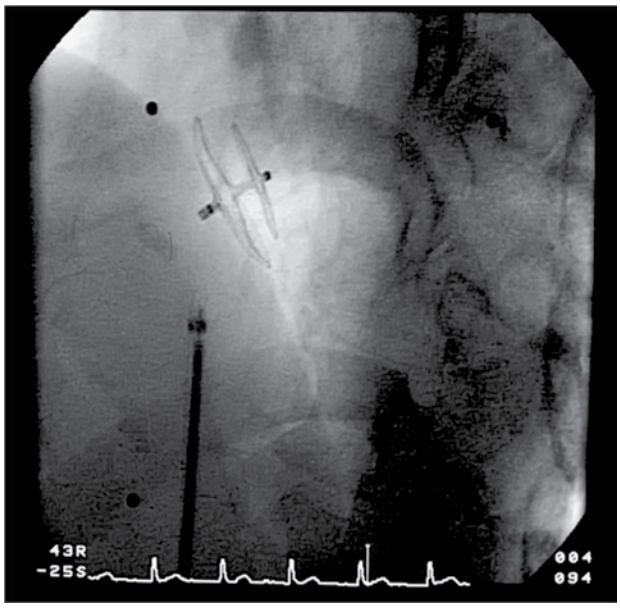

Figure 5. Final release of the Amplatzer occluder under transesophageal echocardiographic and angiographic control. © St. Jude Medical, 2014. Reproduced with permission.

Interventional therapy

Once it has been ascertained that an intervention is indicated, the procedure can be carried out under TEE and angiographic control using an 8-9 F venous access from the femoral vein (Figure 5). One of the most important contraindications is a hypercoagulable state that is predominant on the arterial side, such as the sticky-platelet syndrome or hyperlipoproteinemia.

Different device sizes from 18 mm to 35 mm (right atrium sheet, left atrium sheet up to 25 mm) in diameter are available (e.g. Amplatzer©, Cardioseal©, Helex©), all consisting of a double sheet for both the closure of PFO and stabilization of an atrial septum aneurysm (ASA; Figure 6). The procedure itself can be conducted with low periprocedural risk;[27-30] however, there are some noteworthy pitfalls in long-term follow up. The patency rate is reported to be more than 90%,[27] but very small and residual shunts, detectable only by TCD, occur in up to 21.6% of cases, as underlined by a recent report from an Italian working group around Marchese et al.[28] Several additional shortcomings should also be taken into account. Implementation of a device increases the risk of a new

Figure 6. Amplatzer PFO-occluder. © St. Jude Medical, 2014. Reproduced with permission.

onset of atrial fibrillation (AF), as exemplified in a recent meta-analysis by Kwong and co-workers that included 1856 patients (OR 3.77, 95%CI 1.44-9.87, p=0.007).[29] Other investigators stress the necessity of complete coverage with ASA, challenging the view that favors the use of a small-diameter device in order to promote left atrial function, such as the maintenance of sinus rhythm, and the left atrial conduit function with its active and passive filling and emptying.[30] Most authors recommend periprocedural anticoagulation, predominantly consisting of oral platelet aggregation inhibitors (PAI) for at least three months as mono- or double therapy.[11-13]

Finally, a simultaneous surgical closure during open heart surgery for other reasons should not be ruled out after careful exclusion of the contraindications mentioned above.

Medical therapy

The main goal of PFO closure is to prevent thromboembolic events. In most instances, the use of PAI as a single medication will be sufficient, but some special circumstances, such as DVT, a hypercoagulable state, or an elevated right atrial pressure in cases of expired pulmonary embolism or in patients suffering from chronic obstructive pulmonary disease, may demand further therapy. In daily practice, this frequently consists of heparin during the acute phase and warfarin as a permanent form of medication. Some instances may also involve new oral anticoagulants, represented by the direct thrombin inhibitor dabigatran, or the factor Xa antagonists rivaroxaban or apixaban, which may already be in use for other indications, such as coincident AF.[31] However, none of these substances is approved if PFO is present as a possible underlying cause of stroke.

Bleeding complications and failure in prevention of a second ischemic event are possible disadvantages of an anticoagulation strategy, and are the subject of much discussion. So far, in the prevention of recurrent stroke, aspirin alone has been reported to be non-efficacious in patients with isolated PFO without ASA (2.3 vs. 4.2%).[32] Mas et al, however, demonstrated a significantly higher recurrence rate in the same investigation in cases with an additional ASA.[32] Orgera and colleagues conducted a meta-analysis of five retrospective studies and showed that warfarin was superior to aspirin in preventing an ischemic event (OR 0.37, 95%CI 0.23-0.6).[33] However, another study, published as early as 1996 by Bogousslavsky et al and involving a small sample size of 92 patients, was not able to demonstrate such a benefit.[34] Even prospective studies failed to provide evidence in favor of anticoagulation regimens.[11-13]

The risk of bleeding may increase, especially in older patients with an elevated risk of falls[35] and in patients receiving a combination therapy of warfarin and PAI having undergone coronary stenting.[36]

Ongoing state of clinical investigation

Until the publication of the three studies in 2012/2013, randomized prospective studies involving sufficient numbers of patients were lacking. However, plenty of retrospective surveys and a few prospective studies, with methodological problems due to missing detailed randomization protocols and/or very short follow-up intervals, have been conducted over the past few decades. Van de Wyngaert published data from 66 patients (below 55 years of age) selected for interventional PFO closure in 2008 and reported satisfying results in terms of patency rates. In the follow-up period of 3.73 years, no recurrent stroke was seen.[37] Based on a study involving 16 patients in 1994, Hanna and colleagues reported PFO as a likely cause of stroke and recommended aspirin as first-line therapy.[38] In contrast, the data published by Lee et al in 2010 showed that, of the 181 patients involved, 14 had suffered from recurrent stroke after transcatheter closure, and that

Table 1. Patient characteristics in published observational trials before 2012 (modified from reference #56).

Author/year	Therapy	n	Mean follow up (years)	Age (years)	Male (%)	ASA (%)
Sievert 2001[40]	Closure	281	1.0	46.8 ± 13.2	NA	23
Braun 2002[41]		276	1.3	45.3 ± 13.7	53	22
Onorato 2003[42]		256	1.6	48 ± 15	41	41
Alameddine 2004[43]		272	0.1	51 ± 15.2	47	33
Kiblawi 2006[44]		456	1.5	51.1 ± 15.5	NA	NA
Luermans 2008[45]		430	0.8	50.7 ± 13	53.7	44.9
Taffe 2008[46]		660	0.1	49.3 ± 12.9	55.2	36.4
Wahl 2009[47]		620	1	51 ± 12	60.8	33.4
von Bardeleben[48]		357	3.8	51 ± 14	59.1	28.6
Presbitero 2009[49]		216	1.6	52.5 ± 13.5	54.6	12
Mas 1995[50]	Medical	107	1.9	39.4 ± 10.5	50	35.5
Bougousslavsky 1996[34]		140	3	44 ± 14	60	25
Mas 2001[32]		277	3.2	40.3	53	22
Windecker 2004[51]		158	2.4	50.7 ± 13.5	58.9	20.8
Schuchlenz 2005[52]		113	2.6	47.7 ± 12.7	54.9	23.9
Serena 2008[53]		297	1.9	53.2 ± 14.8	62	38.4
Weimar 2009[54]		234	2.4	57	65.8	20.1
Lee 2010[39]		159	3.5	53 ± 13	73.6	11.3
Paciaroni 2011[55]		117	2	40.9 ± 10.3	50.4	41

ASA – atrial septum aneurysm.

shunts larger than 3 mm (HR 3.0, 95%CI 1.96-4.6) as well as a coincident ASA were predictors for a recurrent event (HR 6.04, 95%CI 1.84-19.86).[39]

Table 1 summarizes the most recent series divided into two categories – interventional closure and medical therapy alone – based on data from at least one hundred patients provided by the PubMed database.

Three new prospective studies

The CLOSURE I,[11] RESPECT,[12] and PC[13] studies were designed as prospective, randomized, open-label multicenter trials (185 centers in North America and Europe) and their results were published in 2012 and 2013. In total, 2294 patients were enrolled. The patients were randomly assigned either to a closure group, subsequently undergoing interventional PFO closure, or to a medical-therapy group, receiving anticoagulation therapy only. In CLOSURE I, the STARFlex® device was used for transcatheter closure, while in other the studies the Amplatzer® device was employed. In the medical therapy groups, therapy consisted of either a PAI or warfarin, while in the closure groups, double PAI therapy was administered six months after closure. The PC study additionally analyzed peripheral thromboembolic events. The primary endpoint was defined as recurrent stroke or TIA (PC and CLOSURE I) during the observation period (between two and seven years). TEE controls were carried out immediately after closure and subsequently at intervals of at least six months for the first two years.

The studies were divided into "intention-to-treat", "modified intention-to-treat", and "as-treated" cohorts, and the data were evaluated accordingly.

In all three studies, demographic data and the underlying medical history showed no significant differences between groups. Table 2 summarizes the main characteristics of all participants:

In the intervention group, CLOSURE statistics showed a significantly higher rate of periprocedural complications, such as the new onset of AF (5.7% vs. 0.7%, $p<0.001$), as well as catheter access-based vascular complications in 13 vs. 0 cases ($p<0.001$). At 86%, the patency rate of the implanted device was the lowest in the CLOSURE-I investigation. Shunt size and the presence of an ASA were slightly more

Table 2. Main characteristics of patients in all three randomized controlled trials.

Study	Characteristic	Closure group	Medical-therapy group	p-value
CLOSURE I	Mean age (years)	46.3 ± 9.6	45.7 ± 9.1	0.39
	Age range (years)	18-60	18-60	
	TIA (%)	27.4	28.6	
	Cryptogenic stroke	72.6	71.4	
	Moderate or substantial shunt (%)	55.9	50.0	0.07
	ASA≥10 mm (%)	37.6	35.7	0.56
RESPECT	Age (years)	45.7 ± 9.7	46.2 ± 10	
	Portion male (%)	53.7	55.7	
	Moderate shunt (%)	27.7	25.2	
	Substantial shunt (%)	49.5	48.0	
	ASA (%)	36.1	35.1	
PC	Age (years)	44.3 ± 10.3	44.6 ± 10.1	
	Portion male (%)	45.1	54.3	
	BMI	26.6 ± 5.6	26.3 ± 4.8	
	ASA (%)	23	24.3	
	Moderate shunt (%)	47	40.9	
	Substantial shunt (%)	23.2	20.2	

ASA – atrial septum aneurysm; BMI – body mass index; TIA – transient ischemic attack.

pronounced in all closure groups, although without being statistically significant. No major bleeding episodes occurred in any group. In the "as-treated" cohort of the RESPECT trial, the closure group showed a significant advantage in relation to the primary endpoint "recurrent stroke" (HR 0.27, 95%CI 0.1-0.75, p=0.007). This, however, was not corroborated by the "intention-to-treat" analysis (HR 0.49, 95%CI 0.22-1.11, p=0.08). Apart from that, no significant difference from the long-term follow-up data could be confirmed in any of the three randomized trials. Table 3 summarizes the main follow-up aspects throughout all studies.

Also comparable was the hazard ratio analysis, especially for risk factors such as shunt size or the presence of an ASA (no significant difference among the groups), although with a slight benefit for the closure groups and the reservation of the smaller sample sizes in the subgroup analyses. The baseline medication (PAI or warfarin) also did not result in a distinct advantage. Table 4 shows the main results of the hazard calculation in all three trials.

Table 3. Crucial endpoints in all three trials after a 2-year follow up, according to the "intention to-treat"-analysis.

Study	Endpoint	Closure group	Medical-therapy group	Hazard ratio (95% CI)	p-value
CLOSURE I	Stroke (%)	2.9	3.1	0.9 (0.41-1.98)	0.79
	TIA (%)	3.1	4.1	0.75 (0.36-1.55)	0.44
	Composite (%)	5.5	6.8	0.78 (0.45-1.35)	0.37
RESPECT	Stroke	9 pts.	16 pts.	0.49 (0.22-1.11)	0.08
PC	Stroke (%)	0.5	2.4	0.2 (0.02-1.72)	0.14
	TIA (%)	2.5	3.3	0.71 (0.23-2.24)	0.56
	Peripheral embolism (%)	0	0		
	Composite (%)	2.5	5.2	0.45 (0.16-1.29)	0.14

CI – confidence interval; TIA – transient ischemic attack.

Table 4. Subgroup analysis with hazard ratio calculation in all three trials according to the "intention-to-treat" analysis or "modified-intention-to-treat" analysis (CLOSURE I).

Study	Subgroup	Closure-group	Medical-therapy group	Hazard ratio (95% CI)	p-value
CLOSURE I	ASA (%)	4.6	6.0	0.78 (0.3-2.13)	0.64
	No ASA (%)	6.2	7.4	0.81 (0.42-1.59)	0.55
	Trace of shunt (%)	6.9	6.8	0.99 (0.39-2.52)	0.99
	Moderate shunt (%)	5.0	7.9	0.61 (0.24-1.55)	0.3
	Substantial shunt (%)	3.5	4.9	0.72 (0.15-3.57)	0.69
	Aspirin (%)	5.3	6.7	0.79 (0.39-1.59)	0.5
	Warfarin (%)	4.2	7.9	0.52 (0.06-4.12)	0.53
RESPECT	Trace of shunt (%)	2.8	2.5	1.03 (0.35-3.08)	0.95
	Substantial shunt (%)	0.8	4.3	0.18 (0.04-0.81)	0.01
	ASA (%)	1.1	5.3	0.19 (0.04-0.87)	0.02
	No ASA (%)	2.2	2.2	0.89 (0.31-2.54)	0.83
	PAI (%)	1.4	3.6	0.34 (0.12-0.94)	0.03
	Other anticoagulants (%)	3.0	2.5	1.14 (0.26-5.1)	0.86
PC	ASA (%)	8.5	3.9	2.09 (0.38-11.4)	
	No ASA (%)	1.9	5.7	0.32 (0.09-1.18)	0.09 (for interaction)
	Index event stroke (%)	3.0	4.9	0.58 (0.19-1.76)	
	Index event TIA or pulm. embolism (%)	5.1	6.4	0.99 (0.29-3.45)	0.78 (for interaction)

ASA – atrial septum aneurysm; PAI – platelet aggregation inhibitors; TIA – transient ischemic attack.

Critical adoption and recommendation to the clinician

Although without crucial cardiological relevance for the most part, a PFO is a widespread congenital defect that can be a native source of thrombus formation and comes to the fore in paradoxical embolism. In most cases, it can be easily diagnosed by TEE. Several concepts involving only PAI, or anticoagulation therapy alone, or interventional and operative closure, have been proposed and debated over the last few decades. The CLOSURE I, RESPECT, and PC trials, three prospective, randomized studies, have published data from approximately 2300 patients. Despite an excellent protocol and thorough statistical analysis, each of these three studies had some minor methodological flaws. Firstly, the observation period of up to seven years was too long, given the likelihood of the interim occurrence of strokes due to concurrent reasons. Secondly, TIA is a relatively imprecise inclusion criterion or study endpoint, as it was used in the CLOSURE-I and PC trials. It was only in the RESPECT investigation that a complete stroke was defined as the primary endpoint in both arms. In addition, the sample size in the PC study may be diminished by general thromboembolic events being accepted as study endpoints. Furthermore, only the RESPECT study showed a significant advantage in the "as-treated" cohort for the primary endpoint in the closure arm. Daily praxis, however, unfortunately implies a common patient behavior that is congruent to an "intention-to-treat" situation and here no significant differences were observed. Baseline anticoagulation regimes also did not show any significant differences in the medical therapy arms, especially in CLOSURE I, and the situation was methodically aggravated by the fact that anticoagulation concepts in the PC study were set by the local attending physicians. Finally, following transcatheter closure, all patients needed at least an initial administration of PAI medication.

Given the lack of well-defined guidelines from North American or European professional societies, there is no definite answer pertaining to the question of PFO closure, as already noted by the editor of the journal that published these three trials.[57] In contrast, general stroke prevention guidelines are well defined by the American Heart/Stroke Association.[58] Administration of aspirin in patients with PFO as a

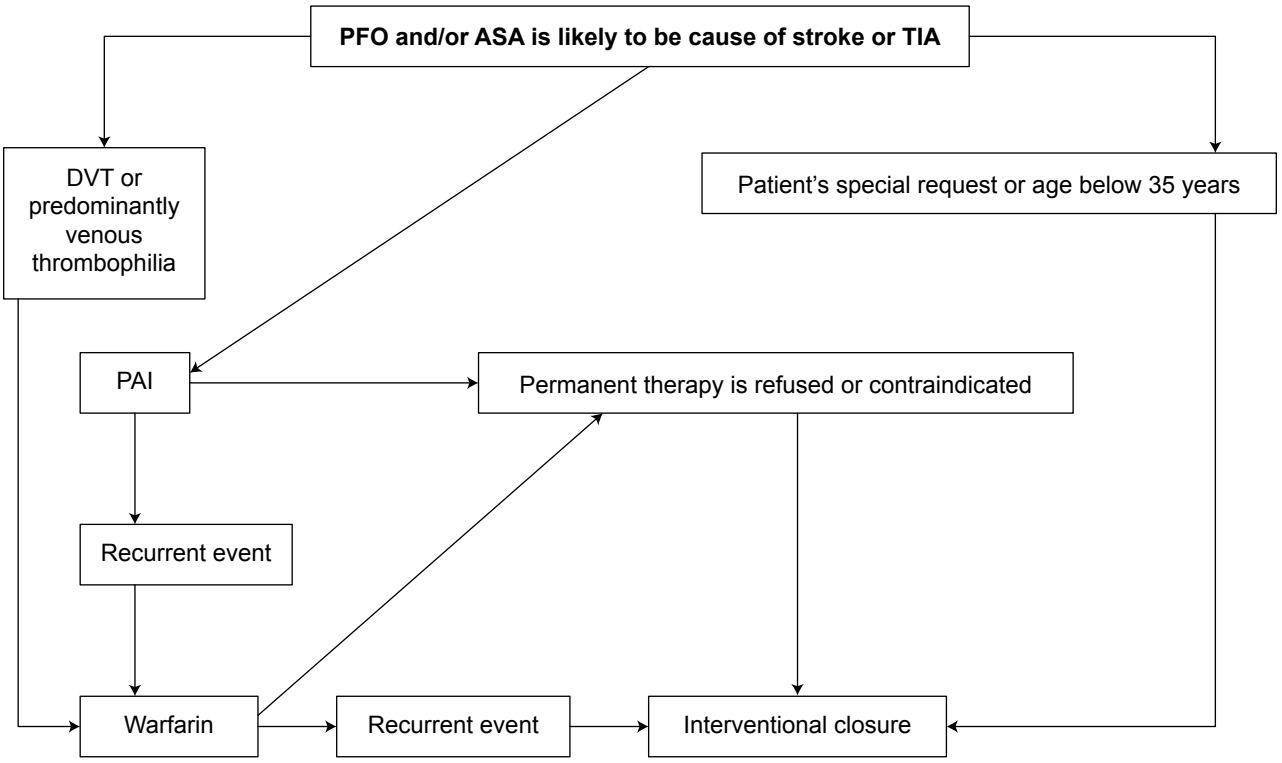

Figure 7. Practical flowchart with recommendations for proceeding in almost all clinical cases.

likely cause of stroke is part of routine practice in our institution. Only in cases of DVT or recurrent ischemic events under aspirin administration does warfarin represent an alternative. Careful diagnosis of thrombophilia is mandatory before an interventional closure can be considered, especially in situations in which anticoagulation is prohibited or the patient refuses enduring medical therapy. Additionally an optional *vena cava* filter may be useful in these cases, or when repetitive embolism is present despite anticoagulation therapy.[59] Figure 7 shows our in-house concept of decision making, which may prove useful to physicians.

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