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CARDIOVASCULAR DISEASE AND STROKE (D LEIFER AND JE SAFDIEH, SECTION EDITORS)

Management of the Stroke Patient with Patent Foramen Ovale: New Insights and Persistent Questions in the Wake of Recent Randomized Trials

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Abstract Stroke without a known cause, or cryptogenic stroke, accounts for up to 30 % of all ischemic strokes. Paradoxical embolism through a patent foramen ovale (PFO) has been implicated as a potential cause of cryptogenic cerebral ischemia, particularly in young patients. Epidemiological studies have noted an association between PFO and cryptogenic stroke and observational studies have suggested the potential superiority of percutaneous PFO closure over medical therapy. However, until recently, there were no randomized data to test the hypothesis that PFO closure reduces the risk of recurrent cerebral ischemia. The publication of three such trials, all failing to demonstrate a therapeutic advantage for closure over medical therapy in intention-to-treat analyses, provides valuable new data in the field. We review epidemiological evidence linking PFO and stroke and recent observational and randomized trial data evaluating different treatment strategies.

Keywords Patent foramen ovale · Cryptogenic stroke · Transient ischemic attack

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Introduction

A common clinical dilemma arises when a patient with ischemic stroke is discovered to have a patent foramen ovale (PFO). Despite the recent publication of three randomized trials addressing this very question, considerable controversy remains about the optimal management for individual patients.

Determination of the cause after an index presentation of ischemic stroke is essential in guiding secondary prevention strategies. Most ischemic strokes can be classified as resulting from large-artery atherosclerosis, cardioembolism, small-vessel disease, or other determined cause [1]. However, a substantial proportion of strokes elude classification into one of these categories, and are designated as strokes of "undetermined cause" or "cryptogenic"[1, 2]. Approximately 30 % of patients presenting with cerebral ischemia have no determined cause [2]. The problem is particularly acute in young adults, with 43 % of ischemic strokes being of undetermined cause despite extensive evaluation in one modern cohort [3].

Paradoxical embolism occurring through a PFO has long been implicated as a mechanism of cryptogenic stroke [4]. It was first described in 1877 by Conheim [5], and it was hypothesized that venous thrombi gained access to the systemic circulation via a PFO, a remnant of the fetal circulation that permits right-to-left shunting of blood at the atrial level in utero. The dramatic clinical scenario of a venous thrombus straddling a PFO is well described [4], but is rarely encountered clinically. In 27 % of adults at autopsy, a valve-like communication between the right and left atria persists as a result of incomplete fusion of the septum primum and septum secundum [6]. This communication can permit right-to-left shunting when right atrial pressure is elevated and/or exceeds left atrial pressure [7]. Such hemodynamic conditions may occur during the initial or

release phase of the Valsalva maneuver, with pulmonary hypertension, or transiently in early systole [7, 8].

A PFO is diagnosed during transthoracic echocardiography with demonstration of right-to-left blood flow by color Doppler imaging or with passage of microbubbles from the right to the left atrium during agitated-saline contrast injection after three to five cardiac cycles. However, color flow imaging alone is often insufficient for diagnosis, with a sensitivity of 22 % in one recent series [9]. Furthermore, provocative maneuvers such as the Valsalva maneuver, cough, or sniff are required in almost half of patients with PFO to raise right atrial pressure and permit visualization of shunting [9]. An atrial septal aneurysm is a redundant portion of the interatrial septum associated with a higher prevalence of PFO and atrial septal defect. It can be defined as bowing of a 1.5-cm portion of the interatrial septum by 1.1 cm or more beyond the central plane of the interatrial septum [7].

Association Between PFO and Stroke

Several case–control and cohort studies have demonstrated an association between the presence of PFO and stroke. In an early case–control study of 160 patients, the prevalence of PFO among patients with stroke was 40 %, as compared with 10 % in normal subjects without stroke [10]. Furthermore, PFO is more often implicated as a potential cause of cryptogenic stroke in the young. In a prospective study of 581 patients younger than 55 years with cryptogenic stroke, PFO was identified in 45.9 %, and these participants were younger and less likely to have cardiovascular risk factors [11]. Handke et al. [12] also demonstrated a higher prevalence of PFO among individuals with cryptogenic stroke in a series of 503 patients. Among patients younger than 55 years the prevalence of PFO among patients with cryptogenic stroke was 43.9 % as compared with 14.3 % in those with a known cause of stroke. In a recent analysis of a case–control study, the Italian Project on Stroke in Young Adults (IPSYS), the stroke risk in patients with PFO and right-to-left shunt diminished with increasing burden of atherosclerotic risk factors such as hypertension, diabetes, smoking, and hypercholesterolemia [13].

Such associations have not been confirmed in prospective studies of general populations initially free of stroke. In a multiethnic, observational cohort of 1,100 participants in the Northern Manhattan Study (NOMAS) with a mean age of 69 years, PFO was discovered by transthoracic echocardiography in 14.9 % of participants. An atrial septal aneurysm was present in 2.5 % of all participants, and was associated with PFO in most of those cases. PFO was not an independent predictor of stroke in this cohort [14]. Similarly, in a cohort of 585 men and women with a mean age of 67 years in the Stroke Prevention: Assessment of Risk in a Community (SPARC) study, PFO was demonstrated by transesophageal echocardiography in 24 % of participants and was not an independent predictor of stroke [15]. These studies focused, however, on older populations, where traditional atherosclerosis risk factors would be expected to drown out an independent signal from PFO and/or atrial septal aneurysm, and included only modest numbers of first-ever strokes, making their power to investigate these associations limited.

Some investigators have attempted to determine whether certain neuroimaging patterns are associated with PFO in patients with cryptogenic stroke [11, 16]. In the Risk of Paradoxical Embolism (RoPE) study, the largest registry of patients with cryptogenic stroke with known PFO status, various associations were noted [17]. Cryptogenic stroke patients with PFO had greater odds of having an index stroke demonstrated on imaging [odds ratio (OR) 1.53, $p=0.003$], a large index stroke (OR 1.36, $p=0.0025$), and a superficial location of the stroke (OR 1.54, $p<0.0001$) [17]. In the same analysis, no particular associations were noted between suspected high-risk PFO features such as resting shunt, hypermobility of the septum, or large shunting and neuroimaging findings [17].

Treatment Approaches for PFO in Stroke

Medical Therapy

To date, no randomized clinical trial has been conducted specifically to compare antithrombotic approaches for prevention of recurrent ischemic events in patients with stroke and PFO. The PFO in Cryptogenic Stroke Study (PICSS), however, an observational study within the Warfarin-Aspirin Recurrent Stroke (WARS) study, which randomized patients with noncardioembolic stroke to treatment with warfarin or aspirin, provides intriguing findings [18]. In this study, Homma et al. [18] evaluated rates of recurrent stroke or death among WARS participants selected by their treating physician to undergo transesophageal echocardiography according to their assigned treatment, either aspirin (325 mg daily) or warfarin (goal international normalized ratio 1.4–2.8), and focused separately on the subgroup whose index stroke was deemed to be cryptogenic. After 2 years of follow up, the rate of primary events in the 98 patients with cryptogenic stroke and PFO was 9.5 % in those treated with aspirin as compared with 17.9 % in those treated with warfarin. (Similar findings were observed in the 152 cryptogenic stroke patients without PFO.) The PICSS results suggest that warfarin may offer greater therapeutic benefit than aspirin in this population, which notably included older participants (mean age 59 years), but the study's limited power precludes reliable conclusions on this question.

Surgical Treatment

Prior to the advent of percutaneous closure devices, mechanical closure of PFO involved open surgery via thoracotomy and cardiopulmonary bypass. There have been no randomized trials comparing surgical closure versus medical therapy or percutaneous closure. In one case series, 30 younger (age less than 60 years) patients with cryptogenic stroke having PFO associated with high-risk features for paradoxical embolism (at least two of the following: large shunt, presence of atrial septal aneurysm, Valsalva maneuver prior to the index event, recurrent event or infarcts in multiple vascular territories) underwent surgical closure, with no recurrent events or complications documented during 2 years of follow-up [19]. In a series of 28 patients who underwent surgical closure, there were no recurrent strokes at 19 months of follow-up among patients younger than 45 years. However, the stroke rate among those older than 45 years was 35 %, underscoring the importance of age for patient selection [20]. Although surgical treatment has been viewed as the gold standard for PFO closure, procedural outcomes can be suboptimal. In a report of 11 patients who underwent open surgical repair, 73 % had evidence of persistent right-to-left shunting on postoperative transesophageal echocardiography.[21] Possible mechanisms for suboptimal results are incomplete apposition of the septum primum and septum secundum or iatrogenic puncture of the septum primum during surgery [21].

Percutaneous Closure

Numerous observational studies have examined treatment strategies for cryptogenic stroke in the context of PFO and have formed the basis for recent randomized trials. For example, in a propensity-score matched analysis of 308 patients with cryptogenic stroke and PFO, the rate of recurrent cerebrovascular events in patients treated with percutaneous closure was 11 % as compared with 21 % in those treated with medical therapy [22]. However, this finding was largely driven by transient ischemic attacks (TIAs). Similarly, the Austrian Paradoxical Cerebral Embolism Trial (TACET) registry found a tendency toward fewer recurrent cerebrovascular events in patients treated with percutaneous closure [23].

A recent meta-analysis of comparative as well as single-arm observational studies evaluating closure with various devices or medical therapy summarizes nonrandomized data to date (Table 1). In single-arm observational studies of percutaneous closure and medical therapy, the incidence rates of recurrent stroke were 0.36 and 2.53 per 100 person-years, respectively. In this analysis, closure was associated with an 86 % reduction in the risk of recurrent stroke, and 76 % reduction in the risk of recurrent TIA [24•]. Furthermore, there was no evidence of interaction by various baseline characteristics such as age, presence or absence of hypertension, atrial septal aneurysm, diabetes, hyperlipidemia, or smoking status. Stratifying recurrent stroke by type of medical therapy received demonstrated lower risk in association with anticoagulation as compared with antiplatelet therapy [incidence rate ratio 0.42, 95 % confidence interval (CI) 0.18–0.98]. Despite the marked effect estimates noted in this analysis, several limitations of observational data are noteworthy. Confounding by indication, differential follow-up of participants treated with closure and medical therapy, and ascertainment bias all raise concern [24•]. Furthermore, these studies used various closure devices and medical therapies, enrolled different patient populations, and used different methods for end-point adjudication [25].

Randomized Trial Evidence

Until recently, randomized trial data testing the hypothesis that closure of PFO reduces the risk of recurrent stroke were lacking. The results of three such trials now inform a clinician's decision about the most appropriate management of a patient with cerebral ischemia and a PFO (Table 2, Fig. 1).

The first trial to test this hypothesis in a prospective, randomized setting was the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke or TIA due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (CLOSURE 1) study [26•]. In this study, 909 patients between the ages of 18 and 60 with a TIA or ischemic stroke in the 6 months prior to randomization and evidence of PFO were randomized to receive percutaneous closure with a STARFlex device (NMT Medical) or medical therapy with warfarin, aspirin, or both medications. After 2 years of follow-up, the incidence of the primary end point of recurrent stroke or TIA was 5.5 % in the closure arm versus 6.8 % in the medical therapy group [hazard ratio (HR) 0.78, 95 % CI 0.45–1.35, p=0.37]. Procedural success was achieved in 89.4 % of patients, and 86 % of patients had effective closure demonstrated at 6 months by transesophageal echocardiography. There was no overall difference in the rates of serious adverse events between groups. However, more participants in the closure group than in the medical therapy group developed atrial fibrillation (5.7 % vs 0.7 %, respectively), and the overall rate of vascular complications in the closure group was 3.2 % [26•].

In the PC trial (Clinical Trial Comparing Percutaneous Closure of PFO Using the Implanter PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism), investigators randomized 414 patients under the age of 60 years with PFO and neuroimaging-proven ischemic stroke, TIA, or peripheral embolism to receive percutaneous closure or medical therapy as directed by the treating physician [27•]. During a mean follow-up period of approximately 4 years, there was no significant difference in the composite outcome

Table 1 Summary estimates from meta-analyses of observational studies

Observational studies	Outcome		
	Total events	Stroke	TIA
Medical arm IR (95 % CI)[a]	4.73 (3.41–6.56)	2.53 (1.91–3.35)	1.93 (1.16–3.20)
Closure arm IR (95 % CI)[a]	0.80 (0.55–1.18)	0.36 (0.24–0.56)	0.46 (0.29–0.74)
IR ratio[b] (95 % CI)	0.17 (0.10–0.28)	0.14 (0.08–0.24)	0.24 (0.12–0.47)

Adapted from Kitsios et al. [24]

TIA transient ischemic attack, *IR* incidence rate, *CI* confidence interval

[a] Incidence rate per 100 person-years

[b] Closure versus medical therapy for all studies (includes single-arm studies and comparative studies)

of death, nonfatal stroke, TIA, or peripheral embolism between participants undergoing closure (3.4 %) and those randomized to receive medical therapy (5.2 %) (HR for closure 0.63, 95 % CI 0.24–1.62, p=0.34). Similarly, there was no significant difference in the rates of individual end points, including stroke. These results were also consistent across various subgroups, with no evidence of interaction according to age, presence of atrial septal aneurysm, or prior cardiovascular event. Atrial fibrillation was noted in 2.9 % of participants in the closure group as compared with 1.0 % in the medically treated arm (HR 3.15, 95 % CI 0.64–15.6, p=0.16) [27•].

The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) Trial enrolled 980 patients with a history of cryptogenic stroke in the 9 months prior to randomization and PFO to receive percutaneous closure with an Amplatzer PFO occluder or antiplatelet therapy in an open-label prospective manner [28•]. Over a mean follow-up period of 2.1 years, there was no difference in the rate of the composite end point of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or death between the groups (HR with closure 0.49, 95 % CI 0.22–1.11, p=0.08). Although the overall intention-to-treat results demonstrated no difference between the two therapies, prespecified per-protocol and as-treated analyses demonstrated significant differences between closure and medical therapy. In the per-protocol cohort, including patients receiving the designated study treatment who did not develop exclusionary criteria, the HR with closure was 0.37 (95 % CI 0.14–0.96, p=0.03). A similar effect estimate was observed in the as-treated cohort, classifying participants according to the actual treatment received (HR 0.27, 95 % CI 0.10–0.75, p=0.007). There was no difference in the rate of serious adverse events between the two study groups. Of note, there was a suggestion of effect modification, wherein patients with larger interatrial shunt or atrial septal aneurysm, or as

Table 2 Summary of randomized trials of percutaneous closure of patent foramen ovale

Study	Population	Closure device arm	Medical therapy arm	Follow-up	End point
CLOSURE 1	909 patients aged 18–60 years, with cryptogenic ischemic stroke or TIA	STARFlex followed by aspirin plus clopidogrel for 6 months followed by aspirin for 2 years	At 2 years, 57.1 % aspirin, 25.2 % warfarin, 9.1 % warfarin plus aspirin, 8.6 % none	2-year period	Composite of early death, late neurologic death, stroke, and TIA
PC	414 patients younger than 60 years with ischemic stroke, TIA, or peripheral embolism	Amplatzer followed by aspirin for 5–6 months plus ticlopidine or clopidogrel for 1–6 months	At 4 years, 75.9 % antiplatelet (aspirin or thienopyridine) 17.7 % oral anticoagulation, 7.1 % none	Mean 4 years	Composite of death, nonfatal stroke, TIA, and peripheral embolism
RESPECT	980 patients aged 18–60 years with cryptogenic ischemic stroke	Amplatzer followed by aspirin plus clopidogrel for 1 month, followed by aspirin for 5 months	At randomization, 75 % antiplatelet (aspirin, clopidogrel, aspirin plus clopidogrel, or dipyridamole-aspirin), 25 % warfarin	Median 2.1 years	Composite of early death and nonfatal and fatal ischemic stroke

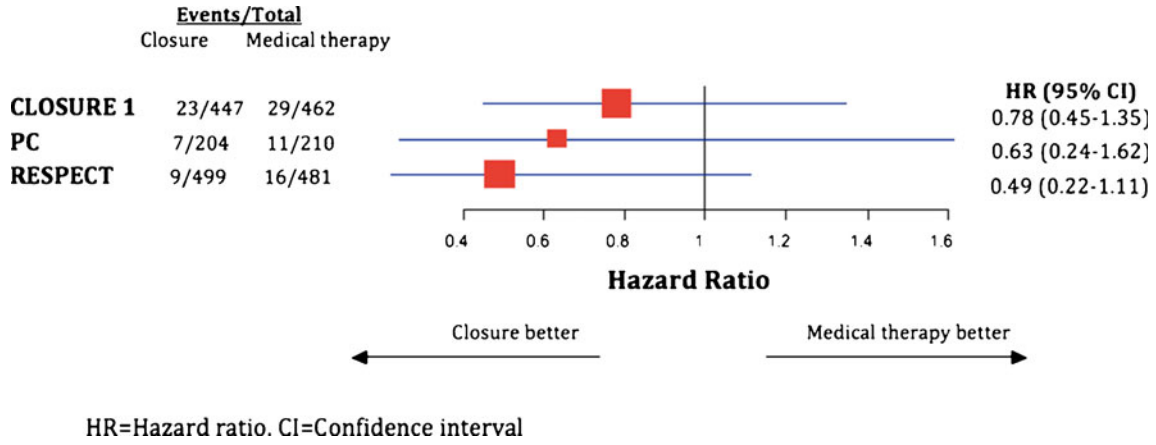

Fig. 1 Forest plot of hazard ratios for randomized trials of percutaneous closure of patent foramen ovale

compared with control patients receiving antiplatelet therapy, appeared to derive greater benefit from percutaneous closure therapy in the intention-to-treat analysis [28•].

However, caution must be exercised in interpreting these trials, and appropriate consideration must be given to their respective study designs and limitations. As highlighted by Thaler et al. [29], several aspects of CLOSURE 1 are noteworthy and may have contributed to a null finding. First, a significant proportion of participants had other risk factors for stroke, and fewer than two thirds of the participants had neuroimaging evidence of acute stroke [29]. The enrolled sample may therefore not have represented a population with cryptogenic stroke. Furthermore, the STARFlex device used in CLOSURE 1 may be associated with higher thrombotic and arrhythmogenic complications than contemporary devices [29]. The rate of recurrent stroke among those randomized to receive device closure in CLOSURE 1 was several times higher than that predicted by observational studies, raising suspicion that patients with non-PFO-related strokes were included in this study, and that the particular device used may have increased thrombogenic complications [29]. Last, given the relatively short follow-up time, there remains the possibility that the trial was not able to detect a benefit afforded by device closure [29].

All three trials were hampered considerably by slow enrollment despite pleas to limit off-label use [30]. In a 7-year period overlapping with attempted enrollment in randomized trials, there was a 50-fold increase in the number of percutaneous PFO/atrial septal defect closure devices inserted in the USA [31]. Lack of statistical power may have also played a role in the observed null findings. In the PC trial, a lower than anticipated event rate resulted in only 40 % power to detect a difference of 66 % between the two treatment arms [27•]. Although all three trials are null, the CIs include the possibility of a clinically significant benefit. Further limitations include sources of bias such as differential loss to follow-up and unblinded end-point reporting [32]. For example, although adjudication of end points was performed in a blinded manner, reporting of end points by investigators was not blinded. Differential adjudication of events in the PC trial was noted, raising concern that end points may have been underreported in the closure arm [27•].

Taken together, the evidence from the three randomized controlled trials published to date, all of which failed to demonstrate benefit of percutaneous closure over antithrombotic therapy, does not support an interventional approach for secondary stroke prevention in the average young or middle-aged patient with cerebral ischemia and PFO. But the benefit of percutaneous closure in the on-treatment analysis of RESPECT leaves open the possibility, although the analysis cannot prove, that this approach could be superior to medical—primarily antiplatelet—therapy in carefully screened patients with cryptogenic stroke. In particular, the possibility of a more pronounced benefit in patients with higher-risk PFO or as compared with antiplatelet therapy is one that will require further study.

Management of Cryptogenic Cerebral Ischemia and PFO

Given the high prevalence of PFO in the general population, a proportion of patients with stroke will harbor a PFO incidental (not accessory) to the pathogenesis of the cerebral ischemic event. Given the increased prevalence of subclinical atherosclerosis of the aorta and of the extracranial and intracranial arteries, along with a heightened risk of (paroxysmal) atrial fibrillation, with advancing age, the relative importance of paradoxical embolism as a potential underlying mechanism for stroke is likely to be reduced in older patients [33].

These considerations must be borne in mind in the approach used for patients with cerebral ischemia found to have a PFO. In such patients, the evaluation of suspected

paradoxical embolism must begin with exclusion of a venous source of thrombus, the detection of which can clinch the diagnosis, and makes systemic anticoagulation indicated [2]. Concurrent venous thromboembolism, however, is infrequently detected, which presents the diagnostic challenge of building a circumstantial case for paradoxical embolism as the basis for the cerebrovascular event [7]. Likewise, although Valsalva-provoking activity immediately preceding onset of the focal neurological deficit favors paradoxical embolism, this historical feature is absent in most patients with stroke in whom a PFO is detected [7].

In impugning PFO as a likely mechanism for cerebral ischemia, one must exclude large-artery sources of (athero)thrombosis or thromboembolism with appropriate vascular imaging [34]. The presence of small, deep infarcts in the context of hypertension or diabetes supports a small-vessel or lacunar cause [35]. Transthoracic echocardiography and, especially in younger patients, transesophageal echocardiography with agitated-saline contrast medium are essential for exclusion of other cardioembolic causes [7]. This requires supplementation with 24-h Holter monitoring to rule out paroxysmal atrial fibrillation or flutter; the advent of noninvasive ambulatory ECG monitoring makes longer screening for atrial fibrillation attractive, especially when the cause of cerebral infarction remains unknown [36]. In the setting of a large cortical infarct without ipsilateral arterial disease or a high-risk cardioembolic source such as left ventricular or left atrial thrombus or tumor, the likelihood of a pathogenic role for PFO increases, particularly in younger subjects. Specific features associated with the PFO itself can strengthen the presumption of paradoxical embolism, such as large magnitude of shunting (appearance of 50 of more microbubbles in the left side of the heart or a two-dimensional separation between the septum primum and septum secundum by transesophageal echocardiography of 4 mm or more) or the presence of an atrial septal aneurysm, although some prospective studies have not confirmed the importance of PFO size as a determinant of risk of recurrence [18]. In addition, in young adults with a personal or family history of premature thromboembolism, testing for thrombophilia may reveal a heritable or acquired predisposition to thrombosis that could influence management, necessitating initiation of systemic anticoagulation [7].

If we leave aside cases of stroke with associated PFO found to have a venous thrombophilia, which were not eligible for inclusion in randomized controlled trials of PFO closure published to date, the latter trials may not apply to instances with high suspicion of paradoxical embolism, because such patients would likely not have been selected for randomization, but would have received anticoagulation or off-label closure according to the judgment of their treating physicians. In these high-risk cases, systemic anticoagulation or percutaneous closure might be proposed to afford superior secondary prevention in comparison with antiplatelet therapy, but no high-level evidence from randomized controlled trials is available to inform management. Nor do the available data directly address the specific instance of a young woman with stroke and PFO contemplating pregnancy, where hypercoagulability, especially associated with the third trimester and puerperium, and pronounced Valsalva-like exertions during labor and delivery introduce risks not present in the nongravid state [37].

Ongoing Studies

Given the shortcomings of randomized trials to date, there remains equipoise for the study of cryptogenic stroke and PFO closure. Ongoing studies include the GORE HELEX Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Gore REDUCE) trial, which plans to randomize over 600 patients with cryptogenic stroke or TIA to closure plus antiplatelet therapy or antiplatelet therapy alone [38], and the Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial [39]. This study aims to determine whether foraminal closure or anticoagulant therapy is superior to antiplatelet therapy for the secondary prevention of stroke in approximately 900 patients. The Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High Risk Patent Foramen Ovale (DEFENSE-PFO) trial plans to randomize approximately 200 patients with cryptogenic stroke and "high-risk" PFO defined as PFO size of 2 mm or greater, atrial septal aneurysm, or hypermobility to receive Amplatzer device closure or standard medical therapy [40].

Conclusions

The gradient from CLOSURE 1 to RESPECT in favor of percutaneous closure versus medical therapy, with a declining rate of periprocedural complications with the Amplatzer versus the STARFlex occluder, in the context of a population more rigorously selected for the presence of a potential paradoxical embolism, suggests that percutaneous closure might be a desirable therapeutic option in high-risk paradoxical embolism patients. Further guidance from regulatory agencies and from ongoing randomized trials is awaited before definitive recommendations can be made in such cases. In the meantime, for most patients with stroke and PFO presenting without a picture strongly suggestive of paradoxical embolism, especially those older than 60 years, available evidence supports antiplatelet treatment and modification of atherosclerosis risk factors as the mainstays of therapy, as detailed in guidelines predating publication of randomized controlled trials of percutaneous closure [2, 41].

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