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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Role of PFO Closure in Ischemic Stroke Prevention

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Abstract

Purpose of review To highlight recent advancements in the management of acute ischemic stroke patients with patent foramen ovale (PFO).
Recent findings One significant recent development was publication of long-term follow-up data from the RESPECT trial demonstrating evidence in favor of PFO closure over medical management. This data subsequently led to FDA approval for AMPLATZER™ septal occluder in the treatment of patients aged 18 to 60 years with both PFO and no other determined etiology for ischemic stroke, otherwise referred to as embolic stroke of undetermined source. Several subsequent closure trial results have recently been published, which also demonstrated benefit of PFO closure over medical management for ischemic stroke risk reduction in select patients. Based on the results of the more recently published REDUCE trial, the FDA granted approval for the GORE™ septal occluder.
Summary There is current, well-established evidence that PFO closure for secondary stroke prevention is effective in select cases.

Introduction

There are approximately 800,000 strokes per year annually in the USA, 700,000 of which are ischemic. Stroke ranks as the fifth highest cause of mortality and one of the highest ranked causes of preventable disability [1]. Between 10 and 40% of stroke cases have no clear etiology despite appropriate and extensive evaluations [2]; these patients have in the past been labeled as having a stroke of cryptogenic etiology [3]. In these cryptogenic cases (which are more appropriately classified using current nomenclature as ESUS, embolic stroke

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of undetermined source), a patent foramen ovale (PFO) was found to be present at a higher rate than the general population (approximately half of patients [4–6]).

During fetal development, the left and right atrial are connected through an opening that closes shortly after birth. Incomplete fusion of the septum primum and secundum occurs in approximately 20–34% of the population, leaving a persistent connection between the left and right atria, or a PFO [5]. Thus, if thrombus were to form on the venous side of the circulatory system, there is possibility of embolization to the arterial side of circulation though the PFO and subsequently to the cerebral circulation.

Considerable investigative effort spanning multiple trials over the last decade and more has attempted to determine if PFO closure is effective in secondary stroke prevention, and if so, which patients should undergo PFO closure (Table 1). The first series of clinical trials, Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale (CLOSURE [7]), Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism (PC [8]), and Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT [9]) each individually failed to reach clinical endpoints that clearly demonstrated superiority of PFO closure over medical management. However, subsequent analysis of RESPECT data including longer-term follow-up suggested potential benefit in favor of closure [10], leading to FDA approval of the AMPLATZER™ septal occluder. More recent data from the Patent

Table 1. Recent PFO trials

	Defense	Reduce	Close
Study overview	Korean trial at two sites	Multinational at 63 sites	Multinational at 32 sites
Patients	1:1 closure or medical, 60 in each arm	664 total, 441 in closure, 223 medical	238 closure, 238 antiplatelet, 187 anticoagulation
PFO	characteristics	Large size, hypermobility, presence of ASA	Moderate or large shunt
Large shunt or atrial septal aneurysm			
Cardiac monitor	Required	Not required	Not done for any timeframe > 30 days
Device	Saint Jude	Helex Occluder (158) Cardioform Occluder (250)	Multiple, most commonly amplatzer PFO Occluder
Complete closure	Residual shunt present in 13% of patients	Residual shunt in 25% of patients	Residual shunt in 7% of patients
Complications	1 pericardial effusion, 1 pseudo-aneurysm	3.9% patients procedure/device-related events	1.3% with device or procedure-related events
Atrial fibrillation	Diagnosed in 2 patients in device arm	6.6% in patients with PFO closure, 0.4% medical	4.6% closure, 0.9% medical
Medical therapy	Investigator discretion: 25% warfarin	Asa, aggrenox, or plavix, no anticoagulation	Anticoagulation (almost all warfarin) or antiplatelet
Follow-up duration	Mean 2.8 years	2–5 years	Mean of 5.3 years
Endpoints	TIMI major bleeding, stroke, vascular death	New stroke, TIA, silent infarct	Stroke, morality, vascular death, bleeding
Outcomes	10% of patients in medication group	Stroke in 1.4% closure, 5.4% medical	Stroke/TIA 3.4% closure, 8.9% antiplatelet

Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke (REDUCE [11••]) trial were published, demonstrating superiority of closure compared to medical management alone, leading to FDA approval for GORE™ Septal Occluder in 2018. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke (CLOSE) trial likewise demonstrated superiority of closure over both defined antiplatelet and anticoagulation medical management groups [12••]. The Cryptogenic Stroke and High-Risk Patent Foramen Ovale (DEFENSE) trial ended earlier than anticipated secondary to recent publications strongly favoring closure interim analysis suggesting a benefit in favor of closure [13••].

Recently, the literature in both cardiology and neurology journals has blossomed with meta-analyses examining prior and more recent major closure trials [14–20]. These meta-analyses have consistently confirmed superiority of closure over medical management in patients meeting enrollment criteria, with relative risk ranging from 0.33 to 0.46 depending on the trials included in the analysis and if shunt characteristics (specifically, size) were taken into consideration. Post-procedure AF is the most common procedure-related complication, and there is no evidence supporting superiority of anticoagulation over antiplatelet medications in medical management.

Certain practice guidelines, position papers, and society recommendations have subsequently been published given this recent information, which support consideration of PFO closure in appropriate patients [21, 22]. Despite mounting evidence in favor of closure over medical management in select cases, knowledge gaps remain.

Detection of PFO

Before a PFO can be closed, it must be found. PFO detection rates vary by modality. Although trans-esophageal echocardiograms are key in both PFO detection and evaluation [23], many medical centers utilize a transthoracic echocardiogram with provocative maneuvers, or a bubble study [24], as a screening test for PFO, as opposed to transcranial Doppler, which is a more sensitive screening detection method for right to left shunt (RLS) detection [25]. Given potential changes in patient management, should a RLS be detected in a stroke patient, more sensitive methods of detection should be considered.

Treatment

Medical and interventional treatment of acute ischemic stroke patients is rapidly evolving. Intravenously administered recombinant tissue plasminogen activator (IV-rtPA) can now be administered in select cases in the field, prior to hospital arrival, with the use of mobile stroke units [26] and in patients with "wake up" strokes outside of the standard timeframe of 3–4.5 h for IV-rtPA administration [27]. Endovascular therapy for large vessel occlusive strokes can be performed in select cases up to 24 h from last known well [28]. However, none of these emergent therapeutic options (particularly those involving extended time windows) are currently different or unique for patients with presumed PFO-mediated stroke; indeed, most emergent treatment takes place before the specific stroke mechanism has even been deduced. Therapeutics that minimize the chance of a second stroke (secondary prevention) are where the majority of treatment decisions lay in patients with PFO and ischemic stroke or transient ischemic attack (TIA), and will therefore be the focus of this review.

Percutaneous closure of PFO

Patient selection is a critical and complex component of effective PFO closure. Patients with ischemic strokes or TIA attributed to a PFO have been traditionally

categorized as cryptogenic strokes. Since its adoption and widespread use in the vascular neurology vernacular, the classification of cryptogenic stroke has evolved, and now more specific subset classifications—such as embolic stroke of undetermined source (ESUS)—have emerged. This more refined ESUS classification includes non-lacunar stroke, exclusion of atherosclerosis ≥ 50%, no high-risk cardio-embolic source, or other etiology identified and emphasizes an embolic phenomenon not-yet-identified as the cause of stroke [29]. ESUS overlaps with the traditional classification of cryptogenic stroke as well as the more recently proposed etiologic classification of PFO-mediated stroke [30, 31].

Inclusion criteria in recent closure trials [11••, 12••] have reflected this shift in stroke classification. The second generation of trials utilized the same upper age limit (60 years), but more definitively excluded alternative etiologies such as lacunar strokes, hypercoagulable states, excessive alcohol or any contributing illicit substance use, and autoimmune disease. Prolonged cardiac monitoring was generally included prior to randomization, as well as enrolling in part based on higher risk characteristics of the PFO (large size, hypermobility, or association with an atrial septal aneurism [13••]).

All of the recent trials [11••, 12••, 13••] enrolled adult patients aged 60 or under with strokes of undetermined source (specifically, those with lacunar strokes, strokes in association with known cardio-embolic source, large artery atherosclerosis, were excluded from these trials). Requirements for cardiac monitoring prior to enrollment varied between these studies, as did shunt characteristics as well as medical treatment arms. No trials had significant differences between baseline patient characteristics.

The REDUCE trial enrolled 664 patients, not all of whom had moderate or large shunts (19% had small shunt size) and atrial septal aneurysm was not evaluated prior to enrollment. Monitoring for atrial fibrillation outside of the hospital setting was not a requirement for enrollment. Patients were randomized in a 2:1 ratio to PFO closure or medical management alone. Closure occurred with either the Cardioform Septal Occluder™ or the Helex Septal Occluder™ and utilized the same antiplatelet regimen as the medical arm at that same site (however, there was significant heterogeneity between sites in both medications and dosing). Follow-up occurred over of a period of 2–5 years, with end points of interest being recurrent ischemic stroke and radiographic infarcts found on MRI, along with PFO closure success and other serious adverse events.

Study approved devices were implanted in 408 total patients, with no residual shunt in 73.2% of patients immediately and in 75.6% of patients at 12 month follow-up. Recurrent ischemic stroke occurred in 1.4% of the study group and 5.4% of the medical group, and radiographic infarcts occurred in 5.7% of the closure group and 11.3% of the medical group; both of which were statistically significant. There were no difference overall in serious adverse events, the closure group experienced a procedure-related adverse event in 2.5% of patients, and a device-related event rate of 1.4% as well as a higher rate of atrial fibrillation (6.6% in the closure group compared to 0.4 in the medical group).

DEFENSE was the most recently published recent trial, which finished enrollment in the 2 Korean sites in patients with higher risk PFO characteristics (including size, hypermobility, presence of atrial septal aneurysm). The Saint

Jude device was utilized in combination with ASA 100 mg and Plavix 75 mg for 6 months, compared to medical management per investigator decision (one quarter of these patients were anti-coagulated with Coumadin). Only 60 patients were enrolled in each group, and 7 of the patients in the treatment arm ultimately declined closure after randomization to this arm. Follow-up occurred over a mean of 2.8 years, with composite endpoints of major bleeding, stroke, and vascular death. The endpoint was not reached in any patients in the closure group during the follow-up timeframe, but occurred at a rate of 10% of patients in the medical arm; 5 ischemic strokes, 1 ICH, 2 major bleeding, 1 TIA. In the closure arm, there were 2 device-related complications, 4 residual shunts on TTE, and atrial fibrillation detected in 2 patients.

CLOSE was unique in that there was a dedicated medical arm involving anticoagulation (generally with Coumadin, target INR 2–3) in patients with large shunts or associated ASA. Attempts were made to enroll in a 1:1:1 closure to antiplatelet or anticoagulation arms, ultimately 238 were assigned to PFO closure (using a wide variety of devices, 2 of whom refused closure and 2 of whom actually did not have PFO present on repeat TEE), 238 to antiplatelet medications, and 187 anticoagulation (93% of which were prescribed Coumadin). The medical antiplatelet arm regimens included asa, plavix, and aggrenox as well as dual asa and plavix with no differences in the medical treatment of those undergoing PFO closure.

Follow-up was slightly over 5 years in mean duration, with the primary endpoint of interest being recurrent stroke, and secondary outcomes of interest including composite of stroke, TIA, systemic embolism as well as serious adverse events and major bleeding. There were no recurrent strokes in the closure group, with 14 of the patients in the antiplatelet group experiencing a recurrent stroke (Kaplan-Meier estimate of stroke in 5 years of 4.9%) as well as 3 stokes in the anticoagulation group. There was not sufficient power for comparison in outcomes between those assigned to antiplatelets and those to anticoagulation. Procedural complications occurred in 5.9% of closure patients, including 4.6% of patients with atrial fibrillation compared to 0.9% in the medical arm ($p = 0.02$). There were no differences between groups overall in rates of serious adverse events.

The Risk of Paradoxical Embolism (RoPE) study used data from 12 component studies to risk-stratify patients based on clinical characteristics (history of hypertension, diabetes, and/or stroke/TIA; smoking status; cortical infarct; age) and estimate whether stroke was attributable to PFO, and predict stroke recurrence [32]. The higher the RoPE score, the more likely the stroke was attributable to PFO. Of note, there is discordance between inclusion criteria in later PFO closure trials and characteristics to obtain a RoPE score; the RoPE cannot be utilized in isolation when making a closure decision. For example, a patient who performed an activity associated with the valsalva maneuver at onset of stroke symptoms may be more likely to have suffered a paradoxical embolus and PFO-mediated stroke. However, that nuance is not accounted for in the RoPE score, nor are high-risk PFO characteristics. Higher ROPE scores in combination with specific PFO characteristics may be useful in predicting stroke recurrence risk [33].

The relevance of an incidental PFO found during stroke hospitalization should be considered in context with patient characteristics, imaging findings, and risk factors. Extensive worldwide studies have noted an increased incidence

of stroke risk in young adults over the last two decades ([34–39]). Possible explanations for this include improvements in diagnostic tools, neuroimaging, and increased public awareness of stroke symptoms. Another explanation is the rising traditional vascular risk factors in the young; one study revealed vascular risk factors traditionally associated with older patients were highly prevalent among young patients with stroke [40]. Additionally, these vascular risk factors (such as hypertension, diabetes mellitus, obstructive sleep apnea, and hyperthyroidism) which are increasing in prevalence in the young can also be associated with atrial fibrillation (AF), another dangerous vascular risk factor [41]. The increasing prevalence of these additional stroke risk factors may complicate PFO closure decisions.

An important component of patient selection is "ruling out" the presence of atrial fibrillation. This is difficult to do with certainty, as the ideal duration of prolonged cardiac monitoring prior to closure is not known. One monitoring study included patients aged 55 years and older with cryptogenic stroke and detected AF of at least 30 s with 30-day cardiac monitoring in 16.1% of patients [42]. Another study included patients > 40 years with cryptogenic stroke, detecting AF of at least 30 s duration with 6 month cardiac monitoring in 8.9% of patients, with longer monitoring associated with higher rates of detection; despite the longer time frame of monitoring, this study had a lower rate of AF detection [43]. To complicate matters further, the standard methods of paroxysmal AF detection (such as holter monitors, patches, or implantable recorders) are being joined by commercially available non-invasive wearable monitors with the capability to detect AF [44]. This could certainly result in higher rates of AF detection, both prior to PFO closure as well as in patients who have already undergone closure (assuming that AF was not detected beforehand).

All of the information required for appropriate patient selection takes time to acquire and analyze. In addition to prolonged monitors for AF detection, laboratory investigations to rule out hypercoagulable states are slow to process and if abnormal should be repeated (for example, diagnosis of the antiphospholipid antibody syndrome generally requires lab work to be positive on 2 occasions 12 weeks apart[45]). The day to day risk of recurrent PFO-mediated stroke should be low [46], and investing the appropriate time to exclude alternative stroke etiologies is recommended over expeditious closure.

Standard procedure

The AMPLATER™ septal occluder and the GORE™ septal occluder are both double disc occluder devices that have been FDA approved for PFO closure. Femoral access is most commonly used, with placement of a sheath of differing sizes depending on the closure system utilized. Trans-esophageal echocardiogram is generally utilized to assess pertinent anatomy, including the presence of a tunnel and length and associated septal aneurysm, which may influence closure device size selection. The catheter is advanced and crosses the PFO, with placement confirmed on echocardiogram. The guidewire is advanced, followed frequently by balloon (although balloon use can sometimes be omitted) then the disk deployment system. The left atrial disk is deployed first, followed by the right atrial disk. Device deployment is evaluated by echo, and the delivery system is subsequently removed, followed by access sheaths. It is recommended

to administer peri-procedural heparin [30]. Successful shunt closure occurs in over 90% of cases [18].

Contraindications and complications

The contraindications for PFO closure include active systemic or cardiac infections, challenging intra-cardiac anatomy that will not allow safe device delivery and deployment, or intra-cardiac mass [47]. Potential complications include AF or atrial flutter, cardiac perforation, cardiac arrest, pulmonary embolism, deep venous thrombosis, gastrointestinal bleeding related to heparin administration, groin or retroperitoneal hematoma formation, and device embolization [30]. The most common side effect in major trials was AF, with relative risk of AF of 3.45–4.97 in the patients undergoing closure [17, 19], the majority of which was transient and did not reoccur. Overall, there has been no significant difference between medical management and closure in rates of serious bleeding, mortality, or serious adverse events [16, 20].

Cost-effectiveness of PFO closure

Several studies incorporating recent data have investigated cost-effectiveness of PFO closure. Two studies examined both 15- [48] and 5-year horizons [49] in the context of the American healthcare system. They estimated that despite the increased upfront cost associated with PFO closure, the additional ischemic stroke prevention benefit provided by closure results in more cost-effective care and downstream savings than medical management alone (which is generally similar between groups as well as inexpensive). One study investigating PFO closure cost-effectiveness in the UK system found that PFO closure is likely to be cost-saving when compared to medical management [50].

Emerging procedures

Alternative closure systems utilizing sutures, such as the NobleStich™ suture delivery system, eliminated shunts entirely in 75% of nearly 200 patients, but left 11% with significant shunts; no significant complications were reported [51]. Clinical trials comparing NobleStich to current FDA-approved double disk devices in PFO closure are starting soon. The Flatstent system has been studied in 88 patients with similar rates of closure success and complications compared to conventional disk devices [52]. There is interest in bio-absorbable devices which may ultimately be associated with fewer device-related complications; however, small trials have not supported this hypothesis [53] and residual shunts have been a frequent occurrence [54].

Surgery

There is understandably little on recent literature regarding open surgery for PFO closure for stroke prevention. The largest single retrospective source of data for open cardiac surgery for PFO closure included 91 patients with suspected PFO-mediated ischemic stroke over a 16-year period, prior to the modern era of

percutaneous closure techniques. Most patients underwent a median sternotomy (81%), with the minority undergoing an inferior sternotomy or right thoracotomy (6.6% and 12%, respectively). There was no mortality in a short follow-up period; morbidity included post-procedure AF (11%), pericardial effusion (6.6%), and requiring return to the operating room (3.3%) [55]. A retrospective study on PFO closure during cardiac surgery for other indications was associated with an increased odds of post-procedure stroke (RR = 2.47 [56]). Given the availability of the less invasive closure options discussed above, open surgery should be generally be limited to those patients undergoing surgery primarily for other indications and/or with contraindications to FDA-approved closure devices.

Medications

Although there are a multitude of medications involved in secondary stroke prevention in addition to antiplatelets and anticoagulants, the emphasis in this review will remain on those agents investigated in trials and clinically utilized in the context of PFO closure. The medical arms of all closure trials as well as post-closure medical regimens suffer from significant degree of heterogeneity between trials. Direct oral anticoagulation agents (DOAC) in particular have not been well-represented in published closure trials (in comparison to warfarin) with only a tiny handful, handful of patients prescribed DOACs. Unless otherwise stated, all agents are associated with potential bleeding risk and can be relatively contraindicated in situations of active or potential serious bleeding; and most concerning interactions are associated bleeding risks when combined with other antiplatelet or anticoagulant medications.

Antiplatelet agents

Acetylsalicylic acid

In closure trials, acetylsalicylic acid (ASA) was the most common antiplatelet regimen utilized in the medical arms and almost universally utilized for varying timeframes post-closure in all trials. It was prescribed in varying doses depending on the trial (and frequently, at discretion of the clinician) in 75, 81, 100, or 325 mg dosing daily. Standard initial dosing for ischemic stroke secondary prevention is 325 mg with recommendations to start within 48 h of ischemic stroke (but not within 24 h of intravenous tissue plasminogen activator administration, [57]). There is evidence based on meta-analysis of over 100,000 patients in favor of weight-based dosing in overall cardiovascular outcomes [58]; however, current American Heart Association guidelines for secondary stroke prevention remain unchanged [57].

Contraindications of note include glucose-6-phosphate deficiency (although it has been administered safely in patients with this condition and acute coronary syndrome [59]), children experiencing or recovering from a viral syndrome [60], and severe thrombocytopenia [61]. It is inexpensive and has been estimated as the most cost-effective antiplatelet for secondary IS prevention for [62].

Clopidogrel

In closure trials, combination of clopidogrel and ASA in the medical treatment arm was allowed in RESPECT [9] until 2006, and dual therapy was frequently used post-closure for a variety of timeframes in multiple trials. A separate [8] trial allowed dosing of either 75 or 150 mg in the closure arm in combination with ASA. Clopidogrel requires loading of dosages between 300 and 600 mg for rapid therapeutic effect, and sometimes given in combination with ASA in the management of high-risk TIA or minor stroke [63] or in secondary prevention in patients with stroke secondary to large artery atherosclerosis [64] for treatment durations of under 3 months.

Clopidogrel interacts with CYP2C8, BCRP/ABCG2, and CYP2B6. It has higher rates of gastrointestinal distress than ASA, but lower rates of GI bleeding [65]. It is likely less cost-effective than when prescribed alone compared to ASA for secondary stroke prevention [62] but cost-effectiveness for short-term treatment should be reevaluated in the context of recent evidence for stroke risk reduction with the combination of ASA and clopidogrel short-term after high-risk TIA or stroke [63].

Aspirin plus extended-release dipyridamole

In PFO closure trials, the combination ASA and dipyridamole was utilized in 8.1% of patients in the medical arm in RESPECT [9], in only 1.3% of patients in the antiplatelet and closure arms of CLOSE [12••], and was prescribed in two possible dosages combinations in REDUCE [11••].

Dosage for secondary stroke prevention is 25 mg of ASA with 200 mg Extended-Release Dipyridamole administered twice daily. Interactions are possible with adenosine [66] and beta-blocking agents. In addition to the slightly increased risk of bleeding given the combination of ASA (and associated side effects with ASA), the main side effect of concern encountered in clinical practice, which can be frequent cause for medication discontinuation, is headache [65, 67] and gastrointestinal distress [68]. If patients are able to remain adherent, there is some evidence that the medication is cost-effective in stroke prevention in comparison to ASA alone [69].

Vitamin K antagonists

In PFO closure trials, warfarin was allowed in the RESPECT [9] and DEFENSE [13••] medical arms (approximately 25% of patients in both trials) and along with approximately 30% of patients in PC [8]. There was an entire arm of CLOSE utilizing anticoagulation, of which 93% received warfarin and only 7% received DOACs [12••]. CLOSURE allowed warfarin in addition to ASA at the clinical discretion in the medical arm [7]. In addition to stroke prevention in patients with AF, warfarin is sometimes prescribed, with some controversy, in patients with low ejection fraction [70] as well as patients with antiphospholipid antibody syndrome [71].

Warfarin dosage is tailored based on international normalized ratio (INR), which varies by indication but most commonly ranges from 2.0–3.0. Interactions are numerous and involve not only vitamin K containing foods but medications that effect CYP2C9, CYP1A1, CYP1A2, and CYP3A4 as well as genetic mutations involving these enzymes [72]. The major side effects of

concern, in addition to bleeding, are paradoxical thrombosis formation and skin necrosis while initiating treatment [73]. In general, fall risk should not be considered a contraindication [74].

Given current evidence, warfarin should not be utilized as an alternative to closure if a patient otherwise is determined to be a candidate for PFO closure. In the context of stroke prevention in patients with AF, it is inexpensive and more cost-effective than ASA given greater efficacy in stroke risk reduction [75], and home testing is likely the most cost-effective method of INR management [76]. Cost analysis incorporating DOACs suggest that despite higher cost of DOACs, these agents may be more cost-effective than warfarin secondary to the greater efficacy of stroke risk reduction [77].

Lifestyle

Diet

There is no current evidence supporting specific dietary modifications in patients with PFO-mediated stroke compared to all other patients with IS, with the exception that patients with PFO-mediated stroke are less likely to have comorbid diagnosis of diabetes, hyperlipidemia, and hypertension [2] and are therefore less likely to have accompanying dietary restrictions in addition to standard recommendations for a diet based upon the meditation diet [78] or dietary approach to stop hypertension (DASH, [79]). There is new preliminary evidence that adherence to a Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND diet, [80]) is associated with lower rates of post stroke cognitive decline [81].

Smoking cessation

Smoking is a well-known risk factor for stroke. There is some evidence of higher rates of smoking in patients considered to have a PFO-mediated stroke [2, 82], potentially in part by increasing risk of DVT formation [83] and associated paradoxical embolism.

Activity and exercise

Although more randomized controlled trials are needed, there is substantial evidence that exercise is likely beneficial in secondary stroke prevention [84, 85]. Exceptions to the general rule of exercise as beneficial may include exercises that involves frequent valsalva maneuvers [86]; for example, it is possible that patients who frequently engage in activities utilizing this maneuverer (such as scuba diving, lifting heavy weights) have an increased risk of PFO-mediated stroke.

Inactivity may be an additional risk factor for those with PFO; as in addition to the widely known association between reduced mobility and deep venous thrombus (DVT) formation, inactivity has been associated with alterations in platelet function [87]. These factors combined may play a role in a higher risk of PFO-mediated stroke (in addition to the established risk of increased risk of stroke associated with reduced mobility, [88]).

Pertinent evolving treatments in other areas of secondary stroke prevention

The clinical picture and etiologic classification of an ischemic stroke patient who may benefit from PFO closure can overlap with the stroke classification ESUS [89]. The optimal management for ESUS patients in addition is unclear at this time, and secondary stroke prevention with anticoagulation in comparison to antiplatelet agents is an area of active investigation. Clinical trials to date comparing anticoagulation with DOACs to antiplatelet agents in ESUS patients have not demonstrated compelling evidence that anticoagulation is superior [90, 91]. Subgroup analysis in patients enrolled in trials with both ESUS as well as PFO have compared ASA to rivaroxaban, but at present, data are not sufficient to recommend anticoagulation over antiplatelet medications in this population [92]. Studies utilizing more selective enrollment criteria [93] and/or future meta-analysis including certain subgroups may potentially yield results in favor of anticoagulation over antiplatelet in the ESUS patient population; this evolving realm of stroke prevention has the potential to complicate current practices of patient selection for PFO closure.

Pediatric considerations

There is a lack of quality data in the pediatric population when compared to the adult population regarding closure, but the available evidence has been excellently summarized [94]. As with other therapeutics in ischemic stroke treatment and prevention, PFO closure has been performed in patients younger than 18 years of age [95] and extrapolation from the adult population in the appropriate clinical settings can be carefully considered.

Closure pre-stroke in high-risk situations and anatomy

The majority of the literature to date has appropriately focused on secondary IS prevention, reducing further ischemic stroke risk in a patient with a known diagnosis of stroke or TIA. There is little on PFO closure in preventing ischemic strokes in patients found to have a PFO with no prior IS or TIA history and who may be at higher theoretical risk for PFO mediate stroke [96]. Further data is required to inform decision-making in this area.

PFO closure in addition to left atrial appendage occlusion

One group has recently published a case series on combined PFO and left atrial appendage (LAA) occlusion procedures, admitting that this practice has yet to find a role in IS secondary prevention [97]. It is possible to imagine a patient potentially benefiting from this with several very specific criteria; for example, an embolic-appearing infarct on brain imaging in a cancer patient who has

severe thrombocytopenia and hypercoagulability. Such patients are somewhat infrequently encountered in clinical practice, limiting the feasibility of clinical trials, and case series may ultimately be the best source of clinical data to assist with decision-making in this limited population.

Conclusion

Continued advancement in optimal patient selection for PFO closure, evolution of devices utilized in closure, and increased procedural and center experience are likely to continue to result in lower procedural complication rates and increase stroke risk reduction. The ideal patient to benefit from closure based upon current evidence should have a stroke or TIA attributable to a PFO, with higher risk PFO characteristics, have no disorders of hypercoagulability, and undergo prolonged cardiac monitoring excluding AF. The duration of cardiac monitoring prior to closure, upper age limit to benefit from closure compared to medication management, optimal device selection and tailoring to patient specific anatomy, and post-closure antiplatelet regimen are all areas that could benefit additional research. Given the continued complexity of decision-making involved in optimal patient selection, the authors agree with the current practice recommendations of involving both neurologists and cardiologists, who can then jointly decide upon optimal management in each individual case.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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