Ma *et al. Ageing Neur Dis.* 2025;5:10
DOI: 10.20517/and.2024.41

Ageing and Neurodegenerative Diseases

Review

Open Access

Management of patent foramen ovale-associated stroke: a review of closure *vs.* medical therapy

Yuanyuan Ma[1], Guo-Yuan Yang[2], Jing Ding[1,*], Xin Wang[1,3,*]

[1]Department of Neurology, Zhongshan Hospital, Fudan University, Shanghai 200032, China.
[2]Med-X Research Institute and School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200030, China.
[3]Department of the State Key Laboratory of Medical Neurobiology, the Institutes of Brain Science and the Collaborative Innovation Center for Brain Science, Fudan University, Shanghai 200032, China.

[*]**Correspondence to:** Prof. Jing Ding, Prof. Xin Wang, Department of Neurology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. E-mail: ding.jing@zs-hospital.sh.cn; wang.xin@zs-hospital.sh.cn

How to cite this article: Ma Y, Yang GY, Ding J, Wang X. Management of patent foramen ovale-associated stroke: a review of closure *vs.* medical therapy. *Ageing Neur Dis.* 2025;5:10. https://dx.doi.org/10.20517/and.2024.41

Received: 9 Dec 2024 **First Decision:** 25 Feb 2025 **Revised:** 28 Apr 2025 **Accepted:** 15 May 2025 **Published:** 23 May 2025

Academic Editor: Weidong Le **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

Patent foramen ovale (PFO) is prevalent in approximately 25% of the general population and the incidence reaches up to 50% among patients with cryptogenic stroke (CS). Extensive research indicates that PFO is linked to paradoxical embolism, leading to CS, embolic stroke of undetermined source, and systemic embolization. Percutaneous PFO closure (PPFOC) has been a promising approach to prevent recurrent ischemic stroke, particularly in selected CS patients under 60 years with a high-risk PFO. Despite advancements, unresolved issues persist. In this review, we provide an updated overview of the diagnosis of high-risk PFOs and summarize recent insights into whether closure or medical therapy alone is effective for reducing recurrent ischemic stroke in CS patients with PFOs. Additionally, we present the current evidence about the safety and effectiveness of PFO percutaneous closure in elderly CS patients. Lastly, we discuss the incidence and the management of atrial fibrillation after PFO closure to guide clinicians in their decision making. Emphasizing the importance of comprehensive assessment, we advocate for a close multidisciplinary collaboration, including neurologists and cardiologists, to avoid unnecessary closure and associated complications in CS patients with a PFO.

Keywords: Closure, cryptogenic stroke, embolic stroke, medical therapy, patent foramen ovale

INTRODUCTION

The foramen ovale is a passage in the interatrial septum of the fetal heart, allowing oxygenated blood from the maternal placenta to bypass the developing fetal lung and flow directly to the left side of the heart[1,2]. Normally, the foramen ovale closes shortly after birth when the pressure in the left-sided cardiac chambers rises due to the initiation of breathing. However, if the foramen ovale fails to close by the age of one, it is termed a patent foramen ovale (PFO)[1].

PFO occurs in approximately 1 in 4 adults, with an even higher prevalence among cryptogenic stroke (CS) patients[3-5]. Additionally, PFO is associated with some other diseases such as obstructive sleep apnea[6], decompression illness[7], secondary migraine headache[8], arterial deoxygenation, and platypnea-orthodeoxia[9], collectively referred to as PFO-associated syndromes.

CS represents approximately one-third of all ischemic strokes, about 16% further classified as embolic stroke of undetermined source (ESUS)[10,11] [Figure 1]. ESUS was introduced in 2014 to categorize stroke presumed to be embolic in nature, lacking evidence of lacunar stroke, ipsilateral arterial stenosis, major sources of cardioembolic, or other definite causes[12,13]. Potential embolic sources in ESUS cases include paroxysmal atrial fibrillation (AF), minor or covert cardiac sources, embolism related to cancer, paradoxical embolism via PFO, or less commonly, a pulmonary fistula, as well as non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries[13-15].

PFO AND ESUS

PFO is identified in 25% of patients with ESUS and is recognized as one of the most important causes of ESUS[16,17]. Paradoxical embolism, meaning a venous thrombus bypasses pulmonary filtration and enters the systemic circulation through the PFO, is a proposed mechanism explaining the involvement of PFO in ESUS[18]. With an average diameter of 9.9 mm, PFOs are sufficiently large to allow thrombi to occlude the middle cerebral artery stem (3 mm) or its cortical branches (1 mm), leading to strokes[19]. Another potential mechanism involves the thrombus formation within the PFO, detectable by high-resolution optical coherence tomography, which may result in embolization into the arterial circulation[20]. Studies have explored the MRI imaging features of patients with CS and PFO. Strokes that were large, radiologically conspicuous, superficially located, or not associated with prior infarcts are more likely to be PFO-associated compared to strokes that were smaller, deeper, or accompanied by chronic infarcts[21]. Furthermore, characteristics such as multiple scattered lesions, small-sized cerebral cortical lesions, or involvement of the posterior circulation are also indicative of PFO-associated stroke[22].

THE DIAGNOSIS OF PFOS

PFOs can be detected using various diagnostic modalities, including contrast transthoracic echocardiography (cTTE), contrast-enhanced transcranial doppler (cTCD), transesophageal echocardiography (TEE) with or without contrast, cardiac computed tomography (CCT), and high-resolution optical coherence tomography[23-25]. Each of these diagnostic techniques has advantages and disadvantages [Table 1]. cTTE is commonly used for PFO screening in selected patients with a high likelihood of a right-to-left shunt, due to its excellent specificity (94%)[29]. However, the cTTE sensitivity is relatively low, ranging from 30%-80%[30]. cTEE is the gold standard for PFO detection due to its high sensitivity (89.2%) and high specificity (91.4%) and superior visualization of cardiac anatomy, although it is invasive and may be intolerable for some stroke patients[26,37,40-42]. In comparison, cTCD offers higher sensitivity (93%) but slightly lower specificity (86%) for PFO detection and may identify small PFOs missed by cTEE[30,43-45]. However, cTCD is a blind test and cannot localize the right-to-left shunt, which may arise from PFOs or pulmonary arterialvenous malformations[5,46]. Therefore, several countries recommend

Table 1. The advantages and disadvantages of different diagnostic techniques for detecting PFOs

Diagnostic techniques	Sensitivity	Specificity	Advantages	Disadvantages	Ref.
cTTE	73% (compared with cTEE)	94% (compared with cTEE)	Noninvasive, easy to operate, commonly used to screen for PFOs	Low sensitivity, require a skilled operator, easily disturbed by subcutaneous fat in the thorax and gas in the lungs, false positive results from the presence of pulmonary Arteriovenous fistulas	[26-30]
cTCD	93% (compared with cTEE)	86% (compared with cTEE)	Noninvasive, low cost, performed at the point of care	Operator-dependent, unable to locate the site of right-to-left shunt	[5,30-32]
cTEE	89.2% (compared with autopsy, cardiac surgery, and/or catheterization)	91.4% (compared with autopsy, cardiac surgery, and/or catheterization)	Gold standard, direct observation of detailed anatomical features of the adjacent atrial septum	High cost, low tolerance (1/3 stroke patients cannot undergo it due to the severity of their stroke, dysphagia, excessive gag reflexes or refusal), inadequate Valsalva maneuver results from the sedation	[19,26,33-35]
HR-OCT	-	-	Investigate *in situ* thrombus within PFOs	Not a common tool to detect PFOs, cannot determine whether it is *in situ* thrombogenesis within the PFOs or a thrombus originating in the venous system	[23,36]
Cardiac CT	25% (compared with cTTE) 89.4% (throughout the full cardiac cycle, compared with cTEE)	96% (compared with cTTE) 92.3% (throughout the full cardiac cycle, compared with cTEE)	Easy to acquire during the acute stroke work-up, identify PFO-specific left atrial flow patterns	Radiation, not a suitable screening method for PFOs	[23,37,38]
Cardiac MRI	-	-	Could detect several cardioembolic sources	High cost, low sensitivity	[23,27,39]

PFOs: Patent foramen ovales; cTTE: Contrast transthoracic echocardiography; cTEE: contrast transesophageal echocardiography; cTCD: contrast-enhanced transcranial doppler ultrasound; HR-OCT: high-resolution optical coherence tomography; MRI: magnetic resonance imaging.

combining multiple diagnostic tools for PFO screening and diagnosis in their clinical guideline[5,47]. Some studies suggested that cTEE and cTCD were complementary and should be used together, particularly in patients with a high suspicion of paradoxical embolism, to enhance diagnostic accuracy[48,49]. CCT can also identify PFOs. However, the limited sensitivity of single-phase CCT and increased radiation exposure with full-cycle CCT limit its utility[23]. Cardiac MRI is sensitive in detecting several cardioembolic sources (e.g., left ventricular thrombus) but has a low diagnostic yield for PFOs. Cardiac MRI's role in exploring the influence of right atrial flow patterns on paradoxical embolism risk remains investigational[23,39]. Although high-resolution optical coherence tomography is not commonly used for PFO detection, recent studies have employed it to investigate the frequency and size of *in situ* thrombi within PFOs in patients with stroke, migraine, and asymptomatic individuals. Microthrombi were observed in the PFO endocardium in 84% of stroke patients, 57% of migraine patients, and none in the control group, although it remains unclear whether these thrombi originate from *in situ* thrombogenesis within PFOs or from paradoxical embolism[36]. Overall, clinicians should strive to develop optimum diagnostic strategies to enhance PFO diagnosis sensitivity, accuracy, and understanding of stroke mechanisms.

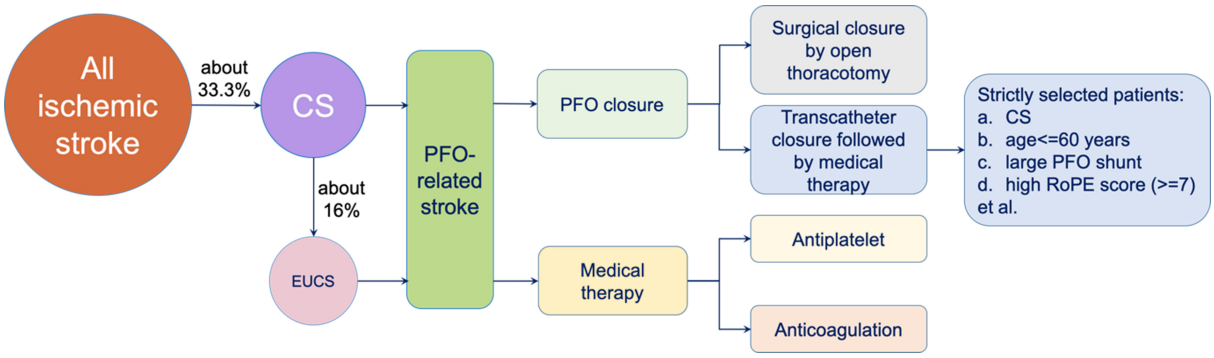

Figure 1. The prevalence of CS or ESUS in all ischemic stroke patients and the therapeutic options for the prevention of the recurrence of ischemic stroke in these patients with PFO-related stroke. Figure 1 was drawn by the authors using Microsoft PowerPoint. CS: Cryptogenic stroke; ESUS: embolic stroke of undetermined source; PFO: patent foramen ovale.

THE RISK OF PFOS FOR STROKE

Although PFOs are common in adults, their association with stroke risk varies among individuals. In many stroke patients with a PFO, other factors such as paroxysmal AF or cervicocerebral atherosclerotic plaque may be the actual causes of the stroke. Thus, PFO may sometimes be an incidental finding rather than a direct cause of stroke[50]. To assist clinicians in determining the pathogenic relevance of PFO in patients with ESUS, two scoring systems have been developed[51]. One is the Risk of Paradoxical Embolism (RoPE) score, which consists of six variables: history of hypertension, diabetes, prior stroke or transient ischemic attack (TIA), non-smoker, cortical infarct on imaging, and age [Table 2]. The scoring system ranges from 0 to 10 points and is positively correlated with stroke risk[51]. The higher score suggests a greater likelihood that the stroke is attributed to the PFO[52]. Studies have demonstrated that a PFO prevalence of over 60% occurs in patients with a RoPE score of 7 or higher, indicating a PFO-attributable fraction of over 80%[51]. Additionally, a RoPE score of 7 or more indicated that the risk of stroke recurrence increased[53]. Despite its widespread clinical use and validation, the RoPE score has limitations, particularly in predicting the causal relationship between a PFO and stroke in elderly patients[18,54,55]. Younger patients (< 40 years) tend to score higher (≥ 7), indicating a high PFO-attributable fraction (> 80%)[51]. Conversely, individuals aged 60 years or older usually have traditional cardiovascular risk factors, including hypertension and diabetes, and often score lower. Even in the absence of these factors and with embolic-like stroke on imaging, older patients may only achieve a RoPE score of 6, indicating approximately a 50% probability of the PFO being pathogenic[51]. Moreover, patients aged 70 years or older receive no additional points based on age in this scoring system. Recent studies have found that older age could predict the recurrence of stroke, especially among patients whose RoPE score was < 6, demonstrating that age is an important risk factor for stroke recurrence[23,53].

To address certain limitations of the RoPE scoring system, the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system was developed. This system integrates the RoPE score with high-risk PFO anatomical features, especially the presence of atrial septal aneurysm (ASA) and a large shunt[11,23,53] [Table 2]. In the PASCAL classification system, ASA is defined as ≥ 10 mm of excursion from midline, and a large shunt size is determined by the presence of > 20 bubbles in the left atrium during TEE[57]. Additionally, PFOs are classified as unlikely, possible, or probable to indicate the likelihood of the stroke association with a PFO[56]. Despite its advancement, the PASCAL system still inherits limitations related to the RoPE scoring system, notably its reliance on age as a primary variable. This dependency on age continues to restrict its applicability among older patients[18].

Table 2. RoPE score[52] and PASCAL classification system[56]

[a]RoPE score		[b]PASCAL classification system		
Characteristic	**Points**	**High RoPE score (≥ 7)**	**High-risk PFO feature (LS and/or ASA)**	**PFO-related stroke**
Absence of hypertension	+1	Absent	Absent	Unlikely
Absence of diabetes	+1			
Absence of stroke/TIA	+1			
Non-smoker	+1			
Cortical infarct on imaging	+1	Absent	Present	Possible
Age, year				
18-29	+5			
30-39	+4			
40-49	+3	Present	Absent	
50-59	+2			
60-69	+1			
> 70	0			
Total RoPE score (sum of individual points) =		Present	Present	Probable

[a]The RoPE score ranges from 0 to 10, with scores of 0 to 3 indicating a negligible likelihood that the stroke is attributable to the PFO and a score of 9 or 10 indicating an approximately 90% probability that the stroke is attributable to the PFO[57]. [b]PASCAL combines the RoPE score with the presence or absence of high-risk PFO features to determine the likelihood that the PFO is causally related to the index stroke. Large shunt size is defined in the database as > 20 bubbles in the left atrium on TEE; ASA is defined as ≥ 10 mm of excursion from midline[57]. RoPE: Risk of Paradoxical Embolism; PASCAL: PFO-Associated Stroke Causal Likelihood; PFO: patent foramen ovale; LS: large shunt; ASA: atrial septal aneurysm; TIA: transient ischemic attack; TEE: transesophageal echocardiography.

Recently, several morphologic characteristics indicating high-risk anatomical features of PFOs have been identified. These characteristics include a large PFO (defined as a maximum separation of the septum primum from the secundum > 2-3 mm), a long tunnel (> 10 mm), ASA (usually defined as hypermobility of the septum with > 10 mm excursion), shunt size, and prominent Eustachian valve[18]. However, current studies have shown slight variations in defining these high-risk anatomical features of PFOs. For instance, Ter Schiphorst *et al.* defined a high-risk PFO with a large shunt as > 30 microbubbles in TEE, while Kanemaru *et al.* defined a large shunt as ≥ 25 microbubbles[58,59]. In addition, previous randomized controlled trials (RCTs) have used different thresholds to define the shunt size through the PFO (ranging from ≥ 20 to > 30 bubbles on TEE), and the presence of an ASA (defined as septal mobility ranging from ≥ 10 mm to ≥ 15 mm)[60]. The role of ASA in converting a PFO into a stroke cause also varies. A systematic review and meta-analysis found that ASA was present in 25.3% of PFO patients and was associated with a higher risk of CS compared to those without ASA. The study enhanced the importance of ASA contribution to stroke in patients with a PFO[61]. However, not all studies have consistently confirmed this relationship. For example, a single-center, retrospective cohort study in the Netherlands did not find a causal relationship between ASA and stroke[62], attributing this discrepancy to the study's small sample size[62]. Furthermore, additional characteristics of PFOs have been identified as independent risk factors for CS, including the length of the PFO tunnel, low-angle PFO (defined as an angle between the inferior vena cava and PFO ≤ 10°), and the presence of ASA. To better understand the pathophysiology of PFOs in CS or ESUS, further studies are needed to standardize definitions of high-risk anatomical features of PFOs and to explore their implications in stroke causation[63].

CLOSURE FOR PFOS

Identifying and effectively managing pathogenic PFOs is crucial for the secondary stroke prevention in PFO patients. Currently, three different therapeutic options for PFO management are available, including surgical closure by open thoracotomy, transcatheter closure followed by medical therapy for several months,

and medical therapy alone, such as antiplatelet or anticoagulation treatment[47,64] [Figure 1]. Compared with the surgical closure, which is not commonly used because of its invasive nature, percutaneous PFO closure (PPFOC) is increasingly favored due to its minimally invasive nature and patient preference[64,65]. However, determining the most appropriate treatment (medical therapy alone or PPFOC followed by medical therapy) for individual patients in routine clinical practice remains challenging. Fortunately, several completed RCTs and updated meta-analyses have shown that PPFOC followed by medical therapy reduced the risk of recurrent stroke in selected PFO patients with a CS compared with medical therapy alone[66-74] [Table 3]. Moreover, the research conducted by Leppert *et al.* has demonstrated that PFO closure in CS patients is cost-effective compared to medical therapy alone[77]. Based on these findings, current guidelines from Germany recommend PFO closure in patients who are aged between 16 and 60 years and have experienced a CS or cardioembolic stroke with a high-risk PFO (class A recommendation, level I evidence)[78]. Similarly, the European Stroke Organisation (ESO) and the 2022 Society for Cardiovascular Angiography & Interventions (SCAI) guidelines also strongly recommend PFO closure plus antiplatelet treatment for patients (age 18-60 years old) with PFO-associated stroke and with no other causes except for PFO[79]. For ischemic stroke patients (age 18-60 years old) with other possible causes, the ESO prefers PFO closure plus antiplatelet to anticoagulation treatment, based on superior results from RCTs and a lower risk of major bleeding[79]. However, the relevant evidence was of low quality. Additionally, Malaysian experts advised PFO closure for embolic stroke patients younger than 60 with a high RoPE score (> 6), provided that they have undergone thorough investigation and multidisciplinary evaluation to rule out other stroke mechanisms[50]. These experts emphasized early closure, as evidence supporting late closure is limited[50]. Studies have shown that early closure in carefully selected patients offers longer protection from PFO-associated strokes and associated morbidity[80].

The effectiveness and safety of PFO closure in older patients (> 60 years) with CS have not been clearly established, as previous RCTs primarily enrolled CS patients under 60 years old. A hospital-based cohort study conducted in Taiwan enrolled 173 patients with CS or TIA and a PFO. The patients were further divided into non-elderly (< 60 years) and elderly (≥ 60 years) groups. The results showed that elderly patients who underwent PFO closure had better functional outcomes at 6 months compared to those without PFO closure[81]. Similarly, two single-center, retrospective cohort studies completed in Japan and Italy also investigated the safety and efficacy of PFO closure in elderly patients with high-risk PFOs[82,83]. Although these studies enrolled smaller samples (14 and 64 CS patients, respectively), the results suggested that PFO closure in elderly patients was as effective and safe as in younger patients. Another multicenter, retrospective study conducted in Korea, which included a larger patient cohort (437 in total, with 161 patients undergoing PFO closure), confirmed that elderly patients with a high-risk PFO could benefit from device closure[84]. Furthermore, a multicenter study crossing 6 centers in Canada and Europe (388 elderly patients were included) also showed that PFO closure was safe in older patients (> 60 years) with a CS event. Meanwhile, the study found that the incidence of recurrent ischemic events was relatively low in these elderly patients at follow-up compared with patients without PFO closure[85]. After a mean follow-up of 5 years, Eichelmann *et al.* reported that patients over 60 years old with high-risk PFOs and CS displayed improved outcomes compared to patients treated with medical therapy alone, as the recurrence of stroke was lower[86]. Using Kaplan-Meier estimates, Wang *et al.* showed that the predicted relative reduction in the rate of stroke recurrence with PFO closure was 12.9% overall, 48.8% in those with a high-risk PFO feature. Therefore, the authors suggested performing PFO closure in older patients with a high-risk PFO and CS[87]. Although the above studies showed promising results, all of them are retrospective studies. Thus, more large-scale RCTs are needed to provide definitive guidance on whether closing PFO improves outcomes in selected elderly patients with CS. Further research in this area will help inform clinical practice and decision making regarding PFO management in older patients with CS.

Table 3. RCTs on PFO closure plus medical therapy *vs.* medical therapy alone in patients with CS

Study	Study object	Country	Objective	Age (year)	Number	Mean age (year)	Definition of high-risk PFO	Size of PFO	Grade of PFO	Closure device	Medical therapy alone	Mean follow-up (year)	Primary end point	Main results	Ref.
CLOSURE I	CS or TIA with a PFO	87 sites in the United States and Canada	Whether PFO closure combination with medical therapy is superior to medical therapy alone	18-60	909 (447/442)	46.3 ± 9.6, 45.7 ± 9.1	-	10.2 ± 5.1 mm	-	The STARFlex device	Warfarin, aspirin (325 mg daily), or both	2	The 2-year rate of TIA, stroke, or death	PFO closure was not superior to medical therapy alone for preventing the recurrence of stroke or TIA	[75]
PC	No other identifiable cause of ischemic stroke, TIA, or a peripheral thromboembolic event with a PFO	29 centers in Europe, Canada, Brazil, and Australia	Whether PFO closure is superior to medical therapy	< 60	414 (204/210)	44.3 ± 10.2, 44.6 ± 10.1	-	-	Grade 0 = none, grade 1 = minimal (1-5 bubbles), grade 2 = moderate (6-20 bubbles), grade 3 = severe (> 20 bubbles)	Amplatzer PFO Occluder	Antiplatelet therapy or oral anticoagulation	4.1, 4.0	A composite of death, nonfatal stroke, TIA, or peripheral embolism	PFO closure did not reduce the risk of recurrent embolic events or death compared with medical therapy	[76]
Gore REDUCE	CS with a PFO presenting a right-to-left shunt	At 63 sites in Canada, Denmark, Finland, Norway, Sweden, the United Kingdom, and the United States	the effect of PFO Closure combined with antiplatelet therapy *vs.* antiplatelet therapy alone	18-59	664	45.2	The presence of more than 25 microbubbles as a large shunt	-	Small shunt size = 1-5 bubbles, moderate shunt size = 6-25, large shunt size ≥ 25 bubbles	Helex Septal Occluder or the CARDIOFORM Septal Occluder	Aspirin alone (75 to 325 mg once daily), a combination of aspirin (50 to 100 mg daily) and dipyridamole (225 to 400 mg daily), or clopidogrel (75 mg once daily)	3.2	Freedom from ischemic stroke and the 24-month incidence of new brain infarction	The risk of subsequent ischemic stroke was lower in the PFO closure combined with antiplatelet therapy group than that in the antiplatelet therapy alone group	[68]
CLOSE	Patients with a CS attributed to PFO	32 sites in France and 2 sites in Germany	Compare the effects of PFO closure with antiplatelet therapy alone	16-60	663	-	ASA or large interatrial shunt[1]	-	Large shunt size ≥ 30 microbubbles	Eleven different devices	Oral anticoagulants (vitamin K antagonists or direct oral anticoagulants), antiplatelet	5.3 ± 2.0 (5.4 ± 1.9), (5.2 ± 2.1)	Occurrence of stroke	The rate of stroke recurrence was lower in the PFO closure combined	[67]

										therapy (aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole)			with antiplatelet therapy group than that in antiplatelet therapy alone	
RESPECT	CS with a PFO	69 sites in the United States and Canada	Whether PFO closure reduces the risk of recurrence of ischemic stroke	18-60	980 (499/481)	45.9	-	5.3 ± 3.9 mm	-	Amplatzer PFO Occluder	Aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole	5.9	A composite of recurrent ischemic stroke or early death	PFO closure lowered the rate of recurrent ischemic stroke	[66]
DEFENSE-PFO	Ischemic stroke with no identifiable cause other than a high-risk PFO with right-to-left shunt	2 sites in South Korea	Investigate the superiority of combined PFO closure compared with medical therapy alone	-	120	51.8 (49 ± 15), (54 ± 12)	PFO with an ASA, hypermobility, or PFO size ≥ 2 mm[2]	3.2 ± 1.5 mm, 3.2 ± 1.1 mm	Large shunt size ≥ 30 microbubbles	Amplatzer PFO Occluder	Antiplatelet therapy (aspirin, aspirin in combination with clopidogrel at a dose of 75 mg/day, or aspirin in combination with cilostazol at a dose of 200 mg/day), oral anticoagulants (warfarin)	2	A composite of stroke, vascular death, or thrombolysis in myocardial infarction-defined major bleeding	PFO closure lowered the rate of the primary endpoint as well as stroke recurrence	[69]

[1]ASA was defined as a septum primum excursion greater than 10 mm detected by cTEE. Large interatrial shunt was defined as the appearance of more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium detected by cTEE. [2]ASA was defined as protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum detected by cTEE; hypermobility was defined as phasic septal excursion into either atrium ≥ 10 mm; PFO size was defined as maximum separation of the septum primum from the secundum during the Valsalva maneuver ≥ 2 mm detected by cTEE. RCTs: Randomized controlled trials; PFO: patent foramen ovale; CS: cryptogenic stroke; TIA: transient ischemic attack; ASA: atrial septal aneurysm; cTEE: contrast transesophageal echocardiography.

The decision to pursue PFO closure in patients with CS should be approached cautiously and thoughtfully due to several complications associated with the procedure, such as new-onset AF, development of scar tissue, risk of aortic root dilation, subsequent erosions, and potential thrombi formation on the device[88]. Studies have shown that quite a few PFO closures were performed in patients older than 60 years, despite these patients having been excluded from previous RCTs[89]. This suggests that trial results are often extrapolated to a broader population, highlighting the need for careful consideration in real-world practice. Additionally, a retrospective cohort study in the Netherlands revealed that a considerable percentage of patients referred for PFO closure had no clearly demonstrated link between the PFO and their stroke, and a subset preferred best medical treatment over percutaneous closure[62]. Recognizing the complexity of PFO-associated strokes, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and SCAI advocated for the establishment of an interdisciplinary Heart-Stroke Team (HST) comprising neurologists and interventional cardiologists to evaluate the causal relationship

between a PFO and stroke[47,90]. Similarly, the guideline from the American Heart Association/American Stroke Association recommended a thorough evaluation by a multidisciplinary team involving cardiology and neurology specialists before considering PFO closure in patients aged 18 to 60 years with ESUS and a high-risk PFO[91]. Additionally, the 2023 National Clinical Guideline for Stroke for the United Kingdom and Ireland recommended PFO closure in selected patients (< 60 years old) who had a stroke or TIA associated with a PFO and a right-to-left shunt or an ASA. However, the guideline stated that it required a careful consideration of the benefits and risks by a multidisciplinary team including the patient's physician and the cardiologist performing the procedure before PFO closure [National guideline for stroke for the United Kingdom and Ireland, 2023 Edition. https://www.strokeguideline.org/app/uploads/2023/04/National-Clinical-Guideline-for-Stroke-2023.pdf. (1 May 2023)]. Therefore, it is essential to establish a multidisciplinary team, including cardiologists and neurologists, to conduct comprehensive discussions regarding the potential benefits and risks, including the risk of AF, associated with the PFO closure procedure[88]. This approach ensures informed decision making tailored to individual patient needs and circumstances.

MEDICAL THERAPY FOR PFOS

Currently, most trials choose temporary dual antiplatelet therapy (DAPT) following PFO closure, but the optimal duration of DAPT followed by a single antiplatelet therapy (SAPT) remains undefined. A recent ambispective cohort study conducted in France and Canada found no significant difference in the effectiveness of DAPT *vs.* SAPT, thus challenging the current recommendations of temporary DAPT[92]. Regarding medical therapy alone, previous RCTs used aspirin alone, clopidogrel alone, aspirin in combination with clopidogrel, aspirin in combination with cilostazol, or aspirin in combination with dipyridamole as the antiplatelet therapy[66-69,75]. The existing problem is that there is a lack of consensus on the management of antiplatelet therapy. For example, which antiplatelet drug is the first choice? How to determine the application of DAPT or SAPT, as well as the duration of DAPT? Further research aiming to answer these questions is needed. In terms of anticoagulant therapy, RCTs predominantly utilized warfarin with a target international normalized ratio (INR) of 2.0 to 3.0 as compared to PFO closure groups, while the CLOSE trial also explored the use of direct oral anticoagulants[66,67,69,75]. However, a recent study noted that direct oral anticoagulants did not confer a net benefit in ESUS, a subtype of CS[93]. For patients with low or uncertain associations between a PFO and stroke and patients with contraindications for PFO closure, some guidelines recommend antiplatelet or anticoagulant therapy[47,94]. Nevertheless, the best drug candidate has not yet been clarified. Five RCTs - including PICSS, RE-SPECT ESUS, NAVIGATE ESUS, ATTICUS, and ARCADIA - have demonstrated that anticoagulation (using warfarin or novel oral anticoagulants) is not superior to antiplatelet therapy in preventing recurrent stroke in these patients [Table 4]. Furthermore, anticoagulant therapy with dabigatran or rivaroxaban has been associated with a higher risk of bleeding compared with antiplatelet therapy[95-99]. Kasner *et al.*, conducting a random-effects meta-analysis combining data from the NAVIGATE ESUS trial with two previous trials (PICSS and CLOSE), suggested that among ESUS patients with PFOs, anticoagulation may reduce the risk of recurrent stroke by approximately half, although the evidence remains somewhat imprecise[100]. In contrast, Diener *et al.* compared the effects of anticoagulant and antiplatelet therapy on ischemic stroke in patients with PFOs (including the RE-SPECT ESUS trials), but did not find a difference between anticoagulant and antiplatelet therapy for preventing the recurrence of ischemic stroke[101]. Given the current evidence, there is insufficient support to recommend anticoagulation over antiplatelet therapy for patients with CS or ESUS and a PFO[101]. Therefore, SAPT was recommended as a long-term antithrombotic therapy for preventing recurrent stroke in ESUS patients[100]. Dedicated trials comparing anticoagulation *vs.* antiplatelet therapy are needed to provide clearer guidance on antithrombotic therapy for patients with CS or ESUS and a PFO who are not suitable candidates for PFO closure.

Table 4. RCTs on antiplatelet *vs.* anticoagulant therapy in patients with CS or ESUS and PFO closure

Study	Study object	Country	Objective	Mean age (year)	Number	Grade of PFO	Medical therapy	Follow-up (year)	Primary endpoint	Main results	Ref.
PICSS	Ischemic stroke	42 clinical sites in the United States	Whether the size of PFO or the concurrent presence of PFO and ASA affects the rate of recurrent stroke or death in CS patients	59.0 ± 12.2, 57.9 ± 13.3	630 in total (312/318), 203 with PFO (97/106)	Large PFO = ≥ 10 microbubbles	Warfarin (2 mg daily, adjusted to achieve and maintain INR 1.4 to 2.8) *vs.* aspirin (325 mg once daily)	2	Recurrent ischemic stroke or death	Larger PFOs were associated with CS; the PFO size or the presence of ASA was not associated with adverse events in stroke patients with PFOs; the effect of warfarin and aspirin in preventing recurrent stroke in CS patients with PFO was similar	[95]
NAVIGATE ESUS	ESUS	480 sites in 31 countries	Comparing rivaroxaban *vs.* aspirin in patients with ESUS	66.9 ± 9.8, 66.9 ± 9.8	7,213 (3,609/3,604)	-	Rivaroxaban (15 mg daily) *vs.* aspirin (100 mg daily)	0.9	Recurrence of ischemic or hemorrhagic stroke or systemic embolism	Rivaroxaban was not superior to aspirin in preventing recurrent stroke after an initial ESUS and increased the risk of bleeding	[96]
RE-SPECT ESUS	ESUS	564 sites in 42 countries from Europe, Asia, North America, and Latin America	Whether dabigatran is superior to acetylsalicylic acid for prevention of recurrent stroke	64.2	5,390 (2,695/2,595)	-	Dabigatran (150 mg twice daily or 110 mg, twice daily if patients ≥ 75 years) *vs.* aspirin (100 mg daily)	1.6	Recurrent stroke (ischemic, hemorrhagic, or unspecified)	Dabigatran was not superior to aspirin in preventing recurrent stroke in patients who had had ESUS, increased the rate of clinically relevant nonmajor bleeding events	[97]
ARCADIA	CS and evidence of atrial cardiopathy without AF	185 sites in the United States and Canada	Compare anticoagulation *vs.* antiplatelet therapy for secondary stroke prevention in patients with CS and evidence of atrial cardiopathy	68	1,015 (507/508)	-	Apixaban (5 or 2.5 mg twice daily) *vs.* aspirin (81 mg, once daily)	1.8	Recurrent stroke	Apixaban did not reduce stroke recurrence compared with aspirin in patients with CS and evidence of atrial cardiopathy without AF	[98]
ATTICUS	ESUS with at least one predictive factor for AF or a PFO	69 sites in the United States and Canada	Whether apixaban is superior to aspirin in patients with ESUS and known risk factors for cardioembolism	68.6 ± 11.1, 68.3 ± 9.8	352 (178/174)	-	Apixaban (5 mg twice daily) *vs.* aspirin (100 mg once daily)	1	Any new ischemic lesion on brain MRI	Apixaban was not superior to aspirin in preventing ischemic stroke in ESUS patients	[99]

RCTs: Randomized controlled trials; CS: cryptogenic stroke; ESUS: embolic stroke of undetermined source; PFO: patent foramen ovale; ASA: atrial septal aneurysm; INR: international normalized ratio; AF: atrial fibrillation; MRI: magnetic resonance imaging.

CHALLENGES AND PERSPECTIVES

Current evidence from RCTs supports the prognostic and economic benefits of PPFOC in selected stroke patient subsets[88]. Compared with the initial RCTs [Closure or medical therapy for CS with patent foramen oval (CLOSURE-1), Percutaneous Closure of PFO Using the Amplatzer PFO Occluder with Medical

Treatment in Patients with Cryptogenic Embolism (PC), Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT)] that showed negative results, the later RCTs receiving positive results used more stringent inclusion and exclusion criteria to investigate whether PFO closure was better than medical treatment alone in preventing stroke recurrence in patients with CS and a PFO[102]. However, a recent retrospective cohort analysis using de-identified administrative claims data from the OptumLabs Data Warehouse did not demonstrate the benefits of PFO closure in preventing stroke recurrence in patients with CS and a PFO compared with medical therapy alone[103]. The potential reason why this observational study showed results that were contrary to those seen in the most recent RCTs was the difference in patient selection between clinical practice and RCTs. In previous completed RCTs, patients undergoing PFO closure had high-risk PFO features like a large shunt or septal aneurysm, which were not often seen in patients in clinical practice. Additionally, patients treated in clinical practice were older than the patients enrolled in clinical trials, which could have also impacted the treatment effect of PFO closure[103]. Thus, strict selection of CS patients who may mostly benefit from PFO closure is imperative for achieving the good outcomes observed in clinical trials.

Another concern is that most clinical trials have excluded patients older than 60 years, although this age group represents a significant portion of acute ischemic stroke cases, many of which are associated with PFOs when characterized as CS[104]. Studies indicated that older age increased the risk of ischemic stroke following cryptogenic TIA or stroke in patients with a PFO who were managed medically[105,106]. Furthermore, current retrospective studies conducted in Asia and Europe showed that PFO closure in elderly patients with CS and a high-risk PFO was safe and reduced the recurrent rate of ischemic events compared to medical therapy alone. Therefore, most researchers suggested performing PFO closure in the selected older patients to improve outcomes, as life expectancy is increasing in almost all regions of the world[84,86,87]. However, more large-scale RCTs are needed to evaluate the efficacy and advantages of early PFO closure in elderly patients with CS, given that unwarranted closure offers no benefits and may lead to complications[107], with AF being the most common adverse event. It was reported that the incidence of AF after PFO closure varied between 2.8% and 5% based on monitoring methods[108]. Notably, studies have shown that PFO closure alongside medical therapy was associated with nearly a fivefold increased risk of AF[73]. Nevertheless, there is no consensus or specific therapeutic algorithm on the management of AF post-PFO closure[80,108]. Fortunately, most AF episodes were transient and self-limiting, occurring in the first 4 to 6 weeks post procedure[80], with a peak increase at 14 days and often resolving spontaneously within 45 days[108]. In addition, studies showed that the burden of AF after PFO closure was low and not associated with recurrent stroke[109]. Moreover, stroke associated with AF was infrequent and comparable between device use and medical therapy[110]. Thus, some researchers emphasized the rhythm rather than the rate control and did not recommend anticoagulation for most AF post-PFO closure due to the benign nature[108]. However, for AF occurring 3 months after PFO closure, anticoagulation should be considered in patients who are older, smoke, have an elevated CHA_2DS_2-VAS score, or present with some comorbidities such as diabetes, hypertension, or dyslipidemia[108]. Considering the low recurrent rate of stroke in both PFO closure followed by medical therapy and medical therapy alone, a comprehensive neurovascular assessment and multidisciplinary evaluation are imperative prior to deciding on PFO closure[74,80]. This necessitates ongoing collaboration between interventional cardiologists, neurologists, and experienced echocardiography operators and cardiac imagers to determine which patients will benefit most from PFO closure based on stroke etiology[23,62,111,112]. Numerous unresolved questions persist regarding PFO management, highlighting the importance of careful consideration of diagnostic findings, stroke risk assessment, and treatment alternatives[113]. Collaboration efforts among physicians across various specialties are crucial for devising personalized strategies and achieving optimal outcomes for patients with CS and a PFO. Further robust clinical trials and research endeavors are essential to address these outstanding queries and refine PFO management for improving patient outcomes[113].

DECLARATIONS

Authors' contributions

Drafted the manuscript: Ma Y
Revised the manuscript: Yang GY
Conceived and revised the manuscript: Ding J, Wang X

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by Shanghai Hospital Development Center Foundation (SHDC22022304).

Conflicts of interest

Yang GY is an Editorial Board member of the journal *Ageing and Neurodegenerative Diseases*. Yang GY was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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