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Opinion Paper

Expert consensus statement for the management of patients with embolic stroke of undetermined source and patent foramen ovale: A clinical guide by the working group for stroke of the Hellenic Society of Cardiology and the Hellenic Stroke Organization

Keywords:
Stroke
Emboic stroke of undetermined source
ESUS
Patent foramen ovale
PFO

1. Introduction

Patent foramen ovale (PFO) is a frequent echocardiographic finding and can be found in approximately 15-25% of the general population (Fig. 1)[1]. The incidence of PFO is 2- to 3-fold higher in patients with stroke of undetermined etiology compared to the general population, a finding that implies a causative role of PFO in patients with stroke of undetermined etiology.[2,3] In this context, percutaneous PFO closure has been increasingly used as a strategy to prevent stroke recurrence in patients with stroke of no apparent cause.[4] During the recent years, evidence about the efficacy and safety of this strategy has accumulated through observational studies and well-designed randomized trials.[5–12]

This paper is a consensus statement of expert panelists from the Hellenic Stroke Organization (HSO) and the Working Group for Stroke of the Hellenic Society of Cardiology (HSC) for the secondary prevention in patients with embolic stroke of undetermined source and PFO. It aims to assist clinicians, patients/families and the Hellenic regulatory authorities to design optimal secondary prevention strategies for this patient population. The recommendations of the panelists are summarized in Table 1.

2. Methodology

A multidisciplinary panel of specialists with expertise in Stroke and Cardiovascular Diseases was established by the HSO and the Working Group for Stroke of the HSC to jointly develop this consensus statement. The panel relied mainly on evidence emerging from randomized controlled trials (RCTs); in case the evidence from RCTs was weak, we also considered data from observational studies. In this context, we used the information yield from a recent systematic review and meta-analysis authored by members of the group, which included evidence available until September 20, 20176. This body of evidence was further enriched through a systematic review of evidence for the time period after this meta-analysis until October the 9th, 2019.

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3. Etiology of ischemic stroke and diagnostic work-up

3.1. Ischemic stroke is an etiologically heterogeneous syndrome

Ischemic stroke is a heterogeneous syndrome, which may be caused by several etiologies.[13,14] Atherosclerotic arteriogenic embolism may be the consequence of several pathologies in any part of the arterial tree which supplies the brain, like the aortic arch, the intracranial and extracranial carotids, and the vertebrobasilar arteries. Non-atherosclerotic arteriogenic embolism may be caused by thrombi formed due to dissected cervical arteries, Takayasu arteritis, Moyamoya disease, and others. Cardiac chamber embolism may occur due to thrombus formed in a cardiac chamber due to various pathologies like blood stasis into the left atrial appendage, atrial fibrillation (AF), atrial flutter or atrial tachycardias, atrial cardiopathy, left ventricular (LV) dysfunction with preserved or reduced ejection fraction, LV regional wall abnormalities after myocardial infarction, non-compaction cardiomyopathy, atrial septal aneurysm, Chiari network, atrial asystole, sick-sinus syndrome, and others. Cardiac embolism may originate from thrombus formed due to cardiac valvular disease like myxomatous valvulopathy with prolapse, mitral annular calcification, aortic valve disease, calcified aortic valves, and others. Patent foramen ovale and other right-to-left shunts can be the underlying cause of stroke. Non-thrombotic cardiac embolism may be caused by myxoma, papillary fibroelastoma, sarcoma and other cardiac tumors, fibrocartilaginous material, and others. Ischemic stroke may be also caused by small vessel disease of the brain (frequently described as lacunar stroke) resulting from occlusion of the small penetrating arteries, which supply blood to the brain's deep structures. Other causes of ischemic stroke may include drugs, vasculitis and others.

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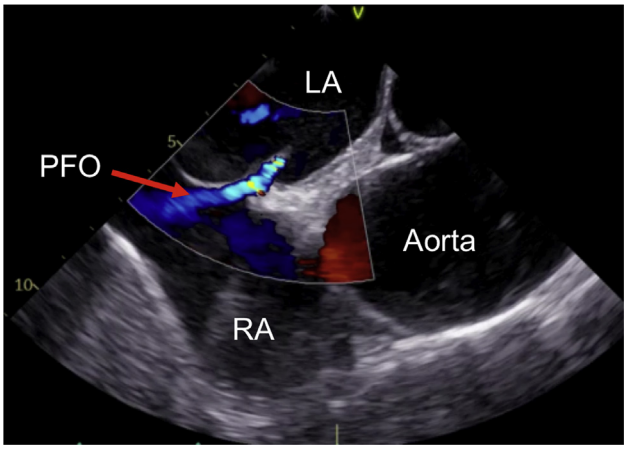

Fig. 1. Transesophageal echocardiogram of a patient with patent foramen ovale that is crossed with a 0.035-inch guidewire. Communication between the right and the left atrium is depicted by color-flow Doppler. LA: left atrium; PFO: patent foramen ovale; RA: right atrium.

3.2. The challenge to identify the underlying etiology in a patient with ischemic stroke

In order to optimize the secondary prevention strategy in a patient with ischemic stroke, it is rational to identify the underlying etiologic pathology. To do so, a thorough diagnostic evaluation, aiming to identify a potential source of embolism and at the same time exclude other potential causes, is necessary. In some cases, this may be rather straightforward, e.g. in a patient with sudden onset of unilateral head and neck pain and ipsilateral carotid dissection a few days after a car accident, or in a patient with recent deep venous thrombosis and a large PFO. However, in the great majority of cases, the identification of the causative pathology is typically less straightforward and more challenging, as several potential etiologies may coexist.[13,15] This vast heterogeneity of the potential underlying etiologies of ischemic stroke, as described above, highlights the pivotal role of a multidisciplinary team of specialists with strong expertise in stroke and cardiovascular diseases (including, but not necessarily confined to, a stroke specialist and a cardiologist) for the critical appraisal of the diagnostic work-up and the role of a detected PFO in a patient with no other apparent cause of ischemic stroke.

Table 1
Summary of recommendations/suggestions

1	We recommend the use of the term “ESUS” (Embolic Stroke of Undetermined Source) instead of the term “cryptogenic stroke”.
2	We recommend that the cardiac rhythm monitoring with automated detection of AF in a patient with ESUS should last for at least 24 hours.
3	We suggest that prolonged monitoring for AF detection could be considered for patients who are older than 40 years and have a high risk for AF (e.g. hypertension, enlarged left atrium, frequent supra-ventricular extrasystoles, prolonged PR interval, multi-territorial infarcts, etc.)
4	We recommend that contrast enhanced trans-esophageal echocardiography should be performed by experienced operators for PFO detection and risk stratification, as well as planning of PFO closure procedures. A PFO should be accordingly classified as low or high-risk for stroke recurrence.
5	We recommend that the decision for the percutaneous PFO closure in a patient with ESUS and PFO should be reached jointly by a multidisciplinary team of specialists (including a stroke specialist and a cardiologist) and the patient/family
6	We recommend percutaneous PFO closure plus long-term single antiplatelet treatment for patients with ESUS and high-risk PFO aged between 18 and 60 years.
7	We suggest that percutaneous PFO closure could be considered for patients with ESUS and low-risk PFO aged between 18 and 60 years, in addition to long-term single antiplatelet treatment.
8	We recommend against routine PFO closure in patients with ESUS and PFO aged <18 or >60 years. It may be considered only on an individual patient basis and after thorough multidisciplinary assessment.
9	We suggest that evidence of PFO closure success is required to inform decision-making on the duration of antiplatelet treatment at follow-up.
10	We recommend dual antiplatelet treatment with low–dose aspirin and clopidogrel for the first 3-6 months after PFO closure and continuation of single antiplatelet treatment thereafter.
11	We recommend single antiplatelet treatment for patients with ESUS and PFO which is not closed percutaneously.

3.3. ESUS vs. Cryptogenic stroke

The term “cryptogenic stroke” has been used historically to describe patients with ischemic stroke for whom the etiology was unclear.[16] Actually, the term “cryptogenic stroke” is a heterogeneous term which includes three distinct subgroups of patients: a) patients for whom the underlying etiology remained unknown because the diagnostic work-up was incomplete; e.g. moribund patient with very severe strokes, b) patients for whom the diagnostic work-up identified more than one potential etiologies; e.g. patients with atrial fibrillation and a significant atherosclerotic plaque ipsilateral to the infarct, and c) patients for whom no underlying cause was identified despite recommended diagnostic work-up.[16] To avoid the confusion raised by the classification of these 3 distinct subgroups into a single category (i.e. cryptogenic stroke), the term embolic stroke of undetermined source (ESUS) was introduced to describe the third subgroup, i.e. patients with ischemic stroke and no apparent cause despite recommended diagnostic work-up (Fig. 2).[14] We recommend and favor the use of the term “ESUS” instead of the term cryptogenic stroke, as it may help avoid unnecessary confusion.

3.4. Recommended diagnostic work-up to consider a patient with ischemic stroke as eligible for PFO closure

It is not infrequent to detect a PFO in patients with ischemic stroke, especially taking into consideration its high prevalence in the general population.[17] In order to assume that PFO is indeed the causative mechanism in a patient with ischemic stroke, it is necessary to exclude other potential causes of ischemic stroke, as mentioned above. There is no strong consensus about the extent and the intensity of the diagnostic work-up that is warranted to exclude other potential etiologies. We recommend the following diagnostic approach presented in Table 2 before a patient with ischemic stroke is considered as potentially eligible for PFO closure. Further investigations may be warranted on a case-by-case basis. If, during the work-up of an ESUS, a serious condition that requires open-heart surgery is discovered, device closure should be omitted and the PFO should be closed surgically.

3.5. Intensity of AF screening

With regard to the duration of automated heart rhythm monitoring, there is accumulating evidence showing that the longer it lasts, the higher the probability of AF detection after an ESUS.[18–20] However, there is a growing debate about the frequency of a causal association between AF detected during follow-up of a patient with ESUS and the index event, especially for episodes of AF detected distant from the event.[20–22] We recommend that the cardiac rhythm monitoring in a patient with ESUS should last for at least 24 hours, but we acknowledge that this is an arbitrary threshold and a longer duration may be considered on a case-by-case basis. For patients >40 years old who are at high risk for having AF (e.g. hyperthyroidism, heart failure, mitral stenosis, hypertension, absence of carotid atherosclerosis, enlarged left atrium, frequent

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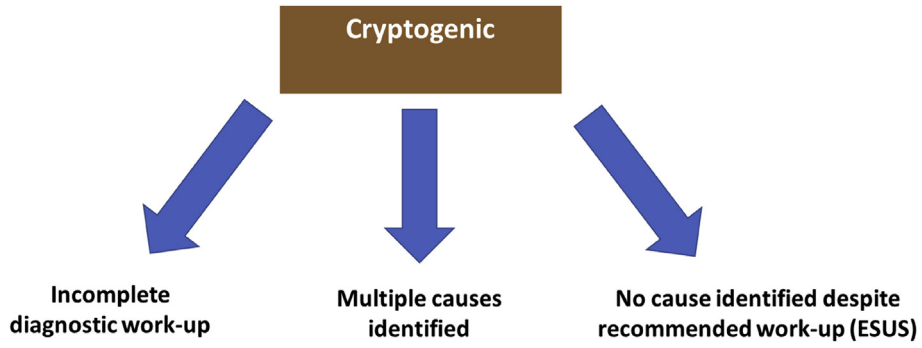

Fig. 2. "Cryptogenic stroke" vs. "ESUS". The use of the term "ESUS" offers the advantage of avoiding the confusion which may be raised by pooling together: a) patients with incomplete diagnostic work-up, b) patients with multiple identified causes, and c) patients with no identified cause despite recommended diagnostic work-up. We recommend and favor the use of the term "ESUS" instead of the term "cryptogenic stroke".

Table 2
Recommended diagnostic approach before a patient with ischemic stroke is considered as potentially eligible for PFO closure

✓ Ischemic stroke detected on CT or MRI, which is not lacunar.
✓ Absence of extracranial and intracranial atherosclerotic plaques in the arteries supplying the ischemic area, that cause stenosis ≥50% or have morphological characteristics associated with high thrombotic risk like presence of ulcer, thrombus, highly lipid rich plaque, intraplaque hemorrhage, and others.
✓ Absence of major-risk source of cardioembolism assessed by 12-lead ECG, cardiac rhythm monitoring with automated detection of atrial fibrillation for at least 24 hours, and contrast-enhanced transesophageal echocardiography.
✓ Absence of any other specific (alternative) cause of ischemic stroke.

supraventricular extrasystoles, and palpitations, prolonged PR interval, multi-territorial infarct, and others), prolonged monitoring for AF detection could be considered.[23–25]

4. Diagnosis and classification of PFO

4.1. Diagnosis

Contrast enhanced transesophageal echocardiography (c-TEE) is considered the gold standard method for the detection and the characterization of PFO. It provides a detailed visualization of the interatrial septum and other relevant structures (coronary sinus, venae cavae, pulmonary veins, eustachian valves, and Chiari network) important for patients with right-to-left shunt. TEE is a widely available, low-cost method with a very low complication rate. However, its sensitivity is limited by the inability to perform an adequate Valsalva maneuver in case the patient needs to be heavily sedated. Moreover, the absence of a left to right shunt seen with color Doppler does not exclude the presence of a PFO. The anatomy and mobility of the atrial septum as well as the presence of a tunnel are strong imaging factors that suggest the presence of a PFO. A contrast-enhanced transthoracic echocardiography (TTE) and/or contrast-enhanced transcranial Doppler are also alternative reliable methods for the initial diagnosis of PFO.

Table 3
PFO variables to be assessed for decision-making and interventional treatment

✓ PFO morphology: size, location, length of the tunnel.
✓ Spatial relationship and distances between the PFO and the aortic root, vena cava, valves, and the free walls of the atrium.
✓ Comprehensive evaluation of the atrial septum, including inspection for atrial septal aneurysms, movement, and other atrial septal defects.
✓ Presence/absence of a Eustachian valve and/or Chiari network.
✓ Thickness of the septum primum and secundum.
✓ Color Doppler evaluation of the shunt at rest and after a Valsalva maneuver.

However, a c-TEE performed by a trained operator is mandatory for risk stratification and planning of PFO closure procedures. The contrast agent should be given by a right cubital vein while lifting this arm and should be synchronized with the release phase of the Valsalva maneuver. A mixture 1:9 of air and serum is the best option for the contrast agent. After injection of the contrast, we should be able to recognize bubbles at the left atrium within the first 3 cycles and then grade the shunt (grade 1:<5 bubbles, grade 2: 5-25 bubbles, grade 3: >25 bubbles; and grade 4: opacification of left atrium). Table 3 summarizes the PFO variables, which need to be assessed for decision making and interventional treatment.

4.2. High-risk PFO

The presence of an atrial septal aneurysm and/or a moderate-to-severe shunt (more than 10-20 microbubbles crossing during the first 3 cardiac cycles) was strongly associated with a causal role of PFO in ESUS patients in observational and randomized studies. These TEE characteristics, together with the presence of simultaneous deep vein thrombosis or pulmonary embolism and stroke, should be used for classifying a PFO as high-risk. Other associated characteristics that may be considered include a large PFO size, atrial septal hypermobility, the presence of a Eustachian valve and/or a Chiari network in the right atrium, and an underlying hypercoagulable state.[26,27]

5. Clinical Evidence for PFO closure in ESUS patients

The CLOSURE (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) was a multicenter, randomized, open-label trial of percutaneous PFO closure (StrarFLex PFO septal Closure System, NMT Medical, Boston) plus antiplatelet treatment versus antiplatelet treatment only, in patients aged 18-60 years with cryptogenic stroke/TIA and PFO. In 909 patients, the Kaplan-Meier estimate of the cumulative incidence of the primary end point (defined as the composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years) was 5.5% in the PFO closure group and 6.8% in the antiplatelet-treatment-only group (adjusted HR: 0.78; 95% CI: 0.45-1.35). There was no significant difference in the rates of stroke (2.9% and 3.1%, $p = 0.79$) and TIA (3.1% and 4.1%, $p = 0.44$). There was no death during the first 30 days, and no death from neurologic causes during the 2-year follow-up period. There were no significant differences between treatment groups in the rate of serious adverse events (16.9% in the PFO closure compared to

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16.6% in the antiplatelet-treatment-only group). Atrial fibrillation was more frequent in the PFO closure group compared to the antiplatelet-treatment-only group (5.7% and 0.7% respectively, $p < 0.001$) and occurred within 30 days after the implantation procedure in 14 of 23 patients (61%); it was transient in 17 patients and persistent in 6 patients.[7] The trial was marked-up by slow recruitment which lead to relatively lower number of patients randomized within the study's protocol. This caused a significant number of potentially eligible patients, to undergo PFO device closure outside the trial, making the patients eventually enrolled not representative of the target population of stroke/TIA patients. This, along with the relatively broad inclusive criteria (e.g. even patients with lacunar stroke may have been eligible for randomization), may have underpowered the study to demonstrate difference between the groups. Nevertheless, the trial demonstrated the crucial need for appropriate selection of patient candidates for device PFO closure.

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) was a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events, in which patients with cryptogenic ischemic stroke and PFO aged 18-60 years were randomized to percutaneous PFO closure (Amplatzer PFO Occluder, St. Jude Medical) group or antithrombotic treatment only (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole). After the device was implanted, patients were treated with dual antiplatelet therapy (aspirin and clopidogrel) for 1 month, followed by aspirin monotherapy for 5 months. Antithrombotic treatment in the PFO closure group was at the discretion of the site investigator from that point afterwards. A total of 980 patients (mean age, 45.9 years) who were followed for a median of 5.9 years i.e. 3,141 patient-years in the PFO closure group and 2,669 patient-years in the antithrombotic-treatment-only group were included. There were 0.58 ischemic stroke recurrences per 100 patient-years in the PFO closure group and 1.07 events per 100 patient-years in the antithrombotic-treatment-only group (HR: 0.55; 95%CI: 0.31-0.99). There were 10 recurrent ischemic strokes of undetermined etiology in 10 patients in the PFO closure group and 23 in the antithrombotic-treatment-only group (HR: 0.38; 95%CI: 0.18-0.79). There was no significant difference between treatment groups in the rate of serious adverse events (40.3% in the PFO closure compared to 36.0% in the antithrombotic-treatment-only group, $p = 0.17$). There were 7 periprocedural episodes of AF in the PFO closure group, all of which resolved before the patients were discharged from the hospital. The rates of serious and non-serious episodes of AF were similar between the PFO closure group and the antithrombotic-treatment-only group (0.48 per 100 patient-years and 0.34 per 100 patient-years, respectively, HR: 1.47, 95%CI: 0.64-3.37).[8] The stricter inclusion criteria and the relatively longer follow-up could be the main reasons accounting for the results of this study, which demonstrated the benefit of PFO closure.

The PC trial was a multicenter, superiority trial with blind assessment of outcome events, in which patients aged <60 years with cryptogenic ischemic stroke, TIA, or a peripheral thromboembolic event and PFO were randomized to percutaneous PFO closure with the Amplatzer PFO Occluder plus antiplatelet treatment (aspirin, ticlopidine or clopidogrel) for at least 5-6 months or antithrombotic treatment only. During a mean follow-up of 4.1 years in the closure group and 4.0 years in the antithrombotic-treatment-only group, the primary end point of death, nonfatal stroke, TIA, or peripheral embolism occurred in 3.4% in the closure group and in 5.2% in the antithrombotic-treatment-only group (HR: 0.63, 95%CI: 0.24-1.62). Similarly, nonfatal stroke occurred in 0.5% in the PFO closure group and 2.4% in the antithrombotic-treatment-only group (HR: 0.20, 95% CI: 0.02-1.72), and TIA occurred in 2.5% and 3.3%, respectively (HR: 0.71, 95%CI: 0.23-2.24). There was no significant difference between treatment groups in the rate of serious adverse events (21.1% in the PFO closure compared to 17.6% in the antithrombotic-treatment-only group, $p = 0.37$). New-onset AF was detected in 6 patients (2.9%) in the PFO closure group (two of which experienced a transient episode, three converted to sinus rhythm either pharmacologically or electrically and one had sustained AF) and two patients (1.0%) in the antithrombotic-treatment-only group (of which one converted to sinus rhythm pharmacologically and one had sustained AF) (HR: 3.15, 95%CI: 0.64-15.6).[9]

The CLOSE trial was a multicenter, randomized, open-label trial, in which patients aged 16-60 years who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, were randomized to percutaneous PFO closure plus long-term antiplatelet therapy (dual antiplatelet treatment for 3 months followed by single antiplatelet afterwards for the whole duration of the trial), antiplatelet treatment only (aspirin, clopidogrel, or aspirin/dipyridamole) or oral anticoagulation only (vitamin K antagonists or non-vitamin-K antagonists). The primary outcome was occurrence of stroke. Among 663 patients followed for a mean of 5.3 ± 2.0 years, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet group (HR: 0.03, 95%CI: 0-0.26). There were 14 (5.9%) patients with procedural complications in the PFO closure group. Atrial fibrillation was more frequent in the PFO closure group compared with the antiplatelet group (4.6% vs. 0.9% respectively, $p = 0.02$), but the number of serious adverse events was not different between the treatment groups ($p = 0.56$).[10] This study established PFO closure as a beneficial treatment option for high-risk PFO patients (as those with large PFOs and atrial septal aneurysms), which significantly reduced the rate of stroke at the expense of increased periprocedural AF.

The Gore REDUCE trial was a multicenter trial in which patients with cryptogenic stroke and PFO were randomized to percutaneous PFO closure (with the HELEX device, Gore & Associates) plus antiplatelet therapy (aspirin, clopidogrel, or aspirin/dipyridamole) or antiplatelet therapy only. Among 664 patients with a mean age of 45.2 years (81% with a moderate or large interatrial shunt) who were followed for a median of 3.2 years, clinical ischemic stroke occurred in 1.4% in the PFO closure group and 5.4% in the antiplatelet-only group (HR 0.23, 95%CI: 0.09-0.62). The rate of serious adverse events was similar in the two groups (23.1% in the PFO closure group and 27.8% in the antiplatelet-only group). Serious device-related adverse events occurred in 1.4% of patients in the PFO closure group and atrial fibrillation occurred in 6.6% of patients after PFO closure.[11] Importantly, in this trial only moderate and large PFO shunts were included, demonstrating once more, that device mediated PFO closure in addition to antiplatelet therapy, result in less subsequent ischemic stroke, with, however, increased rates of AF. Looking at the same, high-risk, PFO population, the DEFENSE-PFO trial randomized patients with cryptogenic stroke and high-risk PFO [defined as PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium $\geq$10 mm), or PFO size (maximum separation of the septum primum from the secundum) $\geq$2 mm] into percutaneous PFO closure plus dual antiplatelet (aspirin or clopidogrel) treatment for at least 6 months or antithrombotic treatment only. Among 120 patients (mean age 51.8 years), the primary endpoint of stroke, vascular death, or major bleeding occurred exclusively in the antithrombotic-treatment-only group (6/60 patients; 2-year event rate 12.9%). The 2-year rate of ischemic stroke was 10.5% ($p = 0.023$). In the PFO closure group, the procedural complications

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included development of AF in 2 patients, pericardial effusion in one patient and pseudoaneurysm in one patient.[12] Both the REDUCE and the DEFENCE-PFO studies, demonstrated a significant benefit for patients undergoing PFO closure. Device mediated PFO closure seems to be associated with reduced stroke and peripheral embolism event rate, suggesting that at least in selected patient population, device PFO closure should be the preferred treatment option.

In the meta-analysis of CLOSURE, RESPECT, PC, CLOSE, and Gore REDUCE trials which included 3,627 patients followed for a mean of 3.7 years, there was significant difference in the rate of ischemic stroke recurrence between the percutaneous PFO closure group and the antithrombotic-treatment-only group (0.53 versus 1.1 per 100 patient-years respectively, OR: 0.43; 95%CI:0.21–0.90). The associated relative risk reduction was 50.5%, the absolute risk reduction was 2.11% and the number of patients needed to be treated with PFO closure to prevent 1 event during 3.7 years was 46.5. There was no significant difference in the rate of TIAs (0.78 versus 0.98 per 100 patient-years respectively, OR: 0.80; 95%CI: 0.53–1.19) and all-cause mortality (0.18 versus 0.23 per 100 patient-years respectively, OR: 0.73, 95%CI: 0.34–1.56). The rate of new-onset AF was higher in the PFO closure arm (1.3 versus 0.25 per 100 patient-years respectively, OR: 5.15, 95%CI: 2.18–12.15) and resolved in 72% of cases within 45 days. There was no difference in the rate of myocardial infarction (0.12 versus 0.09 per 100 patient-years respectively; OR: 1.22, 95%CI: 0.25–5.91) or any serious adverse events (7.3 versus 7.3 per 100 patient-years respectively, OR: 1.07, 95% CI, 0.92–1.25).[6] In the same meta-analysis, the beneficial effect of PFO closure was identified in the subgroup of patients with high-risk PFO (defined as moderate-to-large size of shunt or atrial septal aneurysm) (OR: 0.39. 95%CI: 0.16-0.96), but not in the subgroup of patients with low-risk PFO (OR: 0.79, 95%CI: 0.43-1.43).[6] The main characteristics of the trial are summarized in the supplemental table (Reproduced from Ntaios G, et al Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack. Stroke. 2018; 49:412-418, available at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.020030/-/DC1, with permission.)

In this context, we recommend percutaneous PFO closure for patients with ESUS and high-risk PFO aged between 18 and 60 years. Also, we suggest that percutaneous PFO closure could be considered for patients with ESUS and low-risk PFO aged between 18 and 60 years.

6. Antiplatelet treatment after percutaneous PFO closure

Similar to other implanted devices, there is a requisite time for endothelialization of a PFO closure device that is exposed to circulating blood.[28] The mechanism and the duration of the device healing process are not yet fully understood. Therefore, we recommend that all patients should receive dual antiplatelet therapy (typically a combination of aspirin 80-100 mg and clopidogrel 75 mg) for 3-6 months after percutaneous PFO closure, based on the favorable clinical outcomes of large RCTs that have adopted this strategy. Moreover, we suggest that evidence of PFO closure success is required to inform decision-making on duration of antiplatelet treatment at follow-up. In every day clinical practice, the exact duration of dual antiplatelet therapy is decided on an individual patient basis, depending on their medical history and bleeding risk. After the initial 3-6 months period, clinical data suggest continuation of single antiplatelet therapy for several years or even for life.[29] However, recent observational data suggest that discontinuation of antithrombotic therapy at 1-year may be considered for younger patients without other comorbidities.[1,30] We recommend continuation of single antiplatelet treatment for life after PFO closure. The decision to stop antiplatelets at 1-year post-procedure may be considered on an individual basis after multidisciplinary assessment.

7. Areas of weak evidence

7.1. PFO closure for ESUS patients of <18 or >60 years of age?

There has been no direct comparison between PFO closure and medical-treatment-only in patients with ESUS and PFO aged <18 or >60 years. In patients >60 years, comorbidities which could potentially cause ischemic stroke accumulate significantly, and therefore it is typically challenging to establish a causative association between PFO and ischemic stroke. In this context, we recommend against routine PFO closure in these patient groups. Still, in selected patients with a thorough, negative diagnostic work-up, and a high-risk PFO, percutaneous closure may be considered.

7.2. Oral anticoagulation or antiplatelet treatment for patients with ESUS and non-closed PFO?

In the PICSS trial, among patients with cryptogenic stroke and PFO, there was no significant difference in the time to recurrent ischemic stroke or death between warfarin-treated and aspirin-treated patients (HR: 1.29, 95%CI: 0.63-2.64). The 2-year event rates were 16.5% and 13.2%, respectively.[31]

In the CLOSE trial, stroke occurred in 3 out of 187 patients assigned to oral anticoagulants and in 7 out of 174 patients assigned to antiplatelet therapy alone on an intention-to-treat analysis (HR: 0.44, 95%CI: 0.11–1.48). The effect estimate was similar in the per-protocol analysis (HR: 0.37, 95%CI: 0.07–1.38).[10]

The TAcTiCS-PFO study used individual participant data and rigorous methods to control confounding in order to provide further evidence. Among 2,385 patients (804 on warfarin and 1,581 on antiplatelet) who had 227 composite events (stroke/TIA/death), there was no significant difference between oral anticoagulation and antiplatelet treatment in the rate of the composite event [adjusted HR: 0.76, 95%CI: 0.52–1.12] or of stroke alone (adjusted HR: 0.75, 95%CI: 0.44–1.27). In a sensitivity analysis that was standardized to the patient population who actually received antiplatelet treatment, oral anticoagulation had a statistically significant beneficial effect on the composite outcome (adjusted HR: 0.64, 95%CI: 0.42–0.99).[32]

A meta-analysis comparing oral anticoagulation and antiplatelet treatment for patients with cryptogenic stroke and PFO including data from both randomized and observational studies suggested substantial benefit of oral anticoagulation compared to antiplatelet treatment (incidence rate ratio: 0.42; 95%CI: 0.18-0.98).[33] However, this meta-analysis was limited by the small number of patients and the fact that the included observational studies did not control for confounding.[32]

Recently, an analysis of the NAVIGATE-ESUS trial in patients with ESUS and PFO showed that anticoagulation might reduce the risk of recurrent stroke by about half.[34] Similarly, a meta-analysis of the NAVIGATE ESUS, PICSS, and CLOSE trials showed a significant reduction of ischemic stroke (OR: 0.48, 95%CI: 0.24-0.96; $p = 0.04$) in patients treated with anticoagulation compared to aspirin, without evidence of heterogeneity.[34]

In a recent meta-analysis of 5 randomized controlled trials (1,720 patients, mean follow-up 2.3 ± 0.5 years), the rate of stroke recur-

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rence was 1.73 per 100 patient-years in anticoagulant-assigned patients and 2.39 in antiplatelet-assigned patients (hazard ratio, 0.68; 95% CI, 0.32-1.48). The rate of major bleeding was 1.16 per 100 patient-years in anticoagulant-assigned patients and 0.68 in antiplatelet-assigned patients (hazard ratio, 1.61; 95% CI, 0.72-3.59).[35]

Based on the aforementioned evidence, we recommend single antiplatelet treatment for patients with ESUS and PFO which is not closed percutaneously. A prospective, adequately powered trial of antiplatelet treatment vs. oral anticoagulation is warranted in stroke patients with PFO who are not eligible for PFO closure, preferably with a direct oral anticoagulant given their superior safety profile compared to vitamin K antagonists.[36–38]

Conflicts of interest

Georgios Ntaios: Speaker fees/Advisory Boards/Research support by Sanofi; Boehringer-Ingelheim; Galenica; Elpen; Bayer; Winmedica; BMS/Pfizer; Amgen; European Union.

Apostolos Tzikas: Consultant Abbot Vascular, Gore.

Emmanouil Vavouranakis: Speaker fees/Advisory Boards/Research support/Proctoring by Abbot Vascular; ASTRA; Boehringer-Ingelheim; Bayer; Boston Scientific; Medtronic.

Dimitrios Nikas: speaker fees/Advisory Boards/Research support by Sanofi; Boehringer-Ingelheim; Elpen; Bayer; Pfizer; Amgen; Boston Scientific.

Georgios Katsimagklis: Speaker fees/Advisory Boards support by Boehringer-Ingelheim; ASTRA; Boston Scientific.

Eleni Koroboki: Speaker fees/Advisory boards/Travel grants: Amgen, Bayer, Pfizer. Not related with submitted work.

Antonis S. Manolis: none reported.

Haralampos Milionis: honoraria, consulting fees and non-financial support from healthcare companies, including Amgen, Bayer, Elpen, Mylan, MSD, Pfizer, Servier, Winmedica.

Konstantinos Papadopoulos: Consultant GE Healthcare.

Skevos Sideris: none reported.

Konstantinos Spengos: none reported.

Konstantinos Toutouzas: Speaker fees/Advisory Boards/Research support/Proctoring by Abbot Vascular; Gore; Sanofi; Boehringer-Ingelheim; Elpen; Bayer; Pfizer; Amgen; Boston Scientific; Medtronic.

Dimitrios Tziakas: none reported.

Sofia Vassilopoulou: Travel Grants from Pfizer and Bayer.

Ioannis Kanakakis: speaker fees/Advisory Boards/Research support by Sanofi; Boehringer-Ingelheim; Elpen; Bayer; Pfizer; Amgen; Menarini

Konstantinos Vemmos: none reported.

Konstantinos Tsioufis: speaker and consulting honoraria and research support from Medtronic, Sanofi, Pfizer, Menarini, Servier, Bayer, Amgen, Boehringer Ing, Elpen, Winwedica, Novartis, Mylan

Appendix A. Supplementary data

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