Interventional closure of patent foramen ovale in prevention of thromboembolic events

Consensus document of the Association of Cardiovascular Interventions and the Section of Grown-up Congenital Heart Disease of the Polish Cardiac Society

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ABSTRACT
The presence of patent foramen ovale (PFO) was found to be associated with a number of medical conditions, including embolic stroke and recurrent transient neurological defects. The closure of PFO remains controversial; however, in recently published guidelines from the European Association of Percutaneous Cardiovascular Interventions in collaboration with 7 other European societies, which extensively refer to the latest randomized clinical trials, it is explicitly recommended to perform percutaneous PFO closure in the prevention of recurrent thromboembolic events.
In connection with the above facts and expected increasing number of PFO closure procedures, the joint expert group of the Association of Cardiovascular Interventions and the Grown-Up Congenital Heart Disease Section of the Polish Cardiac Society developed the following consensus opinion in order to standardize the principles of diagnosis, indications, methods of performing procedures, and postoperative care in relation to Polish conditions and experiences.

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Introduction The patent foramen ovale (PFO) is a remnant of fetal circulation, which in utero allows oxygenated blood to flow between the right and left atrium. As a result of pressure changes in the atria after birth, the foramen ovale in most cases closes during the first 2 years of life.[1,2] However, in some cases, it does not close completely and a channel remains between the septum primum and the septum secundum. The channel has an average length of about 5 mm and can be of different shapes. Based on the results of autopsy, the prevalence of PFO in the general population is estimated at 20% to 28%. The mere presence of PFO is not considered a pathology.[3,4] It has been observed that the incidence of PFO in the population decreases with age and is about 34% in the first 3 decades of life, 25% in the fourth to eighth decades, and 20% in the ninth decade.[3-5] This is explained by late spontaneous closures of PFO or greater mortality in patients with PFO.[4] When pressure in the right atrium is increased, the duct may open and a short right-left shunt may occur; moreover, potential embolic material may enter the systemic circulation.[1-8] In addition, thrombus formation and release from the PFO channel is also possible, especially in the presence of atrial septal aneurysm (ASA). Vasoactive substances,

which normally are degraded in the lungs, may also play an important role in various pathologies, and in those with PFO, they affect cerebral circulation similarly to nitrogen bubbles in divers.[6-8]

For many years there has been a debate about the relationship between PFO and thromboembolic complications, including the most serious one, that is, ischemic stroke.[4-10] Cryptogenic stroke or, according to the current nomenclature, embolic stroke of undetermined source (ESUS) is responsible for almost half of all ischemic strokes in patients younger than 55 years, and PFO is found in this group even in 40% to 61% of patients (diagnostic criteria, see TABLE 1).[11,12] It was also found that the presence of PFO increases 3-fold the risk of a recurrent ischemic event.[5-7] The relationship between ischemic stroke has been proved not only in younger (<55 years of age) but also in older patients.[12]

The concept of crossed (paradoxical) embolism as a result of infiltration of embolic material through the persistent connection between the right and left atria as a cause of stroke, transient ischemic attack (TIA) or peripheral embolism, including myocardial infarction, has been well documented in the literature.[3-7,13,14] In addition to ESUS, there is also a suggestion of a causal relationship between PFO and such disease entities as: platypnea-orthodeoxia,[15,16] decompression illness,[17-19] migraine with aura,[20-34] or high-altitude pulmonary edema.[35-37] Relationships between PFO and peripheral embolism have also been described.[38-42] It has also been found that PFO is an independent risk factor for death and adverse clinical events in patients with massive pulmonary embolism.[43] Some anatomical factors also increase the risk of paradoxical embolism. In addition to the above-mentioned ASA, these are: eustachian valve, Chiari network, or a large spontaneous left-right leak.[44-45]

Transcatheter percutaneous PFO closure was first introduced in 1992 by Bridges et al,[46] and in 1997 the most popular 2-disc Amplatzer device was implanted for the first time.[47] Since then, a number of studies have been conducted on the efficacy and safety of closing PFO in patients with ESUS or peripheral embolism using various types of devices. Long-term observational studies have suggested that closure of PFO in patients with ischemic events, compared with antiplatelet or anticoagulant therapy, reduced the incidence of recurrent stroke.[48-50] Recently, the results of several prospective randomized clinical trials were also published and they tested the hypothesis regarding the efficacy of transcatheter PFO closure in the prevention of ischemic cerebral and peripheral thromboembolic events.[51-53] They confirmed the long-term clinical efficacy of PFO closure.[54-56]

On the other hand, there is still a lot of controversy and ambiguity regarding qualifying patients for the procedure, type of device, and optimal peri- and postoperative treatment. European and American recommendations to date have not recommended routine closure of PFO in stroke prevention / TIA, but they were published before new randomized trials appeared.[57-59] However, the recently published guidelines of the European Association of Percutaneous Cardiovascular Interventions and 7 other European societies have been published, which extensively refer to the latest randomized clinical trials, explicitly recommend percutaneous PFO closure in preventing repeated thromboembolic events.[60]

In connection with the above and expected increasing number of PFO closure procedures, the group of experts of the Association for Cardiovascular Interventions and the Section of Grown-up Congenital Heart Disease of the Polish Cardiac Society developed the following consensus opinion in order to standardize the principles of diagnosis, indications, procedures and postoperative care in relation to Polish conditions and experiences.

Current state of scientific knowledge: randomized trials The results of numerous, although nonrandomized, observational studies indicated a decrease in the incidence of recurrent stroke in patients after ESUS who had PFO closure compared with those treated only pharmacologically.[61-63] Unfortunately, the negative results of the first 3 randomized trials (CLOSURE 1 [Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale], PC

TABLE 1 **Diagnostic criteria of embolic stroke of undetermined source (formerly cryptogenic stroke). Adapted from Hart et al.[10]**

Ischemic nonlacunar stroke detected by CT or MRI (subcortical infarct ≥1.5 cm on CT or ≥2 cm on MRI)
Absence of significant atherosclerotic plaques in extra- or intracranial arteries (causing >50% luminal stenosis)
No major risk of cardioembolic source of embolism (atrial fibrillation / flutter, intracardiac thrombus identified, myxoma or other cardiac tumors, mitral stenosis, recent acute myocardial infarction, valvular vegetations, LVEF <30%)
Absence of other specific cause of stroke (eg, vasculitis, dissection, migraine / vasospasm, drug abuse, poisoning)

Abbreviations: CT, computed tomography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging

Trial [Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism] and the results of a short follow-up from the RESPECT [Patent Foramen Ovale Closure or Medical Therapy after Stroke] study) regarding the effectiveness of transcatheter closure of PFO in secondary prevention of cerebrovascular incidents in patients after ESUS were disappointing,[51-53] although they aroused a lot of controversy as well as doubts with regards to methodology.[64] Despite the fact that 2 published meta-analyses of the above studies indicated the advantage of interventional treatment over conservative treatment, the qualification of patients for such procedures remained controversial for many years, especially among neurologists.[64-66]

The publication of the results of 3 randomized studies in 2017 (REDUCE, CLOSE, and long-term follow-up of RESPECT trial) comparing interventional treatment with pharmacotherapy in the group of patients after ESUS and PFO appears to be a real breakthrough.[54-56] In 2018, another randomized DEFENSE-PFO study was published that also confirmed the effectiveness of interventional therapy in high-risk PFO patients.[67]

The most important clinical data of the above studies indicating the advantage of interventional therapy over pharmacological treatment are presented in TABLE 2.

Patent foramen ovale diagnosis Sensitivity and specificity of transthoracic echocardiography in the detection of PFO are 46% and 99%, respectively.[68] The accuracy of the method increases when imaging with the second harmonic component. It also depends on the laboratory's experience and adopted criteria (the number of microbubbles registered in the left atrium and the time of their appearance).[69]

Transesophageal echocardiography is a more detailed examination.[69,70] The assessment should include the size and thickness of the septum secundum, the length of the PFO channel, the width (wall separation) of the channel, the distance between the PFO and the superior vena cava, the mobility of the atrial septum (presence of ASA), as well as the presence of additional structures / cavities within the right atrium. In some cases, it is also possible to visualize the flow in color Doppler imaging, depending on the right-left and left-right atrial pressure ratio.[71] Usually, however, to confirm the patency of the PFO channel it is necessary (as in the transthoracic examination) to use an echocardiographic contrast agent with a simultaneous right atrial pressure maneuver.

A commonly used contrast agent in the diagnosis of PFO is a mixture of saline (0.9% NaCl) with air (to avoid contamination, it is recommended to take air through an antibacterial filter). An additional increase in the stability of the obtained air bubbles and an increase in the sensitivity of the test can be obtained by adding a little blood to the mixture.[69] The Valsalva maneuver is used to temporarily increase the right atrium pressure. This maneuver should be carried out for about 10 seconds, the echocardiographic contrast should be given for about 8 seconds, and then the recording of the echocardiographic image should also begin. For people unable to properly perform this maneuver, gentle pressure of the epigastric region for about 10 to 20 seconds is recommended, with release immediately before contrast administration. Visualization of air bubbles passing through the channel is an unequivocal confirmation of PFO, but the appearance of air bubbles in the left atrium in the third to sixth cardiac cycle after contrast administration is also considered diagnostic. The subsequent appearance can be associated with the presence of communication between high and low circulation on another level (in some centers, bubbles appear in the left atrium only during the first 3 cardiac cycles). The sensitivity of the transesophageal examination with contrast in the detection of PFO is estimated at about 90%.[72-74]

In many cases, 3-dimensional imaging during transesophageal echocardiography allows to accurately depict the anatomy of the PFO channel and to visualize the passage of bubbles during the contrast examination. However, it should be noted that images obtained during contrast examination have significantly lower time resolution.[75]

Right-to-left leakage can also be detected using the transcranial Doppler examination[76] by performing contrast recording (as during echocardiography) during both free breathing and during the Valsalva maneuver. For this purpose, a 2 MHz transducer, most often located in the temporal region, is used. This allows to visualize the flow in the anterior / middle and posterior cerebral arteries on the examined side in about 80% of patients (in other cases, it may be necessary to use other acoustic windows). Higher test accuracy is obtained using power M-mode modality. This test is characterized by high sensitivity and specificity (97% and 93%, respectively); however, it is not possible to determine the level of leakage.[77] The advantage of transcranial Doppler is the possibility to quantitatively assess the degree of leakage and the scale by Spencer et al[73] is commonly used for that purpose (degrees 0–5; grade 3 and more confirm the presence of a leak) (TABLE 3).

Interventional technique: available closure devices Transcatheter PFO closure is performed in patients under general anesthesia, with the use of analgosedation or under local anesthesia, most often using the right common femoral vein access.[4-5,78] During the procedure heparinization is required with the target activated clotting time of 250 to 300 seconds. Prophylactic intravenous administration

TABLE 2 Summary of the results of the latest randomized clinical trials regarding intervention closure of patent foramen ovale in patients after cryptogenic stroke

Trial	Study group	Type of the device	Conservative treatment	Endpoints	Remarks
RESPECT[54]	Previous cryptogenic stroke; age, 18–60 y; n = 980 patients; 1:1 randomization	Amplatzer PFO Occluder	• Aspirin • Warfarin • Clopidogrel • Aspirin with dipyridamole	• Recurrent stroke: 18 patients in intervention group and 28 patients in conservative group (relative risk reduction, 45%; HR, 0.55; 95% CI, 0.31–0.999; *P* = 0.046) • Recurrent stroke (after ASCOD scale consideration) – 10 patients in intervention group 23 patients in conservative group (relative risk reduction, 72%; HR, 0.38; 95% CI, 0.18–0.79; *P* = 0.007)	Subgroups analysis: patients with atrial septal aneurysm and large right-to--left shunt benefit the most from PFO closure in comparison with conservative treatment
CLOSE[55]	Previous cryptogenic stroke with high--risk PFO (atrial septum aneurysm or large left-to-right shunt), age, 18–60 y; n = 663 patients Randomization: 1) Group 1, 1:1:1 randomization (without contraindications to OAT, n = 524): • PFO closure with long-term antiplatelet therapy • Antiplatelet therapy alone • OAT 2) Group 2, 1:1 randomization (with contraindications to OAT, n = 129): • PFO closure with antiplatelet therapy • Antiplatelet therapy alone	11 different types of occludders (at the discretion of the operator)	• Aspirin • Warfarin • Clopidogrel	• In PFO closure group there was no stroke; in conservative treatment group, 14 strokes (HR, 0.03; 95% CI, 0–0.26; *P* <0.001). • The cumulative 5-year risk of stroke based on Kaplan–Meier curves was 0% in the invasive group and 4.9% in the conservatively treated group.	The composite endpoint (stroke, TIA, or peripheral embolism) was less frequent in patients with PFO closure compared with patients treated with antiplatelet therapy alone (3.4% vs 8.9%; HR, 0.39; 95% CI, 0.16–0.82; *P* = 0.01).
REDUCE[56]	Previous cryptogenic stroke with PFO; age, 18–59; y; n = 664 patients; 2:1 randomization	Helex Septal Occluder; Cardioform Septal Occluder	• Aspirin • Clopidogrel	• Recurrent stroke: 6 patients (1.4%) in the intervention group and 12 patients (5.4%) in the conservative group (reduction by 77%) (HR, 0.23; 95% CI, 0.09–0.62; *P* = 0.002). • Clinically apparent stroke or the occurrence of new, clinically silent ischemic foci on imaging studies: 22 patients (5.7%) in whom PFO was closed and 20 patients (11.3%) in the group treated only with antiplatelet agents (relative risk reduction 0.51; 95% CI, 0.29–0.91; *P* = 0.04)	Number of new clinically silent ischemic foci similar in both groups: 17 (4.4%) in the intervention group and 8 (4.5%) in the antiplatelet group (*P* = 0.97)
DEFENSE--PFO[67]	Previous cryptogenic stroke with high-risk PFO (size ≥2 mm, excessive mobility of the atrial septum); n = 120; 1:1 randomization; follow-up duration, 2 y	Amplatzer PFO Occluder	• Aspirin • Clopidogrel • Warfarin (25%)	Composite endpoint: stroke, TIA, cardiac death, TIMI--defined major bleeding. In the PFO group without incidents; in the conservatively treated group: 12.9% of incidents, including 5 strokes, 1 intracranial bleeding, 1 TIA, and 2 major bleeding (log rank *P* = 0.013)	In the intervention group: 2 AF incidents without clinical consequences, 1 pericardial fluid, 1 pseudoaneurysm

Abbreviations: AF, atrial fibrillation; ASCOD, atherosclerosis, small-vessel disease, cardiac pathology, other causes; CLOSE, Patent Foramen Ovale Closure or Anticoagulation versus Antiplatelets after Stroke; DEFENSE-PFO, Cryptogenic Stroke and High-Risk Patent Foramen Ovale; HR, hazard ratio; OAT, oral anticoagulation therapy; PFO, patent foramen ovale; REDUCE, Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke; RESPECT, Long-Term Outcome of Patent Foramen Ovale Closure or Medical Therapy after Stroke; TIA, transient ischemic attack; TIMI, Thrombolysis In Myocardial Infarction

of antibiotic (eg, cephazolin, 1 g IV) is recommended 30 to 60 minutes before the procedure.

The 0.035-inch soft J-tip guidewire is inserted under fluoroscopic guidance into the right atrium from where it is directed by a multi-purpose, Amplatz or Cournand (4.5–6F) catheter through the PFO channel into the left atrium. The end of the catheter is placed in the left upper pulmonary vein. In exceptional situations, puncture of the atrial septum may be required, especially in case of a long PFO channel or coexistence of small leaks through type II atrial septal defects (ASD).[79]

After exchanging for a 3-cm J-tip stiff guidewire (eg, Extra Stiff 0.035 Amplatz Wire), a dedicated device sheath (8-9F) is inserted into the left atrium. The end of the delivery sheath is placed in the central part of the left atrium and the dilator with the guidewire are removed. The dilator removal should be slow with the proximal end of the introducer sheath kept below heart level until abundant blood backflow is seen.

TABLE 3 Recommendations for basic diagnostic methods of patent foramen ovale

It is recommended to diagnose PFO using TEE with an echocardiographic contrast agent and with the right atrial pressure maneuver simultaneously.
The presence of right-to-left shunt can also be detected using TCD by contrast recording (as in echocardiography) during both free breathing and during the Valsalva maneuver.

Abbreviations: TCD, transcranial Doppler; TEE, transesophageal echocardiography, others, see TABLE 2

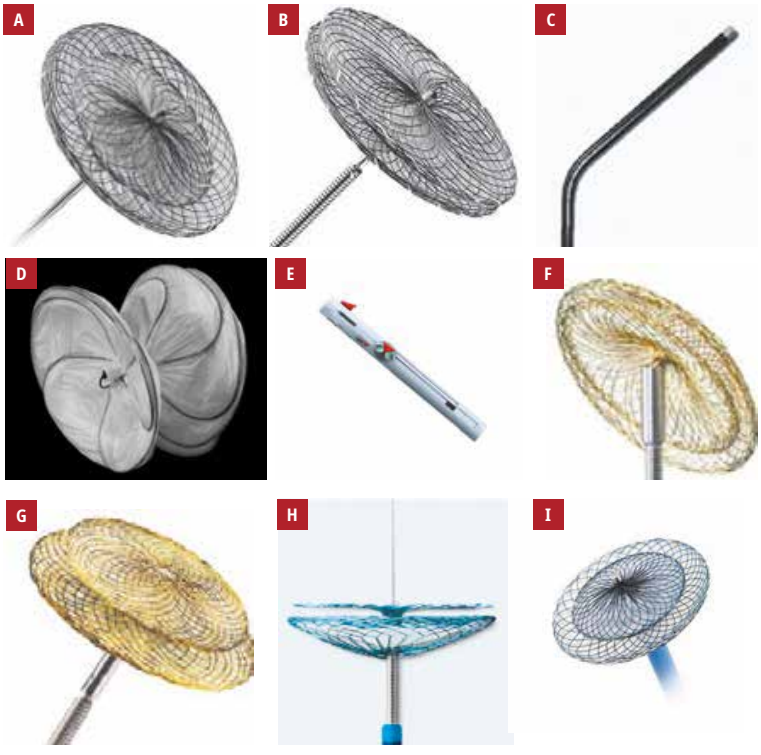

FIGURE 1 **A** – Amplatzer PFO Occluder, Abbott Vascular; **B** – Amplatzer Multifenestrated (Cribiform) Septal Occluder, Abbott Vascular; **C** – Delivery sheath Amplatzer TorqVue 45°; **D** – GORE CARDIOFORM Septal Occluder, Gore Medical; **E** – Delivery knob of GORE CARDIOFORM Septal Occluder, Gore Medical; **F** – Figulla Flex II, Occlutech; **G** – CeraFlex PFO Occluder, Lifetech Scientific, **H** – Nit-Occlud PFO, PFM Medical

This is to avoid air embolization into the heart. In subsequent stages of the procedure, the device is implanted through the delivery sheath. Finally, the delivery system is detached after careful verification of the device position and stability (so-called tug test). There is an increasing number of different types of devices dedicated to transcatheter FPO closure (FIGURE 1). The vast majority are occluders with a 2-disk structure and similar implantation principles.[80] The principles of sizing and implantation as well as the characteristic features of selected devices are presented in TABLE 4. The technology based on transcatheter placement of the suture to seal the PFO channel is currently at the early stages of implementation into clinical practice (eg, NobleStitch EL, Heartstitch, Fountain Valley, California, United States).

At the final stage of the procedure, hemostasis is obtained with a subcutaneous Z-type suture or alternatively a traditional pressure bandage dressing, rarely a dedicated closing device.[81]

Periprocedural imaging Echocardiographic imaging is used to identify PFO and to select those patients for whom PFO is a potential threat.

Qualification to intervention treatment TEE is the gold standard for PFO imaging. The study allows to identify the separation of plaques of foramen ovale channel and estimate the severity of right-left leakage. Measurements of the PFO channel should be made in the longitudinal projection high in the short axis at rest and during the Valsalva maneuver after the contrast is applied to the ulnar vein.

Patients with PFO and right-to-left leakage at rest or in the Valsalva maneuver are eligible for a procedure to close the defect. Only plaque separation without leakage visualized at this level cannot be considered a significant pathology. Such case can be recognized as a partly patent PFO, that is, not fully patent channel that does not cause leakage.

Imaging during the procedure TEE is crucial during percutaneous closure of PFO. At the initial stage, it allows confirming the passage of the catheter through the PFO channel, in "difficult," winding, or narrow channels, the penetration is only possible under the control of TEE. During implantation and expansion of the device, TEE allows for precise visualization of the delivery system and disks. Before releasing the implant, one should confirm the correct position of the device, the presence of a possible residual leak, as well as visualize the anatomical structures near the device—the aorta, mitral valve, circumflex artery, roof of the atrium—and exclude possible collision of these structures with the device. It is important to check

the occluder's stability. In each case, the appearance of pericardial fluid and possible other complications, such as thrombi formation, should be monitored.

Postprocedural follow-up Postoperative control should include transthoracic echocardiography performed regularly up to a year after surgery, followed by an annual follow-up. In case of doubt on the transthoracic examination, the diagnosis should be supplemented with TEE. Echocardiographic examination should show the position of the device, the presence of possible residual leak, assess the presence of fluid in the pericardium or other possible complications such as thrombi or vegetations.

Indications for patent foramen ovale closure

Qualification for PFO closure should be routinely preceded by a neurological consultation. The neurologist's opinion is crucial for the correct diagnosis of ESUS and further qualification of the patient for interventional closure of PFO or pharmacological treatment. Generally, in cases where there are indications for long-term oral anticoagulation (OAC; atrial fibrillation, some cases of venous thromboembolism, thrombophilia), pharmacological treatment rather than transcatheter closure of PFO is indicated. However, patients with OAC used for concomitant pulmonary embolism or at high risk of recurrence of thromboembolic events despite anticoagulant therapy may be considered as candidates for PFO closure.[57,82,83]

Recognition of a causal relationship between PFO and stroke is based on an assessment of the likelihood of other potential causes of embolism and may be difficult. Tests that exclude other causes of stroke, such as 24-hour Holter electrocardiography monitoring (in patients at high risk for atrial fibrillation) and carotid ultrasound, should be performed. Laboratory tests for thrombophilia are also indicated. To assess the clinical probability of casual role of PFO in stroke can be the Risk of Paradoxical Embolism (RoPE) score.[57] Diagnostic workup of PFO and other significant anatomical conditions as well as risk factors are presented in detail in sections Patent foramen ovale diagnosis and Periprocedural imaging. TABLE 5 presents summaries of clinical and anatomical factors that increase the likelihood of ischemic stroke in people with PFO.

Based on available randomized controlled trials and observational studies, the experts recommend percutaneous transcatheter closure of PFO in the indications shown in TABLE 6.

Anticoagulation and antiplatelet treatment in patients after interventional patent foramen ovale closure

The selection of the appropriate type and duration of anticoagulant therapy in patients undergoing transcatheter closure of PFO have not been proved in specially designed clinical trials. The treatment regimens used in everyday clinical practice are the result of expert consensus, best reflected in the protocols of large recently published clinical trials, indicating the potential benefit of interventional treatment compared with conservative treatment in patients with secondary prevention of embolism to the central nervous system. The common point of anticoagulation therapy after PFO closure present in the RESPECT, CLOSE, and REDUCE protocols is the perioperative use of dual antiplatelet therapy for up to 3 months (1–6 months can be used).[54-56] After that, it is recommended to continue treatment with a single antiplatelet drug, most often acetylsalicylic acid (TABLE 7), for an indefinite period (at least for 5 years).

In rare cases, when OAC is required in a patient undergoing PFO closure, therapy should be individualized depending on the risk of bleeding and the risk of recurrence of thromboembolic events (eg, use only OAC or an additional antiplatelet agent for 3 months after surgery).

Complications of transcatheter patent foramen ovale closure

Percutaneous closure of PFO is an effective and safe procedure. A meta-analysis of 10 studies (total number of patients, 1355) showed the occurrence of major and small perioperative complications in 1.5% and 7.9%, respectively.[62]

Complications of the procedure can be divided into nonspecific that can occur during any type of intervention or diagnostic procedure (vascular, infectious, thromboembolic complications, air embolism, transient perioperative cardiac arrhythmias), and specific to this procedure.

Specific complications of PFO closure include residual leakage, thromboembolic complications, including recurrent stroke or TIA, embolization of the occlusion device, damage to heart structures, arrhythmias, damage to the device components, and very rarely atrial wall erosion with possible aortic wall damage.[84]

The frequency of residual leaks is estimated at around 2.3% to 15% and depends on the diagnostic methods used and the time of assessment. Over time, a decrease in the residual leakage frequency is observed, which should be associated with the progressive implant endothelialization. Leak is asymptomatic, but may increase the risk of recurrent stroke or TIA, which is estimated to be around 0% to 4.9%.[62]

Thromboembolic complications usually occur in the first months after implantation. The thrombosis associated with the device require intensified anticoagulation.[85] Complete withdrawal of the thrombus has been described. Large thrombi that may embolize may be an indication for surgical removal.

Some patients experience migraine headaches after PFO closure. These are most often

TABLE 4 Types of devices used in transcatheter closure of patent foramen ovale (continued on the next page)

Device, manufacturer	Description
Amplatzer PFO Occluder, Abbott Vascular, Santa Clara, California, United States	An occluder dedicated to the endovascular closure of PFO; the longest available on the market; great clinical experience; results of multicenter, randomized clinical trials A self-expanding device made of nitinol, lined on the inside with polyester material. It consists of 2 disks connected by a narrow central deck. It is available in 3 sizes: 18 mm, 25 mm, 35 mm corresponding to the size of the right atrial disk. A dedicated delivery sheath with a single-curve device (Amplatzer, TorqVue 45°) is available in sizes 8F for 2 smaller devices and 9F for the largest device. Sizing is based on measurements (TEE or ICE), the distance between PFO, and the aortic root or the superior vena cava. Size selection based on the smaller of the 2 measurements: when measuring from 9.0 mm to 12.4 mm, 18 mm occluder; from 12.5 mm to 17.4 mm, 25 mm occluder; >17.5 mm, 35 mm occluder. If the smallest measurement <9.0 mm device implantation is not recommended. An alternative method using a measuring balloon filled in the PFO channel. The size of the device is not less than twice the size of the balloon waist. In practice, many operators usually choose an 18-mm or 25-mm occluder in the vast majority of cases. Regardless of the sizing method, in the presence of atrial septal aneurysm or a particularly thick secondary septum, it may be optimal to use a larger device to cover the aneurysm and / or to better stabilize the device on the septum. After screwing the occluder to the dedicated delivery cable, placing it in tube, rinsing with heparinized salt, the device is moved to the distal end of the sheath. Under fluoroscopic and TEE / ICE guidance, the left atrial disk is released in the central part of the left atrium by pushing the delivery cable and/or sliding the sheath. The disk is pulled to the atrial septum and subsequently the right atrium disc is released in the right atrium. Before the device is completely unscrewed from the delivery cable, the occluder position and septum tightness in TEE / ICE are verified. The tug test confirms the stable position of the device.
GORE CARDIOFORM Septal Occluder, Gore Medical, Flagstaff, Arizona, United States	An occluder dedicated for endovascular closure of PFO and ASD II. Built of platinum-filled nitinol skeleton coated with polytetrafluoroethylene. It takes the shape of 2 disks of the same size located on 2 sides of the atrial septum. The docking loop includes 3 loops placed in the right atrial disk, waist, and left atrial disk, respectively. The occluder is located in a 75 cm, 10F, delivery sheath with a release handle that allows for configuration the docking loop to load, release, block or re-pull the occluder into the sheath. Pulling the device back into the sheath is possible even after releasing the docking loop. The occluder is available in 4 sizes (15 mm, 20 mm, 25 mm, 30 mm); the size corresponds to the diameter of the disk. The size of the device is not less than 1.8 × the dimension of the measuring balloon waist. As with other types of buckles, many operators use 25 mm in most cases as standard. In the presence of an atrial septal aneurysm or thickened secondary septum, it may be optimal to use a larger device to cover the aneurysm and/or to better stabilize the device on the septum. After flushing the delivery system with heparinized saline and adjusting the release handle, the occluder is moved to the left atrium in the delivery sheath. The left atrial disk is released by retraction of the delivery sheath. The release handle maneuvers allow you to form the left atrial disk, which should be pressed against the atrial septum by pulling the system completely and then release the right atrial disk by the release handle maneuvers. Confirmation of the correct position of the occluder is done using TEE / ICE and in the RAO caudal fluoroscopic projection showing the symmetrical arrangement of the nitinol skeleton of the device (flower-petal shape). Subsequent maneuvers of the handle release the device from the rigid part of the cable, leaving a thin guide connecting the delivery system with the occluder. This allows to reassess the stability and position of the occluder not constrained by a rigid cable.
Figulla Flex II, Occlutech, Helsingborg, Sweden	The device is dedicated to the endovascular closure of PFO. It is built of nitinol mesh formed into 2 disks. Four sizes are available: 16/18, 23/25, 27/30, and 31/35 mm. Size 23/25 mm is available in a version with a left atrial disk with a single layer of nitinol which reduces the amount of artificial material in the left atrium. The left atrial disk forms a uniform surface, without the protruding central core. The system for attaching the occluder to the ball-socket–type lead wire allows greater freedom of position after placing on the septum but before complete release. The principles of sizing and implantation technique are similar to those described for the Amplatzer device.

TABLE 4 Types of devices used in transcatheter closure of patent foramen ovale (continued from the previous page)

Device, manufacturer	Description
CeraFlex PFO Occluder, Lifetech Scientific, Shenzen, China	An occluder dedicated to transcatheter closure of PFO. It has a 2-disk structure. It is made with a nitinol mesh coated with titanium nitride, which aims to reduce the release of nitinol into the blood, accelerate the healing process, and soften the nitinol structure and thereby increase the susceptibility of its structure. The left atrial disk has a uniform surface, with no protruding central core element. Polytetrafluoroethylene filling is intended to increase the tightness of the device. The delivery system allows free positioning of the device in the partition before disconnection from the introductory wire.
Nit-Occlud PFO, PFM Medical, Cologne, Germany	An occluder dedicated to transcatheter closure of PFO. It has a 2-disk structure woven from a single nitinol wire, which means that on both the left and right atrial side it has a smooth surface wiwthout a protruding central core element.[80] The left atrial disk is made of a single layer of nitinol mesh, reducing the amount of artificial material in the left atrium. The device is lined with a Dacron membrane. It is available in 3 sizes: 20 mm, 26 mm, 30 mm, which correspond to the diameter of the discs. Mullins 45°, 9-10F sheaths are used to deliver the device. Sizing is based on measuring the distance of the canal from the aortic root and the superior vena cava ostium on TEE/ICE.
Hyperion PFO Occluder, Comed BV, Heerenven, the Netherlands	An occluder dedicated to the endovascular closure of PFO. It has a 2-disk structure. It occurs in a version with a central core protruding above the surface of the left atrial disk or without a core, and in a symmetrical and asymmetrical version. Available in sizes 18 mm, 24 mm, 30 mm, 34 mm.
Atriasept occluder, Cardia Inc., Eagan, Minnesota, United States	Occluder dedicated to the endovascular closure of PFO. It has a 2-disk structure, each disk consists of 6 nitinol wires forming a skeleton for a polyfluoroethylene covering material. In the current generation of the device, the amount of nitinol and nitinol elements exposed to direct contact with blood has been reduced, which is supposed to reduce the risk of allergic reactions in patients with hypersensitivity to metals. Sizes 20 mm, 25 mm, and 30 mm are available.

Abbreviations: ASD II, type II atrial septal defects; ICE, intracardiac echocardiography; RAO, right anterior oblique projection; others, see TABLES 2 and 3

patients who had this type of ailment before the procedure.

The displacement of the closing device is one of the most serious periprocedural complications. It occurs with a frequency of 0.7% to 1.2%,[86,87] much less frequently than in the case of ASD closure. The device may embolize into both the left and right heart cavities. Percutaneous implant removal is possible using systems dedicated to remove foreign bodies (vascular loops, forceps, bioptomes). Migration of the closure device may be an indication for its operational removal. Late implant migrations are extremely rare.

During implantation of the device, the walls of the atria can be injured and result in pericardial effusion or even cardiac tamponade. Small bleeding may spontaneously stop; larger may require decompression by pericardial puncture or cardiac surgery. Echocardiographic assessment of the pericardium should be one of the important elements of monitoring of the procedure.

An implanted occludder can interact with surrounding cardiovascular structures. This may result in chafing of the heart and tamponade. Abrasion of the aortic wall can cause aortic atrial fistula.

Arrhythmias after implantation of PFO occluder may be manifested by atrial additional beats, less often by transient AV conduction disturbances.[88,89] Implantation of PFO devices significantly increases the likelihood of atrial fibrillation. However, it is definitely smaller than in the case of ASD occlusion, where hemodynamic disorders coexist in addition to the implant's impact. In the CLOSE study, the risk of atrial fibrillation was 4.6% as compared with 0.9% in the pharmacologically treated group.[55] In case of atrial fibrillation, treatment should be in accordance with the current standards.[90]

Isolated cases of damage or fracture of a previous-generation implant have been reported. They may remain asymptomatic or, if affected by heart structures, be the cause of their injury. Device configuration abnormalities on echocardiography are indications for radiological fluoroscopy, which is the most accurate in assessing device damage.[91]

Treatment of patients after interventional closure of patent foramen ovale Management of patients after percutaneous PFO closure includes: 1) antiplatelet therapy; 2) follow-up visits after surgery with clinical and echocardiographic assessment; 3) prevention of infective endocarditis.

The purpose of follow-up visits is to assess the tightness of PFO closure and to diagnose possible complications. The guidelines show ambiguous data on the frequency and time of

TABLE 5 Anatomical and clinical risk factors of recurrent stroke in patients with patent foramen ovale

Anatomical risk factors
• ASA with septum shift >10 mm • Large left-to-right shunt (passage of >25 contrast bubbles during the Valsalva maneuver or spontaneous right-to-left shunt at rest >4 mm on color Doppler TEE) • Presence of Eustachian valve >10 mm or Chiari network • Long PFO tunnel
Clinical risk factors
• Recurrent episodes of ESUS or TIA • Multiple ischemic lesions in brain CT / MRI • History of DVT / PE or thrombophilia • Ischemic event associated with the Valsalva maneuver • Ischemic event connected with long travel / immobilization • Simultaneous pulmonary and systemic embolism • Thromboembolic event during antiplatelet or anticoagulation therapy

Abbreviations: ASA, atrial septum aneurysm; DVT, deep vein thrombosis; ESUS, embolic stroke of undetermined source; MRI, magnetic resonance imaging; PE, pulmonary embolism; others, see TABLES 1–3

TABLE 6 Recommendations for transcatheter patent foramen ovale closure in prevention of recurrent thromboembolic ischemic events

Transcatheter PFO closure should be performed in patients <60 years old
• After ESUS or TIA with confirmed ischemic lesions in neuroradiological imaging (CT or MRI) or after an episode of peripheral embolism (including myocardial infarction) • With PFO with at least 1 anatomical or clinical high-risk factor confirmed by contrast TEE examination
Transcatheter PFO closure PFO should be considered in patients <60 years old
• After ESUS or with TIA with confirmed ischemic lesions in neuroradiological imaging (CT or MRI) or after an episode of peripheral embolism (including myocardial infarction) • With PFO confirmed by contrast TEE
Transcatheter PFO closure should be considered in secondary prevention in patients
• After the episode of decompression divers disease and presence of PFO confirmed by contrast TEE • After the episode of HAPE and presence of PFO confirmed by contrast TEE
Transcatheter PFO closure may be considered, especially if high-risk factors are present, in primary prevention in
• Deep or professional divers • Mountain climbers, alpinists • Professional, military and aerobatic pilots
Transcatheter PFO closure may be considered, especially if high-risk factors are present, in patients with
• Platypnoe-orthodeoxia syndrome • Exercise desaturation (after excluding causes other than PFO) • Sleep-apnea syndrome
Transcatheter PFO closure should not be performed in
• Primary prevention of ischemic episodes in patients with the presence of PFO without ESUS / TIA or ischemic lesions in neuroradiological imaging • Patients with other causes of stroke (carotid atherosclerosis, atrial fibrillation) which, despite PFO coexistence, more likely explaining stroke • Patients with indications for chronic anticoagulation (except of patients with simultaneous incidence of pulmonary embolism) • Patients with migraine headaches without changes in neuroradiological studies

Abbreviations: HAPE, high-altitude pulmonary edema; others, see TABLES 1–3 and 5

TABLE 7 Recommendations for anticoagulation and antiplatelet therapy in patients undergoing transcatheter patent foramen ovale closure

During the procedure, unfractionated heparin should be used in all patients at a dose of approx. 60 IU/kg of bw as bolus under ACT control to achieve a time in the range of 250–300 seconds.
Antiplatelet therapy should be initiated before or immediately after the procedure. In the absence of prior drug saturation, a 300 mg of ASA and 300 mg of clopidogrel loading dose is recommended.
After the procedure, dual antiplatelet therapy should be used at a maintenance dose of 75 mg (both ASA and clopidogrel) for a period of 1–3 months. After this period of time, it is recommended to continue treatment with one antiplatelet drug for the indefinite period, usually ASA.

Abbreviations: ACT, activated clotting time; others, see TABLE 5

postprocedural control, hence each center uses its own follow-up protocol (TABLE 8). The echocardiographic and clinical assessment of the patient is usually made on day 1, after 4 to 6 weeks, after 6, and 12 months after surgery and then every year, indefinitely. In case of any abnormality, the treatment of the patient and subsequent controls should be determined individually. It is important to develop standard procedures in each center.

During the control visit, in addition to the physical examination, electrocardiography and transthoracic echocardiography should be performed. If abnormalities in the TTE are found or suspected, TEE examination should be performed. In some centers, TEE is routinely done 4 to 6 weeks after surgery. If arrhythmias are found or suspected, Holter monitoring should be performed.

According to the general principles from the guidelines, prophylaxis of infective endocarditis should be used for 6 months after surgery, and in patients with persistent residual leakage or other defects (eg, mitral regurgitation), lifetime prophylaxis should be considered.[92]

Return to full physical activity including playing sports is allowed in uncomplicated cases 4 weeks after implantation of the device.[93]

Magnetic resonance imaging is safe (for 1.5–3 T devices) in patients 6 weeks after implantation of the nitinol-containing device (conditional status according to mrisafety.com). For Figulla Flex II (Occlutech, Helsingborg, Sweden), magnetic resonance imaging is safe even immediately after the procedure.

TABLE 8 Recommendations regarding the treatment after the intervention closure of patent foramen ovale

It is recommended to perform clinical and echocardiographic (TTE) examinations on day 1, 4–6 weeks, 6, and 12 months after transcatheter PFO closure.
Prophylaxis of infective endocarditis should be used for 6 months after the procedure, and lifetime prophylaxis should be considered in patients with persistent residual leakage or other defects (eg, mitral regurgitation).
Return to full physical activity including playing sports is allowed in uncomplicated cases 4 weeks after the implantation of the device.
MRI is safe (1.5–3 T devices) 6 weeks after implantation of the occluder containing nitinol.

Abbreviations: see TABLES 1–3

TABLE 9 Recommendations for the training of operators performing percutaneous patent foramen ovale closure

It is recommended that the operator undergoing training in transcatheter PFO closure should first conclude a complete theoretical training on indications, patient preparation, perioperative pharmacotherapy, as well as possible complications and their treatment.
The trainee operator should perform a minimum of 15 PFO closure procedures independently, under supervision, to acquire practical skills.
It is recommended that in a center that concluded less than 25 PFO closure procedures, the procedures should be performed in the presence of an experienced operator (proctor) to train the personnel and to avoid complications during the first procedures.

Abbreviations: see TABLE 2

Recommendations for training physicians to perform patent foramen ovale closure To ensure optimal results, PFO closure should be performed in experienced centers that routinely perform these types of procedures and other structural heart interventions. Cooperation with a neurologist is obligatory. Data from registries regarding ASD and PFO closure procedures show that both individual operators and centers with a small number of procedures performed annually have worse treatment results.[94] Trainee operators should have the theoretical knowledge and technical skills required to safely perform this procedure to ensure the least number of complications. In the United States, in accordance with the recommendations of the Food and Drug Administration, the training program includes, in addition to theoretical training, 25 procedures under the supervision of an experienced operator.

It seems that in the case of experienced interventional cardiologists, 15 to 20 PFO closure procedures performed independently, but under the supervision of an experienced operator, should be required.[95,96]

The team of experts of the Association of Cardiovascular Interventions (ACVI) recommends that the training physician should acquire theoretical knowledge regarding the indications and qualifications for surgery, patient preparation, perioperative pharmacotherapy as well as the selection of the device size and peri- and postprocedural pharmacotherapy. It is also necessary to acquire knowledge of the possible complications, their prevention, and treatment. We recommend observing the procedures during the didactic workshops (see the list of conferences recommended by ACVI), conducted by experienced operators, in an interactive format. In addition, the acquisition of practical experience with the equipment before the procedure, or the possibility of performing the procedure on a simulator can be a very good preparation for the training physicians.

After such training, preferably in a center with extensive experience, the training operator should perform a minimum of 15 PFO closure procedures independently but under the supervision of an experienced operator. In addition, the ACVI team of experts recommends that in a center that carried out less than 25 PFO closure procedures, the procedures should be performed in the presence of an experienced operator (proctor) to train staff and to avoid complications during the first procedures. However, the presence of cardiac surgery department on site is not required (TABLE 9).

SUPPLEMENTARY MATERIAL

The Polish version of the paper is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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