

SUMMARY OF CLINICAL EVIDENCE

Patent Foramen Ovale closure with the Amplatzer™ PFO Occluder for secondary stroke reduction of risk in patients with cryptogenic stroke



THE HEALTH PROBLEM

- A patent foramen ovale (PFO) is a common finding (56%)¹ among patients with a cryptogenic ischemic stroke due to a paradoxical embolism.² A cryptogenic ischemic stroke is diagnosed by excluding other mechanisms for an ischemic stroke. Diagnostic approaches have been proposed to exclude known causes of an ischemic stroke in order to arrive at the diagnosis of a cryptogenic ischemic stroke.
- Clinical findings suggest that a paradoxical embolism through a PFO is the likely mechanism for an ischemic stroke that cannot be explained otherwise (i.e., cryptogenic ischemic stroke).³
- The underlying mechanism for a cryptogenic ischemic stroke is multifactorial. While a PFO is suggested as a pathway for a paradoxical embolism, the likelihood of a PFO-mediated paradoxical embolism may depend on the size of the PFO,⁴ the presence of an atrial septal aneurism,⁵ deep vein thrombosis⁶ and other conditions.
- Costs of an ischemic stroke are composed of a relatively high amount associated with the acute event and ongoing annual costs for patient care following the stroke. Given the relatively young age of such cryptogenic ischemic stroke patients, ongoing annual costs may extend over a considerably long period of time.⁷
- Current clinical management of a cryptogenic ischemic stroke, either in the presence or absence of a PFO, consists of standard antithrombotic therapy.⁸

DEVICE DESCRIPTION AND CLINICAL APPLICATION

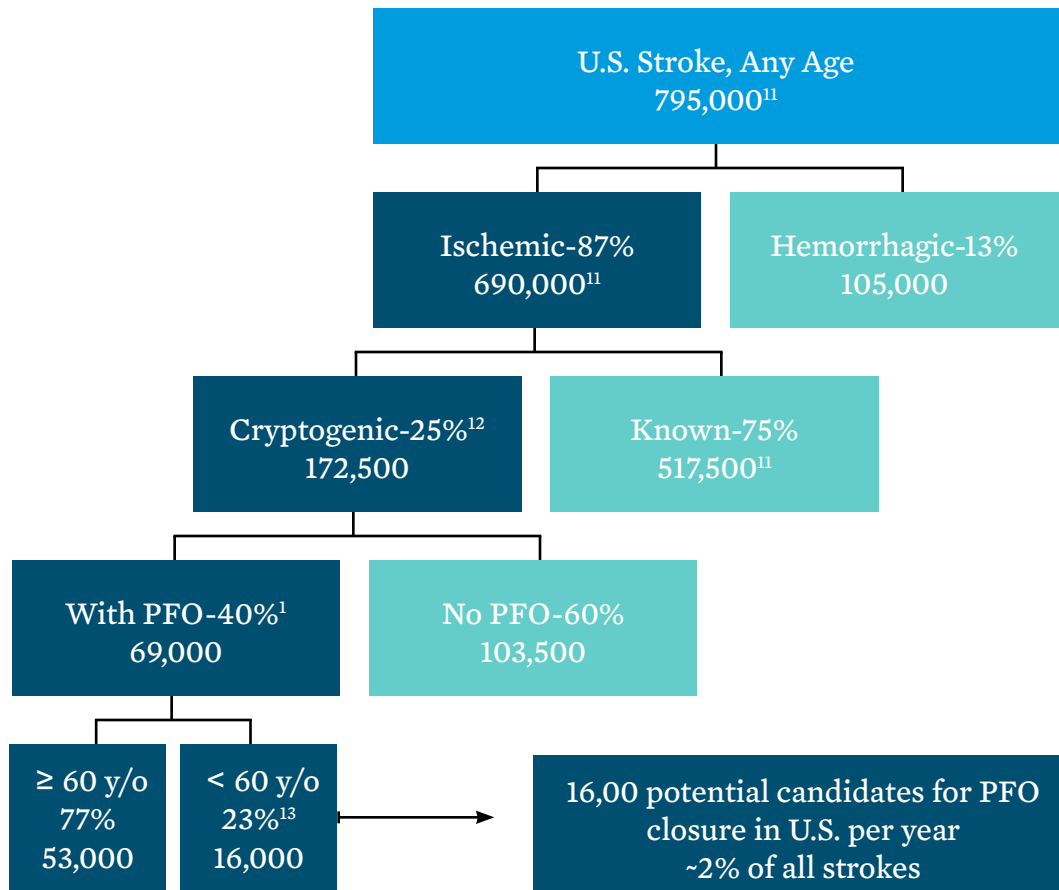
- The Amplatzer™ PFO Occluder is a self-expanding double disc device indicated for percutaneous transcatheter closure of a patent foramen ovale to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. It can be implanted using standard catheterization techniques, guided by fluoroscopy, angiography, transesophageal echocardiography or intracardiac echocardiography.
- In carefully selected patients with a PFO and evidence of a right-to-left shunt, PFO closure with the Amplatzer™ PFO Occluder may be considered to further reduce the risk of a recurrent stroke beyond what can be achieved with antithrombotic therapy alone, while taking into account the risks and benefits of the device. The Amplatzer™ PFO Occluder received European CE Mark in 1998. In addition to commercial approval in Europe, the device is commercially available in 80 countries with more than 100,000 patients receiving the device worldwide over the past 20 years. The device received FDA approval⁹ in 2016 based on the long term follow up results of the RESPECT trial.

- The clinical benefits of PFO closure were reported in 2017 after 10 years of follow up of patients in the RESPECT trial with a median follow-up of 5.9 years.¹⁰
 - Relative risk reduction of 45% was demonstrated by device therapy versus medical management when considering freedom from all recurrent ischemic stroke.
 - Device therapy was particularly effective in reducing the risk of recurrent ischemic stroke of unknown mechanism (cryptogenic stroke), reaching a 62% relative risk reduction.

TARGET POPULATION FOR PERCUTANEOUS PFO CLOSURE

- Patients selected for the Amplatzer™ PFO Occluder should undergo a comprehensive evaluation by a neurologist and cardiologist to confirm the diagnosis of a cryptogenic ischemic stroke due to a presumed paradoxical embolism through a PFO. This comprehensive evaluation should rule out the presence of other known mechanisms for an ischemic stroke. It is recommended that the comprehensive evaluation follow the latest professional society guidelines for diagnosing a cryptogenic ischemic stroke, and should include at a minimum the following assessments:
 - MRI or CT scanning of the head to rule out small vessel disease or lacunar infarct.
 - TEE to rule out non-PFO intra-cardioembolic sources or conditions or aortic arch atheroma.
 - ECG and prolonged cardiac rhythm monitoring (~30 days) to rule out atrial fibrillation and other heart rhythm disturbances that may be associated with stroke.
 - Intra and extracranial artery imaging: MRA, CT angiography or contrast angiography to rule out an ischemic stroke associated with atherosclerotic plaque, arterial dissection or other vascular diseases.
 - Hematological evaluation to rule out an underlying hypercoagulable state.
 - Patients should also be evaluated by an implanting cardiologist to ensure that there are no anatomical contraindications for implanting the device safely. Refer to the Instructions for Use (IFU) for the Amplatzer™ PFO Occluder.
- It is estimated that only a small fraction of stroke patients (2%) will be eligible candidates for transcatheter PFO occlusion. The annual eligible patient population in the U.S. is estimated to include 16,000 patients as demonstrated in the flow chart below, see Figure 1.

Figure 1. Description and size estimation of the target population for PFO closure in the U.S.



MEDICAL NECESSITY

Unlike most stroke patients who are elderly and have a number of age-related diseases, patients who experience a cryptogenic ischemic stroke are typically younger (i.e., average age of 46 years¹⁰), with the potential for the stroke effects to be more disruptive, particularly in working patients supporting a family. Medical management alone does not eliminate the risk for a recurrent stroke.

The Amplatzer™ PFO Occluder addresses an important unmet medical need among patients who suffered a cryptogenic ischemic stroke due to a presumed paradoxical embolism and who remain at risk for a recurrent stroke for decades. Considering the life-long benefit of protection from a recurrent stroke and the low incidence of procedure-related or device-related complications,¹⁴ PFO occlusion is a reasonable and necessary therapy to prevent recurrent strokes.

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AMPLATZER™ PFO OCCLUDER

IMPORTANT SAFETY INFORMATION



INDICATIONS AND USAGE

The Amplatzer™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined

by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

CONTRAINDICATIONS

- Patients with intra-cardiac mass, vegetation, tumor or thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the PFO is gained.
- Patients whose vasculature, through which access to the PFO is gained, is inadequate to accommodate the appropriate sheath size.
- Patients with anatomy in which the Amplatzer™ PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.
- Patients with other source of right-to-left shunts, including an atrial septal defect and/or fenestrated septum.
- Patients with active endocarditis or other untreated infections.

WARNINGS

- Patients who are at increased risk for venous thromboembolic events should be managed with thromboembolic risk reduction regimen after the PFO Closure following standard of care.
- Do not use this device if the sterile package opened or damaged.
- Prepare for situations that require percutaneous or surgical removal of this device. This includes availability of a surgeon.
- Embolized devices must be removed as they may disrupt critical cardiac functions. Do not remove an embolized occluder through intracardiac structures unless the occluder is fully recaptured inside a catheter or sheath.
- Patients who are allergic to nickel can have an allergic reaction to this device.
- This device should be used only by physicians who are trained in standard transcatheter techniques.
- Transient hemodynamic compromise may be encountered during device placement, which may require fluid replacement or other medications as determined by the physician.
- Do not release the device from the delivery cable if the device does not conform to its original configuration, or if the device position is unstable or if the device interferes with any adjacent cardiac structure (such as Superior Vena Cava (SVC), Pulmonary Vein (PV), Mitral Valve (MV), Coronary Sinus (CS), aorta (AO)). If the device interferes with an adjacent cardiac structure, recapture the device and redeploy. If still unsatisfactory, recapture the device and either replace with a new device or refer the patient for alternative treatment.
- Ensure there is sufficient distance from the PFO to the aortic root or SVC (typically defined as 9 mm or greater as measured by echo). See Figure 6. And Figure 7.

PRECAUTIONS

- The safety and effectiveness of the Amplatzer™ PFO Occluder has not been established in patients (with):
 - Age less than 18 years or greater than 60 years because enrollment in the pivotal study (the RESPECT trial) was limited to patients 18 to 60 years old
 - A hypercoagulable state including those with a positive test for an anticardiolipin antibody (IgG or IgM), Lupus anticoagulant, beta-2 glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy
 - A hypercoagulable state including those with a positive test for an anticardiolipin antibody (IgG or IgM), Lupus anticoagulant, beta-2 glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy
 - Unable to take antiplatelet therapy
 - Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels associated with a $\geq 50\%$ luminal stenosis

- Acute or recent (within 6 months) myocardial infarction or unstable angina
- Left ventricular aneurysm or akinesis
- Mitral valve stenosis or severe mitral regurgitation irrespective of etiology
- Aortic valve stenosis (mean gradient greater than 40 mmHg) or severe aortic valve regurgitation
- Mitral or aortic valve vegetation or prosthesis
- Aortic arch plaques protruding greater than 4 mm into the aortic lumen
- Left ventricular dilated cardiomyopathy with left ventricular ejection fraction (LVEF) less than 35%
- Chronic, persistent, or paroxysmal atrial fibrillation or atrial flutter
- Uncontrolled hypertension or uncontrolled diabetes mellitus
- Diagnosis of lacunar infarct probably due to intrinsic small vessel as qualifying stroke event
- Arterial dissection as cause of stroke
- Index stroke of poor outcome (modified Rankin score greater than 3)
- Pregnancy at the time of implant Multi-organ failure must not be used.
- Do not pass the replica end of the TF2000 sizer through the annulus when sizing the valve.
- Use caution when tying knots to avoid bending the stent posts.
- Use on or before the last day of the expiration month that is printed on the product packaging label.
- This device was sterilized with ethylene oxide and is for single use only. Do not reuse or re-sterilize this device. Attempts to re-sterilize this device can cause a malfunction, insufficient sterilization, or harm to the patient.
- The Amplatzer™ PFO Occluder device consists of a nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device for a minimum of 60 days. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. Certain allergic reactions can be serious; patients should be instructed to notify their physicians immediately if they suspect they are experiencing an allergic reaction such as difficulty breathing or inflammation of the face or throat. Some patients may also develop an allergy to nickel if this device is implanted.
 - Store in a dry place.
 - Pregnancy – Minimize radiation exposure to the fetus and the mother.
 - Nursing mothers – There has been no quantitative assessment for the presence of leachables in breast milk.

ADVERSE EVENTS

Potential adverse events that may occur during or after a procedure using this device may include, but are not limited to:

Air embolus Allergic drug reaction; Allergic dye reaction; Allergic metal reaction: Nitinol (nickel, titanium), platinum/iridium, stainless steel (chromium, iron, manganese, molybdenum, nickel); Anesthesia reactions; Apnea; Arrhythmia; Bacterial endocarditis; Bleeding; Brachial plexus injury; Cardiac perforation; Cardiac tamponade; Cardiac thrombus; Chest pain; Device embolization; Device erosion; Deep vein thrombosis; Death; Endocarditis; Esophagus injury; Fever; Headache/migraine; Hypertension/hypotension; Myocardial infarction; Pacemaker placement secondary to PFO device closure; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Peripheral embolism; Pleural effusion; Pulmonary embolism; Reintervention for residual shunt/device removal; Sepsis; Stroke; Transient ischemic attack; Thrombus; Valvular regurgitation; Vascular access site injury; Vessel perforation

CAUTION: This product is intended for use by or under the direction of a physician. Prior to use, reference the Instructions for Use, inside the product carton (when available) or at manuals.sjm.com for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events

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