AMPLATZER™

PFO Occluder

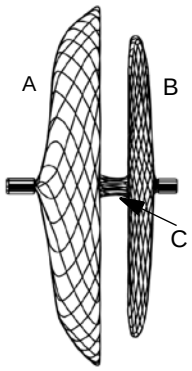
Instructions for Use

Device Description

The AMPLATZER™ PFO Occluder (Figure 1) is a self-expandable, double-disc device made from a Nitinol wire mesh. The 2 discs are linked together by a short connecting waist. In order to increase its closing ability, the discs contain thin polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread.

The device has radiopaque marker bands on the distal and proximal ends of the device. The device contains an end screw on the proximal end to facilitate delivery and deployment. The device is sterilized with ethylene oxide.

Figure 1. AMPLATZER™ PFO Occluder



A. Right atrial disc
B. Left atrial disc
C. Waist

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.

STERILE EO

℞ ONLY

LATEX
Not made with natural rubber latex

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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 is open 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 a 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 ≥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
- 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.

Patient Selection for Treatment

In considering the use of the AMPLATZER™ PFO Occluder, the rationale for seeking PFO closure and the safety and effectiveness of the device compared to antithrombotic therapy alone should be taken into account. A shared decision-making process with the patient and their medical team is recommended when considering the use of the AMPLATZER™ PFO Occluder. See "Patient Counseling Information" and the "Summary of Clinical Studies" sections for additional information.

Ischemic stroke. Most ischemic strokes are due to a known mechanism unrelated to a PFO including thromboembolism from an intracardiac source, large vessel atherosclerosis, artery-to-artery thromboembolism, or small vessel disease. The following are potential etiologies of ischemic stroke:

- Thromboembolic stroke in the setting of atrial fibrillation
- Thromboembolic stroke due to left ventricular mural thrombus
- Thromboembolic stroke due to infectious or non-infectious endocarditis
- Thromboembolic stroke associated with prosthetic heart valves
- Atheroembolic stroke due to thoracic aortic or carotid artery atherosclerotic disease
- Intracranial atherosclerotic disease
- Arterial dissection
- Vasculitis
- Migraine/vasospasm
- Hypercoagulable states
- Thromboembolic stroke via a right-to-left shunt

Ischemic strokes are considered to be *cryptogenic* when there is no identified cause following a comprehensive evaluation to exclude an underlying known stroke etiology.

PFO and ischemic stroke. A PFO persists into adulthood in 25-30% of individuals, and in the vast majority of cases, a PFO is an incidental finding that is not associated with any disease condition. Specifically, the presence of a PFO is not associated with an increased stroke risk among asymptomatic individuals. However, in some patients with cryptogenic ischemic stroke, the presence of a PFO raises the possibility that a thromboembolism from the venous circulation passed through the PFO into the arterial circulation (paradoxical thromboembolism) leading to an ischemic stroke.

Antithrombotic therapy, usually with antiplatelet agents, is the current standard of care to prevent recurrent stroke in cryptogenic stroke patients with PFO.

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. Although a paradoxical embolism through a PFO is one potential mechanism for causing an ischemic stroke, it is an uncommon cause. The AMPLATZER™ PFO Occluder prevents a recurrent ischemic stroke due to a paradoxical embolism through the PFO, but it would not reduce the risk of a stroke from mechanisms or diseases that are unrelated to a paradoxical embolism through the PFO.

Before considering the implantation of the AMPLATZER™ PFO Occluder, other potential mechanisms for an ischemic stroke should be investigated including atrial fibrillation, left atrial appendage thrombus, left ventricular thrombus, significant cardiac valve pathology, aortic arch atheroma, intracranial and extra cranial cerebrovascular disease, small vessel disease, and a hypercoagulable state. Patients selected should undergo an evaluation *by a neurologist* to confirm the diagnosis of a cryptogenic ischemic stroke. This evaluation should exclude the presence of other known ischemic stroke mechanisms that are unrelated to a paradoxical embolism through the PFO. It is recommended that the 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 with a PFO that are first deemed by a neurologist and a cardiologist to have had a cryogenic stroke following an evaluation to exclude known causes of ischemic stroke should next be evaluated by an AMPLATZER™ PFO Occluder implanting physician to ensure that the device can be implanted safely. Specific factors that need to be considered for the AMPLATZER™ PFO Occluder and implantation procedure include the following:

- Overall medical status, including conditions which might preclude the safety of a percutaneous, transcatheter procedure
- Suitability for percutaneous procedures, including considerations of:
  - Cardiac anatomy relating to the size of the PFO and the presence or absence of an atrial septal aneurysm
  - Vascular access anatomy (e.g., femoral vein size, thrombus, or tortuosity)
  - Ability of the patient to tolerate general or local anesthesia

- Ability of the patient to undergo required imaging (i.e., fluoroscopy, intra-cardiac echocardiography, and/or trans-esophageal echocardiography)

- Ability to comply with the recommended post-implant pharmacologic regimen, which includes at a minimum aspirin (81 to 325 mg) and clopidogrel (75 mg) for 1 month after device placement, followed by aspirin (81 to 325 mg) monotherapy for at least 5 additional months. **In the pivotal RESPECT clinical trial, approximately 90% of patients implanted with the AMPLATZER™ PFO Occluder continued taking anti-platelet medications beyond 6 months post-procedure (predominately aspirin alone).**

Patient Counseling Information

Physicians should review the following information when counseling patients about the AMPLATZER™ PFO Occluder and the implant procedure:

- The safety and effectiveness of PFO closure with the AMPLATZER™ PFO Occluder in combination with the required post-implant antiplatelet therapy.
- PFO closure with the AMPLATZER™ PFO Occluder can only reduce the risk for a recurrent stroke due to a paradoxical embolism through a PFO.
  - With aging there is an increased likelihood that non-PFO related risks for stroke may develop and cause a recurrent ischemic stroke independent of PFO closure.
- The procedural risks associated with AMPLATZER™ PFO Occluder. Table 7 and 8 details the major clinical events related to the device or procedure as observed in the RESPECT clinical study.
- The need for adherence to a defined adjunctive antithrombotic therapy following implantation of the AMPLATZER™ PFO Occluder.
- Patients with a history of DVT or PE may benefit from continuation or resumption of anticoagulation therapy following implantation of the AMPLATZER™ PFO Occluder to reduce the risk of recurrent DVT or PE.

It is recommended that the medical team (neurologist and cardiologist) and the patient engage in a shared decision-making process where the risks and benefits of PFO closure in comparison to using antithrombotic therapy alone are discussed while taking into account the patient's values and preferences. Additional counseling information can be found in the Patient Guide and in the Clinical Studies section of the Instructions for Use.

MR Conditional

Non-clinical testing has demonstrated the AMPLATZER™ PFO Occluder is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3.0 Tesla
- Maximum spatial gradient field less than or equal to 30 T/m
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning

In non-clinical testing the AMPLATZER™ PFO Occluder device produced a temperature rise of less than or equal to 1.79° C at a maximum whole-body averaged specific absorption rate (SAR) of 3.4 W/kg for 15 minutes of MR scanning in a 3.0 Tesla MR system (Siemens™ MAGNETOM Trio™, SYNGO™ MR A35 4VA35A software, Erlangen, Germany).

In non-clinical testing the AMPLATZER™ PFO Occluder device produced a temperature rise of less than or equal to 1.61° C at a maximum whole-body averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of MR scanning in a 1.5 Tesla MR system (Siemens™ MAGNETOM Espree™, SYNGO™ MR B17 software, Erlangen, Germany).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the device. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this implant.

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 dye reaction
- Allergic drug 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

Clinical Study

Design

The AMPLATZER™ PFO Occluder was evaluated in a prospective, randomized, multi-center, event driven trial (the RESPECT trial) comparing device closure of a PFO (plus medical management) with medical management alone in the prevention of recurrent ischemic stroke in patients diagnosed with a cryptogenic ischemic stroke and PFO.

A total of 980 patients were enrolled in the study with 499 patients randomized to PFO closure using the AMPLATZER™ PFO Occluder (the Device group) and 481 randomized to the Medical Management (MM) group.

The four medical therapy regimens allowed per protocol in the MM group were: (a) Aspirin alone, (b) Coumadin alone, (c) Clopidogrel alone or (d) Aspirin combined with dipyridamole. Patients implanted with the AMPLATZER™ PFO Occluder were to take clopidogrel for 30 days and aspirin for 6 months. Additional medical therapy beyond six months was at the discretion of the treating physician. Device group subjects were evaluated by transesophageal echocardiogram (TEE) at approximately 6 months post implant to assess PFO closure.

The primary effectiveness endpoint was the composite of recurrent nonfatal stroke, fatal ischemic stroke, or post-randomization mortality within 30 days post-implant or 45 days post-randomization in the Device group and within 45 days after randomization in the MM group. The secondary effectiveness endpoints included the absence of transient ischemic attack (TIA) and the rate of complete PFO closure (assessed by TEE bubble study) at 6 months follow-up (in-the Device group only). The safety endpoint consisted of serious adverse events, which included death, life threatening adverse events, inpatient hospitalization or prolongation of an ongoing hospital stay, persistent or significant disability/incapacity, and medically significant events.

The intention-to-treat (ITT) population was the pre-specified primary analysis population. Analyses were also performed on the Per Protocol population, which consisted of subjects who received their randomly assigned treatment and complied with protocol-mandated medical treatment and excluded subjects who did not receive their randomized therapy, did not comply with the protocol-mandated medical treatment, or had a major inclusion/exclusion criterion violation. In accordance with the pre-specified decision rules, trial enrollment was stopped once 25 primary endpoint events occurred. The initial data lock used for primary analyses occurred on 20 May 2012. The extended follow-up data lock occurred on 14 August 2015.

Patients Studied

Inclusion criteria

- PFO and a cryptogenic stroke within 270 days
  - Stroke was defined as an acute focal neurological deficit, presumed to be due to focal ischemia, and either:
    - Symptoms persisting ≥24 hours, or
    - Symptoms persisting <24 hours with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct
  - Cryptogenic stroke was defined as a stroke of unknown cause
  - PFO was defined as visualization of microbubbles (during TEE) in the left atrium within three cardiac cycles of right atrial opacification at rest and/or with Valsalva

Screening to establish the diagnosis of cryptogenic stroke

- Work-up of qualifying stroke evaluated by a neurologist
- TEE
- ECG or Holter monitor
- Brain MRI or CT scan
- Imaging of intracranial arteries with MR angiography, CT angiography, contrast arterial angiography, or transcranial Doppler
- Imaging of extracranial arteries with MRA, CTA, contrast arterial angiography, or duplex ultrasound
- Hypercoagulable state screening

General exclusion criteria

- Age <18 years and age >60 years
- MI or unstable angina within 6 months
- Mitral or aortic valve stenosis or severe regurgitation
- LVEF <35%
- Kidney, liver or lung failure
- Uncontrolled hypertension or diabetes mellitus despite medications
- Subjects contraindicated for aspirin or clopidogrel
- Subjects not able to discontinue anticoagulation if randomized to the Device
- Qualifying stroke with Modified Rankin score >3
- Anatomy in which the Device would interfere with intracardiac or vascular structures
- Progressive neurological dysfunction or life expectancy < 2 years

Criteria to exclude patients with known causes of ischemic stroke

- Atrial fibrillation/atrial flutter (chronic or intermittent)
- LV aneurysm, intracardiac thrombus, or tumor
- Mitral or aortic valve vegetation or prosthesis
- Aortic arch plaques protruding >4 mm into the lumen
- Atherosclerosis or arteriopathy of intra- or extracranial vessels with >50% diameter stenosis
- Another cause of right-to-left shunting (e.g., an ASD or a fenestrated atrial septum)
- Presence of a hypercoagulable state
- Lacunar infarct probably due to intrinsic small vessel as the qualifying event, defined as an ischemic stroke in the distribution of a single, small deep penetrating vessel in a patient with any of the following:
  - A history of hypertension (except in the first week post stroke)
  - A history of diabetes mellitus
  - Age ≥50 years
  - MRI or CT with leukoaraiosis greater than symmetric, well-defined periventricular caps, or bands (European Task Force on Age-Related White Matter Changes rating scale score >0)
- Arterial dissection as the qualifying event

The RESPECT trial subject demographics and baseline characteristics and baseline stroke risk factors for the ITT population are shown in Tables 1 and 2, respectively.

Table 1. Subject Demographics and Baseline Characteristics – ITT population

Variable	Device Group (N=499)	MM Group (N=481)	p-value[a]
Age, years[b]	N=492 45.7 (9.7) 46.7 [18.1, 61.0]	N=476 46.2 (10.0) 47.6 [18.4, 60.9]	0.491
Time from stroke to randomization, days	499 130 (70) 117 [10, 277]	481 130 (69) 121 [10, 286]	0.891
Sex, male	268/499 (53.7%)	268/481 (55.7%)	0.564
Previous myocardial infarction	5/499 (1.0%)	2/481 (0.4%)	0.452
Previous transient ischemic attack	58/499 (11.6%)	61/481 (12.7%)	0.626
Stroke prior to qualifying cryptogenic stroke	53/499 (10.6%)	51/481 (10.6%)	1.000
Substantial Shunt at Rest or Valsalva[c]	247/499 (49.5%)	231/481 (48.0%)	0.655
Atrial septal aneurysm[d]	180/499 (36.1%)	170/481 (35.3%)	0.842

Continuous variables are reported as n, mean (SD), median [min, max] and categorical variables as n (%).
MM = Medical Management

a. 2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized) or Fisher's Exact test.
b. The IRB at one site did not allow recording of subject birthdates on the case report forms (12 subjects).
c. Substantial shunt defined as Grade III at rest or Valsalva by TEE.
d. Defined as total excursion of the septum primum relative to the plane of the interatrial septum ≥ 10 mm.

Table 2. Baseline stroke risk factors – ITT population

Variable	Device Group (N=499)	MM Group (N=481)	p-value[a]
Current Smoker	75/499 (15.0%)	55/481 (11.4%)	0.109
Former smoker	134/499 (26.9%)	143/481 (29.7%)	0.322
Diabetes mellitus	33/499 (6.6%)	41/481 (8.5%)	0.278
Hypercholesterolemia	196/499 (39.3%)	195/481 (40.5%)	0.696
Hypertension	160/499 (32.1%)	153/481 (31.8%)	0.945
Atrial fibrillation	0/453 (0.0%)	1/442 (0.2%)	0.494
Birth control/HRT	41/499 (8.2%)	51/481 (10.6%)	0.228
Migraine	195/499 (39.1%)	186/481 (38.7%)	0.948
Other risk factor	37/456 (8.1%)	40/443 (9.0%)	0.636

MM = Medical Management
a. Fisher's Exact test.

RESPECT Effectiveness and Safety Results

Subject Follow-up

There was a higher rate of discontinuation in the MM group vs. the Device group for both the initial data lock (19.1% in the MM vs 10.4% in the Device group) and for the extended follow-up data lock (30.1% in the MM group vs 18.2% in the Device group). For the initial data lock (20 May 2012), there was 1476 patient-years of follow-up (mean 3.0 years) in the Device group and 1284 patient-years (mean 2.7 years) in the MM group. For the extended data lock (14 August 2015), there was 2769 patient-years of follow-up (mean 5.5 years) in the Device group and 2376 patient-years (mean 4.9 years) in the MM group.

Medical Therapy Use

In the MM group, antiplatelet therapy (mostly in the form of a single antiplatelet agent) was used in approximately 80% of subjects with approximately 55% of subjects on aspirin alone. Warfarin alone or warfarin in combination with an antiplatelet agent was used in the remaining MM group subjects. Approximately 90% of Device group subjects were taking anti-platelet medications throughout the study (predominately aspirin alone beginning 6-months post-Device implantation).

Primary Endpoint Analysis Results

ITT Population. All primary endpoint events were non-fatal ischemic strokes. The primary endpoint analysis of the initial (20 May 2012) and extended follow-up (14 August 2015) data locks for the ITT population (499 Device subjects and 481 MM subjects) are shown in Table 3. In the initial data lock analysis, there were 25 total primary endpoint events, 9 in the Device group (rate 0.61 per 100 patient-years) vs. 16 in the MM group (rate 1.25 per 100 patient-years), corresponding to a 50% relative risk reduction in favor of the Device group (which did not achieve statistical significance, p=0.089). In the extended follow-up data lock analysis, there were 42 total primary endpoint events (18 in the Device group and 24 in the MM group) and a numerically smaller relative risk reduction (35%) compared with the initial data lock analysis in favor of the Device group.

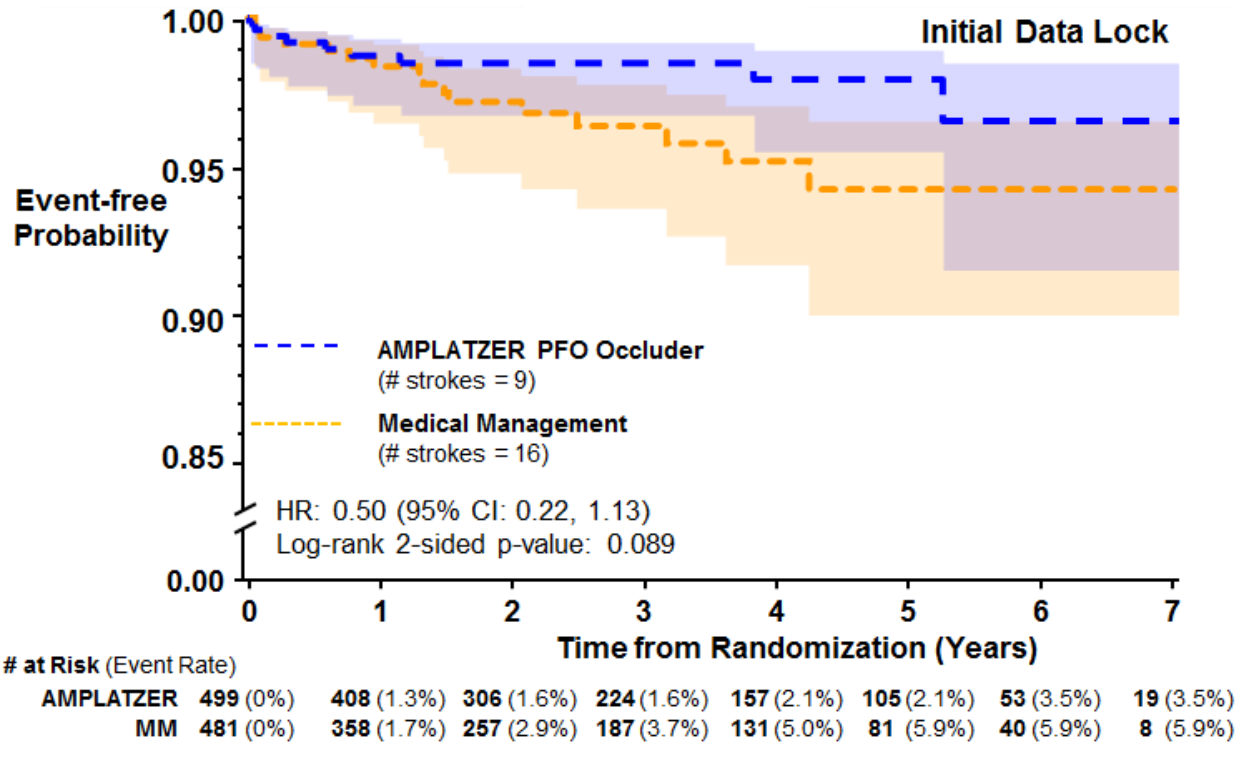
Table 3. Summary of primary endpoint analyses results (ITT Population)

Data Lock	# Events (Rate per 100 Pt-Yrs)[a]		Hazard Ratio[b] (95% CI)	Relative Risk Reduction	p-value[c]
	Device group (N=499)	MM Group (N=481)			
20 May 2012	9 (0.61)	16 (1.25)	0.50 (0.22, 1.13)	50%	0.089
14 August 2015	18 (0.65)	24 (1.01)	0.65 (0.35, 1.2)	35%	–

a. 100 x (Total number of events / total patient years follow-up)
b. Based on a Cox proportional hazards model
c. Based on a log-rank test
MM = Medical Management; Pt-Yrs = Patient-years

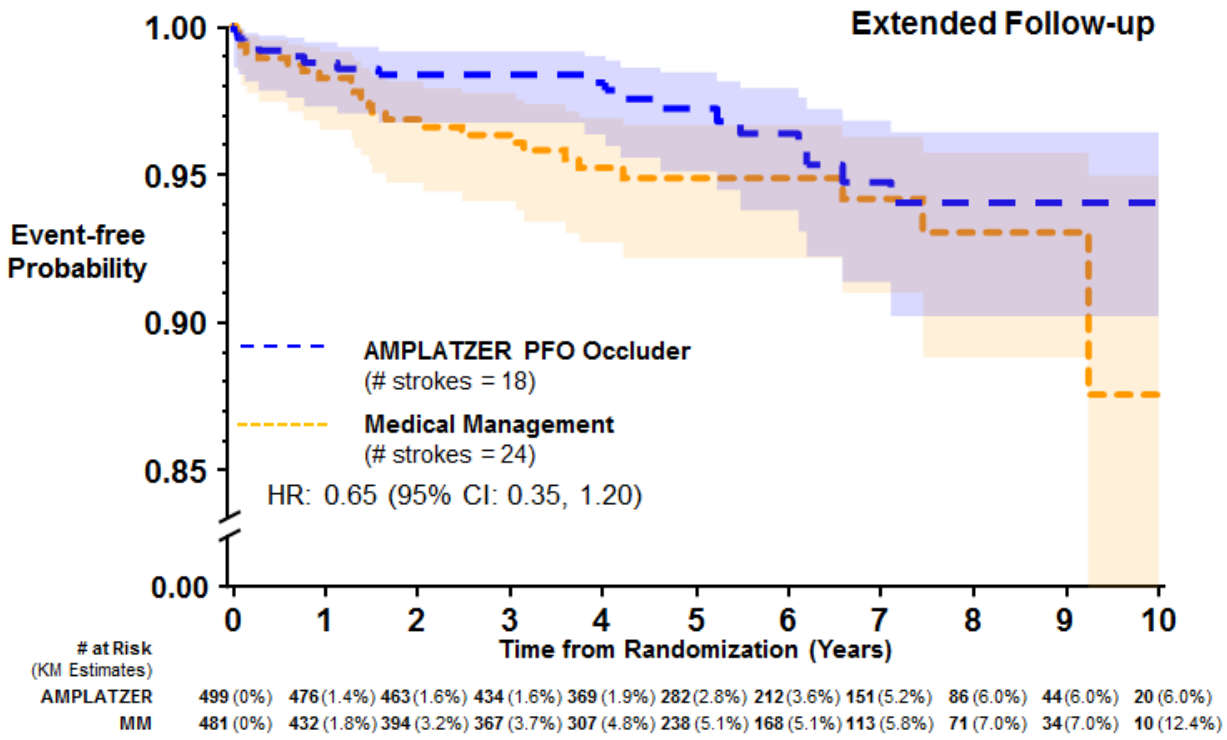
For the initial data lock, the Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 years were 0.021 in the Device group vs. 0.059 in the MM group (Figure 2). For the extended follow-up data lock, the Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 and 8 years were 0.028 in the Device group vs. 0.051 in the MM group, and 0.060 in the Device group vs. 0.070 in the MM group, respectively (Figure 3).

Figure 2. Kaplan-Meier Freedom from Primary Endpoint Event, ITT Analysis - Initial Data Lock



Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

Figure 3. Kaplan-Meier Freedom from Primary Endpoint Event, ITT Analysis - Extended Follow-Up



Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

In the ITT population, the number needed to treat with the AMPLATZER™ PFO Occluder to prevent one recurrent stroke at 5 years was 27 in the initial data lock analysis and was 43 in the extended follow-up data lock analysis.

Per-Protocol Population. The primary endpoint results for the initial (20 May 2012) and extended follow-up (14 August 2015) data locks for the Per-Protocol population (463 Device subjects and 474 MM subjects) are shown in Table 4. In the initial data lock analysis, there were 20 total primary endpoint events, 6 in the Device group (rate 0.42 per 100 patient-years) and 14 in the MM group (rate 1.19 per 100 patient-years), corresponding to a 63% relative risk reduction in favor of the Device group (which reached statistical significance, p=0.034, unadjusted for multiple testing). In the extended follow-up data lock analysis, there were 37 total primary endpoint events (15 in the Device group and 22 in the MM group) and a numerically smaller relative risk reduction (42%) compared with the initial data lock analysis in favor of the Device group.

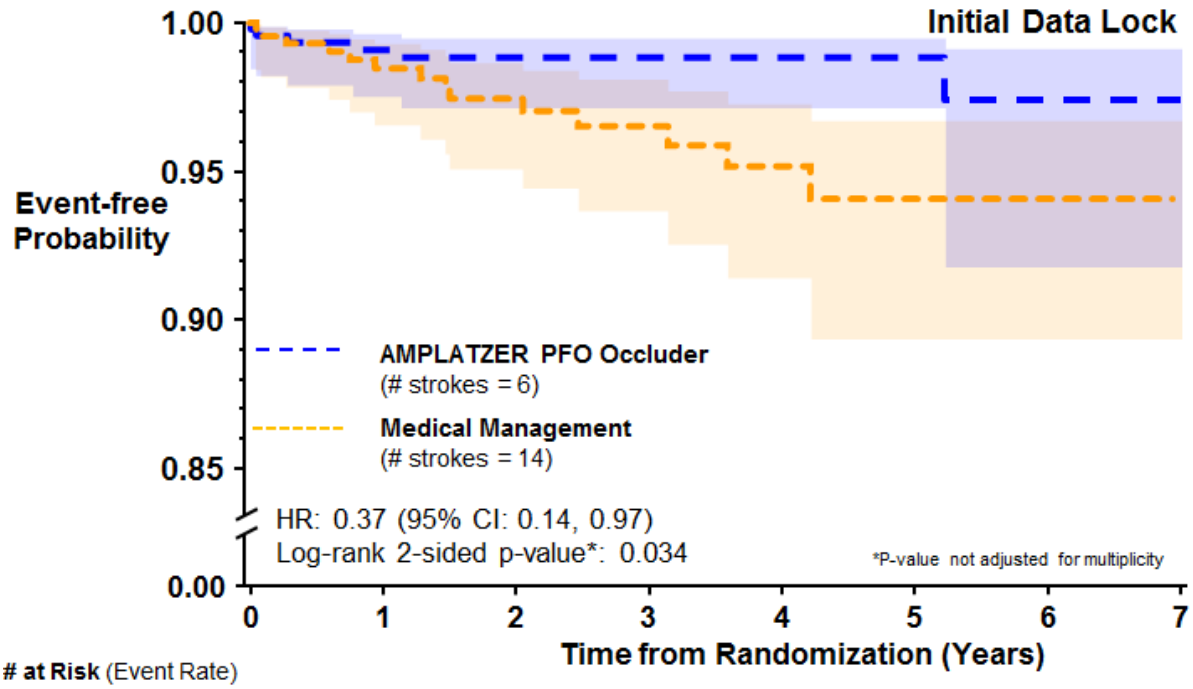
Table 4. Summary of primary endpoint analyses results (Per-Protocol Population)

Data Lock	# Events (Rate per 100 Pt-Yrs)[a]		Hazard Ratio[b] (95% CI)	Relative Risk Reduction	p-value[c]
	Device group (N=463)	MM Group (N=474)			
20 May 2012	6 (0.42)	14 (1.19)	0.37 (0.14, 0.97)	63%	0.034
14 August 2015	15 (0.57)	22 (0.99)	0.58 (0.30, 1.12)	42%	–

a. 100 x (Total number of events / total patient years follow-up)
b. Based on a Cox proportional hazards model
c. Based on a log-rank test, unadjusted for multiple testing
MM = Medical Management; Pt-Yrs = Patient-years

For the initial data lock, the Per Protocol Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 years were 0.012 in the Device group vs. 0.059 in the MM group (Figure 4). For the extended follow-up data lock, the Per Protocol Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 and 8 years were 0.022 in the Device group vs. 0.049 in the MM group, and 0.055 in the Device group vs. 0.069 in the MM group, respectively (Figure 5).

Figure 4. Kaplan-Meier Freedom from Primary Endpoint Event, Per Protocol Analysis - Initial Data Lock

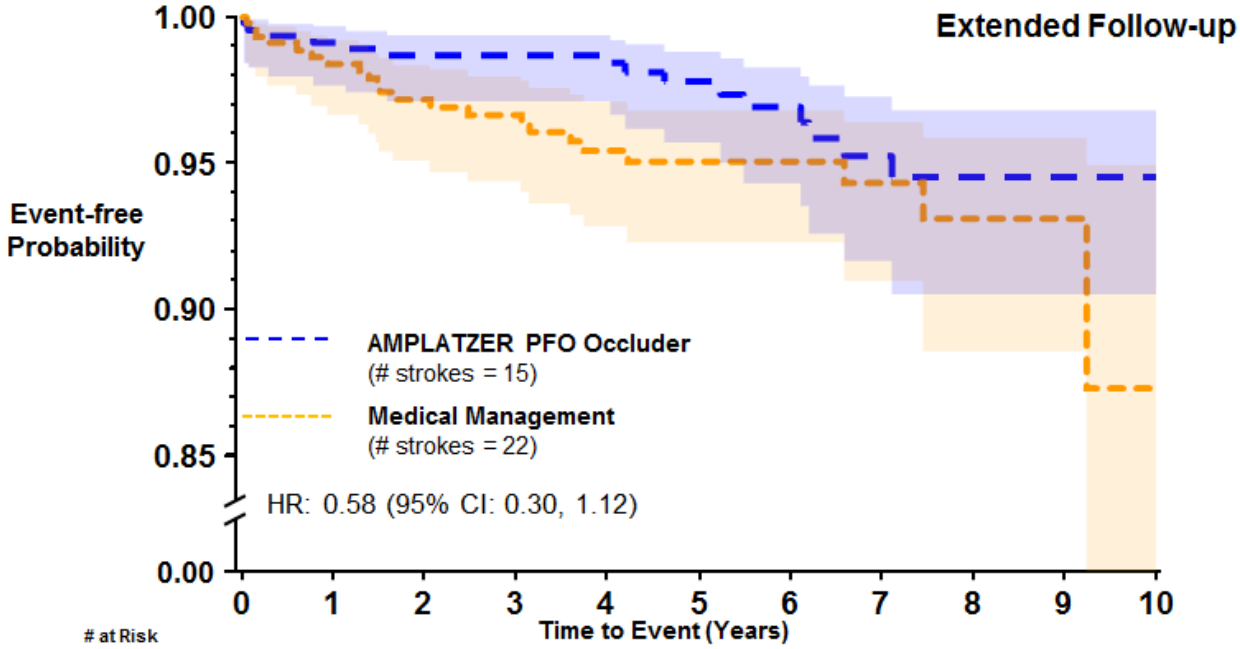


 # at Risk (Event Rate)

AMPLATZER	**463** (0%)	**390** (0.9%)	**293** (1.2%)	**215** (1.2%)	**152** (1.2%)	**102** (1.2%)	**52** (2.6%)	**19** (2.6%)
MM	**474** (0%)	**334** (1.5%)	**238** (2.5%)	**171** (3.4%)	**119** (4.8%)	**72** (5.9%)	**36** (5.9%)	**8** (5.9%)

Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

Figure 5. Kaplan-Meier Freedom from Primary Endpoint Event, Per Protocol Analysis - Extended Follow-Up



 # at Risk (KM Estimates)

AMPLATZER	**463** (0%)	**455** (1.1%)	**444** (1.3%)	**418** (1.3%)	**356** (1.3%)	**273** (2.2%)	**205** (3.1%)	**146** (4.8%)	**82** (5.5%)	**43** (5.5%)	**20** (5.5%)
MM	**474** (0%)	**412** (1.6%)	**376** (2.8%)	**346** (3.4%)	**285** (4.6%)	**221** (4.9%)	**154** (4.9%)	**106** (5.7%)	**66** (6.9%)	**31** (6.9%)	**10** (12.7%)

Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

For the secondary endpoint of the rate of PFO closure in the Device group, 249 of 349 subjects had grade 0 shunt both at rest and post-Valsalva at 6 months, for a complete closure rate of 71.3% (Table 5). The rate of effective closure (Grade 0 or I at Rest and Grade 0 or I at Valsalva) was 94.2% at 6 months.

Table 5. 6-month PFO closure data, Device group subjects who received a Device

Closure	Shunt grade	n/N (%)
Complete	Grade 0 Rest AND Grade 0 Valsalva	249/349[a] (71.3%)
Effective	Grade 0/I Rest AND Grade 0/I Valsalva	323/343 (94.2%)

[a.] 349 subjects includes 338 subjects with a shunt grade assessed both at rest and Valsalva plus 11 subjects with a shunt grade assessed as Grade 1 or higher either at rest or with Valsalva (included in the closure analysis as complete closure failures). PFO closure data were incomplete or missing in 33.2% of subjects

For the secondary endpoint of freedom from TIA, the Kaplan-Meier rate per 100 patient years (initial data lock analysis) in the Device group was 0.47 vs. 0.55 in the MM group.

Safety Evaluation

There were 386 serious adverse events (SAEs) in 189 patients in the Device group and 298 SAEs in 168 patients in the MM group. The proportions of patients experiencing an SAE in the two groups were similar (37.9% in the Device group and 34.9% in the MM group; Table 6). There were 16 deaths: 6 in the Device group (6/499, 1.2%) and 10 in the MM group (10/ 481, 2.1%) None of the deaths were adjudicated by the Data Safety Monitoring Board as being related to the Device, procedure, delivery system, or study protocol.

In the Device group, there were 25 SAEs related to the Device or implantation procedure in 21 subjects. The proportion of patients experiencing an SAE related to the procedure was 2.4% and the proportion of patients experiencing an SAE related to the device was 2.0%. No unanticipated adverse device effects were reported in the trial.

Table 6. Overall rate of SAEs through the extended follow-up data lock

	Device Group (N=499, 2769 patient-years)		MM Group (N=481, 2376 patient-years)	
	n[a] (%)	Events (Rate per 100 Pt-Yrs)	n (%)	Events (Rate per 100 Pt-Yrs)
Any SAE	189 (37.9%)	386 (13.9)	168 (34.9%)	298 (12.5)
Deaths related to procedure or device	0 (0.0%)	0 (0.0%)	N/A	N/A
Related to procedure	12 (2.4%)	12 (0.4)	N/A	N/A
Related to device	10 (2.0%)	13 (0.5)	N/A	N/A

MM = Medical Management; Pt-Yrs = Patient-years

[a.] Subjects could have more than one event

Twelve (12) procedure-related SAEs occurred in 12 patients (2.4%), and are summarized in Table 7.

Table 7. Procedure-related SAEs in the Device group through the extended follow-up data lock (N = 467)

Event	n (%)
Cardiac perforation *(required pericardiocentesis)*	2 (0.4%)
Cardiac perforation *(no treatment required)*	2 (0.4%)
Access site bleeding *(1 required sutures, 1 required transfusion, 1 required no treatment)*	3 (0.6%)
Right atrial thrombus *(detected during procedure - procedure abandoned)*	1 (0.2%)
Deep vein thrombus	1 (0.2%)
Atrial fibrillation	1 (0.2%)
Other *(allergic drug reaction - vasovagal response)*	2 (0.4%)

Thirteen (13) device-related SAEs occurred in 10 patients (2.0%) and are summarized in Table 8.

Table 8. Device-related SAEs in the Device group through the extended follow-up data lock (N = 467)

Event	n (%)
Ischemic stroke *(included in the primary endpoint)*	2 (0.4%)
Pulmonary embolism	2 (0.4%)
Thrombus in right atrium *(not attached to device)*	1 (0.2%)
Explant/surgical intervention	2 (0.4%)
Atrial fibrillation	1 (0.2%)
Residual shunt *(requiring closure with septal occluder device)*	1 (0.2%)
Other (*chest tightness, atrial flutter, non-sustained ventricular tachycardia, sepsis*)	4 (0.8%)

There were a total of 29 reported venous thromboembolism (VTE) events (serious or non-serious events) in 21 subjects: 18 events in 24 Device group subjects, and 5 events in 3 MM group subjects. These events are summarized in Table 9.

Table 9. Venous thromboembolic events through the extended follow-up data lock

	Device Group (N=499)			MM Group (N=481)		
	# Patients	# Events	Rate Per 100 Pt-Yrs	# Patients	# Events	Rate Per 100 Pt-Yrs
All VTEs	18	24	0.87	3	5	0.21
Deep Vein Thrombosis	11	11	0.40	3	3	0.13
Pulmonary Embolism	12	13	0.47	2	2	0.08

MM = Medical Management; Pt-Yrs = Patient-years

There were a total of 30 supraventricular arrhythmia events (serious or non-serious events) reported in the Device group subjects and 12 events in MM group subjects. Most events were atrial fibrillation. These events are summarized in Table 10.

Table 10. Supraventricular arrhythmia events through the extended follow-up data lock

	Device Group (N=499)			MM Group (N=481)		
	# Patients	# Events	Rate Per 100 Pt-Yrs	# Patients	# Events	Rate Per 100 Pt-Yrs
Atrial fibrillation	20	23	0.83	9	12	0.51
Peri-procedural	7	7	0.25	NA	NA	NA
Post-procedural	13	16	0.58	NA	NA	NA
Atrial Flutter	2	2	0.07	0	0	0
Paroxysmal Supraventricular Tachycardia	5	5	0.18	0	0	0

MM = Medical Management; Pt-Yrs = Patient-years

Technical Success

Technical success, defined as successful delivery and release of the device for subjects in whom delivery system entered the body at the time of first procedure, was 99.1%.

Procedural Success

Procedural success, defined as successful implantation with no reported in-hospital SAEs in device subjects, was 96.1%.

Directions for Use

Materials for use with this device

- 0.035-inch AMPLATZER™ Guidewire (9-GW-002)
- AMPLATZER™ TorqVue™ 45. Please refer to the AMPLATZER™ TorqVue™ 45 Instructions for Use.

Preprocedure care

- Aspirin (325 mg/day) (or alternative antiplatelet/anticoagulant, if patient has aspirin intolerance) is recommended to be started at least 24 hours prior to the procedure.
- Antibiotics can be administered periprocedurally at operator's discretion.
- Patients should be fully heparinized throughout the procedure using adequate dosing so as to keep the activated clotting time (ACT) greater than 200 seconds.

Procedure

CAUTION: Transesophageal echocardiography (TEE) or similar imaging equipment (i.e., intracardiac echocardiography) is recommended as an aid in evaluating the PFO and placing the AMPLATZER™ PFO Occluder. If TEE is used, the patient's esophageal anatomy must be adequate for placement and manipulation of the probe.

CAUTION: Fluoroscopic x-ray guidance may be used during placement of the device

1. Puncture the femoral vein and perform a standard right-heart catheterization.
2. Perform an angiogram to demonstrate the PFO. Catheterize the left atrium using a 45° LAO position and cranial angulation of 35°–45°. Inject contrast medium into the right upper lobe pulmonary vein.

   Note: Occluder size and placement are based on the locations of the PFO.
3. Use the J-tip guidewire to gain access through the PFO.
4. Use TEE or similar imaging equipment (i.e., intracardiac echocardiography to measure the distance from the PFO to the aortic root, and the distance from the PFO to superior vena cava orifice.

   Note: If TEE imaging is used, Steps 4-7 can be performed prior to femoral access, if desired.
5. Obtain two linear measurements by TEE or intra-cardiac echocardiography (ICE) as shown below:

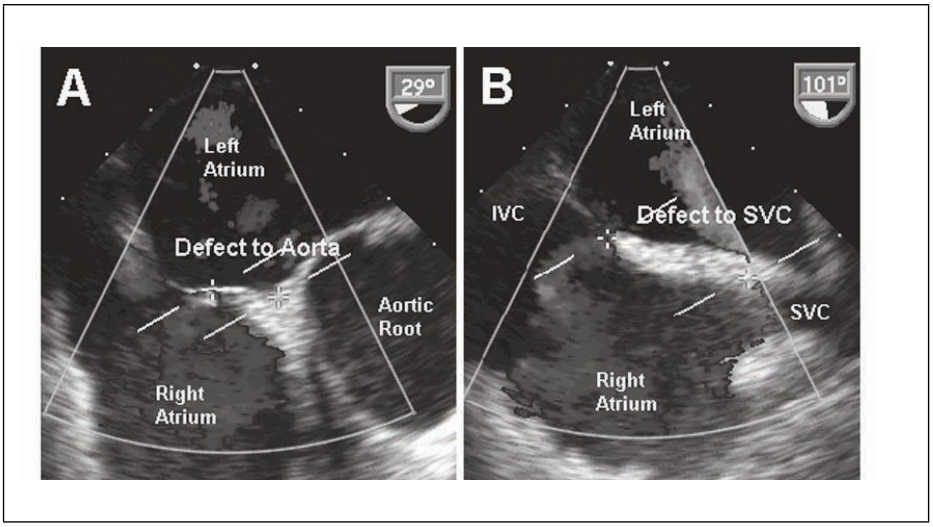


Figure 6.

A	Distance from the PFO to aortic root in the 30 degree view (range 0 to 45 degrees to visualize the aortic root en face)
B	Distance from the PFO to the orifice of the superior vena cava (SVC) in the bicaval 90 degree view (range 80 to 125 degrees to minimize foreshortening of the SVC).

Note: If Imaging cannot clearly localize the PFO, place a wire through the PFO to help with identification.

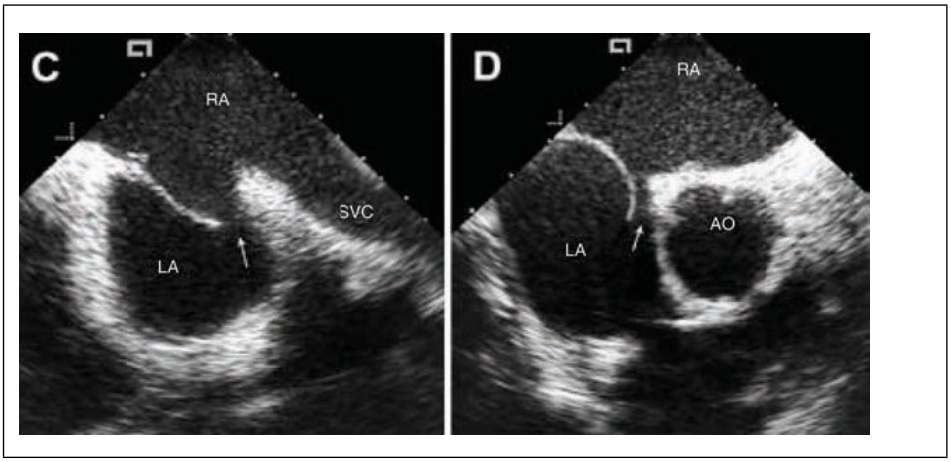


Figure 7.

C	PFO as assessed by ICE in long axis view
D	PFO as assessed by ICE in short axis view

6. Size the device such that the radius of the right atrial disc will not exceed the lesser of the two measurements, except in

the case of an atrial septal aneurysm, where consideration should be given to placing a larger occluder in an effort to cover the aneurysm (refer to Table 11 and Table 12 for sizing guidelines and device selection). Check SVC, inferior vena cava (IVC) and coronary sinus (CS) flows after device deployment, but before detachment.

WARNING: Do not implant a device if the distance from the PFO to the Aortic Root or Superior vena Cava (SVC) is less than 9 mm (as measured by echocardiography).

Table 11. Device Sizing Guidelines

Shortest Distance from PFO to Aortic Root or Distance from PFO to Superior Vena Cava Orifice (mm)	Suggested AMPLATZER™ PFO Occluder Size (mm)
Greater than or equal to 17.5	35
12.5 – 17.4	25
9.0 – 12.4	18
Less than 9.0	Do not implant device

Note: See Table 12 for device specifications and recommended sheath size.

Table 12. AMPLATZER™ PFO Occluder Specifications and Recommended Sheath Sizes

Device Order Number	Right Atrial Disc Diameter	Left Atrial Disc Diameter	Recommended Sheath Size
9-PFO-018	18 mm	18 mm	8 Fr
9-PFO-025	25 mm	18 mm	8 Fr
9-PFO-035	35 mm	25 mm	9 Fr

7. Prepare the delivery system according to the manufacturer's instructions for use.
8. Insert the dilator into the delivery sheath and tighten the rotating luer. Advance the dilator and delivery sheath over the guidewire, through the communication, and into the left atrium, confirming correct movement via echo and/or fluoroscopy.

   CAUTION: Do not use a power injection syringe to put contrast solution through the sheath.

   WARNING: Do not advance the delivery system if resistance is felt. Slowly remove the guidewire and dilator to prevent ingress of air. Allow blood back-flow to purge all air from the system. Flush the delivery sheath with sterile saline.
9. Prepare the device for use.
   - Inspect the sterile pouch.

   CAUTION: Do not use the device if the sterile pouch is open or damaged.

   - Open the sterile pouch. Inspect the device.

   CAUTION: Do not use the device if it is damaged.
10. Pass the delivery cable through the loader. Attach the device to the distal end of the delivery cable by rotating the device clockwise approximately 5 turns until the device is secure. Then, rotate the device counterclockwise 1/8 of one turn to facilitate release of the device.
11. Immerse the device and loader in sterile saline and pull back on the delivery cable to retract the device inside the loader
12. Flush the loader with sterile saline through the hemostasis valve.
13. Attach the loader to the delivery sheath and tighten the rotating luer to lock the components together.
14. Attach the loader firmly to the sheath to ensure that there are no gaps between the inner surfaces of the 2 components. Advance the delivery cable and device through the delivery sheath until the device reaches the tip of the sheath. Do not rotate the cable.

    CAUTION: Do not advance the delivery cable and device if resistance is felt.
15. Use angiography and echocardiography for guidance. Hold the delivery cable in place while retracting the delivery sheath to deploy the left atrial disc and part of the connecting waist. Pull the device gently against the atrial septum. This can be felt and observed by echocardiography.
16. Maintain a slight tension on the delivery cable while retracting the delivery sheath approximately 5–10 cm to deploy the right atrial disc.
17. Confirm correct placement. Use angiography and echocardiography to confirm that the device is in place and evaluate for residual shunt or valve insufficiency.
18. If the position of the device is unsatisfactory:
    - Stabilize the delivery cable and re-advance the delivery sheath until the device is completely within the sheath.

- Reposition the device and deploy it again, or remove the device from the patient. The device may be repositioned and recaptured up to 3 times.

19. Do not release the device from the delivery cable if the device does not conform to its original configuration or if device position is unstable or interferes with any adjacent cardiac structure (such as SVC, PV, MV, CS, AO). Recapture the device and redeploy. If still unsatisfactory, recapture the device and replace it with a new device, or refer the patient for alternative treatment. Detach the device from the delivery cable by turning the delivery cable counterclockwise (indicated by the arrow on the plastic vise). In the unlikely event that this should not be possible, advance the delivery sheath against the right atrial disc to secure the device and to facilitate detachment.

    Note: When the procedure is complete, slowly remove the sheath and delivery cable from the patient.

    WARNING: When the procedure is complete, slowly remove the delivery cable and delivery sheath from the patient. Remove the sheath slowly to prevent an ingress of air.

Post-procedure care

- It is up to the physician discretion whether patient should be kept overnight. Regardless of hospital length of stay, the patient should have a TTE prior to discharge.
- Patients with any observed pericardial effusion following the device implantation should be closely monitored with serial echocardiograms performed until the pericardial effusion resolves.
- Clinical follow-up with a cardiologist are recommended at 1 day post-implant, pre-discharge, and again at 1 week, 6 months, and 12 months post-implant. Clinical follow-up with a cardiologist annually thereafter is also recommended.
- Echocardiography (TTE or TEE) to assess the status of the device and PFO closure is recommended to be performed at either 6 months or 12 months post implant.
- Patients who experience a stroke after device implantation should undergo TEE to evaluate the device for thrombus.
- If a left-sided thrombus is identified following device implant, the patient should be evaluated for a hypercoagulable state and therapeutic anticoagulation (warfarin) should be initiated for a minimum of 3 months. A TEE should be performed following anticoagulation treatment to confirm resolution of the device-related thrombus. Thrombolysis or surgical removal of the device should be considered if the patient does not respond to anticoagulant therapy.
- Patients should be educated to seek immediate medical attention that includes an echocardiogram, if they develop signs or symptoms of hemodynamic instability such as chest pain, arrhythmia, fainting, or shortness of breath.
- Patients should take appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at the discretion of the physician.
- Patients should be treated with antithrombotic therapy (such as aspirin) for 6 months post-implant. The decision to continue antithrombotic therapy beyond 6 months is at the discretion of the physician. **In the RESPECT trial, approximately 90% of patients implanted with the AMPLATZER™ PFO Occluder continued taking anti-platelet medications beyond 6 months post-procedure (predominately aspirin alone).**
- Patients should be instructed to avoid strenuous activity for a minimum of 1 month post-device implant or as directed by physician. Strenuous activities may lead to the increased risk of adverse events including erosion. Patients should be reminded that if they experience any symptoms of shortness of breath or chest pain at any time, and especially after strenuous activity, they should seek medical care immediately.
- For patients with a history of PE or DVT, chronic anticoagulation rather than antiplatelet therapy should be considered post-device implantation.

Post-procedure Instructions

- Registration form – An implant registration form is located in each device box. Complete the patient information section and send the form to St. Jude Medical Corporation.

Disposal

- The carton and IFU are recyclable. Dispose of all packaging materials as appropriate.
- Dispose of device and accessories following standard solid biohazard waste procedures.

Warranty

St. Jude Medical Corporation warrants to buyer that, for a period equal to the validated shelf life of the product, this product shall meet the product specifications established by the manufacturer when used in accordance with the manufacturer's instructions for use and shall be free from defects in materials and workmanship. St. Jude Medical Corporation's obligation under this warranty is limited to replacing or repairing at its option, at its factory, this product if returned within the warranty period to St. Jude Medical Corporation and after confirmed to be defective by the manufacturer.

EXCEPT AS EXPRESSLY PROVIDED IN THIS WARRANTY, ST. JUDE MEDICAL CORPORATION DISCLAIMS ANY REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY AS TO MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

See the Terms and Conditions of Sale for further information.

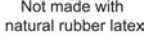
For U.S. --- California Only:

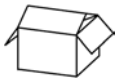
Proposition 65, a State of California voter initiative, requires the following notice:

WARNING: This product contains a chemical known to the State of California to cause cancer and birth defects or other reproductive harm.

Symbol Definitions

The following symbols may appear on the device packaging:

Symbol	Definition
	Manufacturer
	Reference number
	Product serial number
	Product lot number
	Use by date (Use on or before the last day of the expiration month noted on the product packaging.)
	Do not reuse
	Do not resterilize
	Sterilized using ethylene oxide
	Consult operating instructions
	Keep dry
	Do not use if package is damaged
 	Not made with natural rubber latex
	Inner diameter
	Outer diameter
	Length
	Usable length
	Recommended delivery sheath/catheter dimensions

Rx ONLY	Federal law (USA) restricts this device to sale by or on the order of a physician (or properly licensed practitioner).
	Date of manufacture
	Quantity
PFO Occluder	PFO Occluder