Clinical Insights

TECHNICAL PRODUCT FEATURE ANALYSIS

AMPLATZER™ STRUCTURAL INTERVENTIONS

THE INTAGLIO[™] WIRE TREATMENT

KEY MESSAGES

- Intaglio is a chemical etch treatment of Nitinol wire used in the manufacturing of Amplatzer Devices.
- Although Amplatzer products have always met the standards for nickel leaching, they were improved through the use of Intaglio wire treatment.
- The Intaglio wire treatment reduces the amount of nickel that may be leached from the device by more than 95% depending on the model. See next page for Nickel Reduction from Intaglio in Table 1 and PFO example in Graph 1.
- Intaglio is part of Abbott's commitment to increasing quality of all products.

INTRODUCTION

In 2014, a process for applying a chemically etched finish called Intaglio was introduced to the Amplatzer family of heart occluder devices. Prior to 2014, the Amplatzer occluder devices were manufactured using Black Oxide Nitinol wire. This process is part of continuing enhancements and improvements to Abbott's Amplatzer occluder and plug devices.

SIGNIFICANCE OF INTAGLIO

Amplatzer products have been evaluated using a robust in-vitro chemical leaching study to assess the material-related toxicity risks associated with nickel release after implantation. The conversion to the Intaglio chemical etching process has further reduced these toxicological risk factors with respect to nickel leaching. The Intaglio wire treatment reduces the amount of nickel that may be leached from the device by more than 95% depending on the model. Table 1 displays the outcome of this testing and shows that the amount of nickel leach from Amplatzer devices is well below recommended levels. The mechanical performance of the device remains unchanged with the conversion to chemically etched wire. Graph 1 shows the impact on nickel leaching over time as a result of the Intaglio process.



INTAGLIO TREATMENT

The Intaglio treatment is a secondary step applied to the Nitinol material utilized in the production of Amplatzer occluders. The metal wire undergoes a chemical etch as a process during manufacturing which results in a thinner, more consistent oxide layer on the device. The mechanical properties of the wire and finished device are not affected by this process so the proven clinical performance remains unaltered. Amplatzer devices with Intaglio have a slight coloration compared to previous devices with an untreated black oxide finish. this coloration is typically a blue or purple hue but can vary from nearly gold to dark purple as shown in the images below. This color variation can occur as a result of device size variation, wire size, and final device curing process. Color variation does not impact device performance characteristics.



CONCLUSIONS

Amplatzer[™] Occluder devices and the Intaglio[™] chemical etching are part of Abbott's commitment to continuous product improvement. Although Amplatzer products have an excellent safety profile and have always met the standards for nickel leaching, they were improved through the use of Intaglio wire treatment. Testing of Amplatzer Occluder devices with Intaglio chemical etching has demonstrated a significant reduction in nickel leaching compared to devices manufactured with a black oxide finish. Lower levels of nickel is intuitively better for patients and may reduce the potential for an adverse reaction to nickel.

TABLE 1: NICKEL REDUCTION FROM INTAGLIO IN AMPLATZER OCCLUSION PRODUCTS*

Product	Black Oxide, Max Ni Leach 1st Day [µg]	Black Oxide, Max Ni Leach 10th Day [µg]	Intaglio, Max Ni Leach 1st Day [µg]	Intaglio, Max Ni Leach 10th Day [µg]	1st Day Reduction in Nickel Leach with Intaglio (%)	10th Day Reduction in Nickel Leach with Intaglio (%)
PFO	77.1	18.4	1.79	0.17	97. 7%	99.1 %
ADOII	45.2	7.0	0.74	0.08	98.4%	98.9%
ASD	78.1	21.8	3.36	1.05	95.7%	95.2%

• The Intaglio wire treatment reduces the amount of nickel that may be leached from the device by more than 95% depending on the model.

• Lower levels of nickel increase safety and may reduce the potential for an adverse reaction to nickel.

* Chemical Characterization Testing data on file at Abbott. For product specific Nickel precautions, please check the Instructions for Use.

GRAPH 1: NICKEL LEACH REDUCTION WITH INTAGLIO - PFO



IMPORTANT SAFETY INFORMATION AMPLATZER™ PFO OCCLUDER



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 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.

PRECAUTIONS

- The safety and effectiveness of the Amplatzer™ PFO Occluder has not been established in patients (with):
- o 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
- o 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
- o Unable to take antiplatelet therapy
- o Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels associated with a ≥50% luminal stenosis
- o Acute or recent (within 6 months) myocardial infarction or unstable angina
- o Left ventricular aneurysm or akinesis
- o Mitral valve stenosis or severe mitral regurgitation irrespective of etiology
- o Aortic valve stenosis (mean gradient greater than 40 mmHg) or severe aortic valve regurgitation
- o Mitral or aortic valve vegetation or prosthesis
- o Aortic arch plaques protruding greater than 4 mm into the aortic lumen

- o Left ventricular dilated cardiomy opathy with left ventricular ejection fraction (LVEF) less than 35%
- o Chronic, persistent, or paroxysmal atrial fibrillation or atrial flutter
- o Uncontrolled hypertension or uncontrolled diabetes mellitus
- o Diagnosis of lacunar infarct probably due to intrinsic small vessel as qualifying stroke event
- o Arterial dissection as cause of stroke
- o Index stroke of poor outcome (modified Rankin score greater than 3)
- o Pregnancy at the time of implant
- o 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.

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 reactionAllergic 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 thrombusChest pain
- Device embolization
- Device erosion
- Deep vein thrombosis
- Death
- Endocarditis
- Esophagus injuryFever
- Headache/migraine
- Hypertension/hypotension
- Myocardial infarction
- · Pacemaker placement secondary to PFO device closure
- Palpitations
- Pericardial effusion
- Pericardial tamponade
- Pericarditis
- Peripheral embolismPleural effusion
- Pulmonary embolism
- Reintervention for residual shunt/device removal
- Sepsis
- StrokeTransient ischemic attack
- Thrombus
- Valvular regurgitation
- Vascular access site injury
- Vessel perforation

IMPORTANT SAFETY INFORMATION AMPLATZER™ SEPTAL OCCLUDER



INDICATIONS FOR USE

The Amplatzer[™] Septal Occluder is a percutaneous, transcatheter, atrial septal defect closure device intended for the occlusion of atrial septal defects (ASD) in secundum position or patients who have undergone a fenestrated Fontan procedure and who now require closure of the fenestration.

Patients indicated for ASD closure have echocardiographic evidence of ostium secundum atrial septal defect and clinical evidence of right ventricular volume overload (such as, 1.5:1 degree of left-to-right shunt or RV enlargement).

CONTRAINDICATIONS

The Amplatzer[™] Septal Occluder is contraindicated for the following:

- Any patient known to have extensive congenital cardiac anomaly which can only be adequately repaired by way of cardiac surgery.
- Any patient known to have sepsis within 1 month prior to implantation, or any systemic infection that cannot be successfully treated prior to device placement.
- Any patient known to have a bleeding disorder, untreated ulcer, or any other contraindications to aspirin therapy, unless another antiplatelet agent can be administered for 6 months.
- Any patient known to have a demonstrated intracardiac thrombi on echocardiography (especially left atrial or left atrial appendage thrombi).
- Any patient whose size (such as, too small for transesophageal echocardiography probe, catheter size) or condition (active infection, etc.) would cause the patient to be a poor candidate for cardiac catheterization.
- Any patient where the margins of the defect are less than 5 mm to the coronary sinus, inferior vena cava rim, AV valves, or right upper lobe pulmonary vein.

WARNINGS

- Physicians must be prepared to deal with urgent situations, such as device embolization, which require removal of the device. This includes the availability of an on-site surgeon.
- Embolized devices must be removed as they may disrupt critical cardiac functions. Embolized devices should not be withdrawn through intracardiac structures unless they have been adequately collapsed within the sheath.
- Use on or before the expiration date noted on the product packaging.
- This device is sterilized using ethylene oxide and is for single use only. Do not reuse or resterilize. Attempts to resterilize the device may result in device malfunction, inadequate sterilization, or patient harm.
- Do not use the device if the packaging sterile barrier is open or damaged.
- Do not release the Amplatzer[™] Septal Occluder 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)). 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.
- Implantation of this device may not supplant the need for Coumadin[™] in patients with ASD and paradoxical emboli.
- The use of echocardiographic imaging (TTE, TEE, or ICE) is required.

- Balloon sizing should be used to size the atrial septal defect using a stop-flow technique. Do not inflate the balloon beyond the cessation of the shunt (such as, stop-flow). DO NOT OVERINFLATE.
- Patients with a retro-aortic rim of less than 5 mm in any echocardiographic plane, or patients in whom the device physically impinges on (i.e. indents or distorts) the aortic root, may be at increased risk of erosion.
- Do not select a device size greater than 1.5 times the echocardiographic-derived ASD diameter prior to balloon sizing.

PRECAUTIONS

- The use of this device has not been studied in patients with patent foramen ovale.
- Use standard interventional cardiac catheterization techniques to place this device.
- Placement of the Amplatzer™ Septal Occluder may impact future cardiac interventions, for example transeptal puncture and mitral valve repair.
- This device contains 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 seek medical assistance immediately if they suspect they are experiencing an allergic reaction. Symptoms may include difficulty in breathing or swelling of the face or throat. While data is currently limited, it is possible that some patients may develop an allergy to nickel if this device is implanted.

• MR Conditional to 3.0 Tesla

Caution should be used if an MRI is performed with a magnetic field of >3.0 tesla.

Through non-clinical testing, the Amplatzer[™] device has been known to be MR Conditional at field strengths of 3.0 tesla or less with a maximum whole-body-averaged specific absorption rate (SAR) of 3.83 W/kg at 1.5 tesla and 5.57 W/kg at 5.0 tesla for a 20-minute exposure to a Bl of 118 ×T. The Amplatzer[™] device should not migrate in this MR environment. Non-clinical testing has not been performed to rule out the possibility of migration at field strengths higher than 3.0 tesla.

In this testing, the device produced a temperature rise of 1.1°C at 1.5 tesla and 1.6°C at 5.0 tesla.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device.

POTENTIAL ADVERSE EVENTS

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

Air embolus; Allergic dye reaction; Anesthesia reactions; Apnea; Arrhythmia; Cardiac tamponade; Death; Embolization; Fever Hypertension/ hypotension; Infection including endocarditis; Need for surgery; Pericardial effusion; Perforation of vessel or myocardium; Pseudoaneurysm including blood loss requiring transfusion; Stroke; Tissue erosion; Thrombus formation on discs; Valvular regurgitation

IMPORTANT SAFETY INFORMATION AMPLATZER™ DUCT II OCCLUDER



INTENDED USE

The Amplatzer[™] Duct Occluder II is apercutaneous transcatheter occlusion device intended for the non-surgical closure of patent ductus arteriosus.

CONTRAINDICATIONS

The Amplatzer ${}^{\rm TM}$ Duct Occluder II is contraindicated for the following:

- Patients weighing less than 6 kg
- · Patients less than 6 months of age
- Patients with a window-type patent ductus arteriosus (ie, length less than 3mm)
- · Patients with an active infection
- Patients with thrombus at the intended site of implant
- Patients with pulmonary hypertension with pulmonary vascular resistance of greater than 8 Wood units or Rp/Rs of greater than 0.4
- Patients with patent ductus arteriosus greater than 12 mm in length by angiography
- Patients with patent ductus arteriosus greater than 5.5 mm in diameter by angiography

WARNINGS

- Patients at greater risk of complications can include:
- Patients with a descending aorta < 10 mm in diameter
- Patients with cardiac anomalies requiring surgical or interventional correction
- Patients who have had more than 2 lower respiratory infections within the last year
- Do not release the occluder from the delivery wire if the occluder does not conform to its original configuration or if the occluder position is unstable. Recapture the occluder and redeploy. If still unsatisfactory, recapture the occluder and replace with a new occluder.
- The Amplatzer[™] Duct Occluder II should only be used by physicians trained in transcatheter defect closure techniques.
- Physicians must have an on-site surgeon available in the event that surgical removal of an occluder is required.
- Embolized occluders must be removed. Embolized occluders should not be withdrawn through intracardiac structures unless they have been adequately collapsed within a catheter.
- This device has not been studied in patients older than 18 years of age.

PRECAUTIONS

- This device was sterilized with ethylene oxide and is for single use only. Do not reuse or re-sterilize this device. Attempts to resterilize this device can cause a malfunction, insufficient sterilization, or harm to the patient.
- Use before the expiration date noted on the product packaging.
- Patients should have an activated clotting time (ACT) of greater than 200 sec prior to device replacement.
- The Amplatzer[™] Duct Occluder II contains 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 seek medical assistance immediately if they suspect they are experiencing an allergic reaction. Symptoms may include difficulty in breathing or swelling of the face or throat. While data are currently limited, it is possible that some patients

may develop anallergy to nickel if this device is implanted.

- Use in specific populations
- Pregnancy Care should be taken to minimize the radiation exposure to the fetus and the mother.
- Nursing mothers There has been no quantitative assessment of the presence of leachables in breast milk.
- Store in a dry place.
- Do not use if the packaging sterile barrier is opened or damaged.
- Do not use contrast power injection with delivery catheter.
- The physician should exercise clinical judgment in situations that involve the use of anticoagulants or antiplatelet drugs before, during, and/or after the use of this device

MR CONDITIONAL

Abbott Medical's Amplatzer™ Duct Occluder II device is manufactured of chemically etched nitinol wire, 80% platinum, 20% iridium marker band and a 316L end screw.

Non-clinical testing has demonstrated that the Amplatzer™ Duct Occluder II device is MR-Conditional. Patients can be scanned safely immediately after implantation under the following conditions:

- Static magnetic field of 1.5 Tesla (1.5T) or 3.0 Tesla (3.0T)
- 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 with body coil excitation, the Amplatzer[™] Duct Occluder II device produced a differential temperature rise of less than or equal to 3.65°C when exposed to a maximum average whole body specific absorption rate (SAR) of 3.35 W/kg for 15 minutes of scanning in a 3.0 Tesla MR system (Siemens MAGNETOM Trio‡, SYNGO‡ MR A35 4VA35A software, Erlangen, Germany). Scaling of the SAR and observed heating indicates that average whole body SAR of 2.0 W/kg would be expected to yield a localized temperature rise of less than or equal to 1.0°C in Normal Operating Mode.

In non-clinical testing with body coil excitation, the Amplatzer[™] Duct Occluder II device produced a differential temperature rise of less than or equal to 1.91°C when exposed to a maximum average whole body specific absorption rate (SAR) of 2.80 W/kg for 15 minutes of scanning in a 1.5 Tesla MR system (Siemens‡ MAGNETOM Espree‡, SYNGO‡ MR B17 software, Erlangen, Germany). Scaling of the SAR and observed heating indicates that average whole body SAR of 2.0 W/kg would be expected to yield a localized temperature rise of less than or equal to approximately 1.0°C in Normal Operating Mode.

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

POTENTIAL 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; Anesthesia reactions; Apnea; Arrhythmia; Bacterial endocarditis; Bleeding; Cardiac perforation; Cardiac tamponade; Chest pain; Device embolization; Device erosion; Death; Fever; Headache/migraine; Hypertension; Hypotension; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Peripheral embolism; Pleural effusion; Pulmonary embolism; Reintervention for device removal; 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 eifu. abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events.

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