Physician Communication Bulletin

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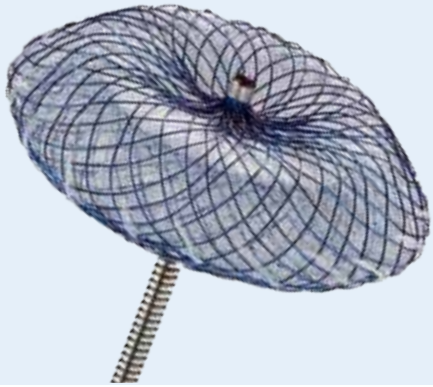
AMPLATZER™ ATRIAL SEPTAL OCCLUDER (ASO)

AMPLATZER™ ATRIAL SEPTAL OCCLUDER (ASO) CLINICAL DATA UPDATE

Notification of US Instructions for Use (IFU) Update Specific to Factors to Consider for Cardiac Erosion

OVERVIEW

This document is intended to inform health care providers of updated data provided in the US AMPLATZER™ Atrial Septal Occluder Instructions for Use (IFU) related to patient and atrial septal defect (ASD) characteristics that present greater risk for cardiac erosion following ASO implants. While erosion events occur at extremely low rates, they have the potential for emergent outcomes. An analysis by McElhinney and colleagues identified risk factors for erosion.[1] These are provided in the updated IFU (https://manuals.sjm.com) and are summarized herein for physician consideration during patient screening and device selection.



BACKGROUND

The AMPLATZER™ Atrial Septal Occluder (ASO) is currently the most commonly used device for transcatheter ASD closure (FDA Premarket Approval P000039). It has been established as a safe and effective alternative to surgical closure.[2,3,4] In a retrospective observational study of 6,585 ASD closure patients from the Pediatric Health Information Systems database, 5,262 received a transcatheter closure device. Their in-hospital death rate was significantly lower with transcatheter ASD closure relative to surgery (0.0% v 0.4%, p=0.001).[4] Long term mortality (median 10 years) on 375 patients from another retrospective analysis reported no differences in survival between transcatheter vs surgical closure cohorts respectively (97% vs 97%, p=.99).[3]

Further, the ASO pivotal IDE study of 442 ASO and 154 surgical closure cases similarly showed lower acute major complications rates (0.2%) in the ASO arm, compared to the surgical arm (5.2%).[2] At 12-months, rate remained low and significantly different between both arms (1.6% v 5.2%, p=0.03). No erosions were reported. While the incidence of adverse events following use of the ASO remain low and clinically acceptable, a 0.3% cardiac erosion rate was observed in the ASO Post-Approval Study (PAS). Erosion is defined as abrasion of the device through the atrial wall into the aorta and/or pericardial space, and has been identified as a rare but potentially serious complication.[6] Deficient aortic rims, protrusion into the aortic root, somewhat undersized device, and device motion against the heart were implicated, but because erosion is so rare, there was insufficient data to confirm this.[6]

Following an FDA Panel review of all commercially approved ASD occluders, the FDA required St. Jude Medical (SJM), now Abbott, to conduct a postmarket surveillance study to better understand how erosion impacts the performance of the ASO and assess potential risk factors related to the occurrence of erosion. The ADVANCE ASO study was initiated in January 2015 as a prospective, multicenter, case-cohort study designed to identify potential risk factors and patient groups at high risk for cardiac erosion. In 2016, McElhinney and colleagues published an analysis which SJM submitted to FDA to address the postmarket surveillance study requirement of which FDA concurred. Upon collective review of this analysis, and the pre- and post-market ASO clinical data, the ADVANCE ASO study was terminated February 2017.

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.

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IFU UPDATES RESULTING FROM CASE-CONTROL ANALYSIS BY MCELHINNEY *ET AL 2016*[1]

McElhinney et al. conducted a retrospective case-control investigation to identify potential risk factors associated with erosion in patients who were implanted with the ASO for occlusion of a secundum atrial septal defect. One hundred twenty-five (125) cases of erosion reported between 2002 and 2014 following ASD closure with an ASO were matched in a 2:1 fashion to controls who had ASD closure with an ASO, but did not develop erosion. The median duration from implant to erosion diagnosis was 14 days and was ≤1 day in approximately one-third of patients (n=40).

Deficiency of aortic or SVC rims, (i.e. aortic rim < 5 mm or SVC rim < 5 mm), stop flow sizing technique, the balloon-sized ASD diameter, the difference between sized and static ASD diameters, the absolute ASO device size, patient age:device size and weight:device size ratios, and the device size-static ASD diameter difference were significantly associated with erosion in the univariate analysis ($p<0.05$). Details on the results of this analysis are provided below [Table 1]. Another possible risk factor for erosion following implantation of the ASO device was indentation of the aortic sinus (Odds ratio: 4.8, 95% Confidence interval: 1.4–17.3, p=0.016).

TABLE 1: BASIC DETAILS OF EROSION AND CONTROL COHORTS (TABLE 2 IN MCELHINNEY *ET AL.*)

	CONTROL (250)	EROSION (125)	OR (95% CI)	P VALUE
Age at procedure, y	28.7±18.6	27.4±18.0 [117]	0.9 (0.7–1.1)	0.49
Female	172 (69)	83 (72) [116]	2.2 (0.7–7.5)	0.21
Weight, kg	60.6±27.2	55.6±25.7 [78]	0.99 (0.96–1.01)	0.25
DEFICIENT RIM(S)				
Any rim	64 (26)	84 (97) [87]	103 (14–741)	<0.001
Aortic rim	61 (24)	82 (94) [87]	51 (12–208)	<0.001
SVC rim	2 (1)	14 (17) [84]	27 (3.6–206)	<0.001
Both aortic and SVC rim	0 (0)	12 (14) [84]	156 (0.9-27333)	0.055
ASD SIZE				
Static (native) ASD diameter, mm	15.7±6.3	16.6±5.0 [96]	1.03 (0.99–1.08)	0.19
BS performed	249 (99)	71 (96) [74]	0.01 (0–154)	0.34
Stop-flow technique used	248 (99)	34 (58) [59]	0.02 (0–0.23)	0.006
BS ASD diameter, mm	19.0±6.7	21.2±5.2 [92]	1.07 (1.03–1.12)	0.003
BS diameter—static diameter difference, mm	3.3±3.7	4.3±3.7 [86]	1.11 (1.03–1.20)	0.007
BS diameter >5 mm more than static diameter	62 (26)	36 (44) [95]	3.2 (1.6–6.1)	<0.001
ASO DEVICE-RELATED DETAILS				
Device size, mm	20.3±7.4	22.6±5.6 [121]	1.07 (1.03–1.11)	0.001
Patient age:device size ratio, y/mm	1.50±1.10	1.21±0.84 [115]	0.03 (0.01–0.22)	<0.001
Patient weight:device size ratio, kg/mm	3.23±1.71	2.52±1.39 [78]	0.01 (0.00–0.10)	<0.001
Device size—static diameter difference, mm	4.5±4.0	5.8±3.8 [94]	1.12 (1.04–1.20)	0.003
Device diameter >5 mm more than static diameter	83 (34)	49 (52) [95]	2.7 (1.6–4.8)	<0.001
Device size—BS diameter difference, mm	1.33±2.15	1.52±1.85 [95]	1.1 (0.9–1.2)	0.33
Device size >3 mm more than BS diameter	37 (15)	18 (18) [97]	1.3 (0.6–2.2)	0.51

Data are presented as number (% of patients with available data) or mean±standard deviation, along with the [number of patients with available data]. ASD indicates atrial septal defect; ASO, AMPLATZER septal occluder; BS, balloon-sized or balloon-sizing; CI, confidence interval; OR, odds ratio; and SVC, superior vena cava.

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In the multivariate analyses, deficiency of aortic or SVC rims, balloon size diameter > 5 mm larger than static (native) ASD diameter, and low patient weight to device size ratio were found to be significantly associated with erosion($p<0.05$). Details on the results of this analyses are provided below [Table 2].

TABLE 2. MULTIVARIABLE CONDITIONAL LOGISTIC REGRESSION MODELS FOR ASSOCIATION WITH EROSION (TABLE 3 MCELHINNEY *ET AL.*)

	OR (95% CI)	P VALUE
MODEL 1		
Any rim deficient	71 (8–682)	<0.001
BS diameter >5 mm more than static	4.4 (1.1–17.2)	0.036
Patient weight:device size ratio, log	0.004 (0.001–855)	0.044
MODEL 2		
Aortic rim deficient	45 (7–292)	<0.001
BS diameter >5 mm more than static	5.4 (1.3–22.2)	0.02
Patient weight:device size ratio, log	0.002 (0.00–0.400)	0.022

BS indicates balloon-sized; CI, confidence interval; and OR, odds ratio.

SUMMARY

The ASO has been established as a safe and effective treatment option for ASD closure. Cardiac erosion is rare but still a concern among implanting physicians; however, more information regarding risk factors and high risk patients has been provided by the McElhinney results. The study identified three major risks associated with cardiac erosion: any rim deficiency, larger ASO diameter relative to native ASD diameter, and low patient weight to device ratio. The US ASO Instructions For Use have been updated with findings from this study. **Physicians should consider these risk factors for erosion at implant and in selection of device size and placement.**

ADDITIONAL RESOURCES

This communication document, along with contact details, a summary of the McElhinney publication, links to the IFU updates and Frequently Asked Questions will be available at: **www.MyAmplatzer.com** which is administered by Abbott.

For further information about this communication, you may also contact your local Abbott Representative or Abbott Customer Service at **1-855-478-5833.**

1. McElhinney D, Quartermain M, Kenny D *et. al.* Relative Risk Factors for Cardiac Erosion Following Transcatheter Closure of Atrial Septal Defects, A Case-Control Study. Circulation. 2016; 133:1738-1746.
2. Du Z, Hijazi Z, Kleinman C, *et. al.* Comparison between Transcatheter and Surgical Closure of Secundum Atrial Septal Defect in Children and Adults. J Am Coll Cardiol. 2002 Jun 5;39(11):1836-44.
3. Kutty S, Hazeem AA, Brown K, *et. al.* Long-term (5- to 20-year) outcomes after transcatheter or surgical treatment of hemodynamically significant isolated secundum atrial septal defect. Am J Cardiol. 2012 May 1;109(9):1348-52
4. O'Byrne ML, Shinohara RT. Am Heart J *et. al.* Increasing propensity to pursue operative closure of atrial septal defects following changes in the instructions for use of the AMPLATZER Septal Occluder device: An observational study using data from the Pediatric Health Information Systems database. Am Heart J 2017; 192:85-97
5. Turner DR, Owada CY, Sang CJ Jr, *et. al.* Closure of Secundum Atrial Septal Defects with the AMPLATZER Septal Occluder: A Prospective, Multicenter, Post-Approval Study Circ Cardiovasc Interv. 2017; 10(8). pii: e004212
6. Moore J, Hegde S, El-Said H, *et. al.* Transcatheter Closure of Atrial Septal Defects. A Safety Review. JACC Cardiovasc Interv. 2013 May;6(5):433-42

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AMPLATZER™ SEPTAL OCCLUDER AND DELIVERY SYSTEM

IMPORTANT SAFETY INFORMATION

℞ ONLY

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 B1 of 118 ^{x}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

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

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