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Transcatheter Device Closure of Atrial Septal Defects

A Safety Review

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This review discusses the current safety issues related to U.S. Food and Drug Administration approved atrial septal defect devices and proposes a potential avenue to gather additional safety data including factors, which may be involved in device erosion.

Atrial septal defects (ASD) are classified into ostium primum, ostium secundum, sinus venosus, and coronary sinus types. The current reported prevalence of ASD is about 10% of congenital cardiac defects (1). ASD, although recognized as a relatively benign form of cardiac disease, if left untreated can eventually contribute to significant morbidity and mortality, as borne out by the natural history studies (2,3). Unrepaired ASD can lead to right ventricular volume overload with resultant right heart failure, elevated pulmonary vascular resistance, systemic embolism,

and atrial arrhythmias. Among the various types of ASDs only the ostium secundum defect is amenable to device closure, whereas all 4 types can be surgically closed. Over the years, routine closure of ASD in childhood has been justified due to the availability of low-risk, curative surgical, and transcatheter options.

Transcatheter device closure of secundum ASD is a maturing technology, now more than a decade old. This therapy has become a well-accepted alternative to surgical therapy and has been regarded as generally safe and effective. Widespread use of devices and fairly

casual post-market surveillance brought device erosion resulting in perforation of the heart, a previously unrecognized and potentially catastrophic adverse event, to light. Erosion events were not identified in the pivotal U.S. Food and Drug Administration (FDA) device studies. Accumulating reports of erosions have been concerning and prompted the FDA to convene a panel to review the approved ASD closure devices.

Our goal is to outline the available information on the safety of ASD devices with a focus on erosion, to report the recommendations from the FDA panel, and to propose a possible mechanism for more comprehensive post-market evaluation and monitoring of devices such as septal occluders, using a national registry.

Surgical Closure

Historically, surgical closure of an ASD was the standard of care. The first experimental surgical closure of ASD, by inverting the atrial appendage through the defect and using fascia lata to seal the defect, was attempted in 1939 at Columbia Presbyterian Hospital. Between 1939 and 1953, many methods of surgical repair of ASD were proposed and studied. John Gibbon in Philadelphia performed the world's first successful closure of ASD using a cardiopulmonary bypass machine. This technique was refined and by the late 1960s was adopted by most surgeons around the world (4).

The surgical technique now consists of approximating the edges of the defect in small ASD to achieve closure or using native pericardium/synthetic patch, in larger ASD, to close the defect. Minimally invasive surgical approaches (nonsternotomy or small incision) are being increasingly adopted to repair ASD. The surgical method allows closure of all sizes and types of ASD regardless of the rims.

Surgical results are excellent, and surgery has altered the natural history of patients with ASD. A prospective longitudinal follow-up of 135 patients who underwent surgical closure of ASD in childhood showed excellent long-term survival and low morbidity (5). Another study of the natural history of surgically corrected ASD showed actuarial 27-year survival rates among patients younger than 25 years to be better than for patients over 25 years of age (6).

Abbreviations and Acronyms

ASD = atrial septal defect(s)

ASO = Amplatzer septal occluder

CCISC = Congenital Cardiovascular Interventional Study Consortium

FDA = U.S. Food and Drug Administration

HSO = Helex septal occluder

IMPACT = Improving Pediatric and Adult Congenital Treatments

MAUDE = Manufacturer and User facility Device Experience

MDR = medical-device report(s)

Device Closure

King and Mills, in 1974, originally described and subsequently demonstrated feasibility of closing ASD using a device. Their device consisted of Dacron-covered stainless steel umbrellas, but it required a large delivery sheath and complicated maneuvering during deployment. William Rashkind developed a device that initially had 3 stainless steel arms covered with medical grade foam and subsequently a device with 6 arms, all of which ended with miniature hooks. In the early 1980s, Rashkind obtained investigational device exemption from the FDA and organized multi-institutional clinical trials in the United States. Due to difficulty in deploying the double-umbrella, Lock et al. modified the Rashkind device in 1989 into a clamshell occluder by introducing a second spring in the arms. Rome et al. and Hellenbrand et al. reported clinical experience with this device in the 1990s. In 1990, Sideris et al. described a buttoned device that consisted of an occluder and a counter-occluder. The first 4 generations of this device were extensively studied and reported by Sideris and Rao et al. In 1993, Pavenik et al. designed a monodisk device, which consisted of a stainless steel ring covered with 2 layers of wire mesh and hollow pieces of braided stainless steel wire. Babic et al. in 1991, Siveret et al. in 1995, and Hausdorf in 1996 described the use of a double umbrella device called an ASD occluding system deployed via an arterio-venous wire loop. In 1993, Das et al. described a self-centering device delivered transvenously called Das Angel Wing with a subsequent modified device that was called Guardian Angel Wing. When the clamshell device was withdrawn due to stress fractures of the stainless steel arms, the device was modified by using MP35N, a nonferrous alloy, with an additional bend in the arms and the device was called Cardio-SEAL (NMT Medical Inc.: Boston, Massachusetts) in 1996. In 1998, the device was further modified by using a self-centering mechanism with microsprings between the umbrellas and the device was called STARFlex (NMT Medical Inc.). The STARFlex device was subsequently further modified by using bioabsorbable material to replace the Dacron, and the devices were called BioSTAR (NMT Medical Inc.) and BioTREK (NMT Medical Inc.) (7).

In 1997, Amplatz developed a self-expanding prosthesis made of nitinol (nickel and titanium alloy) wire mesh with 2 round disks and a connecting short waist. This device was called Amplatzer septal occluder (ASO) and was approved by the FDA in December 2001. The Helex occluder is made of a 0.012-inch nitinol wire covered with an ultra-thin expanded polytetrafluoro-ethylene membrane, and once deployed, the device forms 2 round flexible disks on either side of the septal defect. The FDA approved the Helex occluder in 2006.

Over the years, the devices evolved both in terms of design and technique of deployment, making device closure of ASD a safe and efficacious alternative to surgery. The data from the Nationwide Inpatient Sample, identified 15,482 secundum ASD/patent foramen ovale closures between 1988 and 2005. Of these, 5,495 were percutaneous, 10,278 were surgical, and 1,196 were unspecified or undetermined type (8). The devices currently approved in the United States and widely used for closure of ASD are the ASO and the Helex septal occluder (HSO).

Safety and Efficacy Studies

The pivotal studies for both the ASO (St. Jude Medical Inc., St. Paul, Minnesota) and the HSO (W. L. Gore and Associates, Flagstaff, Arizona), showed no statistical difference in efficacy between surgical and device closure of secundum ASD. There were, however, notable differences in safety (9,10).

The ASO pivotal study was a multicenter nonrandomized trial performed in 29 pediatric cardiology centers from March 1998 to March 2000 with 442 patients enrolled in the device group and 154 patients in the surgical group. This study sought to compare the safety, efficacy, and clinical utility of the ASO for closure of secundum ASD with surgical closure. The inclusion criteria for both groups included: 1) presence of a secundum ASD (diameter ≤38 mm by echocardiogram for the device group, no limit for the surgical group); 2) a left-to-right shunt with a Qp/Qs of ≥1.5:1 or presence of right ventricular volume overload; and 3) patients with minimal shunt in the presence of symptoms. Additional inclusion criteria for the device group required the presence of a distance of >5 mm from the margins of the ASD to the coronary sinus, atrioventricular valves, and right upper pulmonary vein as measured by echocardiography. The exclusion criteria for both groups are shown in Table 1.

The overall complication rate was 7.2% for the device group and 24% for the surgical group with a mortality of 0% for both groups. One death that occurred in the device group was found to be unrelated to the device. The major adverse event rates were 1.6% for the device group and 5.2% for the surgical group. The safety outcomes suggested that patients having device closure encountered lower major and total adverse events (9).

The HSO pivotal study was a multicenter nonrandomized trial performed in 14 U.S. medical centers from March 2001 to April 2003 with 119 patients enrolled in the device group and 128 patients in the surgical group. This study sought to compare the safety and efficacy of the HSO with the surgical repair of secundum ASD. Inclusion criteria for enrollment included the presence of an ostium secundum ASD and evidence of right heart

Table 1
Exclusion Criteria for the ASO Pivotal Study

Exclusion Criteria for Both Groups*
Presence of associated congenital cardiac anomalies requiring surgical repair
Primum ASD
Sinus venosus ASD (including partial anomalous pulmonary venous drainage)
Pulmonary vascular resistance >7 Woods units
Right-to-left shunt at the atrial level with peripheral arterial saturation <94%
Recent myocardial infarction
Unstable angina, decompensated congestive heart failure, or right and/or left ventricular decompensation with ejection fraction of <30%
Sepsis
History of repeated pulmonary infection
Any type of serious infection <1 month before the procedure
Malignancy where life expectancy was <2 yrs
Intracardiac thrombi
Weight <8 kg
Inability to obtain informed consent
Other contraindications to aspirin or other antiplatelet agents

Reprinted, with permission, from Du et al. (9). *An additional exclusion criterion for the device group was patients with multiple defects that could not be adequately covered by device(s).
ASD = atrial septal defect(s); ASO = Amplatzer septal occluder.

volume overload. Additional criteria for the device arm patients was a balloon occlusion defect diameter ≤22 mm and the presence of adequate septal rims to secure the device as judged by the individual investigator at the time of implantation. In the surgical arm, patients could be enrolled retrospectively within 12 months of institutional review board approval. Exclusion criteria for the study included the presence of concurrent cardiac defects requiring surgical repair or significant comorbidities including a history of stroke, pulmonary hypertension, pregnancy, or the presence of multiple ASD requiring the use of more than 1 device (device arm only). The major adverse event rate was 5.9% for the device group and 10.9% for the surgical group. These rates were not statistically different. There were no deaths in the device group, but there was 1 death in the surgical group from pericardial tamponade (10).

Other available studies have confirmed the pivotal studies' safety outcomes (11,12). In the continued access study for the HSO, the rate of major adverse events was 2.2% in 137 patients (13). A recent HSO report (14) on combined data of feasibility, multicenter pivotal, and continued access studies showed a major adverse event rate of 5.8%.

Table 2

Adverse Events Listed in the Instructions for Use for ASO and HSO

Potential Device- or Procedure Related Adverse Events Listed by the Manufacturer for the ASO	Potential Device- or Procedure Related Adverse Events Listed by the Manufacturer for the HSO
Air embolus	Device embolization
Allergic reaction	New arrhythmia requiring treatment
Anesthesia reactions	Repeat procedure to the septal defect
Apnea	Intervention for device failure or ineffectiveness
Fever	Access site complications requiring surgery, interventional procedure
Hypertension/hypotension	Transfusion or prescription medication
Infection including endocarditis	Thrombosis or thromboembolic event resulting in clinical sequelae
Perforation of vessel or myocardium	Impingement on, damage to or perforation of a cardiovascular structure by the device
Pseudoaneurysm	Device fracture resulting in clinical sequelae or surgical intervention
Blood loss requiring transfusion	Air embolism
Stroke	Myocardial infarction
Valvular regurgitation	Pericardial tamponade
Death	Cardiac arrest
	Renal failure
	Sepsis
	Significant pleural or pericardial effusion requiring drainage
	Significant bleeding
	Endocarditis
	Headache or migraine
	TIA or stroke
	Death

Adapted, with permission from AGA (15) and W. L. Gore (16).
ASO = Amplatzer septal occluder; HSO = Helex septal occluder; TIA = transient ischemic attack.

Types of Adverse Events

The instructions for use for both the ASO and HSO provide a list of potential adverse events and include the data from the pivotal studies as shown in Table 2 (15,16).

Cardiac perforations by the ASO arose as a safety signal from reports to the FDA's MAUDE (Manufacturer and User Facility Device Experience) database, which were subsequently reported in the literature (Table 3) (17–19). There have been no instances of erosion with the HSO with

very rare occurrence of partial prolapse of a Helex device associated with early frame fracture and mitral valve perforation (13).

Device Malposition/Embolization

Device embolization is a potential complication of every attempted ASD closure, and the causative factors can be undersized device, inadequate or floppy rim, operator-related technical issues such as malposition during the "push-pull" maneuver, or excessive tension on delivery cable during device deployment.

A survey of AGA proctors carried out in 2003 revealed that there were 21 embolizations out of 3,824 ASO implants (0.55%); of those, 15 were retrieved using a transcatheter approach (71.4%) and 6 were retrieved surgically (28.5%) (20). An analysis of the device embolizations reported to the MAUDE database found it to be the most prevalent adverse event and the device was retrieved surgically in 77.2% of cases and using a transcatheter approach in 16.7% of cases. There were 2 deaths related to embolization (18).

The AGA survey showed that experienced operators were able to successfully retrieve the embolized device using a transcatheter approach. All operators who use the septal occluders should be prepared to perform percutaneous device retrieval in the event of a device embolization. After device embolization, the first objective is simply to get the device into a position in which it will not cause harm. The device may then be stabilized and moved or removed from the body.

Infection

Device closure of ASD is typically performed under strict asepsis, and often the patient receives a dose or more of prophylactic antibiotics. As with all implanted devices there remains a small risk of infection, and there are rare instances

Table 3

Types of Adverse Events Reported to the MAUDE Database Between January 1, 2002 and June 30, 2007

Adverse Event	Percentage of Reported Events for 18,333 (Estimated) Implants
Device embolization	51
Cardiac perforations	23
Thromboembolic complications	5
Residual/recurrent defect	4
Device infection	2

Reprinted, with permission, from DiBardino et al. (18).
MAUDE = Manufacturer and User Facility Device Experience.

of the device needing to be explanted due to suspected endocarditis. The FDA analyses of the MAUDE medical-device reports (MDR) showed that 0.8% of the MDR were related to infection/endocarditis (19).

Arrhythmias

The reported complications from device closure of ASD include development of atrial tachyarrhythmias or heart block, both transient and permanent. The risk of bundle branch block in patients with large ASD, particularly those with deficient rims, may be increased, although the true risk is unknown. A retrospective study of 610 device patients (585 ASO), who underwent device closure of ASD, showed a low overall risk of arrhythmias with clinically significant heart block occurring in 0.3% of patients. A tendency toward atrial arrhythmias appears to increase with device closure (21). In the MAUDE analysis, 5% of the MDR were arrhythmias (19). There is a concern that device closure of ASD may preclude future electrophysiology procedures that require transseptal access.

Thromboembolic Complication

An analysis of the MAUDE database showed that 2.5% (18 of 705) of the MDR were related to device thrombus, and 1 death was attributed to thrombus (19). In one report, 1,000 patients were studied to investigate the incidence and clinical course of thrombus formation following device closure of ASD. This study showed that the incidence of thrombus on closure devices is low. However, significant differences were noted between different devices with the Amplatzer nitinol wire frame filled with polyester fabric and the Helex nitinol wire covered by an ultra-thin membrane of expanded polytetrafluoroethylene to be least thrombogenic. Atrial fibrillation and persistent atrial septal aneurysm after transcatheter closure are significant risk factors for thrombus formation. In most of the patients, the thrombus resolved under medical therapy without clinical consequences (22).

Nickel Allergy

The use of nitinol-containing devices can pre-dispose to nickel allergy. In 2009, a survey of the members of the Congenital Cardiovascular Interventional Study Consortium (CCISC) was conducted to determine the approach of interventional cardiologists to nickel allergy. Whereas 80% of responders believed that nickel allergy exists, only 44% routinely inquired about nickel allergy prior to device closure, and no responders performed skin testing prior to device closure. Reaction reportedly occurred anywhere from 2 days up to 1 month after implantation and manifested as headaches, rash/urticaria, difficulty breathing, fever, or peri-cardial effusion. All patients responded to medical manage-

ment (23). In rare instances, if medical management fails, the devices may need to be explanted.
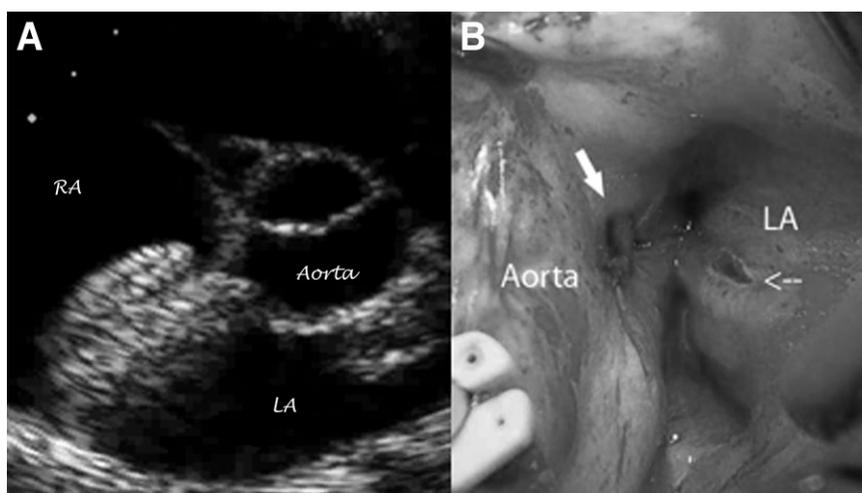
Erosion

Although the pivotal studies reported no cases of erosion or cardiac perforation after ASO implantation, this rare but potentially fatal complication subsequently came to light. AGA Medical Corporation focused on the issue of cardiac perforation when it selected an expert panel to review all cases of hemodynamic compromise reported to the corporation by 2004 (24). A total of 28 cases of hemodynamic compromise were reported with ASO by 26 physicians between 1998 and March 2004. They determined the erosion rate to be 0.1% (9 of 9,000 known U.S. implants). In 25 patients, the aortic rim was deficient and/or the ASD was described as "high" suggesting deficient superior rim. Of the 28 cases with hemodynamic compromise, some deserve mention: 5 involved perforation of the roof of the left atrium and the aorta; 6 involved perforation of the roof of the right atrium and the aorta; in 1 case, both atria were involved; 3 cases, there was no atrial perforation; and in 3 cases with aortic perforations, a fistulous communication was noted. Of 28 patients, 19 had symptoms develop within 72 h. In 8 patients, diagnosis was made between 5 days and 8 months, and in 1 patient, pericardial effusion developed after 3 years. The therapeutic approach to erosion varied with 21 patients requiring surgery. Of those 21 patients requiring surgery, 16 had device removal in addition to perforation or fistula repair. The device was left in place in 5 patients because it appeared to be in optimal position, but the perforation was repaired. In 7 of 28 cases with hemo-dynamic compromise, the patients were managed medically with pericardiocentesis and/or observation. Figure 1 illustrates a typical example of erosion with the ASO device. The AGA expert panel made some recommendations based on their findings as shown in Table 4.

To better understand factors causing device erosion with ASO, a survey was sent by e-mail to all members of CCISC. CCISC was originally founded to design, conduct, and report the findings of scientific studies in interventional cardiovascular care of patients with congenital heart disease. The 57 survey responders had cumulative experience of 12,006 ASO implants. Of those responders, 12 reported 14 erosions out of 3,010 implants. The findings of this survey revealed that the opinions of experienced operators were at odds with the manufacturer's recommendations made following the expert review in 2004. A deficient aortic rim was noted in 90% of patients with erosion. The results of the survey regarding the mechanism of the erosion indicated: devices with lower risk of erosion are those that straddle the aorta, are somewhat oversized, and do not move relative to the heart; devices with higher risk are those with protruding left atrial disk into the aortic root, are somewhat undersized,

Figure 1

Erosion With ASO

(A) Echocardiographic image of device in vivo prior to erosion. **(B)** Intraoperative image of erosion of atrial wall and aorta as shown by arrow. ASO = Amplatzer septal occluder; LA = left atrium; RA = right atrium.

and may have motion relative to adjacent heart structures. The CCISC members were divided in their opinion of the leading risk factor with 84.7% agreeing that the motion of the device relative to the heart causes erosions, whereas 71.7% felt that a somewhat undersized device with tip-disk protrusion into the aortic root was more likely to cause erosions (25).

Table 4

AGA Expert Panel Recommendations

AGA Expert Panel Recommendations Regarding Erosions
Follow instructions for use when performing balloon-sizing.
Avoid overstretching the balloon when balloon-sizing the defect.
Use stop-flow technique for maximum inflation of sizing balloon.
Be gentle with to-and-fro movement of the device to assess stability while the device is attached to the delivery cable.

Follow more closely the categories of patients listed below:
    Those with significantly larger ASO (>1.5×) than native diameter of ASD;
    Those even with development of small pericardial effusion;
    Those with deformation of the ASO at the aortic root (significant splaying of the device edges by the aorta);
    Those with high defects (minimal aortic and superior rims).

Conduct follow-up in all patients.
Educate patients about the risk and need for echocardiography with symptoms.

Reprinted, with permission, from Amin et al. (25).
   Abbreviation as in Table 1.

The MAUDE reports also eventually identified cardiac perforation resulting in hemodynamic compromise as a rare but serious adverse event caused by the ASO. In the analysis by DiBardino et al. (18), there were 51 cardiac perforations, erosions, or ruptures reported to the MAUDE database; 10 of those patients died. The most common site for perforation documented was a combination of the atrium and aorta adjacent to the device suggesting erosion. They estimated a national erosion rate of 0.28% (51 of 18,333 implants). Only 4 events occurred at implantation. Most were clustered in the first 6 months (16 within 24 h, 11 within 1 month, and 8 between 1 and 6 months), but erosions and ruptures are still being reported as late as 3 years after deployment. The mortality from erosions from this MAUDE database analysis is 0.05%, which, as an isolated cause for mortality, is still at a lower rate than the overall surgical mortality of 0.13% determined from the STS (Society of Thoracic Surgeons) database.

A more recent analysis of the MAUDE database by the FDA showed that erosion contributed to 15% of MDR (109 of 705 MDR: 100 documented and 9 suspected). In 80 patients, the device was explanted. There were 13 deaths (8 documented and 5 suspected). Nine of these erosion events occurred in the United States and 4 outside the United States. Some patients developed sudden onset of signs and symptoms and required emergency interventions. The signs and symptoms include cardiac tamponade (9 of 13 erosion death events), pericardial effusion, hemodynamic

Table 5

Summary of the MAUDE Database Analysis of MDR for ASO Compiled by the FDA

ASO and Amplatzer Cribriform	On-Label Use			Off-Label Use for PFO			Total		
	MDR (n = 672)	Patient Death (n = 24)	Explant (n = 505)	MDR (n = 33)	Patient Death (n = 2)	Explant (n = 24)	MDR* (n = 705)	Patient Death (n = 26)	Explant (n = 529)
Erosion	103	13	74	6	0	6	109 (15)	13	80
Documented	95	8	71	5	0	5	100	8	76
Suspected	8	5	3	1	0	1	9	5	4
Perforation/effusion, no erosion	26	2	2	4	2	1	30 (4)	4	3
Device embolization	318	3	315	11	0	10	329 (47)	3	325
Malposition	55	0	46	0	0	0	55 (8)	0	46
Residual/recurrent shunt	0	0	0	2	0	2	2 (0.3)	0	2
Valve dysfunction	8	0	7	0	0	0	8 (1)	0	7
Fracture†	1	0	0	0	0	0	1 (0.1)	0	0
Device malfunction‡	57	0	27	2	0	1	59 (8)	0	28
Neurological events	14	0	4	1	0	1	15 (2)	0	5
Stroke	7	0	4	0	0	0	7	0	4
Other	7	0	0	1	0	1	8	0	1
Device thrombus§	14	1	2	4	0	2	18 (2.5)	1	4
Infection/endocarditis	6	0	6	0	0	0	6 (0.8)	0	6
Air embolus	6	2	1	0	0	0	6 (0.8)	2	1
Arrhythmia	35	0	9	1	0	0	36 (5)	0	9
Allergy	9	0	5	1	0	1	10 (1.4)	0	6
Others‖	20	3	7	1	0	0	21 (3)	3	7

Reprinted, with permission, from FDA (19). Values are n or n (%). *The percentage represents the proportion of the MDR of the reported problem over the total of all ASO MDR. †The fracture event was reported, but investigation did not confirm that it actually occurred. ‡Three MDR categorized as "device malfunction" were also reported with device embolization. §Five MDR categorized as "device thrombus" were also reported with stroke. ‖Others include events such as headache, effusion after CPR, non-device-related stroke, aborted procedure, femoral access site fistula, septal tear to inferior vena cava, guidewire extraction difficulties, respiratory failure, and death (cause unknown).

CPR = cardiopulmonary resuscitation; FDA = U.S. Food and Drug Administration; MDR = medical-device report(s); PFO = patent foramen ovale; other abbreviations as in Tables 1 and 3.

compromise, chest pain, shortness of breath, syncope, and sudden cardiac death. The time to erosion reported in the 13 deaths ranged from 1 day to 821 days (2.2 years) after implantation (Table 5). As reported in the 13 erosion death MDR, 10 patients were women and 3 were men (ratio 3.3:1) (19). This rare complication that was not encountered in the pivotal or post-market approval studies is particularly troubling because it may even occur late after device implantation and may be catastrophic resulting in the patient's death.

A study from the National Cardiovascular Center in Osaka, Japan, sought to further elucidate potential causal factors by conducting a prospective investigation into the morphological changes in the ASO over time and the influences of these changes on the atrial and aortic walls

after ASD closure (26). The researchers studied the relationship of the disks to the atrial and/or aortic walls and also looked at any residual shunts. They enrolled 78 patients and performed transesophageal echocardiography under anesthesia before and soon after device placement on all patients. In some patients, the transesophageal echocardiography was repeated at 3 months, 6 months, and 12 months. This study showed that those with deficient aortic rim, flare device shape on the aortic side immediately after deployment, and thicker device profile at the middle part immediately after deployment were significantly more likely to show a possible worsening in the relation of the disks to the atrial and aortic walls. No major complications such as erosion or device migration were recognized in the 78 patients.

Figure 2

Potential Risk Factors for Erosion With Amplatzer Septal Occluder
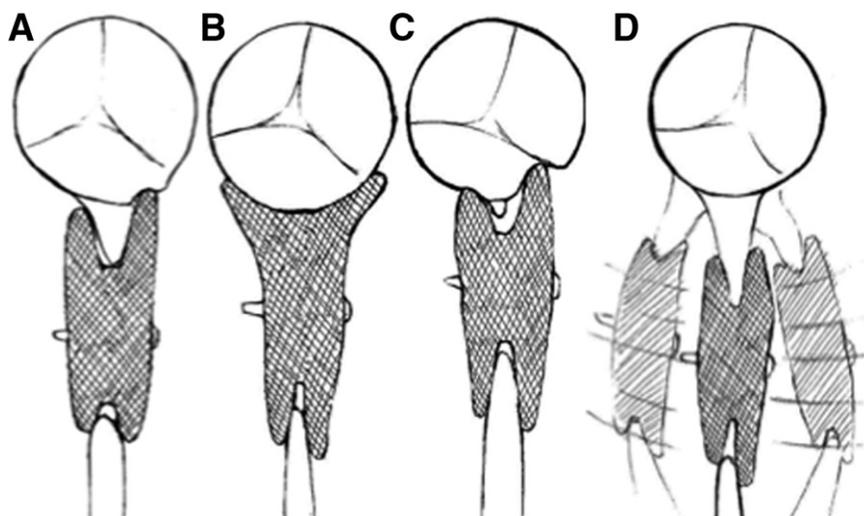
(A) Intermittent contact; **(B)** splaying; **(C)** protrusion; **(D)** motion.

In reviewing the literature and available registry data, it is evident that there is neither conclusive data nor consensus about incidence or root cause(s) of cardiac perforation or erosion by the ASO. Potential risk factors, as gleaned from the AGA study in 2004, the CCISC survey in 2009, and the National Cardiovascular Center study in 2009, may be:

1. Contact by the edge of the device with the atrial wall causing protrusion of the device into wall and into adjacent structures such as the aorta.
2. Splaying or flaring of the device around the aortic root following implantation.
3. Rotation of the device around its central pins during atrial contraction and/or translational movement of the device relative to the motion of the heart after implantation.
4. Absent and/or deficient aortic (anterior-superior) rim.
5. Thicker device profile at the time of deployment.

Figure 2 illustrates some of the potential risk factors. These factors individually or in combination may be predictors of early and late erosions; thus, they warrant close monitoring. The critical assessment of ASD using echocardiography before, during, and after device deployment is of paramount importance. The data gathering by way of obtaining high-resolution images will help us understand the erosion mechanism better. Individual centers have varying degrees of expertise of using different imaging techniques be they transthoracic, transesophageal, intracardiac, or 3-dimensional echocardiography to guide cardiac interventions. Interventionalists should make the best use of the available expertise and ensure that they pay close attention to potential risk factors. Specific recommendations regarding imaging techniques can be made once the issue of erosion is better examined in the light of larger studies.

FDA Panel Review and Recommendations

There is currently insufficient data and no consensus as to whether or how to change clinical practice or alter labeling of ASD occlusion devices. Given the lack of available data pertaining to the potential risk factors for erosion and frequency of adverse events in patients with ASD occlusion devices, the Circulatory System Devices Panel of the FDA met on May 24, 2012, to discuss current knowledge about the safety and effectiveness of the Amplatzer ASO device and Gore Helex ASD occluder as transcatheter ASD occluders used for the closure of secundum ASD.

The panel discussed the clinical significance of erosion, fracture, embolization, and other adverse events in the context of disease, surgical alternatives, and benefits of device closure. They concluded that the overall known safety profile of the class of devices has not changed since marketing approval; however, the awareness of the full spectrum of events/outcomes has been elucidated. The

panel determined that there is insufficient information to confidently determine which patient subgroups are at increased risk for certain events associated with transcatheter ASD device closure (27).

The following are the interim recommendations:

1. As events are more frequent in the first 12 months, there should be frequent follow-up in the first year (e.g., serial echo at 1 week, 1 month, 6 months) and clinical follow-up yearly with less frequent follow-up after the first year. Specific recommendations regarding clinical and imaging follow-up should be further vetted as the issue is further examined. Mandatory device tracking was strongly recommended for both devices (i.e., the device class).

2. Current instructions for use for the Amplatzer device should be modified so that the contraindication related to having a 5-mm anterior-superior aortic rim is clarified and changed to a warning. Both devices should include in the patient and physician labeling a warning regarding patient symptoms that require emergent treatment (e.g., severe chest pain). Also, standard training of echocardiographers, echo laboratories, and standard imaging should be captured.

3. There is no need to reanalyze the data collected from the Helex studies; however, a reanalysis should be performed for the Amplatzer data collected with suggestions to: 1) consider other variables not previously analyzed; 2) use existing data on noncases (either from the pre-market study or post-approval study) to estimate relative risk for events; and 3) assess center volume and user experience.

4. Ongoing post-approval studies should remain unchanged, and it was agreed that a 522 study is indicated for the Amplatzer ASO device. A case cohort study design was suggested under the 522 regulation with an additional suggestion that data on both devices be captured in prospective registries, possibly using the American College of Cardiology/Society of Thoracic Surgeons framework. A majority of the panel members felt that a 522 study for the Helex device to address fracture issues was not necessary.

5. Additional measures should be taken to ensure that patients are informed of the risks/benefits of transcatheter ASD closure. Patients should be informed by: 1) more robust pre-procedural information so patients are aware of risks/benefits prior to the procedure; and 2) direct communication to patients who have already been implanted. Communication should come from the FDA and the sponsors in the form of a letter generated by sponsors given to clinical sites and distributed to the patients.

A Role for IMPACT?

The FDA panel recommendations expressed the need to further define the risk factors and the incidence of erosion by the ASO. To do both, a very large, detailed, longitudinal dataset would be required for study. The NCDR (National Cardiovascular Data Registry) IMPACT (Improving Pediatric and Adult Congenital Treatments) registry (28) was created in part to provide a research tool to evaluate interventional procedures in patients with congenital heart disease. IMPACT began enrolling centers and patients one year ago and is presently in a start-up phase. It has already accumulated data on over 4,000 catheterizations, and it has provided the first reports to its 52 participating centers. These reports include data for 340 ASD occlusions (29). The number of centers in IMPACT is growing steadily. As of the end of 2012, there were 80 centers participating in IMPACT. The NCDR's goal is to enroll the majority of the approximately 200 centers in the United States, which perform catheterization in patients with congenital heart disease, by the end of 2013. It is likely that IMPACT will be able to provide the study power needed to address the problem of erosion. However, IMPACT's current data elements for ASD occlusion are not sufficient to provide further information about risk factors. In addition, the registry does not collect longitudinal data (i.e., erosions occurring after the initial episode of care are not captured). From its inception, a goal for IMPACT has been to develop longitudinal modules to study longer-term outcomes for select interventions. The development of such a dataset for late ASD closure outcomes fits well with the current vision for IMPACT and is perfectly aligned with the FDA panel recommendations.

Conclusions

Post-market approval studies and reports focusing on the ASO and the HSO have confirmed the safety profiles of these devices suggested by their pivotal studies. Overall risk imposed by device closure of ASD compares favorably with the risk of surgical closure. With the exception of cardiac perforation (erosion) caused by the ASO, new safety issues have not come to light. The FDA MAUDE database was most responsible for raising a safety signal with respect to erosion. Erosion has been confined to the Amplatzer device, and it appears to occur only once or twice per 1,000 device patients. It was not encountered during the pivotal study presumably because this study population was not of adequate size to identify rare adverse events. This event, though rare, is particularly troublesome because it may occur late after device implantation and because it may be catastrophic.

As suggested by the FDA panel, additional clinical trials are neither likely to better define the incidence of erosion, nor likely to better identify critical risk factors. The panel

recommended a case-cohort study design because they deemed identification of risk factors to be more important. This recommendation has merit only if the cases identified for study have high quality, comprehensive, and longitudinal clinical data and imaging available. It has been unfortunate that many of the case materials available for retrospective study to date have been incomplete and/or inadequate. It appears that study cases and further data may need to be identified and collected prospectively. A large sophisticated congenital heart disease registry such as NCDR IMPACT is one tool that may be suitable for this task.

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