The Society for Cardiovascular Angiography and Interventions

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The Society for Cardiovascular Angiography and Interventions (*SCAI)* provides this written statement to the U.S. Food and Drug Administration's (*FDA* or *The Agency*) Circulatory System Devices Panel (*The Panel*) regarding the available published safety and effectiveness data for transcatheter Atrial Septal Defect (*ASD*) occluders.

SCAI is the leader in science, education, and advocacy for interventional cardiologists and their patients. SCAI represents over 4,000 invasive and interventional cardiologists and their patients. SCAI promotes excellence in invasive and interventional cardiology through physician education and representation, and through quality initiatives to enhance patient care.

SCAI is committed to providing the best care possible for patients with intra-cardiac defects. We applaud and share the Agency's efforts to ensure the safety and well-being of patients with intra-cardiac defects who are treated with these medical devices.

- While no implanted medical device is 100% safe, SCAI's position is that ASD occluders are safe and effective and both are a vital treatment option.
- As new data will likely be presented at *The Panel* meeting, SCAI will provide an update in a subsequent comment letter.

Background

Pediatric Interventional cardiologists have been at the forefront of treating patients with intra-cardiac defects. The first device closure of secundum ASD dates back to the mid 1970's when Terry D. King, MD, a pediatric cardiologist, partnered with Noel Mills, MD, a cardiac surgeon, at the Ochsner Clinic to perform the first transcatheter closure of an ASD, in a 17 year old female patient.

In 2001, the Agency approved the *Amplatzer Septal Occluder (ASO)* for treatment of secundum ASD and Fontan fenestration with closure rates comparable to those obtained by open-heart surgery. The U.S. study that led to the approval of the device compared open-heart surgery to device closure. That study provided data demonstrating that device closure was as successful as open-heart surgery in closing the defect. However, the two major differences between device closure and surgical closure were the rate of adverse events and the length of hospital stay. Device closure had 7.7% incidence of adverse events (major and minor) compared with 24% incidence for the surgical arm. The length of hospital stay was 1.3 days for the device arm compared to 3.2 days for the surgical arm (1).

Further, in 2006, the FDA approved a second device, the *Gore Helex device (Helex)*. Similar to the *ASO*, a trial was conducted to compare device closure to surgical closure (2) with 119 cases receiving the *Helex* and 128 undergoing surgical repair. Closure success, defined as complete closure or a clinically insignificant residual shunt, was similar in both groups. Major and minor adverse events rates were not statistically different. The most common major adverse events for the

device group was device embolization requiring catheter retrieval (1.7%), and in the surgery group was post-pericardiotomy syndrome (6.3%), including one death due to tamponade. The primary end point, clinical success (a composite of closure success and no major adverse events at 12 months), satisfied the non-inferiority hypothesis comparing device closure with surgery.

Safety and Efficacy

SCAI acknowledges and shares the concerns raised by the surgical community and the FDA about complications related to the use of these devices (i.e., device erosions, embolization and frame fracture). While there are complications associated with the use of any implanted device, our goal is to demonstrate to *The Panel* that device closure using these devices is indeed safe and remains excellent, recognizing that the alternative is open heart surgery for ASD repair with implantation of a patch.

SCAI believes that approval and use of any interventional therapy should meet the following criteria:

1. ***Established safety & efficacy*** of the interventional method.
2. ***Equivalent outcome comparison*** between the common methods used to treat an ASD (i.e., open-heart surgery vs. device closure).
3. ***Favorable long-term outcome*** using the interventional method (i.e., device closure).

Safety and efficacy of device closure: The two pivotal trials in the United States (1, 2) have proved that device closure using the *ASO* or the *Helex* device were indeed as safe and effective as surgical closure of ASD.

For the *ASO* study: This study had 423 patients treated with 433 devices. A total of 154 patients underwent surgical closure in nationally-recognized children's hospitals in the U.S. The safety and effectiveness of the entire cohort of patients:

Technical Success – Successful deployment of the device, or the successful completion of the surgical procedure

Table 5. Principal Effectiveness and Safety Results – Pivotal Study

	AMPLATZER Patients[a]	Surgical Control Patients	90% Confidence Interval
Technical success	423/442 (95.7%)	154/154 (100%)	(-0.084, -0.010)
Procedure success	413/423 (97.6%)	154/154 (100%)	(-0.059, +0.008)
Early (≤ 30 days) composite success	401/442 (90.7%)	148/154 (96.1%)	(-0.096, +0.019)
12-month composite success	331/362 (91.4%)	146/154 (94.8%)	(-0.153, -0.033)
24-hour closure success	404/418 (96.7%)	154/154 (100%)	(-0.073, -0.001)
6-month closure success	376/387 (97.2%)	154/154 (100%)	(-0.068, +0.003)
12-month closure	326/331 (98.5%)	149/149 (100%)	(-0.052, 0.017) [Presumably, second value should be +]
Principal Safety Measures			
Major adverse events 12 months	7/442 (1.6%)	8/154 (5.2%)	(-0.090, -0.002)
Minor adverse events 12 months	27/442 (6.1%)	29/154 (18.8%)	(-0.200, -0.070)
12-month composite success (K-M)	0.934	0.938	[-0.044, +0.036]
Survival at 30 days (K-M)	0.939	0.956	[-0.052, +0.036]
Survival at 180 days (K-M)	0.936	0.947	[-0.048, +0.026]

Further, for patients less than 20 years of age, the safety and effectiveness data are shown below.

Table 6. Principal Effectiveness and Safety Results – Patient Age Less Than 20 Years

	AMPLATZER Patients	Surgical Control Patients	90% Confidence Interval
Technical success	315/328 (96.0%)	149/149 (100%)	(-0.086, -0.005)
Procedure success	306/315 (97.1%)	149/149 (100%)	(0.074, +0.005)
Early (≤ 30 days) composite success	295/328 (89.9%%)	143/149 (95.9%)	(-0.124, -0.007)
12-month composite success	256/281 (91.1%)	142/149 (95.3%)	(-0.108, +0.013)
24-hour closure success	301/310 (97.1%)	149/149 (100%)	(-0.075, +0.005)
6-month closure success	270/278 (97.1%)	149/149 (100%)	(-0.077, +0.006)
12-month closure	246/251 (98.0%)	149/149 (100%)	(-0.068, +0.014)
Principal Safety Measures			
Major adverse events 12 months	6/328 (1.8%)	7/149 (4.7%)	(-0.086, +0.008)
Minor adverse events 12 months	16/328 (4.9%)	29/149 (19.5%)	(-0.221, -0.085)
12-month composite success (K-M)	0.930	0.944	[-0.055, +0.027]
Survival at 30 days (K-M)	0.933	0.954	[-0.059, +0.017]
Survival at 180 days (K-M)	0.930	0.954	[-0.062, +0.014]

For the *Helex* device, the data are presented below and shows no significant difference between device closure and surgery for ASD.

Table 4 Number of Subjects by Category of Major Adverse Events, Successful Device Delivery, or Surgical Closure Events Reported Through 12-Month Follow-up

	Device Non-Training	Surgical Controls	p Value*
Subjects evaluable for safety	119	128	
Subjects with 1 or more major adverse events	7 (5.9%)	14 (10.9%)	0.176
Cardiac	2 (1.7%)	10 (7.8%)	0.036
Bleeding (treatment required)	-†	1 (0.8%)	1.000
Embolization (post-procedure)	2 (1.7%)	Na‡	
Pulmonary edema	-	1 (0.8%)	1.000
Post-pericardiotomy syndrome	Na	8 (6.3%)	
Integument	1 (0.8%)	-	0.482
Allergic reaction	1 (0.8%)	-	0.482
Neurologic	2 (1.7%)	-	0.231
Migraine (new)	2 (1.7%)	-	0.231
Paresthesia	1 (0.8%)	-	0.482
Pulmonary (respiratory)	-	1 (0.8%)	1.000
Stridor	-	1 (0.8%)	1.000
Vascular	1 (0.8%)	1 (0.8%)	1.000
Hemorrhage (treatment or intervention required)	1 (0.8%)	1 (0.8%)	1.000
Wound	-	2 (1.6%)	0.499
Hernia	-	1 (0.8%)	1.000
Scarring or scar related	-	1 (0.8%)	1.000
Device (HELEX septal occluder)	3 (2.5%)	Na	
Allergic reaction	1 (0.8%)	Na	
Device size inappropriate	2 (1.7%)	Na	
Other	-	1 (0.8%)	1.000
Anemia	-	1 (0.8%)	1.000

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Table 6 Clinical Success End Point

	Device Non-Training	Surgical Controls	Difference (90% CI)*	p Value†
Evaluable subjects with successful delivery/surgical closure	117	124		
Clinical success end point				
Subjects evaluated	109	86		
Clinical success	100 (91.7%)	72 (83.7%)	−8.0% (−15.9%, −0.2%)	<0.001
Clinical failure	9 (8.3%)	14 (16.3%)		
Major device/procedure adverse event‡	7 (6.4%)	14 (16.3%)		
Significant leak on final core lab evaluation	2 (1.8%)	0 (0.0%)		
Subjects not evaluated	8	38		
Lost to follow-up prior to evaluation	2	18		
Final defect evaluation missing	6	20		

For the safety data: Major adverse events at 12 months for the device group were 1.6% compared to 5.2% for the surgical group (90% CI -0.090, -0.002). Minor adverse events at 12 months for the device group was 6.1% and for the surgery group were 18.8% (90% CI -0.200, -0.070). Further, when we analyze the data by age (those less than 20 years of age), similar findings are obtained.

For *Helex* device study: Similar data were reproduced and provided below:

Table 3 Procedure Summary

	Device Non-Training	Surgical Controls	p Values*
Delivery attempted/surgery	135	128	
Defect size by direct balloon sizing (mm)			
N	133	NA	
Mean (SD)	14 (4)		
Median	14		
Range	(5, 24)		
Total time under fluoroscopy (min)			
N	134	NA	
Mean (SD)	28 (21)		
Median	22		
Range	(6, 148)		
Total time under anesthesia (min)			<0.001
N	133	128	
Mean (SD)	168 (63)	205 (43)	
Median	160	202	
Range	(55, 360)	(30, 330)	
Days in hospital for procedure			<0.001
N	135	128	
Median	1	3	
Range	(0, 4)	(1, 9)	

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Lost to follow-up prior to evaluation	2	18		
Final defect evaluation missing	6	20		

Based on these data, SCAI believes there is clinical evidence that both of these device closure technologies (*ASO* and *Helix*) are as safe and effective as surgical closure of ASD.

Numerous papers have been published from centers around the U.S. and the world about the results of specific centers' device closure of ASD. These papers documented safe and effective closure of the ASD using the *ASO* and the *Helex* device (3-11)

Outcome comparison with open-heart surgery: There are very few published papers comparing open-heart surgery with device closure, one paper from a reputable center in Berlin, Germany (12) is cited.

In the U.S, the Society for Thoracic Surgery (STS) Registry collects observational data from many U.S. centers and provides some insight on treatment options. In a paper published in 2011, Mascio CE et. al. (13) examined surgical outcome for congenital heart disease, including isolated ASD closure performed by congenital heart surgeons. Although the mortality in that cohort was zero, the morbidity was significant. From 2000-2009, 365 patients underwent surgical repair of an ASD where 20% of the patients had complications, including arrhythmias in 7.7%, pleural effusions in 1.6%, pneumonia in 3.3%, mechanical ventilation for more than 7 days in 0.6% and bleeding requiring reoperation in 0.6%. These authors also examined ASD closure by non-congenital cardiac surgeons (adult cardiac surgeons) and found in-hospital mortality of 2.1% for isolated ASD and 5% if combined with another procedure. SCAI believes there is clinical evidence that the rates of mortality for ASD closure by non-congenital cardiac surgeons far exceed any mortality reported for device closure of ASD.

Long-term outcome: **SCAI looks forward to the publication of a current post-market surveillance study**. This post-market surveillance study on the ASO has enrolled 1000 patients and is nearing completion. These data are expected to be available very soon and will shed light on long-term outcomes of patients who underwent ASD closure with the ASO.

While anecdotal, the longest data currently available comes from the first few patients performed in 1975 by Dr. King who has reported on his 30+ year outcomes. Of the five patients treated, all did well long-term and all are still living except for an 84 year old who died of Hodgkin's disease. All patients are over 50 years of age and two have had atrial fibrillation.

Another paper from Pakistan (15) looked at medium term outcomes from device closure using the ASO. Between the years 1999 and 2009, 205 patients underwent closure of their defect. These authors reported 98% success rate of closure of the defect with no mortality, no thromboembolic events, and no cases of device erosion. Atrial fibrillation occurred in 1.5% of the patients.

SCAI believes that the current incidence of clot formation and thromboembolic episodes are both rare events for these two devices. A paper by Krumsdorf et. al. (16) reported on 1000 patients who had their defect (ASD or PFO) closed with a several devices, including the *ASO* and *Helex*, and found that the *ASO* and the *Helex* device had the lowest incidence for clot formation when used in patients with ASD (0% and 0.8% respectively). **SCAI believes that post implant device thrombus formation remains a concern; therefore, treating all patients with current regimens of antiplatelet therapy (aspirin and aspirin/clopidogrel) for 6 to 12 month period is prudent to minimize the chance of clot formation.**

Finally, a recent paper by Kutty S et al (17) evaluated long-term outcome of ASD closure. Pre-evaluation of all patients for any clotting disorder may be of benefit to rule in-or-out those patients at higher risk of clot formation. Isolated case reports documented the two treatment modalities (device and surgery). The authors concluded that this treatment strategy has excellent outcomes with no significant differences were found between device and surgical closure with regard to survival, functional capacity, atrial arrhythmias, or embolic neurologic events.

Frame fracture: Regarding the issue of frame fracture, to our knowledge, fracture of the *ASO* device frame has not been reported. However, for the *Helex* device, a fracture rate of about 0- 5.5% without clinical sequelae (2, 18) has been reported.

Clinical Topics before *The Panel*

SCAI appreciates the opportunity to provide comments. As new data will likely be presented at *The Panel* meeting, SCAI will provide an update in a subsequent comment letter.

1. Clinical significance of the adverse events experienced with ASD closure devices given the overall context of disease and alternative treatment options - specific categories of events are planned to be discussed, (e.g., erosion, embolization, fracture, etc.)

To date, the adverse event profile reported varies between devices. One paper by Chessa M, et. al. (19) examined the need for surgical repair due to device malposition, embolization, or erosion. Minor complications have included unsatisfactory device position or embolization where device retrieval was needed. Other adverse events, although minor, included pericardial effusion, thrombus formation on the left atrial disc, right iliac vein dissection, groin hematoma, hemorrhage in the retropharynx, and sizing balloon rupture. All such events were self-limiting and within the spectrum of adverse events when primary surgical therapies were applied.

A recent meta-analysis by Butera G et. al. (20) reviewed all reports containing more than 20 patients that compared the two methods of closure (percutaneous and surgical) published through 2008 that assessed primary endpoints including death and major early complications. Thirteen original non-randomized studies (3,082 patients) met inclusion criteria. One death was reported in the surgical group (0.08%; 95% C.I. 0-0.23%). Analysis of post-procedural complications showed a 31% rate (95% CI 21-41%) in surgical patients and a 6.6% rate (95% CI 3.9-9.2%) in those treated percutaneously. The adjusted OR for surgery *vs.* catheter-based closure for total complications was 5.4 (95% CI 2.96-9.84; $p<0.0001$), significantly in favor of percutaneous closure. The post-procedural major complication rate was 6.8% (95% CI 4-9.5%) in surgery patients and 1.9% (95% CI 0.9-2.9%) in the catheter-based closure population patients. The adjusted OR for surgery *vs.* catheter for major complications was 3.81 (95% CI 2.7-5.36; $p=0.006$), again favoring percutaneous closure.

SCAI believes device closure using these devices is indeed safe and remains excellent, recognizing that the alternative is open heart surgery for ASD repair with implantation of a patch.

2. Context of events regarding whether new safety concerns should be further addressed and to what extent these concerns apply to the class of devices or a specific device

No device or procedure (surgery) is 100% safe and as such, safety issues in application of devices or procedures are always of concern, regardless of how successful or long the physician's clinical experience. Transcatheter closure of atrial defects has been applied clinically for over 30 years. The largest experience is with the *ASO* (St. Jude Medical), due to its applications in defects up to 40 mm in diameter, its ease of use, and well-established safety profile. The most significant adverse event (potentially life threatening) is device erosion. The true incidence of this event is not known. Only one paper has provided an estimate, which is no higher than 0.1% (21). Leading clinicians believe this estimate is likely to be an over-estimate (refer to number 4 below for reasons). More importantly, morphological characteristics that increase the risk for such events are not fully characterized, and no recommendations as to high-risk *vs*. no low-risk morphologies can be made at this time due to the rarity of the event. The complexity of this evaluation was highlighted recently in a paper by Bell-Cheddar and Amin (22).

SCAI cannot provide any additional comment. To address the true incidence of this event, and make recommendations as to long-term safety, a long-term prospective post-market study is required, which the device manufacturer has done. Good scientific data from that study should be

available very soon. SCAI requests access to all new data and will provide additional recommendations in a subsequent comment letter.

3. Whether there are any patient characteristics that portend a higher risk of a significant event

The vast majority of secundum type atrial septal defects (>80%), have some degree of deficiency or absence of the so-called retro aortic (anterior-superior) rim. As such, device placement (as applies to the *ASO*) often requires that the implant 'straddles' the roof of the atrium astride the supra-aortic valve portion of the ascending aorta. The experience with the CardioSEAL™ double umbrella disc trials in the late 1980's highlights that this is necessary for closure where residual shunts occurred in this region due to prolapse of the implant arms (23). Devices have been implanted effectively in patients with deficiencies of various components of the septal rim; however, large confluent defects with little or no rim throughout the circumference of the defect have failed device closure. Unknown are the extent and location of rim deficiency that would result in an unsecure placement and whether this contributes to erosion risk. This remains to be seen. So, all of the theories behind mechanisms of erosion remain theoretical with nothing proven to-date. **SCAI advocates "caution" when closing defects with deficiency of such rims, but certainly, there are no data or basis to contra indicate device closure in such patients.**

4. Specific discussion of erosion with respect to root cause and corrective actions

There is no single 'root cause' of erosion. It is multifactorial and likely involves not only the extent of rim deficiency, but also patient characteristics, defect shape, and device size (as applies to the *ASO* device). Some reported erosion events were not associated with a deficient aortic rim, and some classified erosions were due to poor catheter technique and atrial wall trauma during the procedure (personal communications Lee Benson, MD, FSCAI). If an absent aortic rim were the only cause for erosion, and 80% of defects had some degree of rim absence, with 30,000 implants (as of 2004, see reference 20 - an incidence of 0.1%), at least 300 erosions should have been reported by that time. Clearly, no registry from any monitoring body has accumulated this number of events. Thus, there must be a number of modifying circumstances including defect morphology that influence this occurrence, confirming it is multi-factorial with a relatively rare probability of development. **Therefore, SCAI believes that 'corrective action' for events that are rare and influenced by many other factors, cannot be supported, until the true incidence of these events are determined.**

The FDA MAUDE reports often provide information to the FDA which can affect decision-making policy. In May 2011, the FDA requested all reports of pericardial effusion be reported after ASO closure. A sample review of MAUDE reports from 2011 and 2012 noted approximately 50 reports of significant adverse events after ASO closure. All occurred in 2011-12, except 4 that occurred in 1998, 2006, 2007 and 2008, all of which were adjudicated as erosions. In all, there were 6 erosions; but, in two of these, the device was left in place with limited management. Only one erosion from 2006 was unexplained based on the data presented. There were 2 unexplained pericardial effusions. The vast majority of the remaining MAUDE reports noted device embolizations primarily related to operator error, deficient inferior rims, or efforts to undersize the device to avoid erosion.

This limited sample of 2011-12 MAUDE reports suggest:

1. That erosions are extremely rare when operator error and frank device oversizing are excluded. (Only one erosion from 2006 was unexplained).

2. That operator technical errors and inexperience are frequently the cause of most ASO adverse events.

3. There are more device embolizations and retrieval surgery reported which occur primarily to avoid potential liability by under-sizing the device.

5. Assessment of adequacy of current responses to events given current experience (e.g., labeling changes) and whether there is a need for any additional corrective actions such as:

- ***Changes to follow-up recommendations (e.g., times, modality)***

  Patients should never be 'discharged' from follow-up; but, after 3 years, patients may be seen every 5 years with an echocardiogram looking for any new pericardial effusion.

- ***Additional analyses from data already collected (or being collected under post-approval studies)***

  SCAI looks forward to the current post-market study and the new data to be published. Analyzing these patients' outcomes will be of paramount importance before we make any recommendations for any changes to the instructions for use manual. Therefore, SCAI cannot offer comment at this time.

- ***Additional prospective data collection/monitoring (e.g., 522 study).***

  Beyond the post-market surveillance study, SCAI cannot provide recommendations for additional studies until access to the data is provided.

- ***Specific communication to patients and/or physicians***

  All known complications are discussed by the implanting cardiologist to patients undergoing an invasive procedure. At present, there is no information to stratify implanted patients to determine risk. Additional efforts may be necessary to insure adequate physician training has been achieved to avoid technical operator errors and inexperience in directing and managing ASO closure.

6. Finally, additional secondary topics may be discussed such as:

- ***Concerns regarding future treatments in patients with device closure (e.g., atrial fibrillation***).

  Again, all risks associated with device closure including the very small risk of development of atrial fibrillation should be discussed with the family. This is true with surgical closure as well.

- ***What if/any information from experience gathered thus far may be used to inform new ASD device models and occlusion for other indications (e.g., PFO).***

  From what we have gathered so far, there have been some cases of complications encountered using devices outside their intended approval "off label use", again, caution should be exercised and these risks disseminated to clinicians.

Conclusions

The FDA has the critical role of facilitating innovation in the development of medical devices while simultaneously protecting the public. The continued study after introduction occurs to ensure there are no unintended consequences or results that were not identified during the pre-market study. We appreciate the opportunity to discuss any new findings.

SCAI recommends that patients with secundum ASD continue to have access to these treatment options. While no implanted medical device is 100% safe, SCAI believes that these device closure technologies are safe and effective, with low complication rates. The data for transcatheter device closure compares very favorably to data for surgical closure for ASD's suitable for device closure. SCAI believes patients benefit from this technology and with appropriate selection of patients and adequate operator skills, complication rates will remain very low. SCAI believes the data collected are sufficient and caution should be exercised when closing defects with deficient rims. SCAI believes physicians should

not be excluding patients with deficient anterior/superior rims since they comprise the majority of the cases and there are compelling data in this sub-group of patients that device closure success rates remain very high and risk of erosion remains extremely low (0.1%).

Thank you for accepting our written statement and for considering our comments. Please contact Joel C. Harder, MBA, Director of Clinical Documents and Quality Initiatives at jharder@scai.org or 202-552-0910 for questions.

Sincerely,

Christopher J. White, M.D., FSCAI
President

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