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Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience Database for Adverse Events involving Amplatzer Septal Occluder Devices and Comparison with the Society of Thoracic Surgery Congenital Cardiac Surgery Database

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Abstract

Objective—Amplatzer (AGA Medical Corporation, Plymouth, Minn) septal and vascular occluder devices have significantly altered the care of patients with congenital heart disease. The relative frequency and consequence of complications resulting from the attempted placement of such devices, however, have not been well assessed. The purpose of this study is to use large databases to assess the frequency and severity of such complications and compare them with those of surgical atrial septal defect closure.

Methods—The US Food and Drug Administration Manufacturer and User Facility Device Experience database was quarried for all adverse events for Amplatzer septal occluder devices, which were categorized and analyzed with particular emphasis on management and outcome. The Society of Thoracic Surgery database was likewise quarried for the same data regarding atrial septal defect closures over a contemporaneous time period. By using a literature-derived denominator for total Amplatzer implant numbers, the results of the 2 therapies were compared.

Results—Since July 1, 2002, 223 adverse events in patients undergoing Amplatzer atrial septal defect closure were submitted to the Food and Drug Administration, resulting in 17 deaths (7.6%) and 152 surgical rescue operations (68.2%). Society of Thoracic Surgery data demonstrated 1537 primary operations with 2 deaths (0.13%) and 6 reoperations (0.39%). By extrapolating on published estimates of Amplatzer implantation to provide an implant denominator (n = 18,333), there was no difference between overall mortality for surgical (0.13%) and device closure (0.093%, $P = .649$). Rescue operation for device adverse events (0.83%) was 2.1 times more likely than reoperation for surgical closure (0.39%, $P = .063$). Mortality per adverse event was higher for device closure (7.6%) than for surgical closure (1.2%, $P = .004$), and the need for surgery per

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adverse event was higher for device closure (68.2%) than for surgical closure (3.6%, $P < .001$). The mortality for surgical management of a device adverse event (2.6%) was 20-fold higher than for primary elective atrial septal defect closure (0.13%, $P < .0001$).

Conclusion—Overall crude mortality for device and surgical closure atrial septal defect closure is equivalent, and the need for subsequent operation (surgical rescue) is more common in patients undergoing device closure than reoperation is in patients undergoing surgical closure. Complications from device closure tend to be serious and most often require urgent or emergency operative management, whereas the mortality for surgical management of a device complication appears higher than that of elective atrial septal defect closure. Further information is required in the form of postmarketing surveillance, such as a mandatory user registry with periodic end-user notification.

Amplatzer septal and vascular occluder devices (Amplatzer, AGA Medical Corporation, Plymouth, Minn) have significantly altered the care of patients with congenital heart disease and are becoming standard care in many institutions. The relative frequency, consequence, and cost of complications resulting from the attempted placement of the Amplatzer occluder devices, however, have not been well assessed. The overall mortality and need for surgical intervention are unknown. In addition, periprocedural adverse events (AEs) for catheter therapies often mandate operative intervention such that an analysis of the patterns of such failures are germane to the cardiac surgeon and essential to the cardiologist providing informed consent to patients and families. To generate such data, an analysis was undertaken of the US Food and Drug Administration (USFDA) on-line database for device-related AEs, and a denominator of device implants was estimated from published literature. AEs involving surgical atrial septal defect (ASD) and patent foramen ovale (PFO) closure were likewise obtained from the Society of Thoracic Surgery (STS) Congenital Cardiac Surgery Database, such that a comparative analysis could be performed.

Materials and Methods

The Manufacturer and User Facility Device Experience (MAUDE) database was accessed via the USFDA main Web page.[1] A query was performed using the brand name “Amplatzer” to select for AEs involving all Amplatzer devices, and only the results for ASD and PFO closures were included in this analysis. The first such reported AE was received by the USFDA on January 24, 2002, and the search was arbitrarily concluded on June 30, 2007, for a total of a 5.5-year collection period. Events were broadly classified into categories (Table 1). If multiple AEs occurred within a single patient narrative, the event that dominated the clinical presentation and course of the patient was used for classification purposes. Device “embolization” was defined by the movement of a device to a location other than the atrial septum, differentiating it from device “malposition,” an unacceptable position within the atrial septum. Cardiac perforation/erosion/rupture (PER) was defined as any narrative where perforation, device erosion, or rupture of a cardiac structure occurred or was thought to have occurred. This is differentiated from the category of “pericardial effusion,” which would be a serous effusion or one in which a perforation or erosion was not suspected. Infection refers to cases in which the device was thought to be the infectious

source, and the thromboembolitic event category included all stroke, transient ischemic attack, and device thrombus events.

All data regarding the manner in which complications were addressed (catheter intervention, operative management, or both) and the final outcome (mortality) were included in the analysis when sufficient information was provided in the reported narrative. Any patient with death as the outcome of the AE was listed as a device mortality, whereas all patients undergoing operation in the management of the AE were counted as "surgical rescue." To calculate the relative frequency of events, a request was made to AGA Medical for estimates of implants over the study period. This request was subsequently denied via electronic mail correspondence. Thus, a previously published device estimate calculation was used to generate a denominator and allow comparison with STS data.

The STS Congenital Cardiac Surgery Database was likewise quarried for the results of surgical closure of defects at the atrial septum during a similar time frame (beginning January of 2002 with data available through December 2006). Patients with primary closure of PFO, primary ASD closure, and patch closure of ASD as the primary qualifying index operation were included in the analysis, whereas patients with other defects addressed at the time of the index operation were excluded secondary to complexity mismatch with device closure candidates. Outcomes were requested and obtained for discharge mortality, postoperative length of stay, and a complete list of any and all complications. From the complication tally, any patient undergoing an unplanned reoperation of any kind was counted in the "surgical reoperation" group. The overall mortality rate of surgical versus device closure was compared, as was the need for surgical rescue compared with surgical reoperation. The rate of death per AE and need for operation per AE were also compared for device versus surgical closure.

Because the MAUDE database narratives are widely and freely available to the public on the World Wide Web and no patient identification variables are included, there was no requirement for institutional review board permission. Likewise, no such institutional permission is needed for the use of STS data; permission was requested and granted from the STS database committee. All data were coded using an Excel spreadsheet (Microsoft Corp, Redmond, WA), and all percentages all reported with the accompanying raw numeric data in the form of a fraction. Inferential statistics were performed as 2-tailed chi-square analysis[2] for categoric data.

Results

Manufacturer and User Facility Device Experience Database Adverse Events: Embolization and Perforation/Erosion/Rupture

AE reports totaling 274 involving any type of Amplatzer device were received over a 5.5-year period; closure of the atrial septum was involved in 232 reports (84.7%) (Figure 1). Reliable morphologic data on the location within the atrial septum was unavailable, and specific patient demographics and identifiers such as age, weight, body surface area were likewise not found in the online reports. The specific Amplatzer system elements identified as the failing component in the 232 AE narratives are listed in Table 2. Careful review of

each independent event narrative revealed that multiple entries were sometimes found when multiple devices were used for the same patient. Controlling for these duplications resulted in 223 individual patients having AEs.

Death is listed as the outcome for 17 of 223 patients (7.6% mortality per AE, Table 3). Cardiac PER was the most frequent AE type resulting in mortality (10/17, 58.8%). One woman who survived perforation lost her pregnancy, although this was not counted as mortality. To provide a denominator for analysis, we relied on a published precedent for implant estimate calculation used by Delaney and colleagues,[3] which was derived from published estimates by a panel of physicians who were previously chosen by AGA Medical to perform complication analysis and who appear to be financially linked to the company.[4] According to these data, approximately 10,000 implants are estimated over a 3-year period from 2002 to 2004. Extrapolation of this rate over a 5.5-year period starting in 2002 gives 18,333 implants and an overall mortality of 17 of 18.333 (0.093%).

Embolization of Amplatzer occluder devices was the most prevalent AE (114/223 patients, 51.1%), giving a national embolization rate of 114 of 18,333 (0.62%). A 2004 survey of AGA proctors determined the rate of embolization to be 21 of 3824 implants (0.55%), not significantly different from our data ($P = .599$).[5] There were 2 deaths, giving a mortality rate per embolization of 1.8%. Table 4 lists the sites and relative frequencies of embolization, demonstrating the most frequent embolization to the left side of the heart. In 12 of the 114 cases (10.5%), a secondary arrhythmia occurred with embolization and was often the “warning sign” of an AE, triggering further workup (Table 5). Eighty-eight patients with embolization (77.2%) required operation, whereas successful transcatheter management was possible in 19 patients (16.7%). Management is not known for 5 patients (4.4%), and no action was taken in 2 patients (1.8%).

Cardiac PER was the second most commonly reported AE (51/223, 22.9%). Mortality for this complication was 10 of 51 patients (19.6%), with 1 survivor losing her pregnancy and at least 2 survivors described as having serious neurologic morbidity. By similarly applying the previous estimates, the national PER rate is 51 of 18,333 (0.28%). A 2004 publication by investigators affiliated with AGA Medical determined the PER rate to be 9 in the known 9000 US implants, giving a rate of 0.1%, which is significantly lower than in our findings ($P = .0003$).[4] Timing of the AE is listed in Table 6; only 4 events occurred at implant, and whereas most were clustered in the first 6 months, erosions and ruptures are still being reported as late as 3 years after deployment. Table 7 lists the confirmed or suspected locations of cardiac PER; a location is specified in 40 patients and not specified in 11 patients.

Some combination of atrium and aorta was found in 18 patients (35.3%, 18/51), whereas the atria alone were involved in 13 patients (25.5%, 13/51). Both cases involving the ascending aorta and 2 of the 3 left atrial appendage perforations were confirmed at surgery or autopsy. The other left atrial appendage perforation was suspected by the implanting physician after frank hemopericardium occurred within “a few hours” of the procedure. One patient died 4 hours after implant and was found to have a 1.5-mm right upper pulmonary vein perforation at autopsy. A device erosion through the atrial septum resulted in a new ASD that was

confirmed at catheterization and successfully treated with a new device. Hemoptysis secondary to what the implanting physician thought to be a pulmonary vein perforation developed in 1 patient; the procedure was immediately aborted, and this was successfully managed nonoperatively. Likewise, an implanting physician suspected perforation of the "left atrium or pulmonary vein" on review of a case of frank hemopericardium occurring 2.5 hours after the implant; the drainage slowed down, and successful nonoperative management was used.

In the 11 cases of PER where the location is not specified, 3 cases were confirmed by successful surgical exploration, but the location is unlisted in the narrative. An additional 4 cases were described as sudden grossly bloody pericardial effusions, but the location is unknown because each was successfully treated nonoperatively by pericardial drainage. The timing of 3 of these presentations was within 1 hour (n = 1) and within 24 hours (n = 2) such that these were most consistent with PER; in the fourth case, presenting at 1 month postimplant, erosion was suspected such that "surgery was scheduled," but no follow-up details of the operation are given. In 3 cases the location was unknown because each was a death and limited autopsy data are given describing bloody fluid in the pericardium and left side of the chest, making PER the most likely event. In the last unknown case, an infant underwent cardiopulmonary resuscitation several weeks after a device implant and was then found to have a large effusion. It is unclear whether erosion occurred first, mandating cardiopulmonary resuscitation, or erosion occurred during the chest compressions and final outcome is not given.

Surgical Outcome and Comparison Between Databases

According to MAUDE narratives, 112 patients appear to have been sent directly to the operating room (112/223, 50%), resulting in 2 operative deaths. Forty additional patients (40/223, 17.9%) were sent to the operating room after failed catheter intervention to control the AE, resulting in 2 additional operative deaths. Summation gives 152 of 223 Amplatzer AEs (68.2%), ultimately requiring operative management and an overall operative mortality for surgical rescue of 2.6% (4/152).

STS data revealed that surgical closure of ASD and PFO was performed in 1537 patients; primary closure was performed in 457 patients (35 PFO and 422 ASD); and patch ASD closure was performed in 1080 patients. Discharge mortality was 2 patients (0.13%), and median length of stay was 3.0 days (quartiles 2 and 4 days). *Any* complication as defined on the STS data harvest worksheets occurred in 167 of 1537 patients (10.9%). Serious complications, however, were rare; no patient required a pacemaker (no permanent arrhythmia) or any form of dialysis (temporary or permanent), 2 patients had a persistent neurologic finding at discharge (0.13%), 3 patients had postoperative cardiac arrest (0.20%), and 6 patients required unplanned reoperation (0.39%). There were no cases of sternal dehiscence, mediastinitis, endocarditis, systemic or pulmonary venous obstruction, phrenic, or recurrent laryngeal nerve injury, and in no case was tracheostomy or mechanical support required.

A comparison of the benchmark events (operative mortality, need for surgery and operative mortality, or need for surgery *per* AE) for device and surgical closure was performed (Table 8). Overall mortality for surgical (0.13%) and device closure (0.093%) was similar ($P = .649$). Rescue operation for device closure (0.83%) was 2.1 times more likely than reoperation for surgical closure (0.39%), closely approaching statistical significance ($P = .063$). Mortality per AE was higher for device closure than surgical (7.6% vs 1.2%, $P = .004$). Likewise, the need for surgery to control an AE was higher for device closure (68.2% vs 3.6%, $P < .001$).

Discussion

The MAUDE is a USFDA-driven reporting mechanism, the purpose of which is to allow public access and review of AEs involving medical devices.[1] With the 1976 advent of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic act, the FDA was charged with ensuring the safety and efficacy of such devices.[6,7] Although premarket requirements are more stringent for class III (highest risk) devices, there are several relevant examples in cardiovascular medicine in which limitations of premarket analysis have been exposed. Two examples from cardiac surgery include the Bjork-Shiley tilting disk prosthesis (Shiley Inc, Irvine, Calif) and the use of St Jude Silzone (St Jude Medical Inc, St Paul, Minn) valve coating.[7] For these and many other reasons, postmarketing surveillance has become an important focus for the FDA. Voluntary reporting (focusing on the health care professional) has been encouraged in 1973 and was formalized under the “MedWatch program in 1993. Important steps were added in 1984, when Medical Device Reporting regulations enforced mandatory manufacturer reporting, and in 1990, when the Safe Medical Devices Act similarly charged user facilities with the same reporting responsibility. The MAUDE allows rapid access to these reports.

We acknowledge a priory the potentially serious limitations of this analysis and have taken this into consideration regarding the data we have chosen to report. Our experience with MAUDE has confirmed that the events reported are essentially all “sentinel events”; they are the most serious, life-threatening complications (of the device and related hardware) that generated enough concern and exposure that the physicians or user facilities thought that a report was necessary. *Procedural*-related complications such as access site problems (bleeding, infection, arteriovenous fistula), blood transfusion, contrast allergy, anesthesia, and airway problems and other commonly recognized catheter complications are not captured by such a database. Furthermore, data from the General Accounting Office report that less than 0.5% of all medical device AEs actually end up reported to the FDA, a serious source of potential error in using these data as a national estimate.[8] The STS database only includes approximately half of the congenital centers in the country and on a voluntary basis such that extrapolation of results to *all* centers provides a source of potential error. The STS database does not account for perception of pain and other end points that would certainly confirm clear advantages to some aspects of catheter procedures. Perhaps the most serious deficiency of the STS database, however, is that the data are not longitudinal.

It is for these reasons that we choose to analyze death and need for operation (surgical rescue vs surgical reoperation) as benchmark end points; both are definitive categoric (“yes

or no") outcomes of significant interest to clinicians and patients. We believe that the issue of requiring an operation to control an AE is of particular interest given our finding that the mortality rate of surgical rescue is 20-fold higher than for elective repair. Thus, the argument that "the patient is only getting the same operation they would have gotten anyway" does not apply to operations for device complications. Attempts to group certain possible complications from a procedure as "serious" or "potentially serious" are fraught with numerous pitfalls and problems such that the subject has itself become an independent science; it is well beyond the scope of this article to breech this topic, and so we make no such comparisons.

Results of the Manufacturer and User Facility Device Experience Database and Society of Thoracic Surgery

Comparing the embolization, PER, and thromboembolitic event rates from the MAUDE database with the published literature, we find that the current rate of embolization is the same as was found in a 2004 survey of AGA proctors,[5] whereas the PER rate is 3 times that reported in 2004 by AGA investigators.[4] Embolized devices often require operative intervention, and there is a risk of damage to cardiac structures with catheter removal. Comparison of thromboembolitic event rates with other publications reveals that it may be a bigger problem than is currently believed. Only 1 such complication was found in 3 major studies (including 2 specifically aimed at detecting thrombosis rates),[9, 10, 11] and a report in 2006 claims to be first to report stroke from an Amplatzer device.[12]

Comparison with other publications also confirms a lower published rate of death and serious complications than or findings indicate.[13, 14, 15, 16] From 2003 to 2006, 5 case reports of device erosion and perforation are found in the literature, and these seem to be accounted for in the MAUDE database.[17–21] Twice before, investigators have published results of the reported PER events from the MAUDE database,[3,22] and there continues to be debate over the cause of this complication. The findings of Divekar and colleagues[22] highlight that larger devices (>25 mm) do not seem to be overrepresented in the known events and that many patients with oversized devices do not experience perforation. We conclude that this seems to be a more frequently encountered complication with a high mortality but make no conclusions about cause.

Conclusions

The overall mortality for device and surgical closure of the atrial septum seems equivalent, and the need for subsequent operation (surgical rescue) may be more common in patients undergoing device closure than reoperation is in patients undergoing surgical closure. Complications from device closure tend to be serious and most often require urgent or emergency operative management, whereas the mortality for surgical management of a device complication appears higher than that of elective ASD closure. Further information is required in the form of postmarketing surveillance, such as a mandatory user registry with periodic end-user notification.

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Abbreviations and Acronyms

AE	adverse event
ASD	atrial septal defect
MAUDE	Manufacturer and User Facility Device Experience
PER	perforation/erosion/rupture
PFO	patent foramen ovale
STS	Society of Thoracic Surgery
USFDA	US Food and Drug Administration

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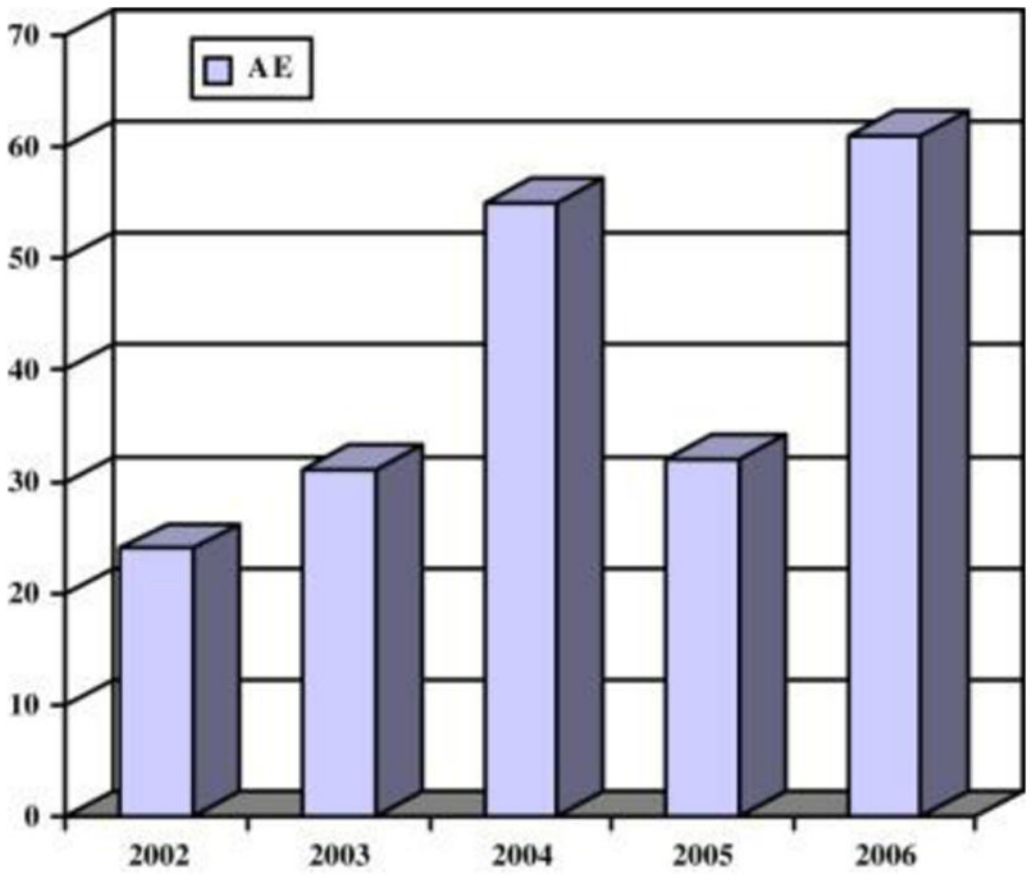

Figure 1.

Histogram demonstrating the number of AEs involving the Amplatzer (AGA Medical Corporation, Plymouth, MN) septal occluder reported to the USFDA between January 2002 and December 2006. *AE,* Adverse event.

Table 1

Major adverse event categories for patients reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Adverse event	No. of reported events	Percentage of reported events
Device embolization	114	51%
Cardiac PERs	51	23%
Thromboembolitic complication	11	5%
Residual/recurrent defect	9	4%
Device infection	5	2%

PER, Perforation/erosion/rupture.

Table 2

Failing component listed for adverse events reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Failing component	No. of reported events	Percentage of reported events
ASD occluder device	197	88.3%
PFO occluder device	16	7.2%
Delivery catheter	10	4.5%
Sizing balloon	6	2.7%
Guidewire	1	0.5%
Unknown	2	0.9%

ASD, Atrial septal defect; *PFO*, patent foramen ovale.

Table 3

Mortality among adverse events in 223 patients reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Number	Failing component catalog number	Adverse event type
1	9-ASD-022	Cardiac PER
2	9-ASD-000	Cardiac PER
3	9-ASD-020	Cardiac PER
4	9-ASD-026	Cardiac PER
5	9-ASD-026	Cardiac PER
6	9-ASD-019	Embolization
7	0-ASD-017	Thromboembolitic event
8	9-ASD-024	Embolization
9	9-ASD-022	Sudden death
10	9-PFO-HDE-025	Myocardial infarction
11	9-ASD-008	Respiratory failure
12	9-PFO-HAD-025	Cardiac PER
13	9-ASD-026	Cardiac PER
14	9-ASD-026	Cardiac PER
15	9-ASD-036	Cardiac PER
16	9-ASD-026	Cardiac PER
17	9-DEL-12F-45/80	Air embolization

PER, Perforation, erosion, rupture.

Table 4

Location of embolized devices among 114 patients reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Location	No. of reported events	Percentage of reported events
Right atrium	2	1.8%
Right ventricle	19	16.7%
Pulmonary artery	18	15.8%
Left atrium	28	24.6%
Left ventricle	12	10.5%
Aorta	21	18.4%
Unknown	14	12.3%

Table 5

Arrhythmia and device location among 114 patients with device embolization reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

No.	Rhythm disturbance (from narrative)	Device location
1	Nonsustained VT	Left ventricle
2	Atrial flutter	Unknown
3	“Significant ectopy”	Right ventricle
4	PVCs	Right ventricle
5	PVCs	Right ventricle
6	PVCs	Right ventricle
7	Atrial fibrillation, complete heart block	Pulmonary artery
8	“Transient arrhythmia”	Left atrium
9	Bradycardia (with hypotension)	Aorta
10	PVCs	Right ventricle
11	“Extreme rhythm changes”	Right ventricle
12	VT	Right ventricle

VT, Ventricular tachycardia; *PVC,* premature ventricular contraction.

Table 6

Timing of 51 cardiac perforations, erosions, or ruptures as reported to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Timing of event	No. of reported events	Percentage of reported events
During implant	4	7.8%
Within 24 h	16	31.4%
Within 1 mo	11	21.6%
1–6 mo	8	15.7%
6 mo to 1 y	2	3.9%
>1 y	3	5.9%
Unknown	7	13.7%

PER, Perforation, erosion, or rupture.

Table 7

Confirmed or suspected locations of 51 cardiac perforation, erosion, or rupture events, as indicated in the reports to the US Food and Drug Administration between January 1, 2002, and June 30, 2007

Timing	No. of reported events	Percentage of reported events
Atrium and aorta	18	35.3%
Left atrium	8	
Right atrium	5	
Unlisted atrium	5	
Atrium alone	13	25.5%
Left atrium	7	
Right atrium	2	
Unlisted atrium	3	
Both atria	1	
Unlisted	11	21.6%
Left atrial appendage	3	5.9%
Pulmonary vein	2	3.9%
Ascending aorta	2	3.9%
Atrial septum	1	2.0%
“Left atrium or pulmonary vein”	1	2.0%

Table 8

Comparison of overall mortality, need for operation to control adverse event mortality per adverse event, and need for operation per adverse event between device closure and surgical closure groups

Benchmark end point	Surgery	Device	*P* value
Overall mortality	0.13%	0.093%	.649
Need for operation	0.39%	0.83%	.063
Mortality per AE	1.2%	7.6%	.004
Operation per AE	3.6%	68.2%	<.001

AE, Adverse event. "Need for operation" is defined as *reoperation* for surgical group and *need for surgical rescue* for device group.