Statement of the American Heart Association to the
Food and Drug Administration
Circulatory System Devices Panel
May 24, 2012

Transcatheter Atrial Septal Defect Occluders

The American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million AHA and ASA volunteers and supporters, appreciates the opportunity to respond to the Food and Drug Administration's (FDA) request for public comment on the safety and effectiveness of transcatheter Atrial Septal Defect (ASD) occluders used for the closure of secundum atrial septal defects.

AHA supports the Agency's decision to examine the safety of these devices and determine if additional measures are needed to protect patients. Subsequent to their approval and widespread use, further data regarding complications related to these devices and the procedure has emerged, necessitating reevaluation of the safety of these devices.

Closure of ASD has evolved from a surgical procedure requiring anesthesia and cardiopulmonary bypass to percutaneous, catheter-based device insertion requiring usually only an overnight hospital stay. Many complications have been described with these procedures including, device malfunction, malposition, embolization, arrhythmias, thromboembolism, infection, vascular damage, pericardial effusion, and tamponade. These complications are infrequent, and the overall safety and effectiveness has compared favorably with surgical repair. Despite being labeled as a Class III device requiring control standards and a rigorous premarket approval process, it is not uncommon for complications that were unknown or under-estimated prior to general use, to be discovered post-approval. These post-approval safety concerns are generally related to special features of pre-approval studies including:

a. Relatively small and carefully selected patient population and anatomic variants studied
b. Protocol based close and generally shorter follow-up
c. Operator training and experience

Pre-approval study characteristics, rate of use, and training of physicians may vary considerably from clinical practice post-approval. Thus, post-marketing surveillance represents an essential component to evaluation of these devices, and in this respect, AHA applauds the Agency's vigilance and decision to reassess these ASD closure devices.

These concerns are relevant and important. However, as the Agency points out, they have to be balanced with the risk of untreated ASD and those associated with surgical repair. ASDs are not uncommon and account for 6% to 10% of all congenital lesions. The most common type of ASD is the secundum ASD that is characterized by incomplete closure of the atrial septum during cardiac development, representing 80% of all ASDs. This causes shunting of blood from the left to the right side of the heart and may lead to right heart volume overload, and ultimately development of heart failure and arrhythmias.

ASD closure is safe and beneficial if performed by an appropriately trained operator in individuals with a clear indication in whom withholding intervention is associated with a high likelihood of developing pulmonary hypertension. In this case, medical treatment alone is not appropriate and there is no debate with regards to appropriateness of closure. Both device and surgical closure have low risks and comparable cost. A recently published meta-analysis compared the two methods of closure for occurrence of death and major complications.[1] Thirteen original non-randomized studies including 3,082 patients were reviewed. Only one death was reported in the surgical group. Analysis of post-procedural complications showed a 31% rate in surgical and a 6.6% in those patients who received percutaneous devices (odds ratio 5.4, 95% confidence interval 2.96-9.84; $p<0.0001$), in favor of percutaneous closure. The post-procedural *major* complication rate was 6.8% in surgery patients and 1.9% with catheter-based closure (OR 3.81, 95% CI 2.7, 5.36; $p=0.006$), again favoring percutaneous closure.

Most patients choose an alternative to open cardiac surgery, especially since the current devices have shown good experience overall thus far. The use of these devices for patent foramen ovale and stroke prophylaxis however is an unresolved issue. AHA however realizes that the Agency's current concern is the safety of these devices for ASD rather than efficacy in patients with patent foramen ovale.

Although these complications can be life threatening, they nevertheless are uncommon. For example, the embolization rate is reported to be 0.5% to 2.0%, and in such cases, the devices are retrievable surgically or through percutaneous approach. Over 90% of these events occur within the first 24 hours of implantation, typically while the patients are being observed in the hospital setting. With an estimated 9,000 implants in the United States, nine confirmed erosions and associated hemopericardium, and three deaths have been reported, yielding an incidence rate of 0.1%, but with a 20% mortality risk if it occurs. Rates of thromboembolism reported varies in the literature but is seen in less than 5% of cases and may be related to different anticoagulation protocols used. Indeed, some are incidental findings on subsequent imaging studies. Other reported complications are less frequent, including bacterial endocarditis. Arrhythmias including atrial fibrillation and heart block may occur as well, and if sustained or recurrent, may require device removal.

It appears that erosions may be related to the deficiency in anatomic rim size. However, if very strict guidelines are put in effect in terms of rim size requirement, that may exclude a majority of patients who currently get these devices and they all will require open surgery. The complications rate in these patients, though higher than those without rim deficiency, is nevertheless comparable or better than surgical closure. The vast majority of secundum type atrial septal defects (>80%) have some degree of deficiency or absence of the retro aortic (anterior-superior) rim. Devices have been implanted effectively in patients with deficiencies of various components of the septal rim, and large confluent defects with little or no rim throughout the circumference of the defect are turned down for device closure. What is unknown is the extent of rim deficiency that would result in an unsecure placement and whether this contributes to erosion risk, remains to be studied further. Certainly caution in this respect needs to be exercised but further large-scale data are needed to be able to derive more specific guidelines. The Agency may therefore consider recommending collection of data in the form of an ongoing registry to further understand the

[1] Butera G et al. Percutaneous versus surgical closure of secundum atrial septal defects: a systematic review and meta-analysis of currently available clinical evidence. EuroIntervention 2011;7:377-85.

nuances and subtleties of the anatomic substrate and the risk of complication in order to inform guideline recommendations.

In summary, these devices appear to be safe and effective, and have a profile of complication rates that compare favorably with the surgical alternative. However, the complication rates are judged to be more common than initially assumed based on pre-marketing approval data and the reported literature. This necessitates further dissemination of these data and information to the individual operators and centers, and the Agency may consider certain steps to further assure patient and procedural safety. However, in the context of the clinical consequences of unrepaired ASDs or the alternative of surgical risks, AHA recommends that these devices remain in clinical use.

Another significant issue appears to be training and credentialing of the individuals performing these procedures. Considering that the overall numbers of procedures performed across the United States still remains modest, a very widespread application guarantees little exposure and in turn expertise for the operators. The Agency might consider recommending that the professional organizations develop training guidelines for these procedures. Moreover, consideration may be given in terms of suggesting that these procedures be limited to large volume centers.

Lastly, post-procedural surveillance with these devices may also be streamlined in terms of both clinical and echocardiographic follow-up to assess the stability of the device implant and the clinical status. This may also require guidelines generated by the professional organizations and will need support from the payers to support the recommended surveillance in terms of reimbursement.

AHA applauds the Agency's constant vigilance and efforts to ensure patient safety. We hope that the Agency will find our perspective and recommendations useful. We look forward to participating in the public hearing and we offer assistance in implementing any further steps to ensure consistent but safe use of these devices.