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Statement of the American Heart Association to the
Food and Drug Administration
Circulatory System Devices Panel
February 18, 2016

Leadless Cardiac Pacemaker Devices

The American Heart Association appreciates the opportunity to respond to the Food and Drug Administration's request for public comment on clinical trial study design, adverse event reporting and physician training requirements for leadless cardiac pacemaker technology.

Since 1924, AHA has dedicated itself to building healthier lives free of heart disease and stroke – the #1 and #5 leading causes of death in the United States – through research, public and provider education, healthcare provider quality improvement programs, and advocacy. We are joined in our efforts by more than 30 million volunteers and supporters, making AHA the nation's oldest and largest voluntary health organization devoted to fighting cardiovascular disease and stroke.

AHA supports the Agency's decision to convene this meeting and examine new developments in pacing technology. Leadless cardiac pacemakers may provide patients and providers with an important new option in treating or preventing abnormal heart rhythms. However, as with any new medical device, the FDA must carefully examine the potential benefits and risks before approving one of these devices for commercial use in the United States.

Potential Benefits and Risks

When evaluating leadless cardiac pacemakers, we encourage the Agency to consider how the risks and benefits compare to currently available pacer technology. The benefits are categorized into three major areas: avoidance of risks associated with intravascular leads, no pocket required for device placement, and an additional option for patients who require a single chamber pacer.

Unlike traditional single- or double-chamber pacemakers, leadless cardiac pacemakers do not contain an intravascular lead. This eliminates the risk of complications such as lead failure, lead fracture, insulation defect, or pneumothorax. The known risks of extraction

such as a torn subclavian vein or tricuspid valve can be avoided because there is no lead to replace or extract. In addition, since there is no lead in the vascular system, the risk of venous thrombosis and occlusion of the subclavian system is eliminated, and the patient has vascular access preserved for other medical conditions (e.g., dialysis or chemotherapy). A leadless device may also decrease the risk of infectious complications since there is less surface area exposed to the bloodstream. And, there could be a decreased risk of tricuspid regurgitation depending on the placement of the device in the right ventricle, the number of devices planted, and the size of the right ventricle.

Because leadless cardiac pacemakers are implanted directly inside the heart, there is no need for a subcutaneous pocket. This eliminates the risk of pocket infections, erosions and pain. A leadless cardiac pacemaker may also be more comfortable and appealing to patients since they are unable to see or feel the device on the chest wall.

These benefits may make leadless cardiac pacemakers a viable option for patients who need a single chamber pacer, such as those with atrial fibrillation with heart block, patients with slow heart rates, those who need rare and intermittent pacing, or patients with many comorbidities who might not have enough benefit from atrioventricular synchrony that ventricular paced/ventricular sensed (VVI) pacing is sufficient. Leadless devices may also be a better option than a surgical endocardial pacemaker for patients with no vascular access due to renal failure or congenital heart disease.

Leadless cardiac pacemakers, however, are not without risk. In the LEADLESS trial, three major adverse events were seen. One reported patient death was due to complications from cardiac tamponade with hemodynamic collapse secondary to repositioning of the leadless cardiac pacemaker. A second patient had the device inadvertently implanted into the left ventricle after the delivery sheath transited an unknown patent foramen ovale (PFO). A third patient required a conventional single chamber pacemaker due to persistent arrhythmias.

There are some additional risks to leadless cardiac pacemakers that must be considered. During implantation, for example, groin access and a larger sheath is required; this can result in increased bleeding, pseudoaneurysm, arterial perforation, or hematoma. Other potential risks include thrombus formation leading to pulmonary embolus or stroke, hemodynamic effects on the right ventricle, and leadless cardiac pacemaker infection. There is also a risk of pacemaker migration, perforation of ventricle during placement leading to cardiac tamponade, as well as long-term erosion through the right ventricular free wall or septum. Like a conventional pacemaker, a leadless cardiac pacemaker can fail to function if it is dislodged.

Monitoring a leadless pacemaker may also be difficult if it is not equipped for remote monitoring. Remote monitoring has been shown to improve outcomes in patients with conventional cardiovascular implantable electronic devices.

Finally, there are questions that remain to be answered. It is unclear how readily leadless cardiac pacemakers can be extracted, especially over the long-term. If there is a problem with the device, can it be removed? Patients and providers will also need a clear

understanding of what happens when the battery on a leadless cardiac pacemaker runs out or the patient needs to upgrade to a double-chamber pacemaker. Is the original device extracted or turned off and abandoned in place? If the original pacemaker remains, can a new device be implanted even if it results in the patient having multiple pacemakers? If a patient has multiple pacemakers, are there concerns related to mechanical interaction or noise?

Clinical Trials and Postapproval Study Design

Another area the FDA has asked the Panel to discuss is clinical trial design and the necessary elements for postapproval study collection. We offer our thoughts on the design of an equivalence trial versus a postapproval trial and/or surveillance as there are different needs for each type of study design. We feel it is very important that the FDA provides guidance for appropriate patient selection in clinical studies.

For the equivalence study, a non-randomized study may be reasonable. We recognize, however, that the patient population included in that study may not reflect the patient population at large. Therefore, product sponsors should be encouraged, if not required, to track comparable patient populations with conventional single-chamber pacemakers to facilitate device comparison over a period of time. For example, product sponsors could use a registry to compare patients enrolled in the study with consecutive patients who decline to participate. The Agency will have to determine the appropriate length of time to follow these patients and whether product sponsors should be required to provide these comparison data and show equivalency in order to obtain FDA-approval.

In the postapproval and/or surveillance setting, product sponsors should be required to follow long-term outcomes. The duration of follow-up may be dependent on the expected battery longevity. We recommend requiring product sponsors to collect data past the pacemaker's expected end-of-life in order to capture information related to device extraction and replacement options. This information can be captured in a patient registry or recorded directly by the manufacturer; the Agency should consult with product sponsors and providers to determine which is preferable.

Postapproval and/or surveillance studies can also be used to answer questions such as:

- Is the use of the device generalizable to all patients or should the device only be used for select populations?
- What are the consequences of shocks administered to patients with a leadless cardiac pacemaker?
- How often will patients need an upgraded or new device?
- When and how should leadless cardiac pacemakers be extracted? (We recommend that product sponsors work with a third party to develop an extraction system).

Finally, postapproval and/or surveillance studies should track patient-centered outcomes, including the patient experience during implantation (e.g., was the patient required to stay in the hospital), and patient quality-of-life after placement. For example, since remote monitoring of these devices is not currently available, patients will be required to regularly

visit their provider, which may impact the patient experience. These types of patient-focused questions must be incorporated into the study design.

Adverse Event Profile and Rates

As noted in the discussion of potential risks, leadless cardiac pacemakers can be associated with a number of adverse events including:

- Bleeding and vascular complications due to the larger sheath size
- Perforation and cardiac tamponade
- Hemodynamic consequences, such as tricuspid regurgitation or heart failure
- Infection
- Migration
- Device failure
- The need for surgery and/or extraction related to the device
- Mortality

There may also be other adverse events that will not be identified until the devices are used in a larger patient population and outcomes are followed for a longer period of time. For example, adverse events resulting from the placement of multiple pacemakers, as discussed above, may not be evident until leadless cardiac pacemakers have been in use for an extended period of time.

In terms of acceptable adverse event rates, we recommend that the Agency examine three different time intervals:

- Acute procedural complication rates
- Shorter-term complications (30 day, 90 day)
- Longer-term complications (1 year, 5 year, and 10 year or specific time period past the expected battery life)

The adverse event rate associated with each time frame may vary, but the acceptable adverse event rate should <u>not</u> be any higher than with conventional pacemakers in comparable patient populations. We recognize, however, that providers will have to familiarize themselves with this new technology and a learning curve will be required. Therefore, the FDA may wish to allow for a slightly higher adverse event rate until a reasonable training period has occurred.

Physician Training Requirements

Leadless cardiac pacemakers represent a new form of pacing technology. The indications for use, patient selection criteria, adverse event profiles, and implant and extraction procedures may differ from the conventional pacemakers providers are familiar with. As such, adequate provider training will be critical to maximizing patient outcomes. Therefore, we strongly support including a physician training requirement as a condition for securing FDA-approval or securing coverage by payors.

Ideally, the required training would not be provided by the product sponsor. We would prefer to see a train-the-trainer model, if possible, in which the product sponsor trains a small cadre of providers who could then take on the role of training providers in other

settings. However, we recognize that each leadless cardiac pacemaker may differ and there will be nuances of each device's implantation and extraction procedures that will likely require some manufacturer participation in the training program, at least in the first few years. A train-the-trainer model may also depend on the patient volume. If these devices are used in settings where the volume is high, a train-the-trainer model might be feasible.

In terms of the specific training requirements, providers will have to learn how to:

- Appropriately select patients
- Correctly place the device, including whether there are additional locations within the right ventricle that the pacemaker (or multiple pacemakers) can be placed
- Address vascular complications associated with the larger sheath size
- Turn off the pacemaker
- Extract the device
- Replace a leadless cardiac pacemaker at the end of its battery life or upgrade the patient to a double-chamber pacemaker

The training program should also address the informed consent process. The informed consent process must include a discussion about the extraction process (including whether or not that is an option); device abandonment (patients should be aware that the device may remain in their body indefinitely); and the possibility that multiple pacemakers will be inserted over the course of the patient's lifetime. Patients should also be educated about what it means to live with a cardiac device long-term, and advised that they will have to visit their provider on a regular basis since remote monitoring of leadless cardiac pacemakers is not currently available.

Lastly, as providers get more experience with these devices, the FDA should examine whether there is a correlation between higher volume providers and patient outcomes. If so, it may be reasonable to limit these devices to providers that perform a minimum number of implantations per year. In addition, as providers learn how to implant these devices, it may be helpful to have just-in-time consultative services available to providers to troubleshoot during a procedure, or a learning laboratory to help educate providers on common problems that could occur when implanting this type of device.

Closing

In summary, AHA appreciates the FDA's efforts to examine leadless cardiac pacemakers and their role as a new form of pacing technology. When evaluating these devices, we encourage the Agency to consider how their risk and benefit profile compares to the conventional single-chamber pacemakers currently on the market. In order to obtain FDA-approval, leadless cardiac pacemakers should have a safety profile that is as good, if not better, than currently available devices. Product sponsors should also be required to initiate a training program with the goal of eventually creating a train-the-trainer model that is not affiliated with the manufacturer. The training program must address patient selection, implantation, extraction, and abandonment, and the risk associated with each, as well as the informed consent process and real-time troubleshooting during device placement.

We hope the Agency will find our perspective and recommendations useful.