PATENT FORAMEN OVALE CLOSURE WITH THE AMPLATZER™ PFO OCCLUDER FOR SECONDARY STROKE REDUCTION OF RISK IN PATIENTS WITH CRYPTOGENIC STROKE

Summary of Clinical Evidence

October 28, 2016
THE HEALTH PROBLEM

- A patent foramen ovale (PFO) is a common finding (56%) among patients with a cryptogenic ischemic stroke due to a paradoxical embolism. A cryptogenic ischemic stroke is diagnosed by excluding other mechanisms for an ischemic stroke. Diagnostic approaches have been proposed to exclude known causes of an ischemic stroke in order to arrive at the diagnosis of a cryptogenic ischemic stroke.

- Clinical findings suggest that a paradoxical embolism through a PFO is the likely mechanism for an ischemic stroke that cannot be explained otherwise (i.e., cryptogenic ischemic stroke).

- The underlying mechanism for a cryptogenic ischemic stroke is multifactorial. While a PFO is suggested as a pathway for a paradoxical embolism, the likelihood of a PFO-mediated paradoxical embolism may depend on the size of the PFO, the presence of an atrial septal aneurism, deep vein thrombosis and other conditions.

- Costs of an ischemic stroke are composed of a relatively high amount associated with the acute event and ongoing annual costs for patient care following the stroke. Given the relatively young age of such cryptogenic ischemic stroke patients, ongoing annual costs may extend over a considerably long period of time.

- Current clinical management of a cryptogenic ischemic stroke, either in the presence or absence of a PFO, consists of standard antithrombotic therapy.

DEVICE DESCRIPTION AND CLINICAL APPLICATION

- The AMPLATZER™ PFO Occluder is a self-expanding double disc device indicated for percutaneous transcatheter closure of a patent foramen ovale to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. It can be implanted using standard catheterization techniques, guided by fluoroscopy, angiography, transesophageal echocardiography or intracardiac echocardiography.

- In carefully selected patients with a PFO and evidence of a right-to-left shunt, PFO closure with the AMPLATZER™ PFO Occluder may be considered to further reduce the risk of a recurrent stroke beyond what can be achieved with antithrombotic therapy alone, while taking into account the risks and benefits of the device. The AMPLATZER™ PFO Occluder received European CE Mark in 1998. In addition to commercial approval in Europe, the device is commercially available in 80 countries. The device received FDA approval in 2016 based on the results of the RESPECT trial data lock date of 2015.

- The clinical benefits of PFO closure have been recently reported after long-term follow-up of patients in the RESPECT trial:

  - Relative risk reduction of 45% was demonstrated by device therapy versus medical management when considering freedom from recurrent ischemic stroke.

  - When results were censored at age 60, the relative risk reduction demonstrated by device therapy reached 58% for recurrent ischemic stroke.

  - Device therapy was particularly effective in reducing the risk of recurrent ischemic stroke of unknown mechanism (cryptogenic stroke), reaching a 62% relative risk reduction.
**TARGET POPULATION FOR PERCUTANEOUS PFO CLOSURE**

- Patients selected for the AMPLATZER™ PFO Occluder should undergo a comprehensive evaluation by a neurologist and cardiologist to confirm the diagnosis of a cryptogenic ischemic stroke due to a presumed paradoxical embolism through a PFO. This comprehensive evaluation should rule out the presence of other known mechanisms for an ischemic stroke. It is recommended that the comprehensive evaluation follow the latest professional society guidelines for diagnosing a cryptogenic ischemic stroke, and should include at minimum the following assessments:
  - MRI or CT scanning of the head to rule out small vessel disease or lacunar infarct.
  - TEE to rule out non-PFO intra-cardioembolic sources or conditions or aortic arch atheroma.
  - ECG and prolonged cardiac rhythm monitoring (~30 days) to rule out atrial fibrillation and other heart rhythm disturbances that may be associated with stroke.

- Intra and extracranial artery imaging: MRA, CT angiography or contrast angiography to rule out an ischemic stroke associated with atherosclerotic plaque, arterial dissection or other vascular diseases.

- Hematological evaluation to rule out underlying hypercoagulable state.

- Patients should also be evaluated by an implanting cardiologist to ensure that there are no anatomical contraindications for implanting the device safely. Refer to the Instructions for Use (IFU) for the AMPLATZER™ PFO Occluder.

- It is estimated that only a small fraction of stroke patients (2%) will be eligible candidates for transcatheter PFO occlusion. The annual eligible patient population in the U.S. is estimated to include 16,000 patients as demonstrated in the flowchart below.

---

**Figure 1.** Description and size estimation of the target population for PFO closure in the U.S.

- **U.S. Stroke, Any Age** 795,000
- **Ischemic–87%** 690,000
- **Ischemic–13%** 105,000
- **Cryptogenic–25%** 172,500
- **Known–75%** 517,500
- **With PFO–40%** 69,000
- **No PFO–60%** 103,500
- **≥ 60 y/o 77%** 53,000
- **< 60 y/o 23%** 16,000
- **16,000 potential candidates for PFO closure in U.S. per year ~ 2% of all strokes**
MEDICAL NECESSITY

Unlike most stroke patients who are elderly and have a number of age-related diseases, patients who experience a cryptogenic ischemic stroke are typically younger (i.e., average age of 46 years10), with the potential for the stroke effects to be more disruptive, particularly in working patients supporting a family. Medical management alone does not eliminate the risk for a recurrent stroke.

The AMPLATZER™ PFO Occluder addresses an important unmet medical need among patients who suffered a cryptogenic ischemic stroke due to a presumed paradoxical embolism and who remain at risk for a recurrent stroke for decades. Considering the life-long benefit of protection from a recurrent stroke and the low incidence of procedure-related or device-related complications,10 PFO occlusion is a reasonable and necessary therapy to prevent recurrent strokes.