**PFO Closure: Role in Prevention of Recurrent Stroke and TIA**

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Cook Medical: Speakers Bureau  
IAC Board: Board Member  
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**Markedly Positive Contrast Study**

**Case Presentation**

- 28 yo native female with hx of amaurosis fugax involving the left eye  
- ECHO revealed normal LV function, a PFO and an intraluminal defect at the IVC/RA junction  
- No prior hx of venothromboembolic disease, but has received Depo-Provera injections for contraception

**Treatment**

- The patient underwent trans-catheter closure with 30mm Cardio-form closure device.  
- Uneventful recovery and was discharged on antiplatelet therapy and Xarelto  
- F/U 1 month later she presented with anemia and black stools  
- GI evaluation was performed identifying gastric erosions  
- Xarelto was discontinued  
- F/U at 3 months was unremarkable with no further events and resolved anemia
Case Presentation

- 39 yo male farmer worker who presented with facial droop, right sided weakness and expressive aphasia.
- MRI head confirmed a left MCA stroke
- Additional evaluation including carotid duplex, special coagulation studies, and ECHO were unremarkable except for PFO

Introduction

- In patients presenting with an acute ischemic stroke, the cause of stroke remains unknown in 30–40%.
- Even after a complete diagnostic evaluation, such strokes are classified as “cryptogenic strokes”
- Patent foramen ovale (PFO) is a fetal remnant of the interatrial septum, which can be considered an anatomical variation given its high prevalence (25%) in the general population
- Using transesophageal echo-cardiogram (TEE), the frequency increases to 50% in survivors of stroke without an identifiable cause
- Although some have argued that a PFO may be an incidental finding in this population, PFO has been found to be independently associated with cryptogenic ischemic stroke in young adults and elderly patients.
Controversy

- More than 20 years have passed since the transcatheter closure of PFO for secondary prevention of paradoxical embolism was first reported.
- Closure remains controversial whether percutaneous PFO closure is superior to medical therapy (i.e., antiplatelet or anticoagulation therapy) for the prevention of recurrent embolic events after a cryptogenic stroke.

Current Level of Evidence

- Multiple observational and nonrandomized studies examining the relationship between PFO closure and stroke have been published in the past two decades.
- Three Randomized Clinical Trials (Closure 1, Respect, PC Trial).
- Two meta-analyses of these studies have suggested that percutaneous closure of PFO in this group of patients may be better than medical therapy alone.

Amplatz Septal Occluder

- Self-Expandable
- Short-connecting Waist
- Nitinol wire
- Sizes: 4-38 mm

Respect Trial

- RESPECT study. From the total 980 patients, the primary end point occurred in 25 patients, 9 in the closure group and 16 in the medical therapy group, with all the events being nonfatal ischemic strokes.
- In the primary time-to-event analysis for the intention to treat population, there was no statistically significant difference between the 2 groups: 0.66 events per 100 patient-years for the closure group versus 1.38 events per 100 patient-years in the medical therapy group (HR = 0.49; 95% CI: 0.22-1.11).

Respect Trial

- However, in two other pre-specified population analyses ("per protocol" and "as-treated") the rate of primary events per 100 patient-years was significantly lower in the PFO closure group compared with the medical therapy group, with 0.46 versus 1.30 events.

PC Trial

- PC trial had a mean follow up period of 4 years.
- 191 patients underwent PFO closure and 200 received the assigned medical therapy.
- The primary end point was confirmed to have occurred in 7 patients (3.4%) in the closure group and 11 patients (5.2%) in the medical-thrapy group (hazard ratio for closure vs. medical therapy, 0.63; 95% confidence interval [CI], 0.24 to 1.62; P = 0.34).
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Pooled Data: Intention to Treat

- The pooled data of the intention-to-treat population of the trials provided 2,303 patients, divided into 1,150 for the PFO closure group and 1,153 for the medical therapy group.
- The individual incidence of TIA and ischemic CVA was similar in both groups, with 24 transient ischemic attacks in the closure group compared with 29 in the medical therapy and 22 ischemic strokes in the closure group compared with 34 in the medical therapy group.
- However, there were 43 events of the composite of TIA and ischemic CVA in the closure group compared with 61 events in the medical therapy group, showing a trend in favor of the PFO closure.

CLOSURE I, RESPECT and PC Trials

- Individual randomized trials have failed to demonstrate the benefit of transcatheter device closure of PFOs in patients with cryptogenic strokes.
- However, when all available transcatheter PFO closure randomized trials data are pooled together in patients with cryptogenic ischemic stroke, the closure of the PFO appears to reduce the risk of recurrent thromboembolic events, namely TIA and ischemic CVA, when compared with medical therapy alone.
- The risk reduction for the composite of both the risk reduction for the composite of both TIA and CVA was of 30% when the “Intention-to-Treat” population was analyzed, a result that did not achieve statistical significance, but showed a trend in favor of the PFO closure (P = 0.08).

Meta-Analysis of “As Treated”

- Analysis of the primary outcome, a composite of TIA and ischemic CVA, in the “As Treated” population, and the pooled data from available studies provided 1,043 patients for the PFO closure group and 1,059 for the medical therapy group.
- There were 38 events in the PFO closure group compared with 61 in the medical therapy group, achieving statistical significance with an OR of 0.62 (95% CI, 0.41–0.94; P = 0.02; Fig. 3).
- When patients who had their PFO actually closed were compared with patients who received the assigned medical therapy (“As-treated” population), percutaneous closure of the PFO significantly reduced the risk of future thromboembolic events, with a risk reduction of 38% (P = 0.02).

Clinical Trial Data

- More recently, Agarwal et al. demonstrated a pooled incidence of recurrent neurological events of 0.76 per person/year (95% CI 0.48–1.05) in the transcatheter PFO closure group compared with 4.39 (95% CI 3.20–5.59) for the medical therapy group, an 84% risk reduction (RR = 0.25; 95% CI 0.11–0.58) using

Percutaneous PFO Closure: Peri-procedural Complications

- What bad things can happen when you put them in?
- Thrombosis
- Device Embolization
- Erosion
- TIA / Stroke

Next Generation Improvements
GORE® CARDIOFORM Septal Occluder

- Improved Delivery System
  - Handle delivery system
  - Simple, intuitive controls
  - One-handed delivery
  - Ease of use

GORE® HELEX® Septal Occluder

Improvements in Technology

- Gore initially developed the Helex device to reduce the risk of erosions and allow for easier retrieval if required

Attributes of GORE® CARDIOFORM Septal Occluder and GORE® HELEX® Septal Occluder

- Soft, conformable discs
- Flat profile
- ePTFE occlusion membrane
- Repositionable
- Retrieval cord enables tension-free assessment
- Pre-assembled with delivery system

Next Generation Improvements (continued)
GORE® CARDIOFORM Septal Occluder

- Five-Wire Frame Design
  - Close septal apposition for rapid defect closure and device stability
  - No post-procedural embolizations in US Pivotal Study and published literature*
  - Conforms to septal anatomy, including challenging defects

*Data as of October 2015
**GORE® CARDIOFORM Septal Occluder Clinical Performance**

- CE Mark in June 2011, FDA approval in April 2015
- Estimated > 7,000 devices implanted
- High closure success in US Pivotal Study and published ASD literature, including challenging defects
  - ≥98% closure success within 24 hours
  - 100% closure success at mid-term follow up
- No post-procedural embolizations in US Pivotal Study or published literature
- No reports of cardiac erosion

*Data as of October 2015

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**Device Indications**

- **US Indication**
  - The GORE® CARDIOFORM Septal Occluder is a permanently implanted device indicated for the percutaneous, transcatheter closure of ostium secundum atrial septal defects (ASDs).

- **CE Mark**
  - The GORE® CARDIOFORM Septal Occluder is a permanently implanted device indicated for the percutaneous, transcatheter closure of atrial septal defects (ASDs), such as ostium secundum and patent foramen ovale.

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**Clinical Indications**

- St. Jude Medical Announces FDA Approval and U.S. Launch of the First and Only Medical Device Indicated to Reduce the Risk of Recurrent Ischemic Stroke in Patients with a PFO (October 28, 2016)

- The AMPLATZER PFO Occluder has been shown to provide a clinically meaningful reduction in the risk of recurrent stroke among patients with a PFO compared to medical management alone. St. Jude Medical, Inc. (NYSE:STJ), a global medical device company, today announced the U.S. Food and Drug Administration (FDA) approval and launch of the AMPLATZER PFO Occluder to help reduce the risk of recurrent ischemic strokes in patients diagnosed with a patent foramen ovale (PFO).

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**Summary**

- The Challenge is to determine when and if a PFO should be closed
- The difficulty with trials is comparing non-standardized medical therapy to closure
- RESPECT clearly favored Closure over medical therapy based on a superiority trial
- PFO closure needs to be targeted for a selective patient population