Devices for Stroke Prevention

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Overview

• Left Atrial Appendage Closure
  – FDA Approved Watchman
  – Investigational Amulet

• PFO Closure
Atrial Fibrillation is a Growing Problem Associated with Significant Morbidity and Mortality

AF = most common cardiac arrhythmia, and growing

AF increases risk of stroke

• Higher stroke risk for older patients and those with prior stroke or TIA
• 15-20% of all strokes are AF-related
• AF results in greater disability compared to non-AF-related stroke
• High mortality and stroke recurrence rate

~5 M people with AF in U.S., expected to more than double by 2050

5x greater risk of stroke with AF

Connection Between Non-Valvular AF-Related Stroke and the Left Atrial Appendage

AF Creates Environment for Thrombus Formation in Left Atrium

- Stasis-related LA thrombus is a predictor of TIA\(^1\) and ischemic stroke\(^2\).
- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA\(^3\).

Atrial Fibrillation

- Atrial fibrillation affects 1.5-2.0% of the general population
- Increases stroke risk by 5-fold
- Accounts for 15-20% of all strokes
- Strokes associated with atrial fibrillation have a 50% greater chance of disability or death
- Anticoagulation is the mainstay of therapy
- Warfarin decreases stroke by 64% and mortality by 26%
Scope of the Problem

• Anticoagulation recommended for CHADS2 or CHADS2-VASc for of ≥ 1

• CHADS2
  – CHF
  – HTN
  – Age ≥ 75
  – Diabetes mellitus
  – Stroke or TIA
Scope of the Problem

- CHADS2-VASc
  - CHF
  - HTN
  - Age > 65
  - Diabetes mellitus
  - Prior stroke or TIA
  - Vascular disease
  - Age > 75
  - Sex (gender)
Scope of the Problem

• Problems with anticoagulation
  – 30-50% of eligible patients do not receive anticoagulation due to absolute contraindication or perceived risks of bleeding
  – Major bleeding risk of 2.1% to 3.6% per year
  – NOACs (daglibitran, riveroxablan, apixablan) reduce intracranial hemorrhage risk compared to warfarin
  – Only apixablan was shown to reduce major bleeding
Indications for Percutaneous LAA closure

- TEE and surgical reports show > 90% of left atrial thrombi are in the LA appendage
- Indication for percutaneous closure generally felt to be high stroke risk and contraindication to long-term oral anticoagulant therapy
HAS BLED

- Hypertension
- Abnormal renal function
- Stroke
- Bleeding
- Labile INRs
- Elderly (≥ 65 years)
- Drugs or alcohol
HAS BLED Annual Bleeding Risk

- 1 → 1%
- 2 → 2-3%
- 3 or greater → 5-20%
LA Appendage Anatomy

- A - Chicken Wing
- B – Windsock
- C – Cauliflower
- D - Cactus
Devices for LAA Closure

- Lariat
- Watchman
- Amplatzer Amulet
Lariat

- Complex hybrid procedure
  - Endocardial approach &
  - Epicardial approach

- FDA approved (and CE marked) for suture and knot tying during surgical applications but not specifically for stroke prevention with atrial fibrillation
Clinical Trial Results -- Lariat

• JACC 2013
  – First published single center experience in Poland
  – 89 patients, mean age 62 yrs
  – CHADS2 1.9
  – CHA2DS2-VASc 2.8
  – Success 96%
  – Two epicardial complications
Clinical Trial Results -- Lariat

- **JACC 2014**
  - Multicenter retrospective US experience
  - 154 patients
  - Procedure time 76.6 min
  - Technical success 94% but procedural success (without complications) was only 86%
  - Significant pericardial effusion requiring intervention in 10.4%
  - Bleeding requiring transfusion 4.5%
  - Emergent cardiac surgery 2%
WATCHMAN LAA Closure Device
Watchman

• Originally owned by Atritech but acquired by Boston Scientific in 2011
• Self expanding frame covered by PET membrane
• 5 different sizes
• CE mark in 2005, US Approval in March 2015
Clinical Trial Results -- Watchman

- PROTECT – AF
  - 707 patients
  - Nonvalvular AF and CHADS2 ≥ 1
  - Randomized 2:1 Watchman vs. warfarin
  - 90.9% successful implantation rate
  - Met noninferiority endpoint (45 month follow-up showed superiority)
  - However, major bleeding was increased 5.5% vs. 3.6% annually
Clinical Trial Results -- Watchman

• Due to early safety concerns in PROTECT-AF, the FDA mandated a second randomized trial

• PREVAIL
  – 407 patients, again 2:1 randomization
  – Successful device implantation in 95.1%
  – Safety endpoint met noninferiority criteria
*Cessation of warfarin is at physician discretion provided that any peri-device flow demonstrated by TEE is ≤ 5mm. **Before 6 months, when seal is adequate, patients can cease warfarin and should begin clopidogrel 75 mg daily and increase aspirin dosage to 300-325 mg daily. This regimen should continue until a total of 6 months have elapsed after implantation.
ASAP TOO Trial

- Randomization between Watchman (followed by ASA/Plavix) vs. Conservative therapy with ASA and/or Plavix
- Planned 888 patients
- Primary endpoints
  - Safety (7 day death, ischemic stroke, embolization, bleeding requiring intervention)
  - Efficacy (time to ischemic stroke or systemic embolization)
- Watson Clinic is one of the U.S. research sites
Amplatzer Amulet

- Self expanding nitinol mesh forming a lobe and a disk connected by a central articulating waist
- 8 sizes available
- CE mark in December 2008 for Amplatzer Cardiac Plug (ACP) and 2015 for Amulet, not US approved
- Watson Clinic is one of the first 10 U.S. sites in a trial randomizing Amulet and Watchman
Amplatzer Amulet
Continued Controversies

• Longer term follow-up of devices for efficacy
• Comparative efficacy of devices versus NOAC
• Direct comparison of device vs. device
• Cost effective analysis
Selection and Comparison of LAA Closure Devices

- **Technical success**
  - Watchman & ACP 95-97%
  - Lariat lower at about 93% (83% without complications)

- **Lariat contraindicated with prior cardiac surgery, LAA > 40mm, and certain LAA anatomy**

- **Watchman can accommodate > 95% of LAA anatomy**
• Watchman
  – Accommodates LAA ostium of 17-31 mm
  – Requires as much LAA depth as the device diameter

• ACP
  – Accommodates maximum landing zone of 12.6-28.5 mm
  – Only requires a depth of approx 10mm
Overview of Patent Foramen Ovale (PFO)

- Embryology
- Incidence
- Diagnosis
- Pathophysiology
- Clinical significance
- Therapeutic options
Embryology

- Remnant of the fetal circulation
- Allows flow of placental blood from IVC to enter the arterial circulation
  - Crista interveniens directs SVC flow away from interatrial septum
  - Coronary sinus blood is also directed away from interatrial septum
Embryology

Figure 1. Normal status — higher left atrial pressure keeps the PFO closed.

Figure 2. Right atrial pressure exceeds left atrial pressure — PFO opens.

Figure 3. PFO track viewed from left atrium.
Embryology

• At birth,
  – PVR and right sided heart pressure drops
  – Flap of the foramen ovale closes against the interatrial septum

• Fusion usually occurs within the first two years of life

• Fusion is incomplete in about 25% of people
Incidence

- Thompson et al (QJ Med 1930)
  - Autopsy study of 1100 subjects
  - “Probe patent” (0.2 - 0.5 cm) in 29%
  - “Pencil patent” (0.6 – 1.0 cm) in 6%

  - Autopsy study of 965 subjects
  - PFO incidence of 27.3%
  - Size 1 – 19 mm
  - Incidence declined with age, suggesting anatomic closure may occur even in adulthood
## PFO Incidence vs. Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 29 Years</td>
<td>30%</td>
</tr>
<tr>
<td>30 – 79 Years</td>
<td>25%</td>
</tr>
<tr>
<td>≥ 80 Years</td>
<td>20%</td>
</tr>
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</table>
Diagnosis of PFO

• Prior to echocardiography, diagnosis was difficult:
  – History normal
  – No physical findings
  – Normal EKG
  – Normal CXR

• Echocardiographic methods:
  – Transthoracic echo
  – Transesophageal echo
  – Transcranial doppler
Diagnosis of PFO

• TEE is currently the reference standard for the diagnosis of PFO
  – Allows direct imaging of IAS
  – Allows direct imaging of saline contrast shunting through PFO

• Cough or Valsalva increases the sensitivity of TEE

• Injection of agitated saline through femoral vein is superior to antecubital vein
Pathophysiology

• With increased right atrial pressure and even at rest in some individuals there can be right to left shunting through the PFO
• Clinical significance
  – Cryptogenic stroke
  – Decompression sickness
    • Scuba divers
    • High altitude aviators and astronauts
  – Migrane headache
Cyptogenic Stroke

• 40% of ischemic strokes have no clear etiology
  – Adults < 55 years of age
    • 60 with ischemic stroke
    • 100 normals
  – All had contrast echo
  – PFO
    • 40% in stroke patients
    • 10% in controls
    • Found in 26 stroke patients (54%) with no other identifiable cause
Cyptogenic Stroke

- PFO-ASA Study (Stroke 2002;33:706-1) – 46% of young cryptogenic stroke patients had PFO
Cryptogenic Stroke

- Cramer et al (Stroke 2004;35:46-50)
  - 18-60 year old stroke patients have higher incidence of pelvic DVT compared to controls (20% vs. 4%)
  - Cryptogenic stroke patients had higher incidence of PFO (59% vs. 19%)
  - Cryptogenic stroke patients younger (42 vs. 49 years) and had fewer atherosclerosis risk factors
Cryptogenic Stroke

- 49 patients with cryptogenic stroke evaluated by TTE, TEE, and TCD
- PFO diagnosis made by:
  - TEE 39%
  - TTE 18%
  - TCD 27%
- Six PFOs not detected by TCD were < 2mm by TEE
- No PFO diagnosed by TTE or TCD was missed by TEE
Cryptogenic Stroke

• Am Heart J 1998
  – TEE study for diagnosis of source of embolism
  – Detected 34 resting PFOs
  – Divided into “small” vs. “large” shunt by size and number of microbubbles
  – All treated with ASA or warfarin
  – Follow-up 21 months

• Ischemic endpoints
  – 31% of “large” group
  – 0% of “small” group
Cryptogenic Stroke

  - Patients < 60 years of age with unexplained neurologic events compared to normal controls
  - TEE in all patients

- Patients with neurologic events:
  - Higher incidence of PFO
  - Larger size of PFO
PFO and Migraine Headache

• Migraine headache is a benign recurring syndrome:
  – Headache
  – Nausea
  – Vomiting
  – Neurologic dysfunction
• Over 2.5 million patients in U.S.A. have migraines
• Lifetime prevalence is 18%
• Associated with cryptogenic stroke
PFO and Migraine Headache

• Neurology 1999;52:1622-5
  – PFO prevalence:
    • 48% in migraine patients
    • 23% in patients without migraine
    • 20% in controls
  – No difference between controls & migraine patients without aura
### PFO and Migraine Headache

<table>
<thead>
<tr>
<th>Author</th>
<th>Prevalence</th>
<th>Migraine with Aura</th>
<th>Migraine w/o Aura</th>
<th>No Migraine</th>
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<tbody>
<tr>
<td>Anzola</td>
<td>48</td>
<td>23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Domitrz</td>
<td>54</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Carod-Artal</td>
<td>51.7</td>
<td>33.7</td>
<td>33.8</td>
<td></td>
</tr>
</tbody>
</table>
PFO and Migraine Headache

- PFO closure has been shown to improve migraine headache with aura
  - 5 of 17 had no further headache
  - 10 of 17 were much improved
  - 2 of 17 unchanged
PFO and Migraine Headache

- J Am Coll Cardiol 2005;45:493-5
  - 162 patients undergoing transcatheter closure of PFO due to paradoxic embolism
  - Complete migraine resolution in 56%
  - 14% had significant reduction in migraine frequency (> 50%)
  - 80% mean reduction in number of migraine headaches per month after PFO closure
MIST I Trial

- Multicenter, randomized, double-blind sham-controlled trial
- Patients age 18-60 years who failed two different migraine medications
- Primary endpoint was migraine cessation
- No difference between groups
  - 3 of 74 in implant group
  - 3 of 73 in “sham” group (p-0.51)
PFO Treatment Options

• Medical therapy
  – Aspirin
  – Warfarin
• Surgical closure
• Percutaneous closure
Medical Therapy for PFO

• Effectiveness ASA or warfarin for primary or secondary prevention of stroke is unclear
• No role for medical therapy to prevent DCS
Medical Therapy for PFO to Prevent Thromboembolism

- To date, there is no randomized study of various treatment regimens for PFO and cryptogenic stroke
- Available data:
  - Observational
  - Nonuniform diagnostic criteria
  - Different inclusion/exclusion criteria
  - Unblinded endpoint determinations
  - Additional therapies/risk factors uncontrolled
Medical Therapy for PFO to Prevent Thromboembolism

- Recurrent stroke risk is low in patients < 60 years of age regardless of the therapy used.
- Annual recurrence 1.9% and type of treatment had no detectable influence.
- However, combination of PFO and atrial septal aneurysm had a recurrence rate of 15.2% despite aspirin therapy.
Medical Therapy for PFO to Prevent Thromboembolism

• Can J Cardiol 1999;15:57-64
  – Retrospective study of 90 patients < 60 years of age with cerebral ischemia
  – 52 had PFO
  – Those treated with nothing or ASA had three fold higher rate of recurrence than those on warfarin
  – NOT BLINDED AND NOT RANDOMIZED
Medical Therapy for PFO to Prevent Thromboembolism

- Circulation 2002;105:2625-31
  - Subgroup of 98 patients with cryptogenic stroke and PFO
  - Nonsignificant reduction in two year incidence of recurrent stroke or death with warfarin vs. ASA (9.5% vs. 17.%) 
  - No difference in major hemorrhage
  - Warfarin increased minor bleeding (22.9 vs. 8.6 events per 100 patient years, p<0.0011)
# Medical Therapy of PFO

## Table 3. Recurrence of stroke and TIA during follow-up of patients with a PFO receiving medical therapy due to a single event of cryptogenic stroke.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Number of patients</th>
<th>Mean duration of follow-up ±SD</th>
<th>TIA n</th>
<th>Recurrent Event Stroke n</th>
<th>TIA+stroke n</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Castro</td>
<td>Prospective</td>
<td>74</td>
<td>31 ± 10</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Mas</td>
<td>Prospective</td>
<td>267</td>
<td>38 ± 10</td>
<td>9</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Homma</td>
<td>Prospective</td>
<td>203</td>
<td>13 ± 11</td>
<td>11</td>
<td>29</td>
<td>40</td>
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<tr>
<td>Meissner</td>
<td>Prospective</td>
<td>140</td>
<td>61 (median)</td>
<td>-</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Thanopoulos</td>
<td>Prospective</td>
<td>44</td>
<td>24</td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Hausmann</td>
<td>Prospective</td>
<td>44</td>
<td>59</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Schuchlenz</td>
<td>Prospective</td>
<td>66</td>
<td>30</td>
<td>17</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Schuchlenz</td>
<td>Prospective</td>
<td>47</td>
<td>31</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td></td>
<td>885</td>
<td>36</td>
<td>54</td>
<td>62</td>
<td>128</td>
</tr>
</tbody>
</table>

- **%**
  - TIA: 7.24
  - Recurrent Event Stroke: 8.32
  - TIA+stroke: 14.5

- **Annual recurrence**
  - %
    - TIA: 20.3
    - Recurrent Event Stroke: 23.3
    - TIA+stroke: 42.7

*mo = months; n = number; pts = patients; SD = standard deviation; TIA = transient ischemic attack.*
Surgical Closure of PFO

- Traditional approach is surgical with open thoracotomy
- Rate of post-operative stroke is 0 – 3.5% at two years
- Mortality is < 1.5%
Transcatheter Closure of PFO

- Efficacy ranges from 86 - 100% among studies
- Recurrent neurologic and peripheral embolic events 0 – 3.8% per year
Transcatheter Closure of PFO

- J Am Coll Cardiol 2004;43:302-9
  - 1000 consecutive patients
  - Nine different technologies used
    - Rashkind PDA umbrella
    - Buttoned Device
    - ASDOS umbrella
    - Angel Wings
    - Cardioseal
    - StarFLEX
    - Amplatzer
    - Helex
    - PFO-Star
  - Excellent results
Transcatheter Closure of PFO
# Transcatheter Closure of PFO

## Table 1. Complications associated with device closure of a PFO

<table>
<thead>
<tr>
<th>Complication</th>
<th>Amplatzer (n = 220)</th>
<th>Device Helex (n = 220)</th>
<th>CardioSEAL-STARFlex (n = 220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>3 (1.4%)</td>
<td>2 (0.9%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Device embolization</td>
<td>0 (0.0%)</td>
<td>3 (1.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hemopericardium</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Thrombus on device</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>8 (3.6%)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>supraventricular tachycardia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Development of fever</td>
<td>2 (0.9%)</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Thrombus of peripheral vein</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Due to anticoagulates</td>
<td>10 (4.5%)</td>
<td>10 (4.5%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>
## Transcatheter Closure of PFO

### Table 4. Comparative stroke and TIA recurrence rates – follow-up period 24 months or greater.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Number of patients n</th>
<th>Mean duration of follow-up ±SD mo</th>
<th>Recurrent Event TIA n</th>
<th>Recurrent Stroke n</th>
<th>TIA+stroke n</th>
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<tr>
<td><strong>Transcatheter closure</strong></td>
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<tr>
<td>Martin⁸³</td>
<td>Prospective</td>
<td>110</td>
<td>47 ± 14</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>Braun⁸⁴</td>
<td>Prospective</td>
<td>307</td>
<td>24</td>
<td>6</td>
<td>0</td>
<td>6</td>
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<td>Thanopolous⁷²</td>
<td>Prospective</td>
<td>48</td>
<td>24</td>
<td>0</td>
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<td>0</td>
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<td>Wahl²⁴</td>
<td>Prospective</td>
<td>525</td>
<td>34.8 (&gt;4 years in 147 pts)</td>
<td>9</td>
<td>6</td>
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<tr>
<td>Schuchlenz⁷⁷</td>
<td>Prospective</td>
<td>167</td>
<td>32</td>
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<td>1</td>
<td>2</td>
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<td><strong>Totals</strong></td>
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<td>n</td>
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<td>%</td>
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<td>1.47</td>
<td>0.69</td>
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<tr>
<td>%</td>
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<td></td>
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<td>6.29</td>
<td>2.96</td>
<td>9.25</td>
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<tr>
<td>%</td>
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<td></td>
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<td>0.54</td>
<td>0.26</td>
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<td>De Castro⁸⁸</td>
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<td>61 (median)</td>
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<td>%</td>
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<td>7.93</td>
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<td>%</td>
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<td>2.68</td>
<td>2.62</td>
<td>5.28</td>
</tr>
</tbody>
</table>

*mo = months; n = number; SD = standard deviation; TIA = transient ischemic attack.*
Transcatheter Closure of PFO

Amplatzer Cribriform Occluder
The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) 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.
In considering the use of the AMPLATZER™ PFO Occluder, the rationale for seeking PFO closure and the safety and effectiveness of the device compared to antithrombotic therapy alone should be taken into account. A shared decision-making process with the patient and their medical team is recommended when considering the use of the AMPLATZER™ PFO Occluder.

Refer to the Instructions for Use, “Patient Counseling Information” and the “Summary of Clinical Studies” sections for additional information.
## RESPECT Study Overview:
Largest randomized clinical trial of PFO closure, event-driven superiority trial

| Design                        | Prospective, multi-center, randomized-controlled study  
|-------------------------------|---------------------------------------------------------------------------------------------------
|                               | - 980 randomized subjects  
|                               | - 69 centers  
| Devices Studied               | AMPLATZER PFO Occluder with 18/25 mm LA disc diameter and 18/25/35 mm RA disc diameter  
| Control                       | Guideline Directed Medical Management  
| Population                    | Cryptogenic stroke within last 270 days  
|                               | Presence of PFO by TEE  
|                               | 18 to 60 years age  
| Primary Endpoint              | Composite:  
|                               | - Recurrence of Non-Fatal Ischemic Stroke  
|                               | - Fatal Ischemic Stroke  
|                               | - Post-Randomization Death at 45 days  
| Follow-up                     | 1, 6, 12, 18, and 24 months  
|                               | Yearly after 24 months  
| National PIs                  | John Carroll, MD – University of Colorado (Intervention Cardiologist)  
|                               | Richard Smalling, MD – University of Texas - Houston (Intervention Cardiologist)  
|                               | Jeff Saver, MD – University of California Los Angeles (Neurologist)  
|                               | David Thaler, MD – Tufts University (Neurologist)  

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## Defining Features of Analysis Populations

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Patients Included</th>
<th>Analysis Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat (ITT)</td>
<td>All randomized</td>
<td>Randomization arm – regardless of whether they received the treatment</td>
</tr>
<tr>
<td>Per-Protocol</td>
<td>Adherent to protocol requirements</td>
<td>Randomization arm</td>
</tr>
<tr>
<td>As-Treated</td>
<td>Adherent to protocol requirements</td>
<td>Treatment actually received</td>
</tr>
<tr>
<td>Device-in-Place</td>
<td>All randomized</td>
<td>Treatment actually received</td>
</tr>
</tbody>
</table>
RESPECT Data Summary

RESPECT 2012
Primary Endpoint

- ITT analysis shows 50% relative reduction in favor of PFO closure for reducing recurrent ischemic stroke
- Per protocol analysis shows significant 63% relative risk reduction in favor of PFO closure for reducing recurrent ischemic stroke
- Statistical significance of ITT primary endpoint was not met
- Primary endpoint analysis focused on any recurrent ischemic stroke
- Cryptogenic stroke was not defined as a primary endpoint of study

RESPECT 2015
Additional Analysis

- Extended follow-up data (average 5 years)
- Additional analysis of ITT population shows statistically significant 54% relative risk reduction in favor of PFO closure for reducing recurrent stroke of unknown mechanism (cryptogenic)

RESPECT 2016
Final Analysis

- This data review was conducted per request from FDA
- Long-term follow-up data (average 5.9 years)
- Primary ITT analysis shows significant 45% relative risk reduction in favor of PFO closure for reducing any recurrent ischemic stroke
- ITT analysis focused on prevention of stroke of unknown mechanism (cryptogenic) shows significant 62% relative risk reduction in favor of PFO closure

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2. FDA Panel Presentation, May 2016
Summary

• Structural heart disease is a growing field in interventional cardiology
• Left atrial appendage and PFO closure have been shown to reduce stroke in selected populations
  – Watchman is approved for LAA closure
  – Watchman being investigated with ASA/Plavix
  – Amulet being compared to Watchman
  – Dedicated PFO closure device recently approved
Questions?