Conflict of Interest

- No financial conflict of interest relating to the talk

- No conflict of interest, except...
  - Interventional cardiologist who performs the procedure
Objectives

- Cryptogenic stroke/Paradoxical embolism
- Role of PFO in cryptogenic stroke
- Role of PFO closure in prevention of recurrent strokes
- Review new long term data
Stroke

- ≈ 800,000 strokes per year
- #1 cause of morbidity
- #3 cause of mortality

Types:

- Hemorrhagic (20%)
- Ischemic (80%):
  - Embolic stroke
  - Large artery atherothrombosis
  - Lacunar stroke
  - Systemic hypoperfusion

25% of Ischemic Strokes are Cryptogenic
**Patent Foramen Ovale**

- In utero, the foramen ovale allows blood to flow from the right atrium to the left, bypassing the lung.
- Usually it closes after birth.
- But in 25% of people it stays open.
Leonardo da Vinci- 1513

“I have found a perforating channel from the left auricle to right auricle
Paradoxical Embolism

- Arterial embolism without evidence of left sided source
- Potential for transient right to left intracardiac shunting and subsequent flow to brain

**Concepts:**

- "Fly-By" Theory: Thrombus in venous system or right atrium passes through the ASD/PFO/ Pulm AVM
“Fly-By” Theory

On Valsalva, $P_{RA} > P_{LA}$
“Lurking Clot” Theory

Clot in a PFO as seen at surgery
Julius Friedrich Cohnheim-1877

German Pathologist
- Protégé of Virchow
- Patent Foramen Ovale
"I recently had a case of a deadly embolus in the frontal lobe of a 35-year-old woman with apoplexy. In the lower extremity a long thrombus was found and ... what I found next I never thought of, to put these two together, until I had a close look at the heart."

“...I found a very large foramen ovale through which I could pass three fingers with ease. Now I could no longer ignore the fact that a torn-off piece of thrombus arising from the lower extremity, while traveling through the heart, passed out of the RA into the LA and to the frontal lobe.”
Smoking
Guns
PFO

Is there any Clinical association between PFO and Stroke?
Risk of Recurrent Stroke

Patients between 18 and 55 years with Prior CVA within 3 months

Mas et al. N Engl J Med 2001;345:1740-
PFO Closure animation
## RANDOMIZED PFO CLOSURE TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Principal Investigator</th>
<th>Planned</th>
<th>Enrolled</th>
<th>F-up</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PC-Trial</strong></td>
<td>APO</td>
<td>Meier B</td>
<td>500</td>
<td>400</td>
<td>5 y</td>
<td>completed</td>
</tr>
<tr>
<td>(2000) Europe &amp; Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>RESPECT</strong></td>
<td>APO</td>
<td>Saver JL</td>
<td>900</td>
<td>980</td>
<td>2 y</td>
<td>completed</td>
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<tr>
<td>(2003) US</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CLOSURE I</strong></td>
<td>STARflex</td>
<td>Furlan A, Reisman M</td>
<td>1600*</td>
<td>900</td>
<td>2 y</td>
<td>completed</td>
</tr>
<tr>
<td>(2003) US &amp; Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>REDUCE</strong></td>
<td>Helex</td>
<td>Kasner SE</td>
<td>664</td>
<td></td>
<td>5 y</td>
<td>Enrolling</td>
</tr>
<tr>
<td>(2008) US &amp; Denmark</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARDIA PFO Stroke Trial</strong></td>
<td>Cardia</td>
<td>Mooney MR</td>
<td>300</td>
<td>100</td>
<td>1 y</td>
<td>Recruiting</td>
</tr>
<tr>
<td>(2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CLOSE</strong></td>
<td>Mas JL</td>
<td></td>
<td>900</td>
<td></td>
<td>3-5 y</td>
<td>Recruiting</td>
</tr>
<tr>
<td>(2007) France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 2007 (april) FDA consent to reduce numbers to 900; APO= Amplatzer PFO Occluder
CLOSURE I enrolled

- Wrong patients
- Wrong PFOs
- Wrong device
Risk of Paradoxical Embolism (Components of RoPE Score)

Statistical Attributability of Stroke to PFO

An index to stratify cryptogenic stroke patients with PFO by their likelihood that the stroke was related to their PFO.

<table>
<thead>
<tr>
<th>Age</th>
<th>Traditional Vascular Risk Factors</th>
<th>Neuroimaging Findings at Index Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age at time of stroke</td>
<td>• Absence of these factors (1 point for each):</td>
<td>• Presence of cortical (superficial) stroke on neuro-imaging (1 point)</td>
</tr>
<tr>
<td>o 5 points for 18-29</td>
<td>o Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>o 4 for 30-39</td>
<td>o Systemic Hypertension</td>
<td></td>
</tr>
<tr>
<td>o 3 for 40-49</td>
<td>o Smoking</td>
<td></td>
</tr>
<tr>
<td>o 2 for 50-59</td>
<td>o Prior stroke or TIA</td>
<td></td>
</tr>
<tr>
<td>o 1 for 60-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o 0 for &gt;70)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Score: Range 0-10

Choice of Patient Population for a Randomized Investigation of Transcatheter Closure of PFO

Figure Modified from Agarwal et al. PFO Closure Versus Medical Therapy. JACC 2012;7:777-89

Prevalence of PFO
73% 67% 54% 47% 34% 35% 23%

Statistical Attributability of Stroke to PFO
PFO-Attributable Fraction
88% 84% 72% 62% 34% 38% 0%

RoPE Score
10 9 8 7 6 5 4 3 2 1 0

Cryptogenic Stroke Population

No PFO Detected

Ideal Sub-Population to Study PFO Closure

Imperfect Cryptogenic Stroke Sub-Population to Study PFO Closure
Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke
for the RESPECT Investigators

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke
for the REDUCE Clinical Study Investigators

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke
for the CLOSE Investigators
RESPECT Trial

- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER™ PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada
Primary Endpoint

• Composite of:
  ▪ Recurrent nonfatal ischemic stroke
  ▪ Fatal ischemic stroke
  ▪ Early post-randomization death (within 45 days)

• Stroke definition:
  ▪ Acute focal neurological deficit due to cerebral ischemia with:
    • Neuroanatomically relevant infarct on imaging
      or
    • Symptoms >24 hours
Enrollment Criteria

**Key Inclusion Criteria**
- Cryptogenic stroke within last 9 months
- TEE-confirmed PFO
- 18-60 years
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

**Key Exclusion Criteria**
- Stroke due to identified cause such as:
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- Inability to discontinue anticoagulation
Patient Flow

Enrolled

Assigned guideline-recommended medication regimen

Randomized 1:1

- Warfarin
- Aspirin
- Clopidogrel
- Aspirin + dipyridamole
- Aspirin + clopidogrel
  (eliminated in 2006)

Device
- Implant within 21 days
- 1 month of aspirin + clopidogrel, then aspirin until 6 months
- Physician discretion thereafter

Medical Management
- Assigned guideline-recommended medication regimen

Follow-up:
- 1, 6, 12, 18, and 24 months
- Yearly after 24 months
RESPECT Final Results

*Freedom from Recurrent Ischemic Stroke (Intention to Treat)*

Risk Reduction: 45%

HR: 0.55 (95% CI: 0.305, 0.999)

Log-rank 2-sided p-value=0.046

# at Risk (KM Estimates)

<table>
<thead>
<tr>
<th>AMPLATZER</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>499 (0%)</td>
<td>481 (0%)</td>
</tr>
<tr>
<td>476 (1.4%)</td>
<td>433 (1.8%)</td>
</tr>
<tr>
<td>464 (1.6%)</td>
<td>394 (3.2%)</td>
</tr>
<tr>
<td>447 (1.6%)</td>
<td>380 (3.7%)</td>
</tr>
<tr>
<td>421 (1.9%)</td>
<td>354 (4.7%)</td>
</tr>
<tr>
<td>352 (2.6%)</td>
<td>282 (5.0%)</td>
</tr>
<tr>
<td>262 (3.3%)</td>
<td>218 (5.0%)</td>
</tr>
<tr>
<td>197 (4.5%)</td>
<td>150 (6.6%)</td>
</tr>
<tr>
<td>128 (5.0%)</td>
<td>104 (7.3%)</td>
</tr>
<tr>
<td>77 (5.0%)</td>
<td>59 (8.5%)</td>
</tr>
<tr>
<td>41 (5.0%)</td>
<td>31 (12.5%)</td>
</tr>
</tbody>
</table>

Event-free Probability

Time from Randomization (Years)
RESPECT Final Results

*Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)*

Event-free Probability

- AMPLATZER PFO Occluder (# strokes = 10)
- Medical Management (# strokes = 23)

Risk Reduction: 62%
HR: 0.38 (95% CI: 0.18, 0.79)
Log-rank 2-sided p-value=0.007

# at Risk (KM Estimates)
- AMPLATZER: 499 (0%), 476 (1.2%), 464 (1.2%), 447 (1.2%), 421 (1.5%), 352 (2.0%), 262 (2.3%), 197 (2.3%), 128 (2.3%), 77 (2.3%), 41 (2.3%)
- MM: 481 (0%), 433 (1.3%), 394 (2.7%), 380 (3.5%), 354 (4.0%), 282 (4.0%), 218 (4.0%), 150 (5.1%), 104 (5.8%), 59 (7.0%), 31 (11.1%)

Time from Randomization (Years)
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke
(Intention to Treat – Patients censored at age 60 years)

Risk Reduction: 58%
HR: 0.42 (95% CI: 0.21, 0.83)
Log-rank 2-sided p-value=0.010

# at Risk
(KM Estimates)
AMPLATZER
475 (0%) 443 (1.3%) 418 (1.8%) 383 (1.8%) 345 (2.0%) 285 (2.6%) 203 (3.0%) 150 (3.0%) 97 (3.0%) 55 (3.0%) 29 (3.0%)
MM
463 (0%) 402 (1.8%) 353 (3.4%) 321 (3.9%) 289 (4.9%) 220 (5.2%) 159 (5.2%) 109 (6.7%) 76 (7.7%) 44 (7.7%) 22 (13.2%)
Interpretation

- These analyses support the hypothesis that PFO closure is preventing PFO-related recurrent strokes.
- PFO-closure cannot prevent strokes from non-PFO related causes.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Relative Risk Reduction</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.55 (0.305-0.999)</td>
<td>45%</td>
<td>0.046</td>
</tr>
<tr>
<td>Stroke without known</td>
<td>0.38 (0.18-0.79)</td>
<td>62%</td>
<td>0.007</td>
</tr>
<tr>
<td>mechanism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-censored analysis</td>
<td>0.42 (0.21-0.83)</td>
<td>58%</td>
<td>0.01</td>
</tr>
<tr>
<td>(&lt;60y)</td>
<td></td>
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</tbody>
</table>
Objective
To assess whether (1) PFO closure with device plus (chronic) antiplatelet therapy on one hand, and (2) oral anticoagulants on the other hand, are superior to antiplatelet therapy, to prevent stroke recurrence in patients 16 to 60 years old with cryptogenic stroke and PFO with atrial septal aneurysm or PFO with large shunt.

Trial design
- Academic-driven, multicenter (32 sites in France and 2 sites in Germany), randomized, open-label, three-arm superiority trial with blinded adjudication of outcome events.
- Funded by the French Ministry of Health.
- 900 patients: 80% power to detect a 50% reduction in the rate of the primary outcome (3.5%/yr in the reference arm) in at least one experimental arm, 5-year study, $\alpha=5\%$.
- 663 patients included from Dec. 2008 to Dec. 2014. Follow-up until Dec. 2016. Mean follow-up 5.3 years (3544 patient-years).
**CLOSE-1**

**Key inclusion criteria**
- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE, TEE) confirmed by echo core lab before randomization

**Key exclusion criteria**
- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

**Outcomes**
- **Primary**: fatal or nonfatal stroke
- **Secondary**: composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety**: major procedural complications and major hemorrhagic complications
CLOSE-1

PFO closure vs. Antiplatelet therapy

HR = 0.03 (95% CI, 0 to 0.25); P < 0.001

Oral anticoagulants vs. Antiplatelet therapy

HR = 0.43 (95% CI, 0.1 to 1.5); P = 0.17

14 strokes in the Antiplatelet arm
(1.2% pryr)

• 0 strokes in the PFO closure arm
The Gore REDUCE Clinical Study (REDUCE) is a randomized, controlled, open-label trial.

- 63 multinational sites, 664 subjects with cryptogenic stroke and Patent Foramen Ovale (PFO) randomized in a 2:1 ratio to:
  - Test: Antiplatelet therapy plus PFO closure (with GORE® HELEX® Septal Occluder or GORE® CARDIOFORM Septal Occluder)
  - Control: Antiplatelet therapy alone

- Subjects prospectively followed for up to five years
- Neuroimaging required for all subjects at baseline and at two years or study exit
**REDUCE**

- **Endpoints**
  - **Two co-primary endpoints:**
    - Freedom from recurrent clinical ischemic stroke through at least 24 months post-randomization (unadjusted log-rank test; adjudicated by CEC)
    - Incidence of new brain infarct (defined as clinical ischemic stroke or silent brain infarct*) through 24 months (binomial test of subject-based proportions)
  - Subjects prospectively followed for up to five years
  - Adjustment for testing multiplicity

- * New T2 hyperintense MRI lesion with diameter \( \geq 3 \) mm; adjudicated by MRI core lab.
REDUCE

• Clinical ischemic Stroke: 1.4% vs 5.4%

• New brain infarctions: 5.7% vs 11.3%
REDUCE

- 77 percent relative reduction in clinical stroke with PFO closure (intention-to-treat analysis)
- PFO closure effect similar across subgroups based on age, sex, region, and baseline shunt size
- Number needed to treat (NNT) = 28 at two years
Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke
for the RESPECT Investigators

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke
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for the CLOSE Investigators

62% reduction

77% reduction

97% reduction
PFO Closure- complications

- Procedural complications
- Atrial fibrillation
- DVT occurrence
Amplatzer® PFO Occluder
Fluoroscopic image of implanted device, canine model

Intra-procedure fluoroscopic image of implanted device in US IDE study subject
Device after endothelialization

Left atrial disc, 30 days post implant in a canine model.


PFO Closure - Clinical Case (1)

27 y/o woman with right hemispheric stroke, no risk factors
• 22 year old woman, 36 weeks pregnant
• CVA @24wks — PFO+ASA
• PFO closure
• Healthy baby delivered
ASD Bidirectional shunt
Clinical Case – ASD Closure

42 y/o woman with severe DOE, prior stroke
Pulmonary AV Fistula
Teddy Bruschi  Bret Michaels
PFO Closure devices....
Conclusions

- Cryptogenic stroke in the young is a devastating problem with risk of recurrence
- PFO (high risk PFO) is common in this population
- Closure of PFO is effective in reducing risk of recurrent stroke
- Careful selection and thorough evaluation and team work across specialties is needed
Atrial septal defect closure using an expanding device

Device passed up inferior vena cava, into the right atrium and into septal defect.
CardioSEAL in a sheep heart explanted at 90 days
Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)