

Diagnosis and Management of PFO

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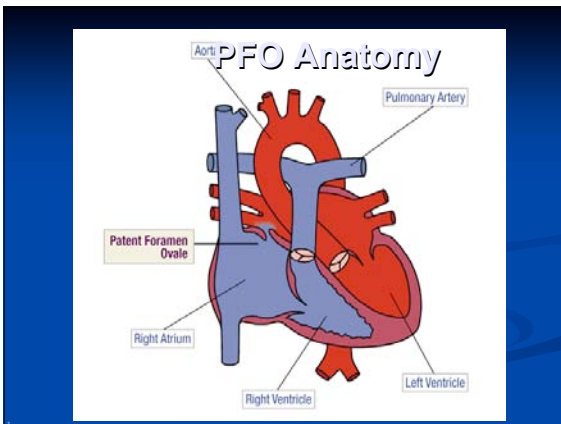
What is a Patent Foramen Ovale (PFO)?

•A patent foramen ovale (PFO) is a persistent, usually flap-like opening between the atrial septum primum and secundum at the location of the fossa ovalis.

•In utero, the foramen ovale serves as a physiologic conduit for right-to-left shunting.

•After birth, with the establishment of pulmonary circulation, the increased left atrial blood flow and pressure results in functional closure of the foramen ovale.

•A PFO is fairly common—it is found in approximately 1 in 5 people, (or 20% of the population).



Cryptogenic Stroke

- 600,000 ischemic strokes per year in the United States
- Up to 40% of all strokes are presumed cryptogenic
- Prevalence of PFO
 - 50% to 60% in patients with cryptogenic stroke
- 30,000 -100,000 strokes per year attributable to PFO

PFO

ASYMPTOMATIC

SYMPTOMATIC CRYPTOGENIC

MIGRAINE

PFO

DIAGNOSIS

ASYMPTOMATIC	TTE + BUBBLE
SYMPTOMATIC	TEE + MRI
	? CTA/MRI

PFO

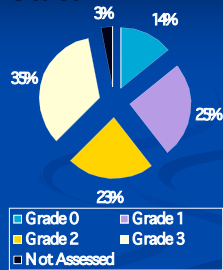
SMALL

MEDIUM – LARGE

PFO + ATRIAL SEPTAL ANEURYSM

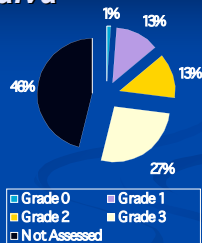
Assessment of Shunting *Resting State*

- Grading: Number of microbubbles in left atrium within 3 beats
 - Grade 1: 1-9
 - Grade 2: 10-20
 - Grade 3: >20



Assessment of Shunting *Valsalva*

- Grading: Number of microbubbles in left atrium within 3 beats
 - Grade 1: 1-9
 - Grade 2: 10-20
 - Grade 3: >20



Stroke

- Do PFO's and Atrial Septal Aneurysm's (ASA) increase the risk of stroke?
- What clinical factors increase this risk?

Atrial Septal Aneurysm

Data not core lab adjudicated

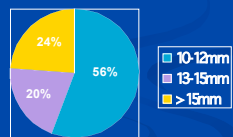
ASA Frequency in All Patients

Atrial Septal Aneurysm: 34.8%
No Atrial Septal Aneurysm: 65.2%

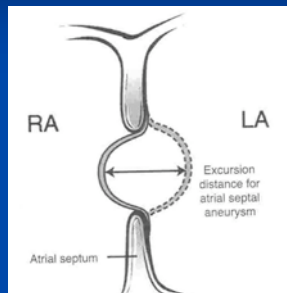
ASA Excursion Direction

RA 8%
LA 32%
Both 60%


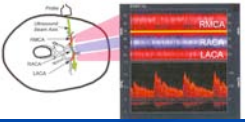
ASA Size % of All ASA

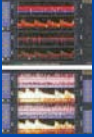


Atrial Septal Aneurysm

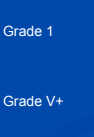


Shunt Detection



Grade 1



Grade V+

SPENCER GRADING SCALE

Grade	Embolic Tracks
0	0
I	1 to 10
II	11 to 30
III	31 to 100
IV	101 to 200
V	>200 ("curtain effect")

**QUANTITATIVE
OBJECTIVE
REPRODUCIBLE
CALIBRATED RESPIRATORY STRAIN**

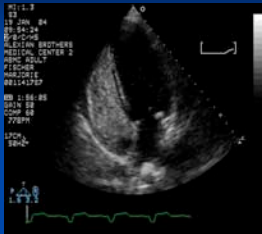
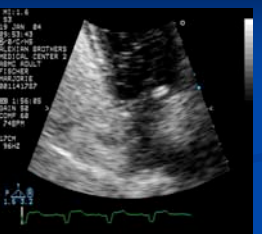
Baseline Characteristics of Patients with Cryptogenic Stroke or with Stroke of Known Cause

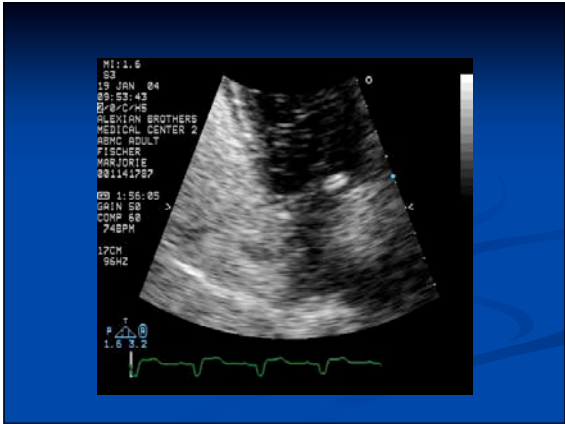
Characteristic	Cryptogenic Stroke (N=227)	Stroke of Known Cause (N=276)	P Value
Age — yr	58.2±13.9	64.5±10.4	<0.001
Female sex — no. (%)	94 (41.4)	97 (35.1)	0.17
PFO — no. (%)	77 (33.9)	34 (12.3)	<0.001
PFO-ASA — no. (%)	33 (14.5)	11 (4.0)	<0.001
Hypertension — no. (%)	143 (63.0)	222 (80.4)	<0.001
Diabetes — no. (%)	48 (21.1)	74 (26.8)	0.15
Hyperlipidemia — no. (%)	81 (35.7)	111 (40.2)	0.31
History of smoking — no. (%)	68 (30.0)	76 (27.5)	0.55
Coronary artery disease — no. (%)	41 (18.1)	82 (29.7)	0.003
Peripheral artery disease — no. (%)	12 (5.3)	20 (7.2)	0.46
Aortic plaque — mm	2.72±1.83	3.06±1.55	<0.001

* Plus-minus values are means ±SD. PFO denotes patent foramen ovale, and ASA atrial septum aneurysm.

Handke M et al. N Engl J Med 2007;357:2262-2268

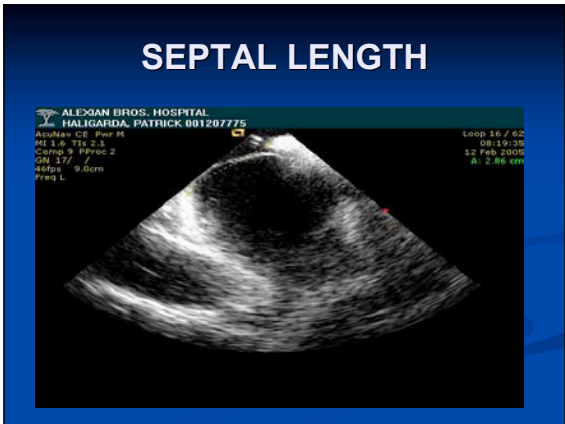
Bubble Study



Sizing a PFO

- Amount of 'bubbles' crossing the septum
- Measurement of opening



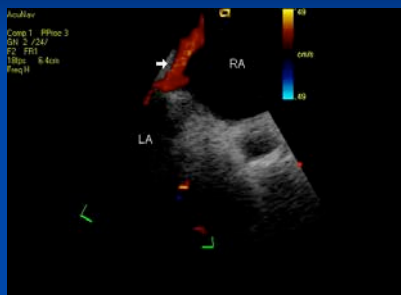
SIZE OF PFO



LENGTH OF TUNNEL



Intra-Cardiac Echo



Device Selection

Shortest Defect to Aortic Root or Defect to Superior Vena Cava Orifice Distance (mm)	Suggested AMPLATZER PFO Occluder Size (mm)
9 - 12.4	18
12.5 - 17.4	25
> 17.5	35

Hematological

RESPECT Trial coagulation parameters:

- * Antithrombin activity assay
- * Prothrombin G20210A mutation
- * Factor V Leiden mutation and/or activated protein C resistance
- * Fasting plasma homocysteine
- * Lupus anticoagulant
- * Anticardiolipin Ab of the IgG and IgM subtypes
- * B2-glycoprotein-1 antibodies
- * Factor VIII activity assay
- * Protein C activity assay
- * Free Protein S antigen assay

PFO

MEDICAL TREATMENT

ASYMPTOMATIC

SMALL	ASA
LARGE	ASA
ATRIAL SEPTAL ANEURYSM	ASA + PLAVIX

SYMPTOMATIC

SMALL	ASA + PLAVIX + ? COUMADIN
LARGE	ASA + COUMADIN
MIGRAINE	ASA + PLAVIX

PFO

TREATMENT WITH CLOSURE DEVICE

PFO ACCESS REGISTRY

2 CRYPTOGENIC STROKE ON ASA, PLAVIX,
COUMADIN

CLOSURE WITH APPROVED ASD DEVICE

MIGRAINE – PREMIUM STUDY

PFO Closure for Strokes?

- No consensus
- No occluder device approved in US
- Two currently ongoing clinical trials
 - CLOSURE I
 - RESPECT

What are the next steps....

- Stroke Randomized trial status-
Closure one –COMPLETED
RESPECT-nearing completion

MIGRAINE

lots need to be sorted out

Current Clinical Trials - problems

- Randomized clinical studies:
 - Medical vs. PFO-closure
- Subjects present with treatment preference:
 - Randomized Controlled Studies
 - Unwilling to participate
- Patients / physicians willing to just close the PFO
 - outside clinical studies
 - devices readily available for off-label closure

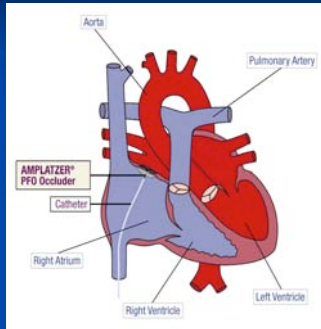
Clinical Trial Design

- The RESPECT PFO Clinical Trial is a randomized evaluation comparing PFO device closure versus medical therapy.
- Maximum 900 patients (450 per arm)
 - Recent cryptogenic stroke (270 days)
 - 18-60 years of age
- Maximum 75 participating institutions across the U.S. and Canada (60 approved sites)

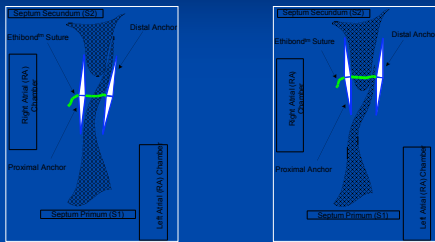
Gore REDUCE Study Design Advantages

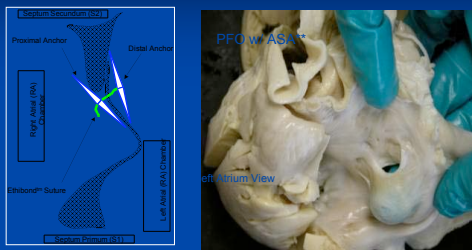
- 2:1 randomization scheme - allows two device arm subjects for every control arm subject
- MR imaging of every subject prior to enrollment and at an endpoint event or two years post-randomization
- Standardized antiplatelet medical therapy across treatment arms
- Multinational study including sites in the US and the Nordic countries
- Utilization of the GORE HELEX Septal Occluder

Device Deployment



Clamshell devices





***Source: Cardiovascular Human Heart, J. Edwards Center, St. Paul, MN

Stroke Prevention: Medical Therapy vs. Transcatheter PFO Closure



Incidence of Recurrent Stroke (%)		
Study Design	Medical Therapy	PFO Closure
Meta-Analysis ¹	3.8-12/year	0-4.9/year
Retrospective ²	24.3/4-year	8.5/4-year (p=0.05)
Retrospective ³	13/year ASA 5.6/year warfarin	0.6/year (p<0.001)

Amplatzer Occluder: Complications

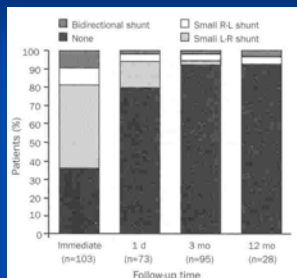
Table 2. Peri-interventional Complications*

Complication	No. of complications	APO	ASO	Intervention
Atrial fibrillation	2	1	1	Cardioversion in 1 patient
Femoral arteriovenous fistula	2	1	1	Surgical repair in 1 patient
Small aneurysm of femoral artery	1	1	1	None
Profound sinus node dysfunction	1	1	1	Pacemaker implantation
Device embolization dislodgement	1	1	1	Device retrieval
Total	7	2	5	4

*APO = Amplatzer PFO (patent foramen ovale) occluder; ASO = Amplatzer septal occluder.

Khositseth, Mayo 2004

Amplatzer Occluder: Residual Shunt



Khositseth, Mayo 2004

PFO Closure Devices

- Umbrella devices
- Suture based techniques
- Non device closure
- Bioresorbable devices
- In-tunnel devices

Amplatzer



18, 25, 30, 35 mm

Nitinol wire frame mesh
Dacron patches inside
Two discs, short connecting waist
The left atrial disc is smaller (exception: 18mm device)

Not FDA approved

CardioSEAL and CardioSEAL-STARFlex



23, 28, 33, 40 mm

Two rectangular discs
each consisting of four wire spring arms
Covered with a polyester patch
Microspring system (CardioSEAL-STARflex)



• Helex

- One single Nitinol wire formed in a spiral
- Two discs
- ePTFE
- Monorail delivery catheter




Occlutech PFO Occluder





AtriaSept PFO PFO-Star 6th Generation

Two discs (Ivalon)
Stranded wires to prevent fractures

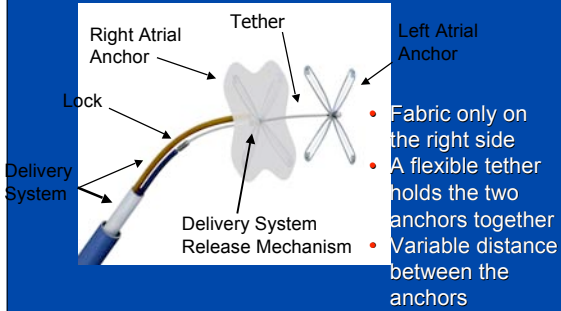
Right side is retrievable and repositionable

Articulated connection to achieve better adaption to the septum

20-35 mm

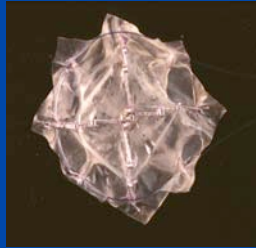
Premere PFO Closure Device



Not FDA approved

BioSTAR (NMT)

- CardioSEAL® framework
- STARFlex® self-centering mechanism
- Bioresorbable collagen matrix, heparin coating
- Only the metallic framework remains



Not FDA approved

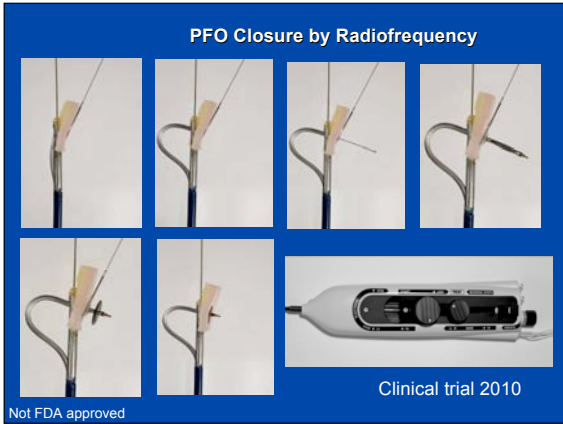
The Sutura SuperStitch® EL Arms and Needles

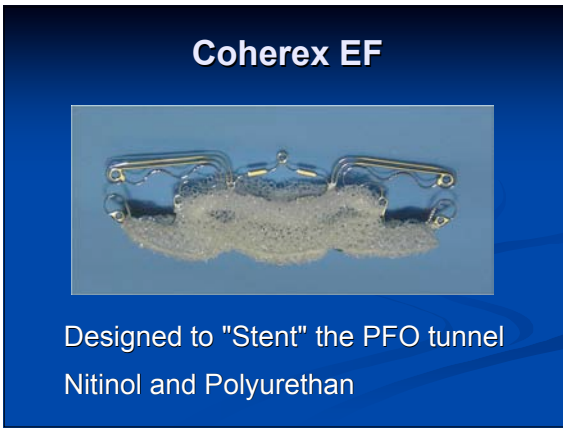
- Based on a puncture site closure technique
- Profile: 12 Fr
- Working length: 90 cm
- Suture type: Polypropylene 4-0



In clinical trials

Courtesy C. Ruiz Not FDA approved





Recent Non-Randomized Studies of PFO Closure in Migraine

	Patients	Follow-up	Results
Reisman et al. JACC 2005;45:493-5	50, ± aura	37±23 weeks	56% resolution 14% ≥50% improvement
Ázarbal et al. JACC 2005;45:489-92	30, ± aura	3 months	63% resolution 80% improvement
Giardini et al. Am Heart J 2006; 151:922-6	35, all + aura 71% F 41±11 yr	1.7±1.3 yr	91% had resolution or significant improvement

MIST –BOTH PRIMARY AND SECONDARY ENDPOINTS WERE

Table 3. Efficacy Analyses: Intention-to-Treat Population

	Implant (n=74)		Sham procedure (n=73)		Statistical Analysis*	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	P
Patients with no migraine attacks, n	0	3	1	3	-0.96% (-6.45-4.54)	1.0
Frequency of migraine attacks, mean±SD	4.82±2.44	3.22±1.80	4.51±2.17	3.52±2.13	0.45 (-0.16-1.05)	0.14
n	66	66	73	73
Total MIDAS score, median (range)	36 (3-106)	17 (0-27)	34 (0-136)	18 (0-24)	1 (-11-10)	0.88
n	66	67	69	72
Headache #/3 mo (MIDAS), median (range)	27 (0-70)	13 (0-30)	20 (0-50)	21 (0-60)	1 (-5-6)	0.79
n	66	67	69	72
HT-6 total score, mean±SD	67.2±4.7	59.5±9.3	66.2±5.1	58.5±8.6	0 (-3-3)	0.77
n	67	67	69	73

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

And Two major US Migraine trials were terminated MIST II and ESCAPE....

Some facts

- Migraine effects roughly 17% of population
- Migraine associated with stroke
- Migraine is now considered a progressive neurological disorder
- Migraine patients have both white and gray matter changes ((cognitive, exec. Function, no longer just “motor track neurology”)
- Migraine is not just a headache it is a functional disorder
- Migraine medications treat symptoms not pathology, especially in the episodic type.
- There is no “pathologic disease signature” or biomarker,

Some facts II

- 4% of migraines “transform from episodic to chronic headache
- There are genetic factors, predominantly in the rare types NOT the common sporadic types
- Migraines have thrombophilia and platelet dysfunction
- Aura appears to be a major component of the PFO headache
- Migraine –“PFO” –stroke complex..... predicting the patient to most benefit from closure
- The Placebo conundrum, nocebo conundrum.

AHA/ASA/ACCF Science Advisory

**Percutaneous Device Closure of Patent Foramen Ovale for
Secondary Stroke Prevention**

A Call for Completion of Randomized Clinical Trials

**A Science Advisory From the American Heart Association/American
Stroke Association and the American College of Cardiology Foundation**

The American Academy of Neurology affirms the value of this science advisory.

Patrick T. O'Gara, MD, FAHA, FACC, Chair; Steven R. Messé, MD, FAHA;
E. Murat Tuzcu, MD, FAHA, FACC; Gloria Catha, BA; John C. Ring, MD, FACC

"The optimal therapy for prevention of recurrent stroke or transient
ischemic attack in patients with cryptogenic stroke and patent
foramen ovale has not been defined. Completion and peer review
of ongoing trials are critical steps to establish an evidence base from
which clinicians can make *informed decisions regarding the best
therapy for individual patients.*"

Circulation. 2009.
