PFO Closure–
Will They Ever Get Any RESPECT?

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Disclosure:

- Consulting/Employment: St. Jude Medical, Boston Scientific, Abiomed, and Covidien
- Stock Equity or Options: Direct Flow
- Speakers' Bureaus/Honoraria: St. Jude Medical, Boston Scientific, and Abiomed

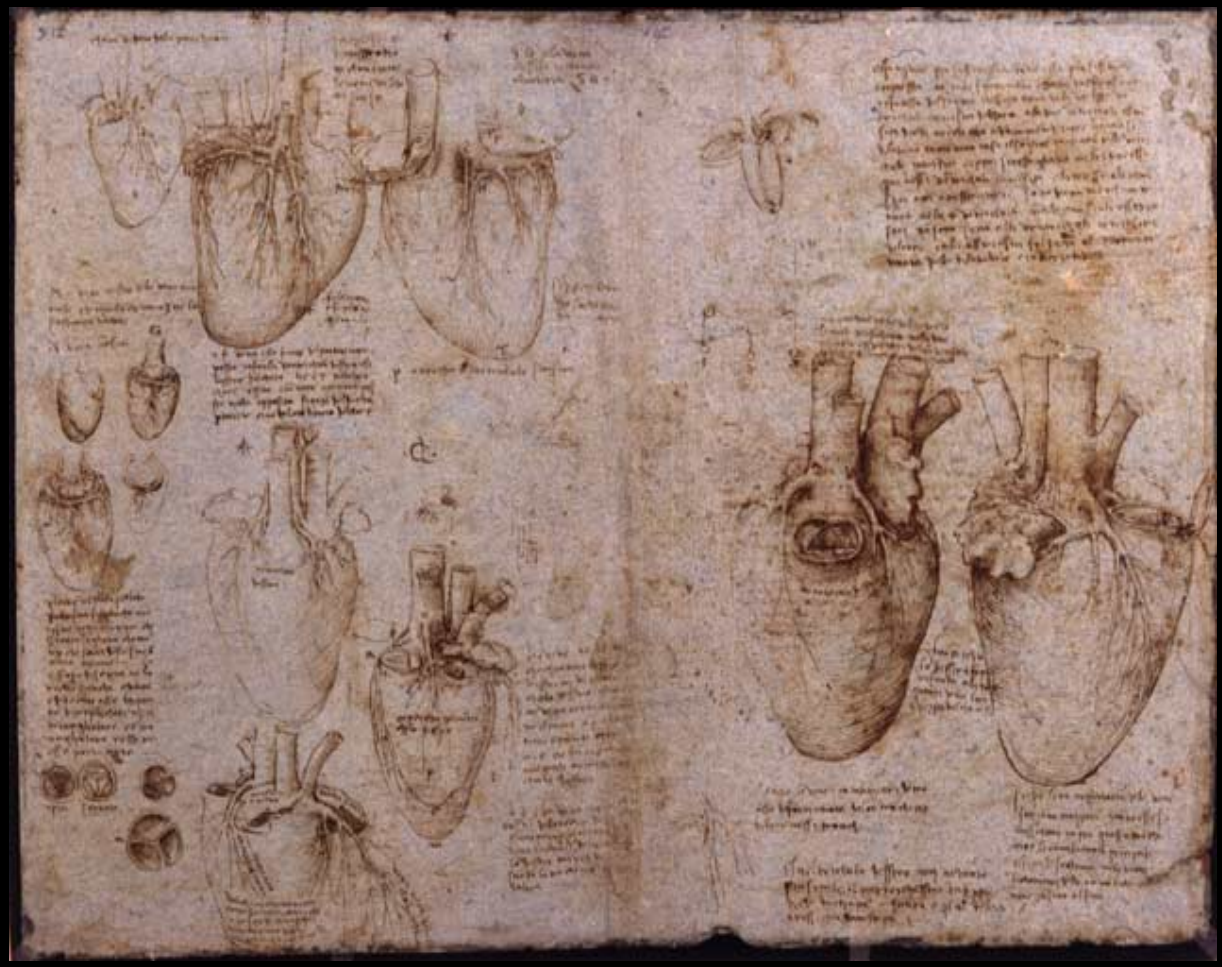
The PFO / Stroke Story

1513

Leonardo da Vinci

- Heart Drawings

“I have found a perforating channel from the left auricle to right auricle.”



Windsor Folios, part of the Royal Collection, held at Windsor

The PFO / Stroke Story

1877

Julius Friedrich Cohnheim

- German Pathologist
- Protégé of Virchow
- Patent Foramen Ovale

Julius Cohnheim (1839–84). (Collec-

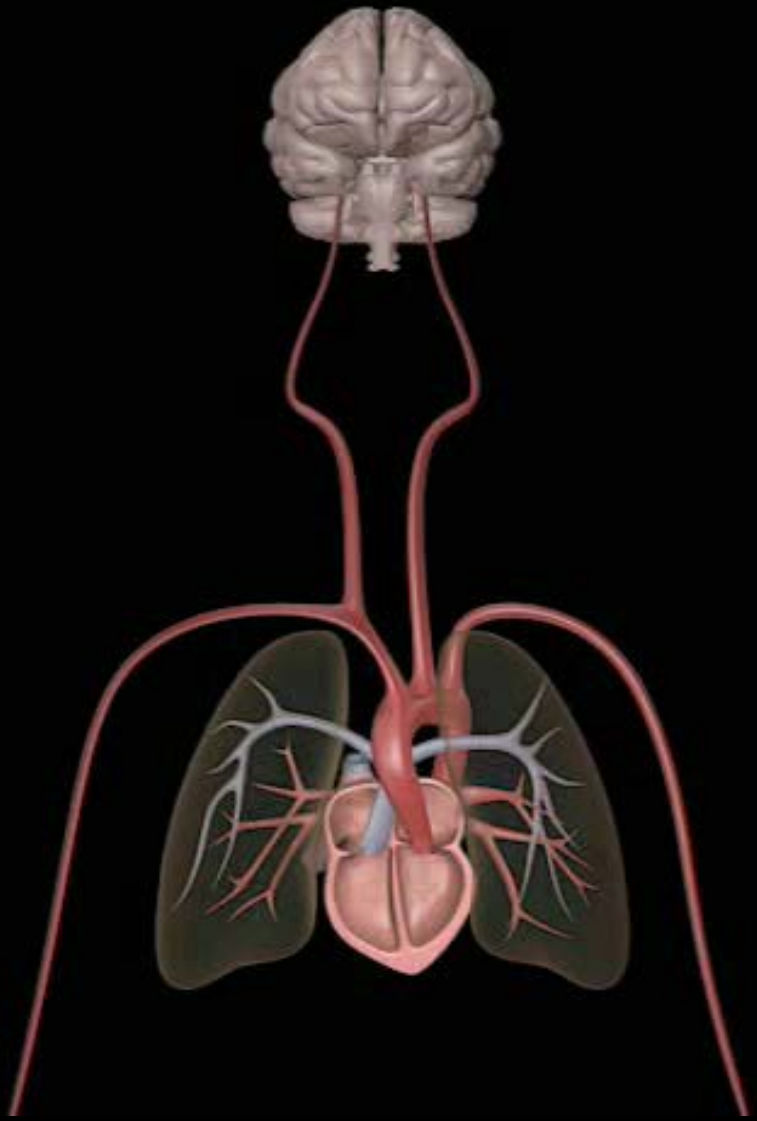
Cohnheim, J. Circulation, Thrombose & Emboli, Vol 1, p. 134. Berlin, 1877. A. Hirschwald.

The PFO / Stroke Story

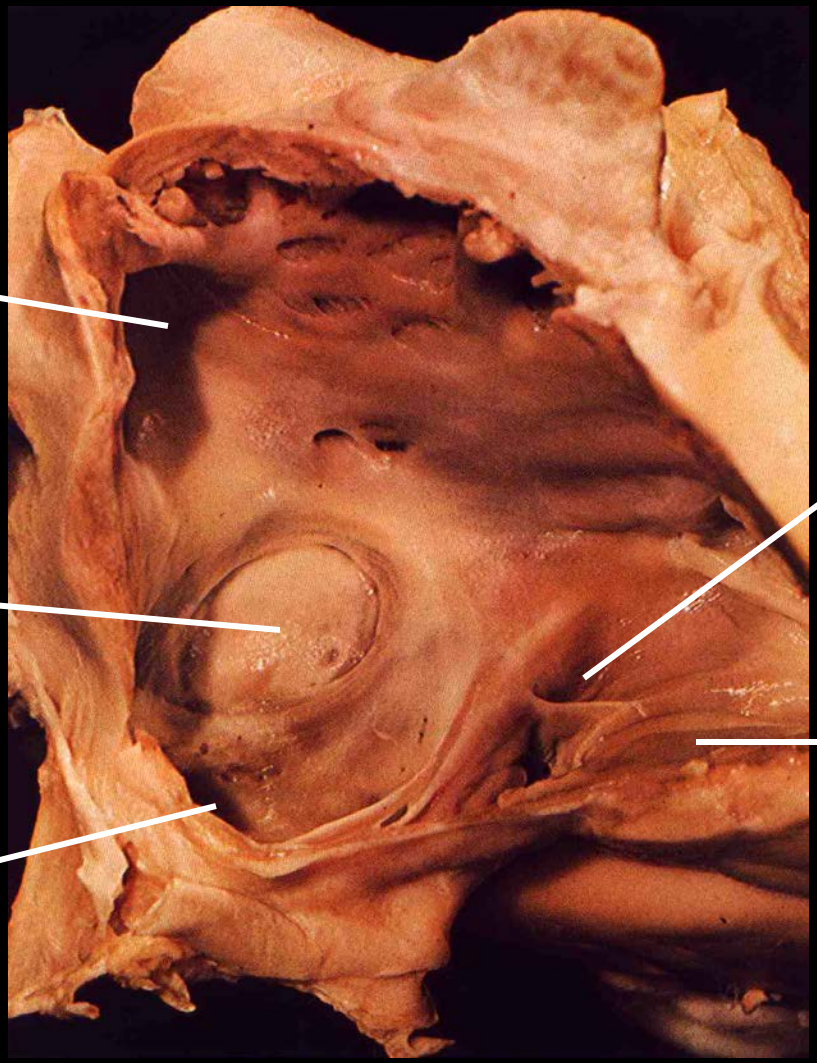
1877

Julius Friedrich Cohnheim

- “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*.”



The Interatrial Septum



Superior Vena Cava

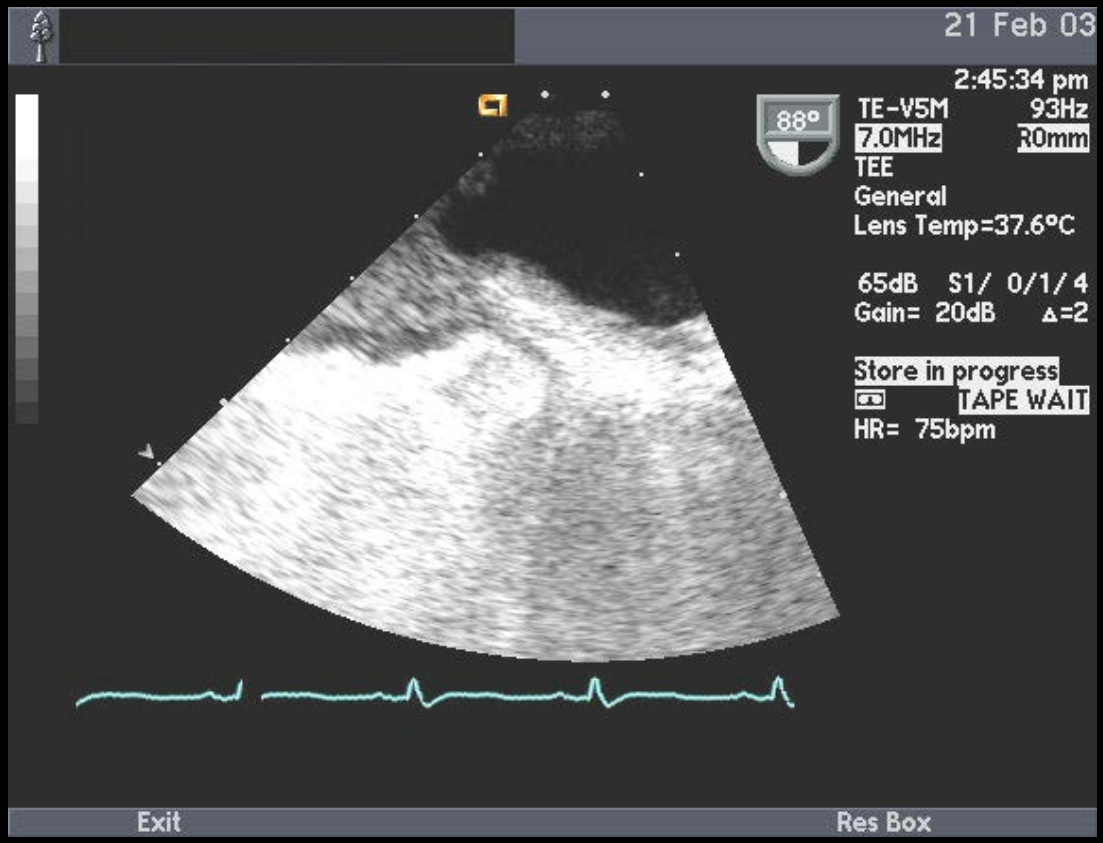
Fossa Ovalis

Inferior Vena Cava

Coronary Sinus

Tricuspid Valve

IV Saline Contrast Study



There are no FDA-approved devices for PFO but off- label use abounds

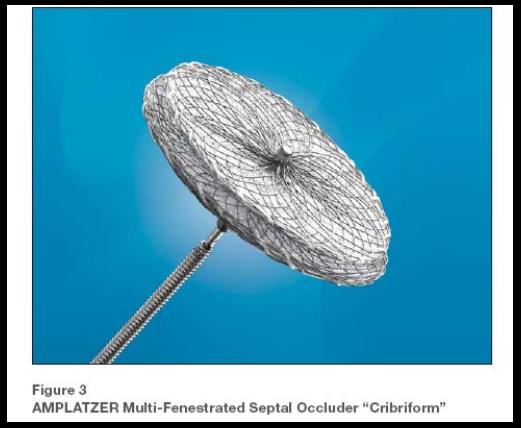
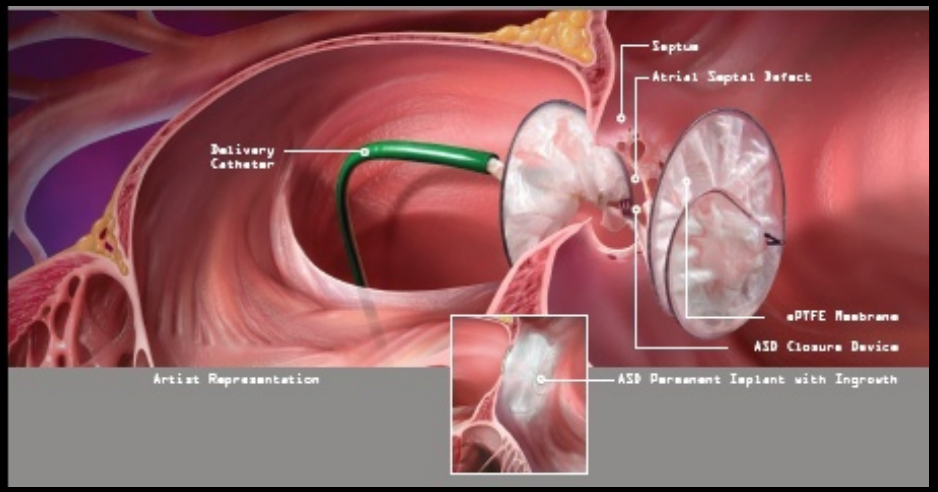


Figure 3
AMPLATZER Multi-Fenestrated Septal Occluder "Cribriform"

Figure 4
AMPLATZER® Septal Occluder

- Amplatzer Septal Occluder
  - AGA Medical Corporation
- Gore Helex Septal Occluder
  - W.L. Gore & Associates



Conditions Associated with PFO (Patent Foramen Ovale)

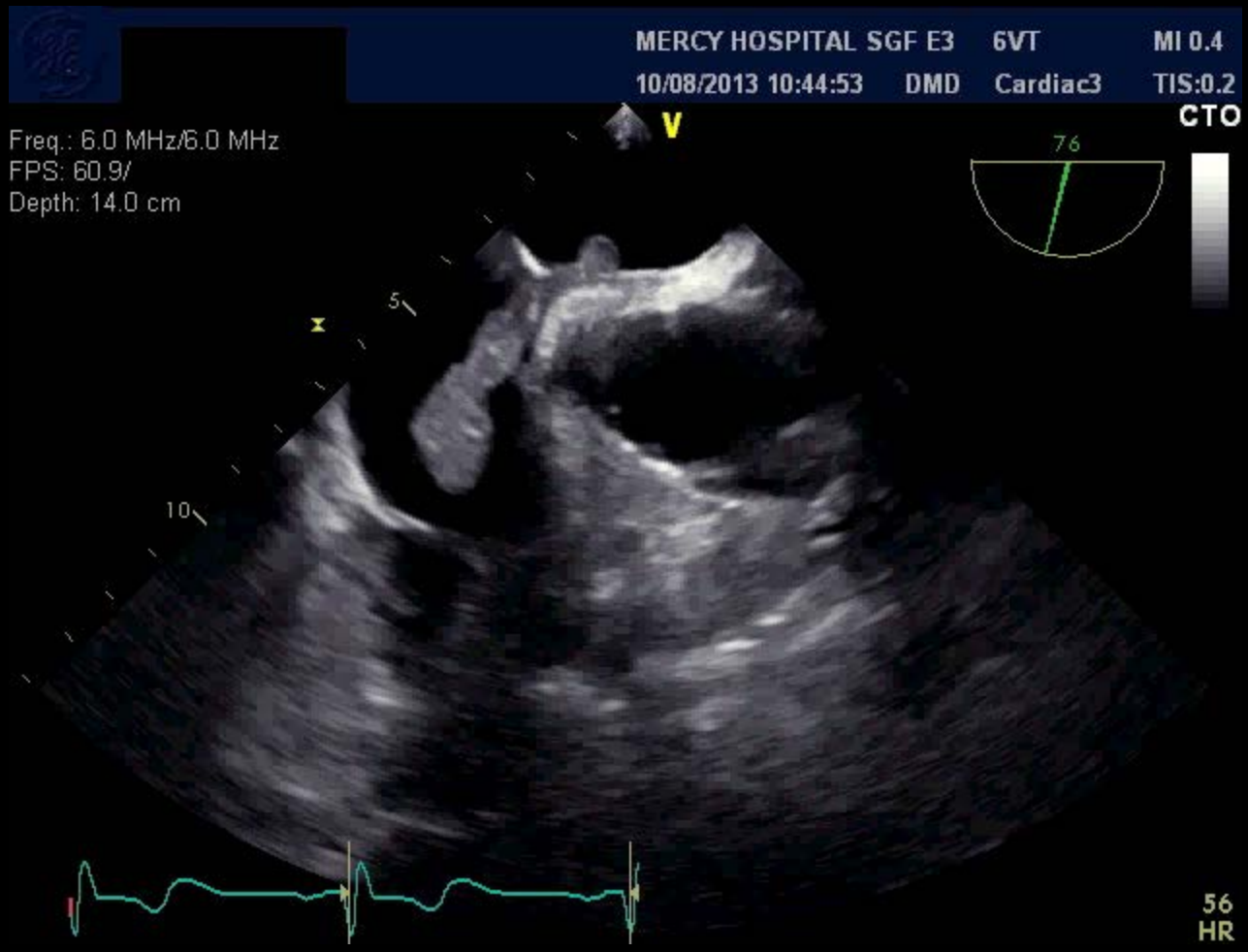
1. Cryptogenic Stroke < 60yo, or older
2. Migraine Headache with or w/o aura
3. Orthodeoxia Platypnea (O_2 Sat < 92%)
4. Acute MI with normal coronaries
5. Decompression Illness
6. High Altitude Pulmonary Edema
7. Obstructive Sleep Apnea Exacerbation
8. Raynaud's Phenomena
9. Dementia ?

Unifying Hypothesis: some venous particulate clot or platelets, or chemical, bypasses the lung and enters the arterial circulation.

Association of PFO and cryptogenic stroke in young adults (< 55 yo)

Study	Pts	PFO (crypto)	PFO (control)	P
Lechat (1988)	26	54%	10%	<0.01
Webster (1988)	40	50%	15%	< 0.01
De Belder (1992)	39	13%	3%	< 0.01
De Tullio (1992)	21	47%	4%	<0.01
Hausmann (1992)	18	50%	11%	< 0.01
Cabanes (1993)	64	56%	18%	< 0.01
Total	202	46% (93/202)	11% (29/271)	< 0.01

Transit in Thrombus Caught in Long Tunnel PFO



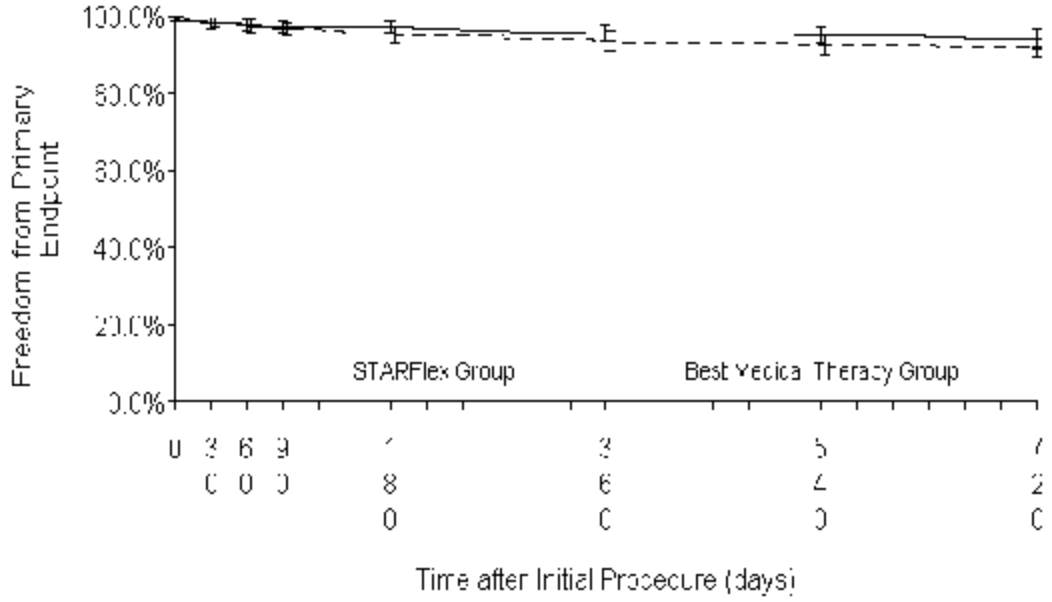
Diagnosis of a Paradoxical Embolic Stroke

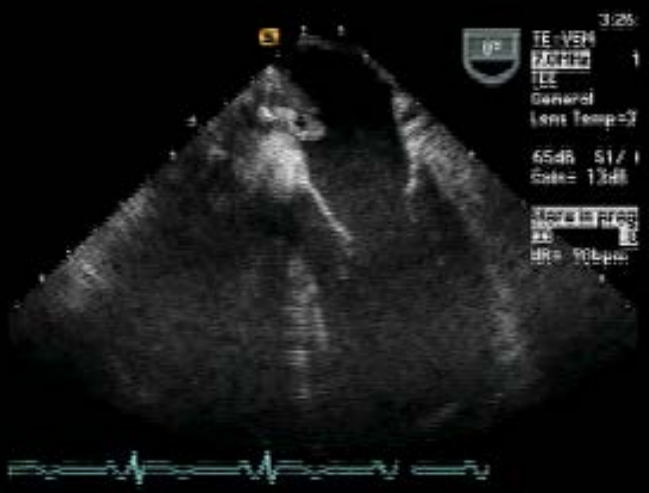
- Non-Paradoxical Embolic Sources Excluded
  - Cerebral Artery Disease (carotid ultrasound)
  - LV Aneurysm (TEE)
  - Aortic Atheromas (TEE)
  - Atrial Fibrillation (Holter monitoring)
  - Hypercoagulability (protein C & S, antithrombin III, Lupus anticoagulant, anticardiolipin antibody, factor V Leiden, Prothrombin 20210A mutation)
- Presence of PFO (or other right to left shunt)
  - Transthoracic echocardiogram with bubble study
  - Transesophageal echocardiogram with bubble study
  - Transcranial Doppler with bubble study

With All This Suggestive Data Many Thought A Randomized Trial Unnecessary

CLOSURE I
Investigating the PFO Stroke Connection

Kaplan-Meier for Primary Endpoint ITT

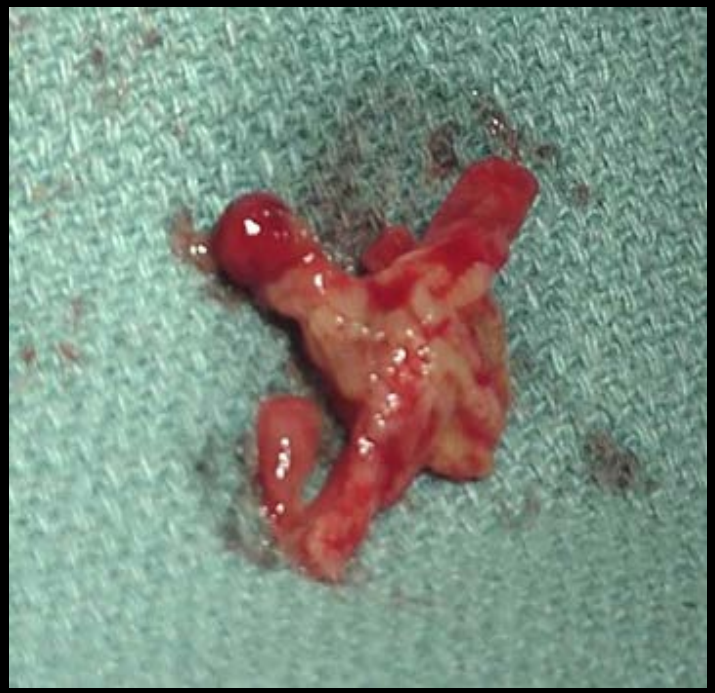




Why StarFlex recurrent stroke rate may not be less than medical Rx:

2) Thrombus on CardioSeal Implant

By TEE: 7 – 22% at 1 mo.



Risk of a PFO occluder device must be less than risk of recurrent stroke!!

Recurrent stroke rate 3.4% with CardioSeal
Reisman, Jesurum: AJC 2007, 99; 1312-15

The Final Results with Primary End Point Analyses

RESPECT

CLINICAL TRIAL

RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

JOHN D. CARROLL, MD, JEFFREY L. SAVER, MD, DAVID E. THALER, MD, PHD, RICHARD W. SMALLING, MD, PHD, SCOTT BERRY, PHD, LEE A. MACDONALD, MD, DAVID S. MARKS, MD, MBA, DAVID L. TIRSCHWELL, MD

FOR THE RESPECT INVESTIGATORS

AMPLATZER PFO Occluder

RESPECT CLINICAL TRIAL

AMPLATZER PFO Occluder*

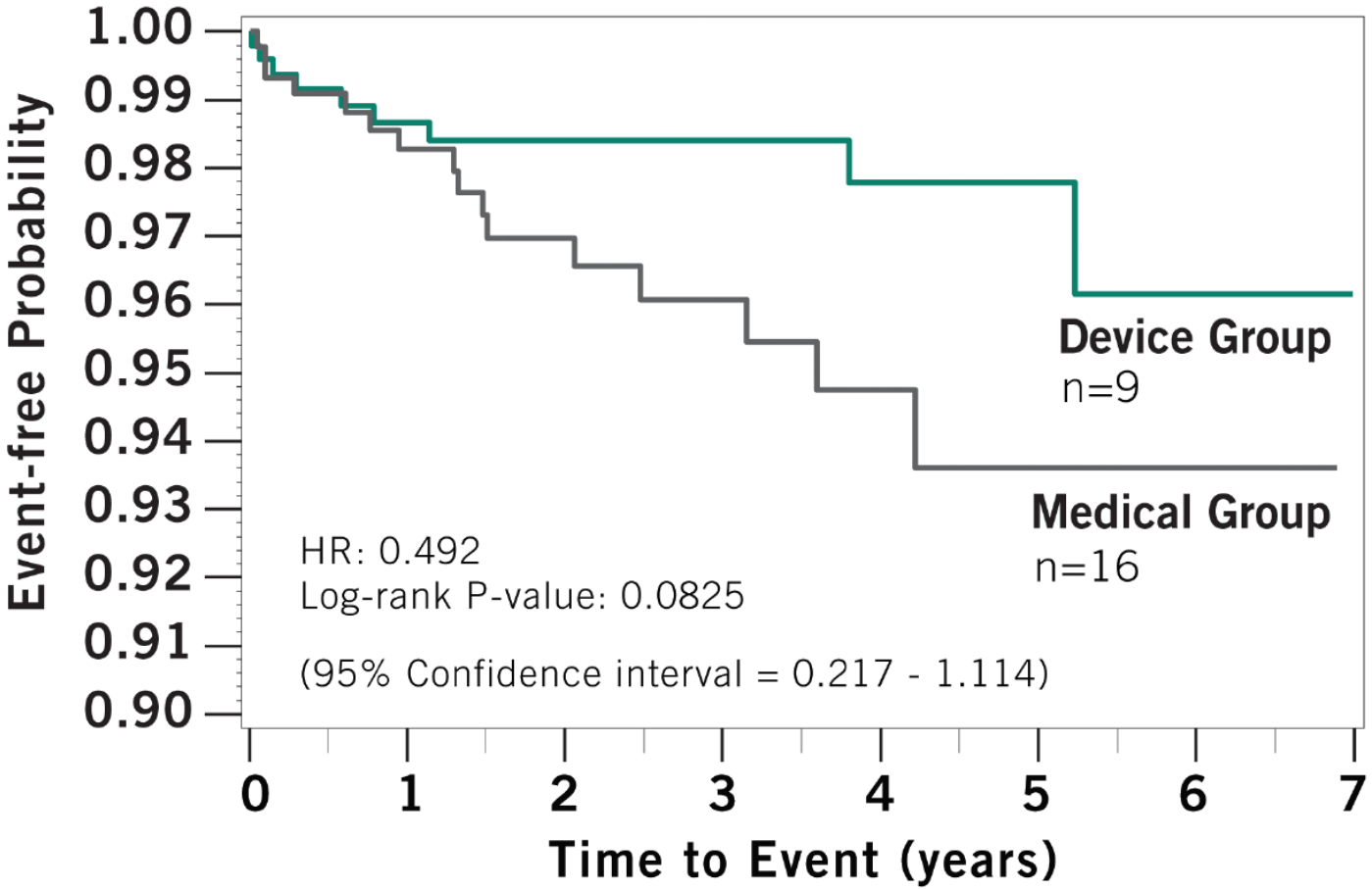
- Percutaneous, transcatheter device
- Self-expanding, double-disc design
- Nitinol wire mesh with polyester fabric/thread
- Radiopaque marker bands
- Sizes: 18, 25, 35 mm
- Recapturable and repositionable

*CAUTION: Investigational device in the United States. Limited by Federal (or U.S.) law to investigational use. Not available for sale in the U.S.

Primary Endpoint Analysis – ITT Cohort

50.8% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL

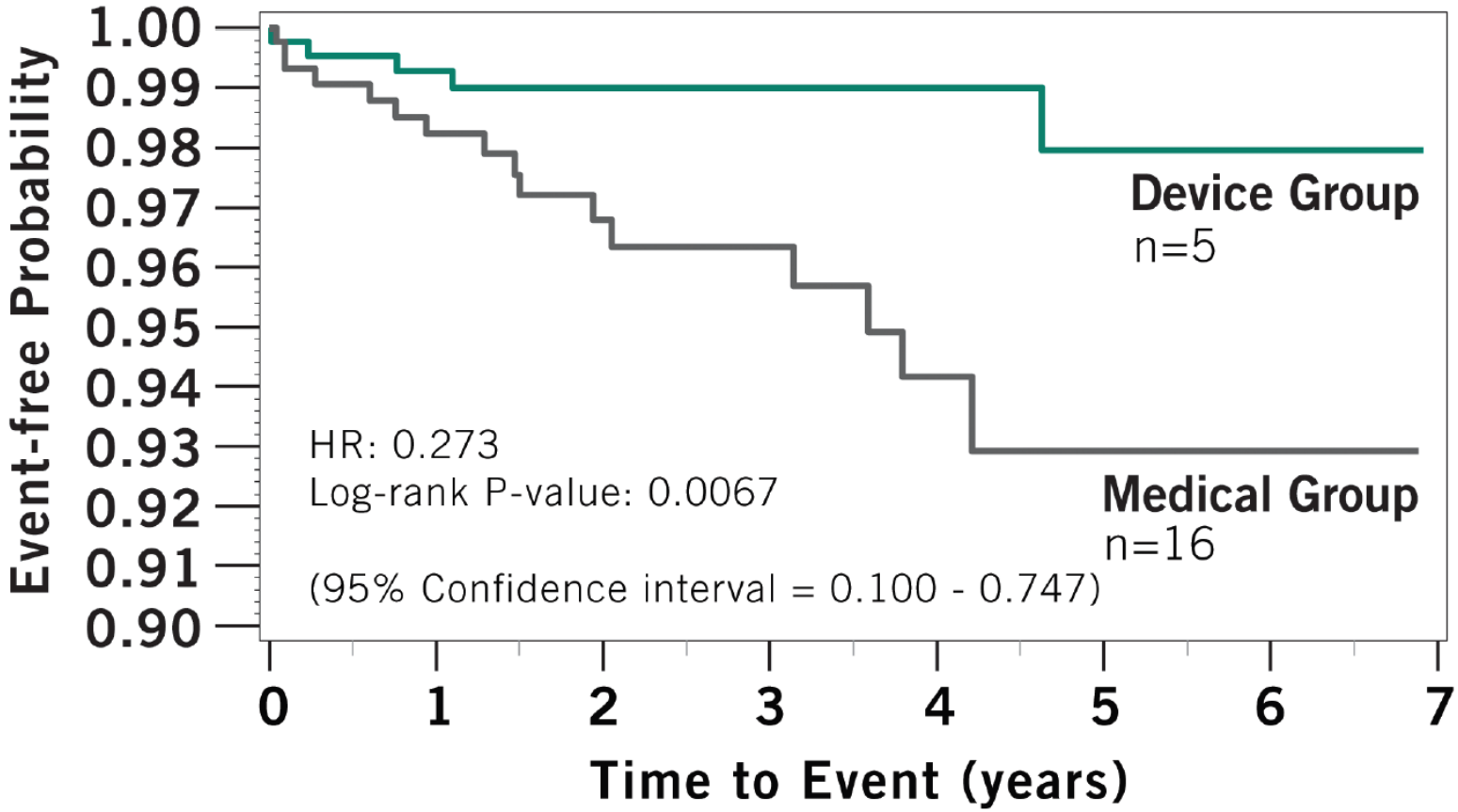


- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL



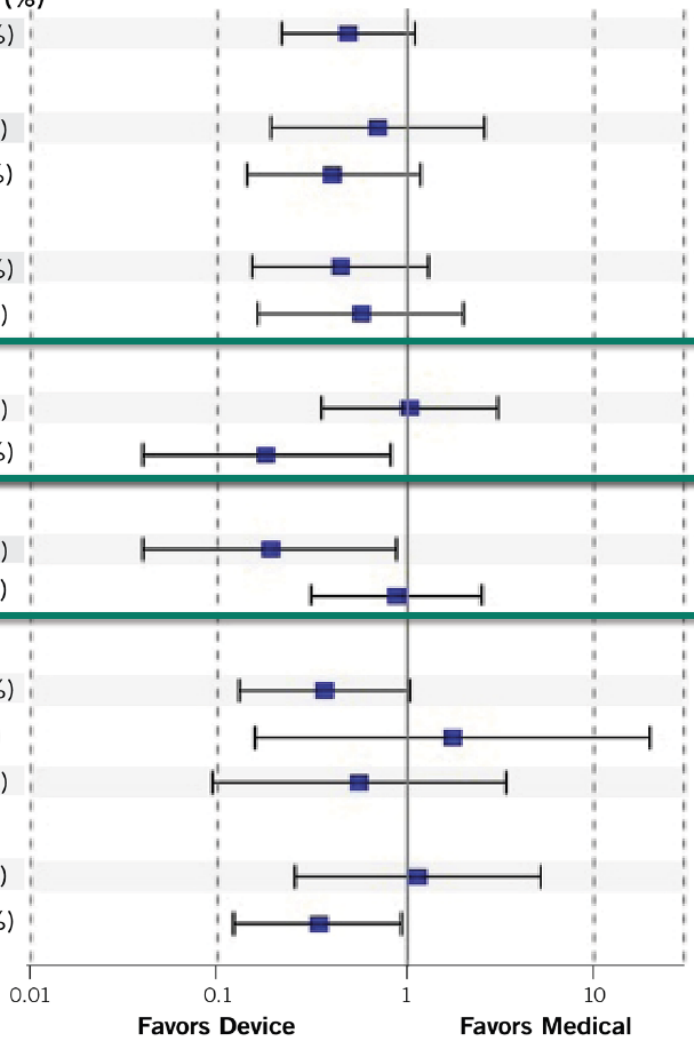
- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI		Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)					
Overall	9/499 (1.8%)	16/481 (3.3%)		0.492 (0.217, 1.114)	0.0825	
Age						0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)		0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)		0.405 (0.140, 1.165)	0.0828	
Sex						0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)		0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)		0.571 (0.161, 2.024)	0.3789	
Shunt Size						0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)		1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)		0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm						0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)		0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)		0.889 (0.312, 2.535)	0.8259	
Index infarct topography						0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)		0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)		1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)		0.558 (0.093, 3.340)	0.5167	
Planned medical regimen						0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)		1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)		0.336 (0.120, 0.944)	0.0299	

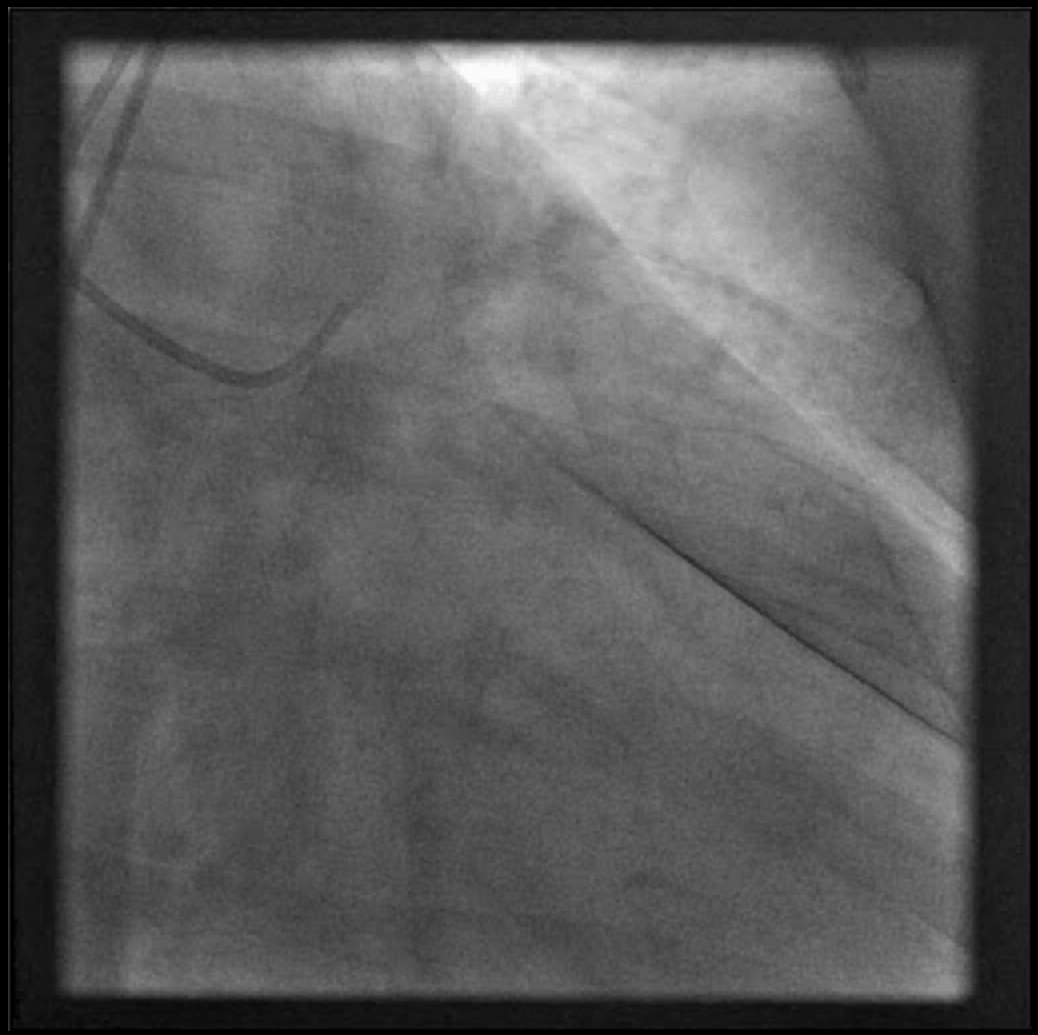


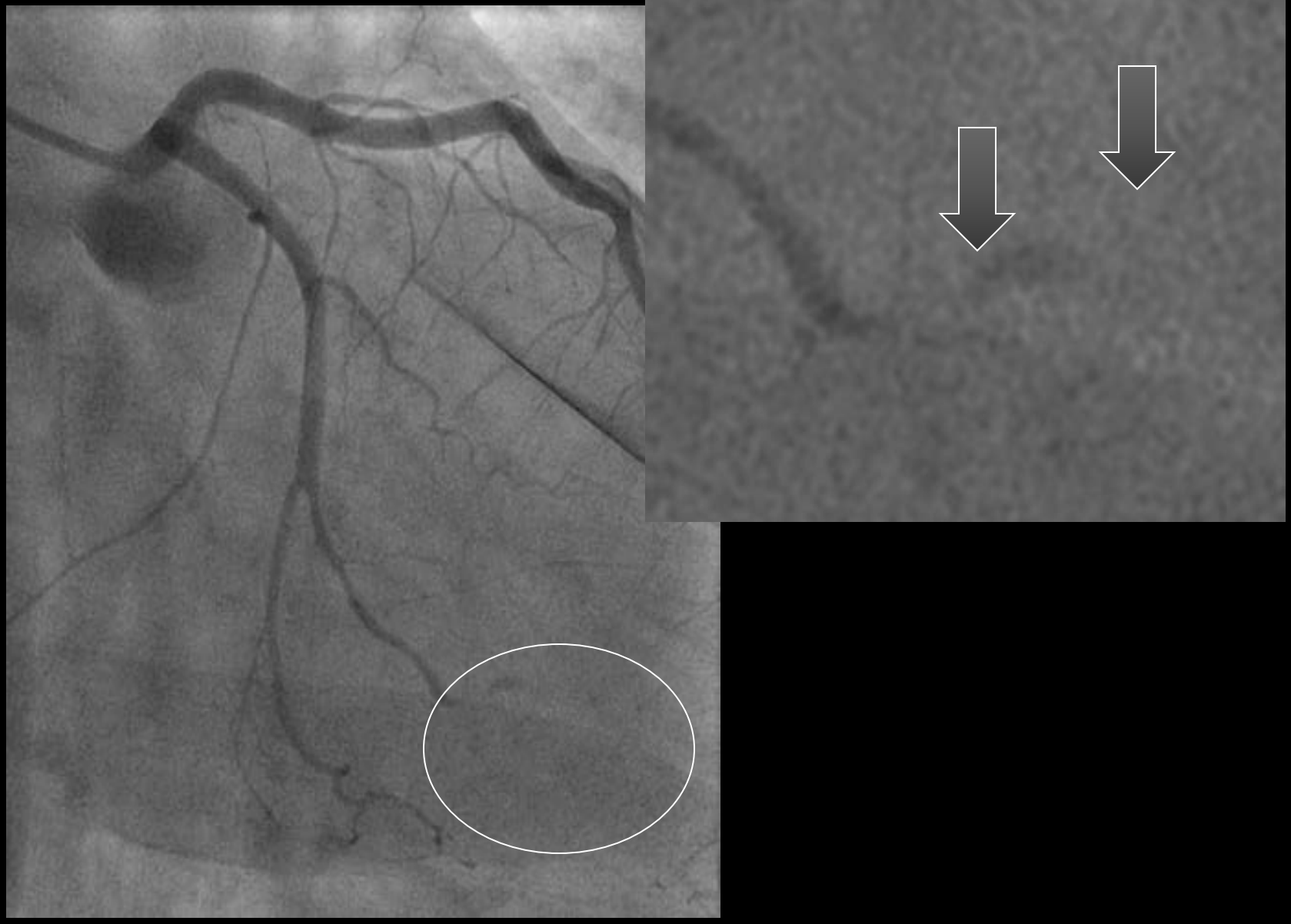
So Who Can We Close ?

Subsets Approved for Closure

Not All Paradoxical Emboli Effect the Brain- A Case Report

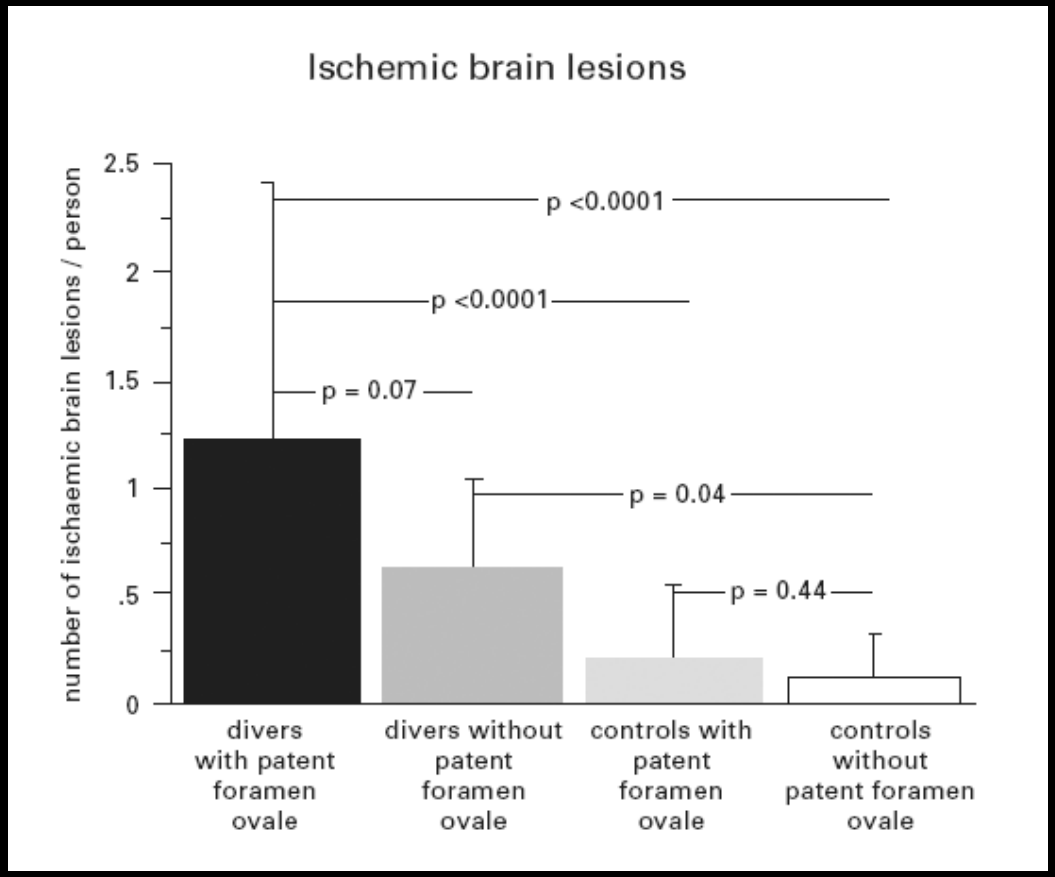
- 47 y/o female with chest, neck and left arm pain and no cardiac risk factors
- On BCPs
- Paramedics brought her to ER, where she has a ventricular fibrillation arrest
- ECG with T wave inversions V5-V6
- Troponins elevated at 21, CKMB at 249





Decompression illness
The Bends

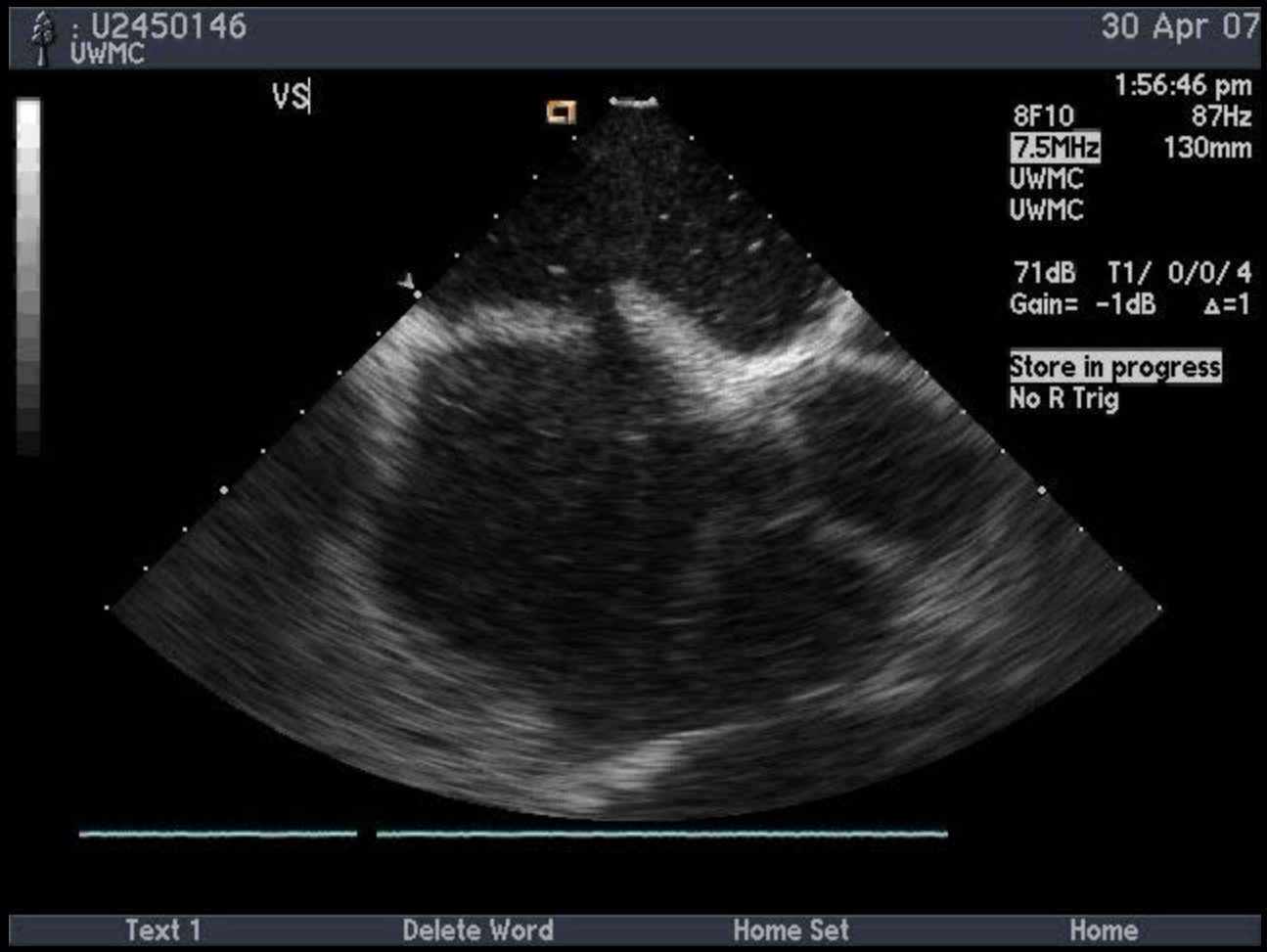
Asymptomatic ischemic brain lesions



Schwerzmann and Seilor Swiss Med Wkly 2001

Platypnea-orthodeoxia

- Hypoxemia due to right to left shunting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71dB T1/ 0/0/4
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Store in progress
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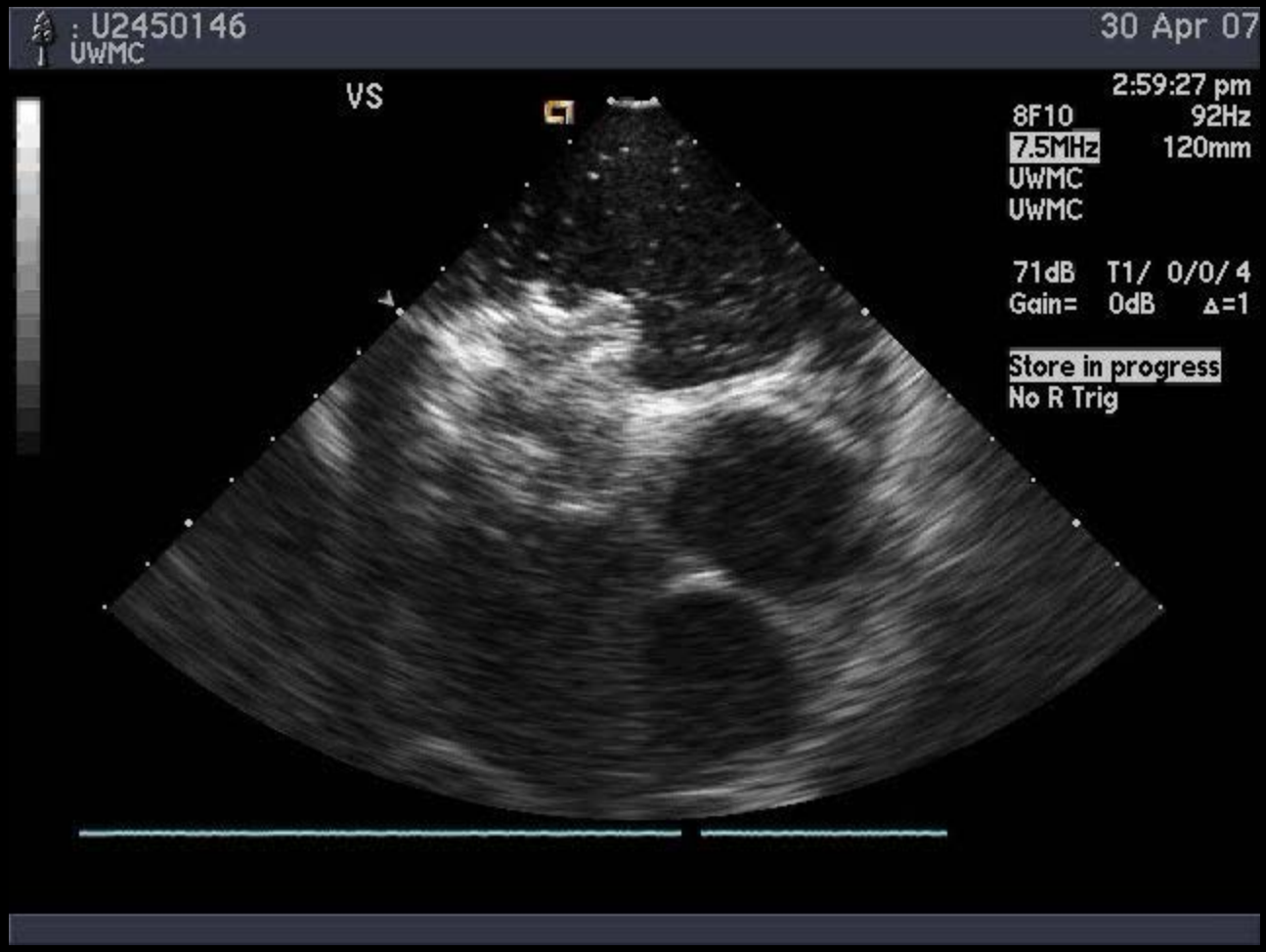
Cath Findings

- Right atrial pressure 16
- Pulmonary artery pressure 42/19
- Pulmonary cap wedge 14

- Pulm vein sats 97%
- LA sats 84%
- AO sats 82%

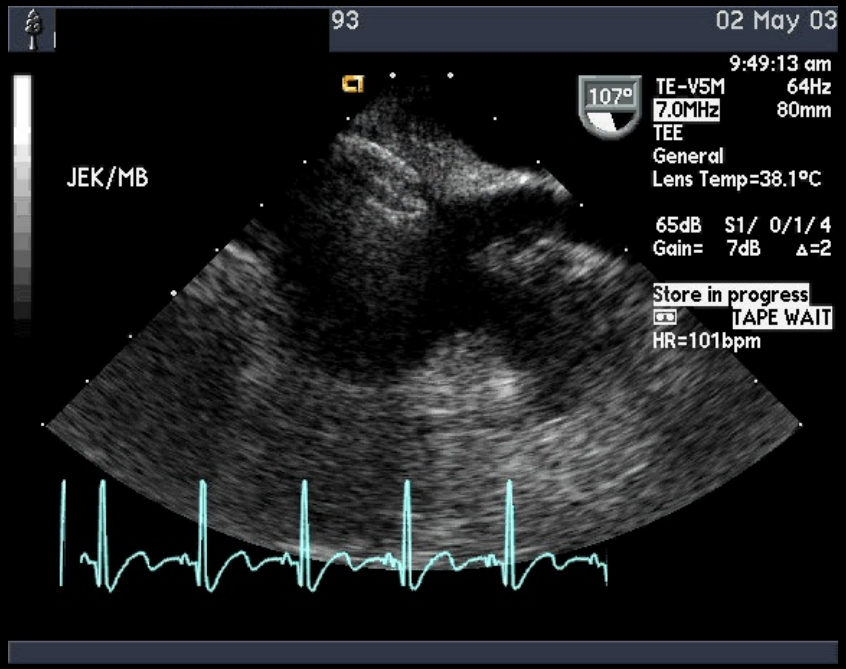
With a device in place O2 sats normalized



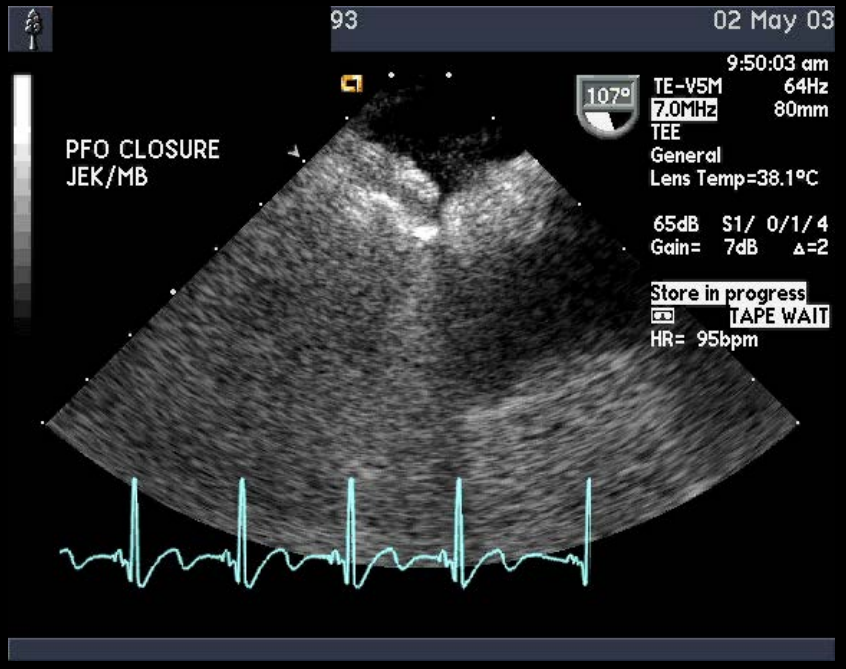
Hypoxia in Patients with Interatrial Septal Defects (IASD)

- Can be persistent, intermittent, or positional
- Mechanism involves transient or persistent elevation in RAP>LAP, or redirection of IVC blood flow toward septum
- Diagnosis can be challenging
  - Requires documentation of R-to-L shunt while hypoxemic
  - Confirmed by improvement in hypoxia after closure
- Associated with a wide variety of conditions
  - Pulmonary AVM
  - Liver Disease
  - Chronic Lung Disease
  - Amiodarone Toxicity
  - Pulmonary Emboli
  - Aortic Aneurysm
  - Carcinoid
  - Hypovolemia
  - Positive Pressure Ventilation
  - Post-pneumonectomy
  - RV Infarction
  - Cardiopulmonary Bypass

Patient with large “eccentrically located” PFO or “acquired” ASD

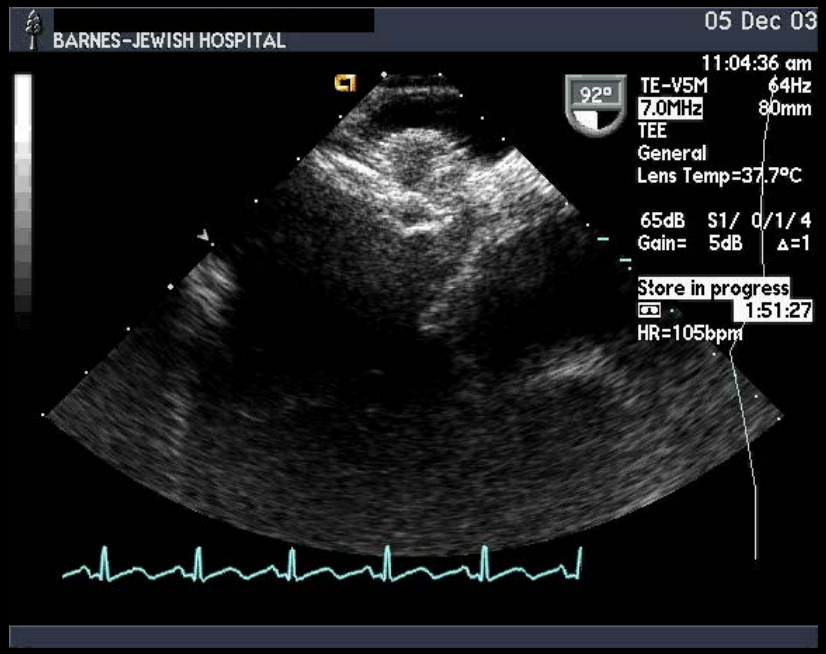


Device fails to cover the defect completely

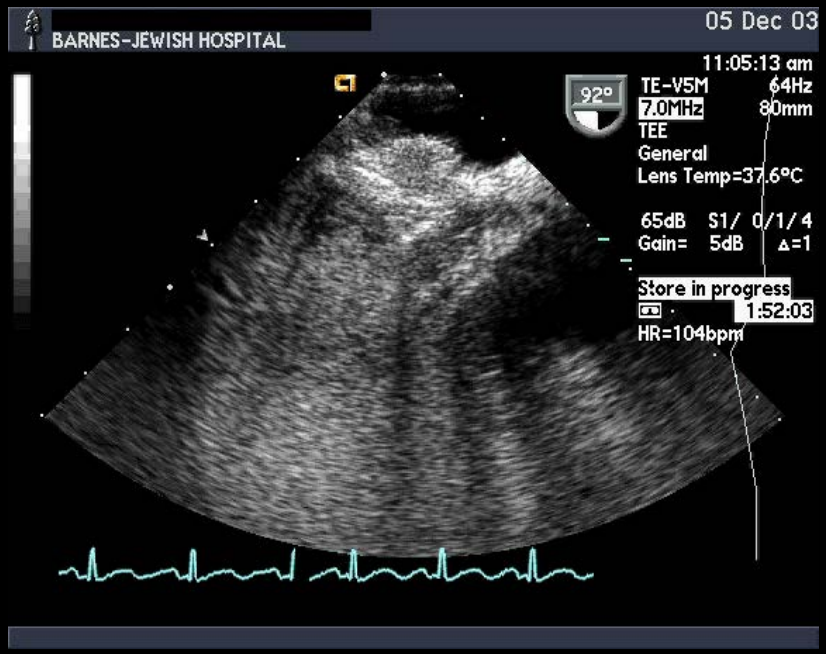


Residual right to left shunt by bubble study

Patient with large eccentrically located PFO /acquired ASD



Second device deployed to cover the residual defect



Bubble study shows elimination of residual right to left shunt

PFO Relationship to Migraines

Observational Studies
Effect of PFO closure on migraine

Study	Prevalence # migraine / # closed (%)	% migraine improved or cured	Length of follow up (months)
Wilmshurst 2000	21/37 (57%)	86%	up to 30
Morandi 2003	17/62 (27%)	88%	all 6
Schwerzmann 2004	48/215 (22%)	81%	all 12
Post 2004	26/66 (39%)	65% cured	all 6
Reisman 2005	57/162 (35%)	70%	all 12
Azarbal, Tobis 2005	37/89 (42%)	76%	mean 18
Total:	206/631 (33%)	78%	

The PFO / Stroke Story

2006

PFO, migraine with aura and cryptogenic stroke

Large atrial shunts (PFO & ASD) are present in:

- 7.3% - population controls
- 38.1% - migraine with aura but no stroke
- 55.6% - stroke but no migraine
- 84% - stroke and migraine with aura

MIST Trial

Migraine Intervention with STARFlex Technology (MIST) Trial

Presented at
The American College of Cardiology Scientific Session 2006

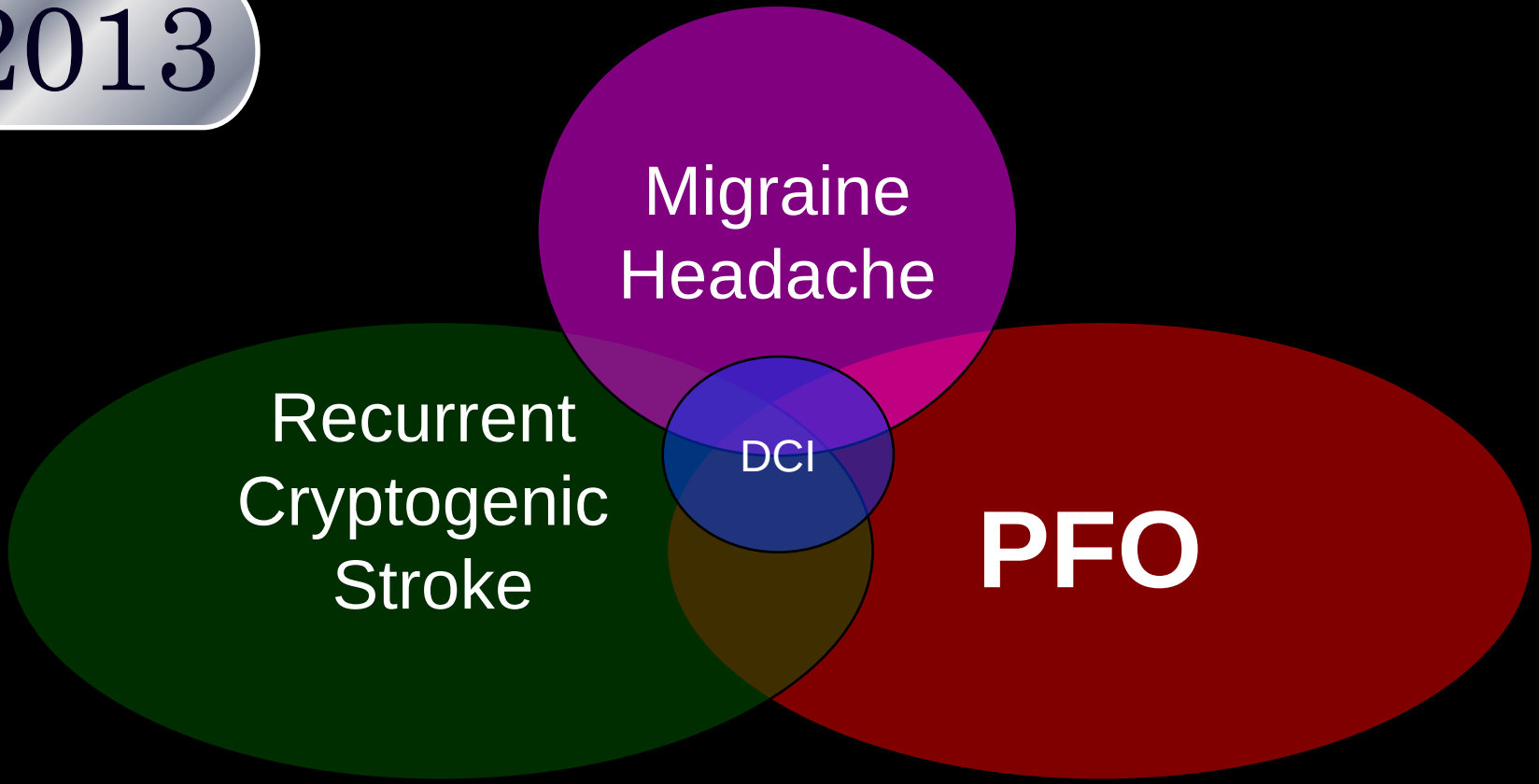
Presented by Dr. Andrew Dowson

Migraine Summary

- Relationship exists between PFO and Migraines.
- Two studies stopped due to modest benefit between closure and relief of symptoms
- Registry data notes 50% elimination and additional 20% improvement in migraines with PFO closure
- The discrepancy is attributable to the patient populations- the registries were PFO closures on suspected patients with paradoxical embolization while the migraine trials excluded any patient with TIA/CVAs!!

The PFO / Stroke Story

2013



The PFO / Stroke Story

2005

Tedy Bruschi

- New England Patriot Linebacker
- Stroke
- PFO Device Closure

The PFO / Stroke Story

2011

Bret Michaels, the
47-year-old singer
of rock group, Poison,
undergoes closure
of a PFO after a TIA.

WHAT IS KNOWN ABOUT PFO AND STROKE

- PFO occurs in 10-15% of all adults
- PFO is diagnosed in 50-70% of patients with stroke of unknown cause.
- After a first stroke due to PFO, ½ of patients still have moderate to severe disability after 1 year.
- After a first stroke due to PFO, second strokes occur at a rate of 2%-9% each year. (depending on risk)
- After several strokes from PFO, repeat strokes occur at a rate of 6%-20% each year.
- The risk of repeat stroke due to PFO is increased in patients with leg clots, migraine headache, atrial septal aneurysm (seen by echo), and large PFO shunting(seen by echo).

PFO TREATMENT OPTIONS
CATHETER CLOSURE OF PFO

- **RISKS**

  - Serious complications (0.2%): death, stroke, infection, bleeding, blood vessel injury, anesthesia, device movement or dislodgement (1:400), incomplete closure (1-5%) clot forming on device (30/10,000 cases)

- **BENEFITS**

  - Stroke reduction to less than 1%
  - No scar; minimal pain
  - Out-patient procedure
  - Return to full activity in 2 days

Summary

- PFOs have been conduits for trouble as recognized for centuries.
- The most recent trials regarding cryptogenic stroke suggest the high risk groups (ASA/ large PFO) benefit from closure.
- The CVA type reduced by the device is the type seen from embolic events.
- Certain indications exist for closure already- DCI, MI/peripheral embolizations.
- Certain anatomies can be closed up front (fenestrated septum or small ASDs) or have been reclassified to allow closure (acquired ASD) .
- Migraines with aura are still in play –if the patient has a history of a TIA/CVA
- Does a trial really need to show superiority or isn't getting off coumadin with equivalent results good enough for the patient?

PFOs ? A Tiger waiting to be released

The Ultimate Irony

Insurance companies may deny some percutaneous PFO closures due to the lack of convincing data however, you can have it closed surgically and be fully covered!