The Patent Foramen Ovale
A Preventable Stroke Etiology ? !

Brian Whisenant, M.D.

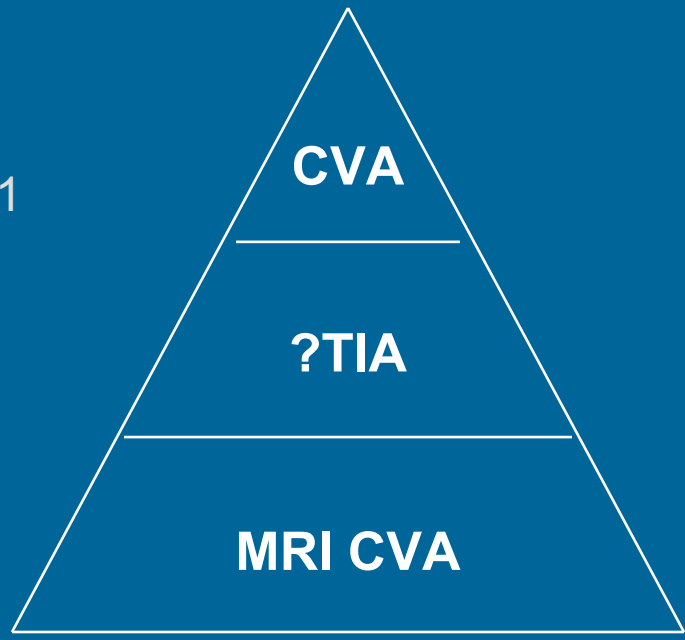
Conflict of Interest Statement

I have a financial interest in Coherex Medical.

Heart Disease and Stroke Statistics 2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee

Circulation 117; January 29, 2008

- 2.7% of men and 2.5% of women >18 years of age have a history of stroke.
- 17.8% of the population over 45 years of age reported at least 1 stroke symptom.
- The prevalence of silent cerebral infarction between 55 and 64 years of age is approximately 11% and increases to 43% above 85 years.



PFO Prevalence:
>20% general population
>40% cryptogenic stroke population

Common Disorders intersecting create the perfect storm.

All or None Polarization

". . . our results offer no justification for the use of potentially dangerous or aggressive treatments. Hence, although this was not one of the objectives of our study, we are led to conclude that invasive treatments such as percutaneous PFO occlusion should be performed only within the framework of a current clinical trial."

Serena, et al. Stroke. 2008 Sep 25. [Epub ahead of print]

Asymptomatic Significant Patent Foramen Ovale: Giving Patent Foramen Ovale Management Back to the Cardiologist

Gianluca Rigatelli,[1]* MD, Paolo Cardaioli,[1] MD, and Mauro Chinaglia,[2] MD

Catheterization and Cardiovascular Interventions 71:573–576 (2008)

Closure of the Patent Foramen Ovale With Dedicated Amplatzer Occluders: Closing in on a Mechanical Vaccination

Bernhard Meier, MD
Cardiovascular Department
University Hospital
Bern, Switzerland

Where are we today?

- Randomized Trials of PFO closure in Stroke and Migraine are ongoing (Closure I completed enrollment last week).
- Many patients referred for PFO consultation do not meet entry criteria for randomized trials.
- Physicians and patients often prefer off-label closure with ASD indicated devices.
- There is little prospective data regarding PFO closure complications and success.
- While PFO closure is technically straightforward, counseling patients regarding PFO closure is challenging.

The PFO Cardiologist?

"We just load the trucks."

No Truck Leaves Empty

Defer to Neurology

Cardiologists must be prepared to discuss complex decisions with intimate knowledge of the PFO space.

Does PFO Closure Prevent Strokes Beyond All or None

Cryptogenic Stroke
- < 55 yo
- > 55 yo

Stroke with suspected alternate etiology

Silent Stroke (MRI)

Transient Ischemic Attack

Systemic Embolism
- MI
- Organs (spleen, bowel)
- Extremities

Venous Thrombus
- DVT
- SVT
- UE thrombus
- PE

Procoagulant Disorders

Central venous foreign body
- permanent pacemakers
- chronic indwelling catheters

PFO Characteristics
- Atrial Septal Aneurysm
- High Flow/Low Flow TCD

Pre-Operative (Liver Transplant, Complex Orthopedic)

Hypoxia (OSA, platypnea orthodeoxia)

Migraine
- migrainous infarction
- non visual aura (TIA-like)
- WMLs MRI

Cheerleader Camp	Cynical Corner
Anecdotal Observations	Observations of Cardiologists
Prevalence Data	Population Observations
Retrospective Comparisons	Lack of Data
Device Safety	Device Complications
Common Sense	Common Sense

Transcatheter Closure vs Medical Therapy
PFO and Presumed Paradoxical Thromboemboli

10 Transcatheter Closures Studies

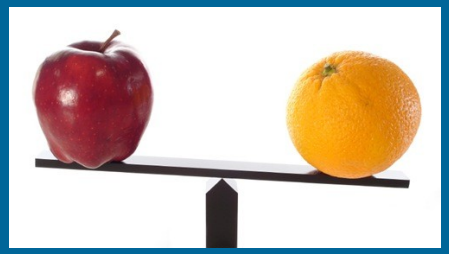
1355 Patients

6 Medical Management Studies

895 Patients

RNTE @ 1 Year

0 - 4.9%

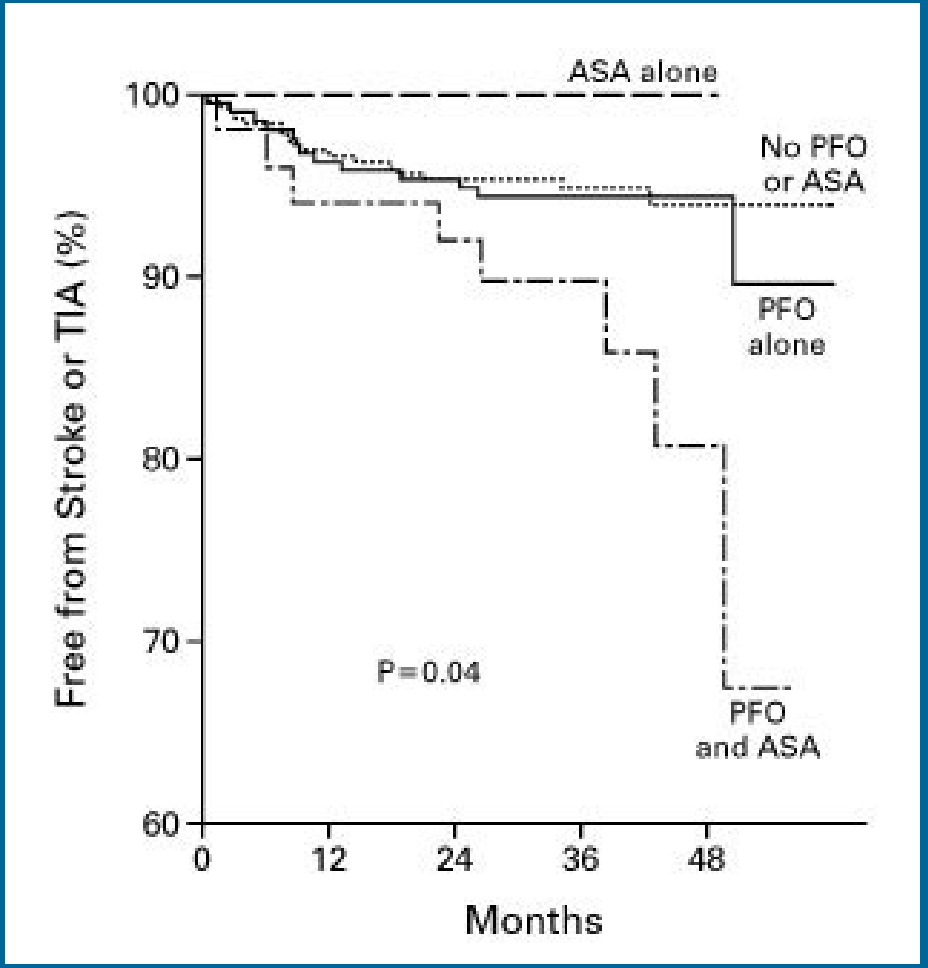


3.8% - 12%

Khairy, et al. Annals of Internal Medicine, 4 Nov. 2003

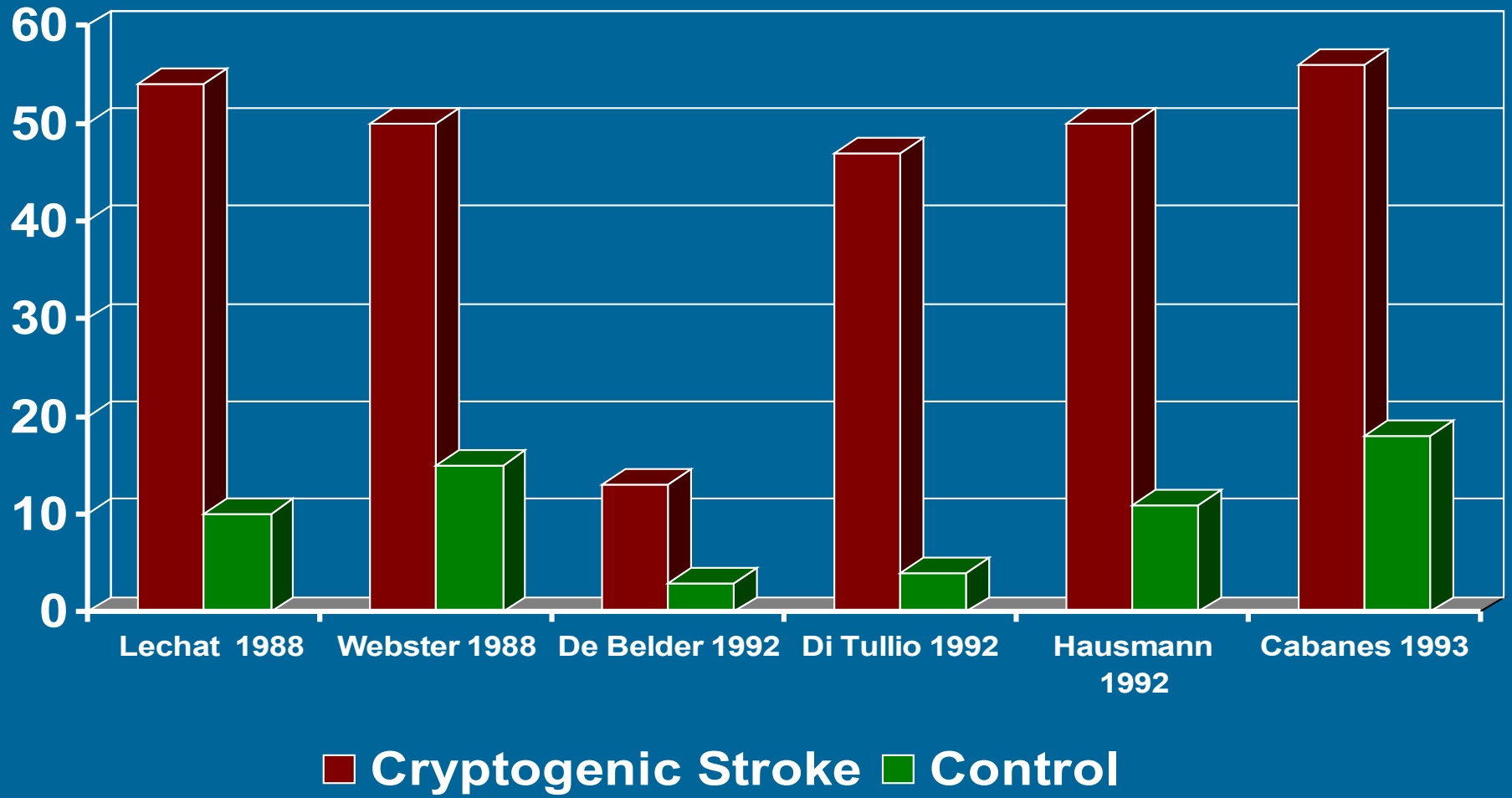
Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U

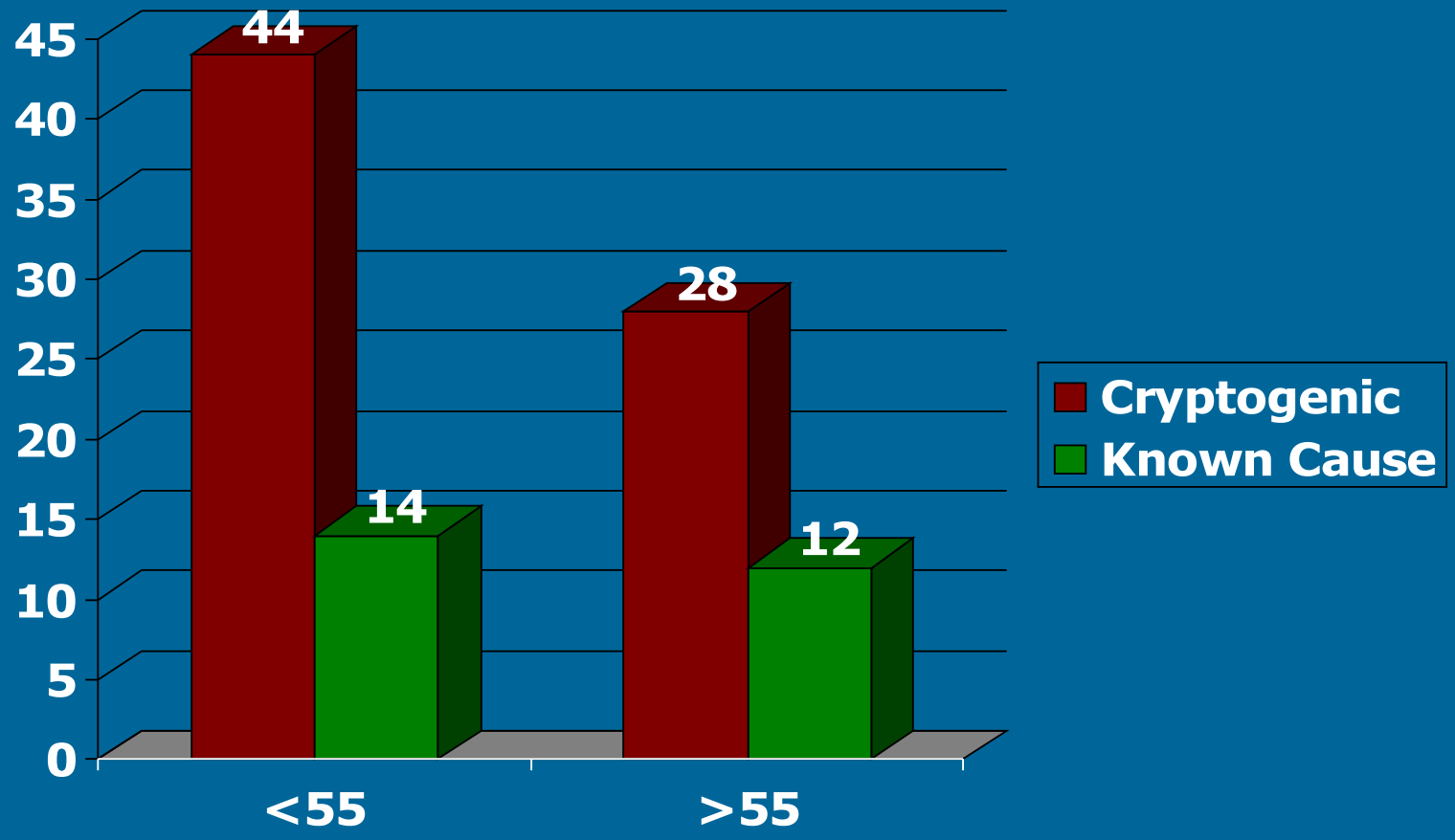


Mas, et al. NEJM Dec 13, 2001

Prevalence of PFO in Patients With "Cryptogenic" Stroke



Patent Foramen Ovale and Older Cryptogenic Stroke Patients



N Engl J Med 2007;357:2262-8.

Force M et al., Clin Neurol Neurosurg. 2008 Jun 3.

Cum Hoc, Ergo Propter Hoc
Association ≠ Causation

PFO prevalence is associated with:

- cryptogenic stroke
- migraine with aura, chronic migraine
- sleep apnea
- chronic fatigue syndrome

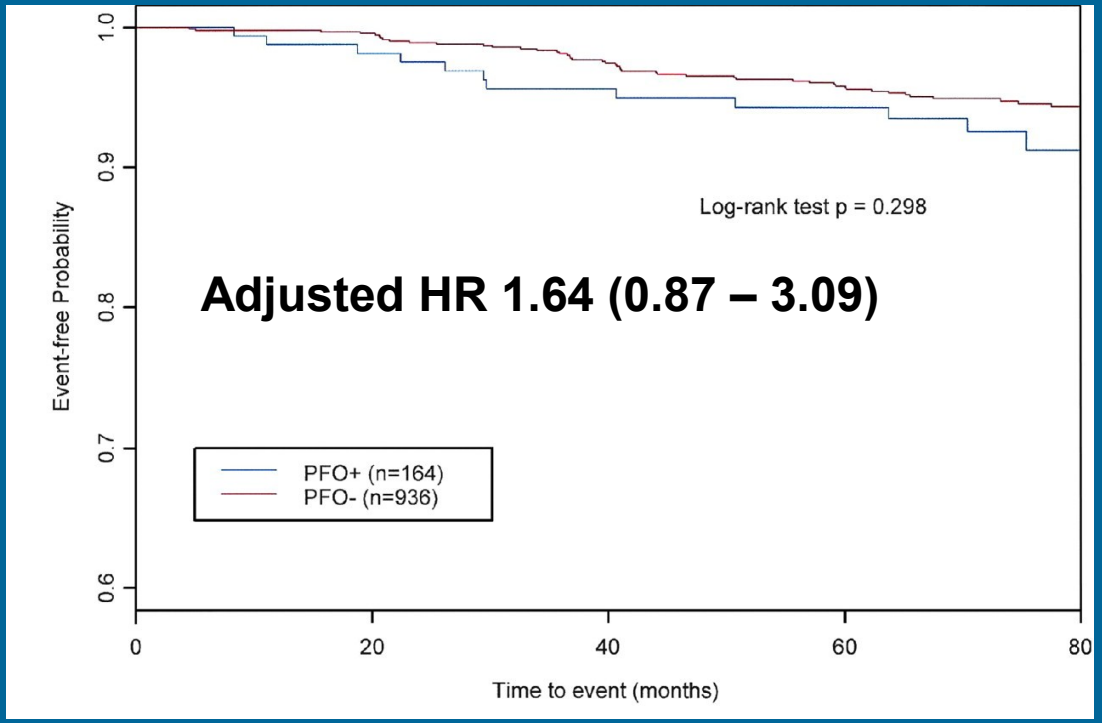
Association intuitively, but not necessarily indicates:

1) contribution to disease process
2) likelihood of impacting treatment with intervention

PFO and the risk of ischemic stroke in a multiethnic population.

Contrast TTE
N= 1,100

PFO 164 (15%)



Although our data suggest that the absolute risk of stroke from a PFO in the general population is low, the search may still be on for individual subjects in whom PFO carries an increased risk. . .

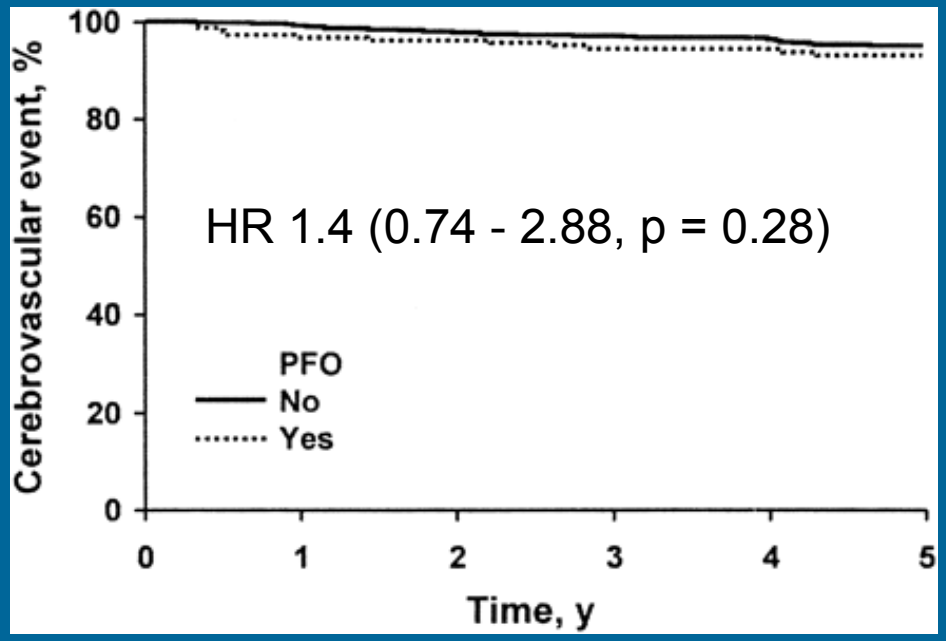
Di Tullio MR, J Am Coll Cardiol. 2007 Feb 20;49(7):797-802.

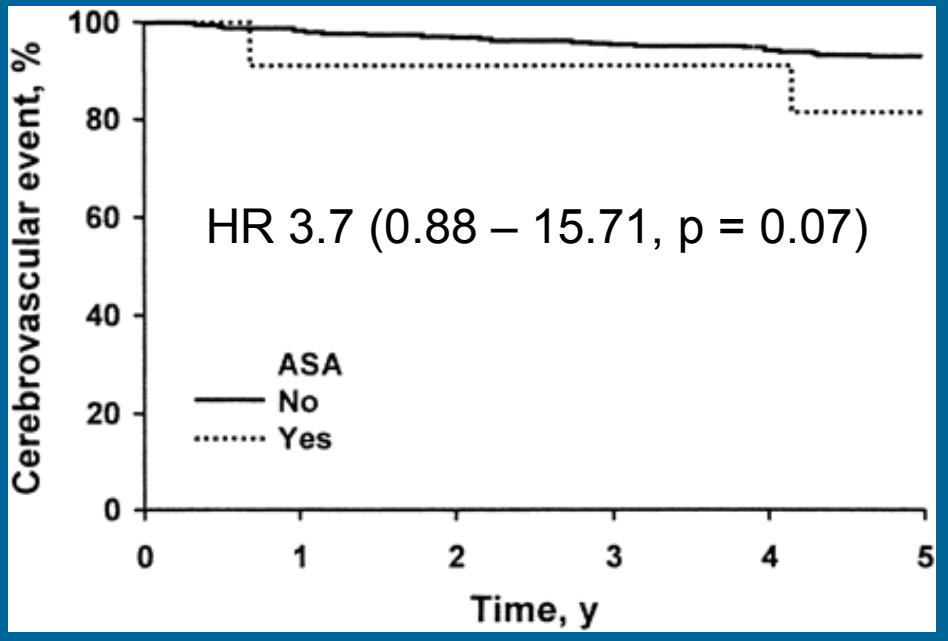
Patent Foramen Ovale: Innocent or Guilty?

Evidence From a Prospective Population-Based Study

Contrast TEE
N= 585
PFO – 140 (24%) No PFO - 437

Atrial Septal Aneurysm
N = 11





Irene Meissner, . . . Jack P. Whisnant , et al. J Am Coll Cardiol, 2006; 47:440-445

WARSS

Warfarin-Aspirin Recurrent Stroke Study Group

2,206 Patients

Ischemic CVA

Warfarin
(INR 1.4 – 2.8)

ASA
325 mg/day

Death or Recurrent CVA at 2 Years

	Warfarin	ASA	p
Total (2206)	17.8%	16.0%	0.25
Cryptogenic CVA (576)	15.0%	16.5%	0.68

NEJM , Vol 345, No. 20, Nov. 15 2001

PICSS

Effect of Medical Treatment in Stroke Patients with Patent Foramen Ovale

601 WARSS Patients evaluated by TEE

	Cryptogenic CVA (250)	CVA etiology suspected (351)	P
PFO	39% (98)	30% (105)	<0.02

	Aspirin	Warfarin	P
Stroke or Death %	17.9	8.5	NS

Circulation 2002 Jun 4;105(22):2625-31

CODICI
A

Recurrent Stroke and Massive (TCD 4 or 5) Right-to-Left Shunt. CODICIA Group

Cryptogenic CVA
N=486

	R-L shunt	TCD 4/5
Total (486)	61.1%	41.2%
Age <55 (229)	70.7%	51.5%

Antiplatelet 79%

F/U 729 +/- 411 Days

Warfarin 21%

Recurrent CVA = 28 (5.8%)

Serena, et al. Stroke. 2008 Sep 25. [Epub ahead of print]

CODICI
A

Recurrent Stroke and Massive (TCD 4 or 5) Right-to-Left Shunt.

Recurrent Stroke (%)

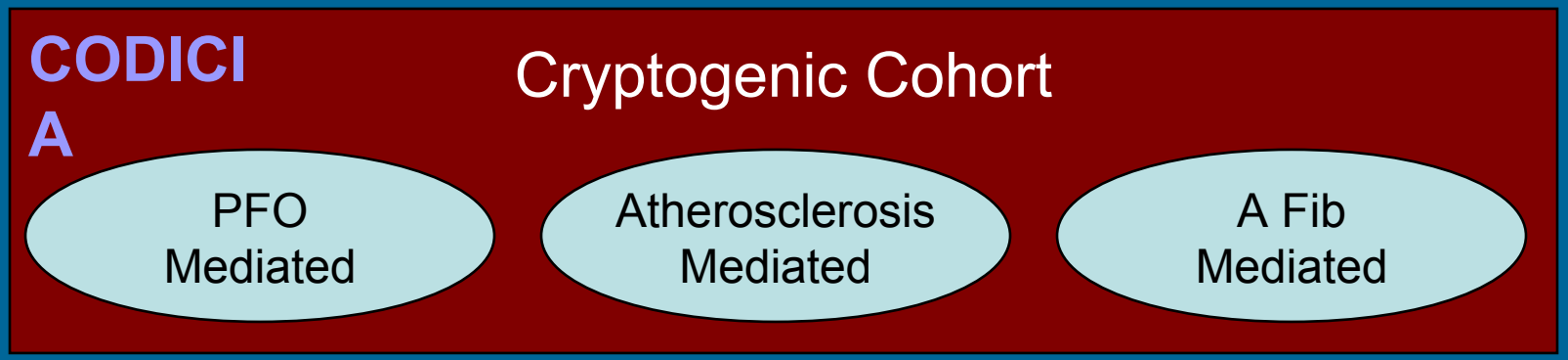
	TCD 4/5	TCD 1/2	TCD 0	p
Total	5.0	6.2	4.5	0.58
Age <55	3.4	2.3	4.5	0.75

"Because the risk of stroke recurrence was low and no significant differences were found between the use of antiplatelet and anticoagulant agents, our results offer no justification for the use of potentially dangerous or aggressive treatments. Hence, although this was not one of the objectives of our study, we are led to conclude that invasive treatments such as percutaneous PFO occlusion should be performed only within the framework of a current clinical trial."

Serena, et al. Stroke. 2008 Sep 25. [Epub ahead of print]

Half Empty or Half Full?

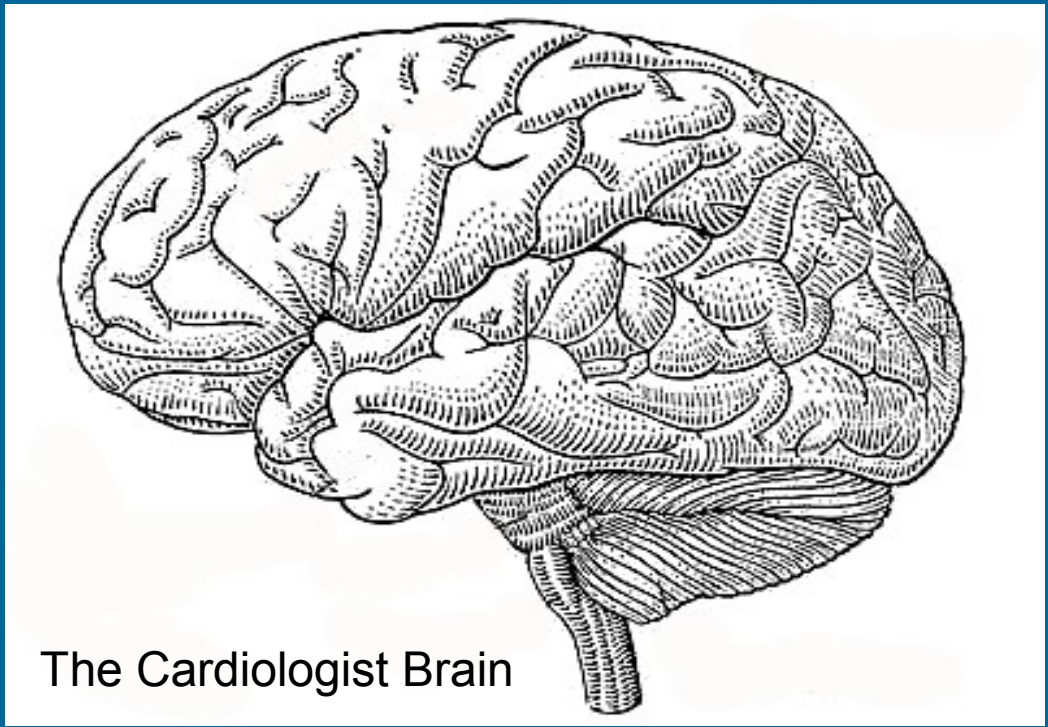
- PFO → CVA Adjusted HR 1.64, 1.4, 3.7 unselected population is provocative
- PICSS 2 year stroke or death: 18% aspirin, 9% warfarin is unacceptable & demands PFO closure



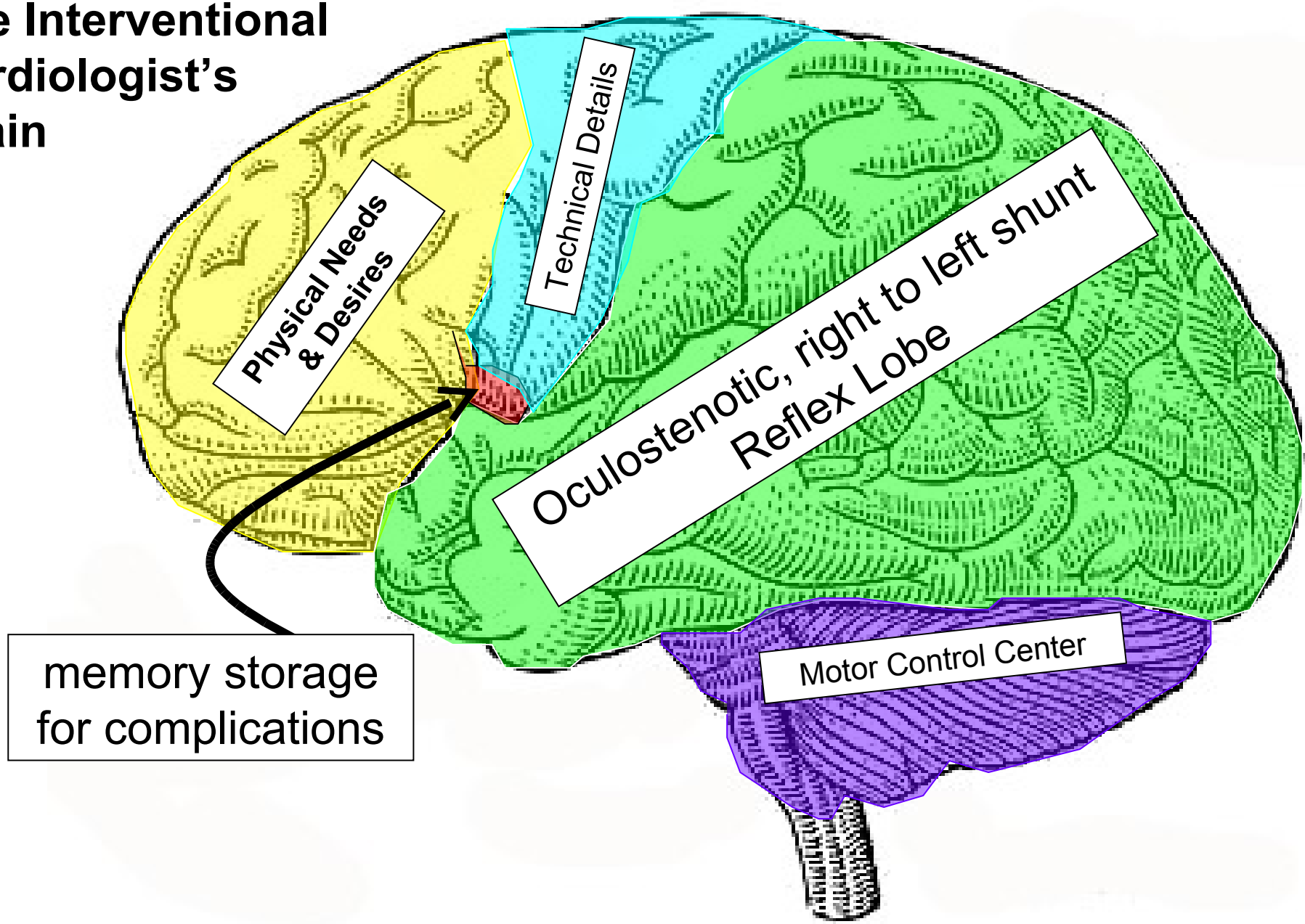
Recurrent Stroke = 5.8% in all patients

Treat HTN, DM, AF, Tob ?PFO

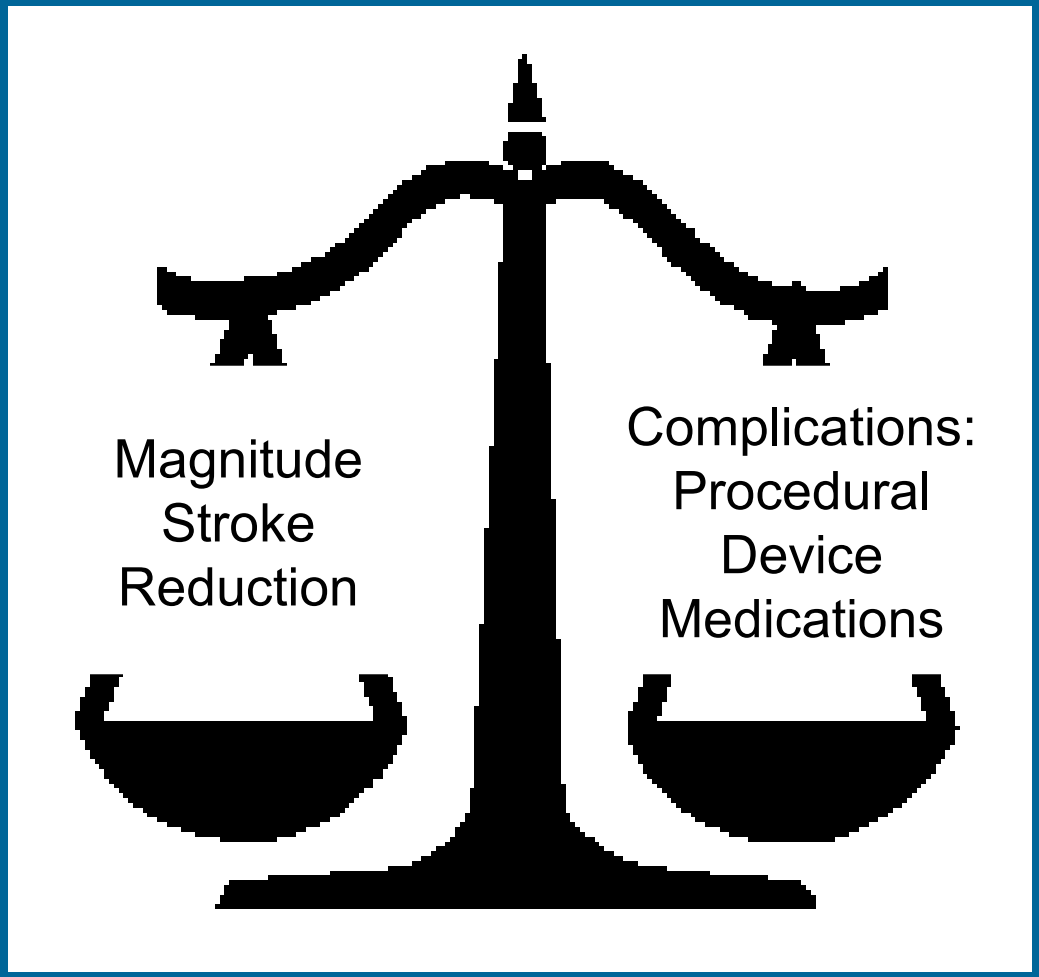
- PFO mediated stroke signals are ubiquitous.
- If there were no PFOs, there would be fewer strokes.
- PFO Closure complications are minimal.
- “PFO Vaccination” ready for prime time?


The Cardiologist Brain

The Interventional Cardiologist's Brain



Stroke Trials



Enrolled population

Operator experience & procedural complications

Device performance

MIST

Migraine Intervention with StarFlex Technology

Adverse Events

Event	Study Arm	Adjudicated Relationship to Device, Procedure, or Medications
A Fib with aberrant conduction	Implant	Possible Device
Tamponade	Implant	Procedure
Pericardial Effusion	Implant	Procedure
Retroperitoneal Bleed	Implant	Procedure
Chest Pain	Implant	Possible Device
A Fib	Implant	Possible Device
Chest Pain	Implant	Possible Device, Procedure, Meds
Stroke	Sham	None
Mennorhagia/Anemia	Sham	Possible Meds
Groin Ooze	Sham	Procedure/Possible Meds

Dawson et al. Circulation. 2008 Mar 18;117(11):1397-404.

Comparison of Three PFO Closure Devices in a Randomized Trial

	Amplatzer (N=220)	Helex (N=220)	CardioSeal/ StarFlex (N=220)
Device Embolization		3	
Hemopericardium		1	
Tamponade & Surgical Explant	1		
Device Thrombus			8
Atrial Fibrillation	3	2	11
30 Day Closure	65%	53%	62%

Taafe M. Am J Cardiol. 2008 May 1;101(9):1353-8.

Recurrent Focal Neurologic Events after Transcatheter PFO Closure

216 Patients

CardioSeal Closure

Retrospective Review

Focal Neurologic Events – 20/216, 3.4%/year

CVA – 4 (2 likely device related)

TIA – 10 (etiology undetermined)

Kutty, et al., Am J Cardiol. 2008 May 15;101(10):1487-92.

Ongoing PFO Stroke Trials

Trial	Respect	Closure I	Reduce
N	500+	900	664
Device (Company)	Amplatzer (AGA)	StarFlex (NMT)	Helex (Gore)
Inclusion	Stroke	Stroke or TIA	Stroke or MRI TIA
Primary Endpoint	Stroke	Stroke or TIA	Stroke or MRI TIA
Key Secondary Endpoints	? Migraine	? Migraine	MRI WMLs

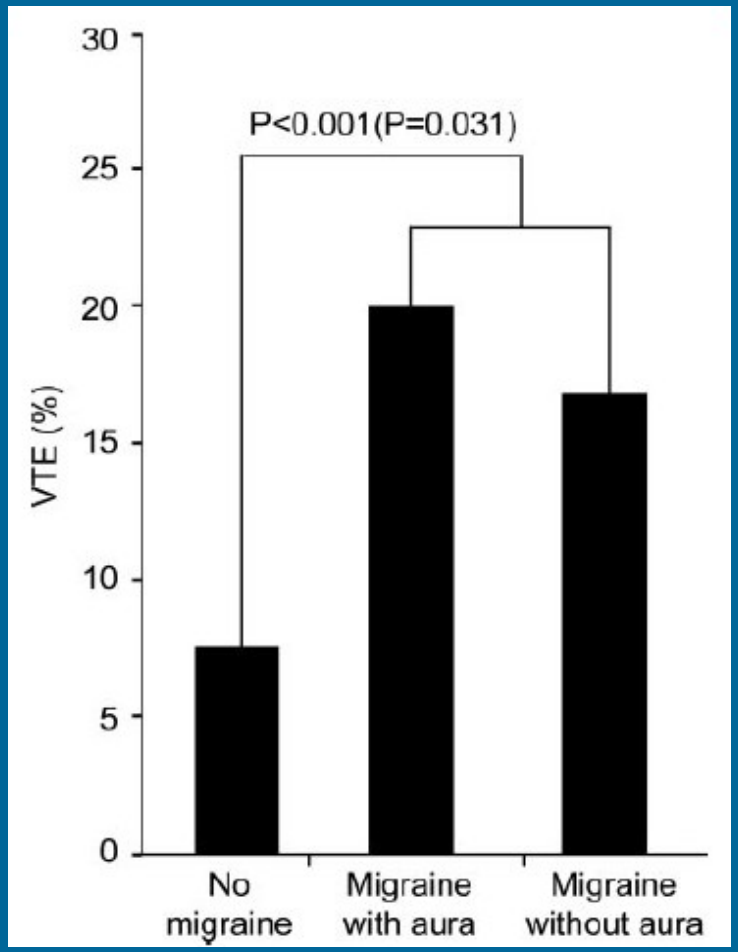
Different Populations, Devices, Endpoints
Essential to Building a Body of Evidence
Translated Results Cannot be Assumed.

Risk of Ischaemic Stroke in People with Migraine: A Meta-Analysis

	Relative Risk
Migraine (any)	2.16
Migraine with aura	2.88
Migraine without aura	1.83
Migraine among women < 45 yrs	2.76
Migraine + oral contraceptives	8.72

Etminan, et al. BMJ January 8, 2005.
Becker, et al. Headache Nov/Dec 2007.

Burden of Atherosclerosis and Risk of Venous Thromboembolism in Patients with Migraine



Schwaiger, et al. Neurology 2008;71:937-943.

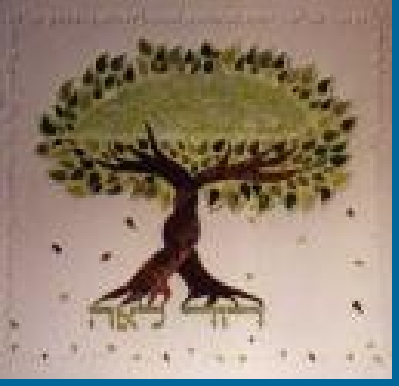
Migraine and Subclinical Brain Lesions.

	Control N=140	Migraine no aura N=134	Migraine with aura N=161
Posterior Circulation Infarct	1 (0.7%)	3 (2.2%)	13 (8.1%)

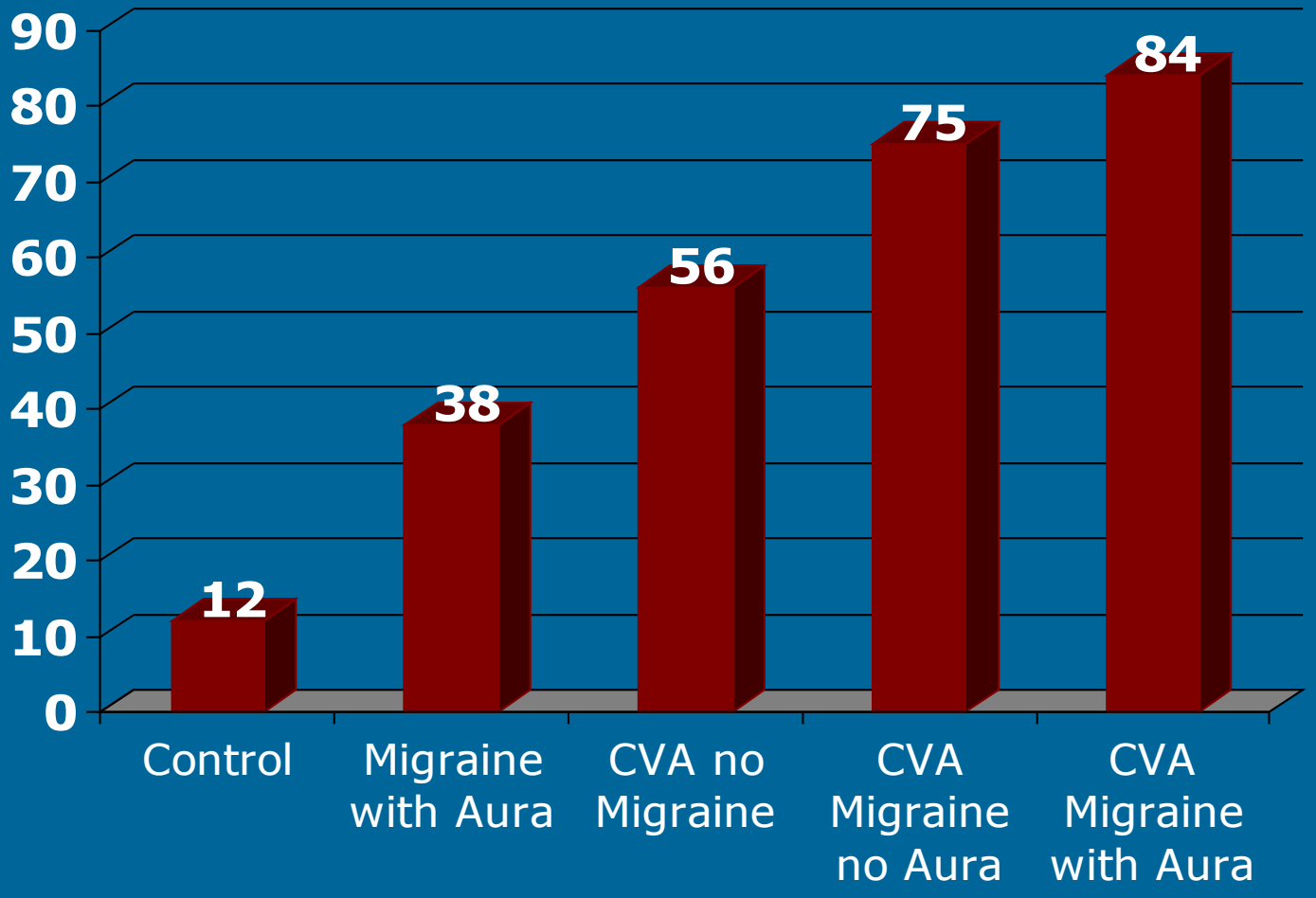
Kruit, et al., JAMA 2004 Jan 28

~50% of migraineurs have MRI white matter lesions
Independent of right to left shunt

Del Sette et al. Cephalalgia, 2008. **28**(4): p. 376-82.
Adami et al. Neurology. 2008 Jul 8;71(2):101-7.



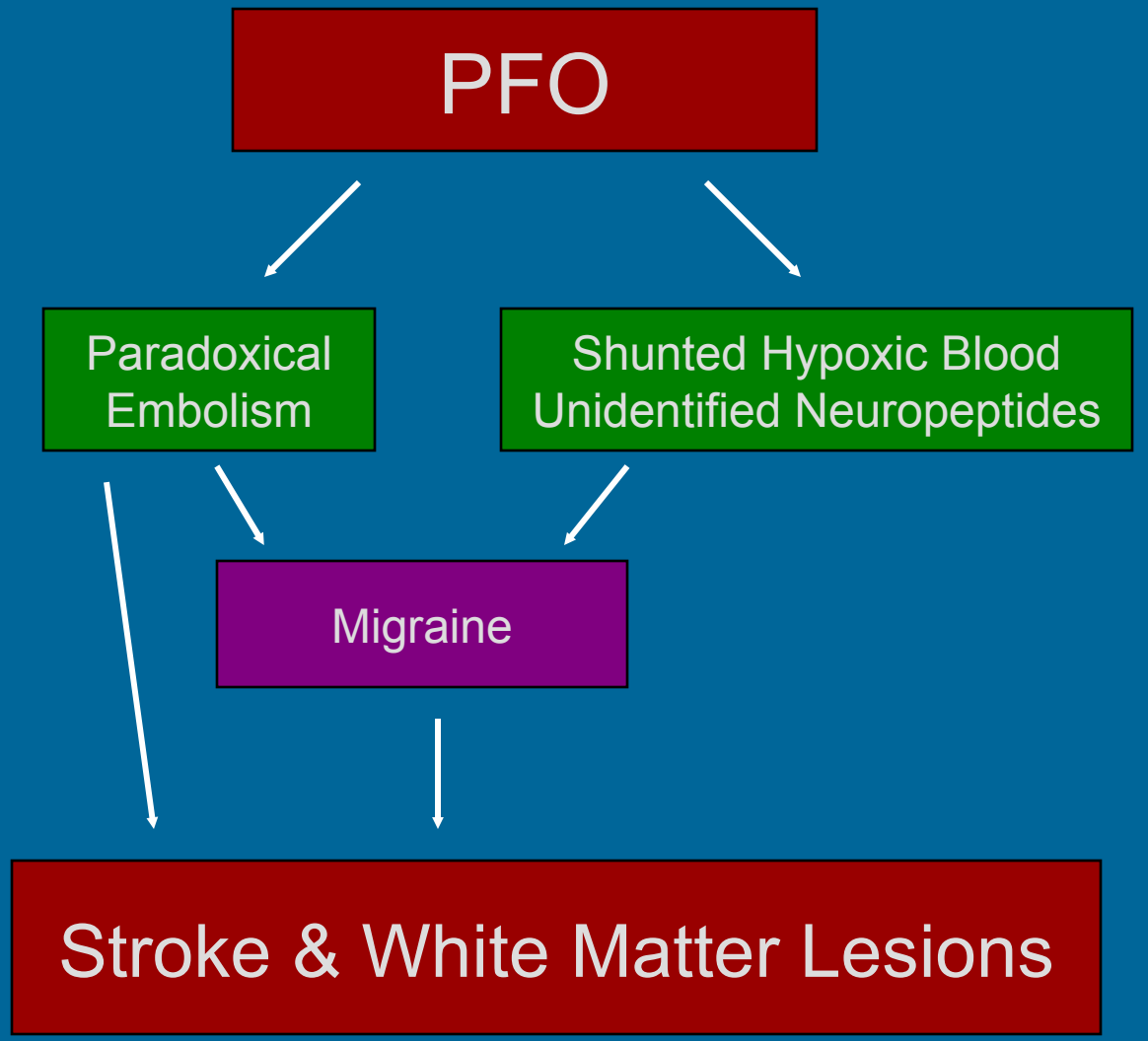
PFO Prevalence: Compounded with CVA + Migraine



Am J Cardiol 2006;98:831-3

Hypotheses

1) Migraine and stroke are associated without causation (PFO causes both).
2) PFO closure diminishes migraine induced brain pathology.
   Assumes:
   - Migraine causes brain pathology
   - PFO closure diminishes migraines



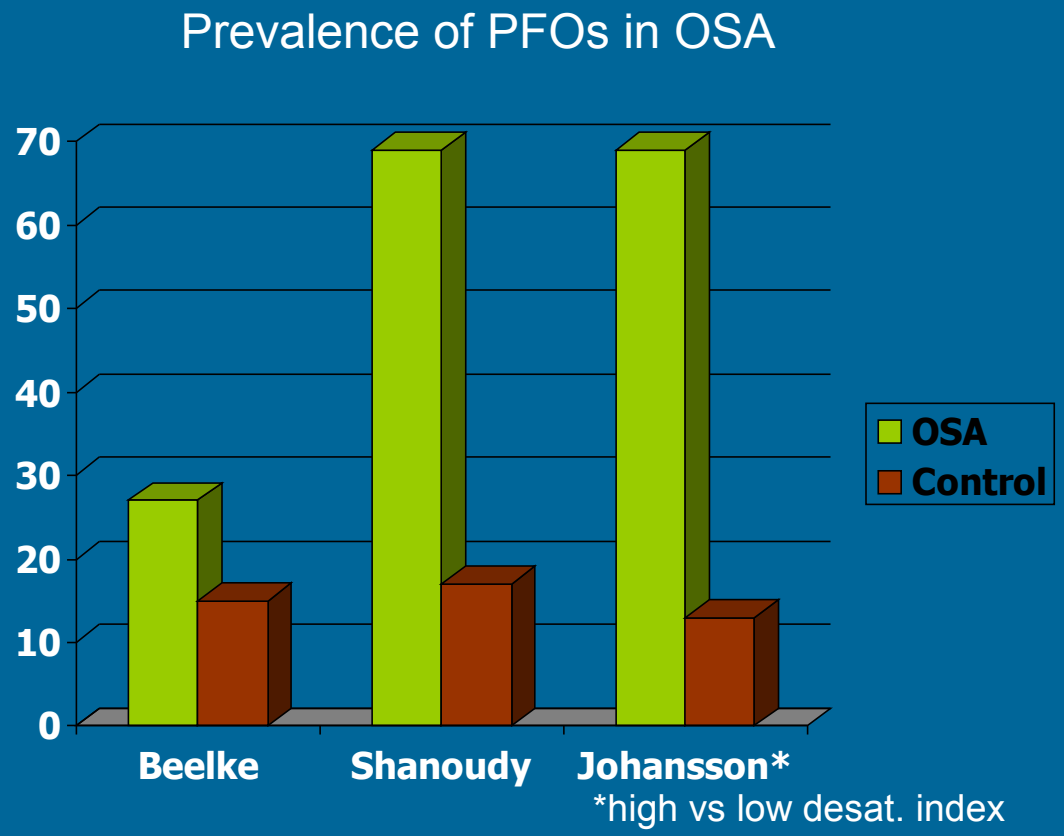
Ongoing, Struggling Research Regarding PFO Closure of Migraine Patients will Provide Little Insight Regarding Stroke Prevention

	Premium	Mist II	Escape
Device (Company)	Amplatzer (AGA)	Biostar (NMT)	Premere (St. Jude)
Inclusion	Refractory To Medications	Refractory To Medications	Refractory To Medications
Exclusion	Stroke TIA	Stroke TIA	Stroke TIA
Endpoint	50% reduction Headache Days	50% reduction Headache Days	50% reduction Headache Days

- **High risk patients are excluded.**

Will closing PFOs in OSA patients prevent strokes?

- Sleep apnea is associated with an increased risk of stroke.
  - Valham et al. Circulation. 2008;118:955-960.
- PFO closure may be associated with diminished sleep hypoxia.
  - Agnoletti et al. Obstructive sleep apnea and patent foramen ovale: successful treatment of symptoms by percutaneous foramen ovale closure. J Interv Cardiol. 2007;18:393-5.
  - Silver et al. Improvement in Sleep Apnea Associated With Closure of a Patent Foramen Ovale. J Clin Sleep Med 2007;3:295-296.



- Beelke et al. Sleep Medicine 2003;4:219-223.
- Shanoudy et al. *Chest.* 1998;113:91–96.
- Johansson et al. Eur Respir J 2007;29:149-155.

Conclusions I

- Closure I, Respect, and Reduce will be scrutinized regarding
  - Closure efficacy
  - Device and procedural related complications
  - Characteristics of enrolled population
- Results of ongoing trials (+ or -) cannot be translated to alternate devices given device specific efficacy and safety profiles.

Conclusions II

- Physicians must respect patients' rights to direct their care.
- PFO consultation should include discussion regarding:
  - Observational population data
  - Ongoing randomized trials
  - Lack of FDA indication for PFO closure
  - Lack of prospective complication and closure data
  - MIST complications
- Randomization should be encouraged when inclusion criteria are met.

Conclusions III

Additional research is indicated beyond ongoing randomized trials.

- Appropriately powered high risk population studies
  - Atrial septal aneurysm
  - Thrombotic risk (PE, DVT, SVT, procoagulant disorders, chronic indwelling catheter, pacemaker)
- PFO closure in high risk migraine population (nonvisual aura, WMLs, thrombotic risk)
- PFO closure in sleep hypoxia

Conclusions IV

Cardiologists participating in PFO closure require a fund of neurology knowledge.

- industry support
- cardiology meetings