

**Patent Foramen Ovale (PFO) Closure
For Stroke and Migraine
How Strong is the Evidence ?**

TCT

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Disclosures

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A Principal Investigator for PREMIUM Trial using the Amplatzer PFO Occluder (AGA Medical) in patients with severe migraines.

MAB for ACCESS LAA Occlusion Trial

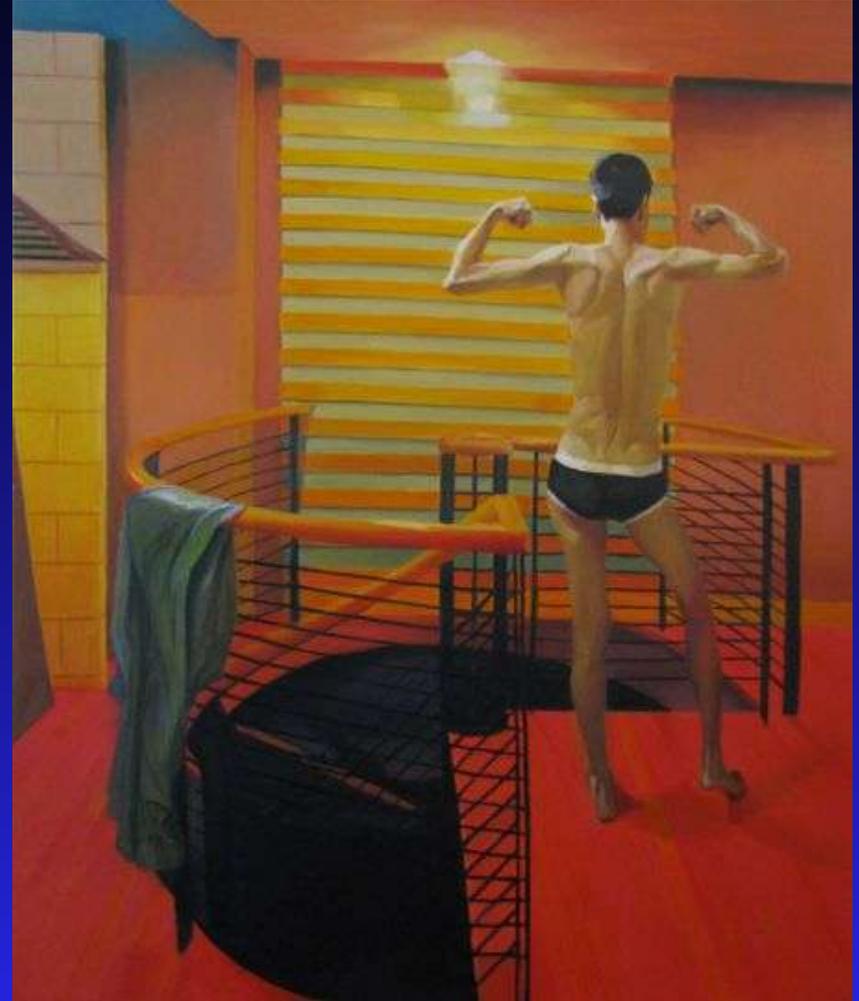
Consultant for the RESPECT stroke trial.

**Consultant to: Boston Scientific
Coherex
WL Gore
Angel Medical**

How Strong is the Evidence?



Is it like this guy?



or like this wanna be?

Controversies in PFO Closure

- 1. There is no FDA approval for any PFO device.**
- 2. Everything we discuss is off-label.**
- 3. The observational data is impressive but only scientifically useful for generating hypotheses, not for proving cause and effect.**
- 4. But, the RCTs are difficult to perform due to availability of using devices off-label.**

Association of PFO and cryptogenic stroke in young adults (< 55 y/o)

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

Determinants of High Risk for Stroke in Patient with PFO

1. ASA (atrial septal aneurysm)¹:
Risk for stroke: PFO alone = OR 3.9
ASA alone = OR 4.3 (rare)
PFO + ASA = OR 33.3
2. Size of PFO: conflicting data, depends how you measure
3. Degree of Shunt: probably
4. Past “silent” strokes on MRI.²
5. Hypercoaguable State (incl Estrogen Rx) 20% of our pts
6. Prolonged immobility = 10%
7. Valsalva (straining) = 5%
8. Size of Stroke is not related to size of PFO.³

1. Cabanes *Stroke* 1993, 24:1865-73.

2. Saver *Current Atherosclerosis Reports* 2007,9:319-325.

3. Tobis and Akhondi *SCAI* 2009

Medical Therapy vs. PFO Closure: A Review of Observational Studies

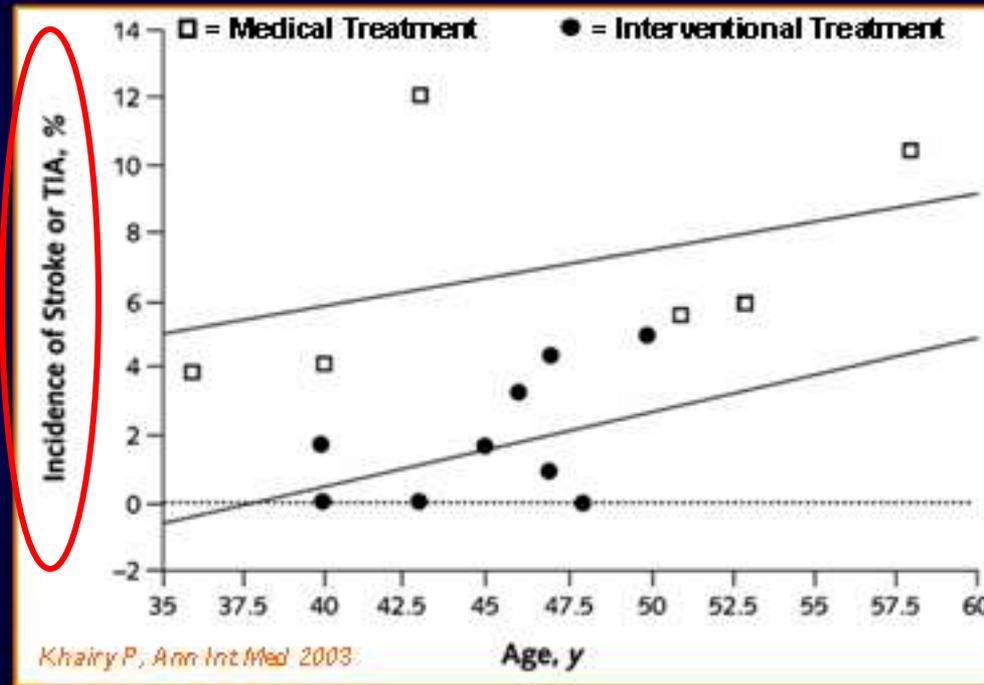
Stroke, Death, or TIA

Events per 100 patient-years

Medical Therapy (9 studies) N = 943	4.9
Percutaneous PFO Closure (12 studies) N = 1430	3.0

This should be $\approx 0\%$

Meta-analysis Medical Rx vs. PFO Closure



What is the problem with these studies?

Meta-analysis

Medical Rx vs. PFO Closure

What is the problem with these studies?

- 1. Observational studies, not RCT.**
- 2. They include TIA which is indistinguishable from a TND (transient neurologic deficit) seen with migraine: motor, sensory, cognitive.**
- 3. They underestimate incidence of PFO by using echo instead of TCD. “Recurrent stroke w/o PFO”**

Current Randomized Clinical Trials

RESPECT Trial (Amplatzer)

CLOSURE Trial (StarFlex)

REDUCE TRIAL (Gore Helex)

Cryptogenic Stroke within 6 months

18-60 yrs old

PFO present

abnl MRI or CT

Medical Rx

PFO Closure

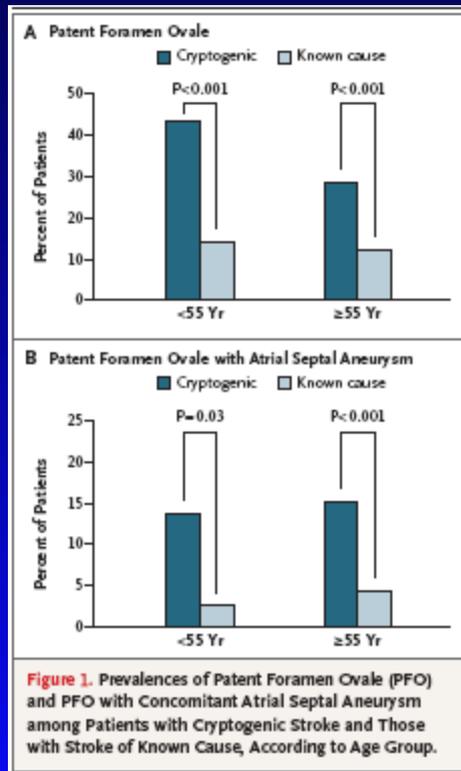
antiplatelet or coumadin

Endpoints: recurrent stroke, death, +/- TIAs

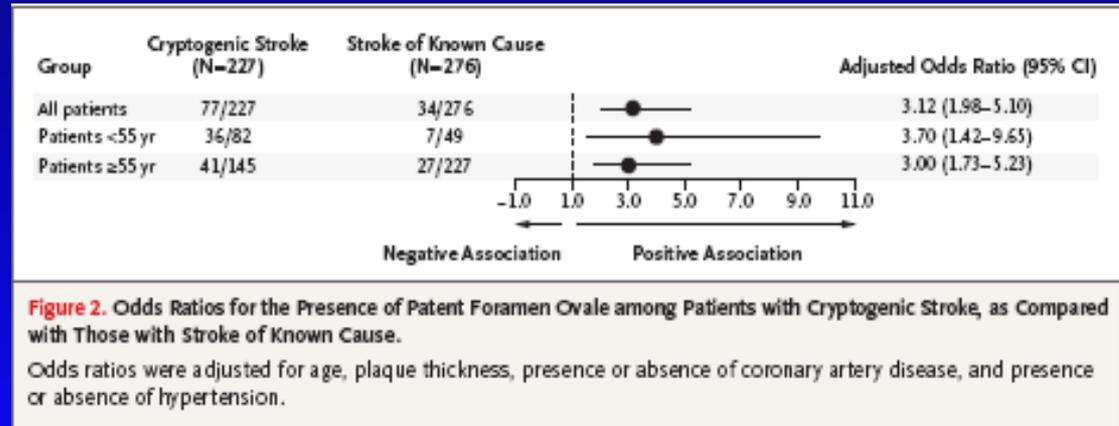
Safety: adverse events

Patent Foramen Ovale and Cryptogenic Stroke in Older Patients

Michael Handke, M.D., Andreas Harloff, M.D., Manfred Olschewski, M.Sc.,
Andreas Hetzel, M.D., and Annette Geibel, M.D.



In all stroke pts (young or >55 yo), PFO is 3x more common with cryptogenic stroke than stroke of known cause.



**70 y.o. woman with Wegener's
Granulomatosis PFO and recurrent strokes**

**No significant atherosclerosis.
PFO closed. In the next year, she
had recurrent strokes and died.**



**20 mm Helex ASD
device Left Atrium**



**Friable ulcerated plaque
in ascending aorta**

Migraine Observations

- 1. Migraine headache affects 12% of population (18%F - 6%M)
or 27 million people in USA**
- 2. Incidence of PFO in pts with migraine:**
 - 48% if migraine with aura ¹
 - 23% if migraine w/o aura and
 - 20% in controls
- 3. Incidence of Migraine in pts with Cryptogenic Stroke and PFO:**
 - 52% had migraine with aura²
 - 10 of 14 (71%) had suppression post closure³
- 4. Migraine pts have 13x incidence of MRI lesions⁴**

1. Anzola, Neurology 52(8):1622-5, 1999
2. Sztajzel, CV Diseases 13(2):102-6, 2002
3. Wilmshurst, Lancet 356(9242):1648-51, 2000
4. Kruit, JAMA 294(4): 427-434, 2004

Observational Studies

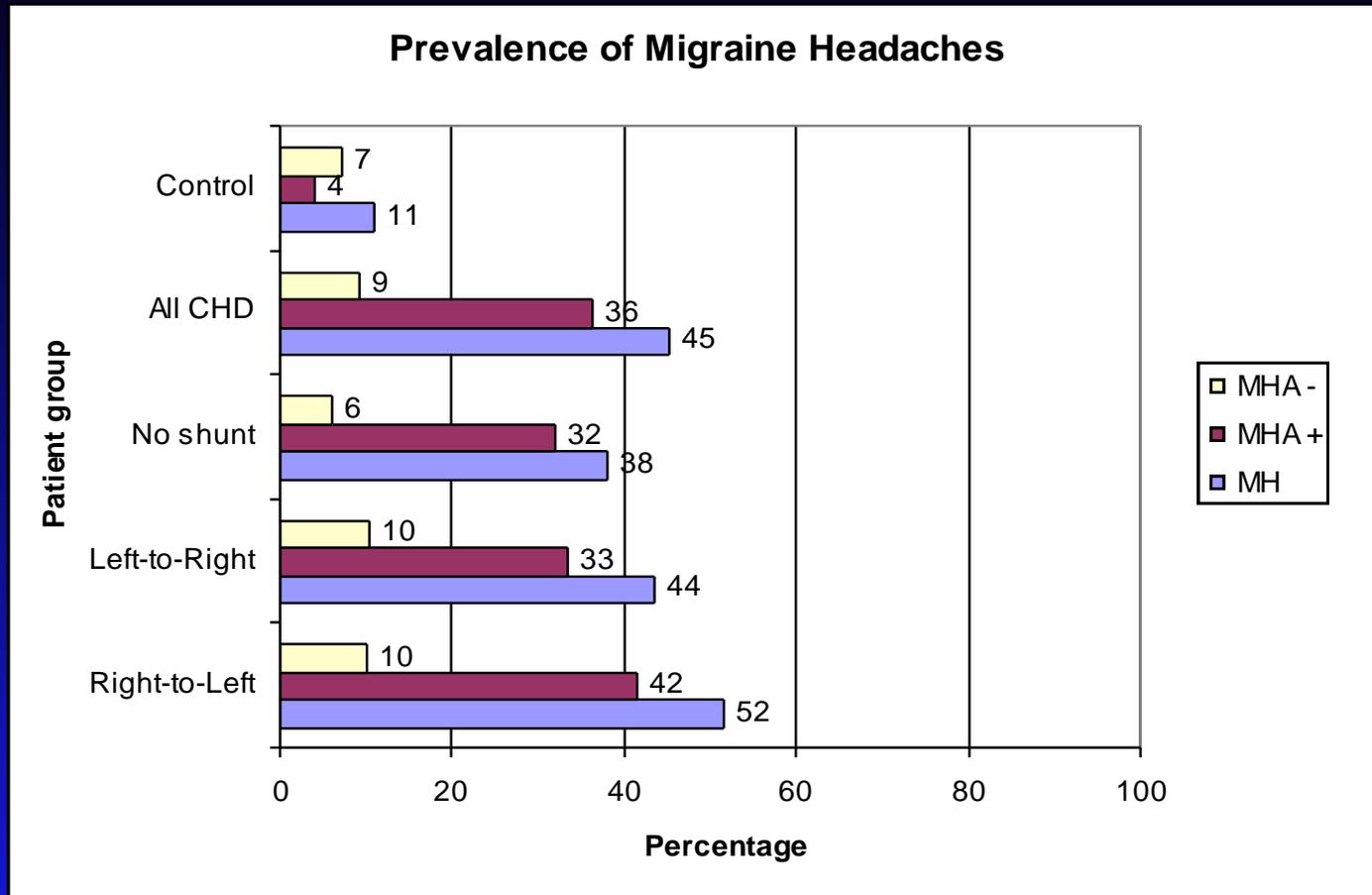
Effect of PFO closure on migraine

Study	<u>Prevalence</u> # 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%

Prevalence of Migraine

UCLA Adult Congenital HD



395 ACHD pts and 252 sex-matched controls



mist

Migraine Intervention with STARFlex® Technology

Migraine with aura

NMT Medical

MIST: Prospective findings in Migraine Patients

Result	Total #	%
Total studied	370	100.0%
Small shunts (atrial and pulmonary)	61	16.5%
Large pulmonary shunt	18	4.9%
ASD	2	0.5%
Large PFO	139	37.6%
Large shunts (all types)	159	43.0%
Total Shunts	220	59.5%

Jan to May 2005



The MIST Trial is sponsored by a research grant from NMT Medical Inc., and is supported by the Migraine Action Association and Migraine in Primary Care Advisors (MIPCA).

MIST Results (Circ. March 2008)

MIST was a negative study....
and we don't really know why.

Is this due to the specific device with residual shunts?

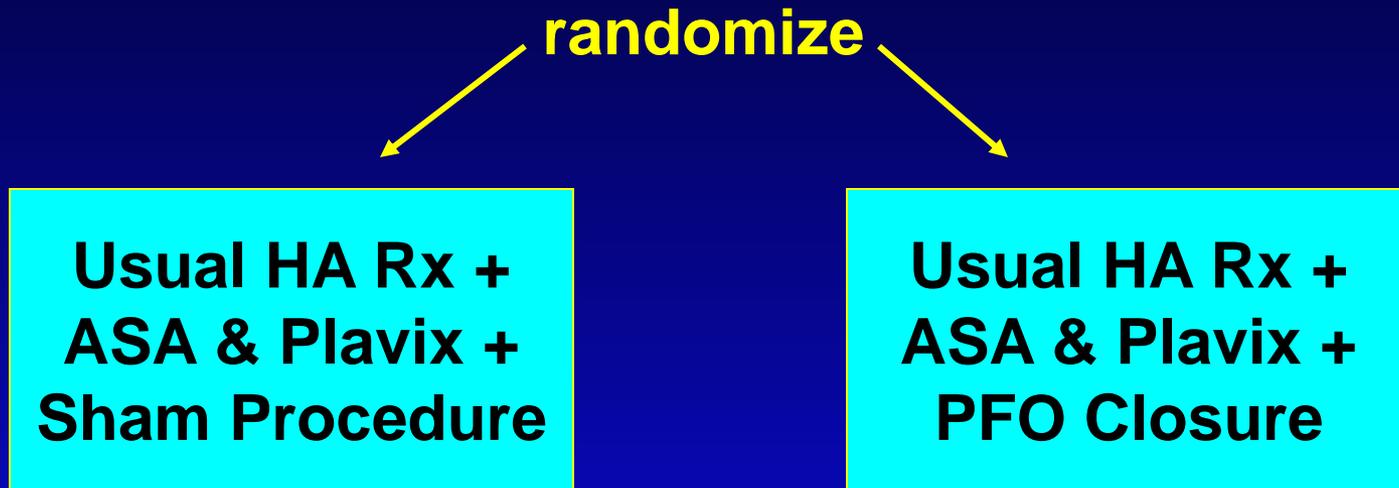
Or a more general problem of patient selection?

**Are some migraine sub-populations more responsive to
PFO closure?**

The PREMIUM Trial

A Randomized Double Blind Trial of PFO Closure for Severe Migraine Headaches

220 patients with migraine \pm aura
assess for PFO with TCD, if +4 or 5, ICE

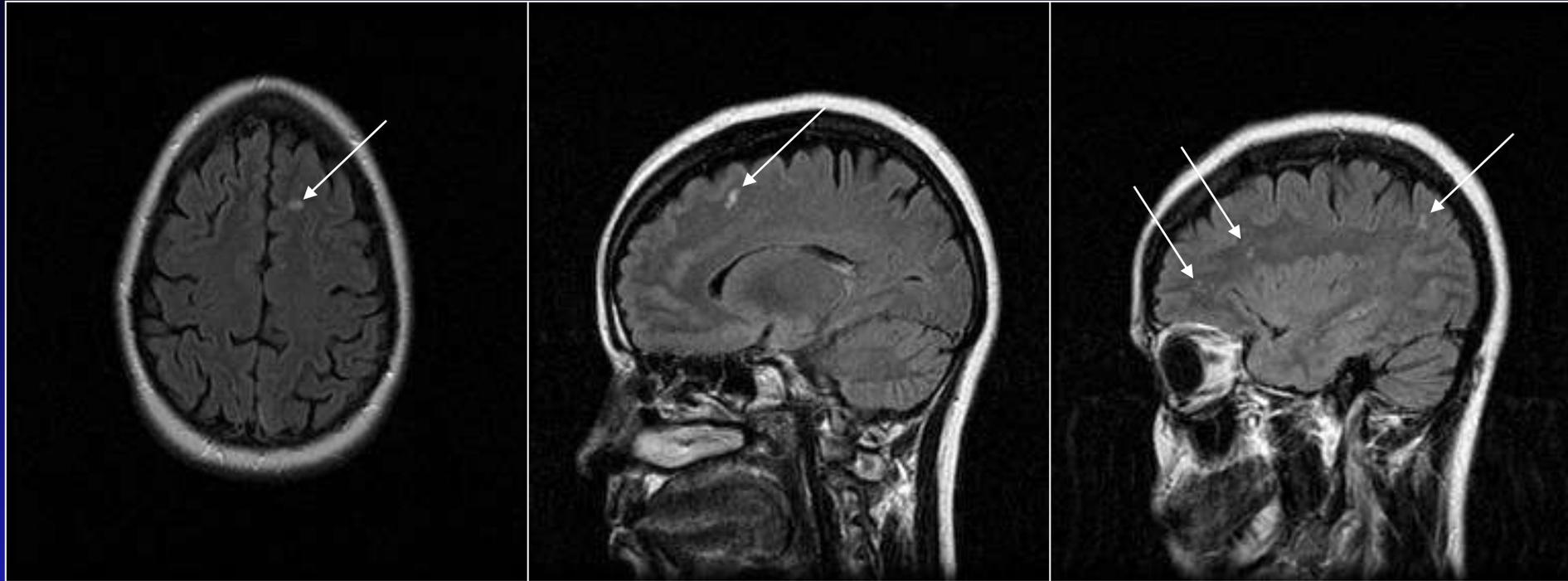


Recent approval by FDA of less restrictive entry criteria

Also: Coherex is expecting to begin a migraine trial

MRI changes in migraine headache

WML = white matter lesion



38yo woman migraine + aura since 12yo

“Few small foci of inc. signal in cerebral white matter.

Ddx: vasculitis, demyelinating disease (MS), chronic ischemia,
or complicated migraine.”

WML = inc. water due to replacement of myelin



JACC cardiovascular Interventions

Improvement of Migraine After Patent Foramen Ovale Percutaneous Closure in Patients With Subclinical Brain Lesions: A Case-Control Study

Carlo Vigna, et.al. *J. Am. Coll. Cardiol. Interv.* 2009;2;107-113

82 pts with migraine, PFO, WMLs

	53 closed	29 not closed
Baseline	32 ± 9	36 ± 13
6 Month Total # Migraines	7 ± 7*	30 ± 21**
	*p < 0.001	**p = ns

Headaches and Heart Attacks (AHA Nov 2006)

Men and Women with migraines have a greater risk of ischemic stroke and heart attack

Physicians' Health Study: 20,084 men

7.2% men with migraine, 56yo, 15.7yrs f/u

**Men with Migraine: 24% inc risk for CVD event:
42% inc MI
12% inc ischemic stroke
7% inc CV death
5% inc revasc.**

Is this due to a shared metabolic disorder?or by paradoxical embolism thru PFO? Perhaps this explains why the incidence of PFO is less in older age groups.

How Strong is the Data ?



As Abraham Lincoln noted about economic distribution:

“You can’t make a weak man strong by making a strong man weak, and you can’t make a poor man rich by making a rich man poor.”

Translated with respect to PFO closure:

“You can’t prove a causal relationship, with observational data alone.”

We need to enroll patients into the RCTs.

Thank you.