PFO: FROM STROKE PREVENTION TO CURE OF MIGRAINES

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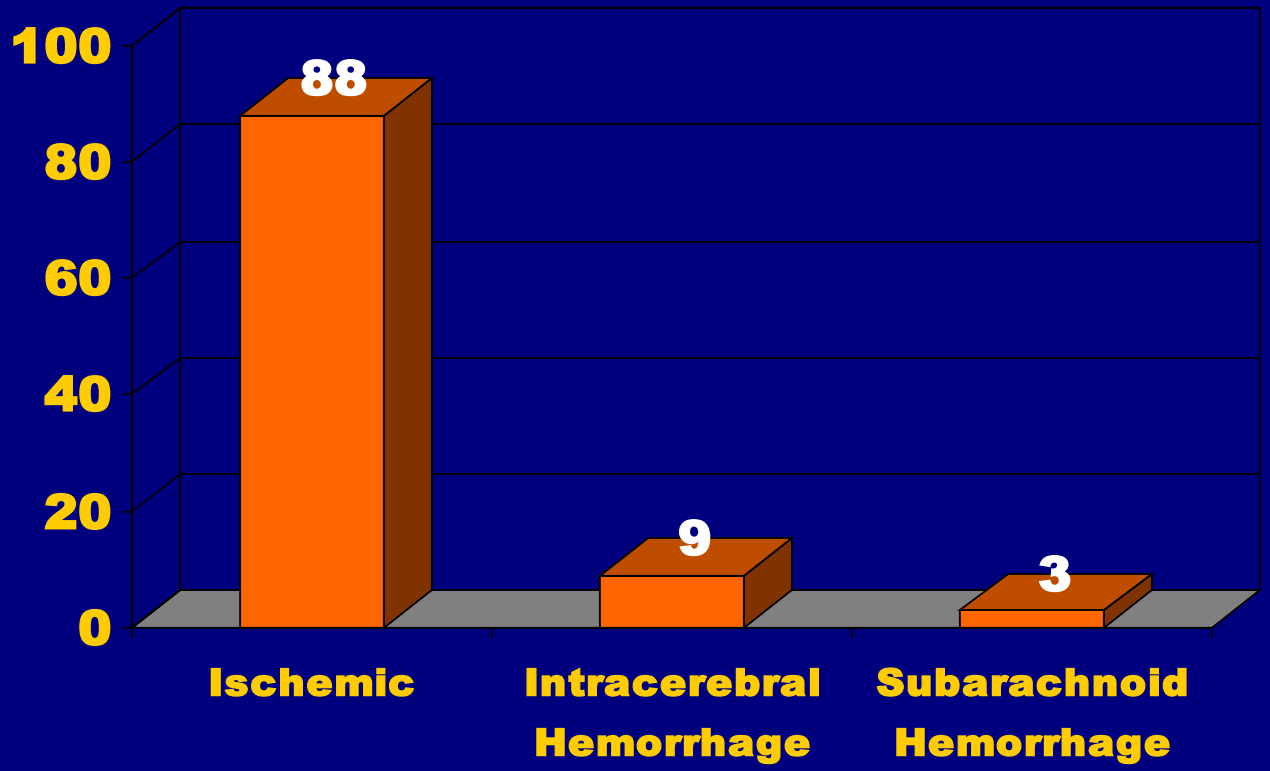
Presenter Disclosure Information

Name: Mark Reisman, M.D.

Within the past 12 months, the presenter or their spouse/partner have had the financial interest/arrangement or affiliation with the organization listed below.

Company Name:	Relationship:
• NMT Medical	National PI for MISTII / CLOSUREI
• Cordis	Advisor
• Abbott	Advisor
• Medtronic	Advisor
• Coaptus	Consultant
• Boston Scientific	Speaker's Bureau

Stroke Classification and Prevalence



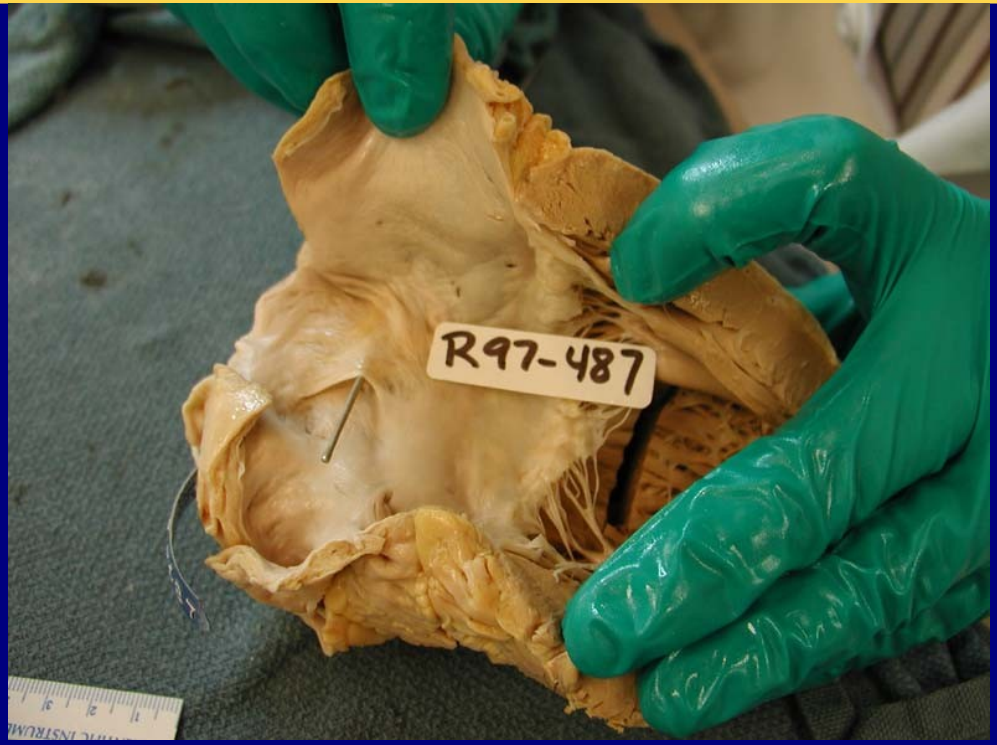
American Heart Association. Heart Disease and Stroke Statistics-2005 Update. Dallas: American Heart Association, 2004

Cryptogenic Strokes

- No identifiable cause
- Over 40% of ischemic strokes
- Associated with young age, presence of superficial infarct, prior transient ischemic attack (TIA)

Sacco et al. Ann Neurol 1989;25:382-90.

PATENT FORAMEN OVALE (PFO)



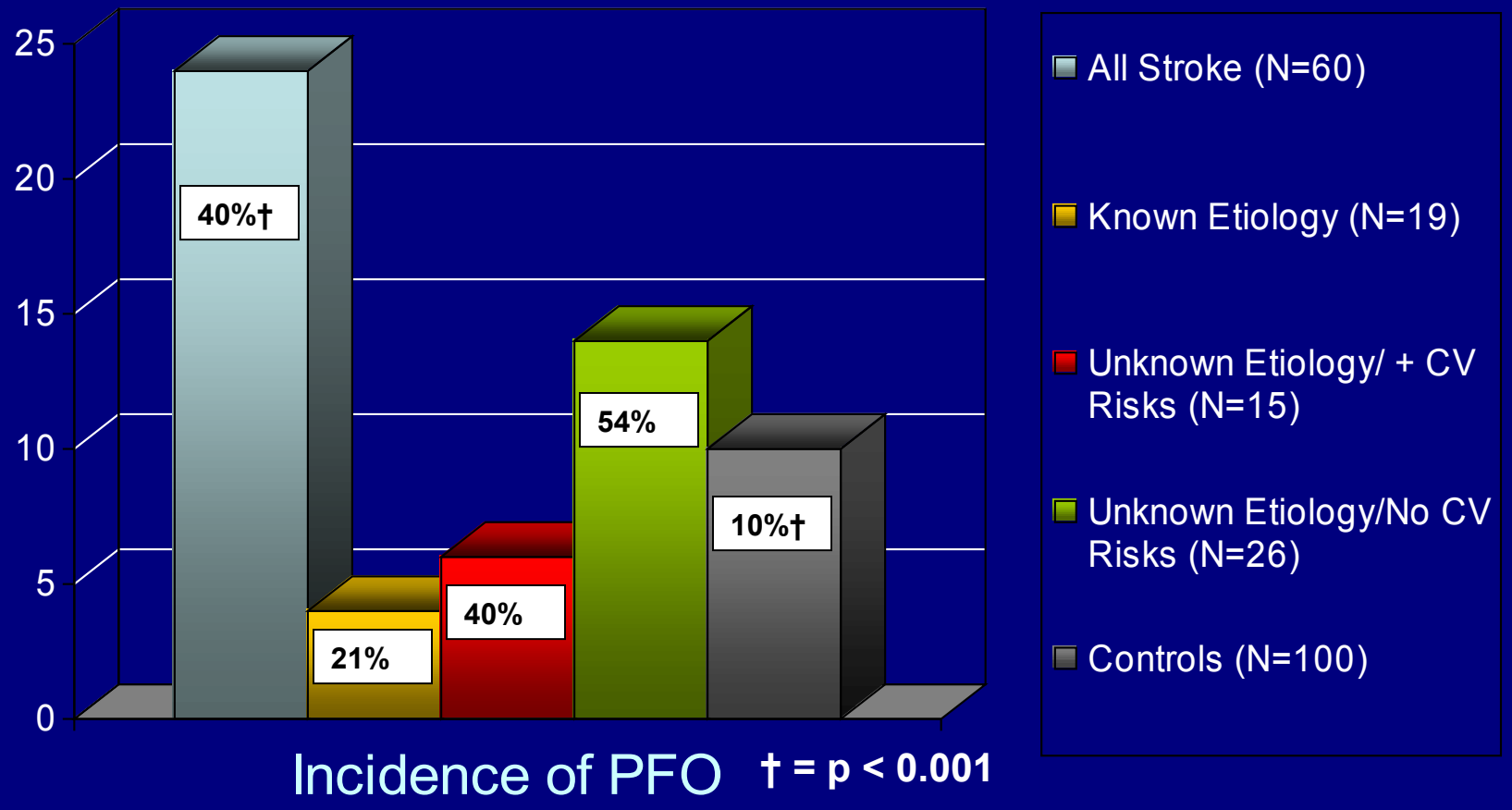
Incidence: about 27% in adults[1]

Occurrence consistent with autosomal dominant inheritance[2]

[1]Hagen et al. Mayo Clin Proc 1984;59:17-20

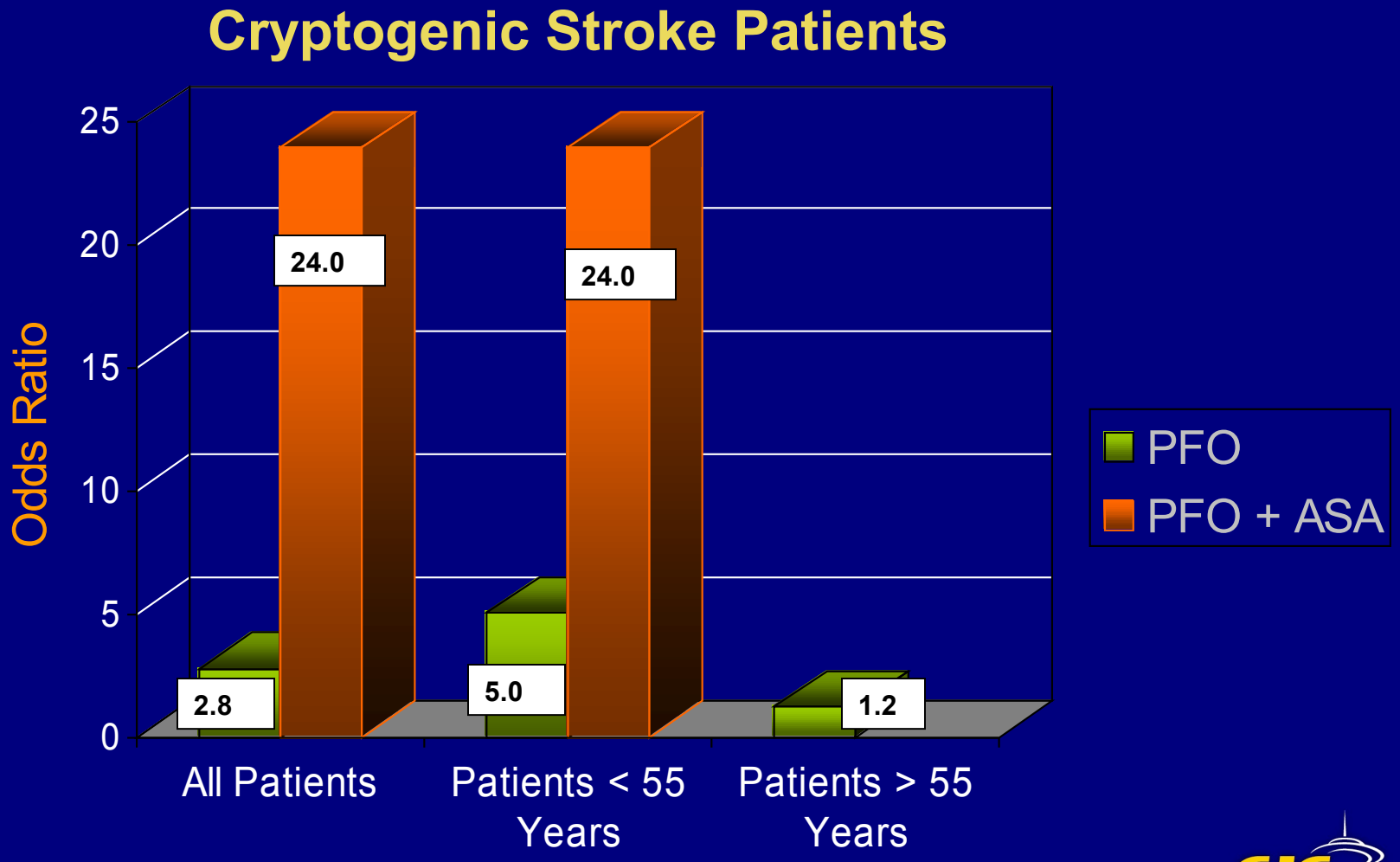
[2]Wilmshurst et al. Heart 2004;90:1315-20

Incidence of PFO in Stroke Patients < 55 Years



Lechat et al. N Engl J Med 1988;318:1148-1152

Interatrial Septal Abnormalities and Cryptogenic Stroke: A Meta-Analysis



Overell et al. Neurology 2000;55:1172-9

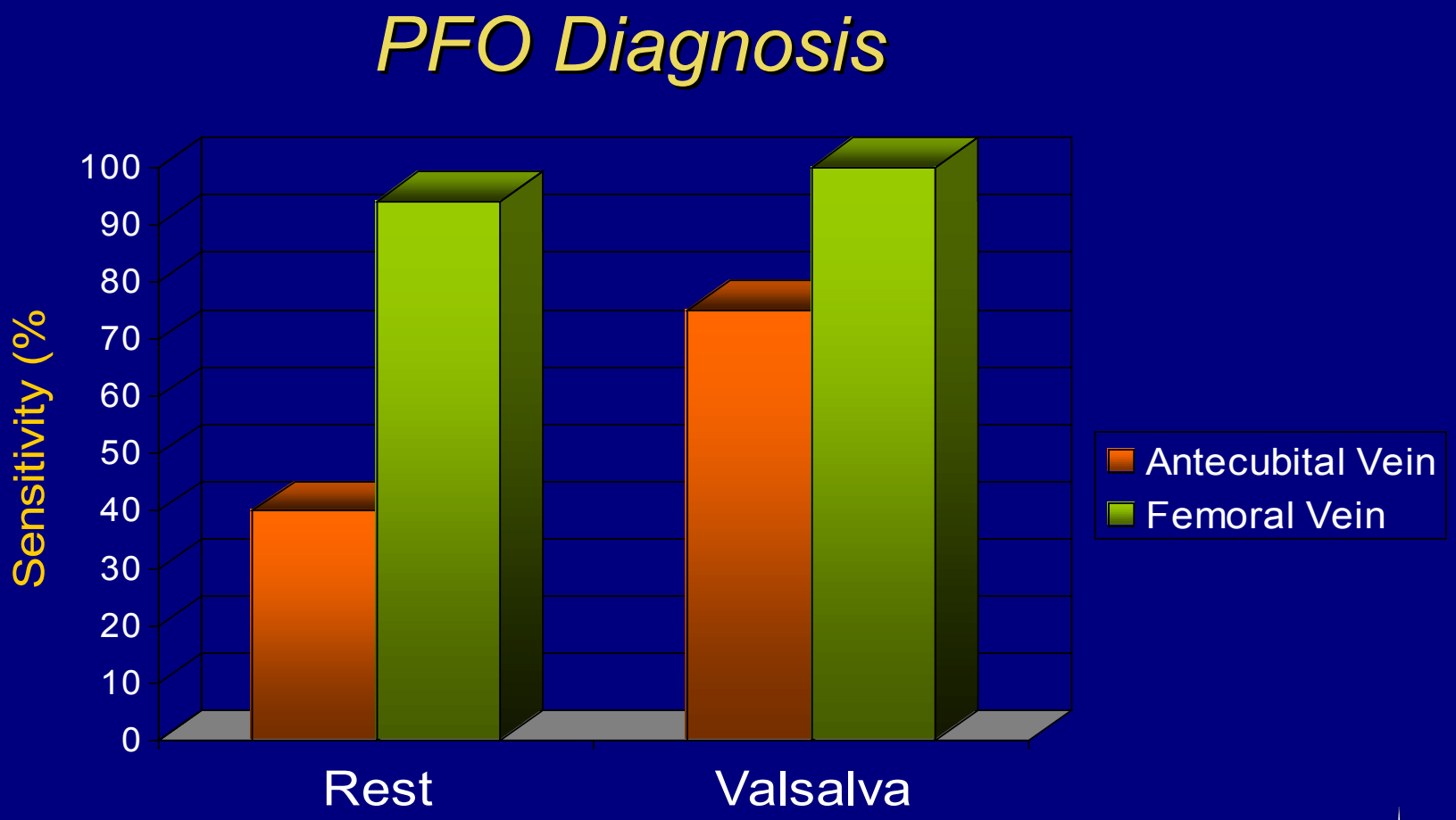
PFO Diagnosis and RLS Detection: TCD vs. TEE

TCD	Sensitivity %	Specificity %	Accuracy %
DiTullio et al.[1]*	68	100	---
Klötzsch et al.[2]*	91	94	93
Spencer et al.[3]†	98	33	94

* Single-gated TCD; †Power M-mode TCD

[1]Stroke 1993;24:1020-4
[2]Neurology 1994,44:1603-6
[3] Spencer, Moehring, Jesurum, Gray, Olsen, & Reisman. J Neuroimaging 2004;14:342-9.

TCD Sensitivity Is Dependent on Contrast Injection Site

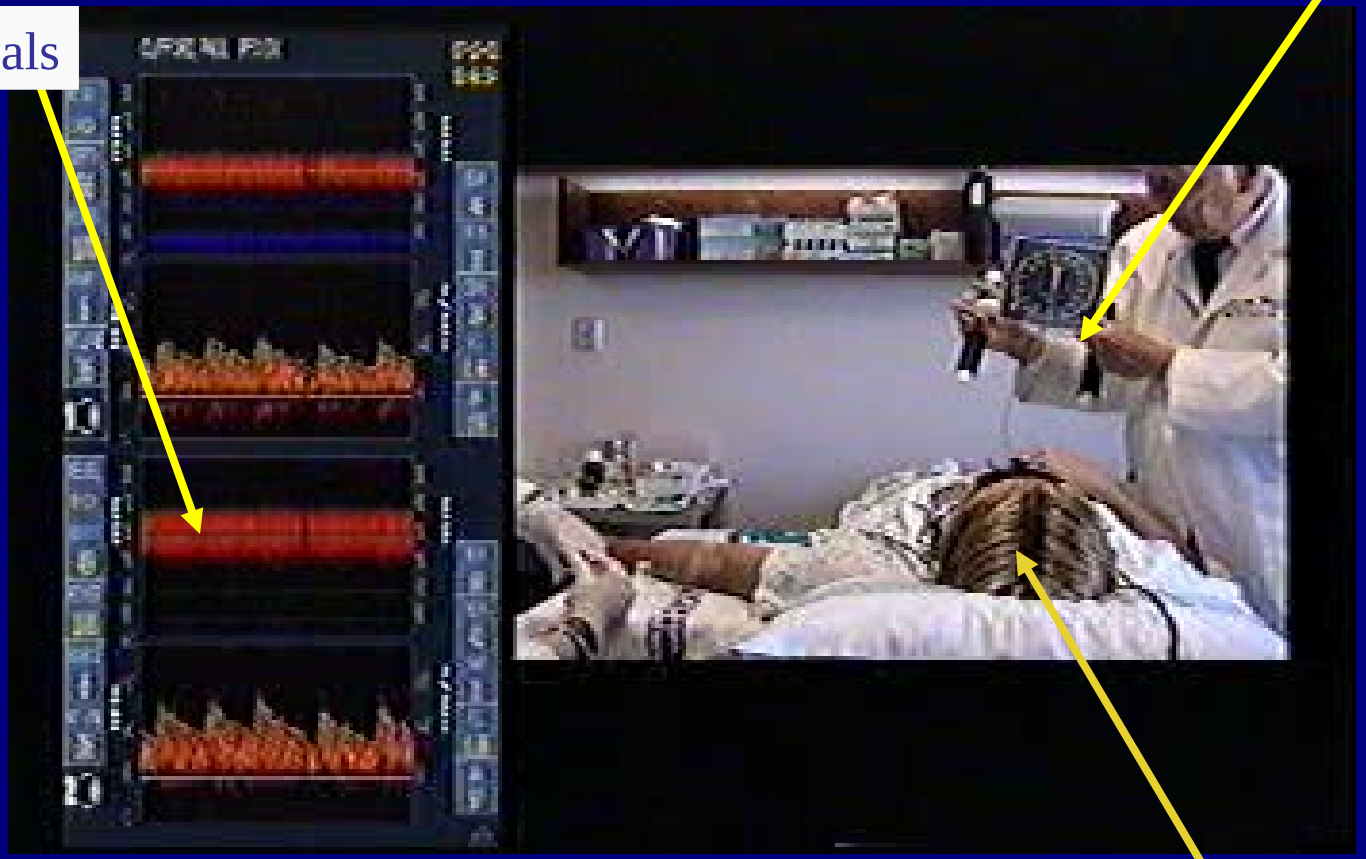


Hamann et al. Neurology 1998;50:1423-8

Diagnostic evaluation

Calibrated Valsalva

Doppler signals



Headset on pt.

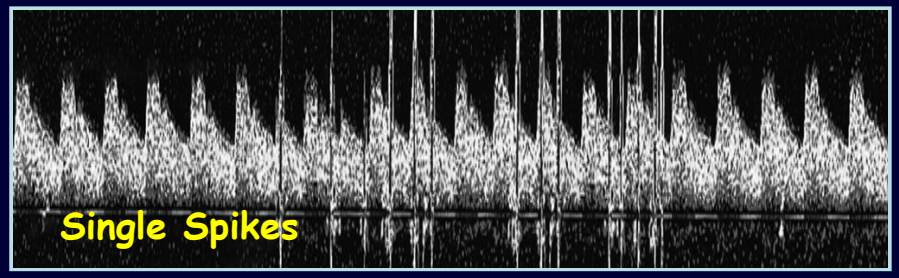
Transcranial Doppler Evaluation

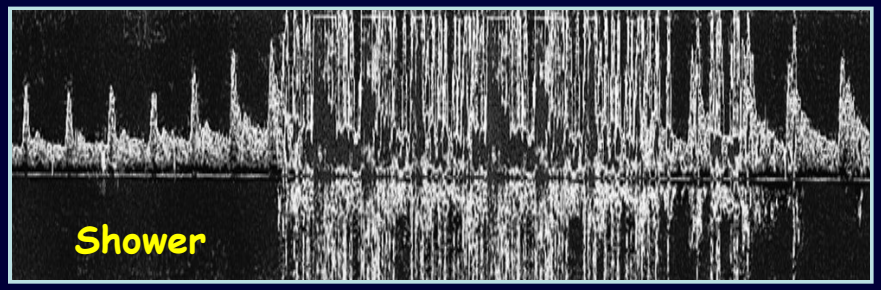
Diagnosis Using TCD

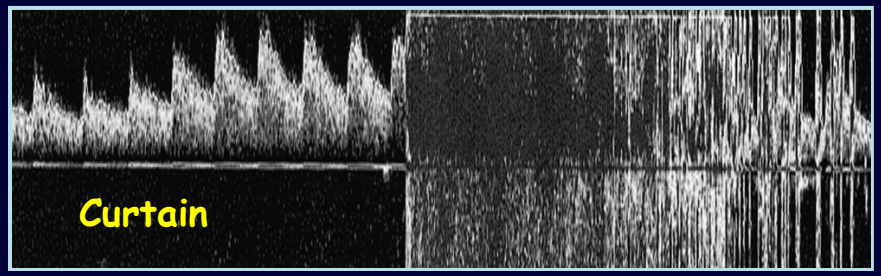
Patent Foramen Ovale (PFO)

HIGH RISK PFO: R-to-L SHUNT VOLUME

The Need to Quantify Right-to-Left Shunt in Acute Ischemic Stroke: A Case-Control Study







"Curtain" or "shower" patterns associated with the highest risk of cryptogenic stroke

(OR 12.4 95% CI 4.08-38.09)

Serena J et al.
Stroke 1998; 29: 1322-1328

Medical therapy-PFO &Stroke

- Anticoagulant-Coumadin
- Antiplatelet- (aspirin, clopidogrel, Aggrenox)

TABLE 3. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without PFO Assigned to Warfarin or Aspirin

	Warfarin	Aspirin	Hazard Ratio (95% CI)	*P*
Entire PICSS cohort				
With PFO (n=203)	16.5% (n=97)	13.2% (n=106)	1.29 (0.63–2.64)	0.49
No PFO (n=398)	13.4% (n=195)	17.4% (n=203)	0.80 (0.49–1.33)	0.40
Cryptogenic cohort				
With PFO (n=98)	9.5% (n=42)	17.9% (n=56)	0.52 (0.16–1.67)	0.28
No PFO (n=152)	8.3% (n=72)	16.3% (n=80)	0.50 (0.19–1.31)	0.16

*From Kaplan-Meier curves.

Recurrent Cerebrovascular events

Group	At 1 Year		At 2 Years		At 3 Years		At 4 Years	
	Risk of Stroke	Risk of Stroke or TIA	Risk of Stroke	Risk of Stroke or TIA	Risk of Stroke	Risk of Stroke or TIA	Risk of Stroke	Risk of Stroke or TIA
	percent (95 percent confidence interval)							
No atrial septal abnormality	2.0 (0.4–3.6)	3.0 (1.1–4.9)	3.7 (1.6–5.8)	4.7 (2.3–7.1)	4.2 (1.8–6.6)	5.2 (2.6–7.8)	4.2 (1.8–6.6)	6.2 (3.0–9.3)
No. at risk	304	304	294	291	270	267	159	158
Patent foramen ovale alone	1.8 (0.05–3.6)	3.7 (1.1–6.2)	1.8 (0.05–3.6)	4.6 (1.8–7.4)	2.3 (0.3–4.3)	5.6 (2.5–8.7)	2.3 (0.3–4.3)	5.6 (2.5–8.7)
No. at risk	216	216	211	207	204	198	125	122
Atrial septal aneurysm alone	0	0	0	0	0	0	0	0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Patent foramen ovale and atrial septal aneurysm	2.0 (0.0–5.8)	5.9 (0.0–12.4)	4.0 (0.0–9.4)	8.0 (0.5–15.5)	6.3 (0.0–13.2)	10.3 (1.7–18.9)	15.2 (1.8–28.6)	19.2 (5.0–33.4)
No. at risk	51	51	48	46	46	44	27	25

*TIA denotes transient ischemic attack.

Mas et.al N.Engl J Med 2001 345:1740-6

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 ($p<0.001$)

[1] Khairy et al. Ann Intern Med 2003;139:753-60

[2] Windecker et al. J Am Coll Cardiol 2004;44:750-8

[3] Schuchlenz et al. Int J Cardiol 2005;101:77-82

Patients with Thrombophilia and PFO Have Comparable Outcomes Post-Closure

PFO (N=72)	With Thrombophilia (N=20)	Without Thrombophilia (N=52)
Multiple ischemic events pre-closure	16 (80%)	5 (10%) *
Event-free rate post-closure	100%	94% NS
Follow-up duration months	20.6±13.5	19.5± 13.2

* $p<0.0001$

Giardini et al. Am J Cardiol 2004;94:1012-6

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PFO Closure (N=242)-Swedish Medical Center Experience

Indication	ALL Patients (N=242)	Patients ≥ 65 (N=62)	Patients < 65 (N=180)
• Stroke/TIA	234	60	174
• Platypnea-Orthodeoxia	1	1	0
• MI	4	1	3
• Other	3	0	3
• Recurrent stroke pre-closure (%)	25	24	27

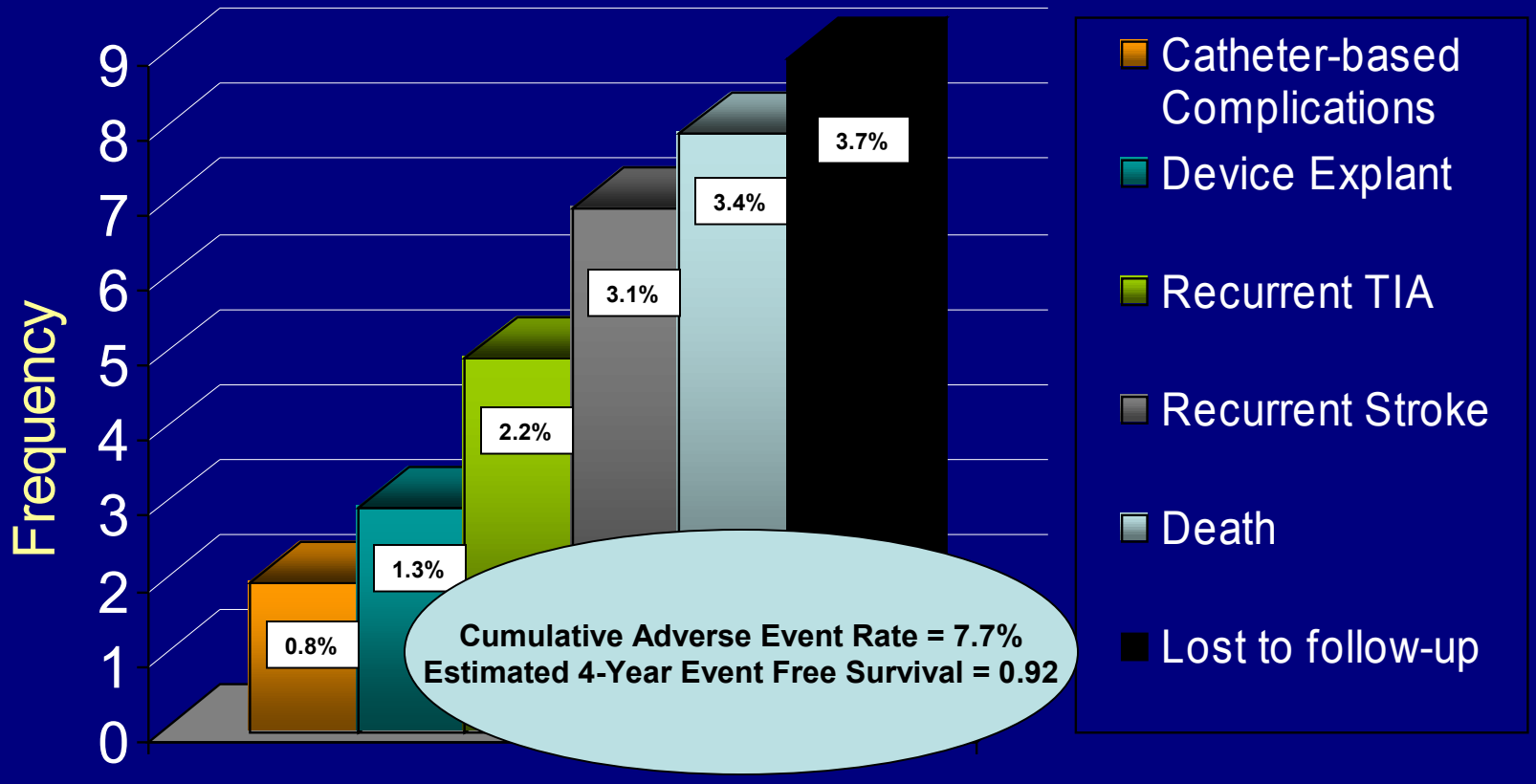
PFO-C: Patient Demographics (N=242)

	All Patients	Age ≥ 65	Age < 65
Age	53 ± 15	73 ± 6	46 ± 11
Male	48%	52%	47%
CAD	22%	27%	20%
Prior MI	6%	12%	4%
Heart Failure	2%	5%	1%
Diabetes	9%	10%	9%
Hypertension	41%	60%	35%
Hyperlipidemia	32%	45%	27%
Renal Failure	2%	2%	2%
COPD	2%	5%	1%

Recurrent Stroke following PFO-C (N=7/242)

Age at Time of PFO-C (years)	Stroke: Days post PFO-C	PFO-C pm-TCD Grade
72	56	6m = G(0)
53	797	1m = G(IV) 6m = G(V)
44	8	1m = G(0) 6m = G(0) 12m = G(I)
72	74	1m = G(V) 6m = G(I)
74	20	12m = G(1)
85	730	1m = G(II) 6m = G(IV) 12m = G(I)
68	105	Unknown

Longitudinal Clinical Outcomes following PFO Closure

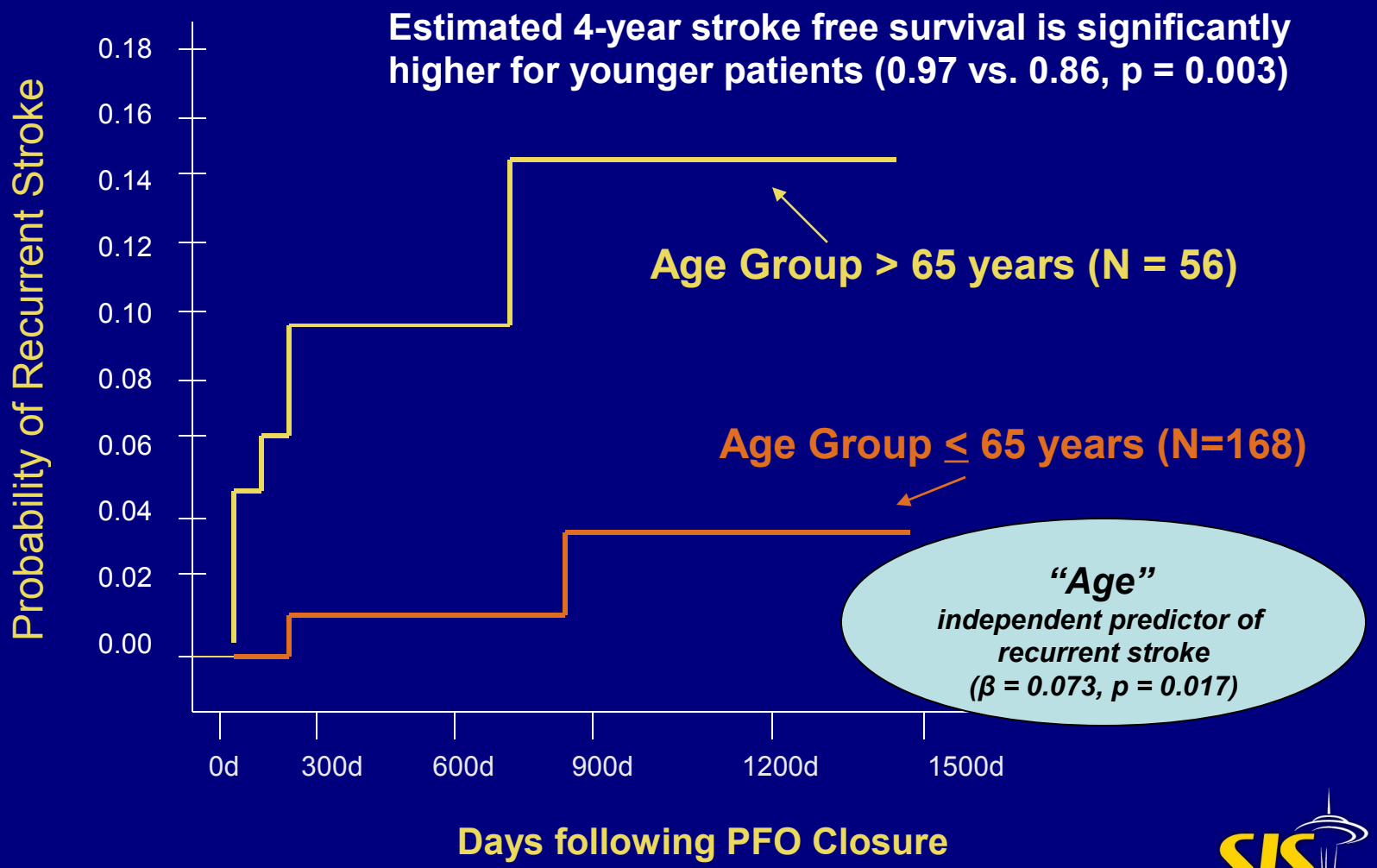


Mean Duration of Follow-up 518 days (95% CI, 480-576)

N=242; Age 53±15 years; 52% female; 97% neurological indication

Harms, Reisman, Jesurum, et al, 2005, unpublished data

Age at Time of PFO Closure: Significant Predictor of Recurrent Stroke



Harms, Reisman, Jesurum, et al, 2005, unpublished data

RLS Grade at Baseline and Following PFO-C

Grade	0	I	II	III	IV	V	N
BL-R	15 (7%)	25 (11%)	35 (15%)	38 (17%)	59 (26%)	58 (25%)	**230**
BL-S	0 (0%)	1 (0.4%)	2 (0.9%)	20 (9%)	52 (23%)	155 (67%)	**230**
1M-S	40 (24%)	41 (24%)	25 (15%)	20 (12%)	17 (10%)	27 (16%)	**170**
6M-S	23 (18%)	53 (41%)	16 (12%)	16 (12%)	8 (6%)	14 (11%)	**130**
12M-S	16 (20%)	32 (40%)	6 (7%)	14 (17%)	6 (7%)	7 (9%)	**81**
>12M-S	10 (23%)	10 (23%)	5 (12%)	8 (19%)	5 (12%)	5 (12%)	**43**

R= rest; S = calibrated Valsalva; BL = baseline; M = month

Change in RLS Grade: Baseline – 1 Month PFO-C (Calibrated Valsalva)

Baseline pm-TCD Shunt Grade (0-V)	pm-TCD Grade: 1 Month Following PFO-C (N=166) N (%)					
	0	**I**	**II**	**III**	**IV**	**V**
0						
I		1 (1)				
II	1 (1)					
III	5 (3)	3 (2)	2 (1)		**1 (1)**	**1(1)**
IV	9 (5)	11 (7)	5 (3)	5 (3)	3 (2)	**3 (2)**
V	23 (14)	25 (15)	18 (11)	15 (9)	13 (8)	22 (13)

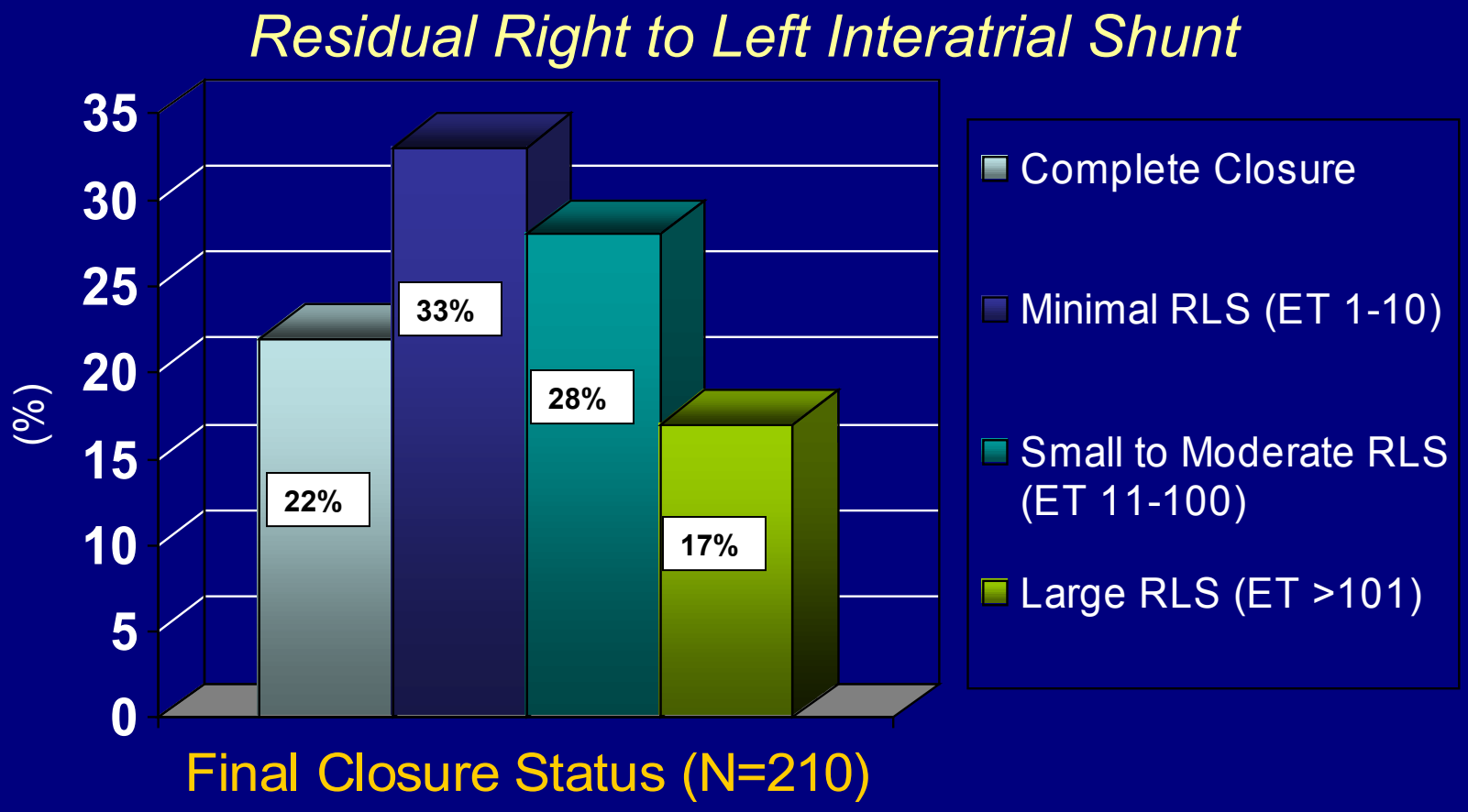
Change in RLS Grade: 1 Month– 6 Months PFO-C (Calibrated Valsalva)

1M PFO-C pm-TCD Shunt Grade (0-V)	pm-TCD Grade: 6 Months Following PFO-C (N=102) N (%)					
	0	**I**	**II**	**III**	**IV**	**V**
0	11 (11)	**12 (12)**	**1 (1)**	**1 (1)**		
I	3 (3)	15 (15)	**3 (3)**	**1 (1)**		
II	1 (1)	6 (6)	3 (3)	**2 (2)**	**1 (1)**	**1 (1)**
III		4 (4)	1 (1)	3 (3)	**1 (1)**	**1 (1)**
IV	1 (1)	1 (1)		3 (3)	2 (2)	**2 (2)**
V	1 (1)	5 (5)	2 (2)	2 (2)	3 (3)	9 (9)

Change in RLS Grade: 6Months– 12 Months PFO-C (Calibrated Valsalva)

6M PFO-C m-TCD Shunt Grade (0-V)	pm-TCD Grade: 12 Months Following PFO-C (N=59) N (%)					
	0	**I**	**II**	**III**	**IV**	**V**
0	3 (5)	**2 (3)**		**1 (2)**		**1 (2)**
I	6 (10)	17 (29)	**1 (2)**	**2 (3)**	**2 (3)**	
II	1 (2)	3 (5)	1 (2)	**2 (3)**		
III	1 (2)	1 (2)	1 (2)	4 (7)	**1 (2)**	
IV		1 (2)			1 (2)	**2 (3)**
V				2 (3)	1 (2)	2 (3)

Longitudinal Outcomes following Transcatheter PFO Closure



- Mean 318 days [95% CI 281–347])
- ET = Embolic Tracks on pm-TCD
- Baseline RLS Grade vs. Final RLS Grade (4.6± 0.73 vs. 1.8± 1.6, p < 0.000).

Harms, Reisman, Jesurum, et al, 2005, unpublished data

Migraines and PFO

Epidemiology of Migraine

- About 12% of population affected [1]
- Women are about 3 times more likely to have migraines than men [1]
- One-year prevalence in children ranges from 3.0-10.6%[1]
- Estimated cost to economy $14.6 billion in terms of medication, missed work days, and lost productivity[2]

[1]Lipton & Bigal Am J Med 2005;118:3S-10S

[2]Hu et al. Arch Intern Med 1999;159:813-8

Psychiatric Costs of Migraine

- Migraineurs are more likely to suffer from major depression, anxiety disorders, and obsessive-compulsive disorder than non-migraineurs[1]
- Migraineurs are more likely to abuse illicit drugs and be dependent on nicotine than non-migraineurs[1]
- Migraineurs with major depression have a high incidence of suicide attempts (38.5 per 100 with aura, 22.2 per 100 without aura)[2]

1Breslau & Davis J Psychiat Res 1993;27:211-21
2Breslau et al. Psychiatry Res 1992;37:11-23

Migraine Severity and Prognosis

- 10-20% of migraineurs are refractory[1]
  - High frequency of days during which they cannot perform normal activities
  - Do not get relief from prophylactic or rescue medications
- 10-15% of migraineurs have aura associated with headache[1]
- Prevalence of migraine appears to fall after age 55[2]
- Subset of population with migraine may progress to chronic daily headache (> 180 days/yr)[2]

1Olesen, Hansen, Welch. The Headaches, 2nd ed. Lippincott, 2001.
2Lipton & Bigal Am J Med 2005;118:3S-10S

Medications For Migraines

RESCUE Medications

- Ergotamine
- Triptans (5-hydroxytryptamine 1B/1D receptor agonists)
- Aspirin and other over-the-counter medications

Migraine Prophylactic Drugs[1-5]

- Anticonvulsants-topiramate, valproate sodium
- Serotonin antagonists*-methysergide
- Selective serotonin reuptake inhibitors (SSRI)*-venlafaxine
- Beta-blockers-atenolol, propanolol
- Calcium-channel blockers*-verapamil
- Tricyclic antidepressants*-amitriptyline, doxepin
- Anticoagulant/anti-platelet drugs-aspirin, clopidogrel*
- Angiotensin-converting enzyme inhibitors-lisinopril*
- Angiotensin II receptor blocker-candesartan*

(* Off-label use)

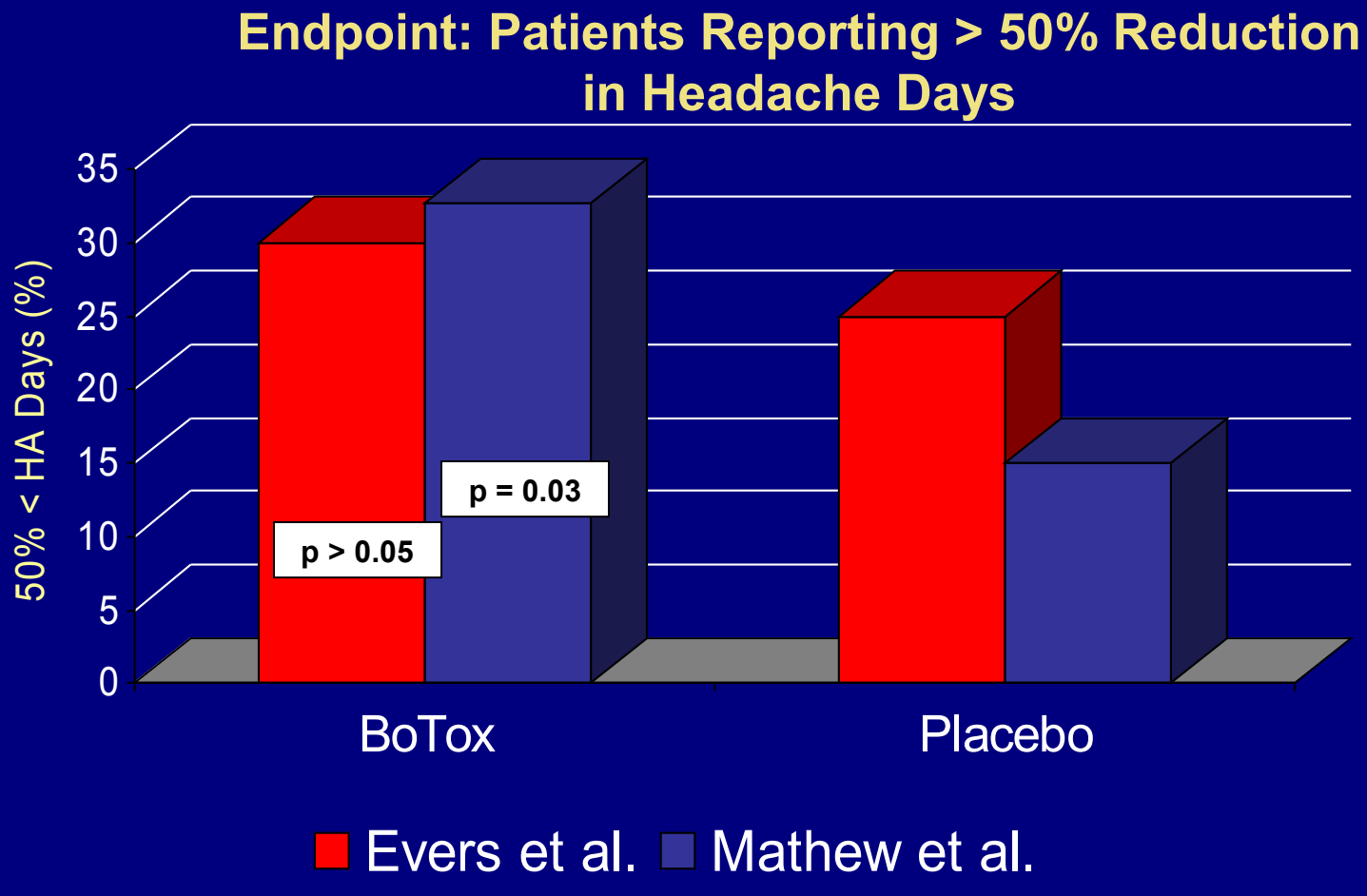
1Holcomb The Nurse Practitioner 2005;30:12-5
2Clinical Courier 2001;19:1-15
3Ozyalcin et al. Headache 2005;45:144-52
4Schrader et al. BMJ 2001;322:1-5
5Tronvik et al. JAMA 2003;289:65-9

Alternative Migraine Prevention Strategies

- Biofeedback-both biofeedback and self-relaxation (control) groups had significant reduction in medication and increased pain-free days[1]
- Feverfew (herbal remedy)-stable extract reduced headaches only in patients with > 4 migraines/mo[2]
- Riboflavin-44% of patients had > 50% decrease in migraines with 25 mg qd[3]

1Vasudeva et al. Headache 2003;43:245-50
2Pfaffenrath et al. Cephalalgia 2002;22:523-532
3Maizels et al. Headache 2004;44:885-90

Botulinum Neurotoxin Type A (Botox) for Treatment of Chronic Daily Headache



Evers et al. Cephalalgia 2004;24:838-43

Mathew et al. Headache 2005;45:293-307

Prophylaxis Trials-THE Placebo Effect

Significant placebo

- 23.5 ± 8.0% of placebo patients vs. 45.5 ± 15.5% of active patients had >50% reduction in attacks
- 16.8 ± 12.7% of placebo patients vs. 41.8 ± 11.7% of active patients had reduced frequency of attacks
- 21 ± 9% of placebo patients had adverse effects in another meta-analysis[2]; nausea, paresthesia, and fatigue most common

1van der Kuy & Lohman Cephalalgia 2002;22:265-70

2Reuter et al. Cephalalgia 2003;23:496-503

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Infarct Location in Ischemic Stroke Patients Aged <45 years

Number (percent)

	Migraineurs N=66	Non-Migraineurs N=353
Global Middle Cerebral Artery (MCA)	3 (5)	46 (13)
Deep MCA	5 (8)*	69 (20)
Anterior Circulation	28 (42)†	219 (62)
Thalamus	9 (14)*	21 (6)
Cerebellum	4 (6)	17 (5)
Posterior Cerebral Artery	14 (21) †	27 (8)
Posterior Circulation	36 (55) †	120 (34)

*p<0.05, †p<0.01 (chi-square or Fisher's exact test)

Milhaud et al. Neurology 2001;57:1805-11

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Migraine and Stroke

- Posterior circulation involvement was a significant predictor of migraine in stroke patients aged <45 [1]

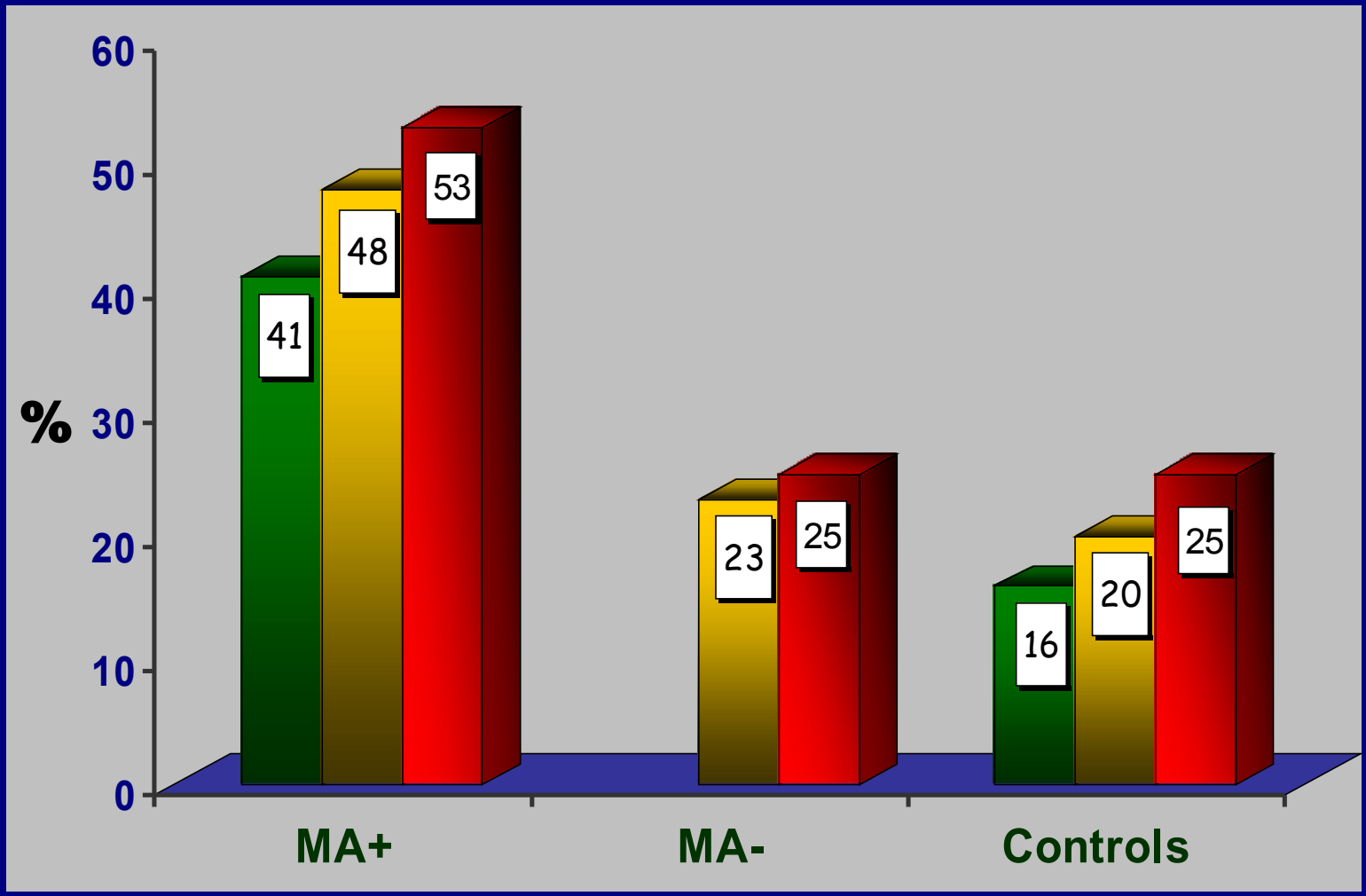
- Migraineurs had significantly higher incidence of subclinical posterior cerebellar infarcts than did age- and sex-matched controls (5.4% vs. 0.7%, p=0.02), due to high incidence in migraine + aura patients (8.1% vs. 2.2% in migraine –aura;p=0.03) [2]

1Milhaud et al.Neurology 2001;57:1805-11
2Kruit et al.JAMA 2004;291:427-434

Incidence of Migraine and PFO in Stroke Patients

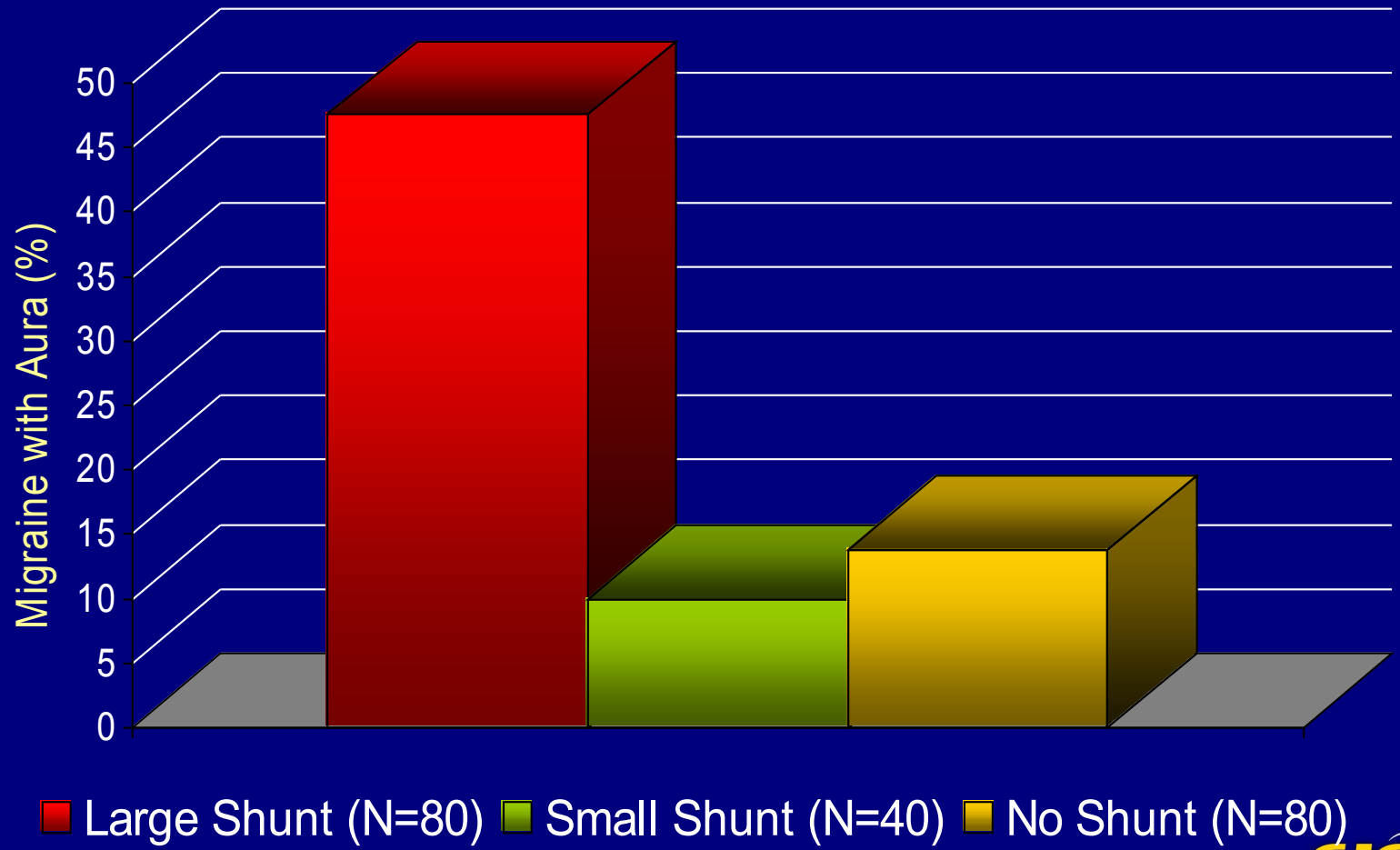
	PFO -	*PFO +*
Lamy et al. Stroke 2002;33:706-11	**14%**	**27%**
Sztajzel et al. Cerebrovasc Dis 2002;13:102-6	**13%**	**52%**

PATENT FORAMEN OVALE: PREVALENCE IN MIGRAINEURS



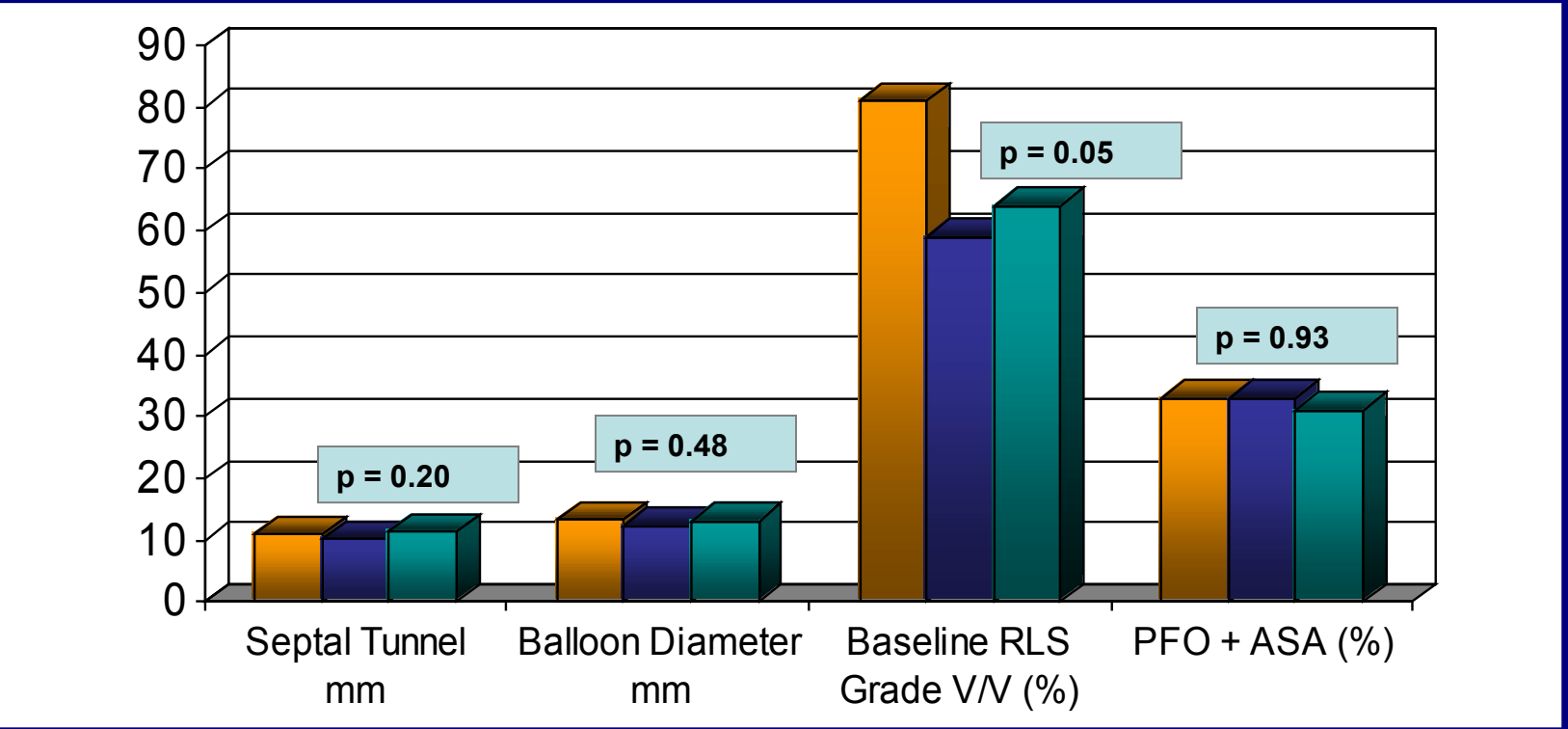
PFO and Migraine Connection

Migraine with Aura in Divers with PFO



Wilmshurst et al. Clin Sci 2001;100:215-20

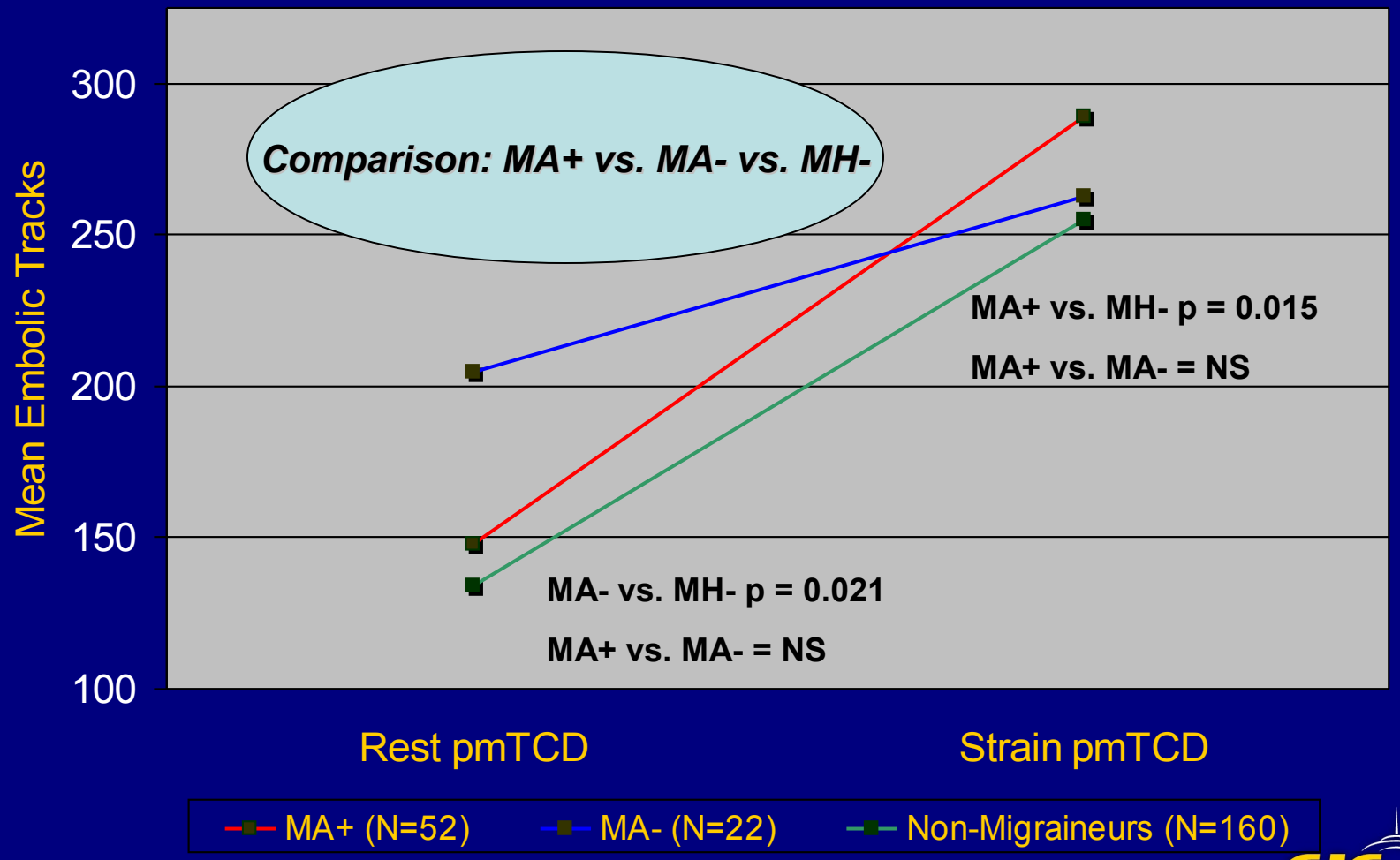
PFO: Septal Morphology Characteristics



- Ischemic stroke patients referred for PFO - closure (246)
- Methods: Pre-closure ICE and pm-TCD evaluation

Harms, Reisman, Jesurum et al., 2005

Baseline Cerebral Conductance in Ischemic Stroke Patients with PFO



Jesurum, Reisman, Krabill et al., *Circulation* 2005, in press

Why might PFO closure reduce migraines?

- Current theory suggests that RLS permits paradoxical microemboli and/or vasoactive chemicals in the venous circulation to bypass lung filtration, thereby triggering migraine symptoms[1]

- Vasoactive agent could be an amino acid or a steroid/prostaglandin[2]

[1]Wilmshurst et al. Clin Sci 2001;100:215-20

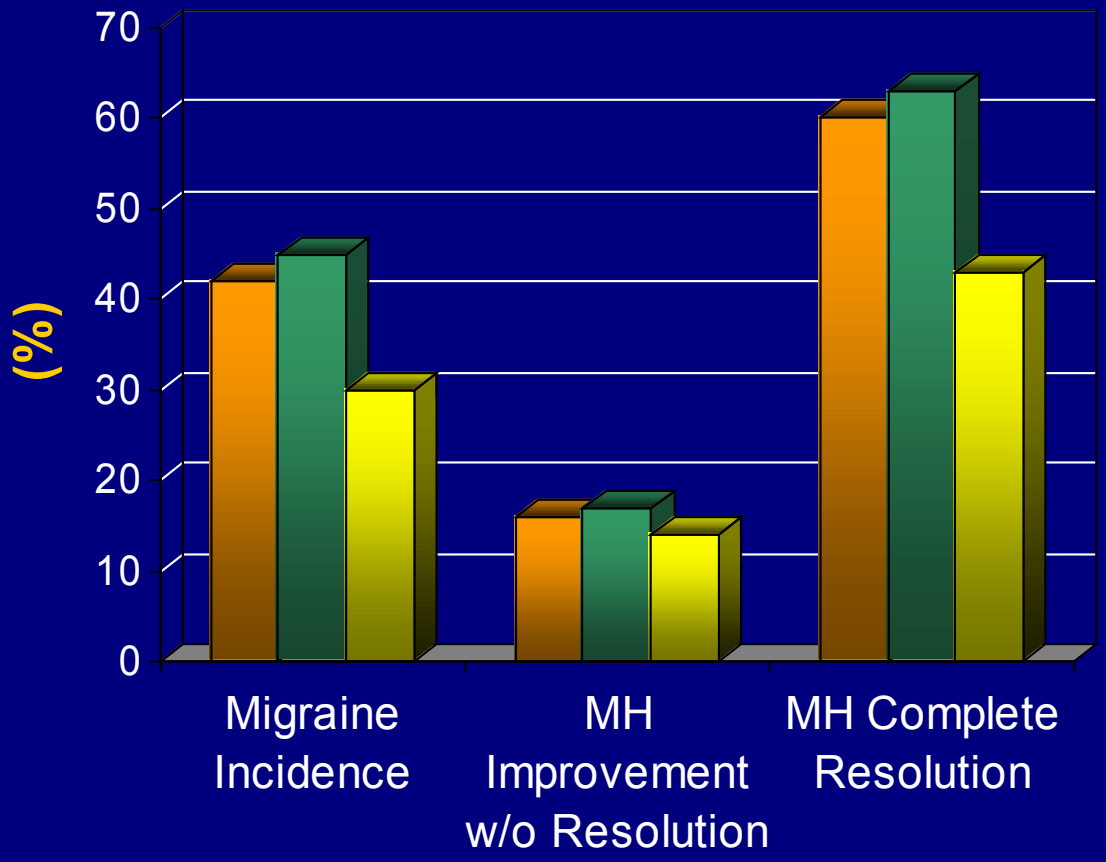
[2]Tobis & Azarbal Curr Issues in Cardiol 2005;32:362-5:

Trials of PFO Closure and Migraine Prevention

Author/Year Study Design	N (%F)	Migraine +Aura Pre-Closure N (%)	Duration of Follow-up	Migraine Resolution	Reduced Severity or Frequency
Wilmshurst et al. Lancet 2000;356:1648-51 Retrospective	21 (48)	16 (76)	NS	48% (44% +aura; 60% -aura)	38% improvement without resolution (50% +aura, 0% -aura)
Morandi et al. J Intervent Cardiol 2003;16:39-42 Prospective	17 (71)	9 (53)	6 mos	29%	59% (intensity, duration, & frequency all reduced)
Post et al. Neurology 2004;62:1439 Retrospective	26 (65)	12 (46)	Median 579 d	2 mo: 31% (33% +aura; 29% -aura)	Frequency reduced ($p<0.05$), but % NS
Schwerzmann et al. Neurology 2004;62:186-90 Retrospective	48 (65)	37 (77)	1.7±0.9 y for pts with all headaches (migraine and other)	NS	Frequency reduced by 54% in +aura, 62% in – aura
Azarbal et al. J. Am. Coll. Cardiol. 2005; 45:489-92 Retrospective	37 (NS)	20 (30)	Mean 12 mo	75% +aura; 40% -aura	Improvement without resolution 5% +aura, 40% -aura

NS = not specified

Migraine Relief Following Transcatheter PFO Closure



75% (15/20) with PFO and MA+ had *complete* migraine relief

- Overall (N=89)
- PFO (N=66)
- ASD (N=23)

Azarbal et al. J Am Coll Cardiol 2005; 45:489-92

PFO Closure and Migraine Relief

Symptom Reduction after PFO Closure

	Complete Resolution of Symptoms %	≥ 50% Reduction in Migraine Frequency[1] %	< 50% Reduction in Migraine Frequency[1] %
Overall (N=50)	56	14	30
MA + (N=38)	54	14	32
MA- (N=12)	62	15	23

- PFO closure performed to prevent recurrent stroke
- Mean follow-up 37±23 weeks
- Migraines/month: 6.8±9.6 baseline; 1.4±3.4 post-PFO-C ($p<0.001$)
- 1 = number of migraine events per month

Reisman et al. J Am Coll Cardiol 2005; 45: 493-5

Late Reversal of Migraine Relief Following Transcatheter PFO Closure: 5 Cases

TCD Readings at Rest/Strain (Number of Migraines per Month/± Aura)

	Baseline	1 Month	6 Months	12 Months	Late (> 12 months)
Patient #1	20/301 (30/MA+)	26/301 (0)	0/97 (0)	33/42 (0)	111/301 (5/MA-)
Patient #2	301/301 (3/MA-)	0/301 (0)	65/301 (0)	75/268 (0)	* (3/MA-)
Patient #3	38/119 (2/MA-)	0/5 (0)	0/0 (0)	0/301 (0)	* (6/MA-)
Patient #4	* (4/MA+)	* (0)	* (0)	1/4 (0)	* (3/MA-)
Patient #5	* (0.6/MA-)	* (0)	0/0 (0)	* *	* (3/MA+)

Jesurum and Reisman, 2005, unpublished data

Lingering Questions

- What is the mechanism of migraine relief after PFO closure?
- What is the trigger for migraine attacks?
- Does size of PFO matter in etiology of stroke and/or migraine?
- Is this a pleomorphic effect?

MIST
(Migraine Intervention with STARFlex™ Technology)

- first prospective, randomized double-blinded study to evaluate PFO/migraine connection
- 147 patients, 1:1 randomization – PFO closure with NMT Medical STARFlex™ implant vs. control
- 15 centers; United Kingdom
- primary endpoint – compare incidence of migraine attacks in both groups
- enrollment completed — July 2005
- follow-up complete — January 2006
  results presented — Q1 2006

Courtesy NMT Medical, Inc.

MIST

(Migraine Intervention with STARFlex™ Technology)

result	Total #	%
total migraine patients studied	370	100.0%
small shunts (atrial and pulmonary)	61	16.5%
large pulmonary shunts	18	4.9%
ASDs	2	0.5%
large PFOs	139	37.6%
Total right to left shunts	220	59.5%

Courtesy NMT Medical, Inc.

Jan to May 2005

Why do we need a prospective study of PFO closure and migraine?

- In the UK, when the MIST I PFO closure study was opened to volunteers for 353 subjects, with half to receive sham procedure, ***14,000 people volunteered in the first week***, and the websites and phones had to be shut down
- This is a measure of the extreme desperation of people with this disorder
- Had the facilities been in place the study could have been completed 6 months early due to rapid recruitment

MIST II

Migraine Intervention with STARFlex® Technology

Mark Reisman, MD
Principal Investigator, Interventional Cardiology

Stewart Tepper, MD
Principal Investigator, Neurology/Migraine

NMT Medical, Inc.
Sponsor

MIST II

MIST II

- Randomized, double-blind, placebo-controlled trial
- 550 patients
- Primary endpoint: Resolution of migraine headache in 40% of patients at 6 months, with sustained 70% reduction of those same patients through 1 year

Conclusion

- Work continues to evolve to investigate optimal therapy for treatment of stroke in the presence of PFO (Closure one, Respect Trials)
- Randomized trials are being developed to further evaluate the relationship of Migraine and PFO
- The FDA continues to work closely with physicians and industry to clearly define the regulatory pathway to reach these endpoints