EBM 2008: What is the Current data for and against PFOs for Stroke, Migraine and Other clinical syndromes

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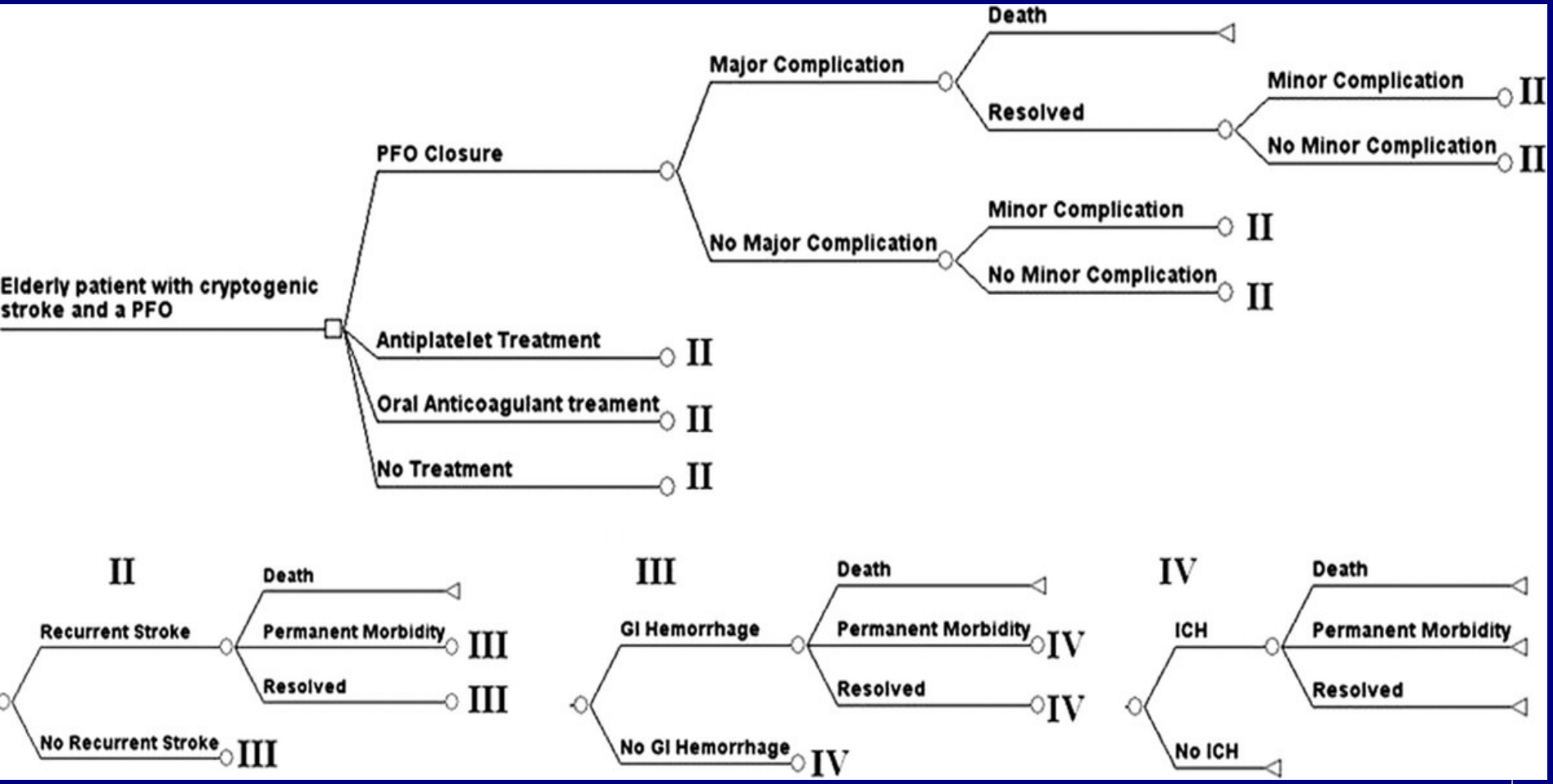
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	*Company*
Grant/Research Support	*NMT, Coherex,*
Consulting Fees/Honoraria	*Boston Sci, Cordis, abbott, Copaptus, Ovalis*
Major Stock Shareholder/Equity	*Biostar*
Royalty Income	
Ownership/Founder	
Intellectual Property Rights	
Other Financial Benefit	

Without EBM our daily conundrum



evolution of a patient……

Born with PFO

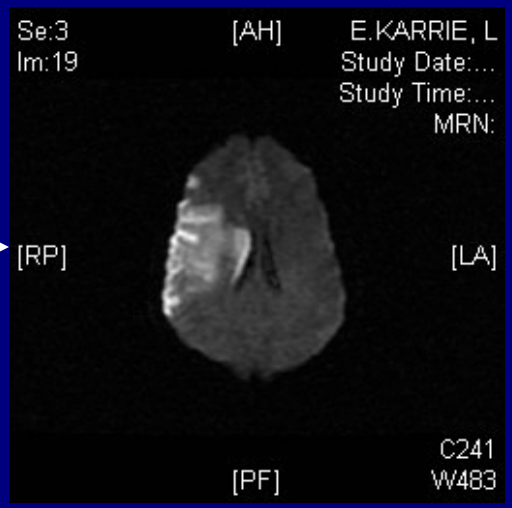
migraine

?

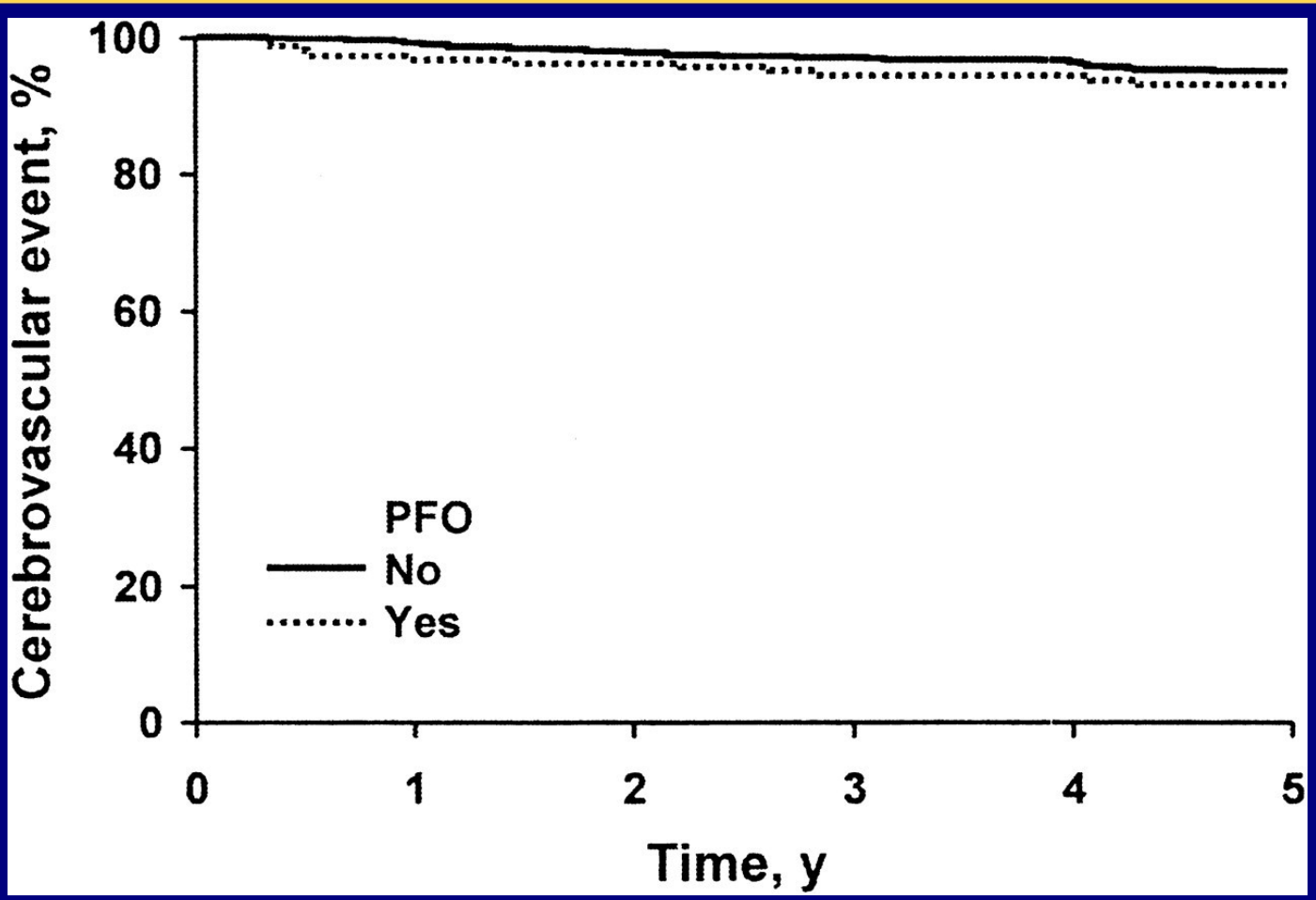
Suffered through
Life with CDH

?

Large debilitating
stroke



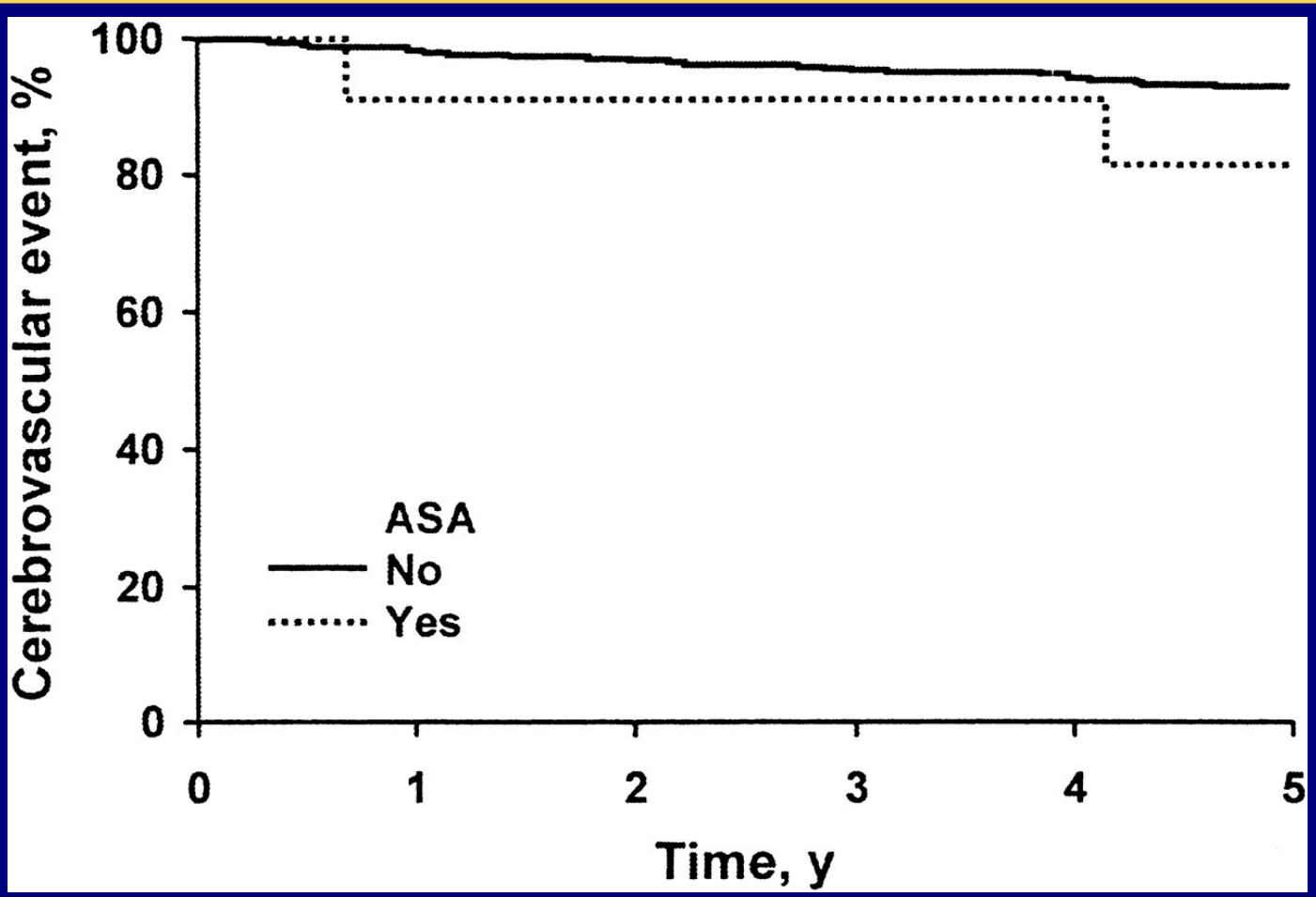
Stroke and PFO



Meissner, I. et al. J Am Coll Cardiol 2006;47:440-445

Kaplan-Meier estimate of survival free of cerebrovascular events in 577 subjects according to presence of patent foramen ovale (PFO)

Stroke –PFO/ASA



Meissner, I. et al. J Am Coll Cardiol 2006;47:440-445

Kaplan-Meier estimate of survival free of cerebrovascular events in 585 subjects according to presence of atrial septal aneurysm (ASA)

PFO is not a significant predictor of stroke in an unselected population sample (total N=585)*

Pathology Strokes/number of subjects	Hazard Ratio (95% CI)	P value
PFO 12/140; none had ASA	1.46 (0.74-2.88)	0.28
Atrial septal aneurysm (ASA) 2/11; none had PFO	3.72 (0.88-15.71)	0.07

Five year follow-up; 41 strokes total

Size of PFO was unrelated to risk of cerebrovascular disease

* Meissner I et al. J Am Coll Cardiol 2006;47:440-5.

Size of PFO does not increase risk of ***recurrent*** stroke or death (PICSS cohort)

	No PFO (N=398)	Small PFO* (N=119)	Large PFO* (N=84)
Event rate, % Hazard ratio (95% CI) P value	15.4 1.0	18.5 1.23 (0.76-2.00) 0.41	9.5 0.59 (0.28-1.24) 0.16

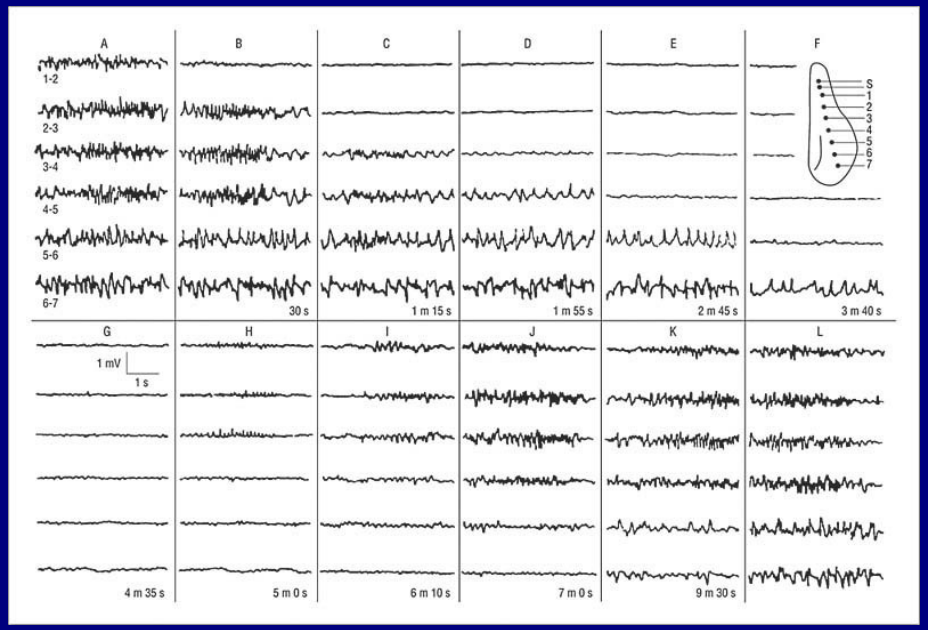
*Large PFO: ≥2 mm separation of septum secundum and primum OR ≥10 microbubbles appearing in left atrium on TEE; all other PFOs classified as small

Homma et al. Circulation 2002;105:2625-31.

….and no difference with respect to presence or absence Of ASA

SIS

Studies of PFO-Migraine



Cortical spreading depression
Seen in migraine suffers

Demographics and Risk Factors in an Overall Cohort of n= 1101 Among Subjects With and Without Self-Reported Migraine

	ALL	M (+)	M(-)	
No. of subjects (%)	1101 (100)	178 (16%)	923 (84%)	
Age, y	69±10	61±9	71±10	<0.01
Women, n (%)	639 (58)	128 (72)	508 (55)	<0.01
Race				<0.01
Black, n (%)	286 (26)	36 (20)	249 (27)	
Hispanic, n (%)	528 (48)	103 (58)	425 (46)	
White, n (%)	264 (24)	36 (20)	231 (25)	
Hypertension, n (%)	738 (67)	123 (69)	618 (67)	0.58
Diabetes mellitus, n (%)	198 (18)	27 (15)	175 (19)	0.23
Dyslipidemia, n (%)	528 (48)	79 (44)	462 (50)	0.17
Current smoking, n (%)	198 (18)	36 (20)	148 (16)	0.17
PFO, n (%)	164 (15)	26 (14.6)	138 (15)	0.91

*Migraine with aura, 22 (16%) of 140; without aura, 4 (11%) of 38 (P=0.42).

Detection of PFO w/migraine

		MA	M	NoM
Del Sette et al[10]	TCD	18/44 (41)	NA	8/50 (16)
Anzola et al[9]	TCD	54/113 (48)	12/53 (23)	5/25 (20)
Schwerzmann et al[8]	TEE	44/93 (47)	NA	16/93 (17)
Dalla Volta et al[31]	TCD	161/260 (62)	12/74 (16)	NA
Carod-Artal et al[33]	TCD	25/48 (52)	32/93 (34)	NA
Domitrz et al[11]	TCD	33/61 (54)	15/60 (25)	16/65 (25)
NOMAS	TTE	26/140 (19)	4/38 (11)	138/923 (15)

TCD indicates transcranial Doppler; TEE, transesophageal echocardiography.

MIST –BOTH PRIMARY AND SECONDARY ENDPOINTS WERE NEGATIVE

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

	Implant (n=74)		Sham procedure (n=73)		Statistical Analyses*	
	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	−0.06% (−6.45–6.34)	1.0
Frequency of migraine attacks/mo, mean±SD	4.82±2.44	3.23±1.80	4.51±2.17	3.53±2.13	0.45 (−0.16–1.05)	0.14
n	66	66	73	73	...	...
Total MIDAS score, median (range)	36 (3–108)	17 (0–270)	34 (2–189)	18 (0–240)	1 (−11–10)	0.88
n	66	67	69	72	...	...
Headache d/3 mo (MIDAS), median (range)	27 (0–70)	18 (0–90)	30 (5–80)	21 (0–80)	1 (−5–6)	0.79
n	66	67	69	72	...	...
HIT-6 total score, mean±SD	67.2±4.7	59.5±9.3	66.2±5.1	58.5±8.6	0 (−3–2)	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….

What are the next steps….

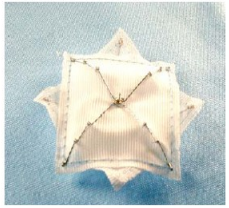
- Stroke Randomized trial status-

Closure one –COMPLETED

RESPECT-nearing completion

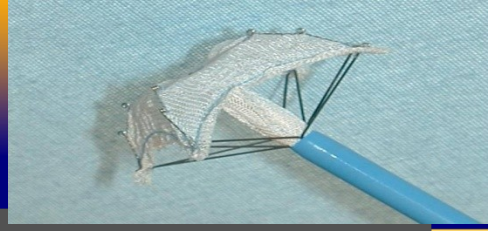
MIGRAINE

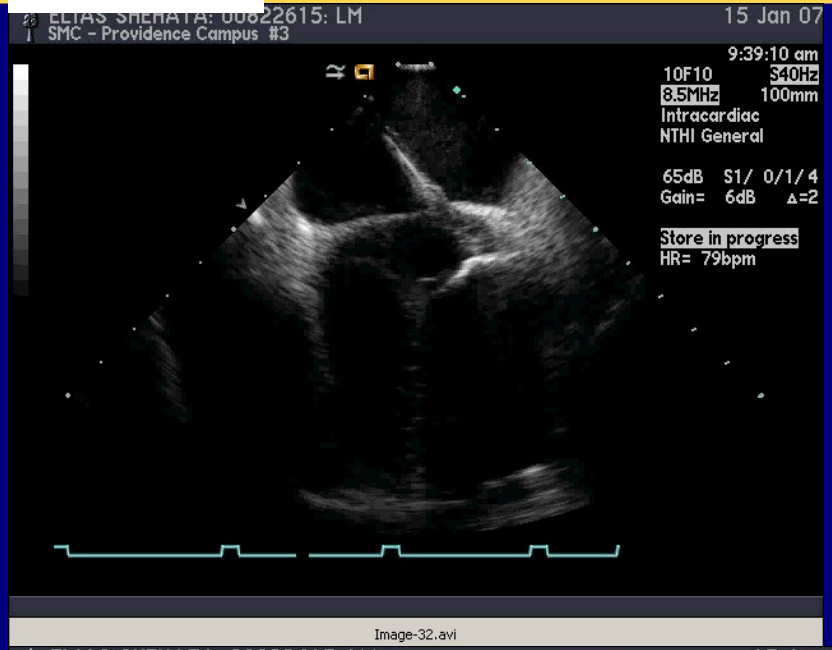
lots need to be sorted out

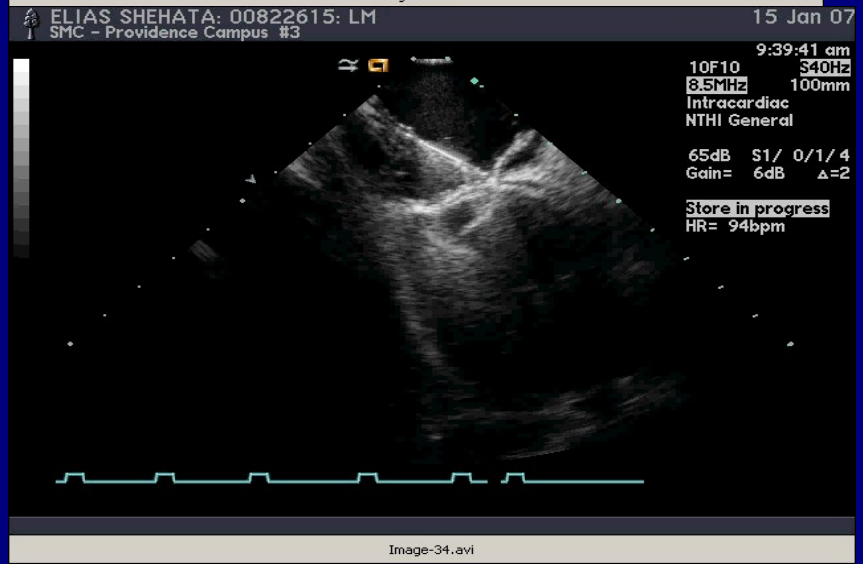


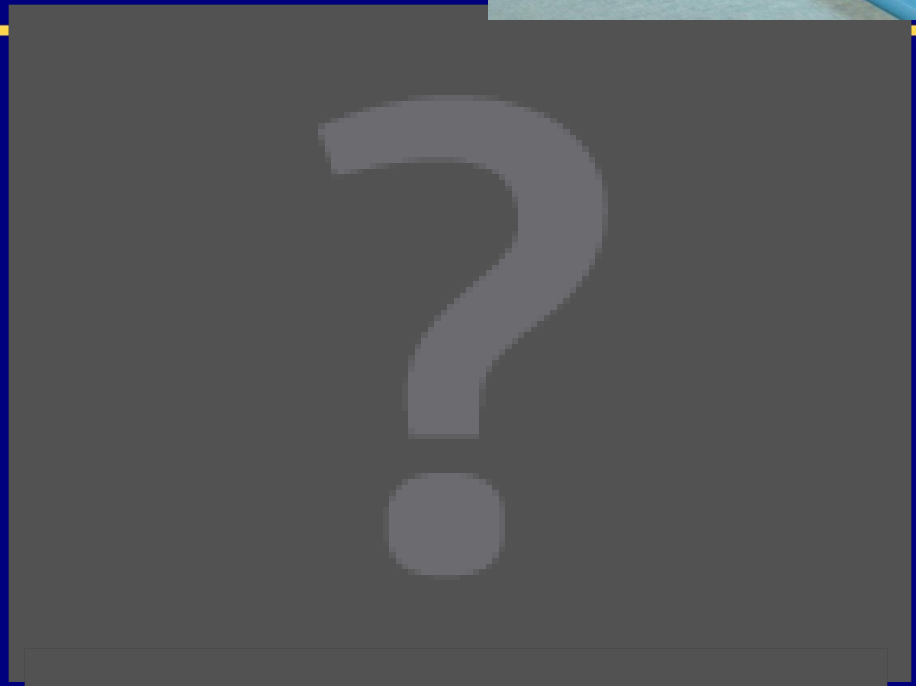
A CardioSEAL Closure Device

The devices for closure

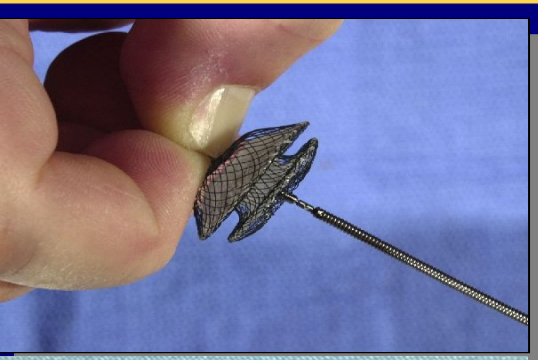








Stroke Prevention: Medical Therapy vs. Transcatheter PFO Closure



Incidence of Recurrent Stroke (%)

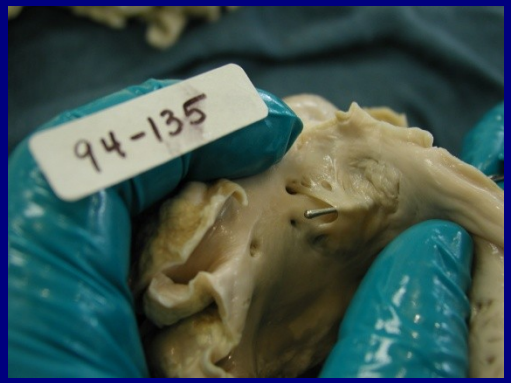
Study Design	Medical Therapy	PFO Closure
Meta-Analysis[1]	3.8-12/year	0-4.9/year
Retrospective[2]	24.3/4-year	8.5/4-year (p=0.05)
Retrospective[3]	13/year ASA 5.6/year warfarin	0.6/year (p<0.001)

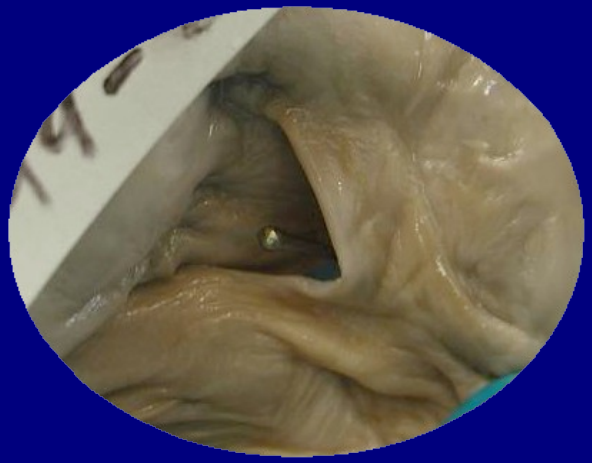
[1] Khairy et al. Ann Intern Med 2003;139:753-60

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

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

What about anatomy…..





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

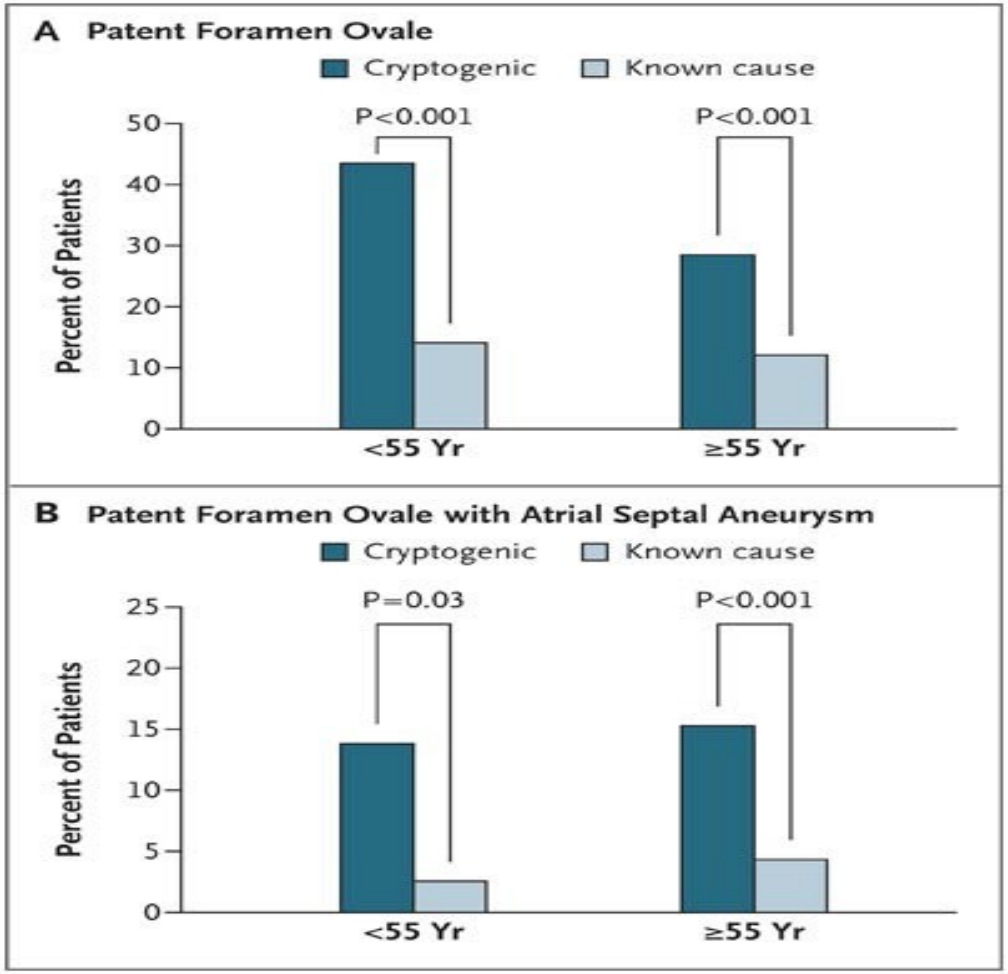
Table 1. Baseline Characteristics of Patients with Cryptogenic Stroke or with Stroke of Known Cause.*

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.

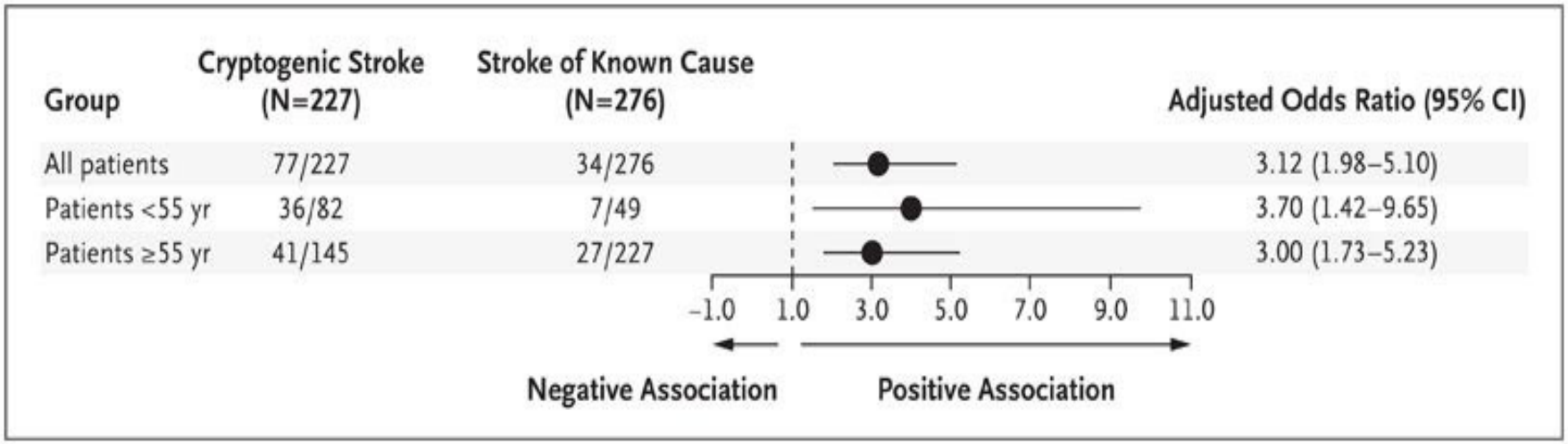
Handke M et al. N Engl J Med 2007;357:2262-2268

Prevalences of Patent Foramen Ovale (PFO) and PFO with Concomitant Atrial Septal Aneurysm among Patients with Cryptogenic Stroke and Those with Stroke of Known Cause, According to Age Group



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

Odds Ratios for the Presence of Patent Foramen Ovale among Patients with Cryptogenic Stroke, as Compared with Those with Stroke of Known Cause



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

Take aways

- In this prospective study, among patients 55 years of age or older, those with cryptogenic stroke (cause of stroke not identified before transesophageal echocardiography was performed) were more likely to have patent foramen ovale diagnosed on transesophageal echocardiography than were patients with stroke of known cause

- This suggests that patent foramen ovale is a cause of stroke in older patients

- There is an association between the presence of patent foramen ovale and cryptogenic stroke in both older patients and younger patients

- These data suggest that paradoxical embolism is a cause of stroke in both age groups

Reported hazards of recurrent ischemic events in medically treated Patients by type of atrial defect and end point (n>100for all studies) Followed for two or more years

Author	Index ischaemic event	Type of defect	Number of patients	Mean age (years)	Time between event and start of follow-up	End point	Mean follow-up (months)	Hazards (%) of a recurrent ischaemic event following the index event during: 30 days	Year 1	Year 2	Year 3	Year 4	Year 5	Year
De Castro *et al.* 2000 [45]	Cryptogenic stroke or TIA	PFO	47	53 ± 14	1 day	Recurrent stroke or TIA	31		4.3[a]	0[a]	0[a]	0[a]		
		PFO + ASA	27				31		7[a]	5.5[a]	0[a]	17.5[a]		
		No PFO	86	47 ± 14			34		3[a]	3[a]	10.3[a]	7[a]		
Mas *et al.* 2001 [44]	Cryptogenic stroke	PFO	216	40	3 months or less	Recurrent stroke or TIA	38 ± 10		3.7	0.9	1.0	0.0		
		ASA	10	40					0.0	0.0	0.0	0.0		
		PFO + ASA	51	40					5.9	3.1	2.3	8.9		
		No PFO	304	45					3.0	1.7	0.5	1.0		
Homma *et al.* 2002 [46]	Is													
Nedeltchev *et al.* 2002 [47]	Fi													
Windecker *et al.* 2004 [48]	C	stroke or TIA – Rx Aspirin				stroke or TIA								
Schuchlenz *et al.* 2005 [43]	Cryptogenic stroke or TIA – Rx aspirin	PFO	66	46 ± 13	Not given	Recurrent stroke or TIA	31		6.0[a]	8.0[a]	15.0[a]	9.0[a]	28.0[a]	16.0[a]
	Cryptogenic stroke TIA - anticc		47	50 ± 12			32		2.0[a]	4.0[a]	8.0[a]	6.0[a]	16.0[a]	0.0[a]

Contrary to the observation that the risk of recurrence
Is highest immediately after the various subtypes of ischemic
Stroke and declines thereafter, the natural history of stroke in
Patients with PFO is uncertain. Some authors have reported
Decline and others have observed an increase in recurrence hazards
during the first three years of f/u of patients
With ischemic stroke and PFO

Variability in duration of follow up may bias the conclusions of cohort studies of patents with patent foramen ovale

J. Benbassat[a] and R. Baumal[b]
[a]Myers-JDC-Brookdale Institute, The Smokler Center for Health Policy Research, Jerusalem, Israel and [b]Department of Laboratory Medicine and Pathobiology, Toronto Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Ischemic stroke treated with PFO closure devices

Table 2 Reported hazards of recurrent cerebrovascular ischaemic event in patients with PFO, with or without ASA, who were treated by transcatheter PFO closure. List of published cohort studies containing 100 patients or more who were followed for two or more years

Author	Number of patients	Mean age (years)	Time between event and PFO closure, (months)	Mean or median follow-up (months)	Hazards (%) of a recurrent ischaemic event, following trans-catheter l PFO closure, during:						
					30 days	Year 1	Year 2	Year 3	Year 4	Year 5	Year 7
Martin *et al.* 2002 [60]	110	47 ± 14	Not given	28 ± 20.		1.8	0.0	0.0	0.0	0.0	0.0
Onorato *et al.* 2003 [61]	256	48 ± 16	Not given	19		0.0	0.0				
Braun *et al.* 2004 [62]	307	43 ± 11	Not given	24		2.0	0.0	0.0	0.0		
Knebel *et al.* 2004 [63]	161	47 + 11	Not given	17 + 11		0.6	0.0				
Khositseth *et al.* 2004 [64]	103	53 ± 14	Not given	8 ± 8		1.0	1.9				
Windecker *et al.* 2004 [48]	150	50 ± 12	Not given	25		5.0[a]	2.8[a]	0.0[a]	0.0[a]		
Schuchlenz *et al.* 2005 [43]	167	44 ± 11	Not given	34		2.0[a]	0.0[a]	0.0[a]	0.0[a]	0.0[a]	
Wahl *et al.* 2005 [65]	361	49 ± 13	Not given	30 ± 19		3.0[a]	3.1[a]	0.0[a]	0.0	0.0	
Post *et al.* 2005 [66]	112	52 ± 13	Not given	23		2.7	1				
Spies *et al.* 2006 [67]	403	49	Not given	13		1.0[a]	1.0[a]	3.0[a]	5.0[a]	0.0[a]	
Kiblawi *et al.* 2006 [68]	456	51 ± 16	Not given	18 ± 11	0.9	1.1	0.4				
Slavin *et al.* 2007 [69]	131	52 ± 14	Not given	30 ± 16		0.0	0.0				

PFO, patent foramen ovale; ASA, atrial septal aneurism.

[a]Recurrence hazards approximated from published Kaplan–Meier curves.

Variability in duration of follow up may bias the conclusions of cohort studies of patients with patent foramen ovale

J. Benbassat[a] and R. Baumal[b]

[a]*Myers-JDC-Brookdale Institute, The Smokler Center for Health Policy Research, Jerusalem, Israel and* [b]*Department of Laboratory Medicine and Pathobiology, Toronto Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

PFO has been linked to Increased risk of:

- Stroke[1]
- Migraine headaches[2]
- Decompression disease in divers[3]
- Obstructive sleep apnea[4]
- Platypnea-orthodeoxia[5]
- "Economy-class" stroke syndrome[6]
- Multiple infarct dementia[7]
- Cerebral microemboli following total knee arthroplasty[8]

1. Lamy C et al. Stroke 2002;33: 706-11.
2. Del Sette M et al. Cerebrovasc Dis 1998;8:327-30.
3. Wilmshurst P et al. Spums J 1997;27:82-3.
4. Agnoletti G et al. J Interven Cardiol 2005;18:393-5.
5. Kerut EK et al. J Am Coll Cardiol 2001;38:613-23.
6. Isayev Y et al. Neurology 2002;58:960-1.
7. Angeli S et al. Eur Neurol 2001;46:198-201.
8. Sulek CA et al. Anesthesiology 1999;91:672-6.

SIS

After a nice long flight and sitting "Economy Class Syndrome"

338 patients admitted to Acute stroke Unit (prospective)

42 had positive travel HX (12.4%)

Frequency of PFO in PTH group was 48%vs. 10% in the NTH

Pts were younger (56yrs of age vs. 67 yr.old) then those in the NTH

PTH had fewer stroke risks

PTH stroke patients had higher frequency of Cardioembolic stroke and more often Ischemia in the posterior circulation (PCA) (29%vs.6.3%)

Heckmann JG et.al Heart2006 92;1265-1268

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)

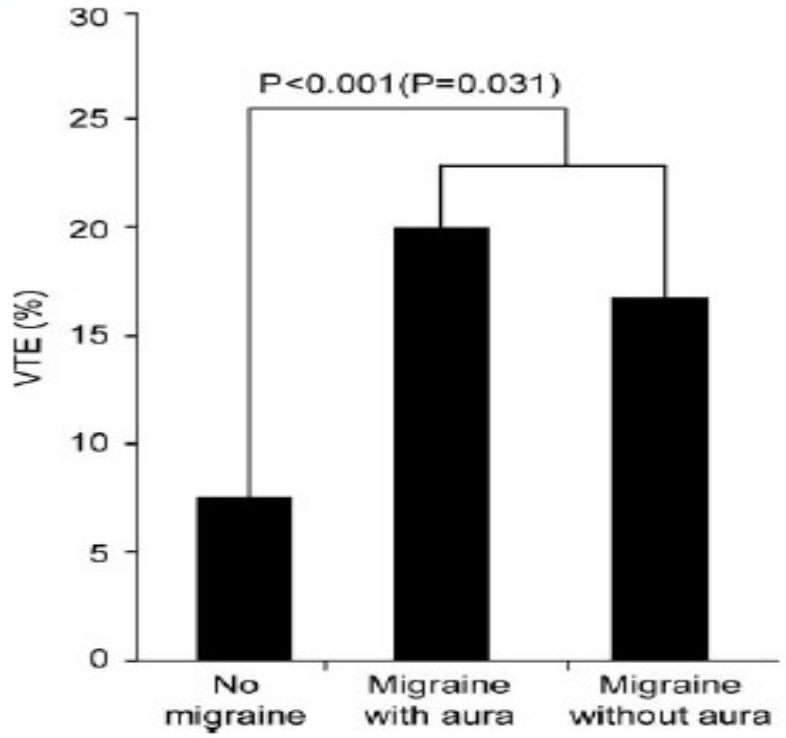
*p<0.05, †p<0.01 (chi-square or Fisher's exact test)

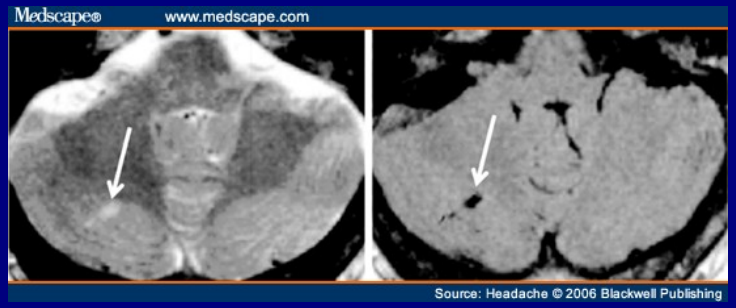
Milhaud et al. Neurology 2001;57:1805-11

Migraine and .....

Burden of atherosclerosis and risk of venous thromboembolism in patients with migraine

Figure Risk of venous thromboembolism (VTE) in patients with migraine with and without aura and in subjects free of migraine headache

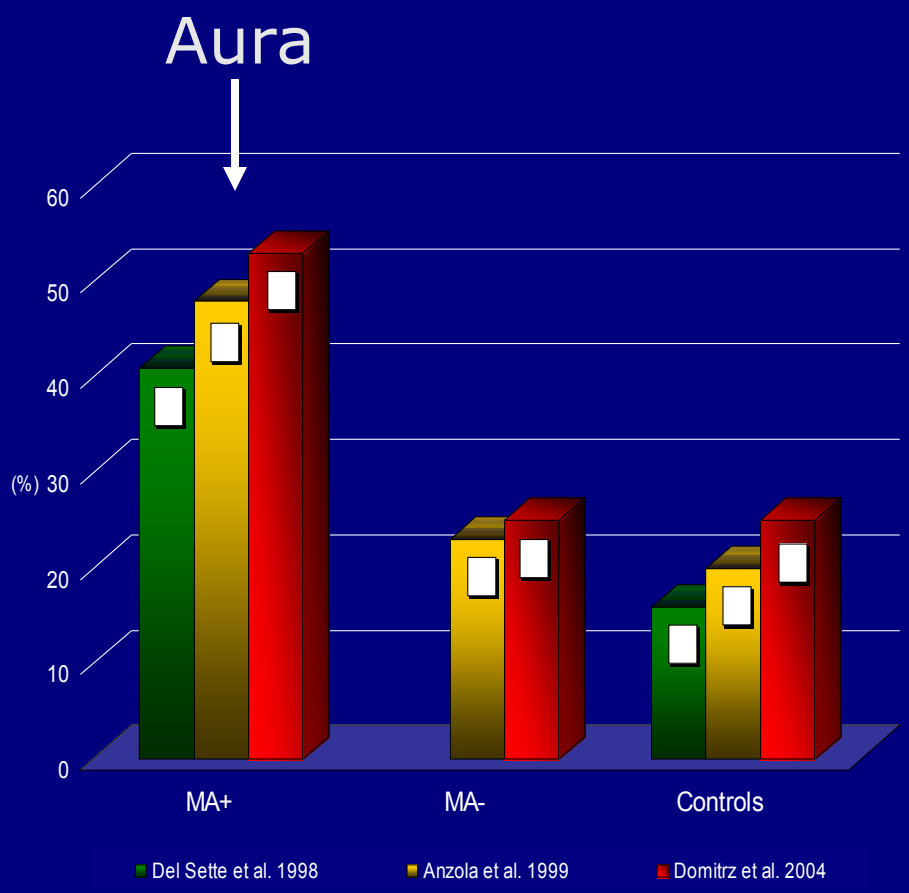




Conclusion: This study is the first to compare the burden of atherosclerosis as quantified by high-resolution duplex ultrasound between migraineurs and nonmigraineurs in the general community, and provides solid evidence against the view that migraine predisposes to atherosclerosis. The higher risk for venous thromboembolism among migraineurs (prothrombotic state) awaits confirmation and elaboration in future research. *Neurology*® 2008;71:937-943

Migraineurs have higher prevalence of PFO's

1. Multiple studies have indicated that patients with Migraine Headaches have higher frequency of PFO's



result	total #	%
total studied	432	100
small shunts (atrial and pulmonary)	72	16.7
large pulmonary shunt	22	5.1
ASD	3	0.7
large PFO	163	37.7
large shunts (all types)	188	43.5
total shunts	260	60.2

Prevalence of PFO among subjects with Migraine

Table 3. Prevalence of PFO Among Subjects With Migraine Selected From the Literature, Including Data From the Current NOMAS Study

Study	PFO Method	Migraine With Aura, n/N (%)	Migraine Without Aura, n/N (%)	No Migraine, n/N (%)
Del Sette et al[10]	TCD	18/44 (41)	NA	8/50 (16)
Anzola et al[9]	TCD	54/113 (48)	12/53 (23)	5/25 (20)
Schwerzmann et al[8]	TEE	44/93 (47)	NA	16/93 (17)
Dalla Volta et al[31]	TCD	161/260 (62)	12/74 (16)	NA
Carod-Artal et al[33]	TCD	25/48 (52)	32/93 (34)	NA
Domitrz et al[11]	TCD	33/61 (54)	15/60 (25)	16/65 (25)
NOMAS	TTE	26/140 (19)	4/38 (11)	138/923 (15)

TCD indicates transcranial Doppler; TEE, transesophageal echocardiography.

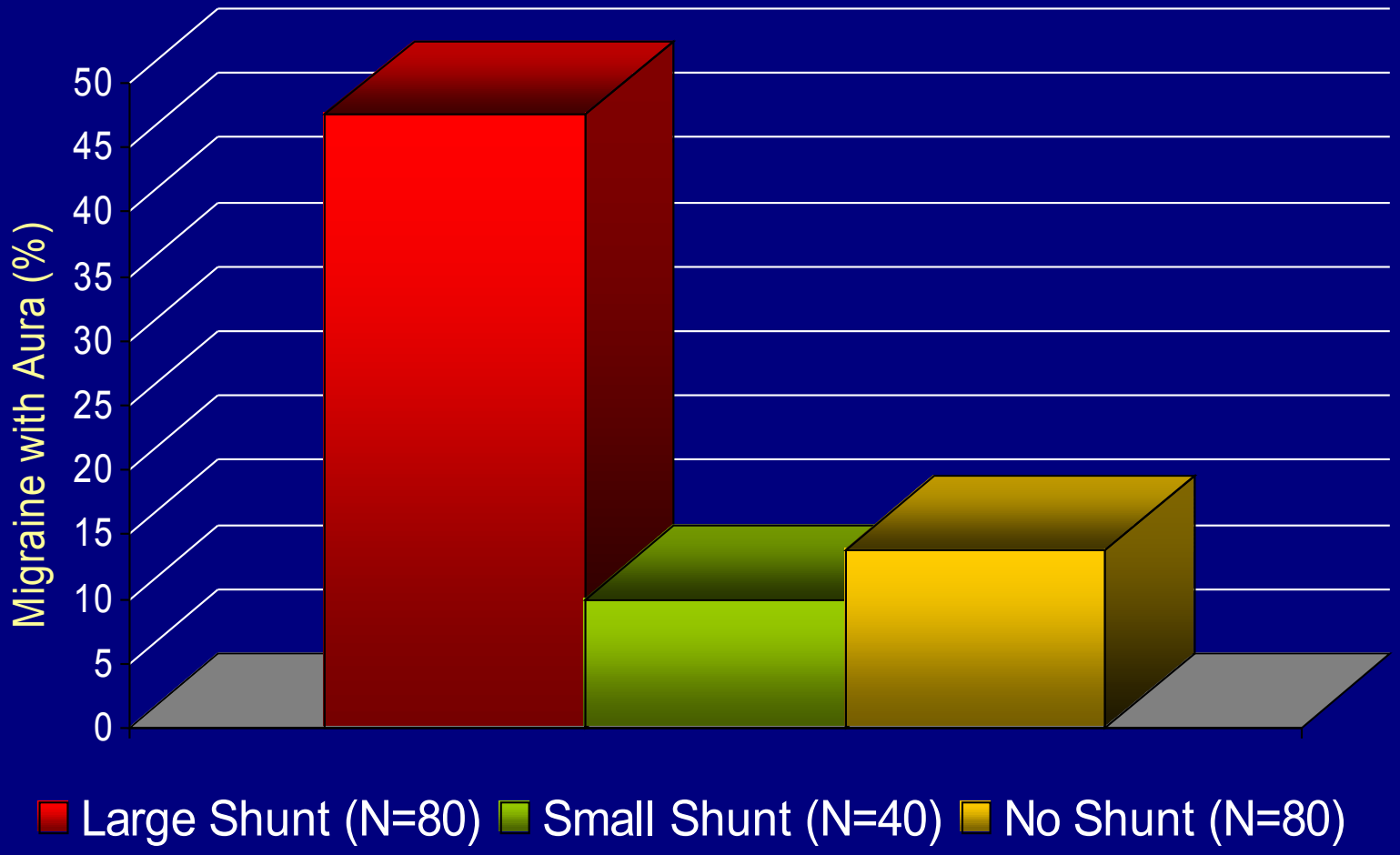
Patent Foramen Ovale and Migraine

A Cross-Sectional Study From the Northern Manhattan Study (NOMAS)

Tatjana Rundek, MD, PhD; Mitchell S.V. Elkind, MD, MS; Marco R. Di Tullio, MD; Emmanuel Carrera, MD; Zhezhen Jin, PhD; Ralph L. Sacco, MD, MS; Shunichi Homma, MD

PFO Size and Migraine

Migraine with Aura in Divers with PFO



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

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
Azarbal 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

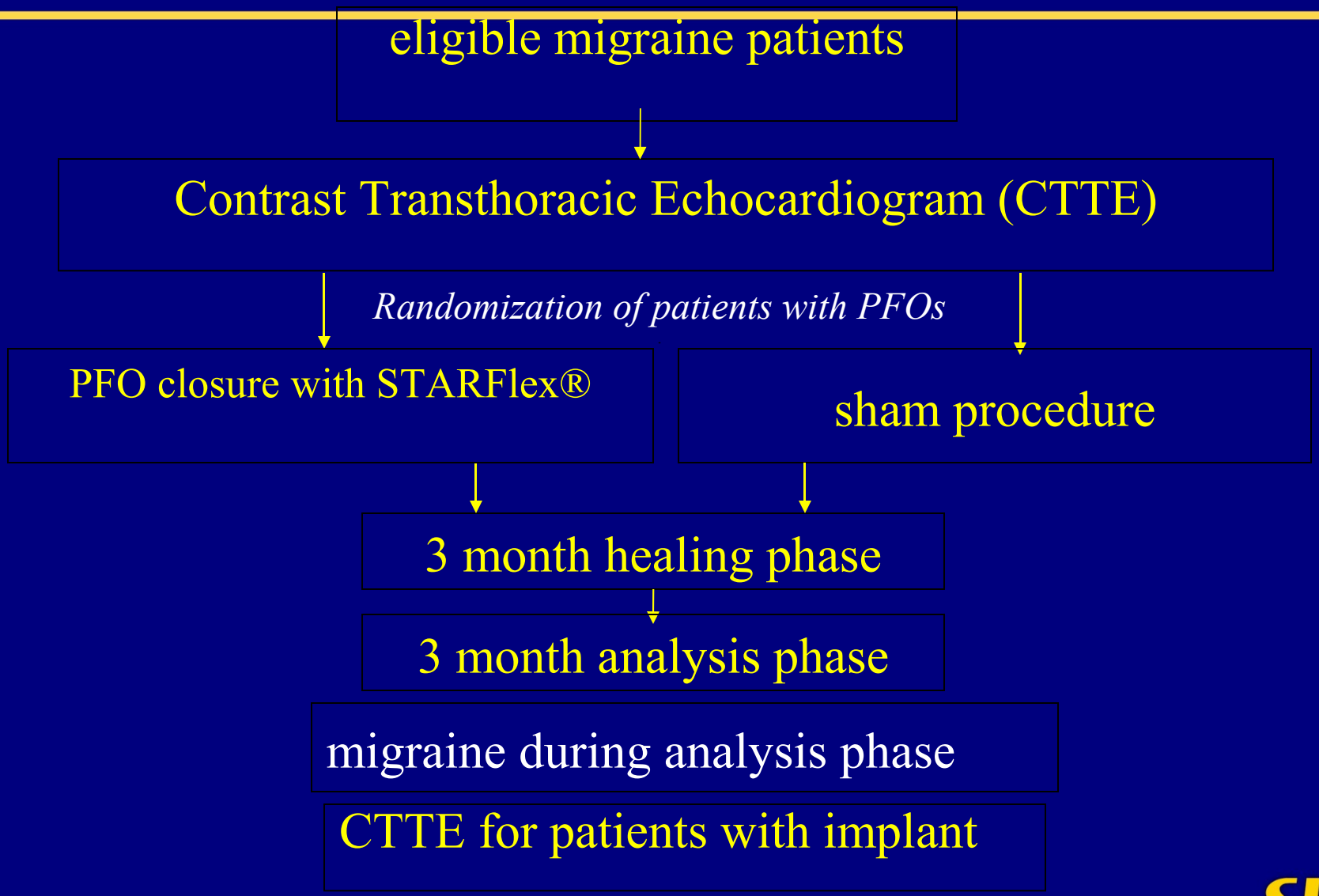
More recent studies

Migraine Headache Relief after Percutaneous Transcatheter Closure of Interatrial Communications

MARK DUBIEL, M.D.,[1] LEONHARD BRUCH, M.D.,[1] INGO SCHMEHL, M.D.,[2] MATTHIAS LIEBNER, M.D.,[3] ANNE WINKELMANN, M.D.,[1] ANNA STRETZ, MARC OLIVER GRAD, M.D.,[1] and FRANZ XAVER KLEBER, M.D.[1]

Conclusions: *Percutaneous transcatheter closure of patent interatrial communications results in significant amelioration of MHA in 87% of patients (complete resolution in 24% and significant improvement in symptoms in 63%). Ongoing randomized trials and larger epidemiologic surveys need to further elucidate the role of device therapy for MHA.* (J Interven Cardiol 2008;21:32–37)

MIST Trial Design



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%

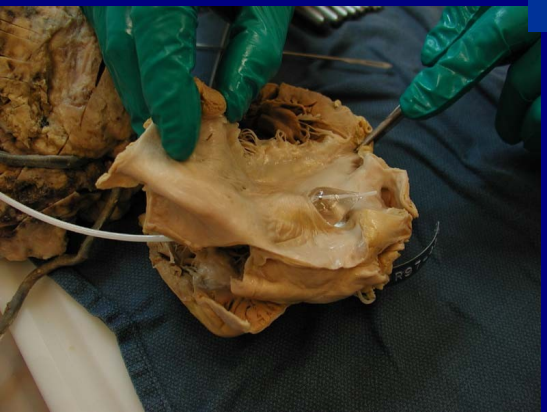
Courtesy NMT Medical, Inc.

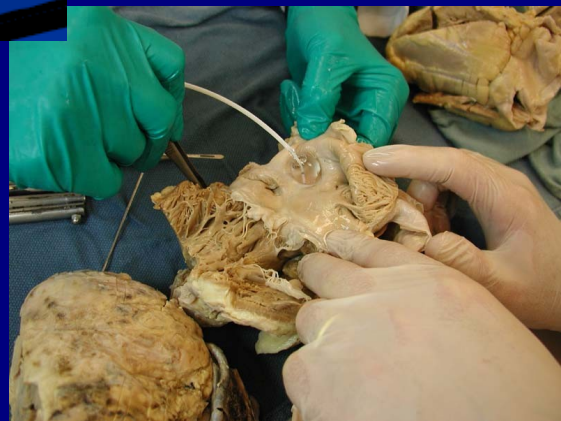
Jan to May 2005

STOPPING FLOW TO ASSESS SECONDARY SHUNTS

MIST TRIAL

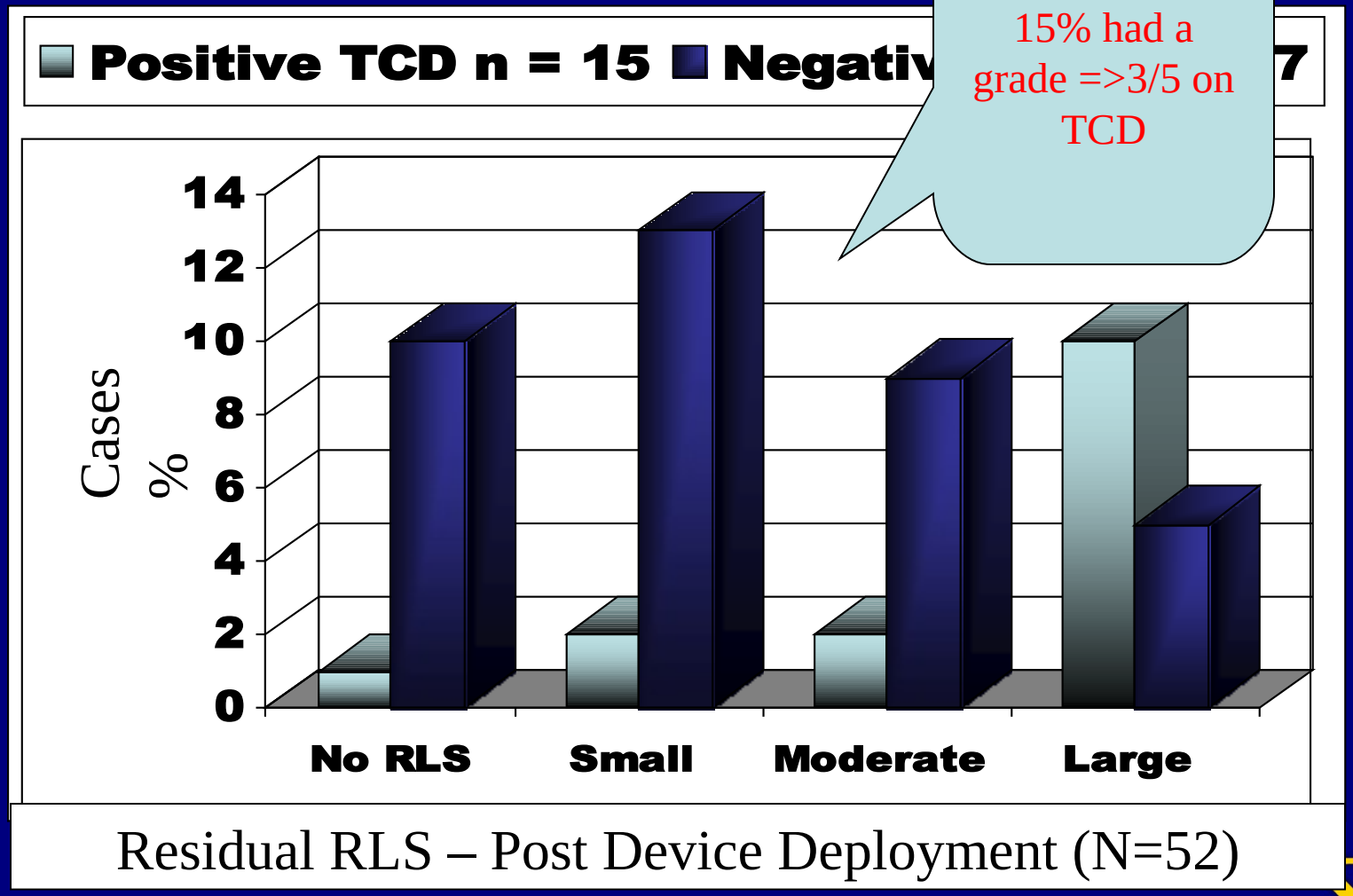
result	total #	%
total studied	432	100
small shunts (atrial and pulmonary)	72	16.7
large pulmonary shunt	22	5.1
ASD	3	0.7
large shunts (all types)	188	43.5
large PFO	163	37.7
total shunts	260	60.2





Fenestrated PFO as eitiogy

Secondary Source of RLS During PFO Closure – Stop flow Balloon Inflation



Residual RLS – Post Device Deployment (N=52)

Renz, Jesurum, Fuller, Reisman – Stroke 2007, in press

The real conundrum of ***MIST***

- The patients had aura √
- The patients had a significant number of headaches√
- The group analyzed had a high frequency of PFO √
- The device (cardioseal) has been shown to be effective √
- Patients had prior hx. Of stroke/TIA **X**
- Type of headache adjudication **X**
- Certainty of device closure **X**

And the data continues to accumulate

Clinical and Brain Magnetic Resonance Imaging Follow-up After Percutaneous Closure of Patent Foramen Ovale in Patients With Cryptogenic Stroke

Carlo Vigna, MD[a,*], Vincenzo Inchingolo, MD[b], Giuseppe Giannatempo, MD[c], Michele A. Pacilli, MD[a], Pietro Di Viesti, MD[b], Saverio Fusilli, BS[d], Cesare M. Amico, MD[a], Tiberio Santoro, MD[a], Pompeo Lanna, MD[a], Raffaele Fanelli, MD[a], Pasquale Simone, MD[b], and Francesco Loperfido, MD[e]

Percutaneous PFO closure results in few clinical or silent events after one year f/u,especially when complete PFO closure is successfully accomplished.

Exclusion of Patients with Arteriosclerosis Reduces Long-Term Recurrence Rate of Presumed Arterial Embolism after PFO Closure

MARK DUBIEL, M.D.,[1] LEONHARD BRUCH, M.D.,[1] MATTHIAS LIEBNER, M.D.,[1] INGO SCHMEHL, M.D.,[2] ANNE WINKELMANN, M.D.,[1] SASCHA RUX, M.D.,[1] STEFFEN SONNTAG, M.D.,[1] HILDEGARD WULFF, M.D.,[1] MARC OLIVER GRAD, M.D.,[1] and FRANZ XAVER KLEBER, M.D.[1]

From the [1]Department of Internal Medicine\Cardiology; [2]Department of Neurology, Unfallkrankenhaus Berlin, Berlin, Germany

At mean f/u of 40months (602 observed patient years) only one patient had a Paradoxical (coronary)emboli.

1. Additional publications ....

1-Prevalence of Patent Foramen Ovale and Usefulness of Percutaneous Closure Device in Carcinoid Heart Disease

Nicolas Mansencal MD, Emmanuel Mitry MD, PhD, Rémy Pillière MD, Céline Lepère MD, Benoît Gérardin MD, Jérôme Petit MD, Iradj Gandjbakhch MD, Philippe Rougier MD and Olivier Dubourg MD

2-

Is migraine a lateralization defect?

hypothesis that PFO and migraine may cooccur as two independent manifestations of lateralization defect during embryonic development. We measured the absolute displacement of a midline

3-

NEUROLOGY 2008;71:101-107

Right-to-left shunt does not increase white matter lesion load in migraine with aura patients

A. Adami, MD, G. Rossato, MD, R. Cerini, MD, V. N. Thijs, MD, PhD, R. Pozzi-Mucelli, MD, G. P. Anzola, MD, M. Del Sette, MD, C. Finocchi, MD, G. Meneghetti, MD, C. Zanferrari, MD On behalf of the SAM Study Group*

Ongoing Research

- Response to Aspirin in Migraineurs
- Platelet Activation in Migraineurs
- Cerebral Vasomotor Reactivity and Blood Flow Distribution in Migraineurs
- Cognitive Function in Migraineurs with Aura and Right-to-Left Shunt: A Pilot Study
- . The Association Between Right-to-Left Shunt and Cognitive Dysfunction in Migraineurs with Aura and Cerebral White Matter Lesions
- . Prevalence of Sleep-Disordered Breathing in Migraineurs with Large Right-to-Left Circulatory Shunts.
- Effect of Daily Aspirin on Headache Symptoms in Aspirin-Responsive Migraineurs
- . Unilateral vs. Bilateral Monitoring for Quantification of Right-to-Left Shunt by Power M-Mode Transcranial Doppler

How to make this complex decision on what to do.

- (1) acknowledge ignorance
- (2) involve the patient and assess personal preferences;
- (3) prioritize good clinical trials before adopting unproven therapies,
- (4) caution should be practiced when extrapolating from results of low-grade evidence because of their inherent biases

Conclusion

- Closure one will provide a essential information on
  - Stroke
  - Migraine (secondary endpoint)
- Migraine trials
  - Future trials will be significantly different then previous ones……..patient selection
- Device iteration
  - Intratunnel,bioabsorbable,radiofrequency sealing,improved umbrella devices
- Regulatory pathway
  - Will continue to be clarified as we focus in on the optimal patient to benefit.
- The “large” population based studies that have been negative regarding PFO/stroke, PFO/migraine are not surprising.

THE PFO Headache

And right now we (I) am color blind

But beginning to see the red jellybeans