



# **PFO Closure for the Management of Migraine and Stroke**

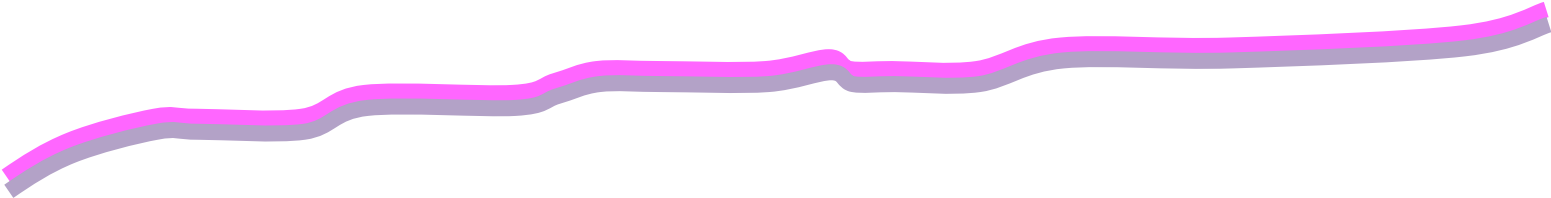
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Asan Medical Center, UUMC**





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- PFO & Migraine
    - PFO causes Migraine or Not?
    - PFO closure for Migraine
  - PFO & Stroke
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    - Benefit of PFO Closure for Ischemic Stroke
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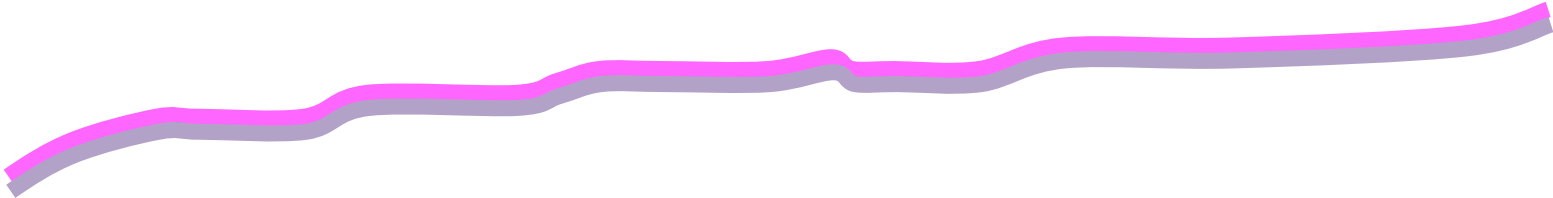
# Hot News

## Interventional Cardiology

### Migraine Intervention With STARFlex Technology (MIST) Trial

**A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to  
Evaluate the Effectiveness of Patent Foramen Ovale Closure  
With STARFlex Septal Repair Implant to Resolve  
Refractory Migraine Headache**

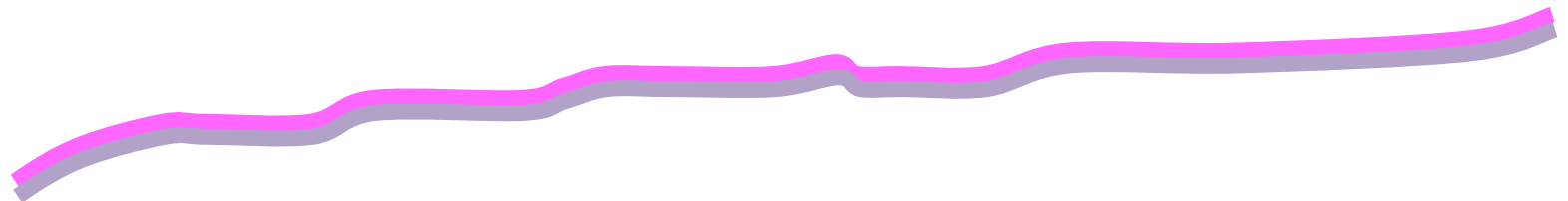
*Conclusions*—This trial confirmed the high prevalence of right-to-left shunts in patients with migraine with aura. Although no significant effect was found for primary or secondary end points, the exploratory analysis supports further investigation. The robust design of this study has served as the model for larger trials that are currently underway in the United States and Europe. (*Circulation*. 2008;117:1397-1404.)



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# Migraine & Stroke

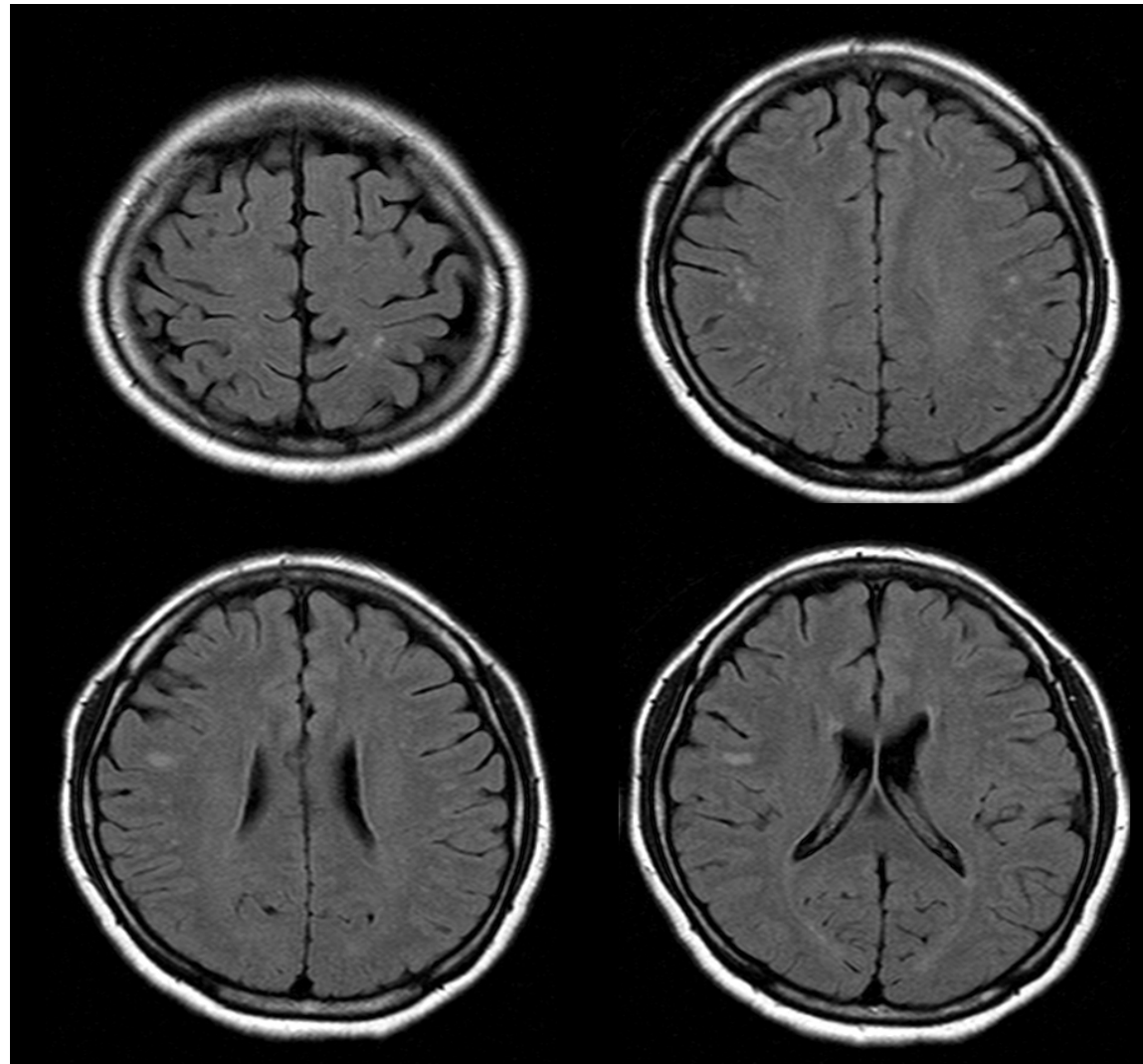
- Etminan M. et al (BMJ 2005;330:63)
  - Meta-analysis of 11 case-control and 3 cohort studies
- RR of ischemic stroke
  - 1.8 in migraine without aura
  - 2.3 in migraine with aura
  - 8.7 in women with migraine + oral contraceptive pill



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# Silent Brain Lesions in Migraineurs

F/50, 10 year history of Migraine



# Migraine as a Risk Factor for Subclinical Brain Lesions

from the Genetic Epidemiology of Migraine (GEM) study, a population-based survey of Dutch adults aged 20 to 60 years

MRI outcome	Control (n=140)	Migraine (n=295)	Migraine without aura (n=134)	Migraine with aura (n=161)
Any location Pt with $\geq 1$ Brain	7(5.0%)	24 (8.1%)	9 (6.7%)	15 (9.3%)
No of infarcts	9	51	19	32
Posterior circulation Pt with brain infarct	1(0.7%)	16(5.4%)	3(2.2.%)	13(8.1%)
No of infarcts	1	33	8	25

# PFO is More Prevalent in Migraineurs

Subjects	RLS + At rest	RLS + only Valsalva	total	RR (95% CI)
Normal	4/50 (8%)	4/50 (8%)	8/50 (16%)	3.2 (1.4-7.2)
Migraine	9/44 (20.5%)	9/44 (20.5%)	18/44 (41%)	

RLS; right to left shunt on TCD

Cerebrovasc Dis 1998, Del Sette M et al

# Prevalence of PFO in Migraineurs

Patient	PFO + (%)	RR (95% CI)	P-value
Migraine with aura	54/113 (48%)	3.32 (1.74-6.34)	0.003
Migraine without aura	12/53(23%)	1.17 (0.32-4.45)	0.07
Control	5(25%)		

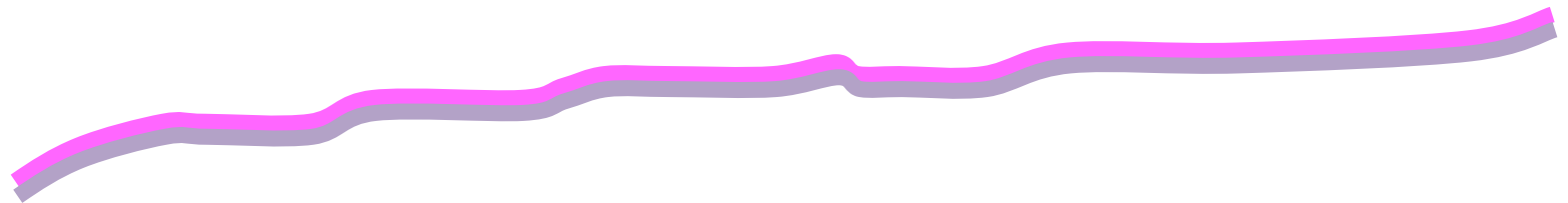
Presence of PFO ; assessed by TCD



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# Migraine & PFO

- PFO; well-known source of paradoxical embolism
- Higher prevalence of PFO in migraine
- PFO may cause ischemic stroke and silent brain lesions in migraineurs



# Migraine-PFO Connection is Independent of Sex

Sex	Diagnosis	Overall RLS prevalence	Grade 2 RLS prevalence
Females	MA+	60/123 (48.8)	31/123 (25.5)
Males	MA+	12/32 (37.5)	4/32 (12.5)
Females	MA-	9/43 (20.9)	6/43 (14)
Males	MA-	5/32 (15.6)	1/32 (3.1)

	RR	p
Female gender	2.8 (1.6–5.1)	0.006
RLS	3.7 (1.9–7.1)	0.001
Gender and RLS	8.9 (3.6–22.0)	<0.0001

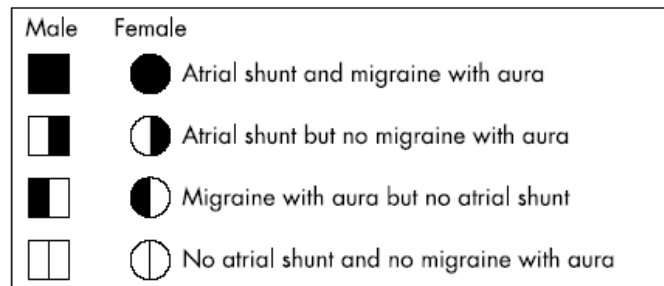
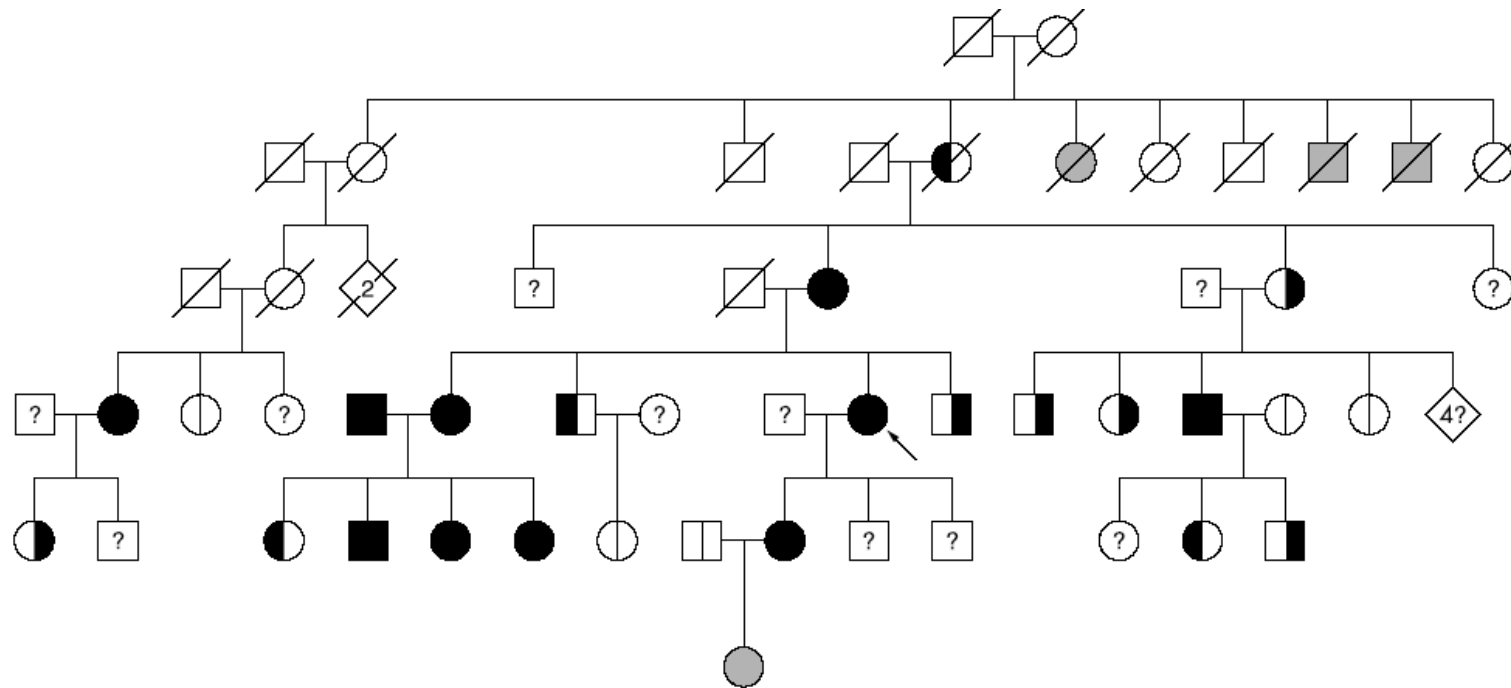


## Inheritance of PFO & Migraine with Aura

- 71 relatives of 20 probands with a significant sized PFO or ASD on TEE
- Atrial shunt has AD inheritance
- Among proband with MWA,
  - 15 of 21 (71.4%) first relatives with atrial shunt had MWA, but 3 of 14 (21.4%) without shunt had MWA

# Migraine & PFO

## Strong genetic association



## Early report

# Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons

*P T Wilmshurst, S Nightingale, K P Walsh, W L Morrison*

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**Findings** 37 of 40 consecutive patients who had had a closure procedure (to permit resumption of diving after decompression illness in 29, after stroke when paradoxical thromboembolism was suspected in four, or to close a large atrial septal defect in four) could be contacted. 21 (57%) had a history of migraine before the procedure (with aura in 16, without aura in five). 11 individuals had fortification spectra in the period immediately after closure. During long-term follow-up, no migraine symptoms were reported by seven individuals who had previously had migraine with aura and three who had previously had migraine without aura. Eight others who had had migraine with aura before closure reported improvement in frequency and severity of migraines. Three (one migraine with aura, two migraine without aura) reported no alteration in migraine episodes.

**Interpretation** These observations suggest a causal association between right-to-left shunts and migraine with aura. There may be a subgroup of patients who have severe migraine associated with a large right-to-left shunt in whom closure of the atrial defect may improve or abolish migraine.

*Lancet* 2000; **356**: 1648–51





**Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine**

*Martijn C. Post, MD; Vincent Thijs, MD; Luc Herroelen, MD; and Werner I.H.L. Budts, MD, PhD*

A patent foramen ovale (PFO) is one of the major causes of right-to-left shunt, and a causal relationship between migraine and a PFO has been suggested.<sup>1</sup> We evaluated whether percutaneous closure of a PFO was associated with changes in the prevalence of migraine.

**Methods.** Patient selection. Patients with a PFO who had a paradoxical embolic event or systemic desaturation and who underwent a percutaneous closure in our center between February 1999 and September 2002 were included. The medical files were reviewed. The ethical committee approved the study.

Evaluation of migraine. A questionnaire was composed in such a way that a neurologist could diagnose migraine with or without aura (MA+ and MA-) according to the criteria of the International Headache Society. The questionnaire was sent to all patients and focused on three periods: 1 year before and 2 months and at least 6 months after percutaneous closure. Two neurologists blinded to the patients' files diagnosed MA+ and MA-.

Statistical analysis. Within-patient comparisons of the absence or presence of migraine were performed with the McNemar's paired  $\chi^2$  test. Interobserver reliability was evaluated by measuring the kappa coefficient. *p* Value < 0.05 was considered significant. All

*Table Characteristics of patients who completed the questionnaire*

	Migraine	No migraine	<i>p</i>
No. of patients (n)	26	40	
Age (y, mean $\pm$ SD)	55 $\pm$ 10	53 $\pm$ 12	0.48
Male/female	9/17	27/13	<0.05
Indication PFO closure			
Stroke (n)	24	37	0.94
Peripheral embolism (n)	2	1	0.33
Brain abscesses (n)	0	1	
Desaturation (n)	0	1	
Frequency of migraine attacks prior to closure			
Almost monthly (n)	9		
Almost weekly (n)	9		
Several times a week (n)	8		

PFO = patent foramen ovale.

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## Mini-Focus: Transcatheter Closure of ASD and PFO

# Association of Interatrial Shunts and Migraine Headaches

## Impact of Transcatheter Closure

Babak Azarbal, MD, Jonathan Tobis, MD, William Suh, MD, Vicki Chan, BA, Catherine Dao, BA,  
Richard Gaster

*Los Angeles, California*

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- Retrospective analysis
- Among 89 pt who underwent transcatheter closure of interatrial shunt
- 42% had migraine before procedure
- Migraine disappeared completely in 75% of MWA and 31% of MOA
- Remaining 40% had significant improvement

## Migraine Headache Relief After Transcatheter Closure of Patent Foramen Ovale

Mark Reisman, MD,\* Ryan D. Christofferson, MD,\* Jill Jesurum, PhD,\* John V. Olsen, MD, FACC,\*  
Merrill P. Spencer, MD,† Kimberly A. Krabill, MD,\* Lance Diehl, MD,\* Sheena Aurora, MD,\*  
William A. Gray, MD\*

*Seattle, Washington*

- 162 pt performed transcatheter PFO closure in patients with paradoxical cerebral embolism
- Active migraine : 35% (57/162)
  - Complete resolution of migraine : 56% (28/50)
  - Significant reduction : 14%(7 of 50)
  - 80% reduction in the mean number of migraine episodes/mo



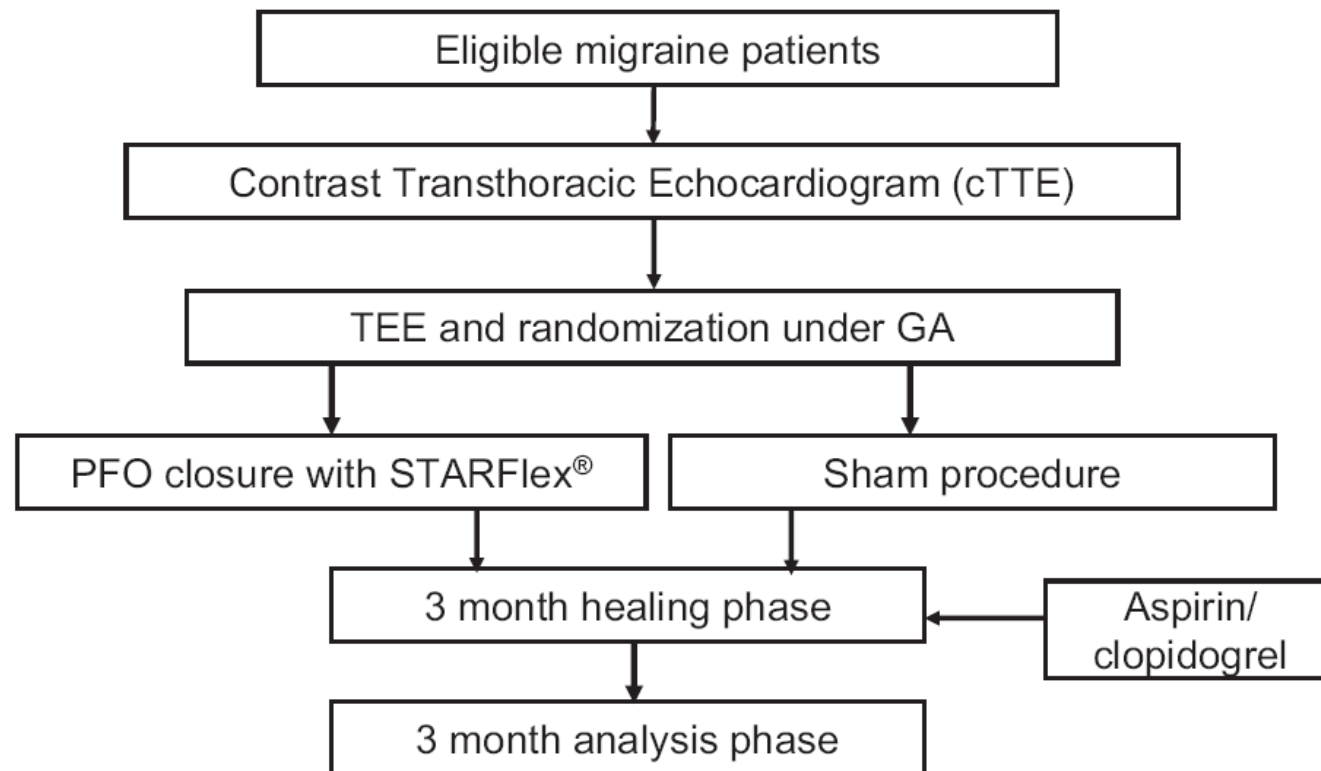
# Transcatheter patent foramen ovale closure mitigates aura migraine headaches abolishing spontaneous right-to-left shunting

Alessandro Giardini, MD,<sup>a</sup> Andrea Donti, MD,<sup>a</sup> Roberto Formigari, MD,<sup>a</sup> Luisa Salomone, MD,<sup>a</sup> Daniela Prandstraller, MD,<sup>a</sup> Marco Bonvicini, MD,<sup>a</sup> Gualtiero Palareti, MD,<sup>b</sup> Donata Guidetti, MD,<sup>c</sup> Oscar Gaddi, MD,<sup>d</sup> and Fernando Maria Picchio, MD<sup>a</sup> *Bologna and Reggio Emilia, Italy*

- 131 consecutive Pt with PFO closure due to cryptogenic stroke
- 35 (27%) had migraine
- 32 (91%) of 35 migraineurs had either complete resolution or significant improvement in headache

# MIST Trial Design

Multicenter, randomized, double-blind sham-controlled trial  
Migraine with aura : >5attacks/mo  
Moderate or large right to left shunt due to PFO

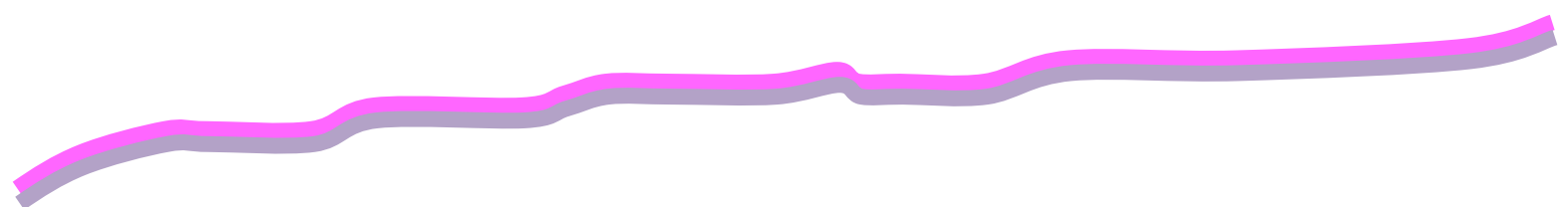


# Closure Makes No Difference

**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.



# Is migraine associated with right-to-left shunt a separate disease? Results of the SAM study

General characteristics of patients with SHUNT and NO SHUNT

	No shunt (type 0–I)	Shunt (type II–III)	<i>P</i>
<i>n</i>	265	195	
M/F	65/200	41/154	NS
Age	37.1 ± 11	34.1 ± 10	0.003
Body mass index	23.01	22.43	NS
Migraine onset (age)	21 ± 11	19 ± 9	NS
<b>FHx for migraine, yes/no</b>	<b>173/87 (66%)</b>	<b>140/45 (76%)</b>	<b>0.045</b>
FHx for CVA, yes/no	105/153	81/102	NS

# Is migraine associated with right-to-left shunt a separate disease? Results of the SAM study

Characteristics of migraine attacks in patients with SHUNT (type III) & NO SHUNT (type 0)

	No shunt (type 0)	Shunt (type III)	<i>P</i>
<i>n</i>	173	110	
M/F	42/131	19/91	NS
Median aura duration, min	20	22	NS
Median aura complexity	2	2	NS
Median pain severity (range 0–3)	3	3	NS
Median <i>n</i> attacks overall*	27	18	0.014
Median <i>n</i> without aura*	12	2	0.011
Relative aura frequency percentage	60	90	0.076

**The SAM study suggests that the effect of RLS on migraine features is not relevant.**

# White matter lesions in migraine & RLS: a conventional and diffusion MRI study

Presence of WMLs as detected by T2-weighted MRI and MRI-derived metrics in migraine patients without RILES and with RILES in migraine with aura

	Absence of RLS <i>n</i> = 44	Presence of RLS <i>n</i> = 36	<i>P</i> -value
Absence of WMLs (number—%)	17—38.6	14—38.9	
Presence of WMLs (number—%)	27—61.4	22—61.1	
Number of WMLs (mean ± s.d.)	6.73 ± 16.15	2.39 ± 3.83	0.65*
WML load (mm <sup>3</sup> ) (mean ± s.d.)	228.74 ± 445.88	84.15 ± 153.05	0.41*
No of DWI-hyperintense lesions	0	0	

**RLS does not increase the likelihood of finding WMLs in migraineurs.**

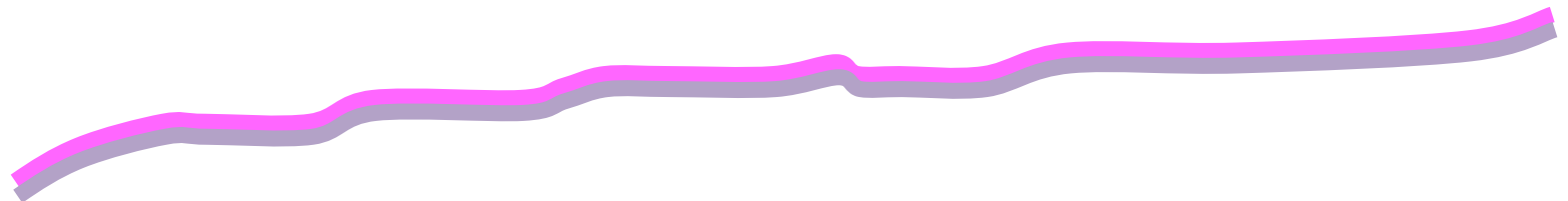
# White matter lesions in migraine & RLS: a conventional and diffusion MRI study

Vascular risk factors in migraine patients with T2-weighted MRI positive for the presence of WMLs vs. patients without MRI-detected lesions

	Absence of WMLs <i>n</i> = 31 Number (%)	Presence of WMLs <i>n</i> = 49 Number (%)	<i>P</i> -value
Diabetes mellitus	0 (0)	1 (2)	0.99*
Smoking	8 (25.8)	13 (26.5)	0.99*
Hypercholesterolaemia	2 (6.5)	7 (14.3)	0.47*
Use of oral contraceptives	6 (19.4)	9 (18.4)	0.99*
Family history of stroke/TIA	1 (3.2)	3 (6.1)	0.99*
Coagulation disorders	10 (32.2)	23 (46.9)	0.25*
Body mass index, (kg/m <sup>2</sup> )	21.89 ± 2.76	22.22 ± 3.06	0.73†
Age, mean ± s.d. (years)	32.52 ± 7.74	39.93 ± 12.91	0.035†

# Migraine - PFO

- Does PFO cause migraine?
  - Strong association between migraine with aura and PFO
  - Circumstantial evidences
    - Higher prevalence of white matter lesions in migraine
    - Higher incidence of stroke in migraine
- Just Association due to Genetic Linkage?
  - Failure of clinical trial
  - Strong family history







# PFO - Ischemic Stroke



# Can PFO Cause Ischemic Stroke?

- PFO
  - Potential source of paradoxical embolism
  - Prevalence of PFO in healthy : about 20%
- Guilty but Only as a Gang member
  - B Meier (JACC 2006:47:446-448)

– Jus Sources with low or uncertain primary risk for ischemic stroke

*Cardiac sources of embolism*

<sup>a</sup>Mitral annular calcification<sup>92</sup>

<sup>b</sup>Patent foramen ovale<sup>93</sup>

Atrial septal aneurysm

Atrial septal aneurysm and patent foramen ovale

Left ventricular aneurysm without thrombus

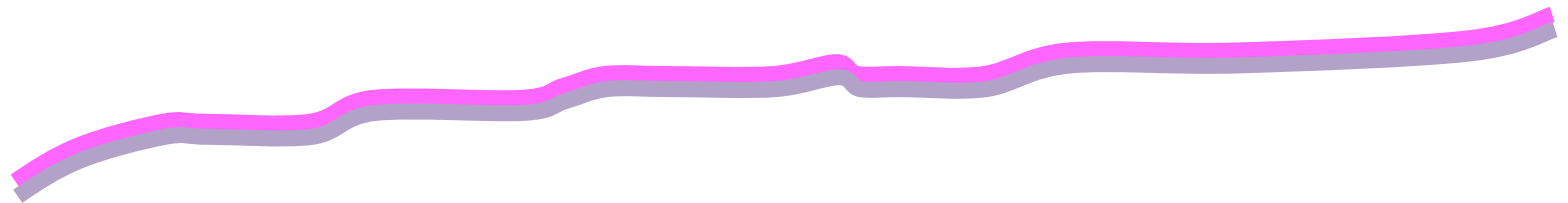
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# Cryptogenic Stroke

- Approximately 30-40% of cerebral infarctions cannot be classified as strokes of determined cause despite a complete diagnostic work-up

Sacco et al (Ann Neurol 1989)

- Cryptogenic stroke
  - Cerebral infarct due to some form of embolism
  - Failure to define a source of embolism
- Presence of PFO in cryptogenic stroke



# Relationship of Cryptogenic Stroke of with PFO among Young Patients

	N	Age	PFO (Cryptogenic)	PFO (Control)	p
Lechat	26	<55	54%	10%	<0.001
Webster	34	<40	56%	15%	<0.001
Cabanes	64	<55	56%	18%	<0.001
De Belder	39	<55	13%	3%	<0.001
Di Tullio	21	<55	47%	4%	<0.001
Hausmann	18	<40	50%	11%	<0.001
<b>Total</b>	<b>202</b>		<b>46%</b>	<b>11%(29/271)</b>	<b>&lt;0.001</b>

# Relationship of Cryptogenic Stroke of with PFO among Old Patients

	N	Age	PFO (Cryptogenic)	PFO (Control)	p
De Belder	64	>55	20%	5%	<0.001
Di Tullio	2434	>55	38%	8%	<0.001
Hausmann	20	>40	15%	23%	N.S
Jones	57	>55	18%	16%	N.S.
<b>Total</b>	<b>165</b>		<b>21%</b>	<b>15%(61/414)</b>	

**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.

# Define Causal Relationship

- As

Impending paradoxical embolism

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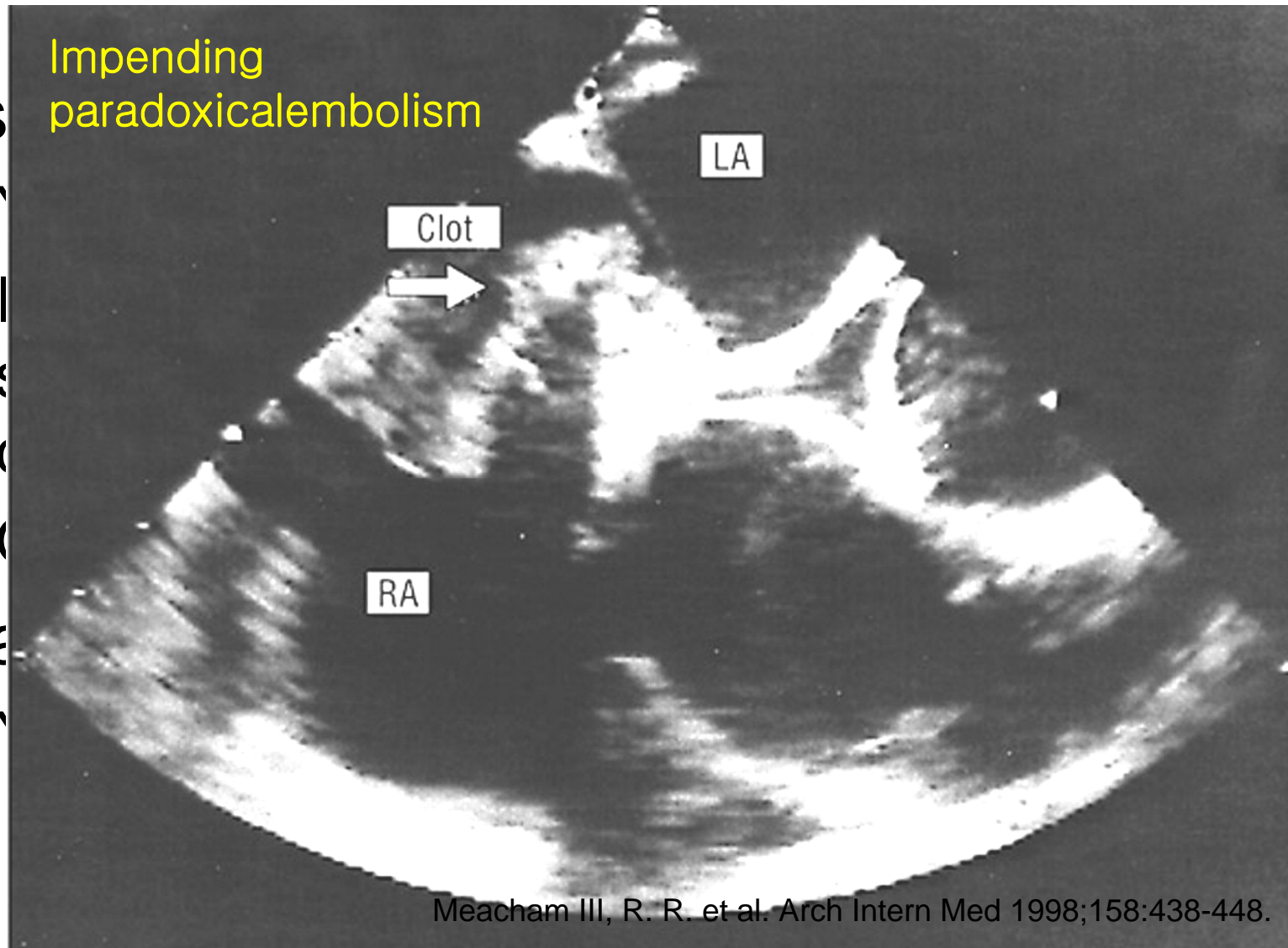
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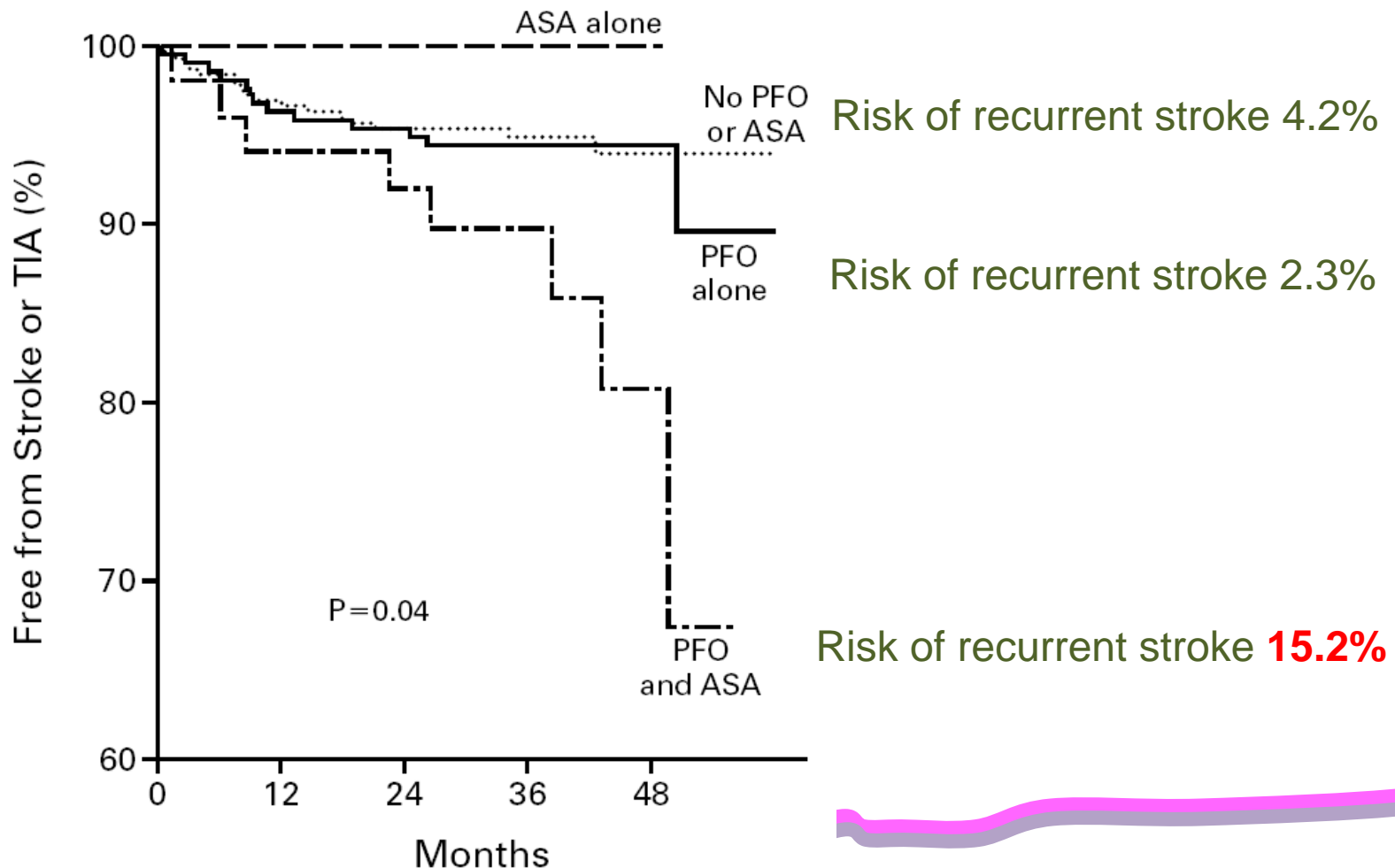
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Meacham III, R. R. et al. Arch Intern Med 1998;158:438-448.

# Recurrent Stroke with PFO & ASA

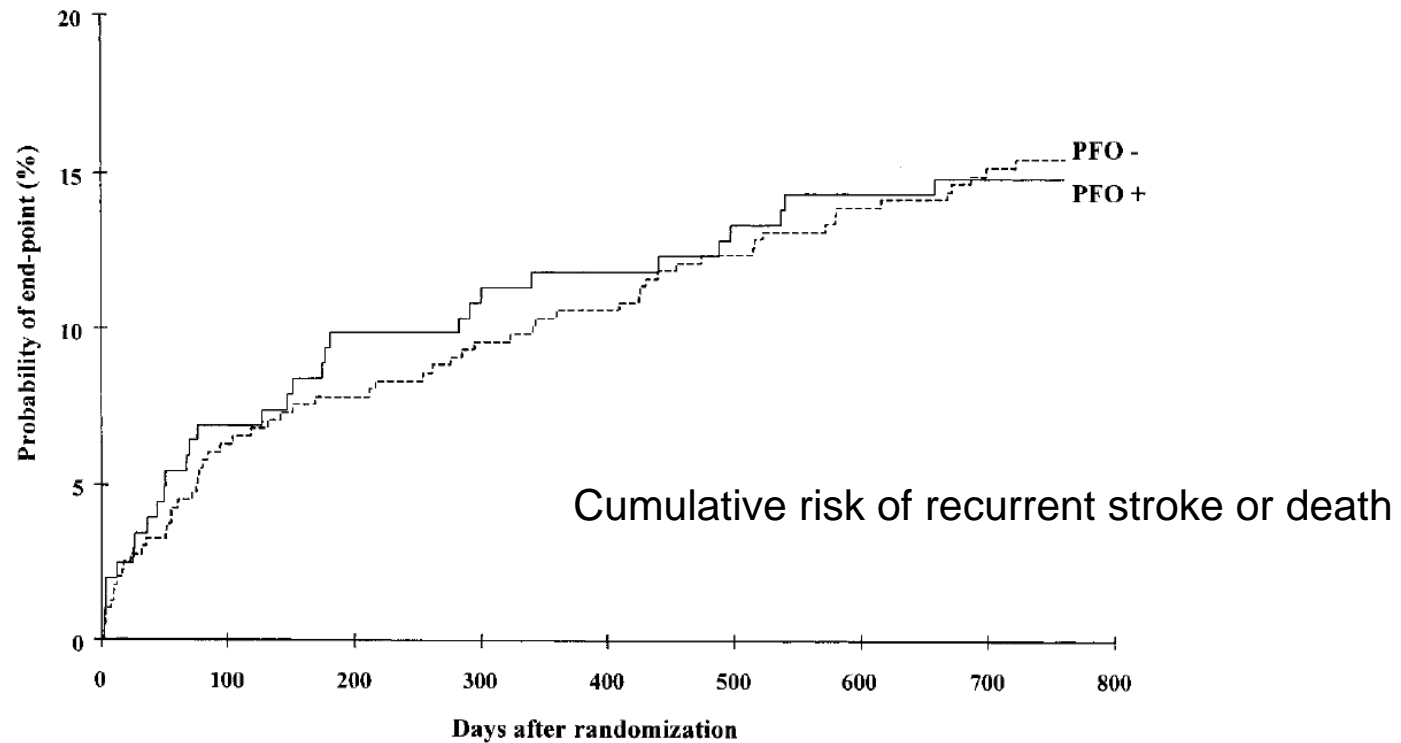
Among 581 pt (18-55yo) with cryptogenic stroke





# PFO in Cryptogenic Stroke Study (PICSS)

630 stroke patients with TEE randomly assigned into warfarin or aspirin group



On medical therapy, the presence of PFO in stroke pt did not increase the chance of event regardless of PFO size or ASA



# Controversies in Stroke

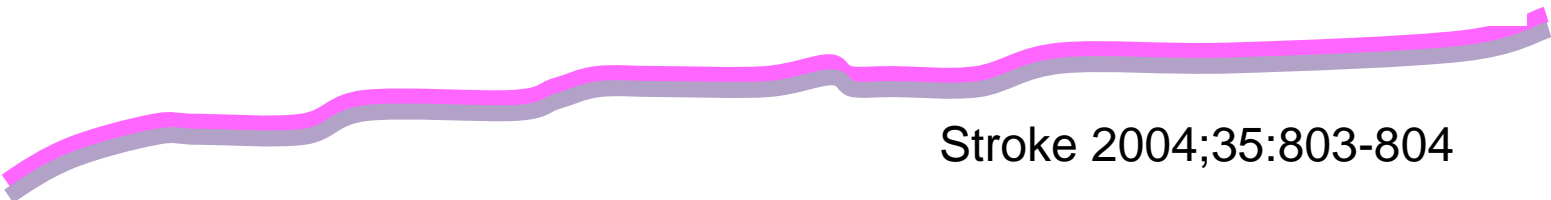
Section Editors: **Geoffrey A. Donnan, MD, FRACP, and  
Stephen M. Davis, MD, FRACP**

## **Patent Foramen Ovale and Recurrent Stroke: Closure is the Best Option: Yes**

Anthony J. Furlan, MD

## **Patent Foramen Ovale and Recurrent Stroke: Closure Is the Best Option: No**

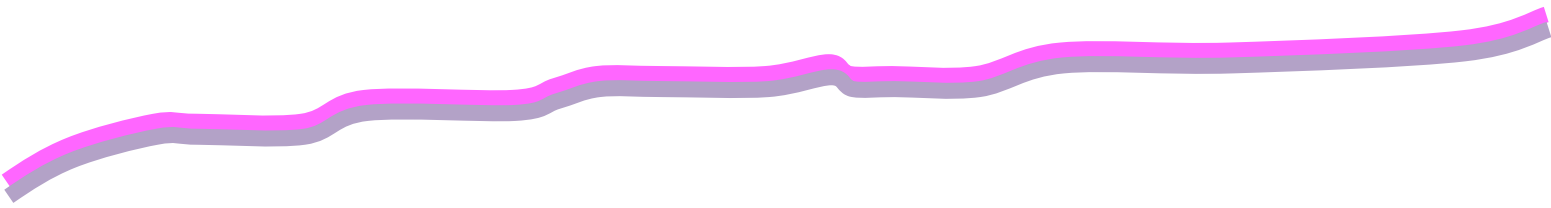
David C. Tong, MD; Kyra J. Becker, MD



Stroke 2004;35:803-804

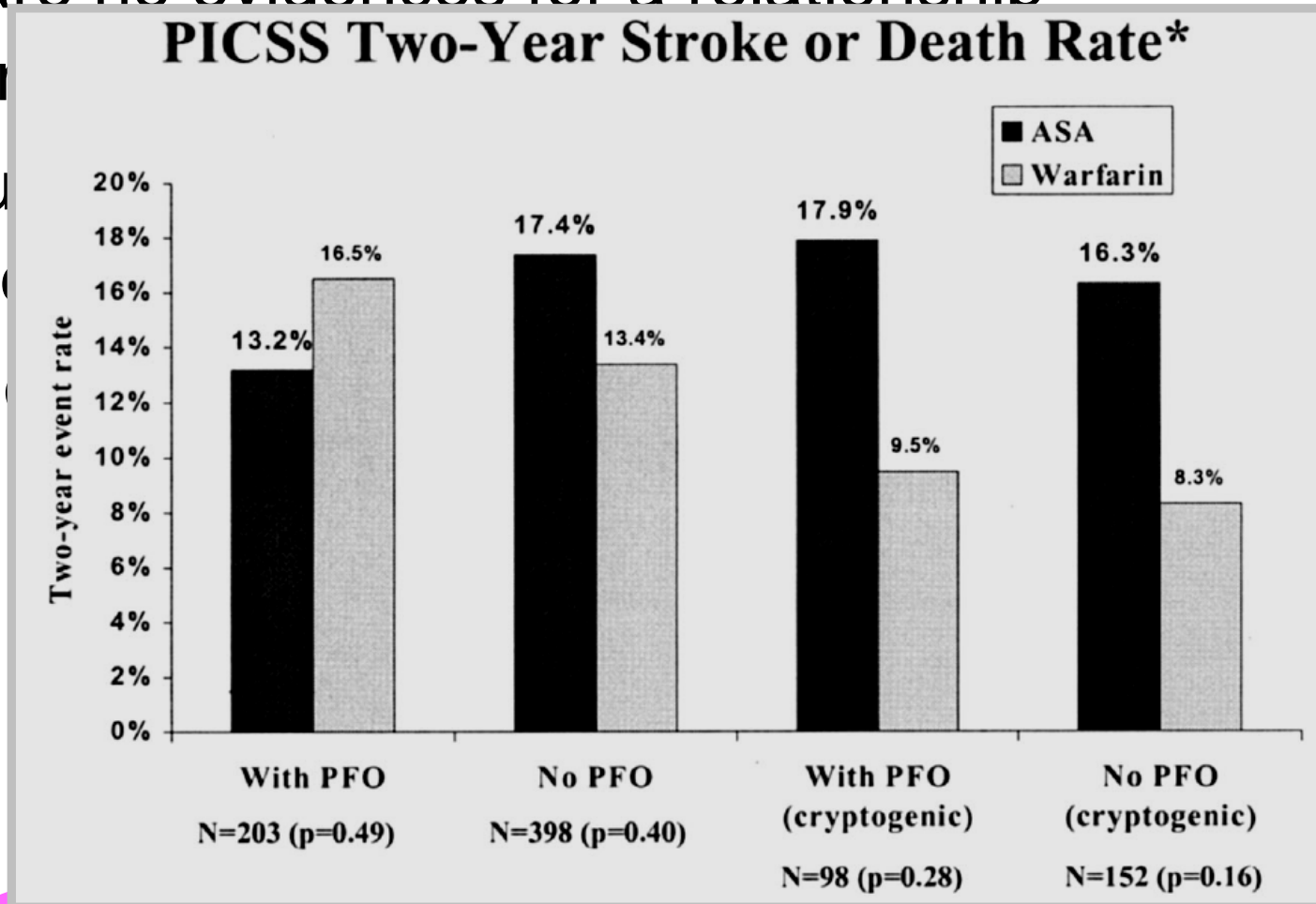
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# Closure is Best Option : Yes

- Warfarin is conventional medical therapy for PFO without hard evidences
  - Warfarin carries 1% per year risk of significant hemorrhage
  - Percutaneous PFO closure has a very low serious complication rate (<1%)
  - Long-term durability of devices is excellent
  - Psychological aspect of the patients
- 

# Closure is Best Option : No

- There are no evidences for a relationship between
- Two stu
- not incre
- PFO is





# **Time to Perform RCTs to Prove the Benefits of PFO Closure in Cryptogenic Stroke**

