

***Is Percutaneous Closure of PFO
indicated for Patients with
Cryptogenic Stroke ?***

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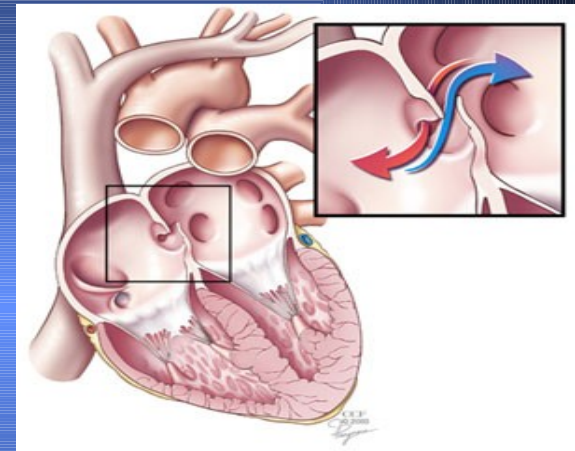
Presenter Disclosure Information

Name: *Shunichi Homma, MD FACC*

***Nothing to Disclose Related to this
Presentation***

Psychology of PFO closure

- *I understand that PFO is more frequent in cryptogenic stroke patients*
- *This makes sense to me and I can explain this to patients*
- *I can easily (learn to) close with different devices*
- *So let's close them !*



Yes, PFO is associated with cryptogenic stroke

<i>Study</i>	<i>N*</i>	<i>Age</i>	<i>PFO</i>	<i>PFO</i>	<i>p</i>
	<u>(patients)</u>		<u>(Crypto)</u>	<u>(Control)</u>	
<i>Lechat</i>	26	<55	54%(14/26)	10%(10/100)	<0.001
<i>Webster</i>	34	<40	56%(19/34)	15%(6/40)	<0.001
<i>Cabanes</i>	64	<55	56%(36/64)	18%(9/50)	<0.0001
<i>De Belder</i>	39	<55	13%(5/39)	3%(1/39)	<0.05
<i>Di Tullio</i>	21	<55	47%(10/21)	4%(1/24)	<0.001
<i>Hausmann</i>	18	<40	50%(9/18)	11%(2/18)	<0.05

46% (93/202) 11% (29/271)

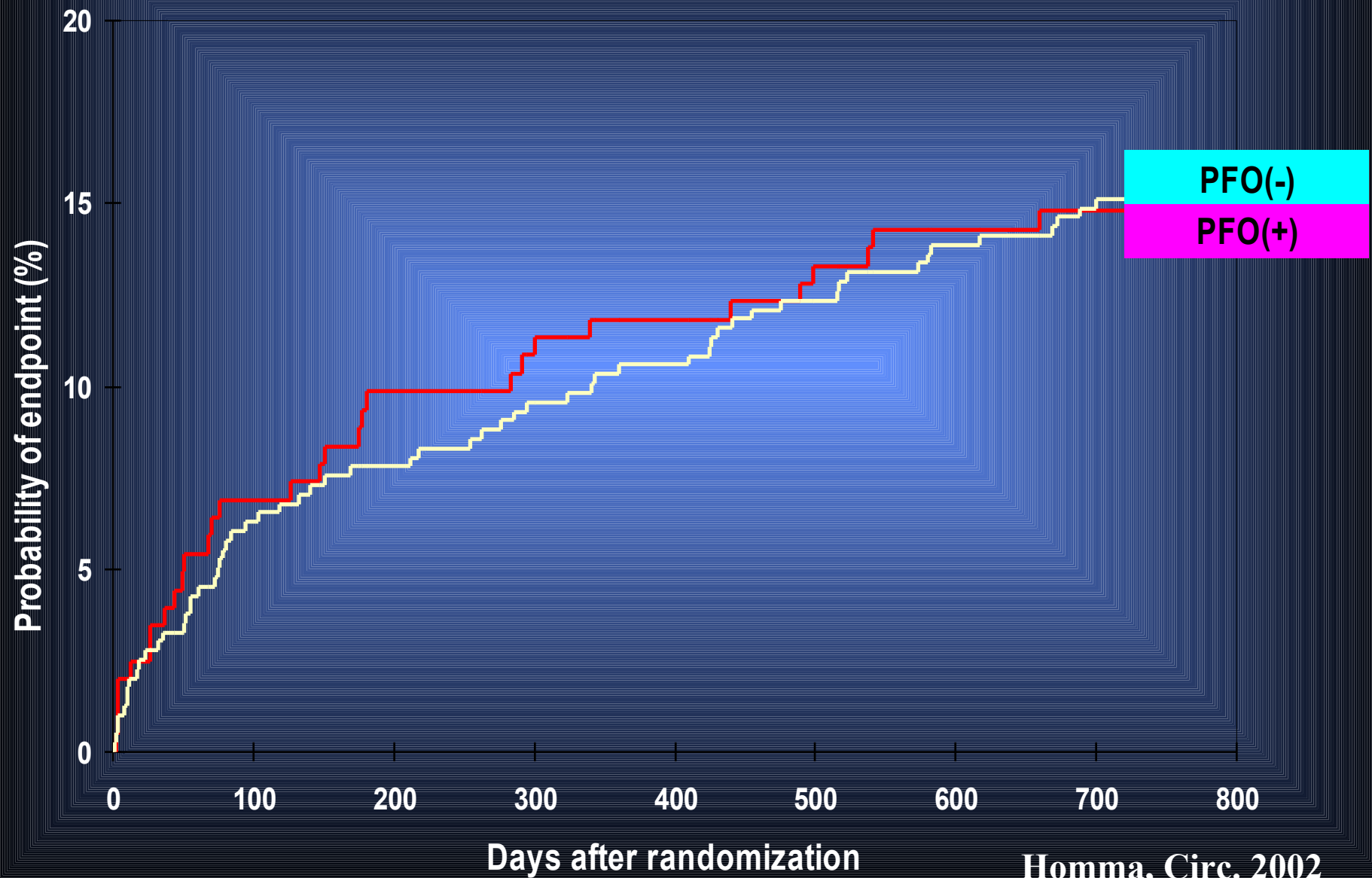
***But is PFO associated with
recurrent stroke while on medical
therapy ?***

- ***4-year stroke rate on aspirin***

<i>No PFO</i>	<i>PFO</i>	<i>PFO / ASA</i>
4.2%	2.3%	15.2%

Mas, NEJM 2002

PFO in Cryptogenic Stroke Study (PICSS)



PFO / ASA

- ***2-year stroke/death rate on warfarin or aspirin***

<i>No PFO / No ASA (N=59)</i>	<i>PFO / ASA (N=69)</i>
<i>14.5%</i>	<i>15.9%</i>

Homma, JACC 2003

Practice Parameter:

***Quality Standards Committee of the
American Academy of Neurology***

- ***No increased risk of subsequent stroke or death in patients with PFO compared to those without***
- ***PFO/ASA combination possibly increases subsequent risk***

April 2004

Messe et al. Neurology,

7th ACCP Conference on Antithrombotic and Thrombolytic Therapy

- ***“in patients with cryptogenic stroke and a PFO, we recommend antiplatelet therapy over no therapy, and suggest antiplatelet therapy over warfarin.”***

Albers et al. Chest, Sept. 2004

But PFO closure studies show such a low rate of stroke after device placement...

- ***Young patients undergo PFO closure***
- ***Many patients with “TIA”***
- ***Long time from stroke to PFO closure***
- ***Medical therapy after closure***
- ***Many lost to follow-up***

Annual Event Rate in Cryptogenic Stroke Patients < 55 years on medical therapy

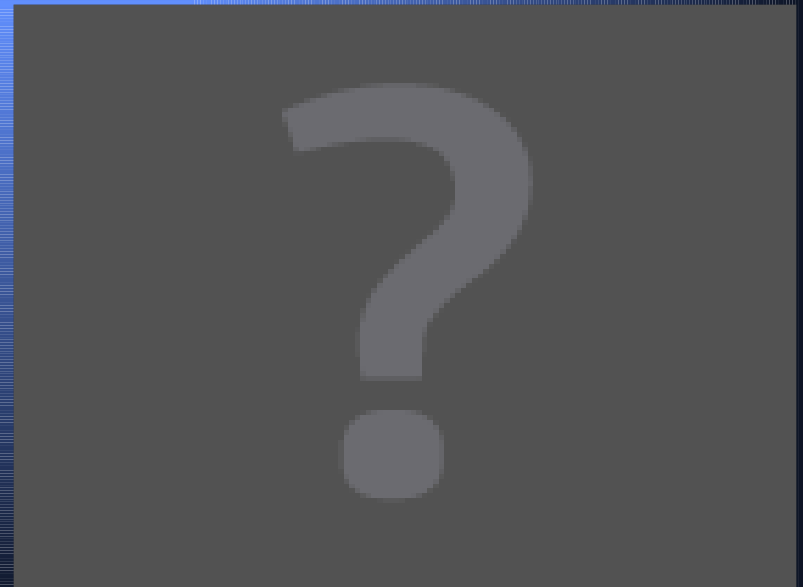
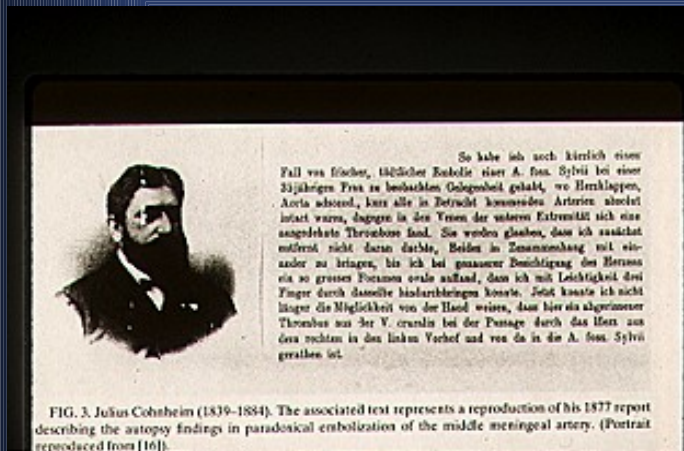
	<i>No PFO (N=54)</i>	<i>PFO (N=49)</i>
<i>Death/Stroke</i>	<i>4.6%</i>	<i>1.0%</i>

Limitations of comparing PFO closure studies to medical therapy studies

- ***“challenges arise as a result of inherent biases and differences in definitions*”**
 - *Khairy, Landzberg, Ann Int Med 2003*
- ***“important limitation is the nonrandomized study design....”***
 - *Windecker, Meier, JACC 2004*



Thrombus in PFO



PFO Prevalence

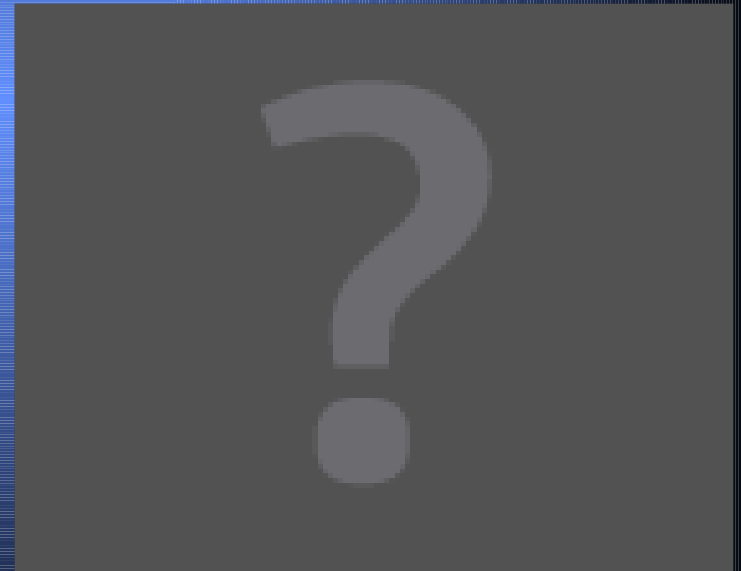
<i>Study</i>	<i>N</i>	<i>Prevalence</i>
<i>Parsons</i>	<i>399</i>	<i>26%</i>
<i>Fawcett</i>	<i>306</i>	<i>32%</i>
<i>Scammon</i>	<i>809</i>	<i>29%</i>
<i>Patten</i>	<i>4,083</i>	<i>25%</i>
<i>Seib</i>	<i>500</i>	<i>17%</i>
<i>Wright</i>	<i>492</i>	<i>23%</i>
<i>Schroeckenstein</i>	<i>144</i>	<i>35%</i>
<i>Sweeney</i>	<i>64</i>	<i>31%</i>
<i>Hagen</i>	<i>965</i>	<i>27%</i>
<i>Thompson</i>	<i>1,000</i>	<i>29%</i>
<i>Penther</i>	<i>500</i>	<i>15%</i>
	<i>9,262</i>	<i>26%</i>

Which PFO is responsible...?



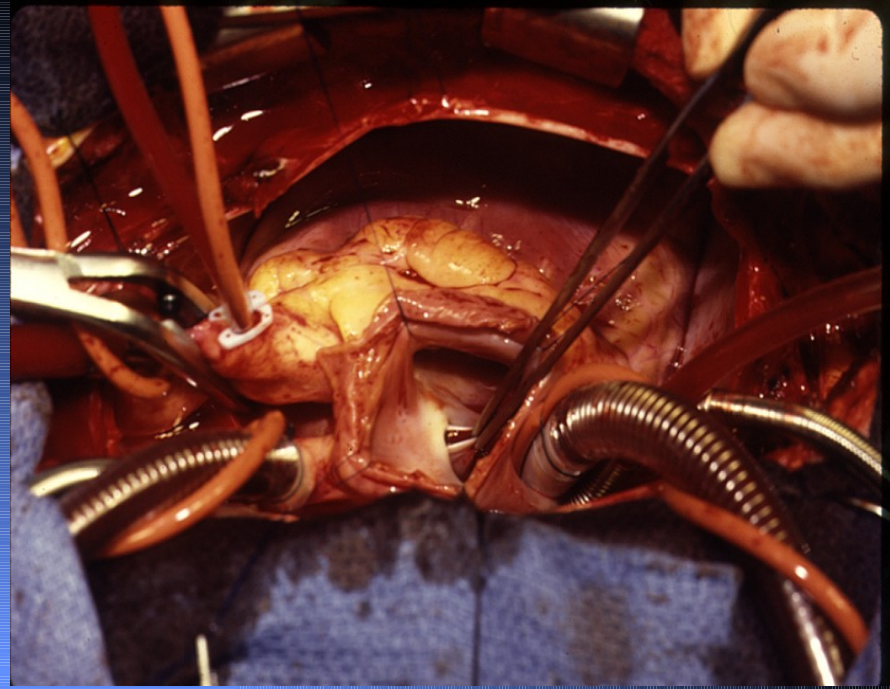
High Risk with PFO

- **VENOUS THROMBUS**
 - *Hypercoagulable state*
 - *Physical inactivity*
 - *Aging*
- **ANATOMY**
 - *Size of Conduit*
 - » *ASA*
 - *Blood flow direction*
 - » *Eustachian valve, Chiari network*
- **HEMODYNAMICS**
 - *RA pressure elevation*





Why do you climb Everest ?



Why do you close PFO ?

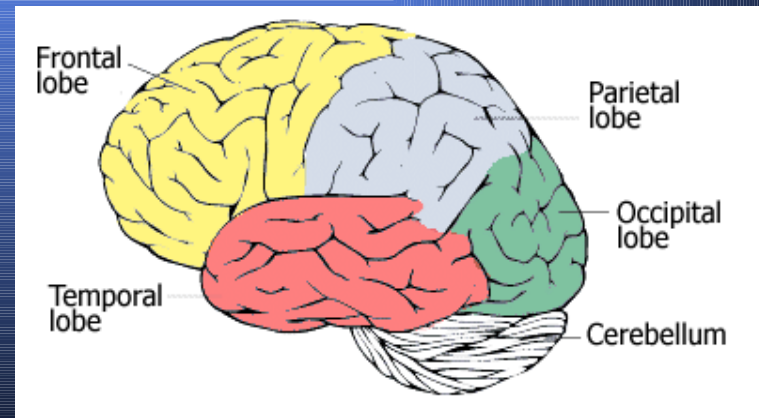
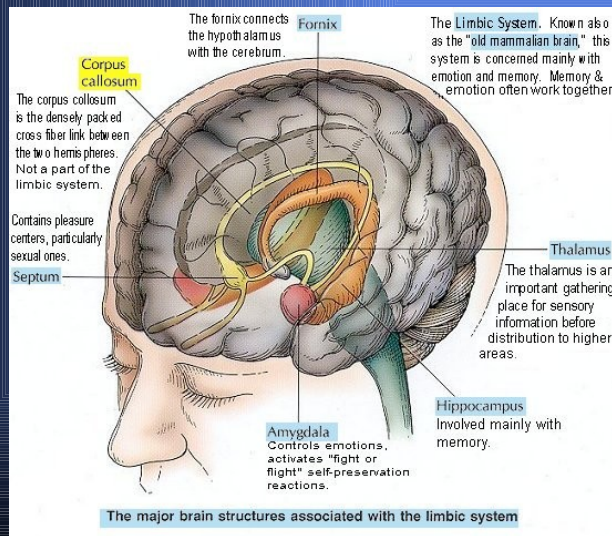


Because
it's there

- *Do we open whatever is closed and close whatever is opened?*

- *Are we dictated by emotion or reason ?*

- *Does limbic system rule us, or do we use frontal lobe?*



So where are we?

- ***No evidence that closure of all PFOs is indicated***
- ***Looking at wrong forest to show effect of device therapy***
- ***Identification of high risk cohort for a trial***

WARSS Bleeding Risk (Mohr, NEJM 2001)

TABLE 3. ADVERSE EVENTS ACCORDING TO TREATMENT ASSIGNMENT. *

EVENT	WARFARIN (N=1103)	ASPIRIN (N=1103)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Death	47 (4.3)	53 (4.8)	0.88 (0.58–1.32)	0.61
Related to hemorrhage	7 (0.6)	5 (0.4)	1.40 (0.42–5.13)	0.77
First hemorrhage‡				
Major	38 (3.4)	30 (2.7)	1.28 (0.78–2.10)	0.39
Minor	261 (23.7)	188 (17.0)	1.51 (1.22–1.87)	<0.001
			RATE RATIO (95% CI)	P VALUE§
	no. of events (rate/100 patient-yr)			
All hemorrhages¶				
Major	44 (2.2)	30 (1.5)	1.48 (0.93–2.44)	0.10
Minor	413 (20.8)	259 (12.9)	1.61 (1.38–1.89)	<0.001

* Maximal follow-up was 25 months. Hemorrhages occurring on the day of the primary event (death or recurrent ischemic stroke) are included. CI denotes confidence interval.

† P values were calculated by the exact test of two independent proportions.

‡ The first hemorrhage is the first or only hemorrhage for each patient.

§ P values were calculated by the exact conditional binomial test for two independent Poisson processes.

¶ All hemorrhages include all hemorrhages in any patient.

PICSS: Event Rate

	<i>PFO</i>	<i>No PFO</i>	<i>RR (95%CI)</i>	<i>P- value</i>
<i>Overall (N=601)</i>	8.17% (N=203)	8.59% (N=398)	0.96 (0.62-1.48)	0.28
<i>Cryptogenic (N=240)</i>	7.96% (N= 98)	6.78% (N=152)	1.17 (0.60-2.37)	0.65

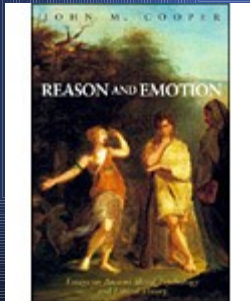
Patients needed to show superiority of closure

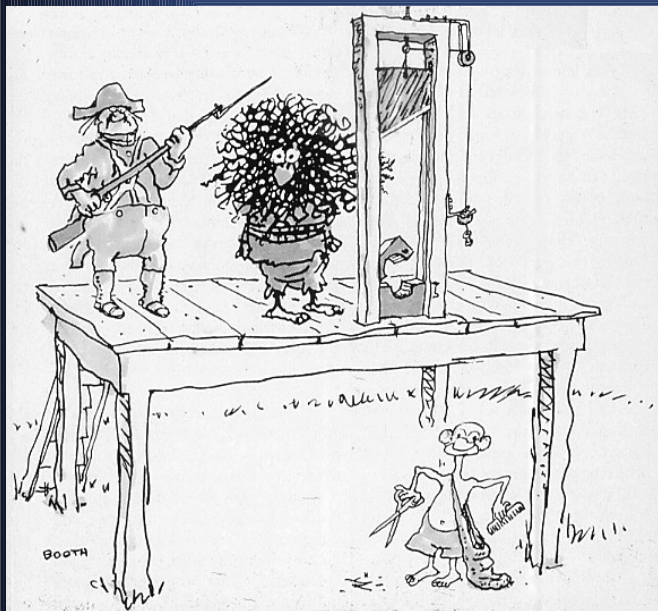
- ***MEDICAL THERAPY*** (*Bogousslavsky, Mas, Homma data*)
 - *2.0% S/D, 3.63% S/D/T*
- ***COMPARED TO CLOSURE THERAPY***
 - *1.5% S/D, 3.0% S/D/T*
 - » *S/D in 2 year study*
 - *5,448 in each group*
 - » *S/D/T in 2 year study*
 - *6,415 in each group*
 - *1.0% S/D, 2.0% S/D/T*
 - » *S/D in 2 year study*
 - *1,135 in each group*
 - » *S/D/T in 2 year study*
 - *802 in each group*

Trial Issues

- ***ALL AGES***
- ***800,000 strokes, 40% crypto 320,000 crypto***
- ***50% PFO***
- ***160,000***

- ***YOUNG PATIENTS***
- ***<50(10%)- 80,000, 40% crypto – 32,000***
- ***<40(3%) - 24,000, 40% crypto - 9,600***
- ***50% PFO***
 - ***<50 - 16,000,***
 - ***<40 - 4,800***





PICSS:

Event Rate in Cryptogenic Patients ≥ 60 years by PFO Status

	<i>PFO (N=39)</i>	<i>No PFO (N=83)</i>	<i>RR (95% CI)</i>	<i>P-value</i>
<i>Death/Stroke</i>	22.44%	9.22%	2.32 (1.09-4.95)	0.03
<i>Death/Stroke/ TIA</i>	25.05%	11.43%	0.74 (0.26-2.08)	0.04

Trial: Practical Problems

- ***Age of patients – low event rate in young***
 - *Large # of patients needed*
- ***Patient preference***
 - *Difficulty randomizing*
- ***Device placebo effect***
- ***Therapy follows “standard of practice”***
 - *Oculo-motor reflex*

Mohr JP, Homma S, Annals Int Med 2003

If closure is better and all cryptogenic stroke patients < 40 get a device

- ***Number of stroke patients < 40 years***
 - $800,000 \times 0.03 = 24,000$
- ***Number of cryptogenic stroke patients***
 - $24,000 \times 0.4 = 9,600$
- ***Number with PFO***
 - $9,600 \times 0.4 = 3,840$
- ***1% reduction in S/D***
 - $3,840 \times 0.01 = 38$
- ***Complication rate from procedure***
 - $3,840 \times 0.01 = 38$
- ***Cost***
 - $3,840 \text{ cases} \times \$10,000 = \$38.4 \text{ million}$

Event Rates in Younger Cryptogenic Stroke Patients

- ***3 studies combined***
 - ***N = 455***
 - ***Mean age = 42***
 - » ***Death/Stroke = 2.00% (1.32-2.91%)***
 - » ***Death/Stroke/TIA = 3.63% (2.69-4.80%)***

Lausanne Study

- ***129 cryptogenic stroke patients <60 years with PFO***
 - ***No randomization***
 - ***Warfarin or aspirin***
 - ***Mean age***
 - » ***44 years***
 - ***Mean follow-up***
 - » ***36 months***
 - ***Death/Stroke: 3.36% (1.79-5.75%)***
 - ***Death/Stroke /TIA: 5.43% (3.36-8.30%)***

Bogousslavsky, Neurology 1996

French PFO/ASA Study

- ***276 cryptogenic stroke patients < 55 years with PFO***
 - *No randomization*
 - *Aspirin*
 - *Mean age*
 - » *40 years*
 - *Mean follow-up*
 - » *36 months*
 - *Death/Stroke: 1.54 % (0.82-2.63%)*
 - *Death/Stroke/TIA: 2.60 % (1.63-3.94%)*
- ***PFO/ASA***
 - *Death/Stroke: 3.71 % (1.36-8.08%)*
 - *Death/Stroke/TIA: 4.96 % (2.14-9.76%)*

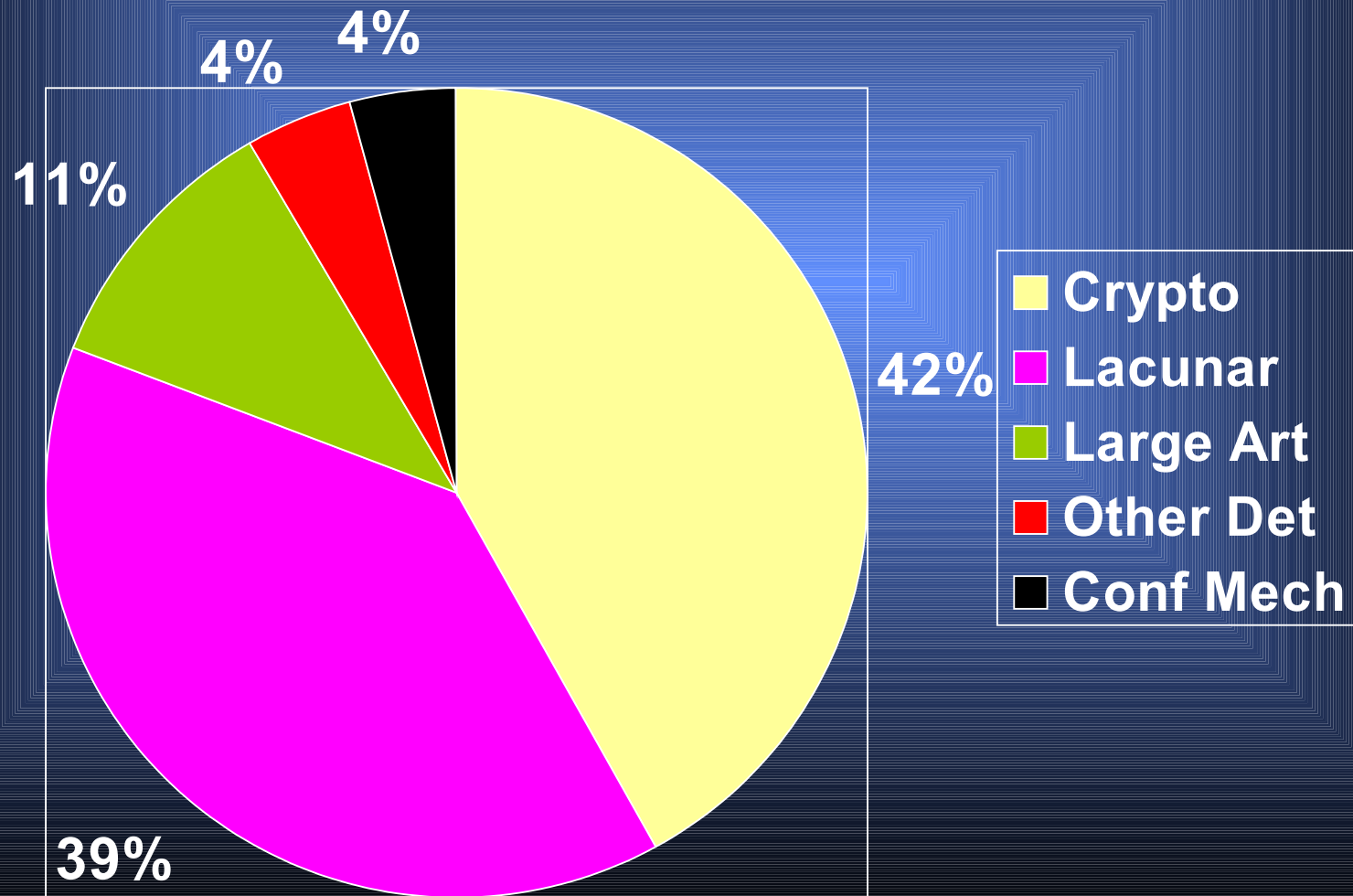
PFO in Cryptogenic Stroke Study (PICSS)

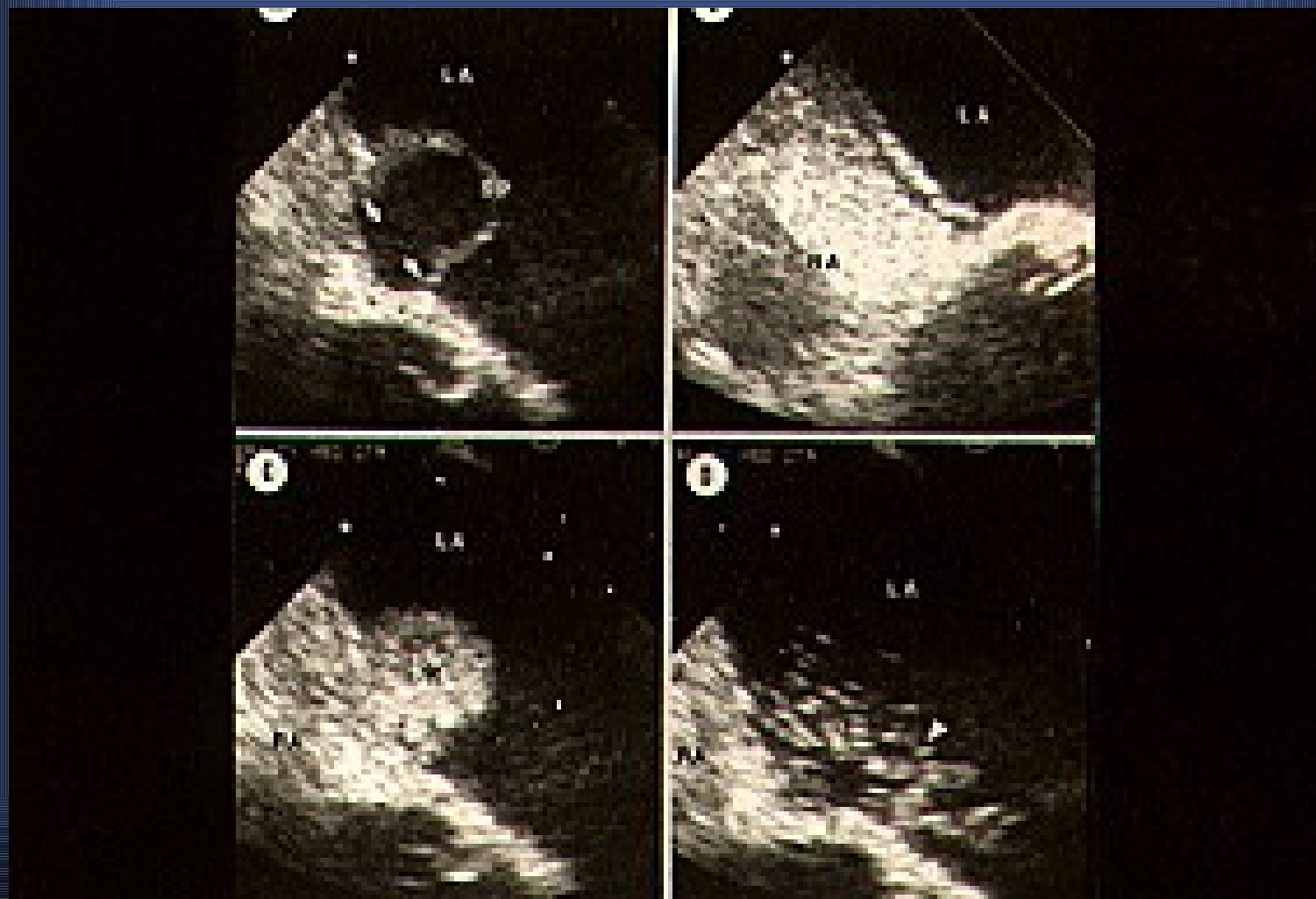
- ***630 stroke patients undergoing TE in WARSS***
 - ***241 cryptogenic stroke patients***
 - ***Randomization to warfarin or aspirin***
 - ***Mean age***
 - » ***59 years***
 - ***Mean follow-up***
 - » ***24 months***

A STROKE
STRIKES EVERY
MINUTE
IN AMERICA.
NOW WE CAN
STRIKE BACK.



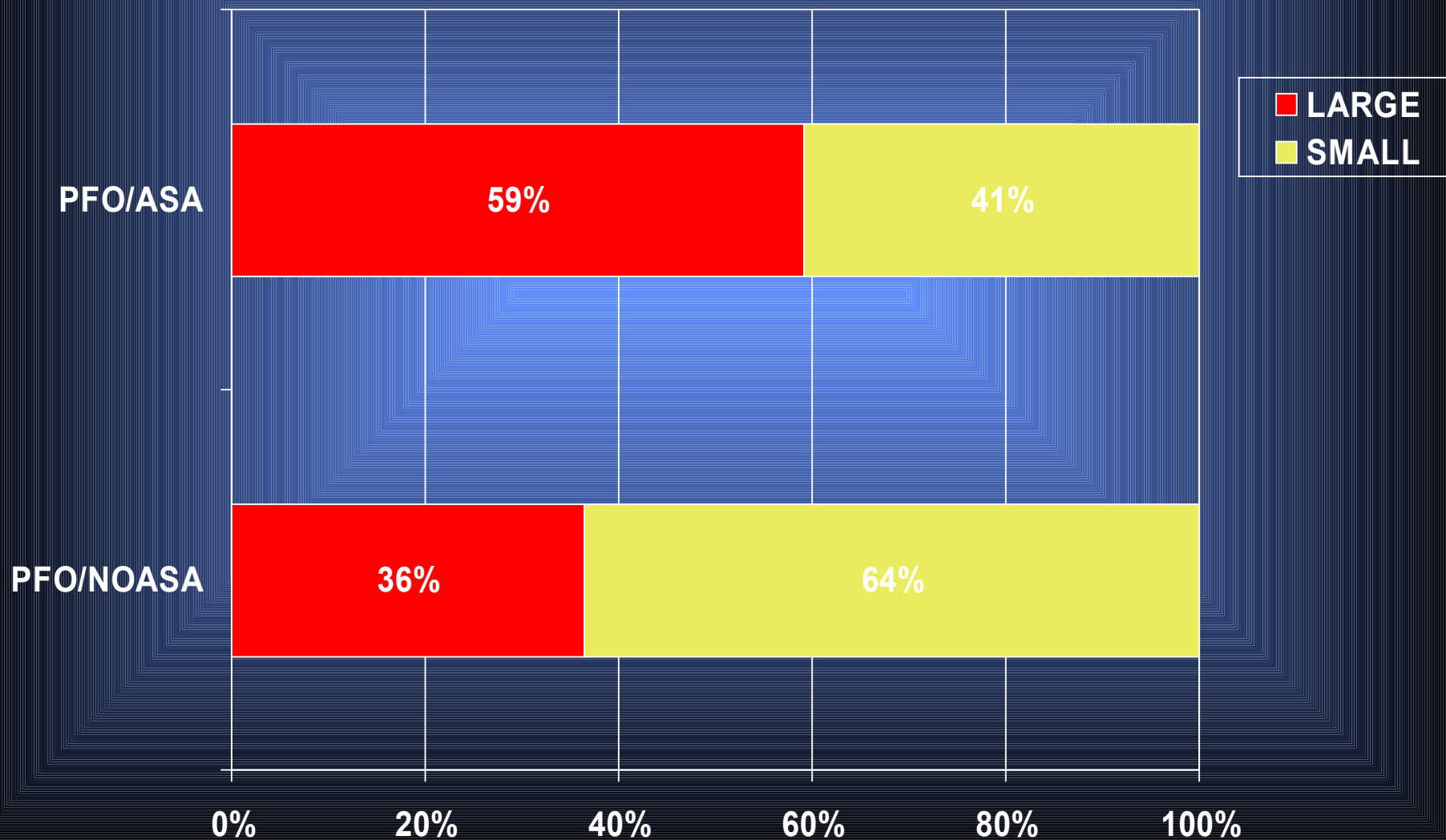
PICSS: Stroke Subtype



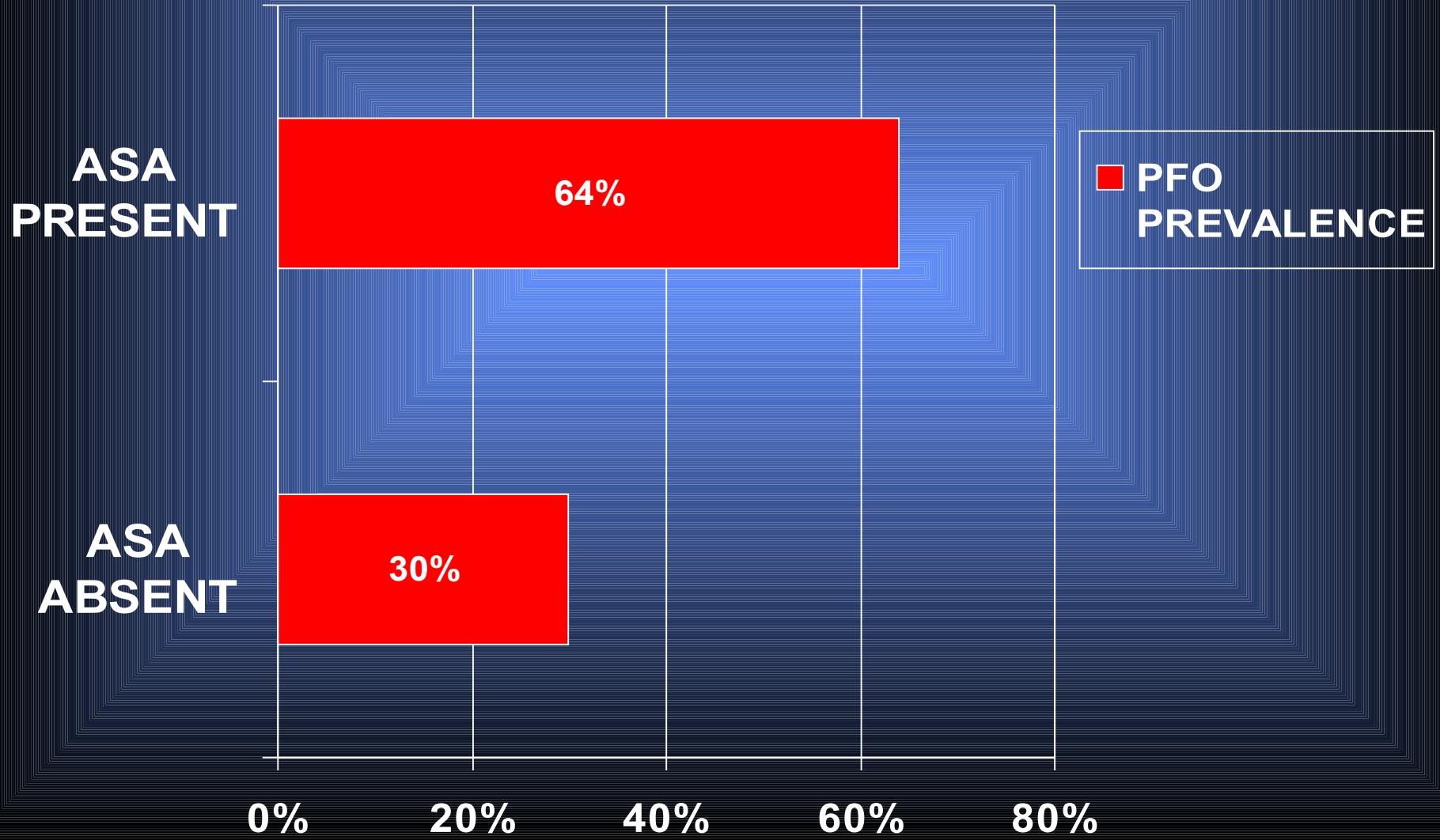


PICSS:

Relationship of PFO Size/Shunt with ASA



PICSS: Relationship of PFO with ASA



PFO and ASA

- **PFO vs. PFO/ASA Event Rates**
– **14.5% vs. 15.7% (p=0.83)**

PFO and ASA

	Event Rate	RR (vs. no PFO or ASA)	95% CI	P-value
No PFO (N=372)	14.8%	---	---	---
PFO only (N=152)	14.5%	0.99	0.61-1.62	0.98
ASA only (N=25)	28.0%	2.10	0.96-4.62	0.06
PFO/ASA (N=44)	15.9%	1.08	0.49-2.38	0.84

Hazard ratios and two-year adverse event rates in patients aged 55 to 64 years with and without PFO

	PFO (N=20)	No PFO (N=36)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Death/Stroke	10.0%	13.9%	0.72 (0.14-3.73) 0.78 (0.14-4.28)	0.70 0.77
Death/Stroke/TIA	10.0%	16.7%	0.59 (0.03-1.92) 0.77 (0.15-4.01)	0.52 0.76
Stroke/TIA	5.0%	13.9%	0.36 (0.04-3.08) 0.46 (0.05-4.13)	0.35 0.49
Stroke	5.0%	11.1%	0.46 (0.05-4.08) 0.48 (0.05-4.57)	0.48 0.52

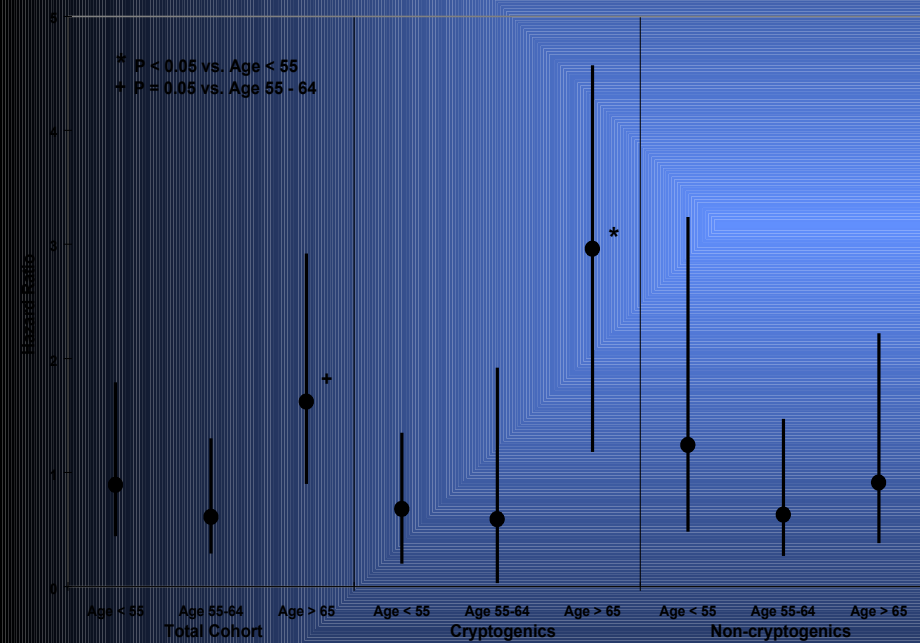
Hazard ratios and two-year adverse event rates in patients aged <55 years with and without PFO

	PFO (N=49)	No PFO (N=54)	Hazard Ratio (95% CI)	P-value
Death/Stroke	2.0%	9.3%	0.21 (0.02-1.78) 0.25 (0.03-2.14)	0.15 0.20
Death/Stroke/T IA	12.2%	16.7%	0.68 (0.20-1.35) 0.79 (0.28-2.26)	0.47 0.66
Stroke/TIA	12.2%	16.7%	0.68 (0.20-1.35) 0.77 (0.26-2.13)	0.47 0.58
Stroke	2.0%	9.3%	0.21 (0.02-1.78) 0.23 (0.03-1.96)	0.15 0.18

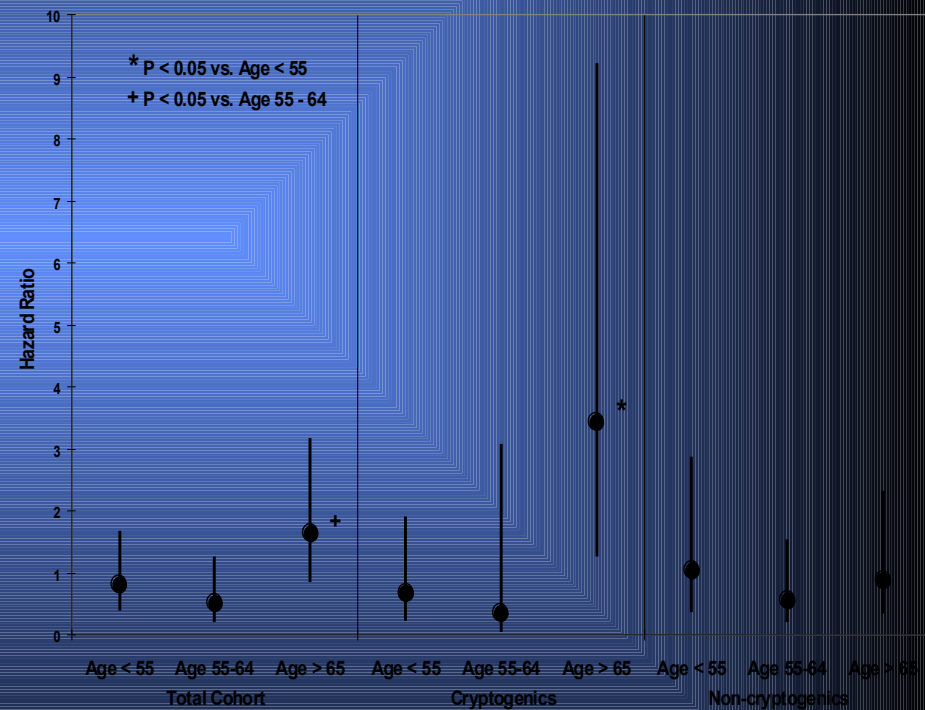
Hazard ratios and two-year adverse event rates in patients aged ≥ 65 years with and without PFO

	PFO (N=29)	No PFO (N=62)	Hazard Ratio (95% CI)	P-Value*
Death/Stroke	37.9%	14.5%	3.21 (1.33-7.75)† 3.32 (1.36-8.10)†	0.01 0.01
Death/Stroke/TIA	41.4%	17.7%	2.96 (1.30-6.72)† 2.92 (1.28-6.68)	0.01 0.01
Stroke/TIA	31.0%	11.3%	3.43 (1.27-9.22)† 3.32 (1.22-8.98)†	0.01 0.02
Stroke	27.6%	8.1%	4.14 (1.35-12.67)† 4.21 (1.36-13.02)†	0.01 0.01

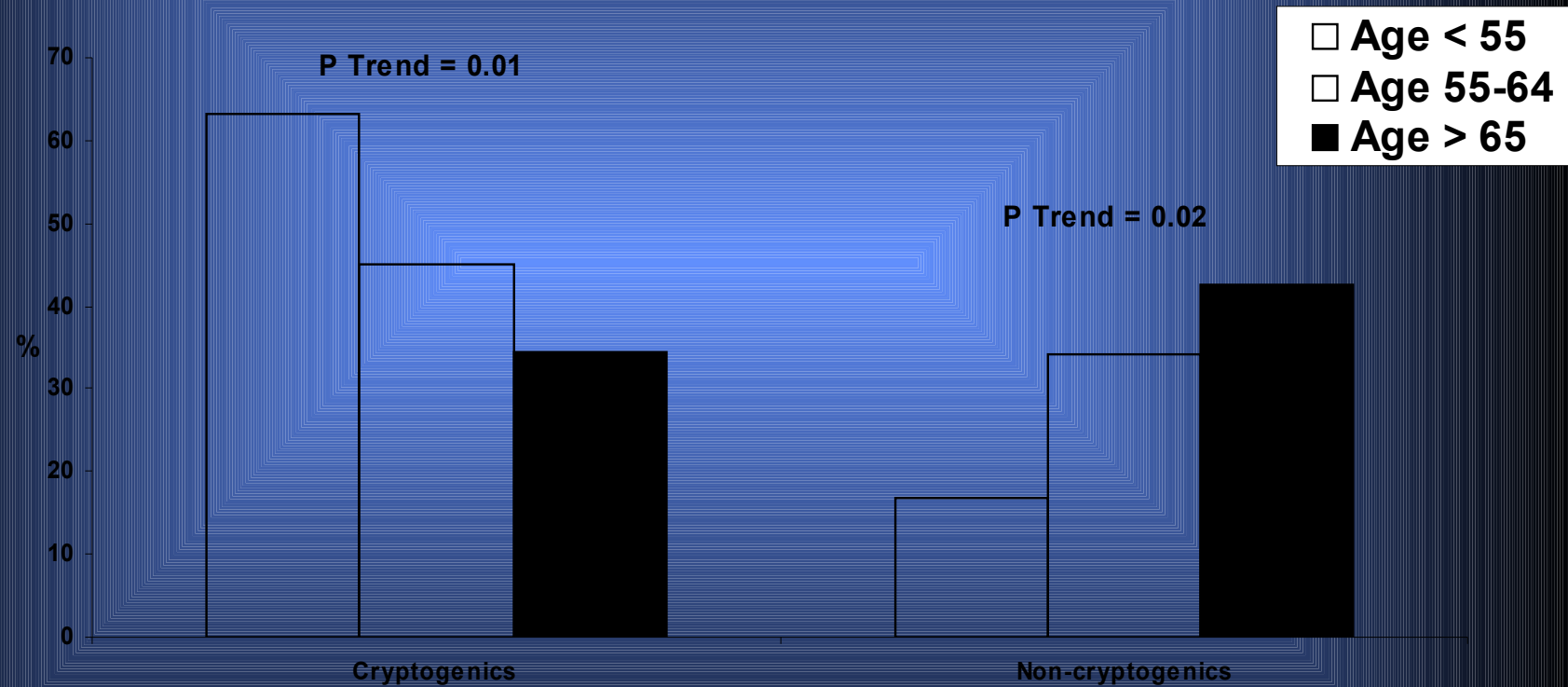
Stroke/Death/TIA



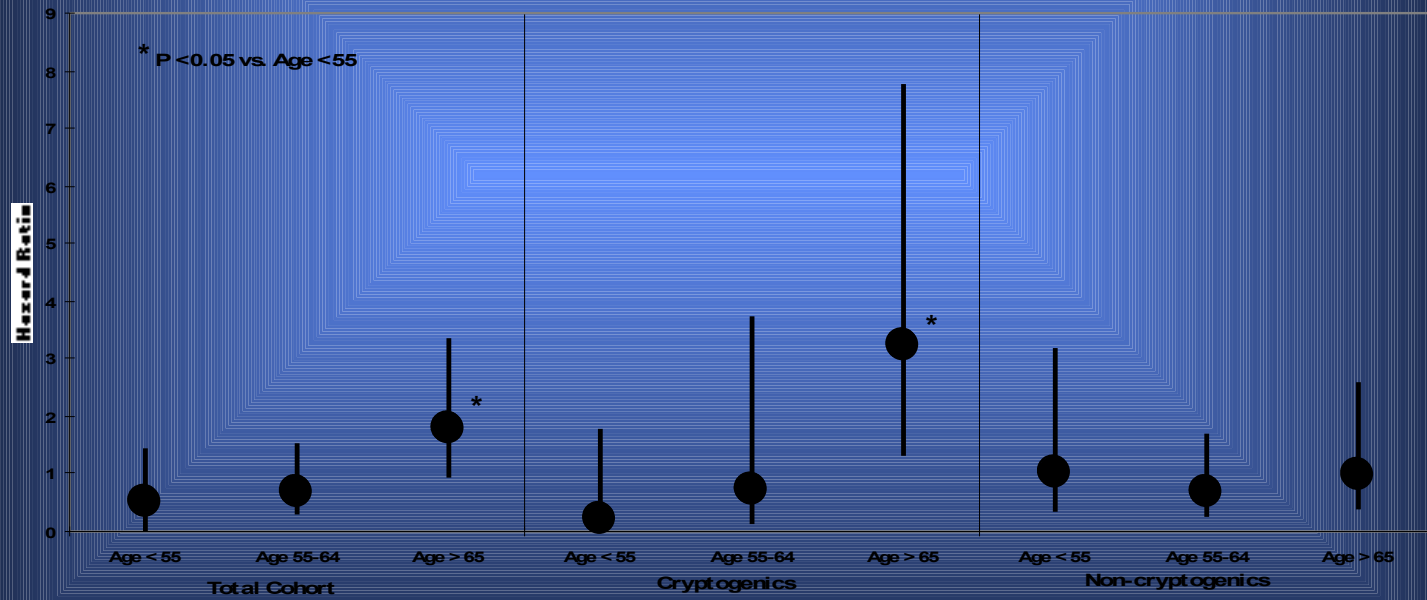
Stroke/TIA



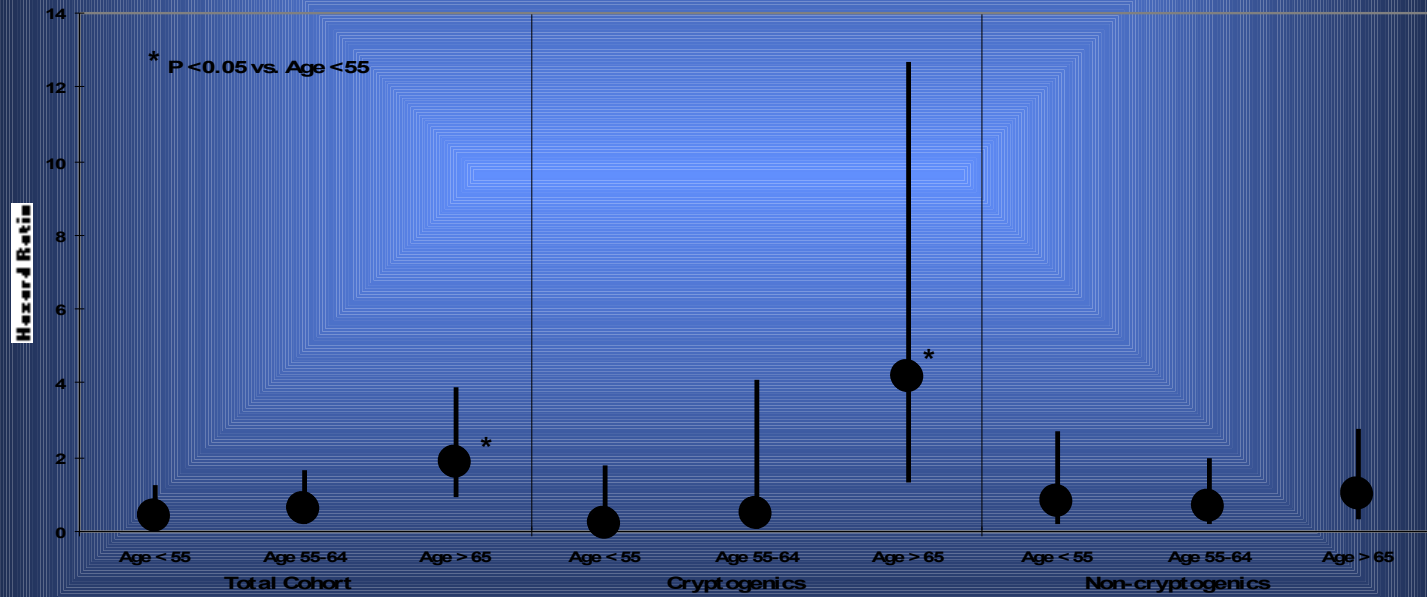
Frequency of Large PFO



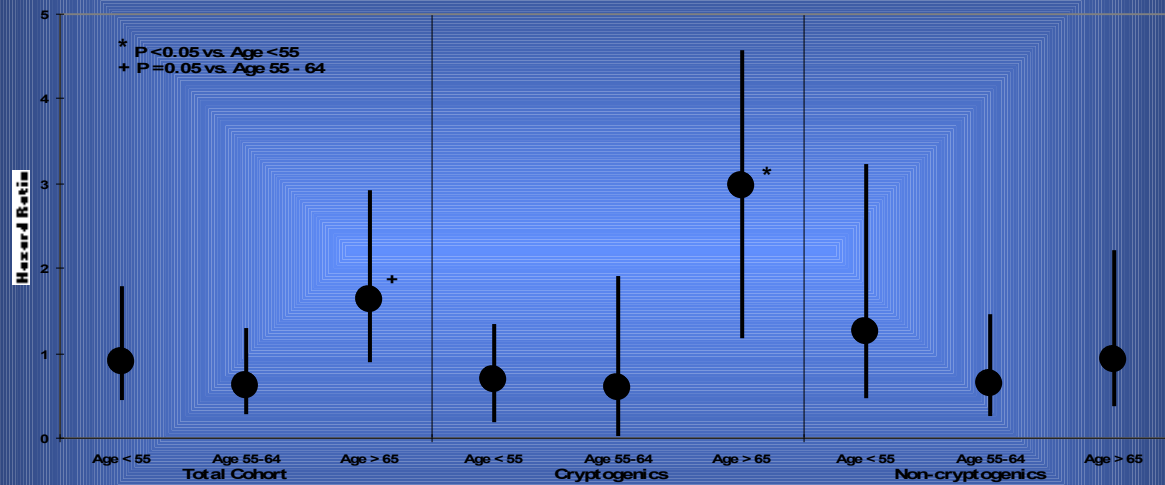
S/D



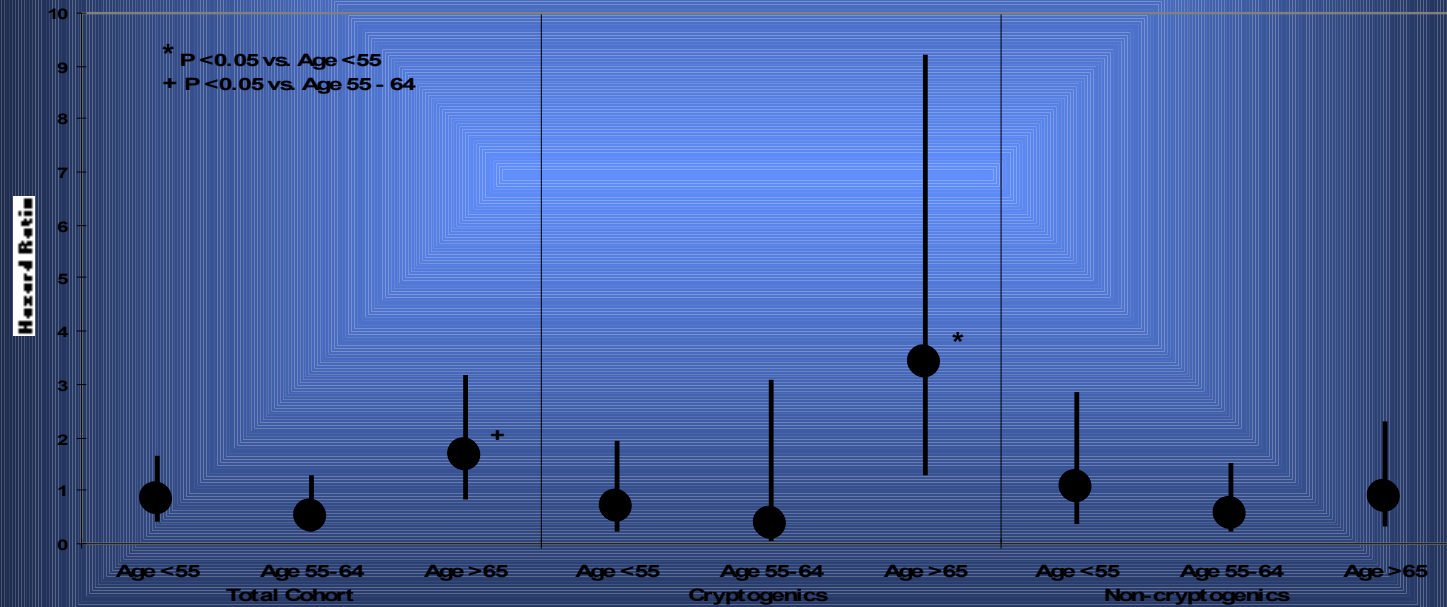
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S/d/t



S/t



Hypercoagulable State and PFO Related Stroke

- **Factor V Leiden mutation**
 - 15.9% in cryptogenic stroke patients vs. 5.3% in control group

(Nabavi, J Neurol 1998)

- **16 patients with stroke and PFO**
 - 5/16 (31%) had hematological abnormality
 - (Anticardiolipin Ab, Protein C abnormality)

(Chaturvedi, J Neurol Sci 1998)

PARTICIPATING CENTERS AND ENROLLMENT

<u># Enrolled</u>	<u>Institution</u>	<u># Enrolled</u>	<u>Institution</u>
82	Columbia-Presbyterian Med. Ctr.	9	Indiana University Med. Ctr.
53	Long Island Jewish Med. Ctr.	8	Wayne State University
47	Georgetown University	8	Cleveland Clinic Florida
41	University of Illinois Med. Ctr.	8	New York University-NY VA
38	Univ. of Iowa Hospitals & Clinics	6	Minneapolis
30	Johns Hopkins Bayview Med. Ctr.	6	Univ. of Southern California
29	U. of Texas Medical School	5	Metrohealth Medical Ctr.
23	Buffalo General Hospital	5	Albert Einstein (PA) Medical Ctr.
21	Massachusetts General Hospital	4	Boston University Medical Ctr.
21	Cleveland Clinic Foundation	4	Marshfield Clinic
19	Montefiore	4	Univ. of Michigan Med. Ctr.
17	University of Miami Sch. of Med.	4	U. Calif. at San Diego Med. Ctr.
17	Henry Ford Hospital	3	St. Paul-Ramsey Medical Ctr.
15	Stanford Stroke Center	3	Yale U. School of Medicine
15	Lankenau Med. Research Ctr.	3	Syracuse VA Medical Ctr.
14	Mt. Sinai School of Medicine	2	University of South Alabama
13	Vanderbilt Medical Ctr.	2	Beth Israel Hospital, Boston
12	Univ. of Kentucky Med. Center	2	Little Rock, AR VA Medical Ctr.
12	Pennsylvania Hospital	1	Maimonides Medical Ctr.
11	Rochester General Hospital	1	University of Vermont
11	New England Medical Ctr.	1	U. of Tennessee at Memphis

Major Hemorrhage Rates

- 2.24 % in warfarin vs.
3.14% in aspirin group

Autopsy PFO Prevalence

- ***Hagen*** (*Mayo Clin Proc*, 1984)

965 Autopsy specimens

<i>Overall</i>	<i>27.3%</i>
<i>0 - 39 years</i>	<i>34.3%</i>
<i>40 - 89 years</i>	<i>25.4%</i>
<i>>90 years</i>	<i>20.2%</i>

- ***Thompson*** (*Quart J Med*, 1930)

1000 Autopsy specimens

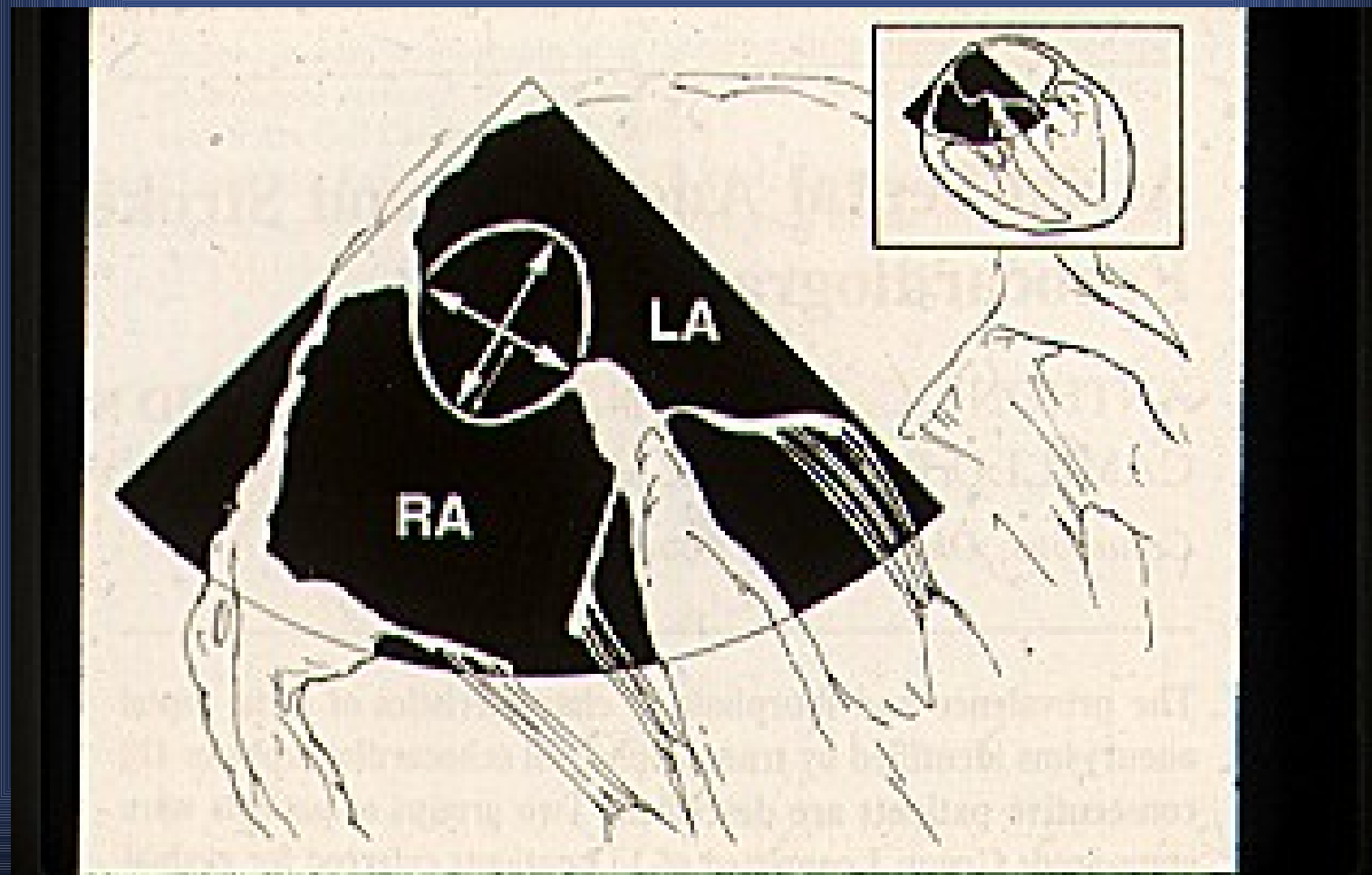
29% - orifice of 0.2 to 0.5 cm (probe patent)

6% - orifice of 0.6 to 1.0 cm (pencil patent)

PFO SIZE/SHUNT in CRYPTOGENIC and NON-CRYPTOGENIC PATIENTS

	<i>Cryptogenic (N=98)</i>	<i>Non-Cryptogenic (N=105)</i>
<u><i>Small PFO</i></u>	49.0% (48/98)	67.6% (71/105)
<u><i>Large PFO</i></u>	51.0% (50/98)	32.4% (34/105)

P<0.01



RELATIONSHIP OF ATRIAL SEPTAL ANEURYSM (ASA) with PFO

- Study prevalence of ASA = 11.5% (69/600)

	ASA PRESENT (N=69)	ASA ABSENT (N=531)	P Value
PFO PREVALENCE	63.8% (44/69)	29.9% (159/531)	< 0.001

OUTCOME: Patients with PFO with/without ASA

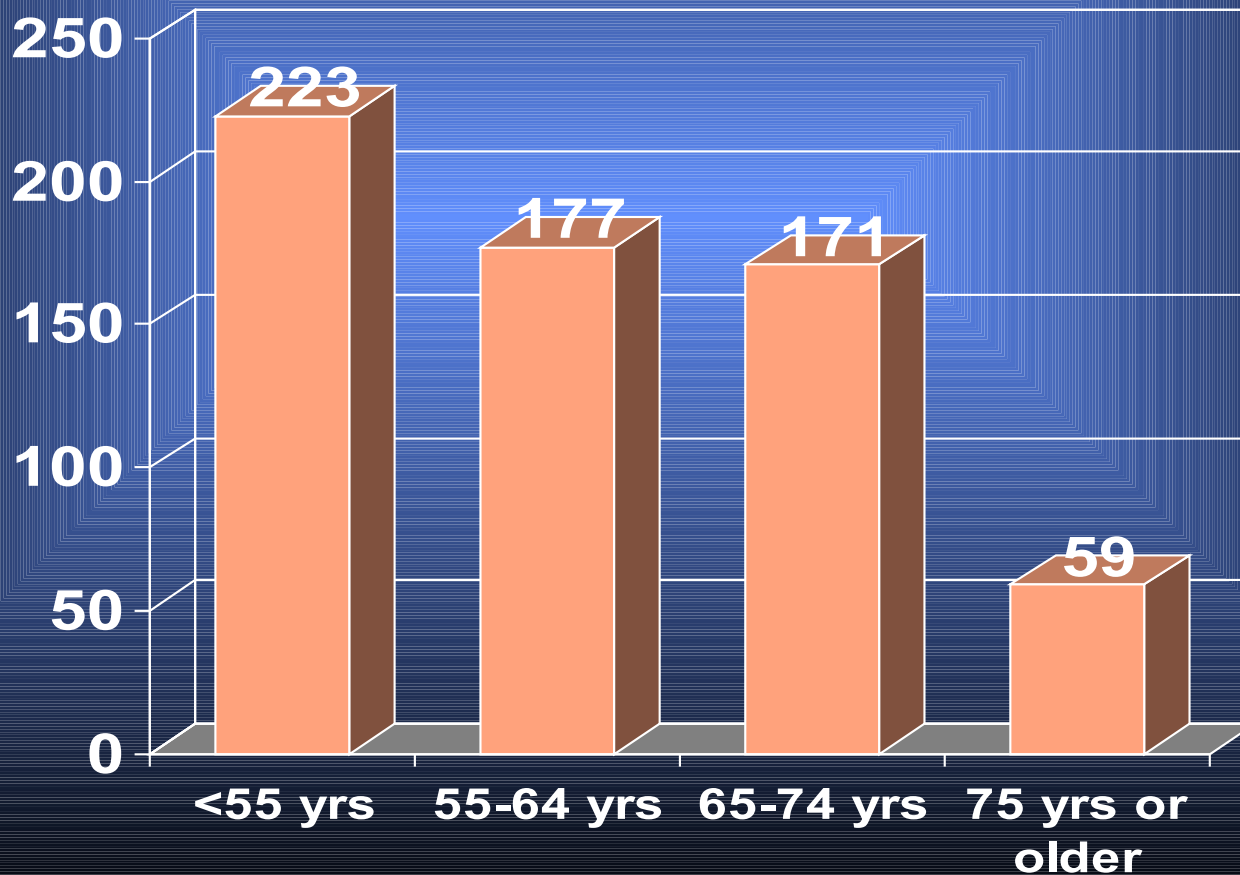
	<i>PFO only (N=159)</i>	<i>PFO + ASA (N=44)</i>
<i>EVENT RATE</i>	<i>14.5% (23/159)</i>	<i>15.9% (7/44)</i>

P=0.84

DEMOGRAPHICS: AGE

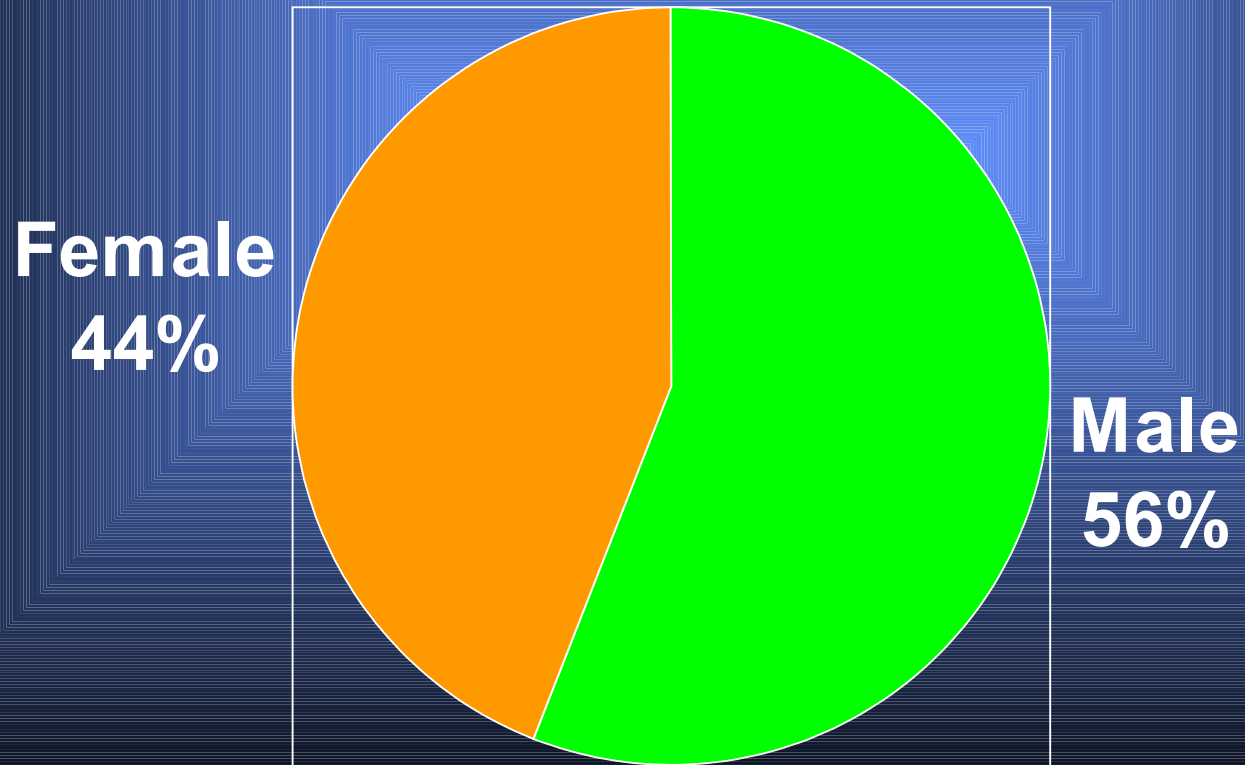
630 patients

59.7 + 12.2 yrs (30-85)



DEMOGRAPHICS: GENDER

- 351 MALE, 279 FEMALE



INR in PICSS Warfarin Treated Patients

- **Warfarin treated patients with PFO**
 - 2.04 ± 1.01 (median 1.85)
 - Time interval between blood draws: 28.3 ± 13.6 days
- **Warfarin treated patients without PFO**
 - 2.04 ± 0.98 (median 1.86)
 - Time interval between blood draws: 28.0 ± 13.3 days

EVENT RATES

- **Overall event rate 16.9% (372/2206)**
 - Aspirin 16.0% (176/1103)
 - Warfarin 17.8% (196/1104)
 - P=0.25, RR 1.13 95% CI 0.92-1.38
- **Warfarin at different INRs**
 - Event rate lower at higher INR approaching that of aspirin

INR in PICSS Warfarin Treated Patients

- **Warfarin treated patients with PFO**
 -2.04 ± 1.01 (median 1.85)
- **Warfarin treated patients without PFO**
 -2.04 ± 0.98 (median 1.86)

OUTCOME: Cryptogenic Patients with PFO

WARFARIN VS. ASPIRIN (N=98)

	<i>WARFARIN</i> (N=42)	<i>ASPIRIN</i> (N=56)
<i>EVENT RATE</i>	9.5% (4/42)	17.9% (10/56)

RR: + PFO on warfarin = 0.52 : P=0.28

**OUTCOME (including TIA):
Cryptogenic Patients with PFO
WARFARIN VS. ASPIRIN (N=98)**

	WARFARIN (N=42)	ASPIRIN (N=56)
EVENT RATE	16.7% (7/42)	23.2% (13/56)

RR: + PFO on warfarin = 0.72 : P=0.48

	Warfarin	Aspirin	RR (95%CI)	P- value
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	8.3% (N=72)	16.3% (N=80)	0.50 (0.19- 1.31)	0.16

SOCIODEMOGRAPHIC FACTORS

	WARFARIN N = 1103	ASPIRIN N = 1103
Mean Age	63.3 ± 11.2	62.6 ± 11.4
Female	447 (41%)	449 (41%)
Race-Ethnicity		
White	627 (57%)	626 (57%)
Black	338 (31%)	325 (30%)
Hispanic	105 (10%)	118 (11%)
Other	33 (3%)	34 (3%)
Education (≤high school)	805 (74%)	796 (73%)

RISK FACTORS

	WARFARIN N = 1103	ASPIRIN N = 1103
Hypertension	746 (69%)	753 (69%)
Diabetes	367 (33%)	338 (31%)
Cardiac Disease	250 (23%)	254 (23%)
TIA/Stroke history	321 (31%)	308 (29%)
Current smokers	306 (28%)	337 (31%)
ETOH >2 drinks/day	125 (11%)	116 (11%)
Physical Inactivity	472 (43%)	456 (41%)

QUALIFYING STROKE FEATURES

	WARFARIN N = 1103	ASPIRIN N = 1103
--	----------------------	---------------------

Duration

≤24 hrs, infarct on CT/MR	74 (7%)	66 (6%)
>24 hrs, infarct on CT/MR	729 (66%)	769 (70%)
>24 hrs, no infarct on CT/MR	300 (27%)	268 (24%)

Glasgow Score

Severe disability	78 (7%)	90 (8%)
Moderate disability	327 (30%)	319 (29%)
No or minimal disability	689 (63%)	694 (63%)

Medication

On aspirin	282 (26%)	290 (27%)
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QUALIFYING STROKE CLINICALLY INFERRED MECHANISM

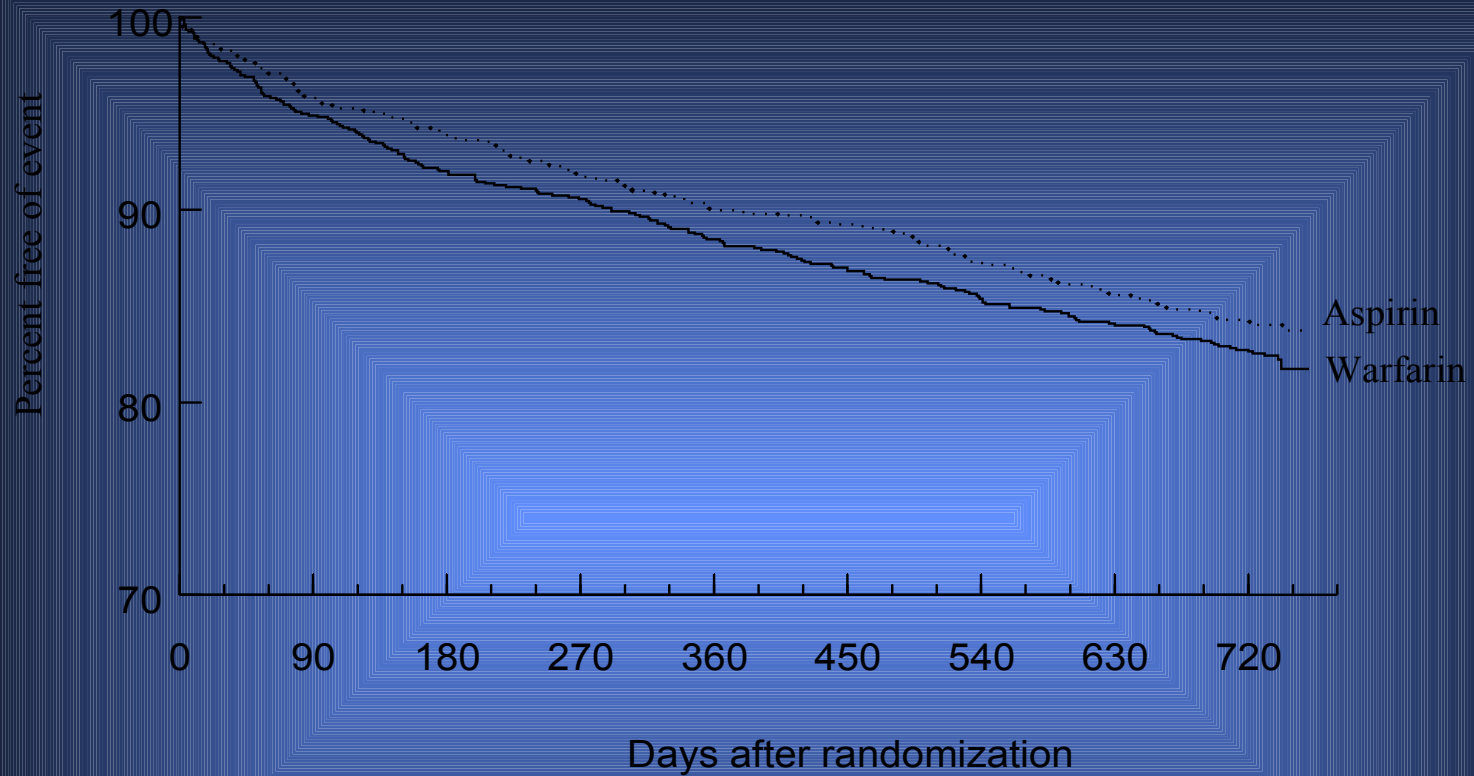
	WARFARIN N = 1103	ASPIRIN N = 1103
Small Vessel/Lacunar	612 (55%)	625 (57%)
Cryptogenic	281 (25%)	295 (27%)
Large Artery/Stenosis	144 (13%)	115 (10%)
Infarct of Other Cause	33 (3%)	30 (3%)
Infarct of Confl.Mech.	36 (3%)	35 (3%)

EVENT RATES

- Overall event rate 16.9% (372/2206)
 - Warfarin 17.8% (196/1104)
 - Aspirin 16.0% (176/1103)

(P=0.25, RR 1.13: 95% CI 0.92-1.38)

Kaplan-Meier Curves for Recurrent Ischemic Stroke or Death

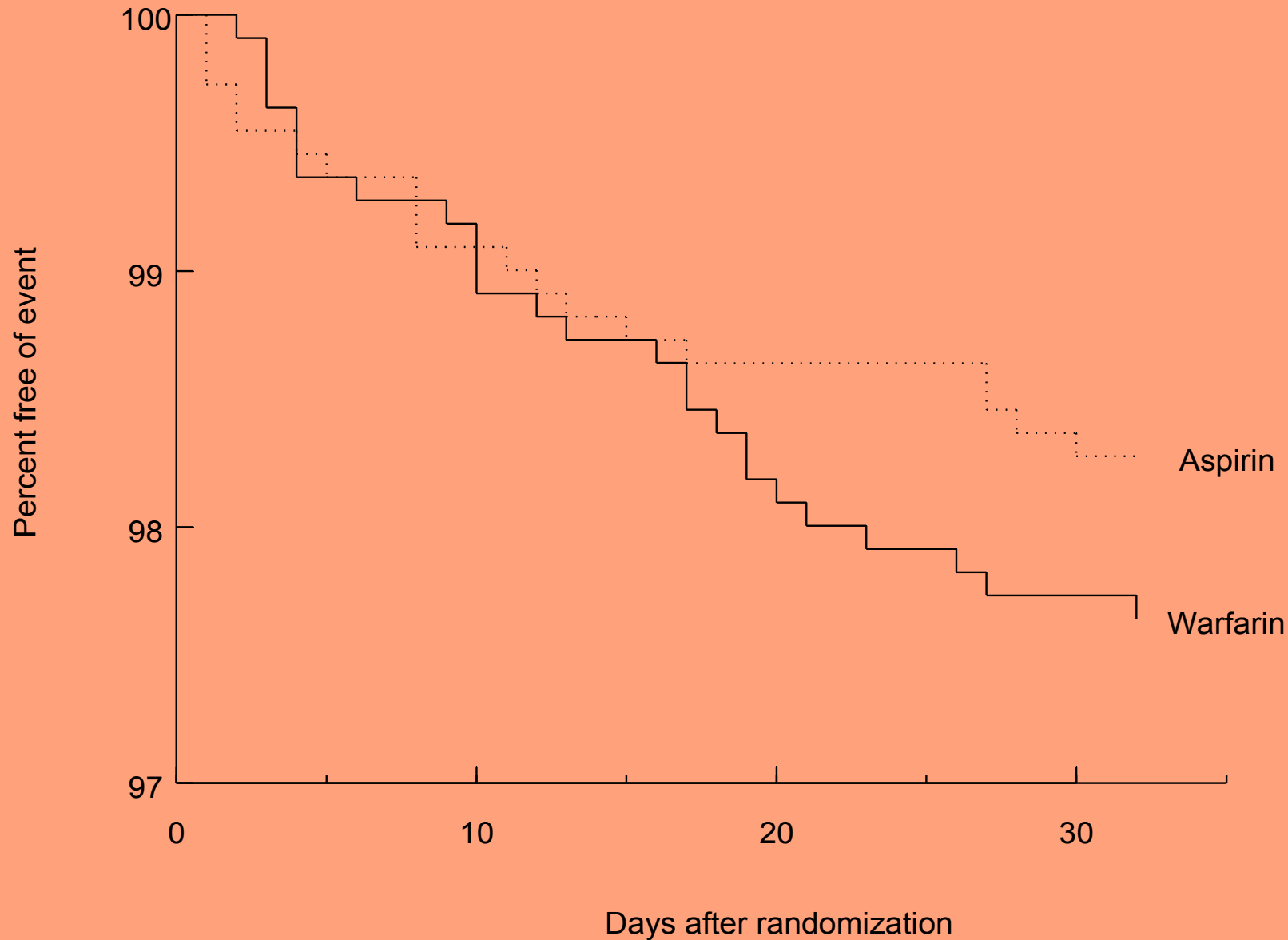


Number at risk

Warfarin	1103	972	885
Aspirin	1103	984	900

Hazard rate ratio=1.13 95% CI 0.92-1.38 two-sided p-value=0.25.

Kaplan-Meier Curves for Recurrent Ischemic Stroke or Death over 30 Days



MAJOR HEMORRHAGE

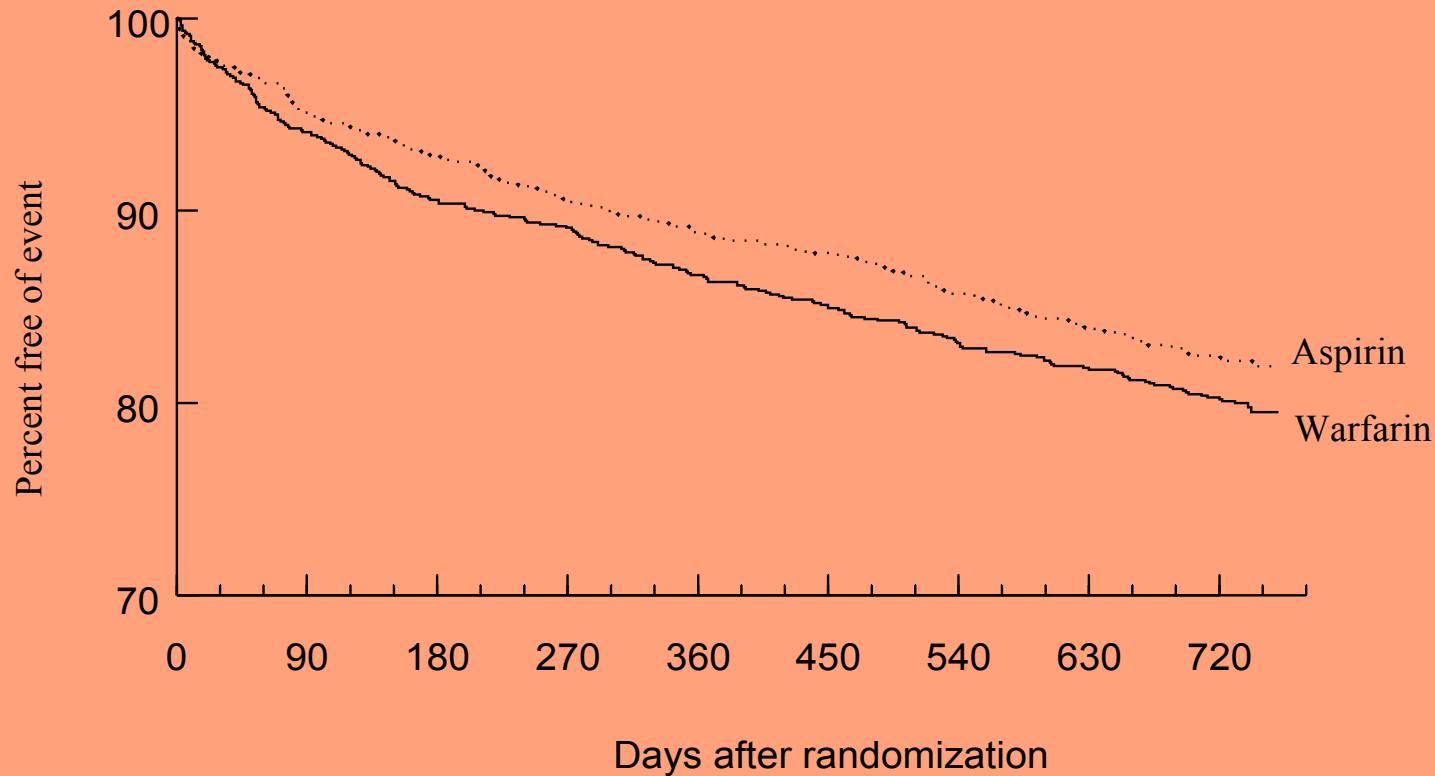
- **GI hemorrhage, hemorrhagic cerebral infarction, subdural hematoma, intracranial hemorrhage, any other requiring transfusion**
- **1.92% warfarin, 1.49% aspirin**

WARSS

Warfarin Aspirin Recurrent Stroke Study

- **J. P. Mohr M.D., M.S.**
- **NIH - NINDS RO1 NS28371**
- **Columbia-Presbyterian Medical Center**

Kaplan-Meier Curves for Earlier of Primary Endpoint or Major Hemorrhage



Number at risk

Warfarin	1103	952	862
Aspirin	1103	971	881

Hazard rate ratio=1.15 95% CI 0.95-1.39 two-sided p-value=0.16.

Demographic Subgroups

**(Risk for death or recurrent ischemic stroke:
warfarin vs. aspirin)**

Race/Ethnicity	P	RR	95% CI
Black (n=663)	0.45	1.14	0.81-1.62
White (n=1253)	0.50	1.10	0.83-1.47
Hispanic (n=223)	0.66	1.14	0.62-2.09
Other (n=67)	0.77	1.18	0.40-3.50
Gender			
Male (n=1309)	0.12	1.23	0.95-1.61
Female (n=897)	0.92	0.98	0.71-1.36

Baseline Stroke Subtype

(Risk for death or recurrent ischemic stroke:
warfarin vs. aspirin)

	P	RR	95% CI
Small vessel/lacunar (n=1237)	0.31	1.15	0.88 - 1.52
Cryptogenic (n=576)	0.68	0.92	0.61 - 1.39
Large artery/severe stenosis/occluded (n=259)	0.51	1.22	0.67 - 2.22
Other determined cause (n=63)	0.15	1.99	0.77 – 5.15
Conflicting mechanism (n=71)	0.79	1.14	0.44 – 2.96

Analysis Summary

Warfarin vs. Aspirin over 2 years, N=2206

- **Primary**
No difference in recurrent stroke or death
- **Major secondary**
No difference in recurrent stroke, death, or major hemorrhage
- **Subgroups**
No difference in recurrent stroke or death by
 - Race/ethnicity
 - Gender
 - Baseline stroke subtype
- **Overall**
The result favors aspirin (11% benefit), but difference not statistically significant

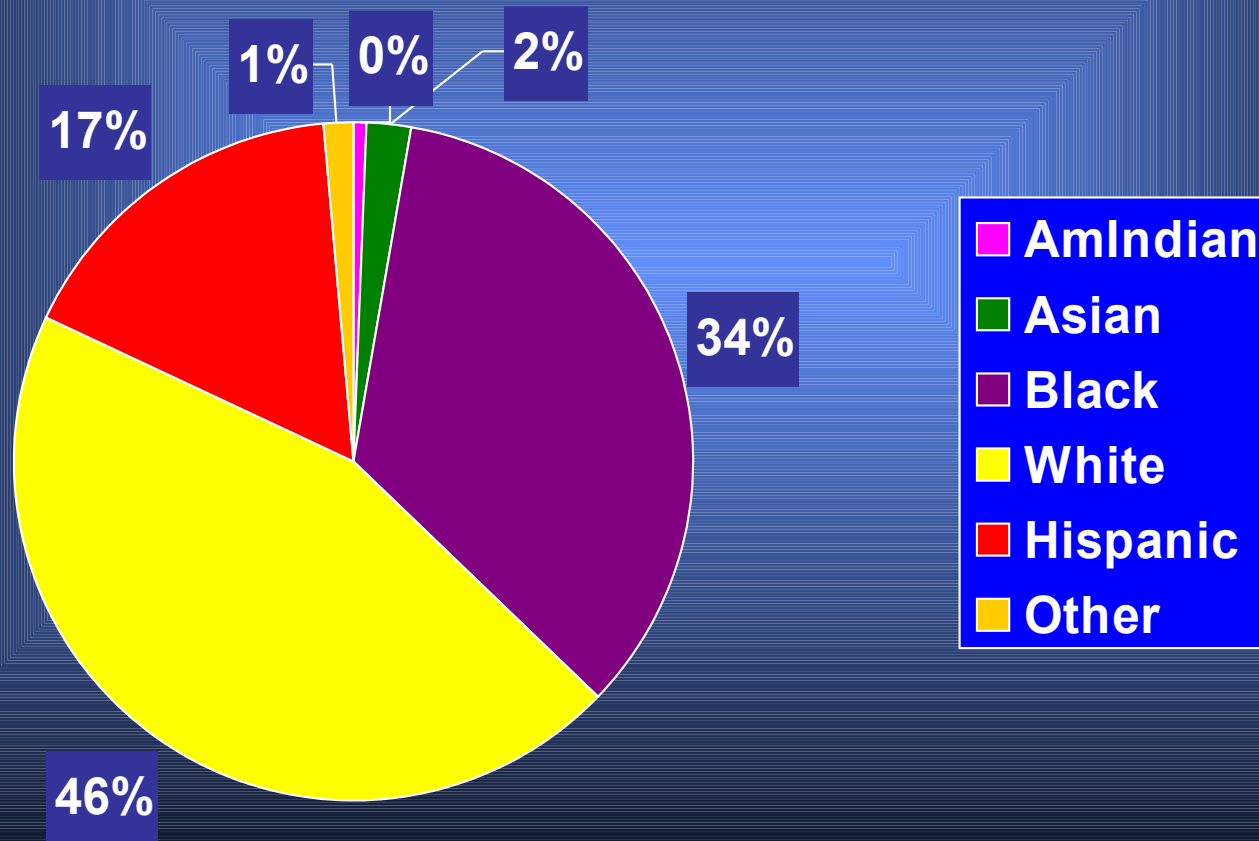
STUDIES ASSOCIATED WITH WARSS

- **PICSS**
 - PFO in Cryptogenic Stroke Study
- **APASS**
 - Antiphospholipid in Stroke Study
- **GENESIS**
 - Genes in Stroke Study
 - » ACE gene
- **HAS**
 - Hemostatic Markers in Stroke Study
 - » Warfarin effect based on initial F1.2

Mechanism for Stroke

- **Paradoxical embolization of venous thrombus through intracardiac right to left shunt**

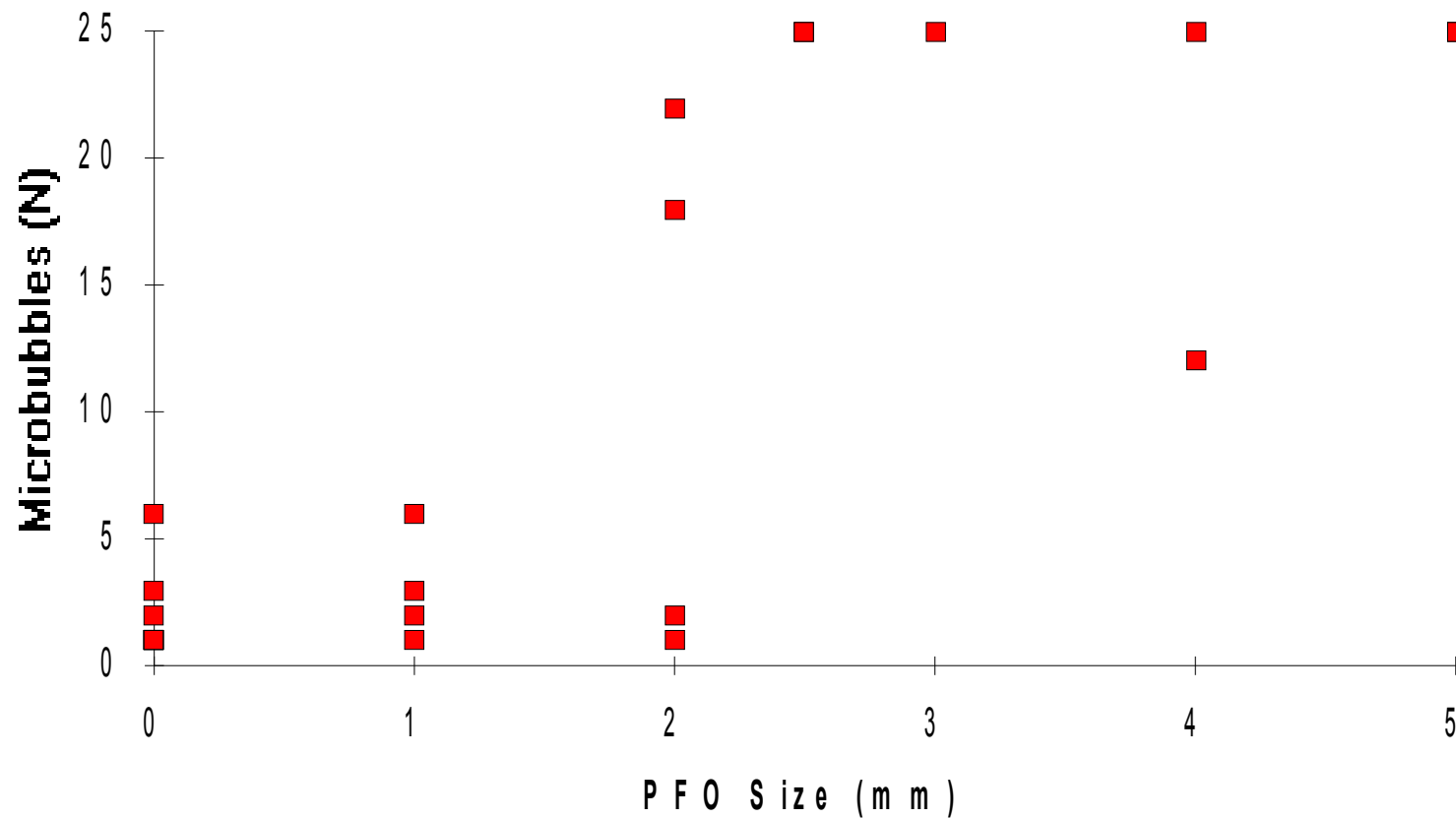
DEMOGRAPHICS: RACE-ETHNICITY



Lost to Follow-up (LTF)

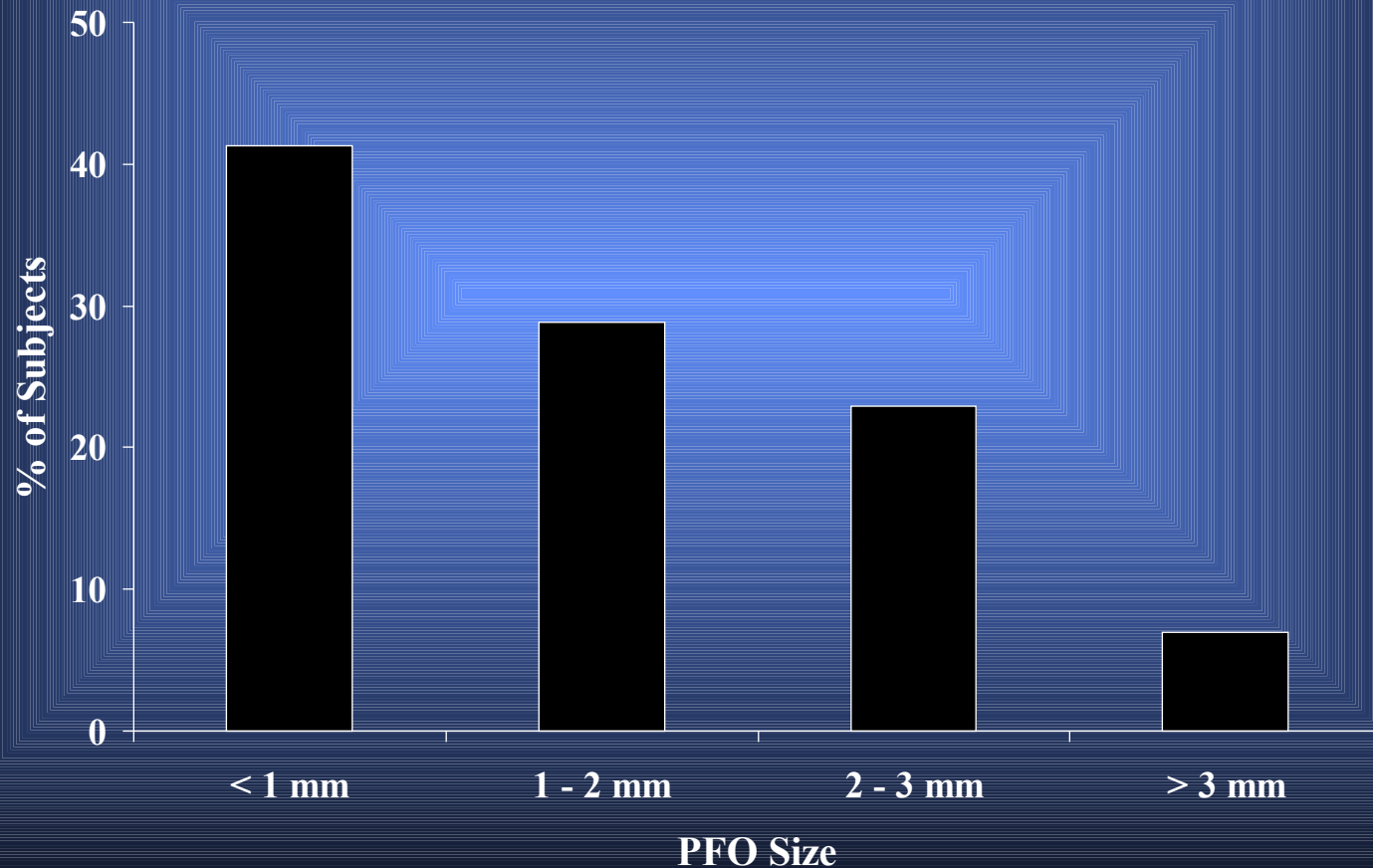
- **10 lost to follow-up**
- **Pre-specified imputation method used stratified by an independent observer**

Relationship between PFO Size and Number of Microbubbles (Homma, Stroke 1994)



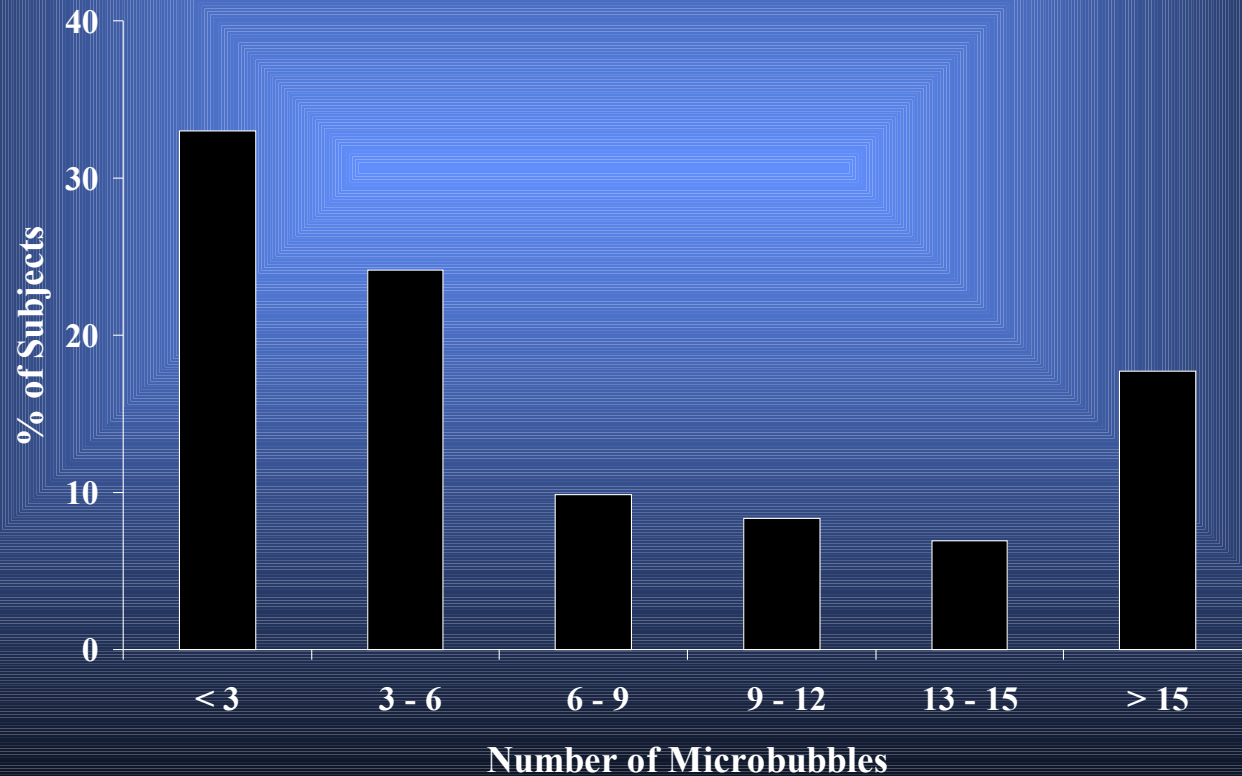
PFO SIZE IN STROKE PATIENTS

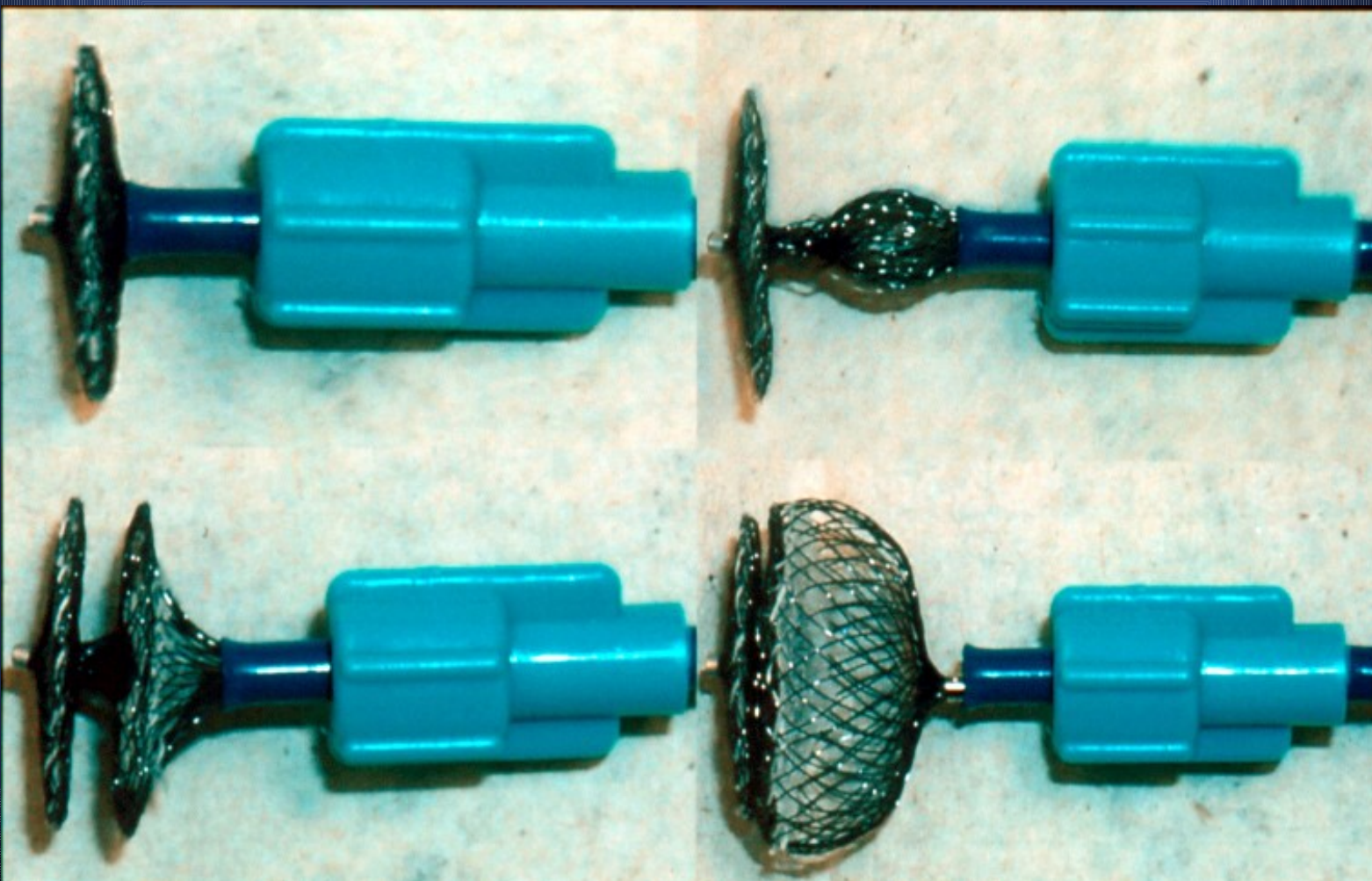
Distribution of PFO Size (N=203)



SHUNT THROUGH PFO IN STROKE PATIENTS

Distribution of Number of Microbubbles in LA (N=203)





METHODS TO ESTIMATE SIZE AND SHUNT

- **TT Echo**
 - **Bubble numbers**
 - » **Qualitative**
 - **Mitral Doppler**
 - » **Number of spikes in Doppler signal**
(Kerr, JACC 2000)

METHODS TO ESTIMATE SIZE AND SHUNT

- **TE**
 - Separation septum primum from secundum
 - Bubble number
 - Area of left atrium occupied by bubbles

METHODS TO ESTIMATE SIZE AND SHUNT

- **TCD BASED**
 - Number of HITS
 - TE large PFO will correspond to “showers” or “curtain” of HITS

VARIABLES IN MEASUREMENTS

- **Site of contrast injection**
 - Lower extremity
- **Amount of injection**
 - Usually 1cc air with
- **Injectate type**
 - Air vs. pre-prepared contrast material
- **Adequacy of Valsalva maneuver or cough**

OUTCOME in Warfarin-treated Patients with PFO Effect of INR

- **INR ≥ 2**
 - **5.5% (95% CI = 1.5 – 15.0%)**
- **INR < 2**
 - **7.2% (95% CI = 2.6-15.2%)**

PFO Size and Brain Imaging

- Although cryptogenic stroke may be due to paradoxical embolism, it is difficult to prove
- We sought to evaluate the brain imaging findings associated with embolism with the presence and characteristics of PFO

PFO Size and Brain Imaging Patient Characteristics

- 95 patients with first ischemic stroke referred for TE

Mean age 64.4 ± 11.1 years

49 woman, 47 man

- Stroke subtyping according to NINDS criteria

Atherosclerotic 6 (27%)

Lacunar 4 (25%)

Cardioembolic 2 (15%)

Cryptogenic 19 (45%)

PFO Size and Brain Imaging Conclusions

- **Stroke patients with larger PFOs have brain imaging features of embolic stroke**
- **Cryptogenic stroke in patients with large PFOs is likely to be due to paradoxical embolization**

WARRS 2

- **Eligible: Ischemic Stroke (Not-cardioembolic, Not-operable Atherosclerotic) within prior 30 days**
- **30 – 85 years old**
- **Sample size: 30% risk reduction (n=2,206)**
- **Secondary Endpoints: TIA, MI**
- **Adverse Experience: Hemorrhage**

PFO Determination

- **Biplane or multiplane transesophageal echocardiography**
 - **Saline contrast injection**
 - **With/without Valsalva**
- **Quality assurance measures**
- **Central analysis**

PICSS ENROLLMENT

ENROLLED IN PICSS
N=630
(42 centers)



TE STUDIES
AVAILABLE N=627

PFO NOT ANALYZED
N=26

PFO ANALYZED
N= 601

ASA and Stroke

- **Atrial septal aneurysm (ASA) is associated with cryptogenic stroke but reason for this association is not clear**

OUTCOME (including TIA): Subjects with and without PFO

	<i>PFO</i>	<i>No PFO</i>
<i>EVENT RATE</i>	19.7%	19.4%

P=0.99, RR with PFO=1.00

OUTCOME: All Patients with PFO WARFARIN VS. ASPIRIN (N=203)

	WARFARIN (N=97)	ASPIRIN (N=106)
EVENT RATE	16.5% (16/97)	13.2% (14/106)

P=0.49, RR with PFO on warfarin = 1.29

Associated Factors

- ***DVT***

10% (3/29) with PFO related stroke

- Gautier, Cerebrovasc Dis '91

8% (1/13) cryptogenic stroke patients with PFO

- Ranoux, Stroke '93

57% (24/42) with PFO and systemic / cerebral embolization

- Stöllberger Ann Int Med, '93

Associated Factors

- ***Chiari Network***

***Directs flow from IVC to interatrial septum
Present in 2% (29/1436) of TE studies***

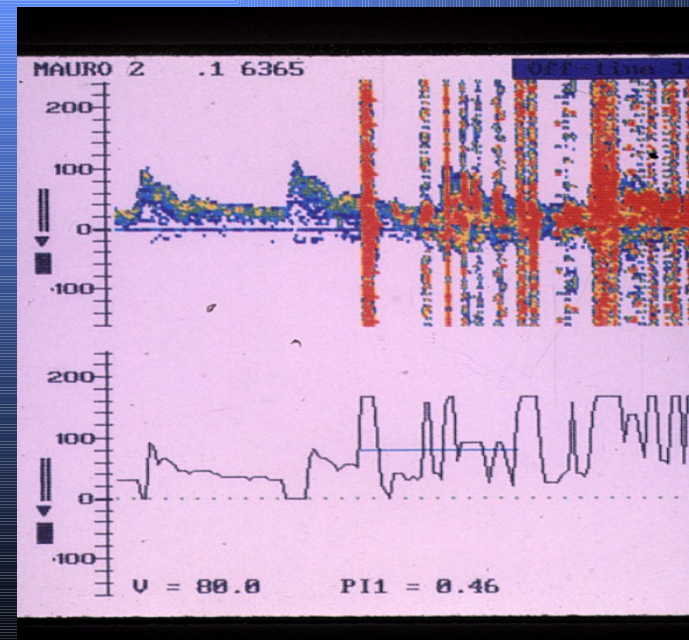
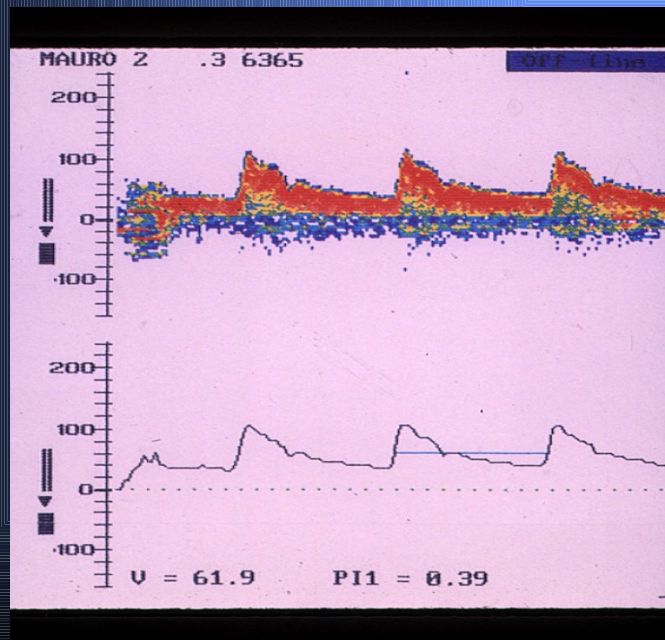
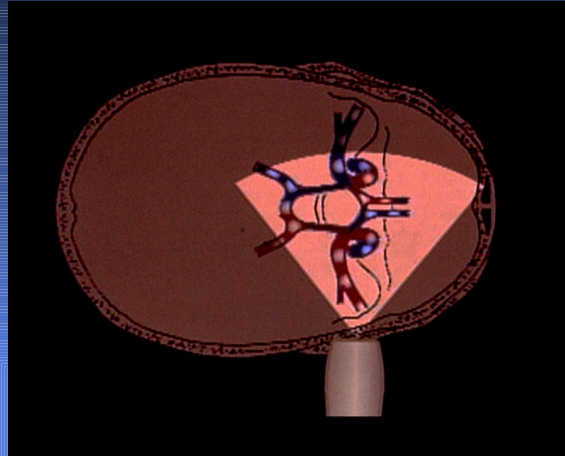
Associated with:

PFO in 83% vs. 28% in control

Intense R-L shunt in 55% vs. 12% in control

ASA in 24% - Schneider JACC '95

TCD with Contrast Injection



Diagnostic Tests for PFO Detection

<u>Study</u>	<u>N</u>	<u>TT Echo</u>	<u>TCD</u>	<u>TE Echo</u>
<u>Teague</u> (Stroke, 1991)	46	26%	41%	----
<u>Di Tullio</u> (Int J Card, 1993)	80	18%	26%	----
<u>Karnik</u> (Am J Card, 1992)	36	----	36%	42%
<u>Jauss</u> (Stroke, 1994)	50	----	28%	30%
<u>Job</u> (Am J Card, 1994)	137	----	42%	47%
<u>Nemec</u> (Am J Card, 1991)	32	23%	41%	41%
<u>Di Tullio</u> (Stroke, 1993)	49	18%	27%	38%
		<u>20%</u> (42/207)	<u>35%</u> (151/430)	<u>41%</u> (126/304)

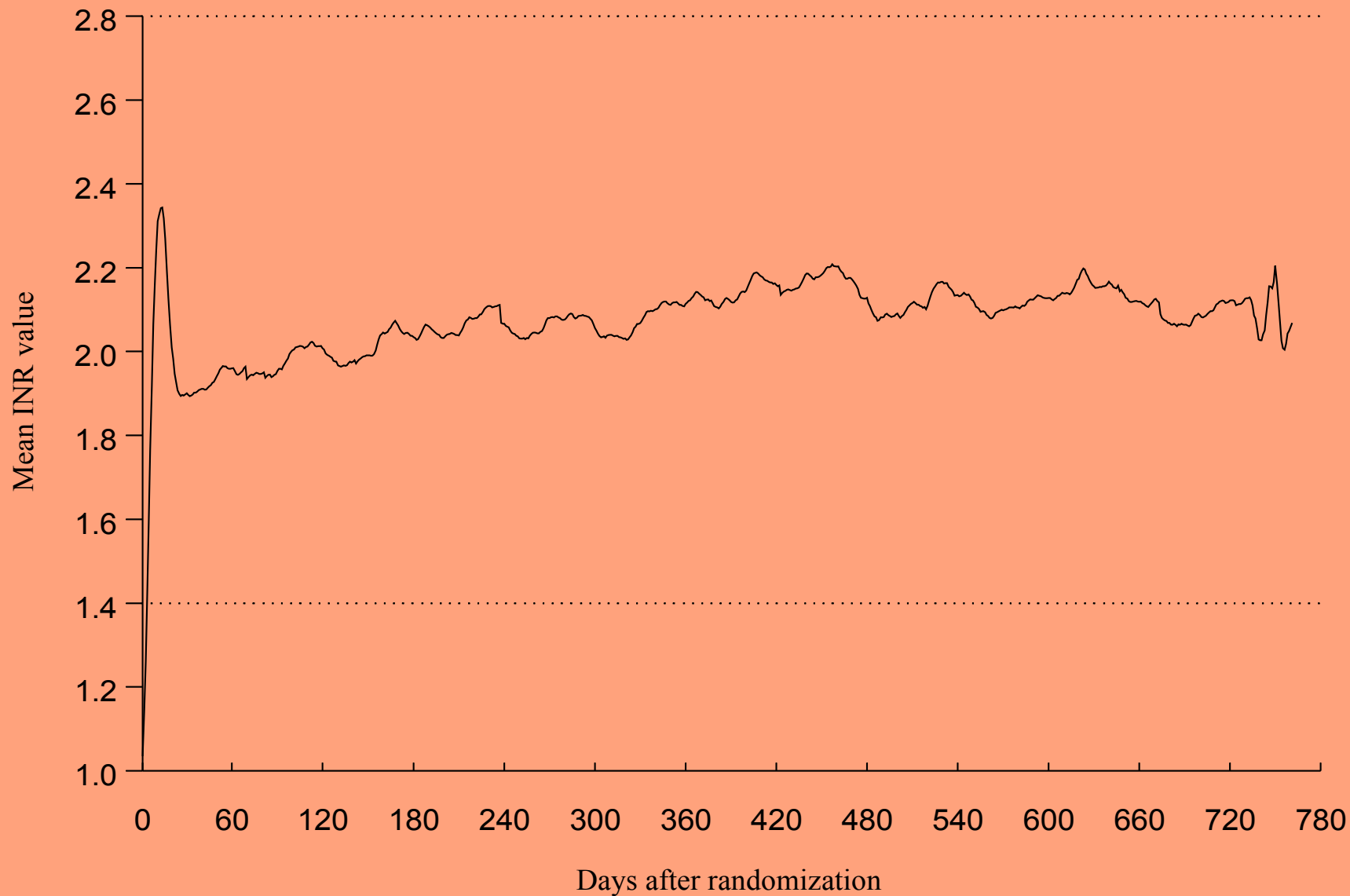
Treatment Blinding 2

- ***Real or fabricated INR reported to each center***
 - ***Fabricated used computer program which took into account changes in doses made at previous report***
- ***Emergency calls made for dangerously high INRs, both for real and fabricated one***
- ***All clinical centers blinded***

INR

- ***49,000 INRs sent/processed at a single laboratory***
- ***Mean interval between blood draws, 28 days***
- ***Mean daily INR 2.07 (median 1.93)***
- ***No difference in INR amongst different stroke subtypes***

Mean INR Value by Day of On-therapy Followup for Warfarin Patients



Auditing / Monitoring

- ***Audits for endpoints at each center by DMC staff***
- ***NIH mandated Performance and Safety Monitoring Board (PSMB) met every 6-12 months***
- ***Outside auditing process of conduct at Columbia by independent firm reporting to NIH directly***

TE Quality Assurance

- ***Test TE studies from each center sent to Columbia for certification***
- ***Central reading of all TE's***
- ***Interpretation by a single cardiologist blinded to all end-points***

PICSS: End-point Adjudication

- ***All endpoints (recurrent stroke or death) confirmed by a panel of 5 blinded neurologists***

Follow-up

- ***Monthly telephone calls***
- ***Quarterly in-person visits***

CT/MRI Brain Imaging Finding and PFO Size

- ***Superficial infarction consistent with embolic events more frequent in patients with larger PFOs***

50% vs. 21% $p=0.02$

Steiner, Stroke 1998

2.5MHZ-M
26 MAR 92
13:50:09
PROC 2/0/C
COLUMBIA PRES. HOS
RM #948

RV

LV

RA

LA

24444:25
50MM/S
XMIT:A
92BPM
20CM
27HZ



IVC Interruption

- ***Greenfield filter - 3 mm diameter thrombus can pass (Dalman 1989)***
- ***IVC ligation - lower extremities edema development of collaterals***

***PICSS:
Relationship of PFO with
Cryptogenic Stroke***

	<i>Cryptogenic (N=250)</i>	<i>Non-Cryptogenic (N=351)</i>	<i>P Value</i>
<i>PFO Prev.</i>	<i>39.2% (98/250)</i>	<i>29.9% (105/351)</i>	<i><0.001</i>

***PICSS:
PFO Size/Shunt in Cryptogenic and
Non-Cryptogenic Patients***

	<i>Cryptogenic (N=250)</i>	<i>Non-Cryptogenic (N=351)</i>
<i><u>Large PFO</u></i>	<i>20.0% (50/250)</i>	<i>9.7% (34/351)</i>

P<0.001

PICSS: Findings

- ***PFO is associated with cryptogenic stroke.***
- ***Large PFOs are associated with cryptogenic stroke.***

PICSS: Findings

- *ASA is associated with PFO*
- *ASA is associated with large PFO*
- *Association of stroke with ASA may derive from the frequent finding of large PFOs*

Homma, JACC in press

PICSS: Enrollment

- ***Cryptogenic stroke patients enrolled in WARSS solicited to undergo TE***
- ***TE studies of WARSS patients undergoing TE for clinical purposes***
- ***All stroke subtyped using defined criteria***
- ***All TE studies sent to Columbia for centralized analysis***

Treatment Blinding 1

- ***All patients received warfarin and placebo aspirin, OR aspirin and placebo warfarin***
- ***All patients underwent blood draw at regular intervals***
- ***All blood samples were centrally analyzed and results reported to Columbia (Data Management Center)***

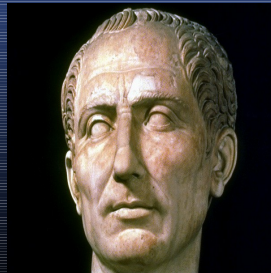
PICSS: Treatment Assignment

	<i>WARFARIN</i>	<i>ASPIRIN</i>
<i>TOTAL (N=630)</i>	<i>49.5% (312/630)</i>	<i>50.5% (318/630)</i>
<i>CRYPTOGENIC (N=265)</i>	<i>47.2% (125/265)</i>	<i>52.8% (140/265)</i>
<i>NON- CRYPTOGENIC (N=365)</i>	<i>51.2% (187/365)</i>	<i>48.8% (178/365)</i>

P=0.56

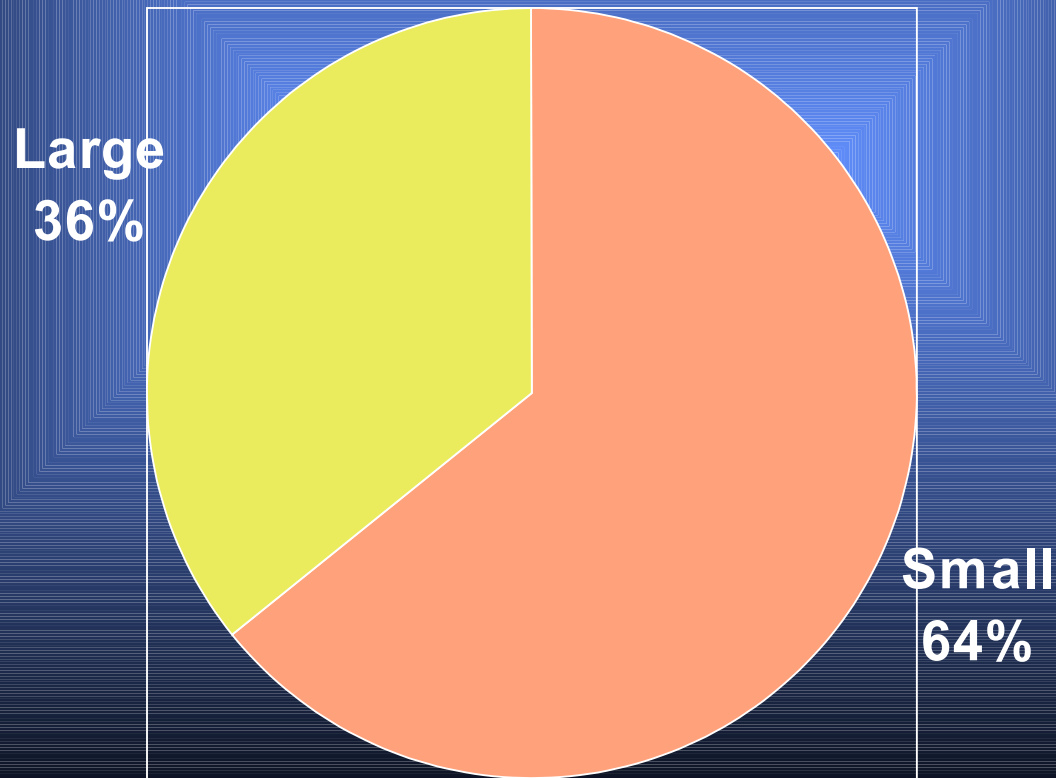
Future Direction

- ***Need for a well-designed randomized trial to determine the role of device therapy, compared with medical therapy***
- ***But difficulty in trial design***
 - ***Age of patients – low event rate in young***
 - » ***Large # of patients needed***
 - ***Patient preference***
 - » ***Difficulty randomizing***
 - ***Device placebo effect***
 - ***Therapy follows “standard of practice”***
 - » ***Oculo-motor reflex Commercial interests***
- ***Primum non-necere***

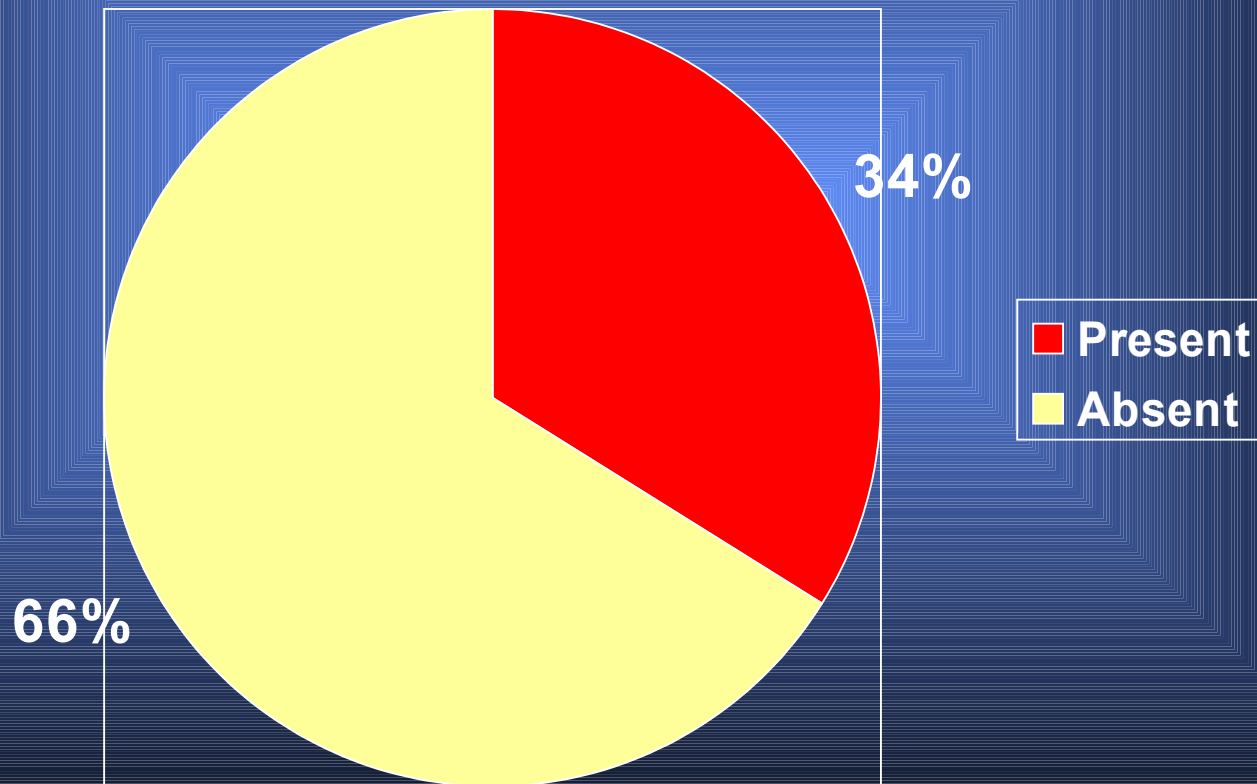


PICSS: PFO Size

- ***Small (N=119) : < 2 mm or 1 to 9 bubbles***
- ***Large (N=84) : ≥ 2 mm or ≥ 10 bubbles***



***PICSS:
PFO Prevalence
203/601 (34%)***



Surgical Closure

- ***Harvey*** (*Ann Int Med* 1986)
4 patients with 7-21 months F/U - No recurrence
 - ***Zhu*** (*Circulation* 1992 abst)
6 patients with 1-10 year F/U - 2 events (1stroke, 1 TIA)
 - ***Devuyst*** (*Nerurology* 1996)
30 patients with 2 years F/U - No recurrence
 - ***Dearani*** (*JACC* 1996 abst)
24 patients with 2.9 yrs F/U - 1 recurrence
 - ***Homma*** (*Stroke* 1997)
28 patients with 19 months F/U - 4 recurrences
- ✎ **92 cases - 7 recurrences with variable F/U**

PICCS: Overall Event Rates

- ***Multivariate Analysis***
- ***Adjustment for unevenly distributed factors***
 - ***Age***
 - ***Marital status***
 - ***Sedentary life-style***
 - ***Diabetes***
 - ***Hypertension***
 - ***Galsgow Score***
 - ***Alcohol consumption***
- ***P = 0.36 (RR =1.24, 95% CI = 0.79-1.95)***

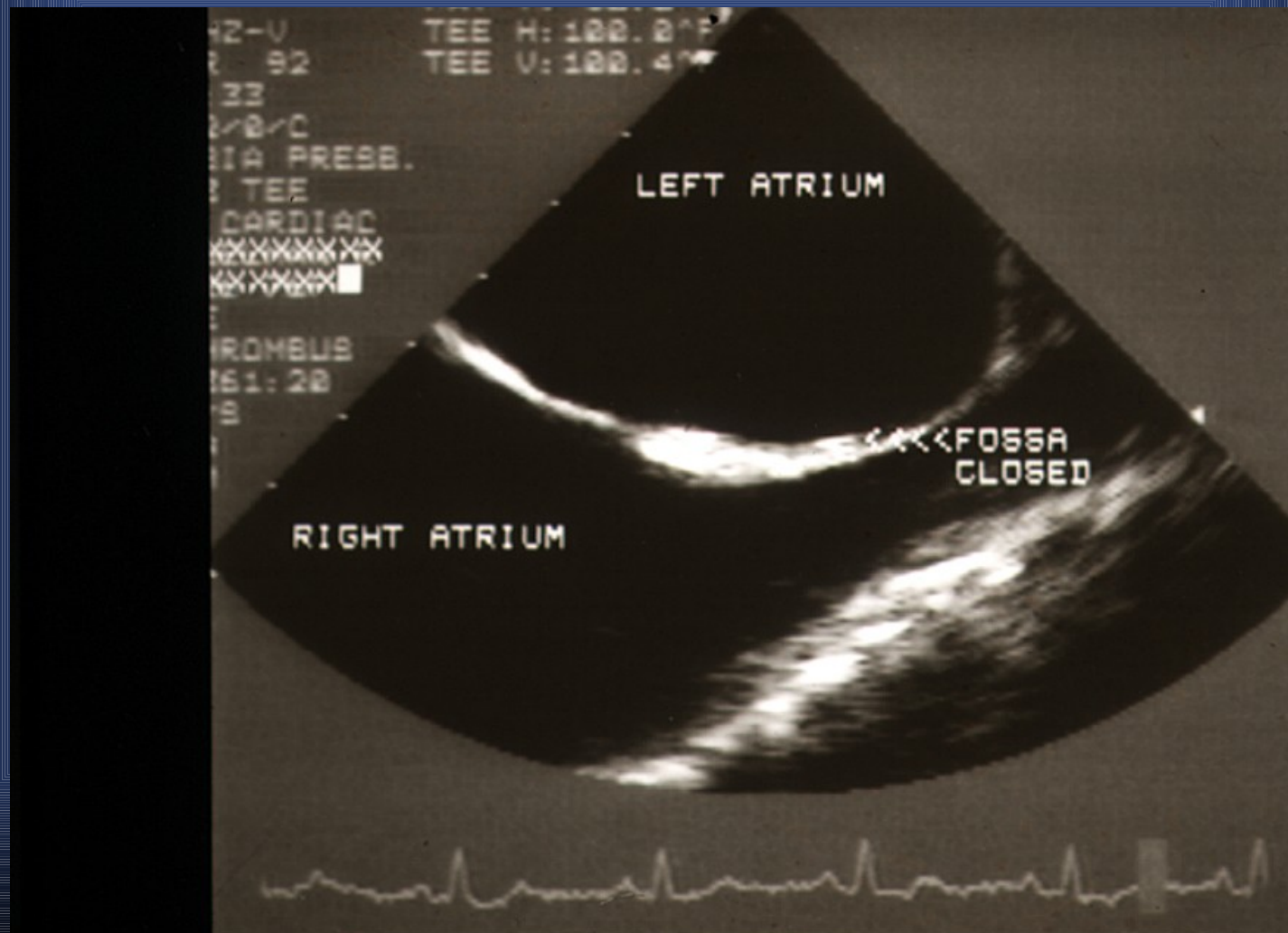
WARRS

(Warfarin Aspirin Recurrent Stroke Study)

- ***Double-blind, randomized, multicenter trial (48 centers in the U.S.)***
- ***Warfarin (INR 1.4-2.8) vs Aspirin (325 mg/day)***
- ***Primary Endpoint: Recurrent Ischemic Stroke or Death***
- ***Recruitment from 06/1993 – 06/2000***

Mohr JP, N Engl J Med 2001

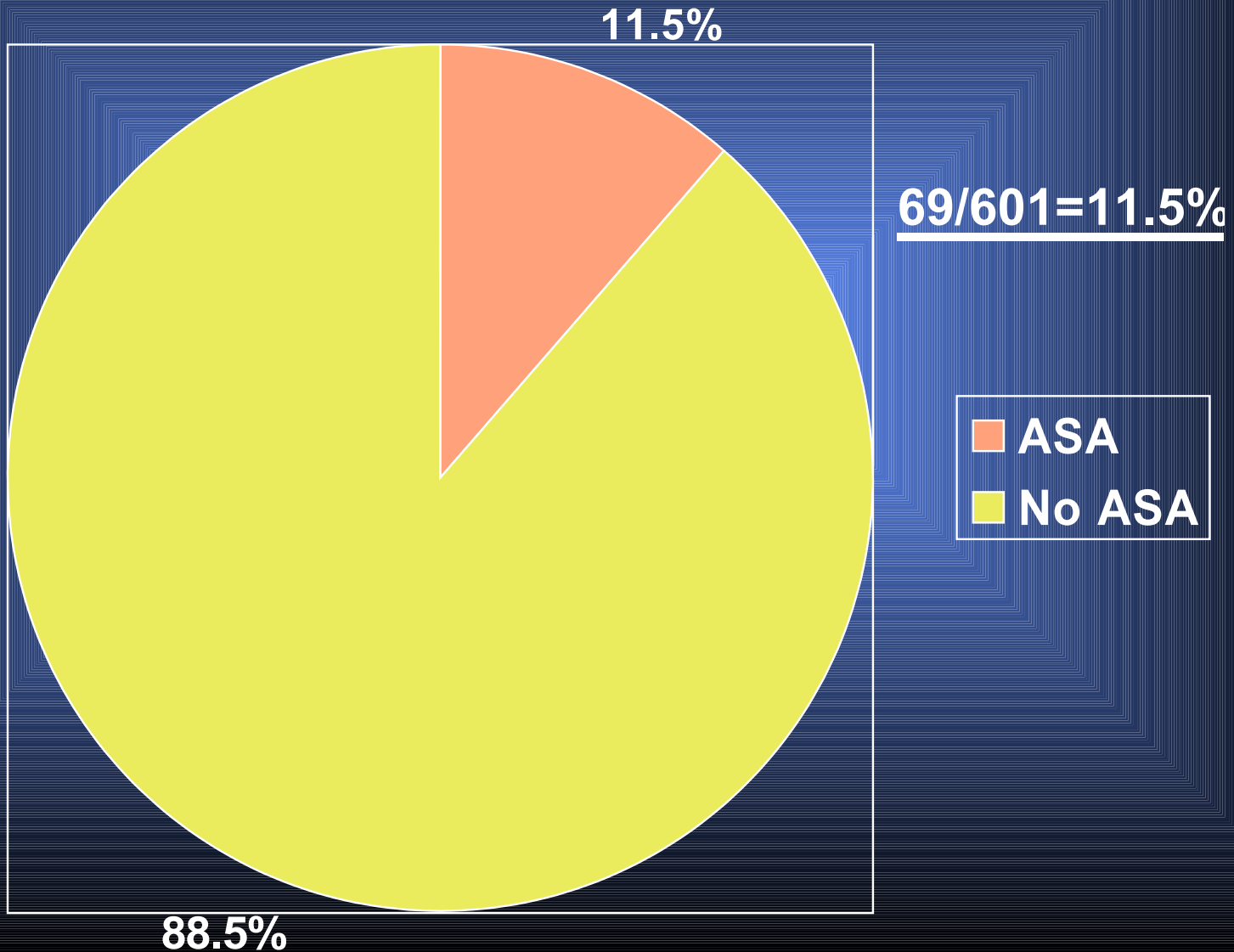
Fossa Ovalis



PFO Characteristics

- **Webster** (*Lancet* 1988)
On TT, cryptogenic stroke patients had larger shunt
- **Bridges** (*Circulation* 1992)
During transcatheter closure, the size of PFO was significantly larger than reported at autopsy
- **Van Camp** (*Am J Cardiol* 1993)
On TE, early and “massive” passage of contrast into left atrium in stroke patients
- **Homma** (*Stroke* 1994)
On TE, larger PFO with more shunt in cryptogenic stroke patients

PICSS: ASA Prevalence



PICSS:
Outcome by PFO Size/Shunt
Either on Warfarin or Aspirin

	<i>NO PFO (N=398)</i>	<i>SMALL PFO (N=119)</i>	<i>LARGE PFO (N=84)</i>
<i>EVENT RATE</i>	<i>15.6% (62/398)</i>	<i>18.5% (22/119)</i>	<i>9.5% (8/84)</i>

P=0.41, RR with small PFO = 1.23
P=0.16, RR with large PFO = 0.59

Sacco RL, Di Tullio MR, Homma S. Treatment of Patent Foramen Ovale and Stroke: to Close or Not to Close, That is Not Yet the Question

***European Neurology* 1997;37:205-6.**

RECURRENCE PREVENTION

- ***IVC occlusion ?***
- ***Surgical Closure ?***
- ***Device Closure ?***
- ***Medical therapy ?***
 - ***Warfarin***
 - ***Aspirin***
 - ***Other antiplatelet agent***

Relationship of Cryptogenic Stroke with PFO in Older Patients

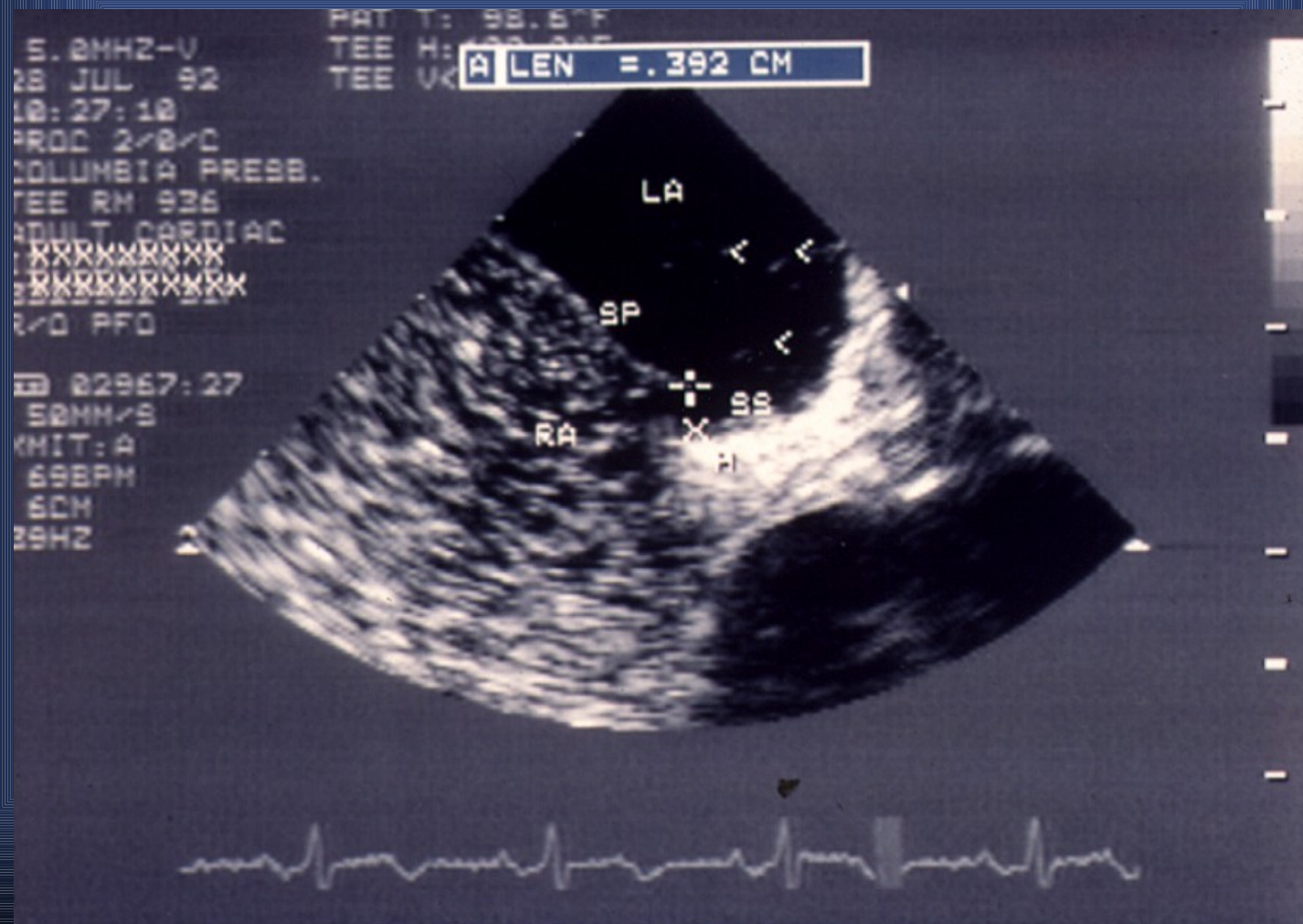
<i>Study</i>	<i>N</i>	<i>Age</i>	<i>PFO (Crypto)</i>	<i>PFO (Control)</i>	<i>p</i>
<i>Di Tullio</i> <i>(Ann Int Med, 1992)</i>	<i>24</i>	<i>≥55</i>	<i>38%</i>	<i>8%</i>	<i><0.001</i>
<i>de Belder</i> <i>(Am J Card, 1992)</i>	<i>64</i>	<i>>55</i>	<i>20%</i>	<i>5%</i>	<i><0.001</i>
<i>Hausmann</i> <i>(Am J Card, 1992)</i>	<i>20</i>	<i>≥40</i>	<i>15%</i>	<i>24%</i>	<i>NS</i>
<i>Jones</i> <i>(Am J Card, 1994)</i>	<i>57</i>	<i>≥50</i>	<i>18%</i>	<i>16%</i>	<i>NS</i>
<hr/>					
			<i><u>21%</u> (35/165)</i>	<i><u>16%</u> (86/530)</i>	

Medical Therapy: Meta-Analysis

- ***12 studies with information on medically treated cryptogenic stroke patients***
 - *1,108 patients*
 - *Mean age, 45 years*
 - *Mean F/U, 34 months*
- ***Annual Event Rate (95% CI)***
 - *Stroke/Death* ***3.12% (2.32-4.11)***
 - *Stroke/Death/TIA* ***4.86% (3.78-5.94)***

Homma, Acta Med Croat 2003

PFO on TE



Patient Selection

- ***280 million population***
- ***26% with PFO – 73 million with PFO***
- ***800,000 strokes***
 - ***40% cryptogenic – 320,000***
 - ***40% with PFO – 128,000***
- ***Then 128,000 of 73 million or 0.17% of those with PFO potentially end up with stroke on a yearly basis***

Patients needed to show superiority of closure

- ***COLLECTIVE FIGURE WITH MEDICAL THERAPY***
 - 3.12% S/D, 4.86% S/D/T
- ***COMPARED TO CLOSURE THERAPY***
 - 2.0% S/D, 4.0% S/D/T
 - » ***For S/D in 2 year study***
 - 1,689 in each group
 - » ***For S/D/T in 2 year study***
 - 4,282 in each group
 - 1.0% S/D, 2.0% S/D/T
 - » ***For S/D in 2 year study***
 - 339 in each group
 - » ***For S/D/T in 2 year study***
 - 313 in each group

IMPORTANCE OF AGE

- ***Mean Age***
 - ***59.7 ± 12.2 yrs (range 30-85)***

PICSS

(PFO in Cryptogenic Stroke Study)

- ***Compared the rates of recurrent stroke or death in patients with PFO to that in patients without PFO while on medical therapy (either warfarin or aspirin)***
- ***Compared the event rates in warfarin treated patients with PFO to that in aspirin treated patients with PFO***

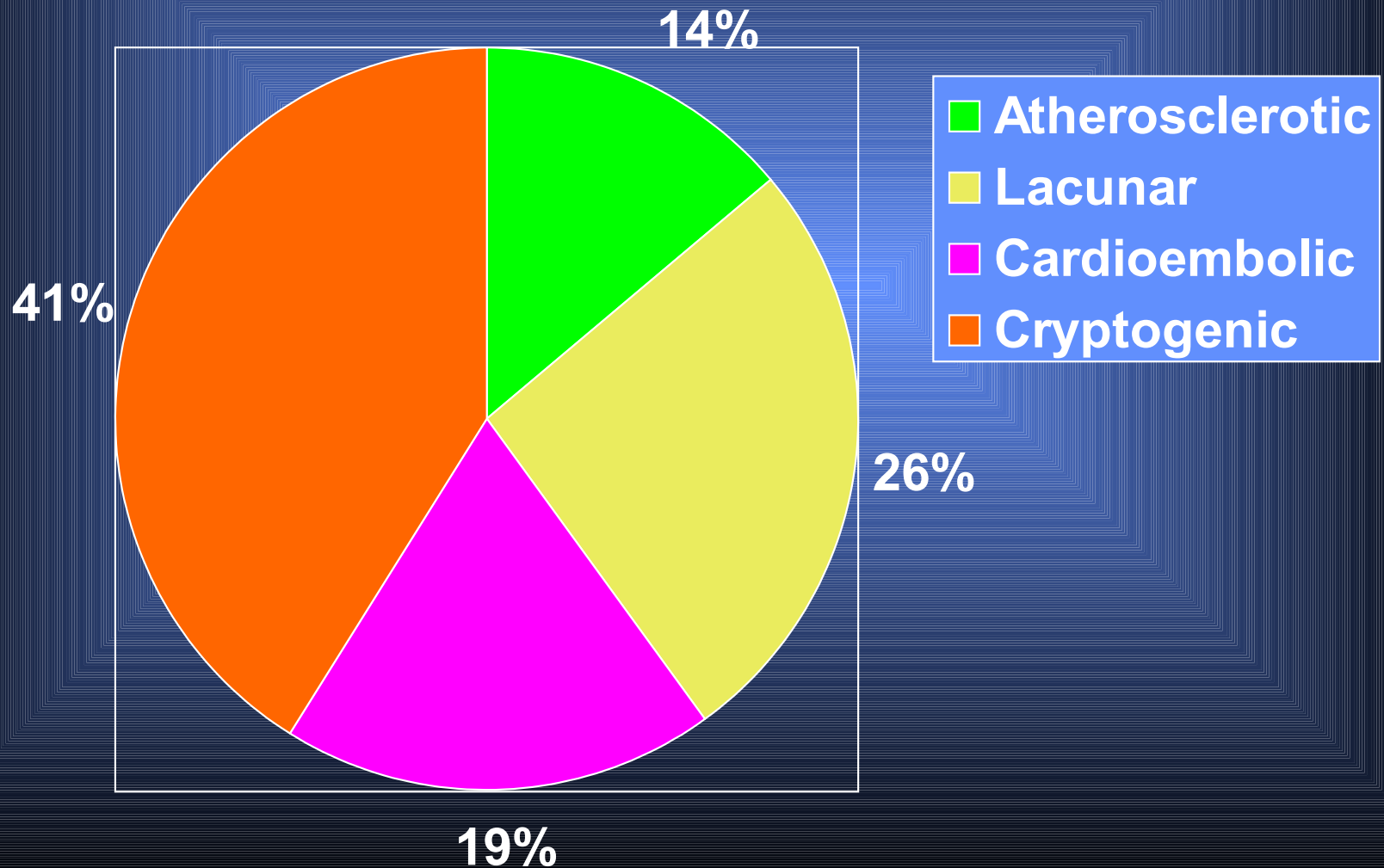
Homma, Circ 2002

Relationship of Cryptogenic Stroke with PFO in Younger Patients

<i>Study</i>	<i>N</i>	<i>Age</i>	<i>PFO (Crypto)</i>	<i>PFO (Control)</i>	<i>p</i>
<i>Lechat</i> <i>(NEJM, 1988)</i>	<i>26</i>	<i><55</i>	<i>54%</i>	<i>10%</i>	<i><0.001</i>
<i>Webster</i> <i>(Lancet, 1988)</i>	<i>34</i>	<i><40</i>	<i>56%</i>	<i>15%</i>	<i><0.001</i>
<i>Di Tullio</i> <i>(Ann Int Med, 1992)</i>	<i>21</i>	<i><55</i>	<i>47%</i>	<i>4%</i>	<i><0.001</i>
<i>Cabanes</i> <i>(Stroke, 1993)</i>	<i>64</i>	<i><55</i>	<i>56%</i>	<i>18%</i>	<i><0.0001</i>
<i>Hausmann</i> <i>(Am J Card,)</i>	<i>18</i>	<i><40</i>	<i>50%</i>	<i>11%</i>	<i><0.05</i>
<i>Jones</i> <i>(Am J Card, 1994)</i>	<i>14</i>	<i><50</i>	<i>29%</i>	<i>11%</i>	<i>NS</i>

53% (93/177) 12% (30/251)

Frequency Distribution of Ischemic Stroke Subtypes: Stroke Data Bank



Stroke Statistics in the U.S.

- ***800,000 new strokes a year***
- ***2 million stroke survivors***

Medical Therapy

- ***Warfarin***
- ***Aspirin***
- ***Plavix (clopidogrel)***
- ***Aggrenox (aspirin / dipyridamole)***

Autopsy PFO Prevalence

<i>Author</i>	<i>N</i>	<i>Prevalence</i>
<i>Parsons (1897)</i>	<i>399</i>	<i>26%</i>
<i>Fawcett (1900)</i>	<i>306</i>	<i>32%</i>
<i>Scammon (1918)</i>	<i>1809</i>	<i>29%</i>
<i>Patten (1931)</i>	<i>4083</i>	<i>25%</i>
<i>Seib (1934)</i>	<i>500</i>	<i>17%</i>
<i>Wright (1948)</i>	<i>492</i>	<i>23%</i>
<i>Schroeckenstein (1972)</i>	<i>144</i>	<i>35%</i>
<i>Sweenwy (1979)</i>	<i>64</i>	<i>31%</i>
<i>Hagen (1984)</i>	<i>965</i>	<i>27%</i>
<i>Thompson (1984)</i>	<i>1000</i>	<i>29%</i>
<i>Penther (1994)</i>	<i>500</i>	<i>15%</i>
	<u><i>10262</i></u>	<u><i>26%</i></u>

U.S !

i.e. 70 million people in

Devices



PICSS:

Efficacy of Warfarin vs. Aspirin

	<i>WARFARIN</i>	<i>ASPIRIN</i>	<i>RR (95%CI)</i>	<i>P- value</i>
<i>ENTIRE PICSS COHORT</i>				
With PFO (N=203)	9.32% (N=97)	7.17% (N=106)	1.29 (0.63-2.64)	0.84
No PFO (N=398)	7.59% (N=195)	9.57% (N=203)	0.80 (0.49-1.33)	0.40
<i>CRYPTOGENIC COHORT</i>				
With PFO (N=98)	5.13% (N=42)	10.20% (N=56)	0.52 (0.16-1.67)	0.28
No PFO (N=152)	4.39% (N=72)	9.06% (N=80)	0.50 (0.19-1.31)	0.16

Anatomy of PFO

