Foramen Oval Perméable: Fermer ou ne Pas Fermer, Là Est la Question…

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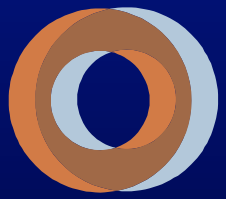


INSTITUT UNIVERSITAIRE
DE CARDIOLOGIE
ET DE PNEUMOLOGIE
DE QUÉBEC

SSVQ 2014
Montréal, Septembre 2014

Divulgation de conflits d'intérêts potentiels

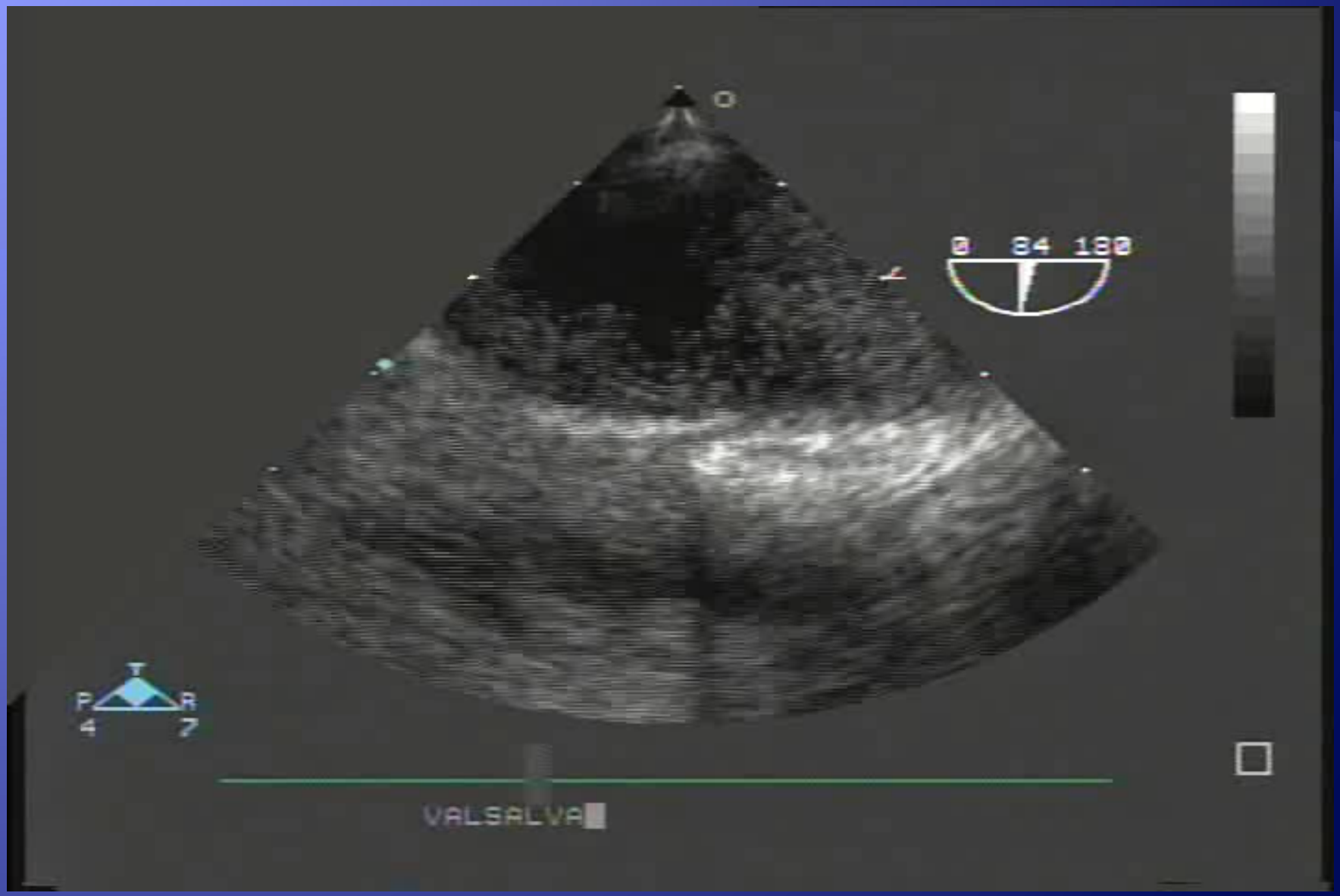
Société des sciences vasculaires du Québec (SSVQ)

Journée d'Actualités en sciences vasculaires

22 novembre 2013

Dr Josep Rodés-Cabau, Conférencier

Research Grant	St-Jude Medical	2013
Research Grant	Boston Scientific	2011-2013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VALSALVA

PFO – Cryptogenic Stroke

Study	Stroke n/N	Control n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Cabanes, 1993 (P)	43 / 100	9 / 50		13.8	3.44[1.51,7.83]
Chen, 1991 (P)	15 / 34	7 / 40		7.2	3.72[1.29,10.74]
Del Sette, 1998 (P)	26 / 73	8 / 50		12.3	2.90[1.19,7.11]
Job, 1994 (P)	38 / 74	27 / 63		28.6	1.41[0.72,2.77]
Jones, 1994 (P)	7 / 26	2 / 19		3.4	3.13[0.57,17.18]
Lechat, 1988 (P)	24 / 60	10 / 100		9.1	6.00[2.61,13.80]
Webster, 1988 (P)	20 / 40	6 / 40		6.0	5.67[1.95,16.46]
Zahn, 1995 (P)	50 / 120	11 / 55		17.7	2.86[1.34,6.07]
de Belder,1992 (P)	5 / 39	1 / 39		1.8	5.59[0.62,50.25]
Total(95%CI)	228 / 566	81 / 456		100.0	3.10[2.29,4.21]
Chi-square 9.40 (df=8) P: 0.31					

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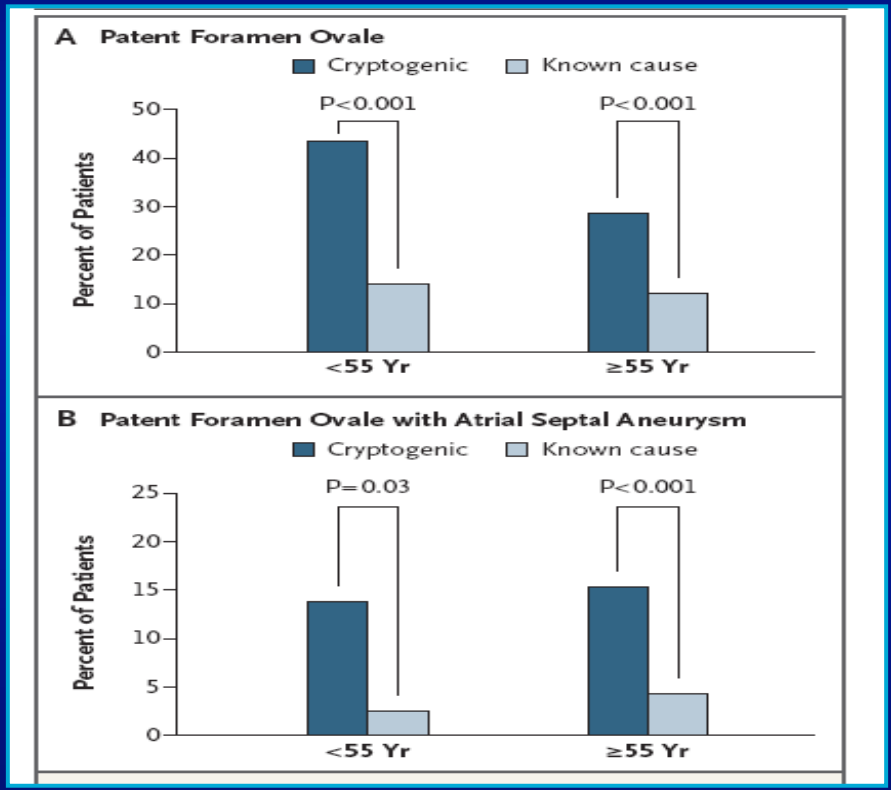
Negative association Positive association

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

Cryptogenic Stroke in Older Patients



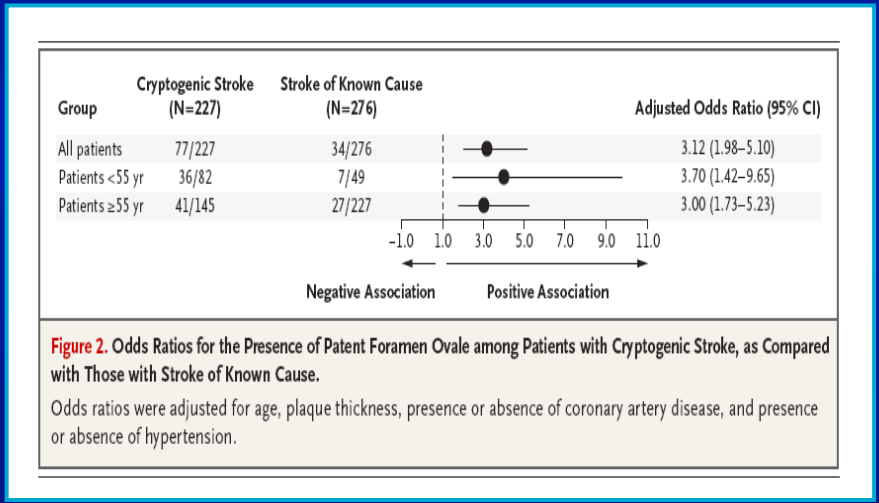
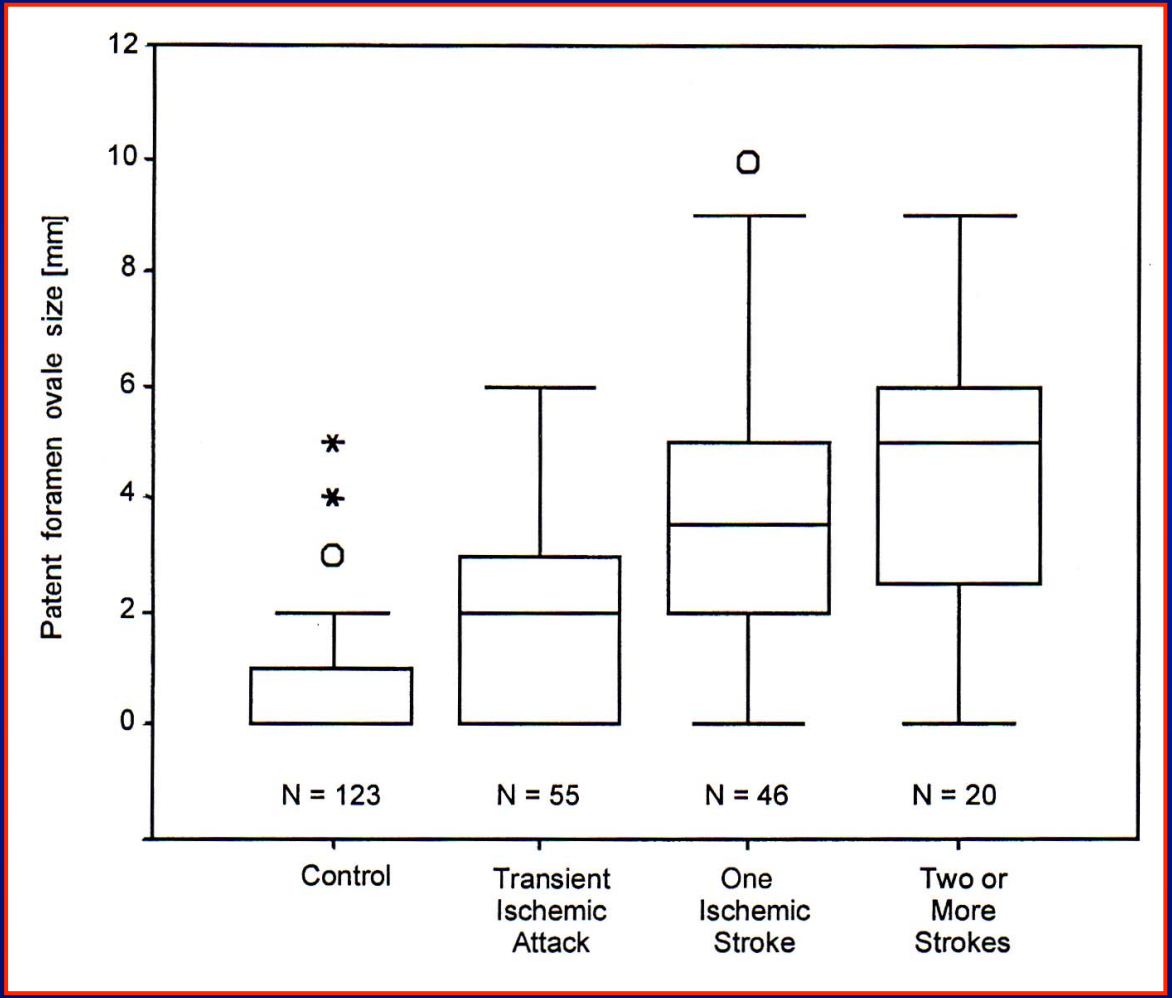


Figure 2. Odds Ratios for the Presence of Patent Foramen Ovale among Patients with Cryptogenic Stroke, as Compared with Those with Stroke of Known Cause.

Odds ratios were adjusted for age, plaque thickness, presence or absence of coronary artery disease, and presence or absence of hypertension.

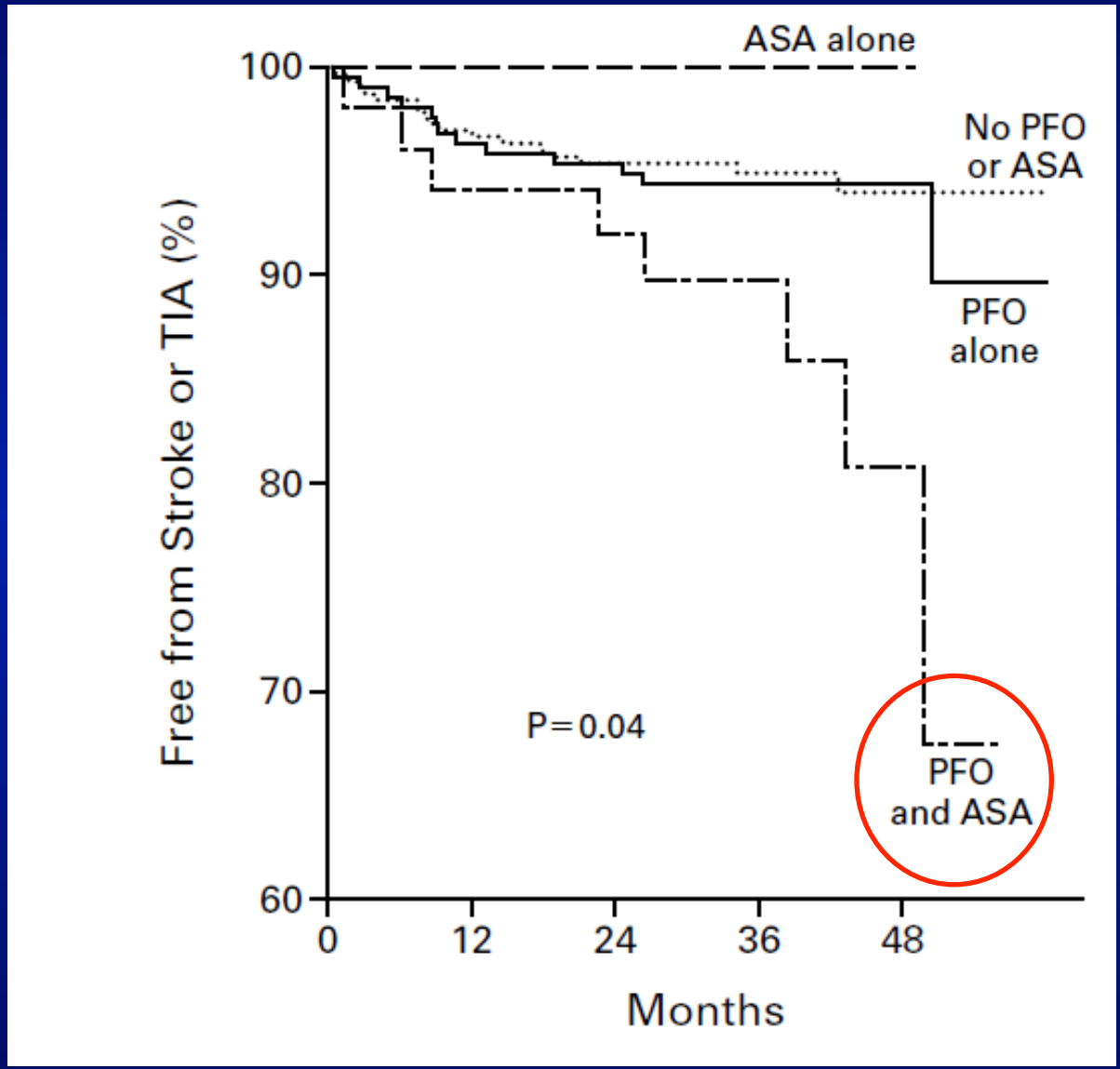
Handke et al. N Engl J Med 2007

PFO Diameter – Number of Events



Schuchlenz et al. Am J Med 2000;109:456-62

PFO and Atrial Septal Anevrysm



Mas et al. N Engl J Med 2001

Atherosclerotic Burden Findings in Young Cryptogenic Stroke Patients With and Without a Patent Foramen Ovale

Josep Rodés-Cabau, MD, FESC; Martin Noël, PhD; Alier Marrero, MD; Donald Rivest, MD; Ariane Mackey, MD; Christine Houde, MD; Elizabeth Bédard, MD; Eric Larose, MD; Steve Verreault, MD; Marc Peticlerc, MD; Philippe Pibarot, PhD; Peter Bogaty, MD; Olivier F. Bertrand, MD, PhD

Background and Purpose—To further determine the mechanisms of cryptogenic stroke or transient ischemic attack in young patients, we evaluated indices of atherosclerosis in patients ≤55 years old diagnosed with cryptogenic cerebrovascular event comparing those with patent foramen ovale (PFO) with those without PFO.

Methods—This was a prospective study including 100 consecutive patients ≤55 years old (mean age, 45±8 years; 56 males) diagnosed with cryptogenic stroke/transient ischemic attack. PFO was identified in 59 of these patients with the use of transesophageal echocardiography with contrast study. The following surrogate markers of atherosclerosis were evaluated in all patients: carotid intima media thickness as measured by carotid ultrasonography and endothelial function as determined by brachial flow-mediated vasodilation. The same measurements were obtained in a control group of 50 age- and sex-matched control subjects.

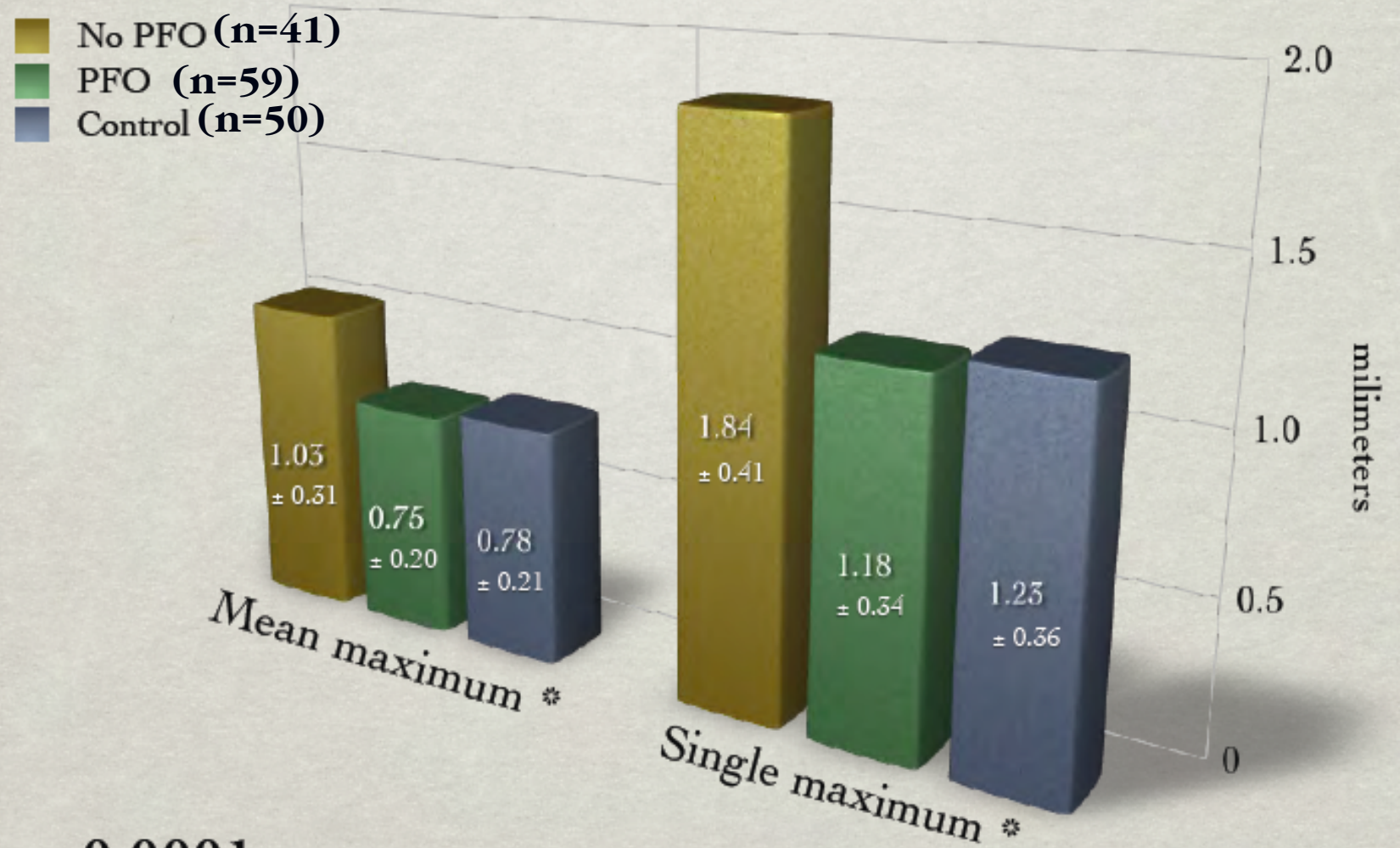
Results—Patients without PFO were more likely to be current smokers and obese and more frequently had a history of hypertension and dyslipidemia. Carotid intima media thickness measurements were higher ($P<0.0001$) in patients without PFO (1.03±0.31 mm) compared with those with PFO (0.75±0.20 mm) and control subjects (0.79±0.17 mm). The absence of PFO was also associated with lower brachial flow-mediated vasodilation (without PFO: 5.04±3.39%; with PFO: 7.16±4.09%; control subjects: 7.33±4.07%; $P=0.02$). There were no differences in carotid intima media thickness and flow-mediated vasodilation between patients with stroke/transient ischemic attack with PFO and control subjects. The presence of PFO was independently associated with reduced carotid intima media thickness ($P<0.0001$) and increased flow-mediated vasodilation ($P=0.019$).

Conclusions—In patients ≤55 years old diagnosed with cryptogenic stroke/transient ischemic attack, the presence of PFO was associated with a lower atherosclerotic burden as measured by carotid intima media thickness and endothelial function with no differences compared with a control group without cerebrovascular event. These results suggest that an atherosclerotic-mediated mechanism may be involved in cryptogenic stroke/transient ischemic attack in patients without PFO, whereas a nonatherosclerotic mechanism may mediate the cerebrovascular event in the presence of PFO. (***Stroke*. 2009;40:419-425.**)

Key Words: atherosclerosis ■ carotid arteries ■ patent foramen ovale ■ stroke

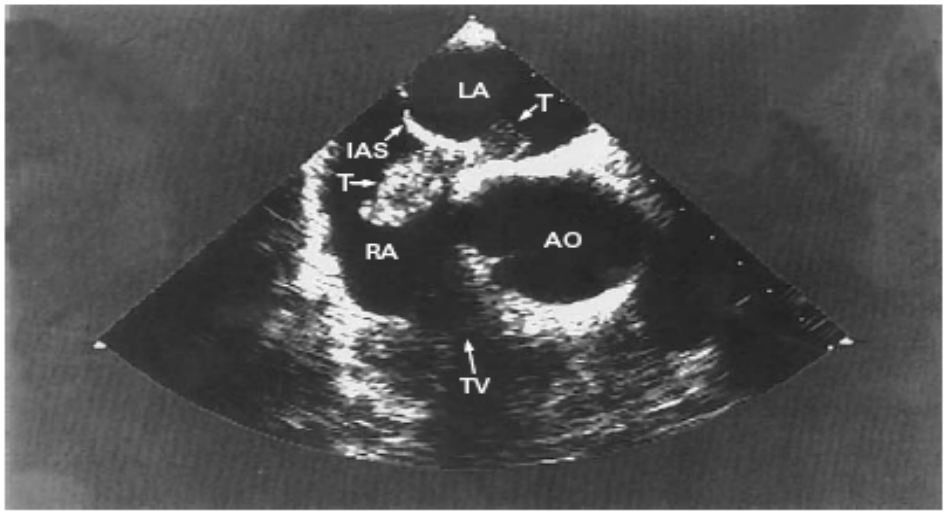
RESULTS
(CAROTID INTIMA-MEDIA THICKNESS)

Cryptogenic Stroke pts ≤55 yrs old (n=100)



* $p<0.0001$

Rodés-Cabau et al. Stroke 2009



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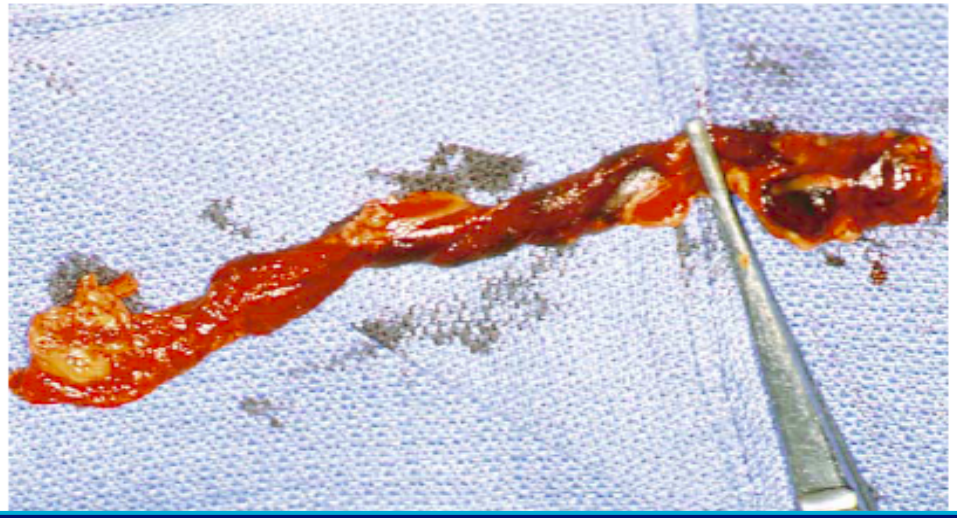


Srivastava et al. N Engl J Med 1997

Silent Cerebral Infarcts in Patients With Pulmonary Embolism and a Patent Foramen Ovale

A Prospective Diffusion-Weighted MRI Study

Marie-Rose Clergeau, MD; Michèle Hamon, MD; Rémy Morello, MD; Eric Saloux, MD; Fausto Viader, MD; Martial Hamon, MD, FESC

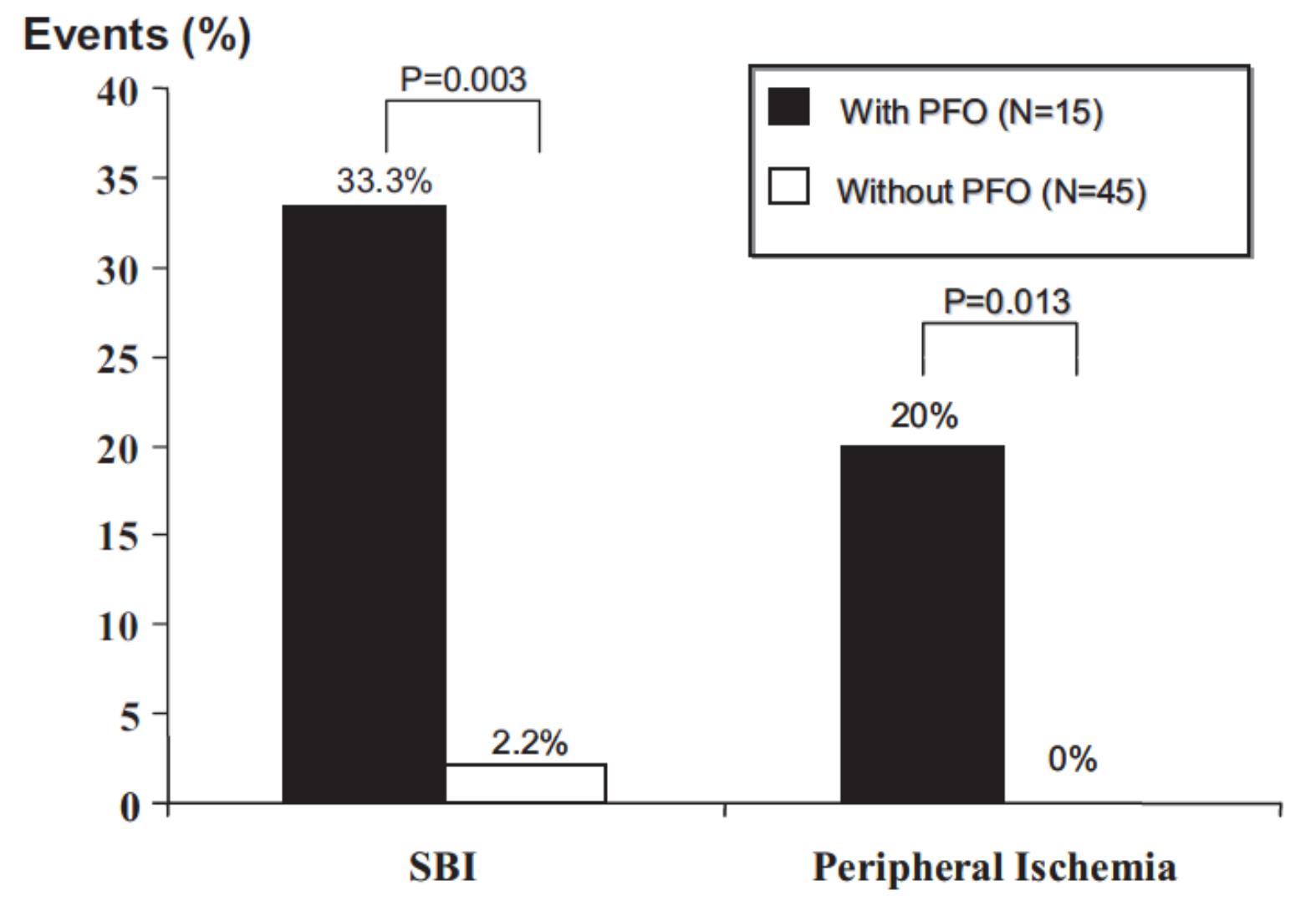
Background and Purpose—Pulmonary embolism is thought to be associated with a small but definite risk of paradoxical embolism in patients with a patent foramen ovale (PFO). Although neurological complications are infrequent, the incidence of clinically silent brain infarction is unknown. We assessed the rate of clinically apparent and silent cerebral embolism in patients with pulmonary embolism in relation to the presence or not of a PFO.

Methods—We used diffusion-weighted MRI in patients hospitalized for a pulmonary embolism to assess cerebral embolic events. Sixty consecutive patients were evaluated at diffusion-weighted MRI. All patients underwent neurological assessment before diffusion-weighted MRI and a contrast echocardiography to detect PFO the next day.

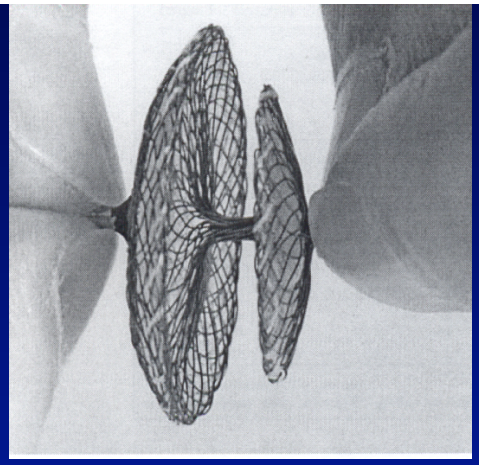
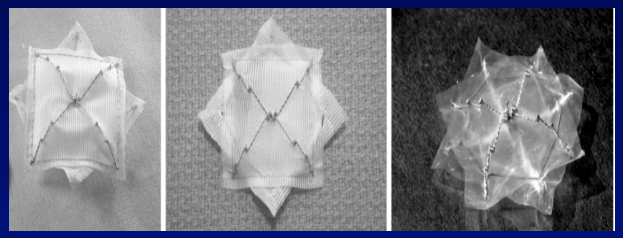
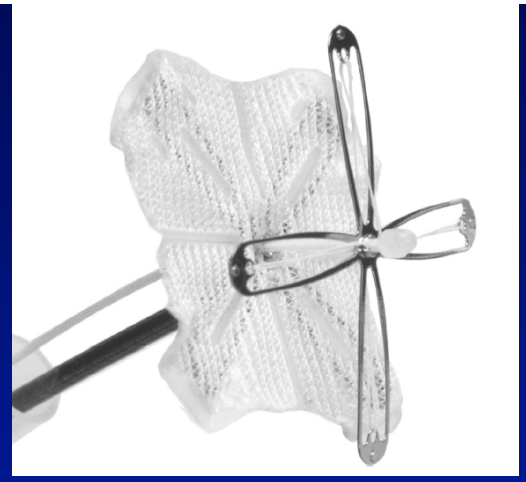
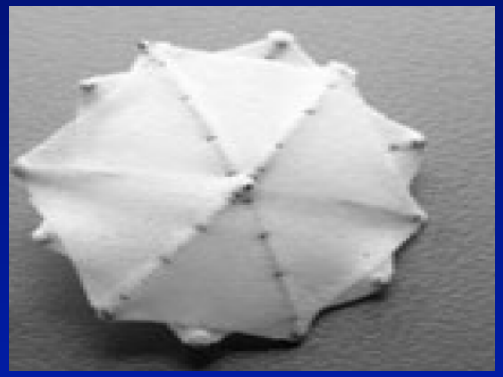
Results—Diffusion-weighted MRI showed bright lesions in 6 patients among the 60 consecutive patients with pulmonary embolism in a pattern consistent with embolic events. There was only one patient with a neurological deficit. After contrast echocardiography, a PFO was diagnosed in 15 patients (25%). The frequency of silent brain infarcts in patients with a PFO was significantly higher than in patients without PFO (5 [33.3%] of 15 versus one [2.2%] of 45 patients, $P=0.003$). By logistic regression analysis, PFO was identified as an independent predictor of silent brain infarcts (OR, 34.9 [3.1 to 394.3]; $P=0.004$).

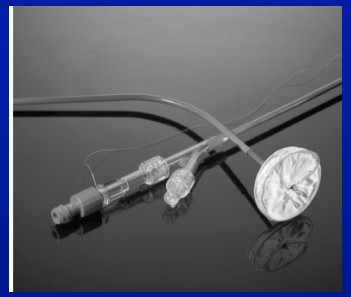
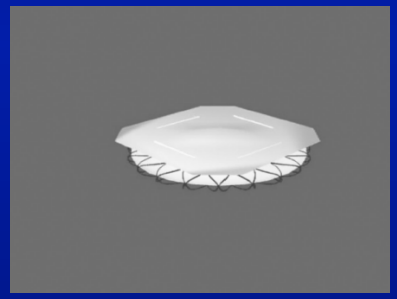
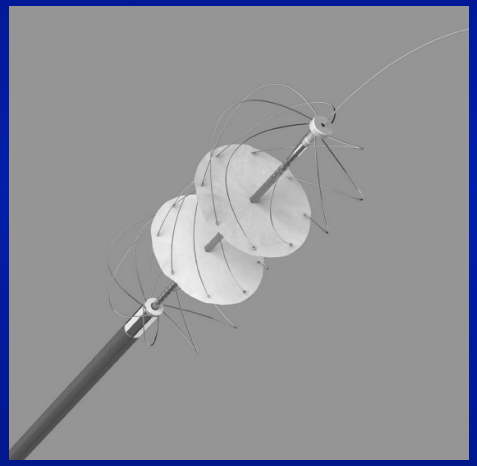
Conclusions—In pulmonary embolism, cerebral embolic events are more frequent than the apparent neurological complication rate. The prevalence of silent brain infarcts is closely related to the presence of a PFO suggesting a high incidence of unsuspected paradoxical emboli in those patients. (***Stroke*. 2009;40:3758-3762.**)

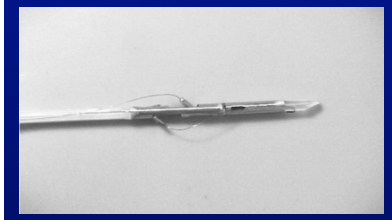
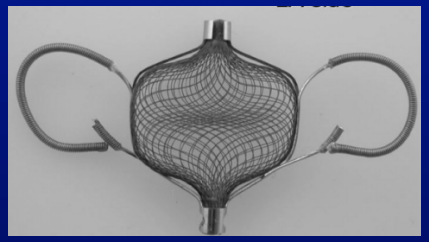
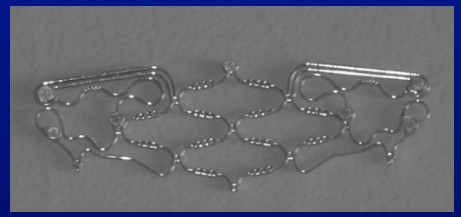
Key Words: embolic stroke ■ embolism ■ MRI ■ patent foramen ovale ■ pulmonary embolism



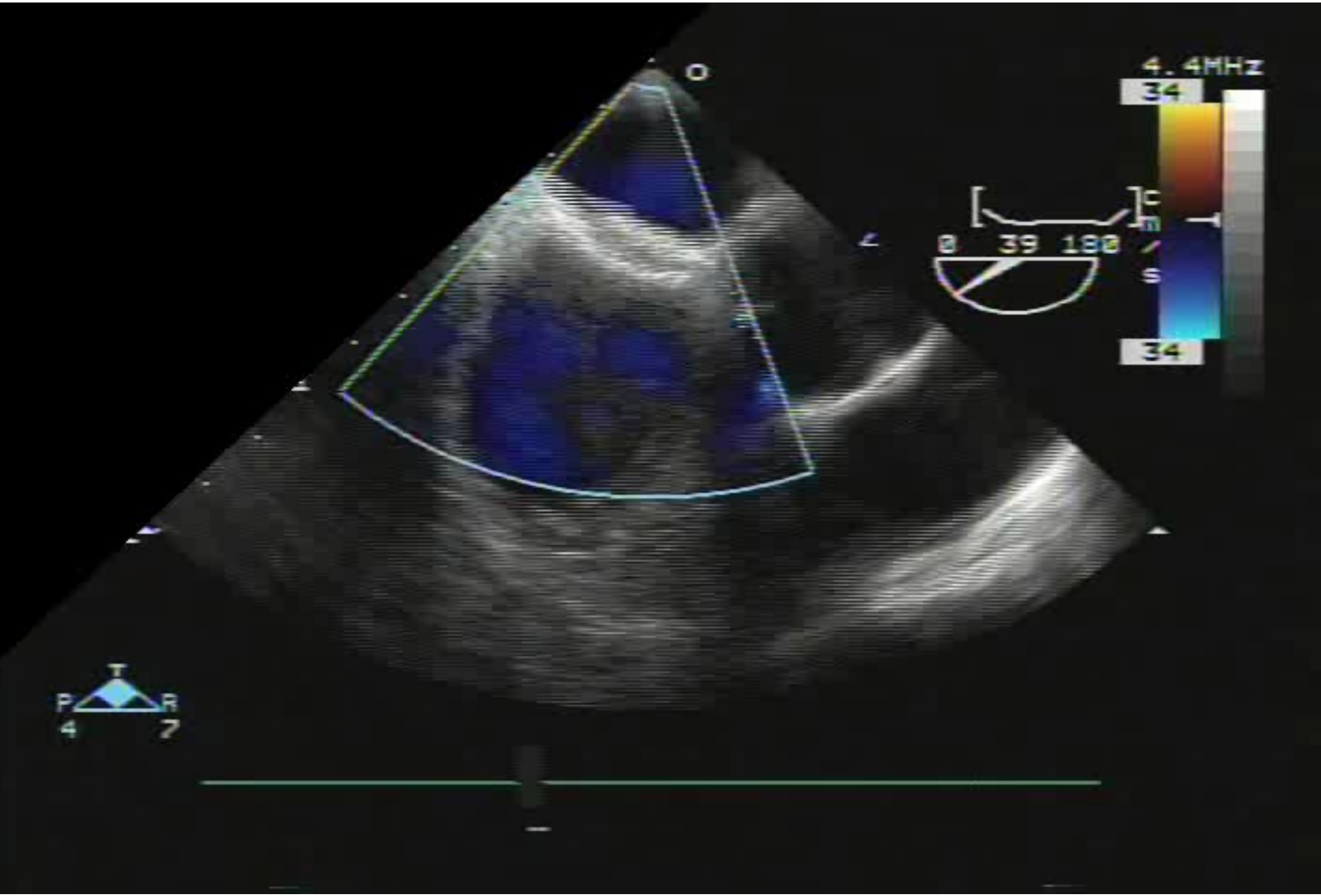
Clergeau et al. Stroke 2009

Majunke and Sievert. J Intervent Cardiol 2007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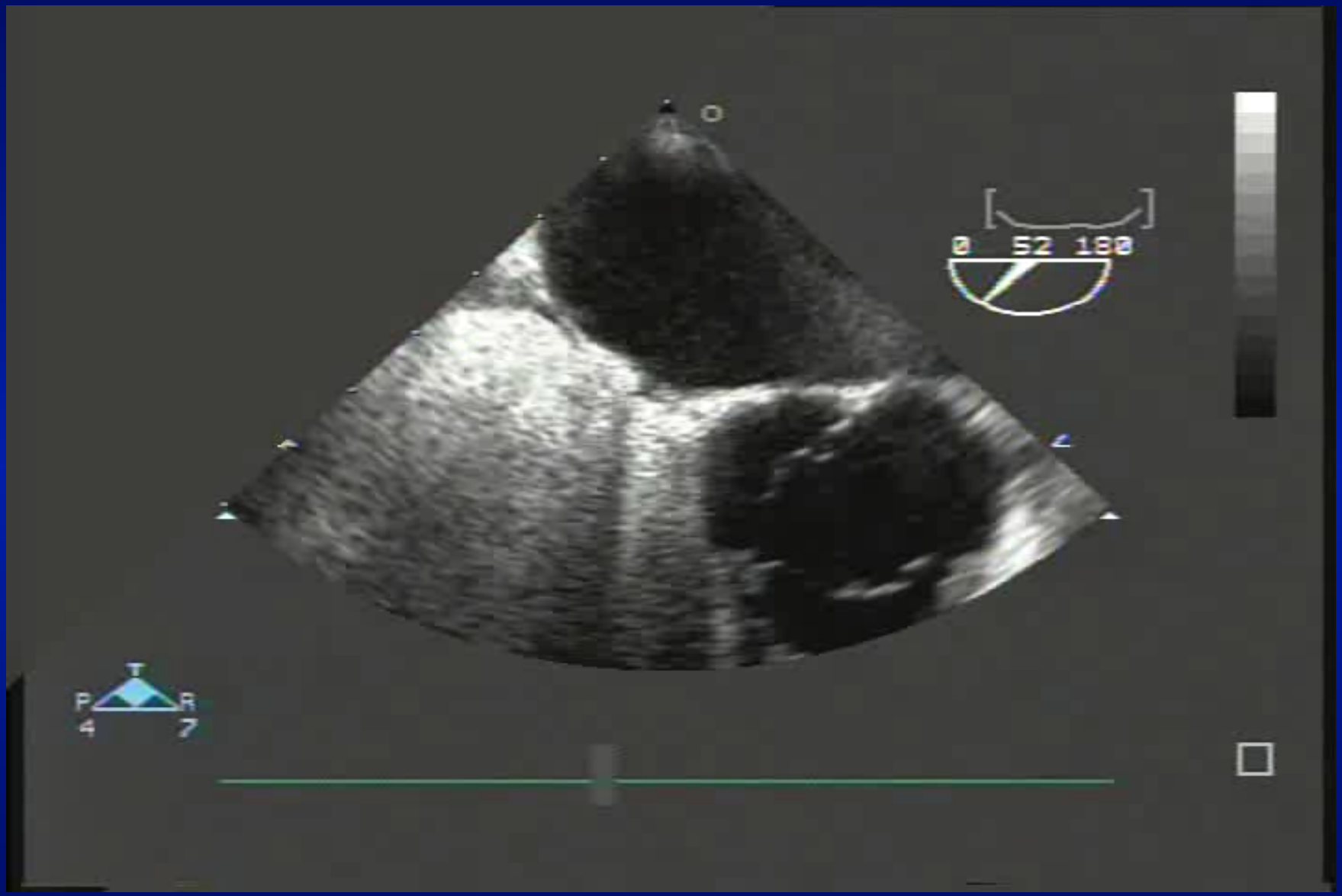
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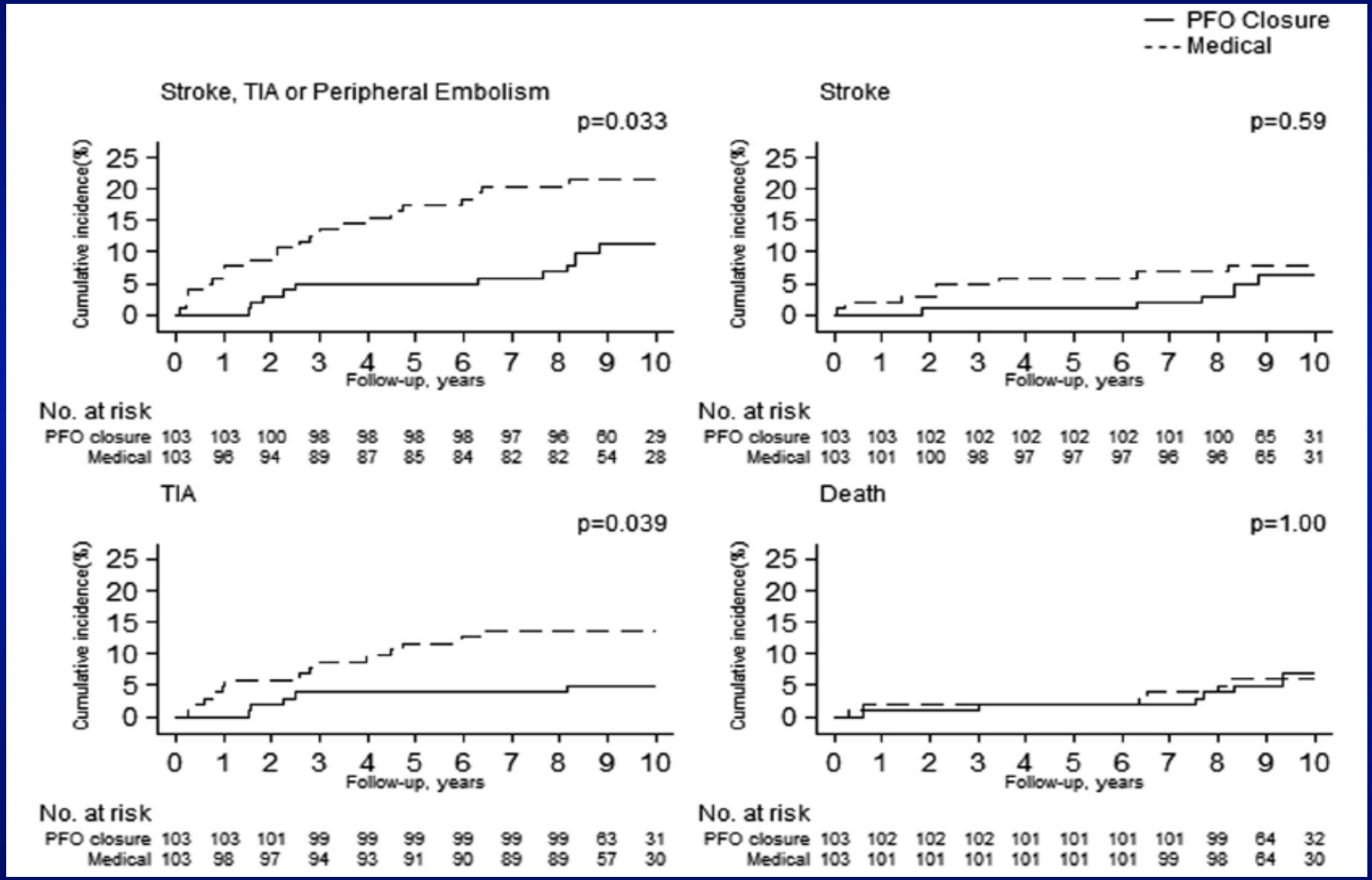
PFO Closure vs. Medical Treatment



Whal et al. Circulation 2012

European Heart Journal Advance Access published July 19, 2013

European Heart Journal
doi:10.1093/eurheartj/eht283

CLINICAL RESEARCH

Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale

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Received 27 March 2013; revised 15 June 2013; accepted 27 June 2013

- 660 patients, 220 patients per group
- Randomization: Amplatzer; CardioSEAL-STARflex, and Helex occluder
- Follow-Up: 5 years
- TEE at 1- and 6-month follow-up

	Amplatzer (n = 220)	Helex (n = 220)	CardioSEAL (n = 220)	*P* Value
Primary Endpoint	1.4%	4.1%	5.9%	0.042[a]
Peripheral Embolism	0	0	0	–
TIA	0	1.8%	2.7%	0.058[a]
Stroke	0.9%	1.8%	2.7%	0.36
Cerebral Death	0.5%	0.5%	0.5%	–
Thrombus Formation	0	0.5%	5%	< 0.0001[b]
Atrial Fibrillation	3.6%	2.3%	12.3%	< 0.0001[b]
Device Embolization	0	1.4%	0	0.049[c]
Complete PFO Closure	100%	96.8%	99.5%	0.004[c]
Severe Residual Shunt Requiring Another Device Implantation	0.9%	6.8%	3.2%	0.0038[c]
Vascular Death	0.5%	0.5%	1.8%	0.22

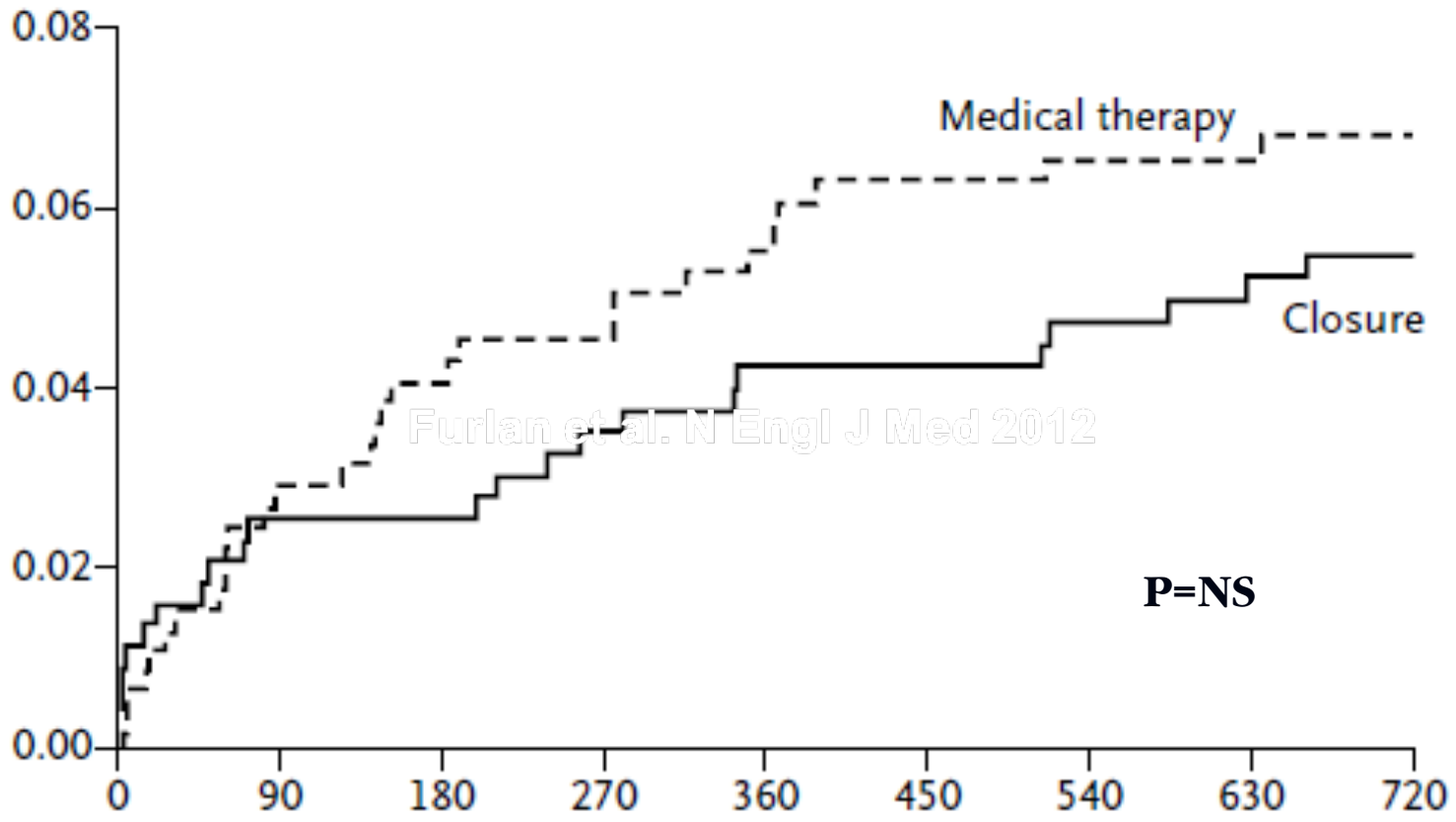
CLOSURE I trial

Table 2. Kaplan–Meier Event Rates for Primary End Point at 2 Years.*

End Point	Closure (N = 447)	Medical Therapy (N = 462)	Hazard Ratio (95% CI)†‡	P Value†
Intention-to-treat population				
Composite end point — no. (%)	23 (5.5)	29 (6.8)	0.78 (0.45–1.35)	0.37
Stroke — no. (%)	12 (2.9)	13 (3.1)	0.90 (0.41–1.98)	0.79
TIA — no. (%)	13 (3.1)	17 (4.1)	0.75 (0.36–1.55)	0.44
Modified intention-to-treat population				
Composite end point — no./total no. (%)	22/400 (5.6)	29/451 (6.9)	0.78 (0.44–1.35)	0.37
Stroke — no./total no. (%)	12/400 (3.1)	13/451 (3.1)	0.94 (0.43–2.07)	0.88
TIA — no./total no. (%)	12/400 (3.0)	17/451 (4.2)	0.72 (0.34–1.51)	0.38
Per-protocol population				
Composite end point — no./total no. (%)	22/378 (5.8)	29/375 (7.7)	0.74 (0.42–1.29)	0.28
Stroke — no./total no. (%)	12/378 (3.2)	13/375 (3.5)	0.91 (0.41–1.99)	0.80
TIA — no./total no. (%)	12/378 (3.2)	17/375 (4.6)	0.68 (0.33–1.43)	0.31

Furlan et al. N Engl J Med 2012

CLOSURE I trial



Furlan et al. N Engl J Med 2012

CLOSURE I trial Limitations

- Only about half of the patients had moderate-to-severe shunt
- Patients at higher risk: PFO closure (out of the trial)
- Underpowered
- No uniform medical treatment
- Significant number of pts on warfarin
- Device with a high rate of significant residual shunt (15% ≥ moderate)

PC TRIAL - PATIENT FLOW

414 PATIENTS
ELIGIBLE FOR THE STUDY

ALLOCATED TO PFO CLOSURE (N=204)
Received allocated intervention (n=191)
Did not receive allocated intervention (n=13)
- No PFO (n=1)
- Withdrawn due to co-morbidity (n=3)
- Logistical problems (n=1)
- Refused PFO closure (n=3)

FOLLOW – UP COMPLETE
Up to 3 years (n=23)
Up to 4 years (n=21)
Up to 5 years (n=127)
Deceased (n=2)

FOLLOW – UP INCOMPLETE
Withdrew (n=7)
Lost to follow-up (n=24)

ANALYSIS FOR PRIMARY ENDPOINT (N=204)
Censored at time of loss to follow-up, or withdrawal (n=31)

ALLOCATED TO MEDICAL THERAPY (N=210)
Received allocated intervention (n=200)
Did not receive allocated intervention (n=10)
- Logistical problems (n=4)
- Received PFO closure (n=6)

FOLLOW – UP COMPLETE
Up to 3 years (n=27)
Up to 4 years (n=24)
Up to 5 years (n=117)
Deceased (n=0)

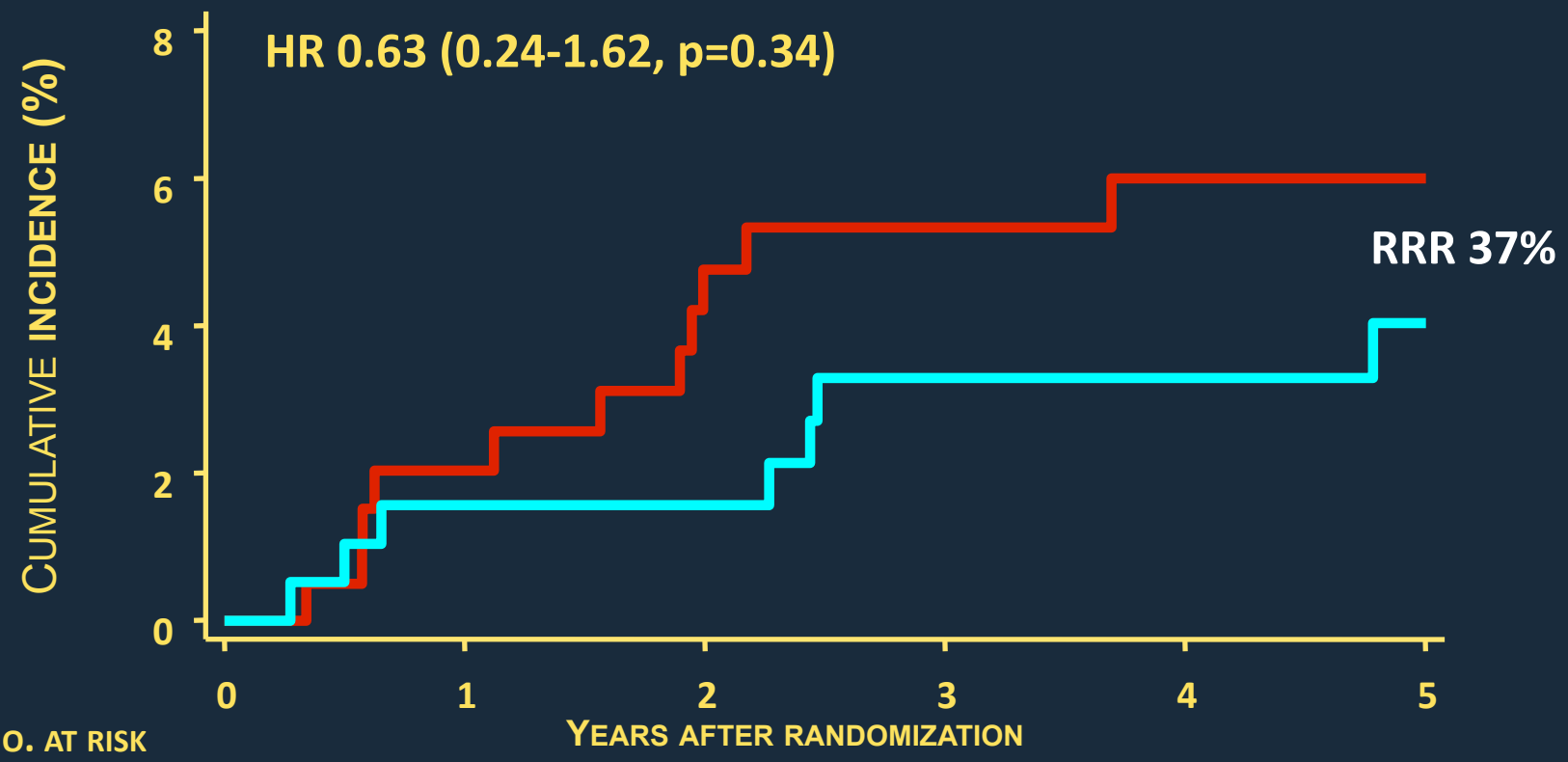
FOLLOW – UP INCOMPLETE
Withdrew (n=11)
Lost to follow-up (n=31)

ANALYSIS FOR PRIMARY ENDPOINT (N=210)
Censored at time of loss to follow-up, or withdrawal (n=42)

Windecker et al. NEJM 2013

Primary Composite Endpoint

Death from any cause, non-fatal Stroke, TIA and peripheral Embolism



No. at risk						
Medical therapy	210	185	170	159	131	90
PFO Closure	204	186	181	163	142	110

TCT2012

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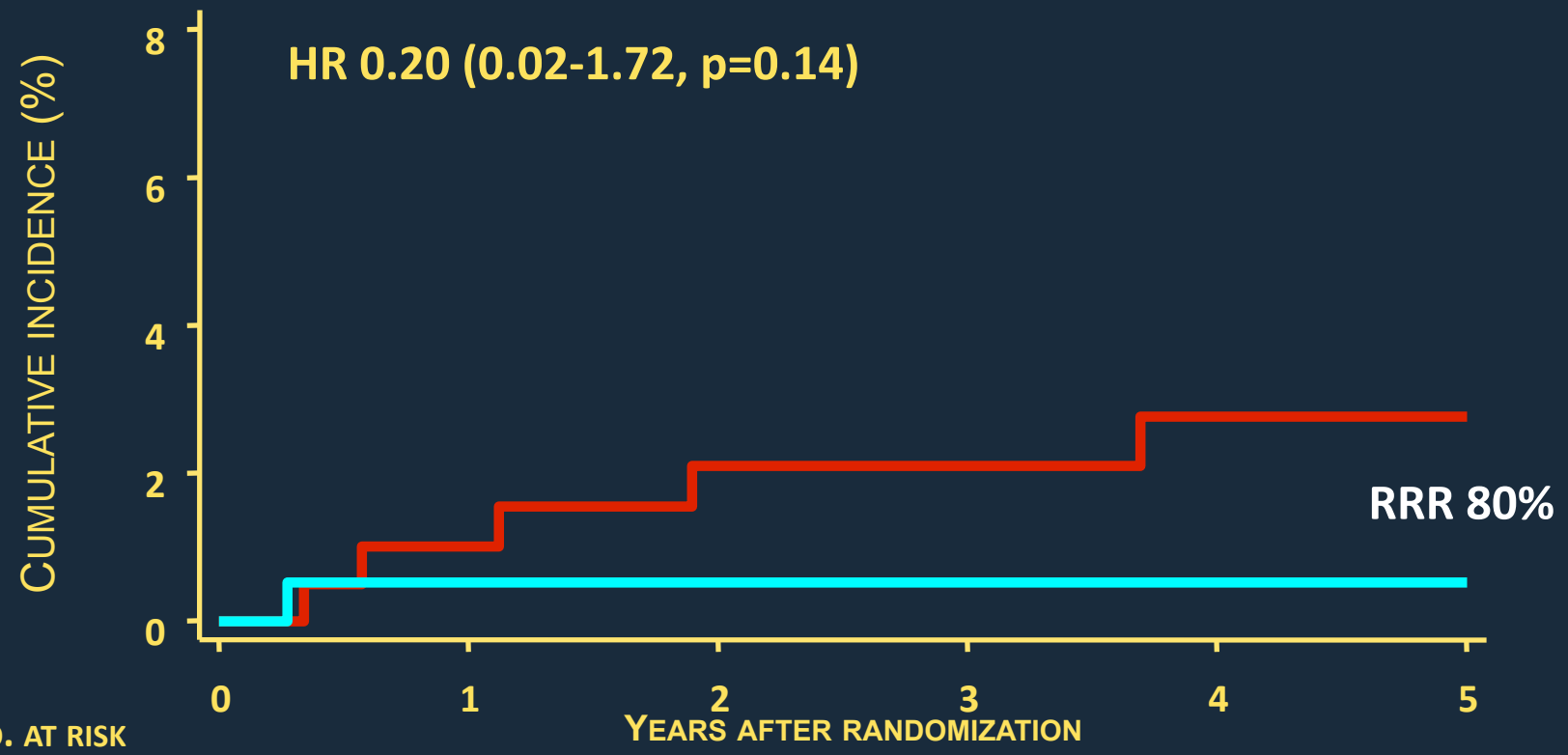
American College of Cardiology

Secondary Endpoint

Stroke



No. at risk	0	1	2	3	4	5
Medical therapy	210	187	175	164	134	92
PFO Closure	204	188	183	167	146	112

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RESPECT TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

Subject Distribution

RESPECT
CLINICAL TRIAL

Enrolled
N=980

Randomization stratified by site and presence/absence of atrial septal aneurysm

Randomized to device group
N = 499

Study device implant attempted
N = 464

Post Implant: clopidogrel 1 month and aspirin 6 months. After 6 months, antiplatelet therapy at discretion of site investigator

TEE with bubble study at 6 months

Randomized to medical group
N = 481

Medical treatment specified pre-randomization by site neurologist

Aspirin only	46.5%
Warfarin only	25.2%
Clopidogrel only	14.0%
Aspirin + dipyridamole	8.1%
Aspirin + clopidogrel[1]	6.2%

Caroll et al. NEJM 2013

1. Aspirin + clopidogrel was removed from the protocol in 2006 based on changes to the AHA/ASA treatment guidelines

Baseline Characteristics

RESPECT CLINICAL TRIAL

	Device Group[1] (N=499)	Medical Group[1] (N=481)	P-value[2]
Age (years)[3]	45.7 (9.7)	46.2 (10.0)	0.491
Gender male (%)	53.7	55.7	0.564
Days from qualifying stroke to randomization	130 (70)	130 (69)	0.891
Atrial septal aneurysm (%)	36.1	35.1	0.790
Maximal baseline shunt Grade II - III (%)[3,4]	77.9	74.1	0.176
Qualifying Stroke Size			
Smaller infarct ≤ 1.5 cm	50.6	51.8	0.714
Larger infarct > 1.5 cm	49.4	48.2	

4.

Right to left shunt grading scale (at rest or post-Valsalva)			
Grade 0	No bubbles	Grade II	10 - 20 bubbles
Grade I	1 - 9 bubbles	Grade III	≥ 20 bubbles

1. Statistics are represented as either mean (standard deviation) or percentages
2. Based on a 2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized), and Fisher's Exact test (sex)
3. Numbers vary by site; Age N=968; Shunt N=969

Serious Adverse Events Adjudicated as Related to Procedure, Device, or Study

RESPECT CLINICAL TRIAL

Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value[7]
Thrombus on device	0 (0%)	N/A	N/A
Device embolization	0 (0%)	N/A	N/A
Atrial fibrillation[1]	3 (0.6%)	3 (0.6%)	1
Transient ischemic attack (TIA)	3 (0.6%)	3 (0.6%)	1
Major bleeding	8 (1.6%)	9 (1.9%)	0.810
Pericardial tamponade (procedure related)[2]	2 (0.4%)	N/A	N/A
Major vascular complications	4 (0.8%)	0 (0%)	0.124
Pulmonary embolism[3]	1 (0.2%)	0 (0%)	1
Cardiac thrombus[4]	2 (0.4%)	0 (0%)	0.500
Ischemic stroke[5]	2 (0.4%)	N/A	N/A
Death[6]	0 (0%)	0 (0%)	N/A

1. For all AE's, atrial fibrillation occurred in 3.0% versus 1.5% in the device and medical groups respectively, p=0.13
2. Pericardial tamponade is a subset of major bleeds, and thus counted in the major bleed category as well
3. For all SAEs, pulmonary embolism occurred in 1.2% and 0.2% in device and medical groups, respectively, p=0.124
4. 1 case of right atrial thrombus resulted in abandonment of device implant procedure (no device received); 1 case of right atrial thrombus (located inferiorly) not attached to device detected in patient with DVT and PE 4 months after procedure
5. 1 ischemic stroke one week post implant; 1 five months post implant with finding of severe shunting related to previously undiagnosed sinus venosus defect, requiring surgical closure
6. For all SAEs, there were 3 device group deaths (0.6%) and 6 medical group deaths (1.2%) all of which were not study related, p= 0.334
7. P-values are calculated using Fisher's Exact test

Device Performance

RESPECT
CLINICAL TRIAL

Procedural Outcomes	n/N (%)
Technical success[1]	460 / 464 (99.1%)
Procedural success[2]	444 / 462 (96.1%)
Effective closure[3]	244 / 261 (93.5%)

Maximum Residual Shunting at Rest and Valsalva at 6 Months
Grade 0: 72.7%
Grade 1: 20.8%
Grade 2-3: 6.5%

1. Defined as successful delivery and release of the device for subjects in whom the delivery system was introduced into the body
2. Defined as successful implantation with no reported in-hospital serious adverse events
3. Defined as complete obliteration or trivial residual shunting (Grade 0 or I at rest and Valsalva) at 6 months, adjudicated by echo core lab

Treatment Exposure and Follow-up

RESPECT
CLINICAL TRIAL

	Device Group (N=499)	Medical Group (N=481)	All Subjects N=980	P-value[1]
Mean (SD), years	2.8 (2.0)	2.5 (1.9)	2.6 (2.0)	
Median, years	2.2	2.1	2.1	
Range, years	0 - 8.1	0 - 8.1	0 - 8.1	
Total exposure, patient-years	1,375	1,184	2,559	0.009

- Total population with greater than 2,550 years of follow-up
- Device group had greater follow-up (fewer drop-outs)
  - 48 drop-outs in the device group versus 90 in the medical group

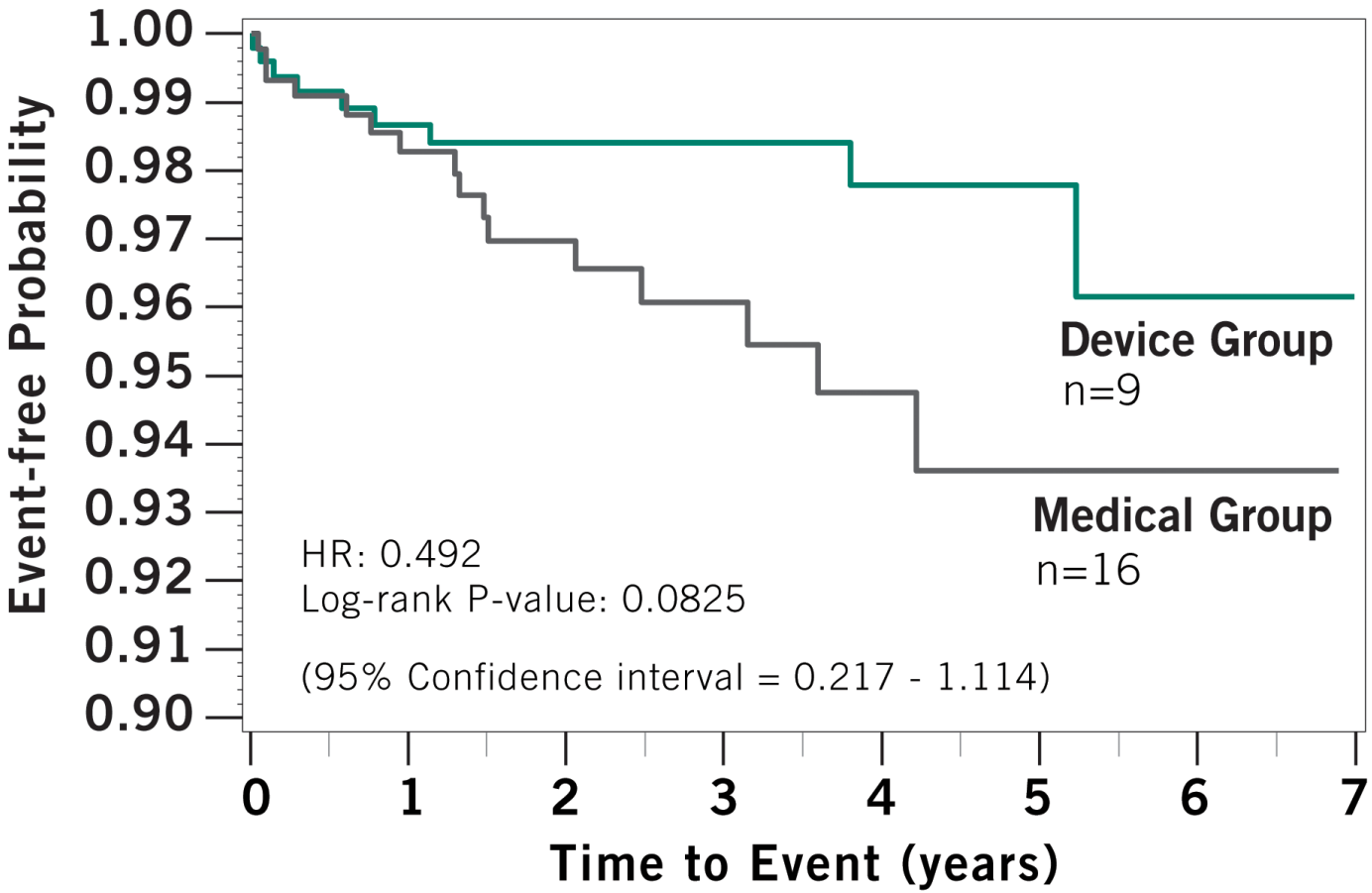
1. P-value calculated using Wilcoxon-Mann-Whitney test

RESPECT
CLINICAL TRIAL

- **Intention to Treat (primary analysis)**
  - All patients according to the group to which they were randomly assigned
    - PFO closure: 499 pts
    - Medical tx: 481 pts
- **Per protocol analysis**
  - Patients who received the randomly assigned treatment
    - - PFO closure: 471 pts
    - - Medical tx: 473
- **As treated analysis**
  - Patients who actually received a protocol-approved treatment, regardless of initial randomization
    - - PFO closure: 474 pts
    - - Medical tx: 484 pts

Primary Endpoint Analysis – ITT Cohort

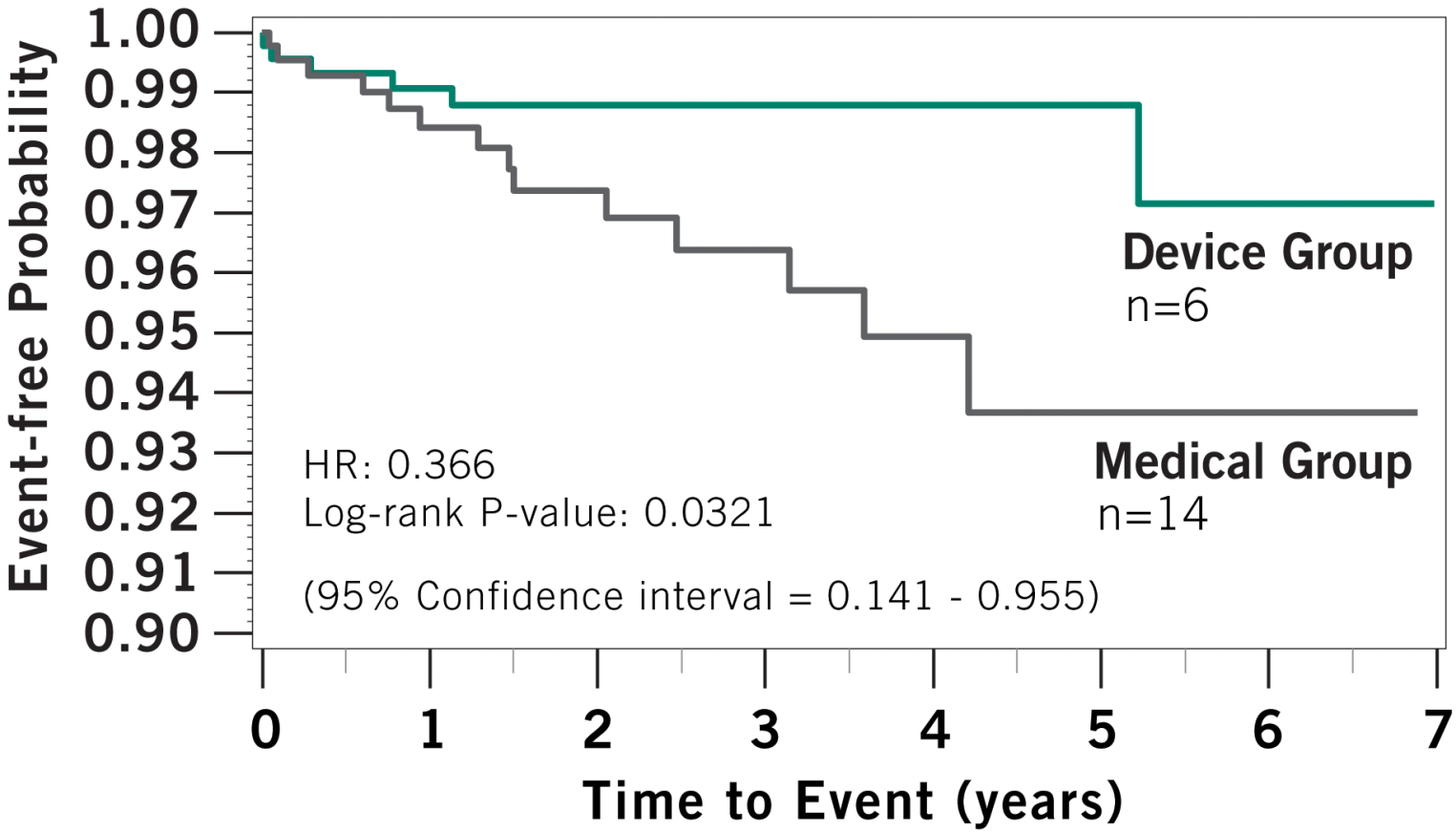
50.8% risk reduction of stroke in favor of device



- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

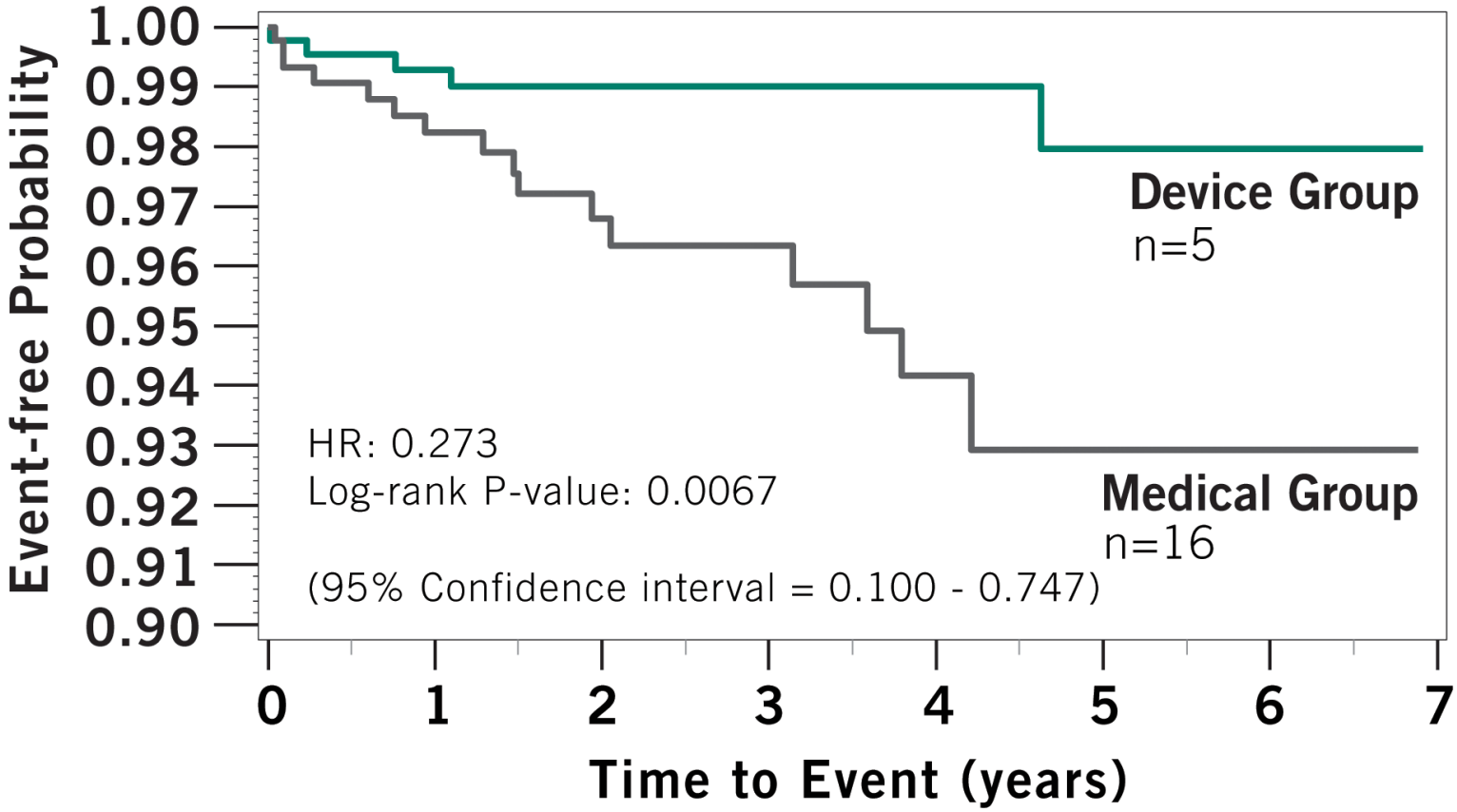
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Totality of Evidence and NNT

46.6%-72.7% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL

Totality of Evidence

Analysis	Risk Reduction	P-Value[1]
Intent to Treat Raw Count	46.6%	0.157
Intent to Treat KM	50.8%	0.083
Per Protocol KM	63.4%	0.032
As Treated KM	72.7%	0.007

Number Needed to Treat (NNT)

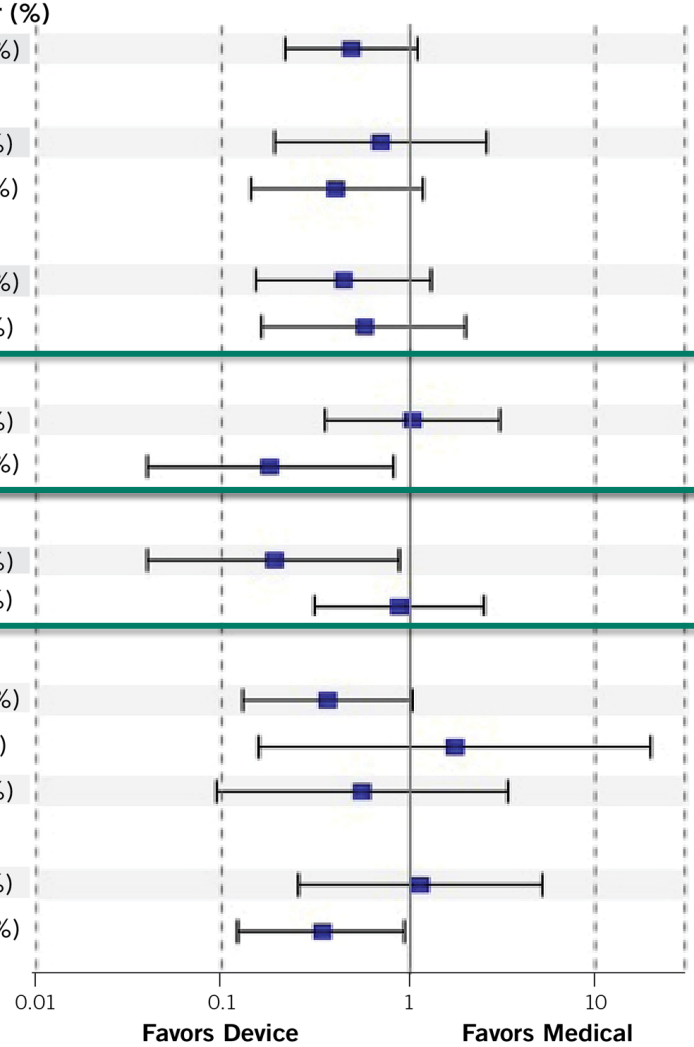
	NNT[2]	Device Group Event Rate[3]	Medical Group Event Rate[3]
1 Year	250	1.33%	1.73%
2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

1. P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
2. The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
3. Calculated using the Kaplan-Meier estimated event rates for each treatment group

Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI	Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)				
Overall	9/499 (1.8%)	16/481 (3.3%)	0.492 (0.217, 1.114)	0.0825	
Age					0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)	0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)	0.405 (0.140, 1.165)	0.0828	
Sex					0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)	0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)	0.571 (0.161, 2.024)	0.3789	
Shunt Size					0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)	1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)	0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm					0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)	0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)	0.889 (0.312, 2.535)	0.8259	
Index infarct topography					0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)	0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)	1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)	0.558 (0.093, 3.340)	0.5167	
Planned medical regimen					0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)	1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)	0.336 (0.120, 0.944)	0.0299	



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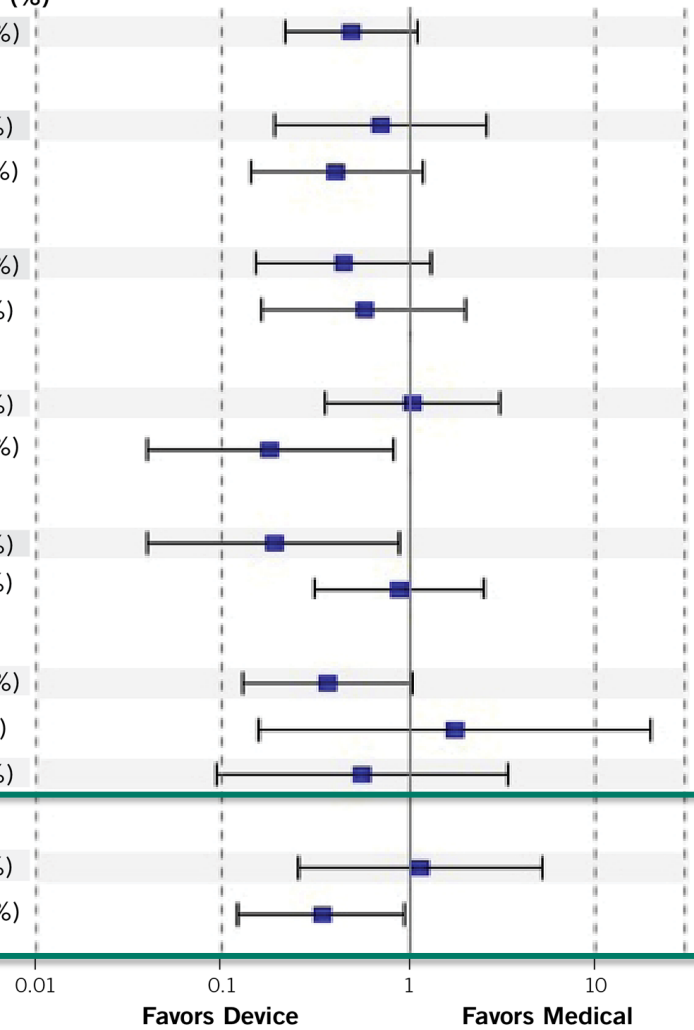

Recurrent Cerebral Infarct Size[1]

Methods pre-specified; analysis post-hoc

Event	Device Group n/N (%)	Medical Group n/N (%)	P-value[2]
Larger infarct >1.5cm	1/7 (14%)	9/13 (69%)	P=0.0573
Smaller infarct ≤ 1.5cm	6/7 (86%)	4/13 (31%)	

- This exploratory analysis of site-reported recurrent cerebral infarct size is provocative in suggesting that recurrent ischemic strokes in the medical versus device group are not only more frequent but also larger

1. Recurrent infarct size reported on primary endpoint population
2. P-value based on Fisher's Exact test

PFO Closure vs. Medical Treatment Randomized Trials

- PC trial
- CLOSURE I trial
- RESPECT trial
- CLOSE trial
  - Age: 18 – 60 yrs; n = 900 pts
  - Study start date: December 2007; estimated study completion date: December 2012
  - PI: Jean-Louis Mas, MD, PhD, Centre Hospitalier Sainte Anne, Paris, France

Catheterization and Cardiovascular Interventions 82:122–129 (2013)

Original Studies

Management of Patients with Patent Foramen Ovale and Cryptogenic Stroke:
A Collaborative, Multidisciplinary, Position Paper: Executive Summary

Christian Pristipino,[1*] MD, Gian Paolo Anzola,[2] MD, Luigi Ballerini,[3] MD, Antonio Bartorelli,[4] MD, Moreno Cecconi,[5] MD, Massimo Chessa,[6] MD, PhD, Andrea Donti,[7] MD, Achille Gaspardone,[8] MD, Giuseppe Neri,[9] MD, Eustaquio Onorato,[10] MD, Gualtiero Palareti,[11] MD, Serena Rakar,[12] MD, Gianluca Rigatelli,[13] MD, PhD, Gennaro Santoro,[14] MD, Danilo Toni,[15] MD, Gian Paolo Ussia,[16] MD, Roberto Violini,[17] MD, on behalf of: Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke Association (ISA-AIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society Of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SICP); Italian Society of Cardiovascular Echography (SIEC); Italian Society of Hemostasis and Thrombosis (SISET).

Cryptogenic Stroke/[redacted] (symptomatic/asymptomatic) & PFO with R-L Shunt

First cryptogenic event without anatomical/clinical risk factors	Cryptogenic event in medical treatment-naïve patients with ≥ 1 risk factor	Any cryptogenic event (first or recurrent) on AP and/or OA therapy
↓	↓	↓
Medical therapy	**Cath PFO closure as an alternative to medical therapy**	**Cath PFO closure**

Anatomical risk factors

- Atrial Septal Anevrysm
- Severe shunt

Clinical risk factors

Multiple ischemic lesions on CT/MR
Recurrent clinical events
History of DVT/PE and/or Thrombophilia
Valsalva-associated embolic event
Ischemic event on arousal (OSAS)
Long travel/immobilization associated event
Simultaneous systemic/pulmorany embolism

Merci Beaucoup!!