PFO trials CLOSURE I, PC and RESPECT: is closure of patent foramen ovale to prevent ischaemic stroke ever justified?

Dott. Luigi Pedon
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ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ESTABLISHED IN 1812 MARCH 21, 2013 VOL. 368 NO. 12

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D.,

CONCLUSIONS

Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy. (Funded by St. Jude Medical; ClinicalTrials .gov number, NCT00166257.)

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*

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

Observational, non-randomized studies show benefit with PFO closure compared with medical therapy for cryptogenic stroke….

	Observational Studies			
Outcome	Closure Arm IR (95% CI), per 100 Person-Years	Medical Arm IR (95% CI), per 100 Person-Years	IRR (95% CI) Closure vs Medical (Comparative Studies Only)	IRR (95% CI) Closure vs Medical (All Studies)
Total events	0.80 (0.55–1.18)	4.73 (3.41–6.56)	0.22 (0.07–0.64)	0.17 (0.10–0.28)
Stroke events	0.36 (0.24–0.56)	2.53 (1.91–3.35)	0.19 (0.07–0.54)	0.14 (0.08–0.24)
TIA events	0.46 (0.29–0.74)	1.93 (1.16–3.20)	0.15 (0.02–1.35)	0.24 (0.12–0.47)

….. but these studies are limited by selection bias and confounding that can not be completely adjusted for by statistical methods.

Kitsios G D et al. *Stroke*. 2012;43:422-431

Medical Therapy versus PFO Closure

Randomized Evidence

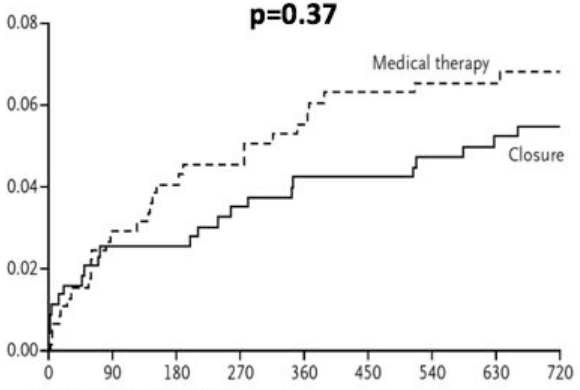
CLOSURE I

Investigating the PFO Stroke Connection

PFO Closure versus Medical Therapy
(N=909)

PFO Closure with the STARFlex Device (n=447)
Medical Therapy (n=462)
Follow-Up Period 24 months

HR 0.78 (95%CI 0.45–1.35)
p=0.37



PRIMARY END-POINT:
COMPOSITE OF STROKE OR TIA DURING 2 YEARS OF FUP, DEATH FROM ANY CAUSE DURING THE FIRST 30 DAYS, AND DEATH FROM NEUROLOGIC CAUSES BETWEEN 31 DAYS AND 2 YEARS

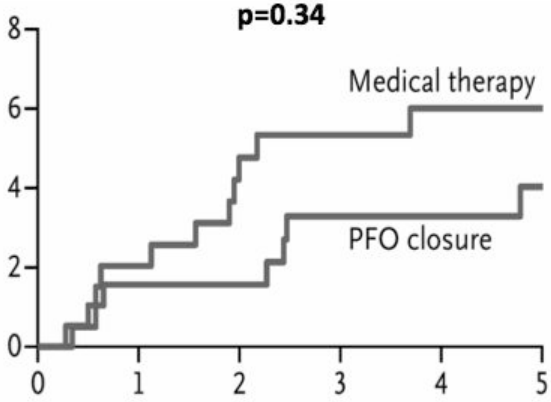
Furlan AJ et al. *N Engl J Med. 2012;366:991-9*

PC – TRIAL

PFO Closure versus Medical Therapy
(N=414)

PFO Closure with the Amplatzer Device (n=204)
Medical Therapy (n=210)
Follow-Up Period 60 months

HR 0.63 (95%CI 0.24–1.62)
p=0.34



PRIMARY END-POINT:
COMPOSITE OF DEATH, NONFATAL STROKE, TIA, OR PERIPHERAL EMBOLISM

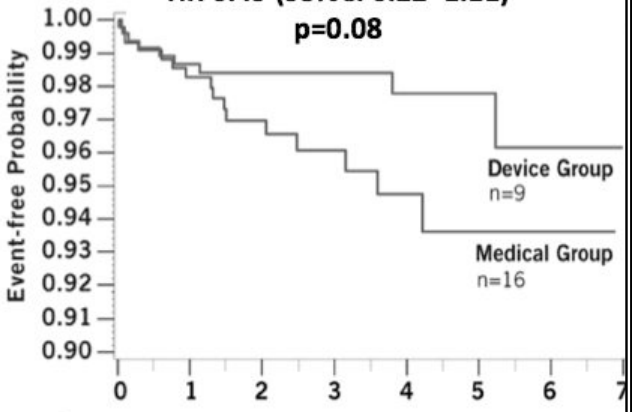
Meier B et al. *N Engl J Med. 2013;368:1083-91*

RESPECT

PFO Closure versus Medical Therapy
(N=980)

PFO Closure with the Amplatzer Device (n=499)
Medical Therapy (n=481)
Follow-Up Period up to 84 months

HR 0.49 (95%CI 0.22–1.11)
p=0.08



PRIMARY END-POINT:
COMPOSITE OF RECURRENT NONFATAL ISCHEMIC STROKE, FATAL ISCHEMIC STROKE, OR EARLY DEATH AFTER RANDOMIZATION

Carroll JD et al. *N Engl J Med. 2013;368:1092-100*

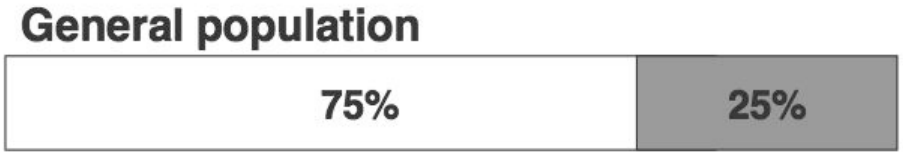
Patent Foramen Ovale in Cryptogenic Stroke

Incidental or Pathogenic?

Alawi A. Alsheikh-Ali, MD; David E. Thaler, MD, PhD; David M. Kent, MD, MS

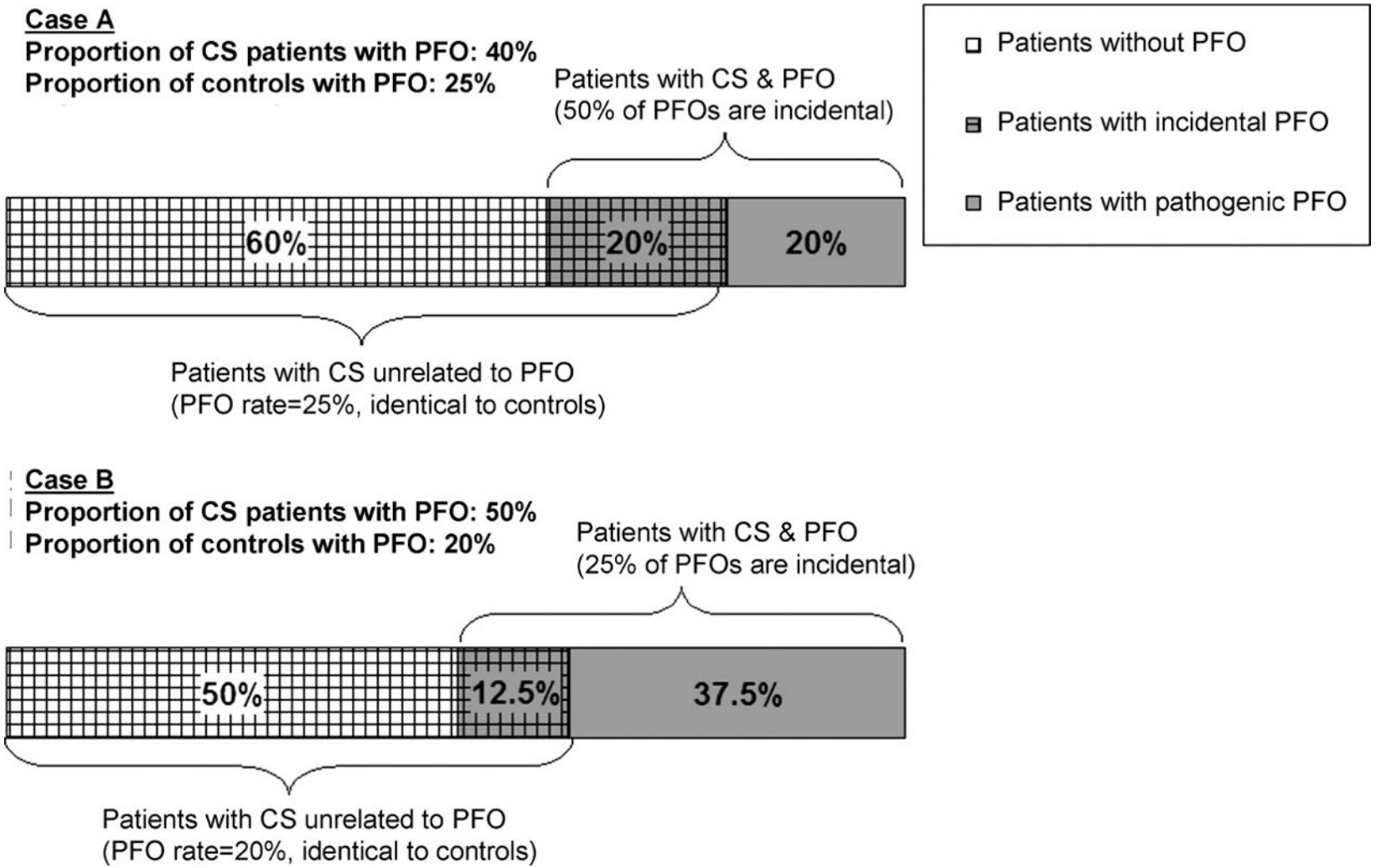
Bayes' theorem

$$\text{PFO Attributable Fraction} = 1 - \left(\frac{\text{Prevalence of PFO in controls} \times [1 - \text{Prevalence of PFO in CS cases}]}{\text{Prevalence of PFO in CS cases} \times [1 - \text{Prevalence of PFO in controls}]}\right)$$



Stroke. 2009;40:2349-2355

Proportion of patients with CS without PFO with incidental PFO and with pathogenic PFO



Alsheikh-Ali A A et al. Stroke 2009;40:2349-2355

Patent Foramen Ovale in Cryptogenic Stroke

Incidental or Pathogenic?

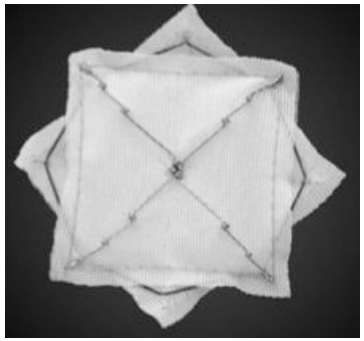
23 case-control studies examining the prevalence of PFO in pts with CS versus control subjects with stroke of known cause.

- One third of PFOs discovered in pts with CS are likely to be incidental and unrelated to the stroke.
- This estimate is sensitive to pts age and is higher in older pts.
- The probability that a PFO is incidental is much lower in any age when associated with ASA.

	Probability PFO Is Incidental	
	Main Analysis	Sensitivity Analysis
PFO		
Age-inclusive	0.33 (0.28–0.39)	0.48 (0.39–0.59)
Young	0.20 (0.16–0.25)	0.20 (0.16–0.25)
Old	0.48 (0.34–0.66)	0.84 (0.60–1.00)
PFO+ASA		
Age-inclusive	0.11 (0.04–0.31)	…
Young	0.09 (0.04–0.18)	0.04 (0.01–0.32)
Old	0.26 (0.12–0.56)	…

Any trial that tests strategies for secondary prevention of paradoxical embolism will enroll patients that have different probabilities of a pathogenic versus an incidental PFO and different recurrence risk.

Alsheikh-Ali AA el al. Stroke. 2009;40:2349-235



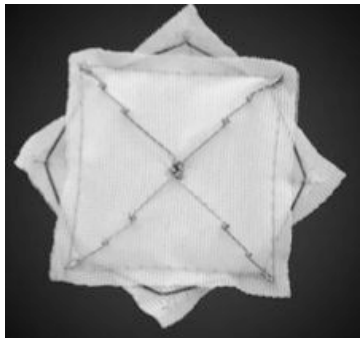
Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

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

	Observational Studies				Randomized Clinical Trial (CLOSURE I)		
Outcome	Closure Arm IR (95% CI), per 100 Person-Years	Medical Arm IR (95% CI), per 100 Person-Years	IRR (95% CI) Closure vs Medical (Comparative Studies Only)	IRR (95% CI) Closure vs Medical (All Studies)	Closure Arm IR (95% CI), per 100 Person-Years	Medical Arm IR (95% CI), per 100 Person-Years	HR (95% CI) Closure vs Medical
Total events	0.80 (0.55–1.18)	4.73 (3.41–6.56)	0.22 (0.07–0.64)	0.17 (0.10–0.28)	2.79 (1.81–4.13)	3.25 (2.19–4.63)	0.76 (0.45–1.29)
Stroke events	0.36 (0.24–0.56)	2.53 (1.91–3.35)	0.19 (0.07–0.54)	0.14 (0.08–0.24)	1.34 (0.69–2.34)	1.41 (0.74–2.41)	0.89 (0.41–1.95)
TIA events	0.46 (0.29–0.74)	1.93 (1.16–3.20)	0.15 (0.02–1.35)	0.24 (0.12–0.47)	1.45 (0.77–2.49)	1.83 (1.10–2.94)	0.73 (0.35–1.50)



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- Wrong Patients
- Wrong Device
- Wrong Outcome Assumptions

CLOSURE I
Investigating the PFO Stroke Connection

Baseline Characteristics ITT

	STARFlex	Medical	P value
N randomized	447	462	
Mean Age	46.3 (18-61)	45.7(18-61)	
Male	52.1%	51.5%	
White	89%	90%	
Index cryptogenic stroke	73%	71%	
Mod/substantial shunt*	58% (231/400)	51% (228/451)	0.04
ASA ≥ 10 mm*	38% (151/400)	35% (160/451)	0.49

* modified ITT

Less than two-thirds of the baseline magnetic resonance imaging scans showed acute stroke (A. Furlan, unpublished data, presented at the 28 Princeton Stroke Conference)

Off-Label Closure During CLOSURE Study

Impact?

Stackhouse KA, Goel SS, Qureshi AM, et al. J Invasive Cardiol 2012;24:608-11.

Between 11/3/2003 and 4/16/2007, there were 100 off-label closures and 33 patients randomized into CLOSURE I.

Compared with off-label closure, patients in CLOSURE I

- **Younger** (41.6 ± 10.1 years vs 50.0 ± 14.0 years; *P*<.001)
- **Fewer** cardiovascular risks factors
- **Less** "High-Risk" PFO Characteristics

Variable	CLOSURE Group (n = 33)	Off-Label Group (n = 100)	*P*-Value
Degree of shunt			.026
Mild	45%	28%	
Moderate	30%	14%	
Severe	25%	58%	
PFO size (mm)	1.4 (IQR, 1.0-2.3)	1.9 (IQR, 1.1-3.0)	.233
Tunnel length (mm)	11.8 ± 6.1	11.3 ± 6.1	.746
Atrial septal aneurysm	21%	40%	.091

Amplatzer PFO Occluder VS StarFlex: implant success and late complication

Event	RESPECT Device Group (%) N=499	Closure I Device group (%) N=402
Procedural Success	96.1%	89.4%
Effective Closure @ 6 m.	93.5%	86.4%
Thrombus on device	0%	1.1%
Atrial Fibrillation	0.6%	5.7%
Major Bleeding	1.6%	2.6%
Major Vascular Complication	0.8%	3.2%

Recurrent Stroke Multiple Etiologies

STARFlex strokes (n =12)

- **3 periprocedural (within 30 days)**
  - 1 a fib
  - 1 clot in LA
  - 1 retinal embolism day 1 presumed procedural embolism
- **3 cryptogenic**
- **3 ASO/lacunar**
- **2 a fib (with LA clot day 52; one day 238)**
- **1 cardiac cath complication day 232 (for CAD)**

Medical therapy strokes (n=13)

- **0 within 30 days of randomization**
- **6 multiple (complex migraine, risk factors, psychogenic)**
- **3 lacunar infarcts**
- **1 arch atheroma**
- **1 afib with off label device**
- **1 cryptogenic**
- **1 vasculitis**

CLOSURE I
Investigating the PFO Stroke Connection

…" A key finding in our trial was that an alternative explanation for recurrent str
TIA, unrelated to paradoxical embolism, was usually apparent".

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

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- Follow-up was stopped at 2 years
- Size population
- Lower-than-expected event rate.

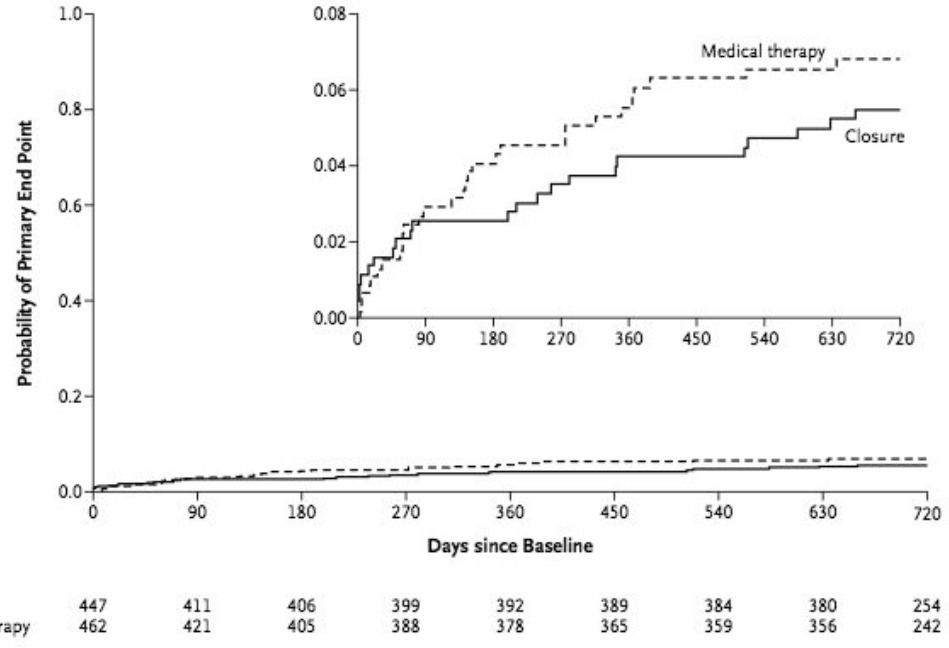
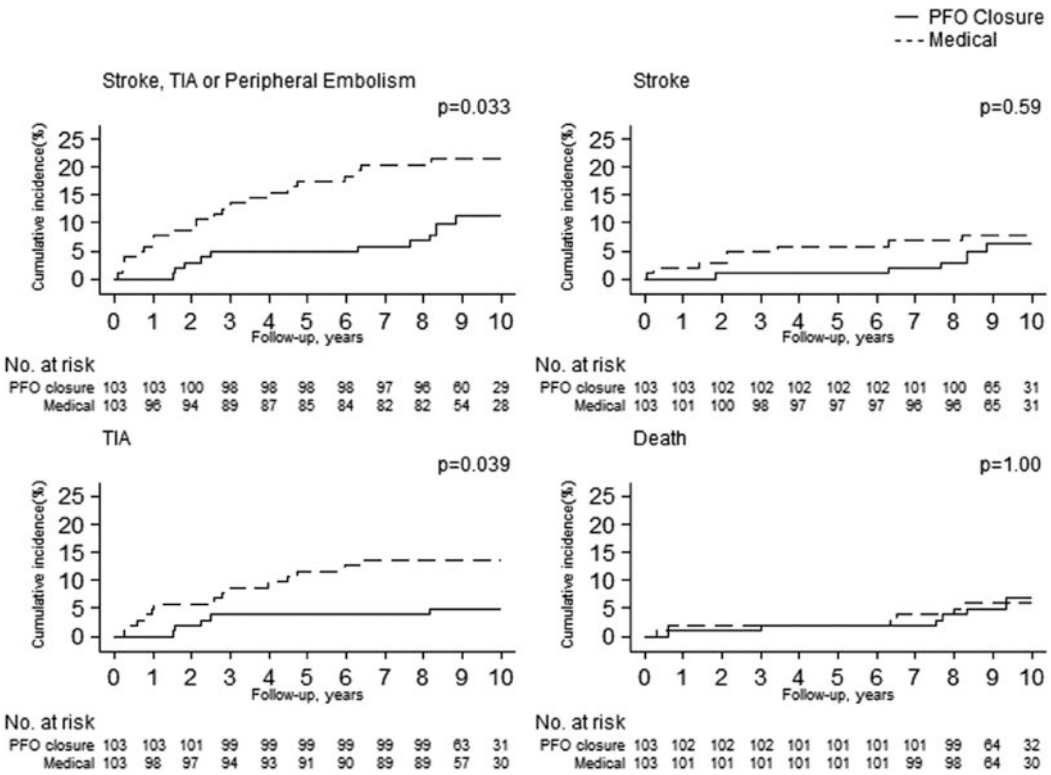


Figure 1. **Kaplan–Meier Curve of Time to Primary End Point through 2 Years of Follow-up in the Closure and Medical-Therapy Groups.**

Long-Term Propensity Score–Matched Comparison of Percutaneous Closure of Patent Foramen Ovale With Medical Treatment After Paradoxical Embolism

Andreas Wahl, MD*; Peter Jüni, MD*; Marie-Luise Mono, MD; Bindu Kalesan, MPH; Fabien Praz, MD; Laura Geister, MD; Lorenz Räber, MD; Krassen Nedeltchev, MD; Heinrich P. Mattle, MD; Stephan Windecker, MD; Bernhard Meier, MD

At a median follow-up of 9 years, the primary composite outcome occurred in 11 patients slated to PFO closure (11%) and 22 patients slated to medical treatment (21%; hazard ratio=0.43; 95% confidence interval=0.20–0.94; *P*=0.033).



Kaplan-Meier estimates for the composite of stroke, transient ischemic attack (TIA), or peripheral embolism (top left); stroke (top right); TIA (bottom left); and death (bottom right) in the propensity score–matched cohort.

Wahl A et al. Circulation. 2012;125:803-812

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PC – TRIAL

PFO CLOSURE VERSUS MEDICAL THERAPY (N=414)

PFO Closure with the Amplatzer Device (n=204)
Medical Therapy (n=210)
Follow-Up Period 60 months

February 2000- February 2009

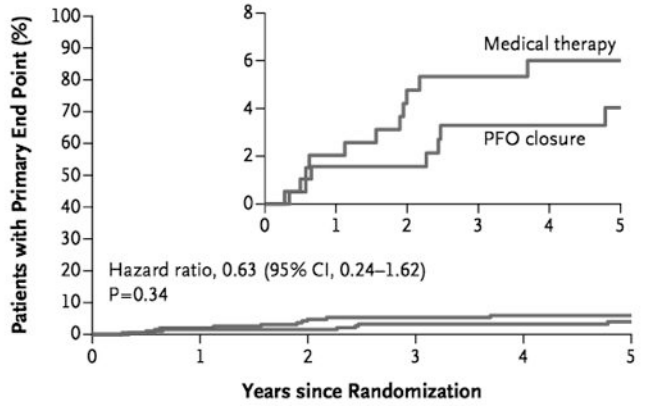
Table 1. **Baseline Characteristics of the Patients.***

Characteristic	PFO Closure (N=204)	Medical Therapy (N=210)
Age — yr	44.3±10.2	44.6±10.1
Male sex — no. (%)	92 (45.1)	114 (54.3)
Body-mass index†	26.6±5.6	26.3±4.8
Family history of cerebrovascular event — no. (%)	53 (26.0)	40 (19.0)
Current smoker — no. (%)	52 (25.5)	47 (22.4)
Arterial hypertension — no. (%)	49 (24.0)	58 (27.6)
Diabetes mellitus — no. (%)	5 (2.5)	6 (2.9)
Hypercholesterolemia — no. (%)	50 (24.5)	62 (29.5)
Valvular heart disease — no. (%)	8 (3.9)	5 (2.4)
Peripheral vascular disease — no. (%)	3 (1.5)	2 (1.0)
Coronary artery disease — no. (%)	4 (2.0)	4 (1.9)
History of myocardial infarction — no. (%)	3 (1.5)	1 (0.5)
Migraine — no. (%)	47 (23.0)	38 (18.1)
Cerebrovascular index event — no. (%)		
Peripheral embolism	6 (2.9)	5 (2.4)
Transient ischemic attack	33 (16.2)	42 (20.0)
Stroke	165 (80.9)	163 (77.6)
>1 Previous cerebrovascular event — no. (%)	76 (37.3)	79 (37.6)
Time from index event to randomization — mo		
Median	4.3	4.5
Interquartile range	1.1–8.2	1.3–8.9
Atrial septal aneurysm — no. (%)	47 (23.0)	51 (24.3)
Interatrial right-to-left shunt — no./total no. (%)‡		
Small	55/185 (29.7)	72/184 (39.1)
Medium	87/185 (47.0)	75/184 (40.8)
Large	43/185 (23.2)	37/184 (20.1)

PC – TRIAL

PFO CLOSURE VERSUS MEDICAL THERAPY (N=414)

PFO Closure with the Amplatzer Device (n=204)
Medical Therapy (n=210)
Follow-Up Period 60 months



No. at Risk

Medical therapy	210	185	170	159	131	90
PFO closure	204	186	181	163	142	110

Figure 1. Kaplan–Meier Cumulative Estimates of the Rate of the Pr End Point.

PFO denotes patent foramen ovale.

Low outcome rate

↓

Modest statistical power

↓

Misclassification of even one or two events can have dramatic effects on the P value

Table 2. Clinical Outcomes.*

Outcome	PFO Closure (N=204)	Medical Therapy (N=210)	Hazard Ratio or Relative Risk (95% CI)†	P Value
	no. of patients (%)			
Primary composite outcome of death, stroke, TIA, or peripheral embolism	7 (3.4)	11 (5.2)	0.63 (0.24–1.62)	0.34
Death‡	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Cardiovascular	0	0	NA	
Noncardiovascular	2 (1.0)	0	5.20 (0.25–107.61)	0.24
Thromboembolic event				
Stroke§	1 (0.5)	5 (2.4)	0.20 (0.02–1.72)	0.14
TIA	5 (2.5)	7 (3.3)	0.71 (0.23–2.24)	0.56
Peripheral embolism	0	0	NA	
Secondary composite outcome of stroke, TIA, or peripheral embolism	5 (2.5)	11 (5.2)	0.45 (0.16–1.29)	0.14

* NA denotes not applicable, PFO patent foramen ovale, and TIA transient ischemic attack.
† Hazard ratios were calculated by means of the Cox proportional-hazards model. For the comparison of deaths (for which one group had no events), the relative risk was calculated instead of the hazard ratio with the use of continuity correction, and the corresponding P value was obtained by means of a two-sided Fisher's exact test.
‡ One patient died of respiratory failure because of chronic obstructive pulmonary disease; the other died from a glioma.
§ All listed strokes were major strokes.

AMPLATZER PFO Occluder*

Trial Design

RESPECT CLINICAL TRIAL

TIAs and lacunar strokes were not enrolled.

Inclusion Criteria	Patients (ages 18 to 60 – mean of 46) with PFO who have had a cryptogenic stroke within 270 days
Follow-up	Up to 8 years with mean approaching 3 years Will continue until a ruling is made by the FDA for US device approval
Primary Endpoints	Composite of: Recurrence of nonfatal stroke Post-randomization death Fatal ischemic stroke
Secondary Endpoints	Closure rate, absence of TIA, absence of recurrent cryptogenic (stroke of unknown cause) non-fatal stroke or CV death
Primary Data Analysis	Four protocol-specified analysis with ITT raw count as primary endpoint analysis

Patient Cohorts

- As directed by the trial's Statistical Analysis Plan, the patient data would be divided into 3 different cohorts – ITT, PP and AT
- ITT raw count data, would be analyzed to determine if the trial met its primary endpoint .
- AT analysis would compare the outcomes of the patients that actually received treatment with the device or medical management alone

Type of analysis	Description
Intent to Treat (ITT) – Raw Count	This is the raw data. All patients are included and analyzed based on the arm they are randomized to, regardless of whether or not they received one of the treatments or dropped out during follow up.
Per Protocol (PP)	Patients are included if they followed the treatment of the arm they are randomized to, e.g. met the inclusion/ exclusion criteria, followed the medical management protocol, etc.
As Treated (AT)	Patients are included based on whether they actually received the treatment, e.g. device vs. medical therapy only, and not based on how they were randomized.

Baseline Characteristics

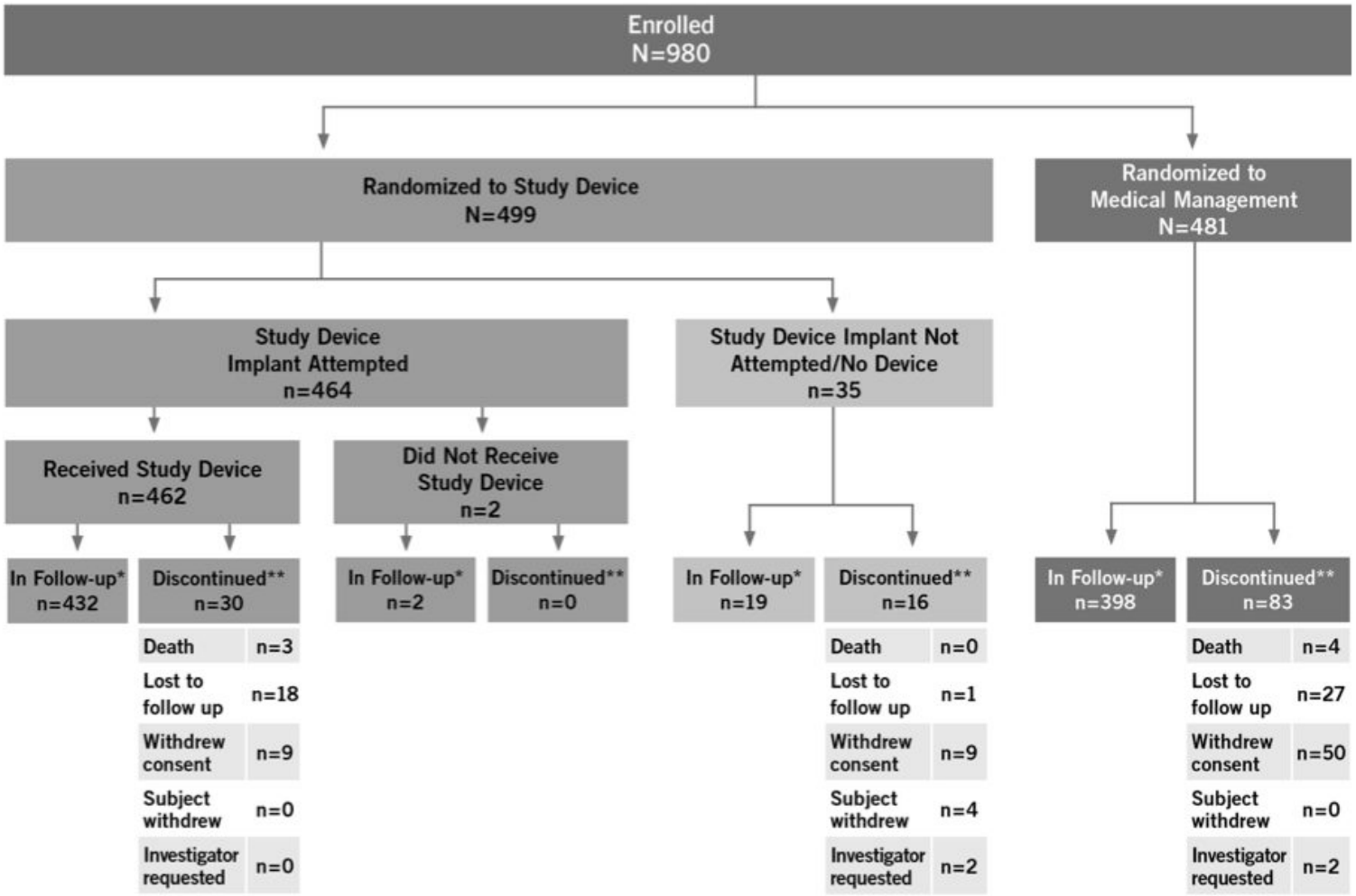
No differences between the two groups

	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	

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

Patient Disposition:
Randomization and Follow-Up



* Completed primary endpoint follow-up
** Discontinued prior to primary endpoint

RESPECT Efficacy Analyses

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

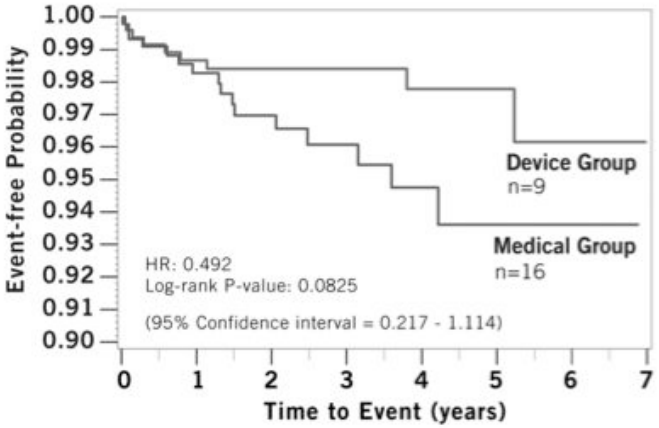
Totality of Evidence

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

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

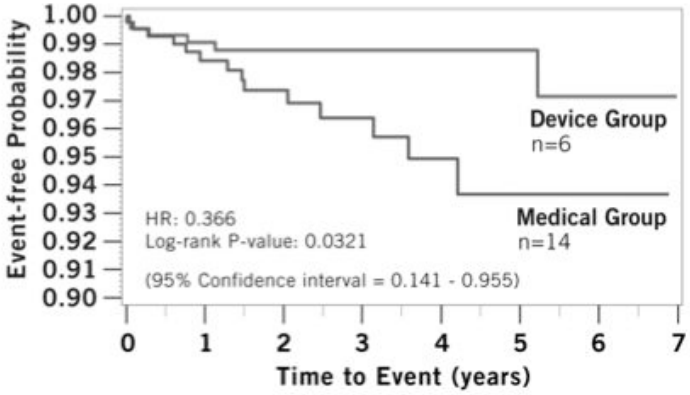
Primary Endpoint Analyses – ITT Cohort

50.8% risk reduction of stroke in favor of device



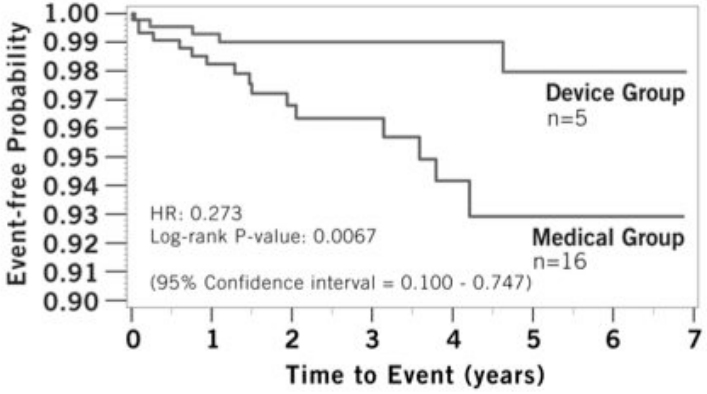
Primary Endpoint Analyses – PP Cohort

63.4% risk reduction of stroke in favor of device



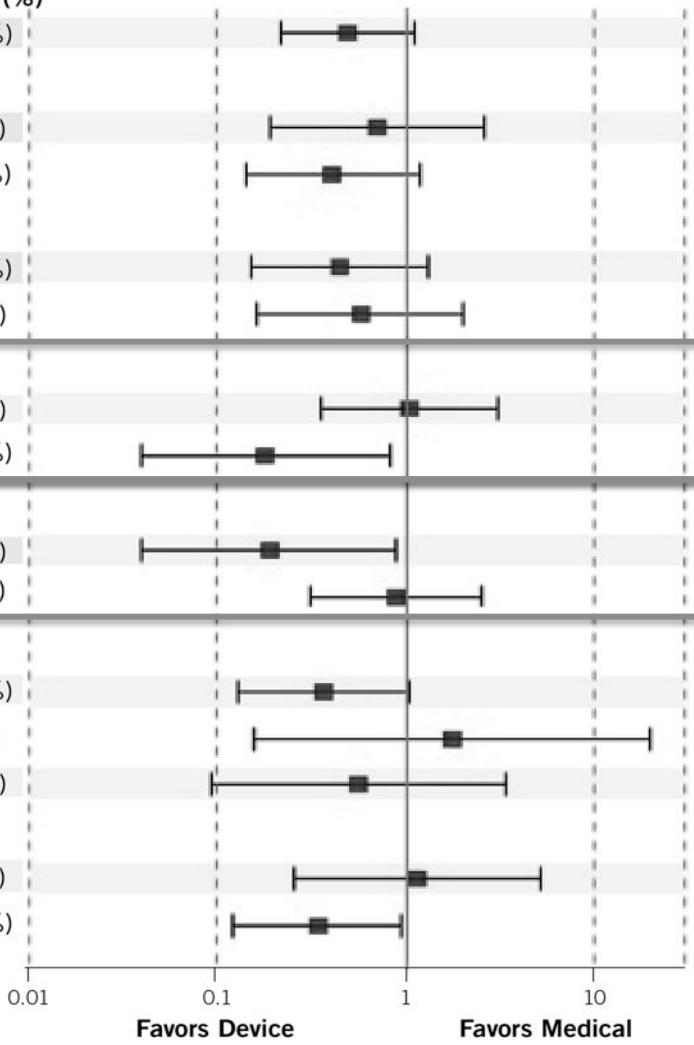
Primary Endpoint Analyses – AT Cohort

72.7% risk reduction of stroke in favor of device



Subpopulation Differential Treatment Effect

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	



Lesion Size of Endpoint Ischemic Strokes

Recurrent larger infarcts were more frequent in the Medical Group at 69.2% vs. 14.3% in the Device Group

RESPECT CLINICAL TRIAL

Lesion size	Device Group n=7	Medical Group n=13	All Subjects n=20	P-value
Small (<0.5 cm)	42.9%	23.1%	30%	0.09[a]
Intermediate (0.5-1.5 cm)	42.9%	7.7%	20%	
Moderate (1.6-3.0 cm)	0.0%	30.8%	20%	
Large (3.1-6.0 cm)	14.3%	15.4%	15%	
Massive (>6.0 cm)	0.0%	23.1%	15%	
Larger (≥ 1.5 cm)	14.3%	69.2%	50%	0.06[b]

a. P-values calculated using Mann-Whitney-Wilcoxon Test
b. P-values calculated using Fisher's Exact test

Stroke Mechanism Aspects of Endpoint Ischemic Strokes – Device Arm

RESPECT CLINICAL TRIAL

- 3 of the 9 device arm ischemic strokes occurred in patients without a device in place
  - 1 after randomization but prior to PFO occluder implant
  - 1 in patient who declined procedure and crossed to medical therapy
  - 1 in patient who required a CABG after randomization but prior to study procedure and who underwent bovine pericardium patch PFO repair during the surgery instead of device closure
- Of the remaining 6 device arm ischemic strokes
  - 2 had alternative causes evident (SLE, radiation)
  - 2 were small, deep only infarcts

The study also showed that PFO closure with the AMPLATZER PFO Occluder has **very low risk of device or procedural complications**.

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%)

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

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

Conclusion

- With stringent patient selection to identify patients with a history of cryptogenic stroke and PFO, closure with the AMPLATZER PFO Occluder showed evidence of benefit over medical management alone.

  Primary analysis of ITT cohort was not statistically significant but trended toward superiority while secondary analyses suggested superiority.

  Stroke risk reduction was observed across the totality of analyses with

  rates ranging from 46.6% - 72.7% .
- PFO closure with the AMPLATZER PFO Occluder exposes patients to a very low risk of device- or procedure-related complications
- Results of the RESPECT Trial have substantial import for the treatment of patients with a history of cryptogenic stroke and PFO
- Follow-up of patients is on-going and will continue to provide additional longer term information regarding benefits, risks, and differential treatment effects in sub-populations

“Meta-analyses”

- **PFO closure better**
  - Renfigo-Moreno P. et al: European Heart Journal 2013
  - Khan AR et al: J Am Coll Cardiol Intv 2013
  - Pineda AM et al: Cath and Cardiovasc Intv 2013
  - Pandit A et. al: Heart, Lung and Circulation 2014

- **No statistical differences**
  - Hakeem A et al: Cardiovascular Revascularization Medicine 2013
  - Wolfrum M et al: Heart 2013 (3RCT + 11 no-RCT)
  - Kwong JSW et al: International Journal of Cardiology 2013
  - Nagaraja V et al: Heart, Lung and Circulation 2013
  - Capodanno D et al: Eurointervention Journal 2014*
  - Ntaios G el at: International Journal of Cardiology 2013*

- **Uncertain Benefit**
  - Kitsios GD et al: Stroke 2013

Device Closure of Patent Foramen Ovale Versus Medical Therapy in Cryptogenic Stroke

A Systematic Review and Meta-Analysis

Abdur R. Khan, MD,* Aref A. Bin Abdulhak, MD,† Mujeeb A. Sheikh, MD,* Sobia Khan, MBBS,* Patricia J. Erwin, MLS,‡ Imad Tleyjeh, MD,§||¶ Sadik Khuder, PHD,# Ehab A. Eltahawy, MD*

Toledo, Ohio; Kansas City, Missouri; Rochester, Minnesota; and Riyadh, Kingdom of Saudi Arabia

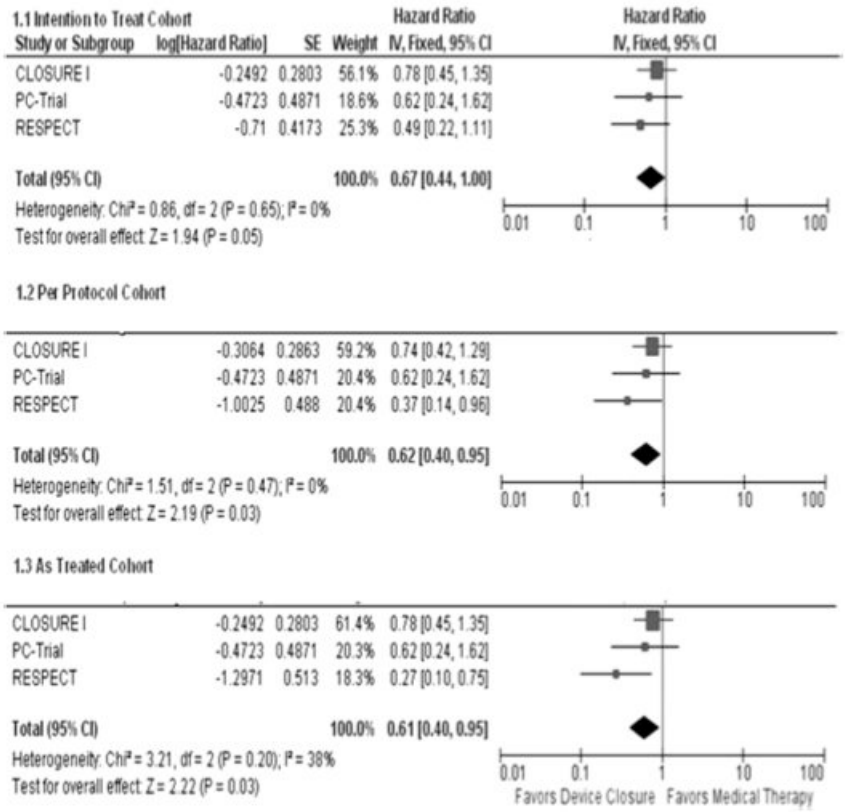


Figure 2. Forest Plot Comparing the Efficacy of Device Closure Arm and Medical Therapy Arm

Stratified based on intention-to-treat, per-protocol, and as-treated cohorts. CI = confidence interval; CLOSURE I = Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale (PFO) (16); df = degrees of freedom; PC Trial = Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism (14); RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (15); SE = standard error.

Device Closure of Patent Foramen Ovale Versus Medical Therapy in Cryptogenic Stroke

A Systematic Review and Meta-Analysis

Abdur R. Khan, MD,* Aref A. Bin Abdulhak, MD,† Mujeeb A. Sheikh, MD,* Sobia Khan, MBBS,* Patricia J. Erwin, MLS,‡ Imad Tleyjeh, MD,§||¶ Sadik Khuder, PHD,# Ehab A. Eltahawy, MD*

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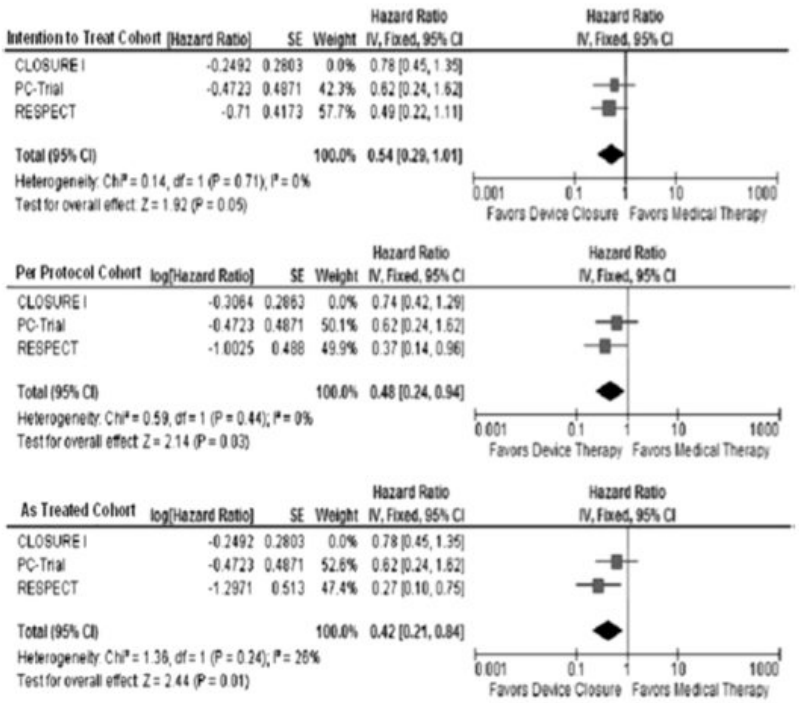


Figure 3. **Forest Plot Comparing the Efficacy of Device Closure Arm and Medical Therapy Arm: Pooled Analysis of RESPECT and the PC Trial**

Stratified based on intention-to-treat, per-protocol, and as-treated cohorts. Abbreviations as in Figure 2.

Conclusions Our meta-analysis suggests that PFO closure is beneficial as compared to medical therapy in the prevention of recurrent neurological events. This meta-analysis helps to further strengthen the role of device closure in cryptogenic stroke. (J Am Coll Cardiol Intv 2013;6:1316–23)

Potentially Large yet Uncertain Benefits
A Meta-analysis of Patent Foramen Ovale Closure Trials

Meta-analysis Results for the Hazard Ratio of Stroke and Additional Outcome

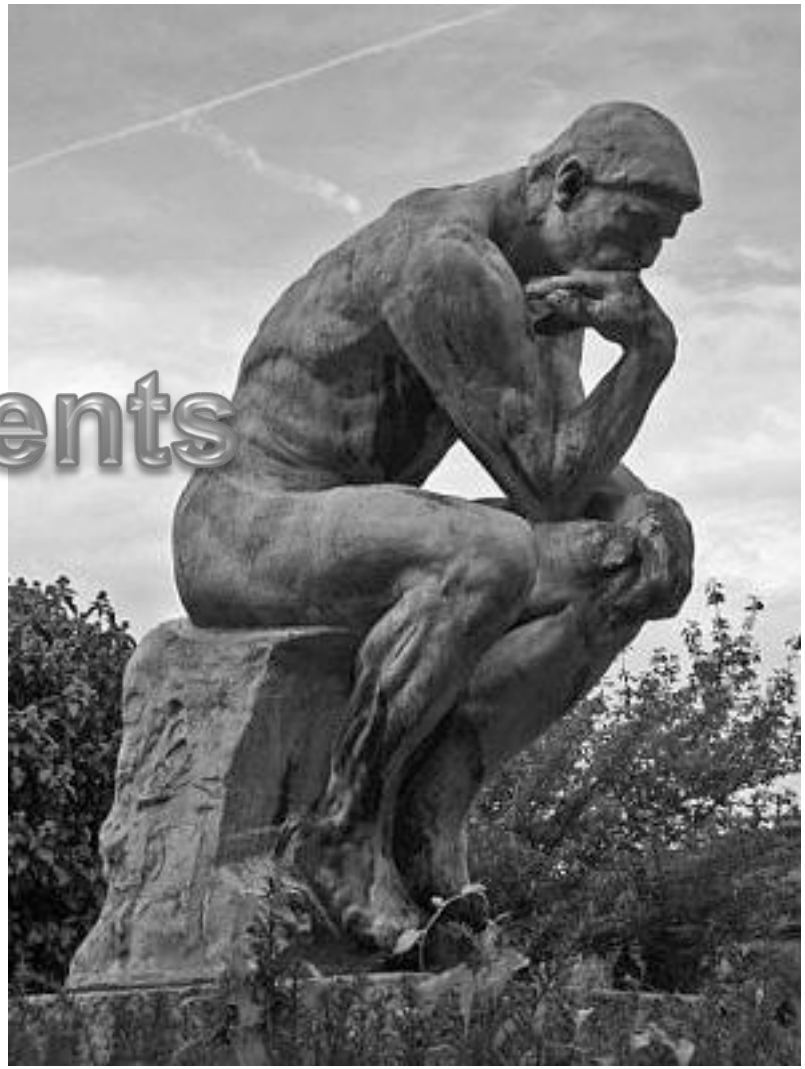
Outcome	All Device (No. Of Studies)	Amplatzer Only RCTs (n=2)	
	Random Effect Model	Random Effect Model	Fixed Effect Model
Stroke (ITT)	0.55 (0.26-1.18), n=3	0.38 (0.14-1.02)	**0.41 (0.19-0.88)**
Stroke/TIA (ITT)	0.69 (0.43-1.13), n=2	NA	NA
Composite primary outcome (ITT)	**0.67 (0.44-1.00), n=3**	0.54 (0.29-1.01)	0.54 (0.29-1.01)
Composite primary outcome (PP)	0.57 (0.32-1.02), n=3	0.44 (0.17-1.12)	**0.44 (0.22-0.89)**

The main message of these analysis is that the uncertainty of the individual trials s n resolved by combining theirs results through meta-analysis.

Kitsios GD et al. Stroke, 2013; 44:2640-264

PFO Closure and Stroke

How to select patients



The RoPe Score

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

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Jean-Louis Mas, MD
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Federica Papetti, MD
David E. Thaler, MD, PhD

ABSTRACT

Objective: We aimed to create an index to stratify cryptogenic stroke (CS) patients with patent foramen ovale (PFO) by their likelihood that the stroke was related to their PFO.

Methods: Using data from 12 component studies, we used generalized linear mixed models to predict the presence of PFO among patients with CS, and derive a simple index to stratify patients with CS. We estimated the stratum-specific PFO-attributable fraction and stratum-specific stroke/TIA recurrence rates.

Results: Variables associated with a PFO in CS patients included younger age, the presence of a cortical stroke on neuroimaging, and the absence of these factors: diabetes, hypertension, smoking, and prior stroke or TIA. The 10-point Risk of Paradoxical Embolism score is calculated from these variables so that the youngest patients with superficial strokes and without vascular risk factors have the highest score. PFO prevalence increased from 23% (95% confidence interval [CI]: 19%–26%) in those with 0 to 3 points to 73% (95% CI: 66%–79%) in those with 9 or 10 points, corresponding to attributable fraction estimates of approximately 0% to 90%. Kaplan-Meier estimated stroke/TIA 2-year recurrence rates decreased from 20% (95% CI: 12%–28%) in the lowest Risk of Paradoxical Embolism score stratum to 2% (95% CI: 0%–4%) in the highest.

Conclusion: Clinical characteristics identify CS patients who vary markedly in PFO prevalence, reflecting clinically important variation in the probability that a discovered PFO is likely to be stroke-related vs incidental. Patients in strata more likely to have stroke-related PFOs have lower recurrence risk. *Neurology*® 2013;81:619–625

GLOSSARY

auROC = area under the receiver operating characteristic curve; **CS** = cryptogenic stroke; **PFO** = patent foramen ovale; **RoPE** = Risk of Paradoxical Embolism.

RoPE Score variables

Table 3 Multivariate regression model predicting presence of PFO

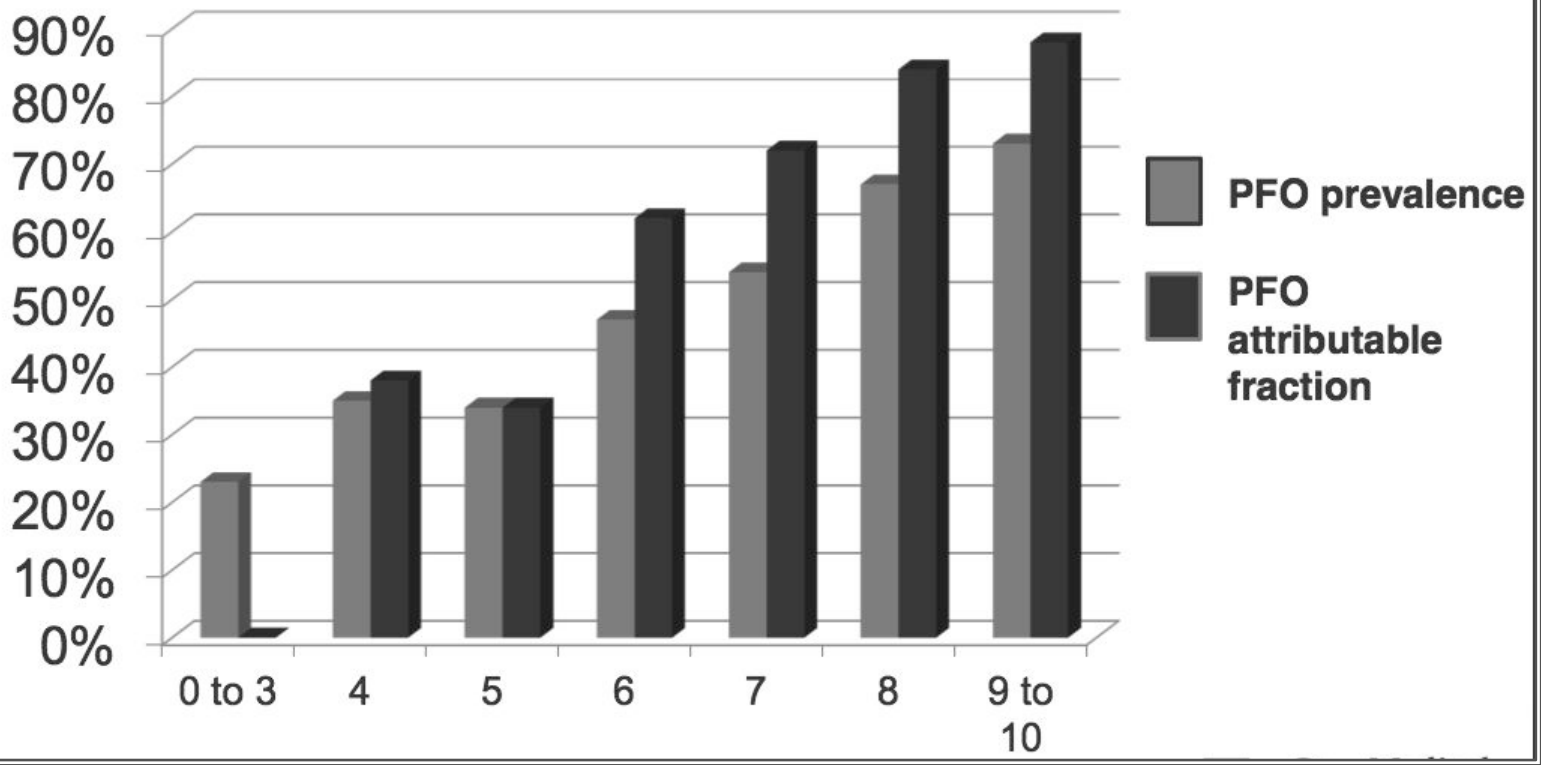
Term in model[a]	OR (95% CI)	*p* Value
Age, per 10-y increase	0.72 (0.67-0.77)	<0.0001
Diabetes	0.65 (0.51-0.83)	0.0006
Hypertension	0.68 (0.57-0.81)	<0.0001
Current smoker	0.60 (0.50-0.71)	<0.0001
History of stroke or TIA	0.78 (0.62-0.99)	0.0375
Radiology, deep (vs superficial)	0.68 (0.54-0.84)	0.0006

Abbreviations: CI = confidence interval; OR = odds ratio; PFO = patent foramen ovale.
[a] Adjusted for sex and index stroke vs TIA.

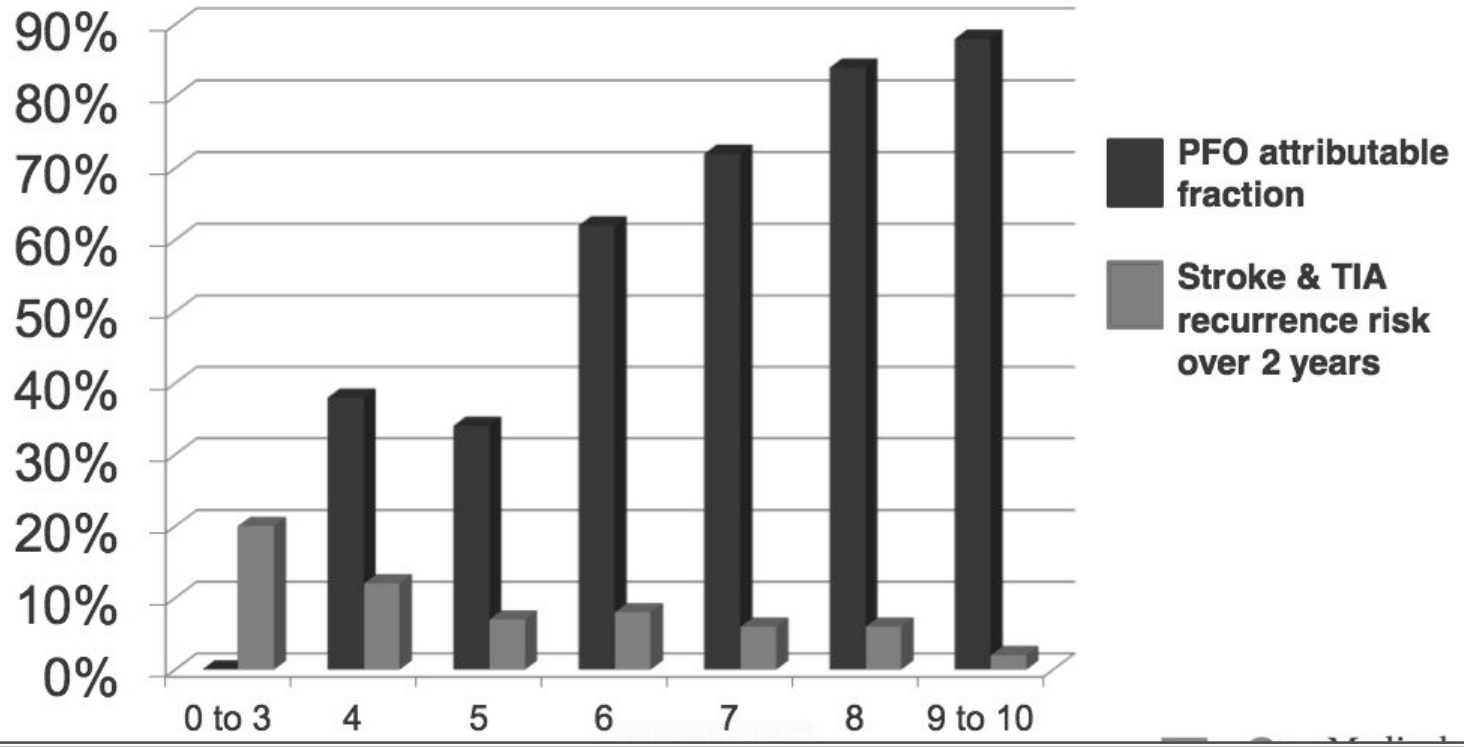
RoPE Score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Increasing RoPE score
→ Increasing PFO prevalence, and
→ Increasing PFO attributable fraction



Increasing RoPE score
→ Increasing PFO attributable fraction
→ Decreasing TIA/Stroke recurrence risk



Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

David E. Thaler, MD, PhD; Robin Ruthazer, MPH; Emanuele Di Angelantonio, MD, MSc; Marco R. Di Tullio, MD; Jennifer S. Donovan, MS; Mitchell S.V. Elkind, MD, MS; John Griffith, PhD; Shunichi Homma, MD, FACC; Cheryl Jaigobin, MD, FRCP, MSc; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Patrik Michel, MD; Marie-Luise Mono, MD; Krassen Nedeltchev, MD, FESC; Federica Papetti, MD; Joaquín Serena, MD, PhD; Christian Weimar, MD; David M. Kent, MD, CM, MSc

Background and Purpose—Patent foramen ovale (PFO) and cryptogenic stroke are commonly associated but some PFOs are incidental. Specific radiological findings associated with PFO may be more likely to indicate a PFO-related cause. We examined whether specific radiological findings are associated with PFO among subjects with cryptogenic stroke and known PFO status.

Methods—We analyzed the Risk of Paradoxical Embolism(RoPE) Study database of subjects with cryptogenic stroke and known PFO status, for associations between PFO and: (1) index stroke seen on imaging, (2) index stroke size, (3) index stroke location, (4) multiple index strokes, and (5) prior stroke on baseline imaging. We also compared imaging with purported high-risk echocardiographic features.

Results—Subjects (N=2680) were significantly more likely to have a PFO if their index stroke was large (odds ratio [OR], 1.36; P=0.0025), seen on index imaging (OR, 1.53; P=0.003), and superficially located (OR, 1.54; P<0.0001). A prior stroke on baseline imaging was associated with not having a PFO (OR, 0.66; P<0.0001). Finding multiple index strokes was unrelated to PFO status (OR, 1.21; P=0.161). No echocardiographic variables were related to PFO status.

Conclusions—This is the largest study to report the radiological characteristics of patients with cryptogenic stroke and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts. There was no association between PFO and multiple acute strokes nor between specific echocardiographic PFO features with neuroimaging findings. **(*Stroke*. 2013;44:675-680.)**

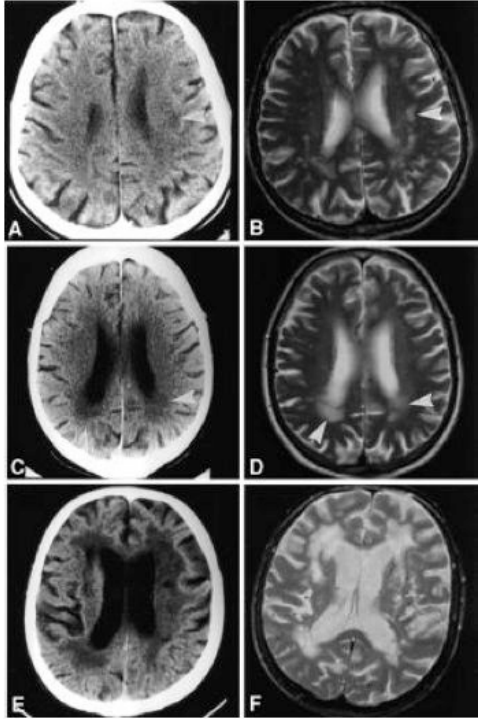


Table 4. PFO Prevalence by Presence or Absence of Radiological Variables

	All			
Variable	Total, n	% With PFO	Adjusted Odds Ratio	*P* Value
Index stroke large				
No	681	37		
Yes	1290	43	1.36	0.0025
Index stroke seen				
No	265	36		
Yes	2040	43	1.53	0.003
Superficial location				
No	779	37		
Yes	1018	48	1.54	<0.0001
Multiple index strokes				
No	1601	41		
Yes	278	43	1.21	0.1614
Prior stroke				
No	1547	43		
Yes	592	33	0.66	<0.0001

Odds ratios and *P* values are adjusted for site as a random effect.
PFO indicates patent foramen ovale.

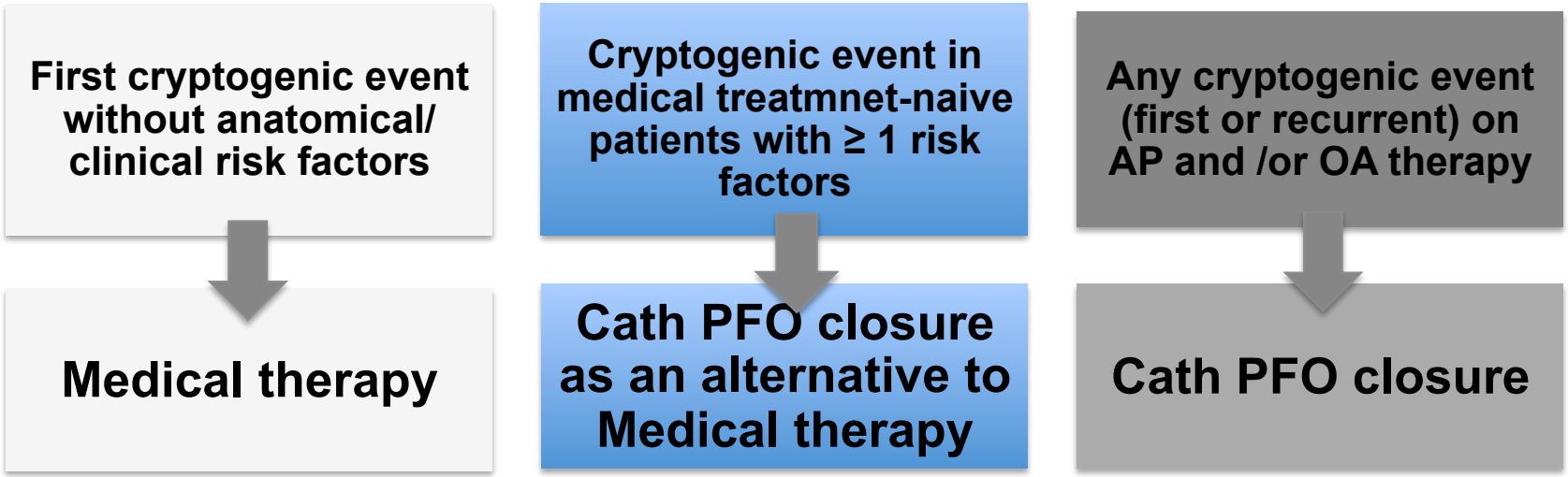
***Conclusions*—This is the largest study to report the radiological characteristics of patients with cryptogenic stroke and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts. There was no association between PFO and multiple acute strokes nor between specific echocardiographic PFO features with neuroimaging findings.**

PFO and Cryptogenic Stroke

- Cryptogenic stroke does not = PFO stroke
- We need a “CHAD score” for PFO’s similar to that in atrial fibrillation
- Anatomy may play a role
- The recurrance rate is low
- We still have no idea what is OMT
- Device does matter
- We don’t know the OMT post closure
- Meta-Analyses…….
- Open, transparent and thorough discussion required prior the closure.

Italian scientific societies position paper

Cryptogenic Stroke/TIA (syntomatic/asyntomatic) & PFO with R-L shun



Anatomical risk factors

- Atrial septal aneurysm
- Large PFO (> 4 mm)
- Basal R-L shunt
- Eustachian valve >10 mm
- Chiari network
- Long PFO tunnel

Clinical risk factors

- Multiple ischemic lesions on CT/MR
- Recurrent clinial events
- History of DVT/PE and/or Thrombophilia
- Valsalva ssociated embolic event
- OSAS
- Long travel/immobilization associated event
- Simultaneous systemic/pulmonary embolism

Catheterization and Cardiovasc Interv. 2013; 82:122-12

Stroke conditions e Linee guida Italiane "SPREAD" marzo 2012

Indicazioni	Terapia	Grado dell'evidenza
Nei pazienti con ictus ischemico o TIA criptogenetico associato a PFO ed esenti da TVP e diatesi trombofilica	**ASA 325 mg**	**A**
Nei pazienti con ictus ischemico o TIA criptogenetico associato a PFO, che hanno altre indicazioni alla TAO, (diatesi trombofilica o evidenza di TVP)	**TAO**	**A**
Nei pazienti con ictus o TIA criptogenetico associato a PFO, con TVP o diatesi trombofilica e controindicazioni alla TAO	**Chiusura PFO**	**D**
Nei pazienti con recidiva di ictus o TIA , in presenza di trattamento con ASA o TAO, dopo un a rivalutazione multidisciplinare del caso e in accordo con il paziente	**Chiusura PFO**	**D**

A almeno una metanalisi, revisione sistematica, o RCT classificato di livello 1++ condotto direttamente sulla popolazione bersaglio; *oppure* revisione sistematica di RCT o un insieme di evidenze costituito principalmente da studi classificati di livello 1+, consistenti tra loro, e applicabile direttamente alla popolazione bersaglio.**B** un insieme di evidenze che includa studi classificati di livello 2++, coerenti tra loro, e direttamente applicabili alla popolazione bersaglio; *oppure* evidenza estrapolata da studi classificati come 1++ o 1+. **C** un insieme di evidenze che includa studi classificati di livello 2+, coerenti tra loro e direttamente applicabili alla popolazione bersaglio; *oppure* evidenza estrapolata da studi classificati come 2++.**D** evidenza di livello 3 o 4; *oppure* evidenza estrapolata da studi classificati come 2+; *oppure* evidenza da studi classificati come – (meno), indipendentemente dal livello.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Walter N. Kernan, Bruce Ovbiagele, Henry R. Black, Dawn M. Bravata, Marc I. Chimowitz, Michael D. Ezekowitz, Margaret C. Fang, Marc Fisher, Karen L. Furie, Donald V. Heck, S. Claiborne (Clay) Johnston, Scott E. Kasner, Steven J. Kittner, Pamela H. Mitchell, Michael W. Rich, DeJuran Richardson, Lee H. Schwamm and John A. Wilson

Stroke. published online May 1, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
PFO	For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B).*	Class changed from IIa to I
	For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A).* When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C).*	New recommendations
	For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure *(Class III; Level of Evidence A).*	Class changed from IIb to III
	In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C).*	New recommendation

EDITORIAL

Still No Closure on the Question of PFO Closure

Steven R. Messé, M.D., and David M. Kent , M.D.

N Engl J Med, 368; 12 March 21, 2013