Why we should close patent foramen ovale (PFO)

SOLACI@EuroPCR Invitation

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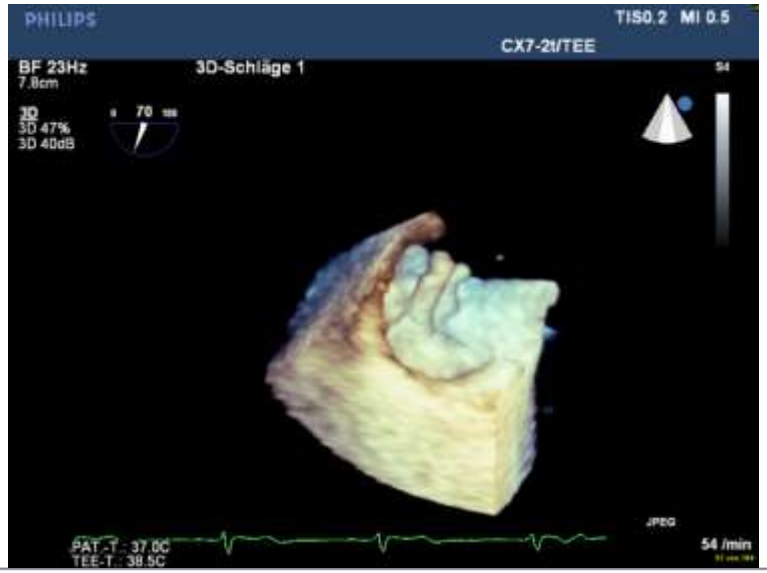
Potential conflicts of interest

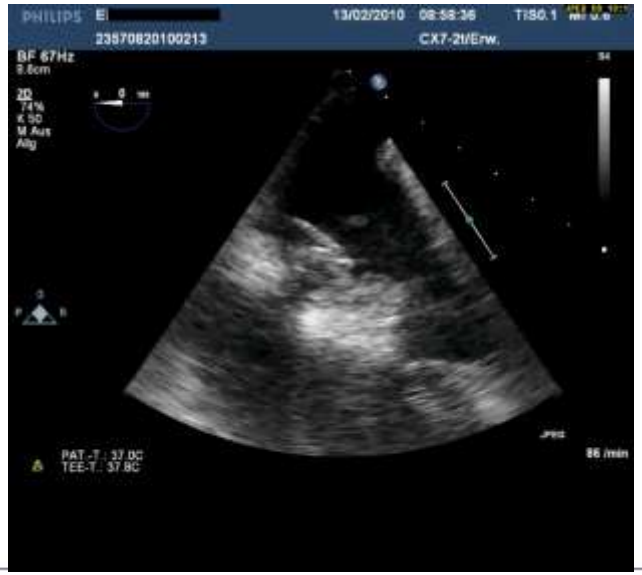
Speaker's name: Ralph Stephan von Bardeleben

None for this presentation

Role of PFO in Stroke

- In cryptogenic stroke in the young (up to 40% of stroke) prevalence of atrial shunt 40% (10-25% in normal population)
  - 2 x times higher than in normal population
  - Clearly some relationship, which patients?
- Evidence for role of PFO
  - Clear cases are rare:
- 48 yo simultaneous PE and TIA, large PFO IASA
  - Is PFO the only potential cause and what the risk of recurrence is
  - Worth intervening if significant risk of recurrence





Sources: Tony Rudd London Csi Congress 2009 / Images von Bardeleben Mainz

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

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

Anthony J. Furlan, MD

Patent foramen ovale (PFO), a common congenital cardiac anomaly in the general population, is more prevalent among patients with stroke <50 years of age, especially patients with "cryptogenic" stroke. That a PFO can serve as a conduit for brain emboli is not in dispute. Right-to-left shunting is easily demonstrated on echocardiography with agitated saline. If the bubbles (ie, emboli) can get from the right heart to the left heart, they can get to the brain.

Although warfarin has been the "conventional" medical therapy for patients with PFO and transient ischemic attack (TIA) or stroke, there are few data to support its routine use and associated risk of bleeding. In a French study,[1] the 2-year risk of stroke or TIA was not increased in patients with cryptogenic stroke and a PFO alone treated with aspirin, but was increased from 4.7% to 8.0% in patients with PFO and

devices also appears excellent, with a 5-year failure rate of <1%.

One of the persuasive arguments for PFO closure is the avoidance of long-term warfarin. Warfarin carries a 1% per year risk of significant hemorrhage, no small consideration especially in younger patients. Of course, the issue of long-term warfarin risk becomes moot if aspirin works just as well. After percutaneous PFO closure, patients are treated with aspirin indefinitely and with clopidogrel usually for 6 months.

In the United States, percutaneous PFO closure is permitted under an FDA Humanitarian Device Exemption (HDE). The specific HDE wording for the CardioSEAL® device is instructive:

Sources:Windecker Circulation and Furlan Stroke 2004

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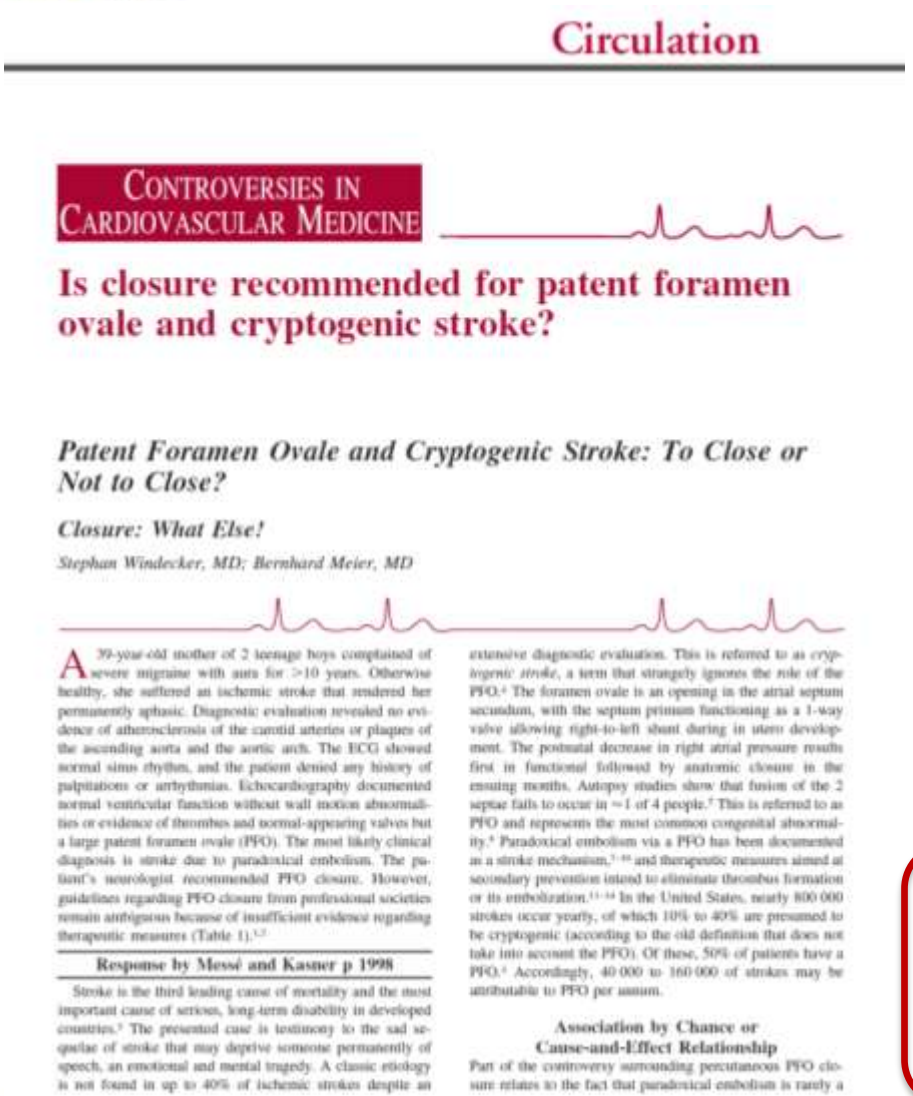
Guidelines



Circulation

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Is closure recommended for patent foramen ovale and cryptogenic stroke?

Patent Foramen Ovale and Cryptogenic Stroke: To Close or Not to Close?

Closure: What Else!

Stephan Windecker, MD; Bernhard Meier, MD

A 39-year-old mother of 2 teenage boys complained of severe migraine with aura for >10 years. Otherwise healthy, she suffered an ischemic stroke that rendered her permanently aphasic. Diagnostic evaluation revealed no evidence of atherosclerosis of the carotid arteries or plaques of the ascending aorta and the aortic arch. The ECG showed normal sinus rhythm, and the patient denied any history of palpitations or arrhythmias. Echocardiography documented normal ventricular function without wall motion abnormalities or evidence of thrombus and normal-appearing valves but a large patent foramen ovale (PFO). The most likely clinical diagnosis is stroke due to paradoxical embolism. The patient's neurologist recommended PFO closure. However, guidelines regarding PFO closure from professional societies remain ambiguous because of insufficient evidence regarding therapeutic measures (Table 1).[1,2]

Response by Messé and Kasner p 1998

Stroke is the third leading cause of mortality and the most important cause of serious, long-term disability in developed countries.[3] The presented case is testimony to the sad sequelae of stroke that may deprive someone permanently of speech, an emotional and mental tragedy. A classic etiology is not found in up to 40% of ischemic strokes despite an extensive diagnostic evaluation. This is referred to as *cryptogenic stroke*, a term that strangely ignores the role of the PFO.[4] The foramen ovale is an opening in the atrial septum secundum, with the septum primum functioning as a 1-way valve allowing right-to-left shunt during in utero development. The postnatal decrease in right atrial pressure results first in functional followed by anatomic closure in the ensuing months. Autopsy studies show that fusion of the 2 septae fails to occur in ≈1 of 4 people.[5] This is referred to as PFO and represents the most common congenital abnormality.[6] Paradoxical embolism via a PFO has been documented in a stroke mechanism,[7–10] and therapeutic measures aimed at secondary prevention intend to eliminate thrombus formation or its embolization.[11–14] In the United States, nearly 800 000 strokes occur yearly, of which 10% to 40% are presumed to be cryptogenic (according to the old definition that does not take into account the PFO). Of these, 50% of patients have a PFO.[4] Accordingly, 40 000 to 160 000 of strokes may be attributable to PFO per annum.

Association by Chance or Cause-and-Effect Relationship

Part of the controversy surrounding percutaneous PFO closure relates to the fact that paradoxical embolism is rarely a

Table 1. Guidelines From Professional Societies[1,2]

	American Academy of Neurology	American College of Chest Physicians
PFO	Insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (level U), but risks of minor bleeding are possibly greater with warfarin (level C); there is insufficient evidence regarding the effectiveness of surgical or percutaneous PFO closure (level U)	...
PFO alone	...	Antiplatelet therapy recommended over no therapy (grade 1C+), and antiplatelet therapy recommended over warfarin (grade 2A)
PFO and ASA	...	Inadequate data available to allow recommendation of optimal therapy
PFO with DVT or PE	At least 3 months of anticoagulation	Anticoagulation recommended

Sources:Windecker Circulation 2008

„HR TIA PFO 0.31 HR death and CV death identical“

Stroke

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

Background—Patients with ischemic stroke or transient ischemic attack presumably related to patent foramen ovale (PFO) are at risk for recurrent cerebrovascular events. Differences in long-term clinical outcome were investigated among patients with percutaneous PFO closure and those who received medical treatment.

Methods and Results—Between 1994 and 2000, 308 consecutive patients with cerebrovascular events presumably related to PFO underwent either percutaneous PFO closure (150 patients) or medical treatment (158 patients). Patients were followed up prospectively for up to 15 years. Seven patients were lost during follow-up. The primary outcome was a composite of stroke, transient ischemic attack, or peripheral embolism. We analyzed 103 propensity score–matched pairs of patients who underwent percutaneous PFO closure or medical treatment. 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). The treatment effect was driven by a decrease in the risk of transient ischemic attack of 5% versus 14%, respectively (hazard ratio=0.31; 95% confidence interval=0.10–0.94; P=0.039). The risk of all-cause (6% in both groups) and cardiovascular (3% in both groups) mortality appeared to be identical.

Conclusion—In this long-term observational, propensity score–matched study, percutaneous PFO closure was more effective than medical treatment for the secondary prevention of recurrent cerebrovascular events among patients with PFO-related transient ischemic attack or stroke. (***Circulation*. 2012;125:803-812.**)

RCT CLOSURE I: failure

Study Design of the CLOSURE I Trial

A Prospective, Multicenter, Randomized, Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients With Stroke or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale

Anthony J. Furlan, MD; Mark Reisman, MD; Joseph Massaro, PhD; Laura Mauri, MD, MSc; Harold Adams, MD; Gregory W. Albers, MD; Robert Felberg, MD; Howard Herrmann, MD; Saibal Kar, MD; Michael Landzberg, MD; Albert Raizner, MD; Lawrence Wechsler, MD; for the CLOSURE I Investigators

Background and Purpose—Some strokes of unknown etiology may be the result of a paradoxical embolism traversing through a nonfused foramen ovale (patent foramen ovale [PFO]). The utility of percutaneously placed devices for treatment of patients with cryptogenic stroke or transient ischemic attack (TIA) and PFO is unknown. In addition, there are no clear data about the utility of medical interventions or other surgical procedures in this situation. Despite limited data, many patients are being treated with PFO closure devices. Thus, there is a strong need for clinical trials that test the potential efficacy of PFO occlusive devices in this situation. To address this gap in medical knowledge, we designed the CLOSURE I trial, a randomized, clinical trial comparing the use of a percutaneously placed PFO occlusive device and best medical therapy versus best medical therapy alone for prevention of recurrent ischemic neurologic symptoms among persons with TIA or ischemic stroke.

Study Design—This prospective, multicenter, randomized, controlled trial has finished enrollment. Two-year follow-up for all 910 patients is required. The primary end point is the 2-year incidence of stroke or TIA, all-cause mortality for the first 30 days, and neurologic mortality from ≥31 days of follow-up, as adjudicated by a panel of physicians who are unaware of treatment allocation. This article describes the rationale and study design of CLOSURE I.

Conclusions—This trial should provide information as to whether the STARFlex septal closure system is safe and more effective than best medical therapy alone in preventing recurrent stroke/TIA and mortality in patients with PFO and whether the STARFlex septal closure device can demonstrate superiority compared with best medical therapy alone.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00201461.

(*Stroke*. 2010;41:2872-2883.)

Key Words: patent foramen ovale ■ cryptogenic stroke ■ atrial septal closure ■ right-to-left shunt ■ percutaneous closure

Device 1265 pat.yrs - 0.7% recurrent TIA/stroke StarFlex 10%Thrombus rate

Long term follow up after percutaneous closure of PFO in 357 patients with paradoxical embolism: Difference in occlusion systems and influence of atrial septum aneurysm

Ralph Stephan von Bardeleben [a], Claudia Richter [a], Julia Otto [a], Ludmilla Himmrich [a], Renate Schnabel [a], Christoph Kampmann [b], Hans-Jürgen Rupprecht [e], Jürgen Marx [c], Gerhard Hommel [d], Thomas Münzel [a], Georg Horstick [a,*]

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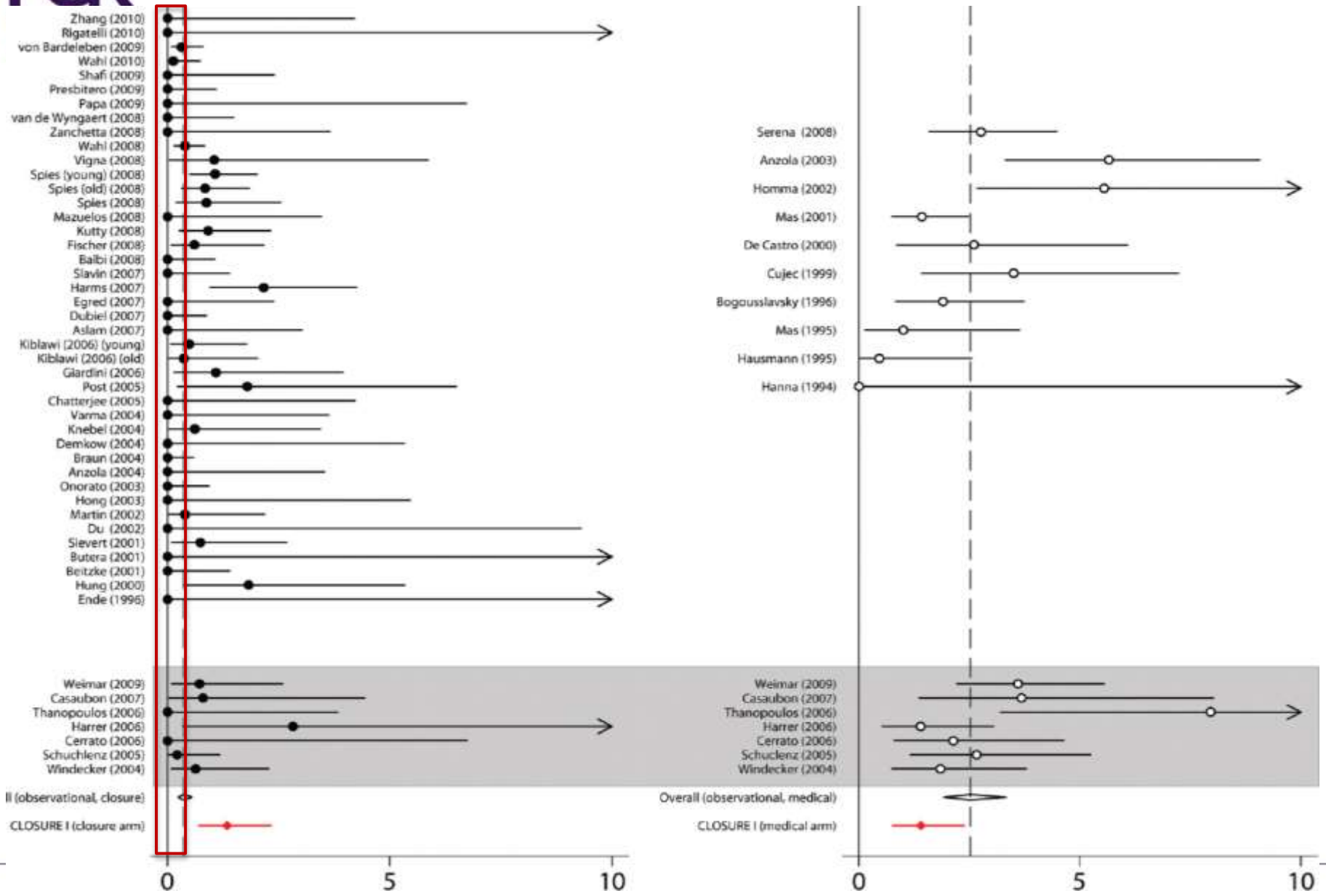
Available online 19 August 2008

Abstract

Background: Percutaneous transcatheter closure of patent foramen ovale (PFO) in cryptogenic stroke or TIA is an alternative to medical therapy especially in patients with atrial septal aneurysm (ASA). The differences in time to complete occlusion for various closure devices in PFO alone and PFO plus ASA are of natural interest.
Methods and results: Between January, 1st 1998 and November, 30th 2006 percutaneous PFO closure was performed in 357 patients with a history of ≥1 paradoxical embolism using three different devices: Amplatzer PFO-(n=199), Starflex-(n=48) and Helex Occluder (n=110). All patients were assigned to a post-interventional protocol with contrast-enhanced transesophageal echocardiography (TOE) at 1 and 6 months and every 6 to 12 months in case of incomplete closure. Definite closure was confirmed in at least two consecutive TOE studies. The closure time curves between the three devices were significantly different (p=0.0072). Devices of 25 mm or less had a better occlusion rate. The difference between the closure time curves of PFO and PFO+ASA concerning each device type was significant for Helex (p=0.006) and Starflex (p=0.030). In regard to the occlusion time for large devices Helex succeeded later than Amplatzer and Starflex (p=0.0029). Concerning the cumulative follow up period of 1265 patient years the recurrence/re-event rate of cerebral and peripheral thromboembolic events was 0.7% per patient year. No relation to residual PFO shunting or to thrombus formation was seen. There were no peri-interventional technical complications. In five patients of the Starflex group thrombi were detected in the four week TOE controls.
Conclusion: The closure rate is dependent on occluder size and type plus the occurrence of an atrial septum aneurysm.

Sources: von Bardeleben Int J Cardiol 2009



Meta analysis PFO vs medical Tx Stroke 2012

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Still No Closure on the Question of PFO Closure

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

In approximately 30% of young survivors of stroke, no clear cause is identified despite a thorough evaluation.[1] Patent foramen ovale is found on transesophageal echocardiography in about half of these patients, as compared with approximately 25% of the general population. Clinicians, then, often assume that the patent foramen ovale was the cause of the stroke, although it may be incidental in some patients.[2-4] The most effective

randomization and were followed for 2 years, the rate of the primary end point of stroke, transient ischemic attack, or systemic embolism was not significantly lower in patients who underwent closure with the use of the STARFlex device (NMT Medical) than in patients who received medical therapy (5.5% and 6.8%, respectively; P=0.37); the rate of the secondary outcome of stroke alone was also not significantly lower in

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Percutaneous Closure of Patent Foramen Ovale versus Medical Treatment in Patients with Cryptogenic Embolism:

The PC Trial

NCT00166257

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

TCT2012

CARDIOVASCULAR RESEARCH FOUNDATION

PROCEDURES

PERCUTANEOUS PFO CLOSURE

Amplatzer PFO Occluder

Acetylsalicylic acid (100-325mg qd)

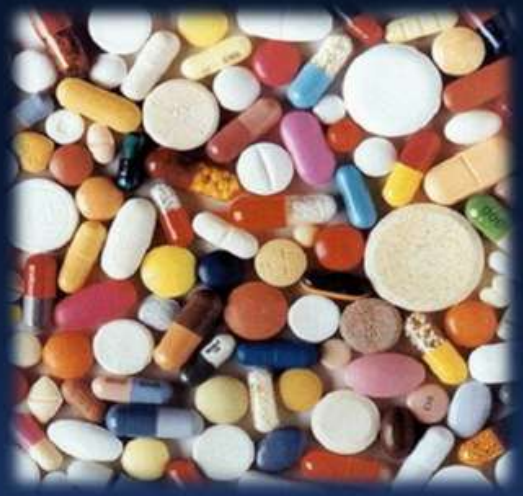
and ticlopidine (250-500mg qd)

or clopidogrel (75mg qd)

for 6 months

1:1

RCT



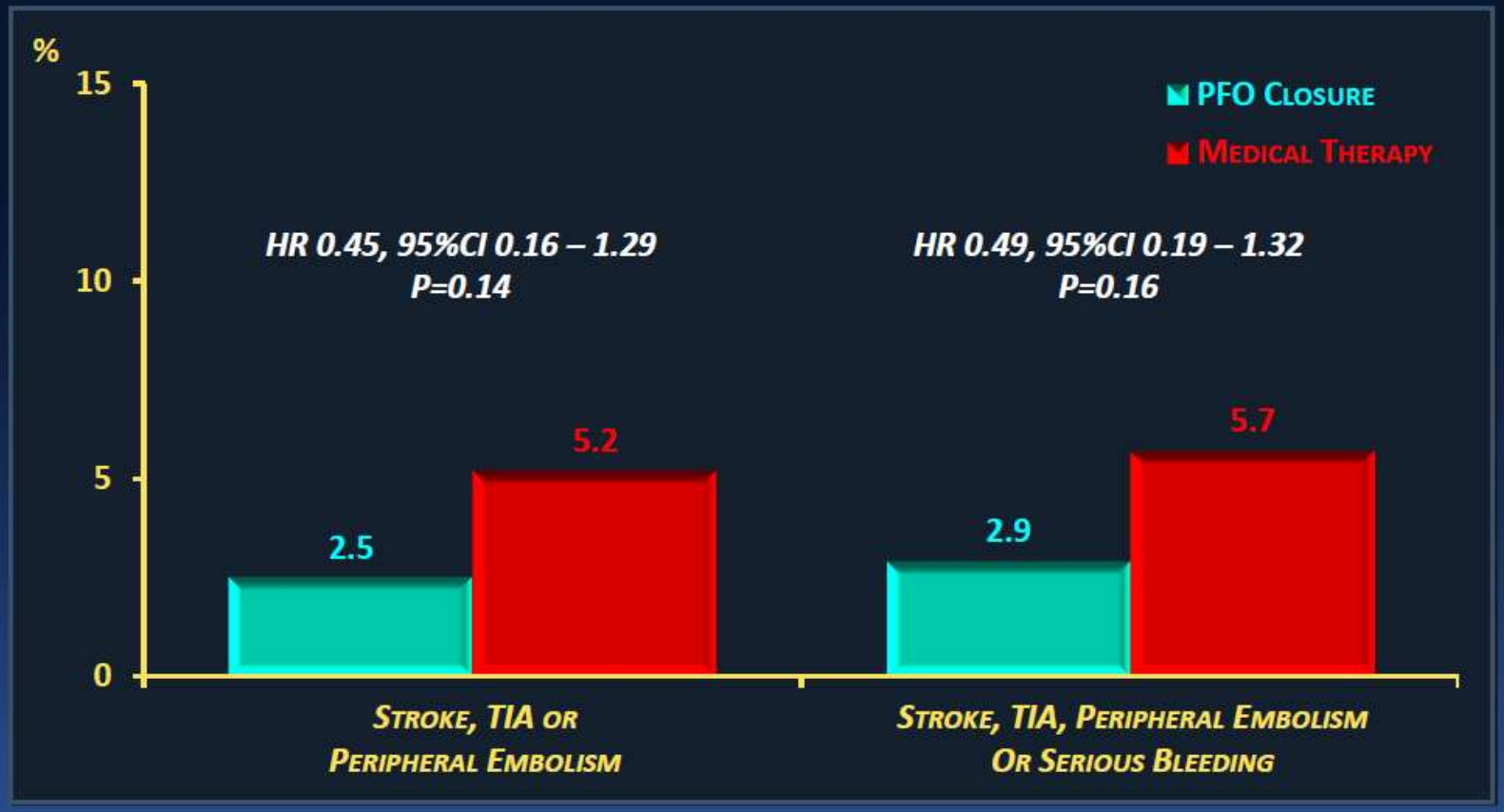
MEDICAL TREATMENT

Oral anticoagulation or

Antiplatelet therapy

at the discretion of the neurologist

Thromboembolic and Bleeding Events



Sources: PC trial NEJM 2013 and TCT 2012 presentation

RESPECT Device safety

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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

Sources: John Carroll RESPECT trial NEJM 2013 and Greg Stone TCT 2012 presentation

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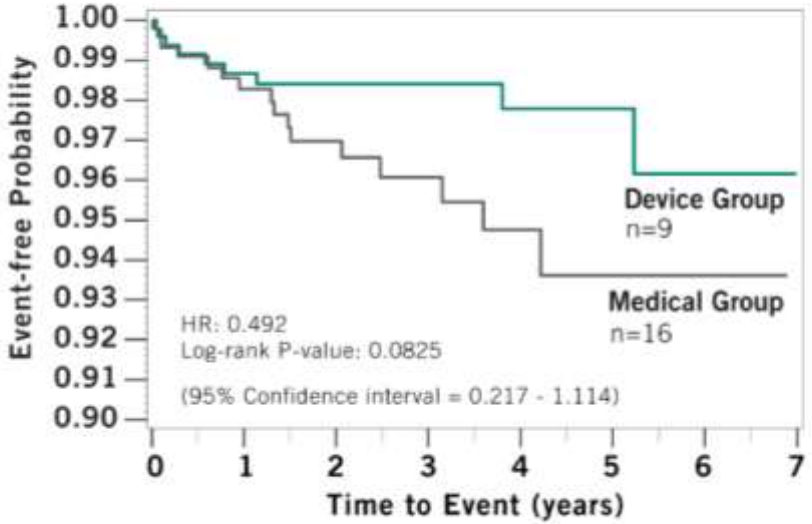
Primary Endpoint Analysis – ITT Cohort

50.8% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL



Recurrent Cerebral Infarct Size[1]

Methods pre-specified; analysis post-hoc

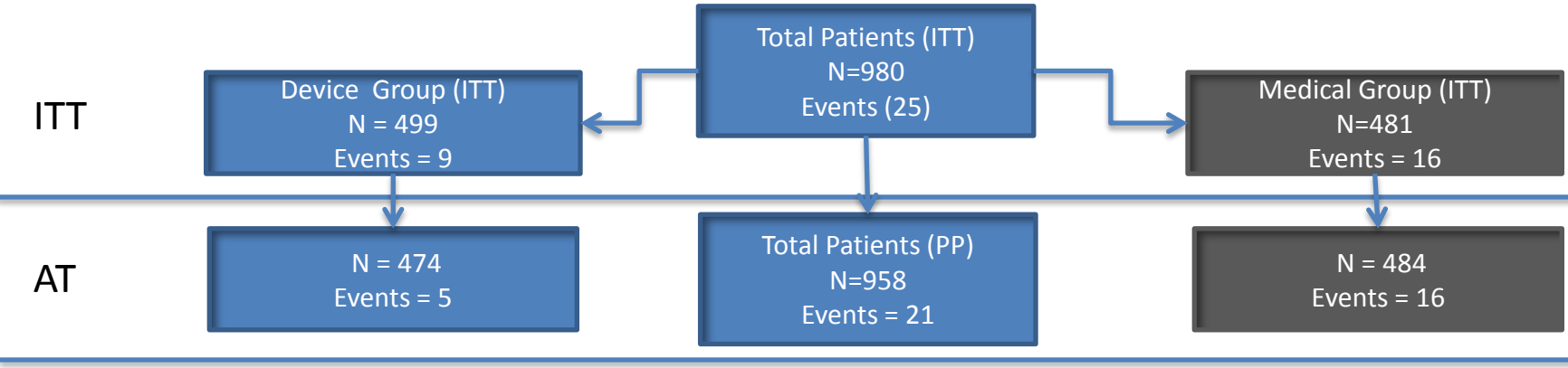
- **3/9** device group patients did not have a device at time of endpoint stroke

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

Sources: John Carroll RESPECT trial NEJM 2013 and Greg Stone TCT 2012 presentation

As Treated Cohort

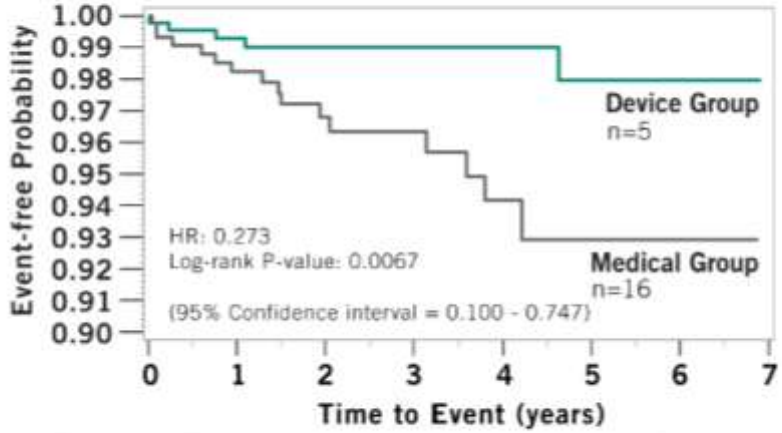


Device Group Exclusion Criteria	N Excluded	Events Excluded & Description
Did not comply with the protocol-mandated medical treatment	1	1 • Compliance rate of 29%
Did not receive randomized therapy or sought alternative protocol approved therapy	16	2 • 1 patient has CABG and patch closure • 1 patient event occurred after randomization but prior to implant procedure (Note: patient included, but event excluded)
Patients did not receive randomized therapy but followed medical treatment protocol	8	1

Medical Group Exclusion Criteria	N Excluded	Events Excluded & Description
Did not comply with the protocol-mandated medical treatment	5	1 • 1 patient discontinued meds (warfarin/ASA) due to biopsy (Note: patient included, but event excluded)
Medical Group Addition (cross over subjects)	**N Added**	**Events Added**
Did not receive randomized therapy but followed medical treatment protocol	8	1

RESPECT RCT AT HR 0.273 and PP HR 0.37

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

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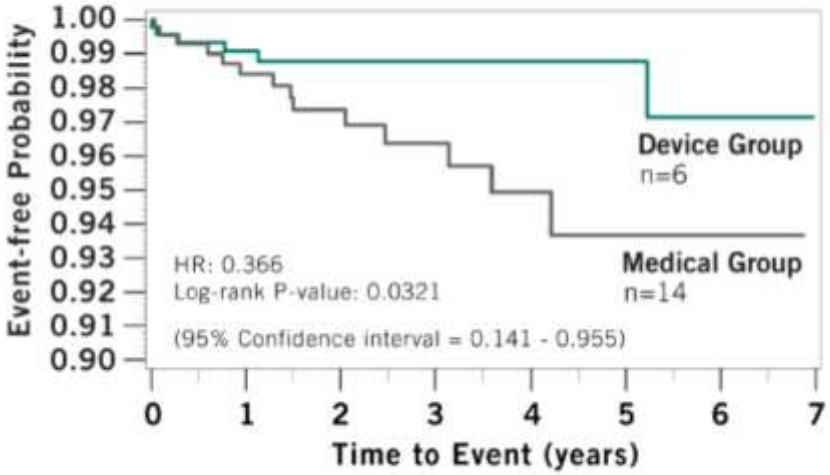
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



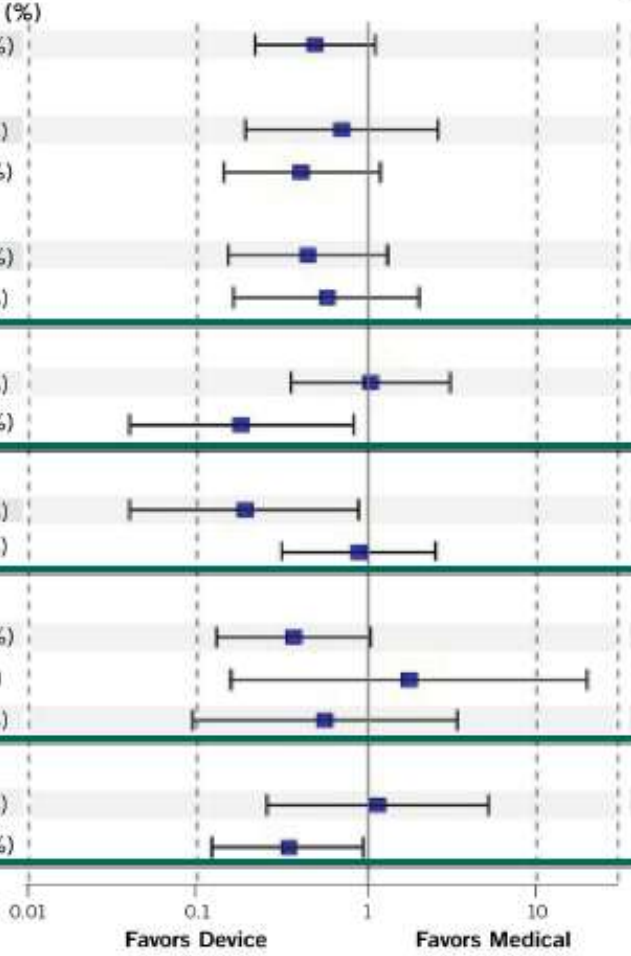
- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

Sources: John Carroll RESPECT trial NEJM 2013 and Greg Stone TCT 2012 presentation

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	



Sources: John Carroll RESPECT trial NEJM 2013 and Greg Stone TCT 2012 presentation

Conclusion

1) 3 RCT failed to show superiority of PFO closure on ITT
2) CLOSURE I had a high thrombus/TIA/Afib (x10) rate in Device Group
3) All RCT suffered from slow inclusion/Cross over/ low event rate due to low comorbidities and too low statistical power to draw solid assumptions (esp. PC trial)
4) Observational Meta-analysis Stroke 2012 and the RESPECT data on AT or PP analysis showed an impressive HR of 0.27 to 0.47 for the device group exceeding medical Tx – trend to smaller/less frequent TIA/stroke

THERE IS STILL NO FINAL CLOSURE ON PFO CLOSURE..