Is A Patent Foramen Ovale Really A Cause of Stroke?

And Would Closing It Help?

Kevin Wolfe M.D.

Sept 29,2017

Faculty/Presenter Disclosure

- **Faculty:** Kevin Wolfe
- **Relationships with commercial interests:**
  - none

Objectives

- To understand what a cryptogenic stroke is
- To understand what a PFO is
- To understand the risks/benefits of PFO closure

Cryptogenic Stroke

- Ischemic stroke of undetermined origin
- 25-40% of strokes are cryptogenic
- brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation

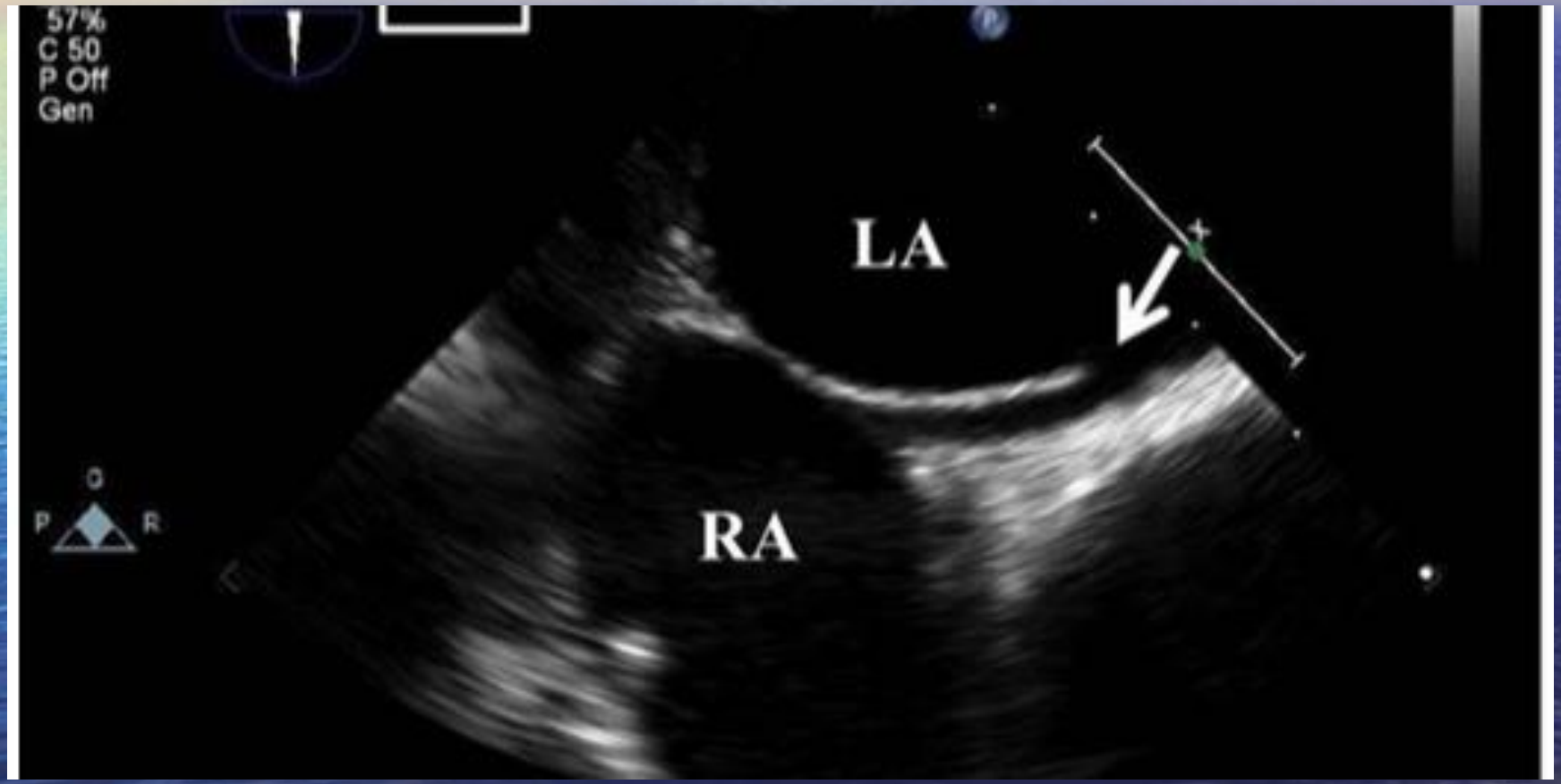
Cryptogenic Stroke

- Compared to strokes of identified cause
  - less severe presenting neurologic deficits, less final disability, and lower mortality.
  - Lower recurrence rates, 1.9% recurrence at one year, and 0.8% per year in years 2-4
    - N Engl J Med 2001;345:1740-6.

Cryptogenic Stroke

- In the setting of Cryptogenic stroke, we do not have a solid clinical cause of the stroke
- Generally a full evaluation by a cardiologist and a neurologist is required, and when they come up empty handed, you have a cryptogenic stroke
- Monitoring for clinically silent atrial fibrillation can be part of the evaluation and Dr Khadem will elaborate

Patent Foramen Ovale

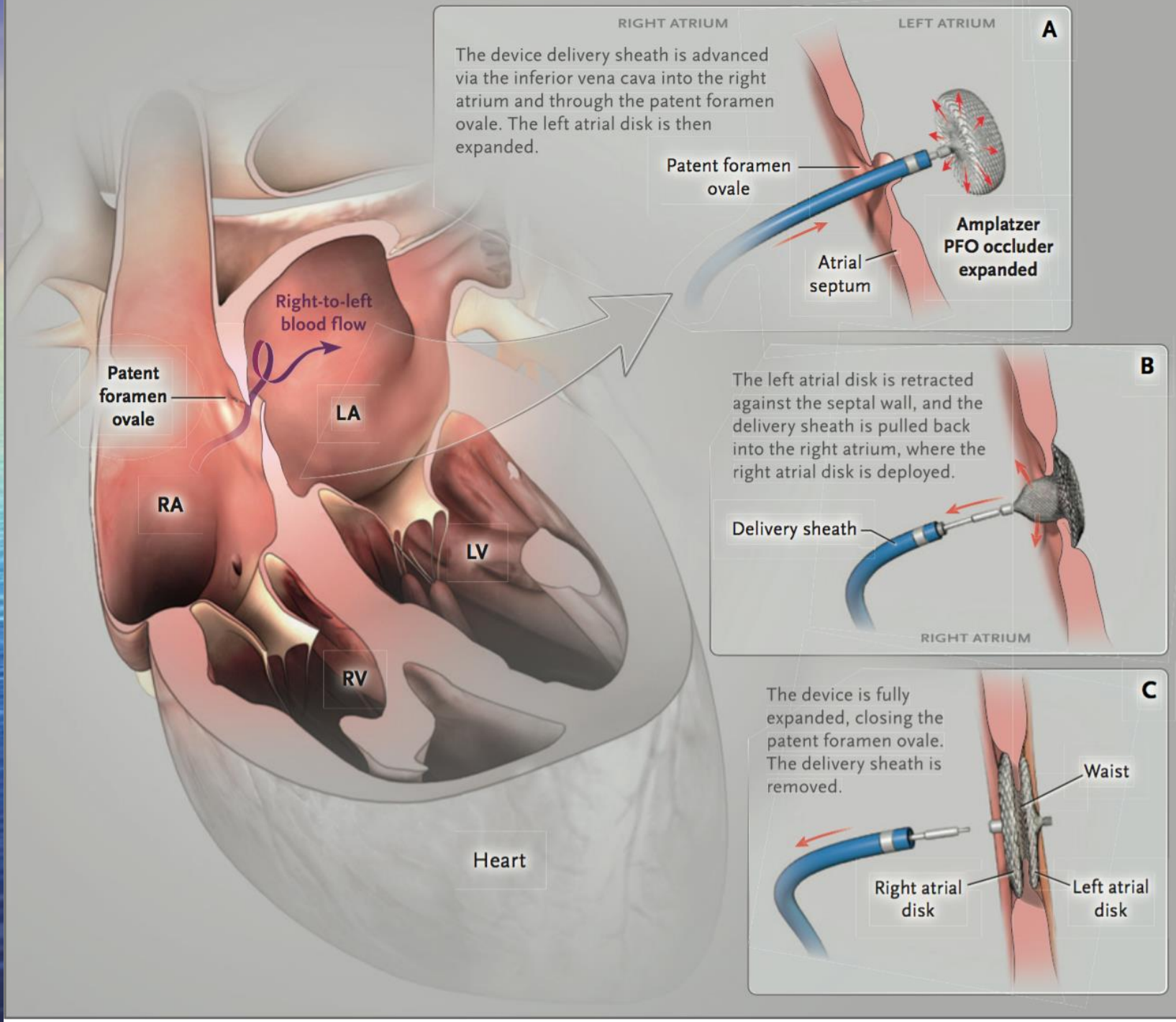


Patent Foramen Ovale

- 25% of the pop are thought to have a PFO and a PFO is present in 50% of cryptogenic strokes
  - Stroke 2009;40:2349-55.
- The role of PFO in stroke remains uncertain.
- Younger age and absence of traditional risk factors like hypertension, diabetes and smoking seem to more strongly suggest PFO as cause
- However patients thought to have a stroke from a PFO seem to have very low recurrence rates

Cryptogenic Stroke/PFO Treatment

- ASA +/- clopidogrel vs warfarin
  - No randomized data. In non randomized trials there is no difference between antiplatelets and anticoagulants
    - low recurrence risk favours antiplatelets
    - History of DVT, VTE, PE, hypercoagulability favours warfarin
- PFO Closure


RIGHT ATRIUM
LEFT ATRIUM
A
The device delivery sheath is advanced via the inferior vena cava into the right atrium and through the patent foramen ovale. The left atrial disk is then expanded.
Patent foramen ovale
Amplatzer PFO occluder expanded
Atrial septum
Right-to-left blood flow
Patent foramen ovale
LA
RA
LV
RV
Heart
B
The left atrial disk is retracted against the septal wall, and the delivery sheath is pulled back into the right atrium, where the right atrial disk is deployed.
Delivery sheath
RIGHT ATRIUM
C
The device is fully expanded, closing the patent foramen ovale. The delivery sheath is removed.
Waist
Right atrial disk
Left atrial disk

Closure Trial

NEJM, 2012,366(11),991

- 909 pts. , 18-60 with CS and a PFO on TEE with saline
- Closure with a starfix device vs medical tx.
- Primary endpoint was a composite of stroke or TIA, death from any cause in the first 30 days, neurologic death 30 days to 2 yrs
- Pts were mean 46 yrs, 89% white

Respect Trial

NEJM 2013 Mar;368(12)1083

- 980 pts, mean age 46(18-60) with CS and PFO by TEE
- Amplatzer PFO Occluder vs ASA, plavix, warfarin, or ASA and dipyridamole
- ASA/plavix 1 month, ASA 5 months post device
- Recurrent nonfatal stroke,fatal stroke, early death after randomization

Primary Endpoint

- Composite of:
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)
- Stroke definition:
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuroanatomically relevant infarct on imaging

      or

    - Symptoms >24 hours

Enrollment Criteria

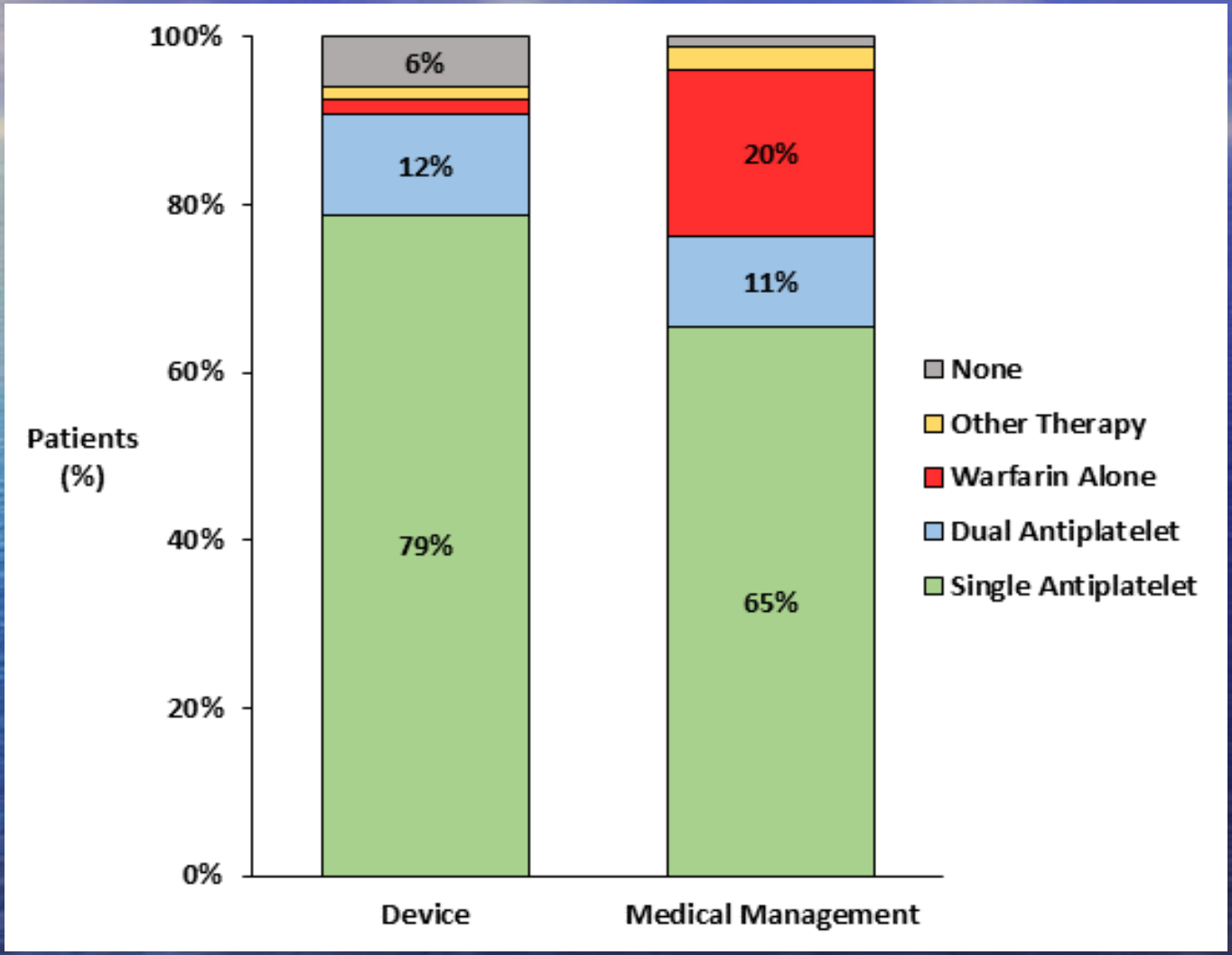
Key Inclusion Criteria

- Cryptogenic stroke within last 9 months
- TEE-confirmed PFO
- 18-60 years
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

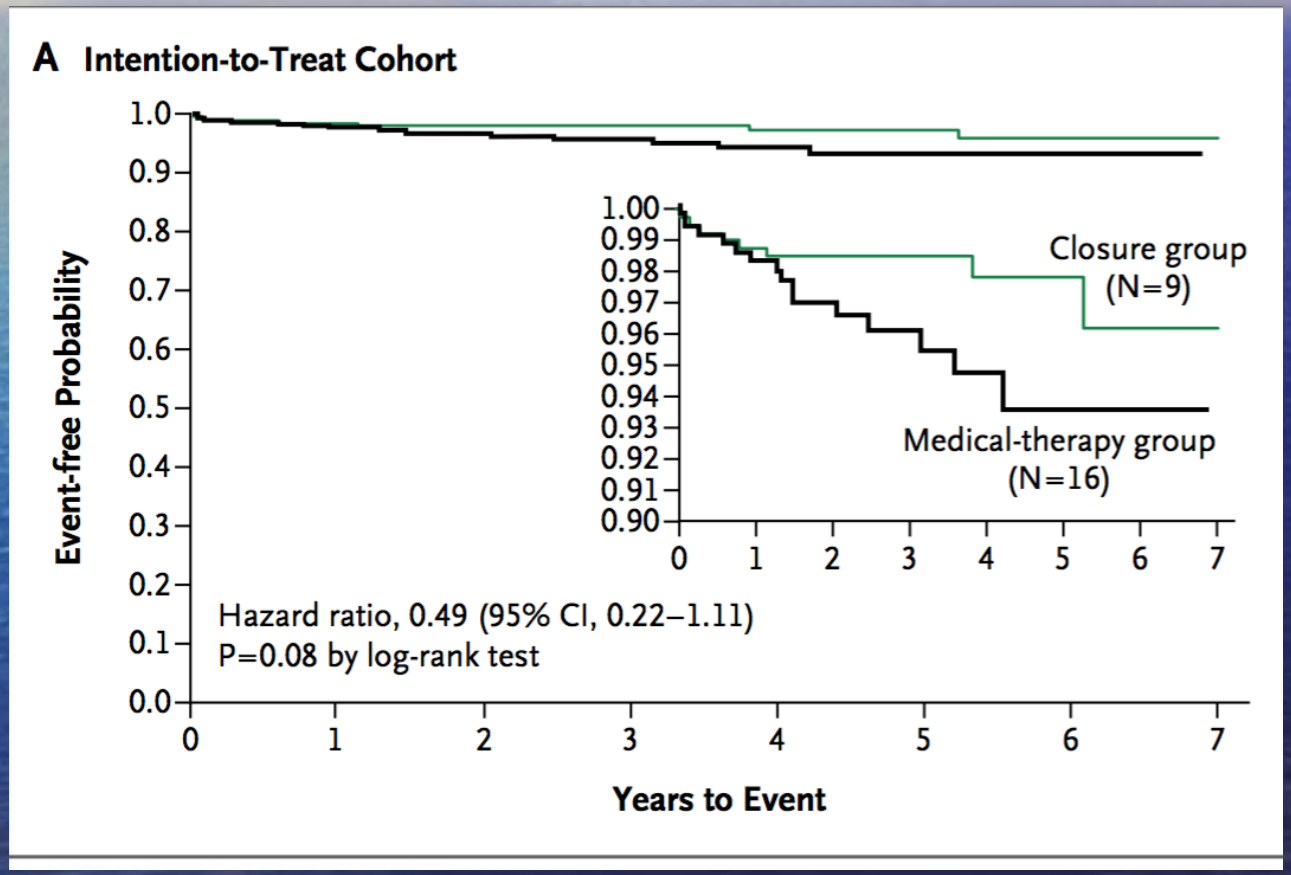
Key Exclusion Criteria

- Stroke due to identified cause such as:
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- Inability to discontinue anticoagulation

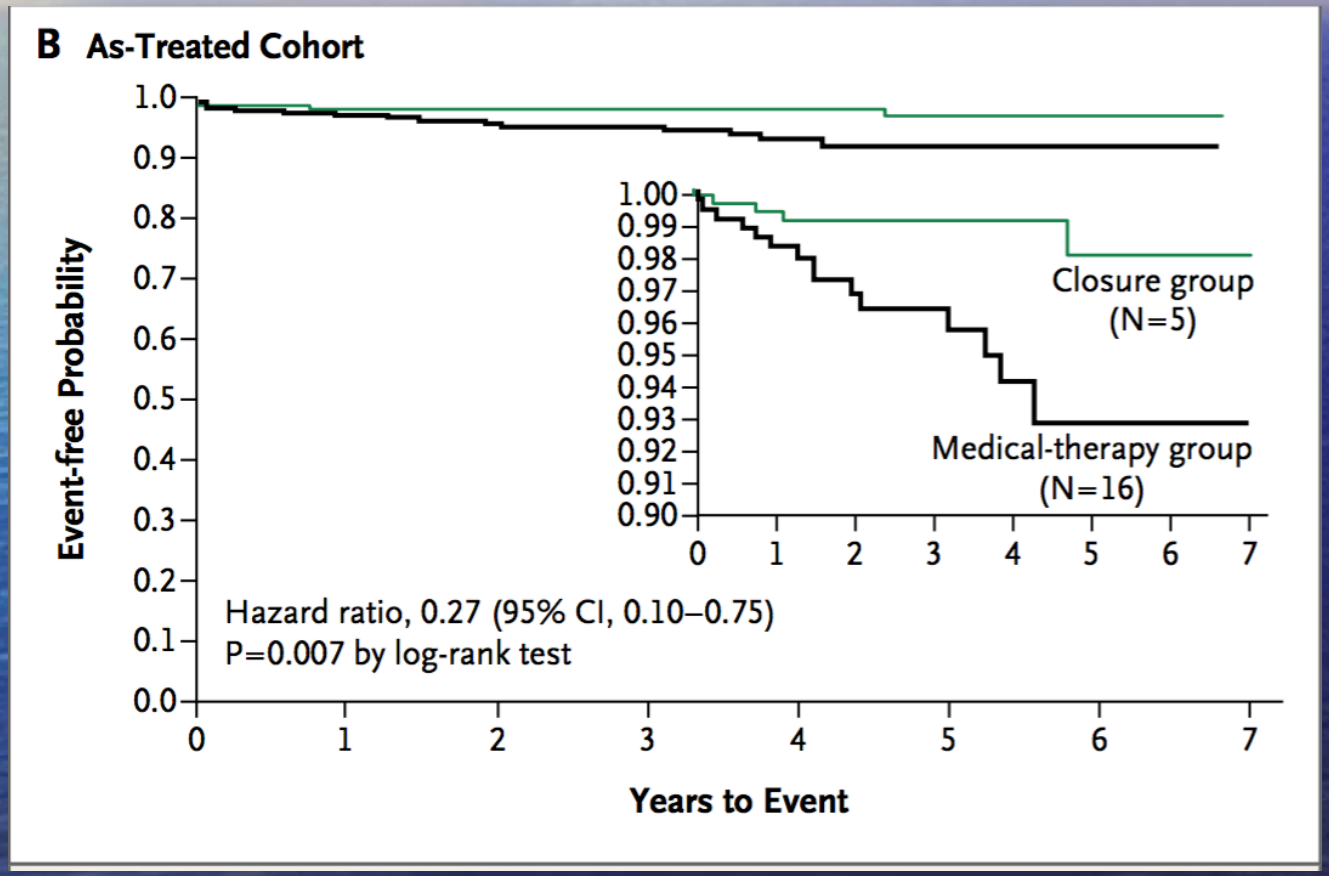
Antithrombotic Medication Use During Follow-up



Respect Trial



Respect Trial



DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)

Conclusions

- In the RESPECT trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone
- Collaboration between a cardiologist and neurologist is important for proper patient selection
- For patients with cryptogenic stroke and PFO, closure with the AMPLATZER™ PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke

American Academy of Neurology

- Practice Advisory: Recurrent Stroke with Patent Foramen Ovale, August 2016
- They are concerned with 129 pts lost to follow up or crossing over in RESPECT
- They estimate an NNT of 56 to prevent one stroke with the amplatzer closure device

American Academy of Neurology

Conclusions: Percutaneous PFO closure with the STARFlex device possibly does not provide a benefit in preventing stroke vs medical therapy alone (risk difference [RD] 0.13%, 95% confidence interval [CI] −2.2% to 2.0%). Percutaneous PFO closure with the AMPLATZER PFO Occluder possibly decreases the risk of recurrent stroke (RD −1.68%, 95% CI −3.18% to −0.19%), possibly increases the risk of new-onset atrial fibrillation (AF) (RD 1.64%, 95% CI 0.07%–3.2%), and is highly likely to be associated with a procedural complication risk of 3.4% (95% CI 2.3%–5%). There is insufficient evidence to determine the efficacy of anticoagulation compared with antiplatelet therapy in preventing recurrent stroke (RD 2%, 95% CI −21% to 25%).

American Academy of Neurology

Recommendations: Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C). In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO (Level C). *Neurology*® 2016;87:815–821

A Ropper MD

NEJM 377;11 Sept14, 2017

Table 1. Six Trials of Patent Foramen Ovale Closure for Stroke with Results Published in the *Journal*.*

Trial Name (Year of Publication)	No. of Patients	Mean or Median No. of Years of Follow-up	Comparator	Primary Outcome	Hazard Ratio†	P Value†
Trials with negative findings						
CLOSURE I (2012)[2]	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)[3]	414	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation‡	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
RESPECT (2013)[4]	980	2.1	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.49	0.08
Trials with positive findings						
Gore REDUCE (2017)[5]	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)[6]	663	5.3	Antiplatelet therapy or anticoagulation‡	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)[7]	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046

Long-Term Efficacy End Points.

Table 2. Long-Term Efficacy End Points.*

End Point	PFO Closure Group (N = 499)		Medical-Therapy Group (N = 481)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate per 100 Patient-Yr	Patients with Event	Event Rate per 100 Patient-Yr		
	no. (%)		*no. (%)*			
Recurrent ischemic stroke	18 (3.6)	0.58	28 (5.8)	1.07	0.55 (0.31–0.999)	0.046
Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD	10 (2.0)	0.32	23 (4.8)	0.86	0.38 (0.18–0.79)	0.007
Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST	1 (0.2)	0.03	11 (2.3)	0.41	0.08 (0.01–0.58)	0.01
Transient ischemic attack	17 (3.4)	0.54	23 (4.8)	0.86	0.64 (0.34–1.20)	0.16

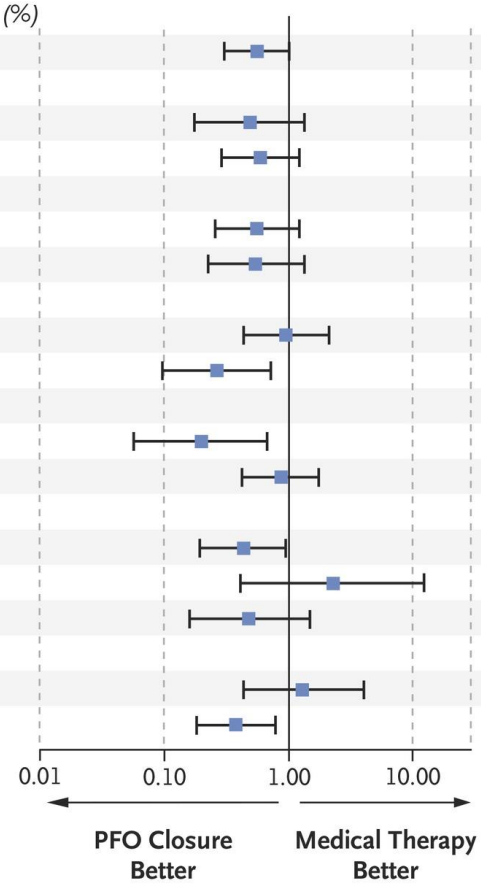
* The end points shown are the first such event that occurred in a patient, not second or later recurrences. ASCOD denotes atherosclerosis (A), small-vessel disease (S), cardiac pathology (C), other causes (O), dissection (D),[12] and TOAST Trial of ORG 10172 in Acute Stroke Treatment.[13]

Saver JL et al. N Engl J Med 2017;377:1022-1032

The NEW ENGLAND JOURNAL of MEDICINE

Rate of Recurrent Ischemic Stroke According to Subgroup.

Subgroup	PFO Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients with event/total no. (%)				
Overall	18/499 (3.6)	28/481 (5.8)	0.55 (0.30–1.00)	0.046	
Age					0.78
18–45 yr	6/230 (2.6)	10/210 (4.8)	0.49 (0.18–1.35)	0.16	
46–60 yr	12/262 (4.6)	18/266 (6.8)	0.59 (0.28–1.23)	0.16	
Sex					1.00
Male	10/268 (3.7)	16/268 (6.0)	0.56 (0.25–1.23)	0.14	
Female	8/231 (3.5)	12/213 (5.6)	0.55 (0.22–1.34)	0.18	
Shunt size					0.04
None, trace or moderate	13/247 (5.3)	12/244 (4.9)	0.96 (0.44–2.11)	0.93	
Substantial	5/247 (2.0)	16/231 (6.9)	0.26 (0.10–0.71)	0.005	
Atrial septal aneurysm					0.04
Present	3/179 (1.7)	13/170 (7.6)	0.20 (0.06–0.70)	0.005	
Absent	15/320 (4.7)	15/311 (4.8)	0.86 (0.42–1.76)	0.68	
Index infarct topography					0.21
Superficial	9/280 (3.2)	18/269 (6.7)	0.43 (0.19–0.96)	0.03	
Small deep	4/57 (7.0)	2/70 (2.9)	2.25 (0.41–12.32)	0.34	
Other	5/157 (3.2)	8/140 (5.7)	0.48 (0.16–1.48)	0.19	
Planned medical regimen					0.07
Anticoagulant	8/132 (6.1)	5/121 (4.1)	1.32 (0.43–4.03)	0.63	
Antiplatelet	10/367 (2.7)	23/360 (6.4)	0.38 (0.18–0.79)	0.007	



Saver JL et al. N Engl J Med 2017;377:1022-1032

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

Jean-Louis Mas, M.D., Geneviève Derumeaux, M.D., Benoît Guillon, M.D., Evelyne Massardier, M.D., Hassan Hosseini, M.D., Ph.D., Laura Mechtouff, M.D., Caroline Arquizan, M.D., Yannick Béjot, M.D., Ph.D., Fabrice Vuillier, M.D., Olivier Detante, M.D., Ph.D., Céline Guidoux, M.D., Sandrine Canaple, M.D., Claudia Vaduva, M.D., Nelly Dequatre-Ponchelle, M.D., Igor Sibon, M.D., Ph.D., Pierre Garnier, M.D., Anna Ferrier, M.D., Serge Timsit, M.D., Ph.D., Emmanuelle Robinet-Borgomano, M.D., Denis Sablot, M.D., Jean-Christophe Lacour, M.D., Mathieu Zuber, M.D., Pascal Favrole, M.D., Jean-François Pinel, M.D., Marion Apoil, M.D., Peggy Reiner, M.D., Catherine Lefebvre, M.D., Patrice Guérin, M.D., Christophe Piot, M.D., Roland Rossi, M.D., Jean-Luc Dubois-Randé, M.D., Ph.D., Jean-Christophe Eicher, M.D., Nicolas Meneveau, M.D., Ph.D., Jean-René Lusson, M.D., Bernard Bertrand, M.D., Jean-Marc Schleich, M.D., Ph.D., François Godart, M.D., Ph.D., Jean-Benoit Thambo, M.D., Laurent Leborgne, M.D., Ph.D., Patrik Michel, M.D., Luc Pierard, M.D., Ph.D., Guillaume Turc, M.D., Ph.D., Martine Barthelet, M.D., Anaïs Chanes-Nestor, M.D., Christian Weimar, M.D., Thierry Moulin, M.D., Ph.D., Jean-Michel Juliard, M.D., Gilles Chatellier, M.D., for the CLOSE Investigators

N Engl J Med
Volume 377(11):1011-1021
September 14, 2017

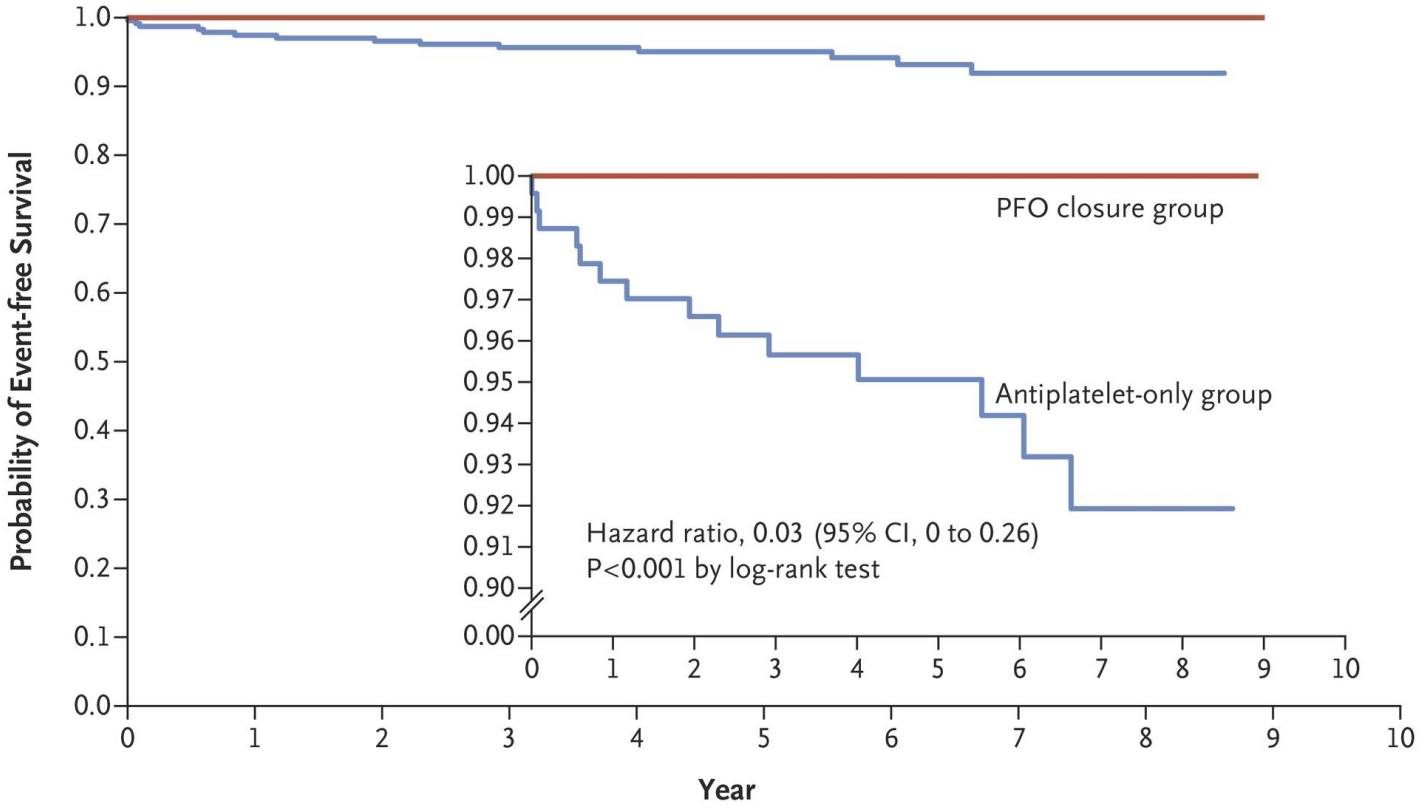
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In patients with cryptogenic stroke and patent foramen ovale with atrial septal aneurysm or large interatrial shunt, closure of the PFO and administration of antiplatelet medications resulted in a lower rate of recurrent stroke than antiplatelet therapy alone.

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.



No. at Risk

PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

Mas J-L et al. N Engl J Med 2017;377:1011-1021

The NEW ENGLAND JOURNAL of MEDICINE

Procedural Complications and Serious Adverse Events.

Table 3. Procedural Complications and Serious Adverse Events.*

Complication or Event	Randomization Groups 1 and 2			Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	P Value	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	P Value
	no. of patients (%)			*no. of patients (%)*		
Major or fatal device-related or procedure-related complication†	14 (5.9)	NA	NA	NA	NA	NA
Major or fatal bleeding complication	2 (0.8)	5 (2.1)	0.28	10 (5.3)	4 (2.3)	0.18
Atrial fibrillation or flutter‡	11 (4.6)§	2 (0.9)	0.02	0	2 (1.1)	0.23
Death	0	0	NA	1 (0.5)¶	0	0.65
At least one serious adverse event	85 (35.7)	78 (33.2)	0.56	62 (33.2)	59 (33.9)	0.88

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.
† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).
‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.
§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.
¶ The one death was due to pancreatic cancer.

Mas J-L et al. N Engl J Med 2017;377:1011-1021

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone.
- PFO closure was associated with an increased risk of atrial fibrillation.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators

N Engl J Med
Volume 377(11):1033-1042
September 14, 2017

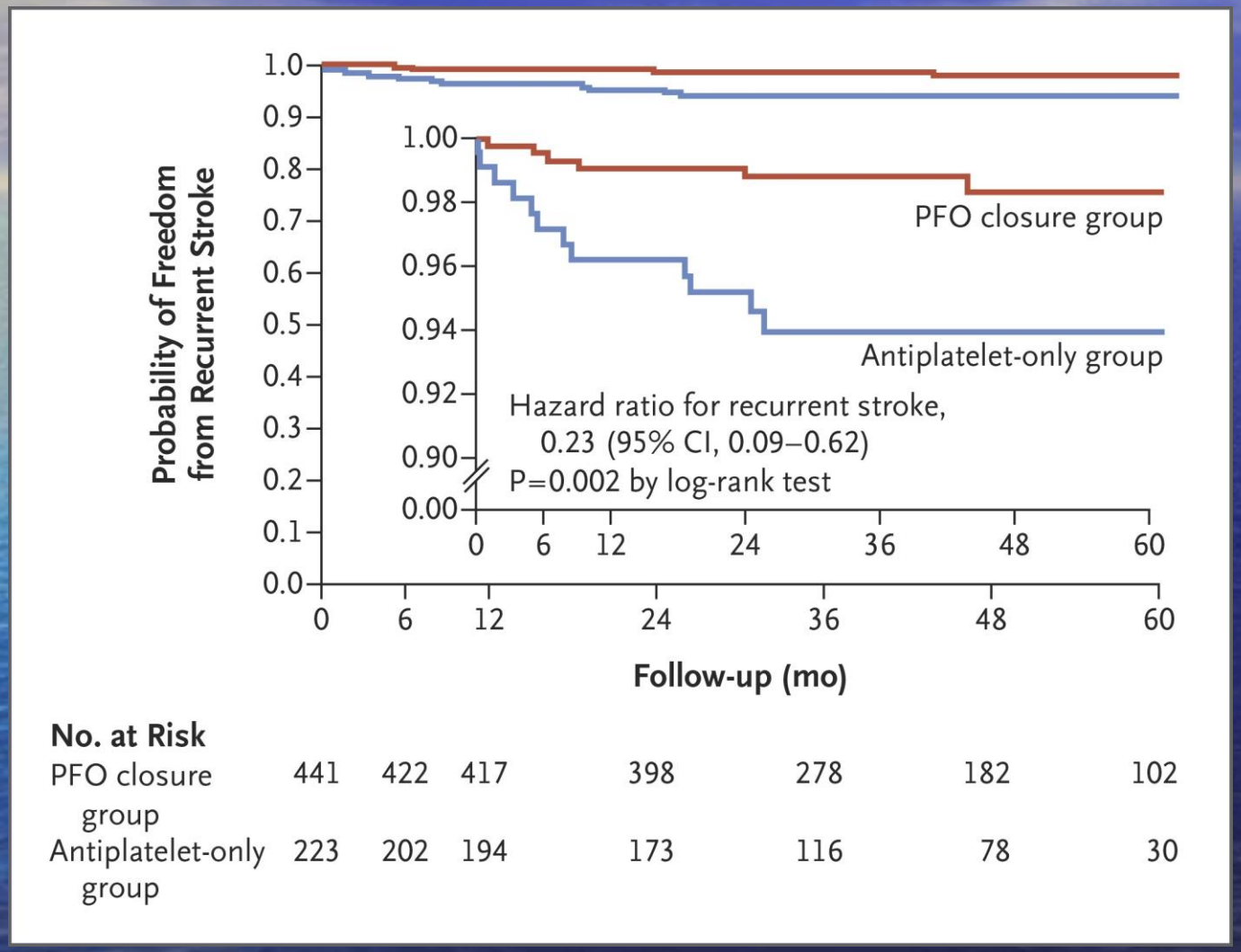
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In a randomized trial involving 664 patients who had had a cryptogenic stroke, closure of a PFO combined with antiplatelet therapy resulted in significantly lower rates of subsequent stroke than antiplatelet therapy alone over a median follow-up of 3.2 years.

The NEW ENGLAND JOURNAL of MEDICINE

Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.



No. at Risk

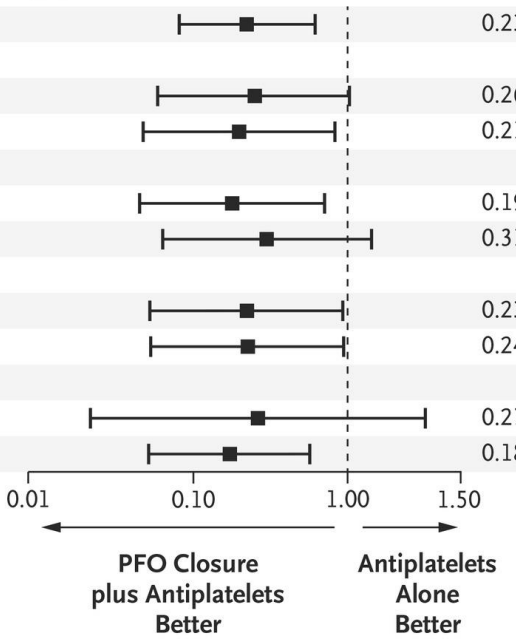
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

The NEW ENGLAND JOURNAL of MEDICINE

Exploratory Analyses to Evaluate Heterogeneity in Relation to Baseline Covariates.

Subgroup	PFO Closure Group	Antiplatelet-Only Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of patients who had recurrent stroke/total no. (%)				
All patients	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)	0.002	
Age					0.85
18–45 yr	3/204 (1.5)	6/114 (5.3)	0.26 (0.07–1.04)	0.04	
46–59 yr	3/237 (1.3)	6/109 (5.5)	0.21 (0.05–0.84)	0.02	
Sex					0.62
Male	3/261 (1.1)	8/138 (5.8)	0.19 (0.05–0.71)	0.01	
Female	3/180 (1.7)	4/85 (4.7)	0.31 (0.07–1.40)	0.11	
Region					1.00
Europe and Canada	3/225 (1.3)	6/108 (5.6)	0.23 (0.06–0.93)	0.03	
United States	3/215 (1.4)	6/115 (5.2)	0.24 (0.06–0.94)	0.03	
Shunt size					0.77
Small	1/77 (1.3)	2/43 (4.7)	0.27 (0.03–3.03)	0.26	
Moderate-to-large	4/348 (1.1)	10/173 (5.8)	0.18 (0.06–0.58)	0.001	



Søndergaard L et al. N Engl J Med 2017;377:1033-1042

The NEW ENGLAND JOURNAL of MEDICINE

Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PFO Closure Group (N=441)	Antiplatelet-Only Group (N=223)
Age — yr	45.4±9.3	44.8±9.6
Days from qualifying event to randomization	100±52	101±53
Male sex — no. (%)	261 (59.2)	138 (61.9)
Medical history — no. (%)		
Current smoking	63 (14.3)	25 (11.2)
Hypertension	112 (25.4)	58 (26.0)
Diabetes mellitus	18 (4.1)	10 (4.5)
Stroke or TIA before the index event	62 (14.1)	23 (10.3)
Previous stroke	42 (9.5)	13 (5.8)
Previous TIA	26 (5.9)	11 (4.9)
Index event — no. (%)		
Ischemic stroke with symptoms lasting ≥24 hr	402 (91.2)	199 (89.2)
Ischemic stroke symptoms lasting <24 hr, with imaging confirmation of infarct	39 (8.8)	24 (10.8)
Patent foramen ovale shunt size — no./total no. (%)†		
Small	77/425 (18.1)	43/216 (19.9)
Moderate	166/425 (39.1)	94/216 (43.5)
Large	182/425 (42.8)	79/216 (36.6)
Atrial septal aneurysm — no./total no. (%)	86/422 (20.4)	NA‡

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. NA denotes not applicable, and TIA transient ischemic attack.

† Shunt size was classified on the basis of the estimated number of microbubbles detected in the left atrium within three cardiac cycles after appearance in the right atrium, as observed on transesophageal echocardiography while the patient was at rest or while a Valsalva maneuver was being performed. The presence of 0 microbubbles was classified as occluded or no shunt, 1 to 5 microbubbles as small, 6 to 25 microbubbles as moderate, and more than 25 microbubbles as large.

‡ The presence of an atrial septal aneurysm was determined at the time of the PFO closure procedure and therefore was not recorded before trial entry or among the patients in the antiplatelet-only group.

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events.

Table 3. Adverse Events.

Adverse Event	PFO Closure Group (N = 441)	Antiplatelet-Only Group (N = 223)	P Value*
	no. of patients (%)		
Any serious adverse event	102 (23.1)	62 (27.8)	0.22
Device related	6 (1.4)	NA	NA
Procedure related	11 (2.5)	NA	NA
Death†	2 (0.5)	0	0.55
Serious bleeding adverse event	8 (1.8)	6 (2.7)	0.57
Procedure associated‡	4 (0.9)	NA	NA
Other§	4 (0.9)	6 (2.7)	0.09
Any atrial fibrillation or flutter	29 (6.6)	1 (0.4)	<0.001
Serious atrial fibrillation or flutter¶	10 (2.3)	1 (0.4)	0.11
Serious device-related adverse event‖	6 (1.4)	NA	NA
Device dislocation	3 (0.7)		
Device-related thrombosis	2 (0.5)		
Aortic dissection	1 (0.2)		
Any deep-vein thrombosis or pulmonary embolism	3 (0.7)	2 (0.9)	1.00

* P values were calculated with the use of Fisher's exact test.
† One suicide related to depression occurred 131 days after randomization, and one fatal myocardial infarction occurred 1045 days after randomization.
‡ Procedure-associated serious bleeding adverse events were events of bleeding within 30 days after the procedure at the vascular access site (three patients) or cardiac tamponade (one patient).
§ Other serious bleeding adverse events were events of bleeding in the reproductive, visual, gastrointestinal, and musculoskeletal systems.
¶ Atrial fibrillation or flutter was classified as a serious adverse event by the local investigator.
‖ A serious device-related adverse event was any adverse event that involved or was related to the device, with the exclusion of arrhythmia.

Søndergaard L et al. N Engl J Med 2017;377:1033-1042

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- If a patient under 60 is felt to have had a CS after careful cardiac and neurologic evaluation
- AND they have a moderate to large shunt from a PFO +/- an atrial septal aneurysm
- They can be considered for PFO closure