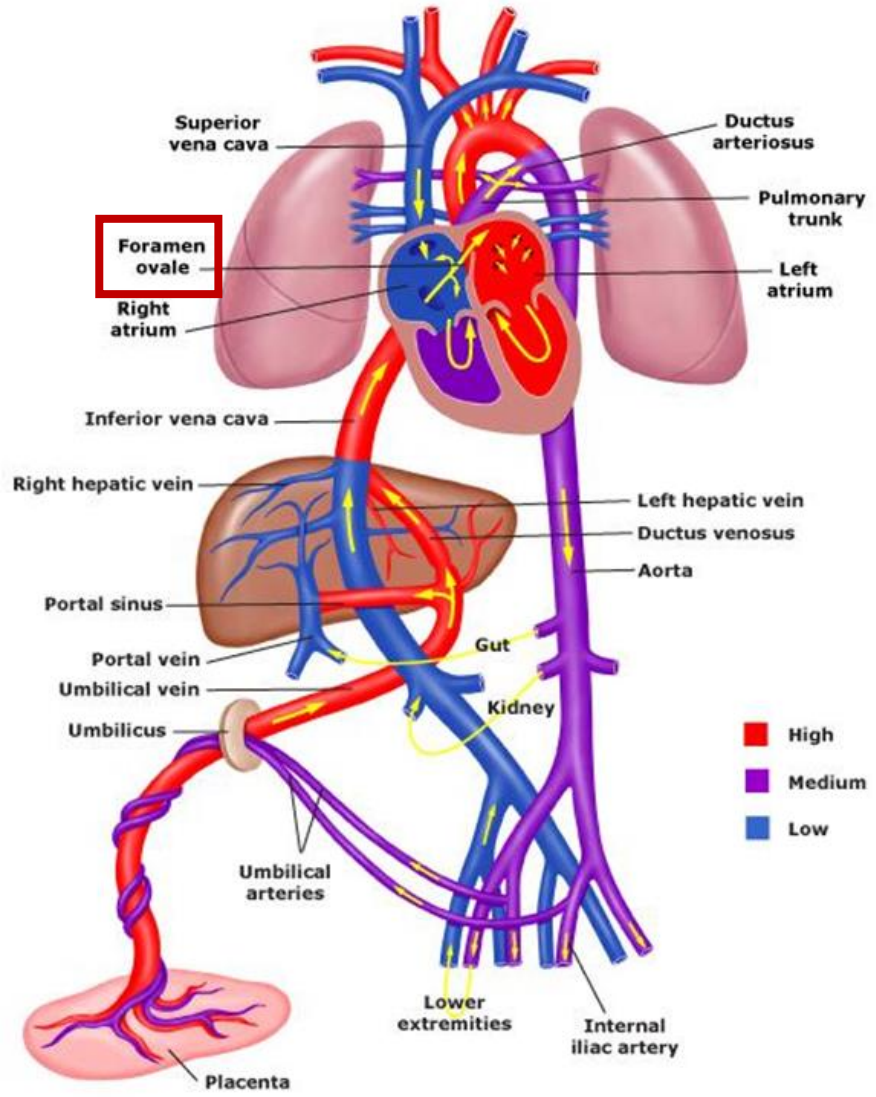
Current status of PFO closure

The Cardiologist perspective – What has changed, which patients benefit from new clinical practice?

Michael Rahbek Schmidt, PhD, DMSc

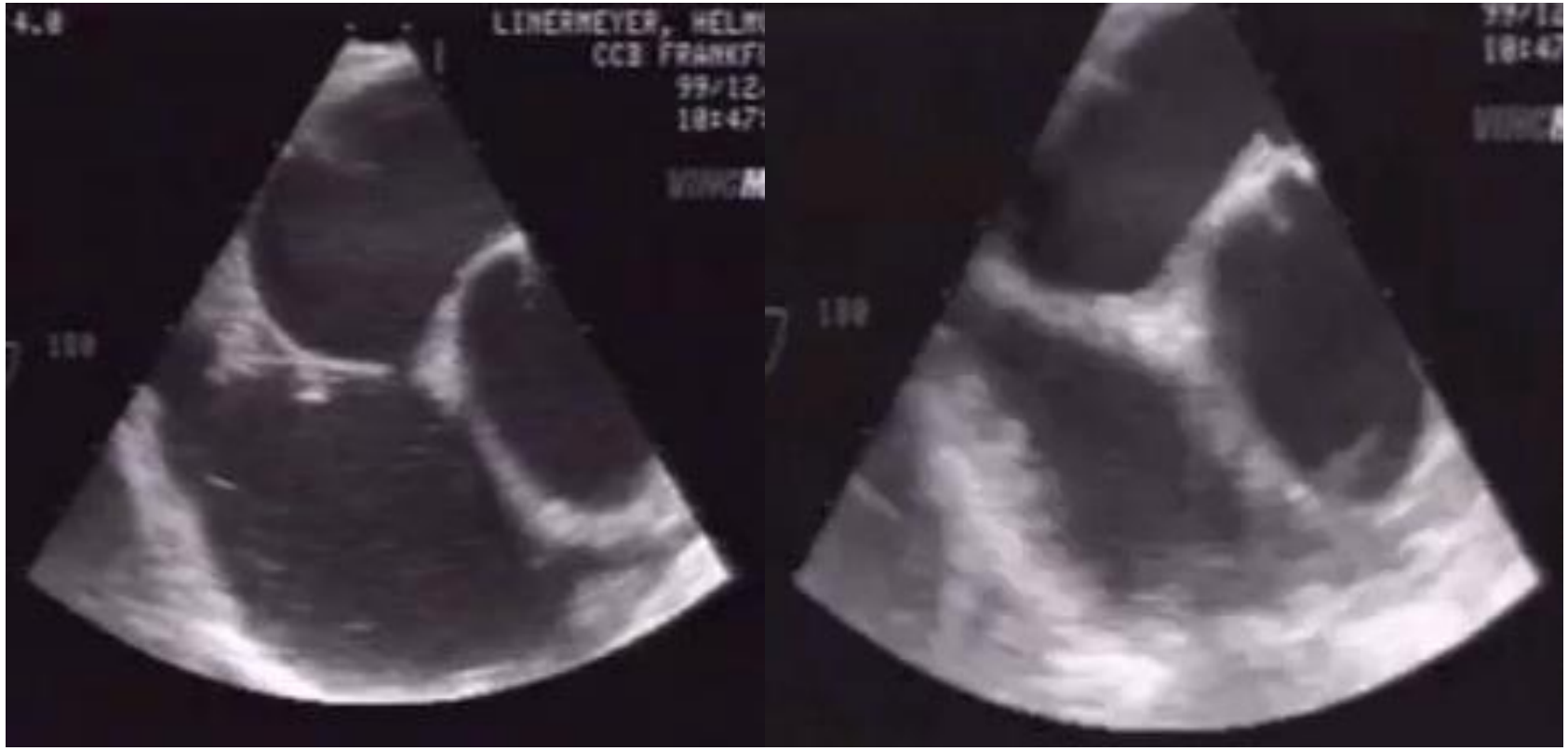
Fetal circulation



Paradoxical emboli

- Valsalva

+ Valsalva



The evidence

CLOSURE-1

The NEW ENGLAND JOURNAL of MEDICINE

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*

PC Trial

The NEW ENGLAND JOURNAL of MEDICINE

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., and Peter Jüni, M.D., for the PC Trial Investigators*

RESPECT

The NEW ENGLAND JOURNAL of MEDICINE

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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*

Any doubts, still?

> “It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of the New England Journal of Medicine.”

Dr. Marcia Angell (2009), editor in chief, NEJM 1999-2000

The evidence

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CLOSE

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

REDUCE

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., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

RESPECT extended f/u

The NEW ENGLAND JOURNAL of MEDICINE

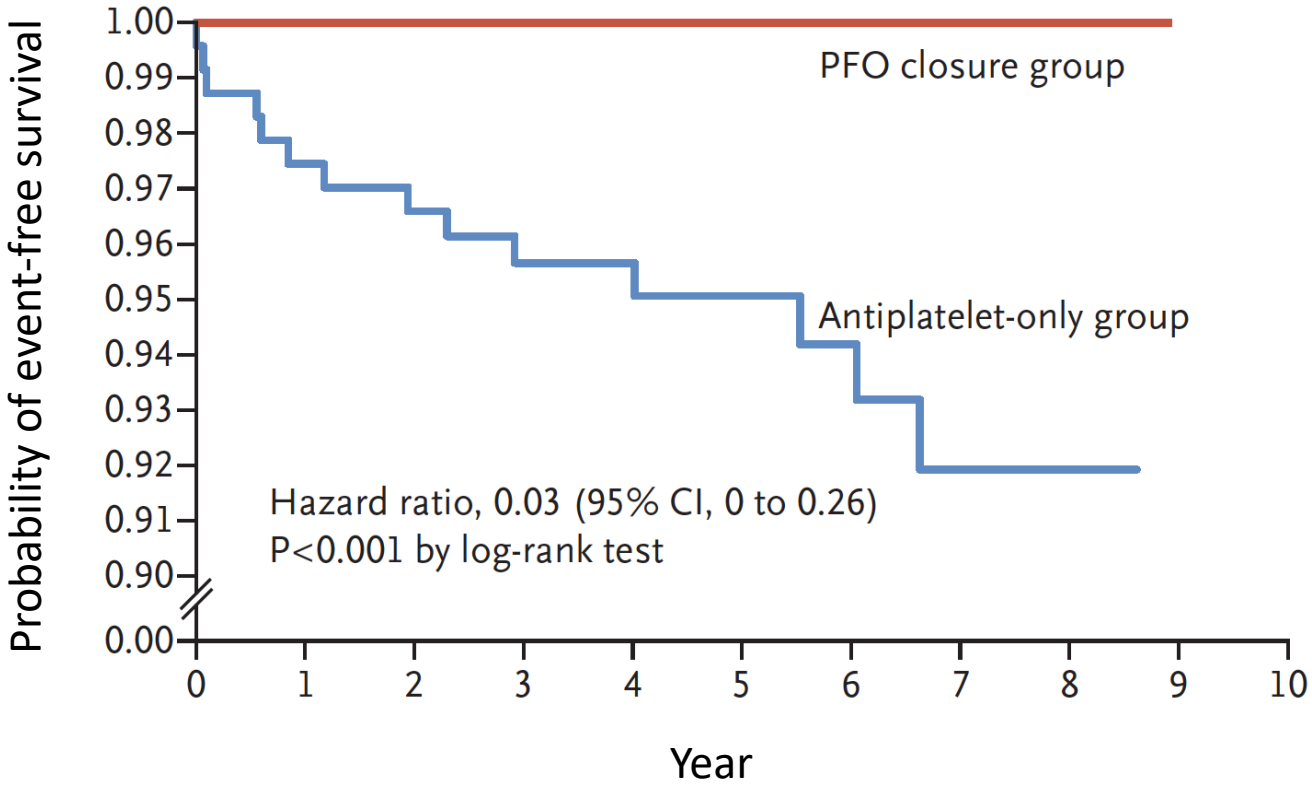
ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

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

CLOSE

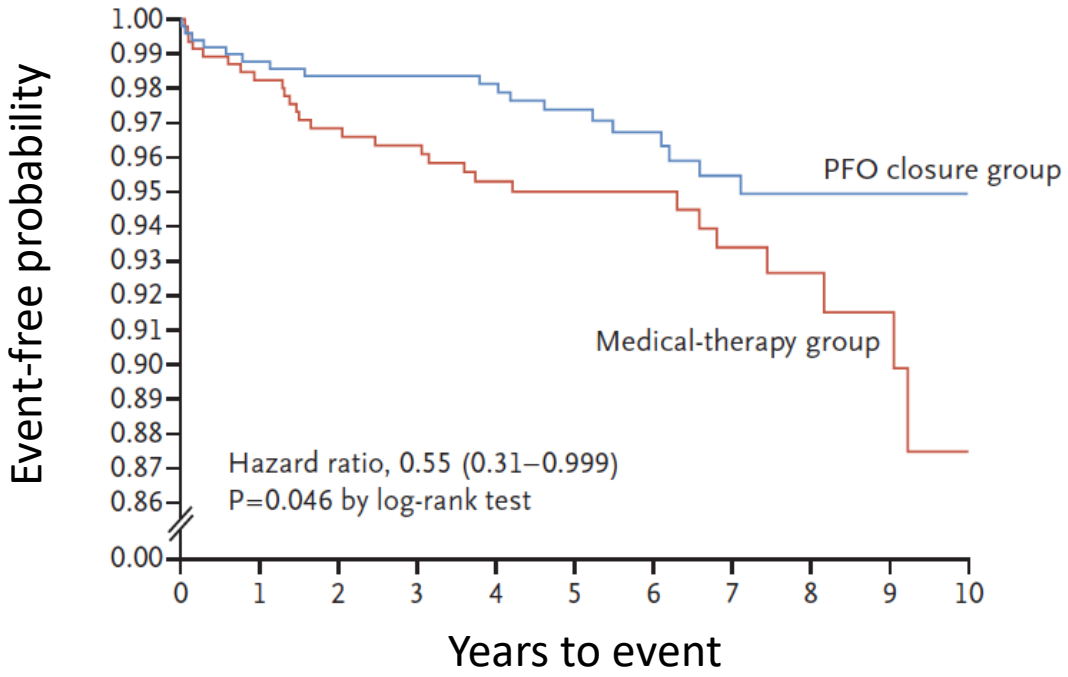
- N=663 patients with ischemic stroke within 6 months
- RCT; 1:1:1 to PFO + DAPT for 3 months followed by SAPT vs. SAPT vs. (D)OAC
  Primary end-point: Fatal or non-fatal stroke. Mean follow-up 5.3 years



Mas et al. NEJM 2017; 377:1011-21

RESPECT extended f/u (mean 2.6 -> 5.9 years)

- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT and aspirin for at least 6 months *or* anti-thrombotic therapy with **VKA (25%) or APT (75%)**
- **Treatment exposure**: 3141 patient-years in the PFO closure group vs. 2669 patient-years in the medical therapy group



Saver et al. NEJM 2017; 377:1022-32

REDUCE Study

- Aim to establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct
- Randomized, controlled, open-label trial
  - 664 subjects randomized in a 2:1 ratio to:
    - Closure: PFO closure plus antiplatelet therapy
    - Medical therapy: antiplatelet therapy alone
- 63 sites in 7 countries
  - Canada, Denmark, Finland, Norway, Sweden, UK, US

Sondergaard et al. NEJM 2017; 377:1033-42

Inclusion and Exclusion Criteria

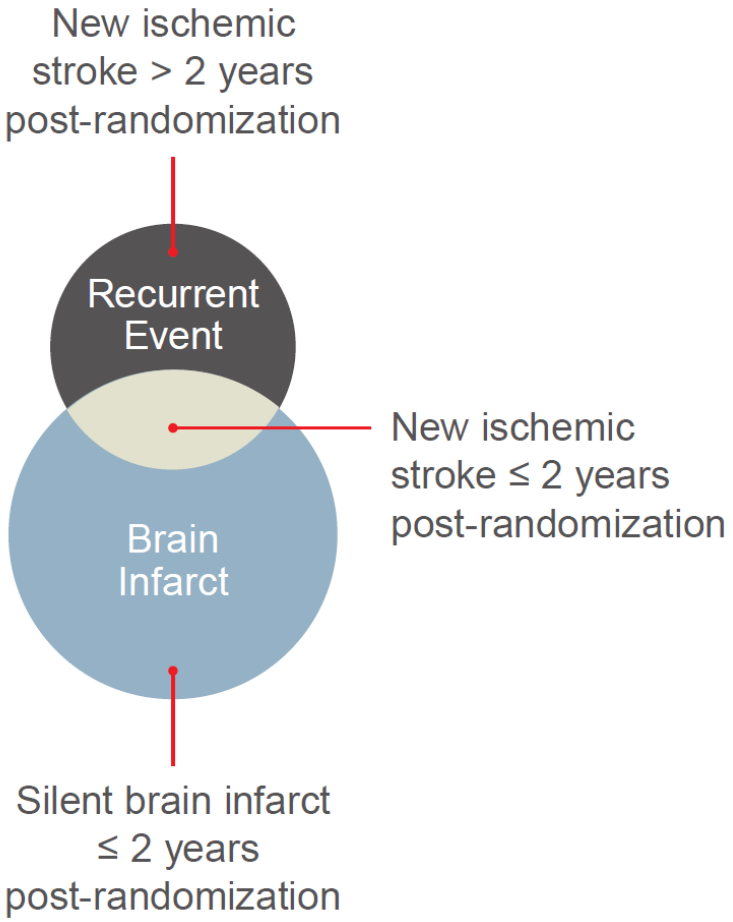
- Age 18-59 years
- Cryptogenic ischemic stroke within 180 days
  - Clinical symptoms ≥24 hours or MRI evidence of infarction
  - Cryptogenic
    - No stenosis >50% or ulcerated plaque in relevant vessels
    - No atrial fibrillation or high risk source of cardioembolism
    - Non-lacunar (based on syndrome and/or size)
    - No evidence of hyper-coagulable disorder
- Patent foramen ovale (PFO)
  - Confirmed by TEE with bubble study (right-to-left shunt)
  - No indication for anticoagulation

Co-Primary Endpoints

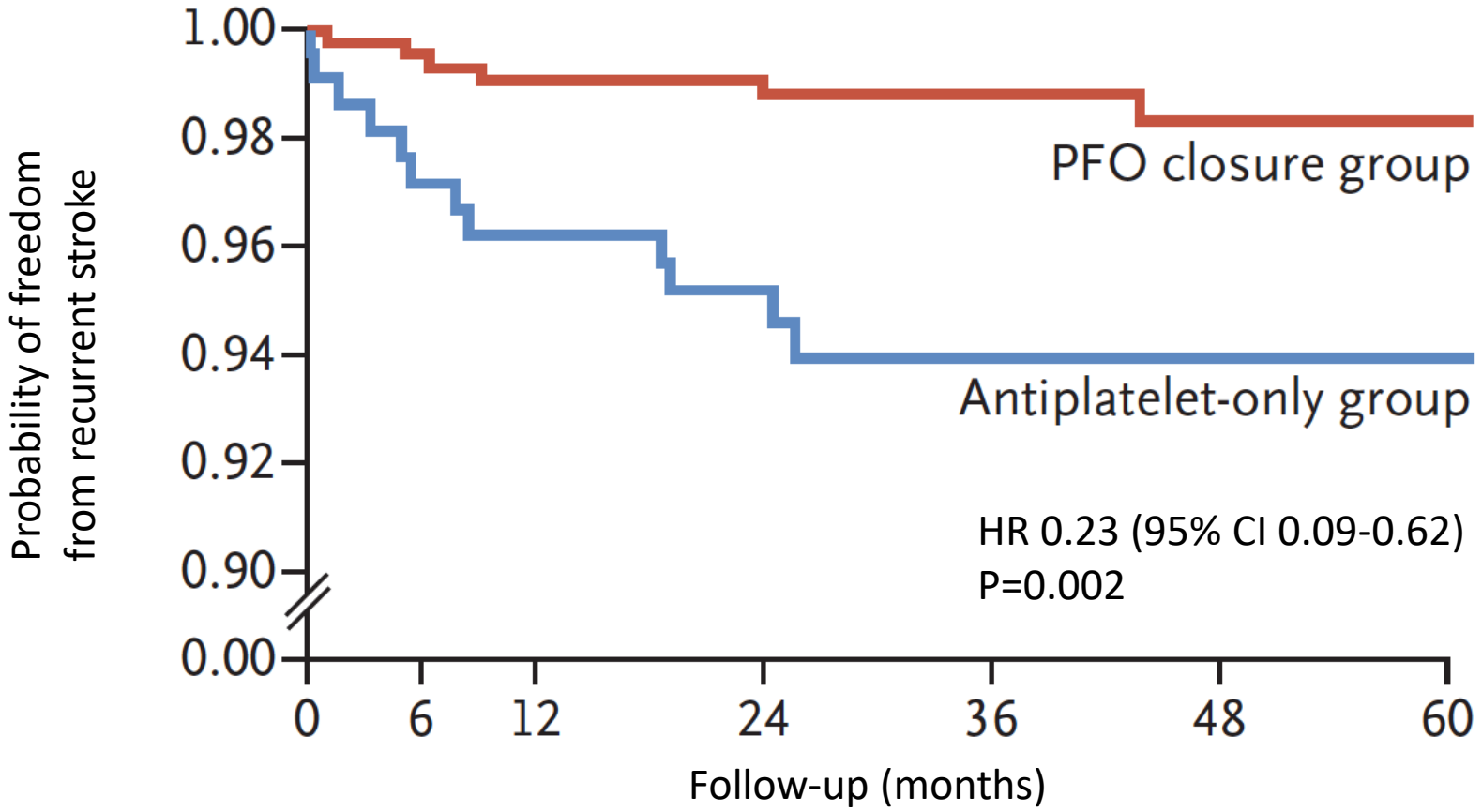
- Freedom from **recurrent clinical ischemic stroke** through at least 24 months

- Incidence of **new brain infarct** (defined as clinical ischemic stroke or silent brain infarct*) through 24 months

*New T2 hyperintense MRI lesion with diameter ≥3 mm; adjudicated by MRI core lab

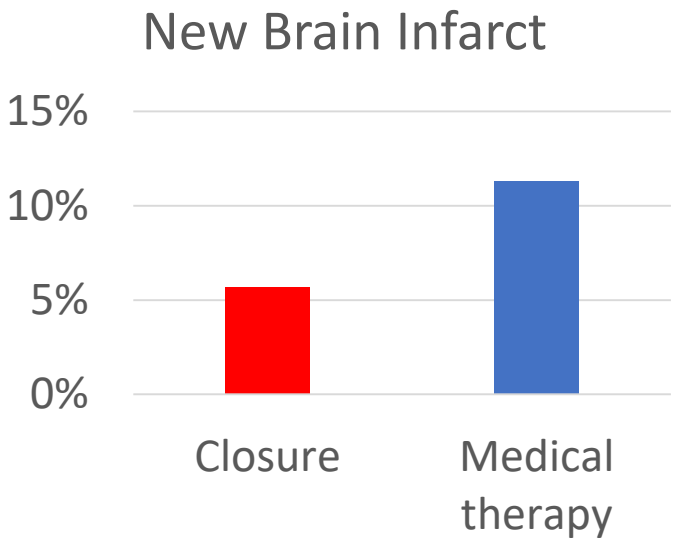


Clinical stroke (ITT)



New brain infarct (ITT)

	Closure (N=441)	Medical (N=223)
Subjects without Evaluation	58	46
Brain Infarct Evaluable	383	177
Brain Infarct Present	**22 (5.7%)**	**20 (11.3%)**
Recurrent Stroke Only	3	6
Both	2	6
Silent Brain Infarct Only	17	8
Brain Infarct Absent	361 (94.3%)	157 (88.7%)



- Difference in incidence of new brain infarct of 5.6%
- Relative risk 0.51 (95% CI: 0.29 to 0.91)
- p=0.024 after adjustment for multiple testing
- silent infarcts about twice as common as clinical stroke

Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	no. of patients/total no. (%)			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)‖	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)‖	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)‖	0.97**

Does PFO closure make infarcts smaller?

Strengths

- Standardized approach to medical therapy
- Selection criteria for cryptogenic stroke similar to recent ESUS definition
- Multi-national trial enhances generalizability
- MRI at baseline and 2 years adds objective confirmation to unblinded trial

Limitations

- Total number of events was small, limiting subgroup and other exploratory analysis
- Potential for bias due to differential drop-out and small number of events relative to drop-out rate
- Limited generalizability due to concurrent closure outside of trial
- Duration of study

What should we tell the patients?

- The evidence is there for prognostic benefit, but
  - Only for patients fulfilling criteria
  - Thorough assessment is required
- The risk reduction is relevant
  - NNT = 28-47
  - ARR= 2-4%, PFO closure brings AR<2%
  - RRR >50%
- While better not perfect
  - The absolute risk of recurrent stroke/brain infarction is low, but important
  - The risk of serious adverse event is low but not negligible

Safety

- Atrial fibrillation/flutter rate higher in the closure group
  - non-serious (63%)
  - onset in 1st month (79%)
  - resolved within 2 weeks (59%)
  - 1/29 patients with AF after PFO closure had a stroke

- REDUCE 6.6% vs. 0.4%
- CLOSURE-1 5.7% vs. 0.7%
- PC Trial 2.9% vs. 1.0%
- RESPECT 3.0% vs. 1.5%
- CLOSE 4.6% vs. 0.9%

All Enrolled Subjects (N=664)	Closure (n=441)	Medical (n=223)	p-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**0.57**
Procedure-related	4 (0.9%)	-	0.31
Other	4 (0.9%)	6 (2.7%)	0.09
Any AF/ flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**<0.001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	<0.001
Serious device adverse events	**6 (1.4%)**	**-**	**-**
Device dislocation	3 (0.7%)	-	-
Device thrombosis	2 (0.5%)	-	-
Aortic dissection	1 (0.2%)	-	-
Any DVT or PE adverse events	**3 (0.7%)**	**2 (0.9%)**	**1.0**

REDUCE

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	

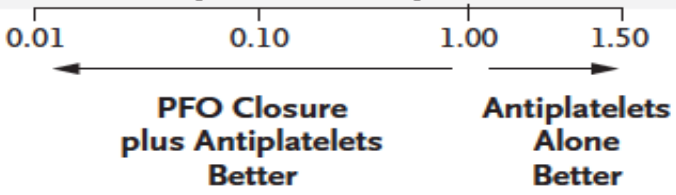


Figure 2. Exploratory Analyses to Evaluate Heterogeneity in Relation to Baseline Covariates.

Subgroup analyses were performed in the intention-to-treat population. The classification of shunt size was based on the maximum number of microbubbles seen in the left atrium in any single frame during the first three cardiac cycles after detection in the right atrium; 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. In one patient in the PFO closure group, the baseline shunt size was unknown according to the site assessment that was used for the analysis.

RESPECT

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	

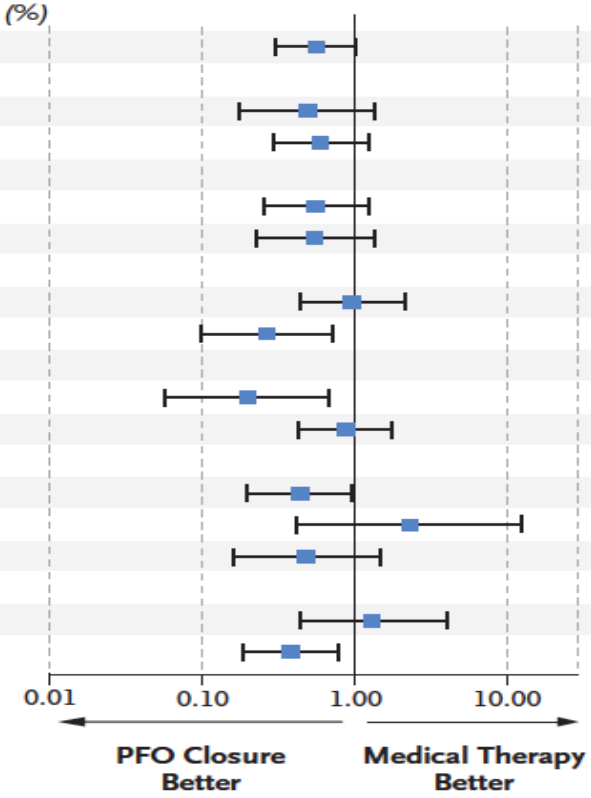


Figure 2. Rate of Recurrent Ischemic Stroke According to Subgroup.

Potential heterogeneity of the treatment effect was noted with respect to three baseline characteristics (threshold for significant interaction, P=0.10), with a suggestion of greater risk reductions with PFO closure than with medical therapy alone among patients with an atrial septal aneurysm, among patients with a substantial shunt size, and among patients whose planned medical regimen was antiplatelet therapy rather than anticoagulant therapy if they were to be randomly assigned to the medical-therapy group. A substantial shunt refers to a shunt size of grade 3. Grades ranged from 1 to 3, with higher grades indicating a larger size.

Risk of Paradoxical Embolism

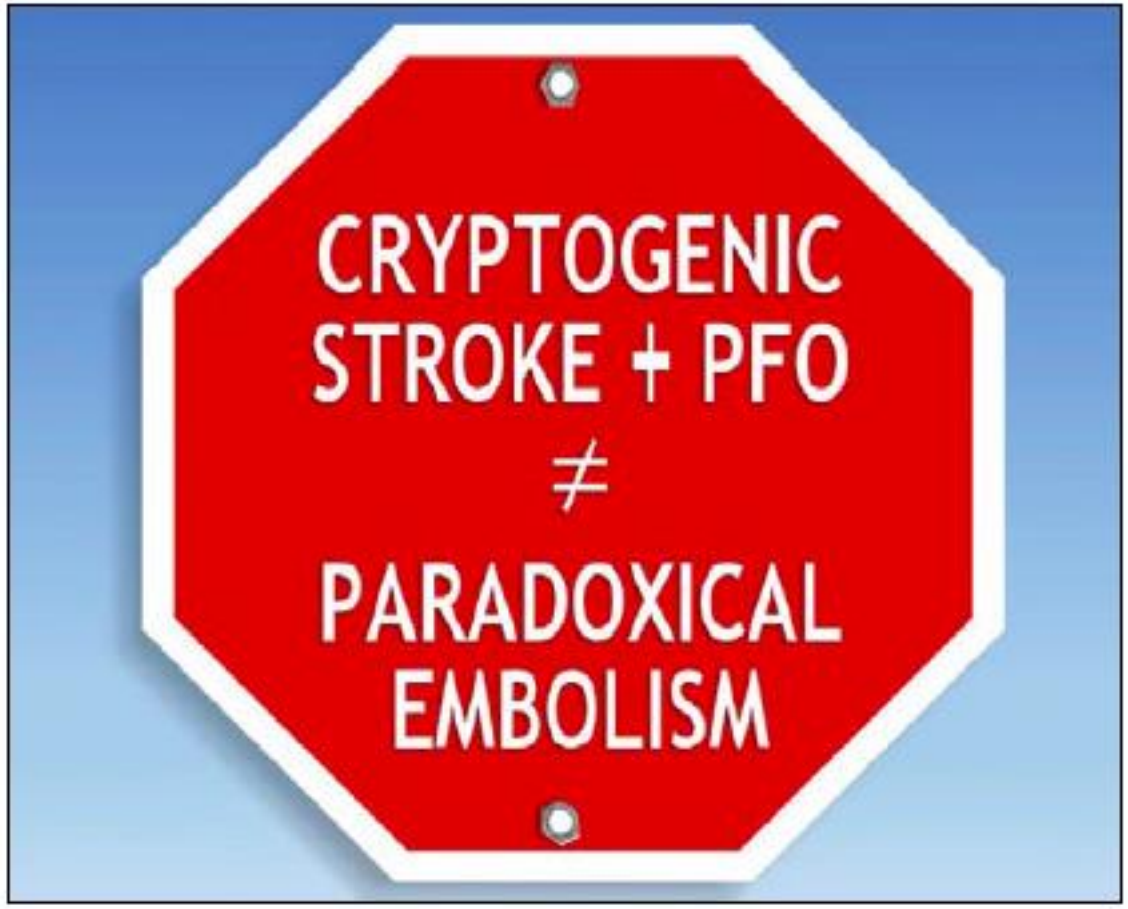


TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**Score**
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	
Total score (sum of individual points)		
Maximum score (a patient < 30 y without vascular risk factors, no history of stroke or TIA, and cortical infarct)		10
Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct)		0

Remaining questions

- Is the ROPE score the best selection tool?
- Is there a better way to estimate shunt size than counting bubbles?
- Is there a relevant difference in safety and efficacy between devices?
- An what about the septal aneurysm?