PFO Closure for Cryptogenic Stroke: Clinical Trial Review and Guidelines

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below:

Affiliation/Financial Relationship	**Company**
Institutional research grant	Abbott Boston Scientific Edwards Lifesciences Medtronic
Consulting Fees/Honoraria	Abbott Boston Scientific Edwards Lifesciences Medtronic

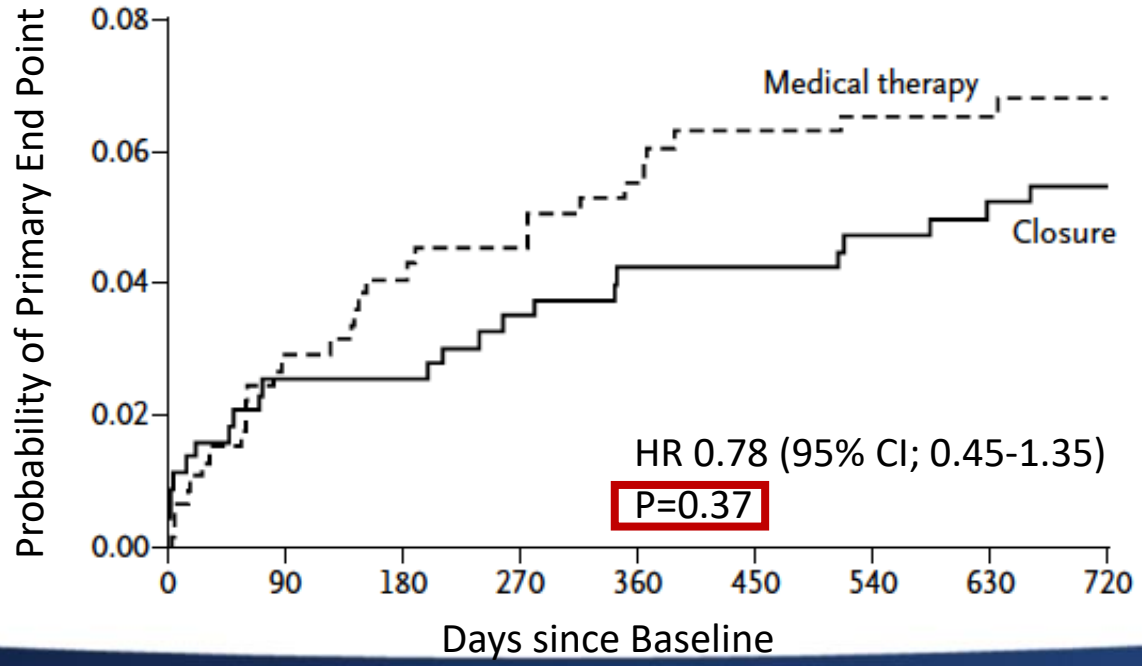
PFO and cryptogenic stroke

Background:

- The contribution of a patent foramen ovale (PFO) to cerebral ischemia has been uncertain
  - PFO is twice as prevalent in patients who have experienced a cryptogenic stroke compared to the general population
  - Observational data suggest a reduction of recurrent stroke with PFO closure, but…
- Three randomized trials of PFO closure did not show significant reduction in stroke risk in their primary intention-to-treat analysis

CLOSURE-1

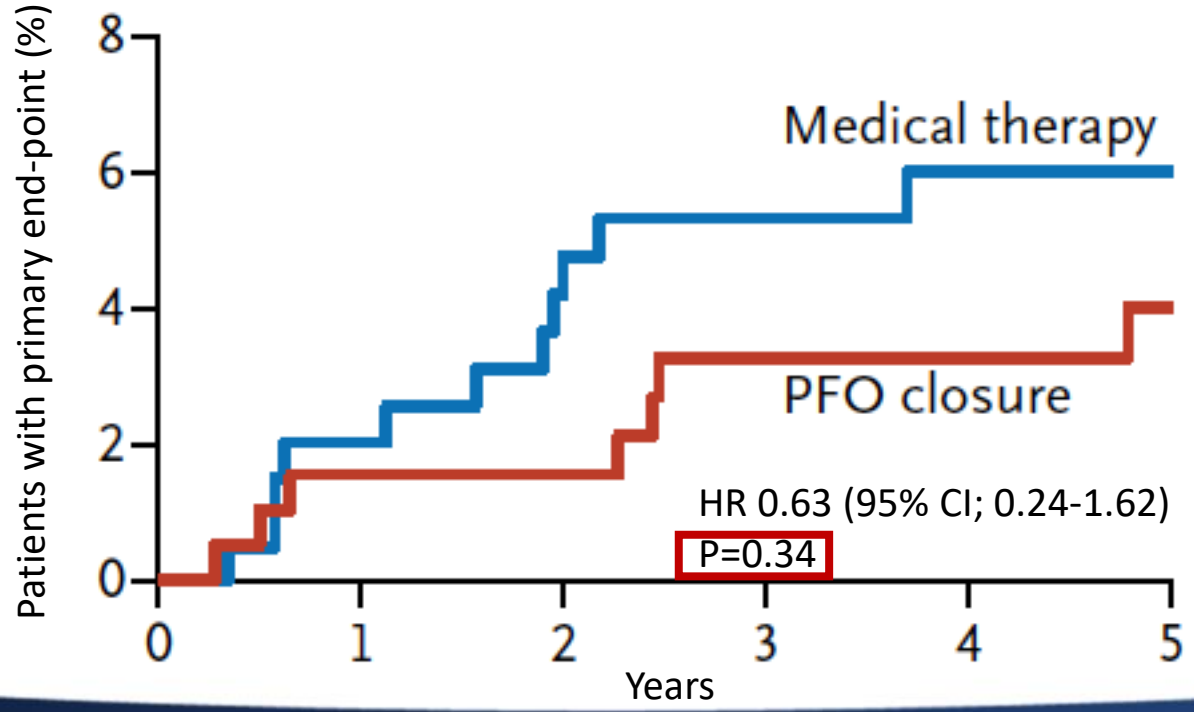
- N=909 patients with stroke or TIA (**not imaging verified**) within 6 months
- RCT, 1:1 PFO closure with STARFlex + 6 months DAPT followed by aspirin for life *or* anti-thrombotic therapy with **VKA, aspirin or both**
- Primary end-point: Stroke/TIA during 2 years, death within 30 days, or death from neurologic cause between day 31 to 2 years



Furlan et al. NEJM 2012; 366:991-9

PC Trial

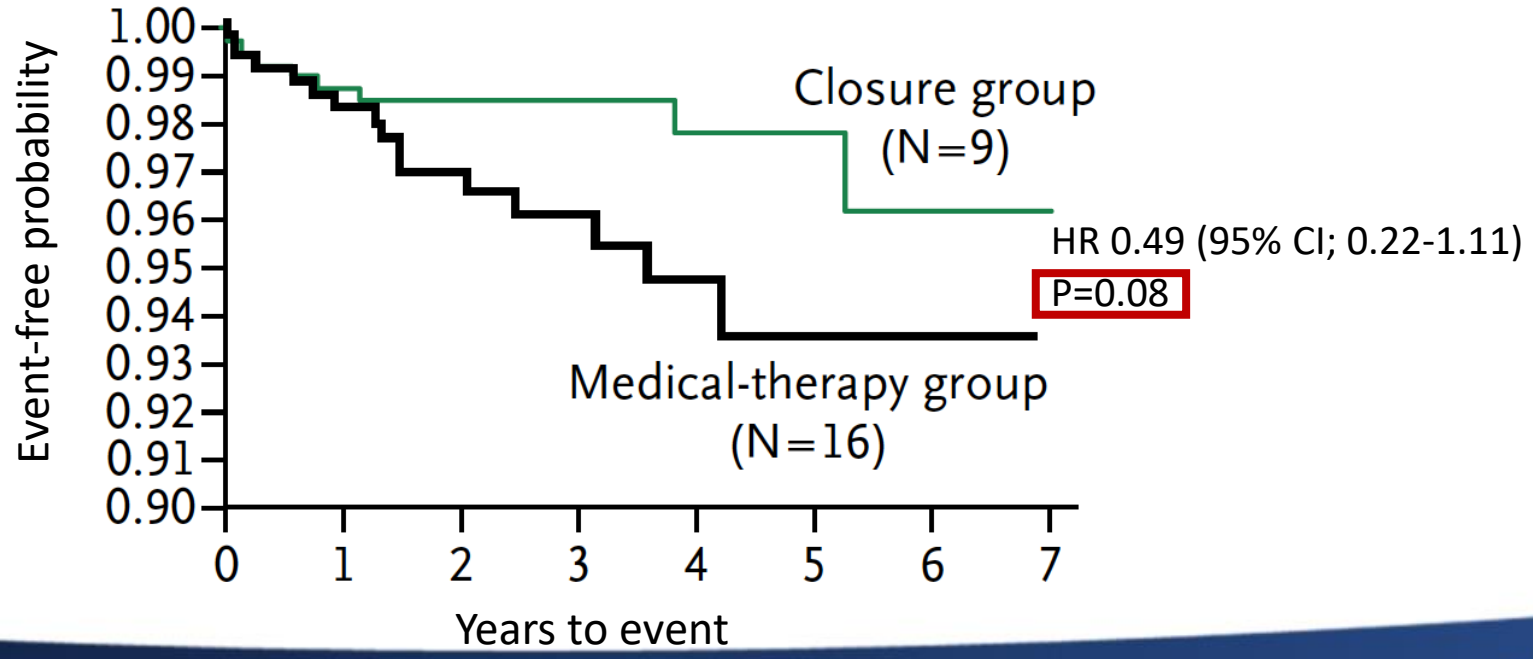
- N=414 patients with stroke, TIA or extra-cranial thrombo-embolic event
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + APT for at least 1-6 months *or* anti-thrombotic therapy with **OAC, aspirin or both**
- Primary end-point: Death, non-fatal stroke, TIA, or peripheral embolism



Meier et al. NEJM 2013; 368:1083-91

RESPECT

- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT followed by aspirin for at least 6 months *or* anti-thrombotic therapy with **VKA (25%) or APT (75%)**
- Primary end-point: Fatal ischemic stroke, non-fatal ischemic stroke, or early death (45 days after randomization/30 days after closure) – event driven trial (N=25)



Carroll et al. NEJM 2013; 368:1092-100

The positive trials - September 14th, 2017

The NEW ENGLAND JOURNAL of MEDICINE

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*

RESPECT extended f/u

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*

REDUCE

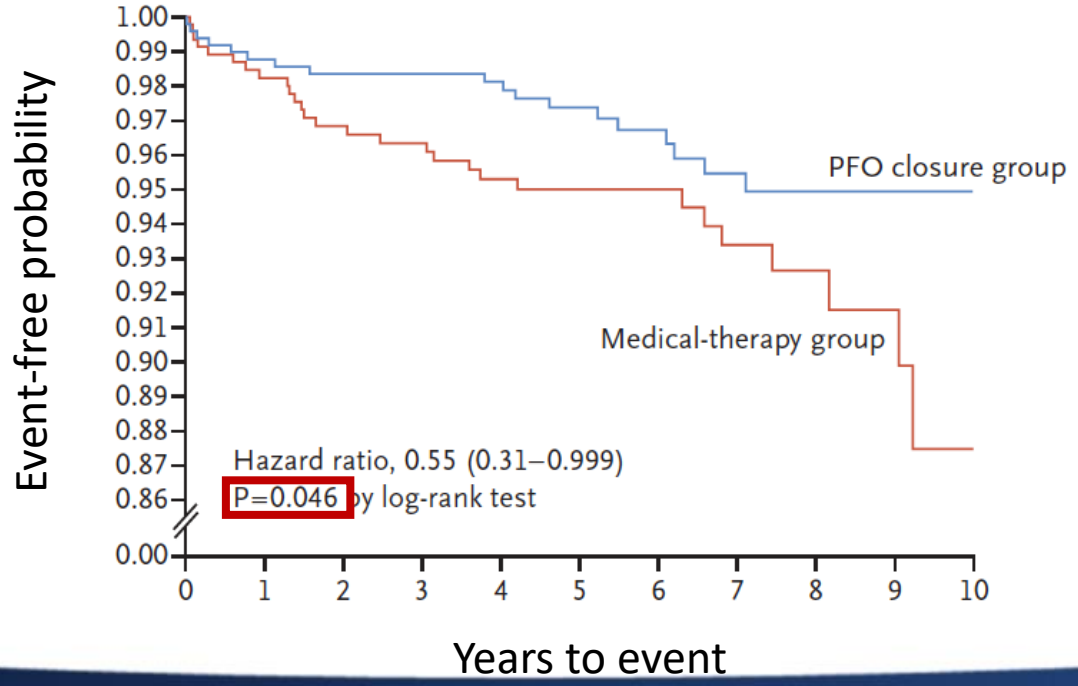
Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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*

CLOSE

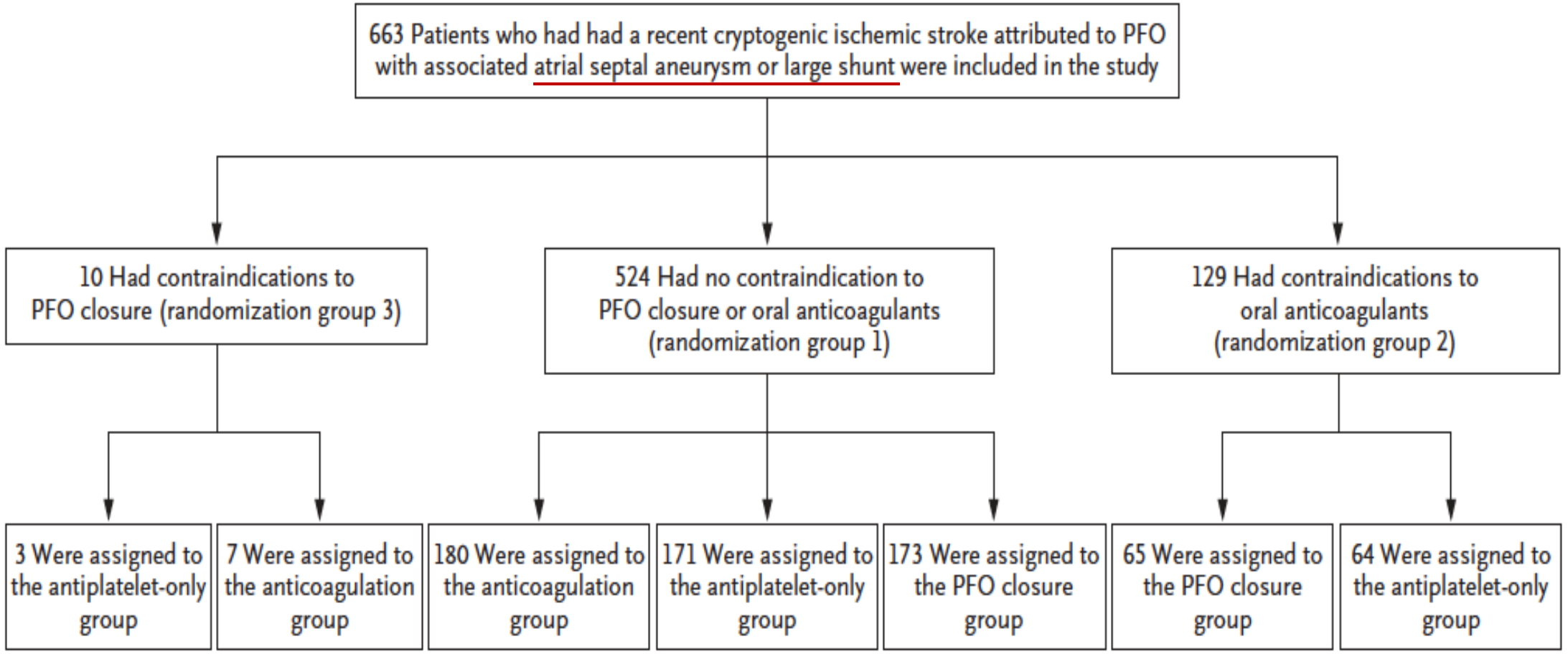
RESPECT extended f/u (mean 2.6 -> 5.9 years)

- 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**: 3,141 patient-years in the PFO closure group vs. 2,669 patient-years in the medical therapy group



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

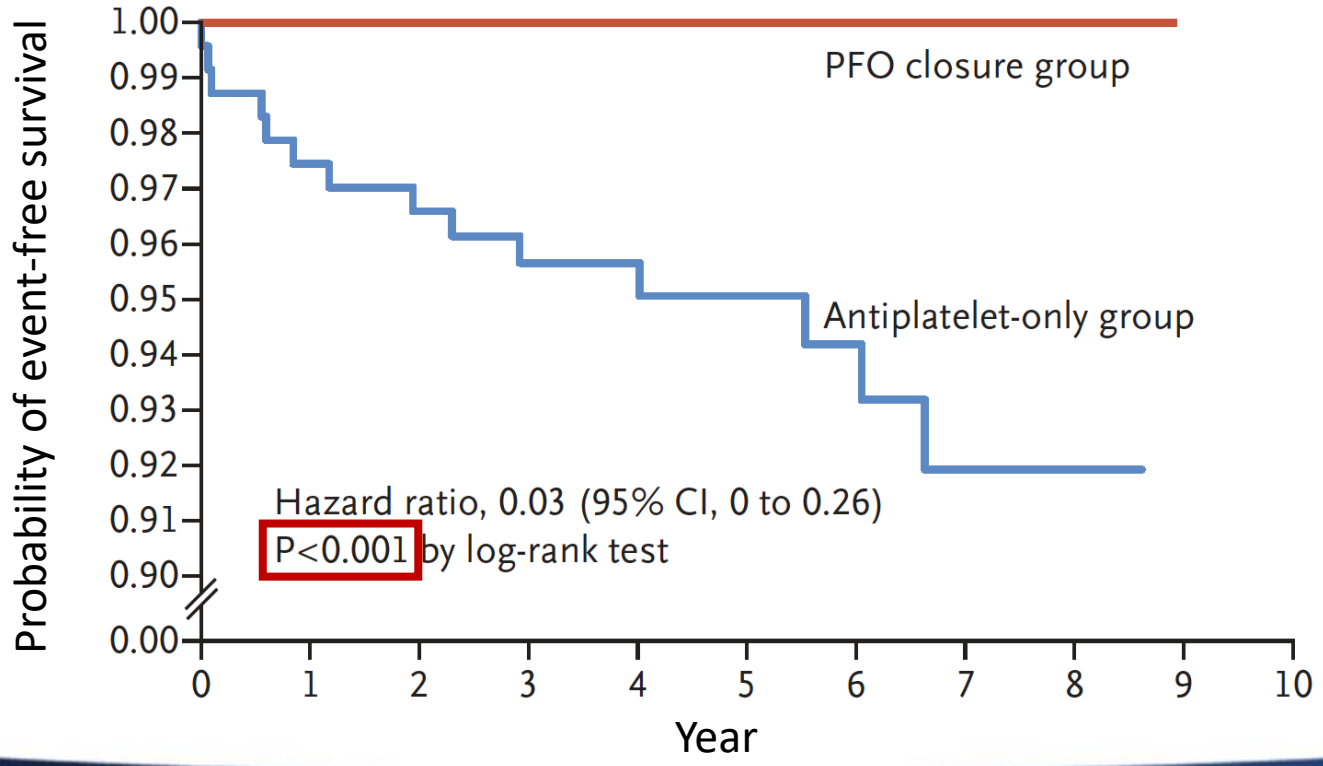
CLOSE



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

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

CLOSE

5-year cumulative estimate of the probability of stroke was:

1.5% in the OAC group and 3.8% in the SAPT group

The study was not adequately powered to compare outcomes in these groups!

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

REDUCE Study

- Aim to establish superiority of PFO closure (WL Gore Septal Occluder) in conjunction with APT over APT 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

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

REDUCE Study Design

Medical Therapy

- Antiplatelet standardized options:
  - Aspirin alone (75-325 mg once daily)
  - Combination aspirin (50-100 mg) and dipyridamole (225-400 mg)
  - Clopidogrel (75 mg once daily)
  - Other combinations or the use of anticoagulants was not permitted
- Prescribed for all subjects for the duration of the study
- Each site was expected to treat all subjects with the same antiplatelet therapy

Follow-up

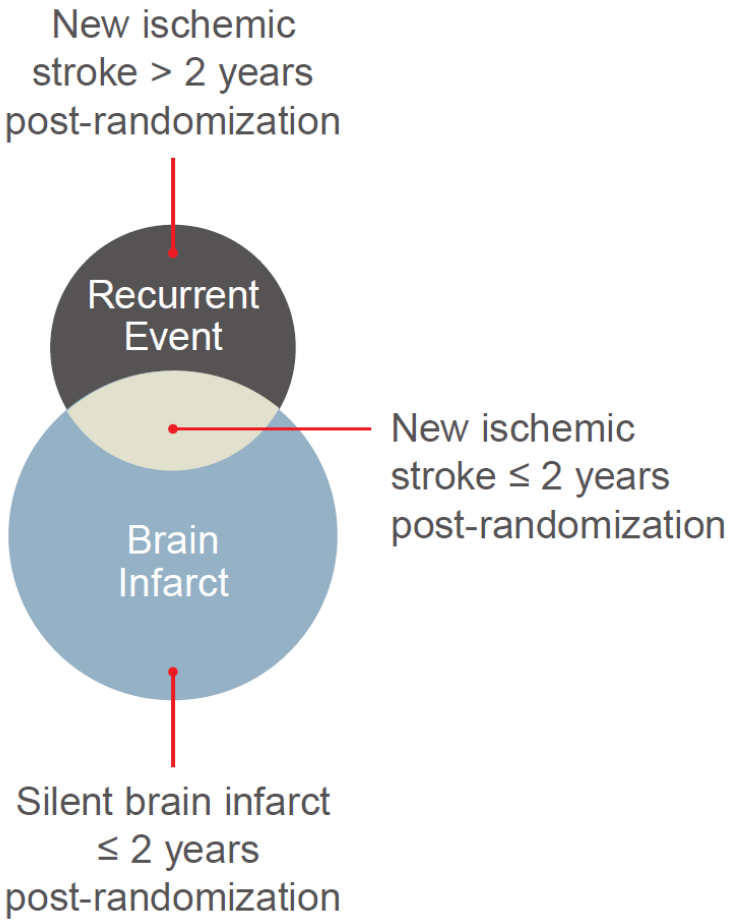
- MRI imaging at baseline and 24 months if not already performed for an endpoint event

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

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

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

Baseline Characteristics

Demographic / Characteristic	Closure (N=441)	Medical (N=223)	p-value
Age, years	45.4 ± 9.3	44.8 ± 9.6	0.41
Days from qualifying event to randomization	100 ± 52	101 ± 53	0.90
Sex, male	59.2%	61.9%	0.56
Current Smoker	14.3%	11.2%	0.30
Diabetes mellitus	4.1%	4.5%	0.84
Hypertension	25.4%	26.0%	0.94
Previous Cerebrovascular Event	14.1%	10.3%	0.22
Maximal baseline shunt grade (# bubbles)	N=425	N=216	0.32
Grade 0 Occluded (0)	0.0%	0.0%	-
Grade I Trivial/Small (1-5)	18.1%	19.9%	-
Grade II Moderate (6-25)	39.1%	43.5%	-
Grade III Large (>25)	42.8%	36.6%	-
Atrial septal aneurysm	20.4%	(did not collect)	-

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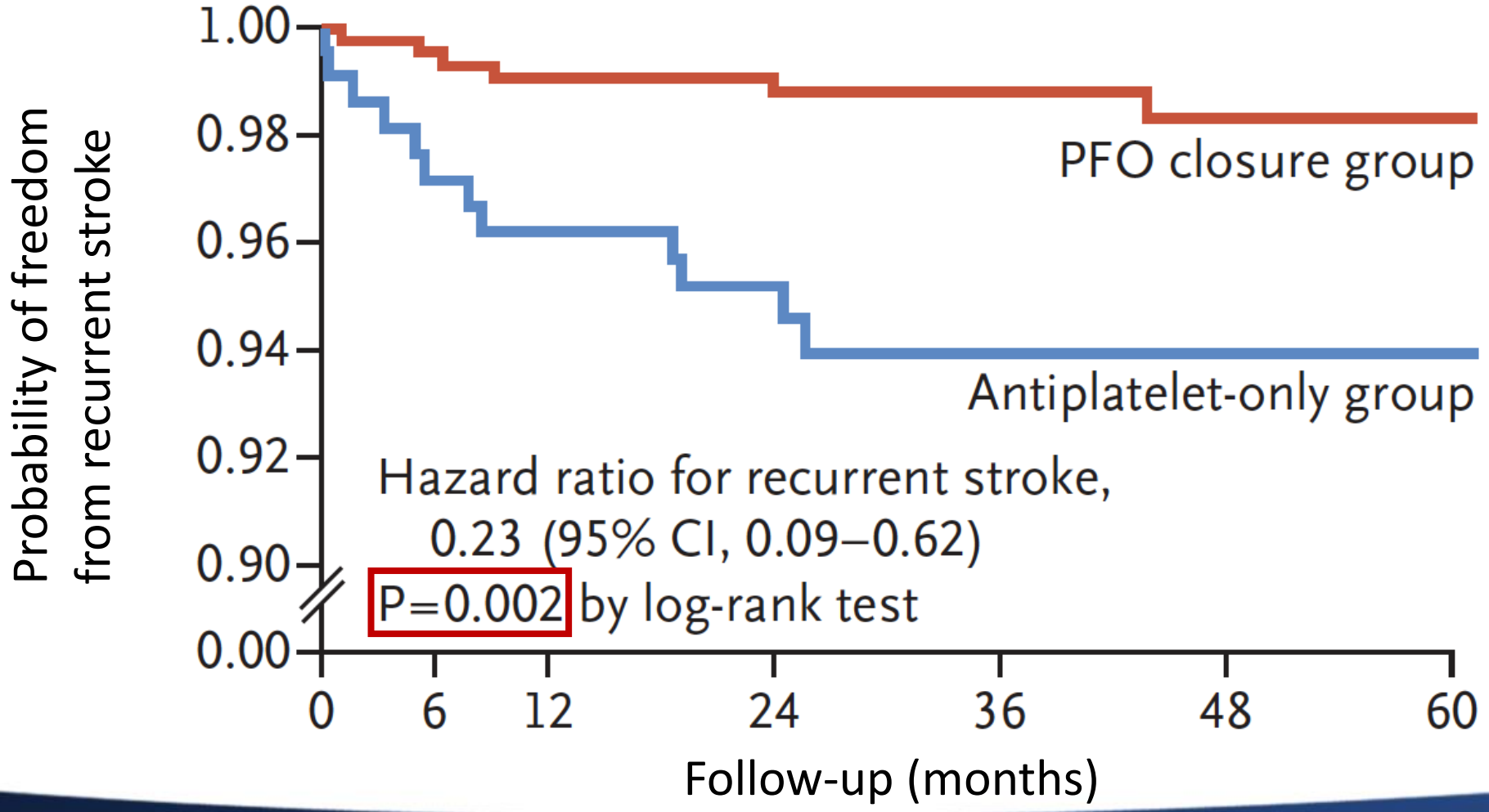
Sondergaard et al. NEJM 2017; 377:1033-42

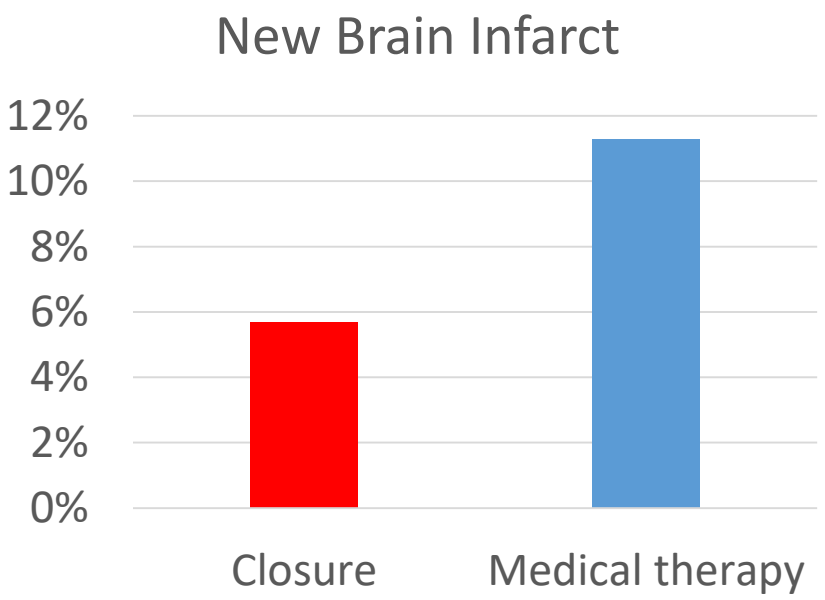
Clinical stroke (ITT)



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

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

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

Safety

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	**3 (0.7%)**	**2 (0.9%)**	**1.0**

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

Safety

- Atrial fibrillation/flutter rate higher in the closure group
  - 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%

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

DEFENCE-PFO

- N=210 -> 120 patients with ischemic stroke within 6 months and high-risk PFO:
  - Atrial septal aneurysm
  - Hypermobility (excursion ≥10 mm)
  - PFO size ≥2 mm (maximum separation of septum primum from septum secundum)

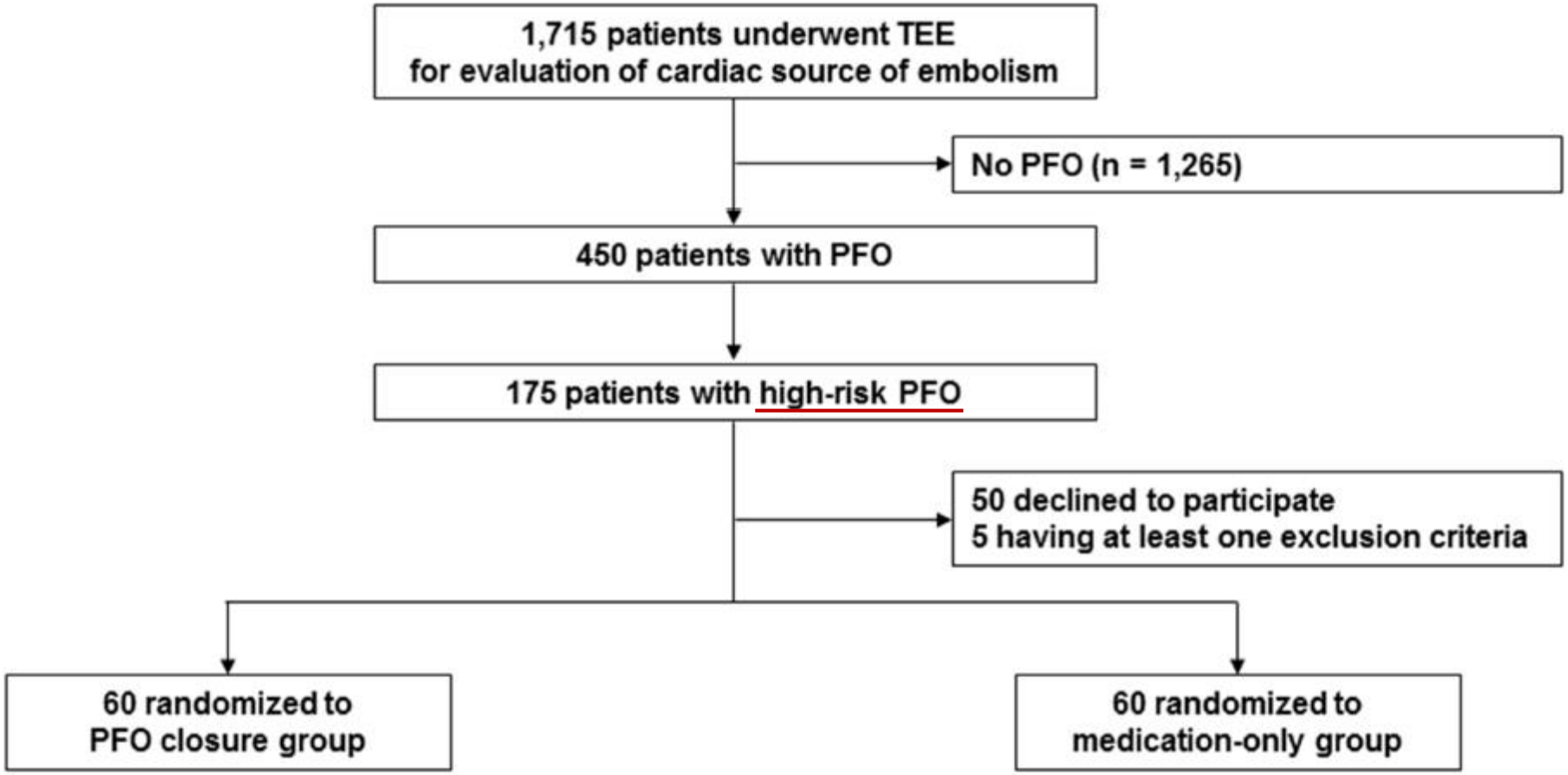
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + DAPT fo r at least 6 months *or* anti-thrombotic therapy with OAC or APT

- Aim: To evaluate whether the benefits of PFO closure can be determined based on morphological characteristics of the PFO

- Primary end-point: Stroke, vascular death, or major bleeding during 2 years f/u

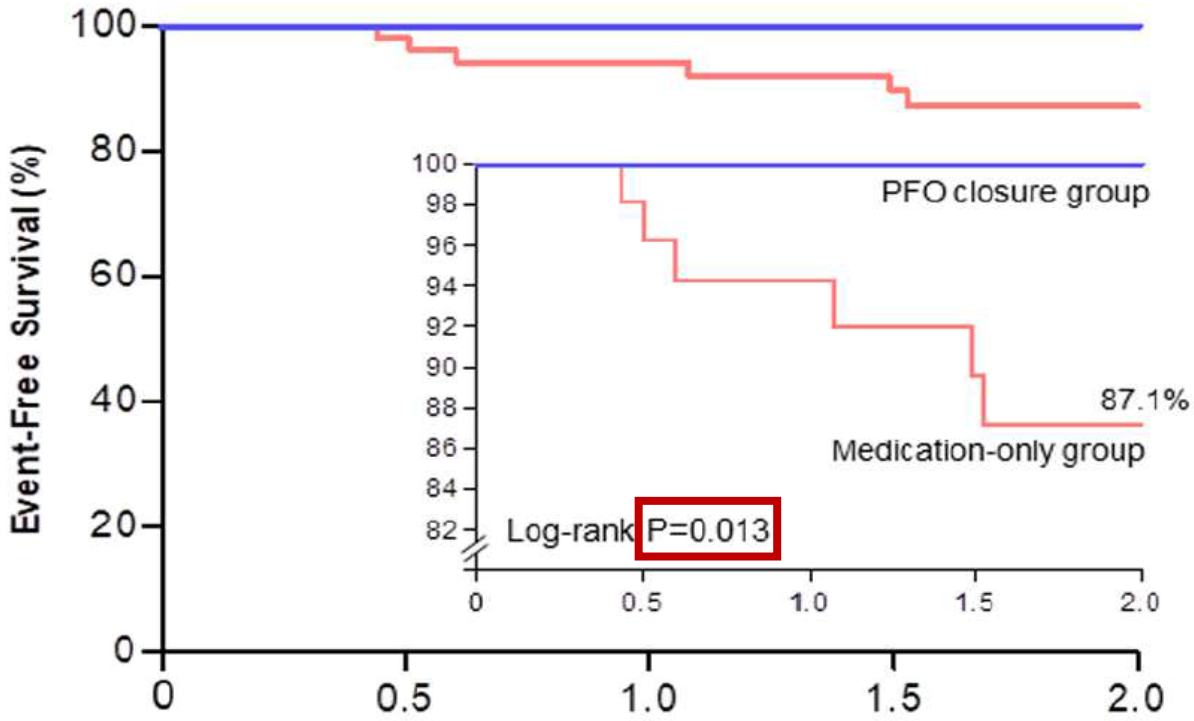
Lee et al. JACC 2018; 71:2335-42

DEFENCE-PFO



Lee et al. JACC 2018; 71:2335-42

DEFENCE-PFO



No. at Risk					
PFO closure	60	52	46	42	40
Medication-only	60	52	45	38	37

Lee et al. JACC 2018; 71:2335-42

American Academy of Neurology

Level A	Clinicians must counsel patients considering percutaneous PFO closure that having a PFO is common; it occurs in about 1 in 4 people; it is impossible to determine with certainty whether their PFOs caused their strokes or TIAs; the effectiveness of the procedure for reducing stroke risk remains uncertain; and the procedure is associated with relatively uncommon, yet potentially serious, complications.
Level C	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 R	Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting.

Messé et al. Neurology 2016; 87:815-21

Canadian stroke best practice recommendation

9.1 Patent Foramen Ovale (PFO) ***(Revised 2017)***

i. Patients with a recent ischemic stroke or TIA attributed to a PFO should have an evaluation by clinicians with stroke and cardiovascular expertise [Evidence Level C].

ii. For carefully-selected patients with a recent ischemic stroke or TIA attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone **provided all** the following criteria are met [Evidence Level A]:

   a. Age 18–60 years;

   b. The diagnosis of the index stroke event is confirmed by imaging as a nonlacunar embolic ischemic stroke or a TIA with positive neuroimaging or cortical symptoms;

   c. The patient has been evaluated by a neurologist or clinician with stroke expertise, and the PFO is felt to be the most likely cause for the index stroke event following a thorough etiological evaluation to exclude alternate etiologies.

iii. For patients requiring long-term anticoagulation, the decision regarding PFO closure remains unclear, and decisions should be based on individual patient characteristics and risk versus benefit profile [Evidence C].

iv. For patients with a recent ischemic stroke or TIA attributed to a PFO who do no undergo PFO closure and are aged 60 years or younger, either antiplatelet or anticoagulant therapy is recommended for secondary stroke prevention, unless there is a separate evidence-based indication for chronic anticoagulant therapy [Evidence Level B].

v. There is insufficient evidence to make a recommendation regarding the comparative effectiveness of PFO closure vs. anti-coagulant therapy.

Wein et al. Int J Stroke 2018; 13:420-43

Conclusions

- In carefully selected patients with cryptogenic stroke, PFO closure significantly reduced the risk of recurrent stroke and new brain infarct compared to anti-platelet therapy alone (REDUCE & CLOSE)

- Low risk of device- or procedure-related complications

- These results are likely to change guidelines and clinical practice for this population