Update on PFO closure for cryptogenic stroke, migraine and more

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Disclosure Statement of Financial Interest

I, Mark Reisman, MD, DO NOT have a financial interest, arrangement, or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- PFO likely responsible for 5% of all ischemic strokes and 10% of ischemic strokes in young and middle-aged adults.
- Cryptogenic stroke makes up approximately 15-30% of all strokes with a higher proportion in the younger population (<60yo)
- PFOs present in 40%-50% of young or cryptogenic ischemic stroke patients versus 10%-15% of controls
- . A meta-analysis of 23 CCS w 3364 pts, demonstrated that the odds of a PFO were 2.9-fold higher in cryptogenic ischemic stroke patients compared with controls.
  - PFOs were especially more frequent in young and middle-aged cryptogenic ischemic stroke patients (age ≤55 years, odds ratio 5.1), but also more frequent among older cryptogenic ischemic stroke patients (age >55 years, odds ratio 2.0)

1) Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke.* 2009; 40: 2349-55.

Objectives

- Review of data
- Advance terminology of PFO and stroke
- Future directions
- Final thoughts

The studies

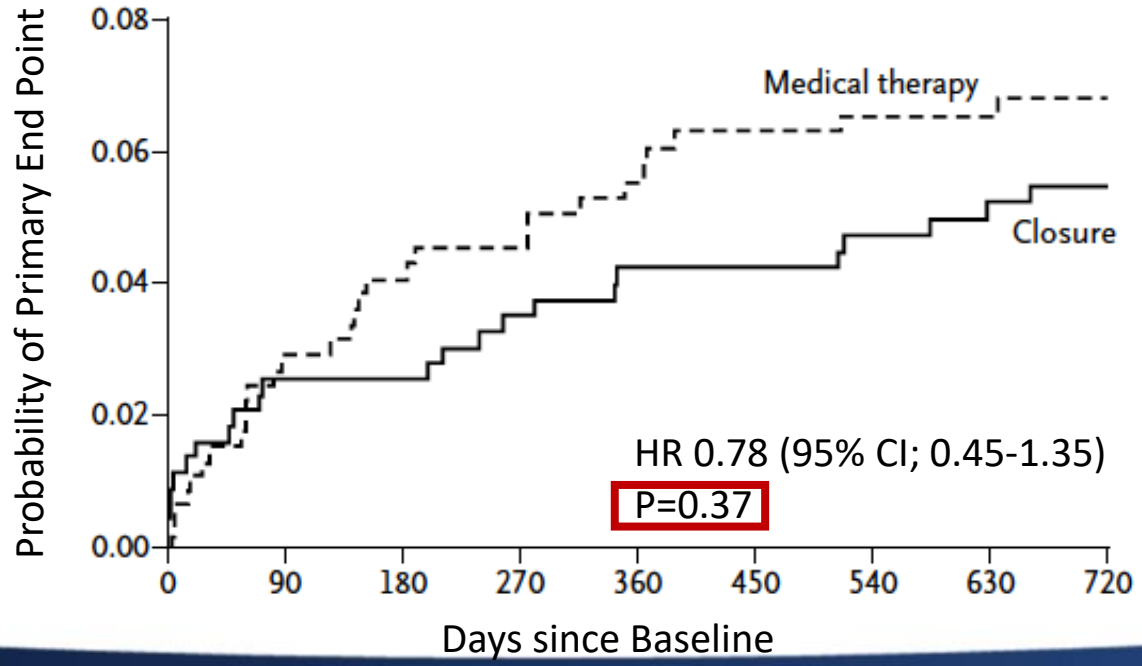
- CLOSURE I (2012)
- PC (2013)
- RESPECT (2013 and 2017)
- REDUCE (2017)
- CLOSE (2017)
- DEFENSE-PFO (2018)

Not a revolution but an evolution

Furlan, AJ, et al. N Engl J Med . 2012;366:991-9.
Meier B, et al. N Engl J Med . 2013;368:1083-91.
Carroll JD, et al. N Engl J Med . 2013;368:1092-100.
Saver JL, et al. N Engl J Med . 2017;377:1022-32.
Søndergaard L, et al. N Engl J Med. 2017;377:1033-42.
Mas JL, et al. N Engl J Med . 2017;377:1011-21.
Lee HP, et al. J Am Coll Cardiol. 2018;71:2335-42.

CLOSURE-1

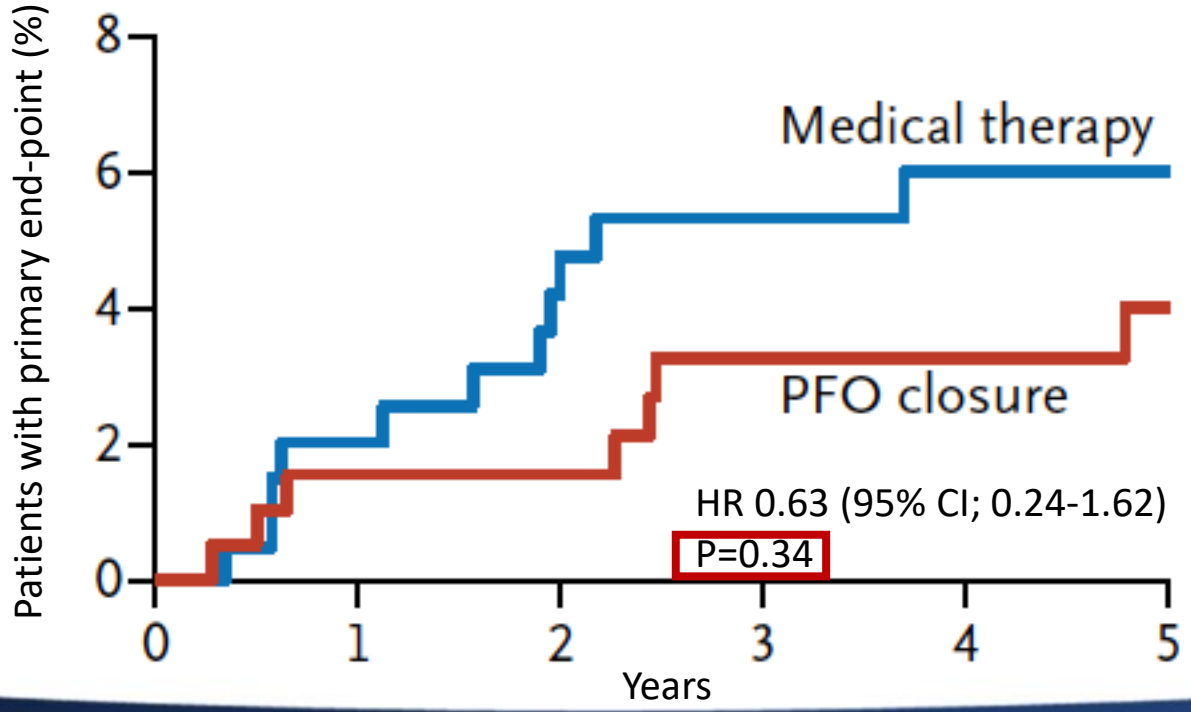
- N=909 patients with stroke or TIA (**not imaging verified**) within 6 months
- RCT, 1:1 PFO closure with STARFlex + 6 months DAPT followed by aspirin for life *or* anti-thrombotic therapy with **VKA, aspirin or both**
- Primary end-point: Stroke/TIA during 2 years, death within 30 days, or death from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



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

PC Trial

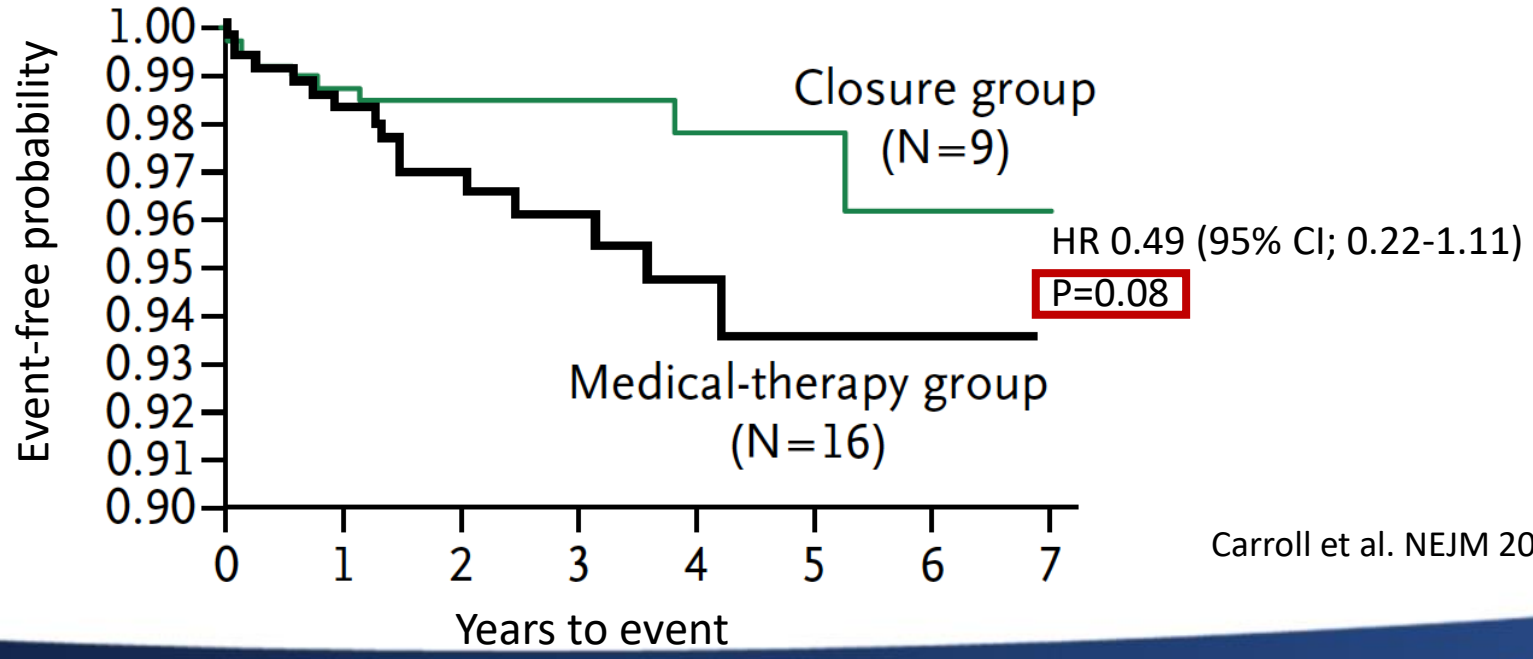
- N=414 patients with stroke, TIA or extra-cranial thrombo-embolic event
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + APT for at least 1-6 months *or* anti-thrombotic therapy with **OAC, aspirin or both**
- Primary end-point: Death, non-fatal stroke, TIA, or peripheral embolism



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

NNT to prevent 1 stroke in 5 years was 42 patients.

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Strok

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

NNT to prevent 1 stroke in 2 years was ~ 28 patients

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

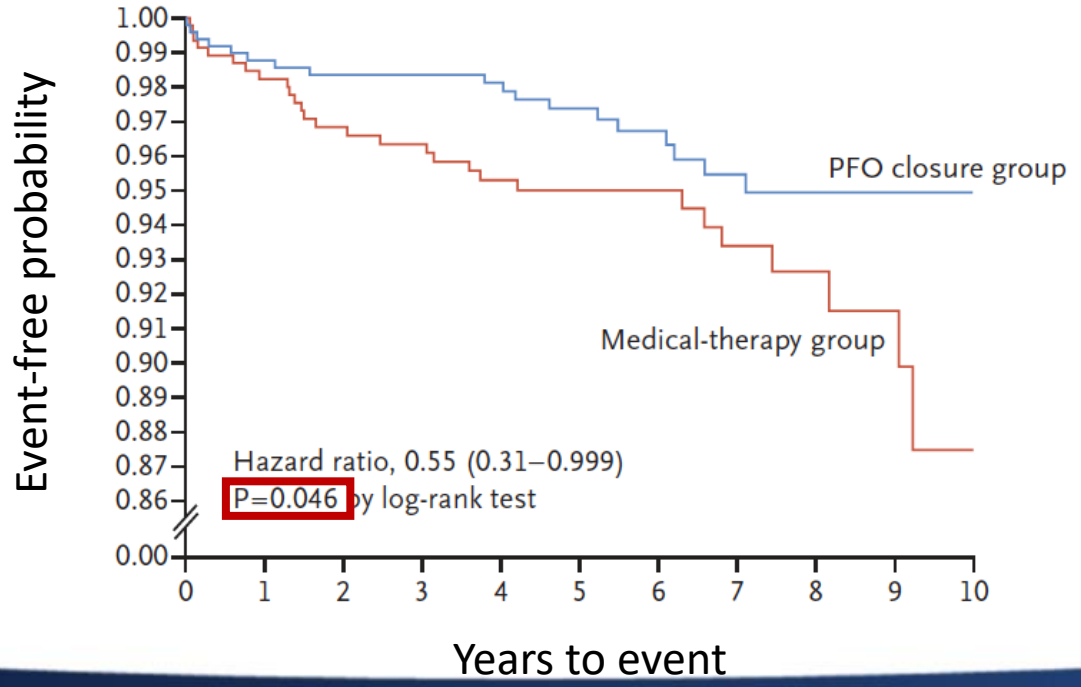
J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. 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

NNT to prevent 1 stroke in 5 years was 20 patients.

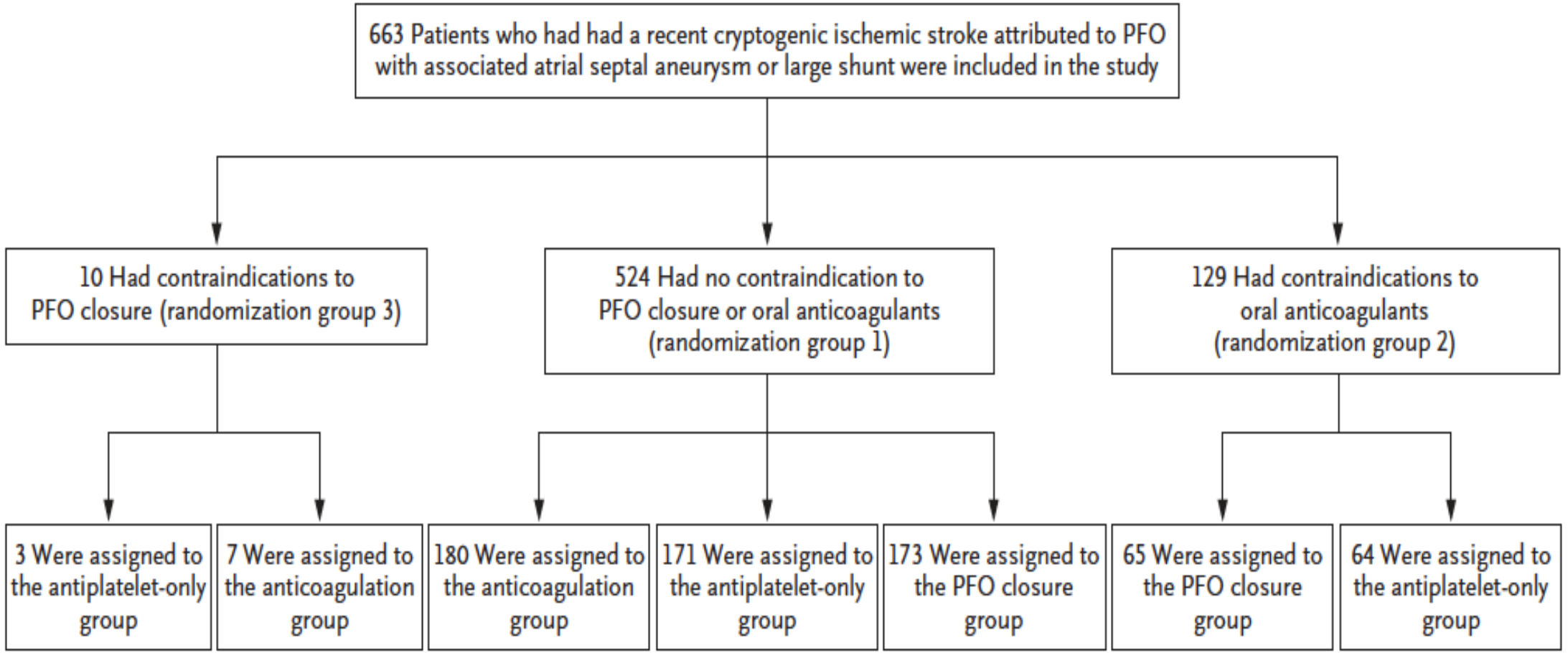
RESPECT extended f/u (mean 2.6 -> 5.9 years)

- 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%)**



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

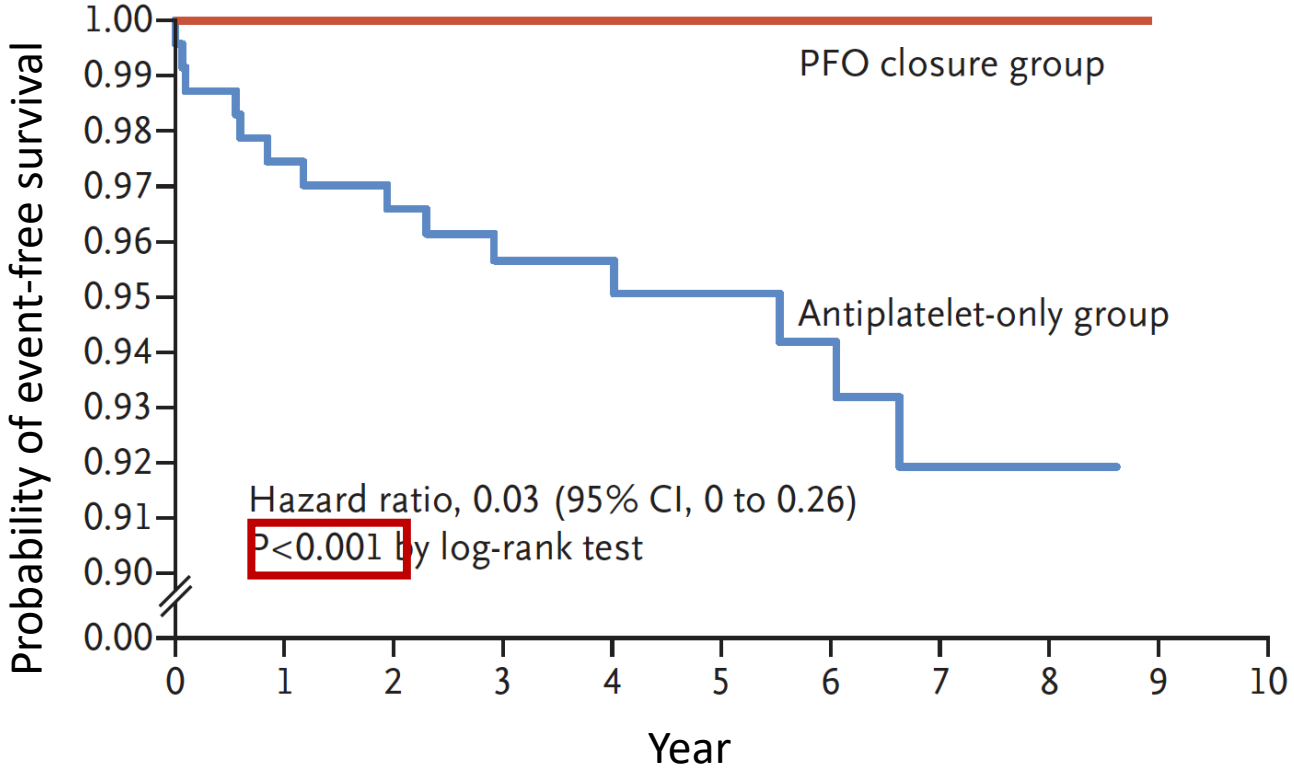
CLOSE



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



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

- PFO closure (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

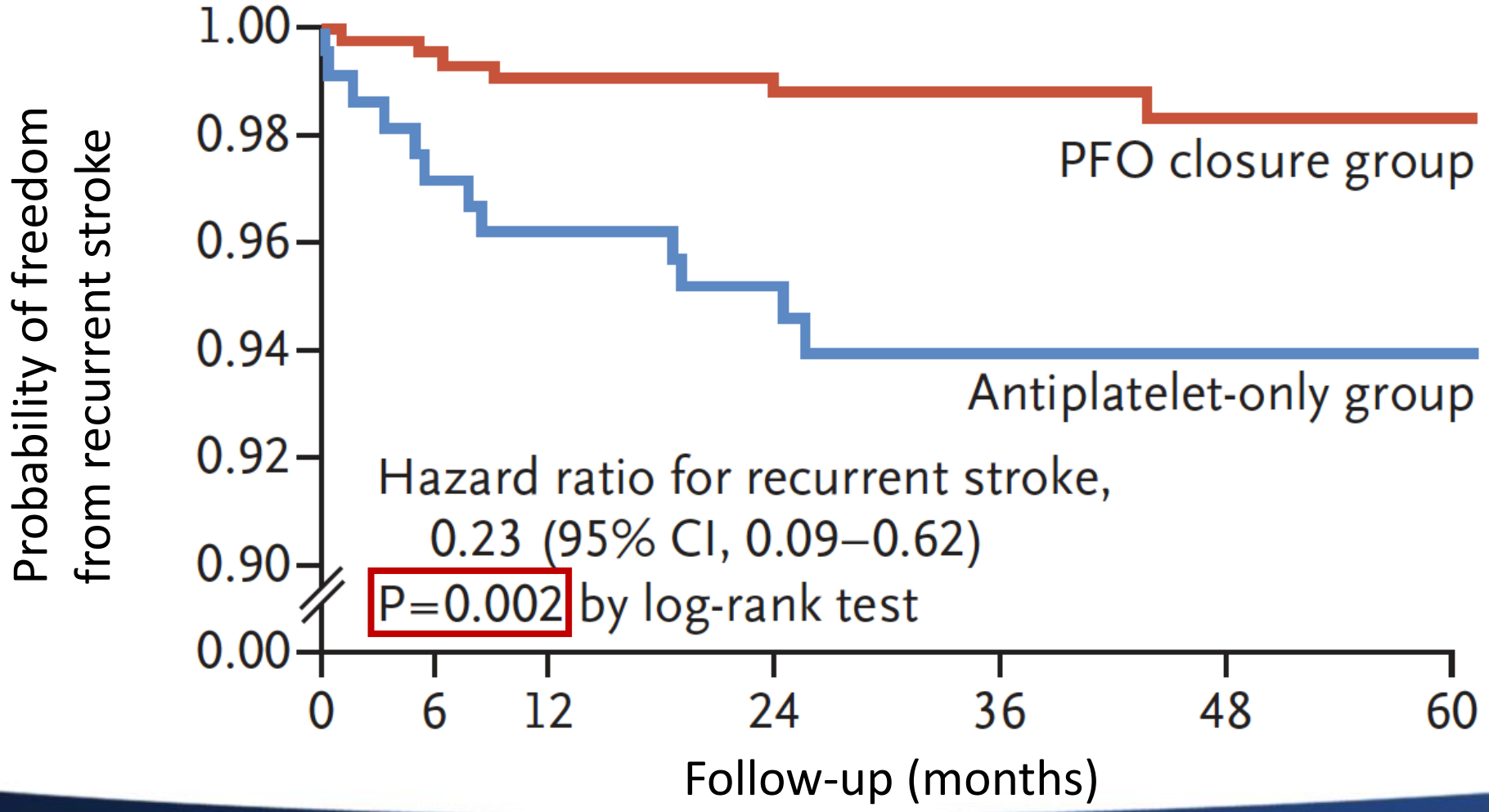
Sondergaard et al. NEJM 2017; 377:1033-42

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)	-

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

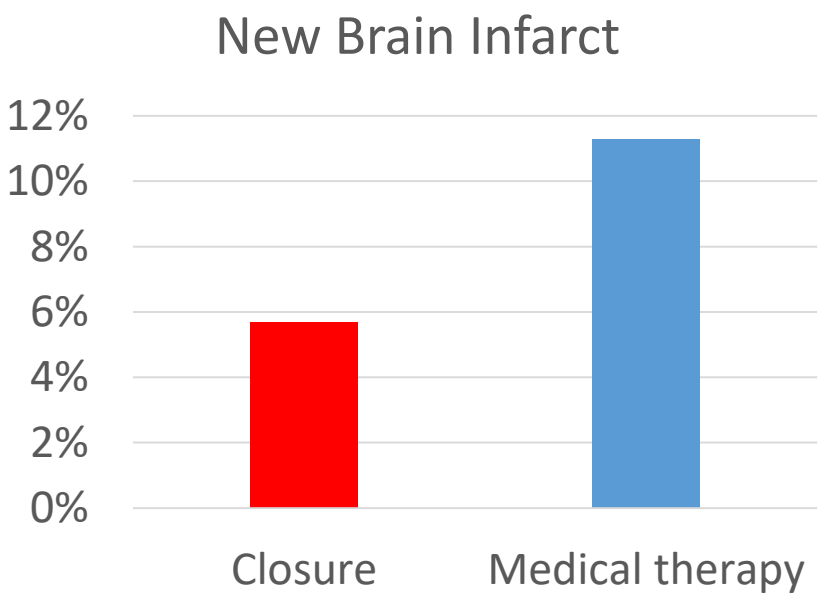
Clinical stroke (ITT)



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

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

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

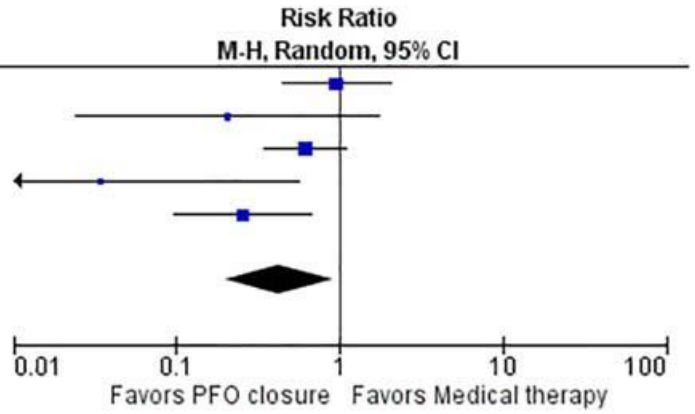
PFO Closure vs. Medical Therapy Alone in the Incidence of Recurrent Stroke

Meta-Analysis of Cryptogenic Ischemic Stroke Randomized Trials

Study or Subgroup	PFO Closure Events	PFO Closure Total	Medical Therapy Events	Medical Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSURE 1	12	447	13	462	28.0%	0.95 [0.44, 2.07]	2012
PC trial	1	204	5	210	9.5%	0.21 [0.02, 1.75]	2013
RESPECT Trial	18	499	28	481	32.2%	0.62 [0.35, 1.11]	2013
CLOSE	0	238	14	235	6.1%	0.03 [0.00, 0.57]	2017
REDUCE	6	441	12	223	24.1%	0.25 [0.10, 0.66]	2017
Total (95% CI)		**1829**		**1611**	**100.0%**	**0.42 [0.20, 0.91]**	
Total events	37		72				

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 9.72$, $df = 4$ ($P = 0.05$); $I^2 = 59\%$

Test for overall effect: $Z = 2.22$ ($P = 0.03$)

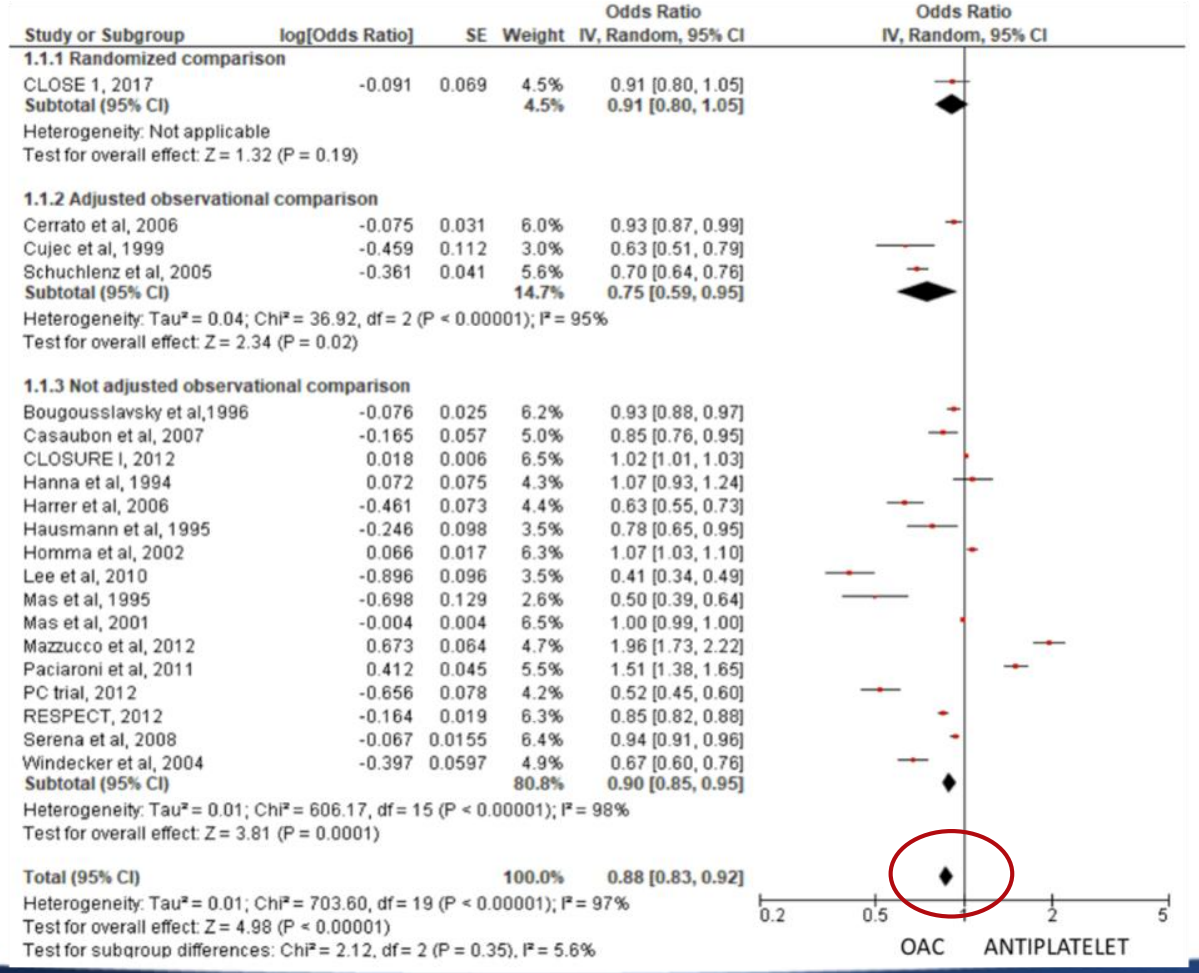


Favors PFO closure (2.0%) over medical therapy alone (4.2%) in decreasing recurrent stroke (p=0.03).

Hakeem A, Cilingiroglu M, Katramados A, Boudoulas KD, et al. Catheter Cardiovasc Interv. 2018.

Anticoagulant vs. Antiplatelet Therapy for Stroke Prevention after Cryptogenic Ischemic Stroke with PFO

Meta-Analysis



Pristipino C, et al. EuroIntervention. 2018.

Rope Score

Table 2: The Risk of Paradoxical Embolism (RoPE) Score

Characteristic	Points
Absence of HTN	1
Absence of DM	1
No history of stroke/TIA	1
Non-smoker	1
Cortical infarct on imaging	1
Age in years:	
18 – 29	5
30 – 39	4
40 - 49	3
50 - 59	2
60 - 69	1
≥ 70	0

The RoPE score is a point system, with a score from a possible 0 to 10.

RoPE score ≥ 7 represents a high probability of the discovered patent foramen ovale (PFO) to be the stroke culprit.

HTN: hypertension, DM: Diabetes Mellitus, TIA: Transient Ischemic Attack.

Classification of PFO Risk as Source of Embolism and PFO Causal Relatedness in Patients with Embolic Infarct Topography and without Other Major Stroke Sources

Risk Grade	Features	Causal Relatedness	
		Low RoPE Score	High RoPE Score
Very high risk source	PFO + straddling thrombus	Very likely	Very likely
High risk source	BOTH of: 1A. PFO + ASA, or 1B. Large shunt PFO, AND 2. Preceding or concomitant PE or DVT	Probable	Likely
Medium risk source	ANY of 1. PFO + ASA 2. Large shunt PFO	Possible	Probable
Low risk source	Small shunt PFO without ASA	Unlikely	Possible

PFO: patent foramen ovale, RoPE: the risk of paradoxical embolism score, ASA: atrial septal aneurysm, PE: pulmonary embolism, DVT: deep venous thrombosis.

And what about migraine…..

Ticagrelor for Refractory Migraine/Patent Foramen Ovale (TRACTOR): An open-label pilot study

- Reisman, Adam M. BS; Robbins, Barbara T. FNP-BC; Chou, Denise E. MD; Yugrakh, Marianna Shnayderman MD; Gross, Giti J. FNP-BC; Privitera, Lauren MS, MPH; Nazif, Tamim MD; Sommer, Robert J. MD

- After completion of the TRACTOR protocol, 9 of 17 ticagrelor MHA responders underwent PFO closure.
- The PFO was successfully closed in all 9 using the Cardioform Septal Occluder
- All had ongoing MHA relief after discontinuation of P2Y12 inhibition, typically clopidogrel, at 3 months after PFO closure.
- There were no PFO closure-related complications.
- Seven of the other 8 MHA responders were unable to get insurance approval for the closure procedure and, at the time of this submission, have remained on thienopyridine therapy with ongoing headache relief. One patient had an excellent response to ticagrelor, but a less effective response to subsequent thienopyridine treatment

Conclusion

- Safe procedure, FDA approved devices
- ~~***Cryptogenic stroke***~~ **PFO Associated Stroke**
- Next steps
  - Focused research in Migraine
  - Rope score~
  - ? High risk scores for primary prevention
    - Elevated right heart pressures ; PHTN, OSA,
    - Pulmonary embolus, VTE
    - High risk : surgery, immobilization, liver transplantation, decompression

  Illness
- More Controversy
  - The presence or absence of competing causes
  - The CODICIA study (PMID: 18818401) did not show an effect of concomitant ASA on stroke risk and size of shunt has been questioned in studies ; consider Transcranial Doppler assessment.

  Long Road to get here, more to come…..