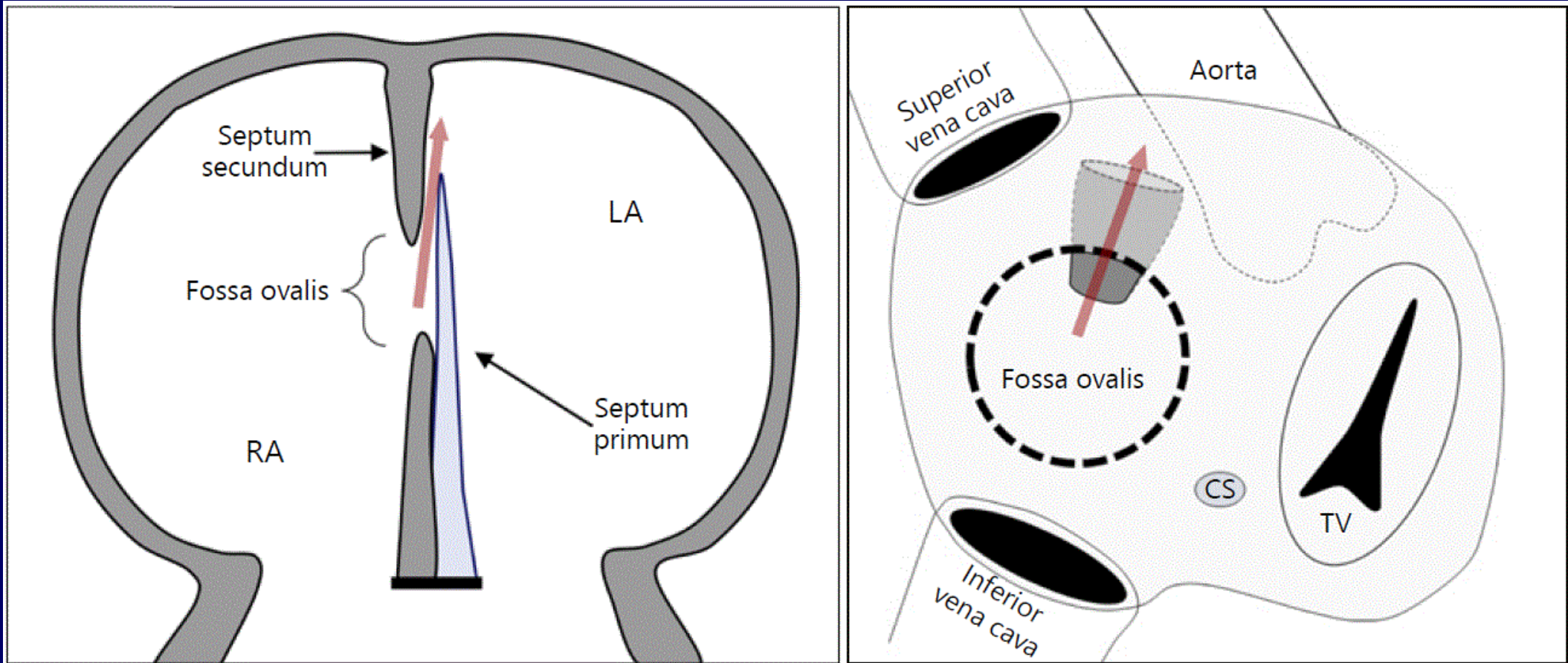


# Intervention for stroke prevention : PFO

Jae Hyung Park

Department of Cardiology, Cardiovascular Center,  
Korea University Anam Hospital

# PFO (Patent foramen ovale)



Cardiology. 2019;143(1):62-72.

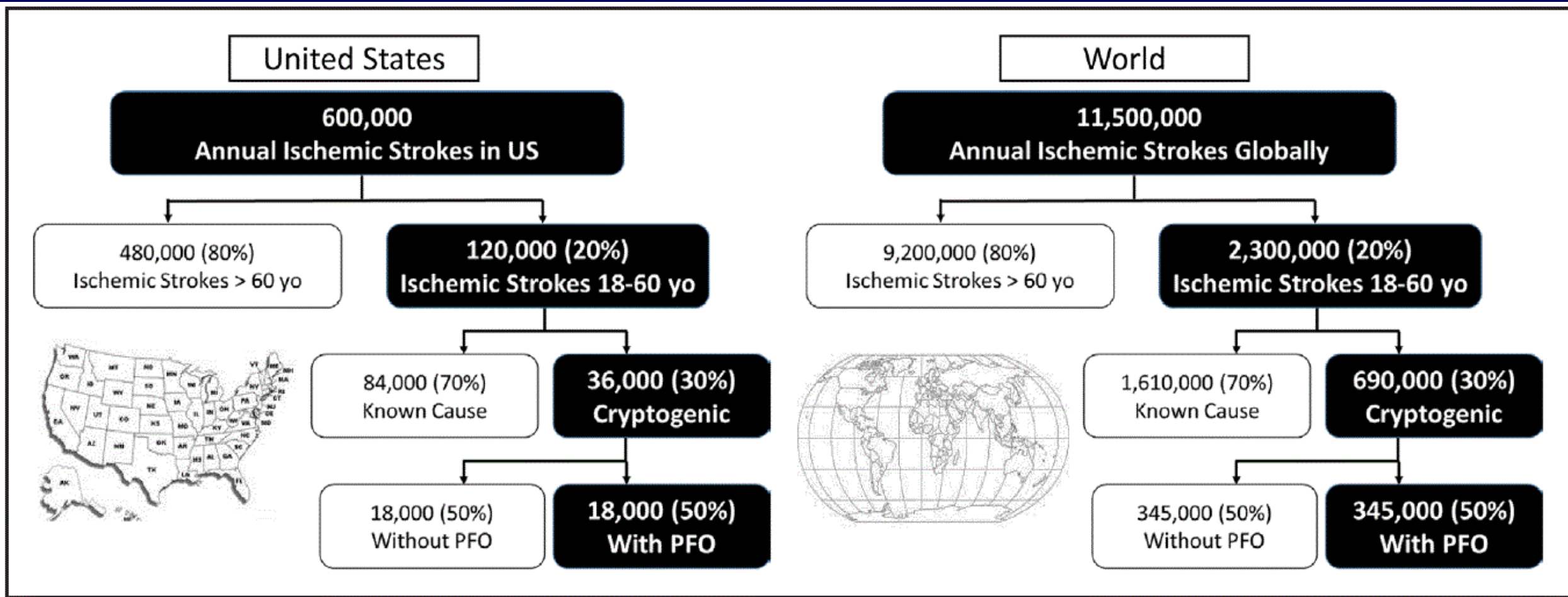
# Is there anybody to have a PFO?



High prevalence : 20~25% of people have a PFO

J Am Soc Echocardiogr. 2015;28(8):910-58.

# Annual incidence of cryptogenic / PFO stroke

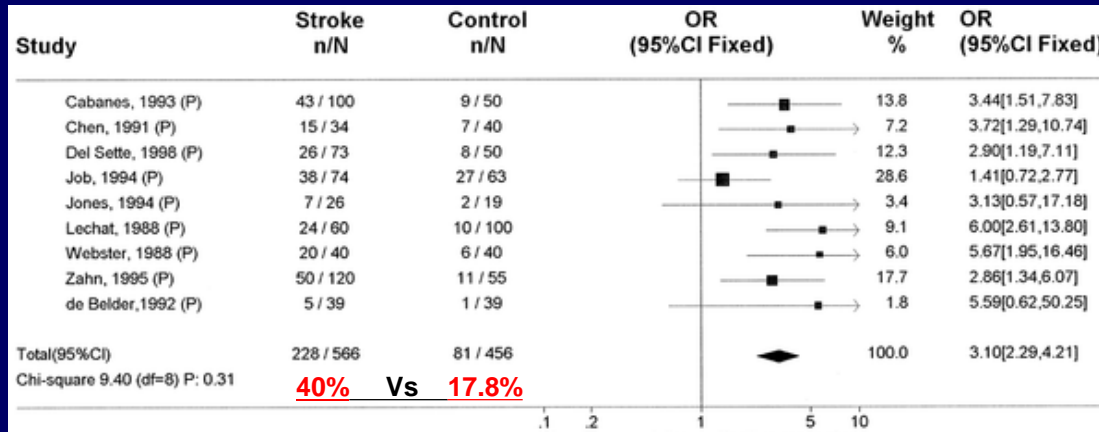


The mean diameter of persisting PFOs : 4.9 mm (1~19 mm)  
 The middle cerebral artery stem (3 mm) and major cerebral cortical branches (1 mm)

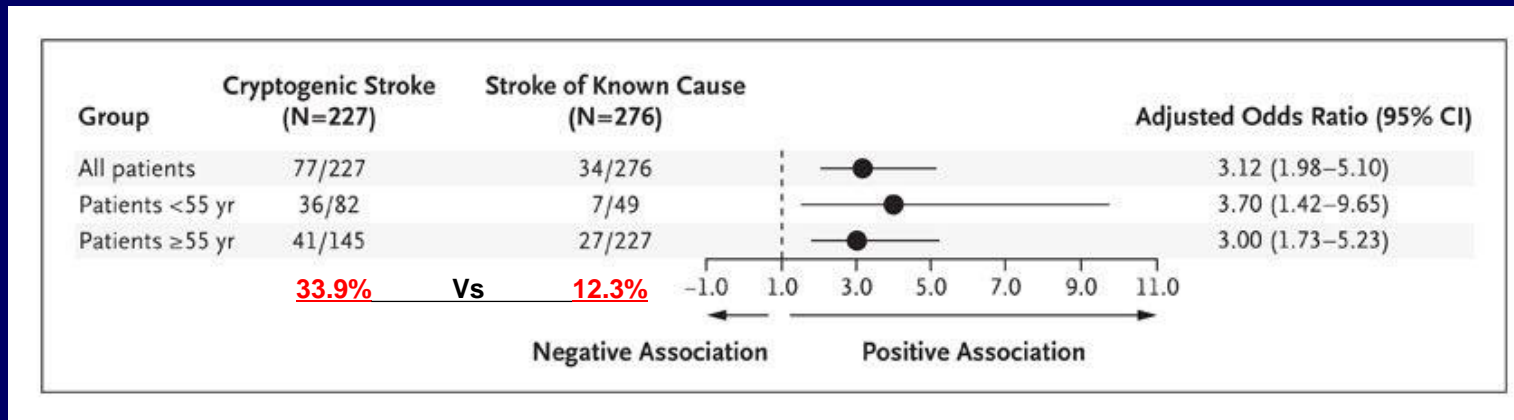
# PFO is associated with Cryptogenic Stroke

- **Lechat et al. (N Engl J Med. 1988)** : first published, case-control study
  - Increased prevalence of PFOs in ~60 patients < 55 years old with cryptogenic stroke
  - **Cryptogenic CVA ; 40%** had PFOs Vs 10% in the control group.

N Engl J Med. 1988;318:1148-52.



Neurology. 2000;55(8):1172-9.

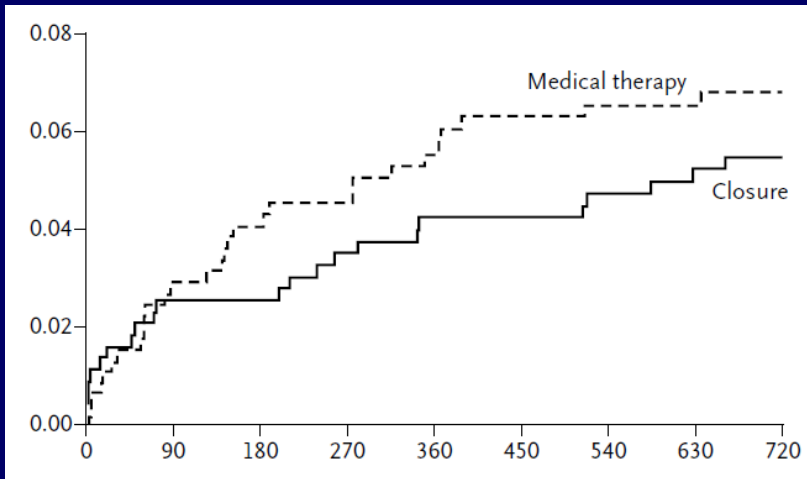


N Engl J Med. 2007;357(22):2262-8.

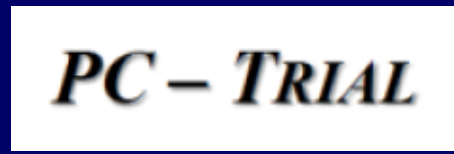
# Medical Vs. Closure (Round-1 RCTs)



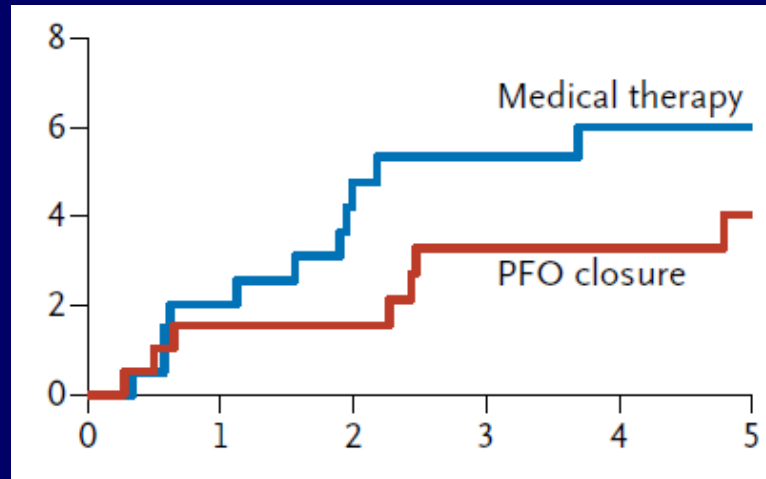
Closure or Medical Therapy for Cryptogenic Stroke/TIA with PFO (N=909) **STARFlex** (N=447)  
24 months fu



HR 0.78 (95% CI 0.45-1.35) p=0.37  
N Engl J Med. 2012;366:991-9.



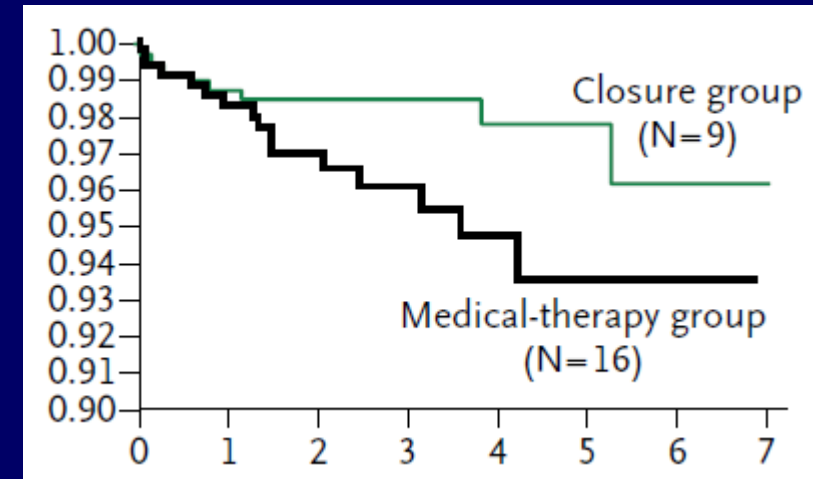
Closure of PFO in Cryptogenic Embolism (N=414)  
**Amplatzer** (N=204)  
60 months fu



HR 0.63 (95% CI 0.24-1.62) p=0.34  
N Engl J Med. 2013;368:1083-91.



Closure of PFO Vs Medical Therapy after Cryptogenic Stroke (N=980)  
**Amplatzer** (N=499)  
84 months fu



HR 0.49 (95% CI 0.22-1.11) p=0.08  
N Engl J Med. 2013;368:1092-100.

**All 3 RCTs failed to meet primary end points!**

# Guidelines for the Prevention of Stroke

## Recommendations

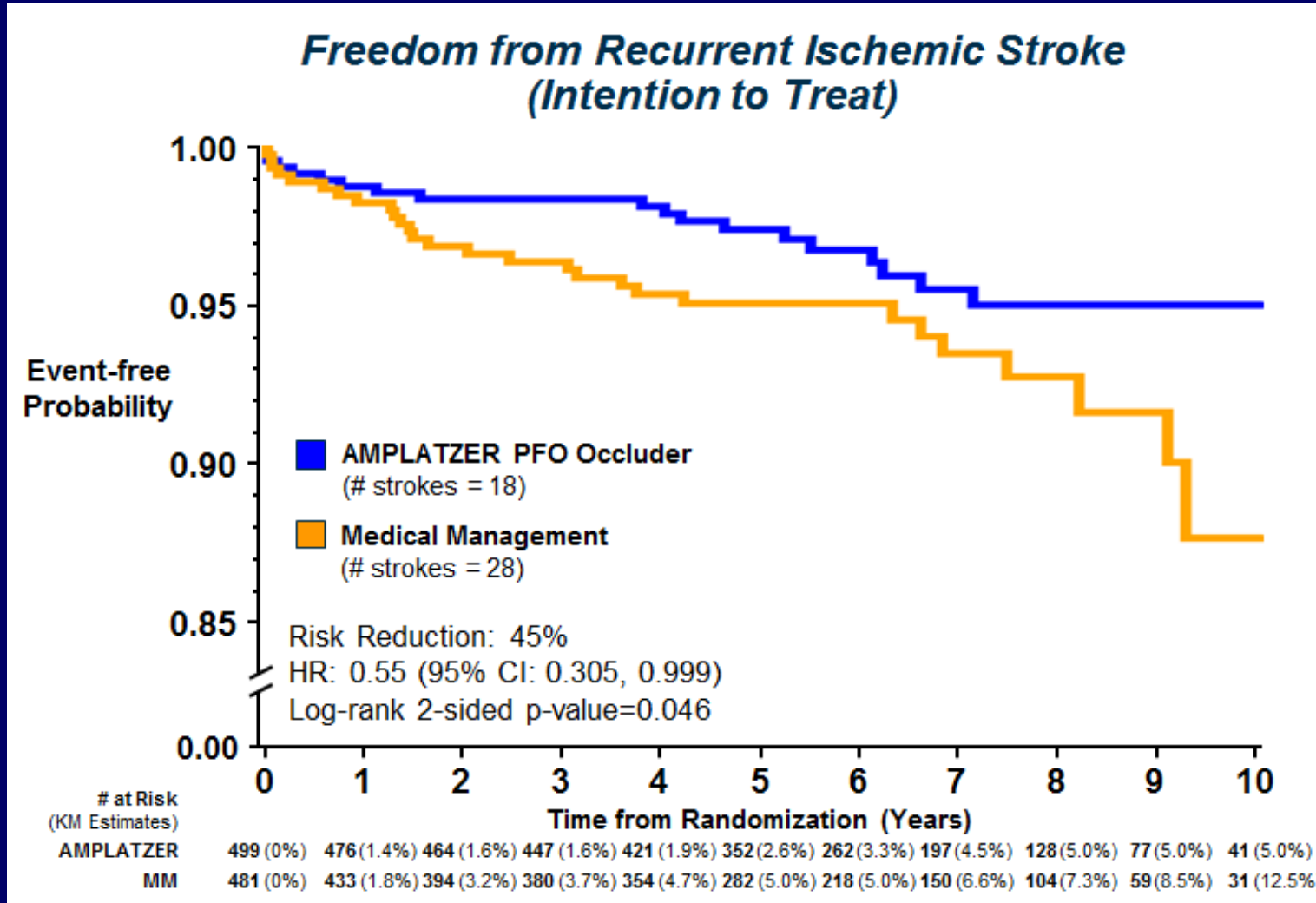
1. For patients with a patent foramen ovale (PFO), a secondary stroke (Class IIa, LOE B)
2. There are no data to support the use of anticoagulation therapy in patients with a patent foramen ovale (PFO) and a secondary stroke (Class IIa, LOE B)
3. There are no data to support the use of anticoagulation therapy in patients with a patent foramen ovale (PFO) and a cryptogenic stroke (Class IIa, LOE B)

2011

Patent Foramen Ovale Recommendations	
2014 Recommendation	Revisions (2011)
For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B)	Class changed from IIa to I
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. (Class I, LOE A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa, LOE C).	New Recommendations
For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. (Class III, LOE A)	Revised Recommendation
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)	New Recommendation

2014

# RESPECT 10 yr Final Results



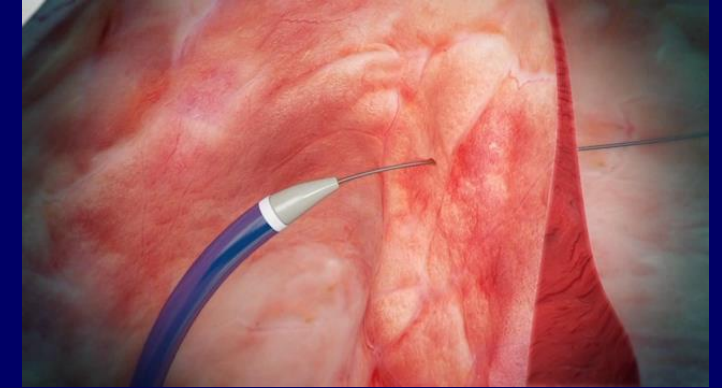
- Mean f/u = 5.9 yrs
- All endpoints were recurrent non-fatal ischemic stroke
- 45% relative risk reduction in favor of device group in the intent to treat cohort
- Age : 18-60, cryptogenic stroke within 270 days.
- TEE visualization of micro-bubbles.

Robert J. Sommer. Presented at TCT 2017.



# FDA Approval 10/28/2016

The **AMPLATZER™ PFO Occluder** is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to **reduce the risk of recurrent ischemic stroke** in patients, predominantly between the ages of **18 and 60 years**, who have had a **cryptogenic stroke** due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
1093 New Hampshire Avenue  
Document Control Center - W066-G609  
Silver Spring, MD 20893-0002

October 28, 2016

St. Jude Medical, Inc.  
Rashmi Bhushan, PhD  
Manager, Regulatory Affairs  
5050 Nathan Lane North  
Plymouth, Minnesota 55442

Re: P120021

Trade/Device Name: AMPLATZER PFO Occluder

Filed: November 30, 2012

Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1, 2014, February 27, 2015, September 17, 2015, October 8, 2015

Product Code: MLV

Dear Rashmi Bhushan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AMPLATZER PFO Occluder. This device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.



## Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter)

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the 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

Scott L. Halperin, MD, PhD,

MSCE

Correspondence to  
American Academy of Neurology:  
guidelines@aan.com

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%).

**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

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

### The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

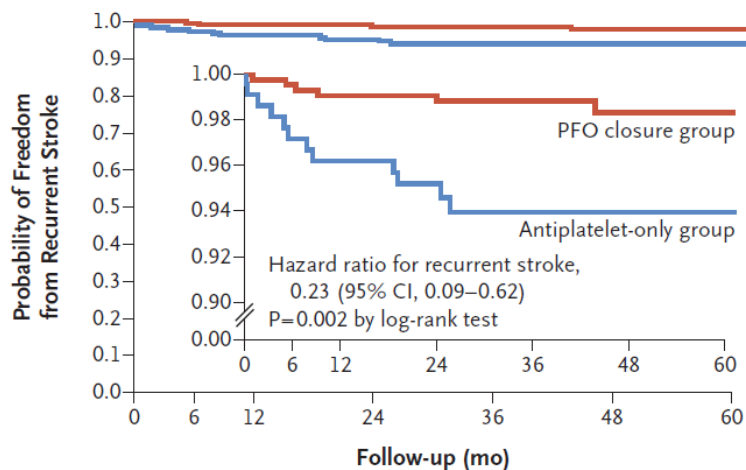
SEPTEMBER 14, 2017

VOL. 377 NO. 11

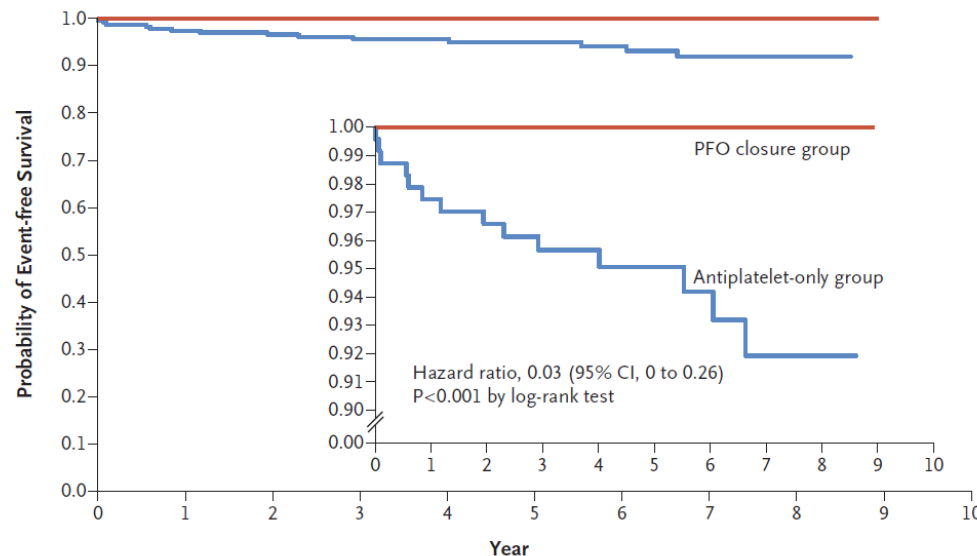
### Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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. Lussion, 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\*

N=664  
Median  
fu 3.2 yrs



No. at Risk	0	6	12	24	36	48	60
PFO closure group	441	422	417	398	278	182	102
Antiplatelet-only group	223	202	194	173	116	78	30



No. at Risk	0	1	2	3	4	5	6	7	8	9	10
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

N=663  
Mean fu 5.3  
yrs

ASA (septum  
primum  
excursion >  
10mm) or  
Large shunt



# Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017

International Journal of Stroke

0(0) 1–24

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DOI: 10.1177/1747493017743062

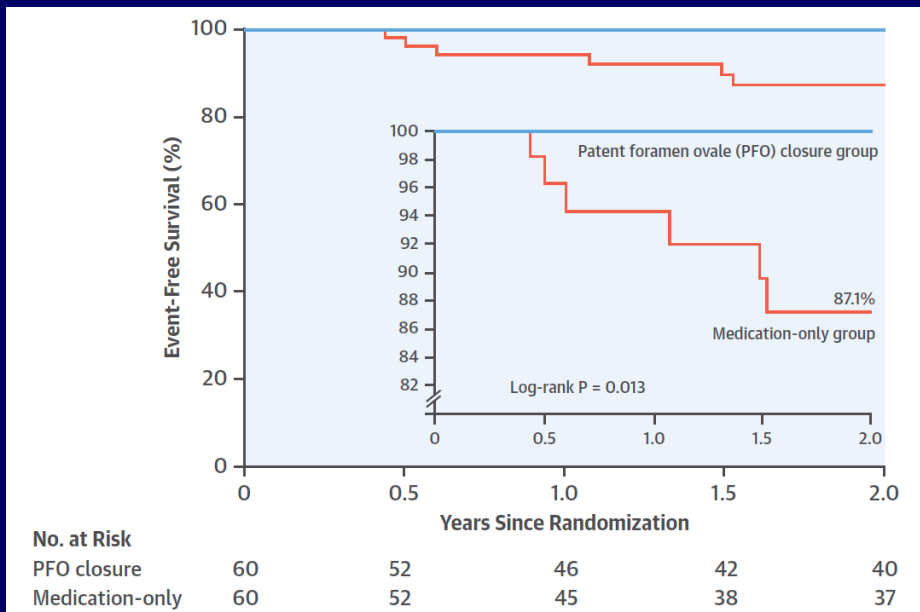
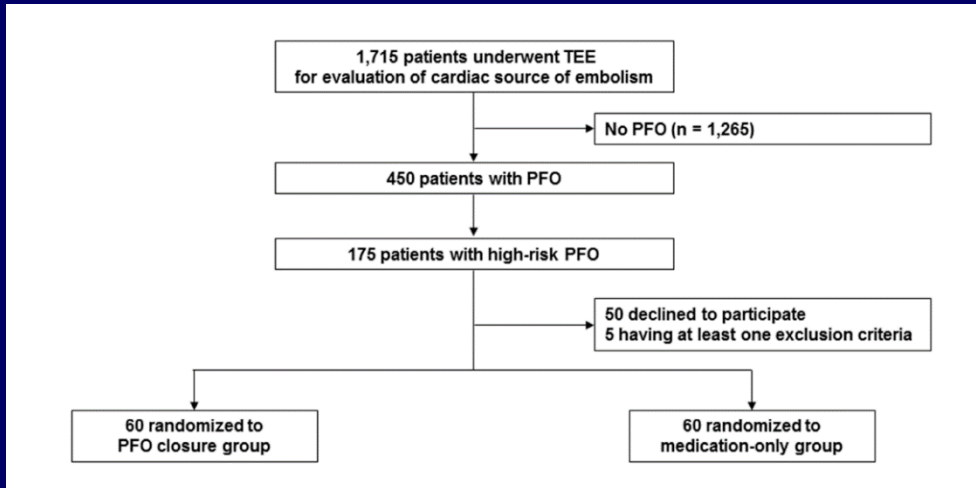
[journals.sagepub.com/home/wso](http://journals.sagepub.com/home/wso)



## 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.**

# Cryptogenic Stroke and High-risk PFO : Defense-PFO



2-Yr Outcome	PFO Closure Group (n = 60)	Medication-Only Group (n = 60)	p Value
Primary endpoint	0 (0.0)	6 (12.9)	0.013
Secondary endpoint			
Ischemic stroke	0 (0.0)	5 (10.5)	0.023
Vascular death	0 (0.0)	0 (0.0)	NA
TIMI-defined major bleeding	0 (0.0)	2 (4.9)	0.15
Hemorrhagic stroke	0 (0.0)	1 (2.5)	0.30
Transient ischemic attack	0 (0.0)	1 (2.0)	0.32
Systemic embolism	0 (0.0)	0 (0.0)	NA
New ischemic lesion on MRI	3/34 (8.8)	7/38 (18.4)	0.24

Values are n (%) (Kaplan-Meier estimates) or n/N (%).

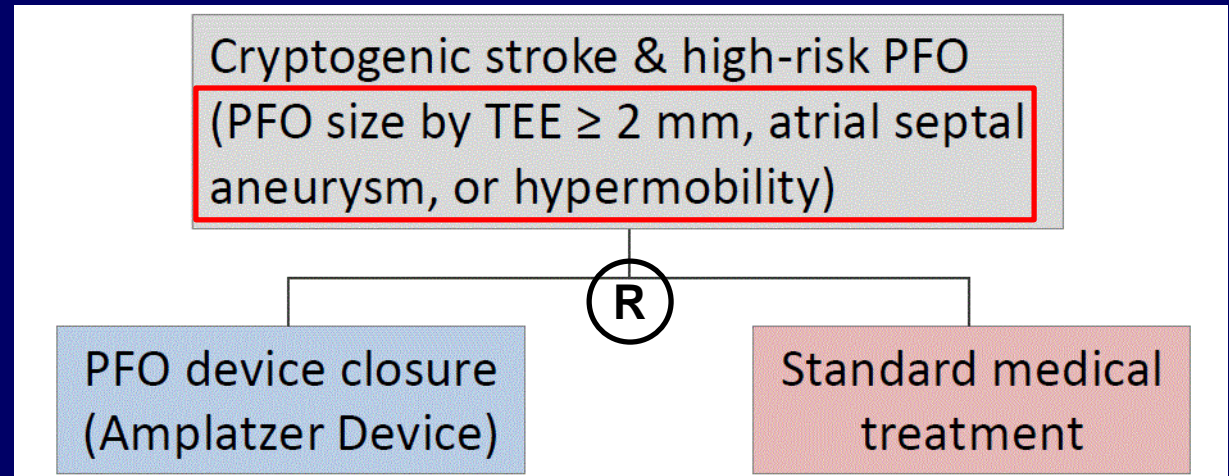
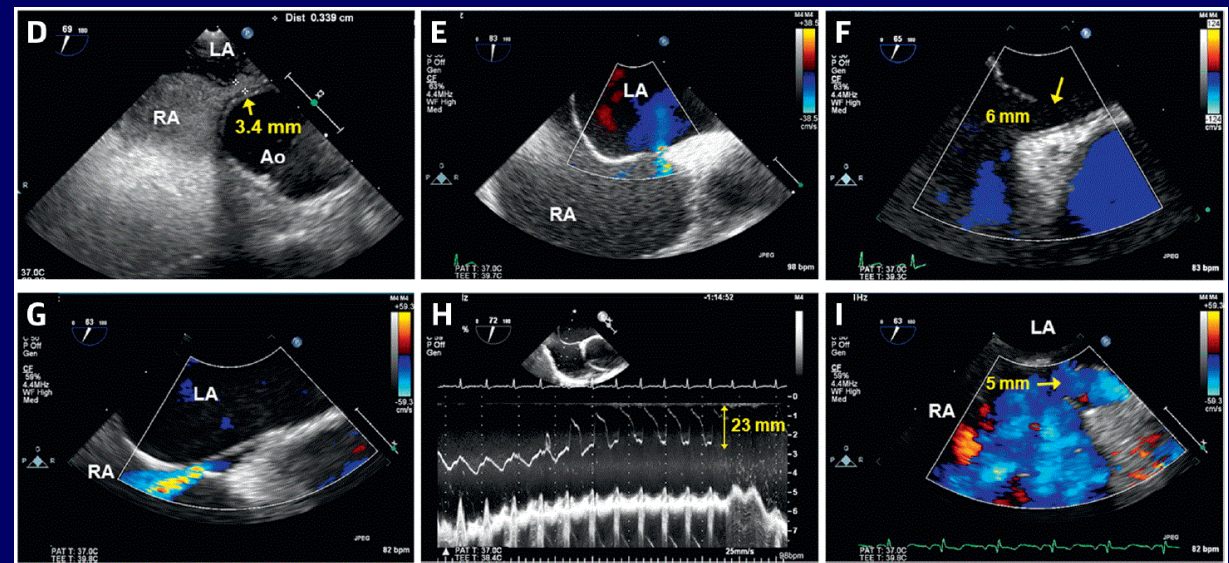
MRI = magnetic resonance imaging; NA = not applicable; PFO = patent foramen ovale; TIMI = Thrombolysis In Myocardial Infarction.

[DEFENSE-PFO] **High-risk PFO**  
 ASA, hypermobility ; excursion  $\geq 10$  mm  
 Large : separation of p from s  $\geq 2$ mm

# Unique definition of morphological 'High-risk' PFO

Baseline demographic and transesophageal echocardiographic characteristics in patients with cryptogenic stroke and patent foramen ovale (PFO) stratified by recurrent stroke during medical treatment

Variable	Recurrence		p Value
	No (n = 145)	Yes (n = 14)	
<b>Demographic data</b>			
Age (years)	52 ± 13	57 ± 15	0.24
Men	108 (75%)	9 (64%)	0.52
Hypertension	72 (50%)	10 (71%)	0.12
Diabetes mellitus	27 (19%)	0 (0%)	0.13
Smoking	55 (38%)	3 (21%)	0.22
Family history of stroke	7 (5%)	1 (7%)	0.52
<b>Echocardiographic data</b>			
Left-to-right shunt	48 (33%)	3 (21%)	0.55
Right-to-left shunt	11 (8%)	1 (7%)	0.34
Shunt grade 3	15 (11%)	6 (43%)	0.010
Atrial septal aneurysm or hypermobility	13 (9%)	5 (36%)	0.011
Patent foramen ovale size (mm)	1.8 ± 1.0	3.9 ± 1.0	<0.001
Length of eustachian valve (mm)	13.0 ± 5.7	13.6 ± 7.2	0.908



Am J Cardiol 2010;106:129-134.

J Am Coll Cardiol 2018;71:2335-42.

# Final Korean knockout-punch

Trial (Year)	FU	Age limitation
--------------	----	----------------

**ROUND 1**

**1**

---

**ROUND 2**

**2**

≤60 yrs  
 (ical Rx)  
 <60 yrs  
 ≤60 yrs  
 ≤60 yrs  
 ≤60 yrs  
 ≤60 yrs  
 No

**UFC FIGHT NIGHT**

FEATHERWEIGHT BOUT

#5 **EDGAR** *vs* **THE KOREAN ZOMBIE** #6

**DEC 21 SAT**

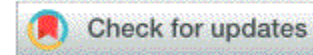
#UFCBUSAN

사직실내체육관  
**SAJIK ARENA**

# High risk PFO Scoring system

## ECHOCARDIOGRAPHIC ASSESSMENT OF PATENT FORAMEN OVALE

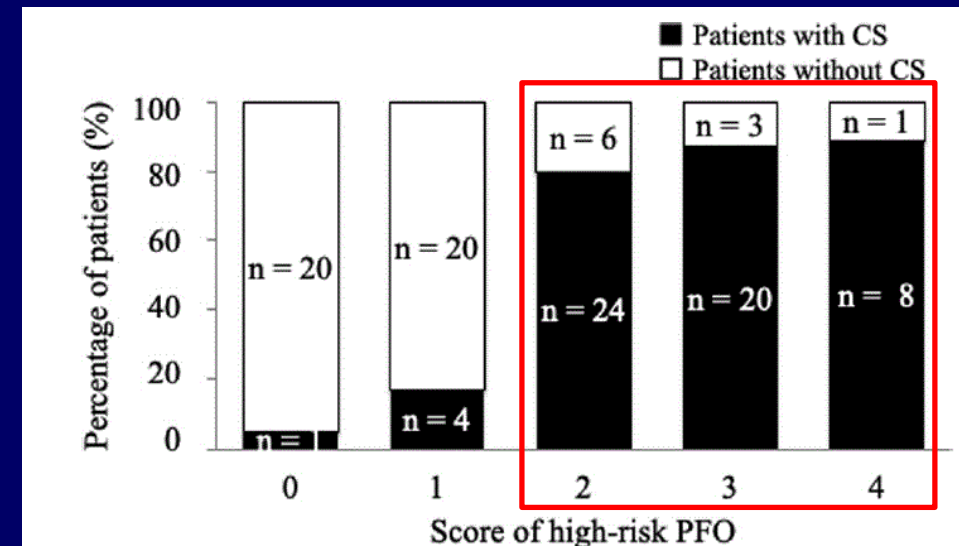
### Identification of High-Risk Patent Foramen Ovale Associated With Cryptogenic Stroke: Development of a Scoring System



Rie Nakayama, MD, Yoichi Takaya, MD, Teiji Akagi, MD, Nobuhisa Watanabe, RDCS, Madoka Ikeda, RDCS, Koji Nakagawa, MD, Norihisa Toh, MD, and Hiroshi Ito, MD, *Okayama, Japan*

**Table 4** Large-size high-risk PFO score calculator

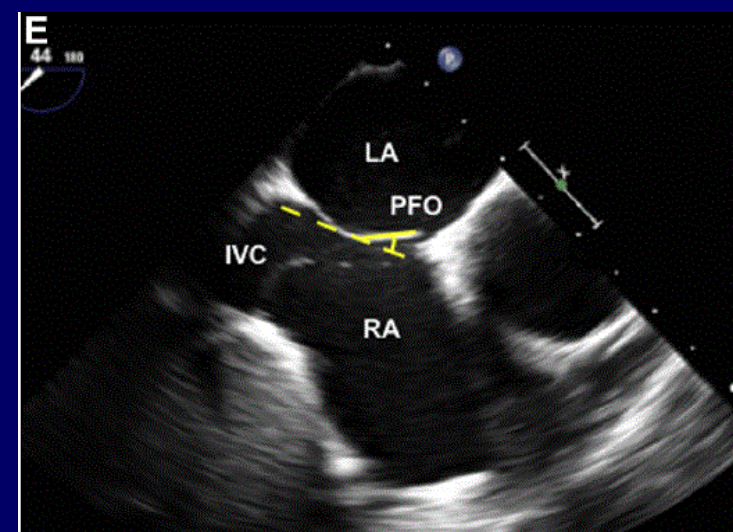
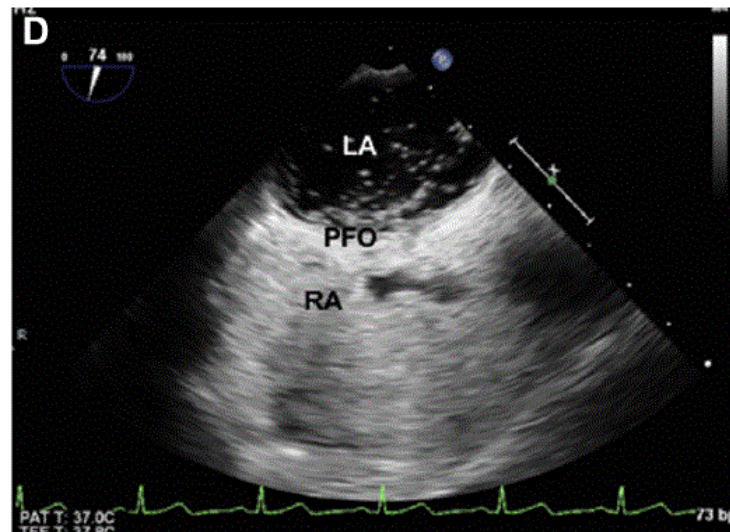
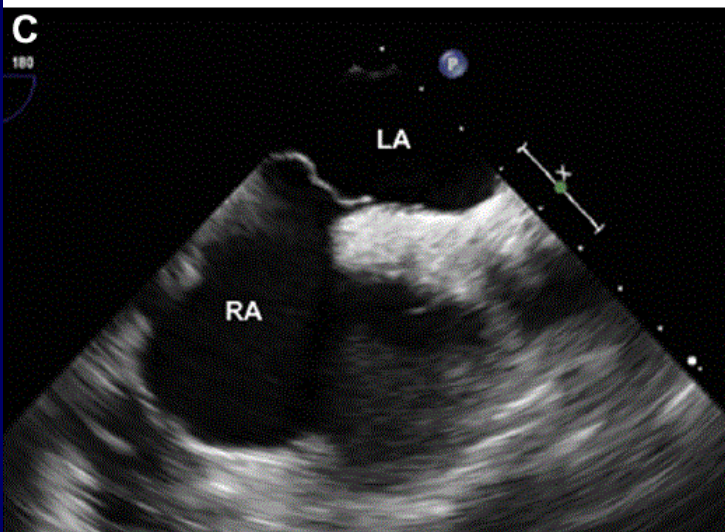
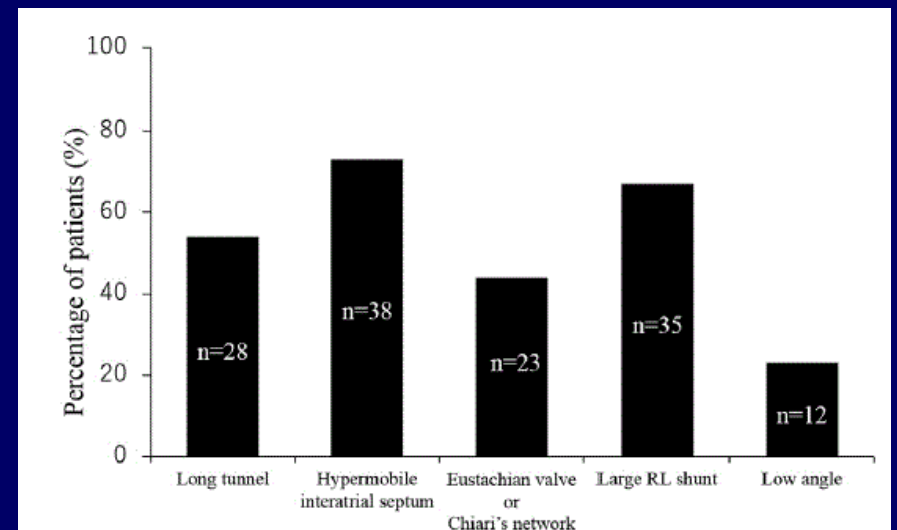
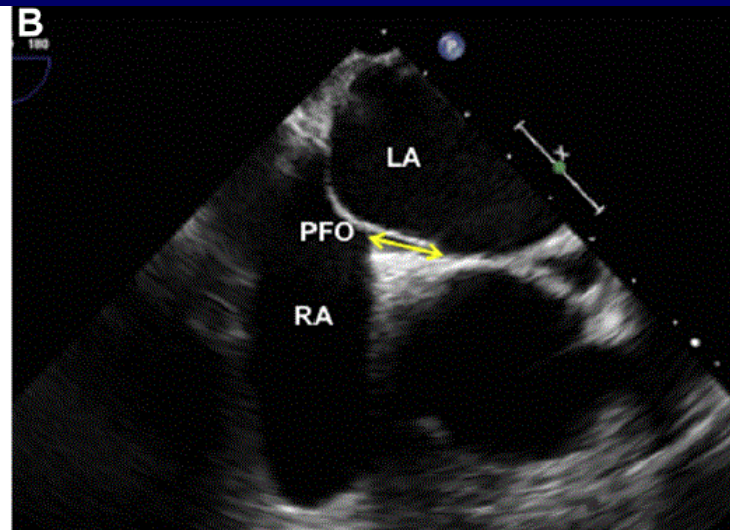
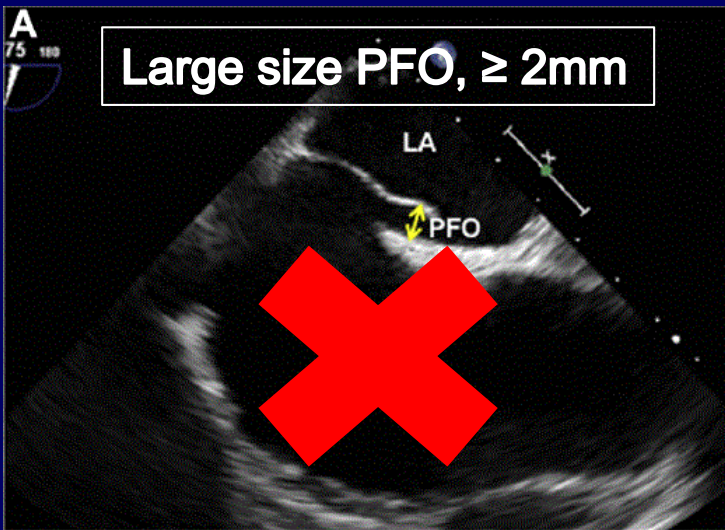
Variables	Point
Long-tunnel PFO $\geq 10$ mm	1
Hypermobility interatrial septum	1
Eustachian valve or Chiari's network	1
Large RL shunt during Valsalva maneuver	1
Low-angle PFO $\leq 10^\circ$	1



J Am Soc Echocardiogr. 2019 Jul;32(7):811-6.



# High risk PFO Scoring system



J Am Soc Echocardiogr. 2019 Jul;32(7):811-6.

# High risk PFO Scoring system

**Table 3** Factors related to CS

Variable	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2	
	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value
Large-size PFO, $\geq 2$ mm	2.54 (1.16-5.59)	.02	0.83 (0.24-2.62)	.754	1.16 (0.33-3.94)	.815
Long-tunnel PFO, $\geq 10$ mm	2.66 (1.19-5.97)	.017	3.27 (1.11-10.6)	.032	3.16 (1.04-10.5)	.042
ASA	4.96 (1.82-13.5)	.002	3.33 (0.94-13.0)	.064	2.51 (0.68-10.3)	.171
Hypermobility interatrial septum	11.4 (4.43-29.1)	<.001	9.09 (2.84-33.5)	<.001	7.26 (2.19-27.5)	.001
Eustachian valve or Chiari's network	4.47 (1.72-11.6)	.002	4.71 (1.45-17.2)	.009	4.58 (1.41-16.9)	.011
Large RL shunt during Valsalva maneuver	5.86 (2.51-13.7)	<.001	3.63 (1.23-11.3)	.020	3.87 (1.27-12.6)	.018
Low-angle PFO, $\leq 10^\circ$	3.74 (1.14-12.3)	.029	5.80 (1.38-29.7)	.016	5.12 (1.10-30.3)	.037
Age	4.34 (1.80-10.5)	.001			2.99 (0.77-12.3)	.112
Hypertension	2.84 (1.12-7.20)	.023			1.64 (0.43-6.77)	.473

Variables for multivariate analysis 1 included large PFO, long-tunnel PFO, the presence of ASA, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and low-angle PFO. Variables for multivariate analysis 2 added age and the prevalence of hypertension.

- CC : Lt weakness & paraesthesia  
(2018.2. other hospital admission)

Rt. MCA infarction, thrombolysis

Recovery of neurology →  
transfer to our hospital for PFO closure

Past history : HTN/DM(-/-)

Smoking/Alcohol(-/-)

RoPE (Risk of Paradoxical Embolism)

No Hx of HTN : 1

No Hx of DM : 1

No Hx of stroke or TIA : 1

Nonsmoker : 1

Cortical infarct on imaging : 1

Age 18-29 : 5

Total score : 10/10

Prevalence of Pts with a PFO : 73%

PFO-attributable fraction : 88%

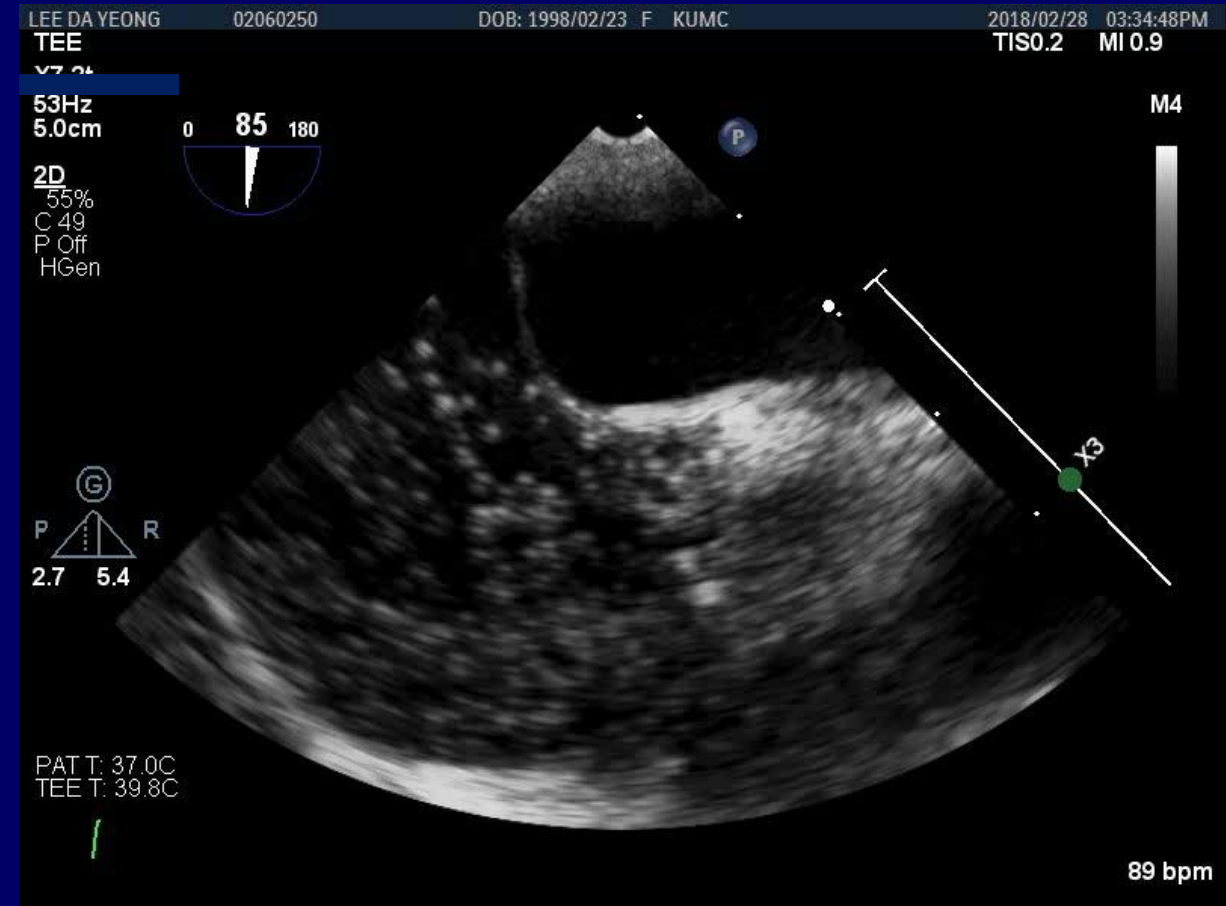
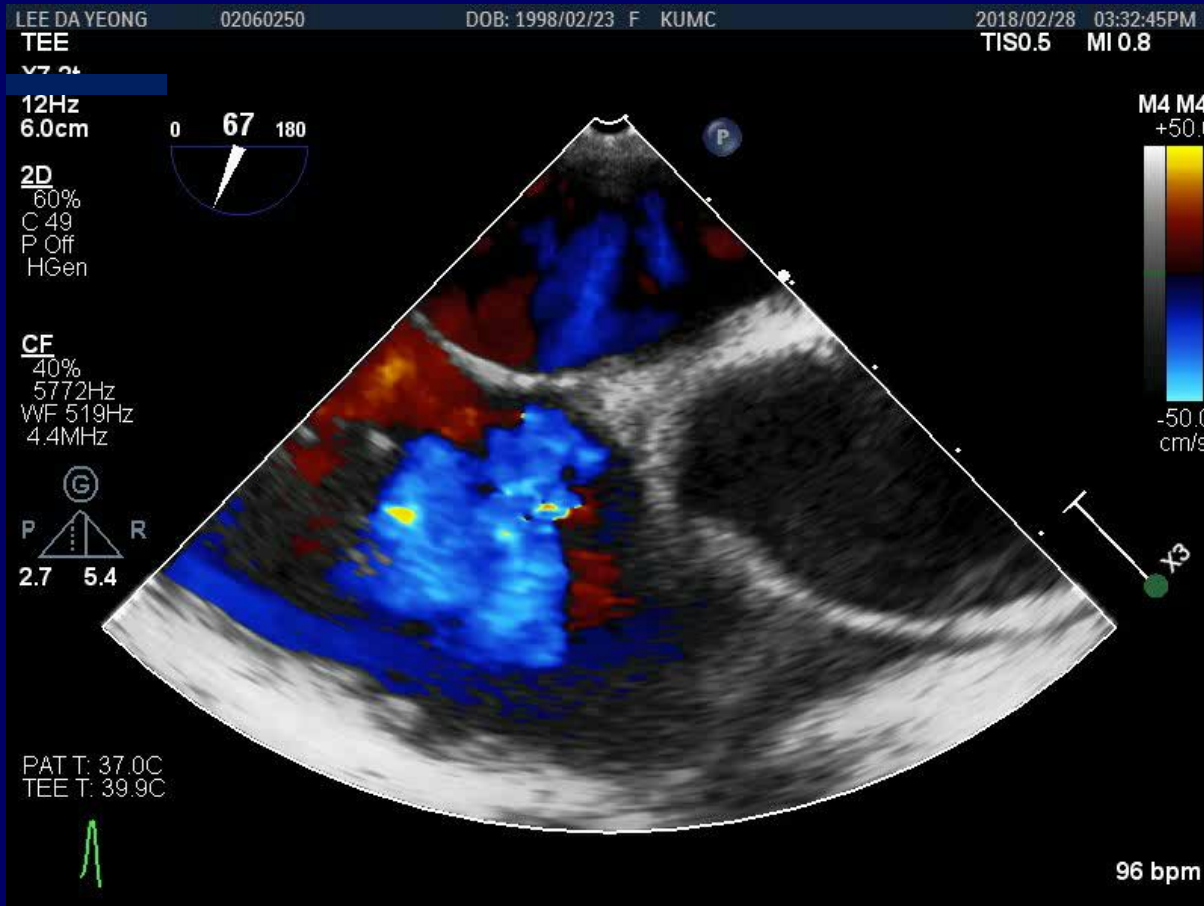
2y stroke/TIA recur rates : 2%

Stroke. 2009;40(7):2349-55.

# CT



# TEE (2018-2-28)



High risk? Small size, small amount of shunt, but, ASA or hypermobility (+)  
& Long tunnel  $\geq 10$  mm, Low angle  $\leq 10^\circ$  [Score 3] High risk PFO.

# What cardiologists & neurologists need to know

## Key Points

- In the presence of a patent foramen ovale (PFO), a transient ischemic attack is indistinguishable from a complex migraine. Both have transient neurologic deficits with a normal MRI.
- The size of a PFO by echo should not be a criterion for closure. A stroke or peripheral embolus associated with a PFO is the indication for closure.
- Informed consent for PFO closure should include the warning that about 1 in 500 cases require device removal through open-heart surgery.

1. PFO closure is a **simple and safe** outpatient procedure that replaces the need for open-heart surgery.
2. 4 RCTs showed that closure is preferable.
3. 50% of migraine with aura have a PFO.
4. **Stroke per year is 1 in 1000 people with a PFO.**
5. **Recurrent stroke is 1% per year, 10 % at 10 years and 50% in lifetime (50 years)**
6. PFO itself does not cause a stroke. We need reduce venous clot.
7. **60%** of first-degree relatives of a proband with a PFO-associated condition will have a PFO.

# Benefit is better only in RCTs with high-risk PFOs

**Table 2** Summary of meta-analyses comparing device closure vs. medical therapy in patients with cryptogenic stroke

Device closure vs. medical therapy	Event rate	OR [95% CI]	$I^2$	NNT/NNH
Stroke recurrence <sup>13</sup>				
Overall <sup>a</sup>	1.96% vs. 4.61%	0.38 [0.18–0.80]	53%	37.7
<b>Only in RCTs with high-risk PFOs</b>	0.81% vs. 5.98%	0.18 [0.07–0.45]	2%	<b>19.3</b>
In Patients with high-risk PFOs in RCTs	1.62% vs. 5.42%	0.34 [0.15–0.76]	49%	26.3
Device closure vs. antiplatelet therapy	2.38% vs. 6.07%	0.38 [0.17–0.84]	60%	27.1
Device closure vs. OAC therapy	2.28% vs. 3.82%	0.74 [0.20–2.74]	31%	N/A
TIA recurrence <sup>13</sup>	3.39% vs. 3.83%	0.85 [0.59–1.22]	0%	N/A
Death <sup>13</sup>	0.37% vs. 0.51%	0.92 [0.31–2.71]	11%	N/A
<b>New onset atrial fibrillation<sup>13</sup></b>				
Overall	<b>4.92% vs. 1.02%</b>	4.15 [2.42–7.13]	1%	<b>25.6</b>
Beyond 45 days	2.01% vs. 1.02%	1.80 [0.99–3.28]	0%	N/A

CI, confidence interval;  $I^2$ , heterogeneity between the included studies; N/A, non-applicable; NNH, number needed to harm; NNT, number needed to treat; OAC, oral anticoagulation; OR, odds ratio; PFO, patent foramen ovale; RCT, randomized clinical trial; TIA, transient ischaemic attack.

<sup>a</sup>Intention-to-treat analysis.

# Key points of safe closure

## Transcatheter Closure of Patent Foramen Ovale

### Devices and Technique

Matthew J. Price, MD

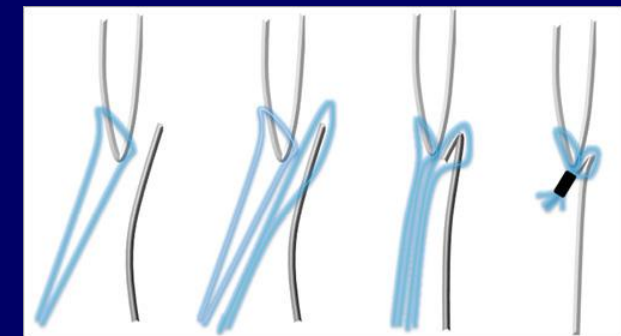
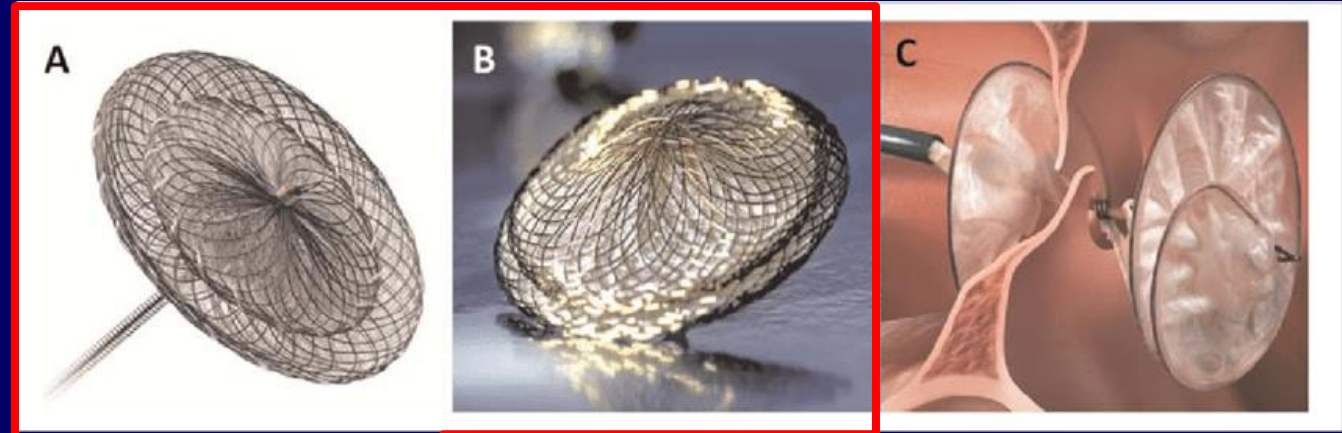
#### KEY POINTS

- A comprehensive preprocedure evaluation should be performed to exclude known mechanisms of ischemic stroke.
- Transesophageal echocardiography is critical to exclude other causes of cardiac emboli, confirm the presence of a patent foramen ovale (PFO), and define its anatomic characteristics.
- Key aspects to reduce procedural complications include performing all catheter exchanges within the left atrium over a stiff wire placed within one of the pulmonary veins and by thorough de-airing and flushing of the delivery sheath and occluder.
- Although device sizing is usually straightforward, special consideration is required in cases that have a redundant, aneurysmal interatrial septum or a thick septum secundum.
- Fastidious technique, combined with intracardiac imaging under conscious sedation, can minimize procedural complications and enhance procedural success.



# Currently available devices for PFO

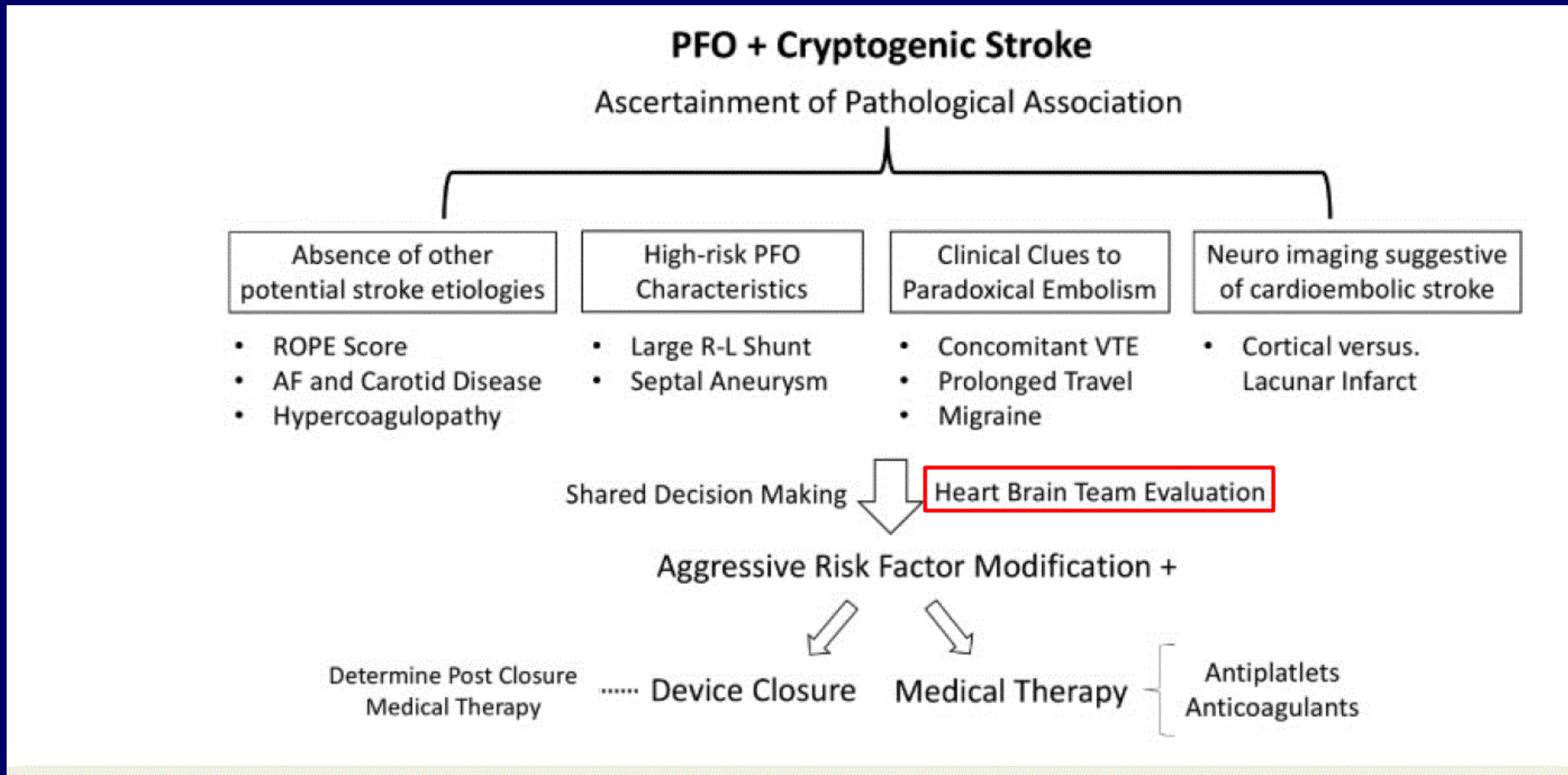
Devices	Approval/distribution/No. of shipment or implantation	Advantages	Disadvantages	Considerations
<b>Amplatzer Septal Occluder</b>	FDA/Worldwide/>500,000	<ul style="list-style-type: none"> <li>General familiarity</li> <li>Largest experience with accumulated data including long-term safety</li> <li>Widest range of sizes</li> </ul>	<ul style="list-style-type: none"> <li>Most of the reported cases of erosion</li> <li>Nickel release</li> <li>Stiff device-cable coupling — device jumping on release</li> </ul>	<ul style="list-style-type: none"> <li>Adverse events have been extensively investigated</li> <li>Non-self-centering version is also available (cribriform devices)</li> </ul>
<b>Occlutech Figulla Flex II ASD Occluder</b>	CE mark/>80 countries/>50,000 including previous generation devices	<ul style="list-style-type: none"> <li>Soft and flexible braiding — conforms to the defect — may reduce erosion risk</li> </ul>	<ul style="list-style-type: none"> <li>Fewer available sizes</li> <li>Larger delivery sheaths</li> <li>Less experience and data — lack of long term data</li> </ul>	<ul style="list-style-type: none"> <li>Usually regarded as a softer device than ASO</li> <li>Non-self-centering version is also available (uniform devices)</li> <li>Order-made fenestrated device is available</li> </ul>
<b>Gore Cardioform Septal Occluder</b>	FDA (CE mark)/ 15 countries/>8,000; >33,000 including HSO	<ul style="list-style-type: none"> <li>Flexible delivery system: 50° angulation + shapeable cable — less tension and jump on release</li> <li>Less material, no hub on LA disk smaller RA hub</li> <li>Titanium oxide coated surface</li> <li>Less exposure of metal to blood stream</li> <li>Softer device with less metal content; not likely cause erosion</li> <li>Thinner device profile</li> <li>Good alignment to the septum after locking of occluder (retrieval is still possible if mis-positioned)</li> </ul>	<ul style="list-style-type: none"> <li>Cannot close &gt; 18 mm defect</li> <li>Only 4 available sizes relatively larger delivery system for smaller defects</li> <li>Rigid coupling between device and control catheter before unlocking</li> <li>Less experience and data — lack of long term data</li> </ul>	<ul style="list-style-type: none"> <li>Non-self-centering device</li> </ul>
<b>Cocoon Septal Occluder</b>	CE mark/22 countries/>40,000	<ul style="list-style-type: none"> <li>Nano-platinum coated surface — prevent nickel release — enhance radio-opacity and biocompatibility</li> <li>Softer and lighter device — may reduce erosion risk</li> </ul>	<ul style="list-style-type: none"> <li>Stiff device-cable coupling — device jumping on release</li> <li>Fewer available sizes</li> <li>Larger delivery sheaths</li> <li>Less experience and data — lack of long term data</li> </ul>	<ul style="list-style-type: none"> <li>Usually regarded as a softer device than ASO</li> </ul>



3 devices are available in Korea.

J Thorac Dis 2018;10:S2909-22.

# Algorithmic approach to patients with CS & PFO



# Patient - centered care

Received: 16 January 2019 | Accepted: 20 January 2019

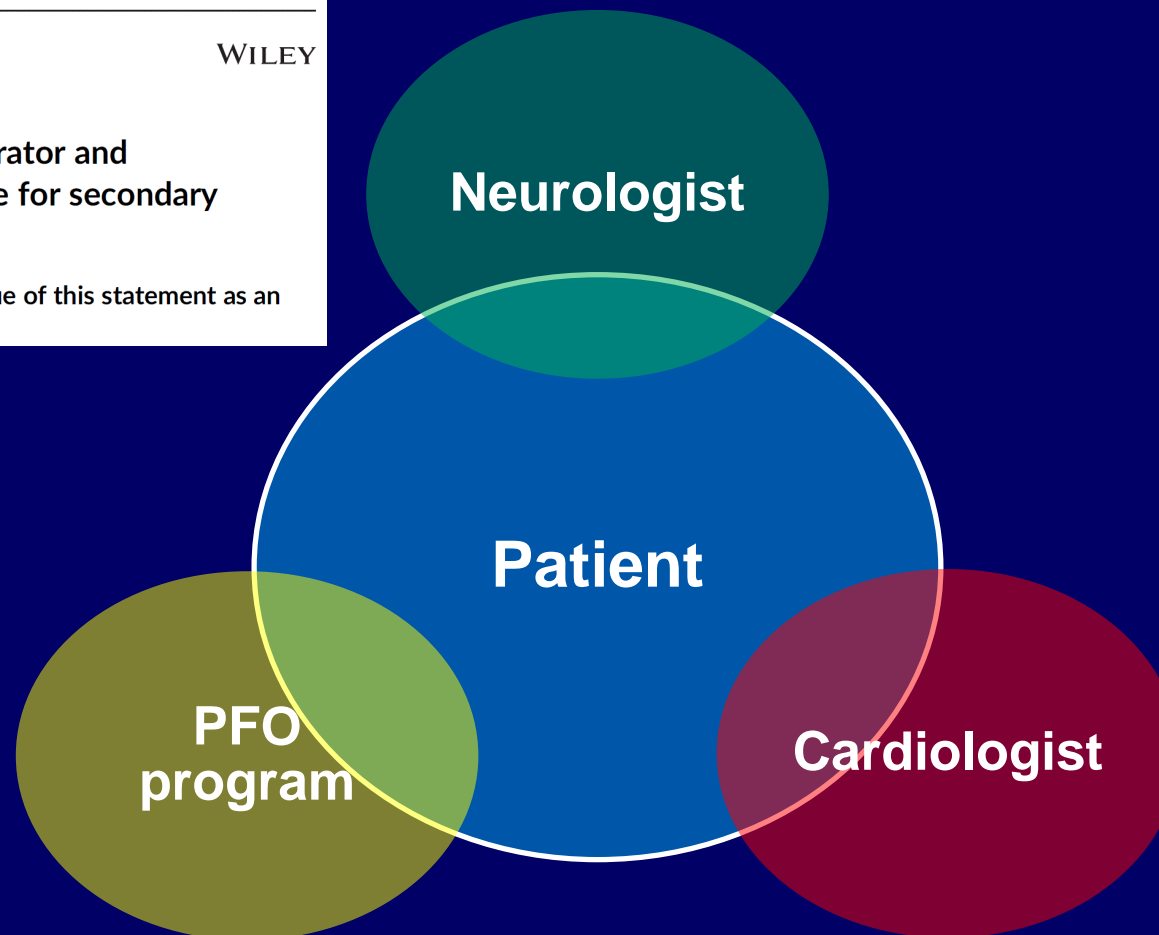
DOI: 10.1002/ccd.28111

WILEY

## CLINICAL DECISION MAKING

**SCAI expert consensus statement on operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke**

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.



Active PFO/stroke program, with emphasis on shared decision making and patient-centered care.

# Not cryptogenic any more, PFO-associated stroke



**ESC**

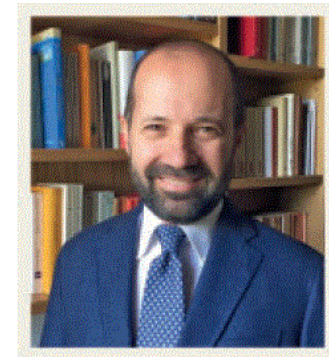
European Society  
of Cardiology

European Heart Journal (2019) **40**, 3182–3195

doi:10.1093/eurheartj/ehy649

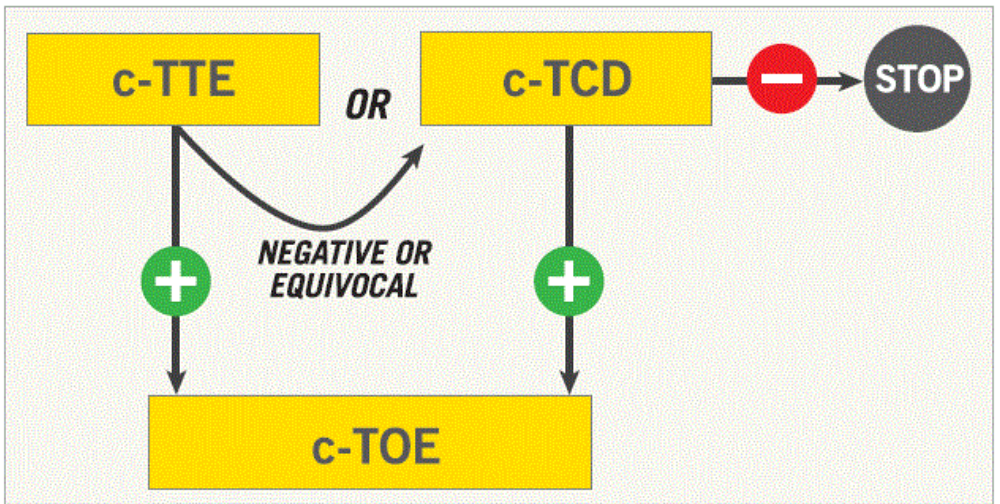
**ESC POSITION STATEMENT**

**European position paper** on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism

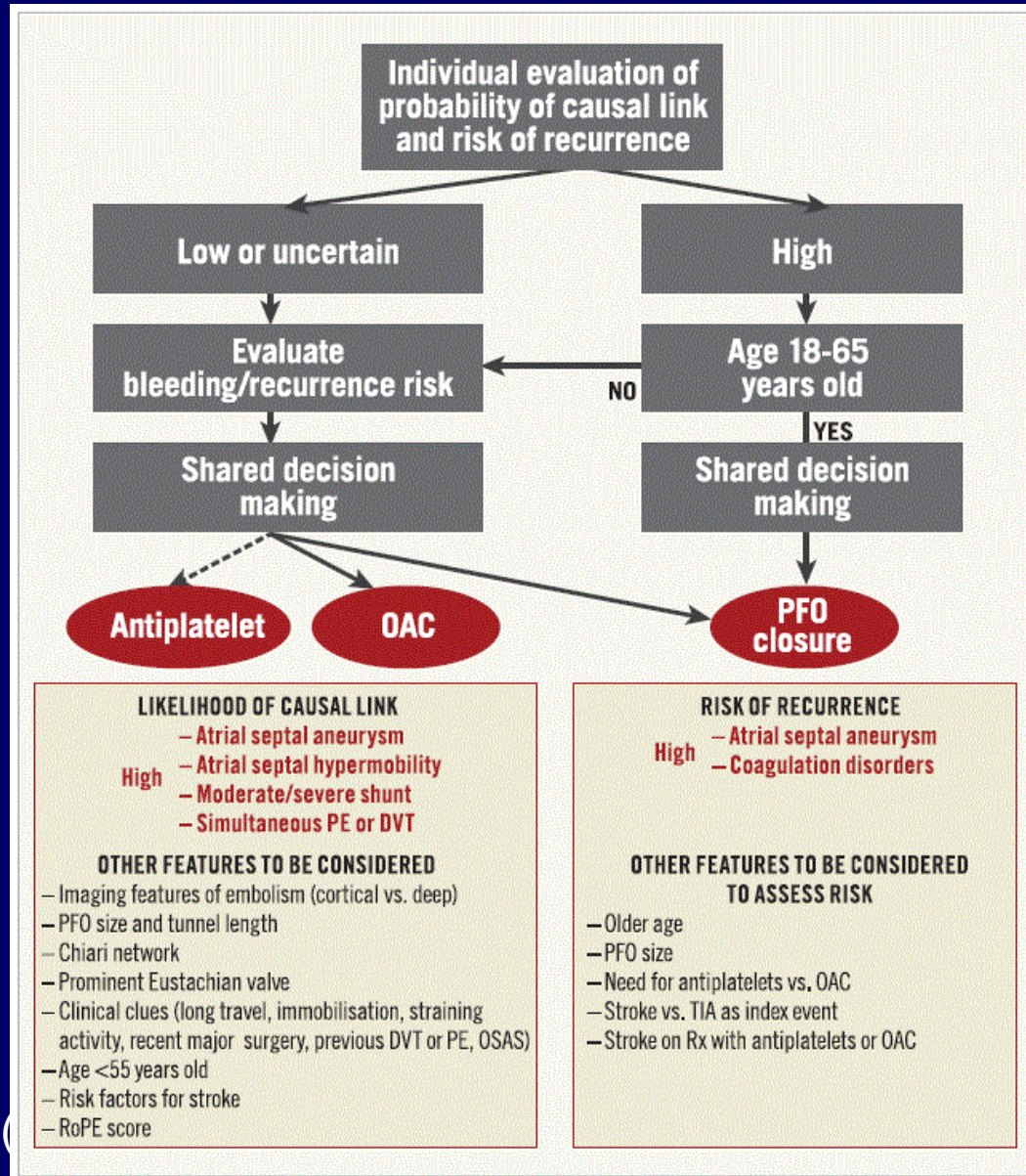


When a PFO is thought likely to be implicated in a cryptogenic embolism, the event should be classified as **PFO-related** instead of cryptogenic.

# Algorithm for the diagnosis & secondary prevention



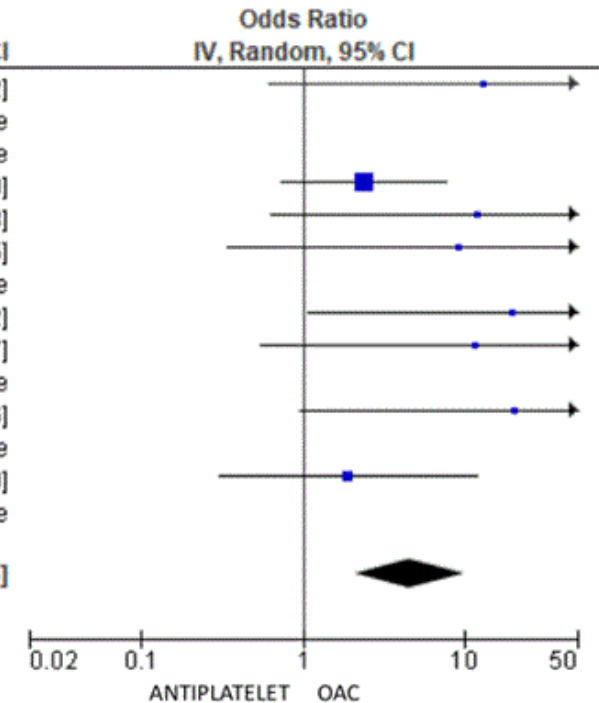
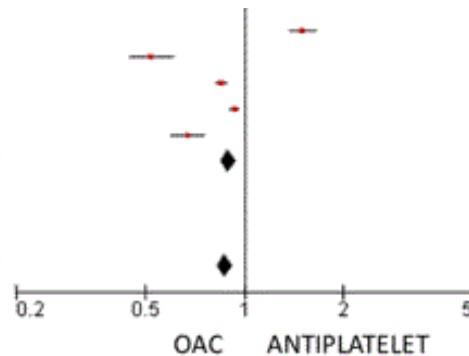
**Figure 1** Algorithm for the diagnosis of PFO. c-TCD: contrast-enhanced transcranial Doppler; c-TOE: contrast-enhanced transoesophageal echocardiography; c-TTE: contrast-enhanced transthoracic echocardiography; –negative test for the presence of right-to-left shunt; +positive test for the presence of right-to-left shunt.



# The risk of stroke recurrence & major bleeding

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
<b>1.1.1 Randomized comparison</b>				
CLOSE 1, 2017	-0.091	0.069	4.5%	0.91 [0.80, 1.05]
<b>Subtotal (95% CI)</b>			<b>4.5%</b>	<b>0.91 [0.80, 1.05]</b>
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.32 (P = 0.19)				
<b>1.1.2 Adjusted observational comparison</b>				
Cerrato et al, 2006	-0.075	0.031	6.0%	0.93 [0.87, 0.99]
Cujec et al, 1999	-0.459	0.112	3.0%	0.63 [0.51, 0.79]
Schuchlenz et al, 2005	-0.361	0.041	5.6%	0.70 [0.64, 0.76]
<b>Subtotal (95% CI)</b>			<b>14.7%</b>	<b>0.75 [0.59, 0.95]</b>
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 36.92, df = 2 (P < 0.00001); I <sup>2</sup> = 95%				
Test for overall effect: Z = 2.34 (P = 0.02)				
<b>1.1.3 Not adjusted observational comparison</b>				
Bougouslavsky et al, 1996	-0.076	0.025	6.2%	0.93 [0.88, 0.97]
Casaubon et al, 2007	-0.165	0.057	5.0%	0.85 [0.76, 0.95]
CLOSURE I, 2012	0.018	0.006	6.5%	1.02 [1.01, 1.03]
Hanna et al, 1994	0.072	0.075	4.3%	1.07 [0.93, 1.24]
Harrer et al, 2006	-0.461	0.073	4.4%	0.63 [0.55, 0.73]
Hausmann et al, 1995	-0.246	0.098	3.5%	0.78 [0.65, 0.95]
Homma et al, 2002	0.066	0.017	6.3%	1.07 [1.03, 1.10]
Lee et al, 2010	-0.896	0.096	3.5%	0.41 [0.34, 0.49]
Mas et al, 1995	-0.698	0.129	2.6%	0.50 [0.39, 0.64]
Mas et al, 2001	-0.004	0.004	6.5%	1.00 [0.99, 1.00]
Mazzucco et al, 2012	0.673	0.064	4.7%	1.96 [1.73, 2.22]
Paciaroni et al, 2011	0.412	0.045	5.5%	1.51 [1.38, 1.65]
PC trial, 2012	-0.656	0.078	4.2%	0.52 [0.45, 0.60]
RESPECT, 2012	-0.164	0.019	6.3%	0.85 [0.82, 0.88]
Serena et al, 2008	-0.067	0.0155	6.4%	0.94 [0.91, 0.96]
Windecker et al, 2004	-0.397	0.0597	4.9%	0.67 [0.60, 0.76]
<b>Subtotal (95% CI)</b>			<b>80.8%</b>	<b>0.90 [0.85, 0.95]</b>
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 606.17, df = 15 (P < 0.00001); I <sup>2</sup> = 98%				
Test for overall effect: Z = 3.81 (P = 0.0001)				
<b>Total (95% CI)</b>			<b>100.0%</b>	<b>0.88 [0.83, 0.92]</b>
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 703.80, df = 19 (P < 0.00001); I <sup>2</sup> = 97%				
Test for overall effect: Z = 4.98 (P < 0.00001)				
Test for subgroup differences: Chi <sup>2</sup> = 2.12, df = 2 (P = 0.35), I <sup>2</sup> = 5.6%				

Study or Subgroup	OAT		Aspirin		Weight	Odds Ratio IV, Random, 95% CI
	Events	Total	Events	Total		
Bougouslavsky et al, 1996	2	37	0	92	6.4%	13.03 [0.61, 278.12]
Casaubon et al, 2007	0	20	0	41		Not estimable
Cerrato et al, 2006	0	17	0	48		Not estimable
CLOSE, 2017	10	187	4	174	43.3%	2.40 [0.74, 7.80]
Cujec et al, 1999	5	38	0	36	7.0%	11.99 [0.64, 225.08]
Hanna et al, 1994	2	5	0	6	5.5%	9.29 [0.34, 252.45]
Hausmann et al, 1995	0	15	0	17		Not estimable
Lee et al, 2010	5	60	0	99	7.1%	19.72 [1.07, 363.32]
Mas et al, 1995	2	22	0	48	6.3%	11.83 [0.54, 257.37]
Mazzucco et al, 2012	0	3	0	49		Not estimable
Paciaroni et al, 2011	2	24	0	93	6.4%	20.78 [0.96, 448.06]
Thanopoulos et al, 2006	0	0	4	44		Not estimable
Wahl et al, 2012	3	46	2	57	17.9%	1.92 [0.31, 12.00]
Windecker et al, 2004	0	79	0	79		Not estimable
<b>Total (95% CI)</b>		<b>553</b>		<b>883</b>	<b>100.0%</b>	<b>4.57 [2.10, 9.93]</b>
Total events	31		10			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 5.32, df = 7 (P = 0.62); I <sup>2</sup> = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						



# Medication after PFO closure

Position statements	Strength of the statement	Level of evidence	Ref.
<b>Drug therapy and follow up after percutaneous closure</b>			
It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure	Conditional	A	27, 29, 51, 112, 132, Supplementary Figure 11
We suggest a single antiplatelet therapy be continued for at least 5 years	Conditional	C	27–29, 51, 112, 132, 128, 138–140
The extension of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient’s overall risk of stroke for other causes and haemorrhagic risk	Strong	C	–
The choice of the type of antiplatelet drug in the follow-up is currently empiric	Strong	A	27–29, 51, 112, 132
The value of residual shunt after percutaneous closure cannot be deduced from available studies	Strong	C	124, 141–47
Systematic, high-quality data on follow-up are needed	Strong	C	–
To obtain comparable data we propose to perform:	Conditional	C	124, 141–147,
a. a TTE prior to hospital discharge			55 +Original meta-analyses
b. c-TCD at least once beyond six months to assess effective PFO closure and there- after, if residual shunt persists, annually until closure			page 4 and Supplementary
c. c-TOE or c-TTE in case of severe residual shunt at c-TCD, or recurrent events, or symptoms during follow-up			Appendix 4
Patients should undergo antibiotic prophylaxis for any invasive procedure performed in the first six months from PFO closure	Conditional	C	–

# Future directions

1. To make **standard criteria** of 'High-risk' PFOs : Predictive models to identify patients who benefit a lot, a little, or not at all.
2. Role of anticoagulation, **NOAC**.
3. Role of **new closure devices** : tunnel insertion, bioabsorbable, suture.
4. Close or not for the anatomical '**Low-risk**' PFOs and the **elderly**.
5. **Refractory migraine** with aura.
6. How to treat **incidental large PFO** without stroke or TIA.



# Take home message

## Risk Stratification

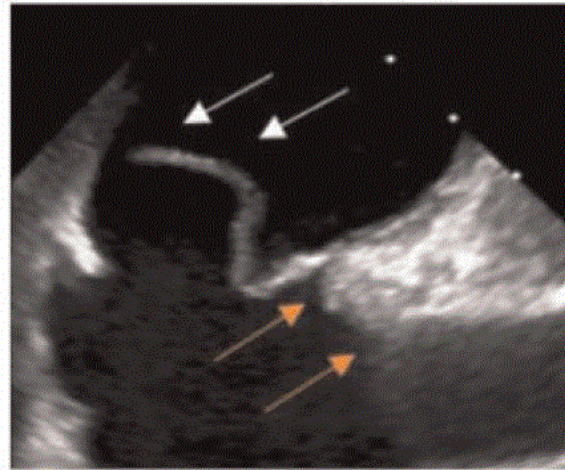
### PFO Characteristics

(Contrast TTE, TOE, TCD)

- ❖ Large Shunt
- ❖ Septal Aneurysm

### Clinical Characteristics

- ❖ Age
- ❖ Stroke Features
- ❖ ROPE Score
- ❖ Hypercoagulopathy
- ❖ Concomitant VTE
- ❖ Competing Risks (e.g., AF)



## Heart Brain Team Decision

Eur Heart J. 2019;40(28):2339-50.

## Data Appraisal

### Round-1 RCT

(PFO closure = Medical Rx)

- ❖ Closure-1
- ❖ PC Trial
- ❖ RESPECT

### Round-2 RCT

(PFO closure > Medical Rx\*)

- ❖ CLOSE
- ❖ REDUCE
- ❖ RESPECT LT
- ❖ DEFENSE PFO

4 - 0

ROUND

1

ROUND

2

**Take home figure** Patent foramen ovale closure in patients with cryptogenic stroke. AF, atrial fibrillation; PFO, patent foramen ovale; RCT, randomized controlled trials; TCD, transcranial Doppler; TOE, transesophageal echocardiography; TTE, transthoracic echocardiography; VTE, venous thromboembolism. \*Predominantly antiplatelets. Orange arrows, patent foramen ovale; White arrows, atrial septal aneurysm.

Individuals most likely to benefit from PFO closure : [ PFO stroke in the Heart Brain Team Decision ]

1. Higher risk of morphology 2. Younger 3. Higher RoPE 4. Concomitant VTE 5. Embolic stroke pattern

# Thank you for your attention

