BERTINORO ULTRASUONI

XXI CORSO NAZIONALE DI
ULTRASONOLOGIA VASCOLARE – DIAGNOSI E TERAPIA
20 – 22 aprile 2023

SINSEC
Società Italiana Neurosonologia ed Emodinamica Cerebrale

PFO: come studiarlo e come interpretarlo

DOTT. GIUSEPPE MICELI

RESPONSABILE DELL'AMBULATORIO DI NEUROSONOLOGIA

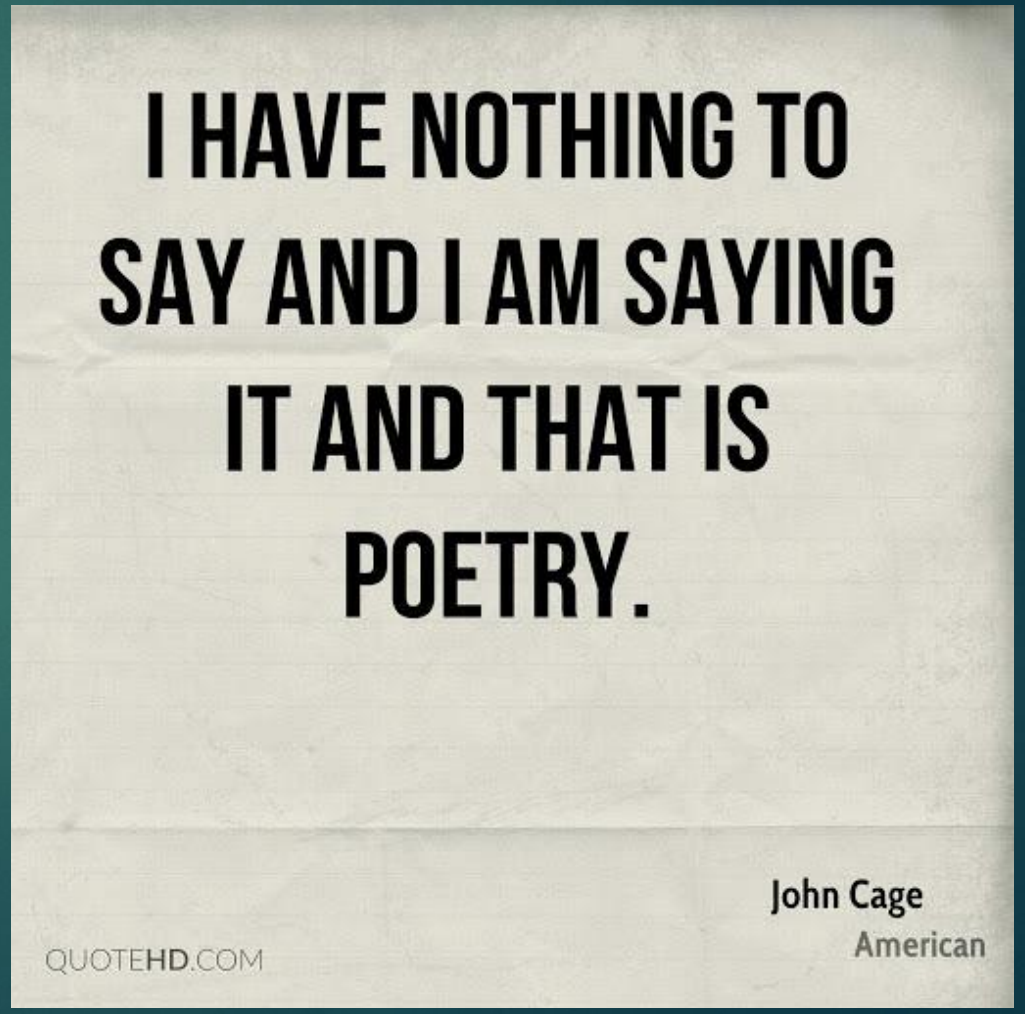
U.O.C. DI MEDICINA INTERNA CON STROKE CARE

AOUP P. GIACCONE PALERMO

PANORMITANÆ STUDIORUM UNIVERSITATIS SICILIA

Conflitti di interessi

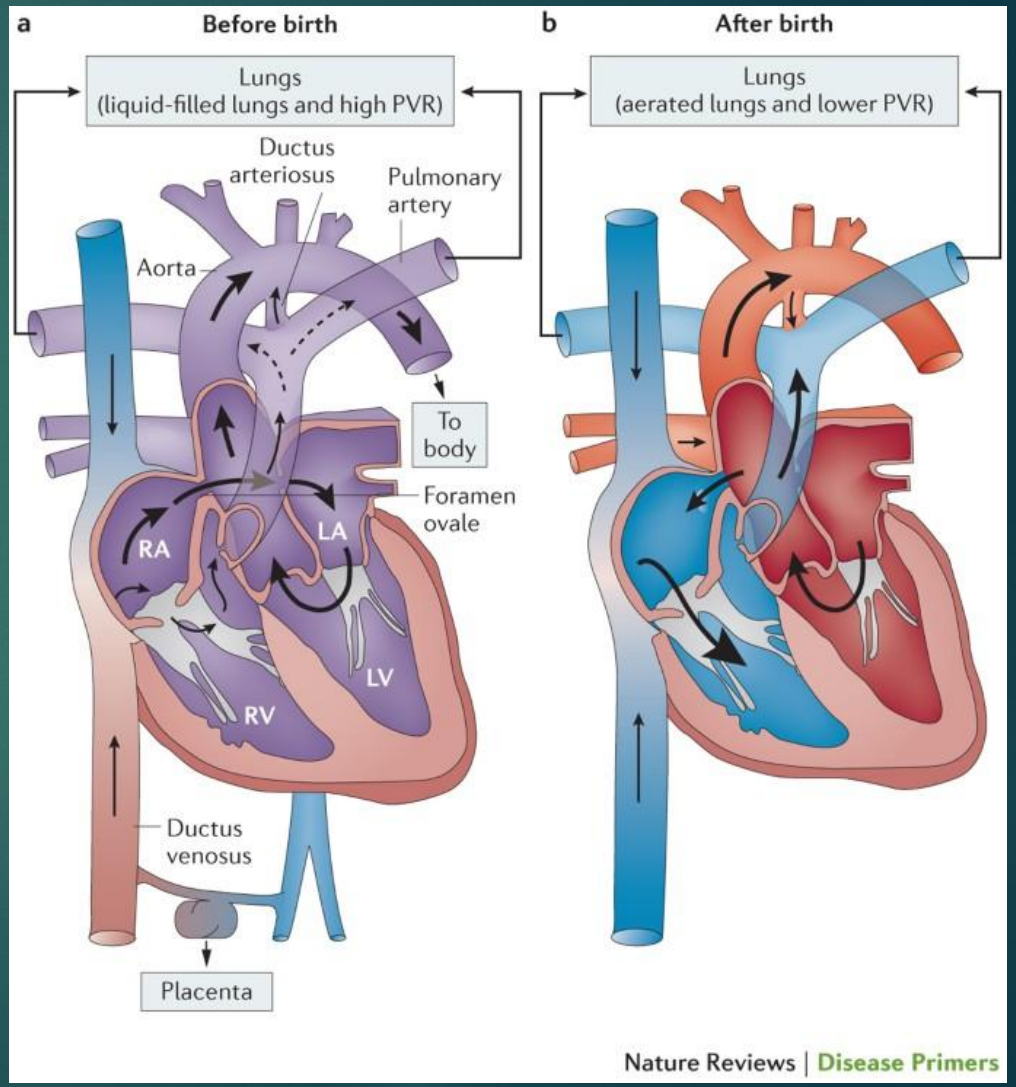
- Nessun conflitto di interessi da dichiarare



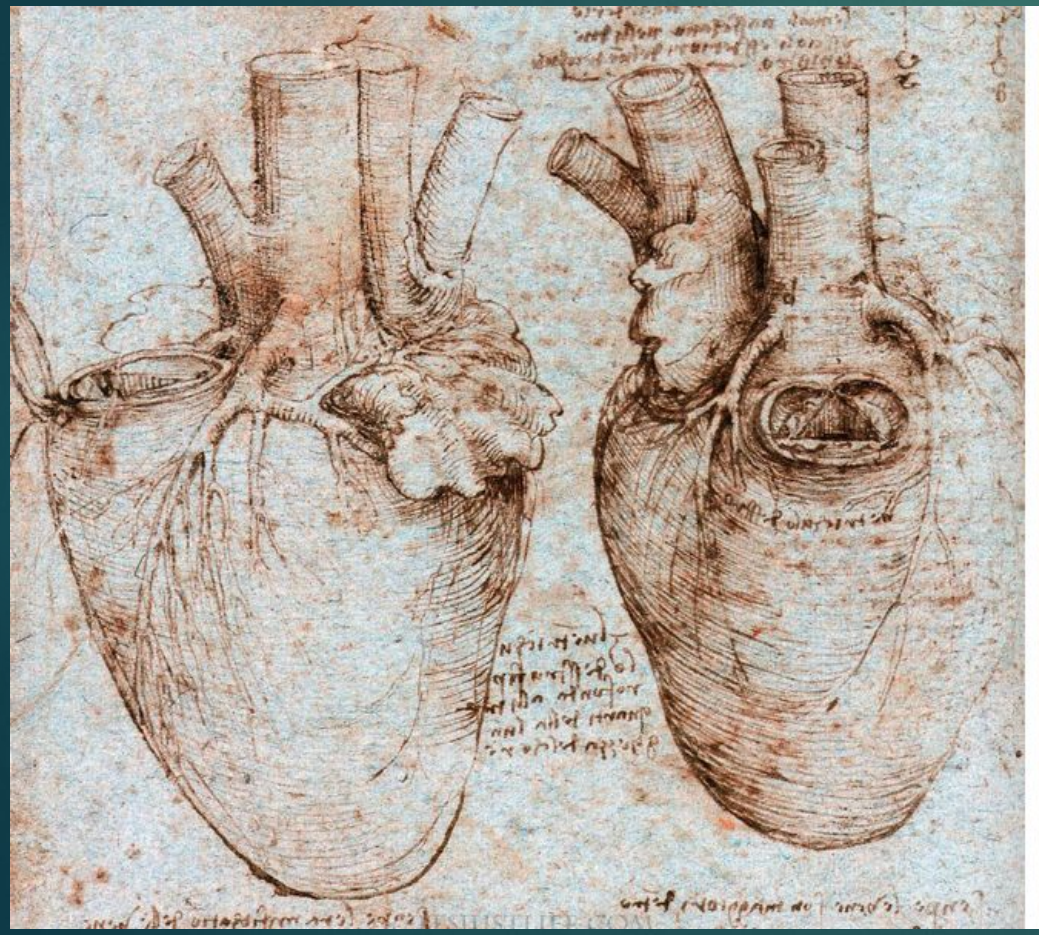
PFO

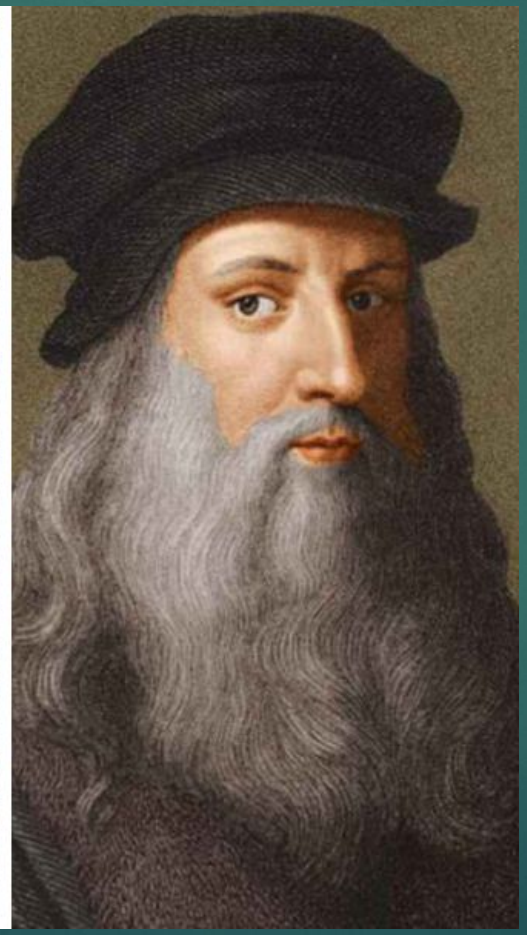
Il Forame Ovale Pervio è una soluzione di continuo del setto interatriale che consente un libero shunt pre-tricuspidalico, la cui entità e direzione dipendono da caratteristiche anatomiche locali e dall'istantaneo rapporto pressorio e di "compliance" tra circolo sistemico e polmonare

- Valvola unidirezionale che permette il passaggio di sangue dall'atrio destro all'atrio sinistro.
- Causato dalla non fusione, nel postparto, del septum secundum al septum primum.



Il PFO è una scoperta recente?





Leonardo da Vinci ha descritto per primo il PFO nel 1513.

«Ho trovato un canale perforante dall'auricola sinistra all'auricola destra»

Le domande «amletiche» sul PFO

- Mi è utile sapere se il mio paziente ha il PFO?
- Come si effettua la diagnosi di PFO?
- Il PFO è responsabile dell'ictus del mio paziente?
- Il PFO del mio paziente va chiuso?

PFO Sì, PFO No…

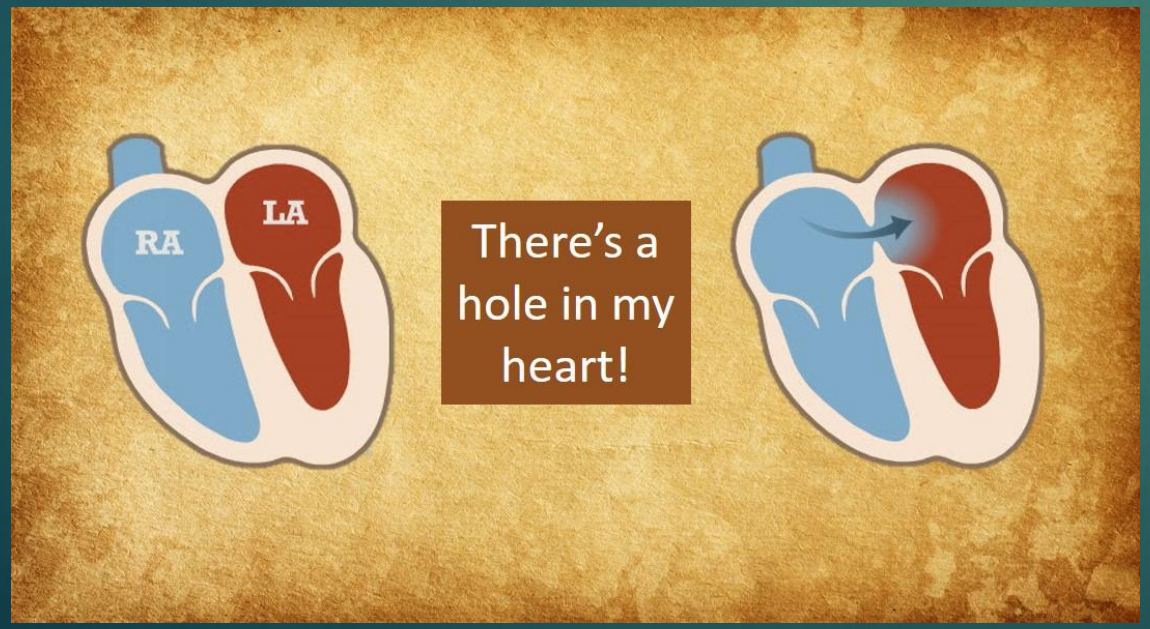
- Mi è ut … te
  ha il PF

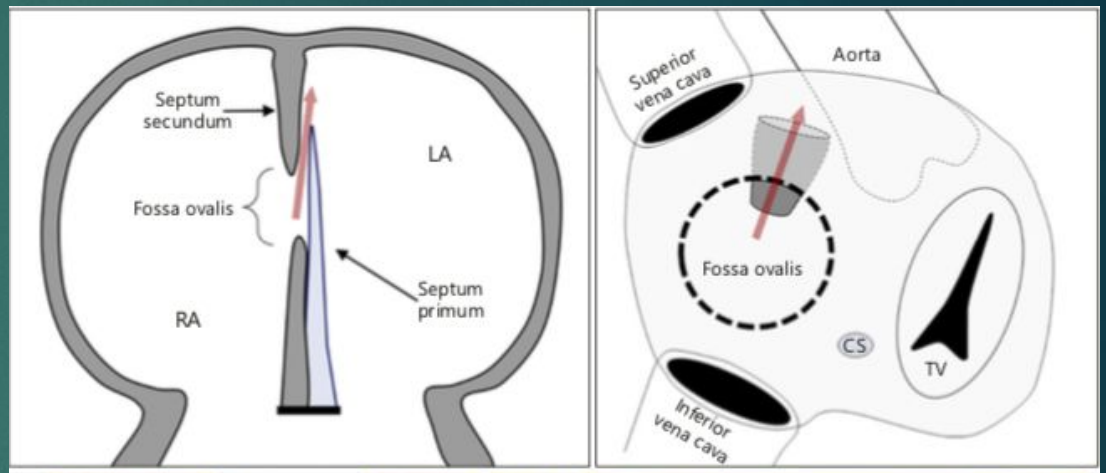
DIPENDE

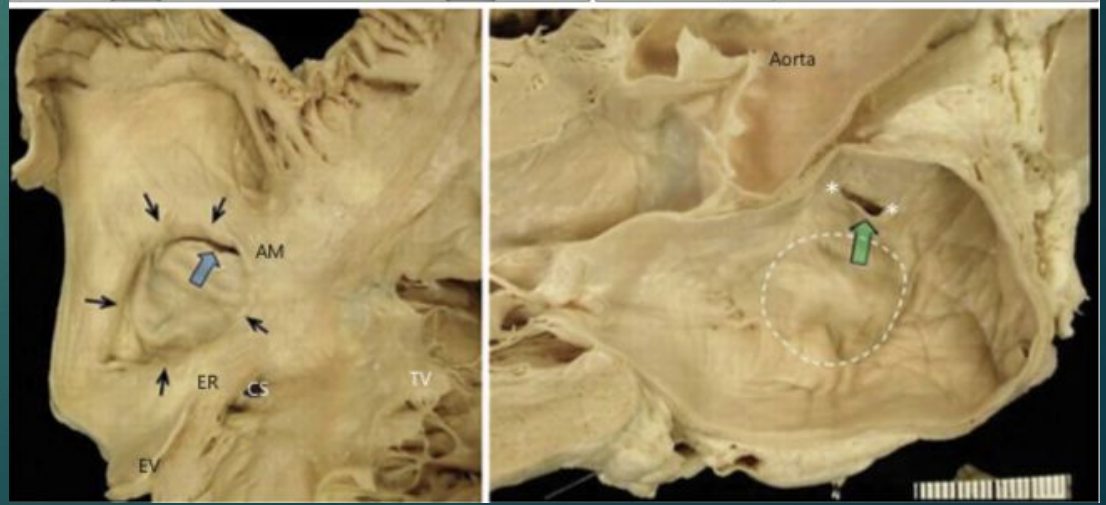
…

Mi è utile sapere se il mio paziente ha il PFO? Ed è utile al paziente?

- 25-30% di prevalenza in riscontri autoptici.
- Corretta comunicazione con il paziente



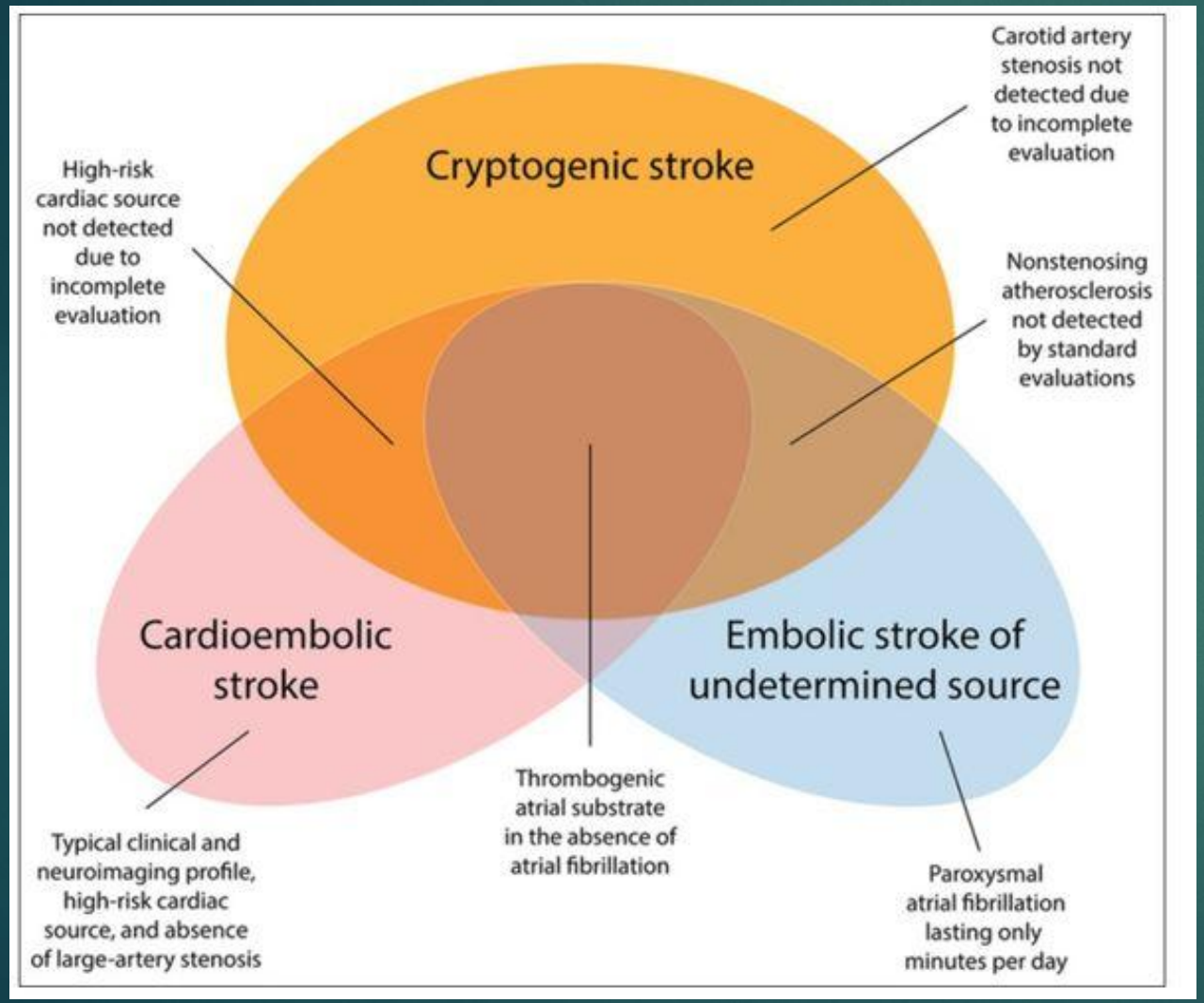


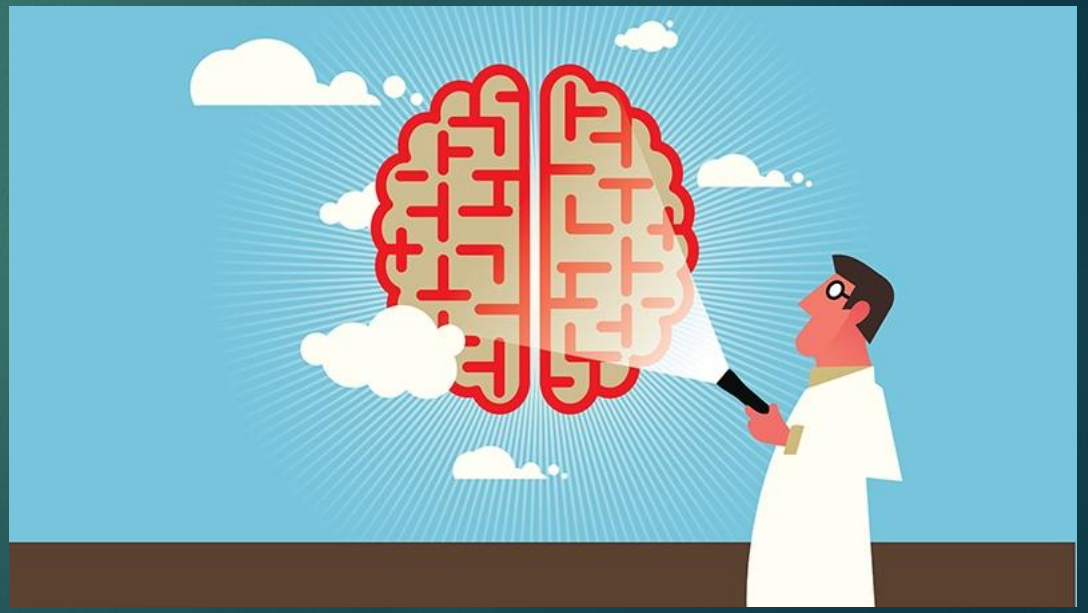


Condizioni cliniche associate a PFO

- Ictus criptogenetico
- Emicrania e cefalea vascolare
- Malattia da decompressione
- Sindrome da platipnea-ortodeossia

ICTUS CRIPTOGENETICO





Cryptogenic strokes

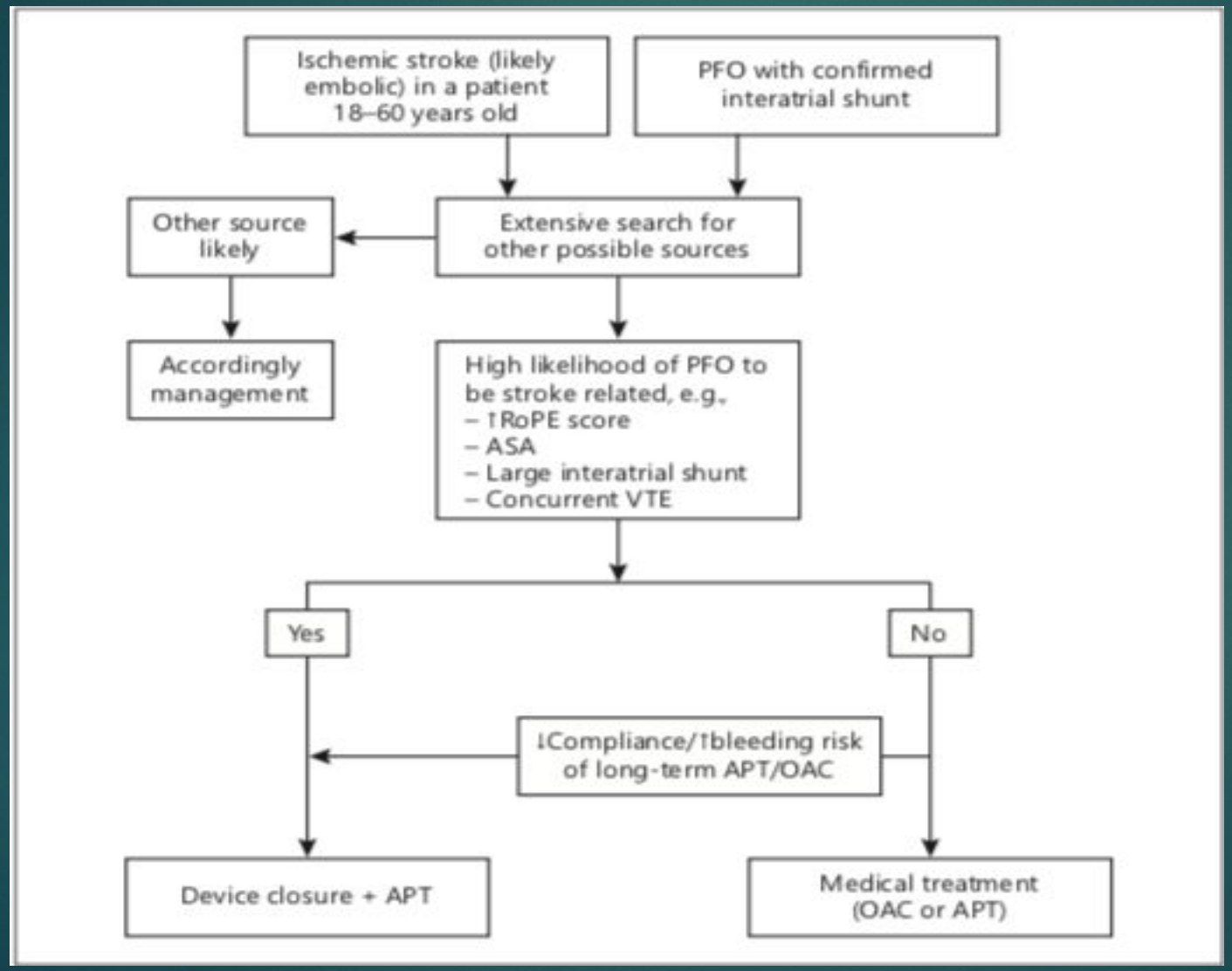
"Brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation'. Amount to 30% -35% of all stroke etiologies"[1]

ESUS *is a subcategory of cryptogenic stroke in patients specifically with non lacunar infarcts in the absence of an apparent cause such as known atherosclerosis, major cardioembolic source or other defined etiology*

Classification	Diagnostic evaluation
TOAST criteria[1]	Not specified
Causative Classification of Stroke (CCS)[2]	Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging
Embolic strokes of undetermined source[3]	Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥24 hours
ASCO(D) phenotyping[4]	Does not include a cryptogenic stroke category

[1]. Adams HP et al. Stroke. 1993;24:35-41; [2]. Causative Classification System for Ischemic Stroke (CCS). Available at: https://ccs.mgh.harvard.edu/ccs_intro.php; [3]. Hart RG et al. Lancet Neurol. 2014;13:429-438; [4]. Amarenco P et al. Cerebrovasc Dis. 2013;36:1-5

ICTUS CRIPTOGENETICO



EMICRANIA E CEFALEA VASCOLARE

Patent foramen ovale and migraine: a quantitative systematic review

TJ Schwedt[1], BM Demaerschalk[2] & DW Dodick[2]

[1]Washington University School of Medicine, Washington University Headache Center, St Louis, MO and [2]Mayo Clinic, Department of Neurology, Scottsdale, AZ, USA

evidence was low. The association between migraine and PFO was OR 2.54 (95% CI 2.01, 3.08). The grade of evidence was low to moderate. Six studies of PFO closure suggested improvement in migraine, but had a very low grade of evidence. The low-to-moderate grade of evidence from observational studies supports an apparent association between PFO and migraine. Although PFO closure seemed to affect migraine patterns favourably, the very low grade of available evidence to support this association precludes definitive conclusions.

Headache disorders, migraine, migraine aura, paradoxical embolism, patent foramen ovale, right-to-left shunt

Epidemiology

Patent Foramen Ovale and Migraine

A Cross-Sectional Study From the Northern Manhattan Study (NOMAS)

Tatjana Rundek, MD, PhD; Mitchell S.V. Elkind, MD, MS; Marco R. Di Tullio, MD; Emmanuel Carrera, MD; Zhezhen Jin, PhD; Ralph L. Sacco, MD, MS; Shunichi Homma, MD

Conclusions—In this multiethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable. (***Circulation***. **2008;118:1419-1424.**)

Association of migraine with patent foramen ovale closure: A systematic review and *meta*-analysis

Yan-Li Wang [a,c,1], Fang-Ze Wang [b,1], Yuan Zhang [a], Jiwei Jiang [a], Ziyan Jia [a], Xiangrong Liu [c], Jian Wang [b,*], Jun Xu [a,c,*]

[a] *Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China*
[b] *Department of Cardiology, Weifang People's Hospital, Weifang Medical University, Weifang, China*
[c] *China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China*

Research Article

Patent Foramen Ovale Closure for Treating Migraine: A Meta-Analysis

Yu Zhang,[1,2] Haijiao Wang,[1] and Ling Liu [1]

[1]*Department of Neurology, West China Hospital, Sichuan University, Wai Nan Guo Xue Lane 37, Chengdu 610041, Sichuan, China*
[2]*Department of Neurology, Chengdu Shangjin Nanfu Hospital, Shang Jin Road 253, Chengdu 610000, Sichuan, China*

Correspondence should be addressed to Ling Liu; deghj333@163.com

Received 3 November 2021; Revised 24 December 2021; Accepted 3 January 2022; Published 2 February 2022

Academic Editor: Thach N. Nguyen

Background. Observational studies have shown percutaneous patent foramen ovale (PFO) closure to be a safe means of reducing the frequency and duration of migraine. *Objective.* This study evaluated the efficacy and safety of PFO closure in patients with migraine using evidence-based medicine. *Methods.* The Pubmed (MEDLINE), Embase, and Cochrane Library databases were searched for randomized controlled trials (RCTs), cohort studies, and retrospective case series from January 1, 2001, to February 30, 2021. The Jadad scale and R 4.1.0 software were used to assess the quality of the literature and meta-analysis, respectively. *Results.* In total, three randomized controlled trials, one pooled study, and eight retrospective case series including 1,165 participants were included in the meta-analysis. Compared with control intervention in migraine, PFO closure could significantly reduce headache frequency (OR = 1.5698, 95% CI: 1.0465–2.3548, $p = 0.0293$) and monthly migraine attacks and monthly migraine days (OR = 0.2594, 95% CI: 0.0790–0.4398, $p = 0.0048$). Subgroup analysis of patients who all completed PFO surgery showed resolution of migraine headache for migraines with aura (OR = 1.5856, 95% CI: 1.0665–2.3575, $p = 0.0227$). *Conclusions.* Treatment with PFO closure could reduce the frequency of headaches and monthly migraine days and is an efficient treatment for migraine attacks with aura.

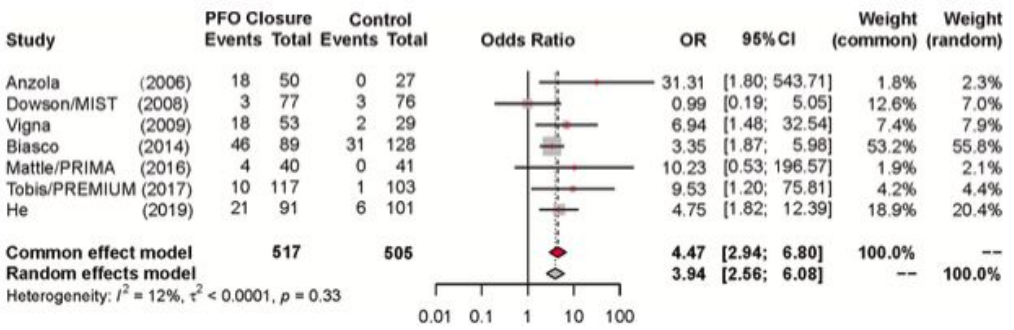


Fig. 1. Associations between complete cessation of migraine and PFO closure.

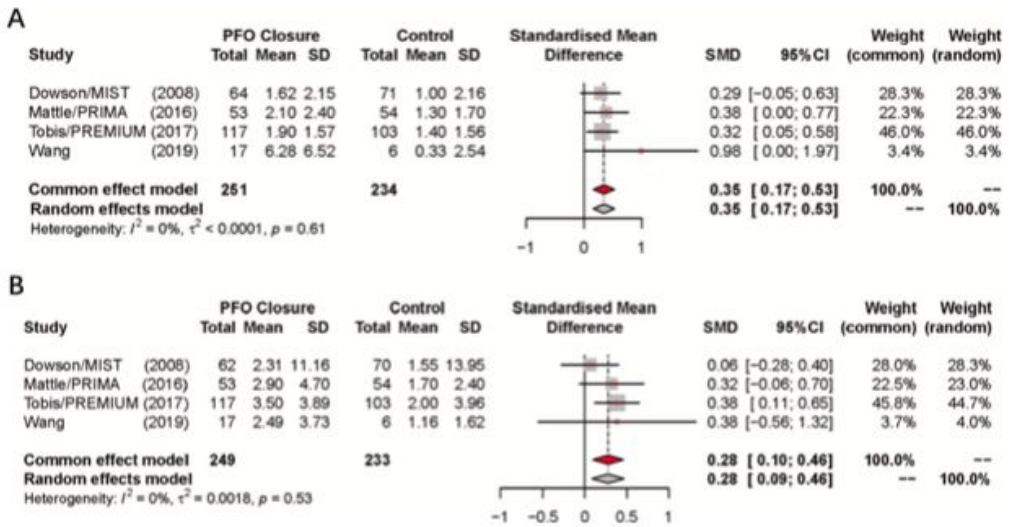
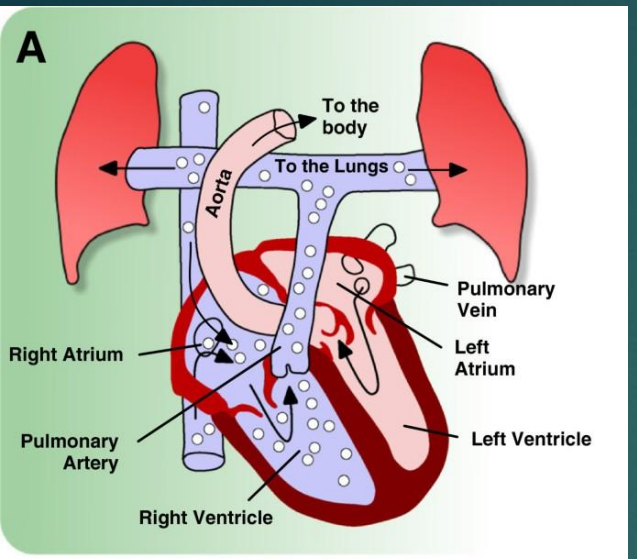
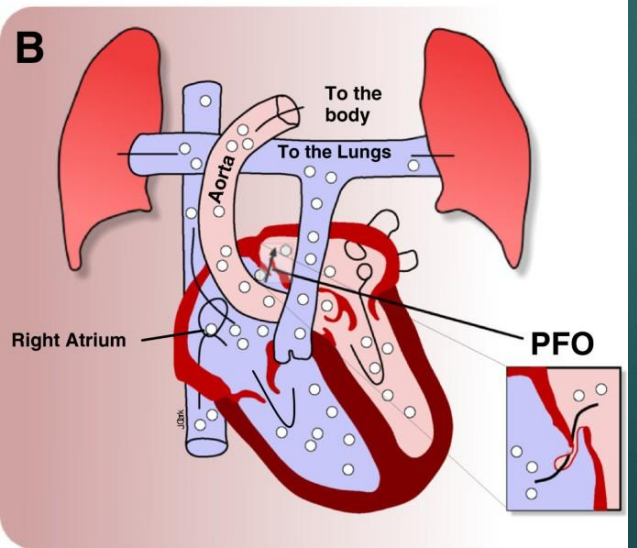


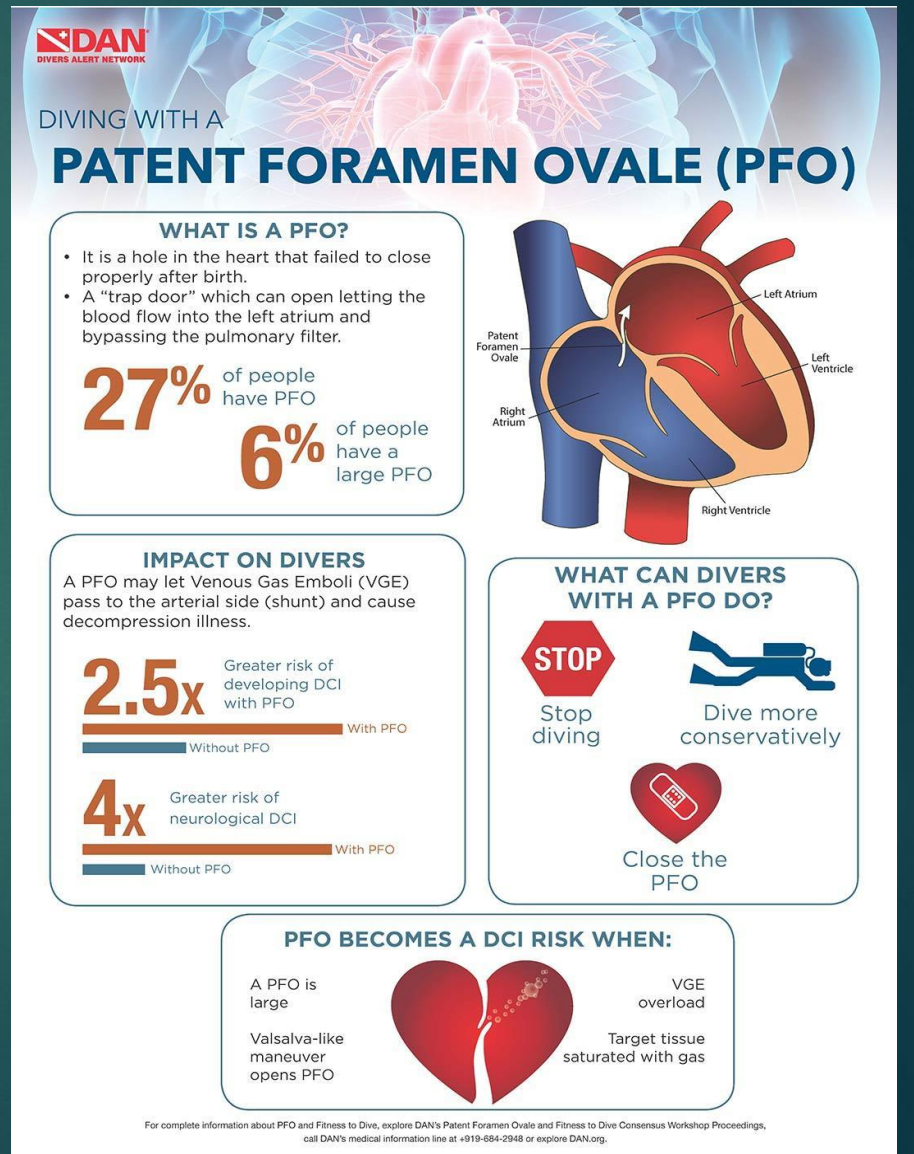
Fig. 2. Associations of PFO closure with migraine frequency (A) and migraine days (B).

MALATTIA DA DECOMPRESSIONE

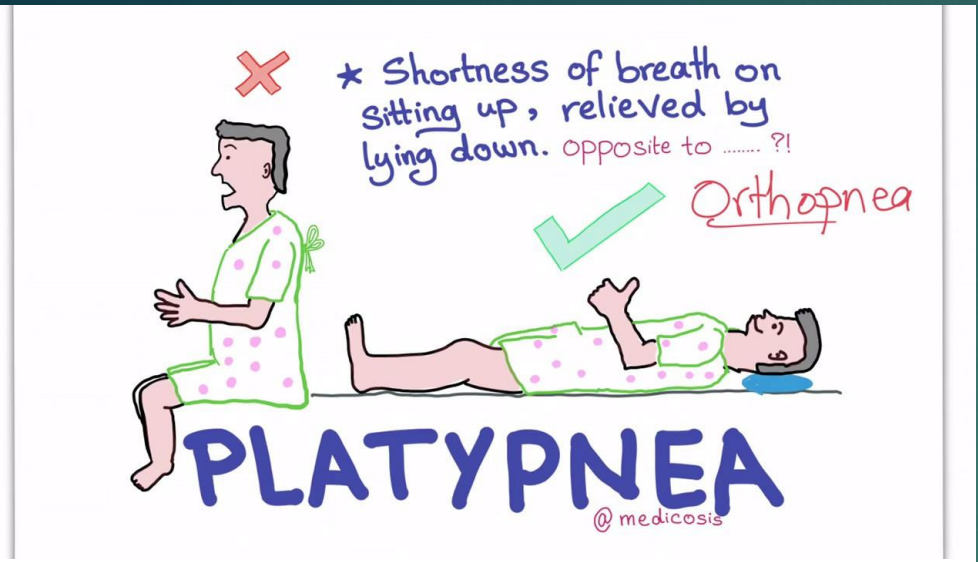




- 25-30% della popolazione ha PFO.
- PFO non rappresenta una controindicazione assoluta.
- La malattia da decompressione si manifesta nello 0,02-0,05% delle immersioni a scopo ricreazionale .
- La chiusura del PFO presenta dei rischi con delle complicanze che hanno incidenza del 2-5%.



Sindrome da platipnea-ortodeossia



CARDIAC PLATYPNEA-ORTHODEOXIA

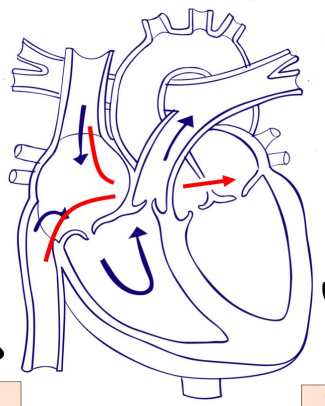
From Recumbent ➡ Standing: Patients Develop Dyspnea (Platypnea) and Hypoxia (Orthodeoxia)
Requires *Anatomic* (i.e., PFO) and *Functional* Component (i.e., PH)
Normally Flow L ➡ R through PFO, but in ❤ POS: R ➡ L in Upright Position

Supine

Causes of R → L Shunt Regardless of Position

Anatomic
- ✓ Atrial Septal Defect
- ✓ Atrial Septal Aneurysm
- ✓ Patent Foramen Ovale

Functional*
- ✓ Pulmonary Hypertension
- ✓ Pericardial Effusion
- ✓ Constrictive Pericarditis
- ✓ RV Failure



Standing

**Cardiac POS* only if ⬆ R → L Flow in Upright vs. Supine*

Anatomic
- ✓ Atrial Septal Defect
- ✓ Atrial Septal Aneurysm
- ✓ Patent Foramen Ovale

Functional*
- ✓ Pulmonary Hypertension
- ✓ Pericardial Effusion
- ✓ Constrictive Pericarditis
- ✓ RV Failure
- ✓ Aortic Aneurysm/Elongation*
- ✓ Persistent Eustachian Valve*

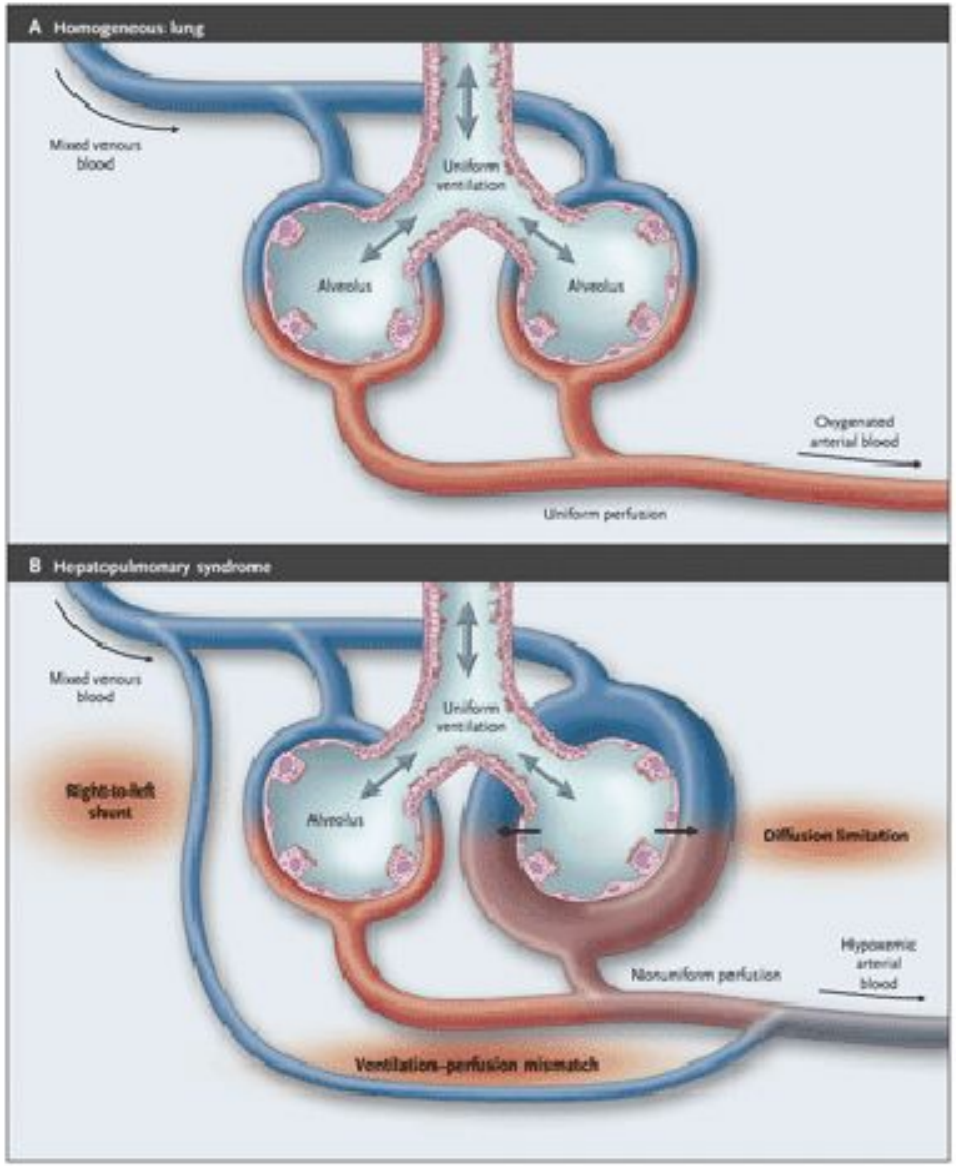
R ➡ L shunt can occur when RA Pressure > LA Pressure including conditions above

Cardiac POS* → R ➡ L shunt can occur in *absence* of ⬆ RA Pressure w/ specific anatomy that directs Caval flow to Atrial Septum

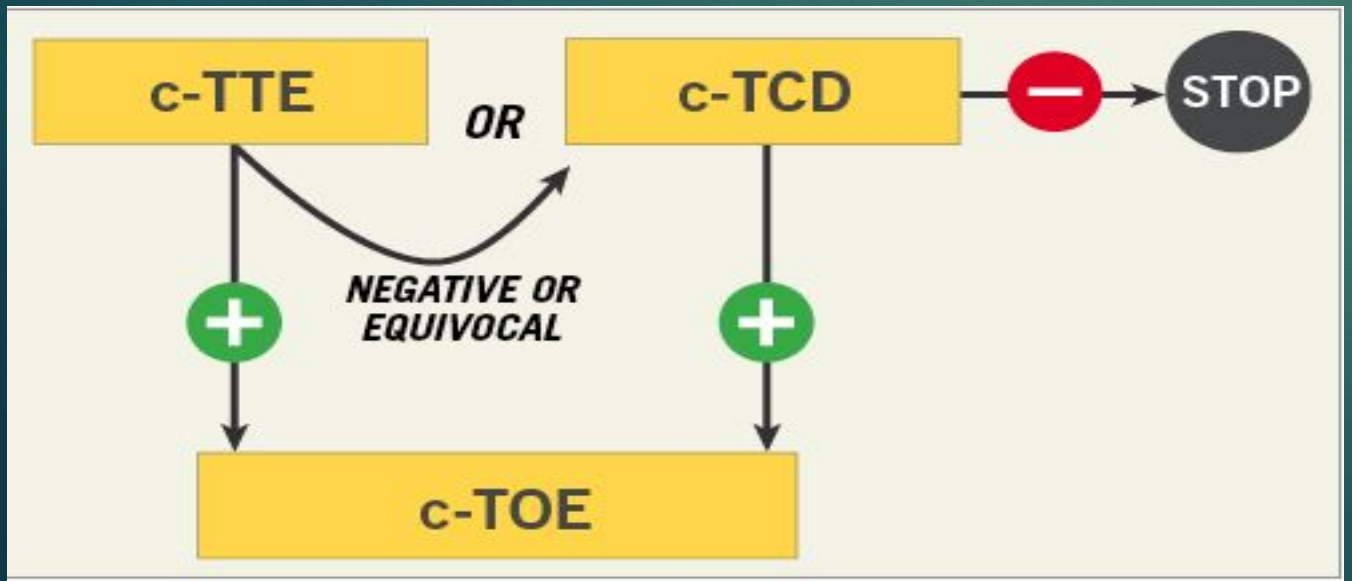
Produced by: @RichardAFerraro | @karanpdesai | #CNCR | www.cardionerds.com

Necessarie 2 componenti:

- Shunt interatriale (PFO, difetto del setto interatriale, ASA,)
- Componente funzionale che promuove shunt in ortostatismo



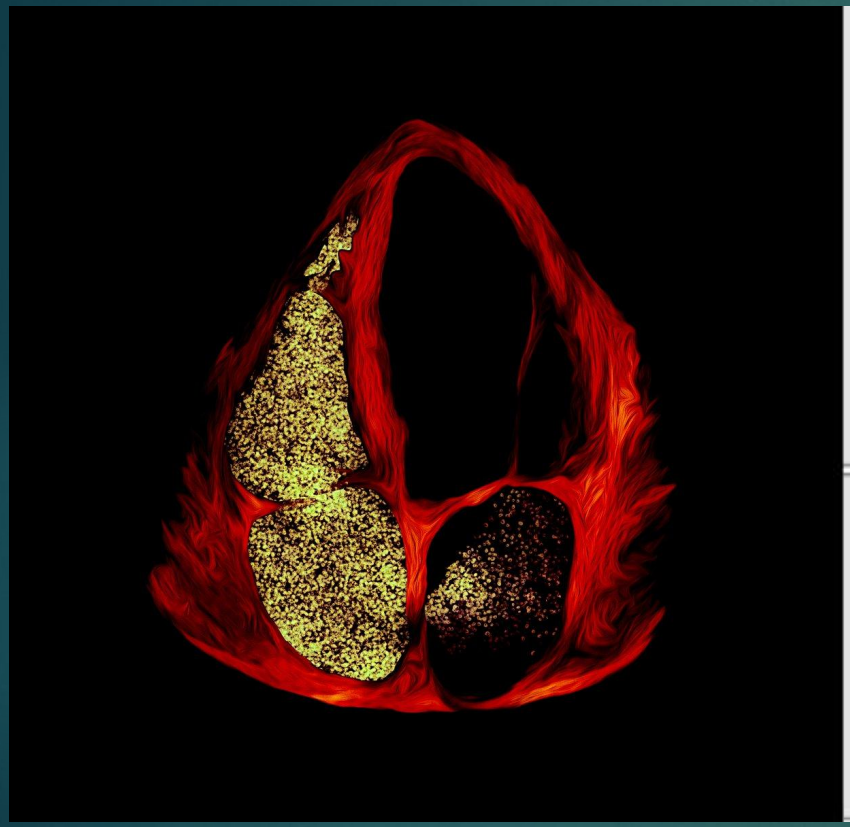
- È semplice la diagnosi di PFO?



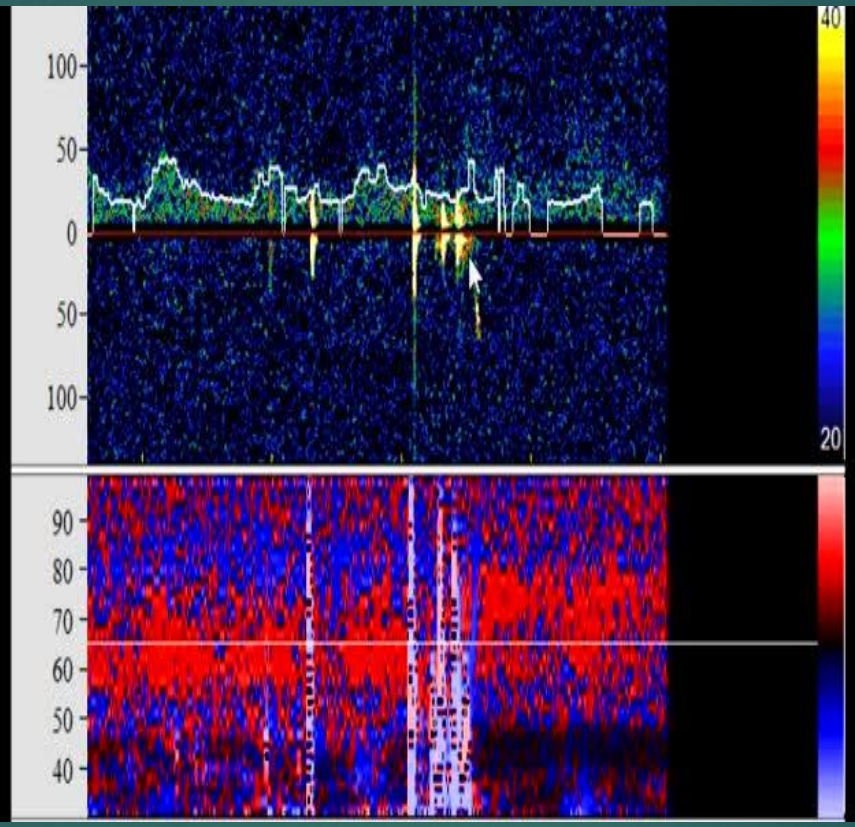
SI!

European position paper .Eurointervention 2019

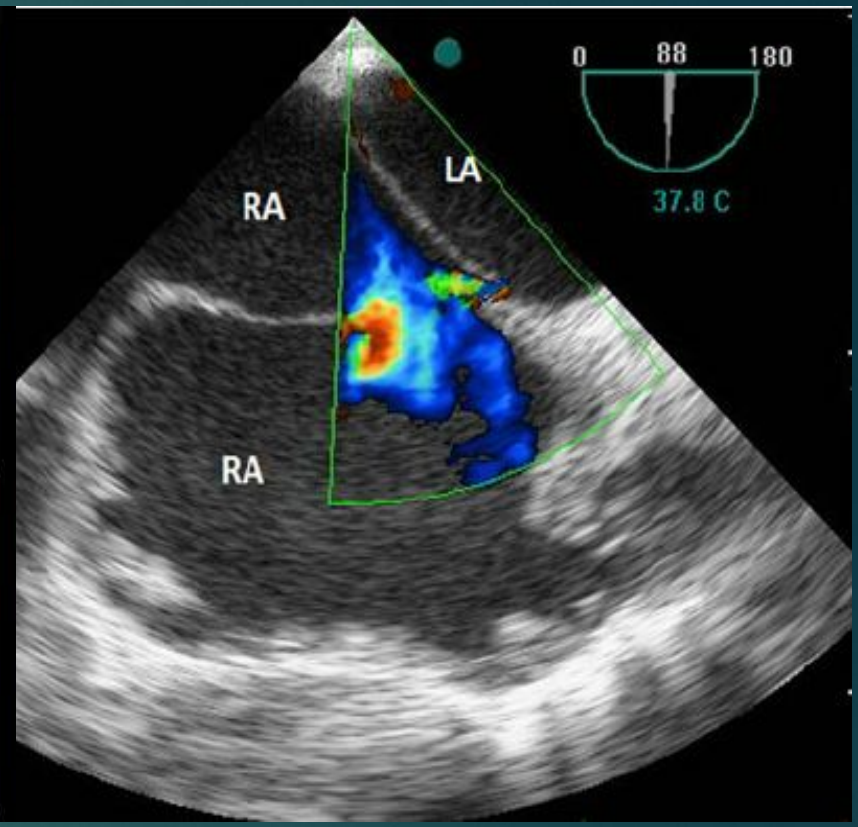
Diagnosi



TTE



TCD



TEE

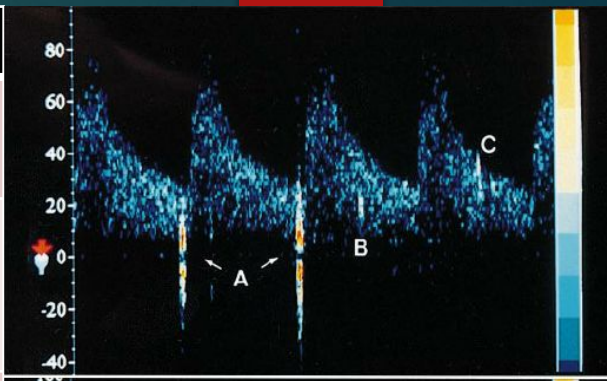
Studio Shunt Dx-Sn

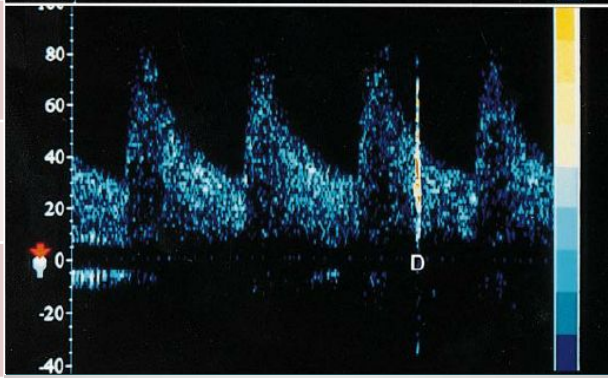
- Latente
- Permanente

Grado di Shunt:

- Assenza di shunt
- Lieve: 1-20 MES
- Moderato: > 20 MES
- Severo: effetto tendina o pioggia in cui I singoli MB non sono più distinguibili

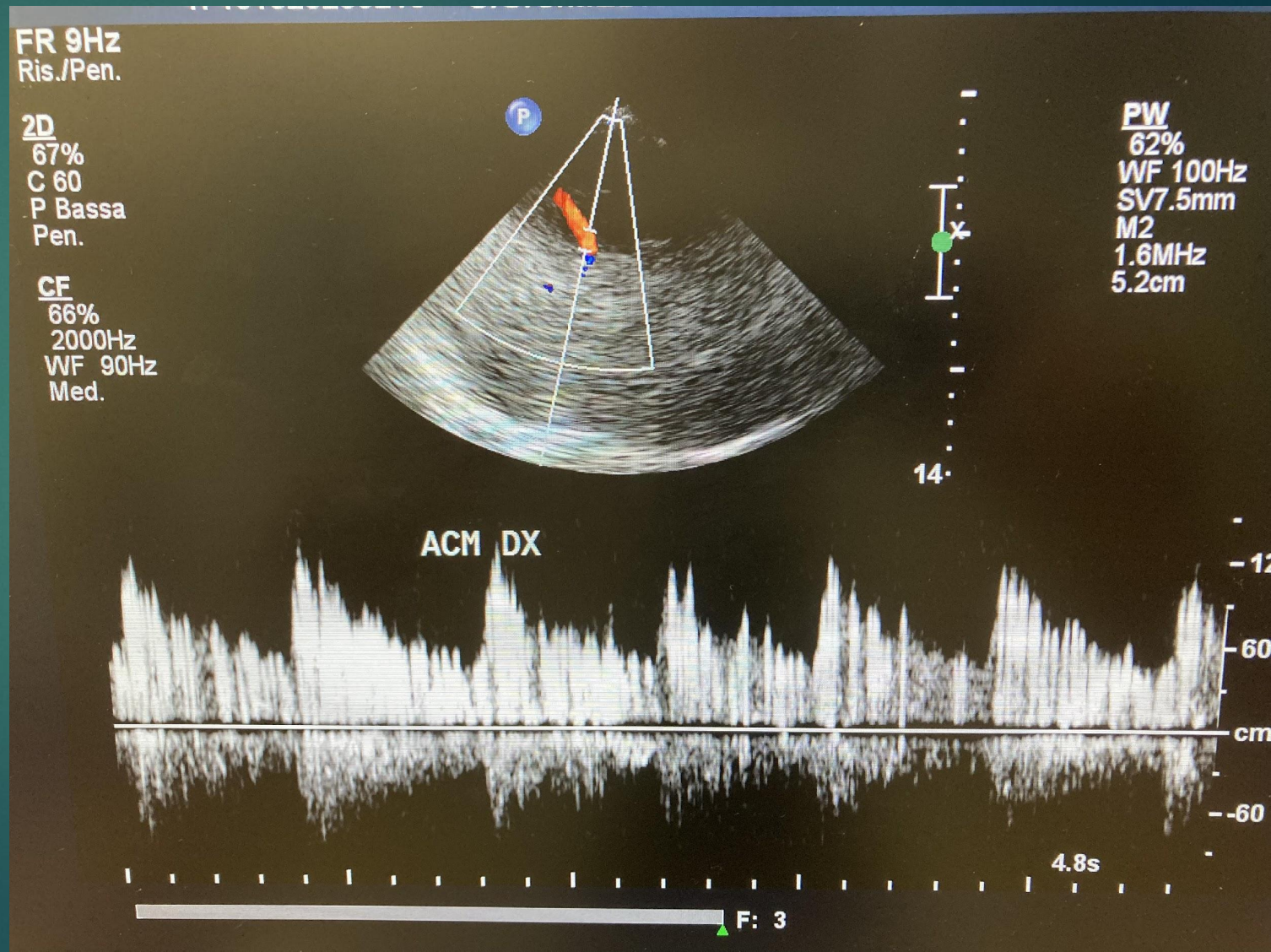
Paziente in posizione supina	**vena brachiale, 18 G**
Monitoraggio	Bilaterale > Unilaterale ACM
Tipo di m.d.c.	m.d.c. commerciali > soluzione salina 9 ml+ 1 ml di aria
Quantità di m.d.c.	10 mL > 5 mL
Manovra di attivazione	Manovra di Valsalva
Inizio MV	5'' dopo inizio infusione del m.d.c.
Durata MV	5''
Soglia MB	1MB
Finestra temporale MB	≤ 40''
N° di tests	1) Basale 2) con MV 3) ripetere MV solo se la prima negativa





EcocolorDoppler Transcranico

- Studio eseguibile con stesse modalità del TCD
- Sensibilità minore
- Il monitoraggio è monolaterale
- Non è possibile pronunciarsi sulla severità dello shunt



Finestra occipitale

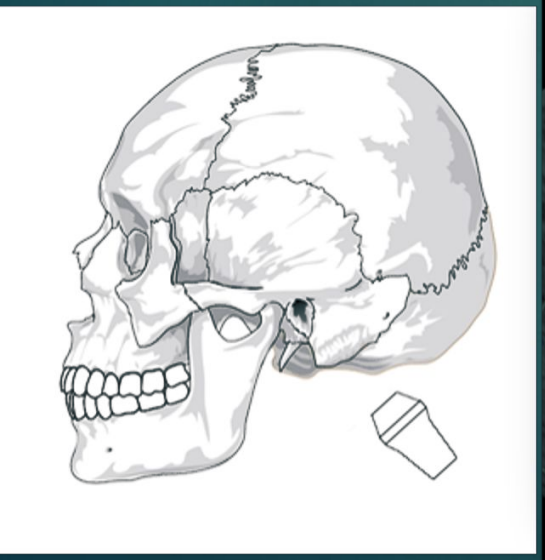
J Neurol Sci. 2017 May 15;376:97-101. doi: 10.1016/j.jns.2017.03.012. Epub 2017 Mar 10.

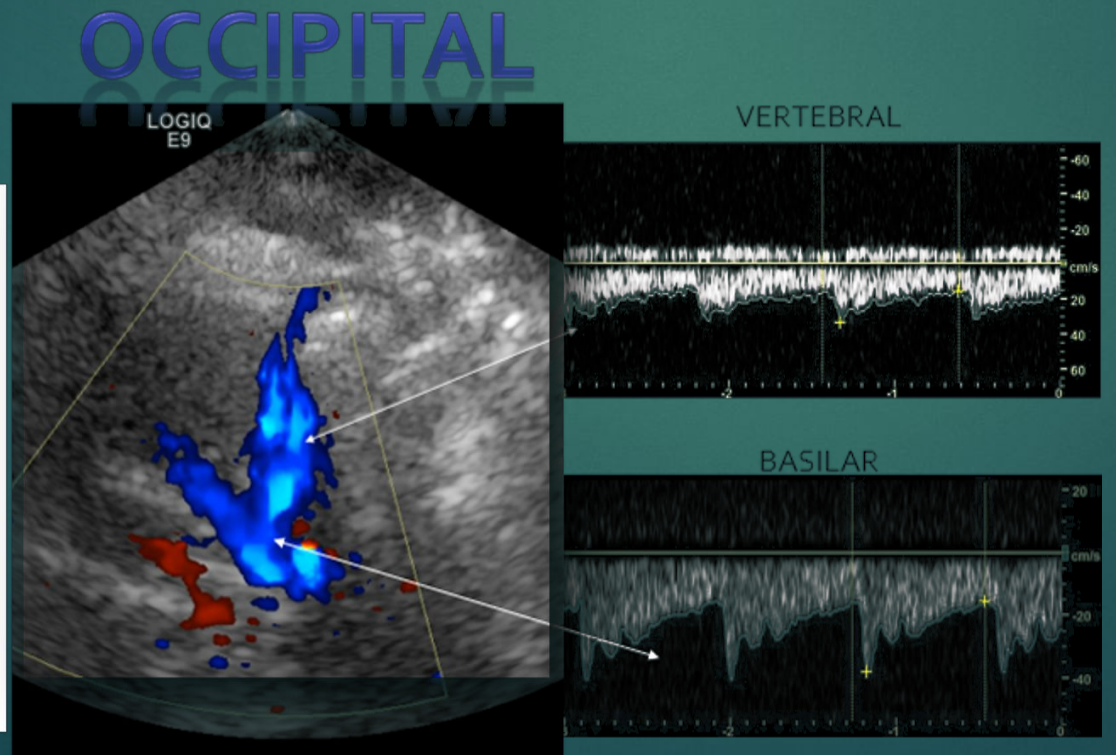
Transcranial color-coded sonography of vertebral artery for diagnosis of right-to-left shunts

Teppei Komatsu [1], Yuka Terasawa [2], Ayumi Arai [2], Kenichi Sakuta [2], Hidetaka Mitsumura [2], Yasuyuki Iguchi [2]

Affiliations + expand

PMID: 28431637 DOI: 10.1016/j.jns.2017.03.012





In the higher-age tertile, the foramen magnum window was significantly more sufficient than the temporal bone window (100% vs. 71%, p<0.001). In 94 patients having both windows, diagnosis of an RLS using cTCCS-MCA revealed a specificity of 42%, and a sensitivity of 84%. Diagnosis of an RLS using cTCCS-VA revealed a specificity of 40%, and a sensitivity of 91%. Analysis of the subgroup with large PFOs revealed a specificity of 71% using both cTCCS-MCA and cTCCS-VA.

Conclusions: cTCCS-VA should play an important role in detecting an RLS, especially in elderly stroke patients having large PFOs.

Komar *et al. Cardiovascular Ultrasound* 2014, **12**:16
http://www.cardiovascularultrasound.com/content/12/1/16

CARDIOVASCULAR ULTRASOUND

RESEARCH Open Access

Transcranial doppler ultrasonography should it be the first choice for persistent foramen ovale screening?

Monika Komar[1*], Maria Olszowska[1], Tadeusz Przewłocki[2], Jakub Podolec[2], Jakub Stępniewski[1], Bartosz Sobień[1], Rafał Badacz[2], Anna Kabłak-Ziembicka[2], Lidia Tomkiewicz-Pająk[1] and Piotr Podolec[1]

Abstract

Background: Persistent foramen ovale (PFO) is considered a cause of cryptogenic stroke and a risk factor for neurological events in young patients. The reference standard for identifying a PFO is contrast-enhanced transesophageal echocardiography (TEE).
The goal of this study was to evaluate the feasibility of transcranial color Doppler (TCD) and its diagnostic sensitiv compared with TEE.

Methods: We investigated 420 patients admitted to our department with cryptogenic stroke, transient ischemic attacks or other neurological symptoms. All patients underwent TCD and TEE evaluation. TCD and TEE examinations were performed according to a standardized procedure: air-mixed saline was injected into the right antecubital vein three times, while the Doppler signal was recorded during the Valsalva maneuver. During TCD the passage of contrast into the right-middle cerebral artery was recorded 25 seconds following the Valsalva maneuver.

Results: We detected a right-to-left shunt in 220 patients (52.3%) and no-shunts in 159 patients (37.9%) with both TCD and TEE. In 20 (4.8%) patients TEE did not reveal contrast passage which was then detected by TCD. In 21 (5.0%) patients only TEE revealed a PFO. The feasibility of both methods was 100%. TCD had a sensitivity of 95% and a specificity of 92% in the diagnosis of PFO.

Conclusions: TCD has a relatively good sensitivity and specificity. TCD and TEE are complementary diagnostic tests for PFO, but TCD should be recommended as the first choice for screening because of its simplicity, non-invasive character, low cost and high feasibility.

Keywords: Persistent foramen ovale, Transcranial color doppler ultrasound, Transesophageal echocardiography

Transcranial Doppler versus Transthoracic Echocardiography for the Detection of Patent Foramen Ovale in Patients with Cryptogenic Cerebral Ischemia: A Systematic Review and Diagnostic Test Accuracy Meta-analysis

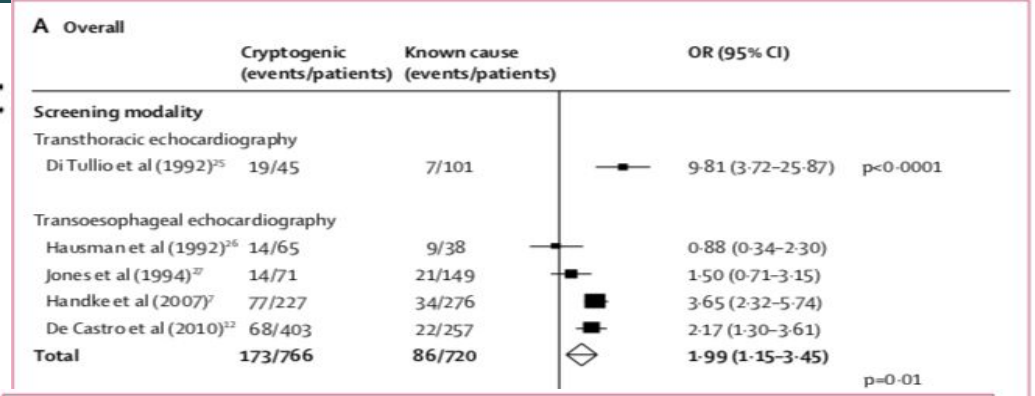
Aristeidis H. Katsanos, MD,[1,2] Theodora Psaltopoulou, MD,[3] Theodoros N. Sergentanis, MD,[3] Alexandra Frogoudaki, MD,[4] Agathi-Rosa Vrettou, MD,[4] Ignatios Ikonomidis, MD,[4] Ioannis Paraskevaidis, MD,[4] John Parissis, MD,[4] Chrysa Bogiatzi, MD,[5] Christina Zompola, MD,[2] John Ellul, MD,[6] Nikolaos Triantafyllou, MD,[7] Konstantinos Voumvourakis, MD,[2] Athanassios P. Kyritsis, MD,[1] Sotirios Giannopoulos, MD,[1] Anne W. Alexandrov, PhD,[8,9] Andrei V. Alexandrov, MD,[8] and Georgios Tsivgoulis, MD[2,8,10]

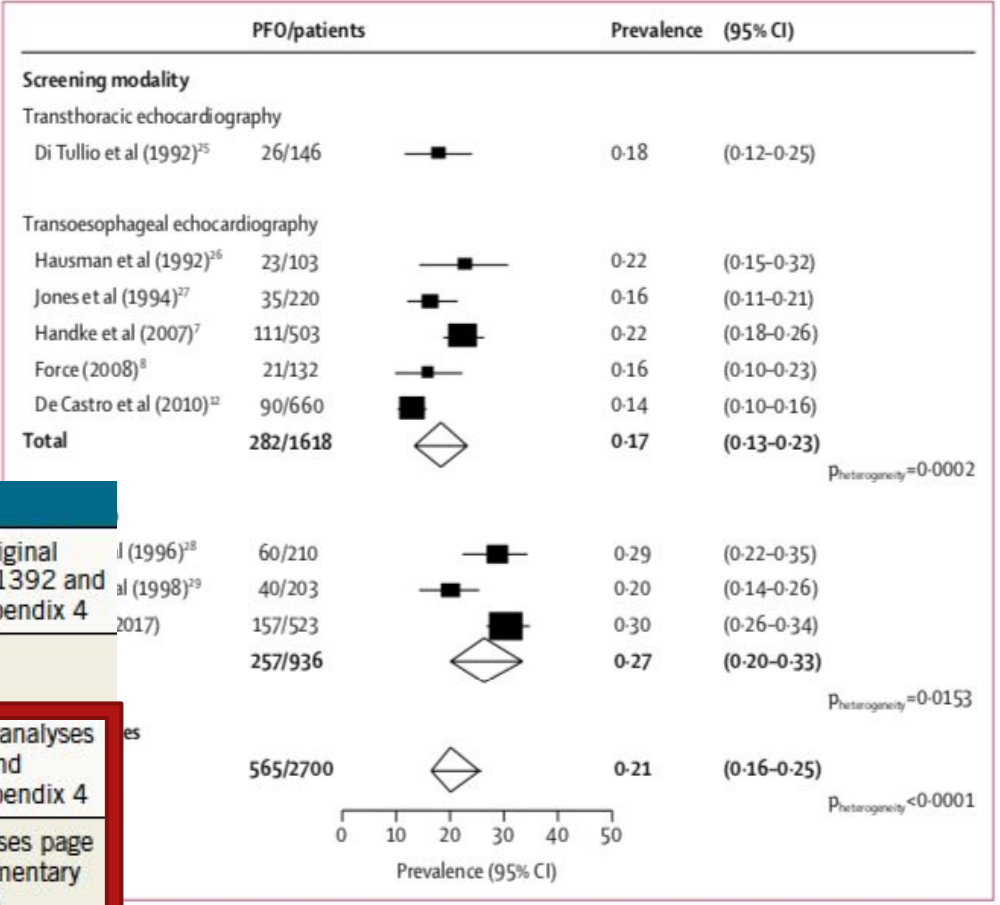
In conclusion, TCD appears to be more sensitive but less specific compared to TTE for the detection of PFO in patients with cryptogenic stroke or TIA. Notably, the overall diagnostic yield of TCD appears to outweigh that of TTE and is nearly comparable to that of TEE. Consequently, it is reasonable to use TCD as the initial screening method for RLS detection in patients with cryptogenic cerebral embolism.

Prevalence of patent foramen ovale in cryptogenic transient ischaemic attack and non-disabling stroke at older ages: a population-based study, systematic review, and meta-analysis

Sara Mazzucco, Linxin Li, Lucy Binney, Peter M Rothwell, on behalf of the Oxford Vascular Study Phenotyped Cohort

« ...we found that **bubble-TCD** is feasible in most older patients with transient ischaemic attack or non-disabling stroke, with a higher rate of RLS than is usually reported in studies of transoesophageal echocardiography»





PFO diagnosis

To achieve the maximal accuracy in PFO diagnosis, the combined use of different techniques is warranted	Strong	A	45, 54, 55 + Original meta-analyses page 1392 and Supplementary Appendix 4
The technique achieving the highest sensitivity should be used as a first-line investigation in PFO diagnosis	Strong	C	–
c-TCD has a higher sensitivity than c-TTE as a first-line investigation to detect a R-T-L shunt	Conditional	A	55 + Original meta-analyses page 1392 and Supplementary Appendix 4
c-TTE has a lower sensitivity for small shunts than other techniques	Conditional	A	Original meta-analyses page 1392 and Supplementary Appendix 4
c-TOE should be performed by experienced operators in PFO assessment	Strong	C	45-47
A strict methodology should be used performing c-TOE	Strong	C	46-47
c-TOE should be performed to stratify the risk	Strong	C	31, 48-52

-analyses of the prevalence of PFO stratified by screening modality
oramen ovale. Bubble-TCD=contrast-enhanced transcranial Doppler. OXVASC=Oxford Vascular Study. of

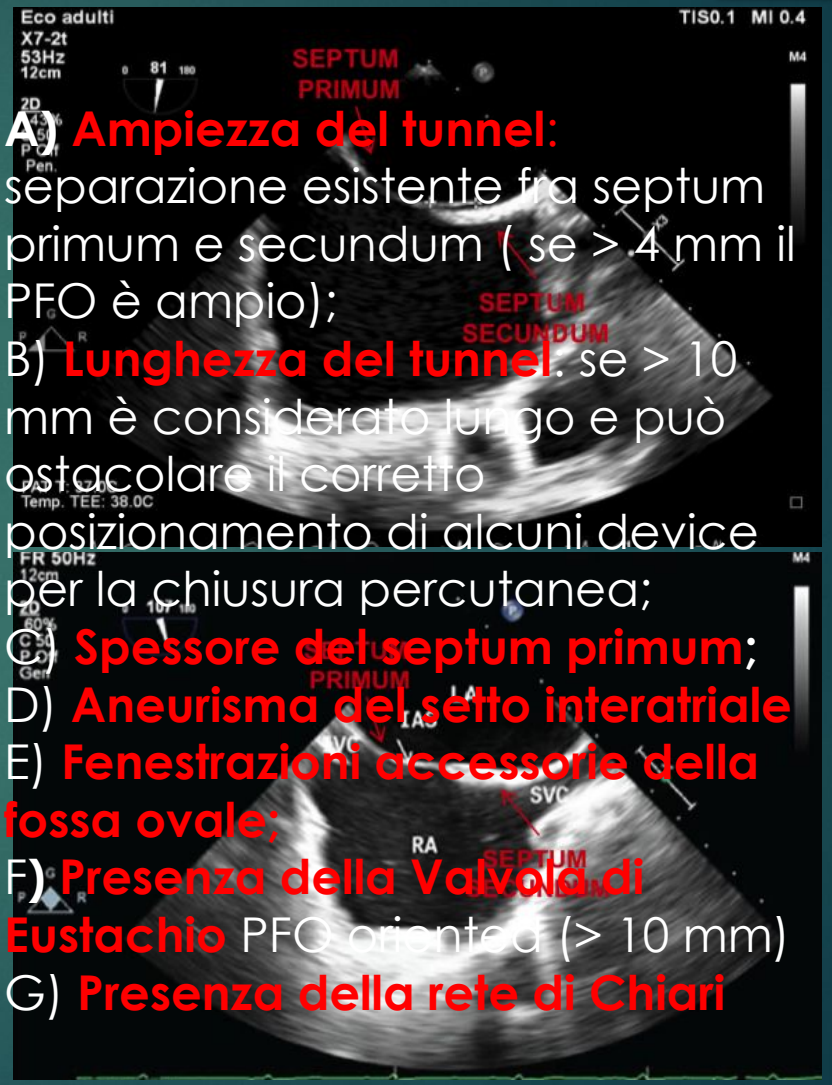
Oxford Vascular Study. *Age cutoff points for the older group in different studies ranged between 40 and

Ruolo dell'Ecocardio Transesofageo

- Escludere altre cause cardiache di embolia sistemica

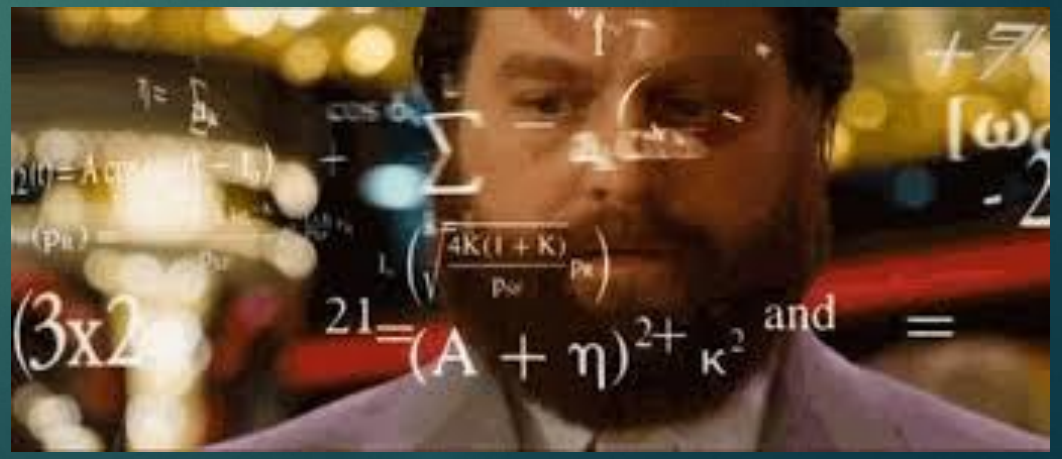
- Conferma diagnosi di PFO

- Stratificazione del rischio e pianificaizone chiusura



A) **Ampiezza del tunnel**: separazione esistente fra septum primum e secundum (se > 4 mm il PFO è ampio);
B) **Lunghezza del tunnel**. se > 10 mm è considerato lungo e può ostacolare il corretto posizionamento di alcuni device per la chiusura percutanea;
C) **Spessore del septum primum**;
D) **Aneurisma del setto interatriale**
E) **Fenestrazioni accessorie della fossa ovale;**
F) **Presenza della Valvola di Eustachio** PFO orientata (> 10 mm)
G) **Presenza della rete di Chiari**

- Il PFO è responsabile dell'ictus del mio paziente?



Mini Review

BIOMEDICAL
Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2019.20.003394

The Challenging Play of PFO in Cerebrovascular Disease: An Actor that can be an Extra or the Protagonist

Carmelo Buttà[1]* and Giuseppe Miceli[2]

[1]*U.O.C. Cardiology, Department of Clinical and Experimental Medicine, Messina (Italy)*

[2]*U.O.C. Internal Medicine with Stroke Care, Department of Health Promotion, Maternal and Child, of Internal and of Excellence, Palermo (Italy)*

- Età del paziente
- Localizzazione ictus (?)
- Caratteristiche anatomiche
- Trombosi venosa, OSAS ,immobilizzazione
- Caratteristiche PFO
- Disordini della coagulazione
- RoPe score

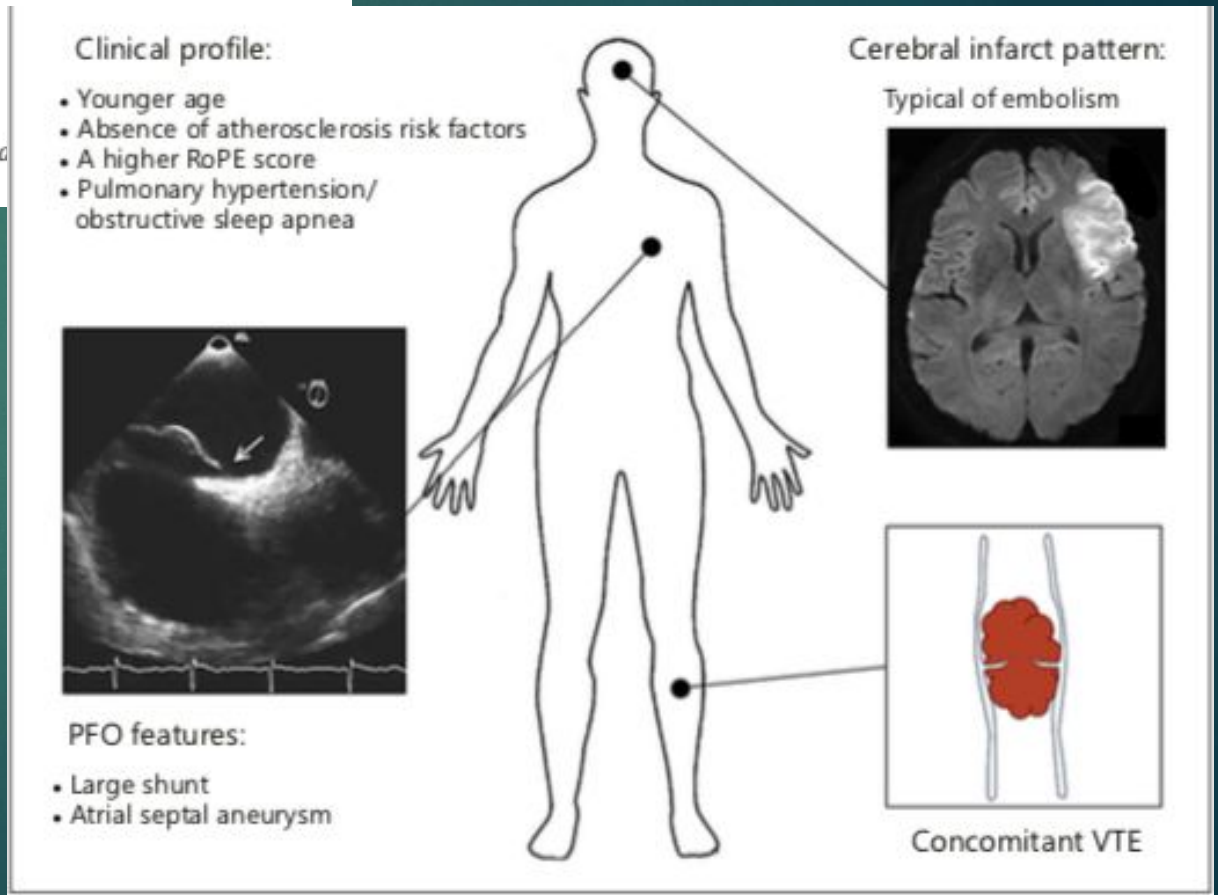
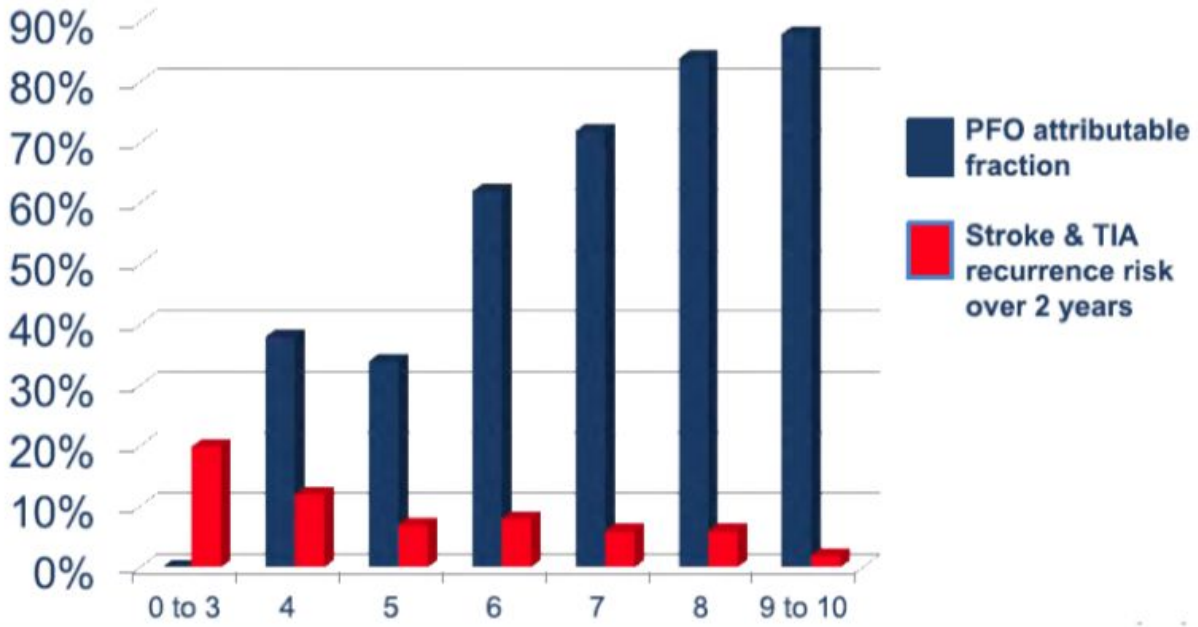


Table 3. Summary of statements on the assessment of PFO role in left circulation thromboembolism.

Position statements	Strength of the statement	Level of evidence	Ref.
PFO can play a pathogenic role in cryptogenic left circulation thromboembolism	Strong	A	9-29, 51, 112, 132, Table 5 and Supplementary Table 7
It is essential to evaluate the role of the PFO in any given left circulation thromboembolism	Strong	A	Table 5
No statement is possible regarding the quantification of the role of PFO in left circulation thromboembolism	Strong	C	13, 18, 27-29, 57-98
The evaluation of the role of the PFO in left circulation thromboembolism should be individualised with critical clinical judgement in an interdisciplinary collaboration between physicians, weighting clinical, anatomical and imaging characteristics	Strong	C	13, 18, 27-29, 57-98
Estimating the probability of a PFO being embolism-related			
No single clinical, anatomical or imaging characteristics are sufficient to make a quantitative estimation of the probability of a PFO causal role	Strong	A	26-28, 51, 112, 128, 132, Table 5, 13, 59, 61, 77-79, 171
When a PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore	Strong	A	26-28, 51, 112, 128, 132, Table 5
The presence of other risk factors does not exclude a causative role of PFO; however, it is more likely when patients are young and lack other risk factors	Strong	B	13, 56-59, 78, 79, 90
Cortical infarcts are commonly embolic but, less frequently, also white matter infarcts can be embolic	Strong	B	59, 60-63, 70
No specific imaging pattern has been associated with a causal role of PFO in stroke patients	Strong	C	59-69, 77
ASA, shunt severity and an atrial septal hypermobility can be linked to a causal role of PFO	Strong	A	27-29, 51, 112, 132, Table 5, Supplementary Figure 5; 78, 79, 90, 122, 170, 171, 71-74, 91
PFO sizes, presence of Chiari network or Eustachian valve can be linked to a causal role of PFO	Conditional	C	64, 75, 76, 208, 256
Deep vein thrombosis, immobilisation, long journeys, straining pre-stroke or obstructive sleep apnoea can be linked to a causal role of PFO	Conditional	C	81, 84, 85
Simultaneous pulmonary embolism and/or deep vein thrombosis strongly suggest a causal role of PFO	Strong	C	15, 18, 80-83
The role of thrombophilia cannot be generalised	Strong	C	86-89
The RoPE score should only be part of a comprehensive individual evaluation.			
Further validation studies on the RoPE score are needed	Strong	B	59, Supplementary Table 3

European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism .Eurointervention 2019

Increasing RoPE score = Increasing PFO attributable fraction = Decreasing risk of recurrent TIA/Stroke



the RoPE score does not account for high-risk PFO features (e.g., septal aneurysm) that have been shown to correlate with higher risk of paradoxical embolisation!

Add points for each risk factor and for age • A patient less than 30 years with no risk factors has a score of 10 • A patient ≥ 70 years with all 5 risk factors has a score of 0		**RoPE SCORE**
	Maximum Score =	**10**
Risk Factor	**(0 to 5 points)**	-
No history of hypertension	(1)	
No history of diabetes	(1)	
No history of stroke or TIA	(1)	
Non-smoker	(1)	
Peripheral infarct on CT or MRI	(1)	
Age at time of index event	**(0 to 5 points)**	-
≥70 years	(0)	
60 – 69 years	(1)	
50 – 59 years	(2)	
40 – 49 years	(3)	
30 – 39 years	(4)	
18 – 29 years	(5)	
	Total Score =	

Pascal Score

eFigure 1. The Extended PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System.

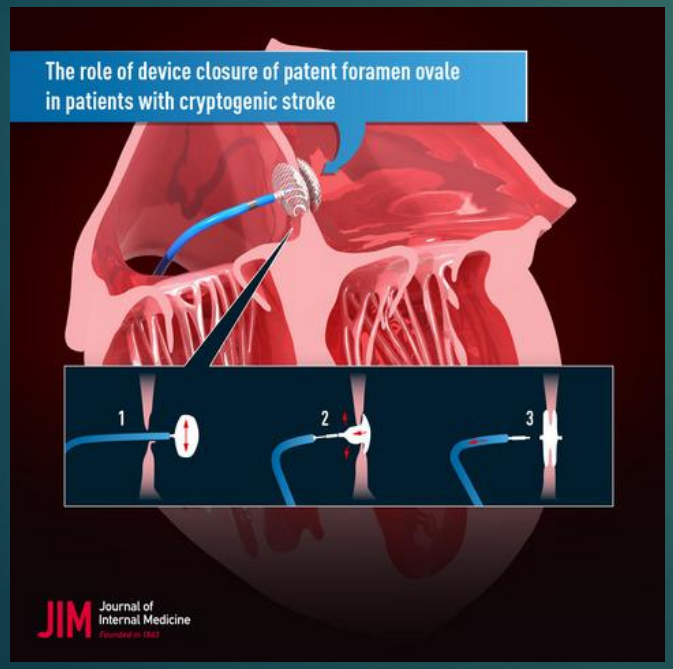
Risk Grade	Features	Casual Relatedness	
		Low RoPE Score[a]	High RoPE Score[a]
Very high risk	PFO + straddling thrombus	Definite	Definite
High risk	BOTH of: 1A. PFO + ASA, *or* 1B. Large shunt PFO, *AND* 2. PE or DVT preceding index infarct	Probable	Highly Probable
Medium risk	ANY of: 1. PFO + ASA 2. Large shunt PFO	Possible	Probable
Low risk	Small shunt PFO without ASA	Unlikely	Possible

1) presence of features that increase likelihood of PFO-stroke mechanisms (high risk PFO physiologic and structural features of large shunt or atrial septal aneurysm)

2) absence of features that increase likelihood of an occult non-PFO stroke mechanisms (older age, vascular risk factors, and stroke topography features) as quantified in the RoPE score.

Based on this combination of factors, the original, extended PASCAL Classification System algorithmically assigns a likelihood of causal relationship among five levels: Definite, Highly Probable, Probable, Possible, and Unlikely.

- Il PFO del mio paziente va chiuso?



Le due probabilità da calcolare di fronte ad un PFO

- Probabilità che il PFO abbia un ruolo nello scenario clinico che ho di fronte

- Probabilità che l'evento clinico a cui sto assistendo possa ripresentarsi.

Estimating the risk of recurrences			
The risk of recurrent embolism in unselected patients with PFO is low	Strong	A	90-92, 259
No single variable allows a quantitative prediction of recurrences	Strong	A	94, 95, 26-28, 51, 112, 128, 132, Table 5, Supplementary Table 7
Variables linked to a higher recurrence rate in PFO patients are: – Atrial septal aneurysm and/or PFO diameter – Older age – Coagulation disorders – Stroke at index – D-dimer >1,000 at admission – Acetylsalicylic acid use vs. OAC	Conditional	B	72, 95-98

TABLE 1 Clinical Trials Randomizing Cryptogenic Stroke Patients to Percutaneous PFO Closure or Medical Therapy

Randomized Clinical Trial (Ref. #)	Cohort (Number of Patients)	Device Arm	Medical Arm	Follow-Up	Primary Outcome	Results
CLOSURE I (20)	Cryptogenic stroke or TIA + PFO; age 18-60 yrs (909)	PFO closure + aspirin and warfarin for 1 month, then aspirin for 2 yrs	Aspirin, warfarin or both	2 yrs	Composite of stroke, TIA, early death from any etiology and late neurological death	PFO closure did not significantly reduce recurrent stroke or TIA compared with medical therapy
PC (23)	Cryptogenic stroke, TIA or peripheral embolism + PFO; age <60 yrs (414)	PFO closure + aspirin for 5-6 months + clopidogrel or ticlopidine for 1-6 months	Antiplatelet or antithrombotic therapy	Mean 4 yrs	Composite of death, nonfatal stroke, TIA, or peripheral embolism	PFO closure did not significantly reduce recurrent embolic events or death compared with medical therapy
RESPECT (27) (extended follow-up)	Cryptogenic stroke + PFO; age 18-60 yrs (980)	PFO closure + aspirin and clopidogrel for 1 month, then aspirin for 5 months	Aspirin, warfarin, clopidogrel or aspirin + extended release dipyridamole	Median 5.9 yrs	Composite of recurrent nonfatal and fatal stroke and early death	PFO closure reduced recurrent stroke events compared with medical therapy
CLOSE (40)	Cryptogenic stroke + PFO with large shunt or atrial septal aneurysm; age 16-60 yrs (663)	PFO closure + aspirin and clopidogrel for 3 months, then single antiplatelet therapy	Aspirin, clopidogrel, or aspirin + extended-release dipyridamole or vitamin K antagonist or direct oral anticoagulant	Mean 5.3 ± 2.0 yrs	Fatal or nonfatal stroke	PFO closure reduced recurrent stroke events compared with medical therapy
Gore REDUCE (41)	Cryptogenic stroke + PFO; age 18-59 yrs (664)	PFO closure + aspirin, aspirin and dipyridamole, or clopidogrel	Aspirin, aspirin and dipyridamole, or clopidogrel	Median 3.2 yrs	Freedom from stroke; incidence of new brain infarct on MRI	PFO closure reduced recurrent stroke events and new brain infarcts on MRI compared with medical therapy






defense PFO 2011-2017 multicenter randomized open label trial Amplatzer PFO closure VS dual antiplatelet OR AND coumadin PFO closure+ antiplatelet reduce risk of stroke VS medical theraphy

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*

Subgroup	Closure	Medical Therapy	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of patients/total no. (%)				
Overall modified intention-to-treat population	22/400 (5.6)	29/451 (6.9)	0.78 (0.44–1.35)	0.37	
Sex					0.16
Male	7/208 (3.4)	15/232 (6.8)	0.50 (0.20–1.22)	0.13	
Female	15/192 (7.9)	14/219 (7.0)	1.13 (0.55–2.34)	0.74	
Atrial septal aneurysm					0.95
No	15/249 (6.2)	20/291 (7.4)	0.81 (0.42–1.59)	0.55	
Yes	7/151 (4.6)	9/160 (6.0)	0.78 (0.30–2.13)	0.64	
Shunt size					0.78
None or trace	8/118 (6.9)	10/155 (6.8)	0.99 (0.39–2.52)	0.99	
Moderate	7/144 (5.0)	12/163 (7.9)	0.61 (0.24–1.55)	0.30	
Substantial	3/87 (3.5)	3/65 (4.9)	0.72 (0.15–3.57)	0.69	
Entry event					0.33
Stroke	15/300 (5.1)	15/324 (5.1)	1.01 (0.49–2.07)	0.98	
Transient ischemic attack	7/100 (7.1)	14/126 (11.6)	0.60 (0.24–1.49)	0.27	
Baseline medication					
None	0/13 (0)	2/38 (5.9)	—	—	0.65
Aspirin alone	15/286 (5.3)	16/252 (6.7)	0.79 (0.39–1.59)	0.50	
Warfarin alone	1/25 (4.2)	8/111 (7.9)	0.52 (0.06–4.12)	0.53	
Aspirin plus warfarin	6/72 (8.5)	2/40 (5.4)	1.59 (0.32–7.89)	0.57	

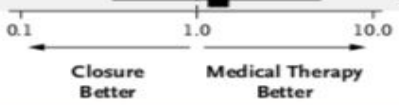


Figure 2. Results of Primary-End-Point Analysis at 2 Years, According to Subgroup, in the Modified Intention-to-Treat Population.
Percentages in parentheses are Kaplan–Meier estimates of the event rates.

CLOSURE I

«In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA».

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*

PC CLOSURE TRIAL

«Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy»

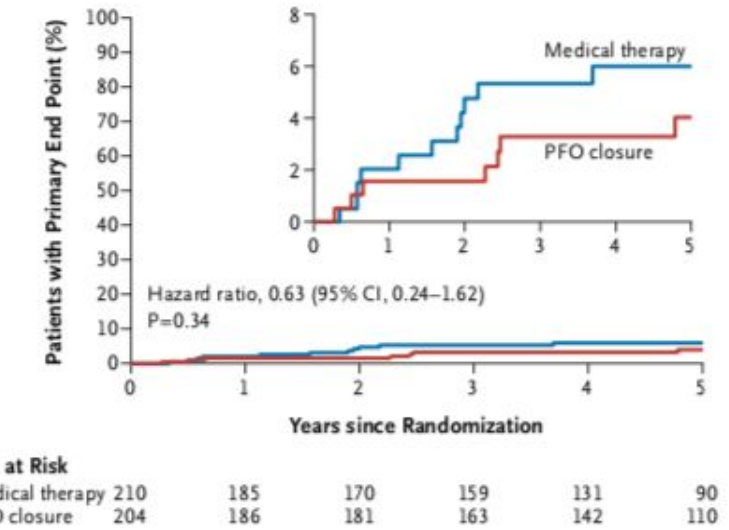


Figure 1. Kaplan–Meier Cumulative Estimates of the Rate of the Primary End Point.
PFO denotes patent foramen ovale.

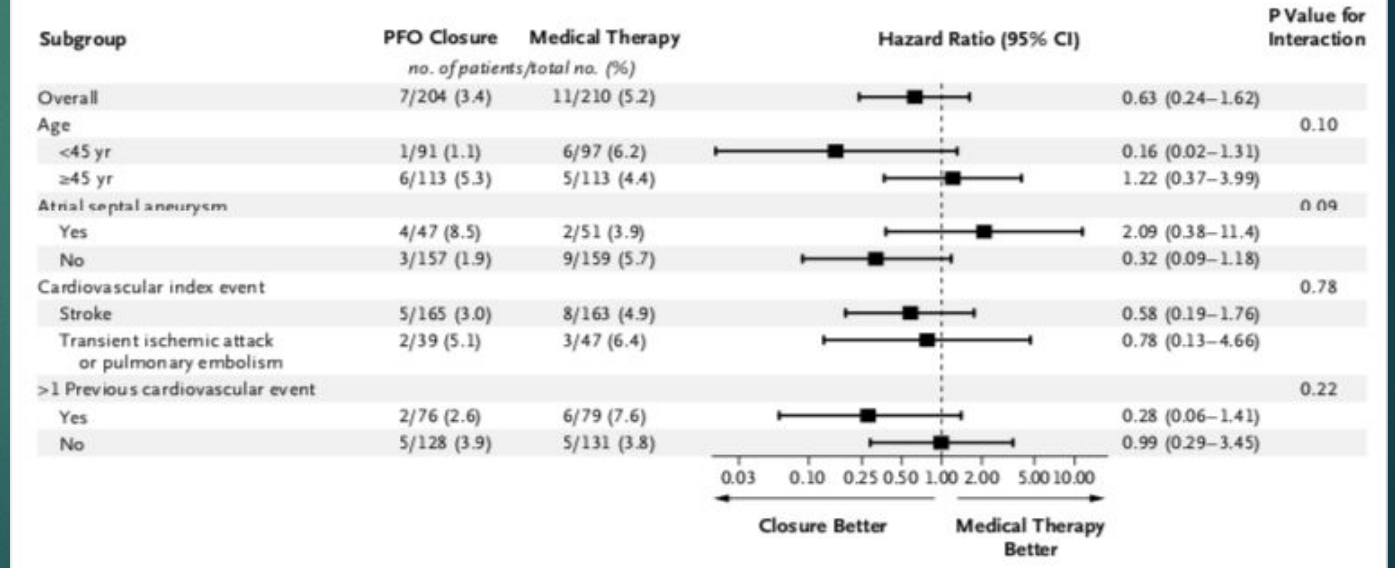


Figure 2. Subgroup Analyses of the Primary End Point.
Hazard ratios were calculated with the use of a Cox proportional-hazards model.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Subgroup	Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients/total no. (%)				
Overall	9/499 (1.8)	16/481 (3.3)	0.49 (0.22–1.11)	0.08	
Age					0.52
18–45 yr	4/230 (1.7)	5/210 (2.4)	0.70 (0.19–2.60)	0.59	
46–60 yr	5/262 (1.9)	11/266 (4.1)	0.41 (0.14–1.17)	0.08	
Sex					0.73
Male	5/268 (1.9)	10/268 (3.7)	0.45 (0.15–1.31)	0.13	
Female	4/231 (1.7)	6/213 (2.8)	0.57 (0.16–2.02)	0.38	
Shunt size					0.07
None, trace, or moderate	7/247 (2.8)	6/244 (2.5)	1.03 (0.35–3.08)	0.95	
Substantial	2/247 (0.8)	10/231 (4.3)	0.18 (0.04–0.81)	0.01	
Atrial septal aneurysm					0.10
Present	2/180 (1.1)	9/169 (5.3)	0.19 (0.04–0.87)	0.02	
Absent	7/319 (2.2)	7/312 (2.2)	0.89 (0.31–2.54)	0.83	
Index infarct topography					0.39
Superficial	5/280 (1.8)	12/269 (4.5)	0.37 (0.13–1.04)	0.05	
Small deep	2/57 (3.5)	1/70 (1.4)	1.76 (0.16–19.93)	0.64	
Other	2/157 (1.3)	3/139 (2.2)	0.56 (0.09–3.34)	0.52	
Planned medical regimen					0.20
Anticoagulant	4/132 (3.0)	3/121 (2.5)	1.14 (0.26–5.10)	0.86	
Antiplatelet	5/367 (1.4)	13/359 (3.6)	0.34 (0.12–0.94)	0.03	

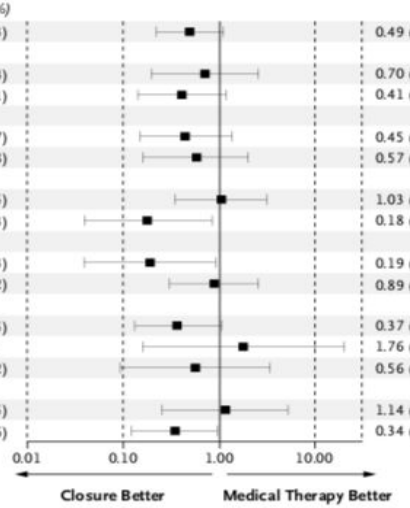
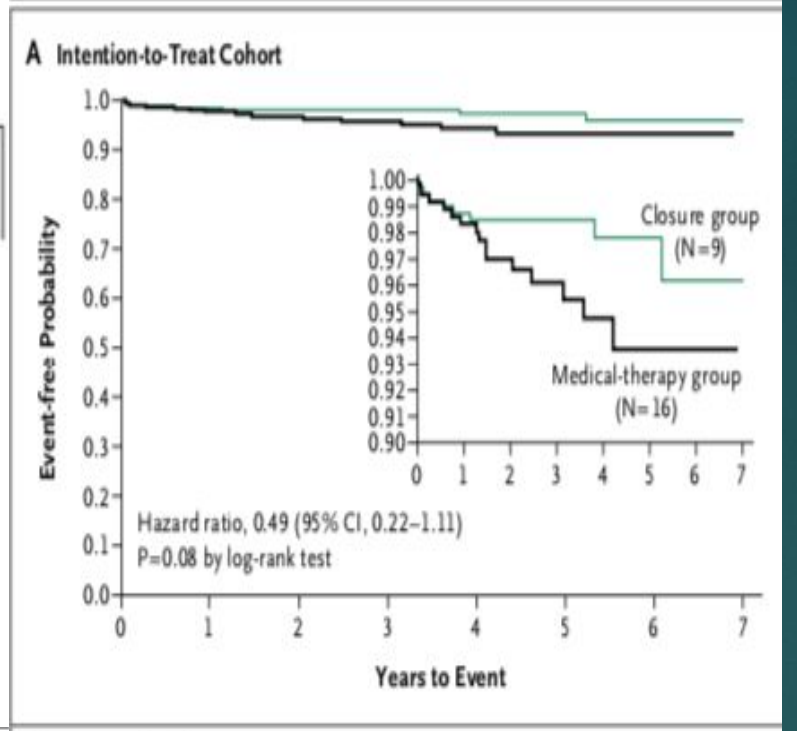
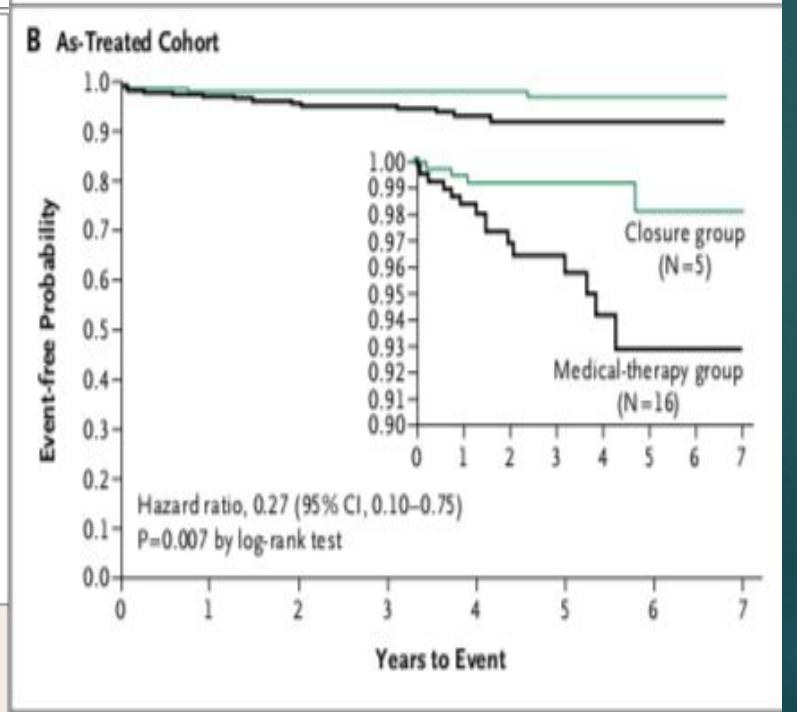


Figure 2. Analysis of the Primary End-Point According to Subgroup, in the Intention-to-Treat Cohort.
Potential heterogeneity of the treatment effect was noted with respect to two baseline characteristics, with a suggestion of greater risk reductions with closure than with medical therapy alone in patients with an atrial septal aneurysm or a substantial shunt size. The percentages are Kaplan–Meier estimates of the event rates.





RESPECT

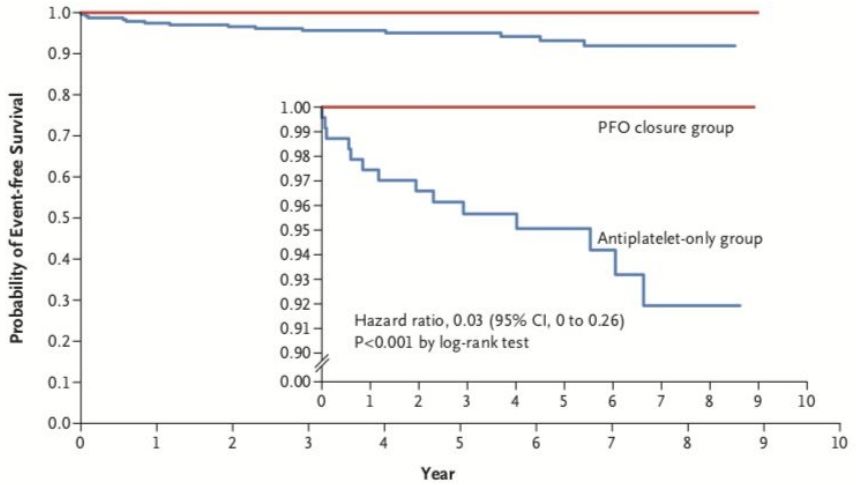
«In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ische- mic stroke. However, closure was superior to medical therapy alone in the pre-specified per-protocol and as-treated analyses, with a low rate of associated risks»

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*



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

Figure 2. Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.

The analysis was performed in the intention-to-treat cohort, which included all patients who were randomly assigned to a treatment. The inset shows the same data on an enlarged y axis.

CLOSE

In conclusion, among patients 16 to 60 years of age who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke was lower with PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone. The effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined.

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

RANDOMIZED CONTROLLED TRIAL

PFO closure + antiplatelet therapy

n=441

Antiplatelet therapy alone

n=223

1.4% Clinical ischemic stroke median of 3.2 years (P=0.002) **5.4%**

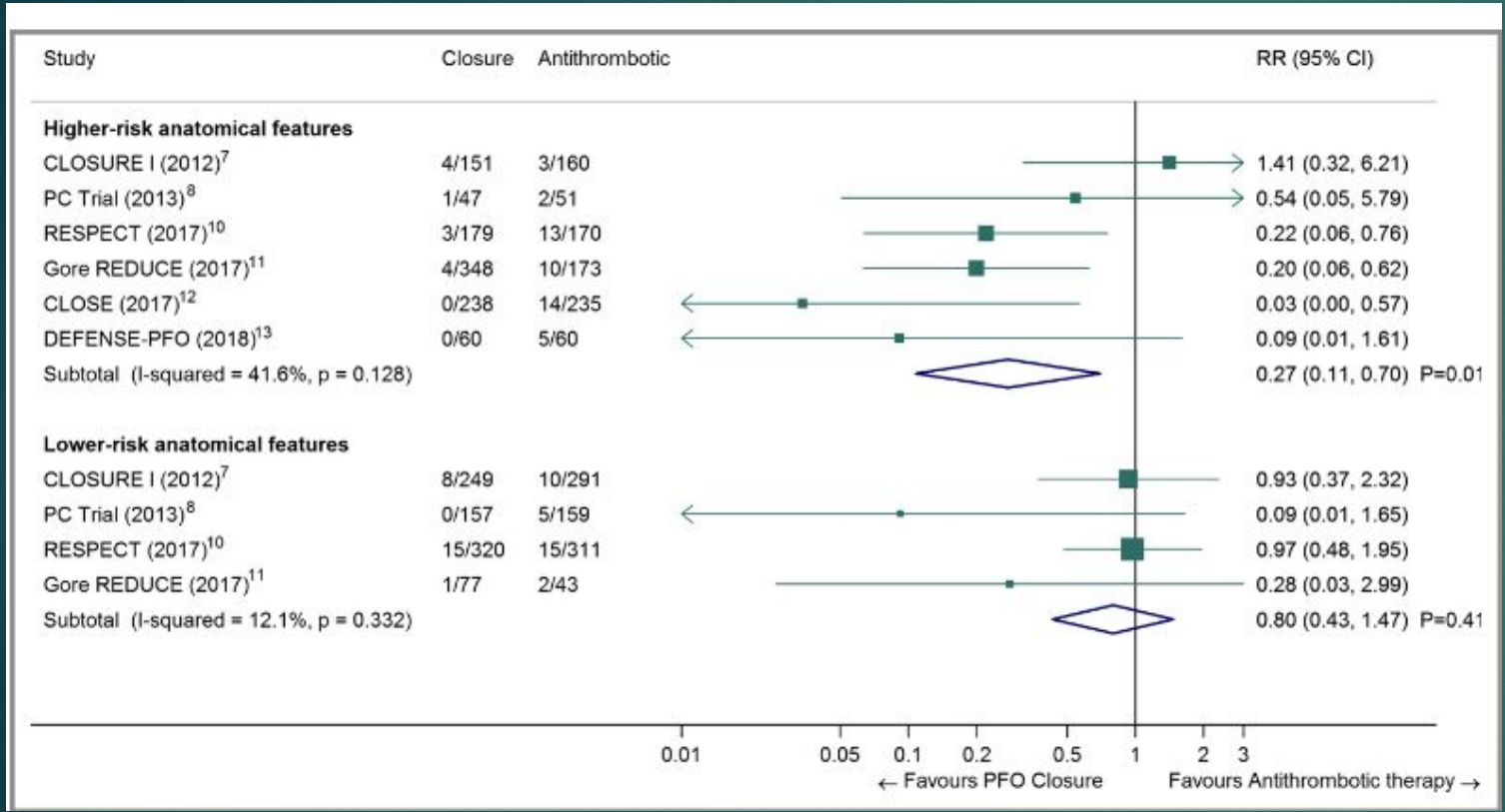
22/383 patients (5.7%) MRI + clinical stroke 20/177 patients (11.3%)

The NEW ENGLAND JOURNAL of MEDICINE

Søndergaard et al. N Engl J Med 2017

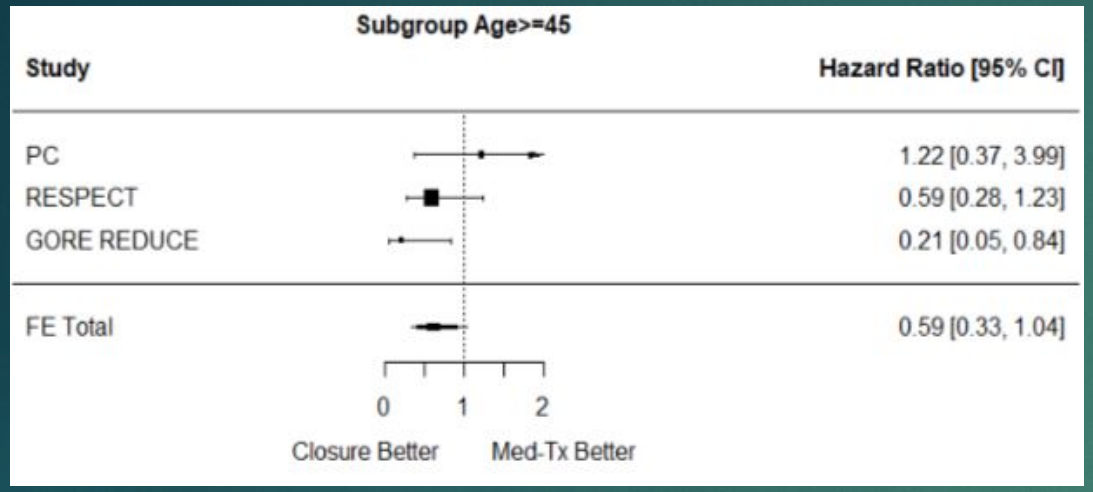
Closure, Anticoagulation, or Antiplatelet Therapy for Cryptogenic Stroke With Patent Foramen Ovale: Systematic Review of Randomized Trials, Sequential Meta-Analysis, and New Insights From the CLOSE Study

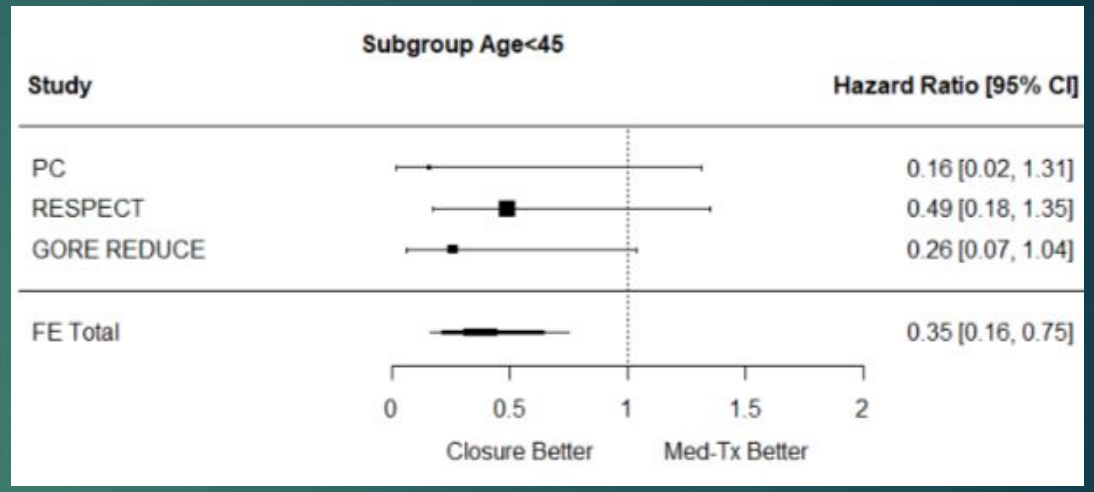
Guillaume Turc, MD, PhD; David Calvet, MD, PhD; Patrice Guérin, MD, PhD; Marjorie Sroussi, MD; Gilles Chatellier, MD, PhD; Jean-Louis Mas, MD; on behalf of the CLOSE Investigators*

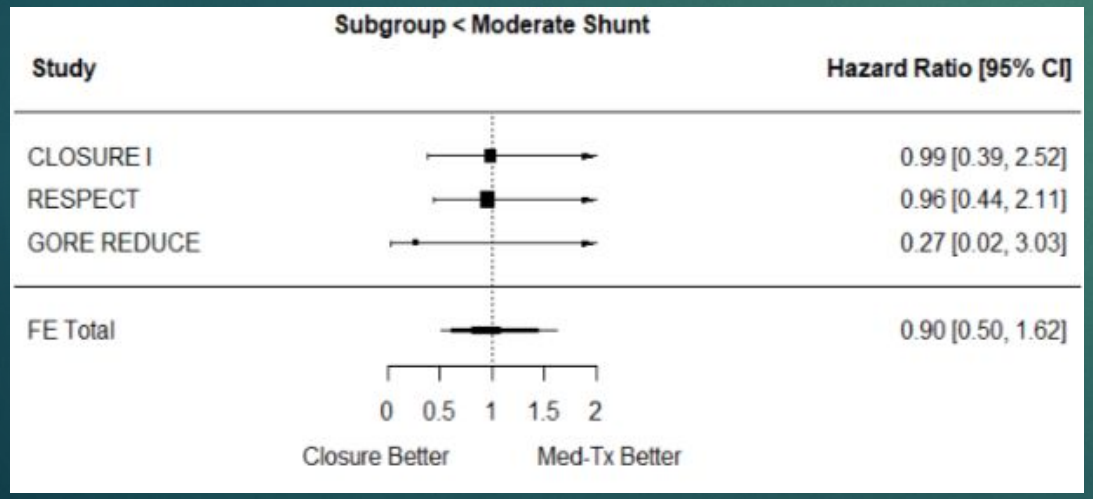


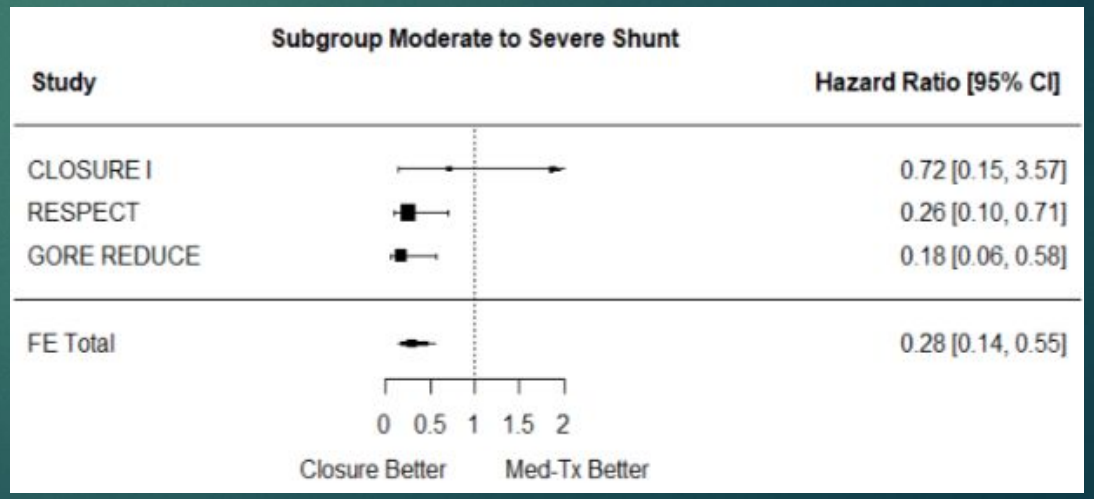
The meta-analysis of all trials found that the number needed to treat with device closure to prevent 1 recurrent stroke was 131 during 1 person-year of follow-up or 13 during 10 person-years of follow-up, which may be clinically important in this generally young population

In tutti i pazienti gli stessi benefici?









Reinthaler M et al. Revival of Transcatheter PFO Closure: A meta-analysis of randomized controlled trials. Am Heart J 2018.

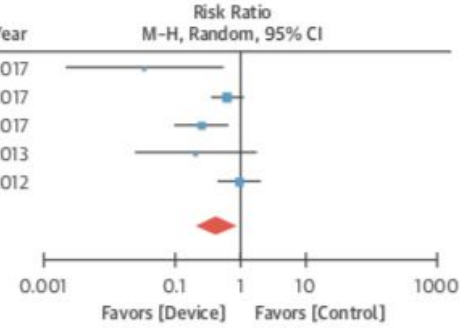
CHIUSURA SENZA RISCHI?

FIGURE 2 Recurrent Stroke and Atrial Fibrillation/Flutter Outcomes in Cryptogenic Stroke Patients Randomized to PFO Closure or Medical Therapy

A Recurrent Stroke

Study or Subgroup	Device Events	Device Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSE (40)	0	238	14	235	6.1%	0.03 [0.00-0.57]	2017
RESPECT (27)	18	499	28	481	32.2%	0.62 [0.35-1.11]	2017
REDUCE (41)	6	441	12	223	24.1%	0.25 [0.10-0.66]	2017
PC (23)	1	204	5	210	9.5%	0.21 [0.02-1.75]	2013
CLOSURE I (20)	12	447	13	462	28.0%	0.95 [0.44-2.07]	2012
Total (95% CI)		1829		1611	100.0%	0.42 [0.20-0.91]	
Total events	37		72				

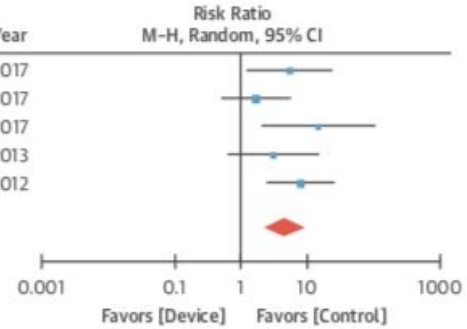
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 9.72$, df = 4 (P = 0.05); $I^2 = 59\%$
Test for overall effect: Z = 2.22 (P = 0.03)



B Atrial Fibrillation/Flutter

Study or Subgroup	Device Events	Device Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSE (40)	11	238	2	235	19.0%	5.43 [1.22-24.24]	2017
RESPECT (27)	7	499	4	481	25.5%	1.69 [0.50-5.73]	2017
REDUCE (41)	29	441	1	223	12.0%	14.66 [2.01-106.95]	2017
PC (23)	6	204	2	210	17.3%	3.09 [0.63-15.12]	2013
CLOSURE I (20)	23	447	3	462	26.2%	7.92 [2.40-26.21]	2012
Total (95% CI)		1829		1611	100.0%	4.55 [2.16-9.60]	
Total events	76		12				

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 5.33$, df = 4 (P = 0.26); $I^2 = 25\%$
Test for overall effect: Z = 3.98 (P < 0.0001)



Summary forest plot for the efficacy outcome of recurrent stroke and safety outcome of atrial fibrillation/flutter. The relative size of the data markers indicates the weight of the sample size from each study. Reprinted with permission from Mojadidi et al. (42). CI = confidence interval; CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE I = Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; M-H = Mantel-Haenszel; PC = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of Patent Foramen Ovale (PFO) With Medical Treatment in Patients With Cryptogenic Embolism; PFO = patent foramen ovale; REDUCE = Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients With PFO; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

Updated meta analysis of closure of patent foramen ovale versus medical therapy after cryptogenic stroke☆

Usama Bin Nasir [a,*], Waqas T. Qureshi [b], Humanatha Jogu [c], Elizabeth Wolfe [a], Abhishek Dutta [c], Chaudhry Nasir Majeed [c], Walter A. Tan [b]

[a] Department of Internal Medicine, University of Connecticut, Hartford, CT, United States of America
[b] Division of Cardiovascular Medicine, Wake Forest University, Winston Salem, NC, United States of America
[c] Department of Internal Medicine, Wake Forest University, Winston Salem, NC, United States of America

Study	PFO Closure Events	PFO Closure Total	Medical Therapy Events	Medical Therapy Total	Weight	Odds Ratio M-H, Random, 95% CI
CLOSE 2017	25	447	3	462	21.0%	9.06 [2.72, 30.24]
CLOSURE 2012	6	204	2	210	16.3%	3.15 [0.63, 15.80]
PC Trial 2013	15	499	7	481	25.0%	2.10 [0.85, 5.19]
REDUCE 2017	29	441	1	223	12.8%	15.63 [2.11, 115.48]
RESPECT 2013	11	238	9	238	25.0%	1.23 [0.50, 3.03]
Total (95% CI)		1829		1614	100.0%	3.45 [1.39, 8.58]
Total events	86		22			

Heterogeneity: $Tau^2 = 0.65$; $Chi^2 = 11.02$, df = 4 (P = 0.03); $I^2 = 64\%$
Test for overall effect: Z = 2.66 (P = 0.008)

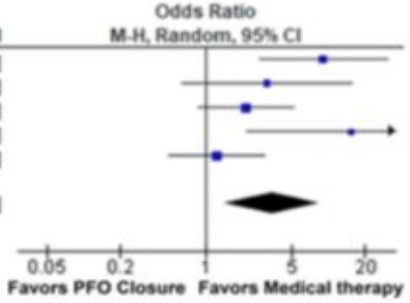


Fig. 7. Forrest plot showing comparison of post procedure atrial fibrillation between patent foramen ovale (PFO) closure and medical therapy groups.

«new onset atrial fibrillation was found to be significantly associated with PFO closure which might be related to irritation of atrium during the procedure. PAF episodes were periprocedural, short lived and self-limiting. On the other hand, there has been no protocolized long-term AF monitoring in all the studies we examined, and such studies are needed to comprehensively quantify subsequent AF burden ».

JACC: Cardiovascular Interventions
ELSEVIER Volume 15, Issue 22, 28 November 2022, Pages 2315-2322

Supraventricular Arrhythmia Following Patent Foramen Ovale Percutaneous Closure

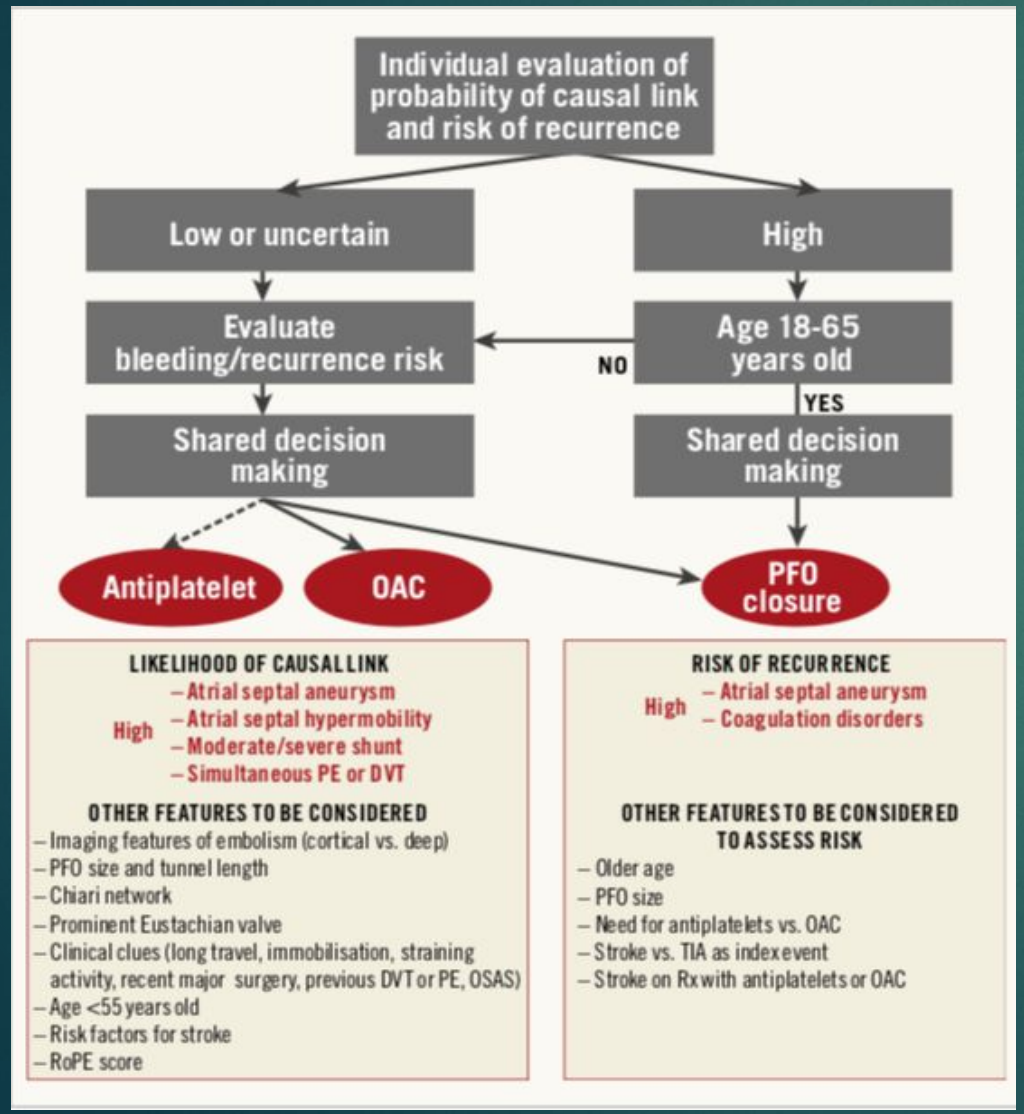
Paul Guedeney MD [a], Mikael Laredo MD [a], Michel Zeitouni MD, PhD [a], Marie Hauguel-Moreau MD [b], Thomas Wallet MD [a], Benjamin Elegamandji MD [a], Sonia Alamowitch MD, PhD [c], Sophie Crozier MD [c], Candice Sabben MD [d], Sandrine Deltour MD, PhD [e], Michaël Obadia MD [d], Nadia Benyounes MD [f], Jean-Philippe Collet MD, PhD [a], Stéphanie Rouanet MS [g], Nadjib Hammoudi MD, PhD [a], Johanne Silvain MD, PhD [a], Gilles Montalescot MD, PhD [a]

«Using loop recorder monitoring for ≥28 days, **supraventricular arrhythmia** was diagnosed in 1 in 5 patients, with a median delay of 14 days, suggesting that this postprocedural event has so far been underestimated.»

…altri rischi…

- Procedural complications had a 2.6% incidence in RCTs.
- Device embolism is a serious event and occurs at a rate of 0.9- 1.3%.
- Tamponade 0,7%.
- The risk of long-term mortality or the need for cardiac surgery is less than one in 1.000.
- The most frequent late complication is device thrombosis, which is seen in 1.0-2.0%.
- Atrial wall erosions are serious events that have been reported anecdotally.

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



EuroIntervention 2019;14:1389-1402 published online ahead of print August 2018

Table 2. PFO variables to be assessed for decision making and interventional treatment.

- PFO morphology: size, location, length of the tunnel
- Spatial relationship and distances between the PFO and the aortic root, vena cava, valves and the free walls of the atrium
- Comprehensive evaluation of the atrial septum, including inspection for atrial septal aneurysms, movement, and other atrial septal defects
- Presence/absence of a Eustachian valve and/or Chiari network
- Thickness of the septum primum and secundum
- Colour Doppler evaluation of the shunt at rest and after a Valsalva manoeuvre

Stroke

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

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

Dawn O. Kleindorfer, MD, FAHA, Chair; Amytis Towfighi, MD, FAHA, Vice Chair; Seemant Chaturvedi, MD, FAHA; Kevin M. Cockroft, MD, MSc, FAHA; Jose Gutierrez, MD, MPH; Debbie Lombardi-Hill, BS, FAHA; Hoonan Kamel, MD; Walter N. Kernan, MD*; Steven J. Kittner, MD, MPH, FAHA; Enrique C. Leira, MD, MS, FAHA; Olive Lennon, PhD; James F. Meschia, MD, FAHA; Thanh N. Nguyen, MD, FAHA; Peter M. Pollak, MD; Pasquale Santangeli, MD, PhD; Anjail Z. Sharrief, MD, MPH, FAHA; Sidney C. Smith Jr, MD, FAHA; Tanya N. Turan, MD, MS, FAHA†; Linda S. Williams, MD, FAHA

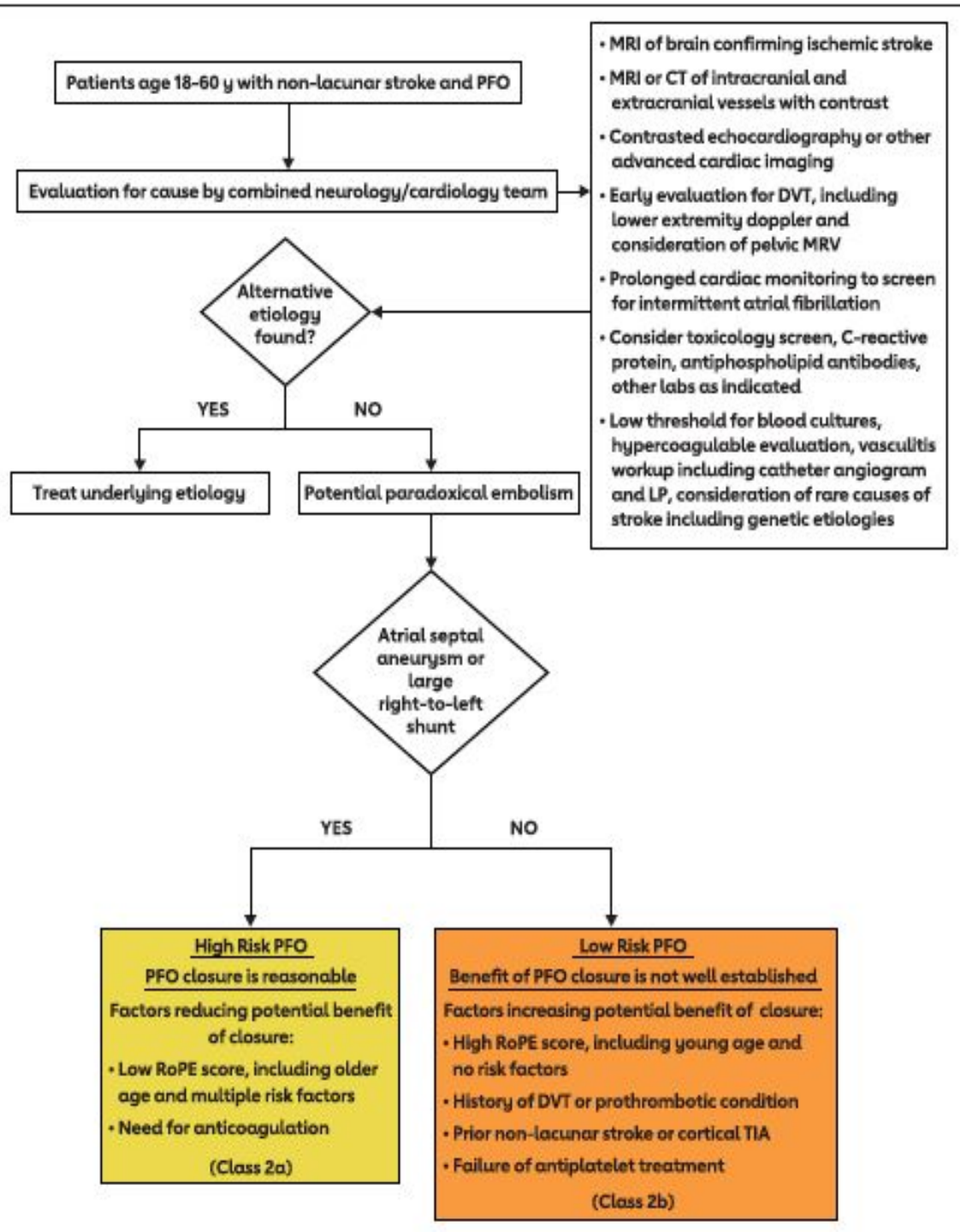
Recommendations for PFO
Referenced studies that support recommendations are summarized in online Data Supplements 38 and 39.

COR	LOE	Recommendations
1	C-EO	1. In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, recommendations for PFO closure versus medical management should be made jointly by the patient, a cardiologist, and a neurologist, taking into account the probability of a causal role for the PFO.

Recommendations for PFO (Continued)

COR	LOE	Recommendations
2a	B-R	2. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features,* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke.[552–557]
2b	C-LD	3. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO without high-risk anatomic features,* the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established.[552–557]
2b	C-LD	4. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown.[554]

*In the evidence, each study defines high-risk anatomic features in a different way.



Il PFO è chiuso…il caso no.

- Quali sottogruppi di pazienti beneficiano molto, poco o per nulla della chiusura del PFO?
- Qual è il ruolo dei nuovi anticoagulanti rispetto alla chiusura del PFO?
- I pazienti non inclusi nei trials (> 60 aa, altre cause possibili di ictus) beneficerebbero della chiusura del PFO?
- Qual è l'impatto clinico della fibrillazione atriale indotta dalla chiusura?
- Quale dovrebbe essere la durata ottimale della terapia antiaggregante dopo chiusura del PFO?
- La chiusura del PFO ha un ruolo nella prevenzione primaria dello stroke?

Priorità ricerca: dove dobbiamo migliorare….

- Individuare fattori di rischio più precisi.
- Identificare nuovi fenotipi e sottogruppi ad alto rischio e avviare nuovi trial randomizzati in queste popolazioni.
- valutare gli outcome della chiusura del FOP rispetto alla terapia con DOAC.
- Disegnare RCT con campioni adeguati che comparino singole terapie mediche (ASA, clopidogrel, warfarin, DOAC…) nei pazienti in cui la chiusura del FOP non è praticabile.
- valutare gli outcome a 5 anni per ognuna di queste terapie.

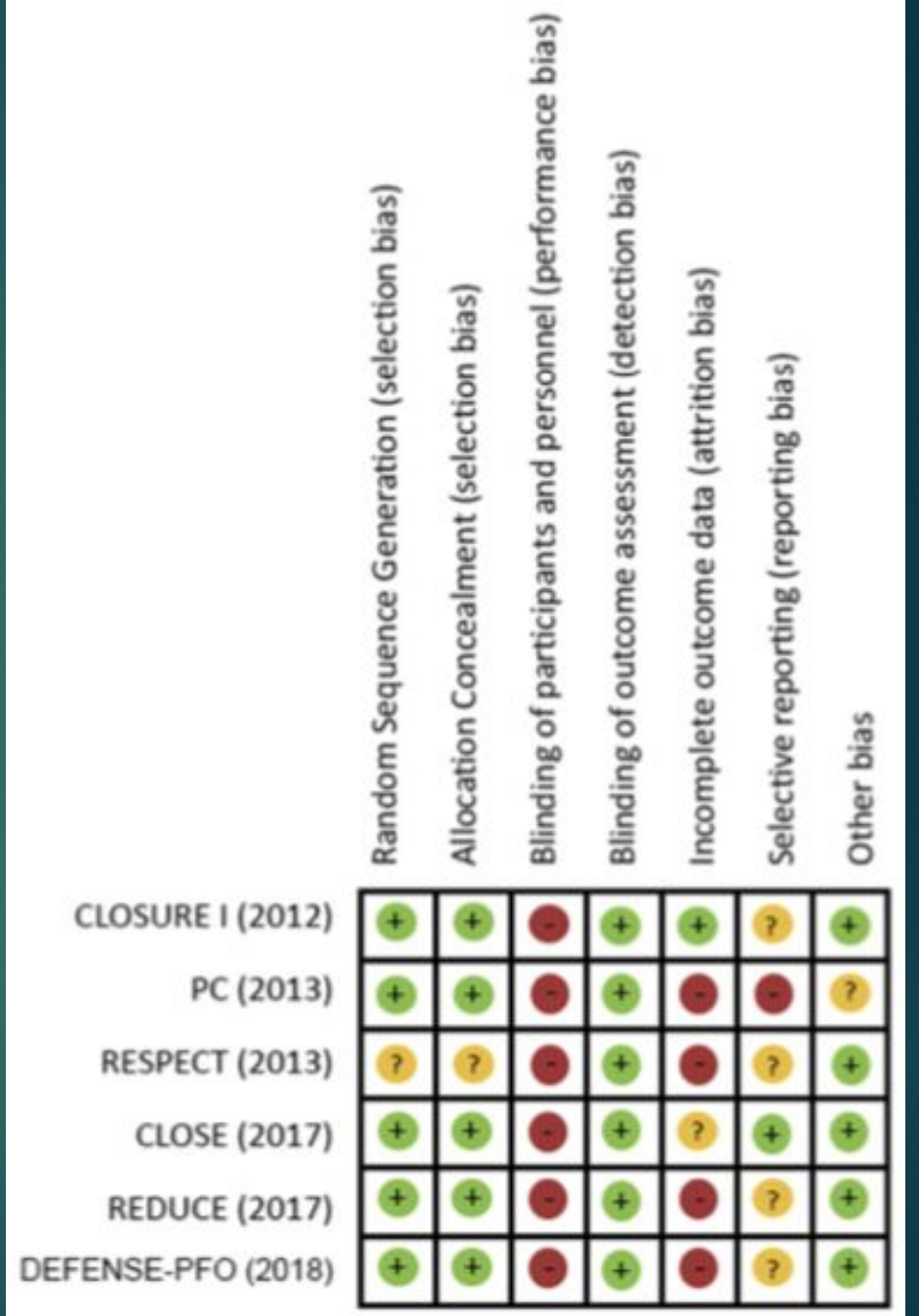
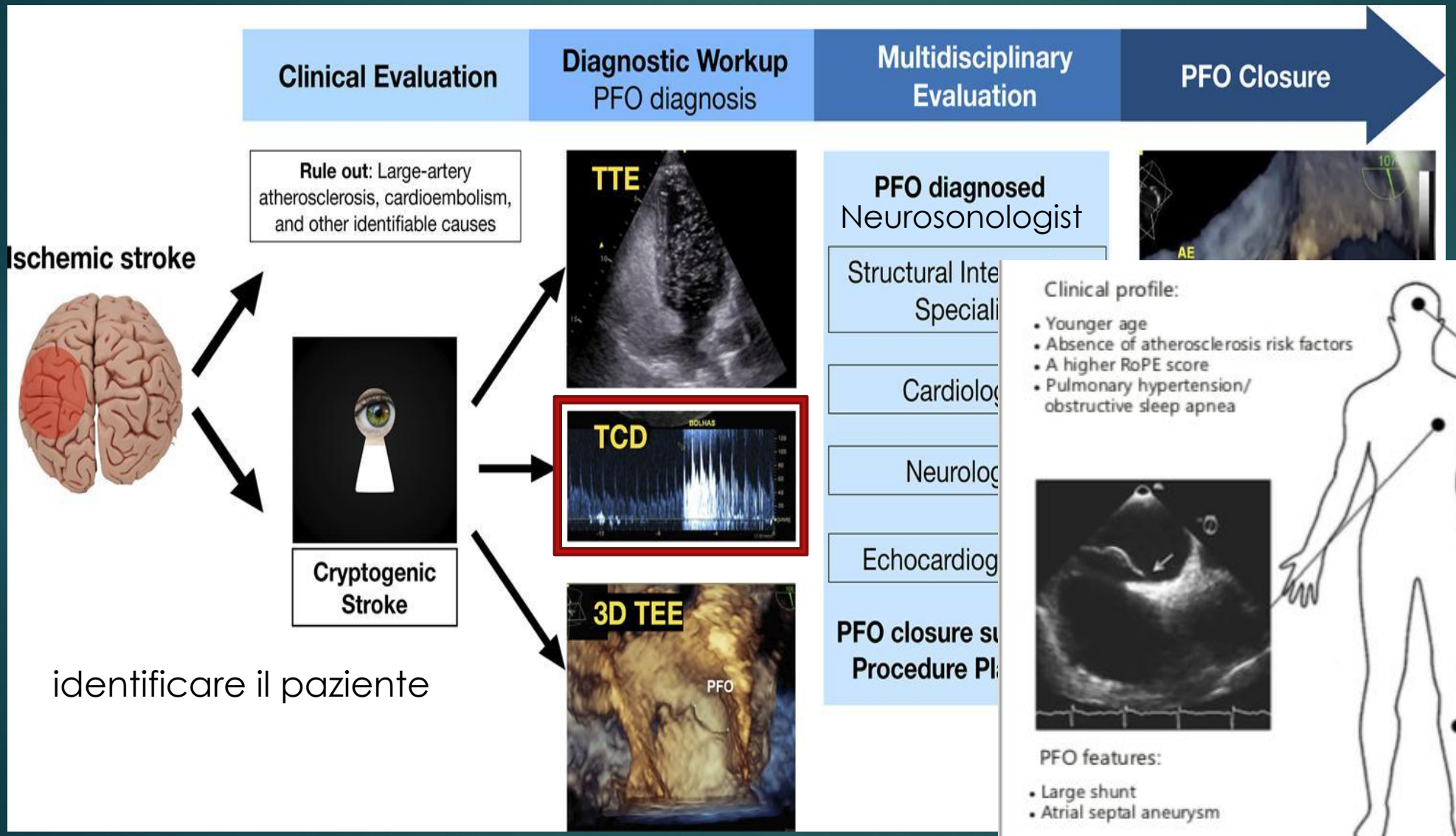


Fig. 2. Newcastle-Ottawa scale assessment of pooled studies.

Tutti i Sì del PFO



identificare il paziente

Drug therapy and follow up after percutaneous closure

It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure

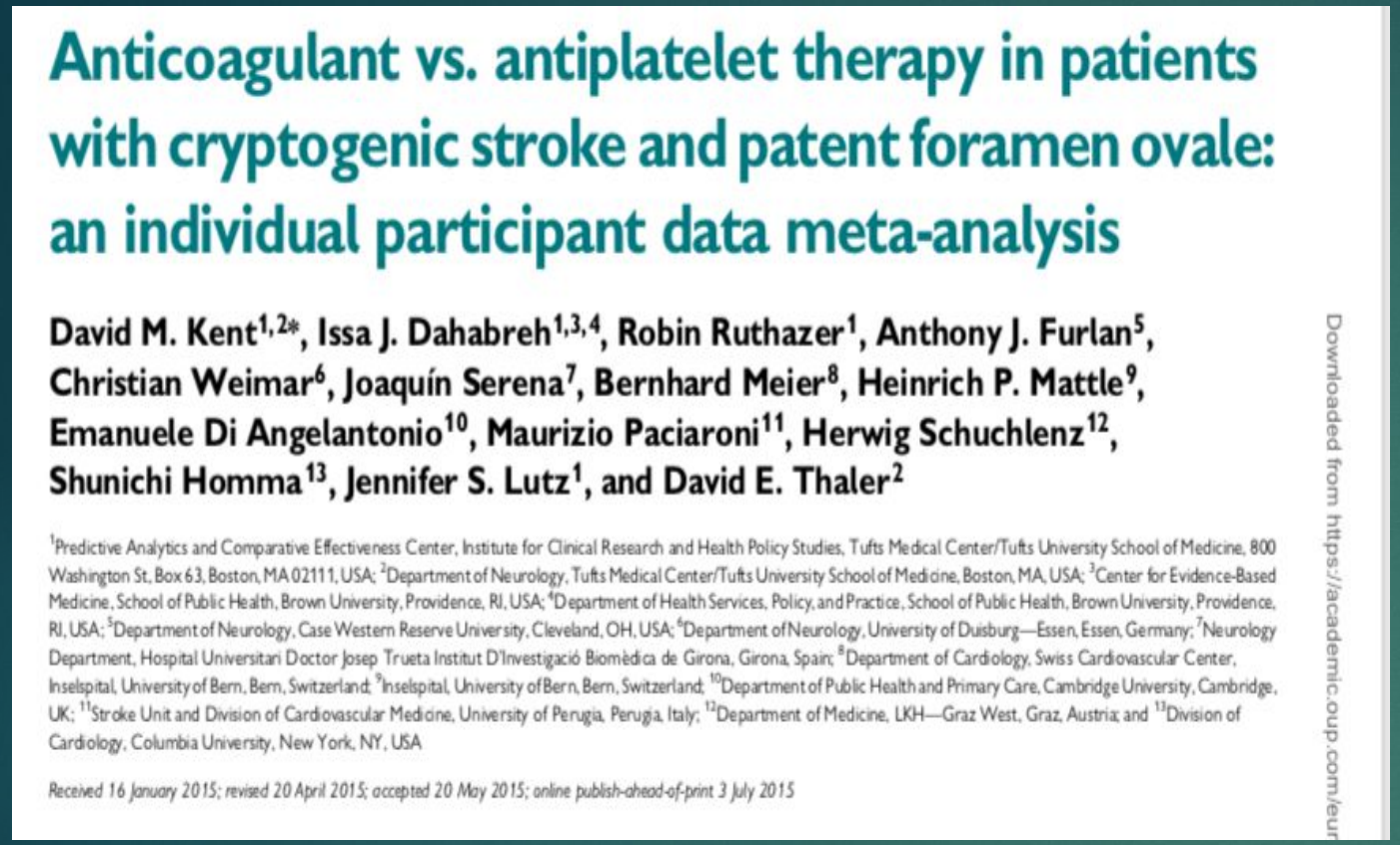
We suggest a single antiplatelet therapy be continued for at least 5 years

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

The choice of the type of antiplatelet drug in the follow-up is currently empiric

The value of residual shunt after percutaneous closure cannot be deduced from available studies

Anticoagulanti



Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis

David M. Kent[1,2*], Issa J. Dahabreh[1,3,4], Robin Ruthazer[1], Anthony J. Furlan[5], Christian Weimar[6], Joaquín Serena[7], Bernhard Meier[8], Heinrich P. Mattle[9], Emanuele Di Angelantonio[10], Maurizio Paciaroni[11], Herwig Schuchlenz[12], Shunichi Homma[13], Jennifer S. Lutz[1], and David E. Thaler[2]

[1]Predictive Analytics and Comparative Effectiveness Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Box 63, Boston, MA 02111, USA; [2]Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, Boston, MA, USA; [3]Center for Evidence-Based Medicine, School of Public Health, Brown University, Providence, RI, USA; [4]Department of Health Services, Policy, and Practice, School of Public Health, Brown University, Providence, RI, USA; [5]Department of Neurology, Case Western Reserve University, Cleveland, OH, USA; [6]Department of Neurology, University of Duisburg—Essen, Essen, Germany; [7]Neurology Department, Hospital Universitari Doctor Josep Trueta Institut D'Investigació Biomèdica de Girona, Girona, Spain; [8]Department of Cardiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Bern, Switzerland; [9]Inselspital, University of Bern, Bern, Switzerland; [10]Department of Public Health and Primary Care, Cambridge University, Cambridge, UK; [11]Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Perugia, Italy; [12]Department of Medicine, LKH—Graz West, Graz, Austria; and [13]Division of Cardiology, Columbia University, New York, NY, USA

Received 16 January 2015; revised 20 April 2015; accepted 20 May 2015; online publish-ahead-of-print 3 July 2015

- in summary, currently available data do not provide definitive evidence on the comparative benefits of OAC vs. APT in patients with CS and PFO. Low outcome rates and the non-comparability of treatment groups resulted in imprecise estimates of the comparative effectiveness of antithrombotic treatments in this patient population. These results support the need for additional comparative studies, including randomized trials.

Economical Gain

- • PFO closure incurs procedural cost. However, cost- effectiveness studies showed that PFO is associated with economic and QUALY gain after 15 years, provided that the procedure was performed in high-risk patients. Performing the procedure in unselected patients translates into a sharp decrease in cost-effectiveness.
- • Moreover, procedural costs and procedure times may be decreased with the use of sedation instead of general anaesthesia or of intracardiac echocardiography versus transoesophageal echocardiography, thereby eliminating the need for an anaesthesiologist

RECURRENT ISCHEMIC STROKE

- As with any stroke, patients who have a recurrent ischemic stroke after PFO closure should have another comprehensive evaluation to determine the stroke mechanism, including assessment of the PFO closure device for defects, device thrombosis, and residual shunt. Recurrent ischemic stroke may occur in patients with a PFO, regardless of whether the PFO was closed, due to mechanisms unrelated to paradoxical embolism, such as cardiogenic embolism, large artery atherosclerosis, small artery disease, and other determined stroke etiologies. In a minority of patients with PFO closure, a residual shunt persists, allowing continued potential risk for paradoxical embolism [46-50]. Alternatively, thrombus may spontaneously form on or adjacent to the PFO device or in the left atrium due to stagnant blood flow [51], particularly given the possible increased risk of atrial arrhythmias (mainly atrial fibrillation) in patients with PFO and/or atrial septal aneurysm [52]. This risk may be augmented after PFO closure [24,25], especially in the first few weeks after device implantation.
- Recurrent stroke should be treated according to the underlying mechanism, if it can be identified:
- ●If the recurrence occurs in a patient who has not had their PFO closed, and the PFO still appears to be the most likely cause of cryptogenic stroke, we suggest PFO closure.
- ●For patients on antiplatelet therapy who have a recurrent cryptogenic stroke (regardless of PFO closure status) and no atrial fibrillation on reevaluation with long-term cardiac monitoring, options include continuing the same antiplatelet agent or switching to another antiplatelet regimen. For patients with recurrent embolic stroke of undetermined source, switching to empiric anticoagulant therapy is also a reasonable option. These issues are discussed in detail elsewhere. (See "Cryptogenic stroke", section on 'Embolic stroke of undetermined source'.)
- ●In rare cases, recurrent thrombus formation on the closure device despite anticoagulant therapy may require device removal [53]

SURGICAL CLOSURE OF PFO

- For rare patients aged ≤60 years with a cryptogenic embolic-appearing ischemic stroke who have a PFO and no other evident source of stroke despite a comprehensive evaluation who have a concurrent indication for cardiac surgery (eg, indication for valve surgery, or the rare PFO that is not amenable to device closure for technical reasons), surgical closure of PFO via standard or minimally invasive (including robotic) techniques for secondary stroke prevention after cryptogenic stroke is a reasonable alternative to percutaneous PFO closure.
- The reported efficacy of surgical closure of a PFO in patients with prior cerebrovascular ischemic events has been variable [14,54-56], and randomized trials comparing surgical PFO closure with percutaneous closure or with medical therapy have not been performed.
- Rates of recurrent cerebrovascular events following surgical closure have ranged from 7 to 14 percent at one to two years [14,54]. Similar to findings from the randomized controlled trials for device closure of PFO, these events are likely due to mechanisms unrelated to paradoxical embolization, as illustrated by a report of 91 patients (mean age 44 years) with one or more cerebrovascular ischemic events who underwent surgical PFO closure [54]. The overall freedom from an ischemic episode at one and four years was 93 and 83 percent, respectively. The recurrent events were transient ischemic attacks (there were no cerebral infarctions), one of which was attributed to giant cell arteritis. Transesophageal echocardiography showed that the closures were intact in all patients, implying that paradoxical embolization was not the cause of the ischemic events.
- In patients with high cardiovascular risk and an incidentally discovered PFO, surgical closure may actually increase the risk of postoperative stroke. This conclusion comes from a retrospective study of over 13,000 adults without a prior diagnosis of PFO or atrial septal defect who had cardiothoracic surgery [57]. A PFO was detected intraoperatively in 2277 patients, and closure was performed at the discretion of the surgeon in 28 percent. Using propensity-matched analysis, the risk of perioperative stroke was significantly higher in patients who had surgical PFO closure than in those who did not (2.8 versus 1.2 percent; odds ratio 2.47, 95% CI 1.02-6.0). There was no difference between the two groups in long-term survival. The uncontrolled retrospective design and small number of events limit the strength of this study.
-