PFO
THE KNOWN UNKNOWNS

Cardio_Cast

Presented by:

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PODCAST OVERVIEW

- PFO diagnostic consideration
- PFO closure device development
- Risk scores
- PFO clinical trials
- Recurrent stroke in PFO
- PFO Management
- PFO and Migraine

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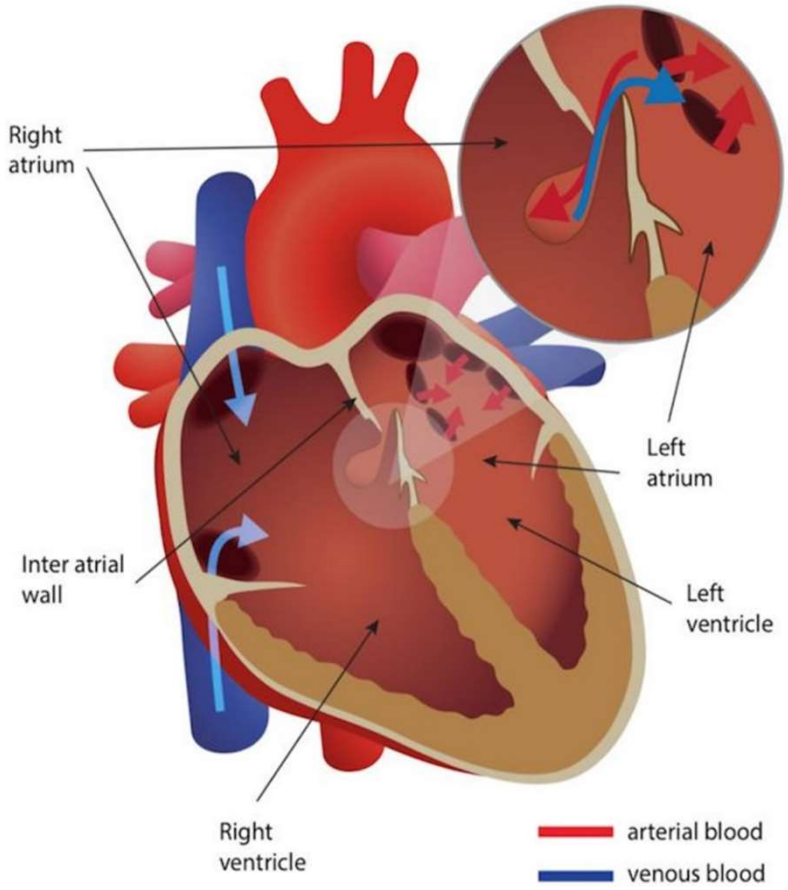

Figure 1 Patent foramen ovale anatomy.

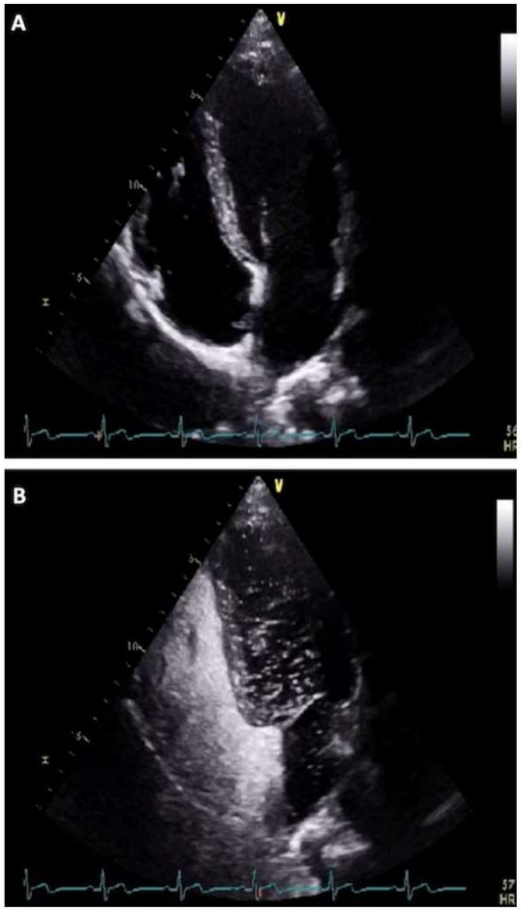

Figure 2 Patent foramen ovale (PFO) detected on transthoracic echocardiography: (A) transthoracic echocardiography detecting large PFO without saline contrast use; (B) transthoracic echocardiography with Valsalva induced rise in the right atrial pressure and increase saline contrast passage through the PFO. Note that the Valsalva technique causes the cardiac chambers to become smaller (confirming that the Valsalva has been effective) and then concentrates the bubbles in the right atrium.

10.1136/practneurol-2019-002450

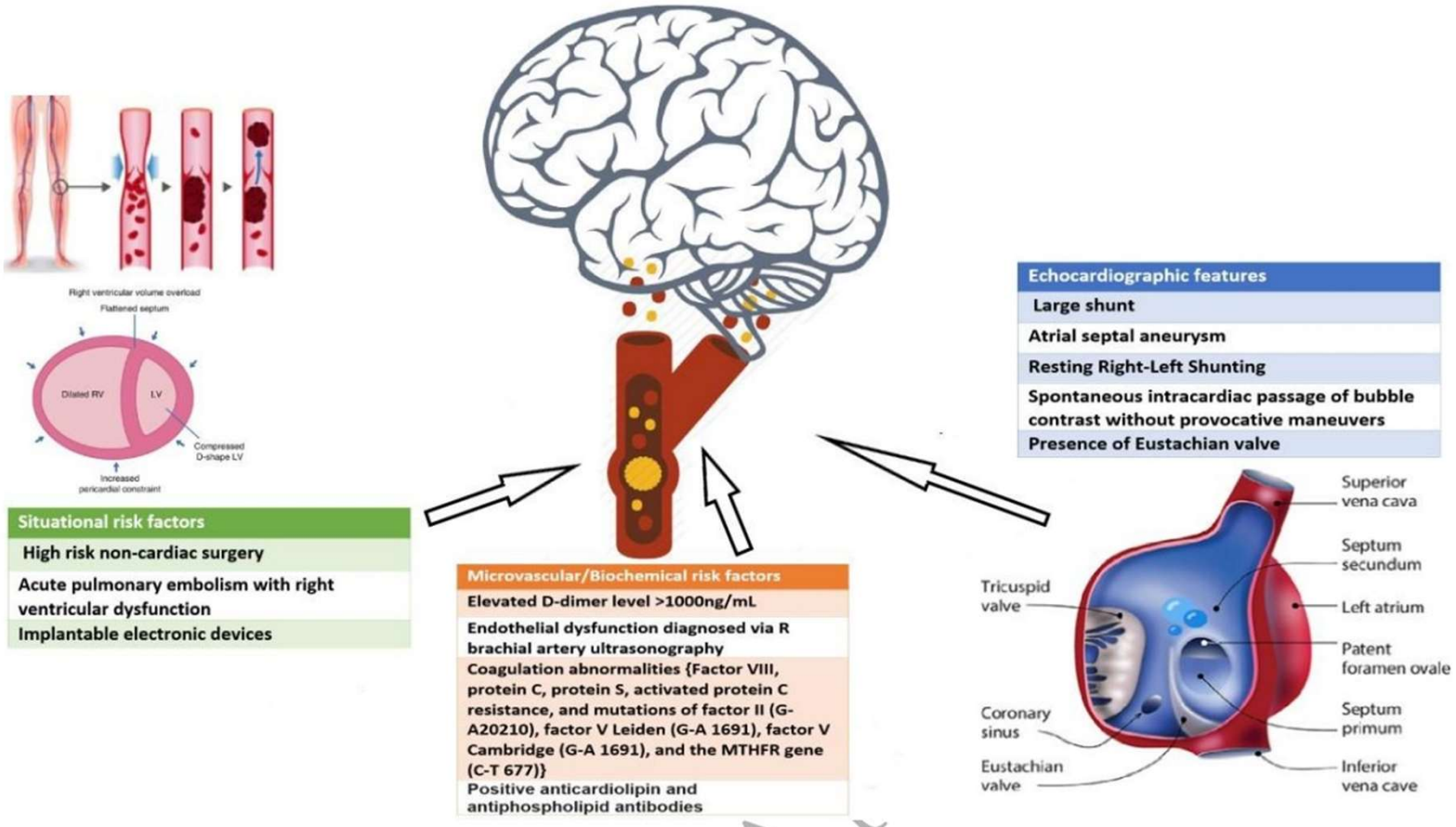

Figure 1-Multiple Risk Factors to be assessed in High-Risk patients

https://doi.org/10.1053/j.jvca.2019.04.017

Table 1
Imaging modalities for the diagnosis of patent foramen ovale and their associated characteristics

Modality	Sensitivity, %	Specificity, %	Advantages	Disadvantages
TEE[a]	90	>95	PFO vs ASD or pulmonary shunt, direct visualization	Patient discomfort, sedation
TCD[b]	97	93	Highest sensitivity, postprocedural residual shunt quantification	Unable to differentiate cardiac vs intrapulmonary shunt
TTE[b]	50–60 90 (with harmonic imaging)	>90	Excellent specificity, widely available	Poor sensitivity without harmonic imaging

Abbreviation: ASD, atrial septal defect.
[a] Compared with right-heart catheterization, surgery, or autopsy.
[b] Compared with TEE.

https://doi.org/10.1016/j.iccl.2019.05.002

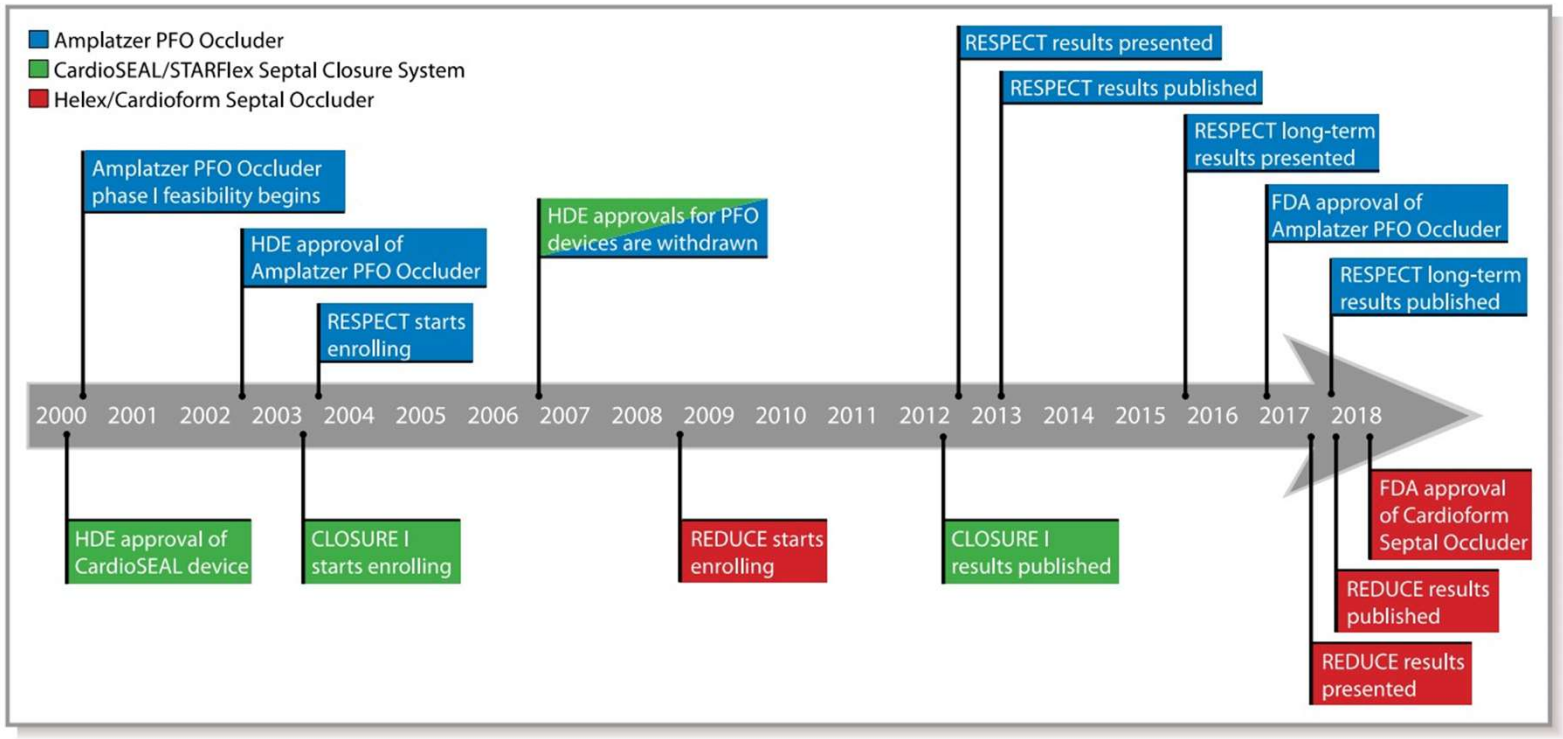

Figure 4. Timeline showing important dates of patent foramen ovale (PFO) closure trials and US Food and Drug Administration (FDA) milestones in the United States. HDE indicates Humanitarian Device Exemption.

DOI: 10.1161/JAHA.117.007146

DEVELOPMENT OF A SCORING SYSTEM

Table 4 Large-size high-risk PFO score calculator

Variables	Point
Long-tunnel PFO ≥10 mm	1
Hypermobile interatrial septum	1
Eustachian valve or Chiari's network	1
Large RL shunt during Valsalva maneuver	1
Low-angle PFO ≤10°	1

Figure 3. The presence of hypermobile interatrial septum and the large RL shunt during Valsalva maneuver were strongly related to CS.

Background: Transcatheter closure of patent foramen ovale (PFO) has become an effective therapeutic strategy for cryptogenic stroke (CS). The identification of high-risk PFO is essential, but the data are limited. This study aimed to clarify the factors related to CS and to develop a score for high-risk PFO.

Methods: We retrospectively analyzed 57 patients with prior CS and 50 without CS who were scheduled for transcatheter closure. PFO characteristics were evaluated by transesophageal echocardiography. Based on factors related to CS, we estimated the risk score.

Results: Patients with CS had a greater frequency of large-size PFO (≥2 mm in height), long-tunnel PFO (≥10 mm in length), atrial septal aneurysm, hypermobile interatrial septum, prominent Eustachian valve or Chiari's network, the large right-to-left shunt at rest and during Valsalva maneuver, and low-angle PFO (≤10° of PFO angle from inferior vena cava), compared with patients without CS. Multivariate analysis showed that long-tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large right-to-left shunt during Valsalva maneuver, and low-angle PFO were independently related to CS. When the score was estimated based on 1 point for each factor, the proportion of CS was markedly elevated with a score of ≥2 points. The probability of CS was markedly different between scores of ≤1 or ≥2 points.

Conclusions: PFO risk can be assessed with a score based on high-risk features. The presence of two or more high-risk PFO features is associated with CS. (J Am Soc Echocardiogr 2019;32:811-6.)

https://doi.org/10.1016/j.echo.2019.03.021

Table 2 Risk of paradoxical embolism (RoPE) score calculator

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Non-smoker	1
Cortical infarct on imaging	1
Age, years	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0
Total score (sum of individual points)	
Maximum score (a patient <30 years with no hypertension, diabetes, stroke or TIA, non-smoker, and cortical infarct)	RoPE score 10
Minimum score (a patient ≥70 years with hypertension, diabetes, stroke or TIA, current smoker, and no cortical infarct)	RoPE score 0

Adapted from Kent *et al*.[35]
TIA, transient ischaemic attack.

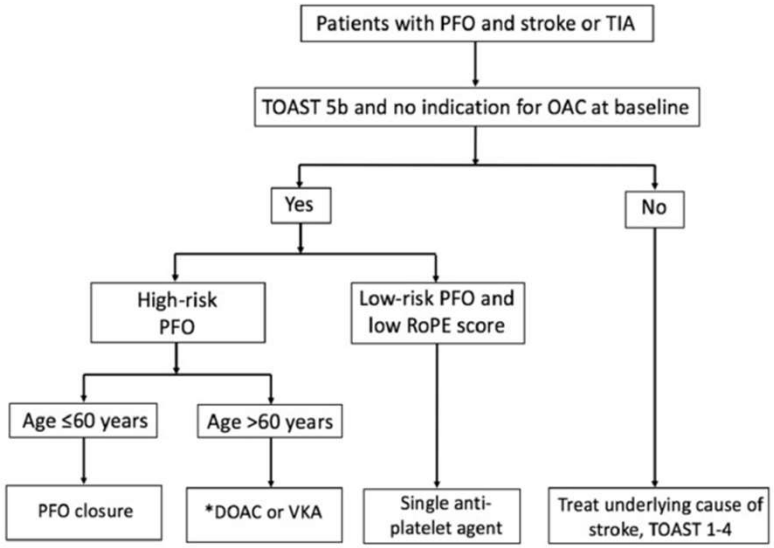

Figure 5 PFO closure in patients who had a stroke.
*Individual treatment decision needed based on bleeding risk.
DOAC, direct oral anticoagulant; PFO, patent foramen ovale; VKA, vitamin K antagonist; TOAST, trial of ORG 10172 in acute stroke treatment; TOAST 1–4, (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined aetiology; TOAST 5, stroke of undetermined aetiology (a) two or more causes identified, (b) negative evaluation, (c) incomplete evaluation; OAC, oral anticoagulant; RoPE, risk of paradoxical embolism; TIA, transient ischaemic attack. Adapted from[23 40 41].

10.1136/practneurol-2019-002450

Table 2
Early randomized controlled trials of patent foramen ovale closure for secondary stroke prevention

Study	Number of Patients	Inclusion Criteria	Device	Follow-up, y	Antithrombotic Therapy	Primary Endpoint	Result
CLOSURE I	909	Patients 16–60 y old & cryptogenic stroke or TIA & PFO	STARFlex septal closure system	2	Device arm: Aspirin & warfarin (1 mo) followed by aspirin (2 y) Medical treatment arm: Aspirin or warfarin or aspirin & warfarin	Early all-cause death, late death due to neurologic cause, stroke, TIA	Percutaneous PFO closure did not significantly reduce recurrent stroke or TIA compared with medical treatment alone
PC	414	Patients <60 y old with cryptogenic stroke, TIA, or systemic embolism & PFO	Amplatzer PFO Occluder	4	Device arm: Aspirin (5–6 mo) & ticlopidine or clopidogrel (1–6 mo) Medical treatment arm: Antiplatelet therapy or anticoagulation therapy	Death, nonfatal stroke, TIA, or peripheral embolism	Percutaneous PFO closure did not significantly reduce death or recurrent embolism compared with medical treatment alone
RESPECT	980	Patients 18–60 y old & cryptogenic stroke & PFO	Amplatzer PFO Occluder	5.9 (median)	Device arm: Aspirin plus clopidogrel (1 mo), followed by aspirin (5 mo) Medical treatment arm: Aspirin or warfarin or clopidogrel or aspirin and extended-release dipyridamole	Recurrent fatal and nonfatal stroke and early death	Percutaneous PFO closure significantly reduced recurrent stroke rates compared with medical treatment alone

https://doi.org/10.1016/j.iccl.2019.05.002

Table 3
Recent randomized controlled trials of patent foramen ovale closure for secondary stroke prevention

Study	Number of Patients	Inclusion Criteria	Device	Follow-up, y	Antithrombotic Therapy	Primary Endpoint	Result
CLOSE	663	Patients 16–60 y old & cryptogenic stroke & PFO associated with an atrial septal aneurysm or large interatrial shunt	Amplatzer, STARFlex, CardioSEAL, Intrasept, PFO-Star, HELEX, Premere, Occlutech, Cardioform	5.3 (mean)	Device arm: Aspirin & clopidogrel (3 mo), followed by single antiplatelet therapy Medical treatment arm: Aspirin or clopidogrel or aspirin combined with extended-release dipyridamole or warfarin or NOAC	Recurrent stroke	Percutaneous PFO closure significantly reduces recurrent strokes compared with medical treatment alone
Gore REDUCE	664	Patients 18–59 y old & cryptogenic stroke & PFO	Helex septal occluder, Cardioform septal occluder	3.2 (median)	Device arm: Clopidogrel (first 3 d) followed by the chosen antiplatelet therapy for the medical treatment arm Medical treatment arm: Aspirin or aspirin & dipyridamole or clopidogrel	Freedom from clinical evidence of ischemic stroke and incidence of new brain infarction (clinical ischemic stroke and silent brain infarction detected on MRI)	Percutaneous PFO closure significantly reduces recurrent strokes and new brain infarcts compared with medical treatment alone
DEFENSE-PFO	120	Patients with ischemic stroke and no identifiable cause other than a high-risk PFO	Amplatzer PFO Occluder	2 (median)	Device arm: DAPT (6 mo), followed by single antiplatelet, DAPT, or anticoagulation Medical treatment arm: Aspirin, aspirin & clopidogrel, aspirin & cilostazol or warfarin	Stroke, vascular death, or TIMI-defined major bleeding	Percutaneous PFO closure significantly reduces recurrent strokes compared with medical treatment alone, in patients with high-risk PFO

Abbreviations: DAPT, dual antiplatelet therapy; NOAC, non-vitamin K oral anticoagulant; TIMI, thrombolysis in myocardial infarction.

https://doi.org/10.1016/j.iccl.2019.05.002

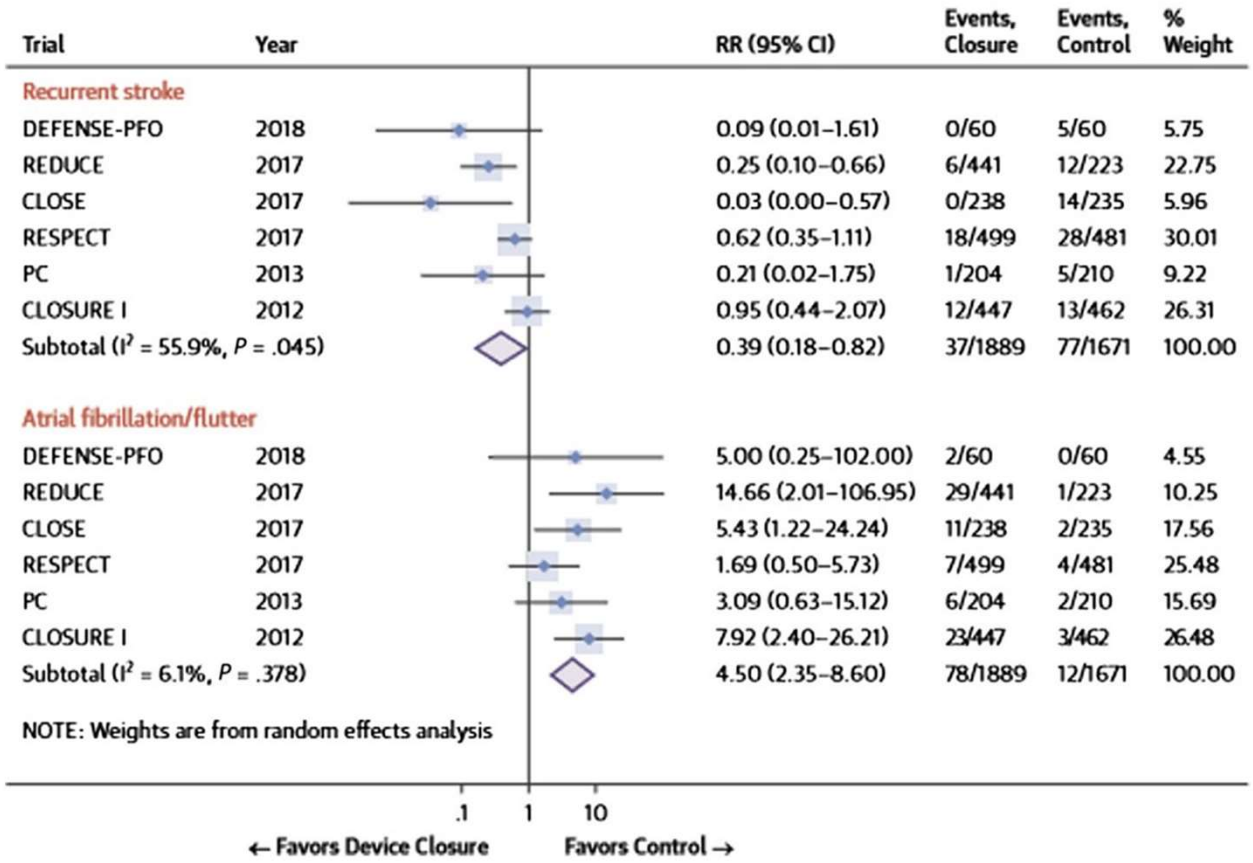

Fig. 1. Meta-analysis of the 6 randomized trials of PFO closure for stroke. Summary plot for primary efficacy (recurrent stroke) and primary safety (atrial fibrillation/flutter). Relative size of data markers indicates weight of sample size. RR, risk ratio. (*From* Mojadidi et al. Cryptogenic Stroke and Patent Foramen Ovale: Ready for Prime Time? J Am Coll Cardiol, 2018;72(10):1183–5. Copyright © year 2018, with permission.)

https://doi.org/10.1016/j.iccl.2019.05.002

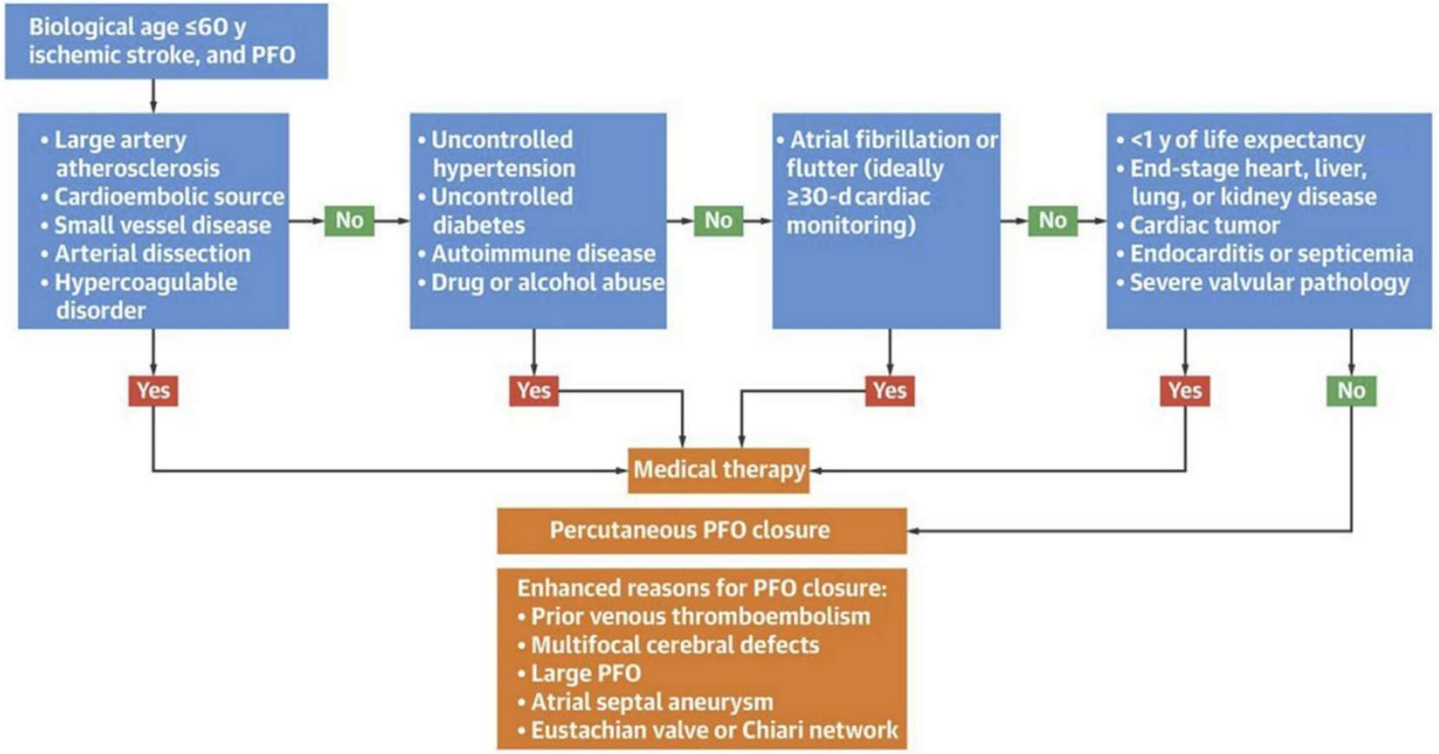

Fig. 2. Evidence-based algorithm for PFO closure in ischemic stroke patients for highest clinical yield, based on the randomized trials. (*From* Mojadidi et al. Cryptogenic Stroke and Patent Foramen Ovale: J Am Coll Cardiol; 2018;71(9):1035–43. Copyright © year 2018, with permission.)

https://doi.org/10.1016/j.iccl.2019.05.002

Table 5. Selected Adverse Events in the RESPECT Trial

Adverse Event	Device		Medical Therapy		*P* Value
	No. of Events (n=499)	%	No. of Events (n=481)	%	
Atrial fibrillation	6	1.2	4	0.8	0.753
Atrial flutter	1	0.2	0	0	1
Cardiac perforation	1	0.2	0	0	1
Cardiac arrest	1	0.2	3	0.6	0.365
Cardiac thrombus	2	0.4	0	0	0.5
Pericardial tamponade	2	0.4	0	0	1
Pulmonary embolism	12	2.4	3	0.6	0.034
Gastrointestinal bleeding	6	1.2	4	0.8	0.753
Hematoma	1	0.2	0	0	1
Transesophageal echocardiogram related event	1	0.2	0	0	1
Residual shunt requiring closure	2	0.4	0	0	0.5
Deep vein thrombosis	5	1.0	1	0.2	0.218
Myocardial infarction	6	1.2	1	0.2	0.124

Reprinted from Saver et al[25] with permission. Copyright ©2017, Massachusetts Medical Society. RESPECT indicates Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

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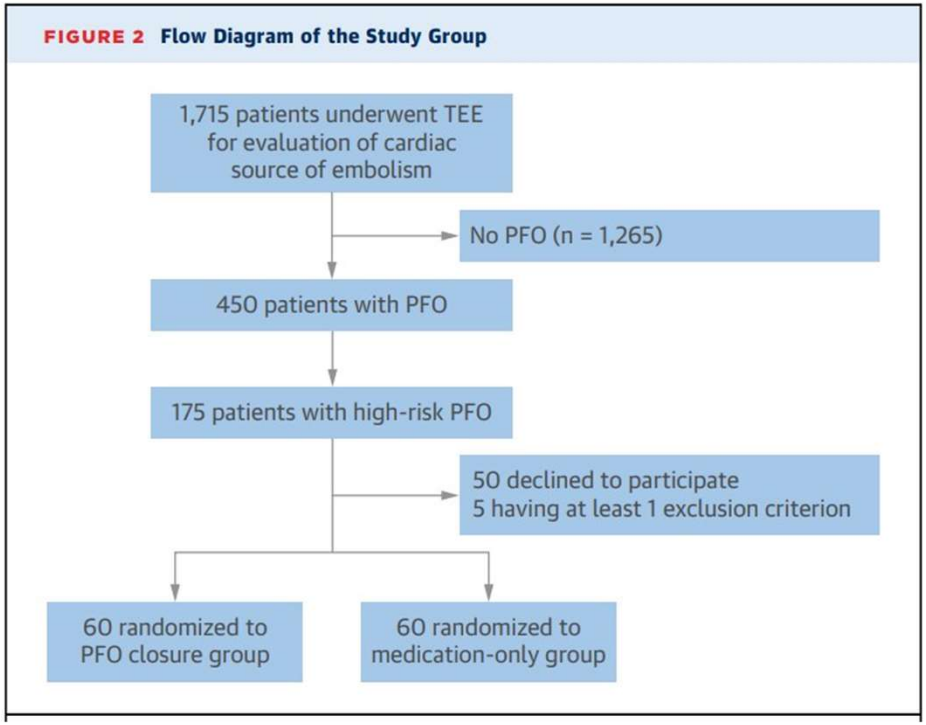
CRYPTOGENIC STROKE AND HIGH-RISK PATENT FORAMEN OVALE THE DEFENSE-PFO TRIAL



JACC VOL. 71, NO. 20, 2018 Device Closure for High-Risk Patent Foramen Ovale MAY 22, 2018:2335 – 4 2

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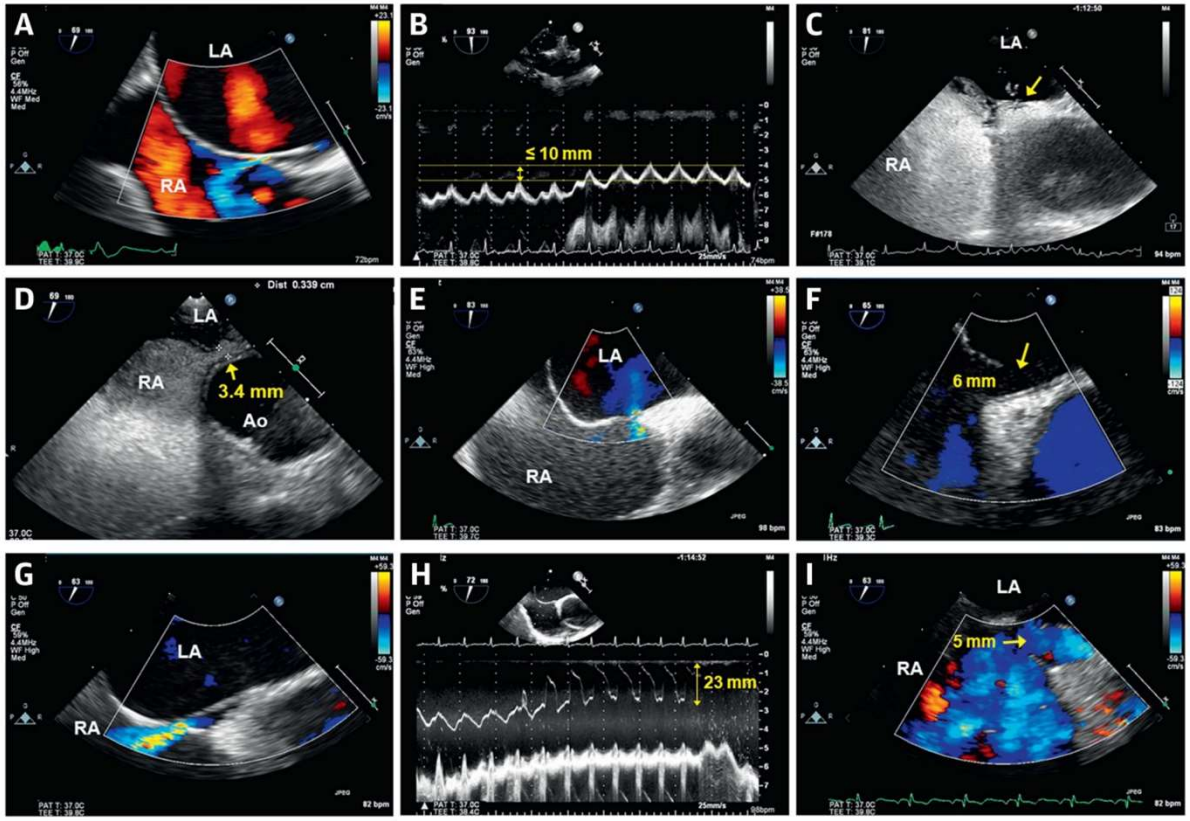
FIGURE 1 Representative TEE Images Showing Low-Risk and High-Risk PFO



Low-risk patent foramen ovale (PFO) is characterized by **(A)** the absence of aneurysmal changes of the interatrial septum **(B)** with limited motion and **(C)** separation of the septum primum and the secundum, resulting in a small PFO size and shunt during the Valsalva maneuver **(arrow)**. High-risk PFO is characterized by **(D)** PFO size of >3 mm **(arrow)** or **(E)** the presence of atrial septal aneurysm with **(F)** hypermobility of the septum during the Valsalva maneuver resulting in a large PFO size **(arrow)**. **(G)** Some patients without a characteristic atrial septal aneurysm may show exaggerated motion of the atrial septum during the Valsalva maneuver, resulting in **(H)** septal excursion >10 mm and **(I)** a large PFO size **(arrow)**. Ao = aorta; LA = left atrium; RA = right atrium; TEE = transesophageal echocardiography.

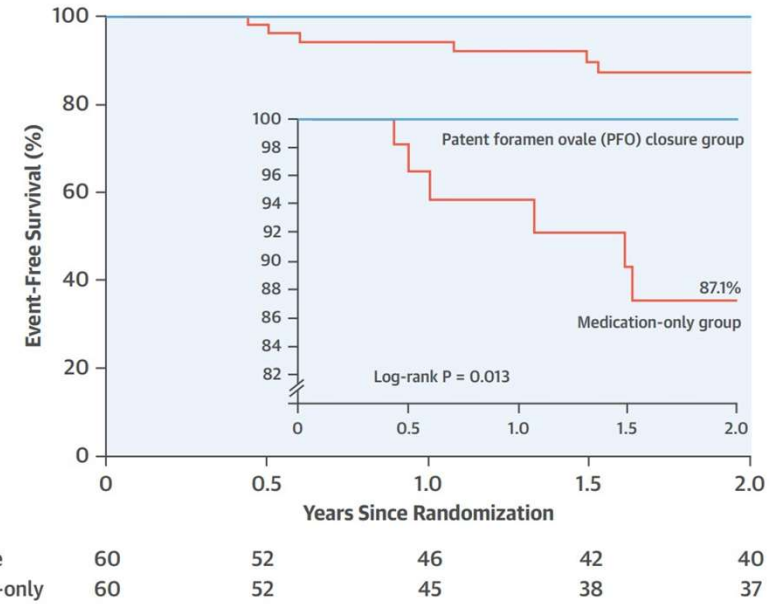
TABLE 3 Clinical Outcomes

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.

CENTRAL ILLUSTRATION Device Closure for High-Risk PFO: Kaplan-Meier Cumulative Estimates



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

Lee, P.H. et al. J Am Coll Cardiol. 2018;71(20):2335–42.

Kaplan-Meier cumulative estimates of the primary endpoint in the patent foramen ovale (PFO) closure group versus the medication-only group.

ATRIAL SEPTAL ANEURYSM, SHUNT SIZE, AND RECURRENT STROKE RISK IN PATIENTS WITH PATENT FORAMEN OVALE

JACC VOL. 75, NO. 18, 2020, Turc et al. MAY 12, 2020:2312 – 2 0 Risk of Recurrent PFO-Associated Stroke

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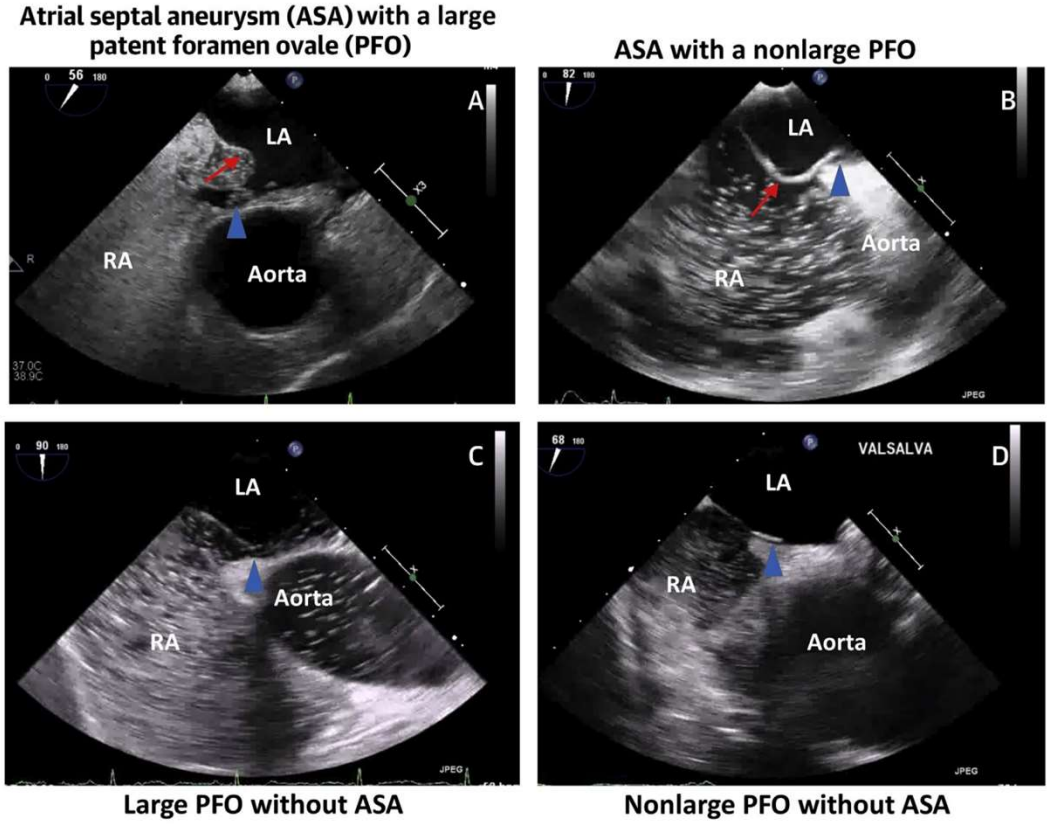
CENTRAL ILLUSTRATION **Representative Transesophageal Echocardiographic Images of 4 Different Anatomical Features of Patent Foramen Ovale in Terms of Hypermobility of the Atrial Septum or Atrial Septal Aneurysm and Patent Foramen Ovale Size**



Turc, G. et al. J Am Coll Cardiol. 2020;75(18):2312-20.

Representative transesophageal echocardiographic images of 4 different anatomical features of patent foramen ovale (PFO) in terms of hypermobility of the atrial septum or atrial septal aneurysm (ASA) and PFO size. Patients with ASA were characterized by hypermobility of the atrial septum (**red arrows in A and B** [Supplemental Videos 1A, 1B, 2A, and 2B]), whereas patients without ASA showed limited motion of the septum (**C and D** [Supplemental Videos 3A, 3B, 4A, and 4B]). Maximum separation of PFO with Valsalva maneuver (PFO size) was measured with injection of hand-agitated saline **(blue arrowheads in A to D)**. LA = left atrium; RA = right atrium.

JACC VOL. 75, NO. 18, 2020, Turc et al. MAY 12, 2020:2312 – 2 0 Risk of Recurrent PFO-Associated Stroke

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TABLE 2 Incidence of Recurrent Ischemic Stroke According to PFO Anatomical Features

PFO Anatomy	Events	Patients	Patient-Years	Incidence Rate of Recurrent Ischemic Stroke per 100 Person-Years (95%CI)
ASA with large PFO	18	178	738	2.4 (1.6-3.8)
ASA with nonlarge PFO	7	71	260	2.7 (1.3-5.5)
Large PFO without ASA	11	397	1,768	0.6 (0.4-1.1)
Nonlarge PFO without ASA	11	252	863	1.3 (0.7-2.3)

Abbreviations as in Table 1.

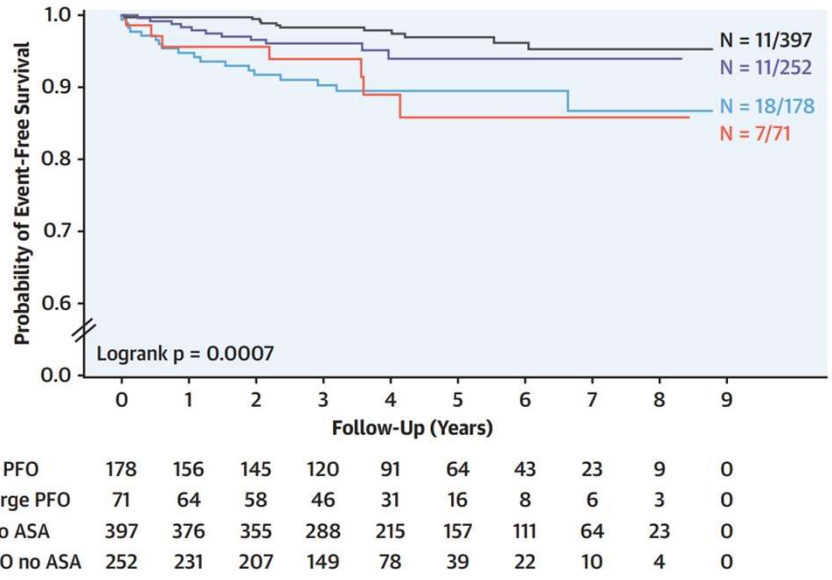
TABLE 3 Association Between ASA and Time to Recurrent Ischemic Stroke, Adjusted for Shunt Size and Other Potential Confounders (Multivariable Analysis, Mixed Effects Cox Regression Model*)

	Adjusted HR (95% CI)	p Value
ASA	3.27 (1.82-5.86)	<0.0001
Large PFO (>30 microbubbles)	1.43 (0.50-4.03)†	0.50
Age, per 10-yr increase	1.29 (0.99-1.69)	0.06
High blood pressure	2.27 (1.16-4.46)	0.02
Anticoagulation (vs. antiplatelets)	0.17 (0.06-0.48)	0.0008

*Cox proportional hazards model with mixed effects incorporating: 1) study-specific random effects that modify the baseline hazard function (random intercepts), to take into account the multilevel structure of the data (patients from 4 different studies with potentially different baseline hazard functions); and 2) random coefficients for PFO size, allowing the association of large PFO and recurrent stroke to vary across the 4 original studies (9). †This represents an averaging of the hazard ratios (HRs) across studies. The adjusted HRs for each study in the model are 4.88, 0.97, 0.98, and 0.89 in Lee et al. (7), DEFENSE-PFO, PFO-ASA and CLOSE, respectively. The variance of the random coefficients for large PFO (vs. nonlarge PFO) across the 4 studies is 0.67.

Abbreviations as in Table 1.

FIGURE 1 Kaplan-Meier Cumulative Estimates of the Probability of Recurrent Ischemic Stroke According to PFO Anatomical Features Categorized in 4 Classes



Atrial septal aneurysm (ASA) was defined as a septum primum excursion ≥10 mm from the plane of the atrial septum into the right or left atrium. Large patent foramen ovale (PFO) was defined by the appearance of >30 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium.

JACC VOL. 75, NO. 18, 2020, Turc et al. MAY 12, 2020:2312 – 2 0 Risk of Recurrent 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

Christian Pristipino[1]*, Horst Sievert[2,3], Fabrizio D'Ascenzo[4], Jean Louis Mas[5], Bernhard Meier[6], Paolo Scacciatella[4], David Hildick-Smith[7], Fiorenzo Gaita[4], Danilo Toni[8], Paul Kyrle[9], John Thomson[10], Genevieve Derumeaux[11], Eustaquio Onorato[12], Dirk Sibbing[13], Peter Germonpré[14], Sergio Berti[15], Massimo Chessa[16], Francesco Bedogni[16], Dariusz Dudek[17], Marius Hornung[2], and Jose Zamorano[18], joint task force of European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Stroke Organisation (ESO), European Heart Rhythm Association (EHRA), European Association for Cardiovascular Imaging (EACVI), Association for European Paediatric and Congenital Cardiology (AEPC), ESC Working group on GUCH, ESC Working group on Thrombosis, European Haematological Society (EHA), European Underwater and Baromedical Society (EUBS)

Table 1 **Summary of statements**

Position statements	Strength of the statement	Level of evidence	Ref.
General management of PFO-associated syndromes			
Interdisciplinary assessment and decision making should be done	Strong	C	–
The decision making should be done taking into account an estimation of the individual: a. Probability of a causal role of the PFO in the clinical picture b. Risk of recurrence	Strong	C	–
Individual risk stratification should take into account clinical, anatomical and imaging characteristics	Strong	C	–
Shared decision making should be documented in an open, individualised, informed consent	Strong	C	–
Decision aids and narrative tools are suggested to enhance patients' involvement	Conditional	C	38–43
Standardised definitions of candidate events should be adopted in research and clinical settings	Strong	C	–
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 4 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 4 and Supplementary Appendix 4
c-TTE has a lower sensitivity for small shunts than other techniques	Conditional	A	Original meta-analyses page 4 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

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

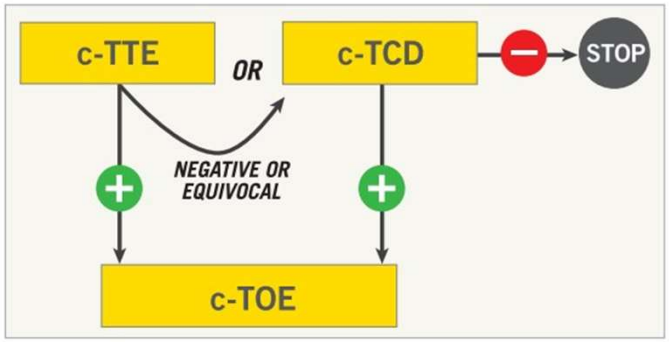


Figure 1 Algorithm for the diagnosis of PFO. c-TCD: contrast-enhanced transcranial Doppler; c-TOE: contrast-enhanced transoesophageal echocardiography; c-TTE: contrast-enhanced transthoracic echocardiography; −negative test for the presence of right-to-left shunt; +positive test for the presence of right-to-left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

Position statements	Strength of the statement	Level of evidence
PFO can play a pathogenic role in cryptogenic left circulation thromboembolism	Strong	A
It is essential to evaluate the role of the PFO in any given left circulation thromboembolism	Strong	A
No statement is possible regarding the quantification of the role of PFO in left circulation thromboembolism	Strong	C
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
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
When a PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore	Strong	A
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
Cortical infarcts are commonly embolic but, less frequently, also white matter infarcts can be embolic	Strong	B
No specific imaging pattern has been associated with a causal role of PFO in stroke patients	Strong	C
ASA, shunt severity and an atrial septal hypermobility can be linked to a causal role of PFO	Strong	A
PFO sizes, presence of Chiari network or Eustachian valve can be linked to a causal role of PFO	Conditional	C
Deep vein thrombosis, immobilisation, long journeys, straining pre-stroke or obstructive sleep apnoea can be linked to a causal role of PFO	Conditional	C
Simultaneous pulmonary embolism and/or deep vein thrombosis strongly suggest a causal role of PFO	Strong	C
The role of thrombophilia cannot be generalised	Strong	C
The RoPE score should only be part of a comprehensive individual evaluation. Further validation studies on the RoPE score are needed	Strong	B

Estimating the risk of recurrences		
The risk of recurrent embolism in unselected patients with PFO is low	Strong	A
No single variable allows a quantitative prediction of recurrences	Strong	A
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

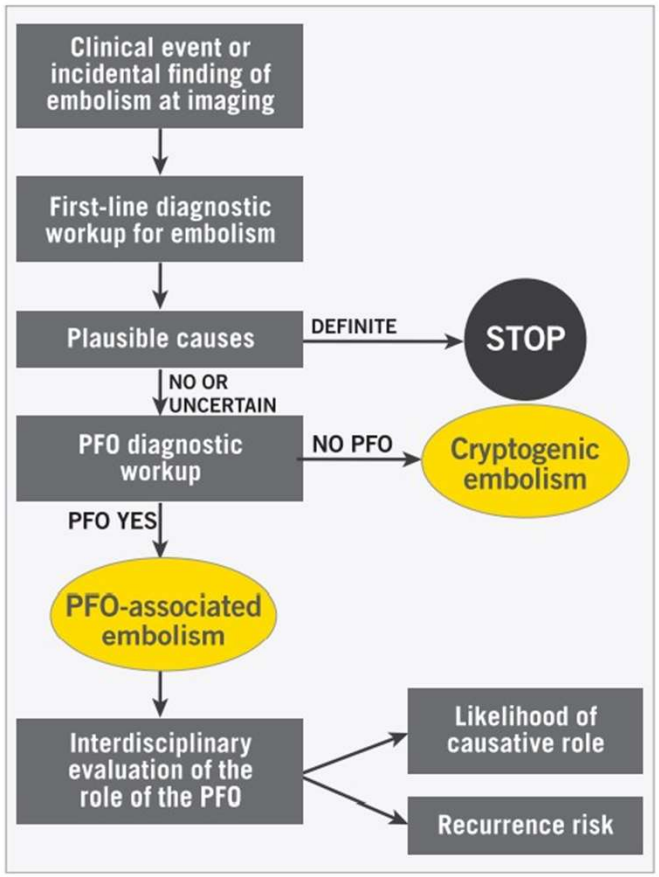


Figure 2 Algorithm for the diagnostic workup of cryptogenic left circulation thromboembolism.

Table 4 **Summary of statements on the evaluation and treatment of concurrent diseases.**

Position statements	Strength of the statement	Level of evidence
AF rule-out strategy		
All patients should undergo a routine 12-lead ECG and either in-patient cardiac telemetry or 24-hour Holter monitoring	Strong	B
In patients >65 years old with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C
ICM evaluation period in cryptogenic left circulation embolism should be at least 6 months before deciding on PFO closure or permanent OAC	Conditional	B
In patients 55 to 64 years old at risk for AF with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C
In patients <55 years old with ≥2 high-risk factors for AF with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C
Patients undergoing diagnostic procedures should be maintained on medical therapy	Strong	B
Medical therapy should be decided according to the statements of this position paper	Strong	C
In patients with clear evidence of a causal PFO (e.g., simultaneous pulmonary embolism), ICM can be withheld so as not to delay percutaneous closure	Strong	C
In patients undergoing ICM, the monitoring should be extended for the full duration of the device life, regardless of the choice of therapy after 6 months	Strong	C
Management of PFO in the presence of concomitant diseases		
Patients on temporary OAC, on OAC for pulmonary embolism or those considered at high risk of recurrences despite OAC may undergo PFO assessment for possible closure	Conditional	C
Paroxysmal AF episodes >30 seconds detected with intermittent recordings, or ≥5 minutes during ICM can be considered sufficient to evaluate the patient for OAC according to current guidelines on AF	Conditional	B
ICM results should always be interpreted with other clinical characteristics in order to weigh the AF embolic risk against the PFO embolic risk	Strong	C
Routine laboratory tests for prothrombotic states (thrombophilia testing) are not warranted to indicate permanent OAC	Strong	C

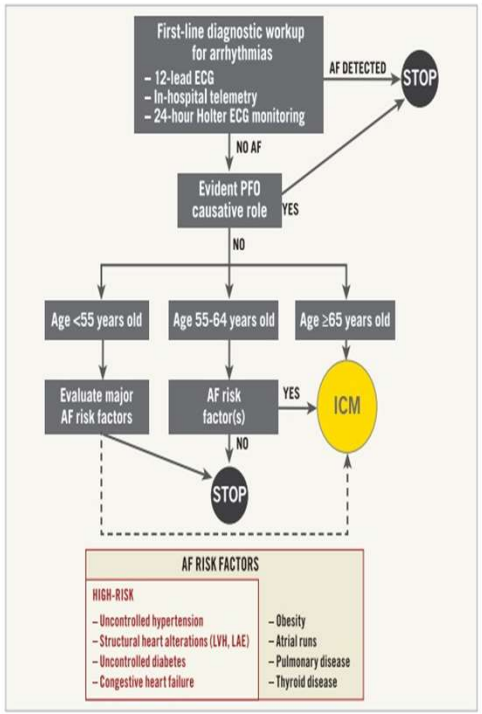


Figure 3 Flow chart for the screening of overt atrial fibrillation in cryptogenic left circulation thromboembolism. The cut-off ages of 55 and 65 years old have been chosen according to data from large epidemiological studies.[166,173] Patients <55 years may be considered for ICM when they have high clinical suspicion of AF (i.e., ≥2 high-risk factors for AF). ECG: electrocardiography; LAE: left atrium enlargement; LVH: left ventricle hypertrophy.

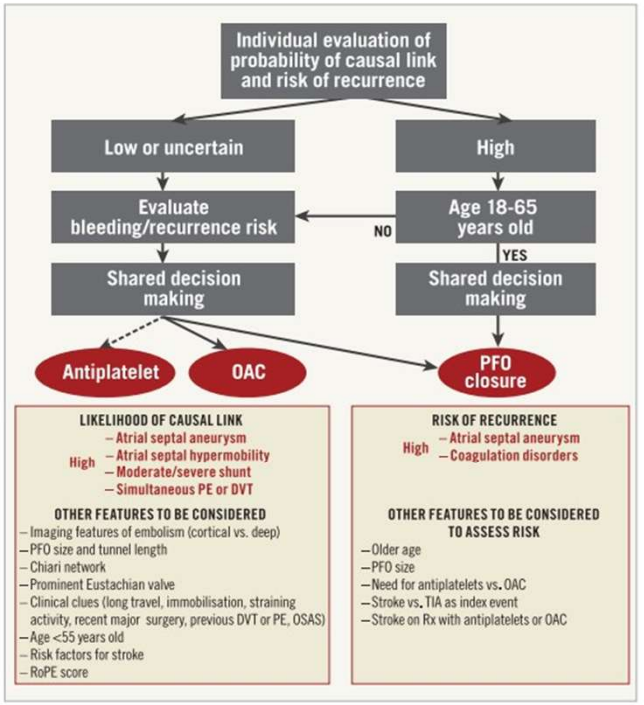


Figure 4 Treatment algorithm for secondary prevention of left circulation cryptogenic thromboembolism. DVT: deep vein thrombosis; OAC: oral anticoagulants; OSAS: obstructive sleep apnoea syndrome; PE: pulmonary embolism; Rx: therapy; TIA: transient ischaemic attack.

Table 7 Summary of statements on the management after percutaneous closure of PFO

Position statements	Strength of the statement	Level of evidence
Drug therapy and follow up after percutaneous closure		
It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure	Conditional	A
We suggest a single antiplatelet therapy be continued for at least 5 years	Conditional	C
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
The value of residual shunt after percutaneous closure cannot be deduced from available studies	Strong	C
Systematic, high-quality data on follow-up are needed	Strong	C
To obtain comparable data we propose to perform: a. a TTE prior to hospital discharge b. c-TCD at least once beyond six months to assess effective PFO closure and thereafter, if residual shunt persists, annually until closure c. c-TOE or c-TTE in case of severe residual shunt at c-TCD, or recurrent events, or symptoms during follow-up	Conditional	C
Patients should undergo antibiotic prophylaxis for any invasive procedure performed in the first six months from PFO closure	Conditional	C

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SPECIAL ARTICLE LEVEL OF RECOMMENDATION

Practice advisory update summary: Patent foramen ovale and secondary stroke prevention

Report of the Guideline Subcommittee of the American Academy of Neurology

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Abstract

Objective

To update the 2016 American Academy of Neurology (AAN) practice advisory for patients with stroke and patent foramen ovale (PFO).

Methods

The guideline panel followed the AAN 2017 guideline development process to systematically review studies published through December 2017 and formulate recommendations.

Major recommendations

In patients being considered for PFO closure, clinicians should ensure that an appropriately thorough evaluation has been performed to rule out alternative mechanisms of stroke (level B). In patients with a higher risk alternative mechanism of stroke identified, clinicians should not routinely recommend PFO closure (level B). Clinicians should counsel patients that having a PFO is common; that it occurs in about 1 in 4 adults in the general population; that it is difficult to determine with certainty whether their PFO caused their stroke; and that PFO closure probably reduces recurrent stroke risk in select patients (level B). In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (absolute recurrent stroke risk reduction of 3.4% at 5 years) and risks (periprocedural complication rate of 3.9% and increased absolute rate of non-periprocedural atrial fibrillation of 0.33% per year) (level C). In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend an antiplatelet medication such as aspirin or anticoagulation (level C).

THE CONNECTION BETWEEN PATENT FORAMEN OVALE AND MIGRAINE

Table 1
Observational studies of the prevalence of migraine in patients referred for PFO closure and the effect of the procedure on migraine

Study	Prevalence of Migraine in Patients Referred for PFO Closure	% Migraine Improved/ Cured Following PFO Closure	Length of Follow-up (mo)
Wilmshurst et al,[32] 2000	21/37 (57%)	86	30
Morandi et al,[33] 2003	17/62 (27%)	88	6
Schwerzmann et al,[34] 2004	48/215 (22%)	81	12
Post et al,[35] 2004	26/66 (39%)	65	6
Reisman et al,[36] 2005	57/162 (35%)	70	12
Azarbal et al,[37] 2005	37/89 (42%)	76	18
Donti et al,[38] 2006	35/131 (27%)	91	20
Anzola et al,[39] 2006	50/163 (31%)	88	12
Kimmelstiel et al,[40] 2007	24/41 (59%)	83	3
Papa et al,[41] 2009	28/76 (37%)	82	12
Khessali et al,[7] 2012	204/590 (35%)	76	12
Total	547/1632 (34%)	80.5	13 ± 7.5

https://doi.org/10.1016/j.nic.2019.01.006

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- KEY POINTS:
- Although observational studies have shown that migraineurs with aura respond well to patent foramen ovale (PFO) closure, randomized trials have not confirmed this. Until a randomized double-blinded study clearly demonstrates a significant benefit of PFO closure to reduce migraines, medical therapy will remain the treatment of choice for migraines.
- One challenge in conducting such a study is adequate patient recruitment in a timely fashion given strict inclusion criteria.

https://doi.org/10.1016/j.nic.2019.01.006

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