“Percutaneous PFO closure in prevention of stroke or transient ischemic attack: is it time to consider it? Neurologist point of view”

Adriana Critelli

U.O NEUROLOGIA - STROKE UNIT
OSPEDALE DELL’ANGELO - MESTRE
Association of CS with PFO

- Meta-analysis of Case-Control Studies
  - Ischemic Stroke vs Controls
    - PFO – OR of 1.83 (95% CI of 1.25 to 2.66) – 15 studies
    - Atrial Septal Aneurysm (ASA) – OR 2.35 (1.46 to 3.77) – 9 studies
    - PFO & ASA – OR 4.96 (2.37 to 10.39) – 4 studies
  - Cryptogenic Stroke vs Stroke of known cause
    - PFO – OR 3.16 (2.30 to 4.35) – 22 studies
    - ASA – OR 3.65 (1.34 to 9.97) – 5 studies
    - PFO & ASA – OR 23.36 (5.24 to 103.20)
  - Association stronger for younger patients (age < 55 yrs)

Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O'Donnell, Ralph I. Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

Panel 1: Causes of embolic strokes of undetermined source

Minor-risk potential cardioembolic sources

Mitrval valve
- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

Aortic valve
- Aortic valve stenosis
- Calcific aortic valve

Non-atrial fibrillation atrial dysrhythmias and stasis
- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

Atrial structural abnormalities
- Atrial septal aneurysm
- Chiari network

Left ventricle
- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction
- Endomyocardial fibrosis

Covert paroxysmal atrial fibrillation

Cancer-associated
- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

Arteriogenic emboli
- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

Paradoxical embolism
- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

PFO Closure Debates

- The management of patients with Cryptogenic Stroke and PFO is controversial

- High level unbiased data do not yet exist to guide our clinical decisions with these challenging patients
### Transcatheter Closure vs Medical Therapy

**SECONDARY STROKE PREVENTION**

(recurrent event rate %)

<table>
<thead>
<tr>
<th></th>
<th>PFO Closure</th>
<th>Medical Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khairy 2003</td>
<td>0-4.9%</td>
<td>3.8-12%</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Windecker 2004</td>
<td>8.5%/4 ys</td>
<td>24.3%/4 yrs</td>
</tr>
<tr>
<td>Retrospective</td>
<td></td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Schuchlenz 2005</td>
<td>0.6%/year</td>
<td>13%/year Aspirin</td>
</tr>
<tr>
<td>Retrospective</td>
<td>5.6%/year Warfarin</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

Windecker et al. J Am Coll Cardiol 2004; 44: 750-758  
Schuchlenz et al. J Cardiol 205; 101:77-82
Transcatheter Closure vs Medical Therapy

Intention to-treat: negative

**CLOSURE**
Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

*Anthony J. Fuhrman, 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., Sahil Kar, M.D., Michael Landzberg, M.D., Albert Rauzen, M.D., and Lawrence Wechsler, M.D., for the CLOSURE Investigators*  


**RESPECT**
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*  


**PC-TRIAL**
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

*Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattie, 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 Schule, M.D., Anthony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Juni, M.D., for the PC-Trial Investigators*  


p=0.3

p=0.08

p=0.34
Meta analysis results

Percutaneous closure of PFO may be more effective than medical treatment for the recurrence of stroke but a statistical significance was not reached.
Transcatheter Closure vs Medical Therapy

Updating the evidence on patent foramen ovale closure versus medical therapy in patients with cryptogenic stroke: a systematic review and comprehensive meta-analysis of 2,303 patients from three randomised trials and 2,231 patients from 11 observational studies

Davide Capodanno\textsuperscript{1,2*}, MD, PhD; Giovanni Milazzo\textsuperscript{1}, MD; Luca Vitale\textsuperscript{1}, MD; Daniele Di Stefano\textsuperscript{1}, MD; Marilena Di Salvo\textsuperscript{1}, MD; Carmelo Grasso\textsuperscript{1}, MD; Corrado Tamburino\textsuperscript{1,2}, MD, PhD

Conclusions: In RCTs, unlike observational studies, PFO closure compared with medical therapy failed to achieve a statistically significant reduction in recurrent stroke. However, pooling RCTs of the AMPLATZER PFO occluder device yielded a statistically significant reduction in stroke over medical treatment that may warrant further investigation.
PFO closure in cryptogenic stroke:

Important Question

Does biologic plausibility = clinical efficacy?
Association ≠ Causation
In patients with otherwise CS, approximately one third of discovered PFOs are likely to be incidental and hence not benefit from closure
CLUES FOR identifying guilty PFOs
In addition to age and conventional stroke risk factors, morphological features of a PFO may influence the association between PFO and CS and hence the probability that the PFO is incidental.
“Pathological” PFOs:

- Association with ASA
- Large (> 4mm) PFO size
- Eustachian valve
- >1 cm long tunnel
- Large shunt on bubble test
- Permanent shunt

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Morphology of the Patent Foramen Ovale in Asymptomatic Versus Symptomatic (Stroke or Transient Ischemic Attack) Patients


The clinical implications of patent foramen ovale (PFO) morphology are still debated. Quantitative analysis by transesophageal echocardiography (TEE) is helpful in characterizing PFO morphology. The aim of this study was to determine whether there were significant differences in anatomy of PFOs on TEE in patients with and without recurrent stroke or transient ischemic attack. The results of TEE in 58 patients who had experienced a cryptogenic cerebrovascular accident (CVA) were compared with those in 58 asymptomatic patients with PFOs found incidentally on TEE. The data were analyzed for differences in PFO size (maximum separation of the septum primum and septum secundum), tunnel length (maximum overlap of the septum primum and septum secundum), and presence of atrial septal aneurysm (>11 mm mobility), the severity of shunts on bubble test, and presence of Eustachian valve. The results showed that patients with CVA had larger PFOs (3.9 ± 1.6 mm vs 2.9 ± 1.4 mm, p < 0.001), longer tunnels (7.3 mm vs 5.5 mm, p = 0.05), and a greater frequency of atrial septal aneurysm (45% vs 17%, p < 0.01) compared with controls. They also had a greater proportion of large (≥4 mm) PFOs, long (≥1 cm) tunnels, and severe shunts on bubble test (55% vs 5%, p < 0.01). The frequencies of prominent Eustachian valves were not significantly different. In conclusion, PFOs in patients with CVAs are larger, have longer tunnels, and are more frequently associated with other anatomic characteristics. This information should be considered when evaluating patients with CVAs. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:124–129)
Pattern neuroimaging

- Cardioembolic stroke
  - DWI multiple early lesions
  - Lesions in different territories
  - Posterior or cortical distribution

RULE OUT DISSECTION

There were no differences in occurrence of multiple lesion pattern in patients with cryptogenic stroke compared to patients with PFO neither for the entire group nor for a subgroup of young stroke patients less than 50 years.

Patients with PFO showed a significantly higher incidence of multiple lesions in the posterior circulation.
Other Evidence

- Factors predisposing to DVT:
  - Prolonged immobilization – recent prolonged travel
  - Leg trauma
  - Surgery – Anesthesia
  - Coagulation disorders [Factor V Leiden - Prothrombin (G20210A)]
- Anatomical variants and DVT in unusual locations
- D-Dimer
- Stroke on awakening (association with OSAS)
- Valsalva at onset

Exclusion of ANY other RF
An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke


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DOI 10.1212/WNL.0b013e3182a08d59

This information is current as of July 17, 2013
Risk of Paradoxical Embolism

• Patient level meta-analysis of 12 cryptogenic stroke cohorts

• RoPE score predicts likelihood of identifying a PFO
  - Start with 10 points
  - Subtract 1 point for each of the following:
    - HTN, DM, smoker, history of stroke, subcortical infarct and each decade from 30 up to 70

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>RoPE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No history of hypertension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No history of stroke or TIA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct on imaging</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total score (sum of individual points)

| Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct) | 10 |
| Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct) | 0  |

Abbreviation: RoPE = Risk of Paradoxical Embolism.

## RoPE Score Predicts Presence of PFO

<table>
<thead>
<tr>
<th>RoPE score</th>
<th>No. of patients</th>
<th>Prevalence of patients with a PFO, % (95% CI)(^a)</th>
<th>PFO-attributable fraction, % (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>613</td>
<td>23 (19-26)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>4</td>
<td>511</td>
<td>35 (31-39)</td>
<td>38 (25-48)</td>
</tr>
<tr>
<td>5</td>
<td>516</td>
<td>34 (30-38)</td>
<td>34 (21-45)</td>
</tr>
<tr>
<td>6</td>
<td>482</td>
<td>47 (42-51)</td>
<td>62 (54-68)</td>
</tr>
<tr>
<td>7</td>
<td>434</td>
<td>54 (49-59)</td>
<td>72 (66-76)</td>
</tr>
<tr>
<td>8</td>
<td>287</td>
<td>67 (62-73)</td>
<td>84 (79-87)</td>
</tr>
<tr>
<td>9-10</td>
<td>180</td>
<td>73 (66-79)</td>
<td>88 (83-91)</td>
</tr>
</tbody>
</table>

RoPE Score Predicts Freedom From Stroke Recurrence

<table>
<thead>
<tr>
<th>RoPE score</th>
<th>No. of CS patients with PFO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>108</td>
<td>20 (12-28)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>12 (6-18)</td>
</tr>
<tr>
<td>5</td>
<td>186</td>
<td>7 (3-11)</td>
</tr>
<tr>
<td>6</td>
<td>236</td>
<td>8 (4-12)</td>
</tr>
<tr>
<td>7</td>
<td>263</td>
<td>6 (2-10)</td>
</tr>
<tr>
<td>8</td>
<td>233</td>
<td>6 (2-10)</td>
</tr>
<tr>
<td>9-10</td>
<td>150</td>
<td>2 (0-4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> CS patients with PFO

Proposed Mechanisms linking PFO to Stroke

- Paradoxical embolism (Small/post infarcts)
- Migrainous stroke
- Thrombi in ASA LA dysfunction
- PFO-unrelated (Low RoPE score)
- Supraventricular arrhythmia (Large infarcts)
Subclinical Atrial Fibrillation and the Risk of Stroke


The Risk of Clinical Atrial Tachyarrhythmias and of Ischemic Stroke or Systemic Embolism, According to the Presence or Absence of Subclinical Atrial Tachyarrhythmias.
Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijss, Ph.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL AF investigators.⁹

Atrial Fibrillation in Patients with Cryptogenic Stroke

Left Atrial Dysfunction in Patients With Patent Foramen Ovale and Atrial Septal Aneurysm

An Alternative Concurrent Mechanism for Arterial Embolism?

Gianluca Rigatelli, MD,* Silvio Aggio, MD,† Paolo Cardaioli, MD,* Gabriele Braggioni, MD,† Massimo Giordan, MD,* Fabio Della'vovatta, MD,* Mauro Chinaglia, MD,‡ Giorgio Rigatelli, MD,§ Loris Roncon, MD,† Jack P. Chen, MD||

Objectives We postulate that, in patients with large patent foramen ovales (PFO) and atrial septal aneurysms (ASA), left atrial (LA) dysfunction simulating "atrial fibrillation (AF)-like" pathophysiology might represent an alternate mechanism in the promotion of arterial embolism.

Background Despite prior reports concerning paradoxical embolism through a PFO, the magnitude of this phenomenon as a risk factor for stroke remains undefined, because deep venous thrombosis is infrequently detected in such patients.

Methods To test our hypothesis, we prospectively enrolled 98 consecutive patients with previous stroke (mean age 37 ± 12.5 years, 58 women) referred to our center for catheter-based PFO closure. Baseline values of LA passive and active emptying, LA conduit function, LA ejection fraction, and spontaneous echocontrast (SEC) in the LA and LA appendage were compared with those of 50 AF patients as well as a sex/age/cardiac risk-matched population of 70 healthy control subjects.

Results Pre-closure PFO subjects demonstrated significantly greater reservoir function as well as passive and active emptying, with significantly reduced conduit function and LA ejection fraction, when compared with AF and control patients. Furthermore, in PFO patients, 66.3% (65 of 98) had moderate-to-severe ASA and basal shunt; SEC was observed in 52% of PFO plus ASA patients before closure. Multivariate stepwise logistic regression revealed moderate-to-severe ASA (odds ratio 9.4, 95% confidence interval: 7.0 to 23.2, p < 0.001) as the most powerful predictor of LA dysfunction. After closure, all LA parameters normalized to the levels of control subjects: no SEC, device-related thrombosis, or aortic erosion were observed on follow-up echocardiography.

Conclusions This study suggests that moderate-to-severe ASA might be associated with LA dysfunction in patients with PFO. The resultant similarities to the pathophysiology of AF might represent an additional contributing mechanism for arterial embolism in such patients.
Increased Incidence of Interatrial Block in Younger Adults with Cryptogenic Stroke and Patent Foramen Ovale

P.E. Cotter\textsuperscript{a}  P.J. Martin\textsuperscript{b}  P.J. Pugh\textsuperscript{c}  E.A. Warburton\textsuperscript{b}  J. Cherian\textsuperscript{d}  M. Belham\textsuperscript{c}

\textbf{Background:} Stroke is often unexplained in younger adults, although it is often associated with a patent foramen ovale (PFO). The reason for the association is not fully explained, and mechanisms other than paradoxical embolism may be involved. Young stroke patients with PFO have more atrial vulnerability than those without PFO. It is plausible that stretching of the interatrial septum may disrupt the interatrial conduction pathways causing interatrial block (IAB). IAB is associated with atrial fibrillation, dysfunctional left atria and stroke. \textbf{Methods:} Electrocardiogram (ECG) characteristics of prospectively recruited young patients (\textasciitilde 55 years of age) with unexplained stroke (TOAST and A-S-C-O) were compared with control data. All stroke cases underwent bubble contrast transthoracic and transoesophageal echography. IAB was defined as a P-wave duration of 6 110 ms. ECG data were converted to electronic format and analysed in a blind manner. 

\textbf{Results:} Fifty-five patients and 23 datasets were analysed. Patients with unexplained stroke had longer P-wave duration (p = 0.013) and a greater prevalence of IAB (p = 0.02) than healthy controls. Case status was an independent predictor of P-wave duration in a significant multivariate model. There was a significant increase in the proportion of cases with a PFO with IAB compared with cases without PFO and with controls (p = 0.005).

\textbf{Conclusions:} Young patients with unexplained stroke, particularly those with PFO, exhibit abnormal atrial electrical characteristics suggesting atrial arrhythmia or atrial dysfunction as a possible mechanism of stroke.
Management of patients with cryptogenic stroke and patent foramen ovale

- Multidisciplinary shared approach may become a basis for a joint management of these patients, while waiting for more consistent evidences

- Team-based, multidisciplinary clinical judgment on an individual basis still remains the core of decision-making

- Un carefully selected patients, off label PFO closure should be considered
Management of patients with cryptogenic stroke and patent foramen ovale

- A consensus statement of recommendations was developed by approaching Italian Scientific Societies to address the urgent need of adopting a comprehensive and rationale workflow in the management of patients with Cryptogenic Stroke and PFO.

- The goal was to organize a common approach that may be shared by different specialists.
Expert Consensus Paper


Christian Pristipino,1 MD, Gian Paolo Anzola,2 MD, Luigi Ballerini,3 MD, Antonio Bartorelli,4 MD, Moreno Cecconi,5 MD, Massimo Chessa,6 MD, Andrea Donti,7 MD, Achille Gaspardone,8 MD, Giuseppe Neri,9 MD, Eustaquio Onorato,10 MD, Gualtiero Palareti,11 MD, Serena Rakar,12 MD, Gianluca Rigatelli,13 MD, PhD, Gennaro Santoro,14 MD, Danilo Toni,15 MD, Gian Paolo Ussia,16 MD, Roberto Violini,17 MD, on behalf of: Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke Association (ISA-AIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society Of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SICP); Italian Society of Cardiovascular Echography (SIEC); Italian Society of Hemostasis and Thrombosis (SISET).

[Epub ahead of print]
Management of patients with cryptogenic stroke and patent foramen ovale

Cryptogenic Stroke/TIA (symptomatic/asymptomatic) & PFO with R-L Shunt

First cryptogenic event without anatomical/clinical risk factors

Medical therapy

Cryptogenic event in medical therapy-naïve patients with ≥ 1 risk factor

Cath PFO closure as an alternative to medical therapy

Any cryptogenic event (first or recurrent) on AP and/or OA therapy

Cath PFO closure

Anatomical risk factors
- Atrial septal aneurysm
- Large PFO (>4 mm)
- Basal R-L shunt
- Eustachian valve >10 mm
- Chiari network
- Long PFO tunnel

Clinical risk factors
- Multiple ischemic lesions on CT/MR
- Recurrent clinical events
- History of DVT/PE and/or Thrombophilia
- Valsalva-associated embolic event
- Ischemic event on arousal (OSAS)
- Long travel/immobilization associated event
- Simultaneous systemic/pulmonary embolism
GRAZIE
CONCLUSION

• The optimal therapy for patient with a cryptogenic ischemic stroke or transient ischemic attack (TIA) who have a PFO is not established

• Currently, no device has been granted an indication for PFO closure

• Nevertheless, un carefully selected patients, off label PFO closure should be considered and expendly performed

• The decision to proced with device closure should only occur after a comprehensive and competent evalutation, shared decision-making with the patient and a commitment to long-term secondary stroke prevention
<table>
<thead>
<tr>
<th>Raccomandazione 12.2.1</th>
<th>A</th>
<th>Prevenzione Secondaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nei pazienti con ictus ischemico o TIA criptogenetico associato a forame ovale pervio (FOP) ed esenti da TVP è indicato il trattamento con ASA 325 mg/die.</td>
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</table>

<table>
<thead>
<tr>
<th>Raccomandazione 12.2.2</th>
<th>A</th>
<th>Prevenzione Secondaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nei pazienti con ictus ischemico o TIA criptogenetico associati a FOP che abbiano altre indicazioni alla TAO, quali evidenza di TVP od embolia polmonare è indicato il trattamento con terapia anticoagulante.</td>
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<thead>
<tr>
<th>Raccomandazione 12.2.3</th>
<th>D</th>
<th>Prevenzione Secondaria</th>
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</thead>
<tbody>
<tr>
<td>Nei pazienti con recidiva di ictus ischemico o TIA associati a (FOP) pur in trattamento con antiaggreganti o con TAO, dopo una rivalutazione multidisciplinare del caso ed in accordo con il paziente, è indicata la chiusura del FOP</td>
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<thead>
<tr>
<th>Raccomandazione 12.2.4</th>
<th>A</th>
<th>Prevenzione Secondaria</th>
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<tbody>
<tr>
<td>I risultati dei tre studi CLOSURE, RESPECT, PC di confronto tra terapia medica e chiusura transcutanea del PFO in ictus ischemici criptogenetici permettono di concludere che non è indicato ricorrere, in prima scelta, alla chiusura transcutanea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent Foramen Ovale Recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2014 Recommendation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. <em>(Class I, LOE B)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Revisions (2011)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class changed from IIa to I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. <em>(Class I, LOE A).</em> When anticoagulation is contraindicated, an inferior vena cava filter is reasonable <em>(Class IIa, LOE C).</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. <em>(Class III, LOE A)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revised Recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. <em>(Class IIb, LOE C)</em></td>
<td></td>
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</tr>
<tr>
<td>New Recommendation</td>
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</tr>
</tbody>
</table>
Transcatheter Closure vs Medical Therapy

Controlled studies

- **Closure I**
  - Investigating the PFO Stroke Connection
  - negative study

- **RESPECT**
  - **CLINICAL TRIAL**
  - negative study

- **PC Trial**
  - negative study
AHA/ASA Guideline
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association
Look for systemic embolization

- Occult PE
- Silent heart lesions
- Renal infarcts (?)

**Conclusions:** Subclinical myocardial infarctions determined in CMRI were observed in **10.8%** of patients with PFO after a first cryptogenic cerebral ischemic event. Our results strengthen the pathophysiologic role of a PFO with paradoxical embolism in patients with cryptogenic cerebral ischemic events.

*Wohlre et al. J Am Coll Cardiol Img, 2010; 3:833-839*
**Background:** Undetected atrial fibrillation (AF) is often suspected as the possible cause in patients with cryptogenic ischemic stroke (IS), especially in elderly population. In young IS patients, the prevalence of AF, particularly paroxysmal form, remains still not enough established. Our aim was to assess the presence of AF in young patients using a long-term electrocardiography (ECG) Holter monitoring. **Methods:** The study set consisted of acute IS patients ≤50 years enrolled in the prospective HISTORY (Heart and Ischemic STROKE Relationship study) study (NCT01541163). In all patients, admission ECG, serum cardiac markers, transesophageal echocardiography, 24-h and 3-week ECG Holter monitoring were performed. **Results:** Out of 634 enrolled patients in the HISTORY study, 98 were ≤50 years (56 males, mean age 39.7 ± 8.4). In total, AF was detected in 10.2% of patients and 70% of them had a paroxysmal form of AF. The elevated serum cardiac markers were present in 70% of patients with detected AF (p = 0.0001). **Conclusion:** AF was detected in 10.2% of young stroke patients and paroxysmal form of AF.
Patent foramen ovale, alone or together with ASA, was not associated with an increased stroke risk in this multiethnic cohort.

Further trial data are needed to confirm the effect of PFO on stroke.
Embolic strokes of undetermined source: the case for a new clinical construct

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Panel 1: Causes of embolic strokes of undetermined source

- Minor-risk potential cardioembolic sources
  - Mitral valve
    - Myxomatous valvulopathy with prolapse
    - Mitral annular calcification
  - Aortic valve
    - Aortic valve stenosis
    - Calcific aortic valve
- Non-atrial fibrillation atrial dysrhythmias and stasis
  - Atrial asystole and sick-sinus syndrome
  - Atrial high-rate episodes
  - Atrial appendage stasis with reduced flow velocities or spontaneous echodensities
- Atrial structural abnormalities
  - Atrial septal aneurysm
  - Chiari network
- Left ventricle
  - Moderate systolic or diastolic dysfunction (global or regional)
  - Ventricular non-compaction
  - Endomyocardial fibrosis
- Covert paroxysmal atrial fibrillation
- Cancer-associated
  - Covert non-bacterial thrombotic endocarditis
  - Tumour emboli from occult cancer
- Arteriogenic emboli
  - Aortic arch atherosclerotic plaques
  - Cerebral artery non-stenotic plaques with ulceration
- Paradoxic embolism
  - Patent foramen ovale
  - Atrial septal defect
  - Pulmonary arteriovenous fistula

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source

- Stroke detected by CT or MRI that is not lacunar
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)
Association of CS with PFO

- Meta-analysis of Case-Control Studies
  - Ischemic Stroke vs Controls
    - PFO – OR of 1.83 (95% CI of 1.25 to 2.66) – 15 studies
    - Atrial Septal Aneurysm (ASA) – OR 2.35 (1.46 to 3.77) – 9 studies
    - PFO & ASA – OR 4.96 (2.37 to 10.39) – 4 studies
  - Cryptogenic Stroke vs Stroke of known cause
    - PFO – OR 3.16 (2.30 to 4.35) – 22 studies
    - ASA – OR 3.65 (1.34 to 9.97) – 5 studies
    - PFO & ASA – OR 23.36 (5.24 to 103.20)
  - Association stronger for younger patients (age < 55 yrs)

Association of CS with PFO

**Figure 2.** Odds Ratios for the Presence of Patent Foramen Ovale among Patients with Cryptogenic Stroke, as Compared with Those with Stroke of Known Cause.

Odds ratios were adjusted for age, plaque thickness, presence or absence of coronary artery disease, and presence or absence of hypertension.

New cerebrovascular events are rare in unselected subjects with PFO, even in those with previous cerebral ischemia and those who have not undergone PFO closure, with an event rate similar to that observed in the general population.
PFO closure in cryptogenic stroke:
Important Question

• How to select PFO patients?

• Does biologic plausibility = clinical efficacy?
PFO closure in cryptogenic stroke: Important Question

• How to select PFO patients?

• Does biologic plausibility = clinical efficacy?
Management of patients with cryptogenic stroke and patent foramen ovale

CLINICIAN’S DECISION TO CONSIDER
PFO CLOSURE
FOR AN INDIVIDUAL PATIENT

VTE Evidence

Patient Characteristics
Age – Risk Factors

Patient Preferences

Neuroimaging Data

PFO and Septum Characteristics

Clinical Clues