DEBATE: PFO MANAGEMENT
TO CLOSE OR NOT TO CLOSE

Matthew Starr, MD
Stroke Attending
DISCLOSURES

None
DEBATE

Should PFO be closed?

* Sometimes yes

NO *
THE CASE AGAINST PFO CLOSURE

1. Did the PFO cause the stroke?
2. Is PFO closure better than anticoagulation?
3. Is risk of procedure worth it?
CRYPTOGENIC STROKE

As discussed last year

Possible etiologies:
1. Hypercoagulable state
2. subclinical afib
3. aortic arch atheroma
4. PFO
5. truly cryptogenic or ESUS
Cryptogenic stroke accounts for 23-40% of all stroke

~1/3 of strokes are cryptogenic, ~200,000 per year

More frequent in younger patients

Hard to know what prognosis for recurrence

It is likely that some portion of cryptogenic stroke is due to PFO
DID PFO CAUSE THE STROKE?

If patient has a lacunar stroke, then PFO closure won’t prevent future event

If patient has underlying afib, then closure won’t prevent future event

If patient has hypercoagulable state then closure MAY not prevent future stroke
TIA VS MIGRAINE

Transient neurological symptoms
Is it TIA
Or is it MIGRAINE
PFO AND STROKE

1\textsuperscript{st} generation trials
CLOSURE, PC Trial and RESPECT

How did these studies assure that stroke was due to PFO?
CLOSURE

909 patients randomized to PFO Closure with STARFlex vs medical therapy

Medical therapy included aspirin or warfarin or both

The number of patients on antiplatelet vs anticoagulation is not readily available

Patients were excluded who had “clinically significant hypercoagulability”, although what this means is not clear

Amount of monitoring for afib also not specified

Index event was Cryptogenic stroke OR TIA (27.4% in closure group vs 28.6% in medical arm)

TIA was also a separate endpoint

Small subcortical stroke (LACUNAR STROKE) was index event in 18% of patients (97 patients enrolled)

PC TRIAL

414 patients with cryptogenic stroke, TIA with infarct on imaging, or peripheral embolism randomized to closure with Amplatzer PFO occluder or medical therapy

Medical therapy included dual antiplatelet therapy for 1-6 months post closure

Medical arm included anticoagulation and/or antiplatelet therapy

Patients followed for 4 years

They included TIA as an endpoint which likely diluted effect of treatment

22 patients crossed over from medical arm to closure arm

Medical arm 42 lost to follow up or withdrew

Closure arm 31 lost to follow up or withdrew
PC TRIAL

PFO vs Medical arm

At baseline:
21.7% vs 21.6% on oral anticoagulation

At end of study
3.1% vs 17.1%

Percutaneous closure of patent foramen ovale in cryptogenic embolism.
PC TRIAL

Testing for hypercoagulability not specified

Extent of monitoring for atrial fibrillation not stated
RESPECT PART 1

980 Patients randomized to Amplatzer PFO occluder vs medical therapy

Medical therapy was antiplatelet (74.8%) or warfarin (25.2%)

Patients excluded if they had history of afib (How long monitoring was not stated)

Patients excluded if they had presence of anticardiolipin antibody, lupus anticoagulant, or hyperhomocysteinemia

Lacunar infarct was an exclusion EXCEPT as defined below:

- Definition: Ischemic stroke in the distribution of a single, small deep penetrating vessel in a patient with any of the following: 1) a history of hypertension (except in the first week post stroke); 2) history of diabetes mellitus; 3) Age ≥ 50; or 4) MRI or CT shows leukoaraiosis greater than symmetric, well-defined periventricular caps or bands

This was 127 patients enrolled

J.D. Carroll, J.L. Saver, D.E. Thaler, et al., RESPECT Investigators

Closure of patent foramen ovale versus medical therapy after cryptogenic stroke

FIRST GENERATION TRIALS

Taken separately, none of these studies showed a statistically significant benefit for closure.

Depending on the Meta-analysis, you could still make a case for or against Closure.

Could strokes enrolled in these studies be due to other etiology?

AF? Lacunar stroke? Hypercoagulable state?

“RESPECT attempted to exclude subcortical lacunar infarcts, yet ≥13% (n=127) of the patients randomized in RESPECT had a single small deep infarct compared with 18% (n=97) in CLOSURE.”

Device Closure of Patent Foramen Ovale After Stroke

Pooled Analysis of Completed Randomized Trials

David M. Kent, MD, a,b Issa J. Dabahreh, MD, c,d,e Robin Ruthazer, MPH, f Anthony J. Furlan, MD, f
Mark Reisman, MD, g John D. Carroll, MD, g Jeffrey L. Saver, MD, h Richard W. Smalling, MD, PhD, i Peter Jüni, MD, j,k
Heinrich P. Mattle, MD, n Bernhard Meier, MD, g David E. Thaler, MD k

ABSTRACT

BACKGROUND The comparative effectiveness of percutaneous closure of patent foramen ovale (PFO) plus medical therapy versus medical therapy alone for cryptogenic stroke is uncertain.

OBJECTIVES The authors performed the first pooled analysis of individual participant data from completed randomized trials comparing PFO closure versus medical therapy in patients with cryptogenic stroke.

METHODS The analysis included data on 2 devices (STARFlex [umbrella occluder] [NMT Medical, Inc., Boston, Massachusetts] and Amplatzer PFO Occluder [disc occluder] [AGA Medical/St. Jude Medical, St. Paul, Minnesota]) evaluated in 3 trials. The primary composite outcome was stroke, transient ischemic attack, or death; the secondary outcome was stroke. We used log-rank tests and unadjusted and covariate-adjusted Cox regression models to compare device closure versus medical therapy.

RESULTS Among 2,303 patients, closure was not significantly associated with the primary composite outcome. The difference became significant after covariate adjustment (hazard ratio [HR] 0.68; p = 0.049). For the outcome of stroke, all comparisons were statistically significant, with unadjusted and adjusted HRs of 0.58 (p = 0.043) and 0.58 (p = 0.044), respectively. In analyses limited to the 2 disc occluder device trials, the effect of closure was not significant for the composite outcome, but was for the stroke outcome (unadjusted HR: 0.39; p = 0.013). Subgroup analyses did not identify significant heterogeneity of treatment effects. Atrial fibrillation was more common among closure patients.

CONCLUSIONS Among patients with PFO and cryptogenic stroke, closure reduced recurrent stroke and had a statistically significant effect on the composite of stroke, transient ischemic attack, and death in adjusted but not unadjusted analyses. (J Am Coll Cardiol 2016;67:907-17) © 2016 by the American College of Cardiology Foundation.

Main results

We included three RCTs involving a total of 2303 participants: 1150 participants were randomized to receive TDC and 1153 participants were randomized to receive medical therapy. Overall, the risk of bias was regarded as high. The mean follow-up period of all three included trials was less than five years. Baseline characteristics (age, sex, and vascular risk factors) were similar across trials. Intention-to-treat analyses did not show a statistically significant risk reduction in the composite endpoint of recurrent stroke or TIA in the TDC group when compared with medical therapy (RR 0.73, 95% CI 0.45 to 1.17). A time-to-event analysis combining the results of two RCTs also failed to show a significant risk reduction with TDC (HR 0.69, 95% CI 0.43 to 1.47). When assessing stroke prevention alone, TDC still did not show a statistically significant benefit (RR 0.61, 95% CI 0.29 to 1.27) (HR 0.55, 95% CI 0.26 to 1.18).

In a sensitivity analysis including the two studies using the Amplatzer PFO occluder, TDC showed a possible protective effect on recurrent stroke compared with medical therapy (HR 0.38, 95% CI 0.14 to 1.02); however, it did not reach statistical significance. Safety analysis found that the overall risks for all-cause mortality and adverse events were similar in both the TDC and medical therapy groups. However, TDC increased the risk of new-onset atrial fibrillation (RR 3.50, 95% CI 1.47 to 8.35) and may be associated with the type of device used.

Authors’ conclusions

The combined data from recent RCTs have shown no statistically significant differences between TDC and medical therapy in the prevention of recurrent ischemic stroke. TDC closure was associated with an increased risk of atrial fibrillation but not with serious adverse events.
RESPECT Long Term Outcomes—same study group as RESPECT

CLOSE

GORE REDUCE

CLOSE: no listed requirement for afib detection. No listed requirement for hypercoagulable testing

Gore REDUCE:

- "6. Patient has no evidence of hypercoagulable state, which requires anticoagulation therapy. This determination will be based on the evaluation of, at a minimum: platelet count, Prothrombin Time (PT) or International Normalized Ratio (INR), Activated Partial Thromboplastin Time (aPTT), and Antiphospholipid Antibodies. All test results are to be evaluated based on the laboratory normals established at the institution. A thorough history of thromboembolic events in first degree family members must be obtained for all patients. For patients who have a first degree family member with such an event prior to age 55, or whose family history is unknown, the following additional tests are required and must be interpreted as normal: Factor V Leiden mutation, Prothrombin Gene G20210A mutation, protein C, protein S, and Antithrombin III"

-Afib detection not listed
“Patients were also excluded if they had had a stroke as a result of small-vessel occlusive disease, which was defined as the presence of a small, deep infarction (<1.5 cm in diameter) or a typical clinical lacunar syndrome.” Gore-REDUCE

“Patients with only one small deep infarction, without hypertension or diabetes, can be included in the study.” CLOSE appendix (unable to find how many patients this included)

Gore-REDUCE prescribed a hypercoagulable work up prior to randomization

They still do not account for atrial fibrillation
**HOW CAN WE ATTRIBUTE STROKE TO PFO?**

RoPE = Risk of ParadoXical Embolism Score

Derived from 12 large cohort studies

Attempt to determine attributable risk of PFO

0-10 points

High score more likely PFO implicated

If fewer traditional stroke risk factors, then more likely related to PFO

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**TABLE 1. RoPE SCORE CALCULATOR**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
<th>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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<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 without vascular risk factors, no history of stroke or TIA, and cortical infarct) = 10
- Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct) = 0
ROPE STUDY

3,674 patients from 12 databases
Determined to be cryptogenic.
48% found to have PFO.

“Complete workup” requires 1) MRI or CT, 2) intra- and extracranial vascular imaging, 3) inpatient or outpatient cardiac monitoring sufficient for the investigator to exclude atrial fibrillation, and 4) transesophageal echocardiography.

It is not listed what constitutes “sufficient” cardiac monitoring

Included TIA (15%)

Infarcts listed as:
Superficial (34%)
Multiple (9%)
Large (43%)

Some amount of infarcts were “small” and “deep” like a lacune.

ROPE STUDY

Followed for 2.2 years
In PFO patients
165 stroke
119 TIAs

After adjudication 17 strokes from known cause, 50 were cryptogenic, 87 could not be determined because of lack of data. 31 events reviewed as not stroke or TIA
PFO prevalence, attributable fraction, and estimated 2-year risk of stroke/TIA by point score strata, using control rate of 25%

<table>
<thead>
<tr>
<th>RoPE score</th>
<th>No. of patients</th>
<th>Prevalence of patients with a PFO, % (95% CI)*</th>
<th>PFO-attributable fraction, % (95% CI)*</th>
<th>CS patients with PFO (n = 1,324)</th>
<th>No. of CS patients with PFO*</th>
<th>Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>613</td>
<td>23 (19-26)</td>
<td>0 (0-4)</td>
<td>108</td>
<td>20 (12-28)</td>
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<tr>
<td>4</td>
<td>511</td>
<td>35 (31-39)</td>
<td>36 (25-48)</td>
<td>146</td>
<td>12 (6-18)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>516</td>
<td>34 (30-38)</td>
<td>34 (21-45)</td>
<td>186</td>
<td>7 (3-11)</td>
<td></td>
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<tr>
<td>6</td>
<td>482</td>
<td>47 (42-51)</td>
<td>62 (54-68)</td>
<td>236</td>
<td>8 (4-12)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>434</td>
<td>54 (49-59)</td>
<td>72 (66-76)</td>
<td>263</td>
<td>6 (2-10)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>287</td>
<td>67 (62-73)</td>
<td>84 (79-87)</td>
<td>233</td>
<td>6 (2-10)</td>
<td></td>
</tr>
<tr>
<td>9-10</td>
<td>180</td>
<td>73 (66-79)</td>
<td>88 (83-91)</td>
<td>150</td>
<td>2 (0-4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; CS = cryptogenic stroke; PFO = patent foramen ovale; RoPE = Risk of Paradoxical Embolism.

*Note: 95% CI for PFO prevalence and attributable fraction based on normal approximation to the binomial distribution.
LIMITATIONS OF ROPE

Does not make it clear whether patients had monitoring for afib

Does not make clear whether hypercoagulable state was evaluated in all patients in database

Some patients studied had lacunar strokes
ATRIAL FIBRILLATION AND CRYPTOGENIC STROKE

Two large trials in 2014 advocating for prolonged HR monitoring

EMBRACE-30 days of monitoring

CRYSTAL AF-3 years of monitoring

EMBRACE Trial did not mention anything about presence or absence of PFO

CRYSTAL AF did look at PFO
CRYSTAL-AF

441 patients 40 or older with cryptogenic stroke

Randomized to insertable cardiac monitor (REVEAL XT) or Conventional treatment

At 6 months, AF detected in 8.9% of loop patients vs 1.4% in control

Median time to detection 41 days

At 12 months 12.4% in loop vs 2.0% in control

At 36 months 30% vs 3% in control

Number needed to screen at 6 months = 14, at 12 months = 10, at 36 months = 4.

Safety — 5 devices, or 2.4%, explanted due to infection or pocket erosion

### PFO AND CRYSTAL AF

“Patients were stratified within the study groups according to the type of index event (stroke or TIA) and the presence or absence of a patent foramen ovale.”

ICM group 52 patients with PFO
Control group 46 patients with PFO

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Atrial Fibrillation Detected by 6 Mo (% of patients)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ICM</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>441 (100.0)</td>
<td>8.9</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>276 (62.6)</td>
<td>4.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>165 (37.4)</td>
<td>17.0</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>161 (36.5)</td>
<td>6.7</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>280 (63.5)</td>
<td>10.1</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>385 (87.3)</td>
<td>8.0</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (6.6)</td>
<td>9.1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>27 (6.1)</td>
<td>20.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>343 (77.8)</td>
<td>8.0</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>98 (22.2)</td>
<td>11.8</td>
<td>0.0</td>
<td></td>
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</tbody>
</table>
PFO AND ATRIAL FIBRILLATION

At 6 months
PFO group 11.8 %
Vs
Non-PFO 8%

Limitations
Mean age 61.6 +/- 11.4 years old
PFO AND ATRIAL VULNERABILITY

Electrophysiology study from 2000

62 patients under 55 with cryptogenic stroke

38 had PFO +/- ASA

24 without PFO

All underwent electrophysiology testing of Latent Atrial Vulnerability and inducibility of sustained atrial arrhythmias

41 patients had sustained atrial fibrillation

29 with PFO, 12 without PFO

(76% vs 50%) P value <0.05

Latent atrial vulnerability in 34 patients

25 with PFO, 9 without

(66% vs 38%) P value <0.03

K. Berthet, T. Lavergne et al.
PFO AND AFIB

There is probably some connection between atrial septal defect and afib.

Attribution of a cryptogenic stroke to a PFO, without prolonged monitoring with an ICM to rule out intermittent AF, especially in patients older than 55 years, may be unreliable.
IS PFO CLOSURE BETTER THAN ANTICOAGULATION?

PICSS Trial

Randomized patients to aspirin vs warfarin

630 patients enrolled.

PFO in 203 patients
Small in 119
Large in 84
ASA in 69 patients

Results:

No significant difference for recurrent cryptogenic stroke
(P=0.84; hazard ratio 0.96; 95% CI 0.62 to 1.48; 2-year event rates 14.8% versus 15.4%)

S. Homma, R.L. Sacco et al.
Effect of Medical Treatment in Stroke Patients With Patent Foramen Ovale
Patent Foramen Ovale in Cryptogenic Stroke Study
Circulation. 2002;105:2625-2631.)
No significant difference in aspirin vs warfarin for stroke prevention

Limited by small sample size

TABLE 3. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without PFO Assigned to Warfarin or Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire PICSS cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With PFO (n=203)</td>
<td>16.5% (n=97)</td>
<td>13.2% (n=106)</td>
<td>1.29 (0.63–2.64)</td>
<td>0.49</td>
</tr>
<tr>
<td>No PFO (n=398)</td>
<td>13.4% (n=195)</td>
<td>17.4% (n=203)</td>
<td>0.80 (0.49–1.33)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cryptogenic cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With PFO (n=98)</td>
<td>9.5% (n=42)</td>
<td>17.9% (n=56)</td>
<td>0.52 (0.16–1.67)</td>
<td>0.28</td>
</tr>
<tr>
<td>No PFO (n=152)</td>
<td>8.3% (n=72)</td>
<td>16.3% (n=80)</td>
<td>0.50 (0.19–1.31)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*From Kaplan-Meier curves.
CLOSE trial compared antiplatelet to anticoagulation in a prespecified manner

187 patients randomized to anticoagulation
174 patients randomized to antiplatelet

3 strokes vs 7 strokes

HR 0.44, (95% CI, 0.11–1.48)

No significant difference
PFO CLOSURE VS ANTICOAGULATION

Studied in CLOSE trial, not in a head-to-head manner though

173 patients with PFO Closure
187 (180 intention to treat analysis)
patients randomized to anticoagulation

0 patient in PFO group had stroke
3 patients in Anticoagulation group had stroke

HR 0.14 (95% CI, 0.00–1.45; P=0.26)
NAVIGATE ESUS

- 7213 patients with Embolic stroke of unknown source
- randomized to Rivaroxaban vs aspirin

- PFO in 7% of the participants (259 patients in the rivaroxaban group and 275 in the aspirin group)

- 4.8 events per 100 person-years in Aspirin vs 2.6 events per 100 person-years in Rivaroxaban

hazard ratio [HR] (0.54; 95% CI 0.22–1.36)—not statistically significant

Hemorrhage risk was similar in PFO vs non-PFO
Random-effects meta-analysis:

summary odds ratio of 0.48 (95% CI 0.24–0.96; p=0.04) for ischemic stroke in favor of anticoagulation

Interesting data but not as convincing as a clinical trial might be.

NO FORMAL STUDIES FOR PFO CLOSURE VS ANTICOAGULATION

No study looking specifically Direct oral anticoagulants vs PFO

In CLOSE only 13/187 patients taking a DOAC

NAVIGATE ESUS subgroup analysis points toward possible benefit

AVERROES Study for apixaban vs aspirin in afib

Bleeding risk similar

44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P=0.57)

May be a future area of study
Atrial fibrillation is common post procedural complication

In Meta-analysis from June of this year 93 out of 1844 patients randomized to PFO closure versus 17 out of 1667 patients randomized to antithrombotic therapy (pooled RR 4.33, 95% CI, 2.37–7.89, P<0.001)

NNT ~25 patients to cause afib

The afib reported in the studies was symptomatic. It is also noted to be transient.

What about subclinical afib?

No prolonged HR monitoring done after PFO closure in these studies

OVERALL

The absolute risk of stroke recurrence was low in both groups: 0.29 and 1.27 per 100 person-years in the closure group and the antithrombotic group, respectively.

NNT 131 to prevent 1 stroke at 1 year
BMJ Rapid Recommendation 7/18

This expert panel make a:

Strong recommendation in favour of PFO closure plus antiplatelet therapy compared with antiplatelet therapy alone

Weak recommendation in favour of PFO closure plus antiplatelet therapy compared with anticoagulants

Weak recommendation in favour of anticoagulants compared with antiplatelet therapy.

AAN guidelines from 2016 still recommend no closure

--This is outdated and ought to change

AHA/ASA do not have updated guidelines either

T. Kuijpers, F. A. Spencer, et al.


BMJ 2018;362:k2515
FURTHER QUESTIONS

What to do for TIA?
What to do for patients over 65?
What to do for small PFO?
What to do for patient with index event >9 months ago (CLOSE 6 months, Gore-REDUCE 3 months, RESPECT 9 months)?
CONCLUSION

PFO should be closed in only carefully selected patients

Determination of PFO closure should be done in collaboration between cardiology and vascular neurology

Other etiologies of stroke should be vigorously investigated
There is a recognized association between PFO and migraine with aura.

There are 3 randomized clinical trials that showed no significant treatment benefit for Migraine:

1. MIST--Migraine Intervention with STARFLex Technology
2. PRIMA--Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura
3. PREMIUM--PFO closure with the AMPLATZER PFO Occluder for the prevention of migraine

PFO CLOSURE NOT RECOMMENDED FOR MANAGEMENT OF MIGRAINE