Patent Foramen Ovale And Stroke

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My wife provides independent consultant services to academia.

We have no personal financial relationships with any for-profit entities.

Unapproved Drugs and Devices

The United States Food and Drug Administration has not approved:
- the STARFLEX Closure System for PFO closure
- the Amplatzer occluder for PFO closure

Patent Foramen Ovale (PFO)

- **PFO has been associated with stroke, particularly in young patients with cryptogenic stroke, in studies from hospital echocardiography laboratories but not in studies conducted in the general population**
- The risk of recurrent stroke on medical therapy is very low and may be lower than in those without PFO
- PFO size and coincident atrial septal aneurysm (ASA) are not consistently related to recurrence
- Warfarin is not better than aspirin in preventing recurrence, inconsistent with a venous thrombosis paradoxical embolism mechanism

Association of PFO with Stroke

	Prevalence in Stroke	Prevalence in Controls	Source
Lechat, et al (NEJM 1988; 318:1148-52)	40%	10%	Hospital Echo Lab
Petty, et al (Mayo Clin Proc 2006; 81: 602-608)	24.8%	24.7%	Community

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Recurrent Cerebrovascular Events Associated with Patent Foramen Ovale on Anti-platelet Therapy

(Mas J-L, et al: NEJM 2001; 345: 1740-1746)

RECURRENT STROKE

	No PFO or ASA	PFO only
2 years	3.7% (1.6 -5.8)	1.8 % (.05 - 3.6)
4 years	4.2% (1.8 - 6.6)	2.3% (0.3 – 9.3)

ASA – atrial septal aneurysm

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Recurrent Cerebrovascular Events Associated with Patent Foramen Ovale and Atrial Septal Aneurysm on Anti-platelet Therapy

(Mas J-L, et al: NEJM 2001; 345: 1740-1746)

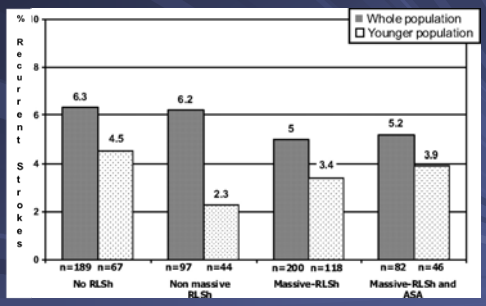
RECURRENT STROKE

	No PFO or ASA	PFO + ASA
2 years	3.7% (1.6 -5.8)	4.0 % (0.0 - 9.4)
4 years	4.2% (1.8 - 6.6)	15.2% (1.8 – 33.4)

ASA – atrial septal aneurysm. No events in 10 patients with ASA alone

Stroke recurrence by Right-Left Shunt (RLSh) magnitude and presence of Atrial Septal Aneurysm (ASA) in the whole and younger (< 55) populations.

Mean follow-up 2.0 ± 1.1 yrs



CODICIA Serena J et al. Stroke 2008;39:3131-3136

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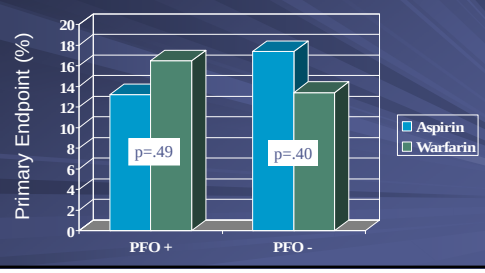
Effect of Medical Treatment on Subsequent Ischemic Stroke and Death for Patients with Stroke and PFO

(Homma, S et al: Circulation 2002; 105:2625-2631)



3 Randomized Controlled Trials of Mechanical Closure of Patent Foramen Ovale to Prevent Recurrent Stroke

- STARFlex device
  - CLOSURE I
- Amplatzer PFO occluder
  - RESPECT
  - PC Trial

CLOSURE I

Furlan, et al: N Engl J Med 2012; 366:991-9

- At two years, there was no difference between the two groups in the primary combined endpoint of stroke, TIA, and neurological death plus all death within 30 days
  - Device 5.5% (23 events)
  - Medical only 6.8% (29 events), p=0.37
- For Stroke alone
  - Device 2.9% (12)
  - Medical only 3.1% (13), p=0.77

Lost-to follow-up

Closure	1.7 % (8/447)
Medical only	0.6% (3/462)

CLOSURE I

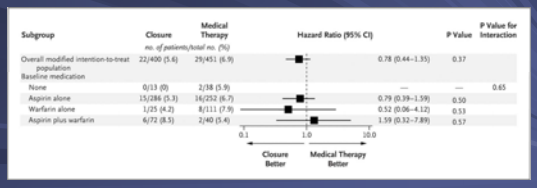
Furlan, et al: N Engl J Med 2012; 366:991-9

- Neither the degree of right-to-left shunt nor the presence of atrial septal aneurysm identified a subgroup that benefitted from PFO closure.
- Certain serious adverse events were more common in the closure group:
  - Major vascular procedural complications (3.2% vs 0%, p < .001)
  - Atrial fibrillation (5.7% vs 0.7%, p < .001)

CLOSURE I

Furlan, et al: N Engl J Med 2012; 366:991-9

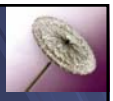
NO Benefit for "Medical Failures"



RESPECT

Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Standard of Care Treatment

N Engl J Med 2013;368:1092-100.



- At a mean follow-up of 2.6 years, there was no significant difference between the two groups in the primary combined endpoint of death within 45 days or ischemic stroke
  - Device group – 9 strokes
  - Medical only group – 16 strokes

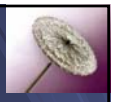
    Hazard ratio 0.49 (95% CI .22 – 1.11), p= .08
- Almost five times more had incomplete follow-up than had endpoints

Closure	8.6 % (43/499)
Medical only	16.4% (79/481)

RESPECT

Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Standard of Care Treatment

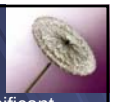
N Engl J Med 2013;368:1092-100.



- Both a substantial degree of right-to-left shunt and the presence of atrial septal aneurysm favored the PFO closure group in multiple subgroup analyses.
- Serious adverse events were uncommon in the closure group:
  - Major vascular procedural complications (0.8% vs 0%, p < .124)
  - Atrial fibrillation (0.6% vs 0.6%, p =1)

The PC Trial

N Engl J Med 2013; 368:1083-1091



- At a mean follow-up of 4 years, there was no significant difference between the two groups in the primary combined endpoint of any death, non-fatal stroke, TIA or peripheral embolism
  - Device Group - 7 events
  - Medical only Group - 11 events

    Hazard Ratio 0.63 (95%CI .24 – 1.62) , p=.34
- For Stroke
  - Device group – 1 stroke
  - Medical only group – 5 strokes

    Hazard ratio 0.20 (95% CI ,.02 – 1.72), p= .14
- Four times more had incomplete follow-up than had endpoints

Closure	15% (31/204)
Medical only	20% (42/210)

Randomized Controlled Trials of Mechanical Closure of Patent Foramen Ovale to Prevent Recurrent Stroke

- All three trials all individually failed to achieve primary endpoint
- What about a meta-analysis?

Meta-analysis of 3 PFO Closure RCTs on Recurrent Stroke

Kitsios, et al. Stroke DOI 10.1161/STROKEAHA.113.001773

	Device	Medical Only	Risk Ratio (95% CI)
CLOSURE I	12/447	13/462	0.90 (.41,1.98)
RESPECT	9/499	16/481	0.49 (.21, 1.11)
PC	1/204	5/210	0.14 (.02,1.17)
Pooled RCTs	Random Effects Model (Trial Heterogeneity)		0.55 (.26,1.18) NOT SIGNIFICANT

. . . but is it appropriate to lump data from two different devices?

Meta-analysis of 2 PFO Closure RCTs with Amplazter Device on Recurrent Stroke

Kitsios, et al. Stroke DOI 10.1161/STROKEAHA.113.001773

	Device	Medical Only	Risk Ratio (95% CI)
RESPECT	9/499	16/481	0.49 (.21, 1.11)
PC	1/204	5/210	0.14 (.02,1.17)
Pooled RCTs	Random Effects Model (Trial Heterogeneity)		0.38 (.14,1.02) NOT SIGNIFICANT
Pooled RCTs	Fixed Effect Model (No Trial Heterogeneity)		0.41 (.19, .88) **SIGNIFICANT**

However, these 2 trials had incomplete follow-up patients > 4 x the total endpoints.
One additional stroke in the lost to follow-up device patients would render the fixed effects model not statistically significant

Mechanical Closure of PFO to Prevent Recurrent Stoke Where are we?

- The importance of PFO as a cause of stroke is marginal at best
- The risk of recurrent stroke on anti-platelet therapy is very low
- Studies that show a trend toward benefit of closure have serious methodological problems
- The long-term safety of the implanted closure devices is unknown

Mechanical Closure of PFO to Prevent Recurrent Stoke

MY ASSESSMENT OF THE DATA

- The evidence is insufficient at this time to recommend mechanical closure of PFO to prevent recurrent stroke, even for those with recurrent events on medical therapy