PFO & Stroke - TIA:

Design and Early Insights from The CLOSURE I Trial

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* Disclosure: Consulting and honoraria from NMT medical

What we know about PFOs

- Present in ~ 10 -12% of population
- Greater frequency in patients with stroke
- Even greater frequency (45-55%) in young patients with cryptogenic stroke
- Suggests treatment of PFO might prevent recurrent stroke

Treatment of PFO

Currently based on questionable opinions:

- PFO closure works better than medical therapy
- Medical therapy is adequate treatment

The Reality? We have equipoise!

Why do cardiologists favor closure of PFO?

- Reports of lower stroke rates in patients after endovascular closure
- Reports of relatively high recurrent stroke rates in some PFO morphologies
- Patient anxiety about stroke recurrence and a "defective heart"
- They like to do procedures

Why do neurologists favor medical therapy?

- Unproven benefit of PFO closure
- Reports of low stroke rates on medical therapy
- They don’t do procedures
  (not yet!)

Medical Therapy: Mas Study - Recurrent Events at 2 and 4 Years

Patients ages 18-55 years (mean 40) with cryptogenic stroke on ASA – Standardized protocol 30 sites in Europe

		2 Yrs		4 Yrs	
	Pts	Stroke	Str/TIA	Stroke	Str/TIA
No PFO/ASA	304	3.7% (1.6-5.8)	4.7% (2.3-7.1)	4.2% (1.8-6.6)	6.2% (3.0-9.3)
PFO	216	1.8% (.05-3.6)	4.6% (1.8-7.4)	2.3% (0.3-4.3)	5.6% (2.5-8.7)
PFO+ASA*	51	4.0% (0.0-9.4)	8.0% (0.5-15.5)	15.2% (1.8-28.6)	19.2% (5.0-33.4)

Deficiencies: Numbers too small. No comparison to closure.

* Atrial Septal Aneurysm

Mas et al. N Engl J Med 2001, 345:1740-6

Medical Therapy: PFO in Cryptogenic Stroke Study (PICSS) 2 Year Event Rates

WARSS substudy – Patients ages 30-85 yrs (mean 59) with cryptogenic stroke

	# Pts	Stroke / Death	TIA/Stroke/ Death
No PFO	152	12.7%	16.6%
PFO	98	14.3%	20.4%

No differences between groups treated with warfarin and aspirin

Deficiencies: Includes other stroke risks; older population; TEE was voluntary.

Homma S: Circulation, Volume 105(22).June 4, 2002.2625-2631

PFO Treatment Options: Closure v. Medical Therapy

	Recurrent event rates @ 1 Yr.	Complications	Problems
Catheter Closure	0% - 4.9%	Major: 1.5% Minor: 7.9%	Selection bias. Significant variation in post implant pharm.
Medical Therapy	3.8 – 12.0%	Major: 1%/yr on warfarin	Poor match to PFO population. Variable medical Rx.

Major conclusion: EQUIPOISE!

Randomized trials needed.

Khairy, Landzberg et al. Ann Int Med 2003;139:753-760.

AAN Practice Parameter on PFO: Quality Standards Subcommittee

- **Insufficient evidence** to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death
- **Insufficient evidence** regarding the effectiveness of either surgical or percutaneous closure of PFO.
- **No evidence that either medical therapy or PFO closure is superior to the other.**

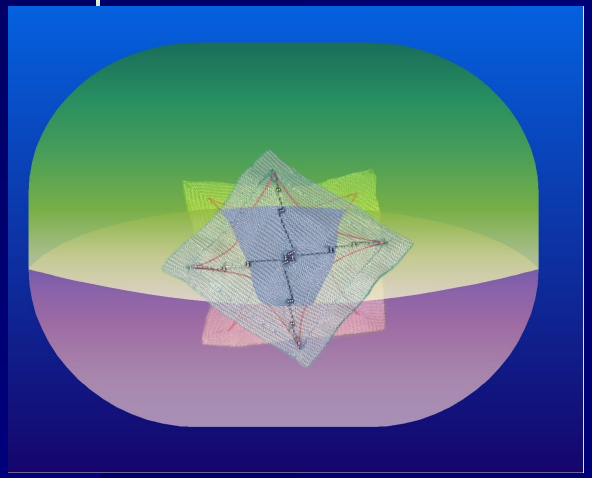
Neurology 2004;62:1042-1050

AAN Practice Parameter on PFO: Quality Standards Subcommittee

"Clinicians who encounter patients with cryptogenic stroke and PFO, with or without atrial septal aneurysm, should encourage them to consider participating in research protocols."

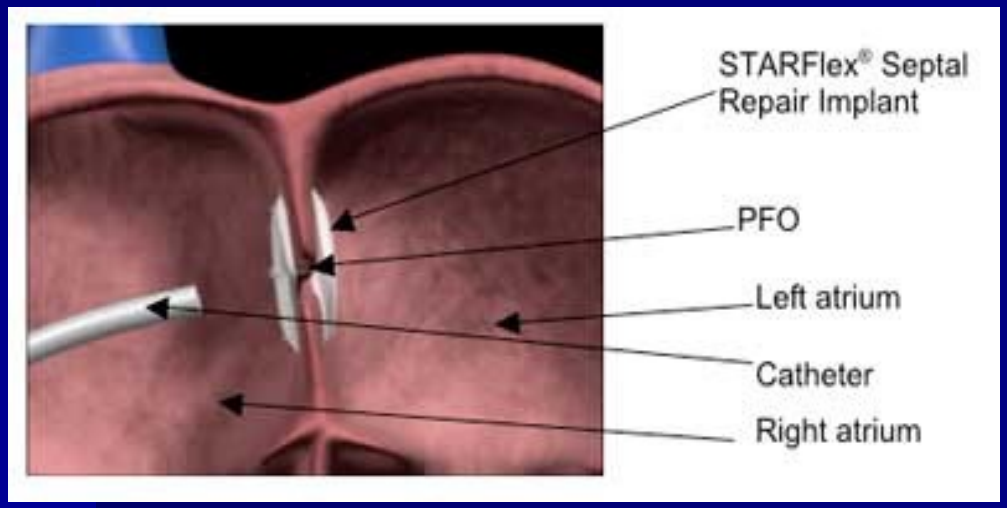
Neurology 2004;62:1042-1050

The STARFlex® Septal Occluder



STARFlex is designed to/for:

- Autocenter in the PFO.
- Higher complete closure rates.
- Lower profile on the septum.



Images courtesy NMT Medical

CLOSURE I*

- Prospective, randomized, multi-center controlled trial comparing endovascular closure with STARFlex device with best medical therapy
- 1600 patients; 1:1 randomization; 100 centers US & Canada
- Best medical therapy: warfarin or aspirin
- Primary endpoint: stroke, TIA and mortality at 2 years
- Neurology / Cardiology executive committee

*** CLOSURE I is sponsored by NMT Medical, Inc. www.CLOSUREI.COM**

CLOSURE I: Inclusion

- Age 18-60
- Cryptogenic stroke or TIA within 6 months
- Positive contrast bubble study by TEE, demonstrating right to left shunting through a PFO during Valsalva.

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CLOSURE I: Exclusions

- Other source of stroke or TIA
- Need for long term warfarin
- Stroke or TIA > 6 months prior to entry
- Contraindication to device

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Closure I: Definitions

- Stroke
  - Acute focal neurological symptoms lasting < 24 hours associated with restricted diffusion on DW-MRI done within 72 hours of clinical event
  - Acute focal neurological symptoms lasting > 24 hours associated with infarction on brain CT or MR
- TIA
  - Acute focal motor weakness, speech/language difficulty, amaurosis fugax or blindness lasting > 10 min

CLOSURE I: Treatment

- Device group
  - Aspirin 81-325 mg daily for duration of study
  - Clopidogrel 75 mg daily for 6 months
  - SBE prophylaxis for 6 months
- Medical therapy group
  - Aspirin 81-325 mg
  - Warfarin INR 2-3

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CLOSURE I

- Patients enrolled to date
  - 65 Medical
  - 65 STARFlex

Other trials also struggling to enroll….

Why isn’t enrollment proceeding faster?

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Barriers to PFO trials

- Neurologists
  - Don't routinely look for PFO
  - Believe medical therapy works well
- Cardiologists
  - Believe closure is a proven, optimal therapy.
  - Misinterpret HDE indication for use.
  - Referral issues
  - Encounter strong patient anxiety about "my hole in my heart"

Barriers to PFO trials

- Patients
  - Hit with a double whammy!
    - Stroke or TIA
    - Hole in the heart
  - Are savvy medical care shoppers
  - Enter the study portal highly biased by local MD.

Recommendations for PFO Stroke - TIA

- "Reality" of the literature must be communicated to referral community:
  EQUIPOISE
- Close cooperation between neurology and cardiology
- Direct ALL patients through neurologists initially
- Strict adherence to HDE requirements
  - Recurrent stroke with failed medical therapy
- No off label use of devices

Conclusions

- PFO frequently associated with cryptogenic stroke, ***but not a proven 'cause'.***
- Medical and endovascular closure both reasonable options but ***best therapy is unproven – unknown.***
- ***We must complete*** prospective randomized controlled trials to determine best therapy

Thoughts on the risks of *not* completing the trials…

- Neurology will not accept closure as a treatment of choice without evidence from randomized trials
- Patients who benefit from device won't get it; those who do not benefit exposed to risks
- Reimbursement for PFO closure limited or nonexistent
- PFO closure will never realize it's full therapeutic potential in preventing recurrent CVA