PFO Closure: Where We Are Going to after CLOSURE I Study?

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Disclosure Statement of Financial Interest

- I, (Issam Moussa) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Patent Foramen Ovale (PFO)
Discussion Plan

- Clinical impact of a PFO
- Decision making in patients with PFO & Cryptogenic stroke – Pre CLOSURE I
- CLOSURE I Trial
  - What did we learn?
- Decision making in patients with PFO & Cryptogenic stroke - Post CLOSURE I
- Future Directions

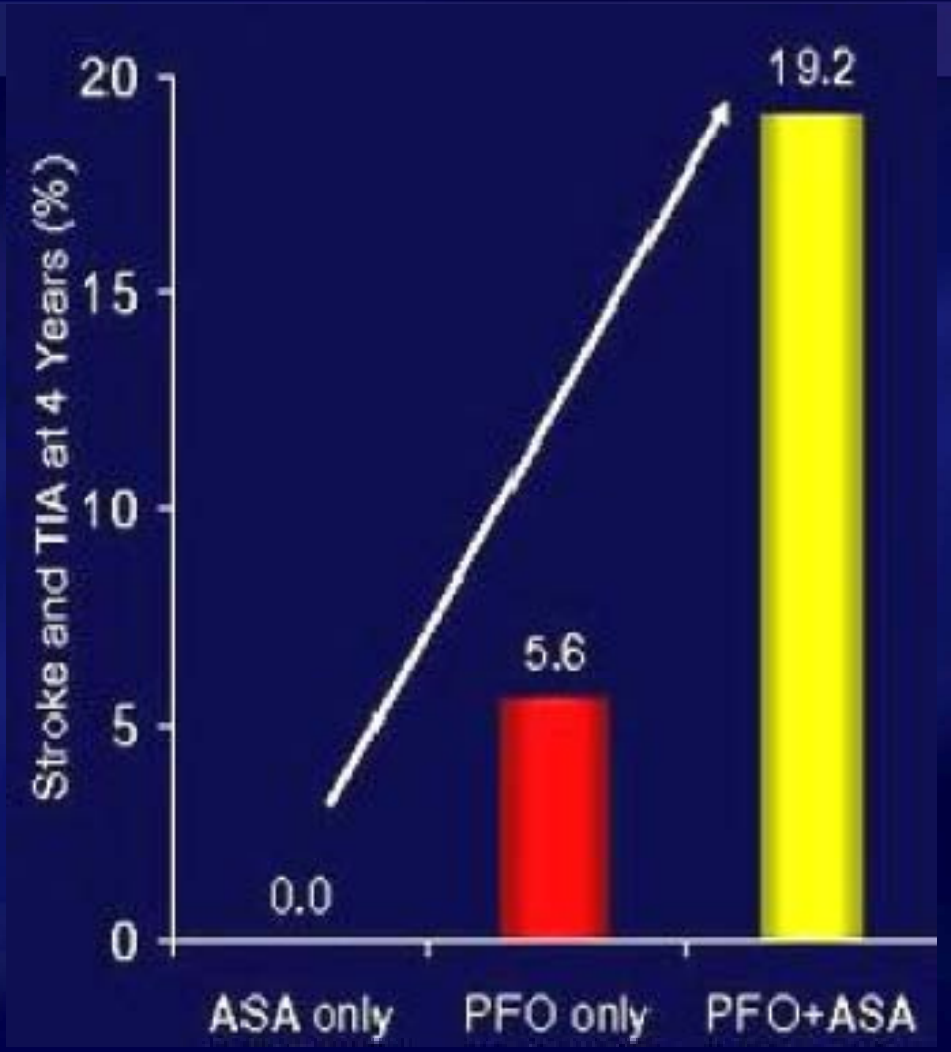
Clinical Impact

- PFO often has no clinical sequelae, but it can be associated with the following disorders:
  - Stroke / TIA
  - Migraine
  - Plathypnea-orthodeoxia syndrome
  - Decompression sickness of the diver

PFO & Cryptogenic Stroke (CS)

There is an Association?

- 581 patients with cryptogenic stroke
- (age 18-55 yrs.)
- TEE
  - n: 304 no septal abnormality
  - n: 216 PFO alone
  - n: 10 ASA alone
  - n: 51 PFO and ASA
- Treatment
  - Aspirin 300 mg qd



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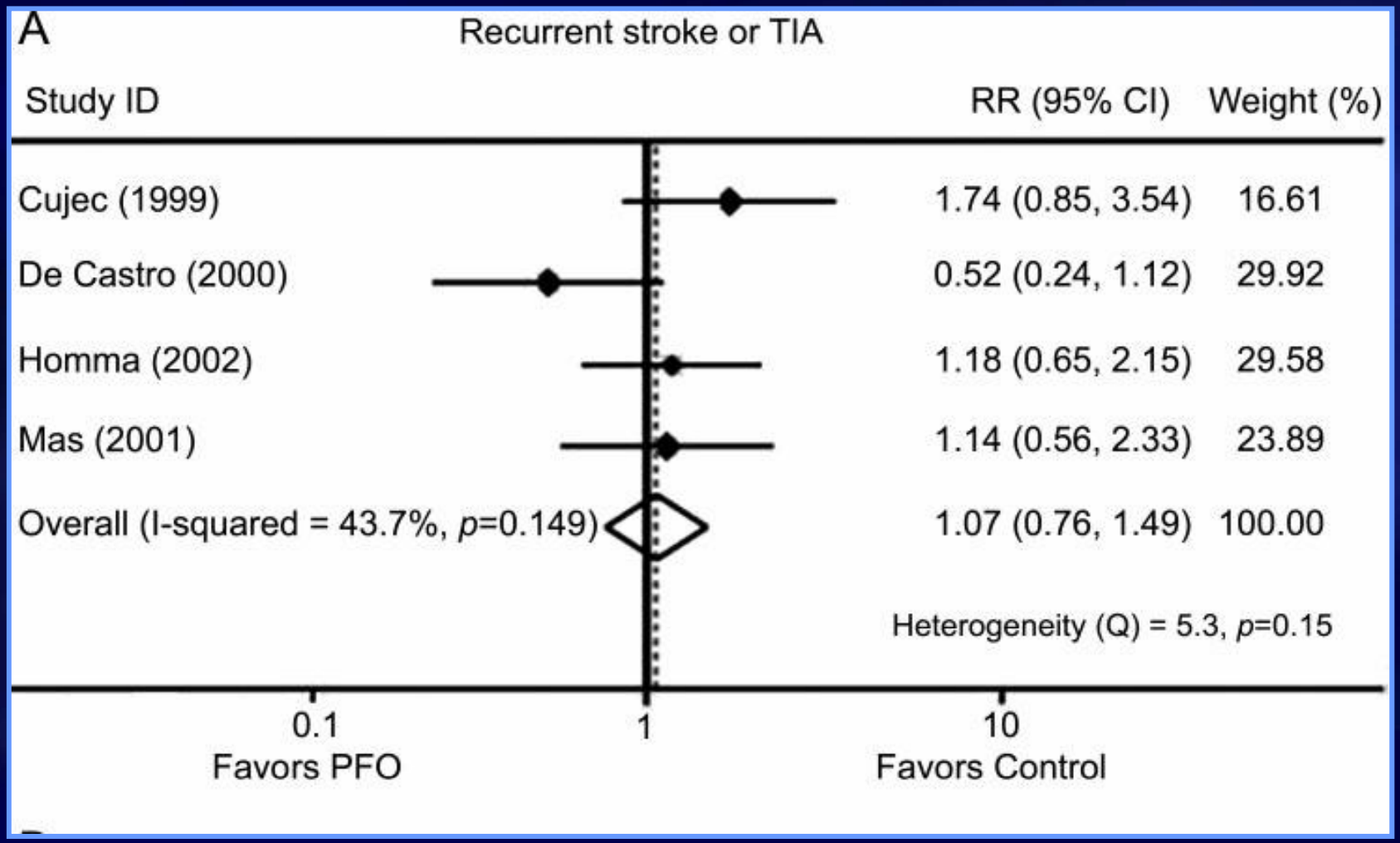
Mas JL, et al. N Engl J Med. 2001; 345: 1740-1746

PFO & Cryptogenic Stroke

There is No Association?



Almekhlafi et al Neurology 72, 2009

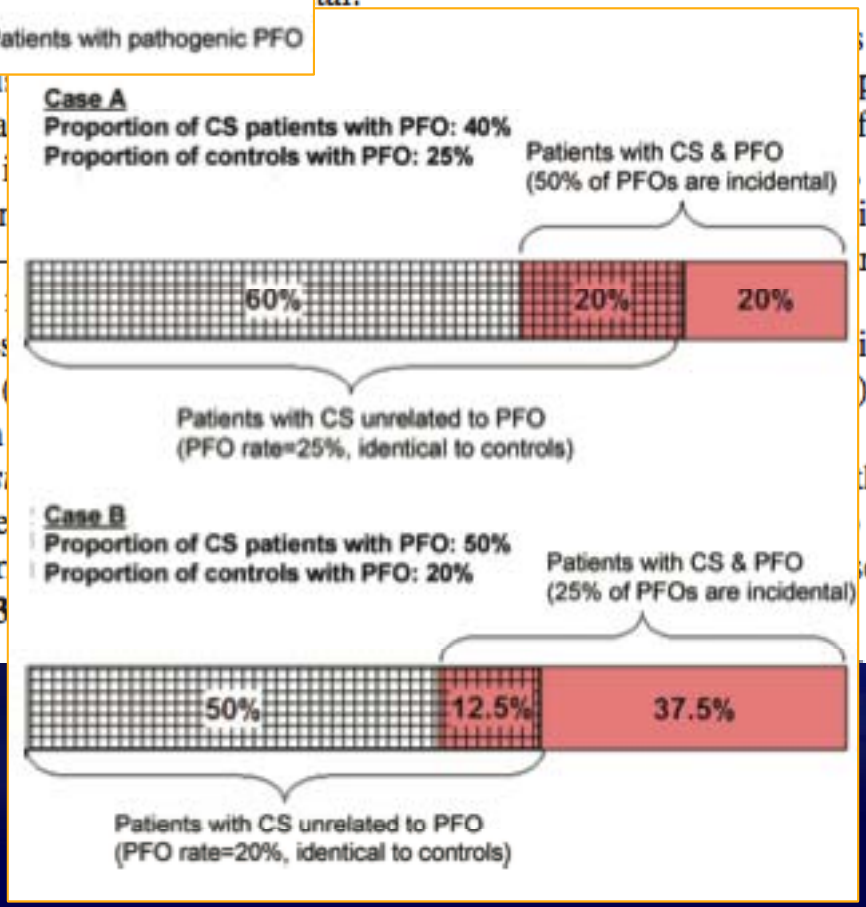
PFO in Cryptogenic Stroke
Incidental or Pathogenic?

Ba Patent foramen ovale (PFO) is significantly associated with cryptogenic stroke (CS). However, a PFO can be an incidental finding. We sought to estimate the probability that a PFO in a tal.

Me examining the prevalence of PFO in patients with CS ple assumptions and Bayes' theorem, we calculated the ffects meta-analyses estimated the odds ratio (OR) of a with or without atrial septal aneurysms, and were used is incidental.

Results– rol subjects was 2.9 (CI, 2.1 to 4.0). The corresponding (3.3 to 7.8) and 2.0 (>1.0 to 3.7), respectively. The idental were 33% (28% to 39%) in age-inclusive studies,) in older patients. These probabilities were much lower

Conclus hird of discovered PFOs are likely to be incidental and patient characteristics such as age and the presence of election in therapeutic decision-making. (***Stroke.*** **2009; 40:23**



approximately one third of PFOs are likely to be incidental and hence not benefit from closure

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Stroke. 2009; 40:2349-2355

Decision Making in Pts with PFO & CS
Pre- CLOSURE I

- Best treatment for an individual patient with "symptomatic" PFO is uncertain
- The patient need to understand:
  - The risk of recurrence on only medical therapy
  - The risk of the procedure (closing a PFO)
  - The extent of uncertainty
  - Having the option to be enrolled in a RCT

The CLOSURE I Trial

CLOSURE I

Study Design

- ***Prospective, multi-center, randomized, open-label, two-arm superiority trial*** **designed to test whether PFO closure using STARFlex® plus medical therapy is superior to medical therapy alone for preventing recurrent stroke or TIA in patients with cryptogenic stroke or TIA and a PFO.**
- ***Study population*****: Patients 60 years old or younger with a cryptogenic stroke or TIA and a PFO documented by TEE, with or without ASA, within 6 months of randomization (DVT, hypercoagulopathy excluded)**
- ***Primary endpoint*** **: 2-year incidence of stroke or TIA, all cause mortality for the first 30 days, and neurological mortality 31 days to 2 years**
- ***Follow-up*** **at 1 month, 6 months, 12 months and 24 months by a board certified neurologist. Repeat TEE at 6 months all patients and 12/24 months if residual leak.**

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Furlan AJ et al. AHA 2010

CLOSURE I
Statistical Design

- *Sample size*:
  expected primary endpoint 6% for medical therapy and 2% for STARFlex
  900 patients (450 per treatment group) provides 80% power and a two-sided significance level (alpha) of 0.05

- *Primary analysis* intent-to-treat

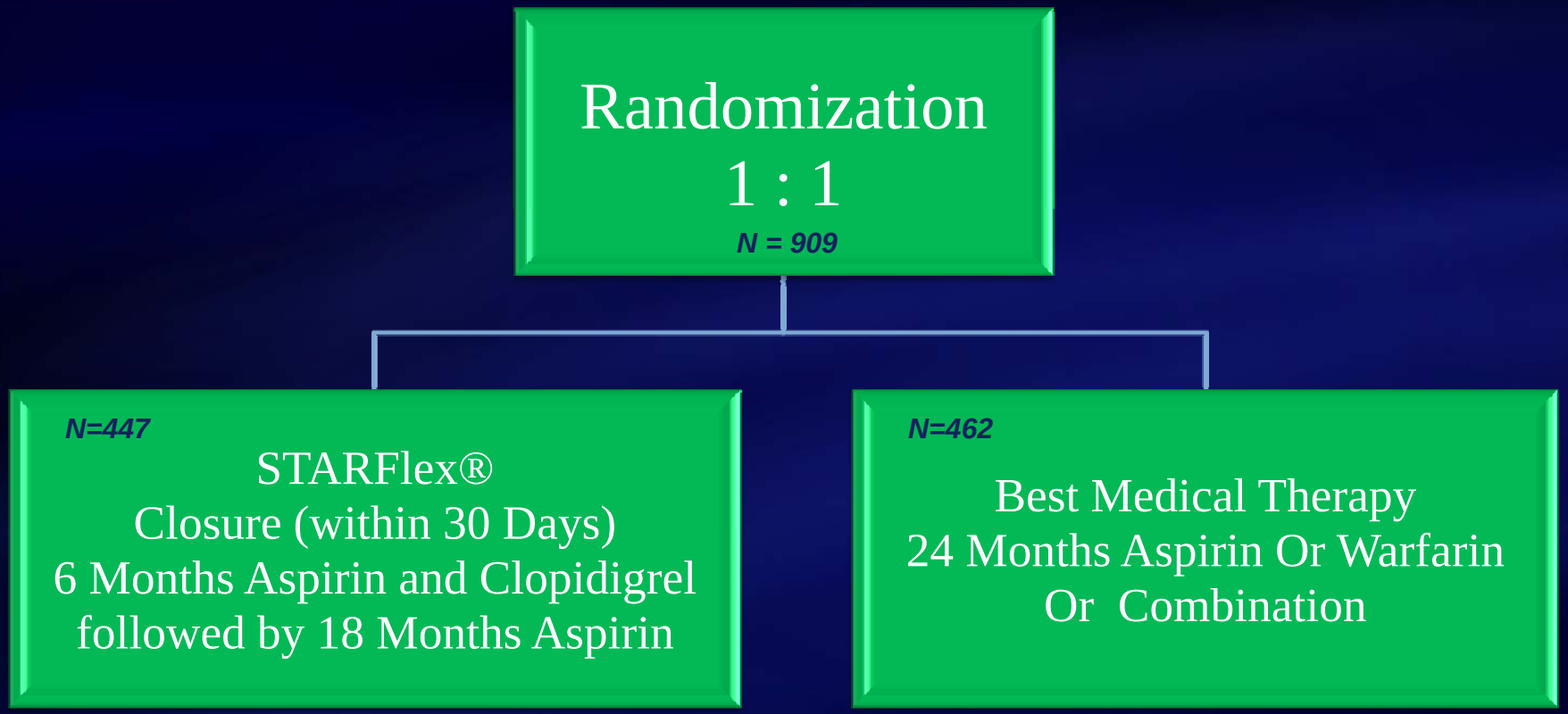
- *Safety analyses* performed on the Safety Analysis population, defined as all randomized patients who received the randomized treatment

STARFlex®

- Double umbrella comprised of MP35N framework with attached polyester fabric
- 23mm, 28mm, 33mm

CLOSURE I

Randomization



Between June 23, 2003 and October 24, 2008, 909 patients were randomized at 87 sites in the United States and Canada. ***Block randomization with stratification by study site and by the presence or absence of an ASA viewed by TEE.***

CLOSURE I
Baseline Characteristics ITT

	STARFlex	Medical	P value
N randomized	447	462	
Mean Age	46.3 (18-61)	45.7(18-61)	
Male	52.1%	51.5%	
White	89%	90%	
Index cryptogenic stroke	73%	71%	
Mod/substantial shunt*	58% (231/400)	51% (228/451)	0.04
ASA ≥ 10 mm*	38% (151/400)	35% (160/451)	0.49

**** modified ITT***

CLOSURE I

2 Year Primary Endpoint ITT

	STARFlex n = 447	**Medical** n = 462	**Adjusted P value***
Composite	5.9% (n=25)	7.7% (n=30)	0.30
Stroke	3.1% (n=12)	3.4% (n=13)	0.77
TIA	3.3% (n=13)	4.6% (n=17)	0.39

Adjusting performed using Cox Proportional Hazard Regression and adjusting for related patient characteristics including: age, atrial septal aneurysm, prior TIA/CVA, smoking, hypertension, hypercholesterolemia

CLOSURE I
Adverse Events

	STARFlex N=402	Medical N=458	P value
Major vascular complications*	3.2% (n =13)	0.0%	<0.001
Atrial fibrillation	5.7% (n= 14/23 periprocedural)	0.7% (n=3)	<0.001
Major bleeding	2.6% (n=10)	1.1% (n=4)	0.11
Deaths (all non endpoint)	0.5% (n=2)	0.7% (n=3)	ns
Nervous system disorders	3.2% (n=12)	5.3% (n=20)	0.15
Any SAE	16.9% (n=68)	16.6% (n=76)	ns

Perforation LA (1); hematoma >5cm at access site (4); vascular surgical repair (1); peripheral nerve injury (1); procedural related transfusion (3);retroperitoneal bleed (3)

CLOSURE I
STARFlex Technical Success

	STARFlex n=402	95% CI
Procedural success	90.0%	(86.7%,92.8%)
Thrombus by TEE	1.0% (n=4; stroke in 2 at days 4, 52)	
Effective closure	No recurrent stroke or TIA in patients with residual leaks	
TEE 6 mos	86.1% closed	(82.1%,89.4%)
TEE 12 mos	86.4% closed	(82.5%,89.8%)
TEE 24 mos	86.7% closed	(82.8%,90.0%)

***Procedural success** was defined as successful delivery of one or more STARFlex devices to the site during the index procedure, deployment of the device at the intended site, and removal of the delivery system without a major procedural complication prior to discharge. **Effective closure** was defined as procedural success with either grade 0 (none) or 1 (trace) residual shunt by TEE.*

CLOSURE I
Aspirin versus Warfarin

	Aspirin alone (n=243)	**Warfarin alone (n=139)**	P value
Composite	6.7% (n=14)	8.1% (n=9)	0.63
Stroke	3.9% (n=8)	2.7% (n=3)	0.67
TIA	2.9% (n=6)	6.3% (n=7)	0.09

CLOSURE I
Conclusions

- CLOSURE I is the first completed RCT independently adjudicated PFO device closure study

- Superiority of PFO closure with STARFlex® plus medical therapy over medical therapy alone was not demonstrated.
  - no significant benefit related to degree of initial shunt
  - no significant benefit with ASA
  - insignificant trend (1.8%) favoring device driven by TIA
  - 2 year stroke rate essentially identical in both arms (3%)

- Major vascular (procedural) complications in 3% of device arm

- Significantly higher rate of atrial fibrillation in device arm (5.7%) (60% peri-procedural)

The CLOSURE I Trial

Limitations

- **Patient selection**

  Qualifying ischemic event (Clinical definition of TIA)

  Extent of baseline work-up

  Type of PFO

- **Patient recruitment**

  2 pt / yr !

  - **Medical treatment**

  Inconsistent in the control arm (Aspirin vs. Warfarin)

  Different between the control and closure arms

- **Device type**

  Thrombus formation, incidence of afib, residual shunt

- **Length of follow-up**: Is 2 yrs long enough?

CLOSURE I

Limitations

- The majority of the stroke endpoint events during follow-up appeared to have a determinable origin, suggesting that these patients likely had alternative explanations for their index stroke.

- Nearly half of the stroke endpoint events in the PFO closure arm appeared to be directly related to the device. A quarter of these occurred in the first 30 days after implantation.

-

- Device-related complications were considered “insignificant”!
  - Incidence of new atrial fibrillation (5.7%) and device thrombus (4 cases and 2 cases lead to a subsequent stroke) associated with recurrent events

Future RCTs of PFO Closure in Patients with Cryptogenic Stroke

Will they Remedy the Limitations of the CLOSURE I Trial?

Randomized PFO Stroke Trials

Trial	Respect	Closure I	Reduce
N	500+	900	664
Device (Company)	Amplatzer (AGA)	StarFlex (NMT)	Helex (Gore)
Inclusion	Stroke	Stroke or TIA	Stroke or MRI TIA
Primary Endpoint	Stroke	Stroke or TIA	Stroke or MRI TIA
Key Secondary Endpoints	? Migraine	? Migraine	MRI WMLs

PFO Morphology

Does It Matter?

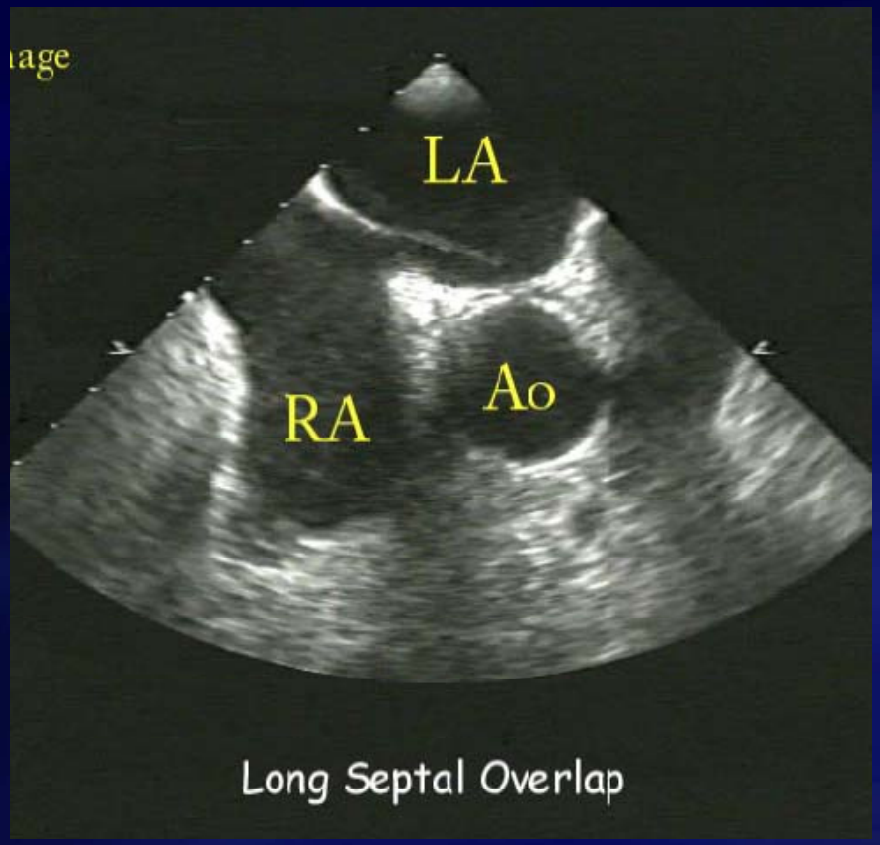
PFO
Are all PFOs the Same?

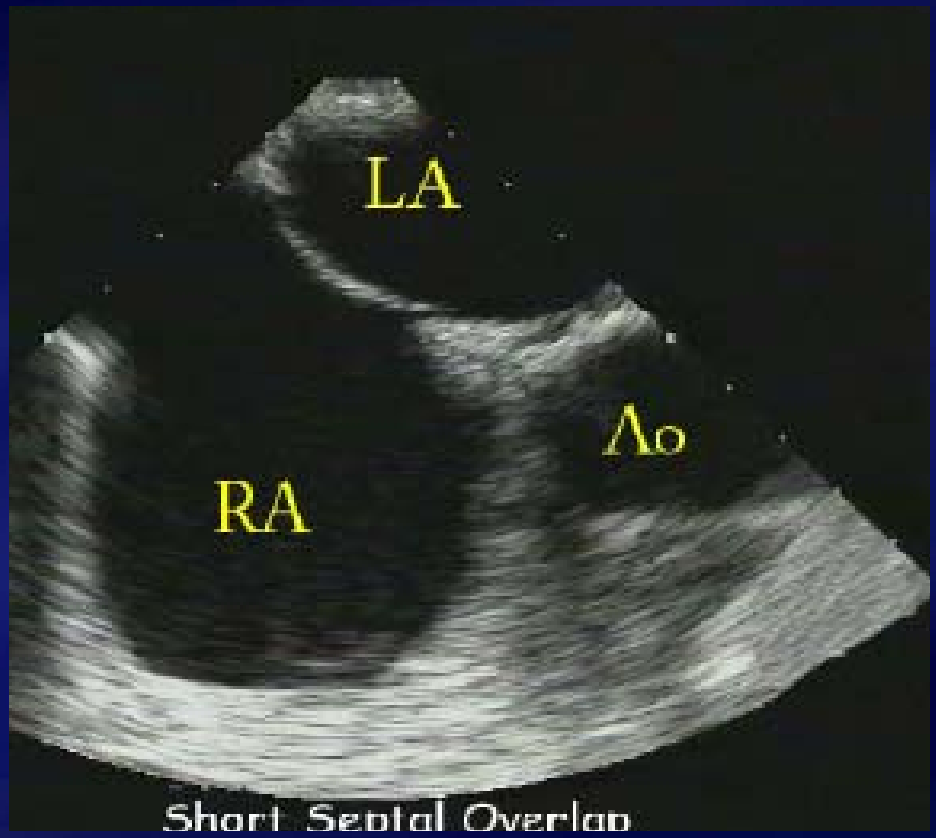
- Characteristics of Septum Primum:
  - Presence of ASA
  - Separation from Septum Secundum
  - Length of Overlap with Septum Secundum
- Characteristics of Septum Secundum:
  - Variable Length
  - Variable Thickness
- Characteristics of Septal Overlap:
  - Length of attachments
  - Complexity of overlap

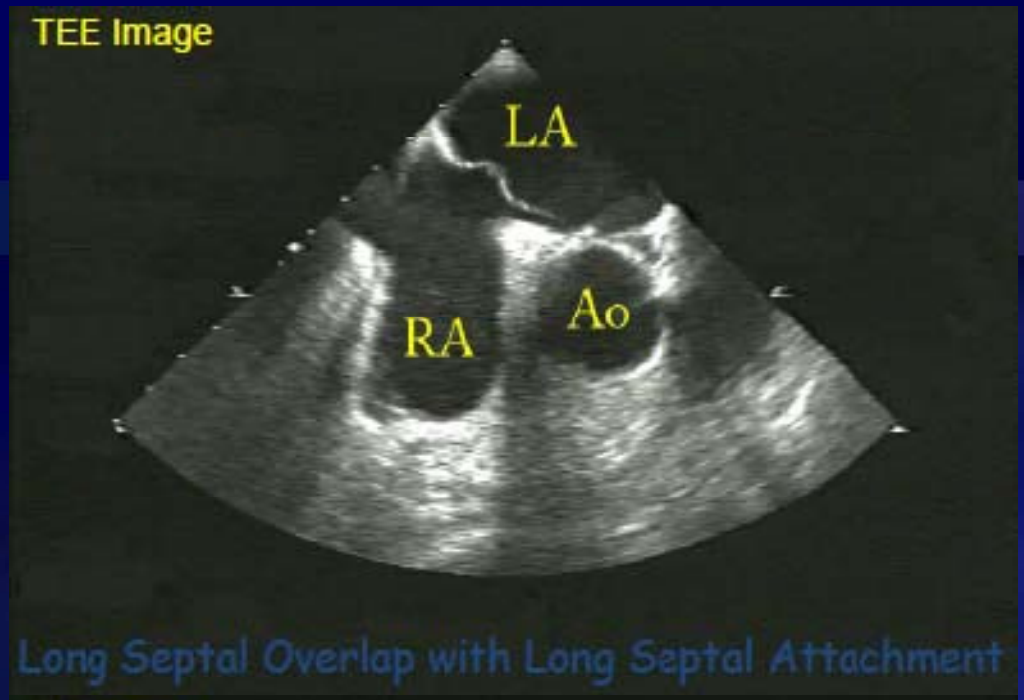
PFO Variations

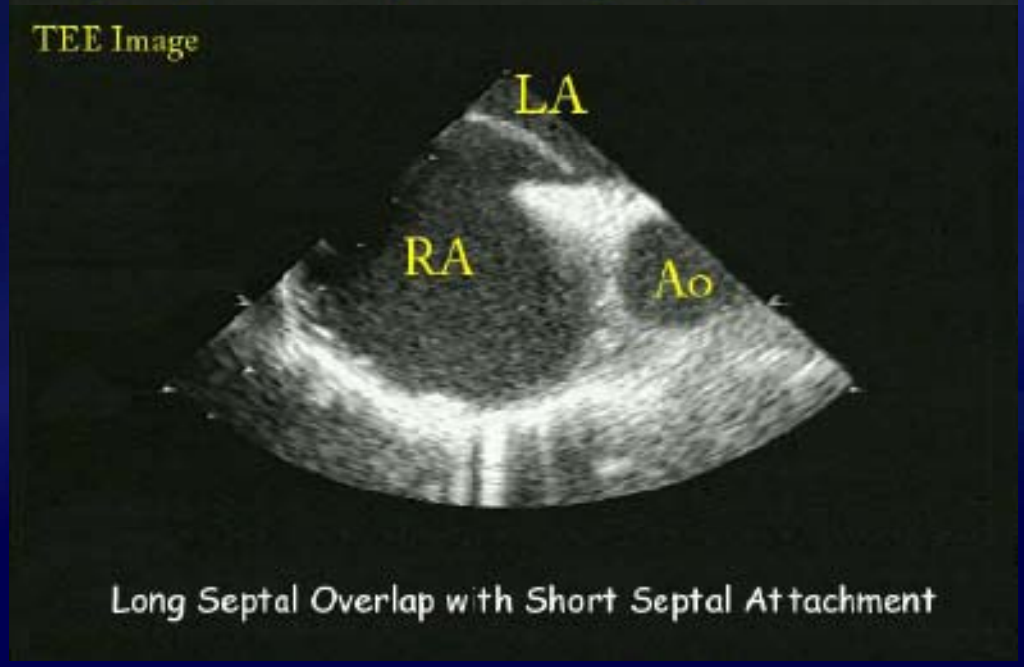
- Long/short septal overlap
- Long/short septal attachment
- Minimal/wide septal separation
  - Stiff/floppy septum primum
  - Aneurysmal septum primum
- Thin/thick septum secundum
- Long/short septum secundum

PFO Variations






TEE Image
LA
RA
Ao
Long Septal Overlap with Long Septal Attachment


TEE Image
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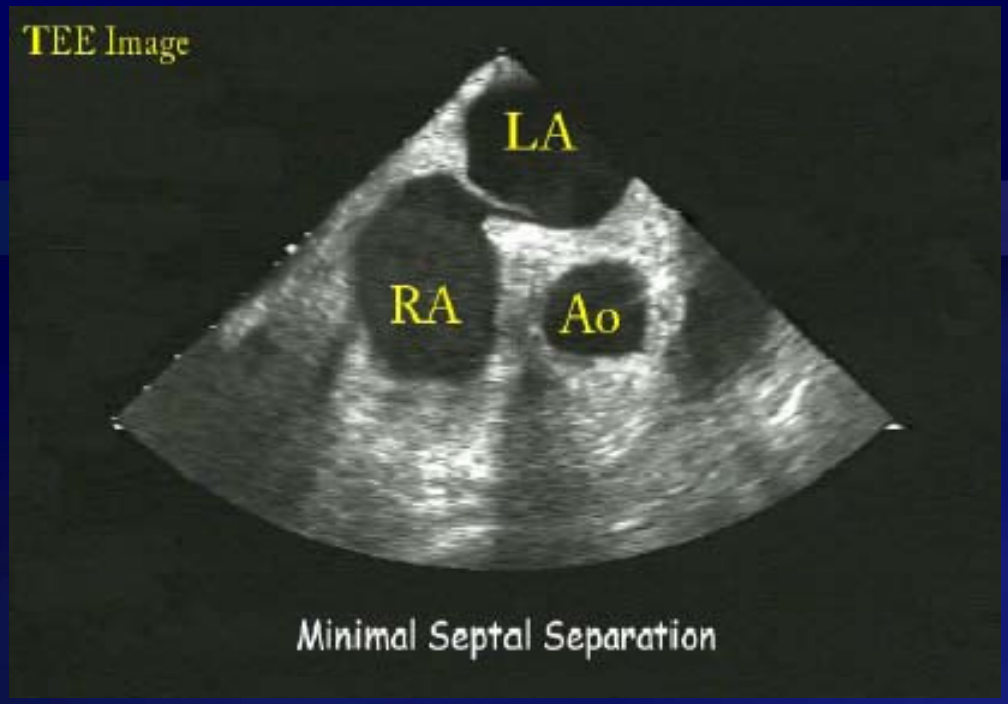
Long Septal Overlap with Short Septal Attachment


TEE Image
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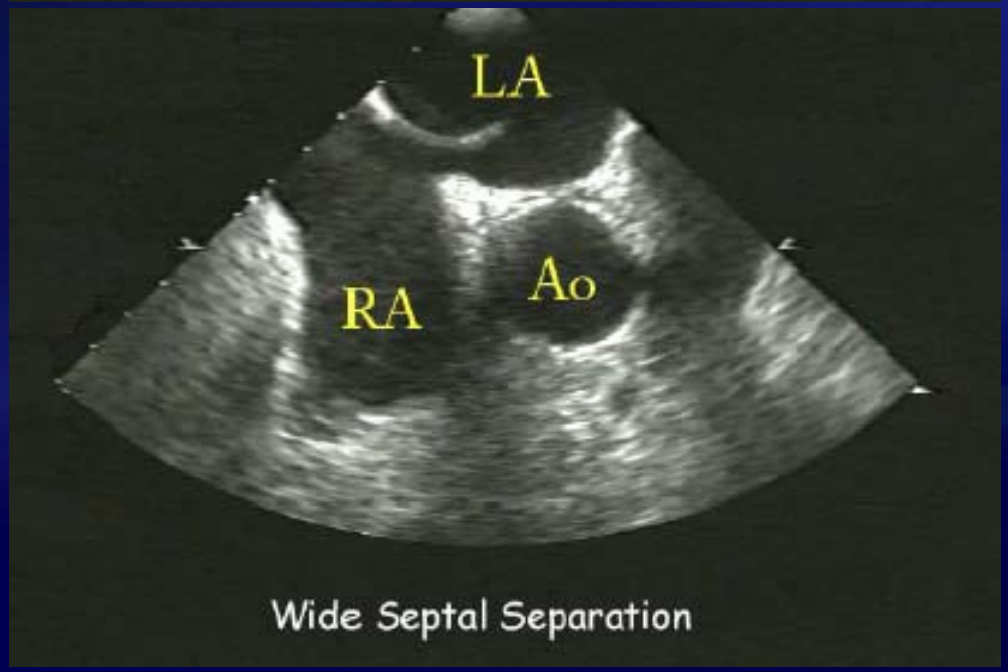
Minimal Septal Separation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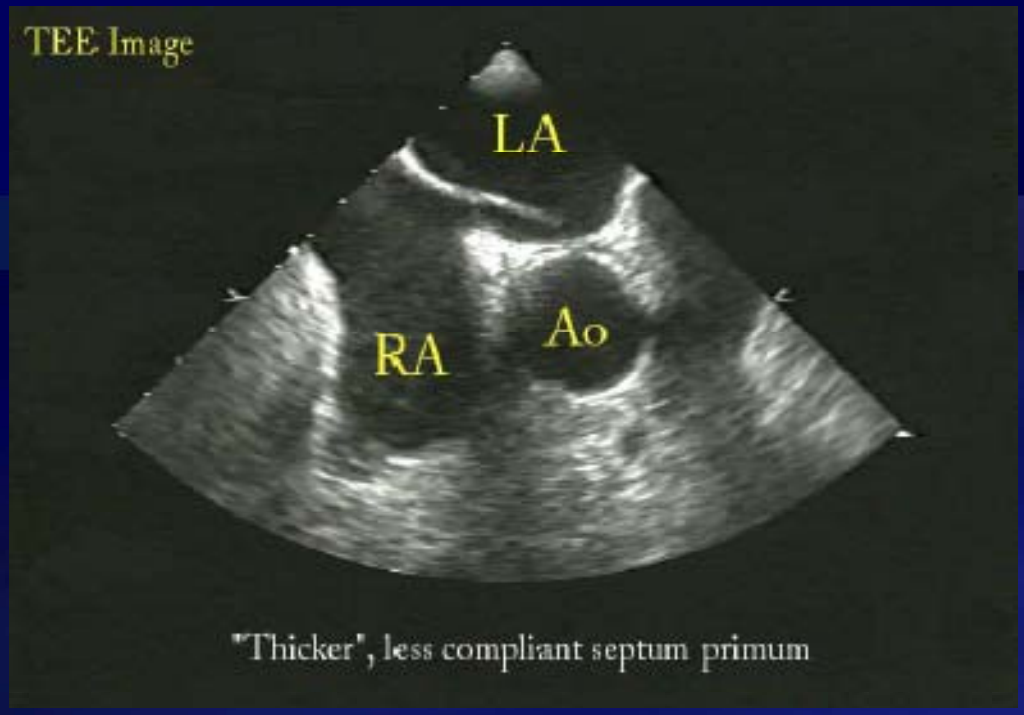
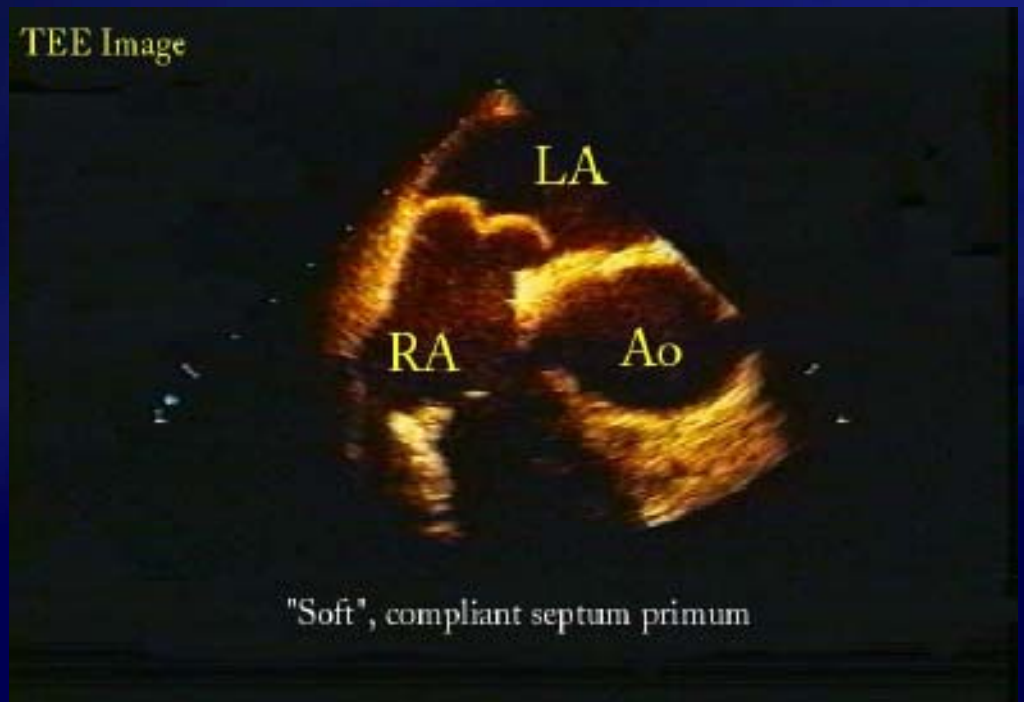
Wide Septal Separation


TEE Image
LA
RA
Ao
"Thicker", less compliant septum primum


TEE Image
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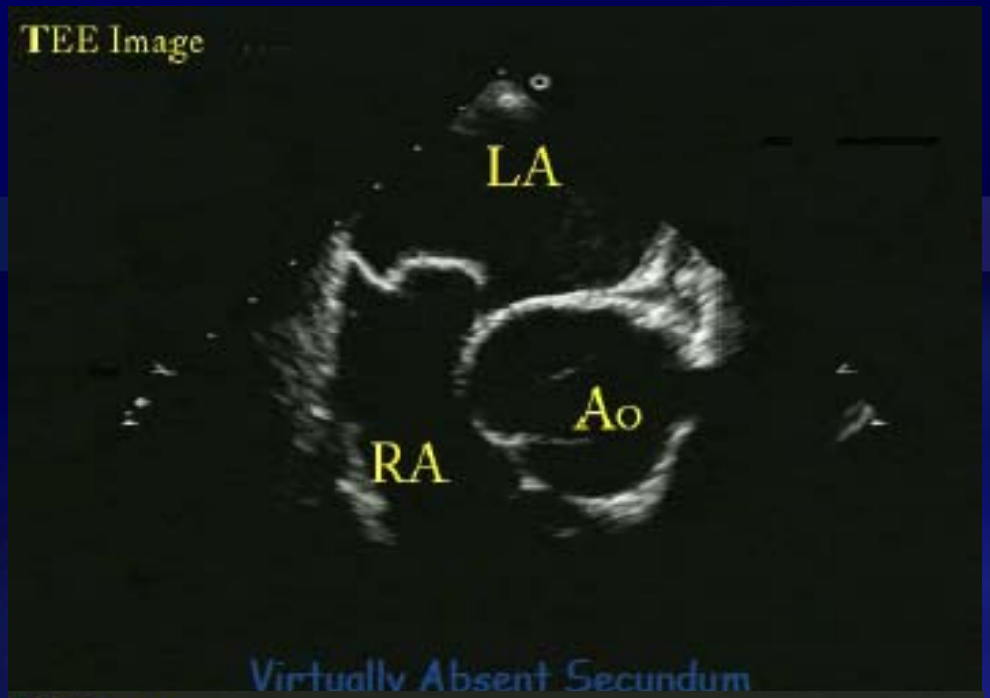
RA
Ao
"Soft", compliant septum primum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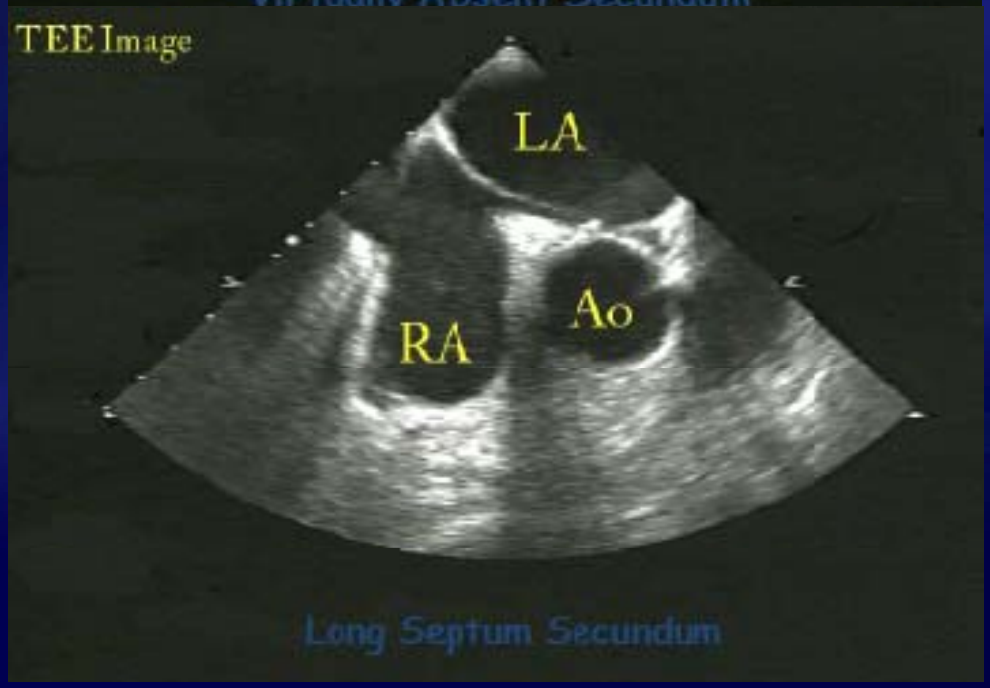
Ao
RA
Virtually Absent Secundum


TEE Image
LA
Ao
RA
Long Septum Secundum

Decision Making in Pts with PFO & CS
Post-Pre- CLOSURE I

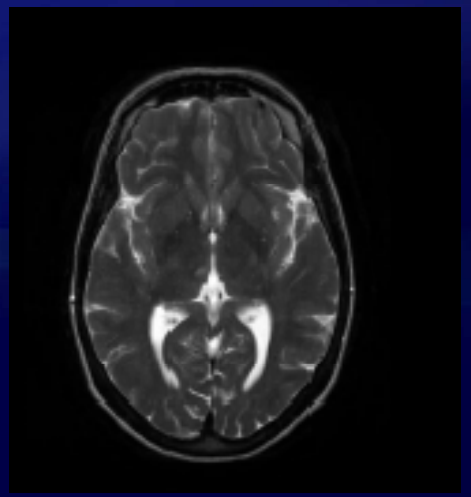
- Best treatment for an individual patient with "symptomatic" PFO is uncertain
- The patient need to understand:
  - The risk of recurrence on only medical therapy
  - The risk of the procedure (closing a PFO)
  - The extent of uncertainty
  - Having the option to be enrolled in a RCT

Who Should undergo PFO Closure?
Post-CLOSURE I

- Cryptogenic stroke with *large* PFO and ASA and *spontaneous* right to left shunt.
- Cryptogenic stroke which recurs and patient does not want long term drug therapy or would not comply.
- Cryptogenic stroke which recurs despite anticoagulation.

Case 1

- 51 year old female with no cardiovascular risk factors
- Sudden onset diplopia and loss of balance. Which resolved after 2 hours
- Negative work-up except for a large PFO with ASA
- PFO closed



Small right paramedian thalamic infarct

Case 2

- A 53 year old male physician without prior medical history.
- Presented with TIA lasting about 4 hours with left sided weakness.
- MRI scan showed old large right cerebellar infarct suggestive of embolism (asymptomatic) and new large infarct in right frontal lobe
- No evidence of carotid or coronary artery disease
- TTE showed large PFO with spontaneous flow of bubbles from right to left
- Patient very reluctant to consider long-term drug treatment

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