Device Closure versus Medical Therapy for Secondary Prevention in Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale

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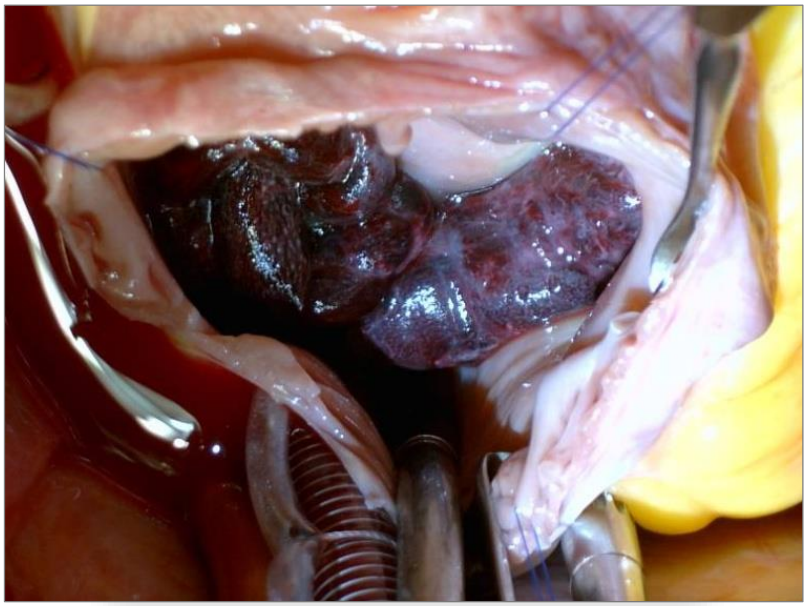
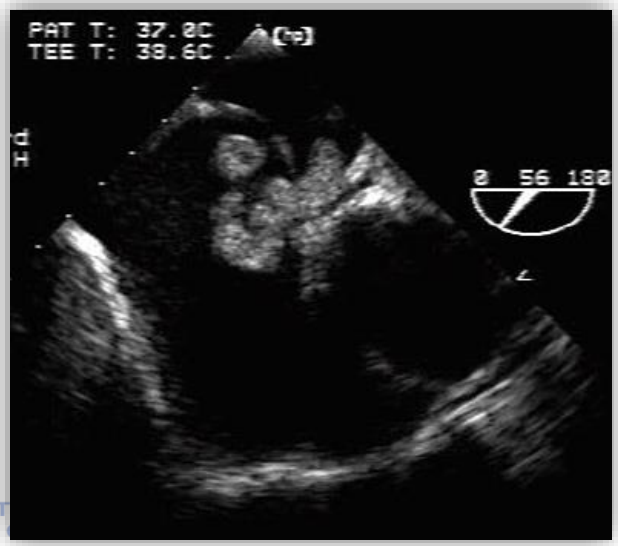
Background:
PFO & Cryptogenic Stroke





- A controversial issue for several decades
- Clinical benefit of closing a PFO – an open and rapidly evolving question

Background: Device Closure of a PFO

- Amplatzer PFO Occluder – approved by the FDA on October 28, 2016
- Conversion from a negative to a positive outlook in the past 5 years (REDUCE, CLOSE, & RESPECT_long term)
- Key to appropriate device use – selecting optimal candidates

Background: Assessment before PFO Closure

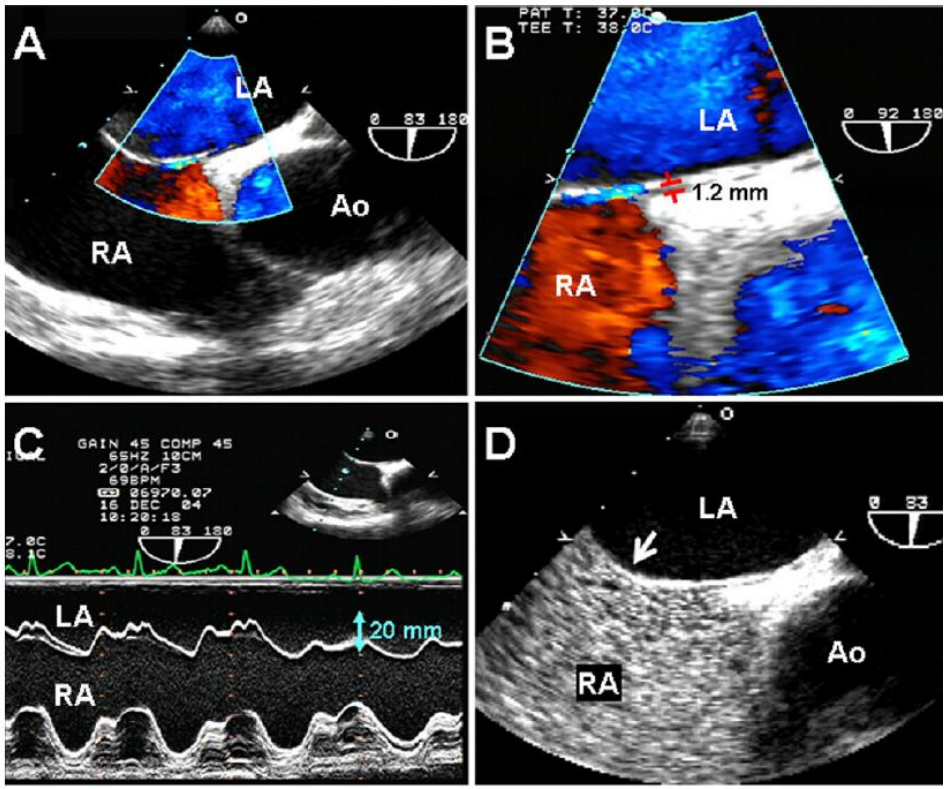
Cryptogenic stroke?

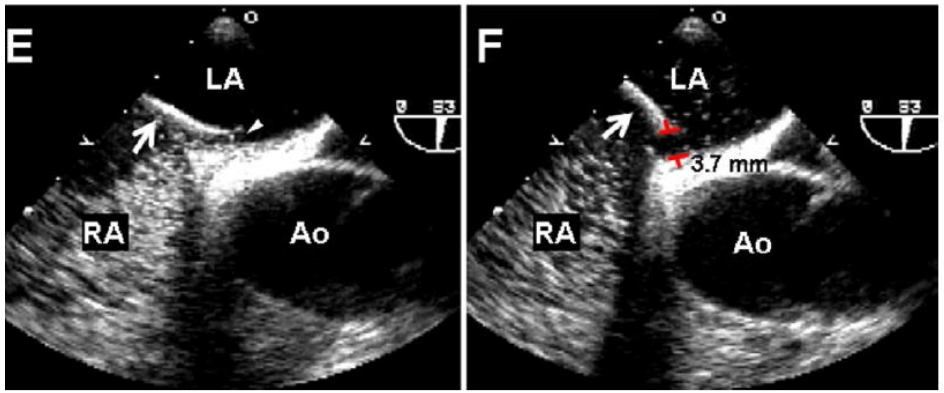
- large-artery atherosclerotic d's
- small-vessel occlusive disease (lacunar stroke)
- cardiac mass
- hypercoagulable disorder
- atrial fibrillation

Morphologic characteristics of the PFO?

A Standardized Omni-Plane TEE Protocol for Diagnosis of a 'High-Risk PFO'

Association Between Anatomic Features of Atrial Septal Abnormalities Obtained by Omni-Plane Transesophageal Echocardiography and Stroke Recurrence in Cryptogenic Stroke Patients with Patent Foramen Ovale





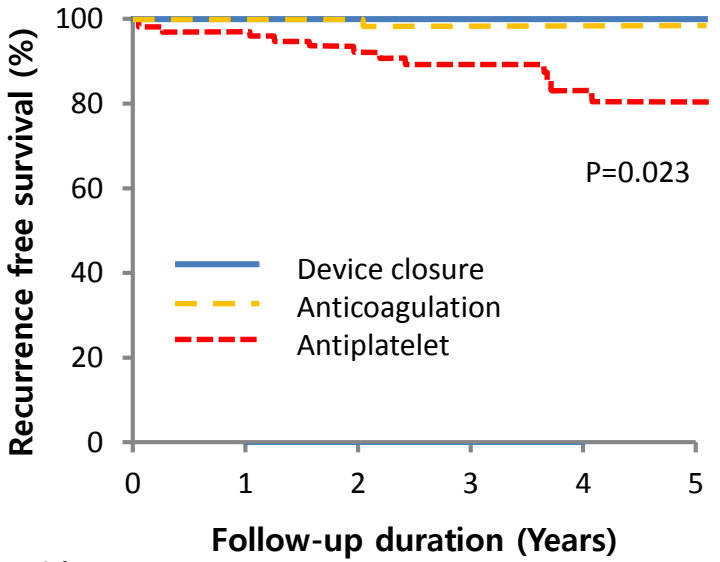
Am J Cardiol 2010:106;129

A Standardized Omni-Plane TEE Protocol for Diagnosis of a 'High-Risk PFO'

- 181 cryptogenic stroke patients with PFO
- Stroke recurrence – 7.7% (median 3.5 years)

1) atrial septal aneurysm or hypermobility (HR 6.04, 1.84-4.6)

2) PFO size (HR 3.0, 1.96-4.60; 3 mm)



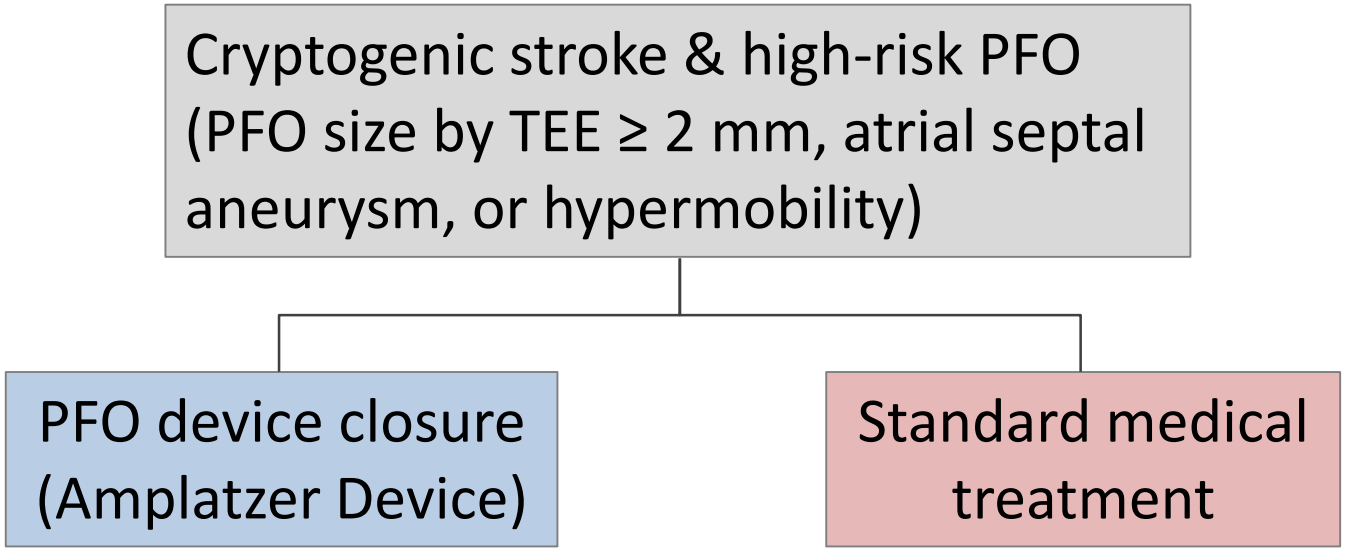
Number at Risk						
Device closure	22	21	17	11	9	7
Anticoagulation	60	53	46	41	33	24
Antiplatelet	99	87	72	59	38	21

Am J Cardiol 2010:106;129

Purpose of the DEFENSE-PFO Trial

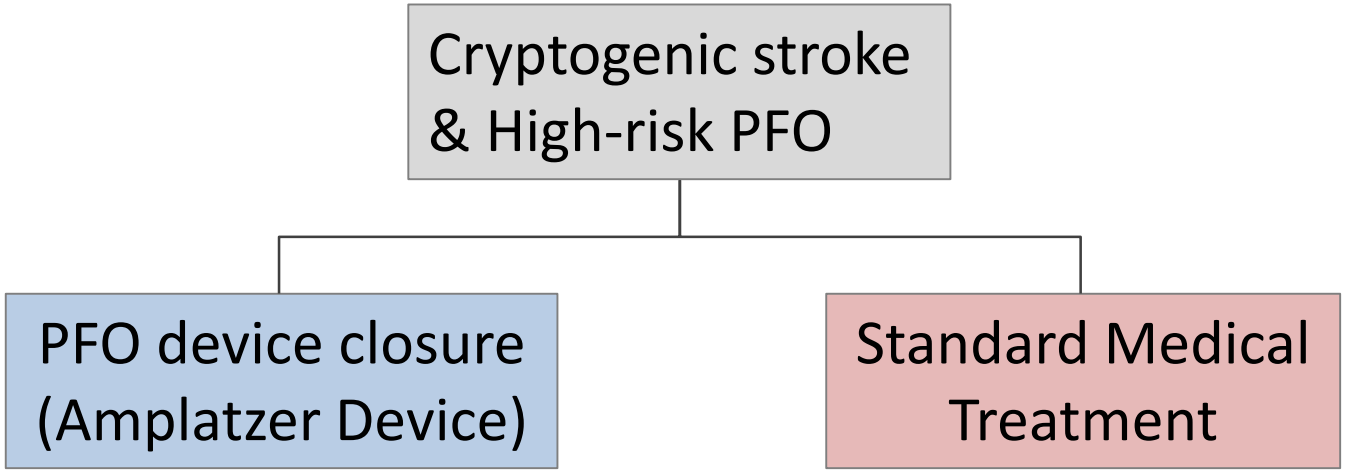
- We sought to evaluate whether the benefit from device closure of a PFO can be determined on the basis of the morphologic characteristics of the PFO

DEFENSE-PFO Trial



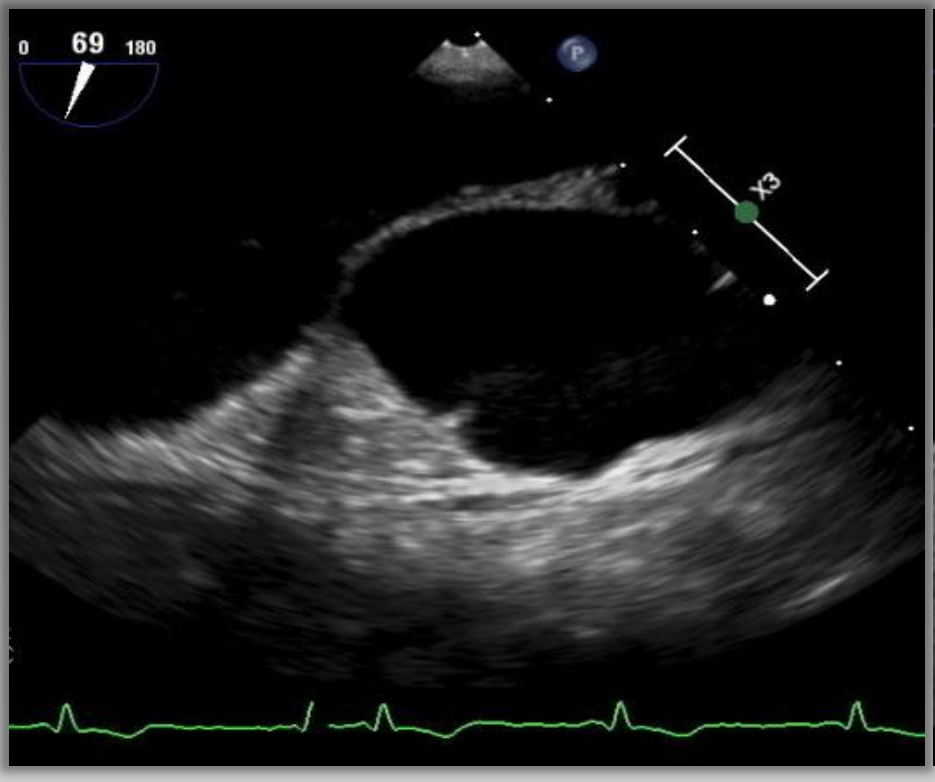
- Primary endpoint:
  - a composite of stroke, vascular death or TIMI-defined major bleeding during 2 years of follow-up

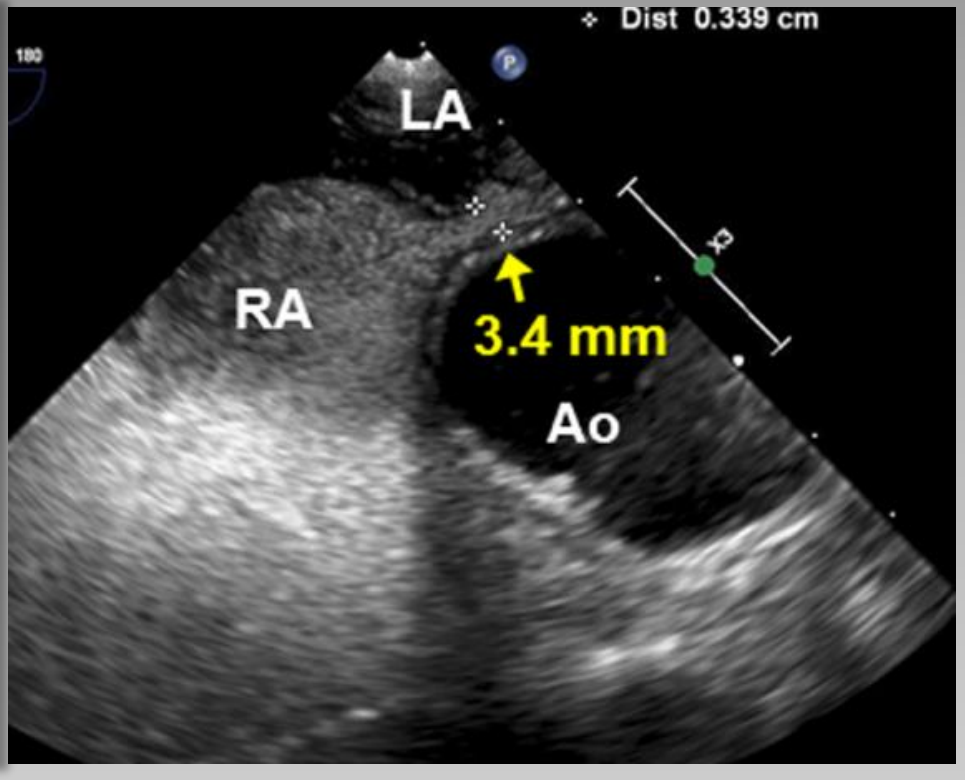
DEFENSE-PFO Trial



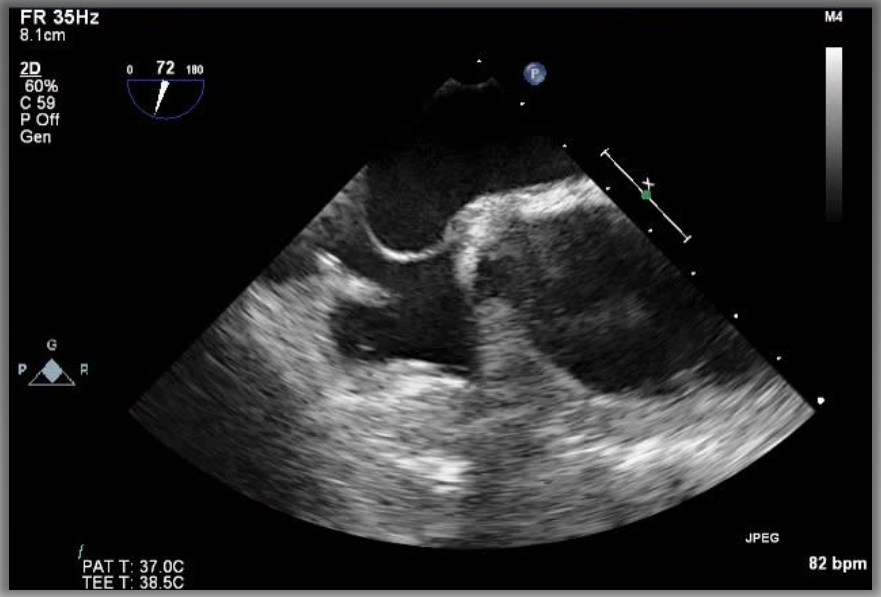
- Sample size estimation:
  - assuming an event rate for 2 years as 4% for the PFO closure group and 15% for the medication-only group
  - 99 patients in each group with a statistical power of 80%
  - attrition rate of 10%
  - 105 patients in each group (total sample size of 210 patients)

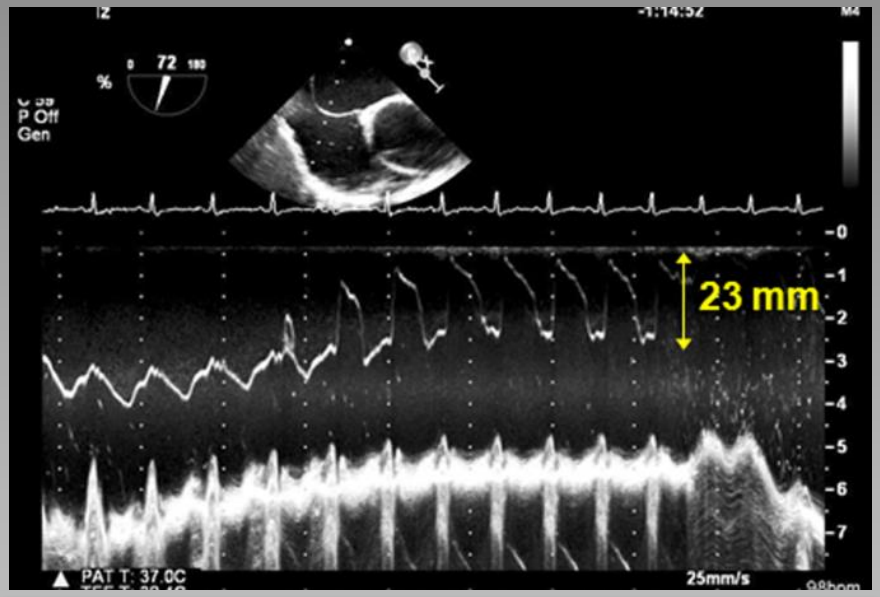
High-Risk PFO: PFO size ≥2 mm

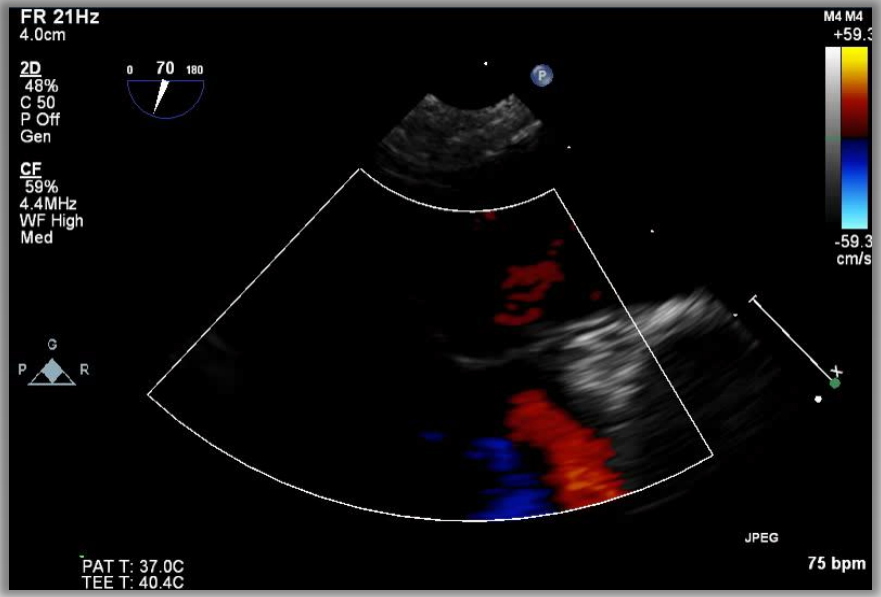


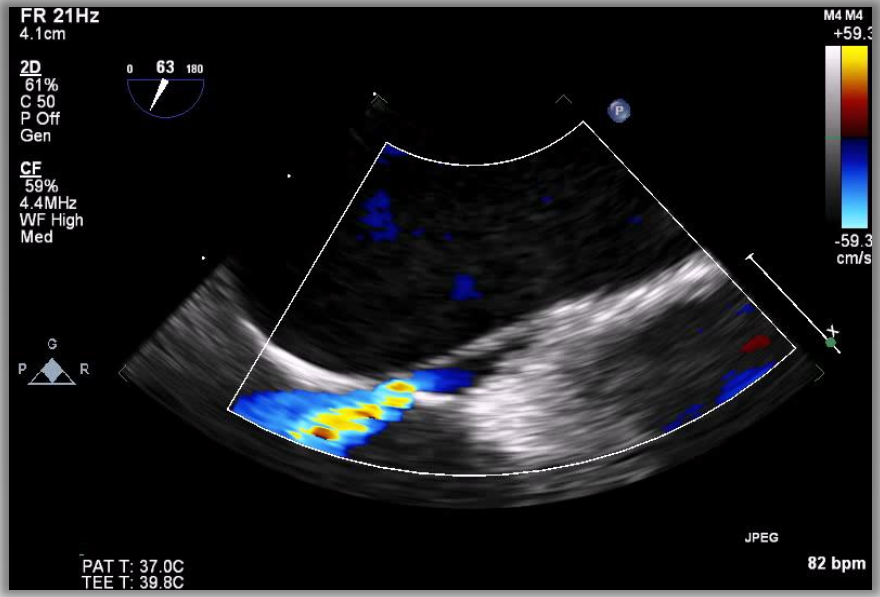


High-Risk PFO: atrial septal aneurysm or hypermobility (septal excursion ≥10 mm)

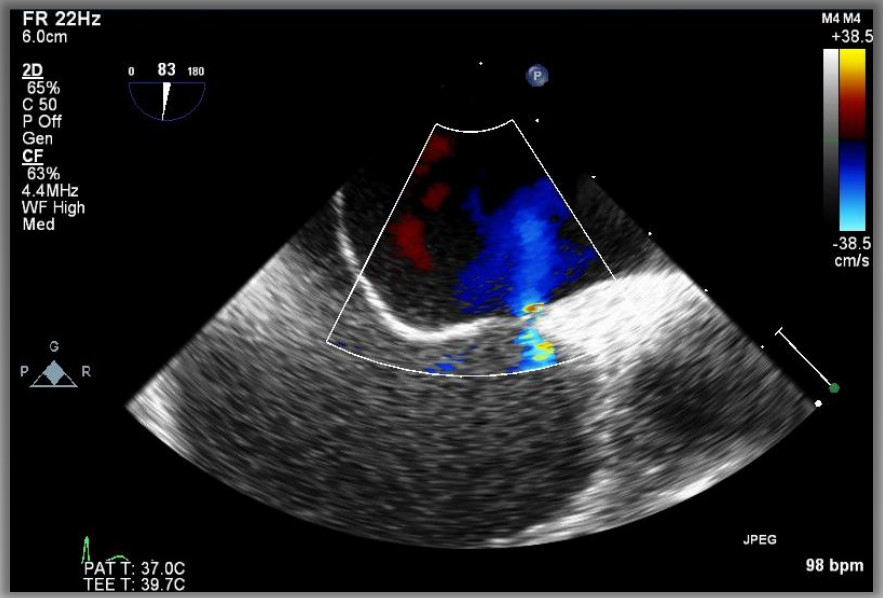


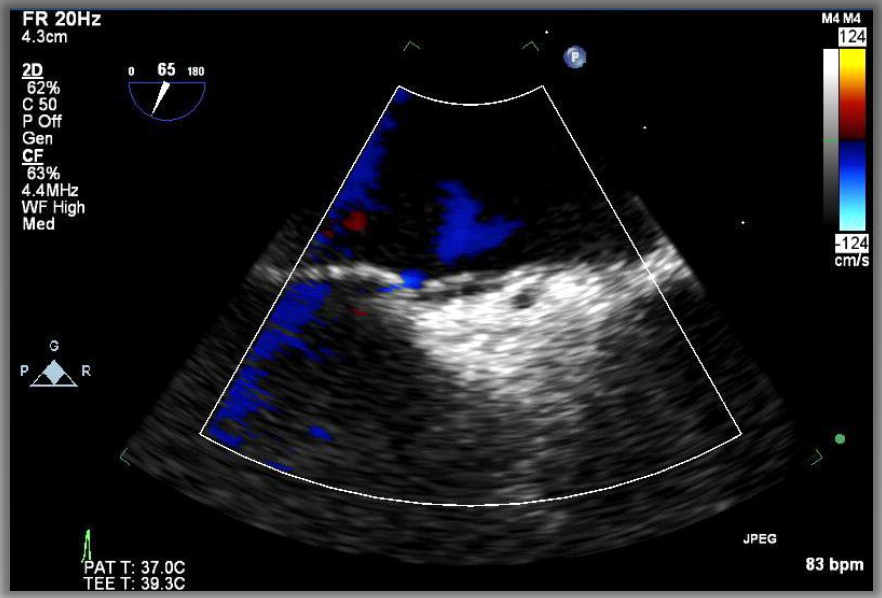


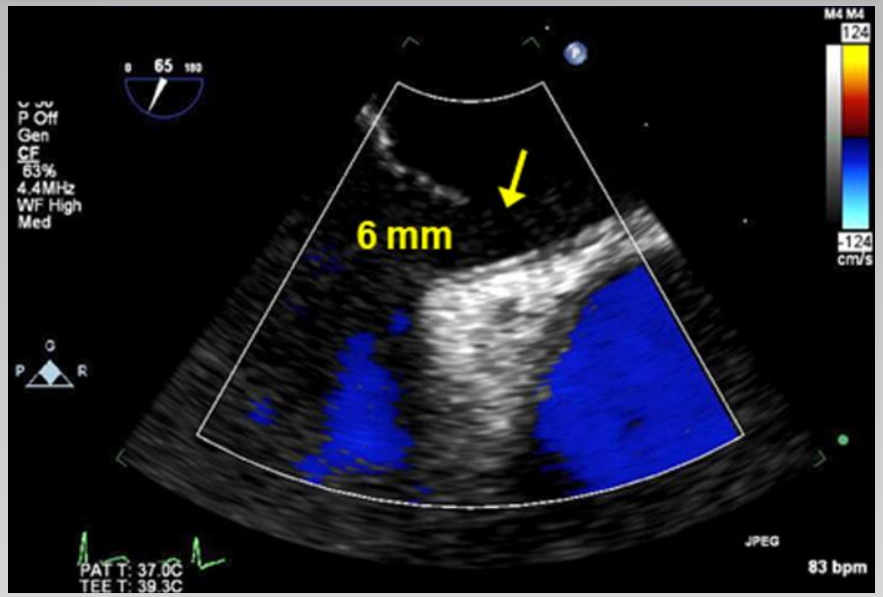


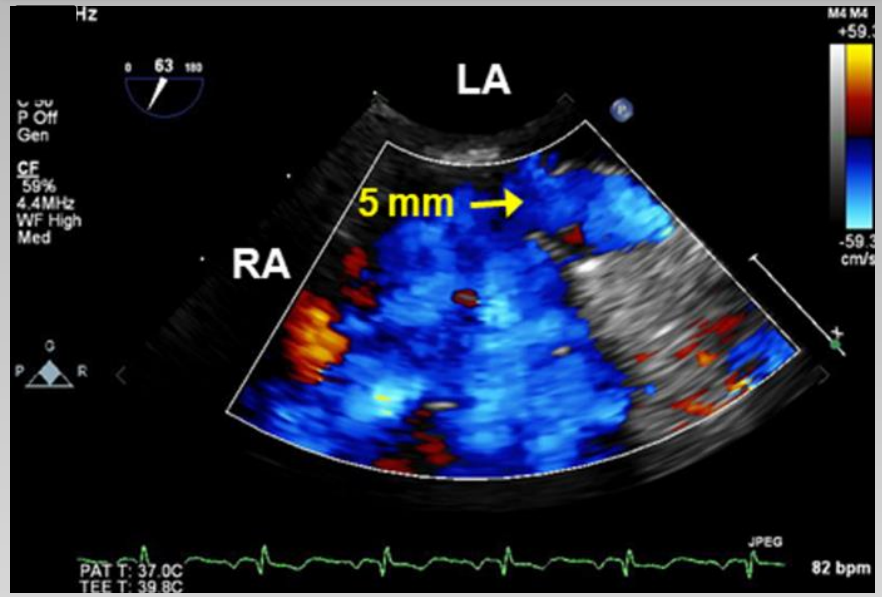


High-Risk PFO: PFO size ≥2 mm

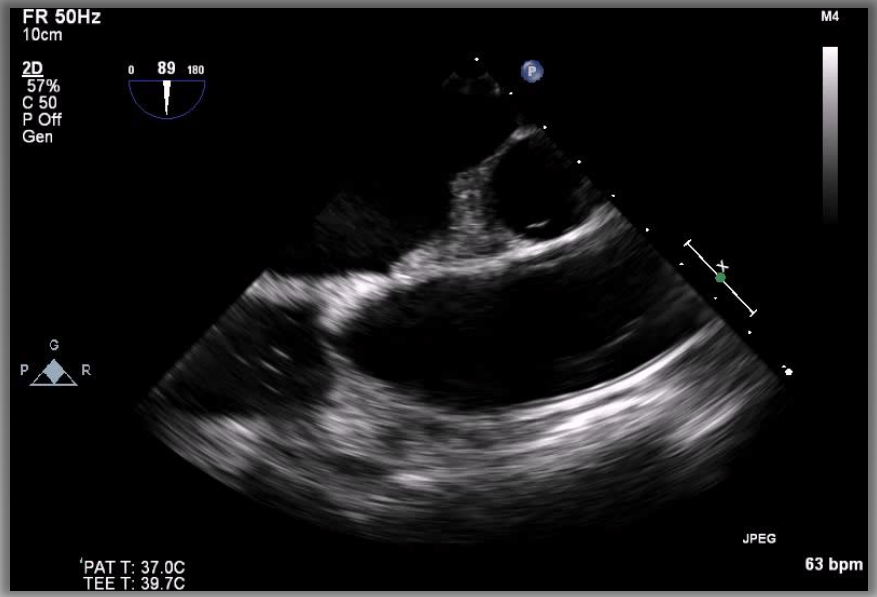








Low-Risk PFO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M4
2D
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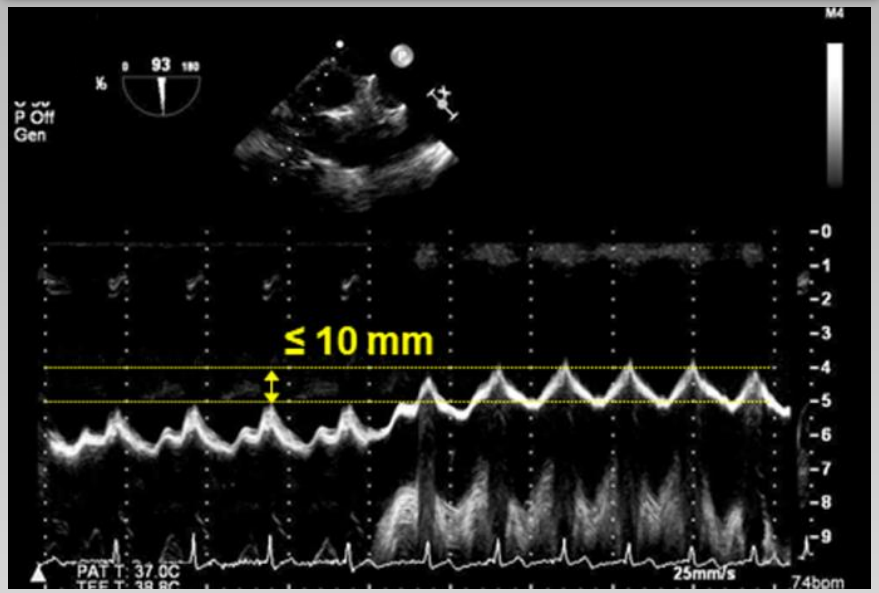
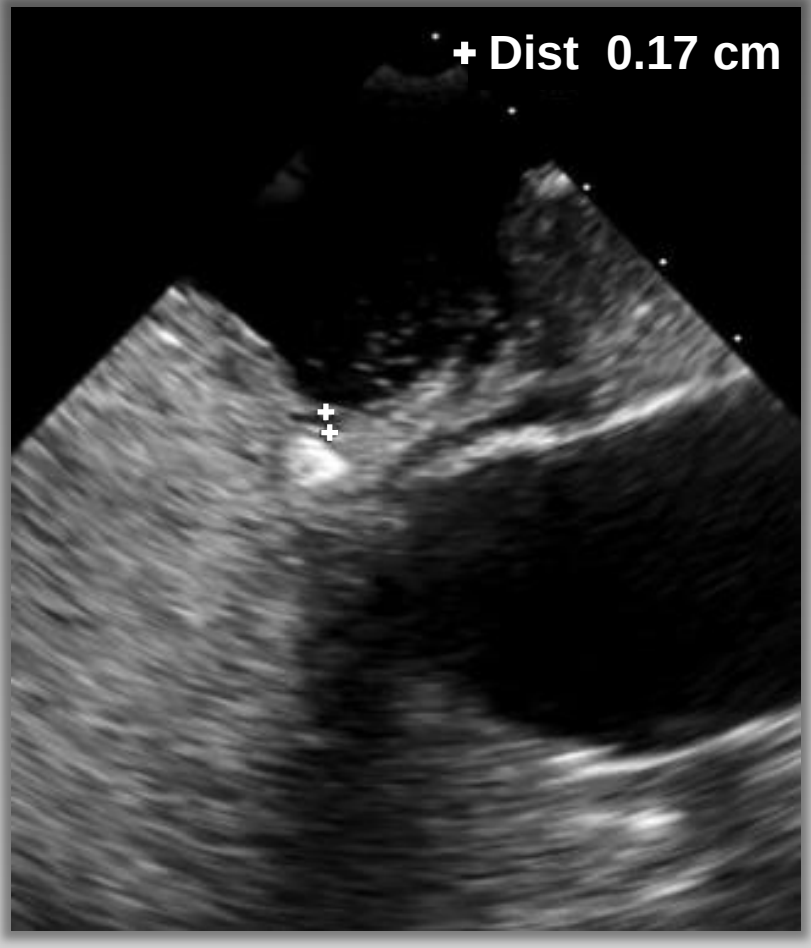
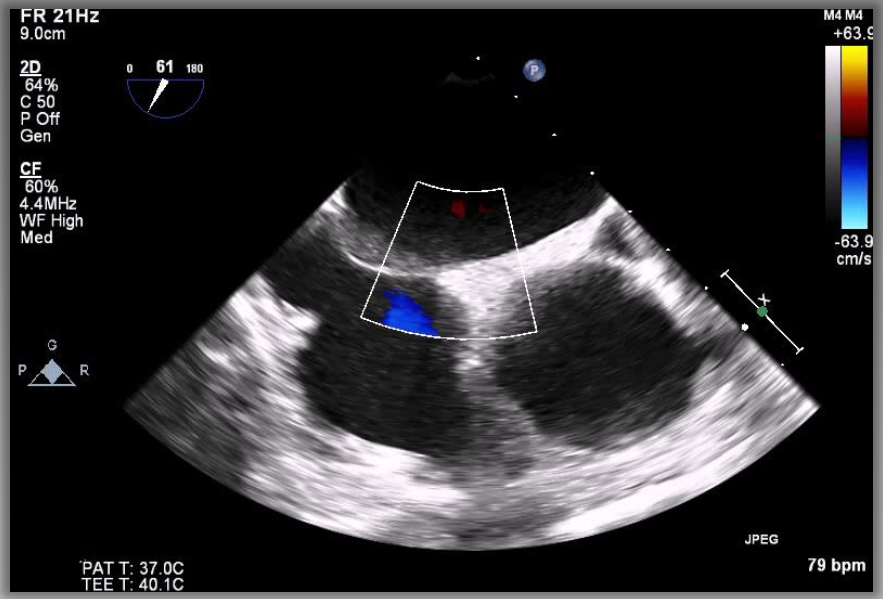
C 50
P Off
Gen
0 89 180
G
P R
JPEG
PAT T: 37.0C
TEE T: 39.7C
63 bpm


M4
P Off
Gen
≤ 10 mm
-0
-1
-2
-3
-4
-5
-6
-7
-8
-9
PAT T: 37.0C
25mm/s
74bpm


+ Dist 0.17 cm

Low-Risk PFO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9.0cm
2D
64%
C 50
P Off
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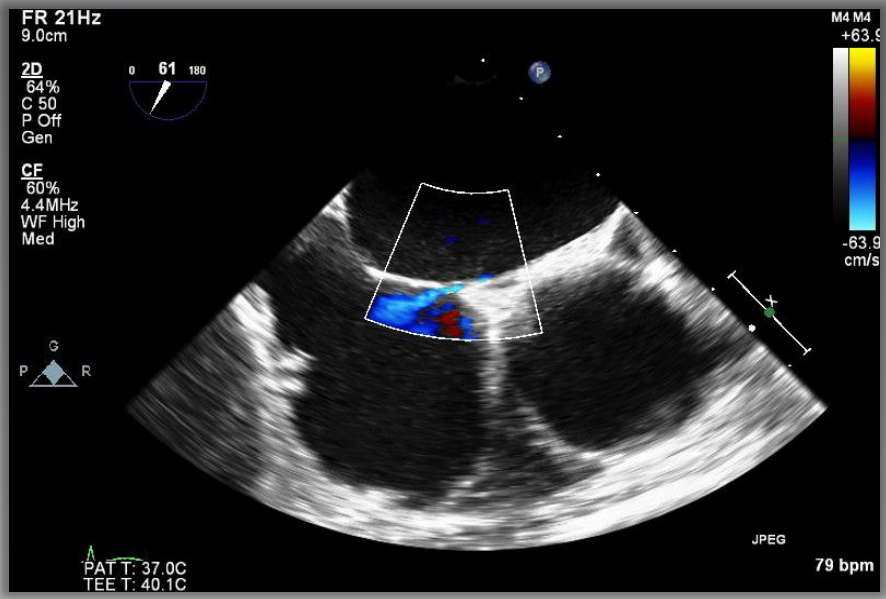
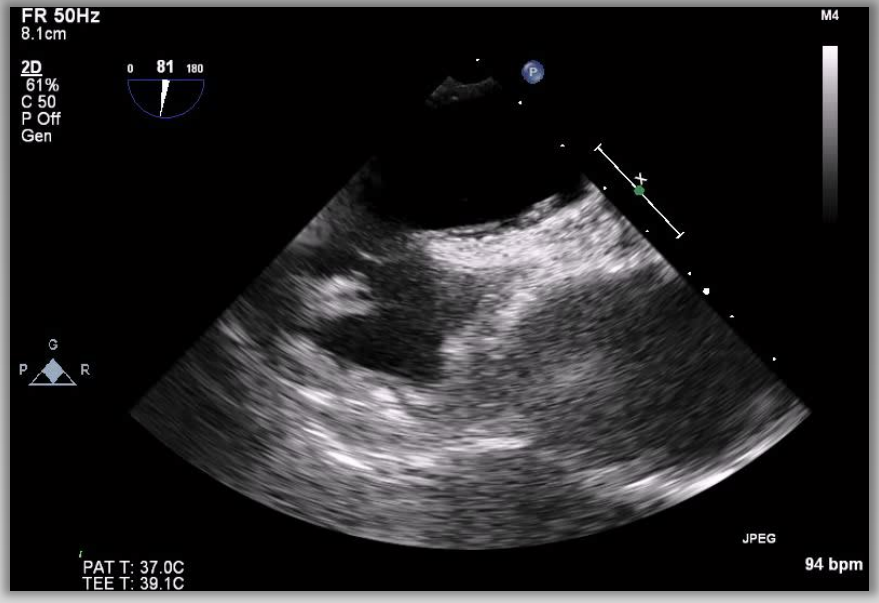
CF
60%
4.4MHz
WF High
Med
61
JPEG
PAT T: 37.0C
TEE T: 40.1C
79 bpm


FR 21Hz
9.0cm
2D
64%
C 50
P Off
Gen
CF
60%
4.4MHz
WF High
Med
61
JPEG
PAT T: 37.0C
TEE T: 40.1C
79 bpm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C 50
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Gen
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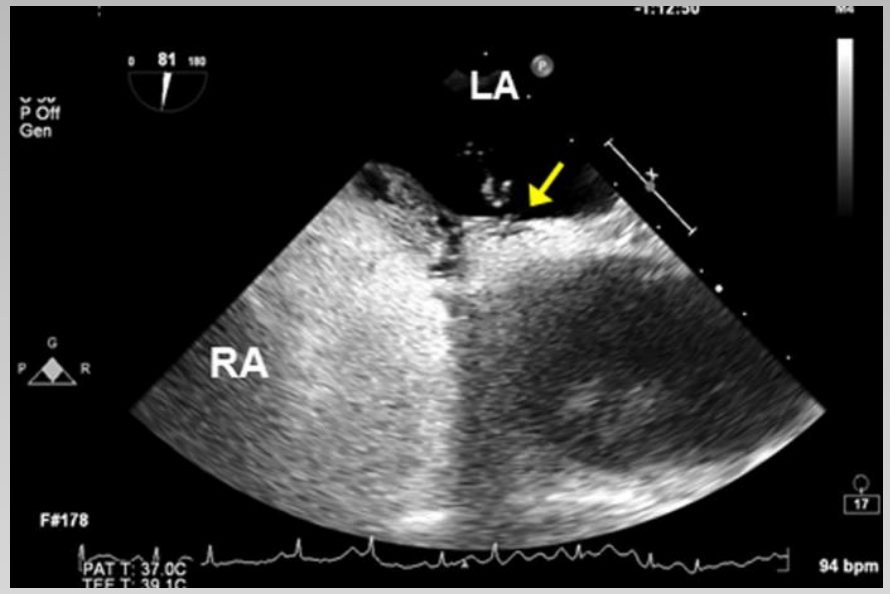
JPEG
PAT T: 37.0C
TEE T: 39.1C
94 bpm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LA
RA
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Gen
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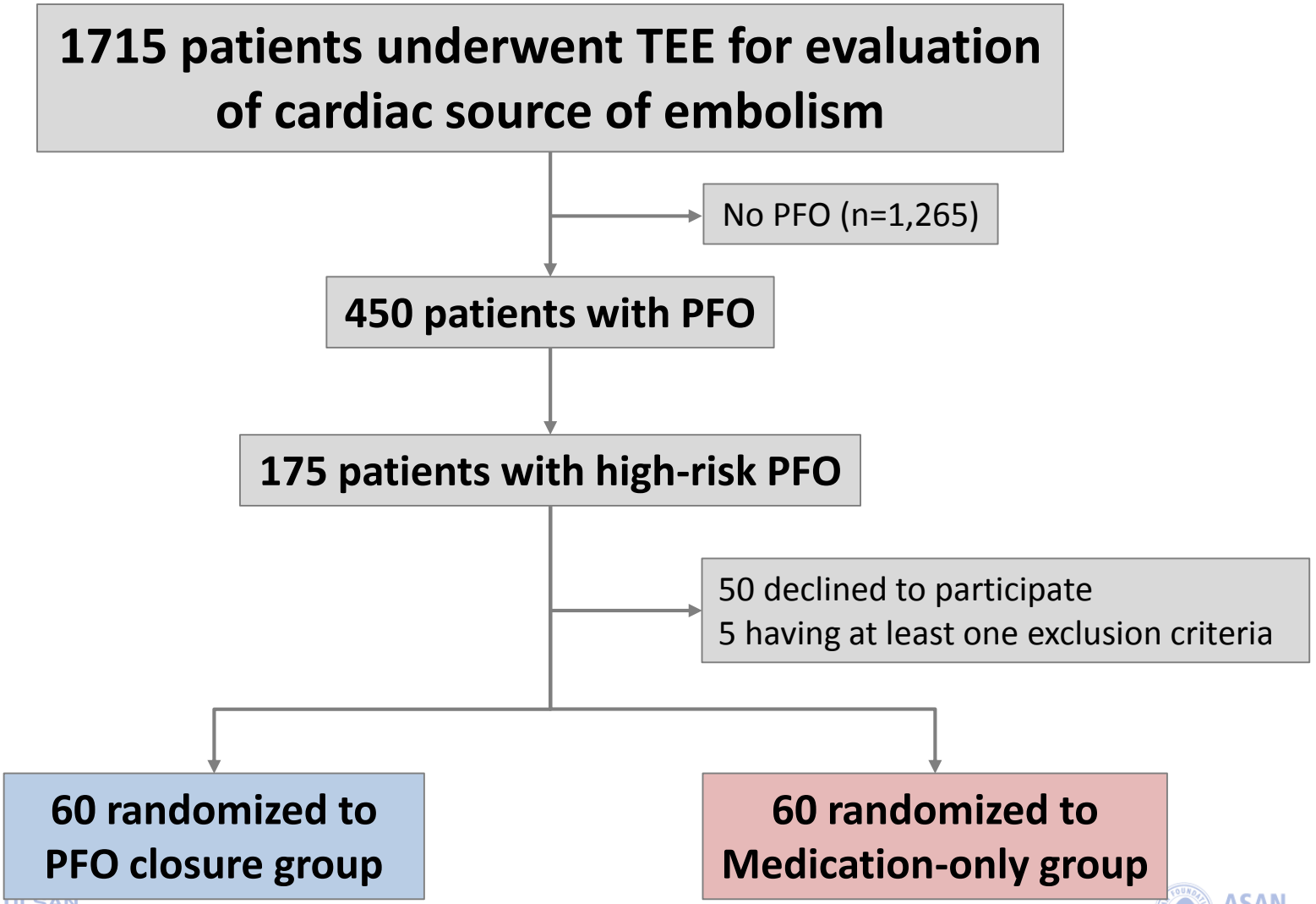
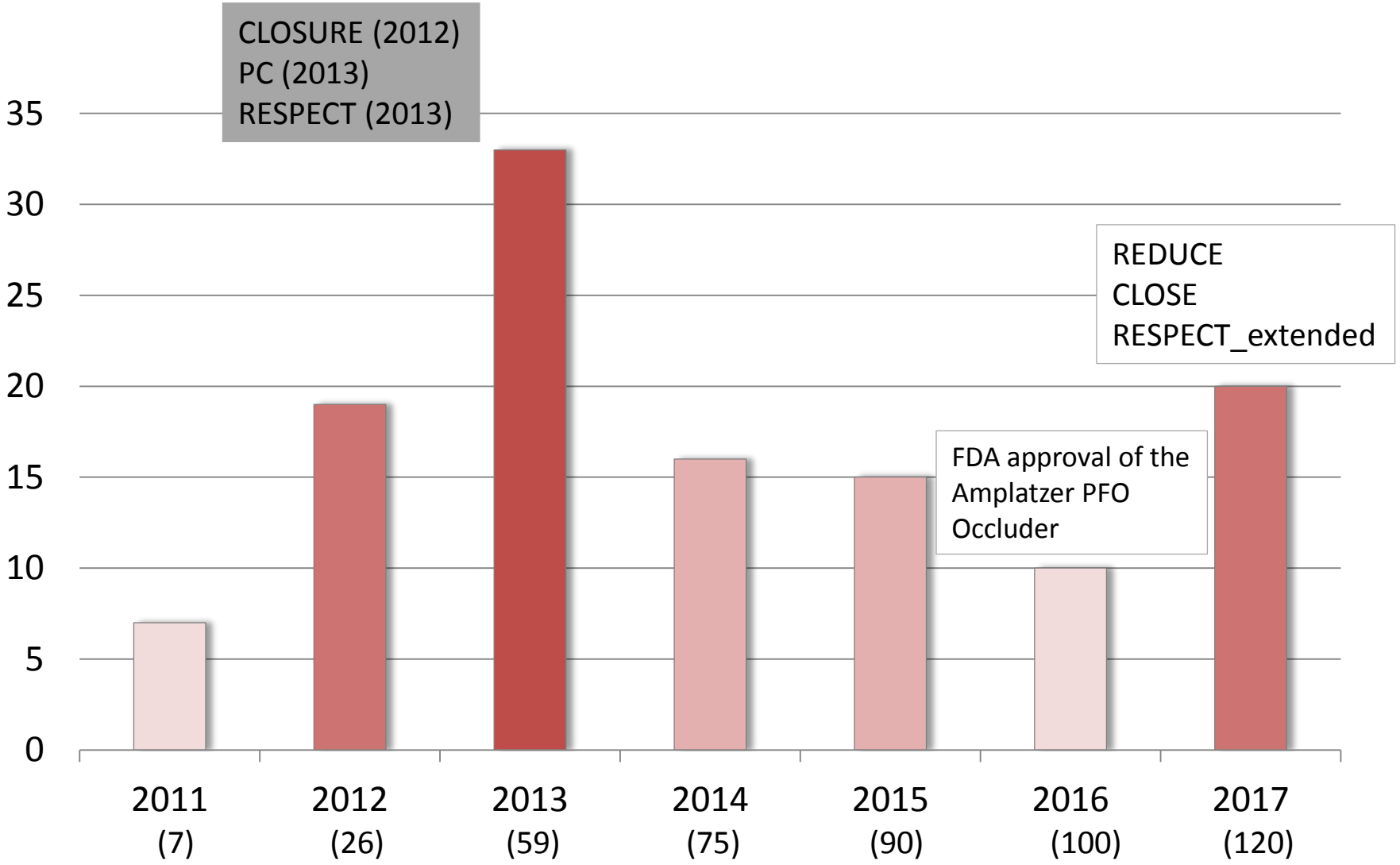
94 bpm

Flow Diagram of the Study Population (Sep 2011 – Nov 2017)

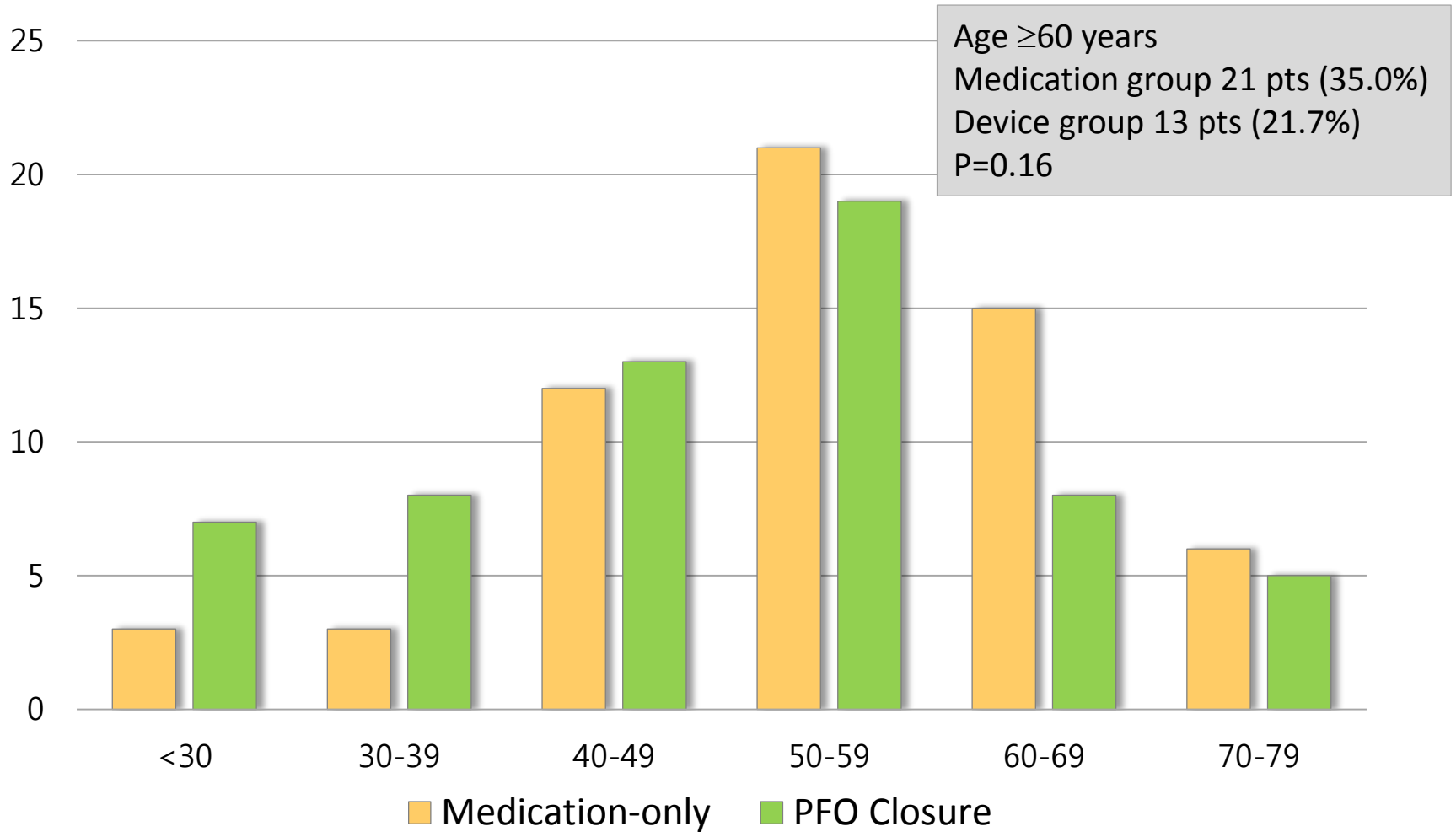


DEFENSE-PFO trial: Enrollment

(Asan Medical Center/Chungnam National University Hospital)

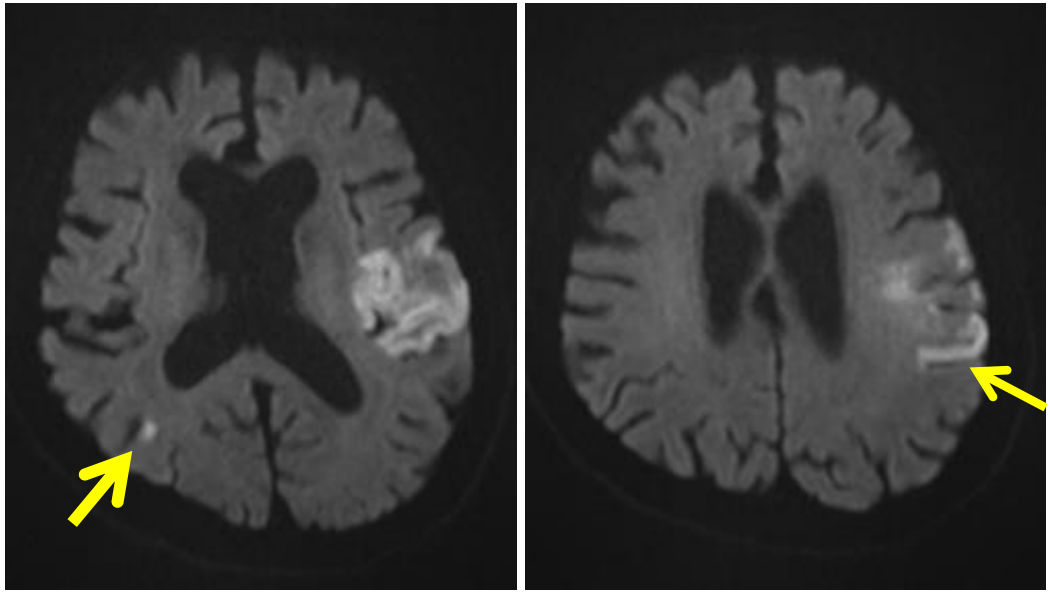


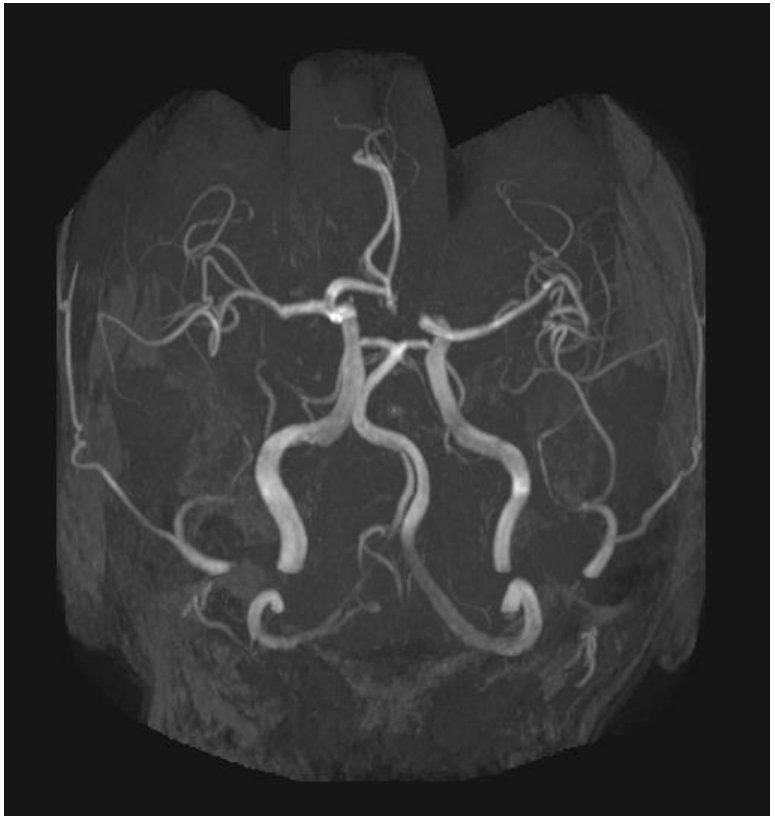
DEFENSE-PFO: Age Distribution



DEFENSE-PFO: Age Distribution

79-year old man presented with aphasia





Baseline Clinical Characteristics

	Medication-only Group (N = 60)	PFO Closure Group (N = 60)	P-value
Age, years	54 ± 12	49 ± 15	0.06
Male sex, n (%)	34 (56.7)	33 (55.0)	>0.99
Medical history, n (%)			
Hypertension	17 (28.3)	12 (20.0)	0.39
Diabetes	8 (13.3)	6 (10.0)	0.78
Current smoker	16 (26.7)	10 (16.7)	0.27
Hypercholesterolemia	25 (41.7)	18 (30.0)	0.25
Qualifying event, n (%)			
Ant./Post. Territory	34/23	28/30	0.28
Multiple territory	2 (3.3)	0	

Anatomic Characteristics of PFO

	Medication-only Group (N = 60)	PFO Closure Group (N = 60)	P-value
Shunt at rest, n (%)			
No shunt	26 (34.3)	25 (41.7)	
L-to-R shunt	34 (56.7)	31 (51.7)	0.06
R-to-L shunt	0	3 (5.0)	
Bi-direnctional	0	1 (1.7)	
PFO size, mm	3.2 ± 1.1	3.2 ± 1.5	0.85
Atrial septal aneurysm, n (%)	8 (13.3)	5 (8.3)	0.56
Atrial septal hypermobility, n (%)	27 (45.0)	28 (46.7)	>0.99

DEFENSE-PFO: Intervention

- Among 60 patients in the combined PFO closure group, 7 declined the intervention
- Amplatzer PFO Occluder was used for PFO closure
- Device closure was successful in all patients without fatal complications

DEFENSE-PFO: Medication

- Medication-only group: either antiplatelet therapy (single or dual) or anticoagulation with warfarin chosen by the local investigator

- Device closure group – dual antiplatelet therapy was recommended for at least 6 months, and, based on the individual risk to benefit ratio, the attending neurologist could stop medication

DEFENSE-PFO: Medications

	PFO Closure Group (N = 60)	Medication-only Group (N = 60)
At 30 days		
Single antiplatelet therapy	10.0% (6/60)	16.7% (10.60)
Dual antiplatelet therapy	75.0% (45/60)	58.3% (35/60)
Warfarin	15.0% (9/60)	25.0% (15/60)
At 6 months		
Single antiplatelet therapy	34.6% (18/52)	25.0% (13/52)
Dual antiplatelet therapy	57.7% (30/52)	51.9% (27/52)
Warfarin	7.7% (4/52)	23.1% (12/52)*
At 12 months		
Single antiplatelet therapy	42.6% (20/47)	37.0% (17/46)
Dual antiplatelet therapy	34.0% (16/47)	41.3% (19/46)
Warfarin	6.4% (3/47)	21.7% (10/46)*
No antiplatelet therapy or warfarin	17.0% (8/47)	0%*

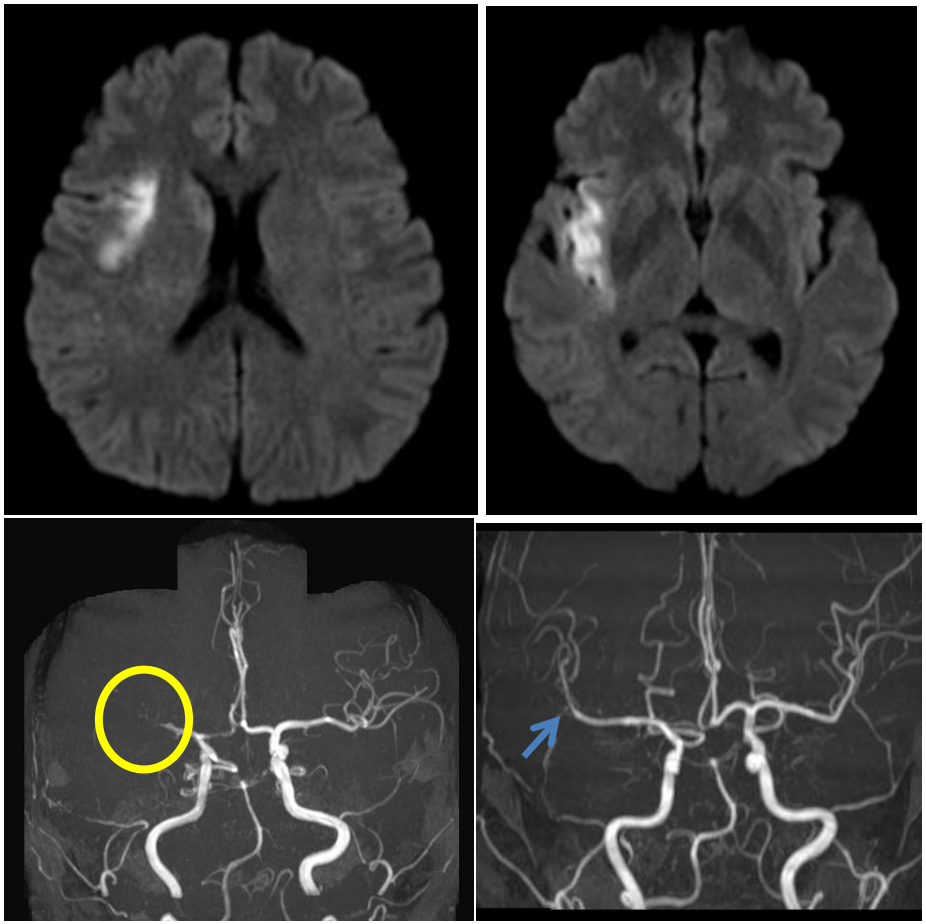
* P <0.05

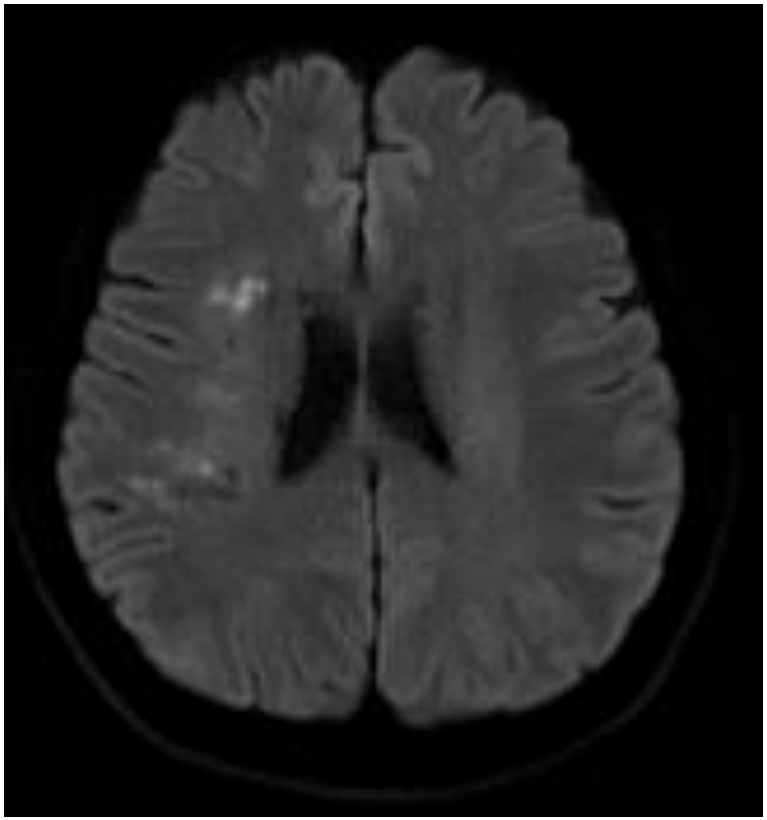
DEFENSE-FPO: Outcome data

- F/U duration (median): 2.8 years (0.9 – 4.1)
- Non-fatal procedural complication:
  - pericardial effusion (n=1)
  - pseudoaneurysm (n=1)
  - atrial fibrillation (n=1)
- No event of primary endpoint in the PFO closure group, whereas 6 of 60 patients in the medication-only group developed the events

DEFENSE-PFO: Clinical outcome

51-year old woman presented with left hemiparesis





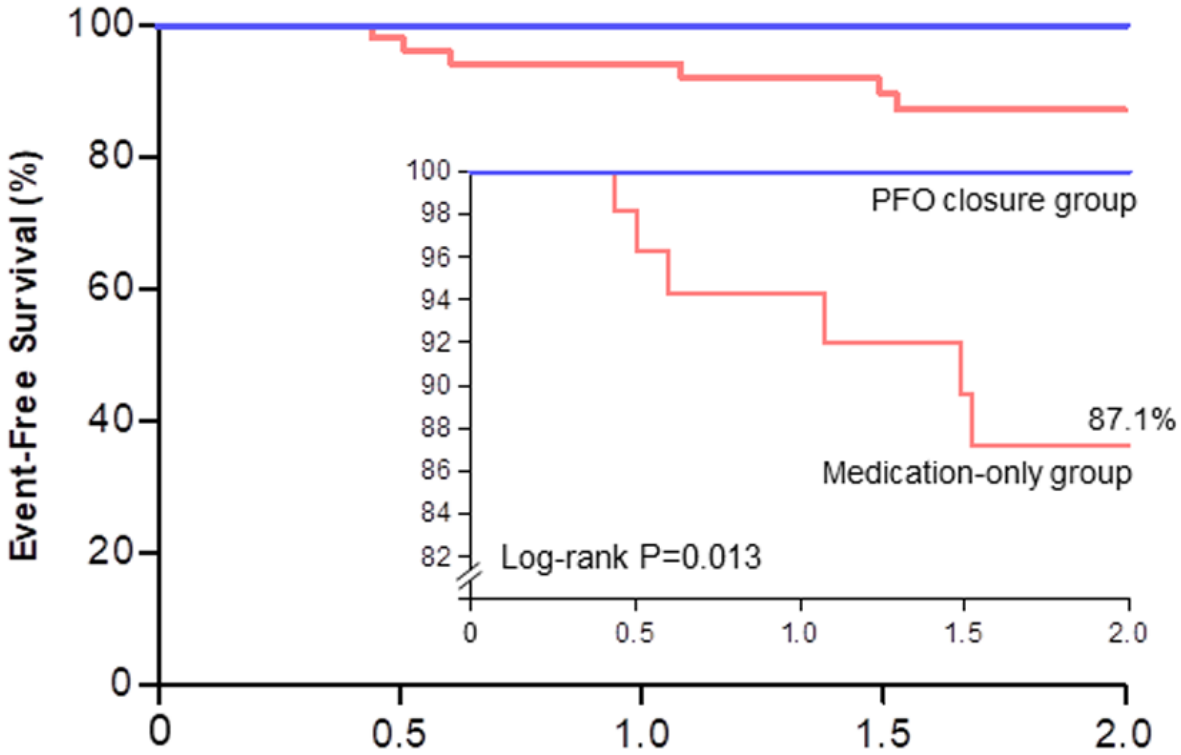
Recurrent left hemiparesis 6 months later

DEFENSE-PFO: Outcome data

	PFO Closure Group (N = 60)	Medication-only Group (N = 60)
Primary endpoint	0	6 (10.0%)
Secondary endpoint		
Ischemic stroke	0	5 (8.3%)
Vascular death	0	0
TIMI-defined major bleeding	0	2 (3.3%)
Hemorrhagic stroke	0	1 (1.7%)
Transient ischemic attack	0	1 (1.7%)
Systemic embolization	0	0
New silent ischemic lesion on MRI	3/34 (8.8%)	7/38 (18.4%)

- 2-year event rate of the primary endpoint = 12.9% (95% CI 3.2-22.6; SE 5.0)
- 2-year event rate of stroke = 10.5% (95% CI 1.68-19.32; SE 4.5): the number of patients needed to treat to avoid one stroke recurrence at 2 years would be 10.

Outcome data: Intention-to-Treat

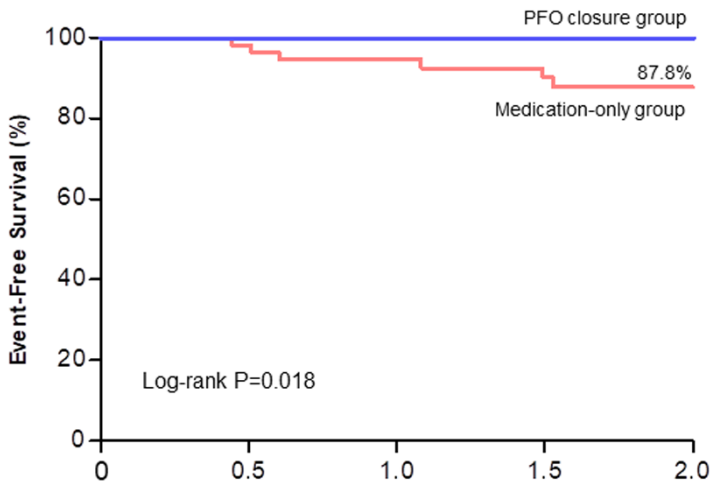


No. at Risk					
PFO closure	60	52	46	42	40
Medication-only	60	52	45	38	37

DEFENSE-PFO: Outcome data

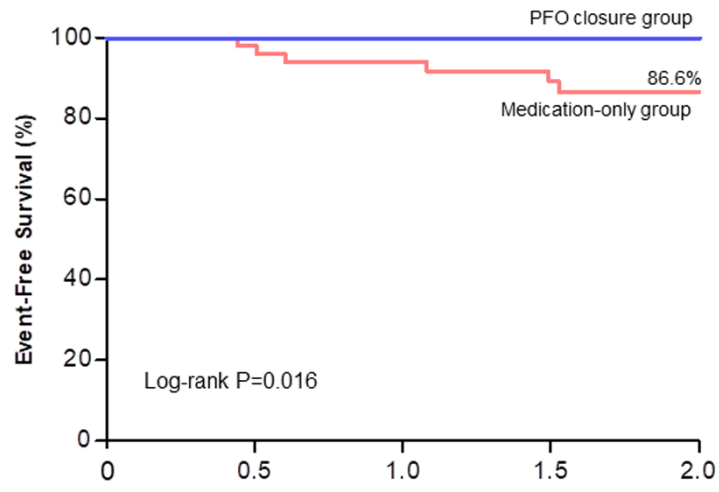
- 7 patients in the PFO closure group did not undergo the device closure and 4 in the medication-only group underwent the device closure during F/U: No one in 11 patients who changed treatment arms after randomization developed the primary endpoint

A. As-treated population



No. at Risk					
PFO closure	57	48	43	40	38
Medication-only	63	56	48	40	39

B. Per-protocol population



No. at Risk					
PFO closure	53	46	41	38	26
Medication-only	56	50	43	36	27

Limitations

- Two centers only – potential selection bias
- A lower-than-expected rate of patient recruitment
- Early termination of the trial for patient safety – underpowered study

Summary

- Among patients with a recent cryptogenic stroke attributed to PFO with high-risk echocardiographic features, the rate of primary endpoint as well as stroke recurrence was lower among those assigned to device closure with medical therapy than those assigned to medical therapy alone.

Conclusions

- The benefit of closing a patent foramen ovale (PFO) for secondary prevention in patients with cryptogenic stroke can be determined on the morphologic characteristics of the PFO and the adjacent interatrial septum

Conclusion

Stringent Definition of Cryptogenic Stroke

Morphologic Characteristics of the PFO

Summary of Event Cases

Sex	Age	TEE Criteria of High Risk PFO			Event day	Drug at event	Baseline territory	Qualifying event	Event territory
		PFO size	ASA	Hypermobility					
F	73	2.0	–	+	220	Clopidogrel	Lt. ant.	Stroke	Lt. ant.
F	72	6.0	+	+	395	Aspirin and Clopidogrel	Lt. ant.	Stroke	Rt. ant.
F	51	3.0	–	+	185	Warfarin	Rt. ant.	Stroke	Rt. ant.
F	75	3.0	–	–	545	Aspirin and Clopidogrel	Rt. ant.	Stroke with hemorrhagic transformation	Lt. ant.
M	50	2.1	–	+	161	Aspirin and Clopidogrel	Lt. ant.	Stroke	Rt. ant
M	59	2.2	+	+	558	Warfarin	Rt. ant	Putaminal ICH	

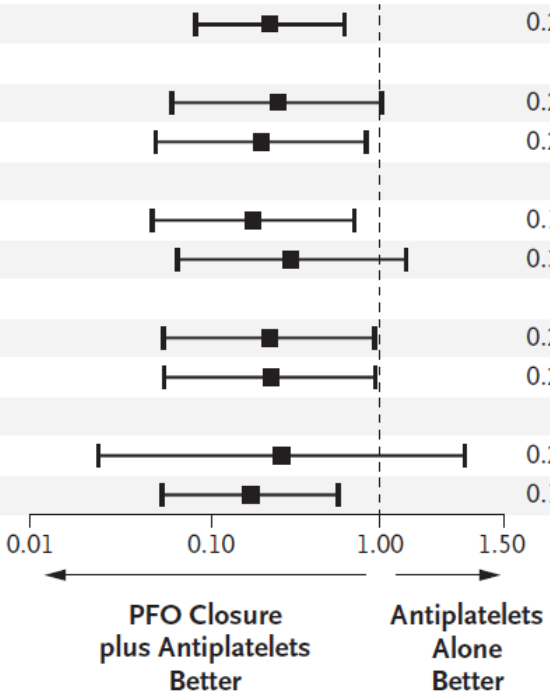
#Case; *Atrial Fibrillation*

- F/62
- Primary event; Lt multiple territory (2012.3.4)
- PFO closure; (2012.5.4)
- AF 1 day after the procedure
- Warfarin thereafter
- No event

- M/58
- Primary event; Lt MCA ter ritory (2013.4.16)
- PFO closure; (2013.5.3)
- AF detected (2015.3.19, on aspirin)
- Warfarin thereafter
- No event

REDUCE

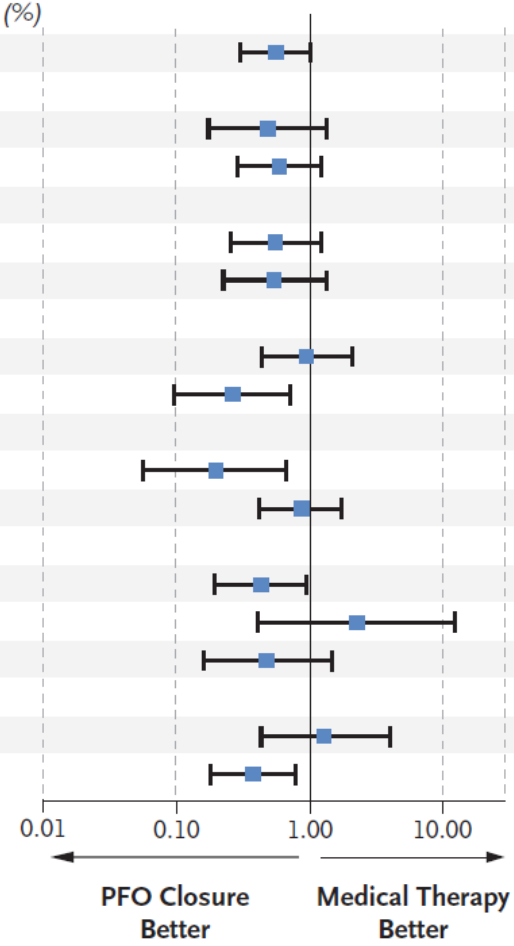
Subgroup	PFO Closure Group	Antiplatelet-Only Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of patients who had recurrent stroke/total no. (%)				
All patients	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)	0.002	
Age					0.85
18–45 yr	3/204 (1.5)	6/114 (5.3)	0.26 (0.07–1.04)	0.04	
46–59 yr	3/237 (1.3)	6/109 (5.5)	0.21 (0.05–0.84)	0.02	
Sex					0.62
Male	3/261 (1.1)	8/138 (5.8)	0.19 (0.05–0.71)	0.01	
Female	3/180 (1.7)	4/85 (4.7)	0.31 (0.07–1.40)	0.11	
Region					1.00
Europe and Canada	3/225 (1.3)	6/108 (5.6)	0.23 (0.06–0.93)	0.03	
United States	3/215 (1.4)	6/115 (5.2)	0.24 (0.06–0.94)	0.03	
Shunt size					0.77
Small	1/77 (1.3)	2/43 (4.7)	0.27 (0.03–3.03)	0.26	
Moderate-to-large	4/348 (1.1)	10/173 (5.8)	0.18 (0.06–0.58)	0.001	



N Engl J Med 2017:377;1033

RESPECT_LONG TERM

Subgroup	PFO Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients with event/total no. (%)				
Overall	18/499 (3.6)	28/481 (5.8)	0.55 (0.30–1.00)	0.046	
Age					0.78
18–45 yr	6/230 (2.6)	10/210 (4.8)	0.49 (0.18–1.35)	0.16	
46–60 yr	12/262 (4.6)	18/266 (6.8)	0.59 (0.28–1.23)	0.16	
Sex					1.00
Male	10/268 (3.7)	16/268 (6.0)	0.56 (0.25–1.23)	0.14	
Female	8/231 (3.5)	12/213 (5.6)	0.55 (0.22–1.34)	0.18	
Shunt size					0.04
None, trace or moderate	13/247 (5.3)	12/244 (4.9)	0.96 (0.44–2.11)	0.93	
Substantial	5/247 (2.0)	16/231 (6.9)	0.26 (0.10–0.71)	0.005	
Atrial septal aneurysm					0.04
Present	3/179 (1.7)	13/170 (7.6)	0.20 (0.06–0.70)	0.005	
Absent	15/320 (4.7)	15/311 (4.8)	0.86 (0.42–1.76)	0.68	
Index infarct topography					0.21
Superficial	9/280 (3.2)	18/269 (6.7)	0.43 (0.19–0.96)	0.03	
Small deep	4/57 (7.0)	2/70 (2.9)	2.25 (0.41–12.32)	0.34	
Other	5/157 (3.2)	8/140 (5.7)	0.48 (0.16–1.48)	0.19	
Planned medical regimen					0.07
Anticoagulant	8/132 (6.1)	5/121 (4.1)	1.32 (0.43–4.03)	0.63	
Antiplatelet	10/367 (2.7)	23/360 (6.4)	0.38 (0.18–0.79)	0.007	



N Engl J Med 2017:377;1022

Table 1. Six Trials of Patent Foramen Ovale Closure for Stroke with Results Published in the *Journal*.*

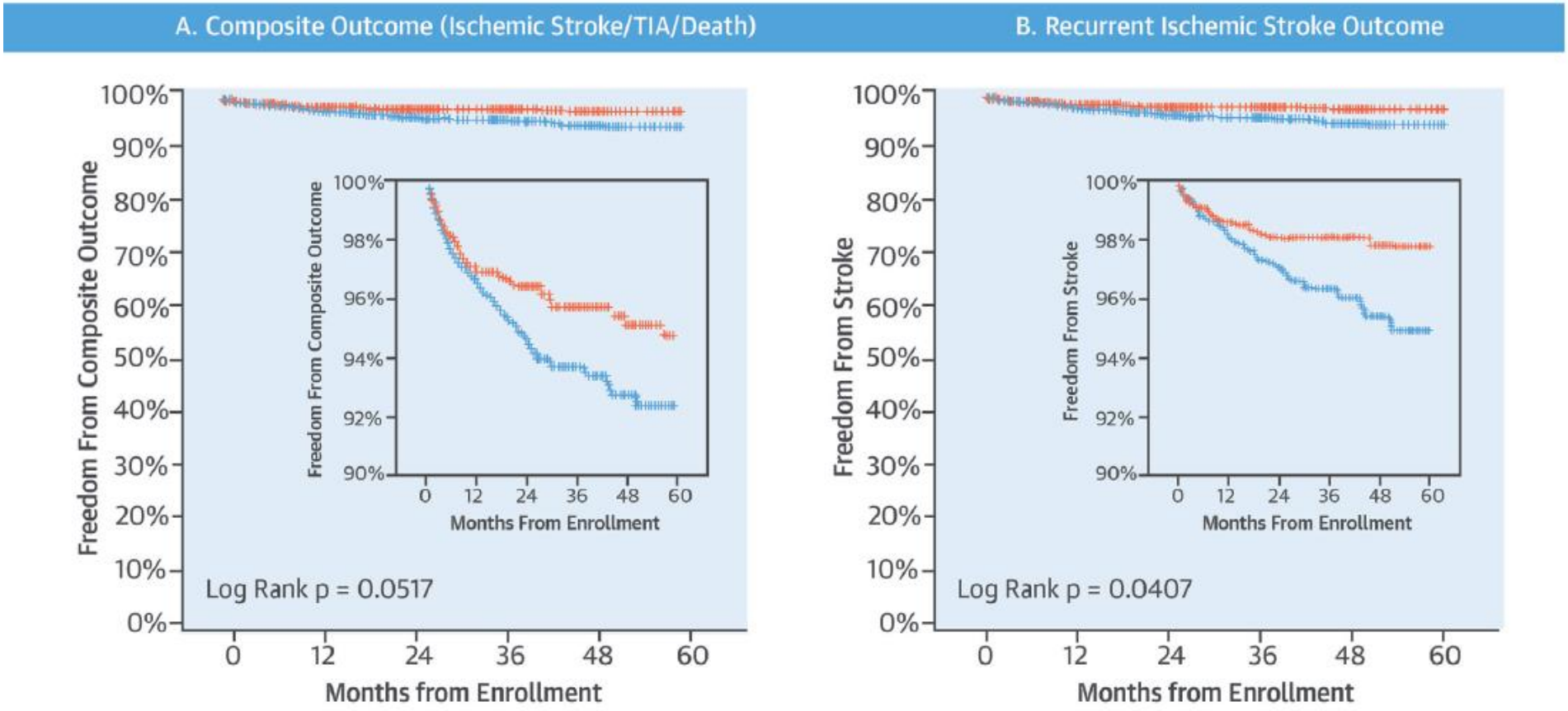
Trial Name (Year of Publication)	No. of Patients	Mean or Median No. of Years of Follow-up	Comparator	Primary Outcome	Hazard Ratio†	P Value†
Trials with negative findings						
CLOSURE I (2012)[2]	909	2	Antiplatelet therapy, warfarin, or both	Composite of stroke or transient ischemic attack at 2 years, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years after randomization	0.78	0.37
PC (2013)[3]	414	4.1 (PFO closure group), 4.0 (medical-therapy group)	Antiplatelet therapy or anticoagulation‡	Composite of death, stroke, transient ischemic attack, or peripheral embolism	0.63	0.34
RESPECT (2013)[4]	980	2.1	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.49	0.08
Trials with positive findings						
Gore REDUCE (2017)[5]	664	3.2	Antiplatelet therapy	Ischemic stroke and new brain infarction on imaging	0.23	0.002
CLOSE (2017)[6]	663	5.3	Antiplatelet therapy or anticoagulation‡	Stroke	0.03	<0.001
RESPECT extended follow-up (2017)[7]	980	5.9	Antiplatelet therapy or warfarin	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	0.55	0.046

Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis

Individual participant data from 12 databases of medically treated patients with CS and PFO were analysed with Cox regression models, to estimate database-specific hazard ratios (HRs) comparing OAC with APT, for both the primary composite outcome [recurrent stroke, transient ischaemic attack (TIA), or death] and stroke alone. Propensity scores were applied via inverse probability of treatment weighting to control for confounding. We synthesized database-specific HRs using random-effects meta-analysis models. This analysis included 2385 (OAC = 804 and APT = 1581) patients with 227 composite endpoints (stroke/TIA/death). The difference between OAC and APT was not statistically significant for the primary composite outcome [adjusted HR = 0.76, 95% confidence interval (CI) 0.52–1.12] or for the secondary outcome of stroke alone (adjusted HR = 0.75, 95% CI 0.44–1.27). Results were consistent in analyses applying alternative weighting schemes, with the exception that OAC had a statistically significant beneficial effect on the composite outcome in analyses standardized to the patient population who actually received APT (adjusted HR = 0.64, 95% CI 0.42–0.99). Subgroup analyses did not detect statistically significant heterogeneity of treatment effects across clinically important patient groups.

Eur Heart J 2015;36:2381

Pooled Analysis of RCT



JACC 2016:67;907

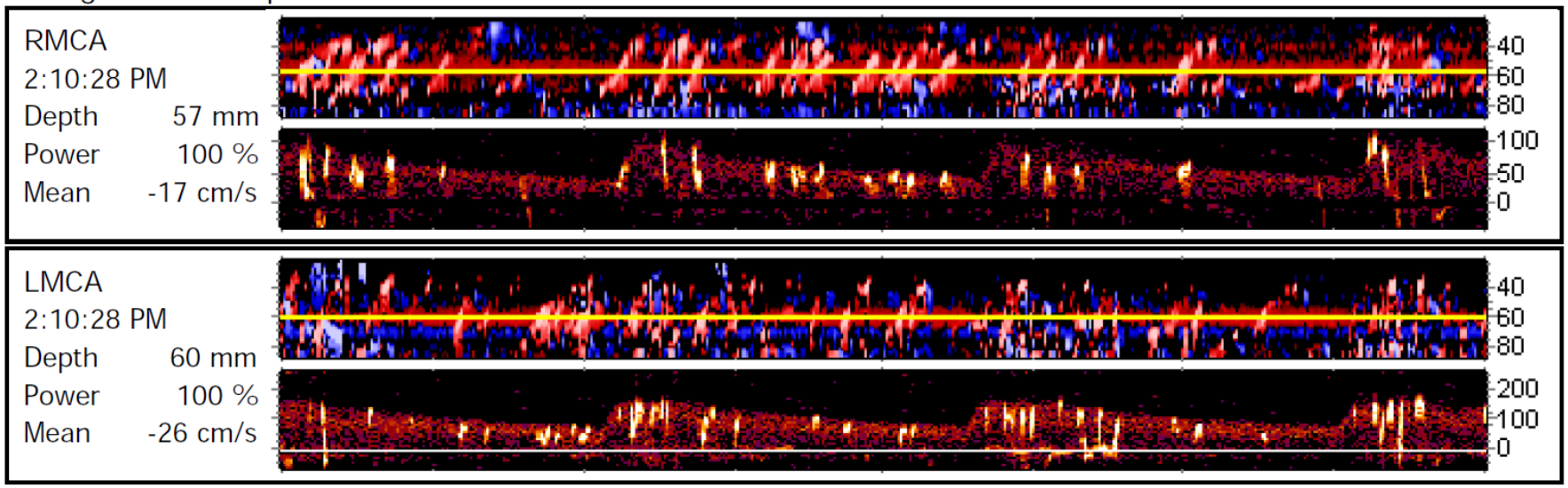
Case Study (1)

- 55/Female, left MCA infarction in Jan 2010

Findings

Embolic tracks counted during normal respiration: 250.

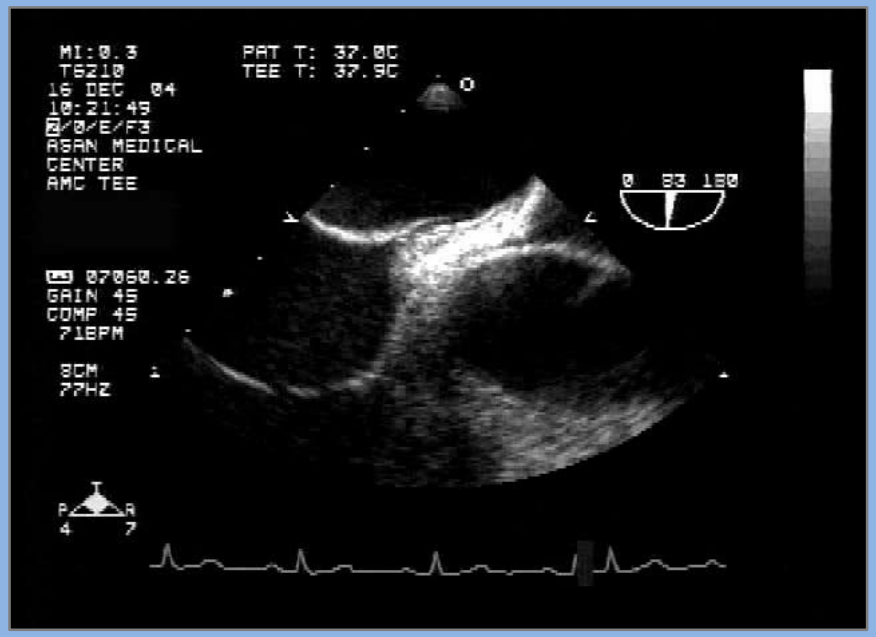
During Normal Respiration



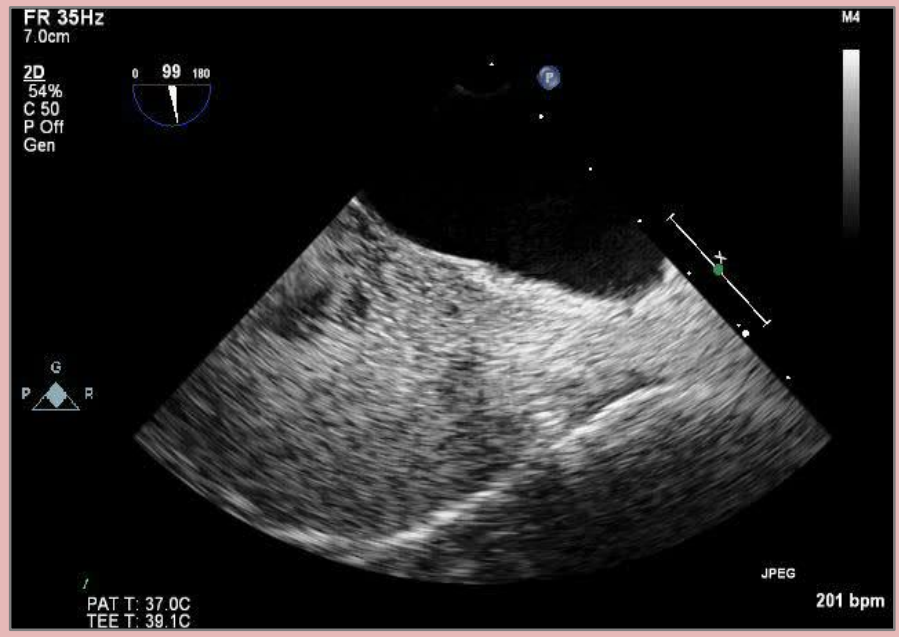
Transcranial Doppler

HITS (high intensity transient signal)

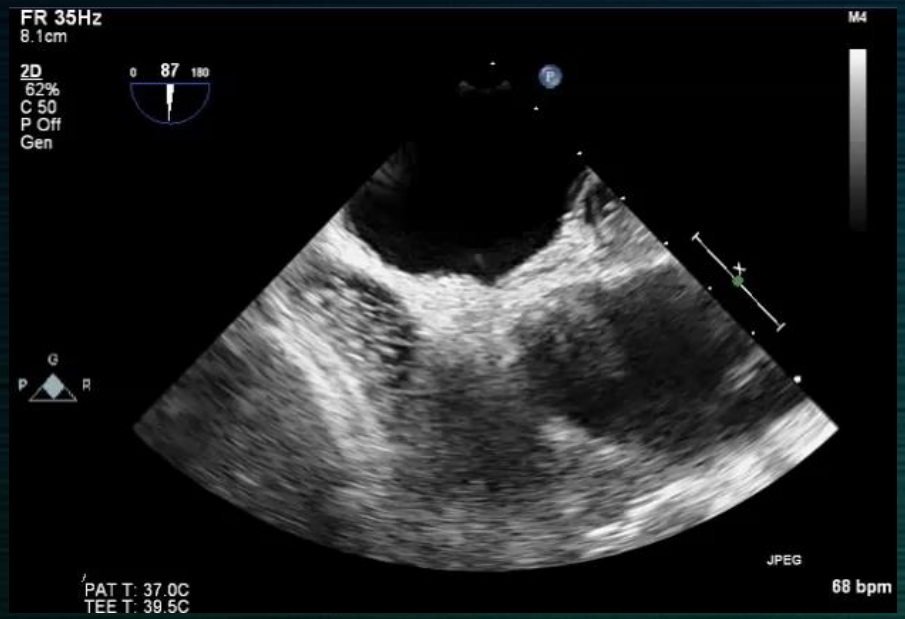
Case Study (1)



PFO



Case F/55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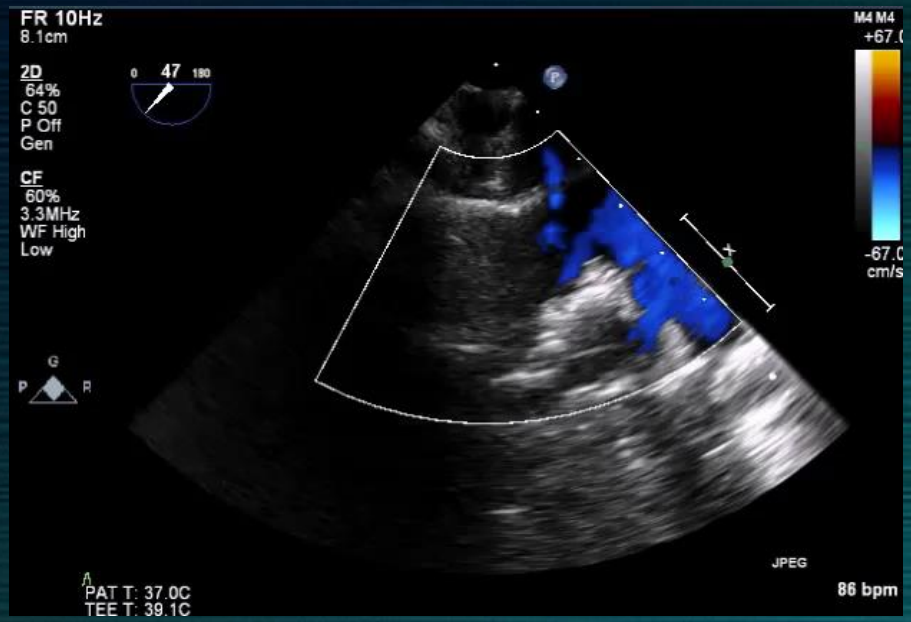
TEE T: 39.5C
68 bpm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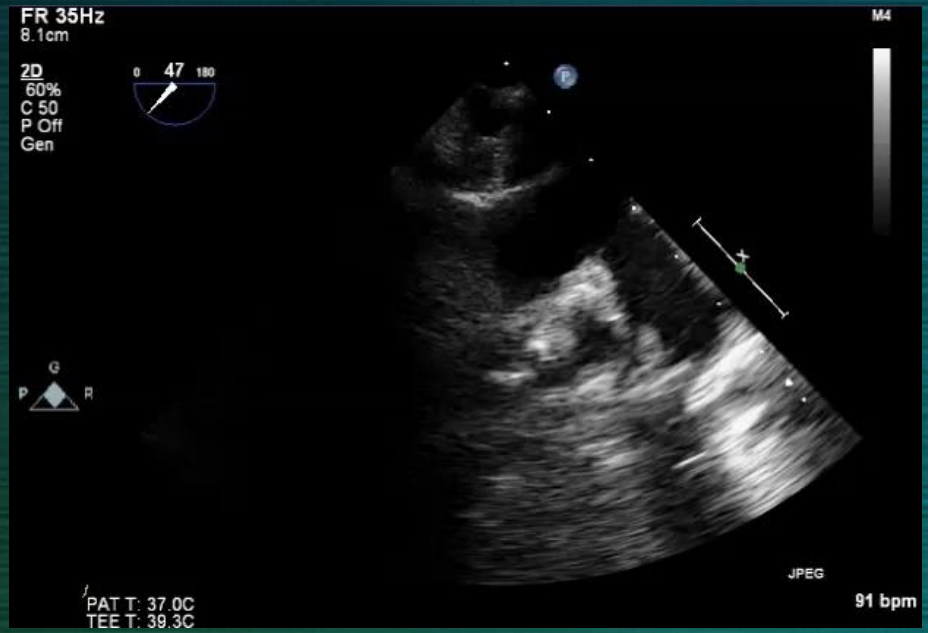
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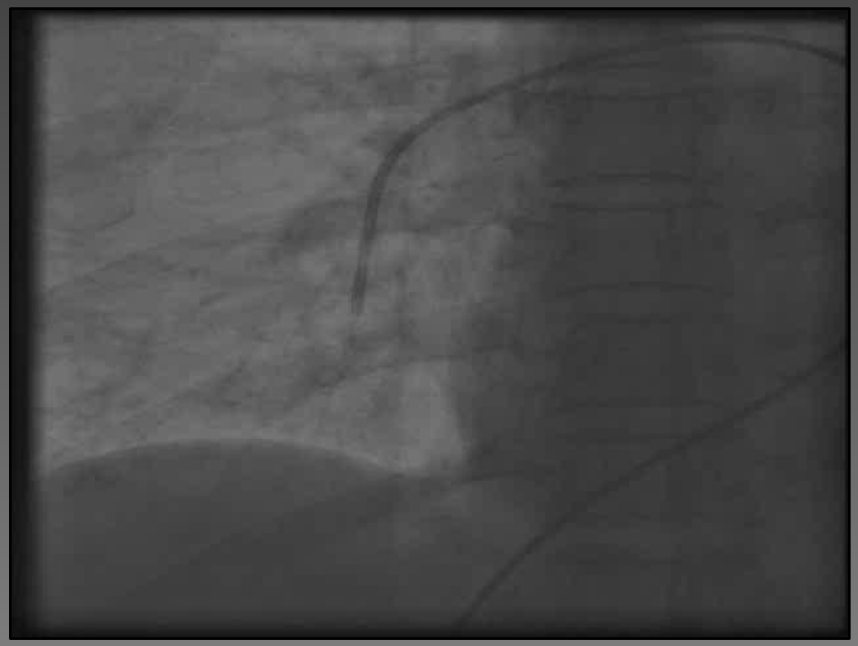
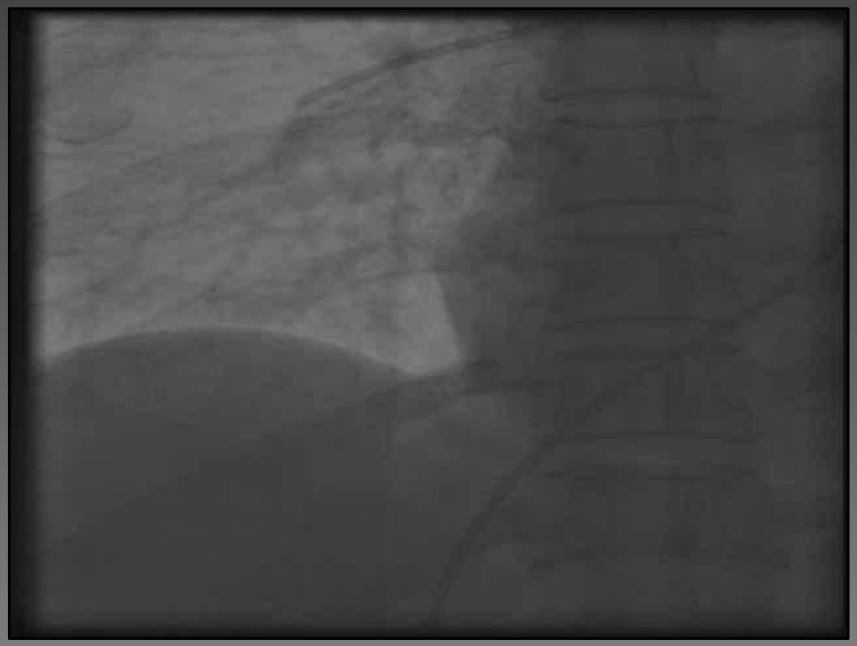
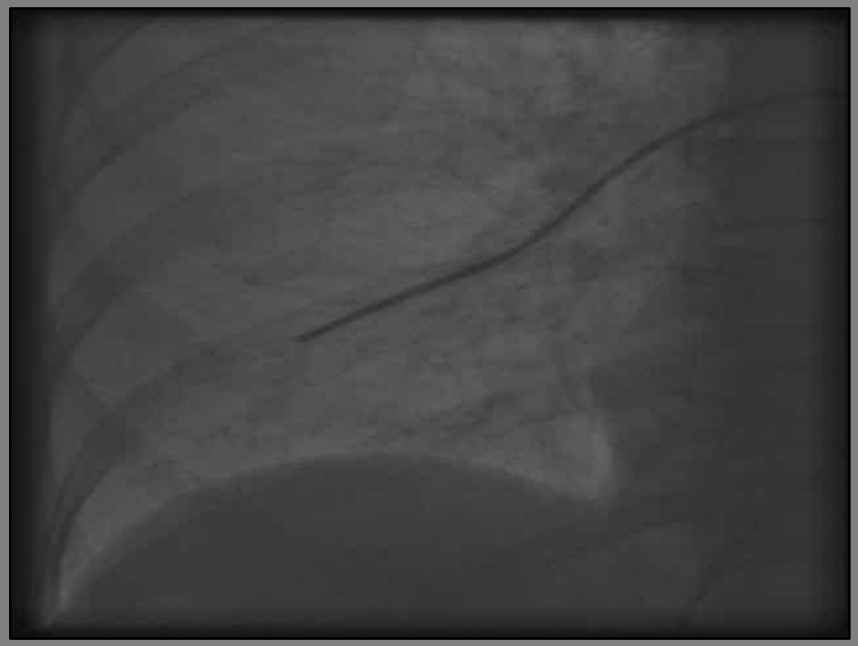
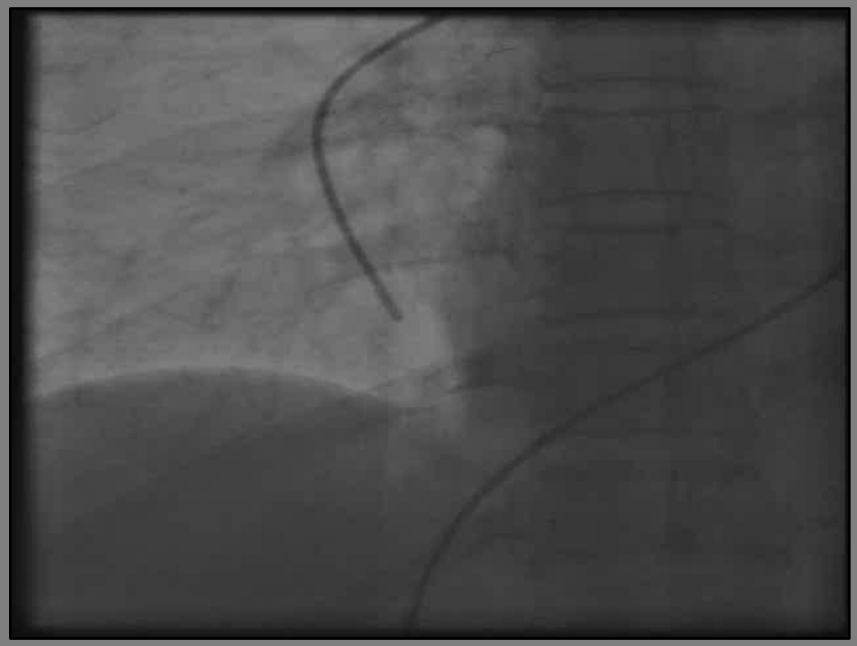
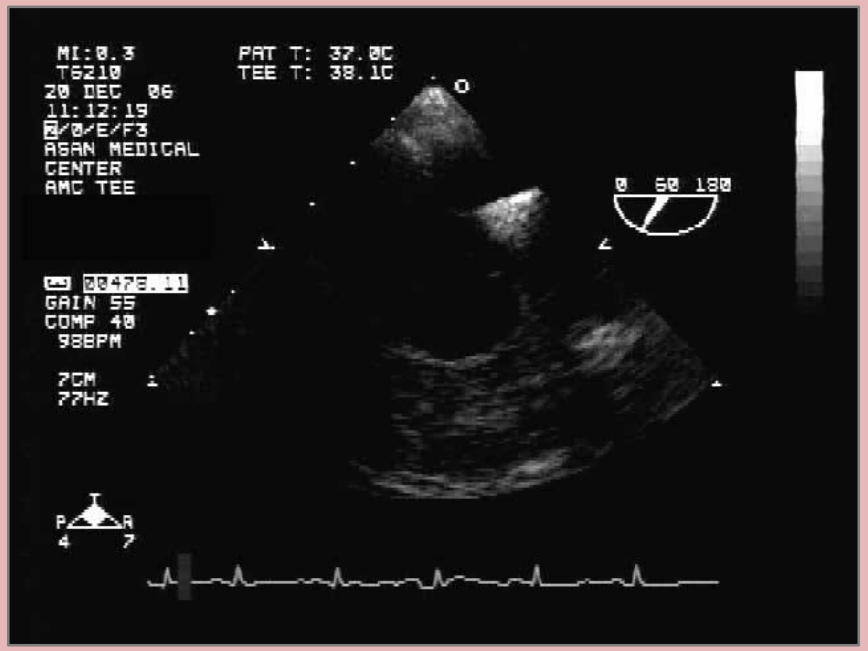




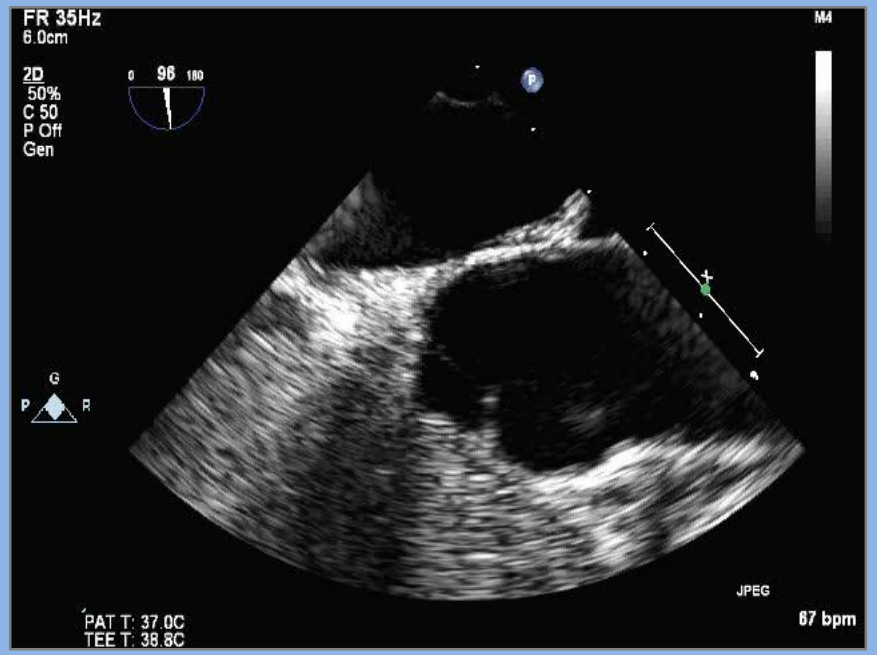




Pulmonary AV Fistula vs. PFO

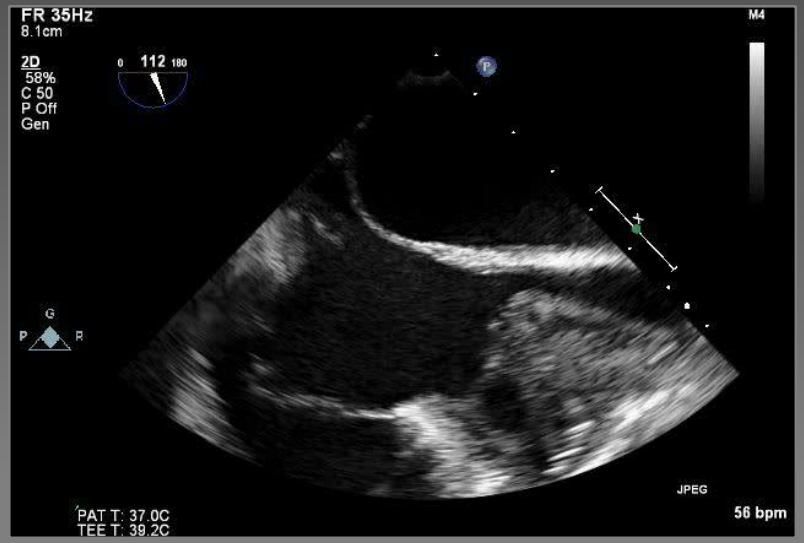


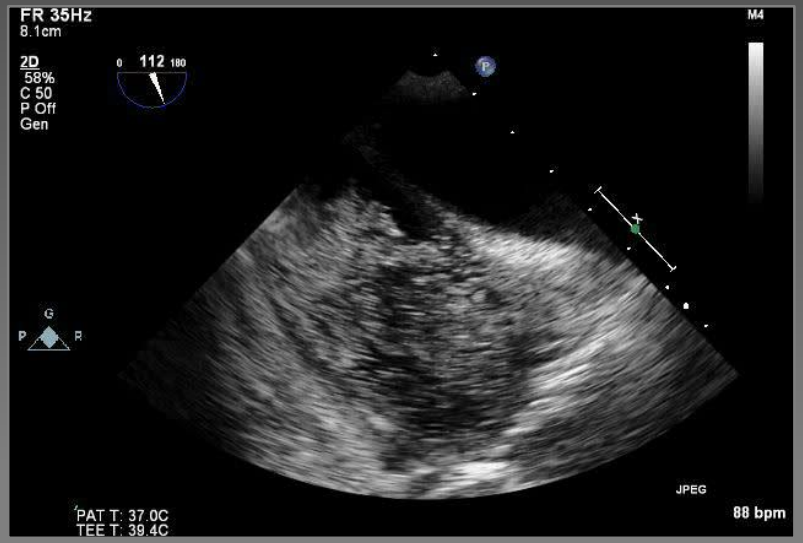
Pulmonary AV Fistula

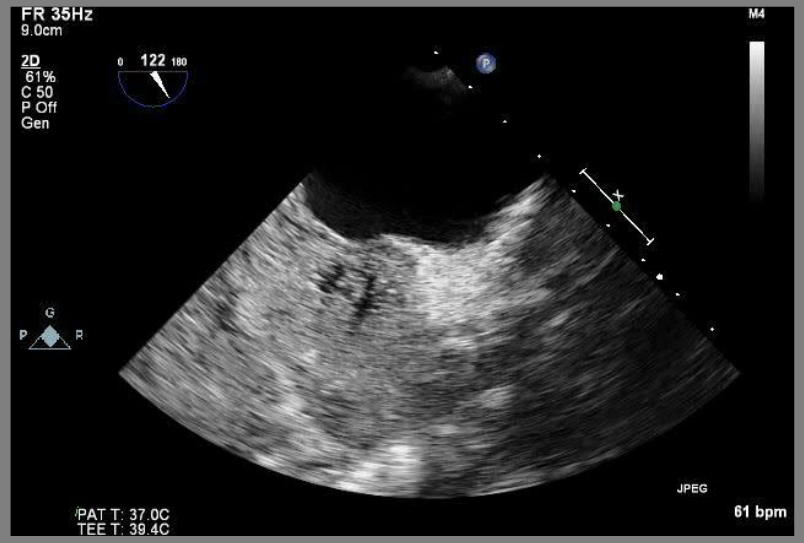


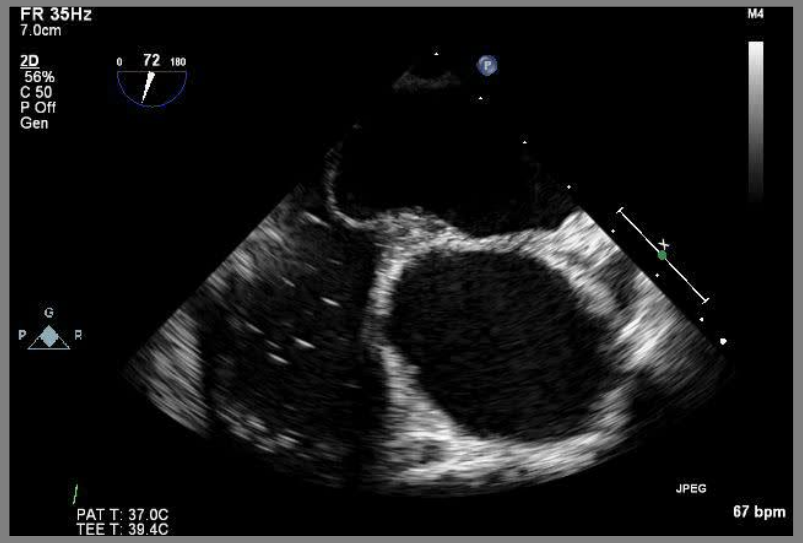
PFO

PFO with Dynamic Features



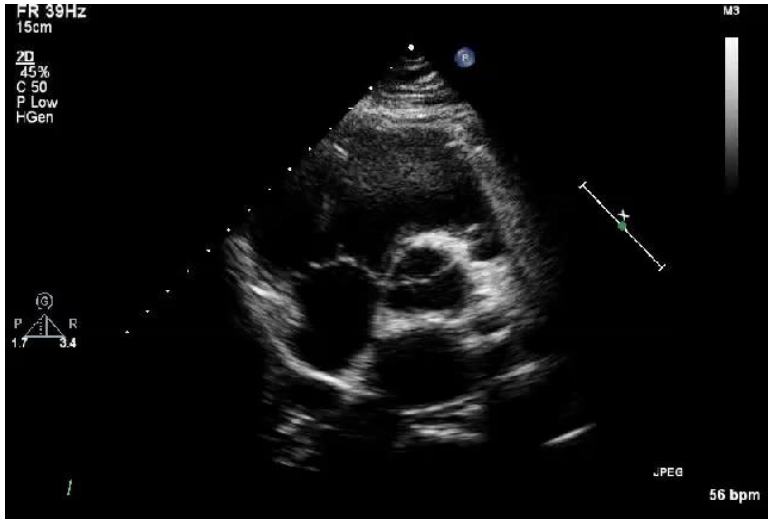


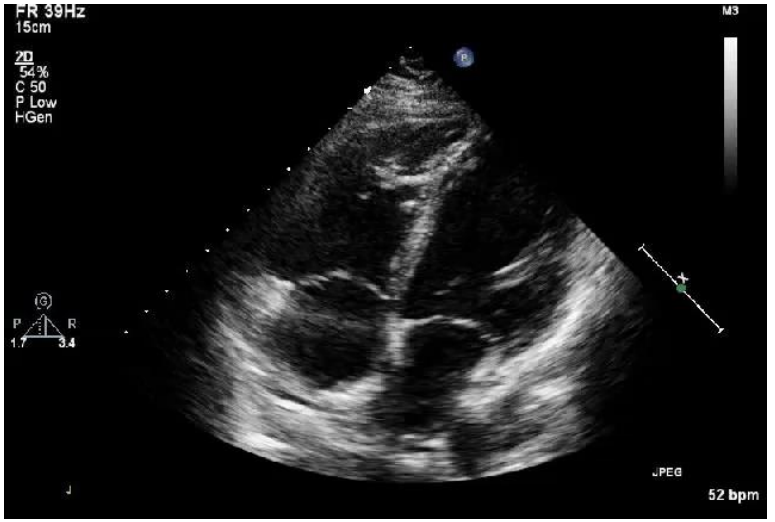


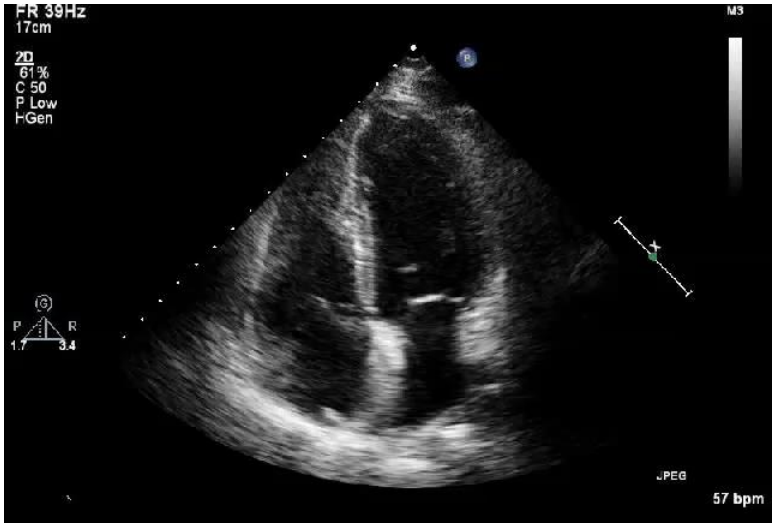


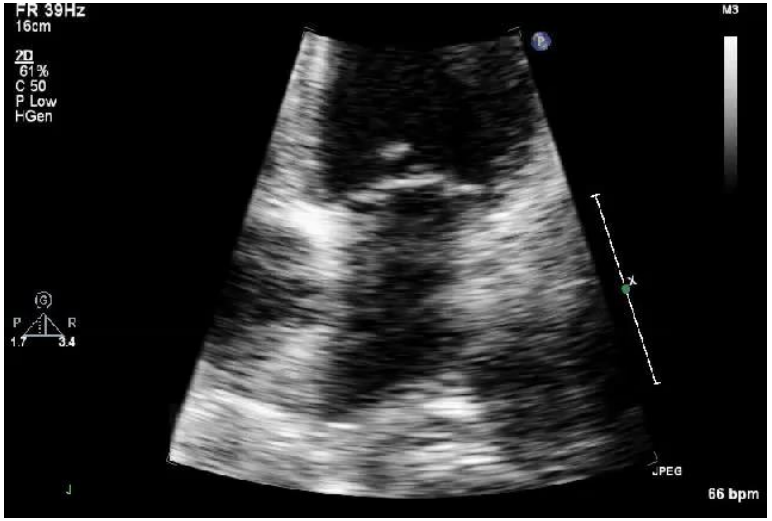
PFO with Dynamic Features

- F/43, s/p appendectomy; sudden syncope and chest pain (POD #4) and right-sided weakness with drowsy mentality (POD #6)



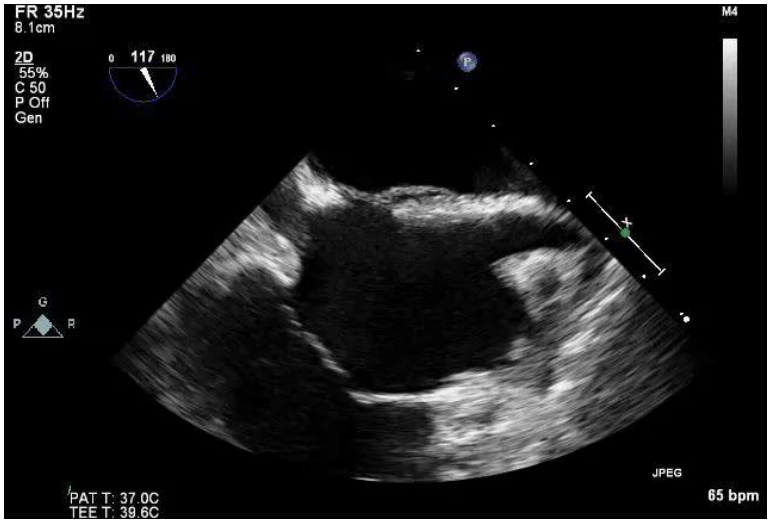


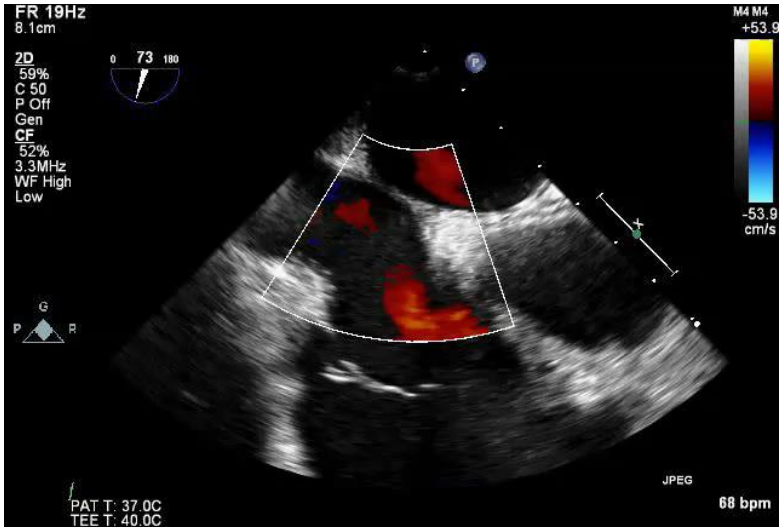


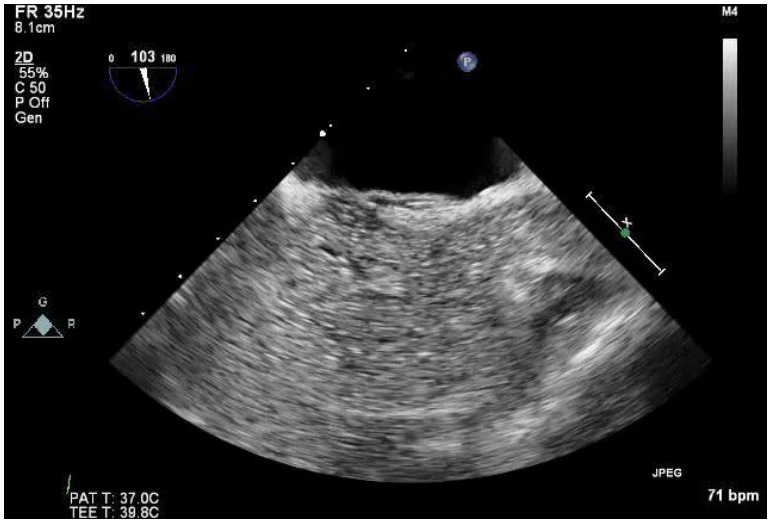


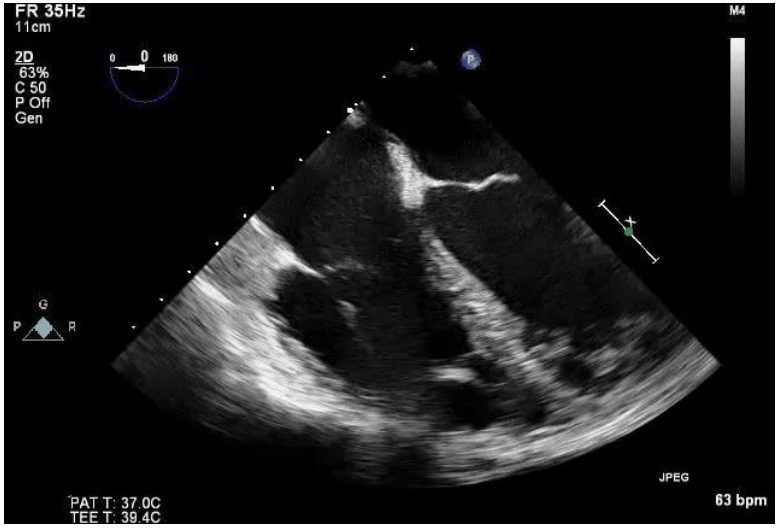
PFO with Many Dynamic Features

- TEE after anticoagulation (POD #9)









Valsalva Maneuver During PFO Device Closure