Interventional Closure of Patent Foramen Ovale 2019

Where We Are and Where we are Going

POMA 2019

Bryan W Kluck, DO,FACC

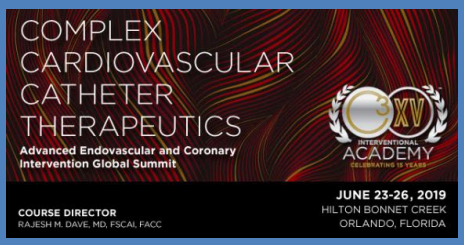
Interventional Cardiologist
Lehigh Valley Health Network
Allentown, PA

#POMA19

1

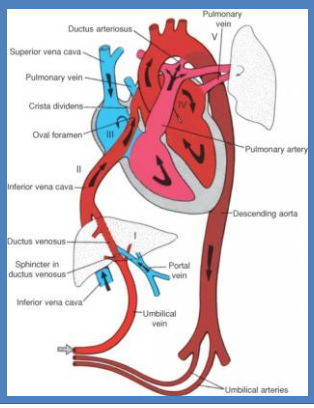
Disclosures

- I have no disclosures related to this topic



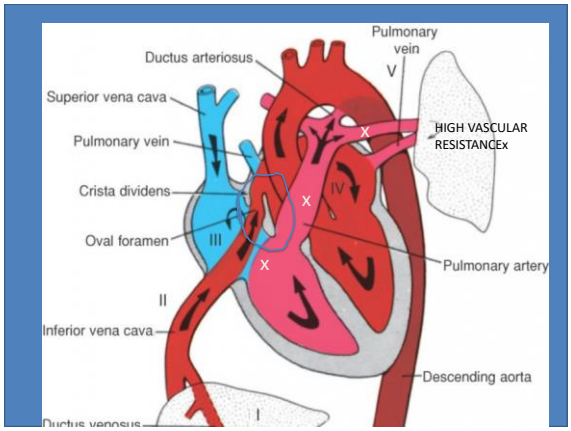
#POMA19

2

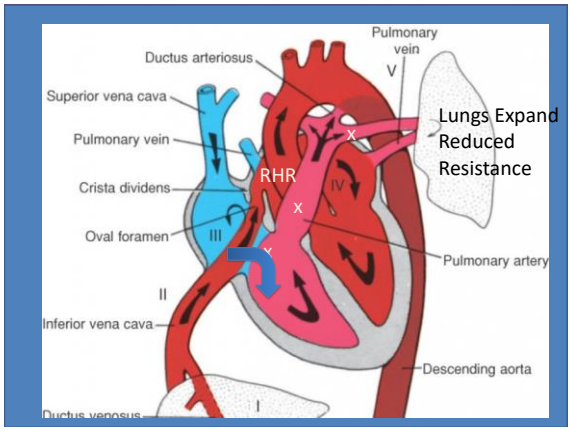


#POMA19

3



4



5

Cryptogenic Stroke- PFO

- Foramen Ovale Closes Shortly after Birth in the Majority
- Up to 25% The foramen remains open but is functionally closed as LA Pressure >> RAP

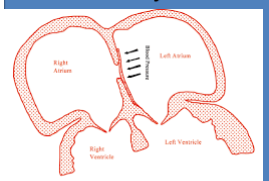


Figure 1. Normal status — higher left atrial pressure keeps the PFO closed.

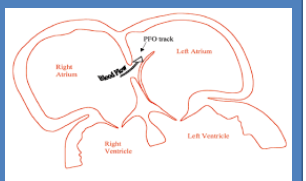


Figure 2. Right atrial pressure exceeds left atrial pressure — PFO opens.

#POMA19

6

Transient or Sustained Reversal of the Left Atrial to Right Atrial Pressure Gradient

- Early Systole
- Valsalva/ Mueller
- Coughing
- Pulmonary Hypertension
- COPD
- Pregnancy
- Asthmatics
- Wind Instruments
- Decompression Sickness (Diving)
- High Altitude Flying
- Obstructive Sleep Apnea

#POMA19

7

PFO Has Been Linked to Increased Risk of:

- Stroke
- Migraine Headaches
- Decompression Illness in Scuba Divers
- Platypnea-Orthodeoxia
- Economy Class stroke Syndrome
- Multi-Infarct Dementia
- Cerebral microemboli following TKR

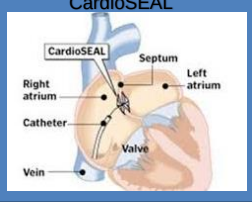
#POMA19

8

First LVHN PFO Closure patient-1/12/2001

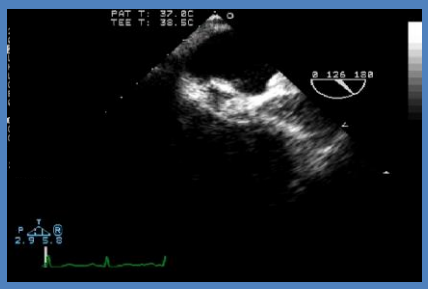
- 50 YO RHWM Brief episode of visual change ; later that morning R leg weak, R arm numb- MRI L parietal stroke
- Workup negative except PFO
- Treated w Coumadin and then closed with 28 mm Cardioseal – complicated due to long tunnel and incomplete R sided expansion – no residual flow by TTE
- 6/08/2007 – L Arm ataxia, dysarthria, R cerebellar infarction- tPA
- Repeat Closure 35 mm Amplatzer PFO device

CardioSEAL



9

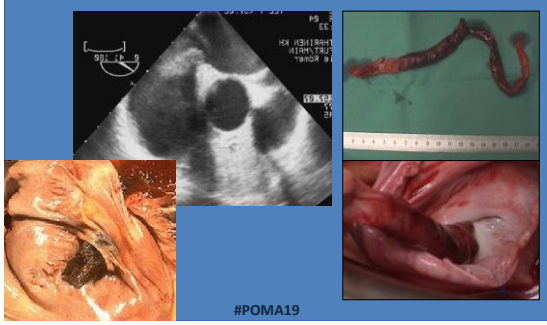
First LVHN PFO Closure patient



#POMA19

10

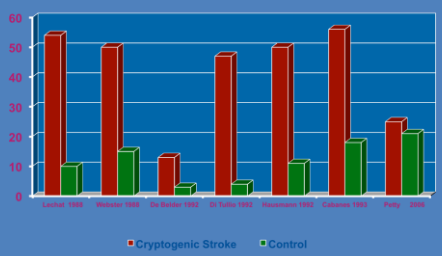
PFO Story Began with Observation of DVT's passing through PFO, causing Stroke



#POMA19

11

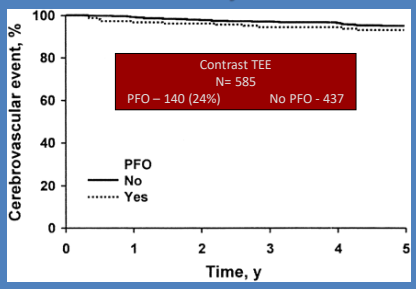
Circumstantial Evidence: Prevalence of PFO in Patients With "Cryptogenic" Stroke



#POMA19

12

Patent Foramen Ovale
Evidence From a Prospective Population-Based Study



Irene Meissner , et al. J Am Coll Cardiol, 2006; 47:440-445

13

PFO and cryptogenic stroke

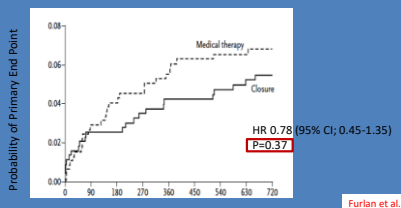
- The contribution of a patent foramen ovale (PFO) to cerebral ischemia-suspected but unproven
  - PFO - twice as prevalent in patients who have experienced a cryptogenic stroke compared to the general population
  - Observational data suggest a reduction of recurrent stroke with PFO closure, but…
- Three randomized trials of PFO closure did not show significant reduction in stroke risk in their primary intention-to-treat analysis

#POMA19

14

CLOSURE-1

- N=909 patients with stroke or TIA (**not imaging verified**) within 6 months
- RCT, 1:1 PFO closure with STARFlex + 6 months DAPT followed by aspirin for life *or* anti-thrombotic therapy with **VKA, aspirin or both**
- Primary end-point: Stroke/TIA during 2 years, death within 30 days, or death from neurologic cause between day 31 to 2 years



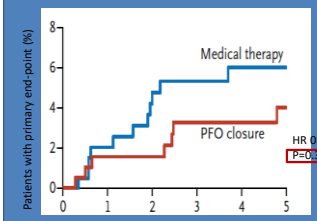
Furlan et al. NEJM 2012; 366:991-9

#POMA19

15

PC Trial

- N=414 patients with stroke, TIA or extra-cranial thrombo-embolic event
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + APT for at least 1-6 months *or* anti-thrombotic therapy with **OAC,ASA or both**
- Primary end-point: Death, non-fatal stroke, TIA, or peripheral embolism



HR 0.63 (95% CI; 0.24-1.62)
P=0.34

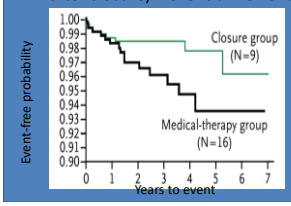
Meier et al. NEJM 2013; 368:1083-91

#POMA19

16

RESPECT

- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT followed by aspirin for at least 6 months *or* anti-thrombotic therapy with **VKA (25%) or APT (75%)**
- Primary end-point: Fatal ischemic stroke, non-fatal ischemic stroke, or early death (45 days after randomization/30 days after closure) – event driven trial (N=25)



HR 0.49 (95% CI; 0.22-1.11)
P=0.08

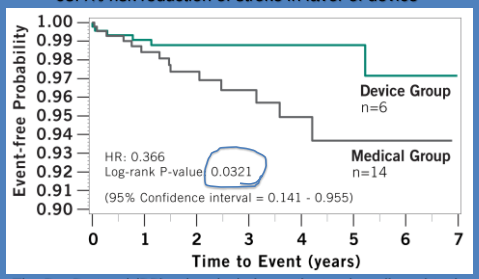
- **3/9** device group patients did not have a device at time of endpoint stroke

Carroll et al. NEJM 2013; 368:1092-100

17

RESPECT PFO-Primary Endpoint Analysis – Per Protocol Cohort

63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

18

American Academy of Neurology (Not Yet Updated)

Level A	Clinicians must counsel patients considering percutaneous PFO closure that having a PFO is common; it occurs in about 1 in 4 people; it is impossible to determine with certainty whether their PFOs caused their strokes or TIAs; the effectiveness of the procedure for reducing stroke risk remains uncertain; and the procedure is associated with relatively uncommon, yet potentially serious, complications.
Level C	In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available.
Level R	Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting.

Messé et al. Neurology 2016; 87:815-21

#POMA19

19

ACC/AHA guidelines 2011-update 2014 (Not Yet Updated To Include 2017 Data)

Patent Foramen Ovale Recommendations

2014 Recommendation	Revisions (2011)
For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B)	Class changed from IIa to I
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. (Class I, LOE A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa, LOE C).	New Recommendations
For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. (Class III, LOE A)	Revised Recommendation
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)	New Recommendation

#POMA19

20

ACC/AHA guidelines 2011-update 2014 (Not Yet Updated to Include 2017 data)

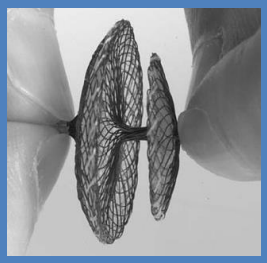
Patent Foramen Ovale Recommendations

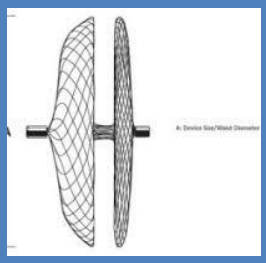
2014 Recommendation	Revisions (2011)
For patients with an ischemic stroke or TIA and a PFO who are not on anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B)	Class changed from IIa to I
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. (Class I, LOE A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa, LOE C).	New Recommendations
For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data does not support a benefit for PFO closure. (Class III, LOE A)	Revised Recommendation
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C)	New Recommendation

#POMA19

21

Amplatzer PFO and Cribriform ASD devices





PFO Device

Cribriform ASD Device

#POMA19

22

The positive trials - September 14th, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

RESPECT extended f/u

REDUCE

CLOSE

#POMA19

23

The positive trials - September 14th, 2017

1.) Longer Follow up
2.) Cortical Strokes only-
3..) No TIA
4.) New Brain Infarct- No Lacunes
5.) Restricted Age 18-60

NGLAND MEDICINE

Closure progenic Stroke

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

RESPECT extended f/u p=0.046

REDUCE P=0.002

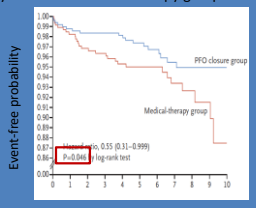
CLOSE P<0.001

#POMA19

24

RESPECT extended f/u (mean 2.6 -> 5.9 years)

- N=980 patients with stroke or TIA within 9 months
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + 1 month DAPT and aspirin for at least 6 months *or* anti-thrombotic therapy with **VKA (25%) or APT (75%)**
- **Treatment exposure**: 3,141 patient-years in the PFO closure group vs. 2,669 patient-years in the medical therapy group

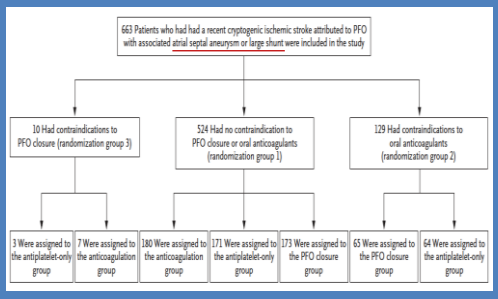


#POMA19

Saver et al. NEJM 2017; 377:1022-32

25

CLOSE



#POMA19

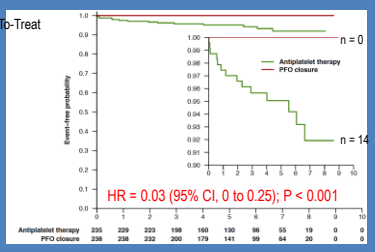
Mas et al. NEJM 2017; 377:1011-21

26

CLOSURE versus ANTIPLATELET THERAPY

Mean follow-up (years) = 5.4 +/-1.9 (CLOSURE) vs. 5.2 +/-2.1 (APT)

Intention-To-Treat



5-yr absolute risk reduction = 4.9%
1 avoided stroke at 5 years for every 20 (17 to 25) patients treated with closure

#POMA19

27

CLOSE

5-year cumulative estimate of the probability of stroke was:

1.5% in the OAC group and 3.8% in the SAPT group

The study was not adequately powered to compare outcomes in these groups!

- #POMA19

Mas et al. NEJM 2017; 377:1011-21

28

REDUCE Study

- Aim to establish superiority of PFO closure (WL Gore Septal Occluder) in conjunction with APT over APT alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct
- Randomized, controlled, open-label trial
  - 664 subjects randomized in a 2:1 ratio to:
    - Closure: PFO closure plus antiplatelet therapy
    - Medical therapy: antiplatelet therapy alone
- 63 sites in 7 countries
  - Canada, Denmark, Finland, Norway, Sweden, UK, US

- #POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

29

Inclusion and Exclusion Criteria

- Age 18-59 years
- Cryptogenic ischemic stroke within 180 days
  - Clinical symptoms ≥24 hours or MRI evidence of infarction
  - Cryptogenic
    - No stenosis >50% or ulcerated plaque in relevant vessels
    - No atrial fibrillation or high risk source of cardioembolism
    - Non-lacunar (based on syndrome and/or size)
    - No evidence of hyper-coagulable disorder
- Patent foramen ovale (PFO)
  - Confirmed by TEE with bubble study (right-to-left shunt)
  - No indication for anticoagulation

- #POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

30

REDUCE Study Design

Medical Therapy

- Antiplatelet standardized options:
  - Aspirin alone (75-325 mg once daily)
  - Combination aspirin (50-100 mg) and dipyridamole (225-400 mg)
  - Clopidogrel (75 mg once daily)
  - Other combinations or the use of anticoagulants was not permitted
- Prescribed for all subjects for the duration of the study
- Each site was expected to treat all subjects with the same antiplatelet therapy

Follow-up

- MRI imaging at baseline and 24 months if not already performed for an endpoint event

#POMA19

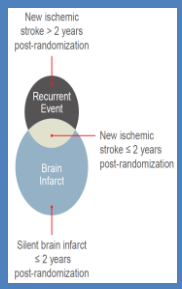
Sondergaard et al. NEJM 2017; 377:1033-42

31

Co-Primary Endpoints

- Freedom from **recurrent clinical ischemic stroke** through at least 24 months
- Incidence of **new brain infarct** (defined as clinical ischemic stroke or silent brain infarct*) through 24 months

*New T2 hyperintense MRI lesion with diameter ≥3 mm; adjudicated by MRI core lab



#POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

32

Baseline Characteristics

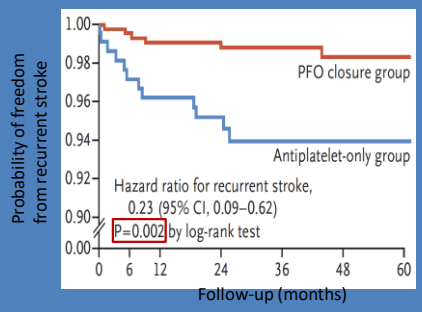
Demographic / Characteristic	Closure (N=441)	Medical (N=223)	p-value
Age, years	45.4 ± 9.3	44.8 ± 9.6	0.41
Days from qualifying event to randomization	100 ± 52	101 ± 53	0.90
Sex, male	59.2%	61.9%	0.56
Current Smoker	14.3%	11.2%	0.30
Diabetes mellitus	4.1%	4.5%	0.84
Hypertension	25.4%	26.0%	0.94
Previous Cerebrovascular Event	14.1%	10.3%	0.22
Maximal baseline shunt grade (# bubbles)	N=425	N=216	0.32
Grade 0 Occluded (0)	0.0%	0.0%	-
Grade I Trivial/Small (1-5)	18.1%	19.9%	-
Grade II Moderate (6-25)	39.1%	43.5%	-
Grade III Large (>25)	42.8%	36.6%	-
Atrial septal aneurysm	20.4%	(did not collect)	-

#POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

33

Clinical stroke (ITT)

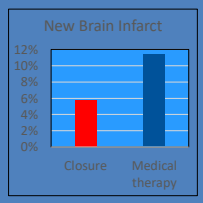


- #POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

34

New brain infarct (ITT)



	Closure (N=441)	Medical (N=223)
Subjects without Evaluation	58	46
Brain Infarct Evaluable	383	177
Brain Infarct Present	**22 (5.7%)**	**20 (11.3%)**
Recurrent Stroke Only	3	6
Both	2	6
Silent Brain Infarct Only	17	8
Brain Infarct Absent	361 (94.3%)	157 (88.7%)

- Difference in incidence of new brain infarct of 5.6%
- Relative risk 0.51 (95% CI: 0.29 to 0.91)
- p=0.024 after adjustment for multiple testing
- silent infarcts about twice as common as clinical stroke

Sondergaard et al. NEJM 2017; 377:1033-42

35

Safety

All Enrolled Subjects (N=664)	Closure (n=441)	Medical (n=223)	p-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**0.57**
Procedure-related	4 (0.9%)	-	0.31
Other	4 (0.9%)	6 (2.7%)	0.09
Any AF/ flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**<0.001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	<0.001
Serious device adverse events	**6 (1.4%)**	**-**	**-**
Device dislocation	3 (0.7%)	-	-
Device thrombosis	2 (0.5%)	-	-
Aortic dissection	1 (0.2%)	-	-
Any DVT or PE	**3 (0.7%)**	**2 (0.9%)**	**1.0**

- #POMA19

Sondergaard et al. NEJM 2017; 377:1033-42

36

Safety

- Atrial fibrillation/flutter rate higher in the closure group
  - onset in 1st month (79%)
  - resolved within 2 weeks (59%)
  - 1/29 patients with AF after PFO closure had a stroke
- REDUCE 6.6% vs. 0.4%
- CLOSURE- 5.7% vs. 0.7%
- PC Trial 2.9% vs. 1.0%
- RESPECT 3.0% vs. 1.5%
- CLOSE 4.6% vs. 0.9%

- #POMA19

All Enrolled Subjects (N=664)	Closure (n=441)	Medical (n=223)	p-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**0.57**
Procedure-related	4 (0.9%)	-	0.31
Other	4 (0.9%)	6 (2.7%)	0.09
Any AF/ flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**<0.001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	<0.001
Serious device adverse events	**6 (1.4%)**	**-**	**-**
Device dislocation	3 (0.7%)	-	-
Device thrombosis	2 (0.5%)	-	-
Aortic dissection	1 (0.2%)	-	-
Any DVT or PE	**3 (0.7%)**	**2 (0.9%)**	**1.0**

Sondergaard et al. NEJM 2017; 377:1033-42

37

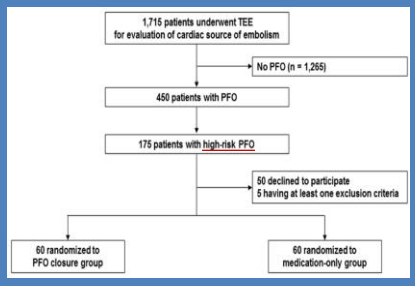
DEFENCE-PFO

- N=210 -> 120 patients with ischemic stroke within 6 months and high-risk PFO:
  - Atrial septal aneurysm
  - Hypermobility (excursion ≥10 mm)
  - PFO size ≥2 mm (maximum separation of septum primum from septum secundum)
- RCT, 1:1 PFO closure with Amplatzer PFO occluder + DAPT for at least 6 months *or* anti-thrombotic therapy with OAC or APT
- Aim: To evaluate whether the benefits of PFO closure can be determined based on morphological characteristics of the PFO
- Primary end-point: Stroke, vascular death, or major bleeding during 2 years f/u

Lee et al. JACC 2018; 71:2335-42

38

DEFENCE-PFO

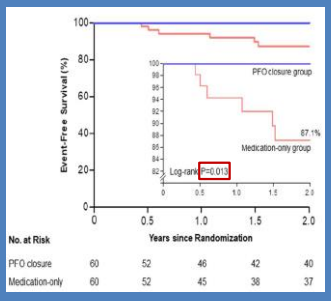


#POMA19

Lee et al. JACC 2018; 71:2335-42

39

DEFENCE-PFO

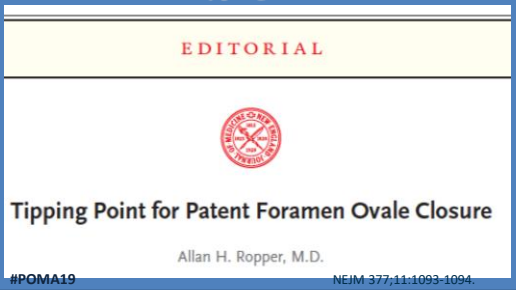


#POMA19

Lee et al. JACC 2018; 71:2335-42

40

"…. it seems reasonable that the presence of a PFO and a sizable interatrial shunt should …. no longer result in the categorization of a stroke as cryptogenic."


EDITORIAL

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

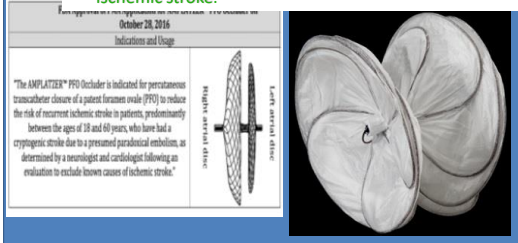
#POMA19

NEJM 377;11:1093-1094.

41

Devices

"… as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke."


October 28, 2016

Indications and Usage

"The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke."

Right atrial disc

Left atrial disc

#POMA19

42

FDA Indications

- Indication for secondary prevention of stroke – not primary
  - Patients who have had a stroke – TIA not included
- No indication for hypoxemia from right to left shunting
- No indication for migraine

#POMA19

43

Screening/Imaging PFO

1.) Transcranial Doppler (TCD-Bubble)
a.) Highest Sensitivity
b.) Low specificity
c.)No PFO Features (PFO, L Atrium, Appendage)
d.) Allows for Valsalva /Mueller
2. Transthoracic Echo (TTE) Specific
Both are initial Screen recommendations in new (and only current) European Guidelines

#POMA19

44

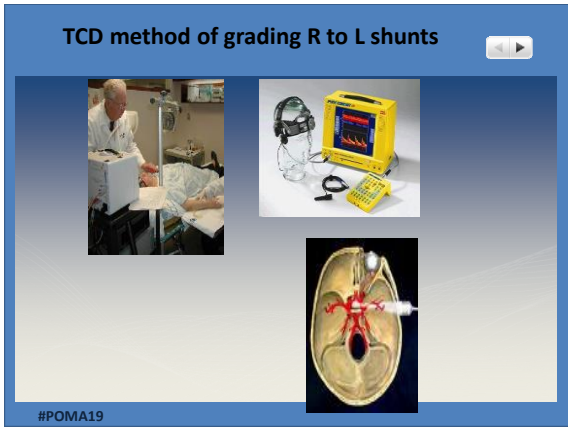
TCD

- Four level visual categorization:
  (i) Grade 0: no occurrence of micro-embolic signals
  (ii) grade I, 1-10 signals;
  (iii) grade II, >10 signals but no curtain pattern
  (iv) grade III, Copious bubbles , not curtain
  (v) Grade IV. Curtain effect

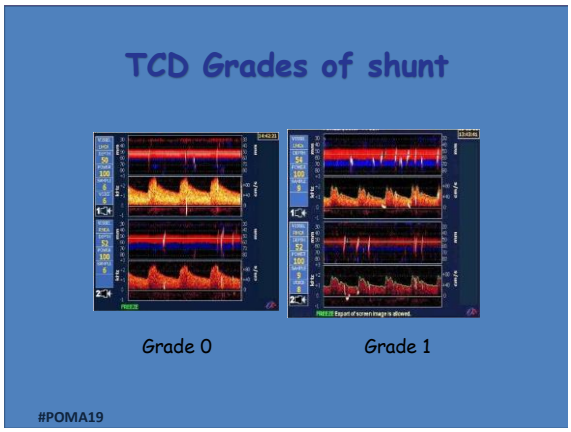
- Test negative: no microbubble
- Low grade shunt: 1–10 microbubbles
- Medium grade shunt: >10 microbubbles but without "curtain effect"
- High grade shunt: curtain effect, seen when the microbubbles are so numerous as to be no longer distinguishable separately

#POMA19

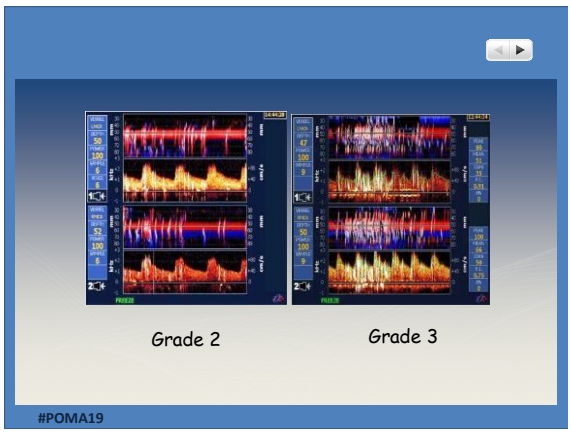
45


TCD method of grading R to L shunts
#POMA19

46


TCD Grades of shunt
Grade 0
Grade 1
#POMA19

47


Grade 2
Grade 3
#POMA19

48

Grade 4 Grade 4

#POMA19

49

TEE

- Specific, But Sensitivity quite varied, False - as high as 15-30% with large R-L shunts missed often
  - a.) number of attempts- inj. agitated saline
  - b.) bulge R to L at time of Recording
  - c.) Arm vs. Leg vein injection

Diagnosis of Patent Foramen Ovale Using Different Imaging Techniques.

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Transcranial Doppler ultrasound	97	98	99	93
Transthoracic echocardiography	100	100	100	100
Transesophageal echocardiography	86	100	100	76

NPV, negative predictive value; PPV, positive predictive value.

#POMA19

50

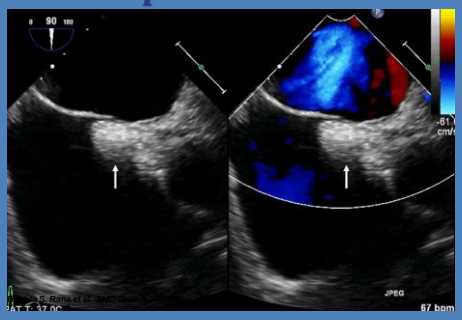
TEE

Additional features : ASA, Septal Anatomy, Tunnel length, LAA Thrombus

#POMA19

51

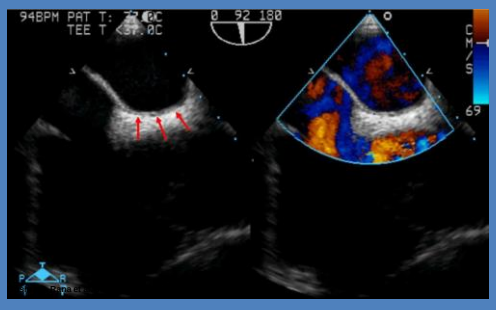
Septal Thickness



#POMA19

52

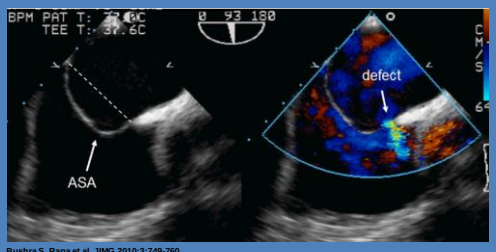
Tunnel Length



#POMA19

53

ASA

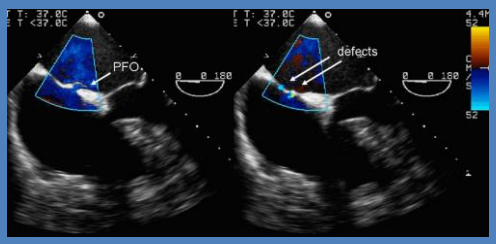


Bushra S. Rana et al. JIMG 2010;3:749-760

#POMA19

54

Hybrid Defects



Bushra S. Rana et al. JIMG 2010;3:749-760

#POMA19

55

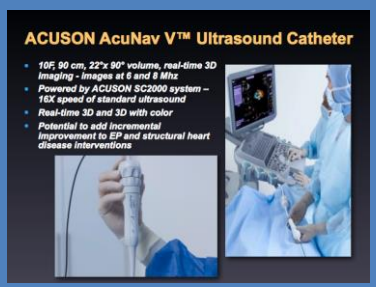
Intracardiac Echo (ICE)

- Only Real Role is For Intraprocedural Imaging- no Role in Diagnostic Evaluation
- Comparable Imaging to TEE; Single Operator
- Avoids General Anesthesia
- Costly
- Second Vascular Access

#POMA19

56

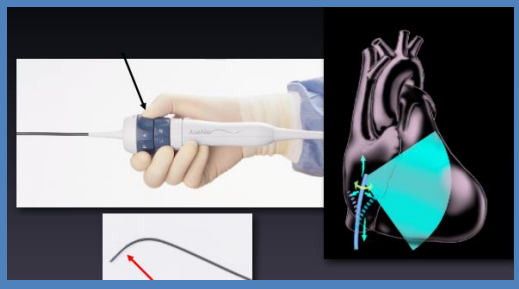
Intracardiac Echo (ICE)



#POMA19

57

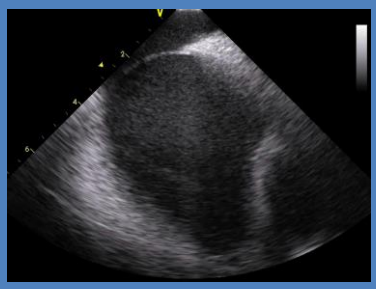
Intracardiac Echo (ICE)



#POMA19

58

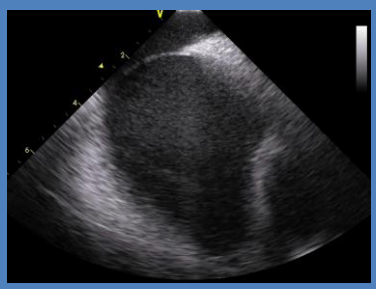
Patient with initial negative bubble study ICE



#POMA19

59

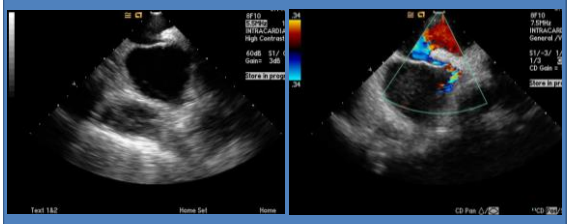
Snoring patient with initial negative ICE bubble study



#POMA19

60

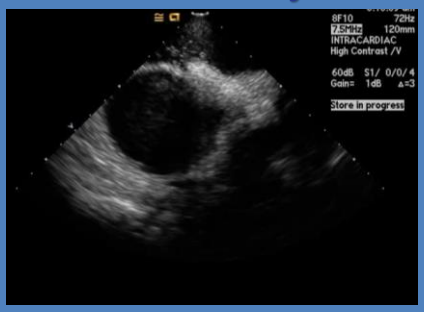
Inter-atrial septum



#POMA19

61

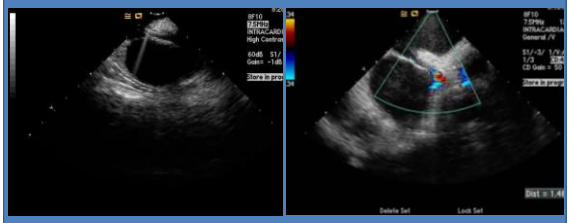
Bubble study



#POMA19

62

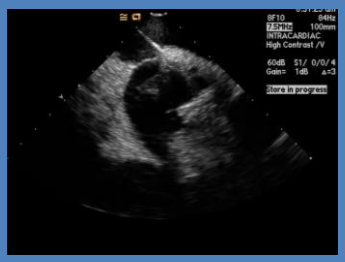
Tunnel length

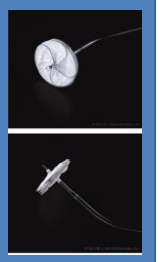


#POMA19

63

30mm Gore Cardioform Septal Occluder



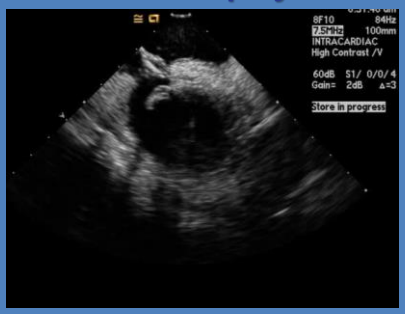


Butera G et al. CCI 2013

#POMA19

64

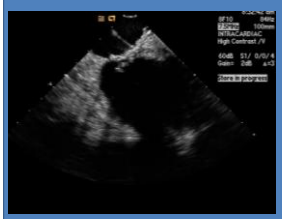
RA disc deployed

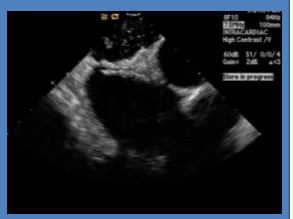


#POMA19

65

Confirmation of device position

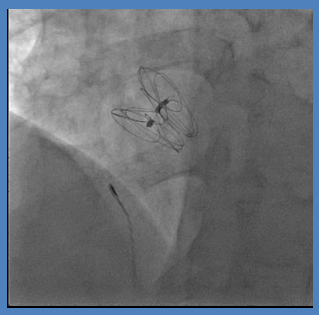




#POMA19

66

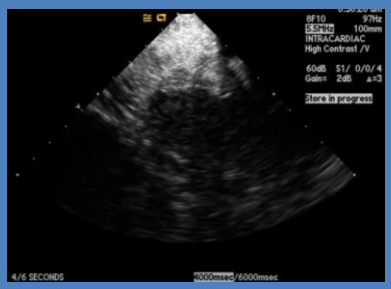
Fluoro



#POMA19

67

Final bubble study



#POMA19

68

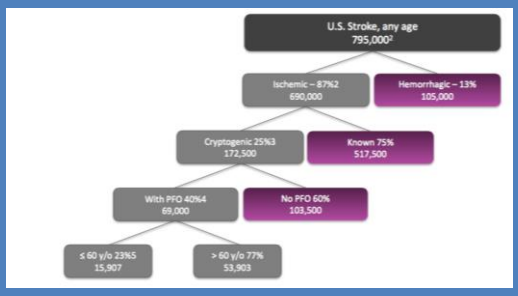
Who Do We Close?

#POMA19

69

Is There a Pathogenic PFO ?

US PFO Incidence



#POMA19

70

Is There a Pathogenic PFO ?

Risk of Paradoxical Embolism (RoPE Score)

Age	Traditional Vascular Risk Factors	Neuroimaging Findings at Index Stroke
• Age at time of stroke ○ 5 points for 18-29 ○ 4 for 30-39 ○ 3 for 40-49 ○ 2 for 50-59 ○ 1 for 60-69 ○ 0 for ≥70)	• Absence of these factors (1 point for each): ○ Diabetes mellitus ○ Systemic Hypertension ○ Smoking ○ Prior stroke or TIA.	• Presence of cortical (superficial) stroke on neuro-imaging (1 point)

#POMA19 **Total Score: Range 0-10**

71

Is There a Pathogenic PFO
Risk of Paradoxical Embolism (RoPE Score)

Total RoPE Score	Prevalence of PFO (%)	PFO-attributable fraction (%)	Estimated 2-year stroke/TIA recurrence rate (%)
0-3	23	0	20
4	35	38	12
5	34	34	7
6	47	62	8
7	54	72	6
8	67	84	6
9-10	73	88	2

65 year old man has a lacunar stroke. He is a smoker, diabetic and hypertensive with history TIA.
RoPE= 1

35 year old woman has a cortical stroke. She has no vascular stroke risk factors.
RoPE= 9

72

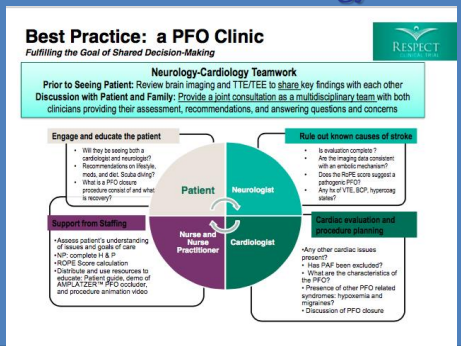
Is There a Pathogenic PFO ? Additional Clues

- Shunting At Rest
- Large Volume of Shunting
- Atrial Septal Aneurism plus PFO
- Anatomically opens > 10 mm
- Prominent Eustacian Valve on Echo

#POMA19

73

LVHN Neurocardiology Clinic



74

Pharmacology and Follow-up

Drug therapy and follow up after percutaneous closure		
Position statements	**Strength of the statement**	**Level of evidence**
It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure	Conditional	A
We suggest a single antiplatelet therapy be continued for at least 5 years	Conditional	C
The extension of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient's overall risk of stroke for other causes and haemorrhagic risk	Strong	C
The choice of the type of antiplatelet drug in the follow-up is currently empiric	Strong	A
The value of residual shunt after percutaneous closure cannot be deduced from available studies	Strong	C
Systematic, high-quality data on follow-up are needed	Strong	C

Pristipino et al, Euro Interventions, 2018

#POMA19

75

Pharmacology and Follow-up

Drug therapy and follow up after percutaneous closure		
Position statements	**Strength of the statement**	**Level of evidence**
It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure	Conditional	A
We suggest a single antiplatelet therapy be continued for at least 5 years	Conditional	C
The extension of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient's overall risk of stroke for other causes and haemorrhagic risk	Strong	C
The choice of the type of antiplatelet drug in the follow-up is currently empiric	Strong	A
The value of residual shunt after percutaneous closure cannot be deduced from available studies	Strong	C
Systematic, high-quality data on follow-up are needed	Strong	C

Pristipino et al, Euro Interventions, 2018

#POMA19

76

Follow up

To obtain comparable data we propose to perform: a) a TTE prior to hospital discharge b) c-TCD at least once beyond six months to assess effective PFO closure and thereafter, if residual shunt persists, annually until closure c) c-TOE or c-TTE in case of severe residual shunt at c-TCD, or recurrent events, or symptoms during follow-up	Conditional	C	124,141-147, 55 + Original meta-analyses and Supplementary Appendix
Patients should undergo antibiotic prophylaxis for any invasive procedure performed in the first six months from PFO closure	Conditional	C	-

Pristipino et al, Euro Interventions, 2018

#POMA19

77

Atrial fibrillation Management

- First, make sure no AF before the procedure
  - 30 day monitor
  - ILR in older patients
  - Prefer Amplatzer in older patients (? Stitch devices)
- If develops after procedure (due to irritation and inflammation)
  - Rate control
  - Anticoagulation (drop one or both antiplatelets)
  - Cardioversion if doesn't resolve during 24 hours
  - Rarely need to use anti-arrhythmics
  - All have resolved on own – discontinued anticoagulation

#POMA19

78

Complications of PFO Closure

#POMA19

79

Intra-procedural Complications

- Air embolism (coronary, brain, systemic)
- Cardiac or vessel damage
- Device embolization
- Bleeding or access site injury
- Thrombus
- Migraine/headache

#POMA19

80

Post-procedure Complications

- Chest pain
  - Nickel allergy (steroids, prefer Gore)
  - Cardiac or vascular damage (effusions)
  - Erosion
- Device embolization
  - Imaging next day
- Pulmonary embolism/DVT
  - Avoid excessive compression
  - Rule out pre-procedure DVT, especially on inpatients
- Atrial fibrillation
  - Device choice
  - Monitoring

#POMA19

81

Post-procedure Complications: Longer Term

- **Endocarditis**
  - Antibiotic prophylaxis X 1 year
- **Residual shunt**
  - Imaging with bubble study at regular intervals
  - May close over time
  - Associated with recurrent stroke – need further closure
- **Thrombus formation**
  - Seen more with earlier devices
- **Device erosion**
  - Most dreaded complication, extremely rare with PFO devices

#POMA19

82

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

N Engl J Med 2017;377:1022-32.

#POMA19

83

Table 3. Serious Adverse Events Related to the Procedure or Device among the 499 Patients in the PFO Closure Group.*

Serious Adverse Event	Patients with Event	Total No. of Events	Procedure-Related Events	Device-Related Events
	no. (%)		no. (%)	
Allergic drug reaction	1 (0.2)	1	1 (0.2)	0
Atrial fibrillation	2 (0.4)	2	1 (0.2)	1 (0.2)
Atrial flutter	1 (0.2)	1	0	1 (0.2)
Cardiac perforation	1 (0.2)	1	1 (0.2)	0
Cardiac thrombus	2 (0.4)	2	1 (0.2)	1 (0.2)
Chest tightness	1 (0.2)	1	0	1 (0.2)
Deep-vein thrombosis	1 (0.2)	1	1 (0.2)	0
Infective endocarditis	1 (0.2)	1	0	1 (0.2)
Ischemic stroke	2 (0.4)	2	0	2 (0.4)
Pericardial effusion	1 (0.2)	1	1 (0.2)	0
Pericardial tamponade	2 (0.4)	2	2 (0.4)	0
Pulmonary embolism	2 (0.4)	2	0	2 (0.4)
Residual shunt requiring closure	2 (0.4)	2	0	2 (0.4)
Sepsis	1 (0.2)	1	0	1 (0.2)
Nonsustained ventricular tachycardia	1 (0.2)	1	0	1 (0.2)
Major vascular complications				
Bleeding	2 (0.4)	2	2 (0.4)	0
Hematoma	1 (0.2)	1	1 (0.2)	0
Vasovagal reaction	1 (0.2)	1	1 (0.2)	0
Total	21 (4.2)	25	12 (2.4)	13 (2.6)

84

Safety Outcomes After Percutaneous Transcatheter Closure of Patent Foramen Ovale

Merkler AE, et al. Stroke 2017;48:3073-3077

- 2005 – 2013
- Closure within 1 year of TIA/stroke
- New York, California and Florida
- Total adverse events 7%
  - Atrial fibrillation / flutter 3.7%
  - Vascular complication 3.0%
  - Hematoma/hemorrhage only 2.7%
  - Cardiac tamponade/perforation 0.5%
  - Death 0.3%
  - Pneumothorax/hemothorax 0.1%

#POMA19

85

- **In general, PFO closure is one of our safest procedures**
  - **Benefits from almost 20 years of experience**
- **New operators should be heavily vetted and only launched once current operators are "maxed out"**
  - **Reference SCAI/AAN Credentialing Document**
- **>90% of complications can be avoided or classified as "never events" in experienced hands**
- **Patients at risk for DVT/PE pre-procedure should remain on warfarin post-procedure**
- **Erosion exceedingly rare – avoid oversizing**
- **Atrial fibrillation is best avoided by pre-procedure monitoring, sometimes extensive**
  - **PAF post-procedure is almost always self-limited**

#POMA19

86

Remaining or Re-Emerging Questions

- 1.) PFO mediated stroke beyond 60
- 2.) PFO in Migraine
- 3.) Primary Prevention

#POMA19

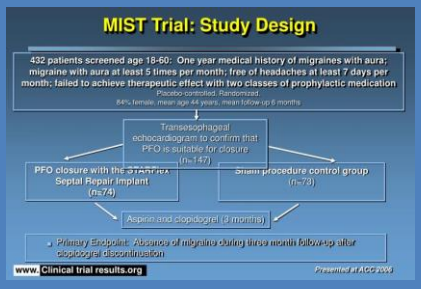
87

MIGRAINE

#POMA19

88

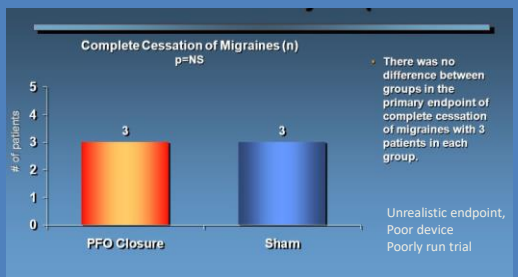
MIGRAINE



#POMA19

89

MIGRAINE



Unrealistic endpoint,
Poor device
Poorly run trial

#POMA19

90

PFO – Migraine
Columbia University Experience (2011-2017)

- treated 136 severe MHA patients with PFO and with no stroke, with clopidogrel (open-label)
  - 86% Female
  - 61% Migraine with aura
  - Mean Age = 37.9 +/- 14.7 years (Range 14 – 71)
  - Average headache burden: 14.7 +/- 9.3 days/month

#POMA19

91

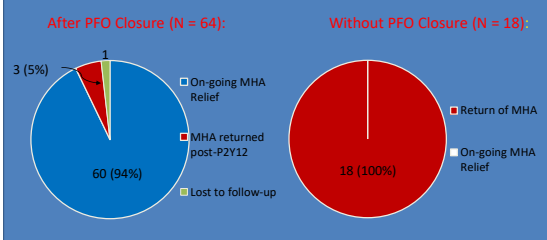
PFO – Migraine
Columbia University Experience (2011-2017)

- Patient response prospectively defined as:
  - Clopidogrel RESPONDER:
    - ≥ 50% Reduction in Monthly MHA days
    - Migraine Elimination/Near Elimination: ≥ 90% reduction in monthly MHA days
  - Clopidogrel NON-RESPONDER:
    - < 50% Monthly Headache Reduction
  - PFO CLOSURE PERFORMED ON "RESPONDERS"

#POMA19

92

PFO – Migraine
P2Y12 Inhibitor Withdrawal in MHA RESPONDERS



Columbia University Experience (2011-2017)

#POMA19

93

PFO – Migraine

MHA Effect of P2Y12 Inhibition

- Suggests that PFO MHAs are "platelet-mediated" and specific to the P2Y12 receptor
- Suggests that the trigger substance crossing PFO is likely a platelet aggregation or platelet activation byproduct
- Suggests that we may be able to predict closure benefit from a beneficial MHA response to P2Y12 inhibition

Columbia University Experience (2011-2017)

#POMA19

94

PFO – Migraine

What's Really New

- Thienopyridine responsiveness will be used to enrich the study population
- Responding subjects will be randomized/blinded to PFO closure or sham, subsequent P2Y12 withdrawal
- Protocol is being submitted to the FDA for IDE
- Site recruitment Q4 2018, enrollment anticipated to begin Q1 – Q2 2019

#POMA19

95

That's All Folks!!!

#POMA19

96

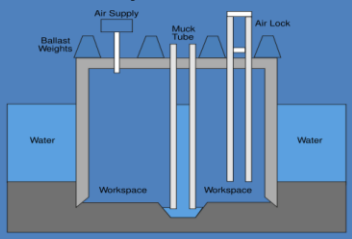
Back-Up Slides

#POMA19

97

Decompression

19th Century "Caisson Disease"



Pressurized air prevents water from entering workspace.

#POMA19

98

Decompression

Brooklyn Bridge

- ~20% of caisson workers developed permanent neurologic deficits
- 1872: Washington Roebling, chief engineer on the Brooklyn Bridge is paralyzed.
- Construction halted on Manhattan tower 30 feet short of bedrock.

The Builders of the Bridge, D.B. Steinman; Harcourt, Brace and Co., 1945

#POMA19

99

Decompression

Mechanism	Affected Organ	Clinical Manifestations
Arterial Precipitates	Large Joints & Skin (BENDS)	• Localized, deep, mild to excruciating pain, aggravated with motion • Mottled, edema, pain, itching
Venous Precipitates	Lungs	• Pulmonary Embolism – CP, SOB, hypoxia
Paradoxical Embolism	Brain	• Confusion, memory loss, erratic behaviour • Headache • Scotoma, tunnel vision, diplopia, blurry vision • Seizures, dizziness, vertigo, nausea, vomiting, loss of consciousness • Chest pain • Ascending weakness or paralysis • Urinary and rectal incontinence • Paresthesias

#POMA19

100

Decompression Illness

- Increased incidence of PFO/ASD among divers with decompression illness (56%) Koopsen et al. Neth Heart J 2018
- Divers with PFOs are 2.5 to 4.5 times as likely to develop decompression illness as divers without PFOs. Bove 1998, Schwerzmann. Ann Int Med. 2001; 134(1)24-1.
- PFO shunt size predicts risk of DCI, although absolute risk remains low. Torti European Heart Journal (2004) 25, 1014–1020; Am J Cardiol. 2004 Jul 15;94(2):270-273

#POMA19

101

Position Statement

South Pacific Underwater Medicine Society (SPUMS)
United Kingdom Sports Diving Medical Committee (UKSDMC)

- Routine screening for PFO is not currently justifiable.
- Divers with a history of decompression illness or congenital heart disease are considered to be at higher risk and may consider screening.
- If a shunt is present, advice should be provided by an experienced diving physician taking into account the clinical context and the size of shunt. Reduction in gas load by limiting depth, repetitive dives may be appropriate.
- Divers with decompression illness may consider PFO closure in order to return to diving.

#POMA19

102

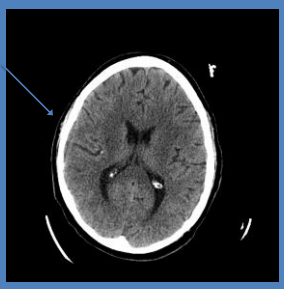
47 Year Old RH Male

- Admitted to hospital with acute R MCA Stroke
- Returned from the Outer Banks by car within the last 2 weeks
- Straining at stool when he noted weakness of L hand
- Tried to stand and his family found him down
- Hospital stroke alert: NIHSS 9,CT R MCA sign 2h ; tPA given at 2h15m

#POMA19

103

CT Scan



#POMA19

104

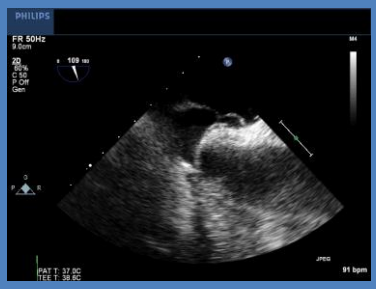
47 Year Old RH Male

- 24 h: Improved- mild L hemi neglect, mild L Sensory loss, no ataxia; NIHSS=3
- 48 h: Improved- NIHSS=0

#POMA19

105

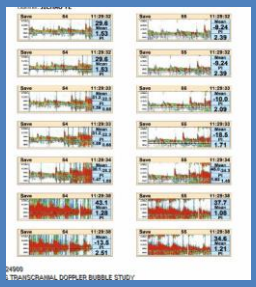
TEE



#POMA19

106

TCD Bubbles



#POMA19

107

30 d Cardiac Event Monitor

- Time: 27d 23h 12m
- AF-Sx: None Indicated
- AF-ASx: None Found
- SVT- Sx: None Indicated
- SVT-ASx: None Found
- Pause/Heart Block-none

#POMA19

108

RoPE Score:

- 7 – suggests a 72% chance stroke due to PFO
- 6% risk at 2 years
- Works in Maintenance Department- heavy lifting
- Combined Cardio/Neuro conference decision: Close PFO

#POMA19

109

PFO Closure

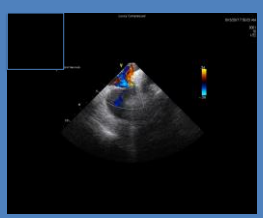
- ACCESS :RRA/RCFV /LCFV
- ACCUNAV ICE
- Gore 30mm ASD Occluder
- Uncomplicated
- Discharged following day DAPT

#POMA19

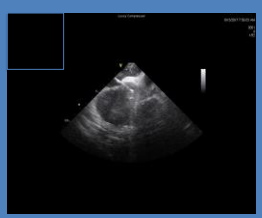
110

ICE

Baseline



Device across

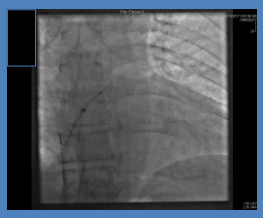


#POMA19

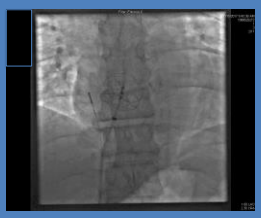
111

Deployment

Gore Device



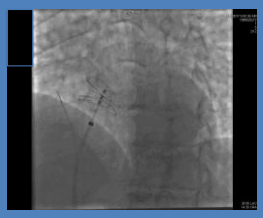
Deployed, Attached

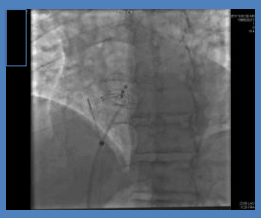


#POMA19

112

Deployment



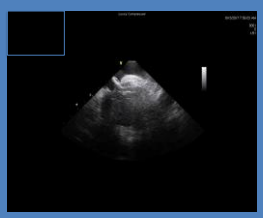


#POMA19

113

ICE

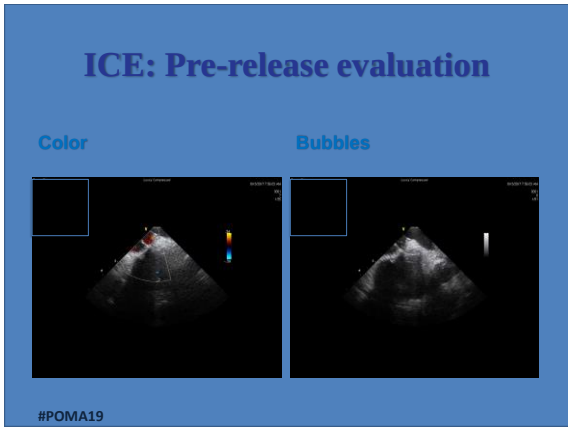
Deployment



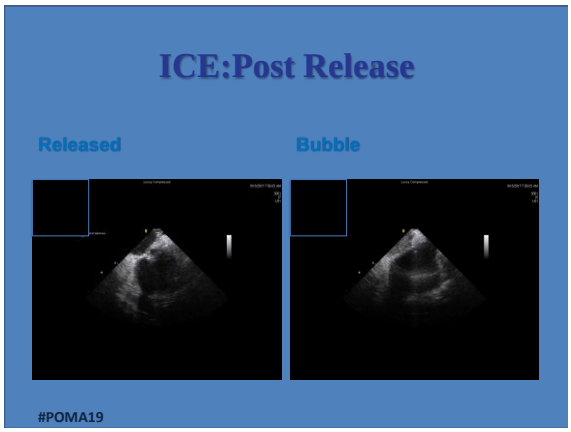
Deployment

#POMA19

114


ICE: Pre-release evaluation
Color
Bubbles
#POMA19

115


ICE:Post Release
Released
Bubble
#POMA19

116