PFO Closure:
Closing the Gap Between Data and Action

Ramin Hastings, MD
Director, Structural Heart and Valve Program
Englewood Health

How Can We Help Our Neurology and Non-Invasive Cardiology Colleagues

- Maybe we Need to Change the Name
- Maybe We Need to Be Better About Predicting When a PFO is the Problem
- Maybe We Need to Translate The Data Better to Our Colleagues
- Maybe We Need Better Screening for PFOs After Stroke
- Maybe We Need Different PFO Closure Devices
- Maybe We Need More Indications
- Maybe We Need An Instagram Star!

Maybe we Need an Instagram Star

MUSIC NEWS

Hailey Bieber Marks 1-Year Anniversary of Her Mini-Stroke: 'A Life-Changing Event'

"I wanted to share all the information I've learned about PFO and share resources to donate," the model wrote.

By Mitchell Peters
03/11/2023

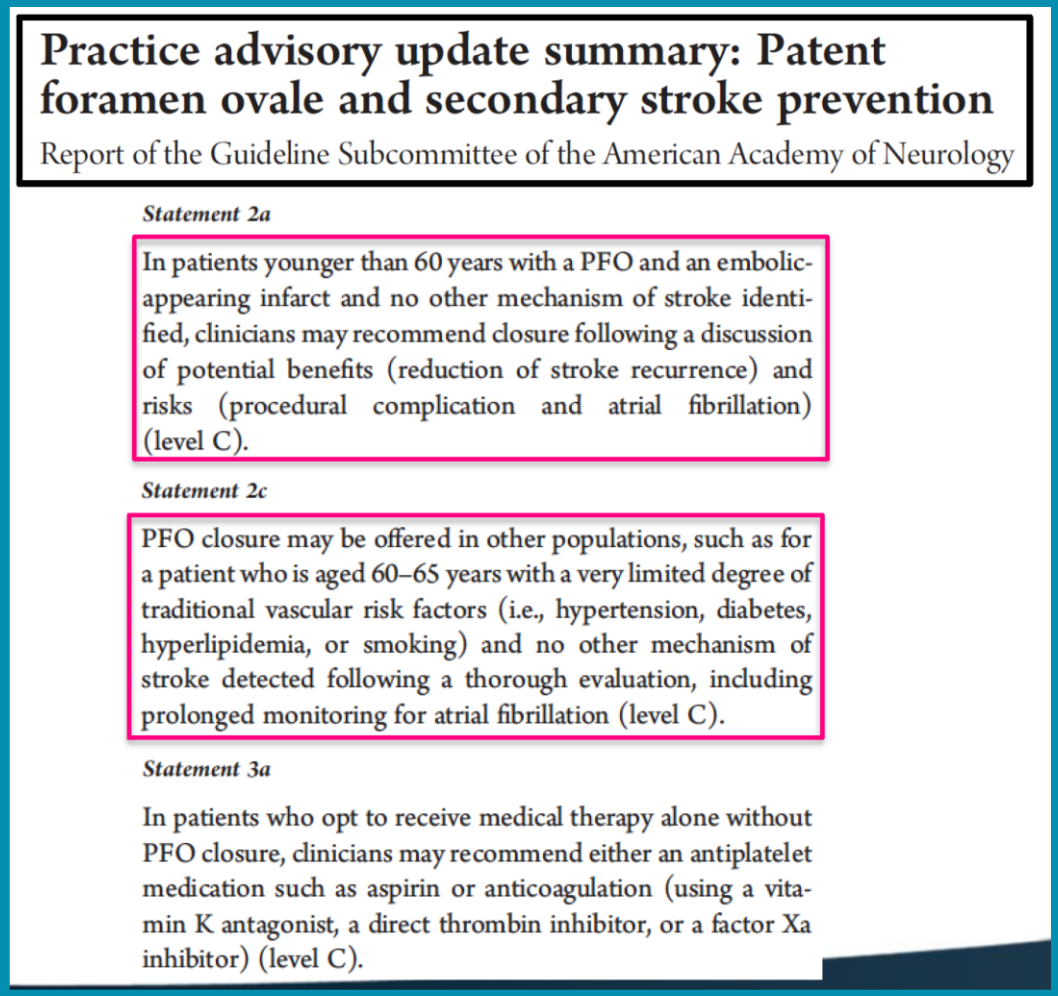
Hailey Bieber attends the 2022 Vanity Fair Oscar Party hosted by Radhika Jones at Wallis Annenberg Center for the Performing Arts on March 27, 2022 in Beverly Hills, California.

Axelle/Bauer-Griffin/FilmMagic

Cors at the Shore 2023

Maybe we Need to Change the Name

- "Cryptogenic Stroke" with a PFO
  - Implies that the PFO isn't playing a Role
- PFO-Associated Stroke
  - Sounds more like we need to do something with the PFO



Practice advisory update summary: Patent foramen ovale and secondary stroke prevention

Report of the Guideline Subcommittee of the American Academy of Neurology

Statement 2a

In patients younger than 60 years with a PFO and an embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (reduction of stroke recurrence) and risks (procedural complication and atrial fibrillation) (level C).

Statement 2c

PFO closure may be offered in other populations, such as for a patient who is aged 60–65 years with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation (level C).

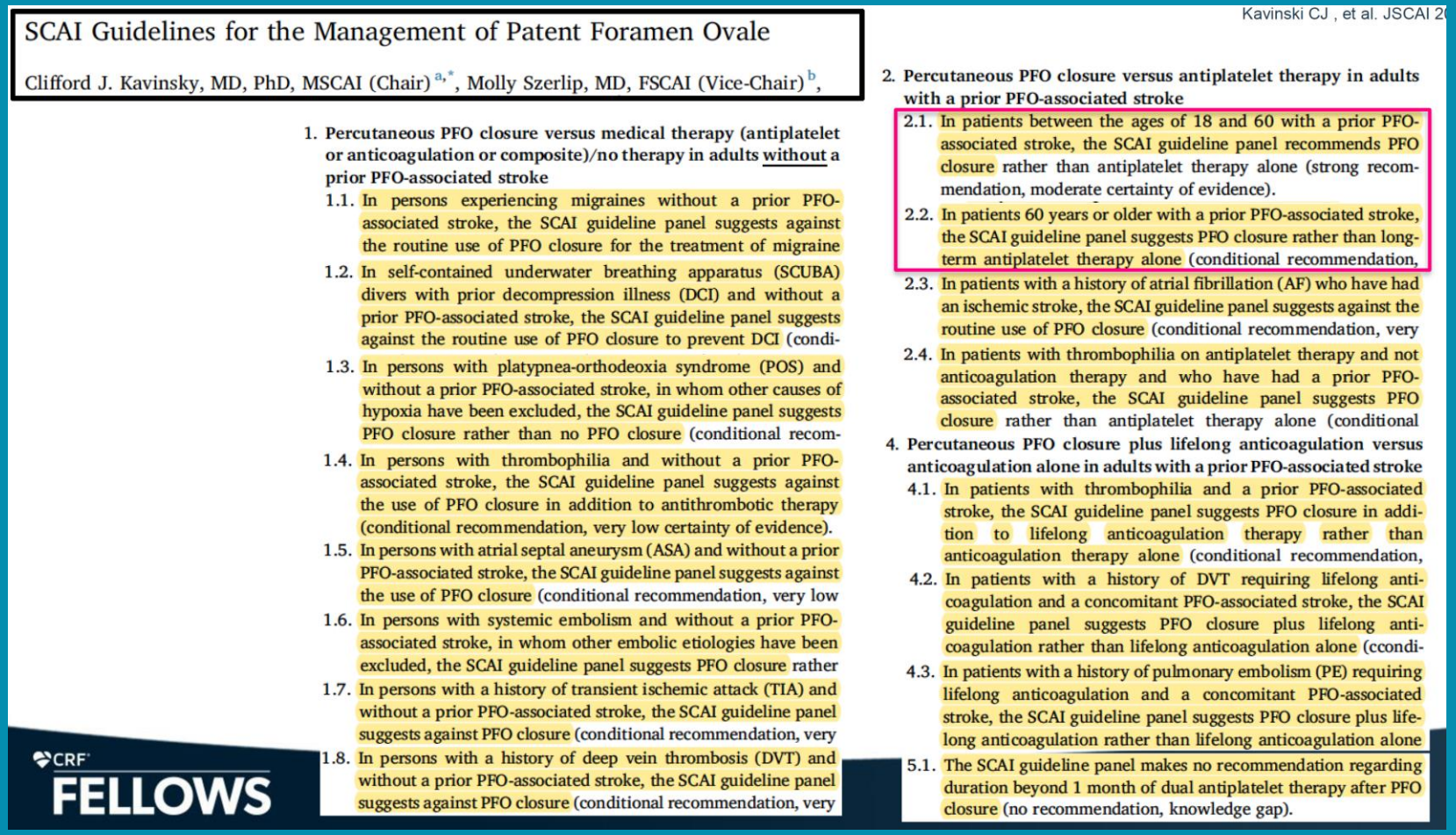
Statement 3a

In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend either an antiplatelet medication such as aspirin or anticoagulation (using a vitamin K antagonist, a direct thrombin inhibitor, or a factor Xa inhibitor) (level C).

American Academy of Neurology – Practice Advisory
Called them PFO and an embolic-appearing infarct

Cors at the Shore 2023

Maybe we Need to Change the Name



SCAI Guidelines for the Management of Patent Foramen Ovale

Clifford J. Kavinsky, MD, PhD, MSCAI (Chair) [a,*], Molly Szerlip, MD, FSCAI (Vice-Chair) [b],

1. **Percutaneous PFO closure versus medical therapy (antiplatelet or anticoagulation or composite)/no therapy in adults without a prior PFO-associated stroke**
   - 1.1. In persons experiencing migraines without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure for the treatment of migraine
   - 1.2. In self-contained underwater breathing apparatus (SCUBA) divers with prior decompression illness (DCI) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure to prevent DCI (condi-
   - 1.3. In persons with platypnea-orthodeoxia syndrome (POS) and without a prior PFO-associated stroke, in whom other causes of hypoxia have been excluded, the SCAI guideline panel suggests PFO closure rather than no PFO closure (conditional recom-
   - 1.4. In persons with thrombophilia and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure in addition to antithrombotic therapy (conditional recommendation, very low certainty of evidence).
   - 1.5. In persons with atrial septal aneurysm (ASA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure (conditional recommendation, very low
   - 1.6. In persons with systemic embolism and without a prior PFO-associated stroke, in whom other embolic etiologies have been excluded, the SCAI guideline panel suggests PFO closure rather
   - 1.7. In persons with a history of transient ischemic attack (TIA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very
   - 1.8. In persons with a history of deep vein thrombosis (DVT) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very

2. **Percutaneous PFO closure versus antiplatelet therapy in adults with a prior PFO-associated stroke**
   - 2.1. In patients between the ages of 18 and 60 with a prior PFO-associated stroke, the SCAI guideline panel recommends PFO closure rather than antiplatelet therapy alone (strong recommendation, moderate certainty of evidence).
   - 2.2. In patients 60 years or older with a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than long-term antiplatelet therapy alone (conditional recommendation,
   - 2.3. In patients with a history of atrial fibrillation (AF) who have had an ischemic stroke, the SCAI guideline panel suggests against the routine use of PFO closure (conditional recommendation, very
   - 2.4. In patients with thrombophilia on antiplatelet therapy and not anticoagulation therapy and who have had a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than antiplatelet therapy alone (conditional

4. **Percutaneous PFO closure plus lifelong anticoagulation versus anticoagulation alone in adults with a prior PFO-associated stroke**
   - 4.1. In patients with thrombophilia and a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure in addition to lifelong anticoagulation therapy rather than anticoagulation therapy alone (conditional recommendation,
   - 4.2. In patients with a history of DVT requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone (ccondi-
   - 4.3. In patients with a history of pulmonary embolism (PE) requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone

5. 5.1. The SCAI guideline panel makes no recommendation regarding duration beyond 1 month of dual antiplatelet therapy after PFO closure (no recommendation, knowledge gap).

CRF FELLOWS

SCAI – Guidelines for PFO

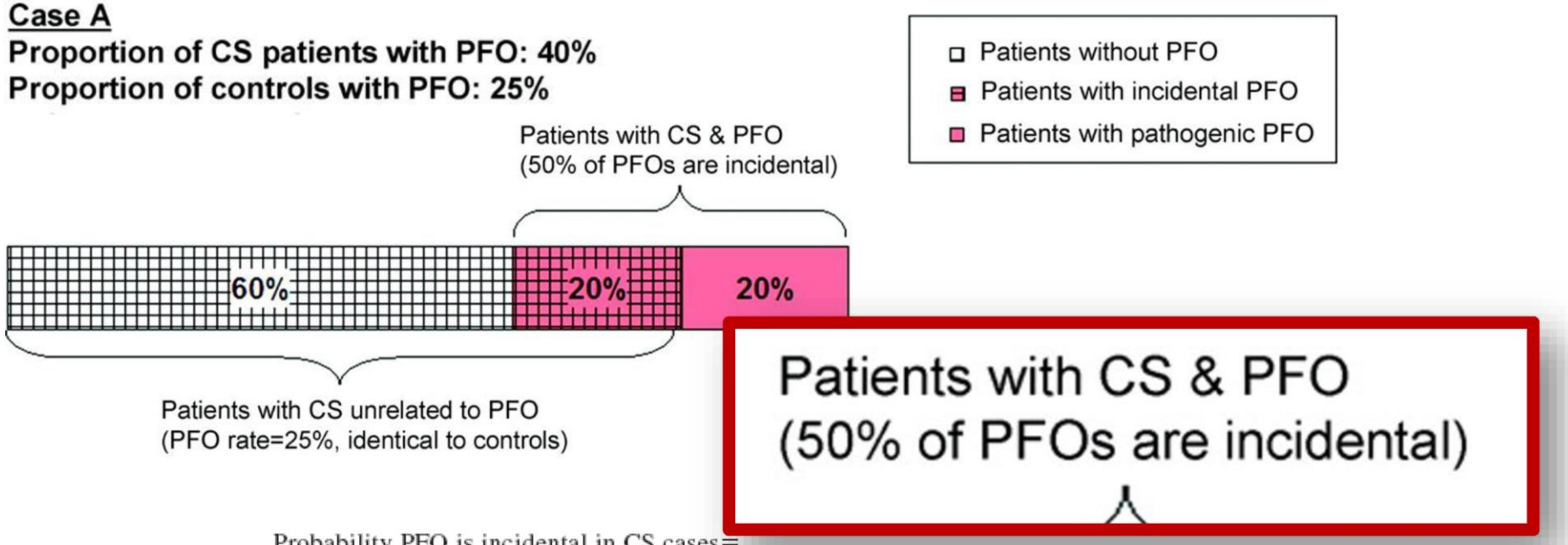
Named them PFO-associated strokes

Cors at the Shore 2023

Maybe We Need to Be Better About Predicting That a PFO Caused the Stroke
In the End It's a Probability Game

Proportion of CS patients with incidental PFO

Case A
Proportion of CS patients with PFO: 40%
Proportion of controls with PFO: 25%



$$\text{Probability PFO is incidental in CS cases} = \frac{\text{Prevalence of PFO in controls}*(1-\text{Prevalence of PFO in CS cases})}{\text{Prevalence of PFO in CS cases}*(1-\text{Prevalence of PFO in controls})}$$

Alsheikh-Ali, A. A. et al. Stroke 2009;40:2349-2355

Cors at the Shore 2023

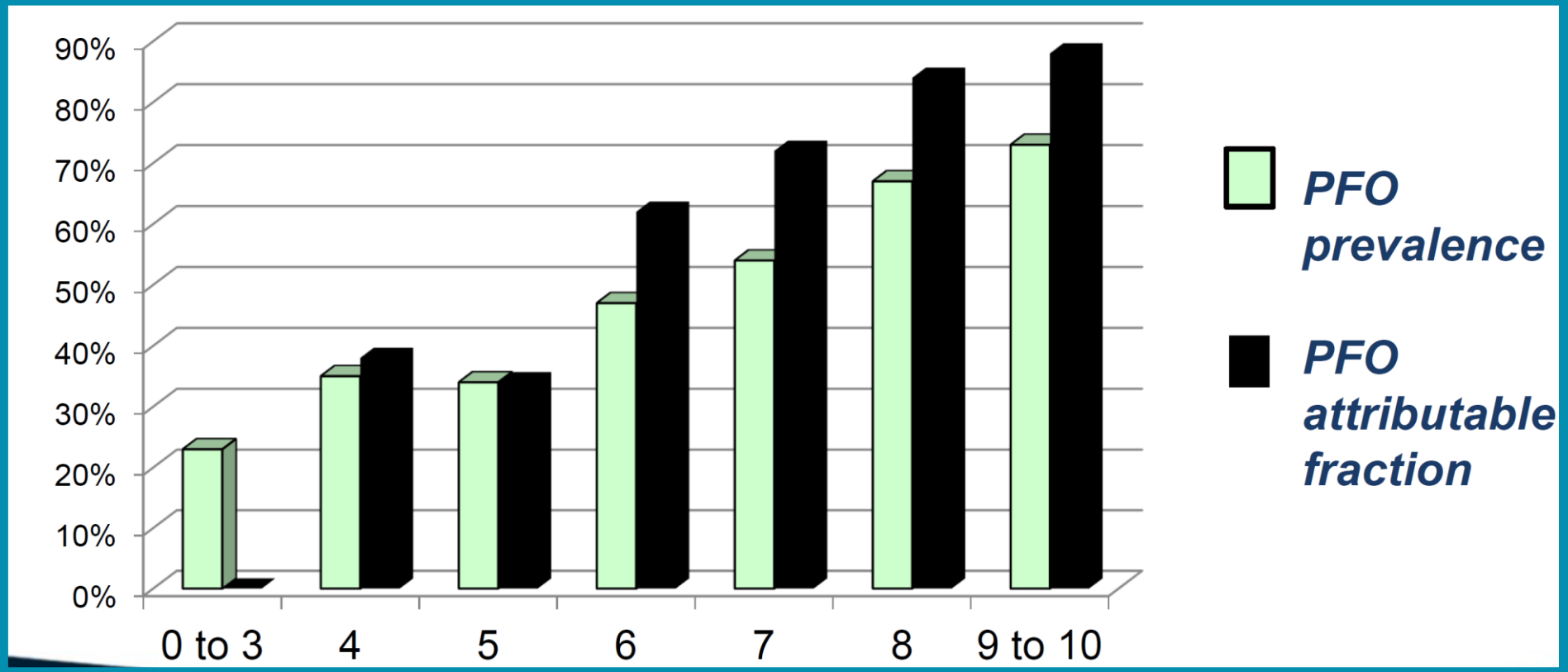
RoPE Score – Way to Classify Patients After Stroke

- Risk of Paradoxical Embolism Score
- More risk factors for Vascular Disease → Lower score
- Younger, healthier → Higher Score

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18-29	5	
30-39	4	
40-49	3	
50-59	2	
60-69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

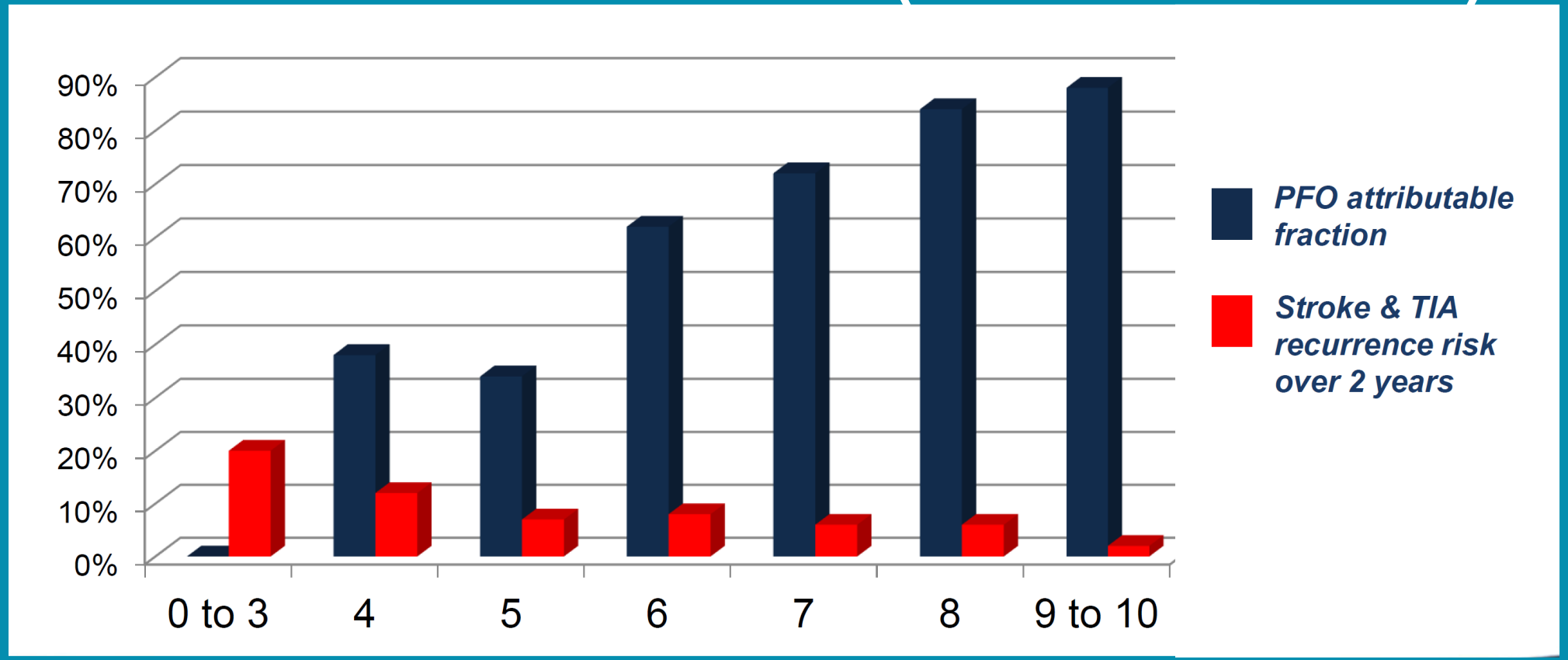
Cors at the Shore 2023

Higher RoPE Score – Higher PFO Prevalence and Greater PFO Attributable Fraction



Cors at the Shore 2023

Those with Higher RoPE Score – Less Recurrent Strokes (Makes sense)



ROPE SCORE

Cors at the Shore 2023

RoPE Score as a Way to Differentiate High probability of PFO-Associated Stroke

ROPE SCORE	Cryptogenic Stroke (N=3023)			
	Number of Patients	Prevalence of Patients with a PFO % (95% CI)	PFO-Attributable Fraction* % (95% CI)	PFO-Attributable Fraction
0-3	613	23% (19% to 26%)	0% (0% to 0%)	40% (36% to 43%)
4	511	35% (31% to 39%)	38% (30% to 46%)	
5	516	34% (30% to 38%)	35% (28% to 42%)	
6	482	47% (42% to 51%)	62% (56% to 69%)	
7	434	54% (49% to 59%)	72% (66% to 77%)	80% (77% to 83%)
8	287	67% (62% to 73%)	84% (79% to 88%)	
9-10	180	73% (66% to 79%)	88% (82% to 93%)	

"Low"

"High"

* Assumes PFO prevalence in the general population of 25%

Cors at the Shore 2023

Utilizing RoPE Score and PFO Anatomy To Further Stratify Likelihood That PFO Caused a Stroke

PFO-Associated Stroke Causal Likelihood (PASCAL)

- The RoPE Score does not take into account high-risk PFO features.
- PASCAL combines the RoPE score with anatomic and physiologic features of the PFO to classify patients

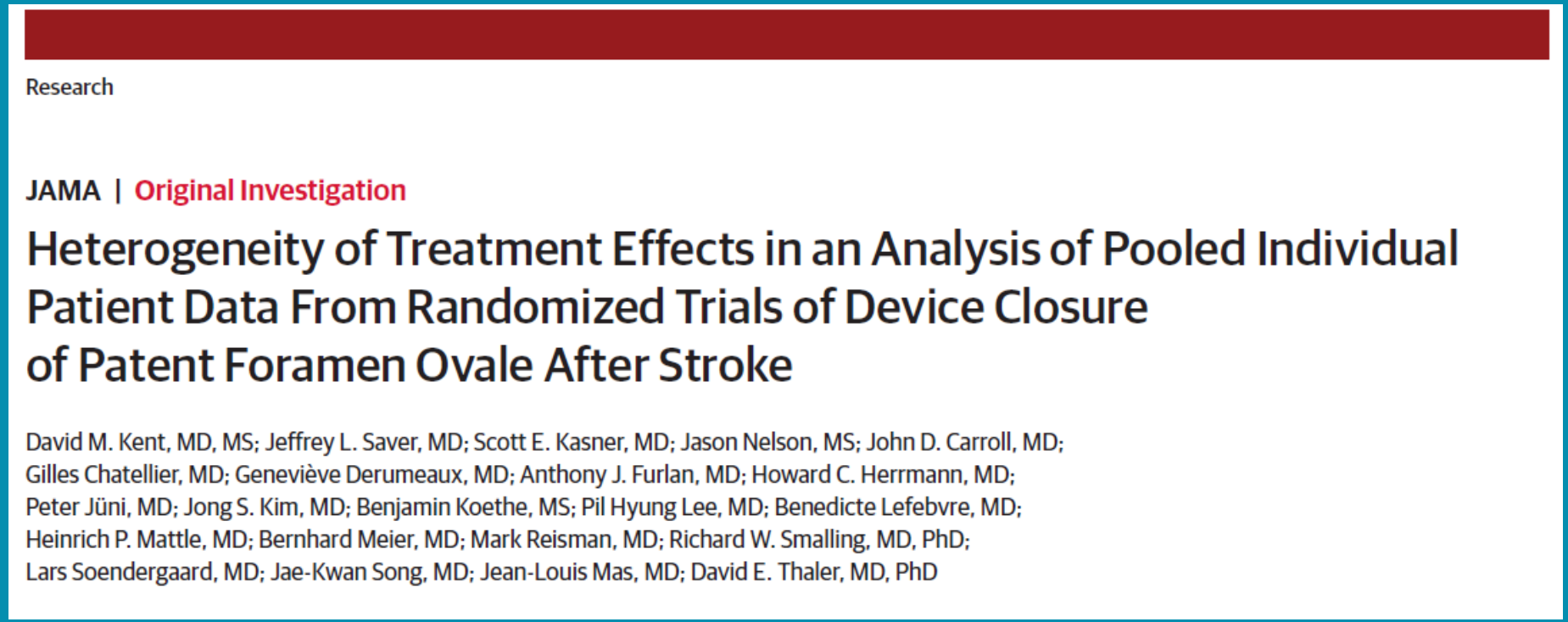
		RoPE Score	
		< 7	≥7
High Grade PFO	Present	Possible	Probable
	Absent	Unlikely	Possible

*High Grade PFO = ASA or large shunt

Cors at the Shore 2023

Maybe We Need to Translate The Data Better to Our Colleagues

- Recent Large Patient-Pooled Meta-Analysis
  - 3600 Patients from 6 Randomized Trials



Research

JAMA | Original Investigation

Heterogeneity of Treatment Effects in an Analysis of Pooled Individual Patient Data From Randomized Trials of Device Closure of Patent Foramen Ovale After Stroke

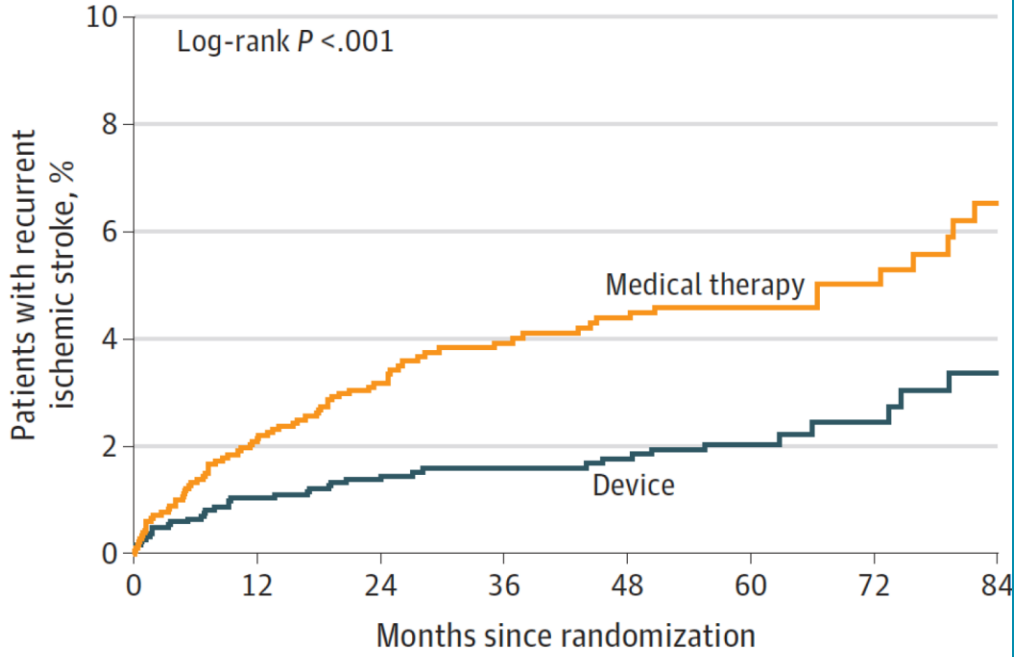
David M. Kent, MD, MS; Jeffrey L. Saver, MD; Scott E. Kasner, MD; Jason Nelson, MS; John D. Carroll, MD; Gilles Chatellier, MD; Geneviève Derumeaux, MD; Anthony J. Furlan, MD; Howard C. Herrmann, MD; Peter Jüni, MD; Jong S. Kim, MD; Benjamin Koethe, MS; Pil Hyung Lee, MD; Benedicte Lefebvre, MD; Heinrich P. Mattle, MD; Bernhard Meier, MD; Mark Reisman, MD; Richard W. Smalling, MD, PhD; Lars Soendergaard, MD; Jae-Kwan Song, MD; Jean-Louis Mas, MD; David E. Thaler, MD, PhD

PFO Closure Is Superior To Medical Management in Reducing Recurrent Strokes

- Patient-pooled Meta Analysis
  - 6 Randomized Trials
  - 3740 Patients
- Trials all had Age cutoff of either 60/65 years old
  - Some had “high risk” PFO
  - All were in “cryptogenic” stroke
- Medical Therapy Arms
  - Included mostly anti-plt therapy
  - Some with Warfarin

Cors at the Shore 2023

Figure 1. Kaplan-Meier Curve of Recurrent Ischemic Stroke



No. at risk								
Device	1889	1771	1338	1245	1155	854	365	26
Medical therapy	1851	1668	1194	1094	971	699	390	25

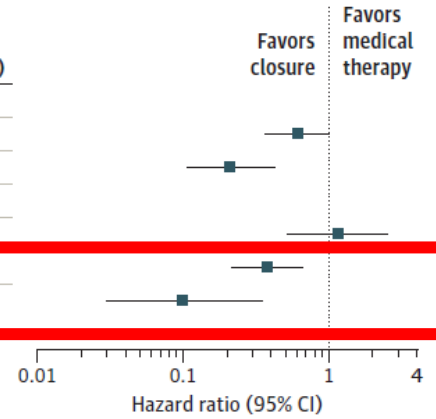
Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7; n = 121).

Can We Utilize RoPE Score and PFO Anatomy To Further Stratify Who Benefits

Figure 2. Recurrent Ischemic Stroke Heterogeneity of Treatment Effect (HTE) Analyses for RoPE and PASCAL

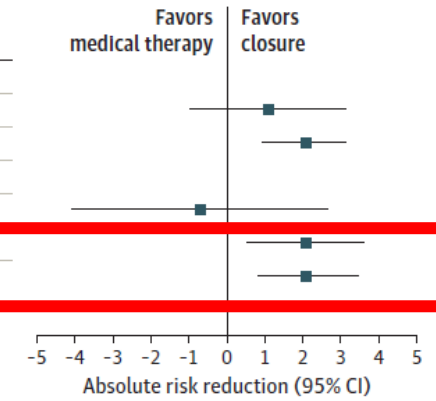
A Hazard ratios of the primary outcome of recurrent ischemic stroke

	Device, overall events/No. of patients	Medical therapy, overall events/ No. of patients	Hazard ratio (95% CI)	P value for interaction
RoPE categories				
<7	29/700	41/704	0.61 (0.37 to 1.00)	.02
≥7	11/1189	41/1147	0.21 (0.11 to 0.42)	
PASCAL categories				
Unlikely	17/293	11/254	1.14 (0.53 to 2.46)	
Possible	19/897	46/914	0.38 (0.22 to 0.65)	.003
Probable	3/700	25/683	0.10 (0.03 to 0.35)	



B Absolute risk reductions of the primary outcome of recurrent ischemic stroke

	Device, 2-y events/No. (%)	Medical therapy, 2-y events/ No. (%)	Absolute risk reduction at 2 y (95% CI)	No. needed to treat (95% CI)
RoPE categories				
<7	20/700 (2.9)	27/704 (4.0)	1.1 (-0.9 to 3.1)	91 (-112 to 32)
≥7	7/1189 (0.6)	28/1147 (2.6)	2.1 (1.0 to 3.1)	49 (100 to 32)
PASCAL categories				
Unlikely	11/293 (4.1)	8/254 (3.4)	-0.7 (-4.0 to 2.6)	-153 (-25 to 38)
Possible	13/897 (1.5)	31/914 (3.6)	2.1 (0.6 to 3.6)	47 (166 to 27)
Probable	2/700 (0.3)	16/683 (2.5)	2.1 (0.9 to 3.4)	47 (111 to 29)

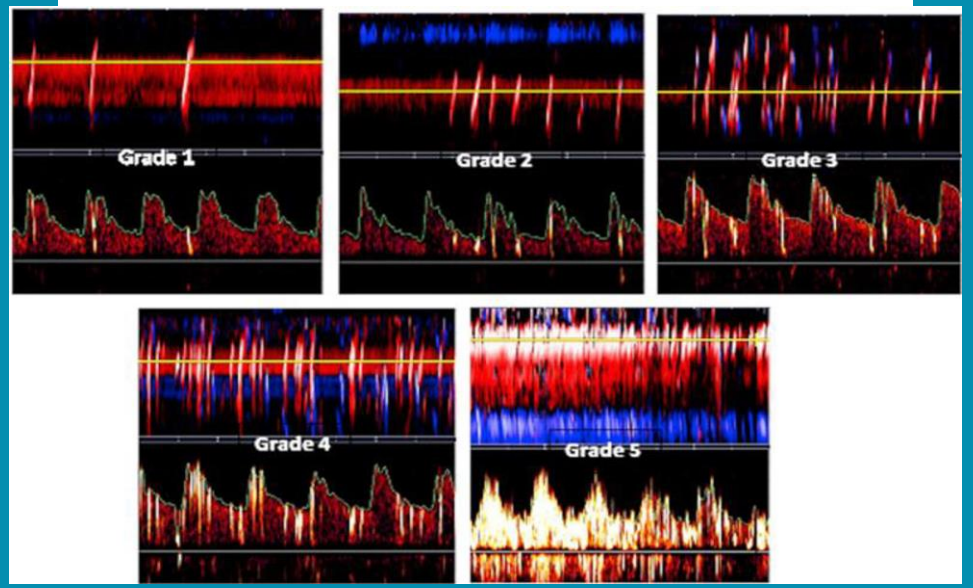


In Probable Group – Only 3/700 (0.4%) patients had a recurrent stroke after closure of PFO

NNT to Prevent a Stroke is 47 in the possible/probable Group at 2 Years

Maybe We Need Better Screening for PFOs After Stroke

- Trans-Cranial Doppler
- High Sensitivity (>95%)
  - Valsalva doesn't affect sensitivity
  - Grading criteria for degree of shunt
  - Found to be more sensitive than TEE
- Easy to perform
- Problems w/ TCD
  - No cardiac visualization
  - Poor windows in ~ 10%

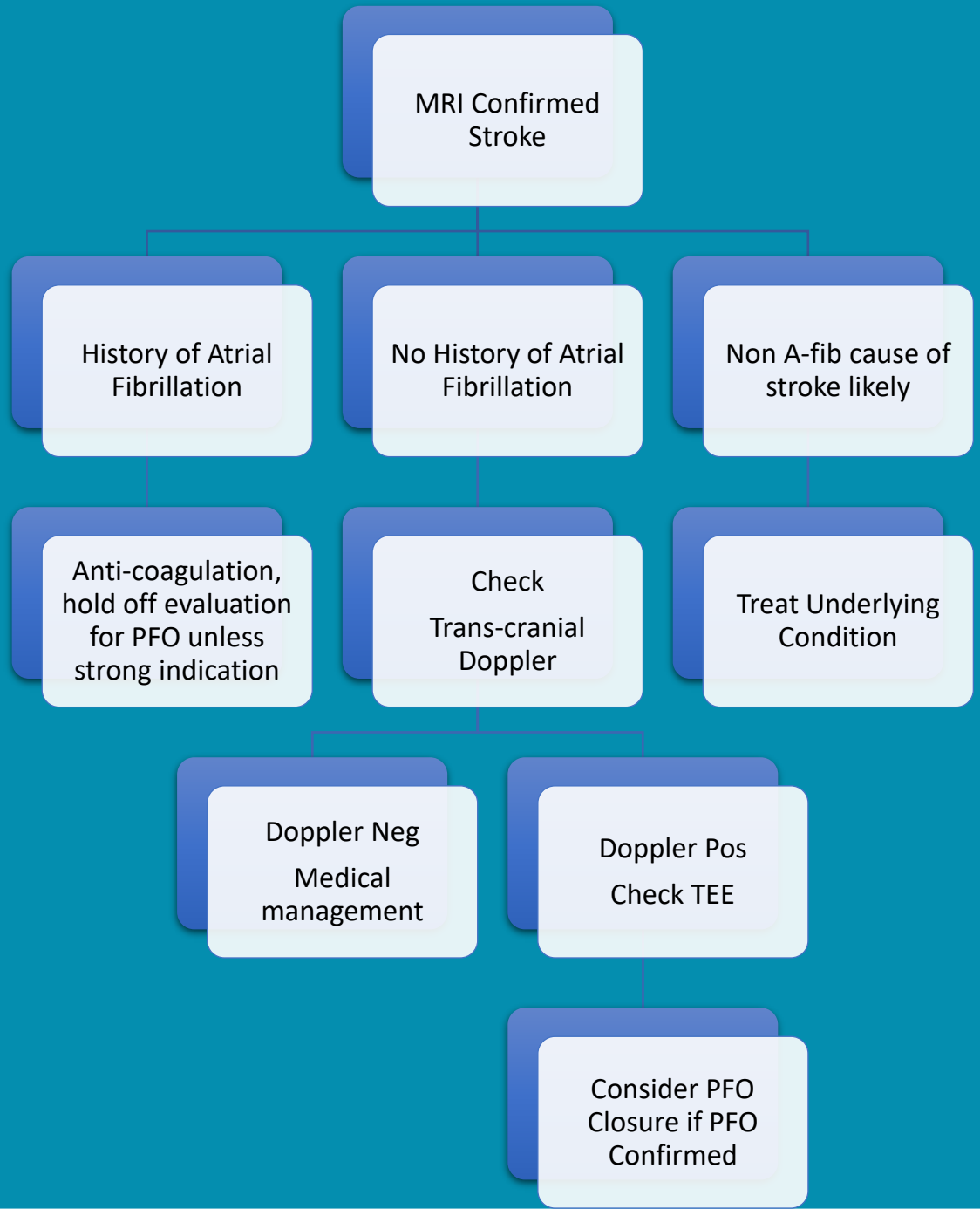


Australas J Ultrason Med, Volume: 23, Issue: 4, Pages: 210-219, First published: 13 November 2020, DOI: (10.1002/ajum.12232)

Cors at the Shore 2023

Creating a Protocol for Screening Within Your Stroke Program

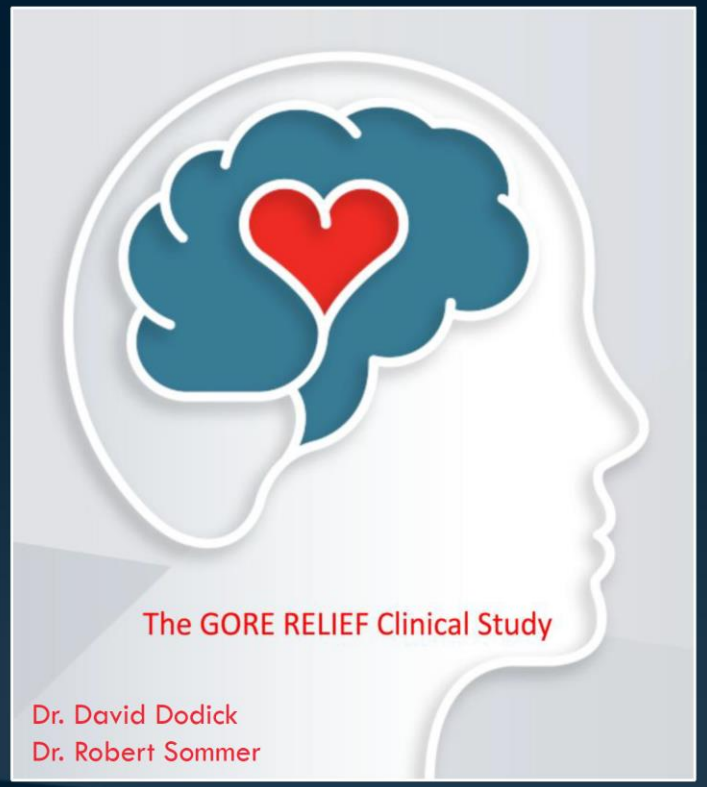
PFO Screening Program Rolled Out at Englewood Health



Cors at the Shore 2023

Future PFO Directions - ? Migraines

The GORE RELIEF Clinical Study

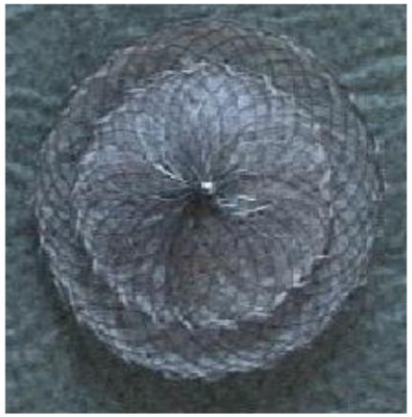


- Randomized, prospective, placebo and sham controlled trial enrolling currently at 25 US sites

1. Screen migraineurs for PFO
2. Test with P2Y12 inhibition or placebo
3. Bring only “Responders” to cath lab for randomized PFO closure vs. sham
4. Stop P2Y12 inhibition in 4 months
5. Re-assess headaches

Future PFO Directions – ? New Devices

FDA approved



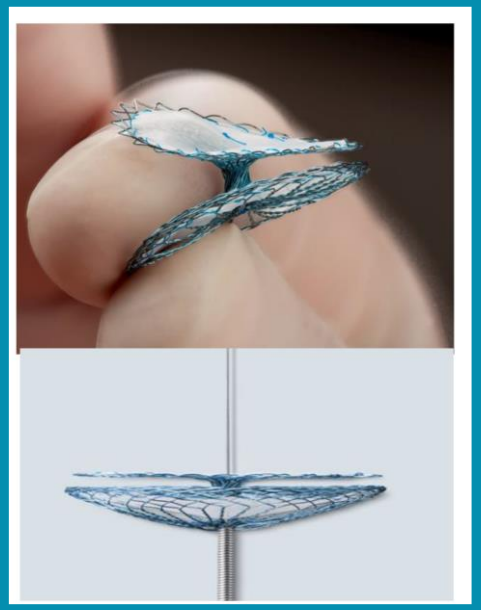
Amplatzer PFO occluder
2016

GORE Cardioform Septal Occluder
2019

Cors at the Shore 2023

Future PFO Directions
New Devices?

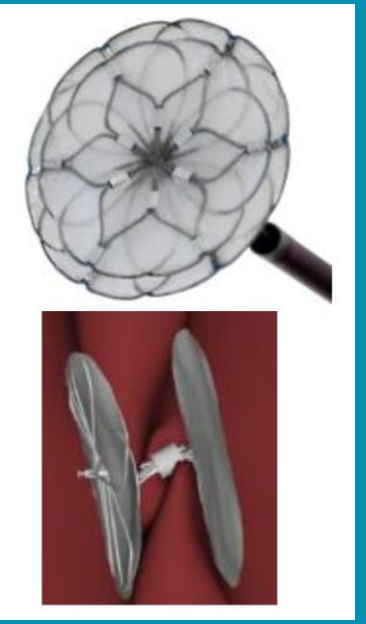
Hyperion



Nit-Occlud PFO

Lifetech CeraFlex

Occlutech
Figulla Flex II

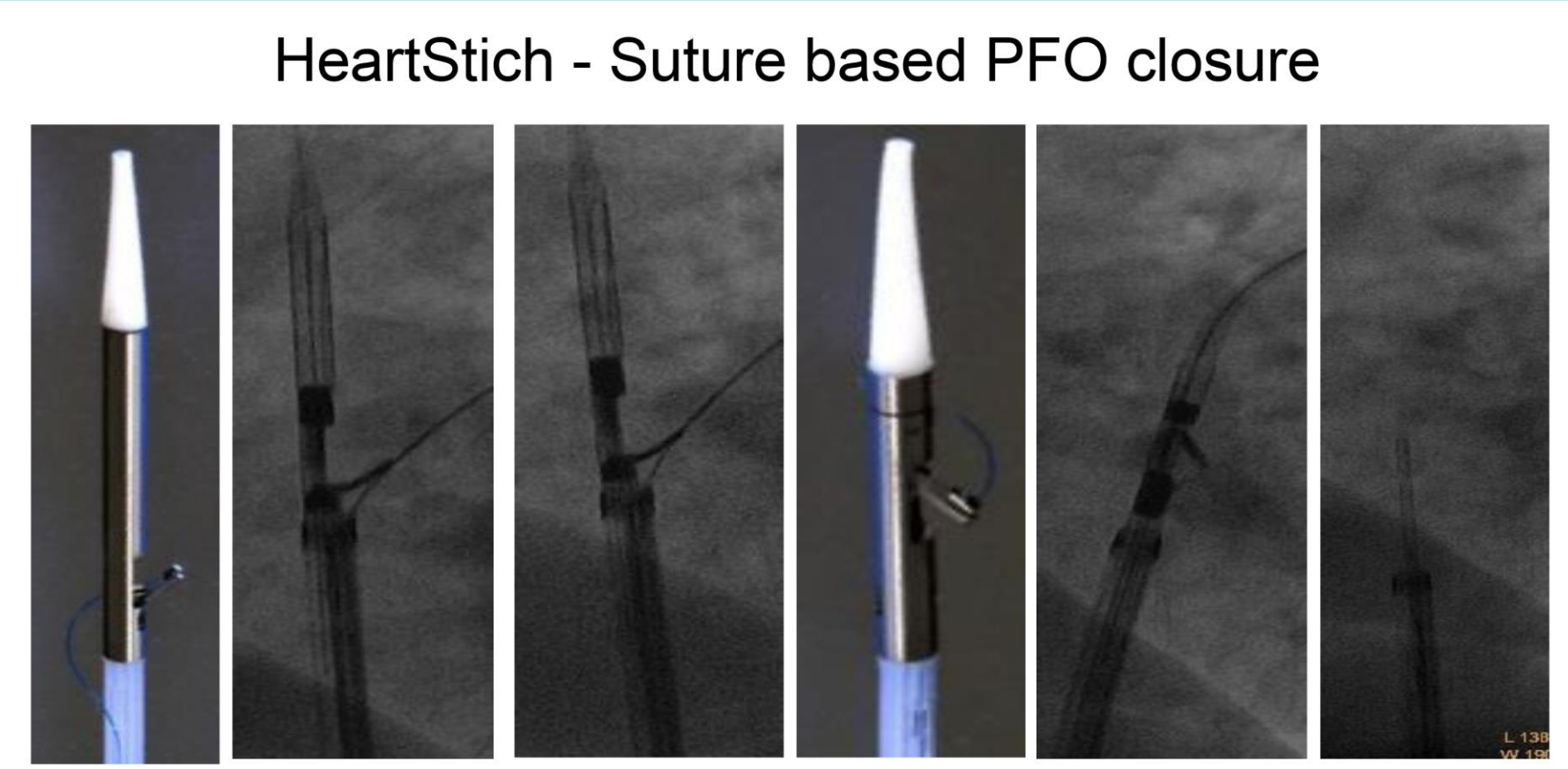


Ultrasept
PFO

Cocoon PFO

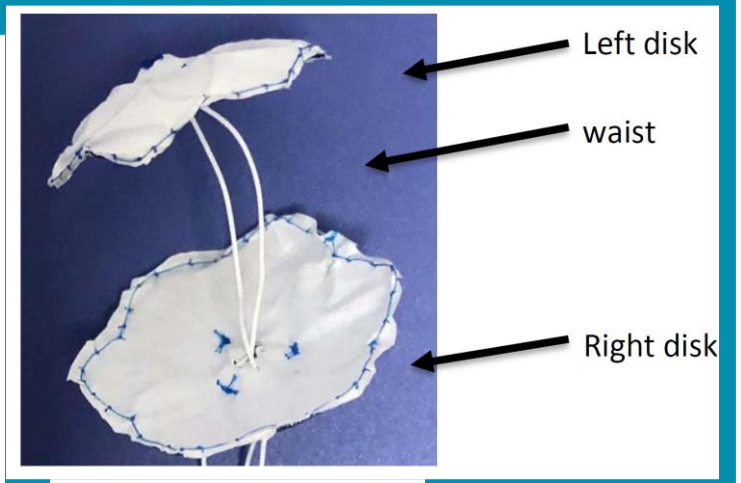
Cors at the Shore 2023

Novel PFO Devices



Novel PFO Devices - Bioresorbable Occluders

Mallow Degradeable Occluder



Dinova PFO Occluder

Memosorb PFO

AbSnow Occluder

Cors at the Shore 2023

Take Home Message for Our Neurology and Non-Invasive Cardiology Colleagues

- Need to change our thinking about PFO
  - Use nomenclature of PFO-Associated Stroke
- Understand the data for PFO
  - RoPE Score and PASCAL classification to help differentiate those who might benefit from PFO closure
  - Multiple randomized trials revealed a reduction in stroke with closure in the correct patient population
- Need standardized programs for PFO screening post CVA
- Future devices may offer more options for our PFO population
  - Future indications for PFO closure may arise as well
- We need to be the biggest advocates for our patients

Cors at the Shore 2023

Thank You!

Cors at the Shore 2023