Getting Closure on PFO Closure: Are we there yet?

Wisconsin ACC

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ASCENSION

Financial Disclosures

- None

Learning Objectives

- Understand the most recent data and guidelines on PFO closure
- Identify which patients would benefit from closure procedures

Outline

- Why do we care about PFOs?
- Pathophysiology of stroke
- History of PFO trials
- Guideline updates
- Future directions

Patient #1

- 55 year old woman with a history of HTN
  - Presented to outside hospital with right sided hemi paresthesia and expressive aphasia
  - MRI showed multifocal infarcts in left MCA territory
  - CTA occlusion of superior division of left MCA M3 segment
  - Received tPA and transferred to CSM, complete resolution of symptoms
  - 30 Day event monitor no afib
  - Carotid US no plaque
  - LE Dopplers no DVT
  - Echo showed “right to left atrial level shunt”

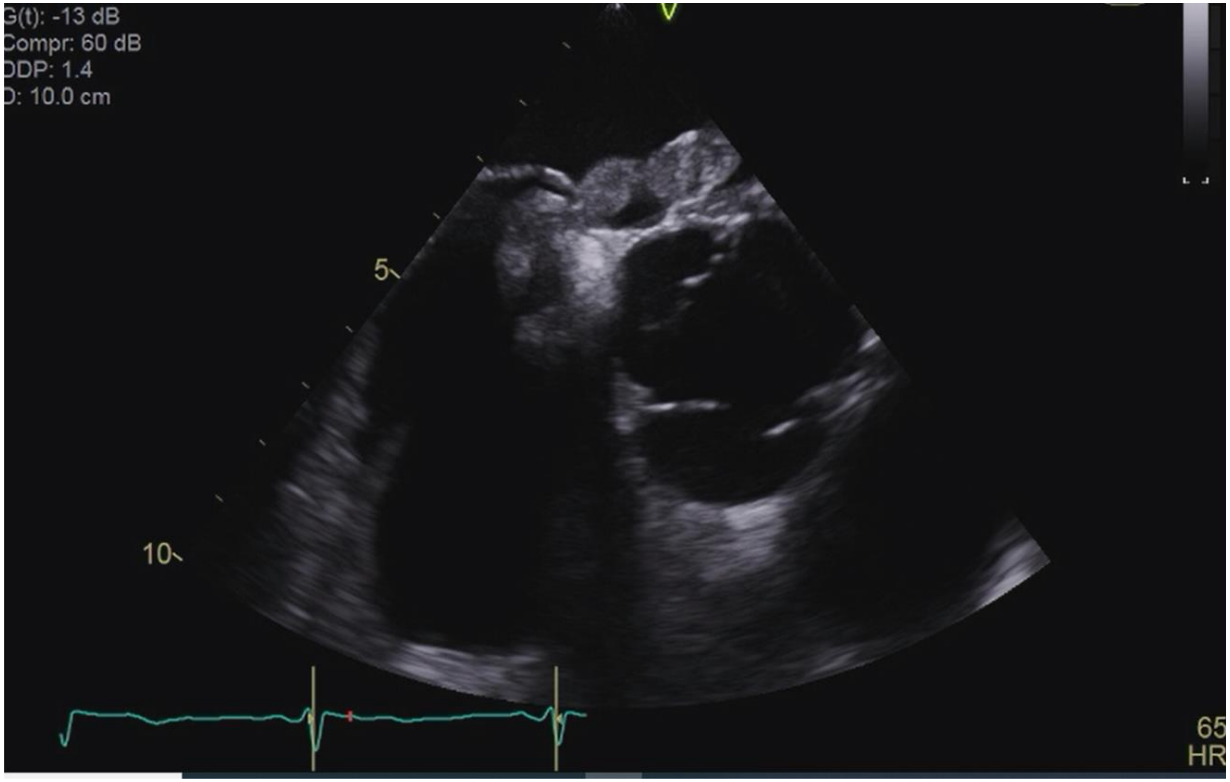
Patient #2

- 45 year old woman, history of migraines.
  - Presents for evaluation of episode of word finding difficulty and clumsiness, accompanied by headache that lasted 5 minutes.
  - MRI done 10 days following the event showed no evidence of acute or subacute stroke
  - Echo showed atrial septal aneurysm with moderate sized PFO with shunting in the baseline state

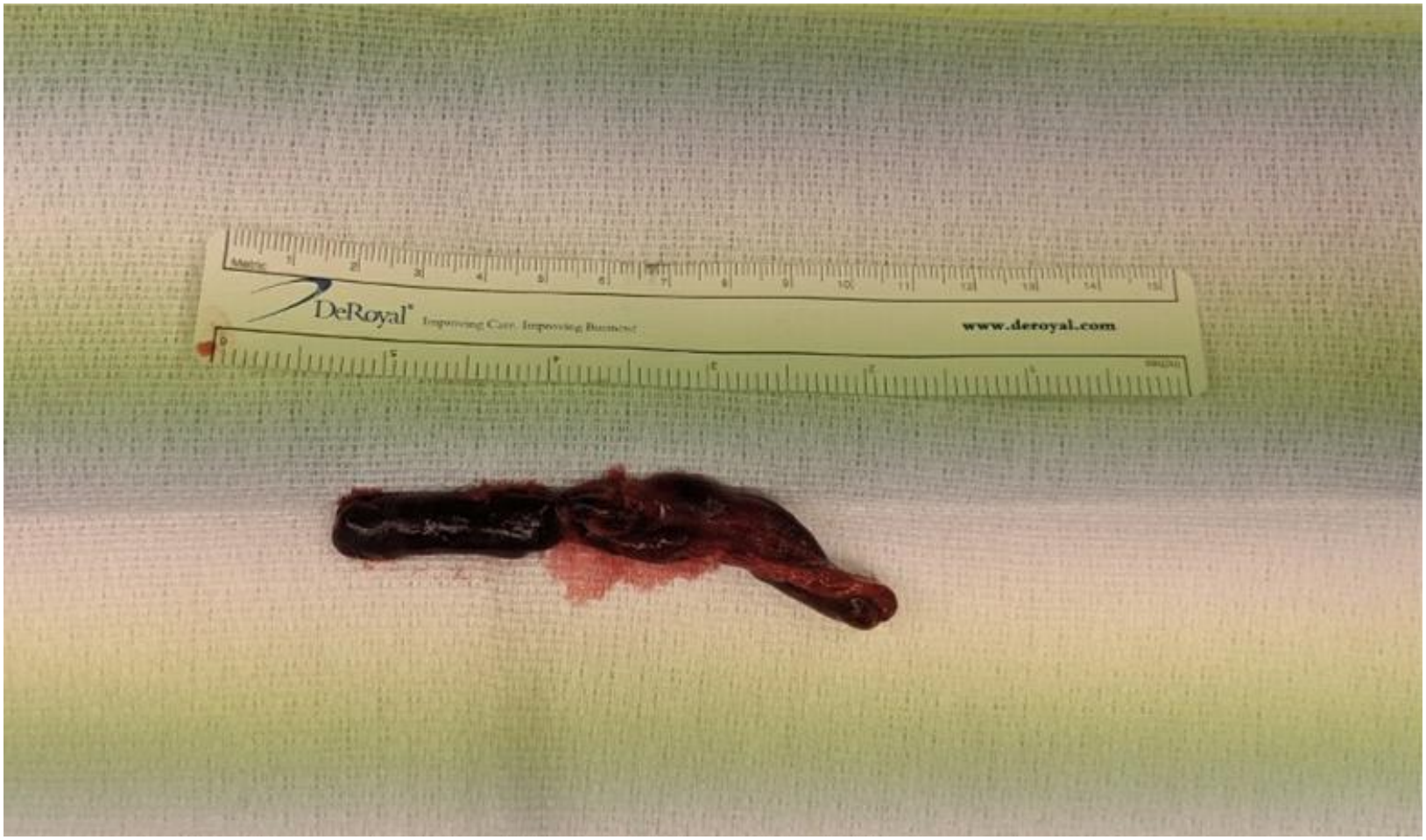
Patient #3

- 61 year old gentleman with a history of HTN hyperlipidemia
  - Presented to ER with complaints of left arm numbness
  - Symptoms resolved by the time he was evaluated
  - He had been taking Aspirin 81 mg daily
  - MRI brain showed small areas of subacute infarct in the right caudate and globus pallidus
  - Transthoracic echo showed evidence of PFO with atrial septal aneurysm

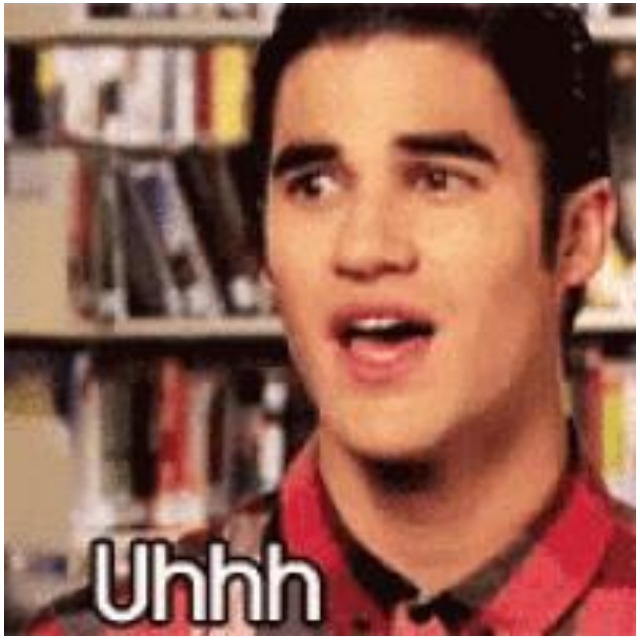
Why do we care about PFOs?



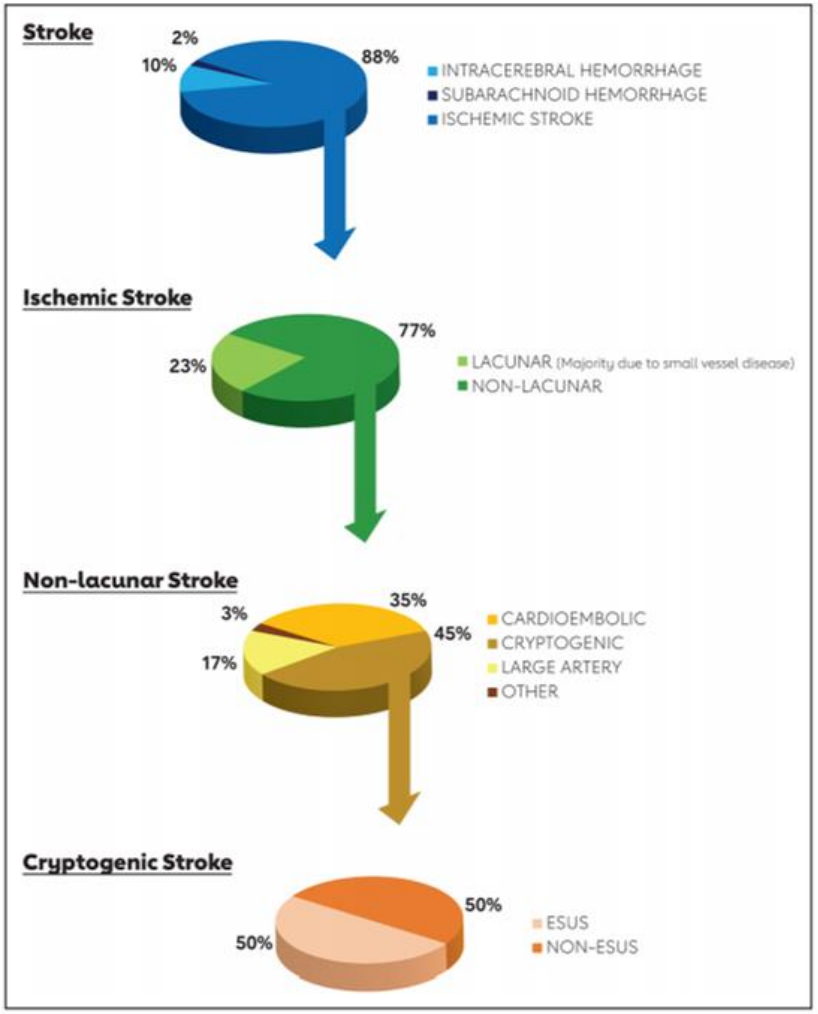
Why do we care about PFOs?



Closure should be a “no-brainer”

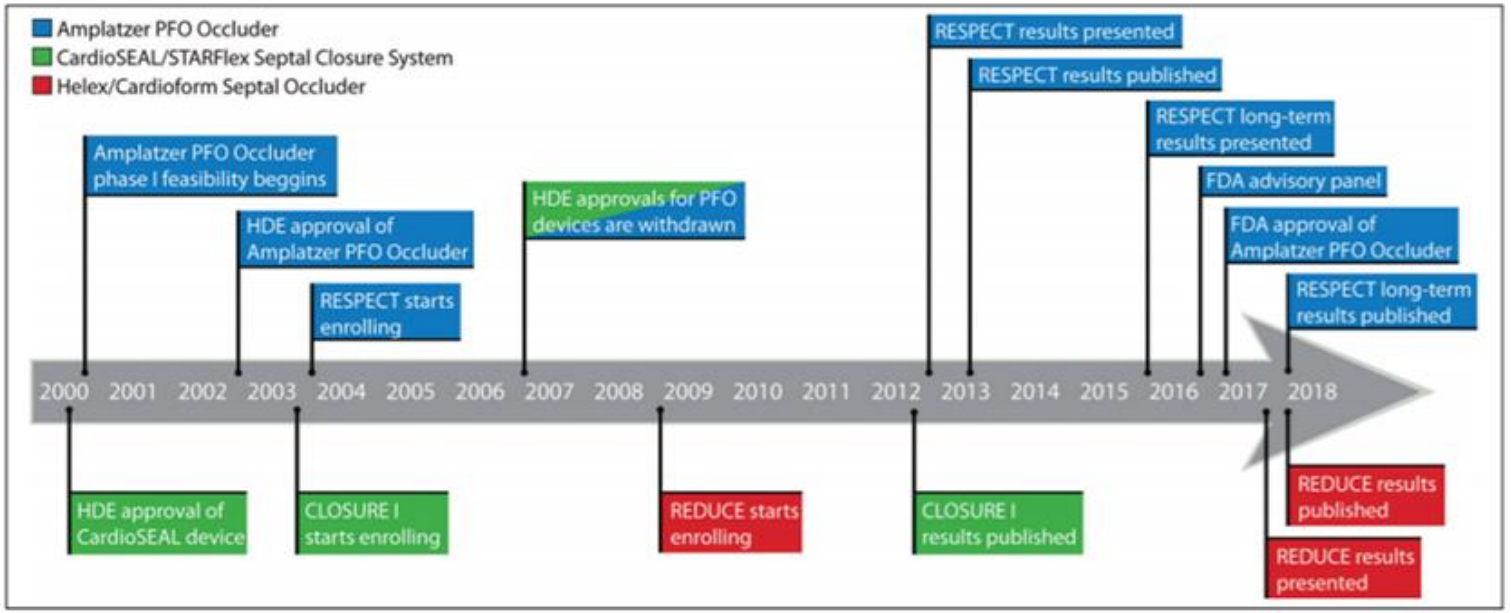


Etiology of Stroke



D Kleindorfer, A Towfighi, S Chaturvedi et al, Stroke. 2021;52:e364–e467

History of PFO Trials

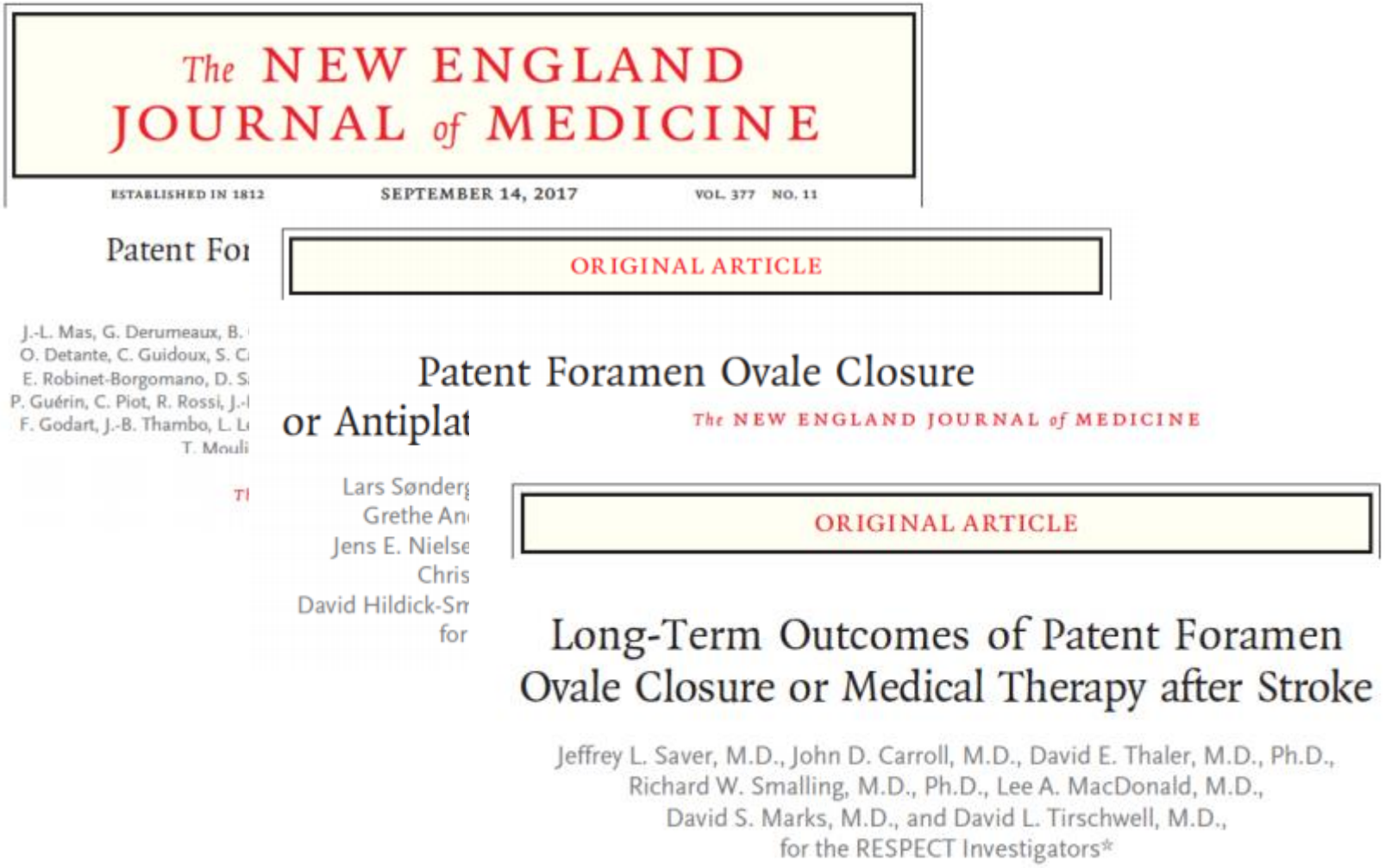


PFO Trials

- Historically, Randomized controlled PFO trials (2011-2016) have had a hard time demonstrating effectiveness of closure vs. medical management
  - Lower rate of events than expected
  - Difficult to enroll patients
  - Older devices not as effective
  - Significant closures outside of trials

  All failed to show statistically significant secondary prevention with closure vs. medical management
  - All trended in this direction

September 2017



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Patent For

ORIGINAL ARTICLE

J.-L. Mas, G. Derumeaux, B.
O. Detante, C. Guidoux, S. C
E. Robinet-Borgomano, D. S
P. Guérin, C. Piot, R. Rossi, J.-
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Patent Foramen Ovale Closure
or Antiplat

The NEW ENGLAND JOURNAL of MEDICINE

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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*

May 2018

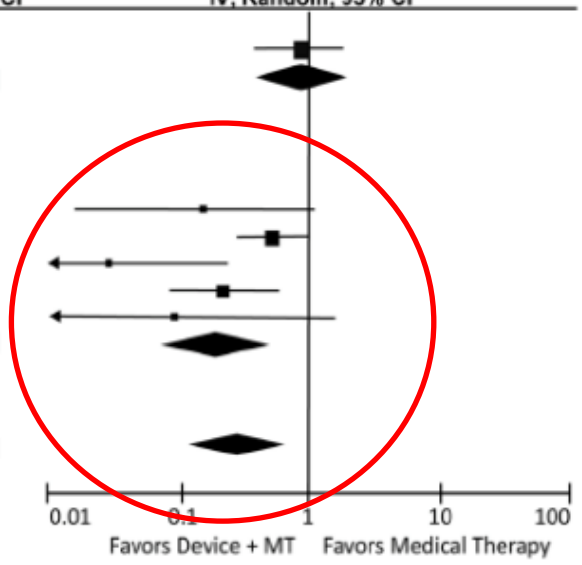
Cryptogenic Stroke and High-Risk Patent Foramen Ovale

The DEFENSE-PFO Trial

Pil Hyung Lee, MD,[a] Jae-Kwan Song, MD, PhD,[a] Jong S. Kim, MD, PhD,[b] Ran Heo, MD,[a] Sahmin Lee, MD,[a] Dae-Hee Kim, MD, PhD,[a] Jong-Min Song, MD, PhD,[a] Duk-Hyun Kang, MD, PhD,[a] Sun U. Kwon, MD, PhD,[b] Dong-Wha Kang, MD, PhD,[b] Dongwhane Lee, MD,[b] Hyuk Sung Kwon, MD,[b] Sung-Cheol Yun, PhD,[c] Byung Joo Sun, MD, PhD,[d] Jae-Hyeong Park, MD, PhD,[d] Jae-Hwan Lee, MD, PhD,[d] Hye Seon Jeong, MD, PhD,[e] Hee-Jung Song, MD, PhD,[e] Jei Kim, MD, PhD,[e] Seung-Jung Park, MD, PhD[a]

Analysis of RCTs

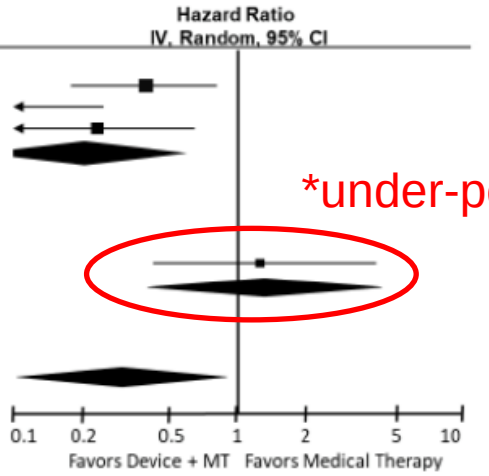
Study or Subgroup	log[HR]	SE	Device + MT Events	Device + MT Pt-Yrs (Pts)	Medical Therapy Events	Medical Therapy Pt-Yrs (Pts)	Weight	Hazard Ratio IV, Random, 95% CI
Umbrella-clamshell devices								
CLOSURE	-0.11	0.40	12	789 (447)	13	766 (462)	24.6%	0.90 [0.41, 1.98]
Subtotal (95% CI)			**12**	**789 (447)**	**13**	**766 (462)**	**24.6%**	**0.90 [0.41, 1.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z =0.27 (P = 0.79)								
Double disk devices (all or predominantly)								
PC	-1.97	1.09	1	845 (204)	7	836 (210)	10.1%	0.14 [0.02, 1.17]
RESPECT-Extended	-0.60	0.30	18	3080 (499)	28	2608 (481)	27.5%	0.55 [0.31, 0.99]
CLOSE	-3.51	1.11	0	1231 (238)	14	1222 (235)	9.7%	0.03 [0.00, 0.26]
REDUCE	-1.47	0.50	6	1529 (441)	12	703 (223)	21.7%	0.23 [0.09, 0.62]
DEFENSE-PFO	-2.40	1.47	0	95 (60)	5	92 (60)	6.4%	0.09 [0.01, 1.62]
Subtotal (95% CI)			**25**	**6780 (1442)**	**66**	**5461 (1209)**	**75.4%**	**0.20 [0.08, 0.54]**
Heterogeneity: Tau^2 = 0.61; Chi^2 =9.46, df = 4 (P = 0.05); I^2 = 58%								
Test for overall effect: Z = 3.20 (P = 0.001)								
Total (95% CI)			**37**	**7579 (1889)**	**79**	**6227 (1671)**	**100.0%**	**0.30 [0.13, 0.68]**
Heterogeneity: Tau^2 = 0.54; Chi^2 = 13.52, df = 5 (P = 0.02); I^2 = 63%								
Test for overall effect: Z = 2.89 (P = 0.004)								
Test for subgroup differences: Chi^2 = 5.38, df = 1 (P = 0.02), I^2 = 81.4%								



Medical Management

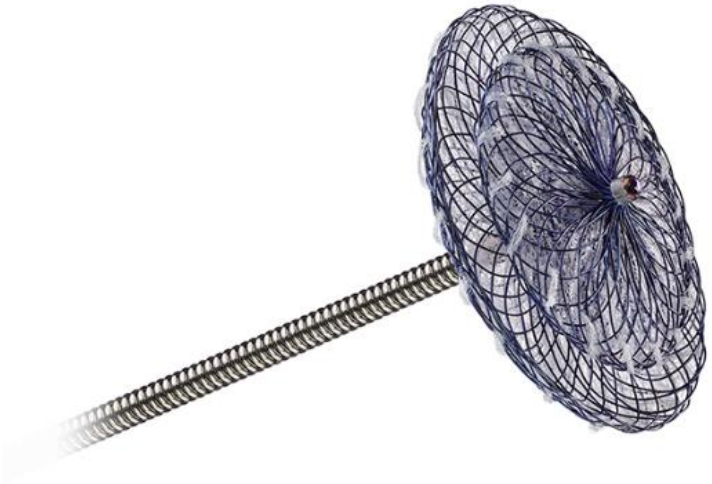
- No clear consensus on which antiplatelets to use (Aspirin 81, Aspirin 81 + Plavix, Aspirin 325)
- No clear consensus on anticoagulant vs. antiplatelet
- In the absence of known thrombotic event (i.e. DVT/PE) the use of AC for Cryptogenic stroke from PFO has fallen out of favor.

Study or Subgroup	log[HR]	SE	Device + MT Events	Device + MT Pt-Yrs (Pts)	Medical Therapy Events	Medical Therapy Pt-Yrs (Pts)	Weight	Hazard Ratio IV, Random, 95% CI
Antiplatelet								
RESPECT-Extended	-0.97	0.38	10	2265 (367)	23	1952 (360)	31.2%	0.38 [0.18, 0.79]
CLOSE	-3.51	1.11	0	1231 (238)	14	1222 (235)	14.6%	0.03 [0.00, 0.26]
REDUCE	-1.47	0.50	8	1411 (441)	12	714 (223)	27.9%	0.23 [0.09, 0.62]
Subtotal (95% CI)			**18**	**4937 (1046)**	**49**	**3912 (818)**	**73.8%**	**0.19[0.06, 0.56]**
Heterogeneity: Tau² = 0.46; Chi² = 4.86, df = 2 (P = 0.09); I² = 59%								
Test for overall effect: Z =3.01 (P = 0.003)								
Anticoagulant								
RESPECT-Extended	0.28	0.57	8	815 (132)	5	656 (121)	26.2%	1.32 [0.43, 4.03]
Subtotal (95% CI)			**8**	**815 (132)**	**5**	**656 (121)**	**26.2%**	1.32 [0.43, 4.03]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								
Total (95% CI)			**26**	**5752 (1178)**	**54**	**4568 (939)**	**100.0%**	**0.27 [0.11, 0.92]**
Heterogeneity: Tau² = 0.82; Chi² = 11.03, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 2.11 (P = 0.04)								
Test for subgroup differences: Chi² = 5.73 df = 1 (P = 0.02), I² = 82.5%								



*under-powered

Available Devices



Amplatzer ™ PFO Occluder
FDA Approved October 2016

Gore ® Cardioform Septal Occluder
FDA Approved March 2018

Patient Selection

- FDA mandates close collaboration between PFO proceduralist and a neurologist (preferably a stroke neurologist).
- Discussions with the patient regarding the risks and benefits of the procedure.
- Patient selection should adhere closely to the FDA labeling which is based on inclusion criteria for the major RCTs.
  - patients with documented stroke 60 years of age or less
  - Patients with transient ischemic attack (TIA) were not included.
  - Stroke is defined as an acute neurologic deficit, presumably due to ischemia, that either resulted in clinical symptoms lasting 24 hr or longer, or symptoms lasting less than 24 hr but associated with a new, neuro-anatomically relevant, cerebral infarction on noninvasive imaging.

Horlick E, Kavinsky CJ, Amin Z, et al. Catheter Cardiovasc Interv. 2019;93:859–874

Guideline Updates

Canadian Best Practice Stroke Recommendation

9.1 Patent Foramen Ovale (PFO) ***(Revised 2017)***

i. Patients with a recent ischemic stroke or TIA attributed to a PFO should have an evaluation by clinicians with stroke and cardiovascular expertise [Evidence Level C].

ii. For carefully-selected patients with a recent ischemic stroke or TIA attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone **provided all** the following criteria are met [Evidence Level A]:

   a. Age 18–60 years;

   b. The diagnosis of the index stroke event is confirmed by imaging as a nonlacunar embolic ischemic stroke or a TIA with positive neuroimaging or cortical symptoms;

   c. The patient has been evaluated by a neurologist or clinician with stroke expertise, and the PFO is felt to be the most likely cause for the index stroke event following a thorough etiological evaluation to exclude alternate etiologies.

iii. For patients requiring long-term anticoagulation, the decision regarding PFO closure remains unclear, and decisions should be based on individual patient characteristics and risk versus benefit profile [Evidence C].

iv. For patients with a recent ischemic stroke or TIA attributed to a PFO who do no undergo PFO closure and are aged 60 years or younger, either antiplatelet or anticoagulant therapy is recommended for secondary stroke prevention, unless there is a separate evidence-based indication for chronic anticoagulant therapy [Evidence Level B].

v. There is insufficient evidence to make a recommendation regarding the comparative effectiveness of PFO closure vs. anti-coagulant therapy.

2021 Guidelines

Recommendations for PFO
Referenced studies that support recommendations are summarized in online Data Supplements 38 and 39.

COR	LOE	Recommendations
1	C-EO	1. In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, recommendations for PFO closure versus medical management should be made jointly by the patient, a cardiologist, and a neurologist, taking into account the probability of a causal role for the PFO.
2a	B-R	2. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features,* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke.[552–557]
2b	C-LD	3. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO without high-risk anatomic features,* the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established.[552–557]
2b	C-LD	4. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown.[554]

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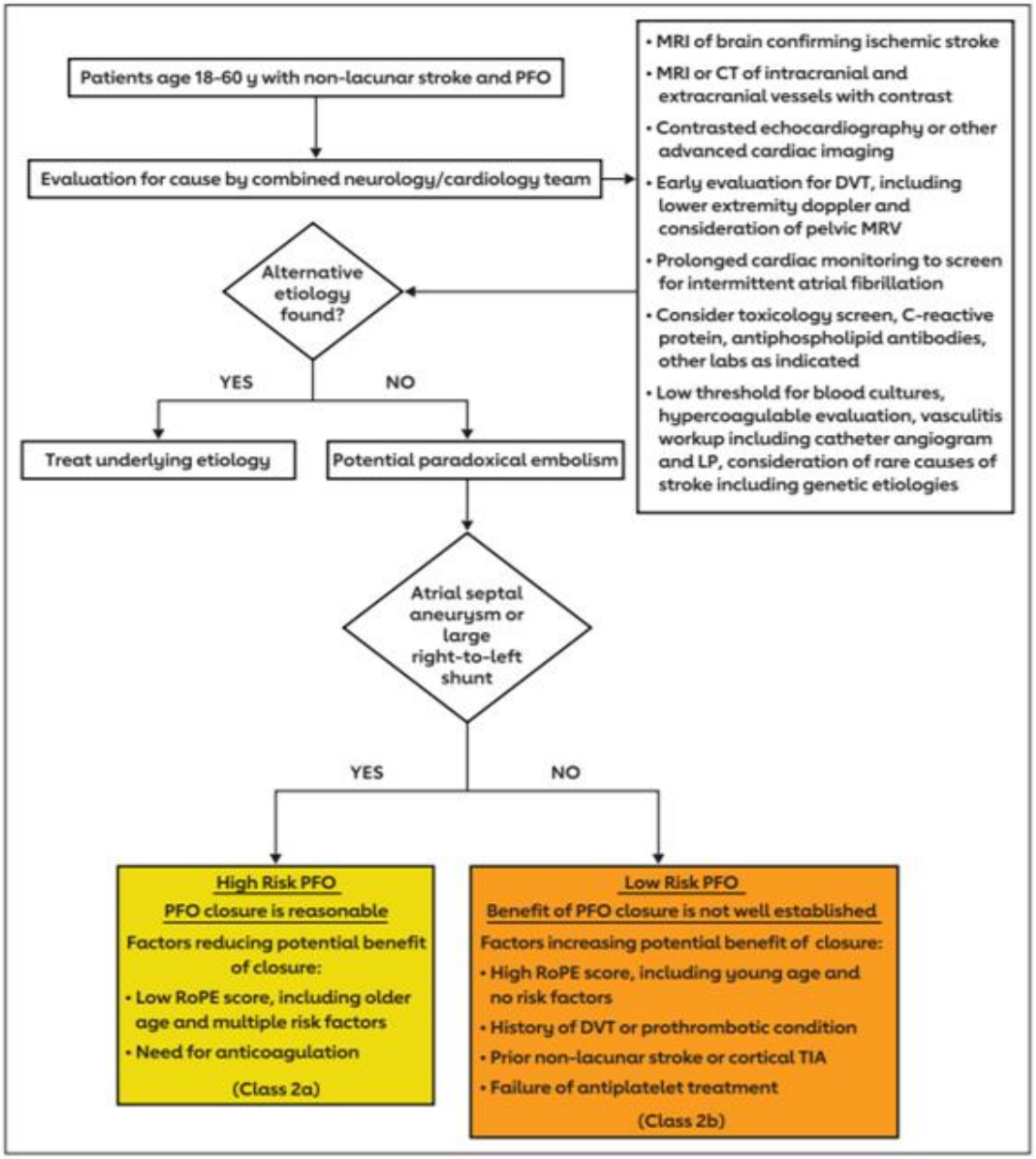

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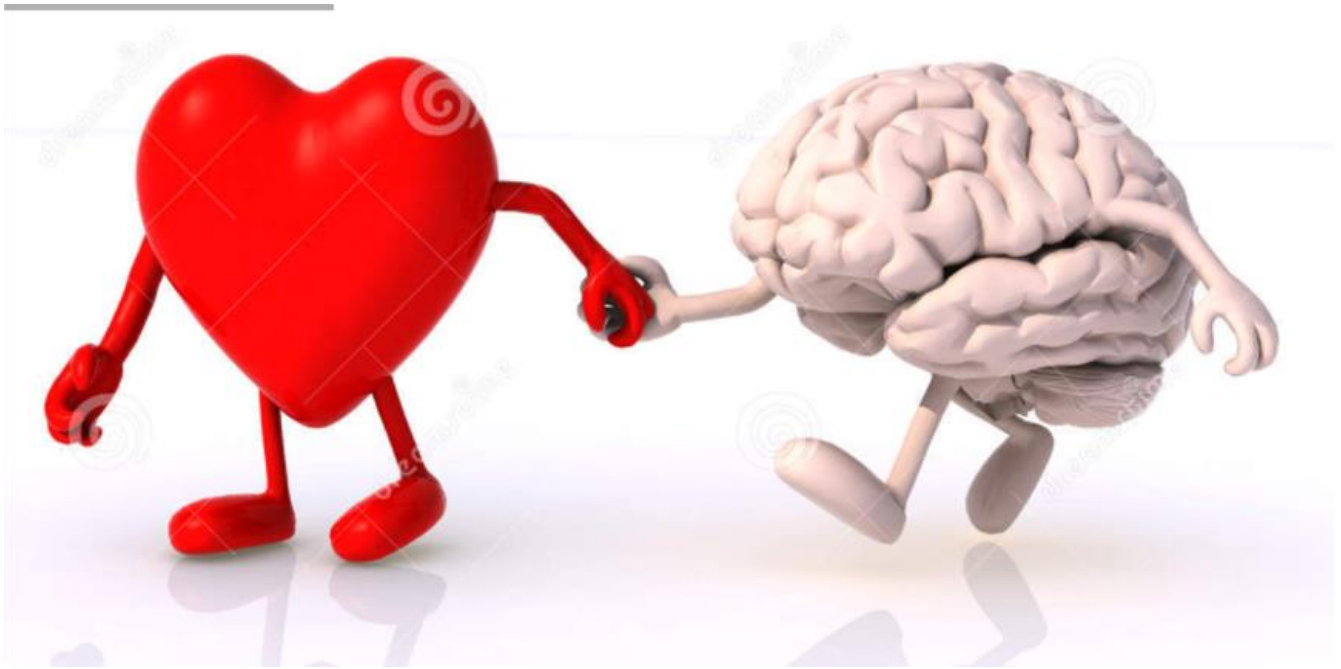
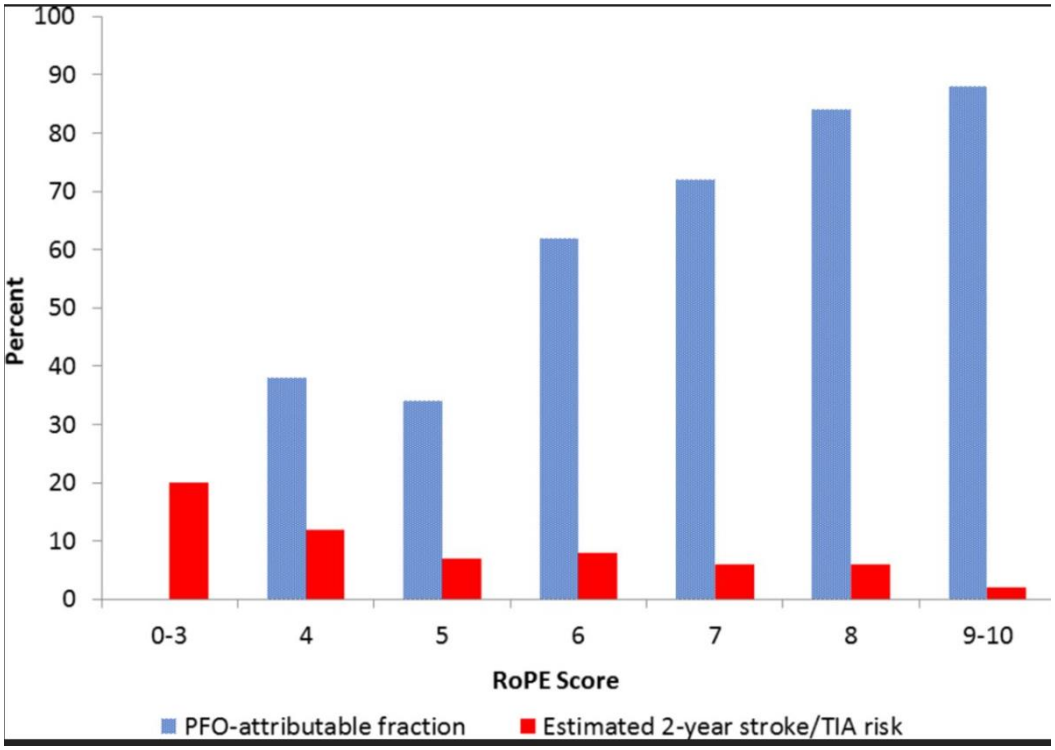
Heart-Brain Team Evaluation



RoPE (Risk of Paradoxical Embolism) Score

Table 1 The Risk of Paradoxical Embolism score (maximum of 10 points)

Characteristics	Points
Vascular risk factors	
No hypertension	1
No diabetes mellitus	1
No prior stroke or transient ischaemic attack	1
Non-smoker	1
Age (years)	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0
Stroke features	
Cortical infarction	1



Yuan K, Kasner SE. Patent foramen ovale and cryptogenic stroke: diagnosis and updates in secondary stroke prevention. Stroke and Vascular Neurology 2018;3: e000173. doi:10.1136/svn-2018-000173

Echo Scoring System

Table 4 Large-size high-risk PFO score calculator	
Variables	**Point**
Long-tunnel PFO ≥10 mm	1
Hypermobile interatrial septum	1
Eustachian valve or Chiari's network	1
Large RL shunt during Valsalva maneuver	1
Low-angle PFO ≤10°	1

A score of ≥ 2 points associated with cryptogenic stroke (sensitivity 91% and specificity 80%)

JASE, 2019-07-01, Volume 32, Issue 7, Pages 811-816

Future Directions

- Trials of closure versus medical management in patients ≥60 years of age
- Further trials and meta-analysis of all randomized trial data in patients <60 in patients with a PFO without high-risk anatomic features.
- Further trials and individual-level meta-analysis of all randomized trial data addressing the benefit of PFO closure compared with long-term anticoagulation.

Future Directions

- Individual-level meta-analysis of all randomized trials to determine whether PFO size is independently associated with response to treatment.
- Prevention of residual shunt at the time of closure
- Large long-term prospective registries of PFO closure patients to assess the risk of device associated AF and the risks associated with device complications such as device erosion, fracture, and endocarditis

Patient #1

- 55 year old woman with a history of HTN
  - Presented to Outside Hospital with right sided hemi paresthesia and expressive aphasia
  - MRI showed multifocal infarcts in left MCA territory
  - CTA occlusion of superior division of left MCA M3 segment
  - Received tPA and transferred to CSM, complete resolution of symptoms
  - 30 Day event monitor no afib
  - Carotid US no plaque
  - LE Dopplers no DVT
  - Echo showed “right to left atrial level shunt”

Patient #1

- PFO closed 10/2018.
- Now on Aspirin 81 mg only, no further neurologic events to date.

Patient #2

- 45 year old woman, history of migraines.
  - Presents for evaluation of episode of word finding difficulty and clumsiness, accompanied by headache that lasted 5 minutes.
  - MRI done 10 days following the event showed no evidence of acute or subacute stroke
  - Echo showed atrial septal aneurysm with moderate sized PFO with shunting in the baseline state

- Neuro Eval Possible TIA vs. Complex migraine
- Did not recommend PFO closure.
- DC OCP, start Aspirin

Patient #3

- 61 year old gentleman with a history of HTN, hyperlipidemia
  - Presented to ER with complaints of left arm numbness
  - Symptoms resolved by the time he was evaluated
  - He had been taking Aspirin 81 mg daily
  - MRI brain showed small areas of subacute infarct in the right caudate and globus pallidus
  - Transthoracic echo showed evidence of PFO with atrial septal aneurysm
- Further Workup
  - Carotid Dopplers, LE Dopplers, 30 day monitor were all unremarkable
  - Review echocardiogram (done at OSH)
  - Formal evaluation with neurologist
  - Ultimately PFO not closed secondary to age and comorbidities