

Beyond Cryptogenic Stroke: PFO Closure for Migraine and More

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Study Investigator

- Physician Training

Company

- WL Gore & Associates (REDUCE)
- WL Gore & Associates (ASSURED)
- WL Gore & Associates (Migraine/PFO Trial)
- Abbott Medical (Amulet)
- Edwards Medical (COMPASSION S3)
- BSCI (PREVAIL, CAP2)
- Conformal Medical (Animal Work, First-in-Man Feasibility Trial)

- Abbott Medical (Amplatzer PFO)
- BSCI (Watchman)

4 Randomized PFO/Cryptogenic Stroke Trials

RESPECT NEJM 2017

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

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

REDUCE NEJM 2017

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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CLOSE NEJM 2017

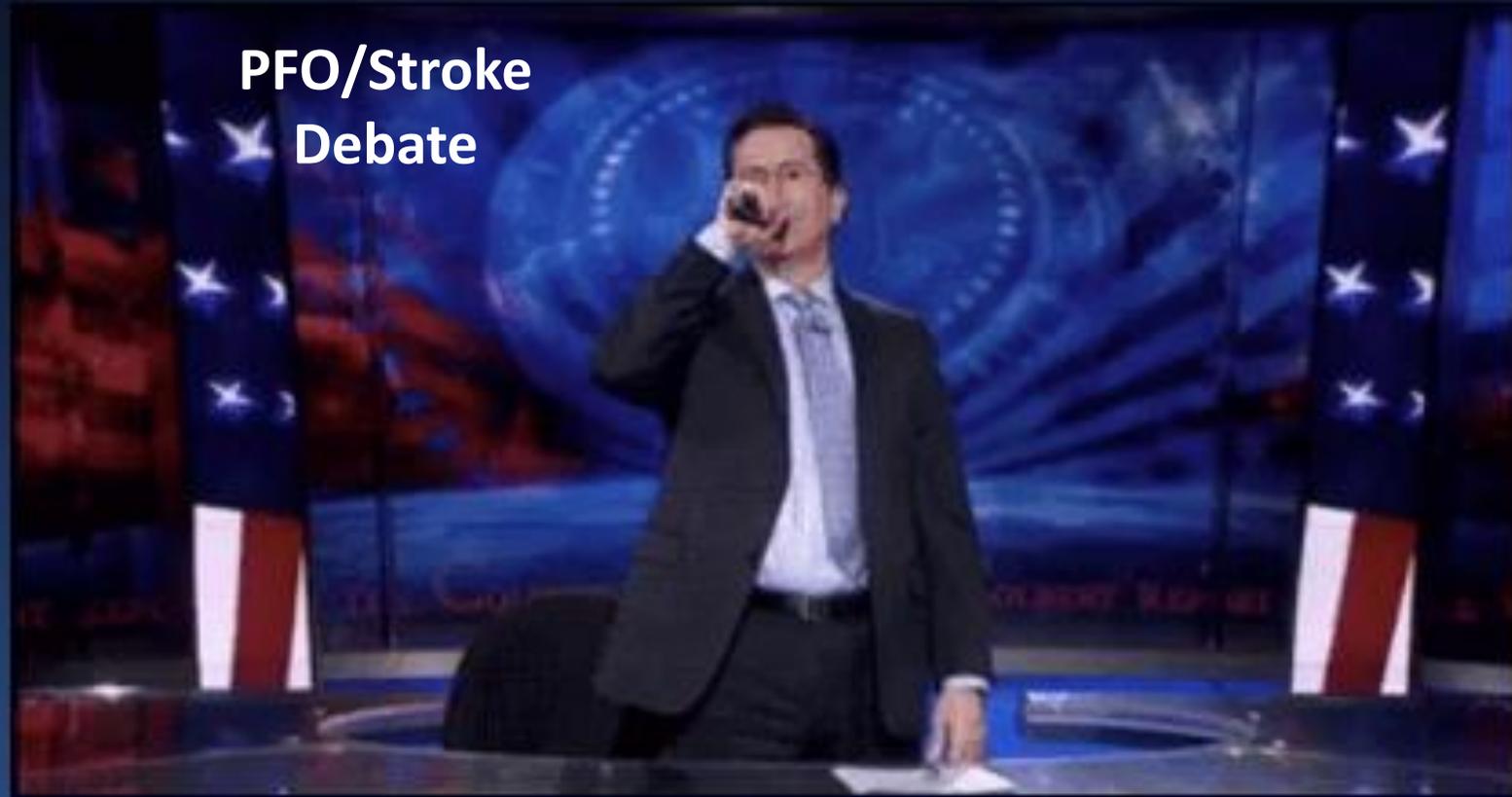
Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial

Running title: Device closure for high-risk PFO

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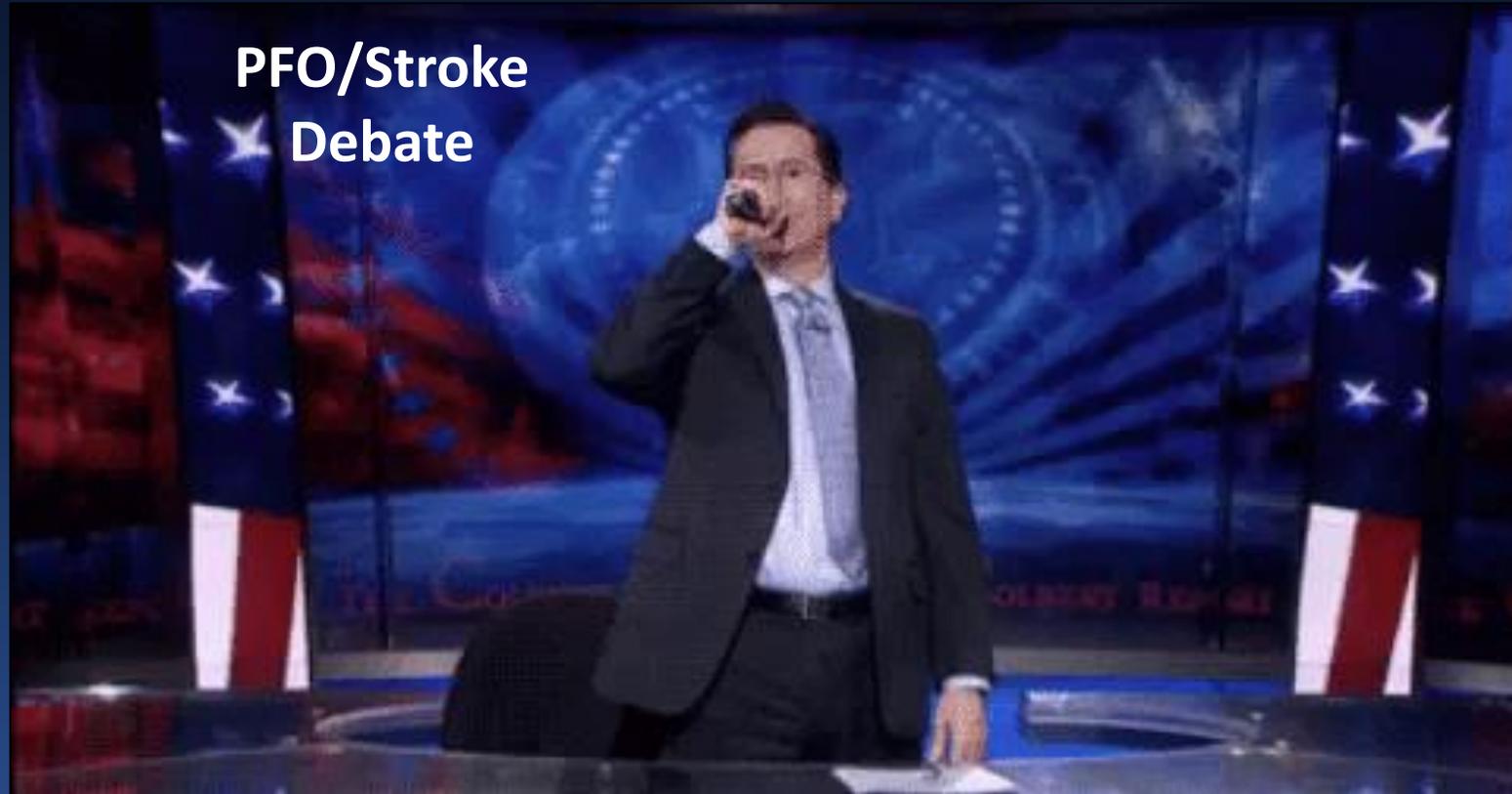
DEFENSE PFO JACC 2018

4 Randomized PFO/Cryptogenic Stroke Trials



**PFO/Stroke
Debate**

4 Randomized PFO/Cryptogenic Stroke Trials



What's next?

PFO – What's Next?

- Systemic (non-cerebral) paradoxical embolization
- Hypoxemia
- Decompression Illness
- Obstructive Sleep Apnea
- High Altitude Pulmonary Edema
- Migraine Headache

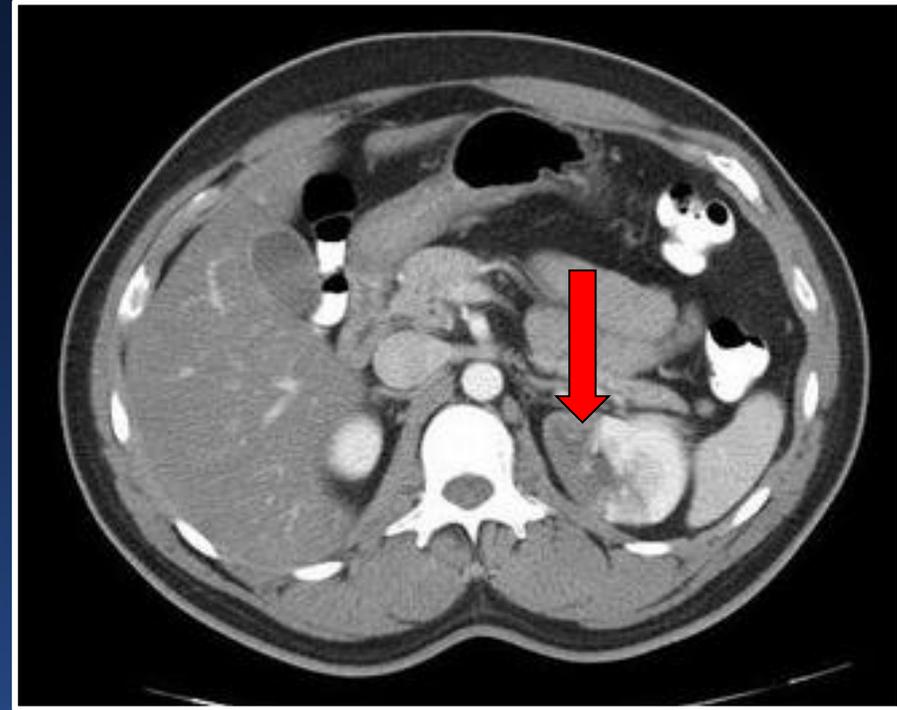
Systemic (Non-cerebral) Paradoxical Thromboembolism

“The clot doesn’t have to go to the brain.”

Systemic Embolization

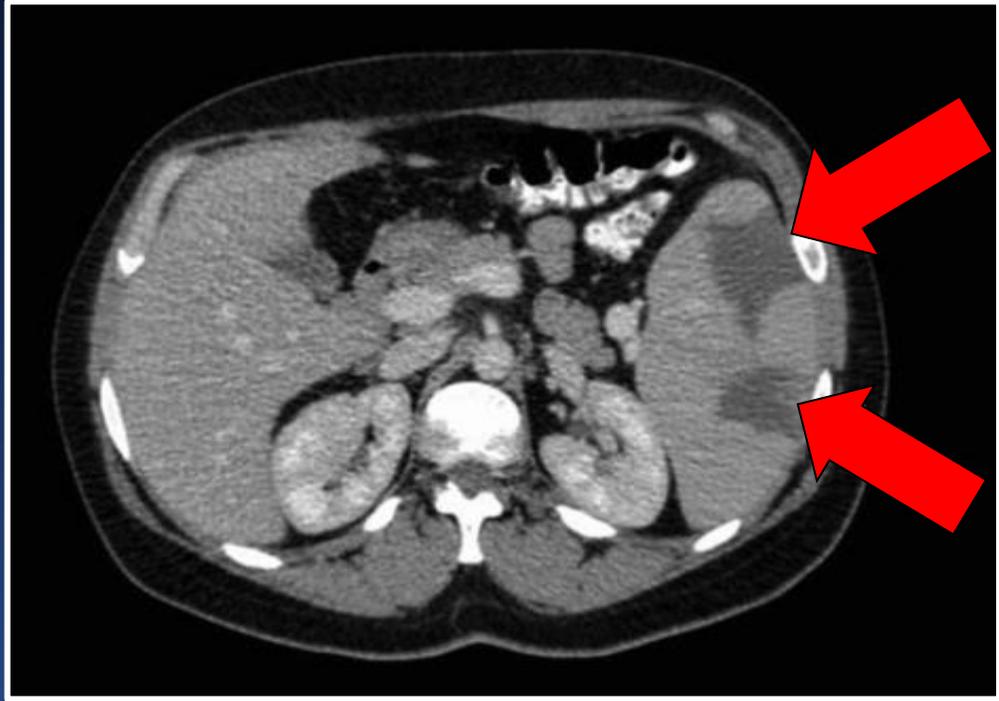


Hepatic Infarct

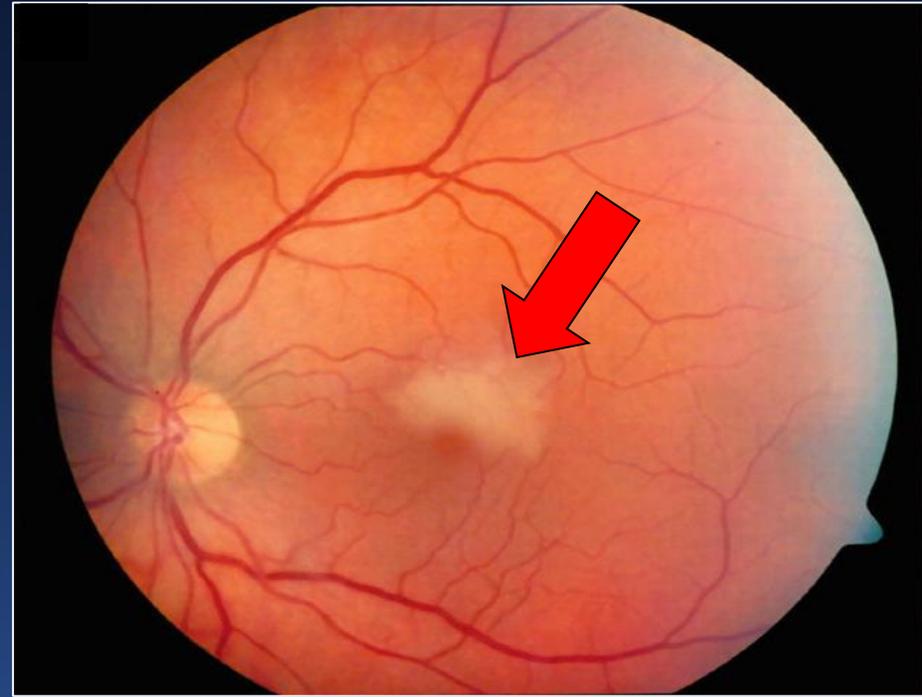


Renal Infarct

Systemic Embolization

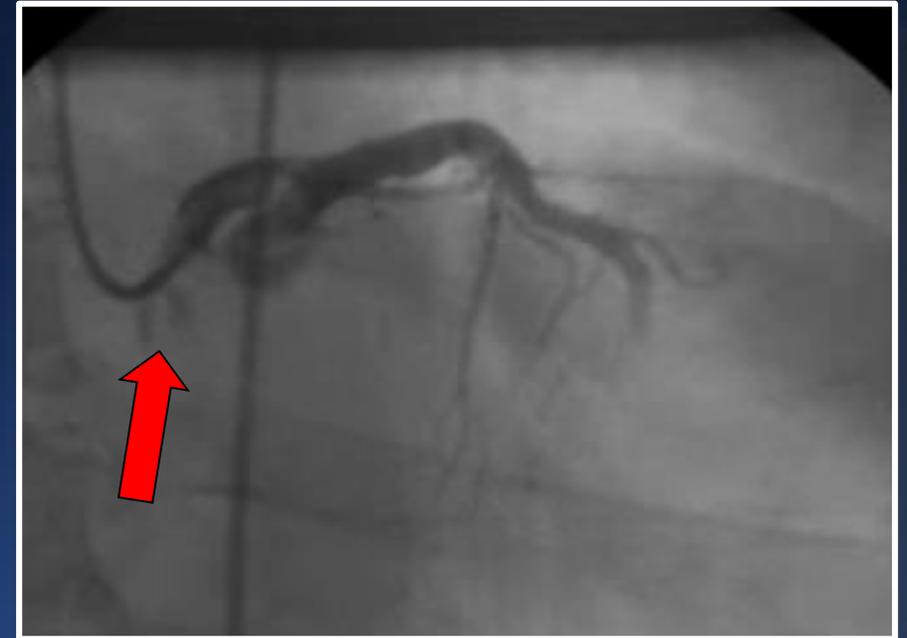
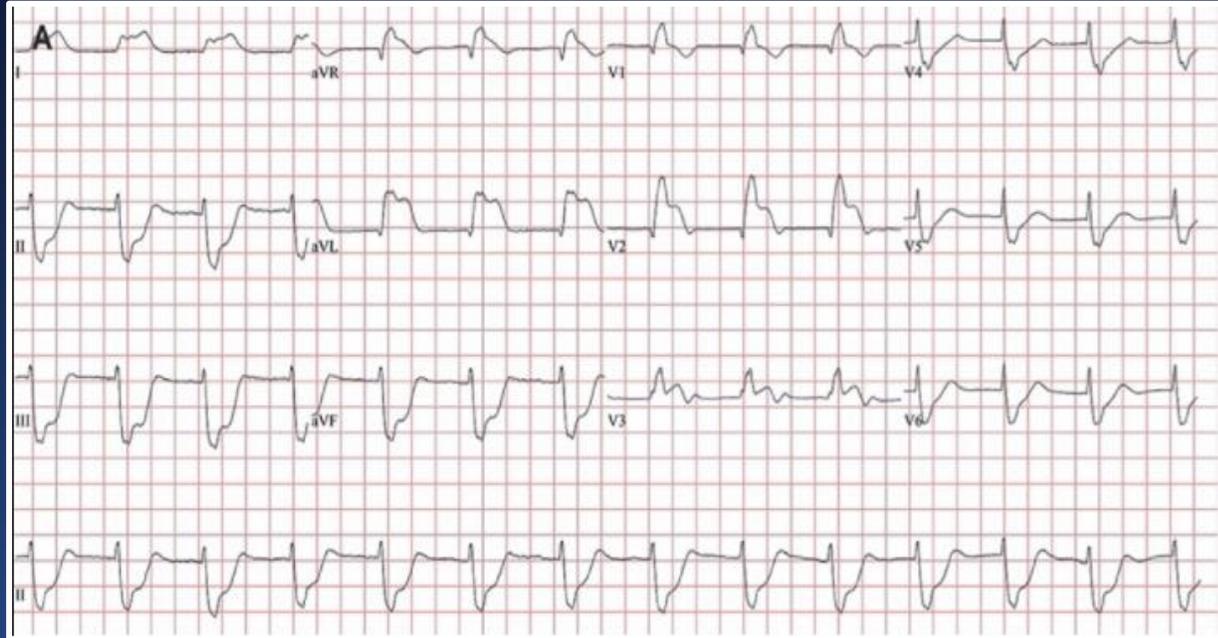


Splenic Infarcts



Retinal Infarct

Systemic Embolization



18 year old with acute myocardial infarct
(thrombus in L main CA)

Systemic Embolization

✓ Why the historical focus on Stroke?

- Largest portion of CO goes to the brain
- Other organs have functional redundancy that the brain does not
- The clinical impact of a smaller clot is more often clinically apparent



Cerebral Infarct

Systemic Embolization

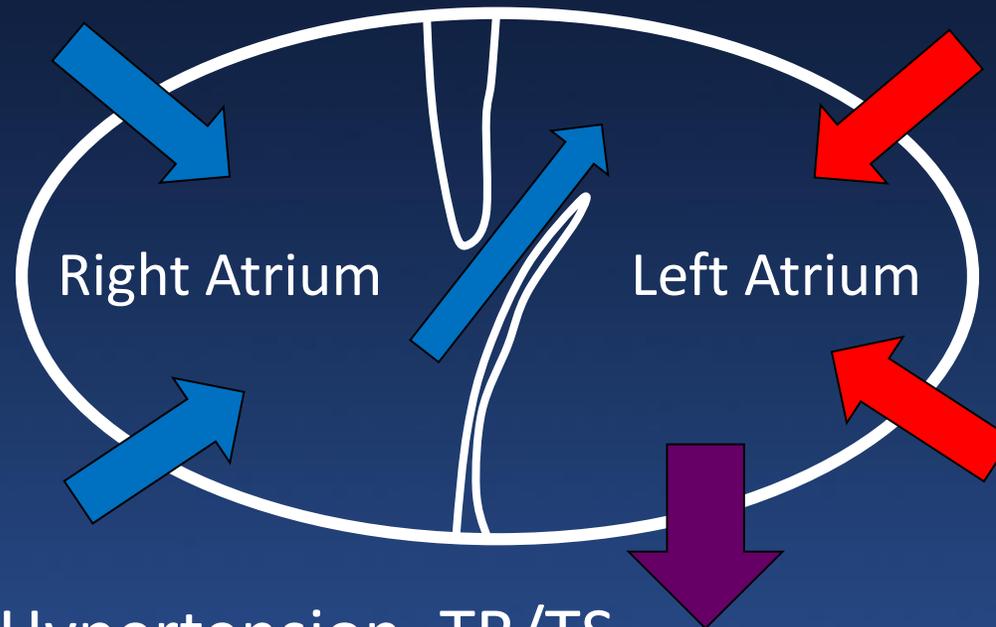
Conclusion (without data)

- Systemic thromboembolism has the same differential diagnosis as cardioembolic stroke and is a “stroke equivalent”.
- In the absence of another source, the PFO in a patient with a systemic thrombotic event should also be closed.

PFO – Hypoxemia

PFO – Hypoxemia: Physiology

With $LAp > RAp$ throughout the cardiac cycle in most patients, the PFO is closed or opens phasically



- RA Hypertension, TR/TS
- RV Non-compliance, normal PAp
- Platypnea – Orthodeoxia: Streaming of IVC inflow

Closure of PFO for Hypoxemia: Literature

Transcatheter Device Closure of Interatrial Septal Defects in Patients with Hypoxia

J Intervent Cardiol 2005;18:227–232

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- N = 10
- Immediate resolution of hypoxemia

Effectiveness of Percutaneous Closure of Patent Foramen Ovale for Hypoxemia

Brett E. Fenster, MD^{a,*}, Bryant H. Nguyen, MD^b, J. Kern Buckner, MD^a, Andrew M. Freeman, MD^a,
and John D. Carroll, MD^b

- N = 97
- Procedural success in 96/97
- Immediate resolution of low O₂ sats in 70%.

PFO Closure for Hypoxemia

- No randomized studies. But it works.
- With continuous R to L flow, balloon occlusion of PFO can assess change in RA pressure and prove that Ao sat will rise.
- Pulmonary hypertension as an underlying cause of R to L shunt is a contraindication to PFO closure.

PFO – Migraine Headache

PFO – Migraine

History

- 2000 – First reports of migraine amelioration with PFO closure for recurrent stroke prevention, followed by numerous retrospective series reporting similar migraine effect
- Four failed PFO-Migraine trials: MIST, ESCAPE, PREMIUM, PRIMA
- In part likely due to our inability to select the PFOs which were “causal” from those which were incidental to the migraines

PFO – Migraine

Columbia University Experience

- ✓ In 2011:
 - PFO/cryptogenic stroke patients with aspirin contraindication
 - Treated with clopidogrel as an alternative agent
 - Some noted dramatic reduction/elimination of pre-existing MHA
- ✓ We postulated that some product of platelet aggregation or activation might be acting as a “trigger” substance, crossing the PFO to reach the brain in supra-physiologic levels

PFO – Migraine

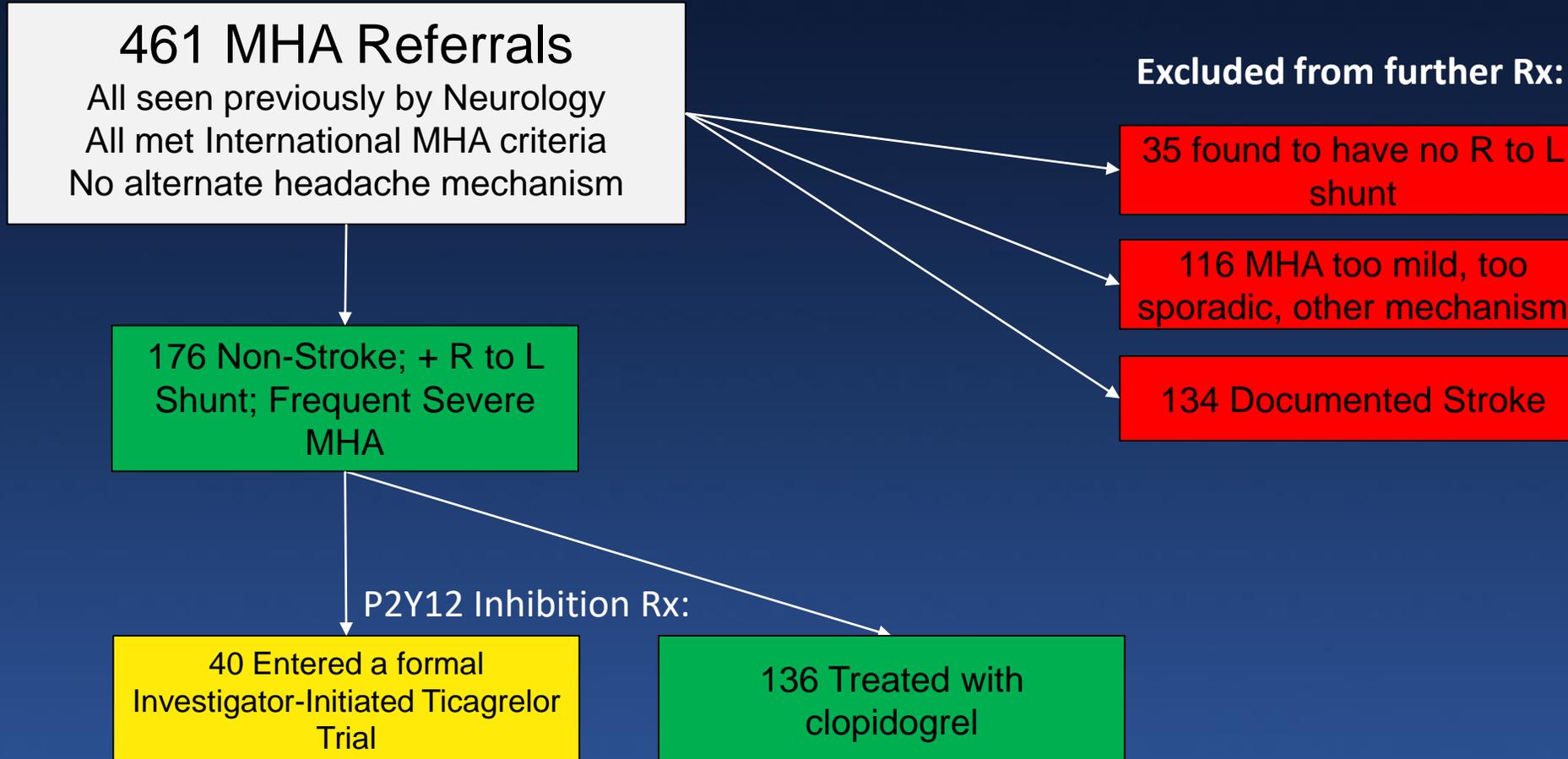
Columbia University Experience 2011-2017

✓ Over 6 years at our site:

- Began an exploratory off-label (open-label) use of clopidogrel therapy for refractory non-stroke / MHA / PFO population
- No patients excluded on basis of:
 - aura/non-aura
 - headache frequency
 - episodic/chronic or any other specific MHA characteristic

PFO – Migraine

Columbia University Experience (2011-2017)



PFO – Migraine

Columbia University Experience (2011-2017)

✓ Population:

- 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 (Range 0.5 – 28)

PFO – Migraine

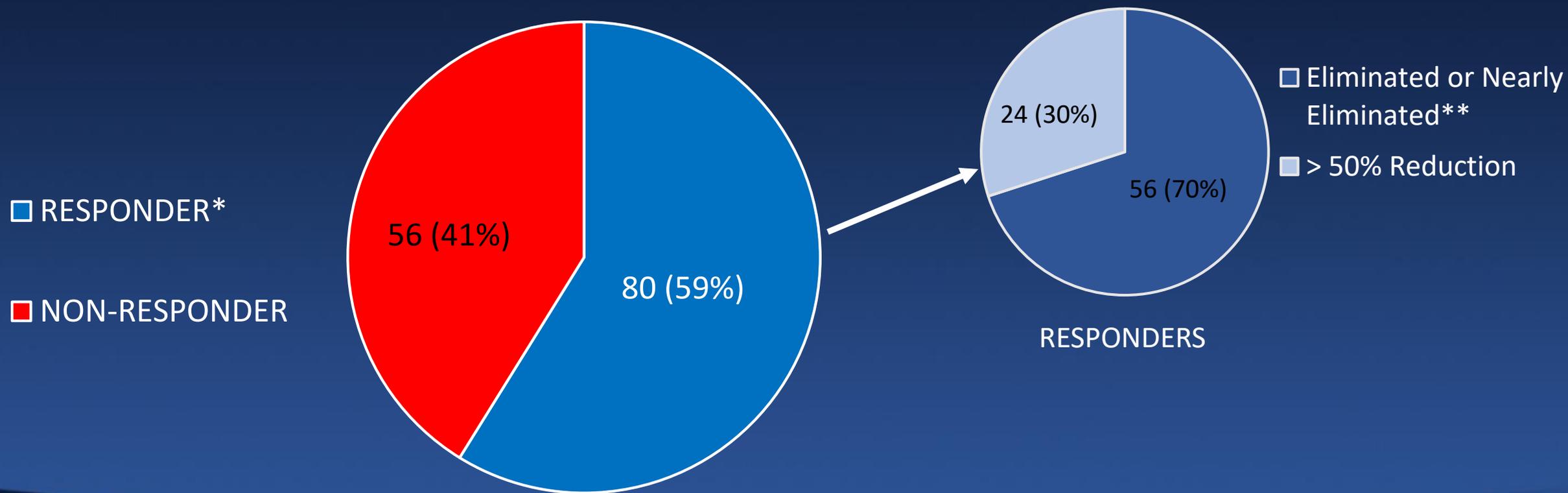
Columbia University Experience (2011-2017)

- ✓ Patient Response prospectively defined as:
 - Clopidogrel RESPONDER:
 - $\geq 50\%$ Reduction in Monthly MHA days
 - Migraine Elimination/Near Elimination: $\geq 90\%$ reduction in monthly MHA days
 - Clopidogrel NON-RESPONDER:
 - $< 50\%$ Monthly Headache Reduction

PFO – Migraine

Columbia University Experience (2011-2017)

Response to clopidogrel



PFO – Migraine

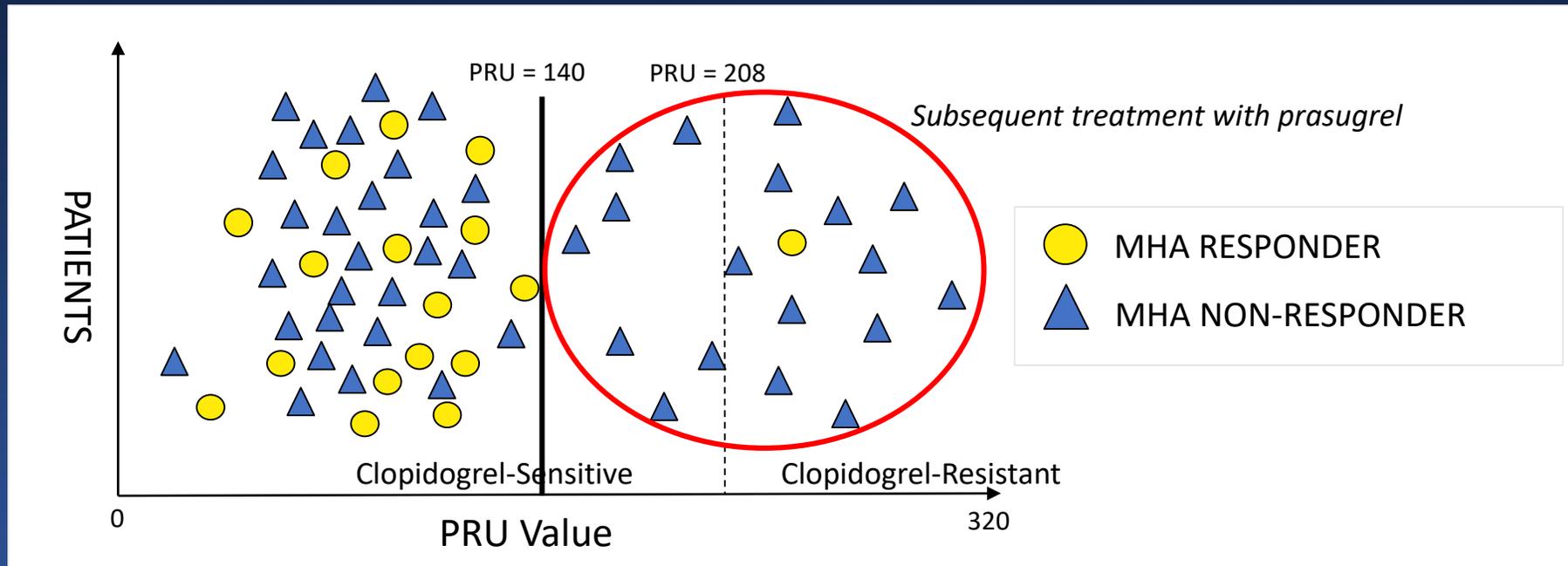
Columbia University Experience (2011-2017)

- ✓ No difference in response rate to clopidogrel:
 - Aura vs. Non-aura (58% vs. 59%)
 - Chronic vs. Episodic (61% vs. 57%)
 - Large vs. small R to L shunt magnitude (73% vs. 59%)

PFO – Migraine

Columbia University Experience (2011-2017)

- 17 RESPONDERS, 45/56 NON-RESPONDERS were tested for adequacy of P2Y12 platelet inhibition (PRU testing)

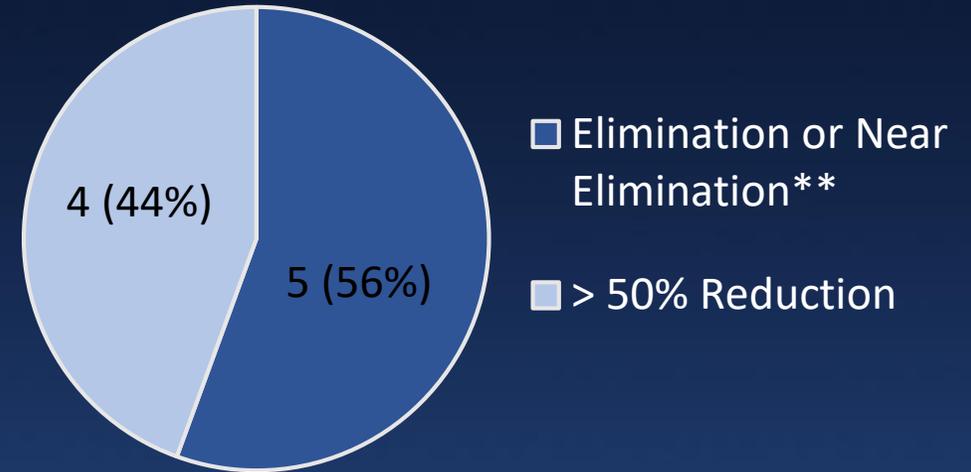
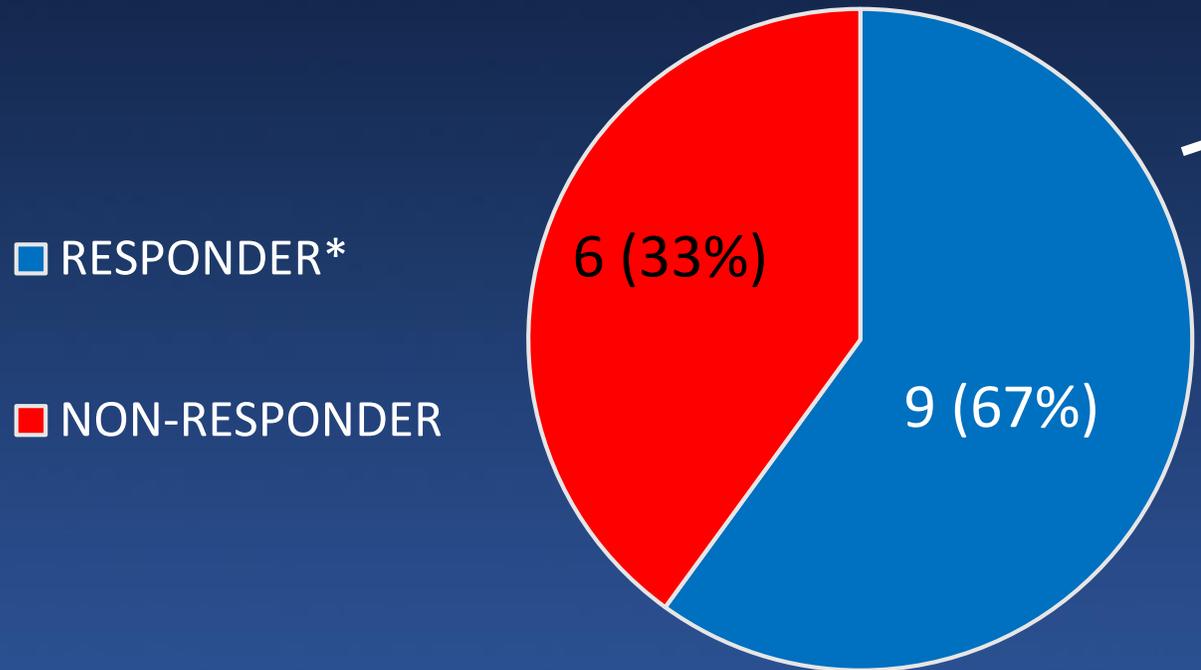


PRU Testing –
VerifyNow[®],
Accriva
Diagnostics,
San Diego CA

PFO – Migraine

Columbia University Experience (2011-2017)

Response to prasugrel in clopidogrel-resistant MHA NONRESPONDERS

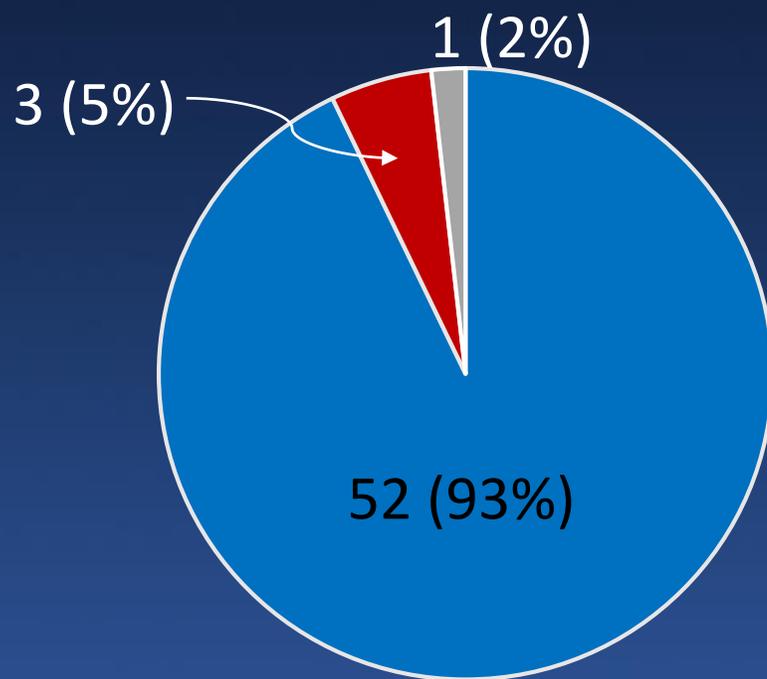


- All patients had PRU < 100 on prasugrel
- Suggested that headache response was related to P2Y12 inhibition
- Implied that PFO Migraines are “platelet-mediated”

PFO – Migraine

Columbia University Experience (2011-2017)

Response to PFO Closure/Drug Withdrawal (N = 56):

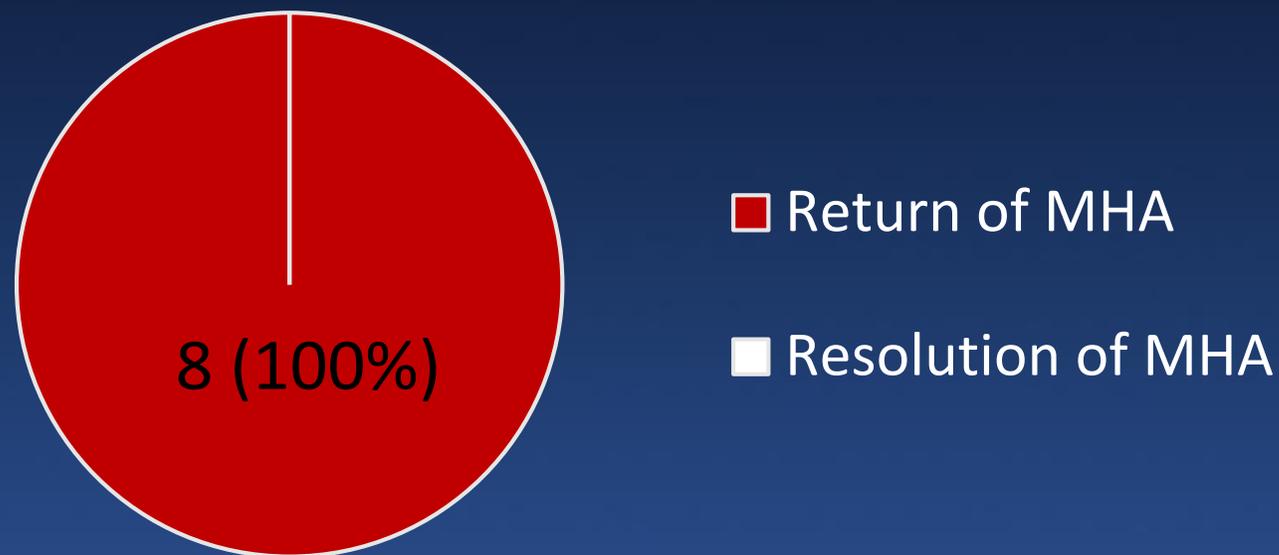


- 1 pt with moderate persistent leak of the PFO device
- 1 patient with no MHA X 1 yr then onset of new/different headaches
- 1 patient with 3 years of complete relief, with mild MHA return when became pregnant

PFO – Migraine

Columbia University Experience (2011-2017)

Response to Drug Withdrawal without PFO Closure (N = 8):



Typical MHA return time = 4- 5 days (the effective elimination time of the thienopyridine)

PFO – Migraine

Columbia University Experience (2011-2017)

- ✓ Formal Ticagrelor feasibility trial (N = 40)
 - 48% Migraine RESPONDERS:
 - Less effective MHA relief
 - 9/9 had same or better response to PFO closure
- ✓ New National MHA/PFO Trial (End of 2018)
 - Thienopyridine responsiveness will be used as final screening step prior to randomized PFO closure or sham procedure