Finally the Feds Will Allow Us to Treat Paradoxical Emboli Leading to Stroke.

What About PFO Closure for Migraines, is There Convincing Evidence to Treat?

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Disclosure Statement of Financial Interest

I, Robert Sommer, have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

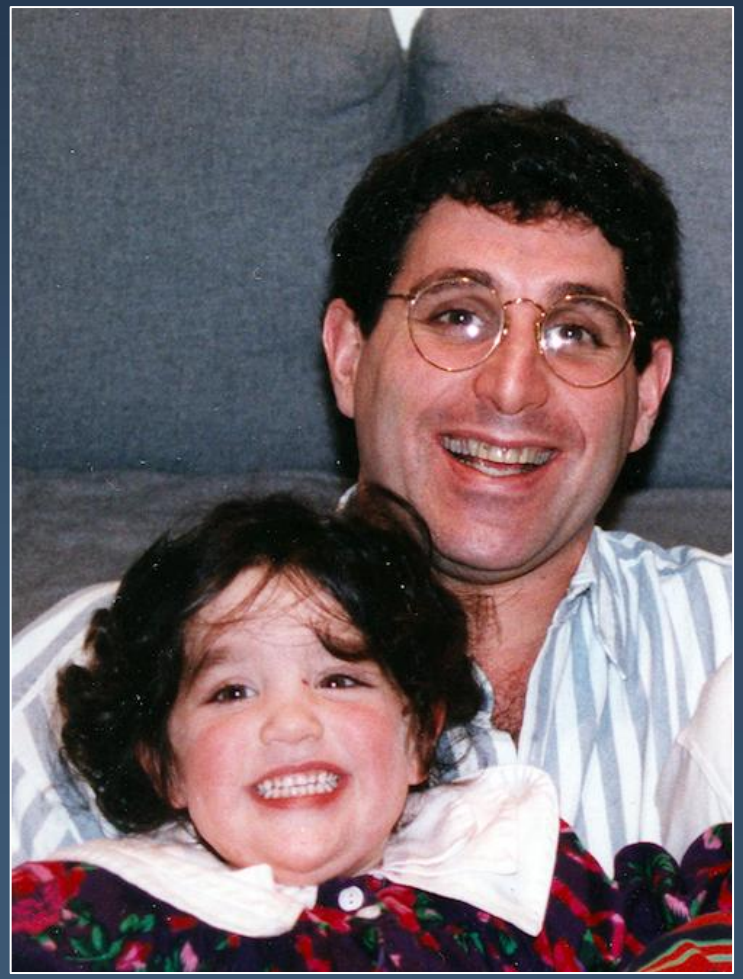
W.L. Gore & Associates:	Cardology PI for upcoming Gore RELIEF Migraine - PFO Trial
Astra-Zeneca:	Investigator-initiated Grant to perform TRACTOR Migraine Trial

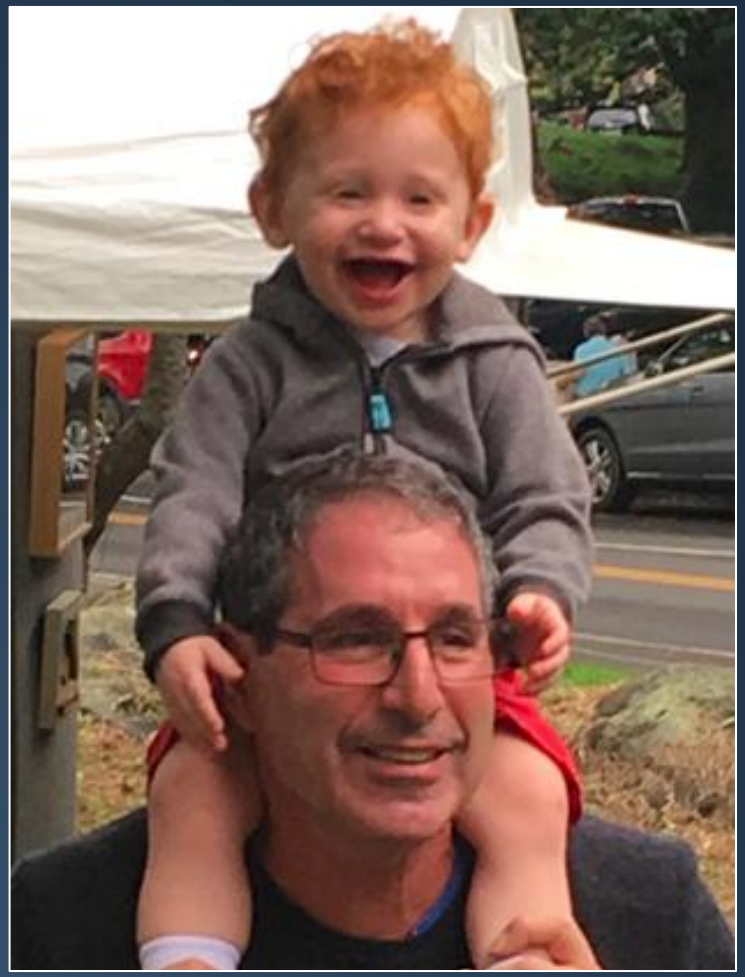
Additional Disclosure

I, Robert Sommer, am not a Neurologist.

PFO: A Lot of History/Controversy

1992 – Today





PFO and Migraine Headache

Migraine vs. TIA

What distinguishes migraine aura symptoms from CVA symptoms (aura can occur w/o headache – acephalgic MHA)?

- Stereotypic nature of recurrent neurologic events!!!
- Multiple events without lesions on MRI
- Duration of symptoms 20 – 30 minutes typical of MHA aura with or without headache

Case Report

A 22 year old woman:

- Suffered left hand weakness lasting for 3 hours during a migraine.
- Neurologist thought this was a TIA, with negative MRI
- Now with a transient visual field loss that lasted ~90 minutes
- TEE reveals a large PFO/ASA and strongly positive bubble study.

Case Report

Do these two events represent atypical migraine or TIA?

□ Atypical MHA □ TIA □ Can't tell

- Symptoms not consistent with prior MHA events. Very different from one another, affecting brain in markedly different distributions.
- High risk PFO/ASA features for recurrent embolic events.
- Manage this like a patient with TIA/stroke: Close the PFO based on data from RESPECT/REDUCE/CLOSE/DEFENSE PFO (may have beneficial side effect of reducing/eliminating the headaches).

Alternate Case Report

26 year old woman, MHA since puberty

- Typically with unilateral head pain, light and sound sensitivity with nausea. No preceding aura. MHAs respond well to early administration of triptans.
- ~ 4 times a year, intense visual aura, progressing to L sided hemiparesis lasting 20 - 30 minutes
- Unilateral headache follows with emesis which can last up to 72 hours. Triptans rarely effective in these episodes. Multiple hospitalizations to r/o stroke, for MHA pain management, and for IV fluid replacement therapy.
- MRI normal. TEE reveals a “probable PFO” with small R to L shunt at the atrial level by bubble study, confirmed by TCD (Spencer Grade 2).

Alternate Case Report

Do these quarterly events represent migraine?

□ Yes □ No □ Can't tell

- Symptoms stereotypical, w/ multiple events, less likely to be embolic.
- Small PFO less consistent with recurrent embolic events.
- MHA can be associated with very small PFOs.
- Now what?

PFO Migraine - Background

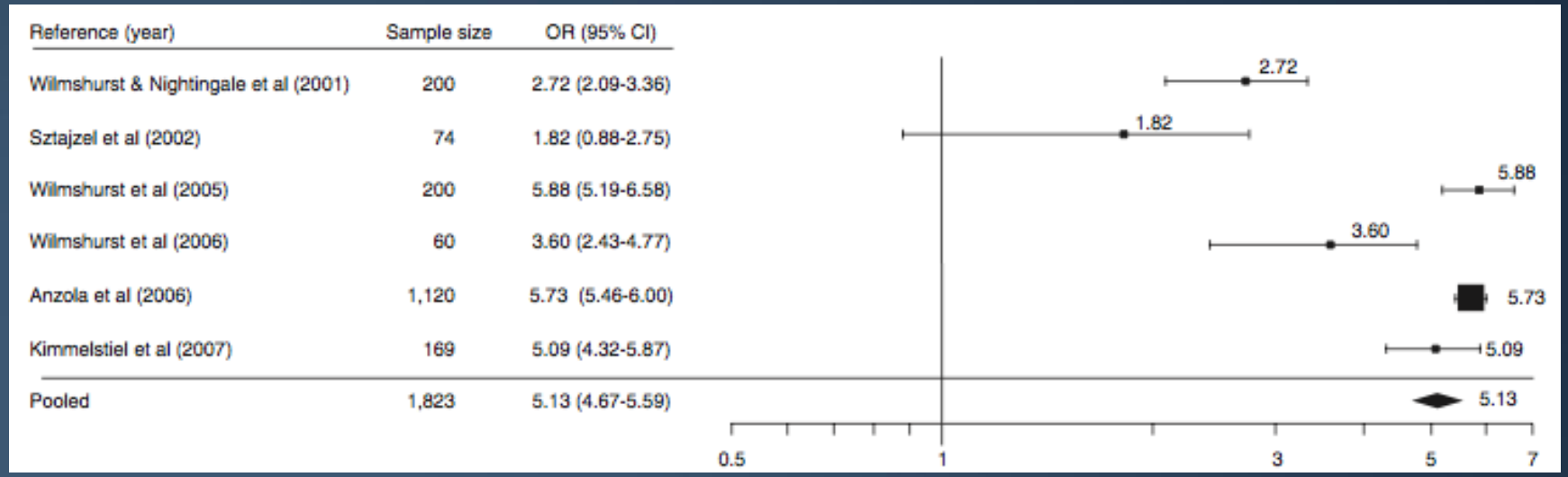
Clinical – Observational Evidence

PFO Prevalence

Patent foramen ovale and migraine: a quantitative systematic review

TJ Schwedt[1], BM Demaerschalk[2] & DW Dodick[2]

PFO Prevalence in Migraineurs



Reference (year)	Sample size	OR (95% CI)
Wilmshurst & Nightingale et al (2001)	200	2.72 (2.09-3.36)
Sztajzel et al (2002)	74	1.82 (0.88-2.75)
Wilmshurst et al (2005)	200	5.88 (5.19-6.58)
Wilmshurst et al (2006)	60	3.60 (2.43-4.77)
Anzola et al (2006)	1,120	5.73 (5.46-6.00)
Kimmelstiel et al (2007)	169	5.09 (4.32-5.87)
Pooled	1,823	5.13 (4.67-5.59)

Cephalalgia. 2008;28:531-40.

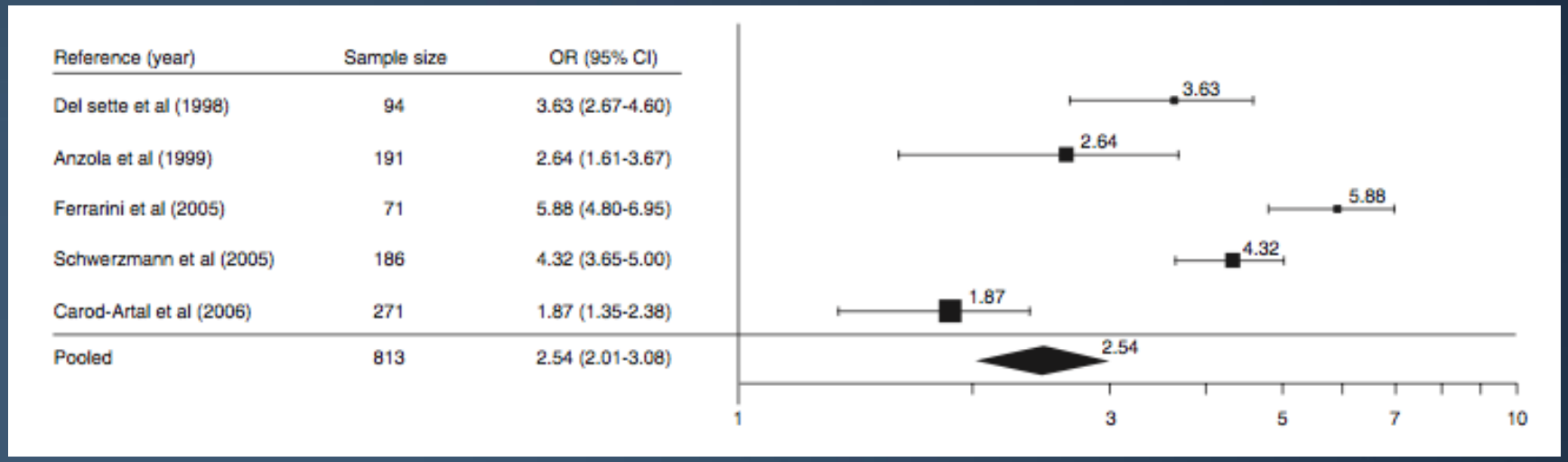
Clinical – Observational Evidence

PFO Prevalence

Patent foramen ovale and migraine: a quantitative systematic review

TJ Schwedt[1], BM Demaerschalk[2] & DW Dodick[2]

Migraine Prevalence in Patients with PFO

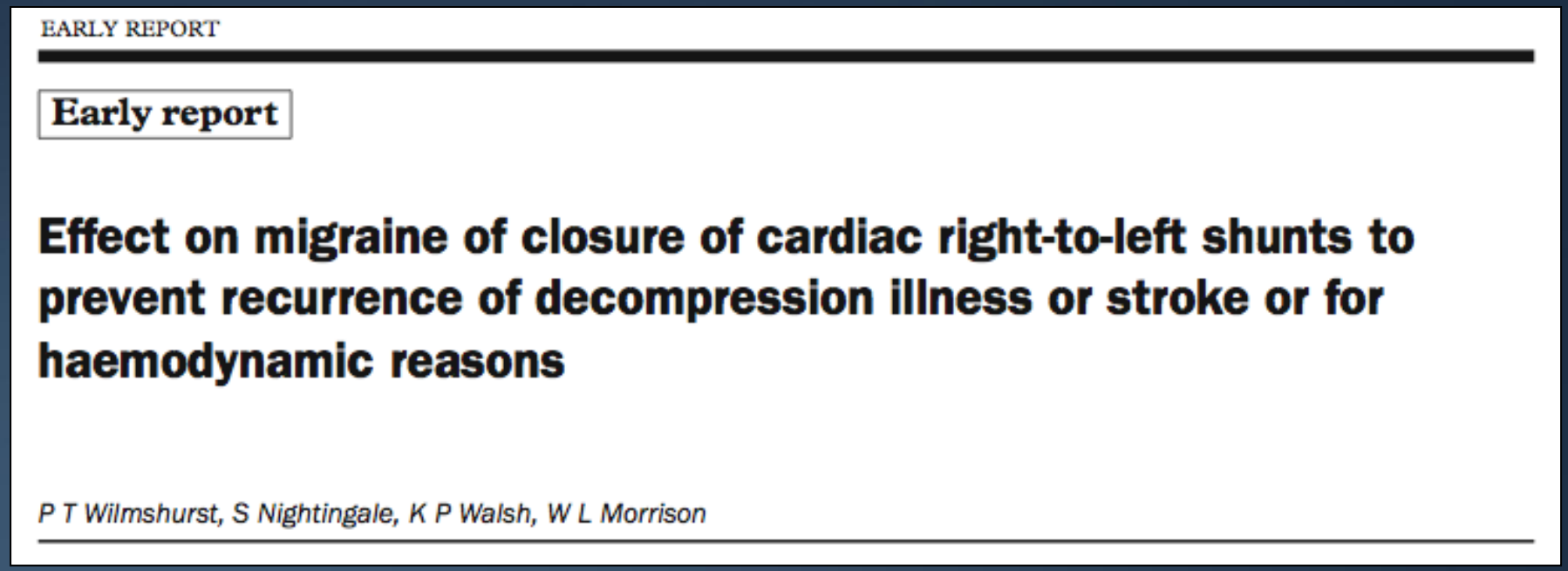


Reference (year)	Sample size	OR (95% CI)
Del sette et al (1998)	94	3.63 (2.67-4.60)
Anzola et al (1999)	191	2.64 (1.61-3.67)
Ferrarini et al (2005)	71	5.88 (4.80-6.95)
Schwerzmann et al (2005)	186	4.32 (3.65-5.00)
Carod-Artal et al (2006)	271	1.87 (1.35-2.38)
Pooled	813	2.54 (2.01-3.08)

Cephalalgia. 2008;28:531-40.

Migraine – 1st Observational Report

Effect of PFO Closure



EARLY REPORT

Early report

Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons

P T Wilmshurst, S Nightingale, K P Walsh, W L Morrison

- ✓ 17/21 had resolution/improvement of migraines symptoms after PFO closure following DCI or stroke

Wilmshurst et al. Lancet 2000;356:1648-51.

Clinical – Observational Evidence

Effect of PFO Closure

Study	Improved?
Morandi. J Int Cardiol 2003;16:39.	76%
Schwerzmann. Neurology 2004;62:1399.	73%
Giardini. Am Heart J 2006;151:922.	91%
Reisman. JACC 2005;45:493.	70%
Slavin. Am J Cardiol 2007;99:1316.	85%
Kimmelstiel. CCI 2007;69:740.	57%
Wahl. Heart 2010;96:967.	82%
Khessali. JACC CV Int 2012;5:682	76%

✓ Numerous retrospective series document migraine relief after PFO closure for recurrent stroke prevention

PFO – Migraine

PFO Pathophysiology

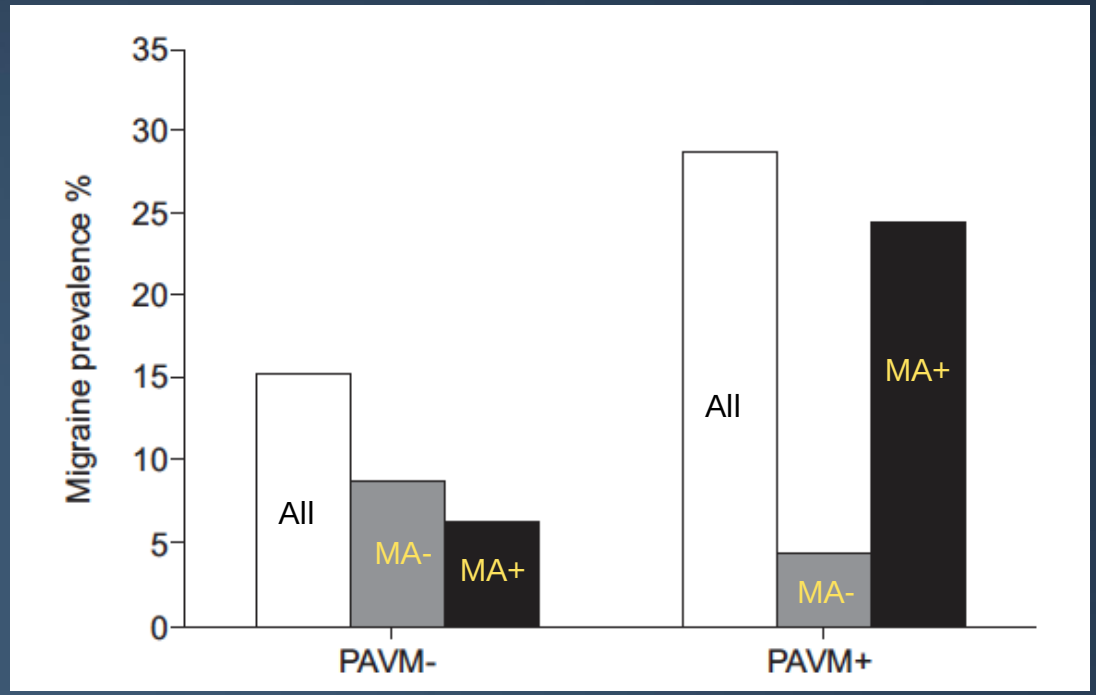
- R to L shunt allows systemic venous blood to reach the cerebral circulation without oxygenation/filtration
  - Known to be associated with paradoxical embolization
  - Known to be associated with hypoxemia
  - Perhaps allows substances, normally “filtered” in the lungs to reach the brain in supra-physiologic levels
    - Directly triggering MHA
    - Changing a MHA threshold
- Migraine association is not unique to PFO

PFO – Migraine: Observational Evidence

Relationship to R to L Shunt

Pulmonary arteriovenous malformations associated with migraine with aura

M.C. Post*, M.W.F. van Gent*, H.W.M. Plokker*, C.J.J. Westermann#, J.C. Kelder*, J.J. Mager#, T.T. Overtoom¶, W.J. Schonewille+, V. Thijs§,ƒ and R.J. Snijder#



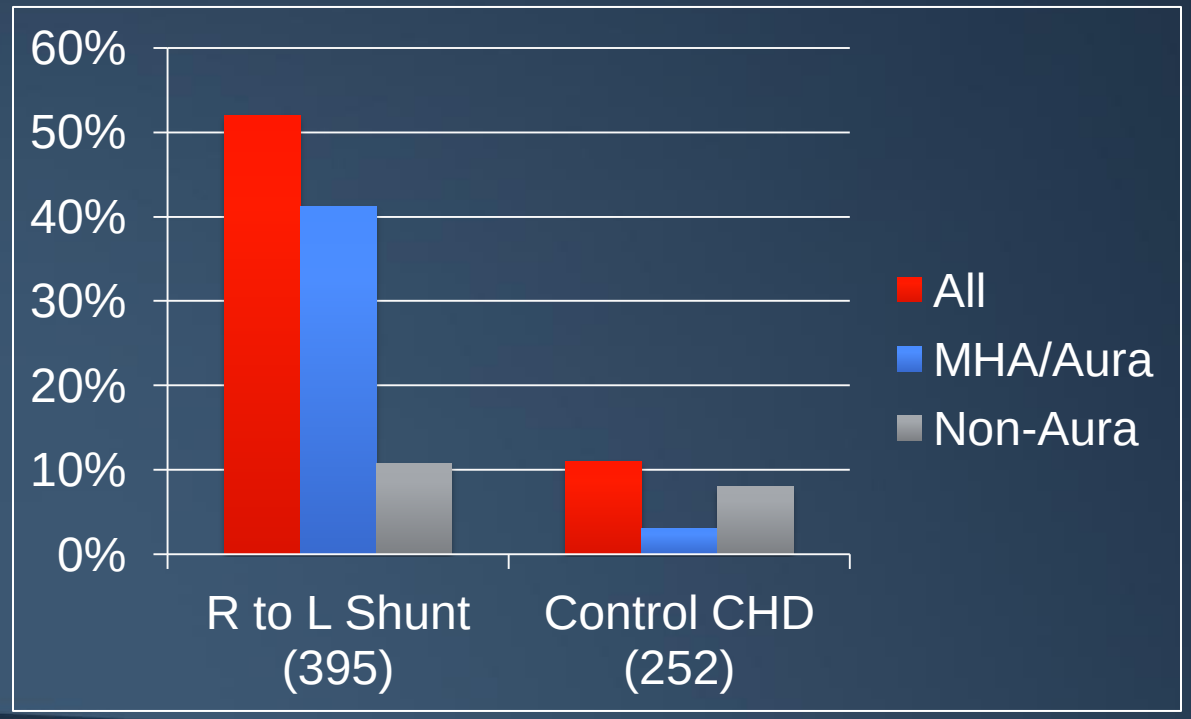
Post et al. Eur Respir J 2009;34:882-7

PFO – Migraine: Observational Evidence

Relationship to R to L Shunt

Prevalence of Migraine Headaches in Patients With Congenital Heart Disease

Tam Truong, MD, Leo Slavin, MD, Ramin Kashani, BA, James Higgins, MD, Aarti Puri, BS, Malika Chowdhry, BS, Philip Cheung, BS, Adam Tanious, BA, John S. Child, MD, FAHA, Joseph K. Perloff, MD, and Jonathan M. Tobis, MD*



Truong et al. Am J Cardiol 2008;101:396-400

What is Crossing the PFO?

- Micro-emboli theory: platelet aggregates or clots (too small to cause CVA) cross PFO to cerebral circulation and trigger migraine
  - Moscowitz – PET scans in mice (cortical spreading depression)
  - Severe migraine symptoms post agitated saline injection, foam sclerotherapy in patients with PFO

What is Crossing the PFO?

- Chemical theory:
  - Vasoactive compounds released locally by platelets usually removed/inactivated in first pass through the lungs (e.g. serotonin)

The Randomized Trials

Effect of PFO Closure

- MIST (2006)
- ESCAPE Migraine (2008)
- PRIMA (2015)
- PREMIUM (2015)

  - All small trials, various designs
  - Two failed to enroll
  - None achieved primary endpoint for headache remediation with closure

Randomized Trials

Effect of PFO Closure

- Trial Failures – What's going on?
  - Closure has placebo effect only?

    Probably not. Today there is general agreement that there is a mechanistic link between PFO and MHA. Just not understood.

  - Poor device performance/incomplete closure?

    Probably not. Studies have shown MHA relief with incomplete closure.

Randomized Trials

Effect of PFO Closure

- Trial Failures – What's going on?
  - The presence of a PFO does not mean that MHA symptoms are PFO-related.
  - Even in MHA with aura, PFO present in only 40%. Thus the other 60% have non-PFO mediated MHA.
  - Trial failure was likely based on the inability to select those PFOs which were mechanistically linked to the MHA from those which were incidental.

Randomized Trials

Effect of PFO Closure

- Trial Failures – What's going on?
  - Ultimately, it was the inability to select the right patients for the therapy.

What's going on today?

Clinical – Observational Evidence

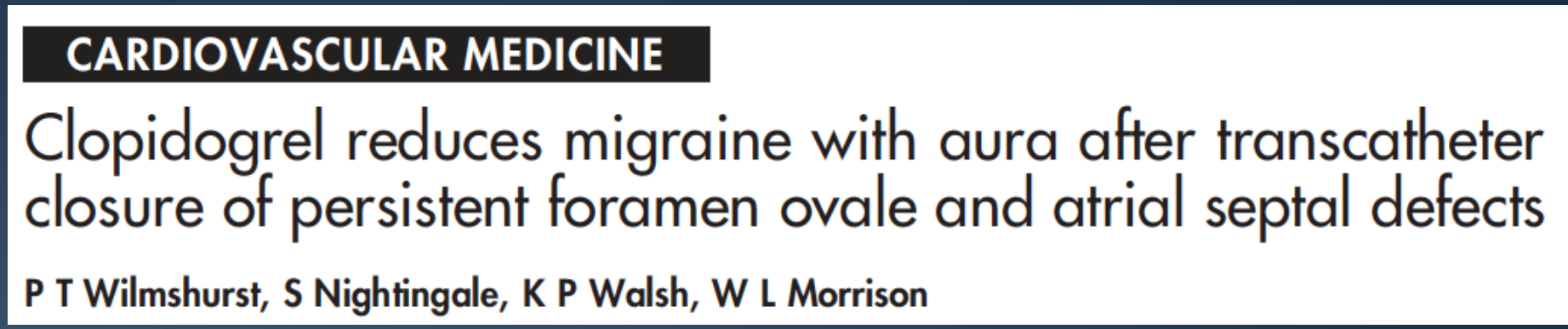
Effect of Platelet Inhibition

PFO – Migraine

Columbia University Experience

- In 2011:
  - Prior to stroke PFO trial evidence – pts offered closure or medical therapy (aspirin)
  - Some PFO/cryptogenic stroke patients treated instead with clopidogrel because of aspirin allergy/sensitivity
  - Noted dramatic reduction/elimination of pre-existing MHA
  - We postulated that a product of platelet aggregation or activation might be the substance crossing the PFO reaching the brain

Clinical – Observational Evidence
Role of Platelets



CARDIOVASCULAR MEDICINE

Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects

P T Wilmshurst, S Nightingale, K P Walsh, W L Morrison

- ✓ 12.2% had MHA after PFO Closure on ASA/Clopidogrel
- ✓ 42.3% MHA after PFO Closure on ASA alone ($p<0.001$)

- ✓ “Platelets may have a role in the pathogenesis of MHA”

Heart 2005;91:1173-5.

Clinical – Observational Evidence

Role of Platelets

Original Investigation

Effect of Clopidogrel and Aspirin vs Aspirin Alone on Migraine Headaches After Transcatheter Atrial Septal Defect Closure

The CANOA Randomized Clinical Trial

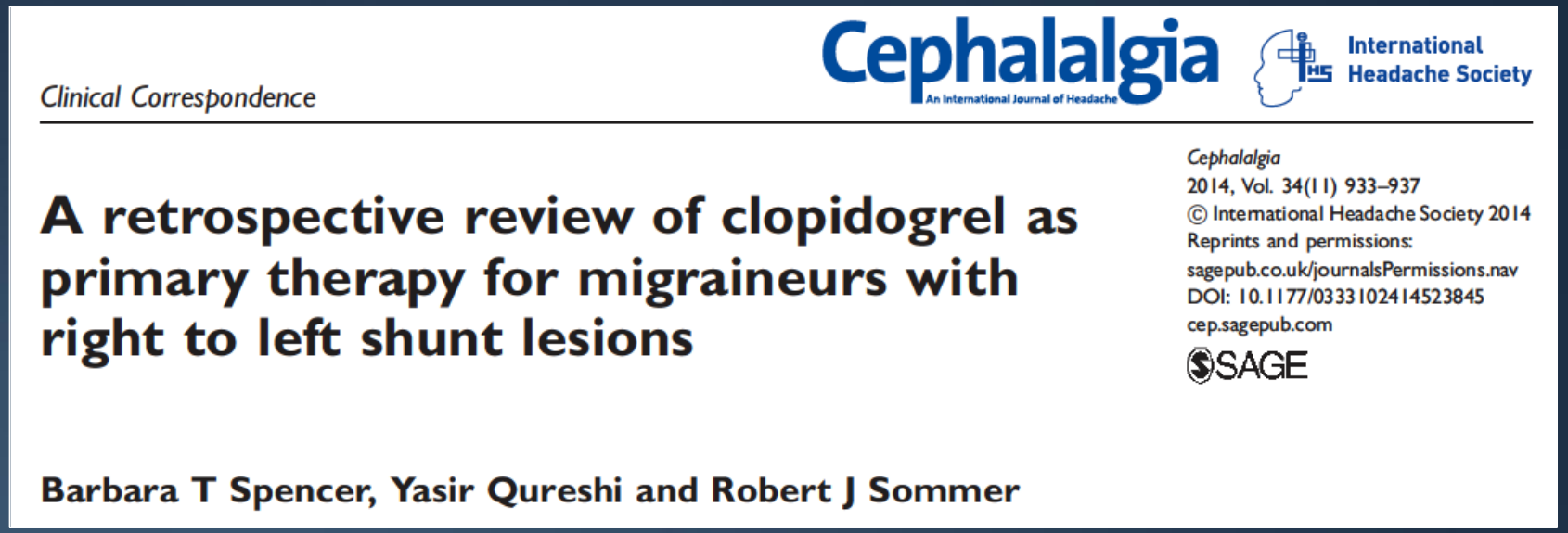
Josep Rodés-Cabau, MD; Eric Horlick, MD; Reda Ibrahim, MD; Asim N. Cheema, MD; Marino Labinaz, MD; Najaf Nadeem, MD; Mark Osten, MD; Mélanie Côté, MSc; Josep Ramon Marsal, MSc; Donald Rivest, MD; Alier Marrero, MD; Christine Houde, MD

- ✓ Patients treated with DAPT post-implant had fewer de novo migraine symptoms (9.5% vs. 21.8%, p = 0.03)
- ✓ Patients treated with DAPT had fewer disabling MHA events (0% vs. 37%, p = 0.046)

JAMA. 2015;314(20):2147-2154.

Clinical – Observational Evidence

Role of Platelets



Clinical Correspondence

Cephalalgia
An International Journal of Headache

International Headache Society

A retrospective review of clopidogrel as primary therapy for migraineurs with right to left shunt lesions

Barbara T Spencer, Yasir Qureshi and Robert J Sommer

Cephalalgia
2014, Vol. 34(11) 933–937
© International Headache Society 2014
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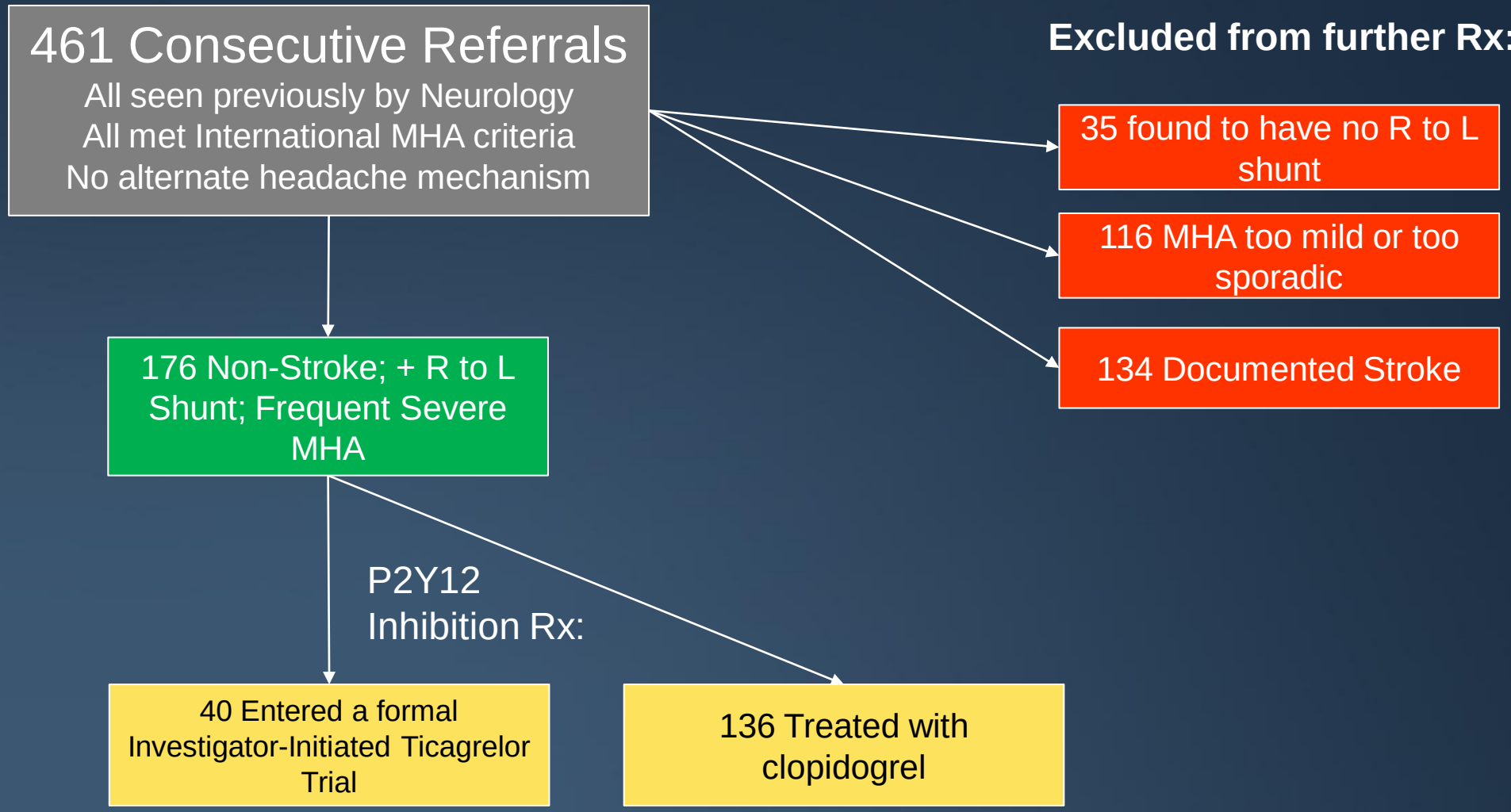
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0333102414523845
cep.sagepub.com
SAGE

- ✓ Small, non-randomized, open-label 15 patient series
- ✓ Clopidogrel added to regimen of severe migraineurs
- ✓ 13/15 had ≥50% reduction in MHA symptoms

Cephalalgia. 2014;34(20):933-937.

MHA-PFO Referrals



Columbia University Experience (2011-2017)

PFO – Migraine

- Population (N = 136): Severe MHA, no stroke, PFO
- Presence of aura, chronic vs. episodic, shunt size not considered
  - 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

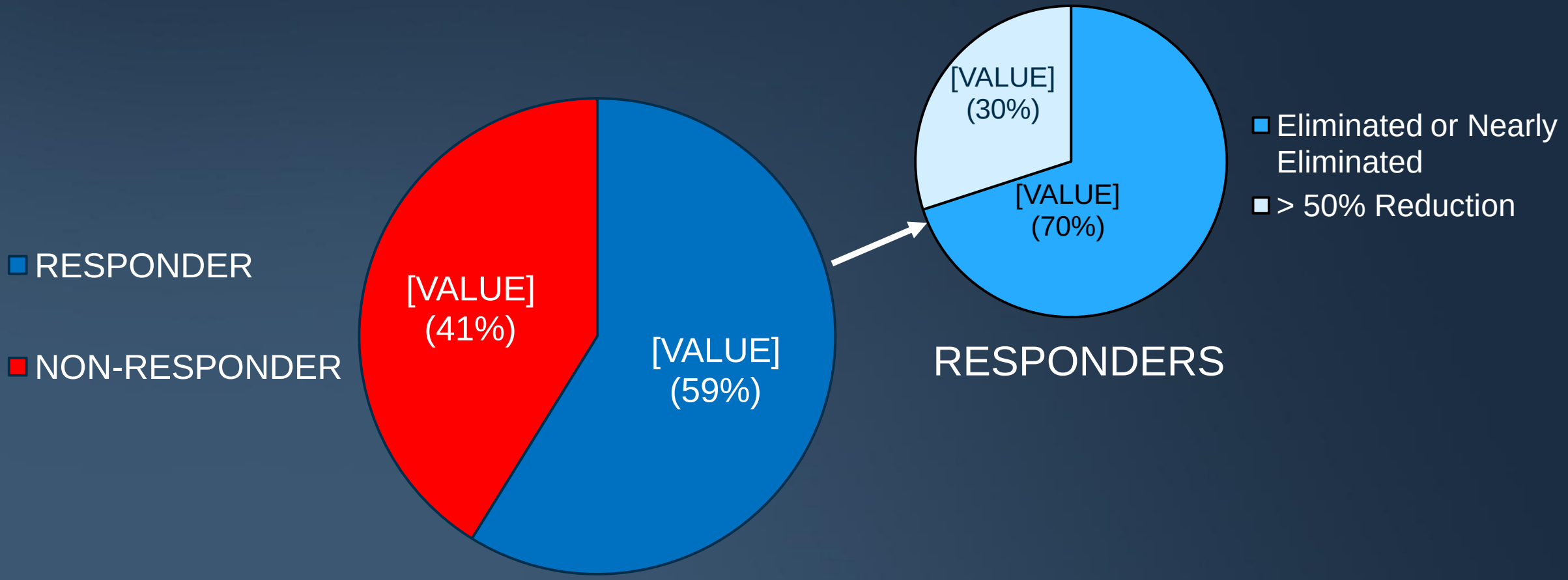
PFO – Migraine

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 – Migraine

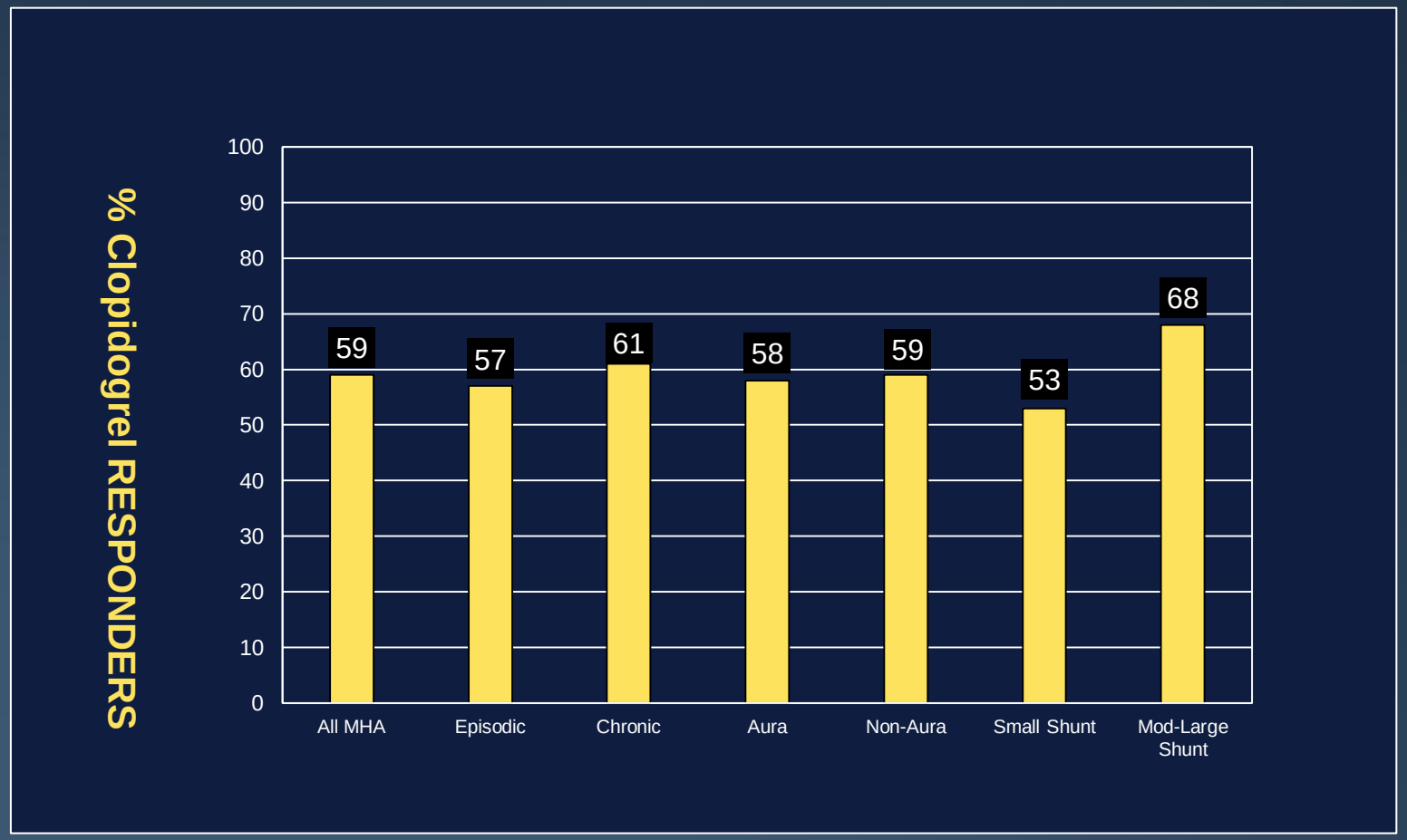
Migraine Headache Response to Clopidogrel



Columbia University Experience (2011-2017)

MHA/PFO Pts Treated with Clopidogrel

(N = 136)

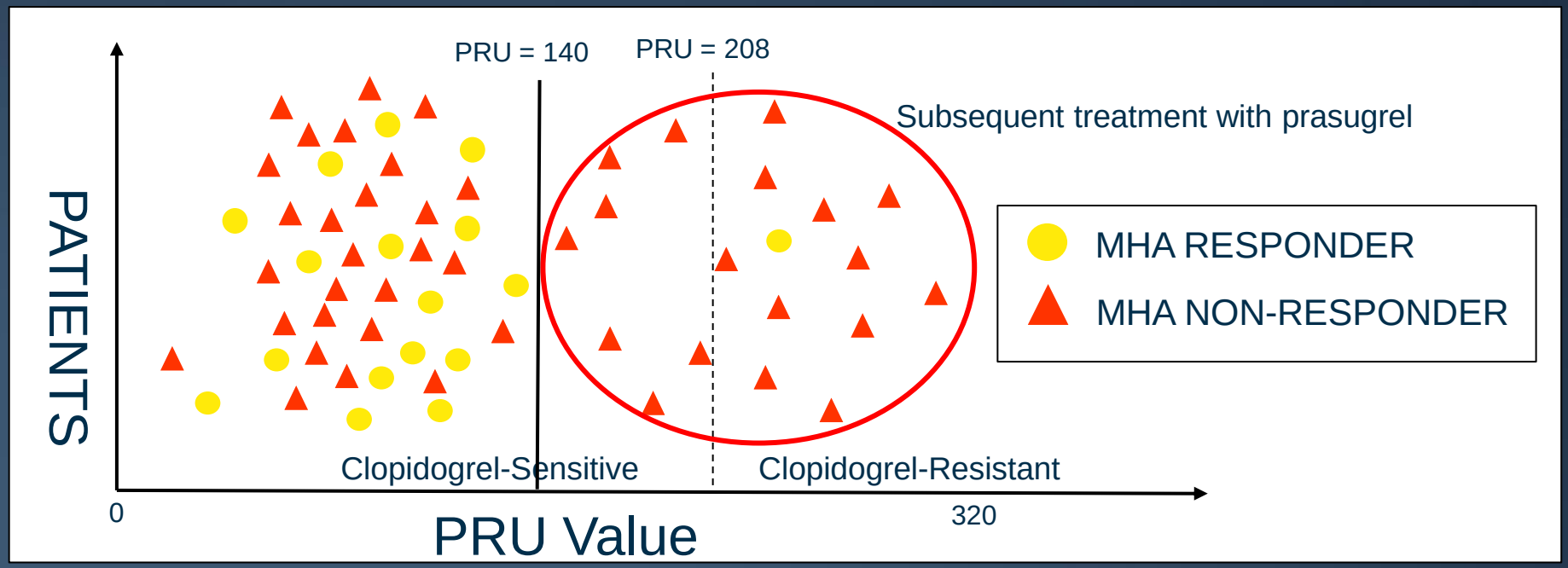


- ✓ No clear difference in response rate to clopidogrel among MHA subtypes:

PFO – Migraine

Effectiveness of Platelet Inhibition on Clopidogrel

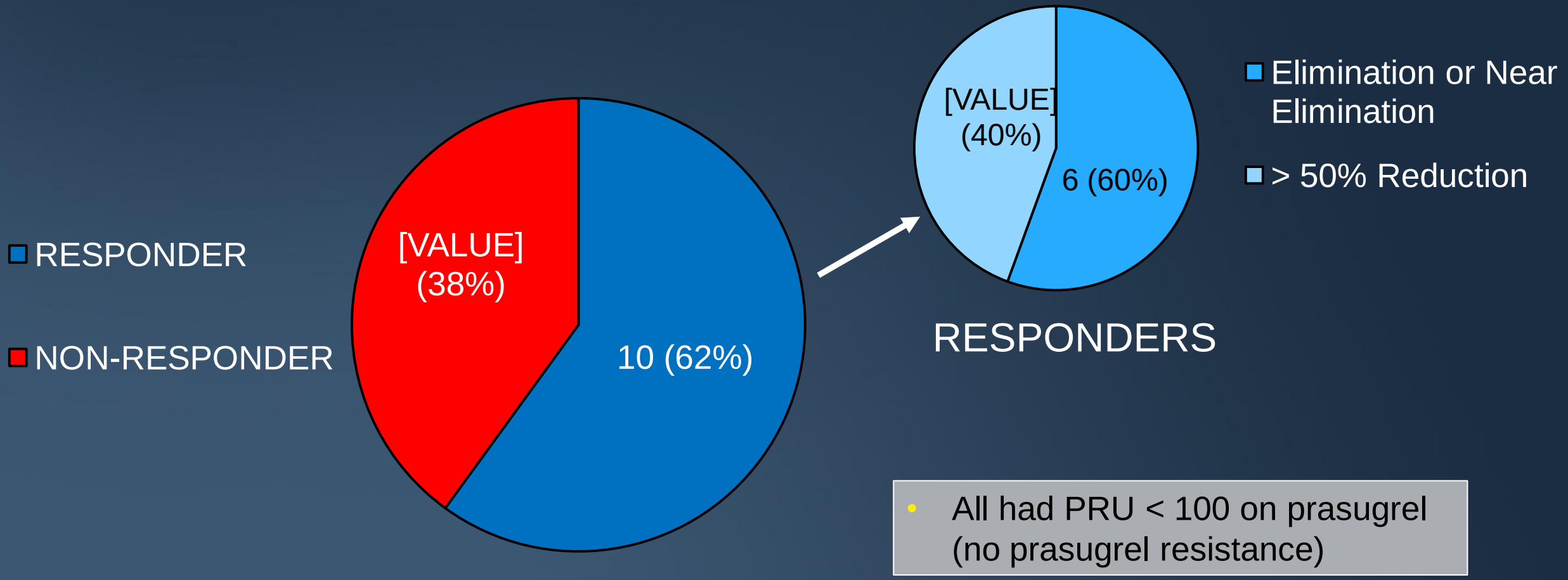
- 17 RESPONDERS, 45/56 NON-RESPONDERS were tested for adequacy of P2Y12 platelet inhibition (PRU testing)



PRU Testing:
VerifyNow®
Accriva Diagnostics,
San Diego CA

PFO – Migraine

MHA Response to Prasugrel in Clopidogrel-resistant NONRESPONDERS



- All had PRU < 100 on prasugrel (no prasugrel resistance)

PFO – Migraine

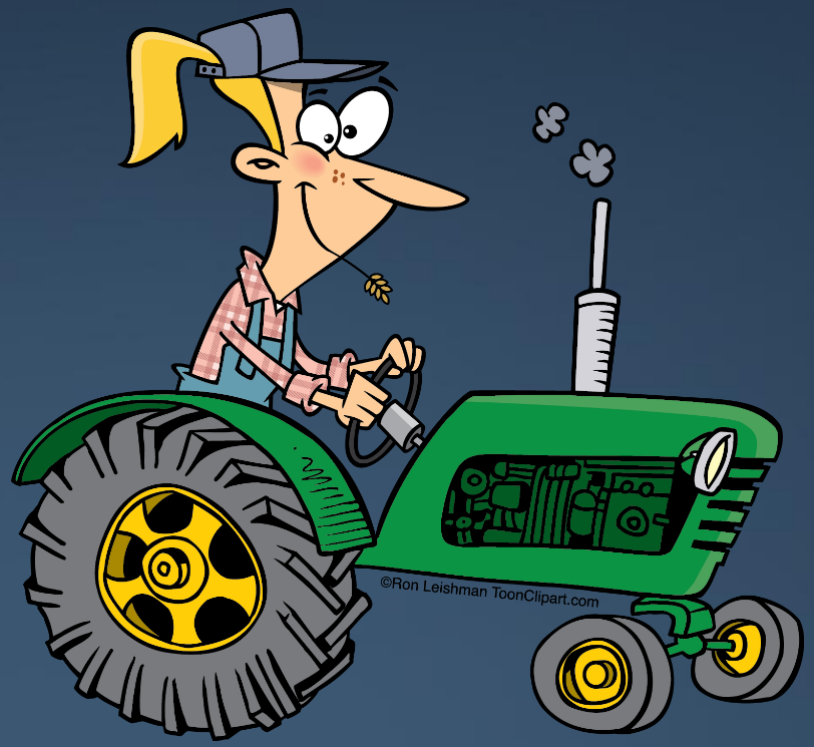
MHA Effect of Thienopyridine P2Y12 Inhibition

- Overall 65% RESPONDER rate to successful P2Y12 inhibition of 65% (89/136)
- Suggested that PFO MHAs are “platelet-mediated” and specific to P2Y12 receptor
- Suggested that the trigger substance crossing PFO is a platelet aggregation or platelet activation byproduct

TRACTOR Migraine Trial

Investigator-Initiated Grant

FDA IDE # 125,532



- Ticagrelor: non-thienopyridine agent
- Does not require metabolic agent
- 40 MHA/PFO patients
- Open-label use of ticagrelor

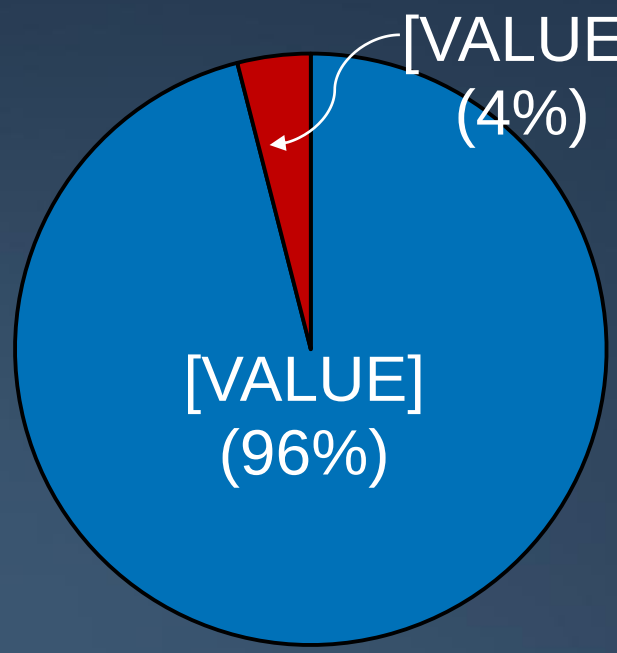
PFO – Migraine

TRACTOR Ticagrelor Trial (N = 40)

- MHA response:
  - Similar MHA benefits, confirming P2Y12 effect
  - Slightly lower RESPONDER rate (43%), slower to best response, fewer patients with complete or near complete headache elimination
  - Extracellular adenosine effect (dipyridamole)
  - More medication side effects than thienopyridines
  - Less well suited to a randomized trial

Subsequent PFO Closure/Drug Discontinuation

In Thienopyridine Responders, N = 50

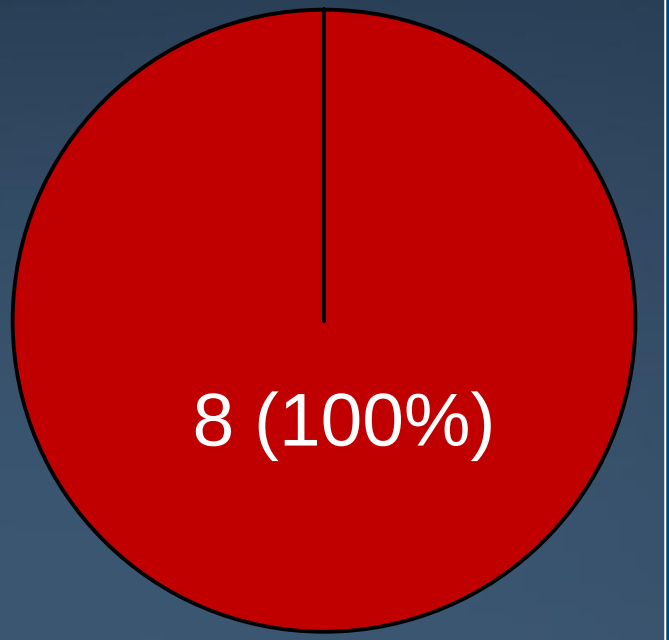


- 1 patient with moderate persistent leak of the PFO device, headaches returned after discontinuing clopidogrel
- 1 patient with resolution for a full year, then headache resumption, but not consistent with prior migraine

9 of 9 Ticagrelor responders also had elimination of MHA symptoms with PFO closure

Withdrawal of Thienopyridine

In Responders without PFO closure



- 1 patient withdrawn by referring neurologist for confirmation of drug effect
- 3 withdrawn for elective procedures (surgical/dental)
- 3 withdrawn for bruising/bleeding
- 1 withdrawn for planned pregnancy

- Typical MHA return time = 4- 5 days (the effective elimination time of the thienopyridine)
- Same return of MHA in 8/8 patients when ticagrelor discontinued

PFO – Migraine

WL Gore Sponsored RELIEF Migraine Trial

- National MHA/PFO Trial
  - Protocol submitted to the FDA for IDE
  - Recruiting sites, enrollment anticipated to begin Q1 – Q2 2019
  - Thienopyridine responsiveness will be used as final screening step prior to randomization to PFO closure or sham
  - David Dodick (Mayo Clinic) is the National Neurology PI

Conclusions

✓Our current recommendations for migraineurs:

- PFO screening for all migraine pts with:
  - Aura (40 – 50%)
  - Refractory headaches despite all Rx
  - Families with multiple members with migraine
  - Atypical aura symptoms (TIA-like)
- Please discuss with your neurologists and enroll patients in the RELIEF Trial
- Consider PFO closure in patients with positive MHA response to P2Y12 inhibition