Perspectives on PFO Closure: Clinical Trials for Stroke Prevention and Migraines

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Disclosure

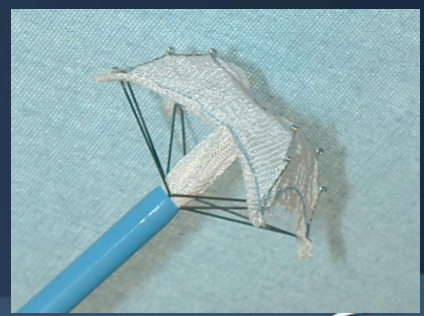
- National PI for the MIST trial-
  - No financial disclosure
- Consultant to Coaptus

The Dark side of the present clinical PFO-Stroke trials

- **Presence of off label device use continues to plague enrollment.**
- **Physician/patient bias for "closure" remains an enormous obstacle….despite limited evidence**
- **Directing "high risk" anatomy towards closure may undermine the outcomes of the clinical trials.**

And now the "good news" regarding the PFO stroke clinical trials-I

- The New CLOSURE I (NMT): New N = 900
- * Interim analysis suggests higher event rate than expected allowing;
- sample size reduction with the *NEW* N=900 (from 1600) – maintaining
- * Superiority trial design.
- * Randomization remains 1 : 1
- * Based on June 07 DSMB review, 900 "will provide an answer".
- ***With over 700 enrolled to date, end of enrollment is in sight.***



And now the "good news" regarding the stroke clinical trials-II

- The RESPECT Trial (AGA)
  - Total randomization is 500 patients
  - Present enrollment is approximately 350

  With significant increase over the last two years.

<u>This trial should fully enroll</u>

PFO Stroke Clinical trials must be completed

- Without the presence of completed prospective randomized clinical trials we will be limited in our ability:
  - Give accurate guidance to our patients
  - Insurance companies may no longer support closure of PFO's for stroke indication
  - Device iteration will be "stalled" due to limited opportunity for commercialization

Perspective on PFO closure for Migraine Relief

- Affects 28 million Americans, 75% of whom are female
- 17% of female, 5.7% of males experience at least one migraine per year
- 30-40% of migraineurs pain is preceded by aura, focal neurological deficits that involve the visual field.
- Effects persons between 25-55yrs old

Perspective on PFO closure for Migraine Relief

- Patients with prior stroke, TIA, and Hemiplegic migraine appear to respond well to PFO closure with reduction in headache burden
- It appears to be a “load” of right to left shunt that impacts outcome in Migraine patients
- Migraine with Aura responds more than those patients without Aura

What do we know to date from prior studies related to PFO-Migraine

- Patients with prior stroke, TIA, and Hemiplegic migraine are the basis for the retrospective data supporting PFO-Migraine connection (between 40-90%resolution or significant reduction in Migraine headaches
- It appears to be a “load” or burden of material that impacts outcome in Migraine patients
- Aura responds more than those patients without Aura

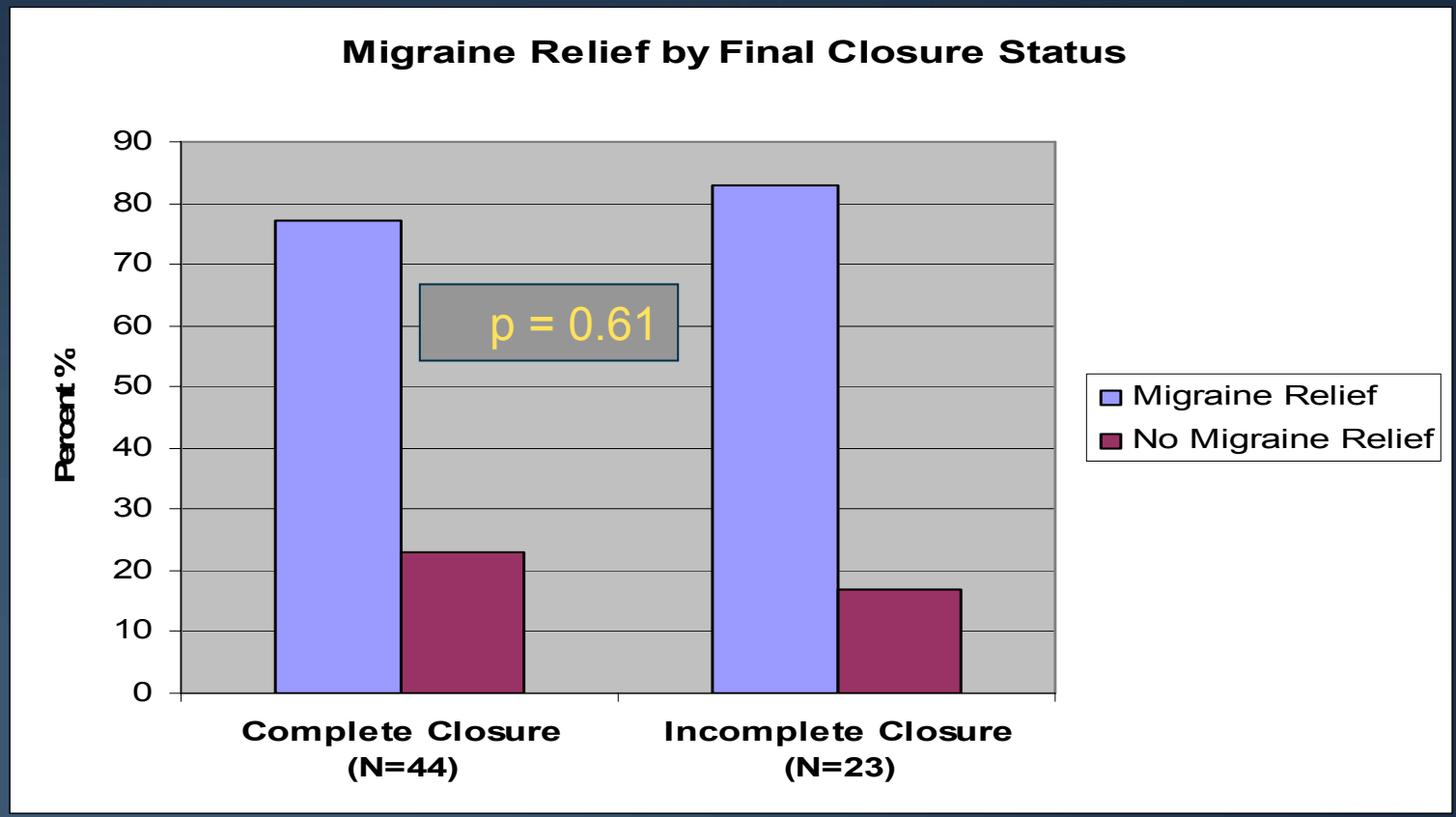
Recent Non-Randomized Studies of PFO Closure in Migraine

	Patients	Follow-up	Results
Reisman et al. JACC 2005;45:493-5	50, ± aura	37±23 weeks	56% resolution 14% ≥50% improvement
Azarbal et al. JACC 2005;45:489-92	30, ± aura	3 months	63% resolution 80% improvement
Giardini et al. Am Heart J 2006; 151:922-6	35, all + aura 71% F 41±11 yr	1.7±1.3 yr	91% had resolution or significant improvement

What do we know to date from prior studies related to PFO-Migraine

- Patients with prior stroke, TIA, and Hemiplegic migraine are the basis for the retrospective data supporting PFO-Migraine connection (between 40-60%resolution or significant reduction in Migraine headaches
- It appears to be a “load” or burden of material that impacts outcome in Migraine patients
- Aura responds more than those patients without Aura

Migraine relief occurs despite incomplete PFO closure

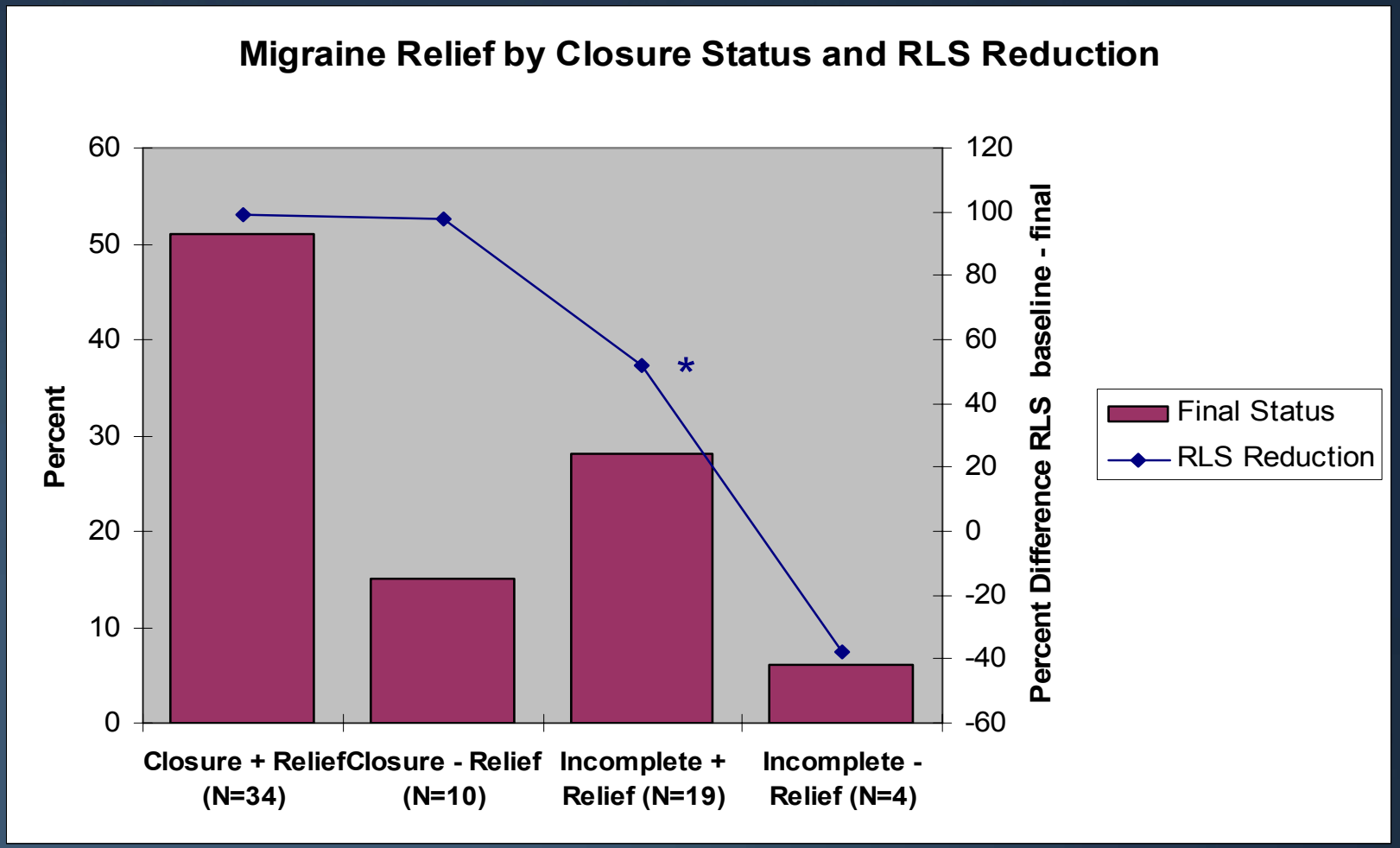


Complete closure = ≤30 ET following calibrated Valsalva/pm-TCD 12 months post closure

Migraine relief = ≥50% reduction in migraine frequency 12 months post closure

Jesurum, Fuller, Reisman *et al. in press*

Migraine Relief: Reducing Cerebral Load Below Threshold

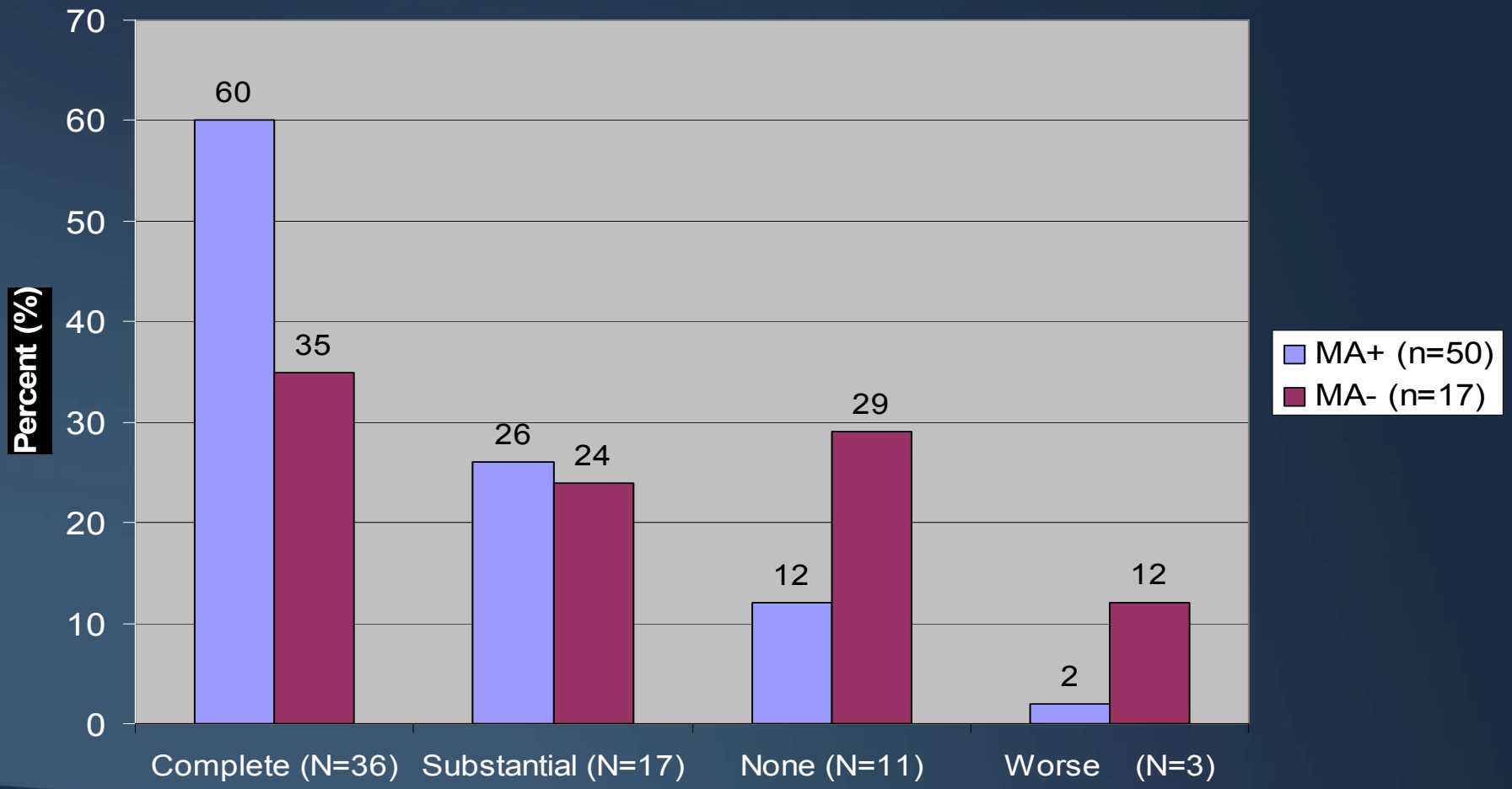


P = 0.001 vs. closure + relief; p = 0.002 vs. closure - relief
Jesurum, Fuller, *et al. JACC 2007, in review*

What do we know to date from prior studies related to PFO-Migraine

- Patients with prior stroke, TIA, and Hemiplegic migraine are the basis for the retrospective data supporting PFO-Migraine connection (between 40-60%resolution or significant reduction in Migraine headaches
- It appears to be a “load” or burden of material that impacts outcome in Migraine patients
- Aura patients may respond differently than those w/o Aura

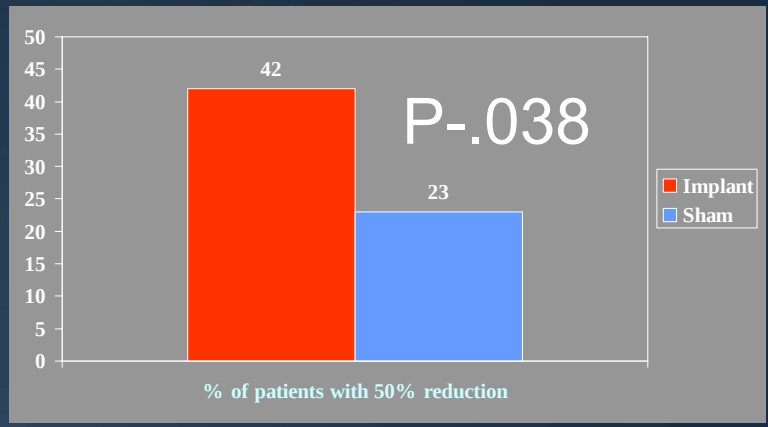
Migraineurs with Aura are 4.6 Times More Likely to have Migraine Relief Post-PFO Closure than Migraineurs without Aura (p = 0.02)

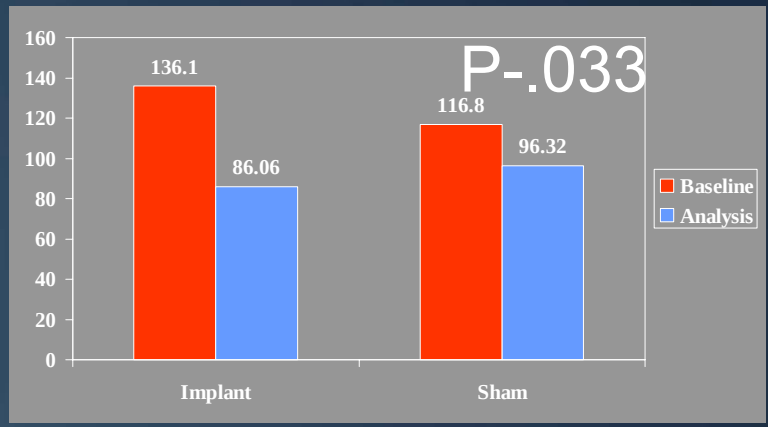


Jesurum, Fuller, et al, JACC 2007, in review

What do we know to date from prior studies related to PFO-Migraine

- That patients enrolled in the prospective MIST trial were "somehow" different then those in the retrospective trial (*NOT EXPLAINED BY PLACEBO EFFECT*), Primary endpoint was not achieved of complete resolution
- MIST secondary endpoint of 50% reduction in migraine days: Implant (I) (42%) vs. placebo (23%): as well as reduction in headache burden (frequency x duration) of 37%(I) vs. 17% placebo





White Matter abnormalities and Migraine

- **Humans- 55% of Brain is White Matter**
  - **Data suggests increased incidence of White Matter abnormalities in Migraineurs**

    - **White Matter requires significant blood flow to meet its demands and is predominantly supplied by penetrating vessels.**

    Thus White Matter should incur 50% of the strokes

    White Matter increase is associated with cognitive dysfunction, which is seen in Migraine patients

    - **They are stable or they progress, they do not *regress***

The Present ongoing Migraine Trials

- Primary endpoints are looking at "reduction" in headache frequency
- Trials are including aura alone or aura/nonaura patients
- Must be refractory to medications with frequent headaches, …*but not to many*
- Be willing to participate in a sham "arm".

Challenges of migraine studies

- Migraine type- aura, exertional, hemiplegic……
- Are there markers that can help better define the population-
    - White matter abnormalities, triggers etc
- Need greater understanding and interpretation of the initial MIST trial
- New devices being tested at same time as new indication……..