A Critical Assessment of PFO Closure for Stroke and Migraine: Why it Might or Might Not Work

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PFO Closure for Stroke and Migraine

Why it might work…..from the perspective of Pathogenesis

- The device or method must achieve reduction in stroke or headache frequency compared to the gold standard
- Must be safe
- Superior to medical therapy, as long as medical therapy does *NOT pose significant side effects or risks (i.e. bleeding, cognitive dysfunction*
- *Relatively easy technically to deploy*

Recurrent Stroke with PFO and ASA: AAN Practice Parameter*

	Relative Risk (95% CI)	Number of Studies (Level of Evidence)
Recurrent stroke with PFO alone	0.95 (0.62-1.44)	2 class I and 1 class II studies
Recurrent stroke with PFO & ASA	2.98 (1.17-7.58)	1 class I (C for younger patients)
Stroke/death medical vs. surgical or endovascular closure (PFO or ASA)	----------	None (U)

Only 4 studies met AAN's criteria for inclusion
C=possibly effective; U=unproven
*Messé SR et al. Neurology 2004;62:1042-50

Stroke Prevention: Medical Therapy vs. Transcatheter PFO Closure

Incidence of Recurrent Stroke (%)		
Study Design	Medical Therapy	PFO Closure
Meta-Analysis[1]	3.8-12/year	0-4.9/year
Retrospective[2]	24.3/4-year	8.5/4-year (p=0.05)
Retrospective[3]	13/year ASA 5.6/year warfarin	0.6/year (p<0.001)

[1] Khairy et al. Ann Intern Med 2003;139:753-60

[2] Windecker et al. J Am Coll Cardiol 2004;44:750-8

[3] Schuchlenz et al. Int J Cardiol 2005;101:77-82

Ground Rules-For why it might work

- PFO Closure *must*
  - *Reduce stroke therefore must be able to select the patients that would benefit*

Stroke and PFO

- Stroke
  - Cyptogenic stroke
    - 40% of strokes occur w/o a clear etiology
    - PFO is more common in patients with Cryptogenic stroke (45-54%) vs. those with a known cause of CVA(20%).
    - Atrial Septal Aneurysm has increase risk- this may or may not be due to increasing the size of the PFO.
  - younger population (less than 60yrs.of age)

Lamy C et al. Stroke 2002;33: 706-11.
Del Sette M et al. Cerebrovasc Dis 1998;8:327-30.
Wilmshurst P et al. Spums J 1997;27:82-3.
Agnoletti G et al. J Interven Cardiol 2005;18:393-5.
Kerut EK et al. J Am Coll Cardiol 2001;38:613-23.
Isayev Y et al. Neurology 2002;58:960-1.

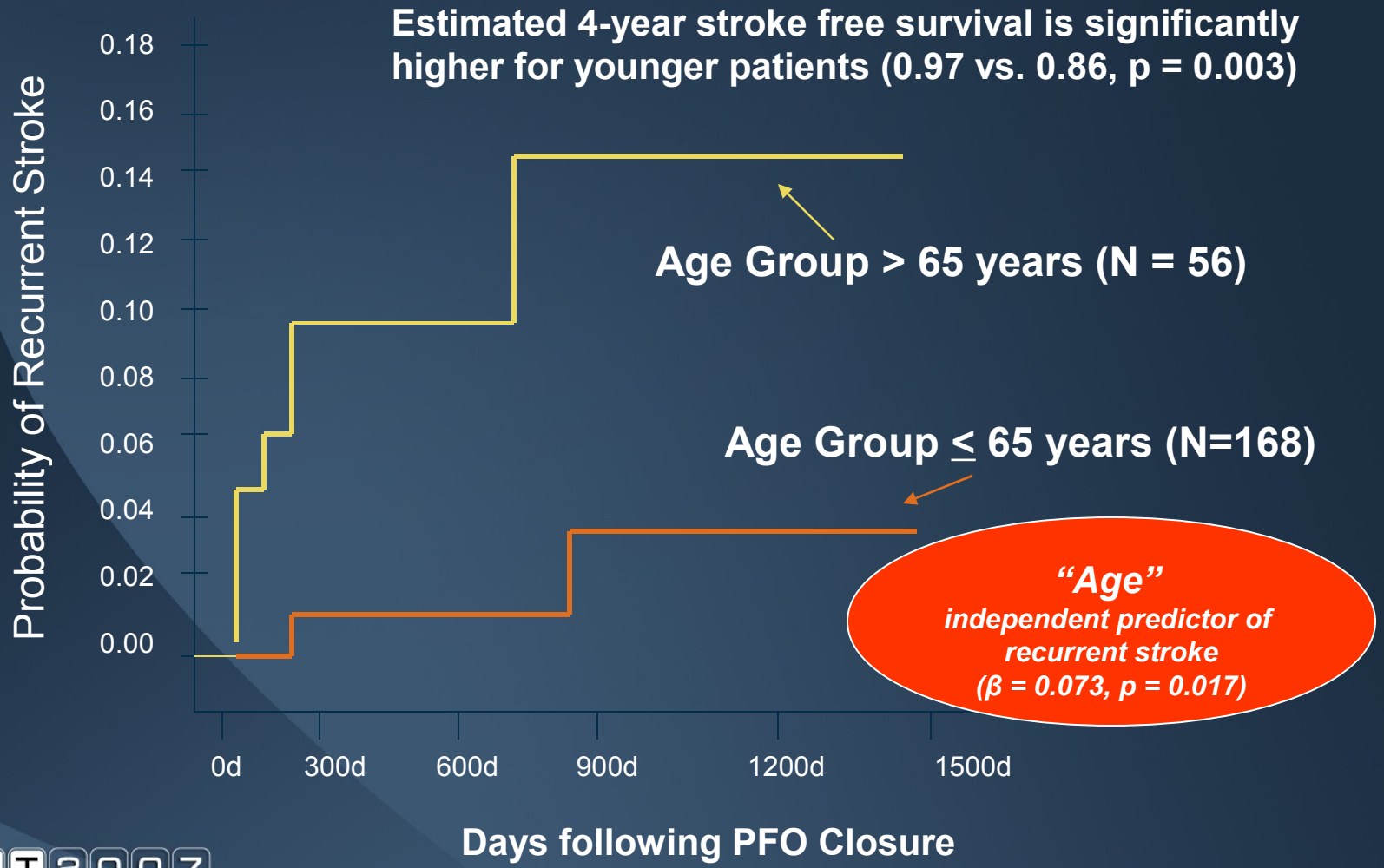
Lechat et al. N Engl J Med 1988;318:1148-1152

The source of emboli in cryptogenic stroke with PFO is unknown*

- Thrombus crossing PFO? Rarely seen
- Calf vein thrombi? Rarely screened
- Pelvic vein thrombi? Even more rarely screened
- Atrial fibrillation? Rarely documented

*Kizer JR, Devereux RB. N Engl J Med 2005;353:2361-72.

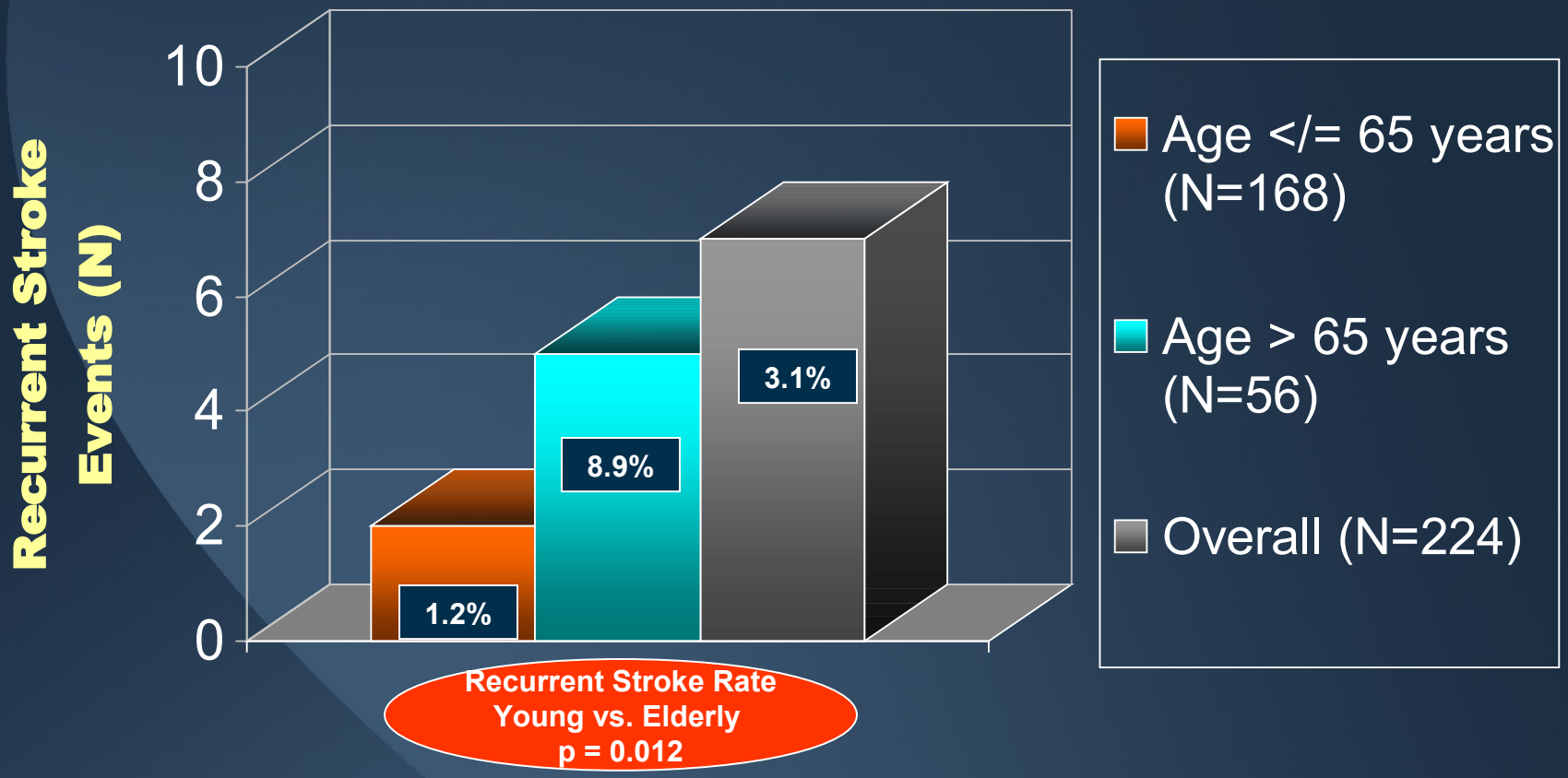
Age at Time of PFO Closure: Significant Predictor of Recurrent Stroke



Harms, Reisman, *et al. Am. J. Cardiol.* 2007;99:1312-5.

Recurrent Stroke Following Transcatheter PFO Closure: Late Results

Indication for PFO Closure: Paradoxical Cerebral Embolism



■ Risk unrelated to gender, HTN, history of multiple strokes/TIA, PFO + ASA, residual RLS

Harms V, Reisman M, Jesurum JT, et al.

After a nice long flight “Economy Class Syndrome”

338 patients admitted to Acute stroke

42 had positive travel HX (12.4%)

Frequency of PFO in PTH gr

10% in the NTH

Pts were younger (56yrs of age vs. 67 yr

NTH

PTH had fewer stroke risks

PTH stroke patients had higher frequency o

Cardioembolic stroke and more often Ischemia i

(PCA) (29%vs.6.3%)

Heckmann JG et.al Heart2006 92;1265-1268

Ground Rules-For why it might work

- **PFO Closure *must***
  - ***Reduce stroke therefore must be able to select the patients that would benefit***
  - ***Be able to handle large and small shunts as well as Atrial Septal Aneurysms***

Size of PFO or Degree of RLS as a Risk Factor for Stroke

Author	N	Results
Stone[1]	34	31% of stroke patients with lg RLS (≥ 20 bubbles on TEE) had recurrent events vs. 0 with sm shunts (P=0.03)
Serena[2]	208+ 100	Lg RLS on TCD seen in patients with cryptogenic stroke> known stroke cause (P<0.0001) or controls (P<0.001)
Schuchlenz[3]	244	Patients with TIA or stroke had larger PFO size than controls (P<0.0001)
Homma[4]	630	No difference in 2-yr event rates for stroke patients with lg or sm PFO
Anzola[5]	59	Amount of RLS only independent variable associated with recurrent stroke
Mesa[6]	90	91% of stroke patients with PFO had RLS at rest vs. 57% of controls with PFO (P<0.05)

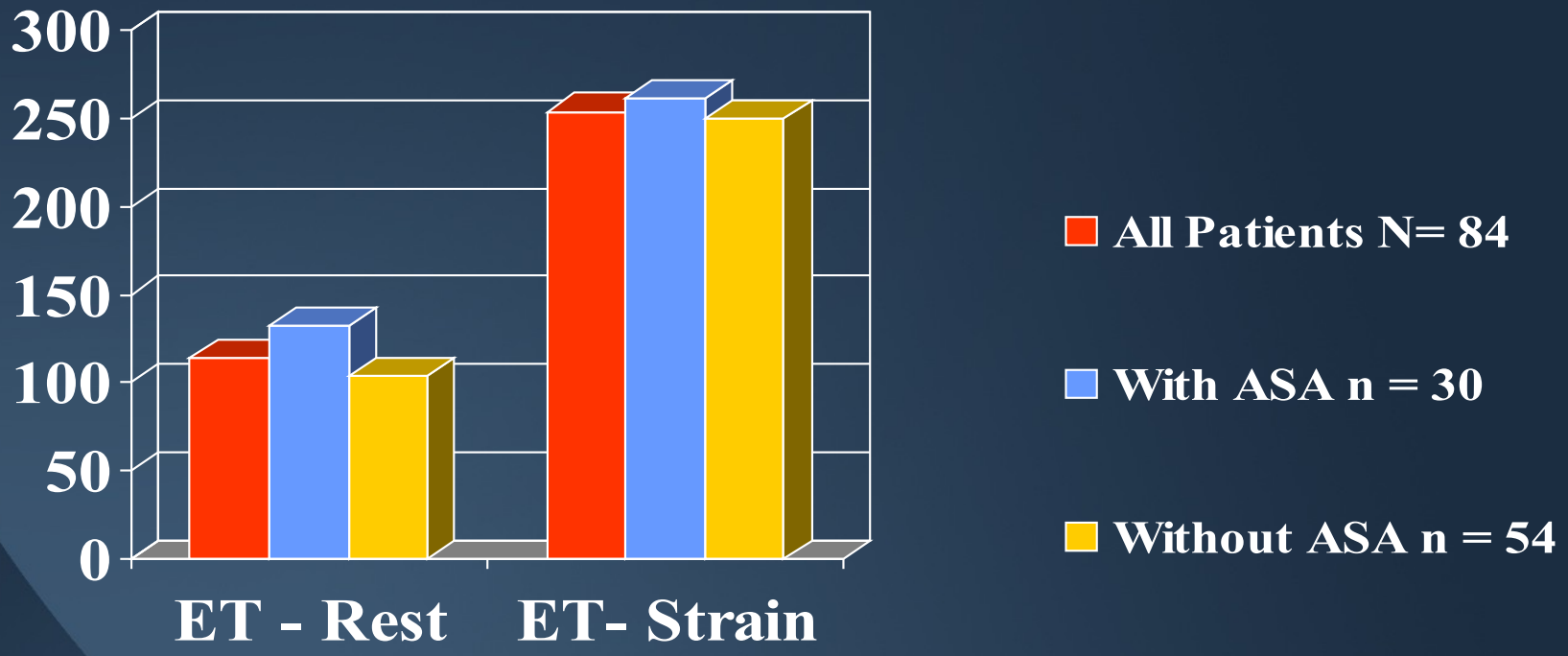
[1]Am Heart J 1996;31:158-61
[2]Stroke 1998;29:1322-8.
[3]Am J Med 2000;109:456-62
[4]Circulation 2002;105:2625-31
[5]Eur J Neurol 2003;10:129-35
[6]Rev Esp Cardiol 2003;56:662-8

Risk of Recurrent Stroke with PFO and ASA

Author, year Design Age, years	Results
Mas et al., 2001[1] Prospective ≤55	Hazard ratio for recurrent stroke (4 year follow-up): 15.2 (1.8-28.6)
Homma et al., 2002[2] Prospective (PICSS) 59.0±12.2	No significant difference in recurrent stroke rates between PFO and PFO+ASA (14.5% vs. 15.9%, respectively)

1. N Engl J Med 2001;345:1740-6.
2. Circulation 2002;105:2625-31.

Cryptogenic Stroke Patients With PFO

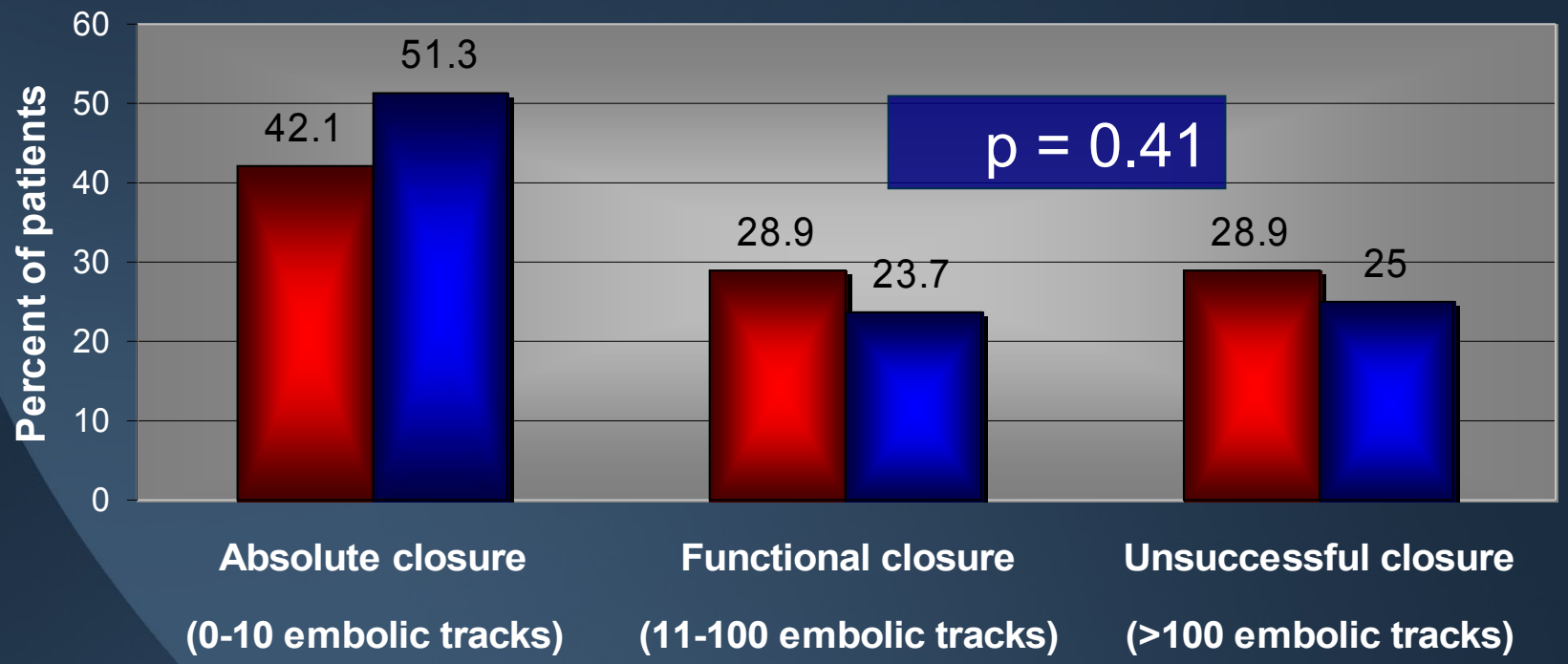


Embolic Tracks pm - TCD

No significant group differences ($p < .05$)

Jesurum, Reisman et al., Stroke 2004 35(1): 237

Final Closure Status
PFO + ASA vs Isolated PFO



† pm-TCD calibrated Valsalva

Jesurum, Reisman, et al., Stroke 2004 35(1): 257

Ground Rules-For why it might work

- **PFO Closure *must***
  - ***Reduce stroke therefore must be able to select the patients that would benefit***
  - ***Be able to handle large and small shunts as well as Atrial Septal Aneurysms***
  - ***Does the device indeed have to "close the hole ???***

Patients with large residual right-to-left shunt (RLS)* at ≥6 months post-PFO closure

	Patients with large residual RLS N=19	Patients without large residual RLS N=150	P value
Balloon stretch diameter, mm	15.9 ± 3.0	13.1 ± 3.6	0.001
Septal tunnel length, mm	10.2 ± 2.9	11.1 ± 3.3	0.25
Presence of atrial septal aneurysm	9 (47.4%)	46 (30.7%)	0.19
Device size > 33 mm	14 (73.7%)	35 (23.3%)	<0.0001

* >200 embolic tracks after calibrated Valsalva on pm-TCD
Fuller CJ, Jesurum JT, Spencer MP, et al. International Stroke Conference 2006.

Large residual RLS after PFO Closure does NOT mean more adverse outcomes

	Patients with large residual RLS N=19	Patients without large residual RLS N=150	P value
Recurrent Stroke	1 (5.3%)	5 (3.3%)	0.52
All Cause Death	1 (5.3%)	2 (1.4%)	0.30
Surgical Device Explantation	1 (5.3%)	1 (0.7%)	0.21

Fuller CJ, Jesurum JT, Spencer MP, Reisman M,et al. Stroke 2006

Why may these be true….that complete closure is not required

- Structure of “clamshell device”
- Disruption of the tunnel confers the benefit
- Simply a result of a low event rate

This may have significant implications for second generation devices…

Why it might not work

Complications of Device placement

Occur in 6-10% of patients

- device embolization or fracture
- air embolism
- vascular complications
- device-related thrombus
- cardiac tamponade
- death

Windecker et.al JACC 2004;44;750-58
Khairy P et. al Ann Int.Med.2003;139;753-60

complete PFO closure does NOT mean freedom from adverse outcomes

- Anzola et al. [1]: TIA occurred in one patient at 3 weeks post-procedure who had no RLS on TCD evaluation at one month
- Hung et al. [2]: One patient had recurrent stroke 6 months post closure; follow-up TEE showed no RLS
- Braun et al. [3]: 5/6 patients who had TIA within 6 months of PFO closure had no RLS on TEE
- Jesurum et al.[4]: One patient who had stroke 72 days after closure had complete closure based on pm-TCD at 76 days

1. Stroke 2004;35:2140-44.
2. J Am Coll Cardiol 2000;35:1311-6.
3. J Am Coll Cardiol 2002;39:2019-25.
4. Jesurum et al., unpublished data

Might closure devices themselves lead to adverse outcomes?

- 48 yo F with stroke 2 months after implantation with CardioSEAL had 2 large pedunculated thrombi on left atrial side of device despite post-implantation aspirin therapy[1]
- Thrombi formed more frequently on CardioSEAL device (22%) than Amplatzer (0%) 1 month after implantation (p=0.02)[2]
- 38 yo M developed pericarditis, atrial fibrillation, and had more frequent migraines with aura due to nickel hypersensitivity from Amplatzer occluder[3]

1. Schuchlenz HW et al. J Thorac Cardiovasc Surg 2005;130:591-2.
2. Anzai H et al. Am J Cardiol 2004;93:426-31.
3. Lai DW et al. Catheter Cardiovasc Interv 2005;66:424-6.

The Question: Who will benefit (might work)

that will be based on identifying the appropriate patient selection

- For Stroke
  - risk factors
    - absence of Atherosclerotic disease, age less than 60
    - Coagulopathy
      - Intrinsic vs. “extrinsic”
    - Travel history
  - Type of stroke
    - Embolic stroke- predominantly posterior circulation
    - Size/distribution of defect on MRI-single or both hemispheres, presence or absence of WMA’s
    - TIA-
      - Differentiation from Migraine, Multiple Sclerosis, other potential confounding medical illnesses.

Will the clinical trials for stroke give us answers.

- Both Clinical trials will be completed
  - Closure one -900 patients
  - RESPECT- 500 patients
- With off label use concerns about biased entry and thus not appropriate guidance for the clinician
- The often concomitant use of antiplatelet therapy prior and after the procedure may confer benefit.

Migraine assessment

- **Migraine studies**
  - **Early encouraging data was often on patients with neurologic events to the gray matter (TIA, stroke, Hemiplegic migraine)**
  - **Trials presently following "*MIST*"** guidance, which achieved secondary endpoint of reduction in headache .
    - *Which would be acceptable for a drug primary endpoint*
  - Subgroups: Aura vs No aura – who derives most benefit?

Migraine –who might benefit

- Patients with larger PFO's

result	total #	%
total studied	432	100
small shunts (atrial and pulmonary)	72	16.7
large pulmonary shunt	22	5.1
ASD	3	0.7
large shunts (all types)	188	43.5
large PFO	163	37.7
total shunts	260	60.2

The Question: Who will benefit

that will be based on patient selection

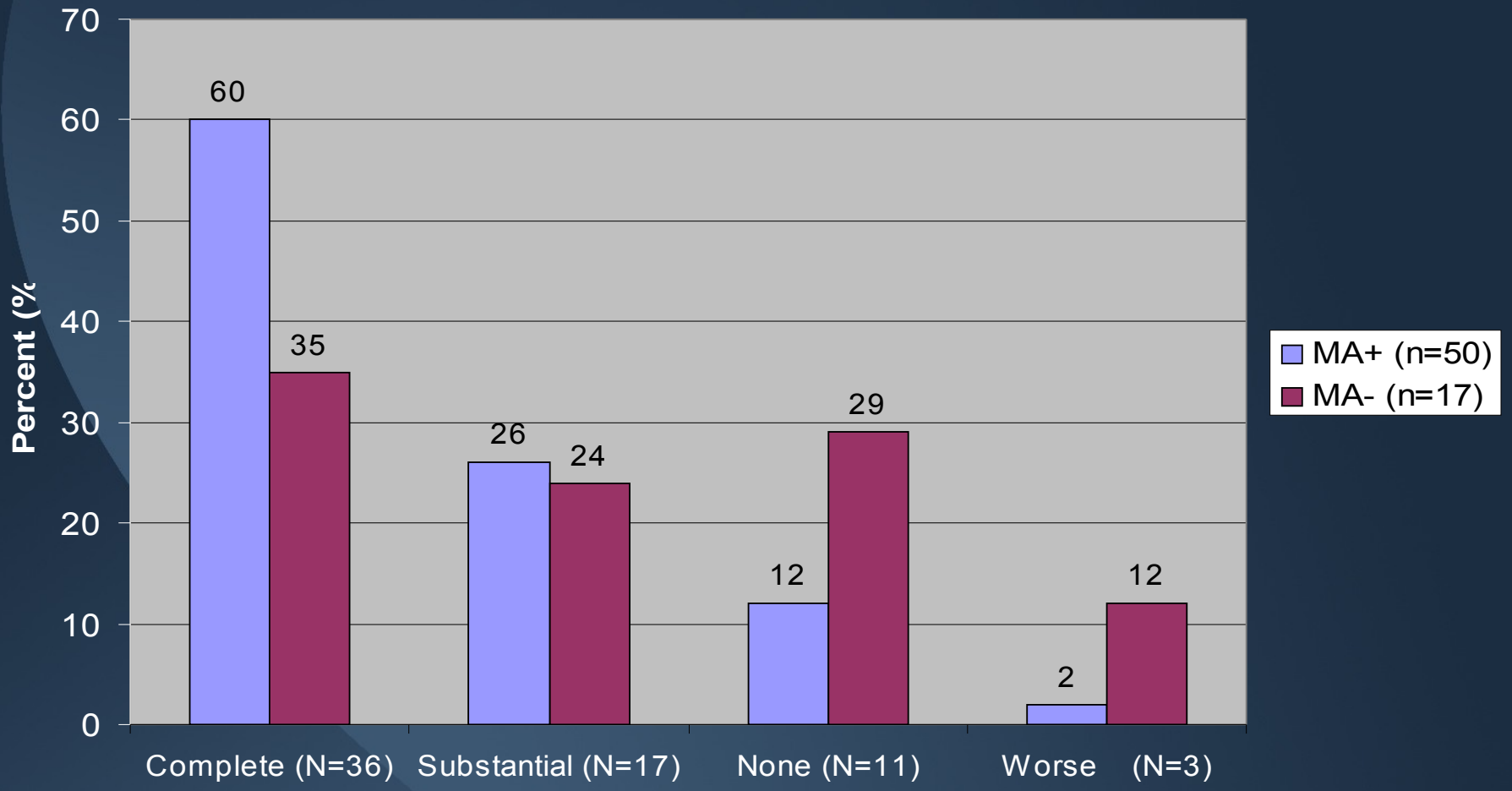
Migraine

Aura vs. absence of aura

Headache reduction has been seen in both groups

Aura is "attractive" based on similarity to TIA/stroke

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

The Question: Who will benefit

that will be based on patient selection

Migraine

Neuro

- Presence or absence of aura
- The question of White Matter Abnormalities
- The question of prior stroke/TIA/DCI

White Matter

- **Data suggests increased incidence of White Matter abnormalities**

In Migraine patients compared to the general population

- **12% of mice brain WM, Humans 55%**
  - **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

The Question: Who will benefit
that will be based on patient selection

Migraine

Neuro

- **Presence or absence of aura**
- **The question of White Matter Abnormalities**
- **The question of prior stroke/TIA/DCI/exertional migraine or hemiplegic migraine**
  - **The majority of "positive" PFO closure data comes from this group of migraine patients.**

Conclusion

- Stroke
  - Clinical trials will be helpful
  - Device iteration will further make the procedure more efficacious and safe
- Migraine
  - Pathogenesis needs to be identified
  - Clinical trials of PFO closure as well as studies looking at PFO and migraine type will be helpful in identifying the population to optimally benefit.