# FDA approval for a PFO closure device – now what?


## David Thaler, MD, PhD, FAHA

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***Professor of Neurology*, Tufts University School of Medicine**
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***October 26, 2017***

# Disclosure Statement of Financial Interest

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

| Affiliation/Financial Relationship | Company |
| --- | --- |
| • Research Support for clinical trial | • WL Gore Associates |
| • Research Support for clinical trial | • Abbott (prev St. Jude Medical) |
| • Consulting Fees for RESPECT/ACP Steering Committees | • Abbott (prev St. Jude Medical) |

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager, Regulatory Affairs
5050 Nathan Lane North
Plymouth, Minnesota 55442

Re: P120021
Trade/Device Name: AMPLATZER PFO Occluder
Filed: November 30, 2012

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

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Patient selection

Patient selection

Patient selection

Patient selection

Patient selection

# Patient selection!

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# 3 dimensions of “risk”

1) Who has the disease
2) Who has the disease and has a high risk of recurrence
3) Who is likely to benefit from treatment

# Is it a stroke?

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**Is it a stroke? Ask a neurologist.**

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# Stroke mimics and chameleons

| | Stroke like presentation | Atypical presentation |
|---|---|---|
| True stroke | Stroke | |
| Not a stroke | MIMIC | |

***Lancet Neurol* 2011, 10: 550-60**

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# Stroke mimics

- Migraine
- Seizure
- Subdural hematoma
- Tumor
- Syncope
- Cardiac arrhythmia
- Panic attack
- Hypoglycemia
- Demyelinating disease
- Amyloid angiopathy
- Brain abscess
- Encephalitis

# Stroke mimics and chameleons

| | Stroke like presentation | Atypical presentation |
|---|---|---|
| True stroke | Stroke | CHAMELEON |
| Not a stroke | MIMIC | Non-stroke |

***Lancet Neurol* 2011, 10: 550-60**

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# Stroke chameleons

| Condition | Prevalence |
|---|---|
| Altered mental status | 31% |
| Syncope | 16% |
| Hypertensive emergency | 13% |
| Systemic infection | 11% |
| Suspected acute coronary syndrome | 10% |
| Other (seizure, peripheral vertigo, cord compression, myasthenia gravis, Bell palsy, migraine, hypoglycemia) | 20% |

***J Stroke Cerebrovasc Dis* 2014 23: 374-378**

# Stroke mimics and chameleons

| | Stroke like presentation | Atypical presentation |
|---|---|---|
| True stroke | Stroke | CHAMELEON |
| Not a stroke | MIMIC | Non-stroke |

***Lancet Neurol* 2011, 10: 550-60**

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# Is it a cryptogenic stroke?

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**Is it a cryptogenic stroke? Ask a neurologist.**

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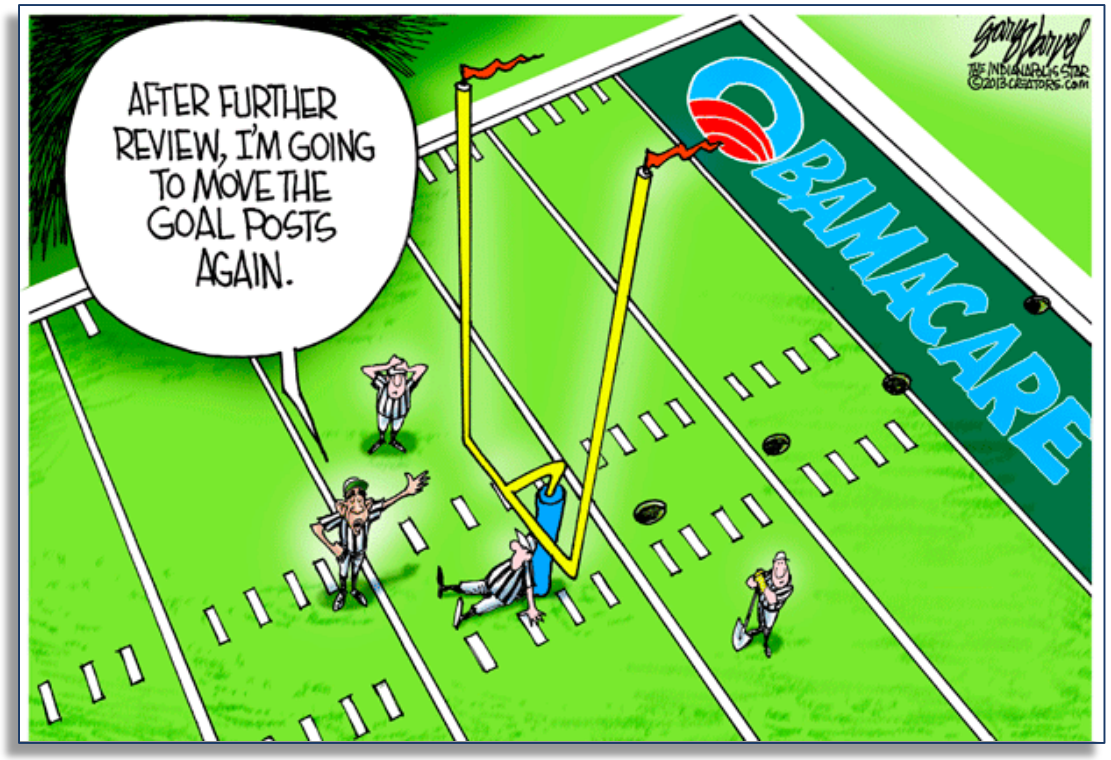
# Cryptogenic stroke c. 2003 ≇ CS c. 2017

- Atrial fibrillation
- Small vessel disease
- Substenotic atheroembolism
- Aortic-source embolism



# What is the underlying mechanism?

*"Stroke is an observation not a diagnosis."*

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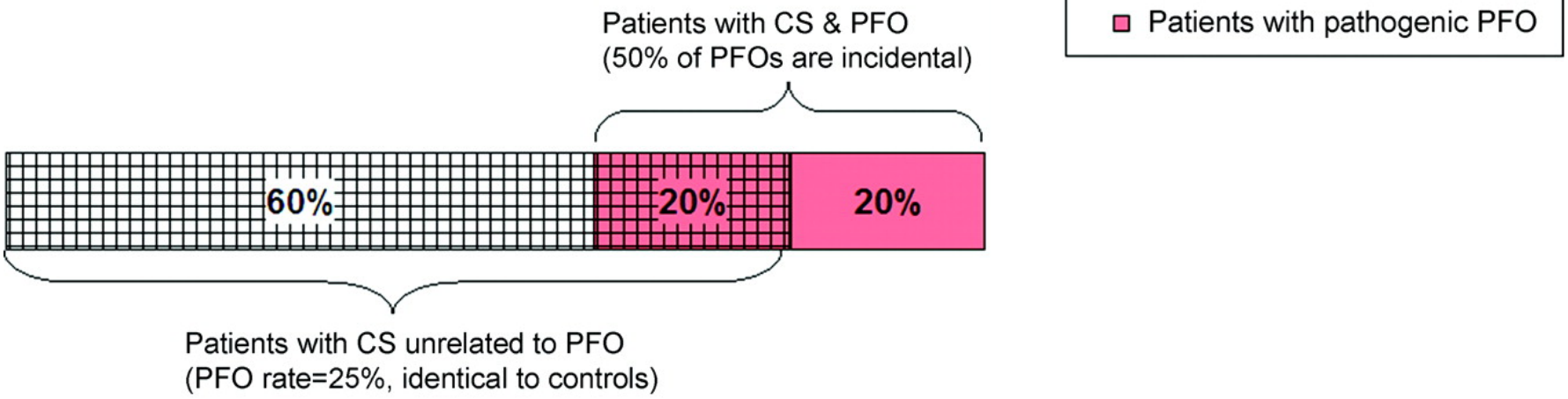
# Proportion of CS patients with incidental PFO

**Case A**
**Proportion of CS patients with PFO: 40%**
**Proportion of controls with PFO: 25%**




$$\text{Probability PFO is incidental in CS cases} = \frac{\text{Prevalence of PFO in controls}*(1-\text{Prevalence of PFO in CS cases})}{\text{Prevalence of PFO in CS cases}*(1-\text{Prevalence of PFO in controls})}$$

Alsheikh-Ali, A. A. et al. Stroke 2009;40:2349-2355

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# Can RoPE help us tell who has had a "PFO stroke?"


*Yes, probably*

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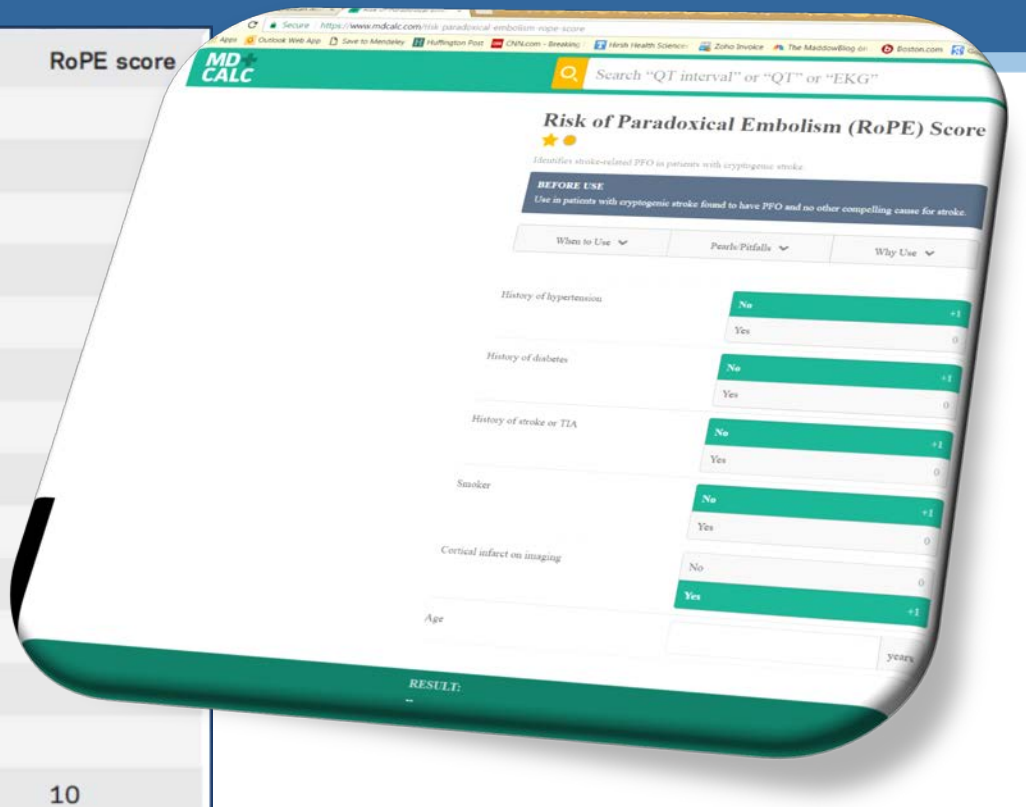
# The RoPE Score Calculator

| Characteristic | Points | RoPE score |
|---|---|---|
| No history of hypertension | 1 | |
| No history of diabetes | 1 | |
| No history of stroke or TIA | 1 | |
| Nonsmoker | 1 | |
| Cortical infarct on imaging | 1 | |
| Age, y | | |
| 18-29 | 5 | |
| 30-39 | 4 | |
| 40-49 | 3 | |
| 50-59 | 2 | |
| 60-69 | 1 | |
| ≥70 | 0 | |
| Total score (sum of individual points) | | |
| Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct) | | 10 |
| Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct) | | 0 |




https://www.mdcalc.com/risk-paradoxical-embolism-rope-score

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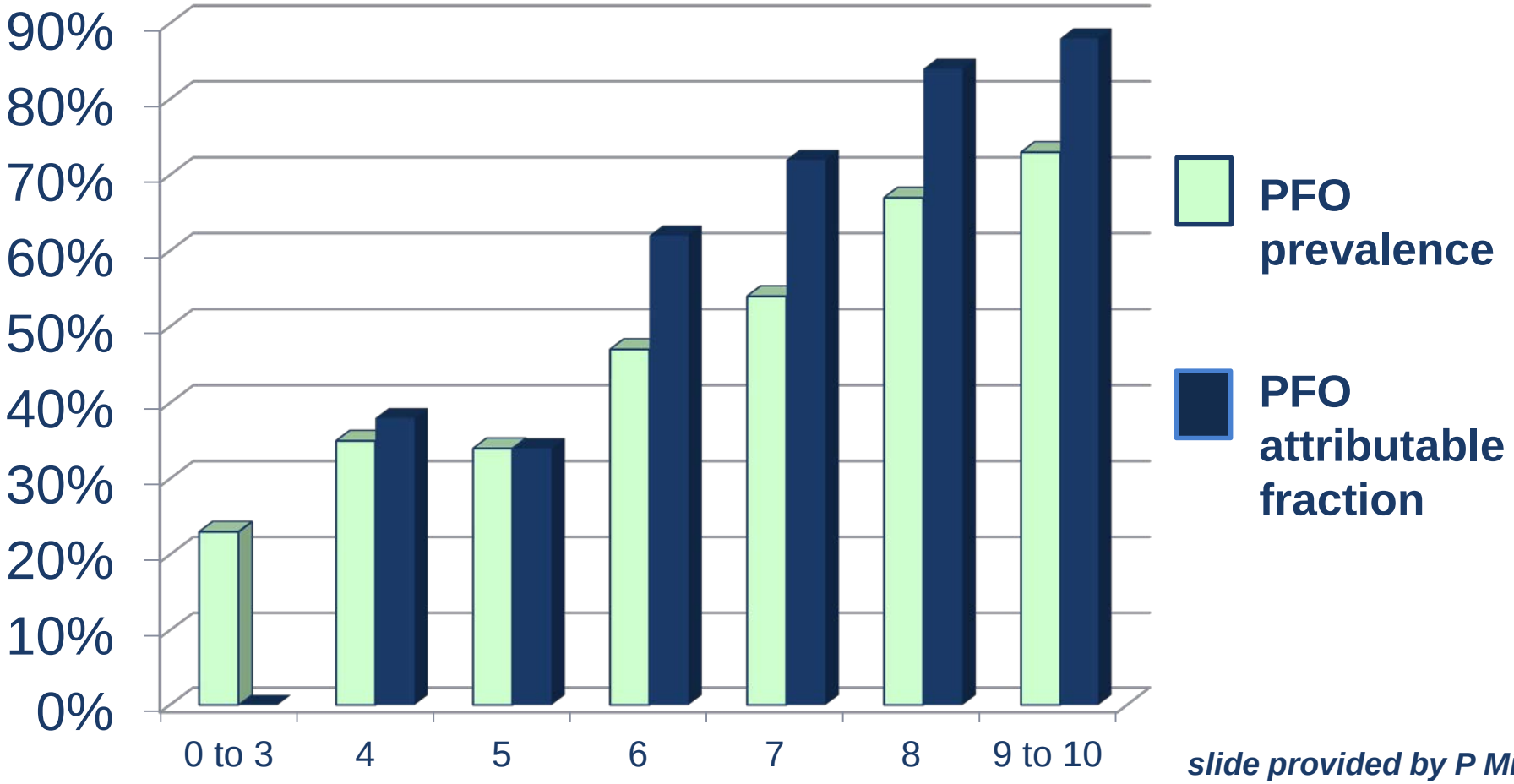
# Increasing RoPE score
## → Increasing PFO prevalence, and
## → Increasing PFO attributable fraction




*slide provided by P Miche*

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# Misconception

**If *you know the RoPE Score then you know who has a "high risk" PFO***

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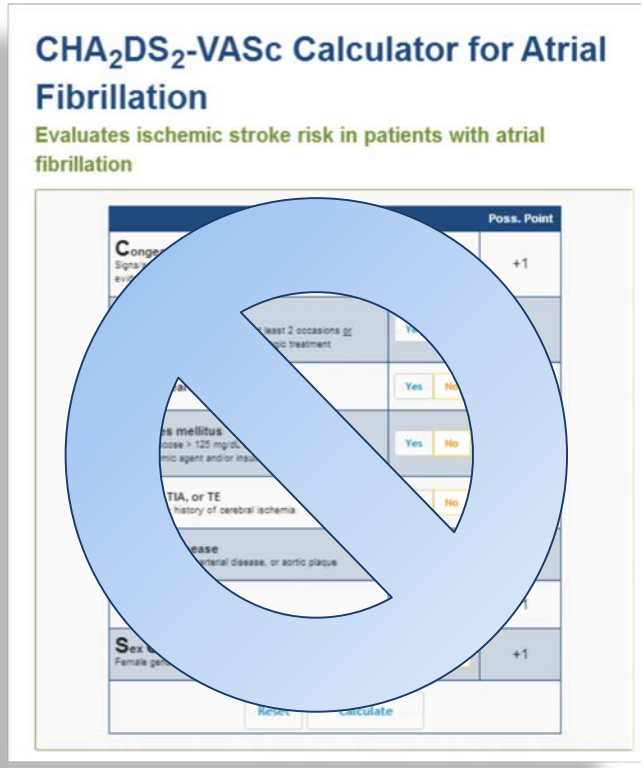
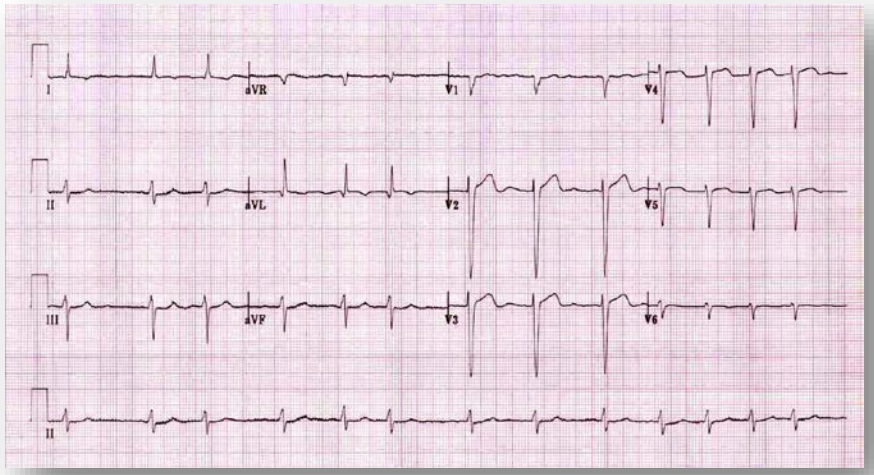
# Analogy with atrial fibrillation diagnosis/risk stratification

RoPE ≠ $CHA_2DS_2$-VASc




RoPE ~ EKG/Holter monitor

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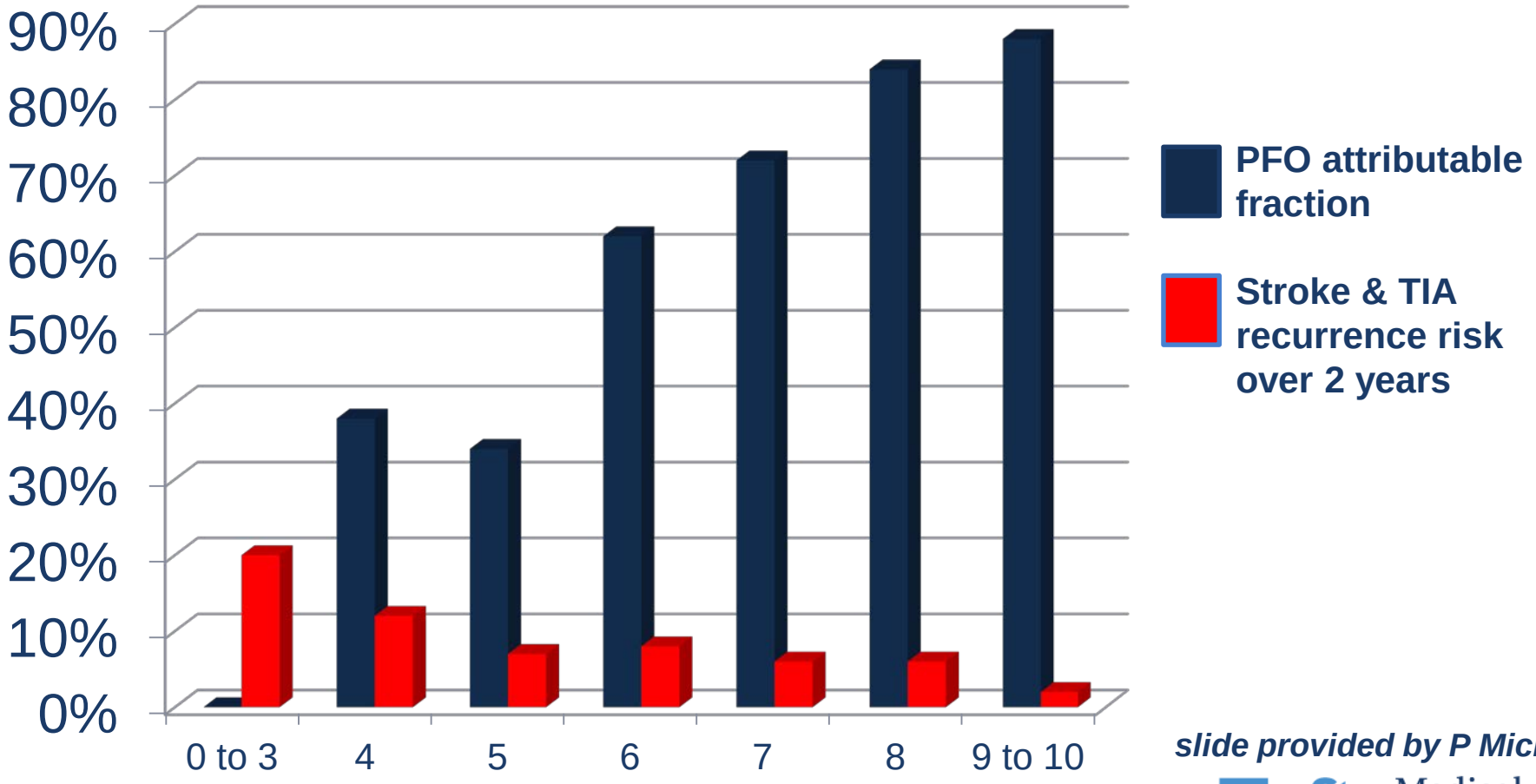
# Increasing RoPE score
## → Increasing PFO attributable fraction
## → Decreasing TIA/Stroke recurrence risk




*slide provided by P Miche*

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**So, are there baseline variables that predict recurrent stroke and do those predictors differ by RoPE Score?**

*Yes (but not what we thought)*

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Recurrent stroke predictors differ in medically treated patients with pathogenic vs other PFOs

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ABSTRACT

**Objective:** To examine predictors of stroke recurrence in patients with a high vs a low likelihood of having an incidental patent foramen ovale (PFO) as defined by the Risk of Paradoxical Embolism (RoPE) score.

**Methods:** Patients in the RoPE database with cryptogenic stroke (CS) and PFO were classified as having a probable PFO-related stroke (RoPE score of >6, n = 647) and others (RoPE score of ≤6 points, n = 677). We tested 15 clinical, 5 radiologic, and 3 echocardiographic variables for associations with stroke recurrence using Cox survival models with component database as a stratification factor. An interaction with RoPE score was checked for the variables that were significant.

**Results:** Follow-up was available for 92%, 79%, and 57% at 1, 2, and 3 years. Overall, a higher recurrence risk was associated with an index TIA. For all other predictors, effects were significantly different in the 2 RoPE score categories. For the low RoPE score group, but not the high RoPE score group, older age and antiplatelet (vs warfarin) treatment predicted recurrence. Conversely, echocardiographic features (septal hypermobility and a small shunt) and a prior (clinical) stroke/TIA were significant predictors in the high but not low RoPE score group.

**Conclusion:** Predictors of recurrence differ when PFO relatedness is classified by the RoPE score, suggesting that patients with CS and PFO form a heterogeneous group with different stroke mechanisms. Echocardiographic features were only associated with recurrence in the high RoPE score group. **Neurology® 2014;83:1–6**

GLOSSARY

**CS** = cryptogenic stroke; **HR** = hazard ratio; **PFO** = patent foramen ovale; **PH** = proportional hazard; **RoPE** = Risk of Paradoxical Embolism; **TEE** = transesophageal echocardiography.

Randomized trials comparing endovascular patent foramen ovale (PFO) closure with antithrom-

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**Table 2** Adjusted hazard ratios from multivariable model of recurrent stroke/TIA

| Variable | Adjusted hazard ratio (95% confidence interval) | | Interaction *p* value[a] |
|---|---|---|---|
| | Point score ≤6 (raw event rate: 87/677 = 13%) | Point score >6 (raw event rate: 35/647 = 5%) | |
| Age (linear), hazard ratio per 10-y increase | 1.47 (1.18–1.83)[b] | 0.83 (0.57–1.20) | 0.0083 |
| Treated with antiplatelets | 1.69 (1.05–2.74)[b] | 0.74 (0.37–1.48) | 0.0554 |
| History of prior stroke or TIA | 1.58 (0.89–2.44) | 3.79 (1.43–10.09)[b] | 0.0911 |
| Small shunt | 1.29 (0.82–2.03) | 3.26 (1.59–6.67)[b] | 0.0306 |
| Hypermobile interatrial septum | 0.83 (0.49–1.42) | 2.31 (1.05–5.05)[b] | 0.0350 |
| | All subjects (raw event rate: 122/1,324 [9%]) | | |
| Incident TIA (vs stroke) | 1.69 (1.05–2.74)[b] | | |

Hazard ratio >1 indicates positive association with outcome.

[a] If the *p* value of the variable or the interaction with the categorized point score (≤6, >6) was ≤0.10, then the interaction term was left in the model and hazard ratios were estimated separately for the point score subgroups. If the interaction *p* value was ≥0.10, then the interaction term was not included in the model and a single hazard ratio for the variable was estimated.

[b] 95% Confidence interval for hazard ratio is above or below 1 (with a corresponding *p* value of ≤0.05).

*Neurology* 2014 83: 1-6

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# Shunt size conundrum?

It's either wrong...

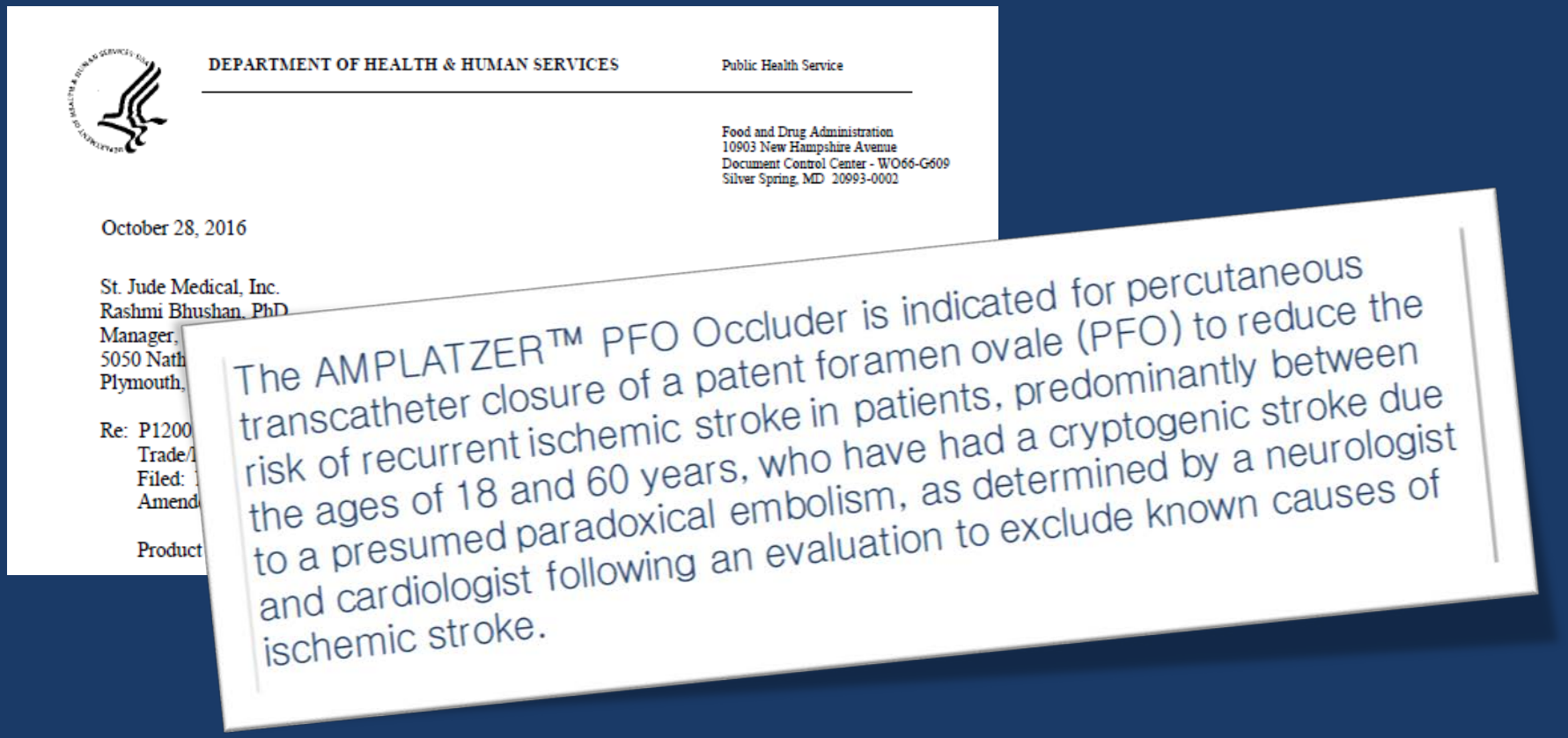
- Unreliable variable? → should revert to null
- Type 1 error
- Biases in the dataset – "informative censoring"
- Poor primary data in RoPE databases

… or right.

- More than 1 PFO-related stroke mechanism?

# Treatment options for CS+PFO

- All guideline directed secondary prevention recommendations
- Antithrombotic Rx
  - Antiplatelet
  - Anticoagulation
- PFO specific Rx
  - Endovascular PFO closure
  - Direct surgical closure




# FDA language doesn't mention subgroups…

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## Do we know who benefits from closure?

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## Do we know who benefits from closure? And who doesn't?

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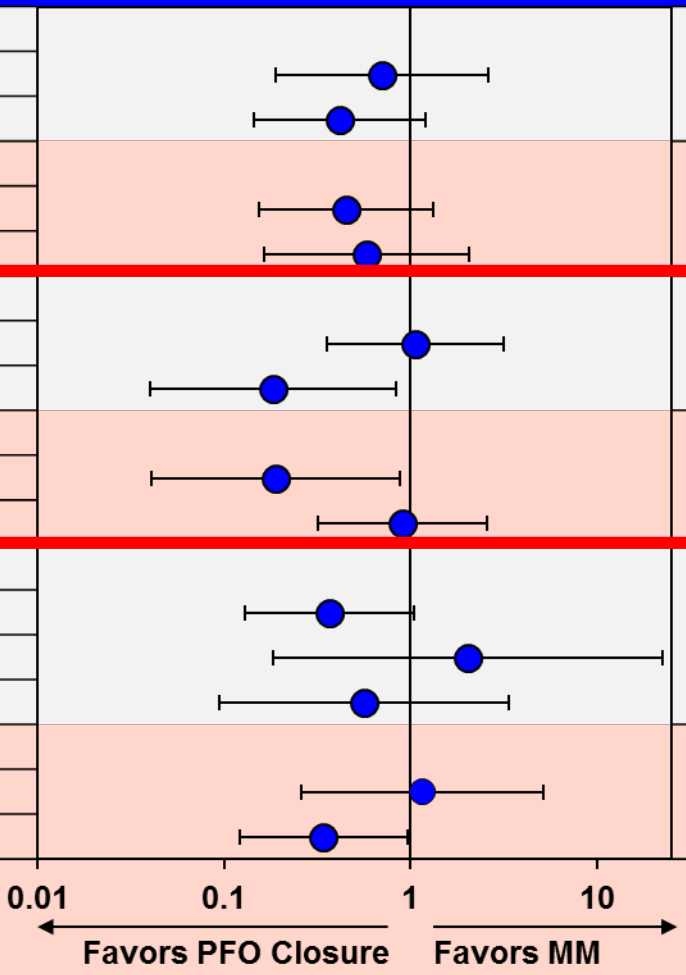
# Subpopulation Differential Treatment Effect: RESPECT

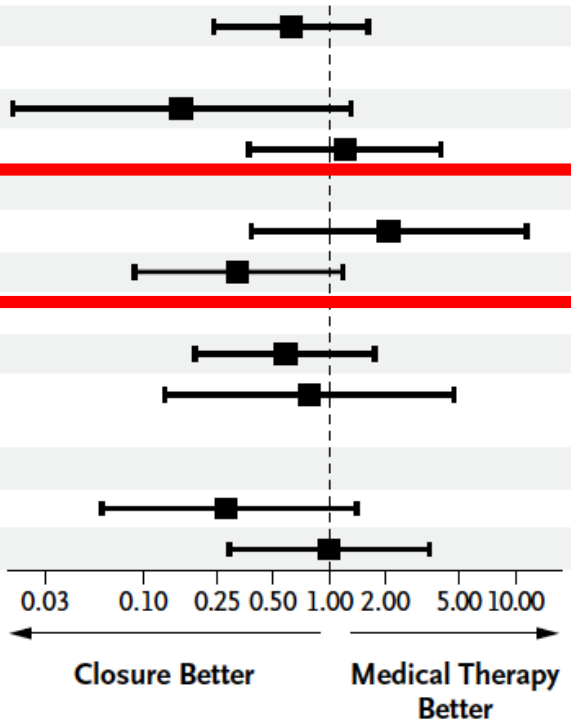
| | PFO Closure n (%) | Medical Management n (%) | Interaction P-Value |
|---|---|---|---|
| **Age** | | | |
| 18-45 | 4 (1.7%) | 5 (2.4%) | **0.53** |
| 46-60 | 5 (1.9%) | 11 (4.1%) | |
| **Sex** | | | |
| Male | 5 (1.9%) | 10 (3.7%) | **0.74** |
| Female | 4 (1.7%) | 6 (2.8%) | |
| **Shunt Size** | | | |
| None, trace or Moderate | 7 (2.8%) | 6 (2.5%) | **0.07** |
| Substantial (Grade 3) | 2 (0.8%) | 10 (4.3%) | |
| **Atrial Septal Aneurysm** | | | |
| Present | 2 (1.1%) | 9 (5.3%) | **0.10** |
| Absent | 7 (2.2%) | 7 (2.2%) | |
| **Index Infarct Topography** | | | |
| Superficial | 5 (1.8%) | 12 (4.5%) | **0.39** |
| Small Deep | 2 (3.5%) | 1 (1.4%) | |
| Other | 2 (1.3%) | 3 (2.2%) | |
| **Planned Medical Regimen** | | | |
| Anticoagulant | 4 (3.0%) | 3 (2.5%) | **0.19** |
| Antiplatelet | 5 (1.4%) | 13 (3.6%) | |




**Primary Assessment**

# PC Trial: Subpopulation Differential Treatment Effect

| Subgroup | PFO Closure | Medical Therapy | Hazard Ratio (95% CI) | P Value for Interaction |
|---|---|---|---|---|
| | *no. of patients/total no. (%)* | | | |
| Overall | 7/204 (3.4) | 11/210 (5.2) | 0.63 (0.24–1.62) | |
| Age | | | | 0.10 |
| <45 yr | 1/91 (1.1) | 6/97 (6.2) | 0.16 (0.02–1.31) | |
| ≥45 yr | 6/113 (5.3) | 5/113 (4.4) | 1.22 (0.37–3.99) | |
| Atrial septal aneurysm | | | | 0.09 |
| Yes | 4/47 (8.5) | 2/51 (3.9) | 2.09 (0.38–11.4) | |
| No | 3/157 (1.9) | 9/159 (5.7) | 0.32 (0.09–1.18) | |
| Cardiovascular index event | | | | 0.78 |
| Stroke | 5/165 (3.0) | 8/163 (4.9) | 0.58 (0.19–1.76) | |
| Transient ischemic attack or pulmonary embolism | 2/39 (5.1) | 3/47 (6.4) | 0.78 (0.13–4.66) | |
| >1 Previous cardiovascular event | | | | 0.22 |
| Yes | 2/76 (2.6) | 6/79 (7.6) | 0.28 (0.06–1.41) | |
| No | 5/128 (3.9) | 5/131 (3.8) | 0.99 (0.29–3.45) | |

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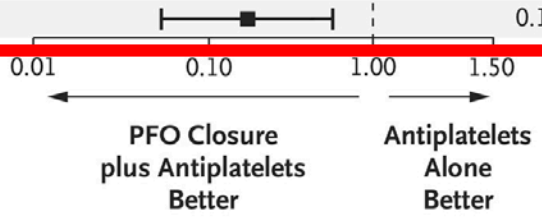
# REDUCE TRIAL
## Exploratory Analyses to Evaluate Heterogeneity in Relation to Baseline Covariates

| Subgroup | PFO Closure Group | Antiplatelet-Only Group | Hazard Ratio (95% CI) | P Value | P Value for Interaction |
|---|---|---|---|---|---|
| | *no. of patients who had recurrent stroke/total no. (%)* | | | | |
| All patients | 6/441 (1.4) | 12/223 (5.4) | 0.23 (0.09–0.62) | 0.002 | |
| Age | | | | | 0.85 |
| 18–45 yr | 3/204 (1.5) | 6/114 (5.3) | 0.26 (0.07–1.04) | 0.04 | |
| 46–59 yr | 3/237 (1.3) | 6/109 (5.5) | 0.21 (0.05–0.84) | 0.02 | |
| Sex | | | | | 0.62 |
| Male | 3/261 (1.1) | 8/138 (5.8) | 0.19 (0.05–0.71) | 0.01 | |
| Female | 3/180 (1.7) | 4/85 (4.7) | 0.31 (0.07–1.40) | 0.11 | |
| Region | | | | | 1.00 |
| Europe and Canada | 3/225 (1.3) | 6/108 (5.6) | 0.23 (0.06–0.93) | 0.03 | |
| United States | 3/215 (1.4) | 6/115 (5.2) | 0.24 (0.06–0.94) | 0.03 | |
| Shunt size | | | | | 0.77 |
| Small | 1/77 (1.3) | 2/43 (4.7) | 0.27 (0.03–3.03) | 0.26 | |
| Moderate-to-large | 4/348 (1.1) | 10/173 (5.8) | 0.18 (0.06–0.58) | 0.001 | |




Søndergaard L et al. N Engl J Med 2017;377:1033-1042

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# Device Closure of Patent Foramen Ovale After Stroke

## Pooled Analysis of Completed Randomized Trials

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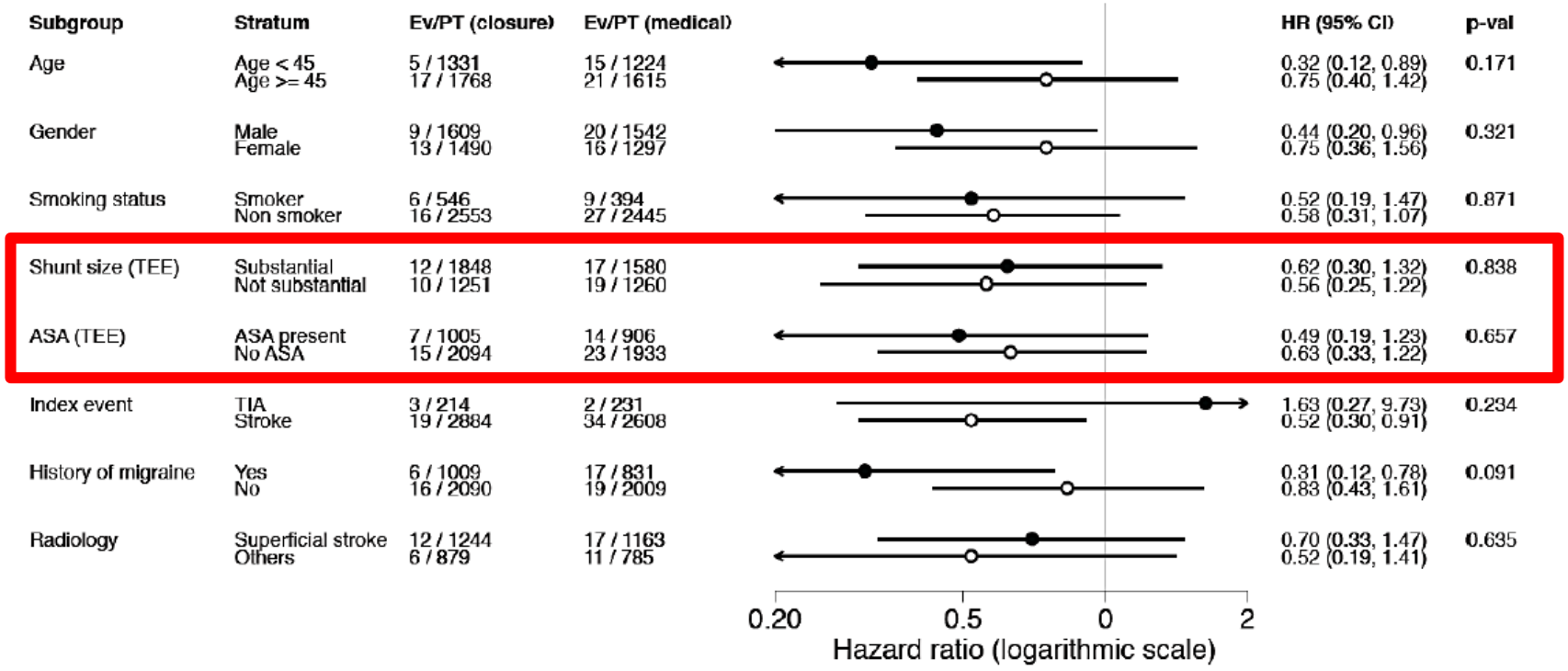
# Subpopulation Differential Treatment Effect: IPDMA

**Unadjusted Hazard Ratios for Study-stratified Cox Proportional Hazard Models for STROKE Outcome**

**Appendix Figure 1. Subgroup analysis for recurrent ischemic stroke (intention-to-treat analyses)**




**Subgroup analyses did not identify statistically significant heterogeneity of treatment effects.**

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# There are always two sides of a coin


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# There are always two sides of a coin: the flip side


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# Results

## Heterogeneity by RoPE Strata

| RoPE Stratum | # Patients | Device (events/100 pt yr) | Med Therapy (events/100 pt yr) | Absolute Risk Reduction | Hazard Ratio* (95% CI) |
|---|---|---|---|---|---|
| RoPE <7 | 912 (43%) | 1.4 | 1.7 | 0.3 | 0.82 (0.4 to 1.6) p=0.56 |
| RoPE ≥7 | 1229 (57%) | 0.3 | 1.0 | 0.7 | 0.31 (0.1 to 0.9) p=0.02 |

*Interaction p-value 0.12

Presented at ISC (Feb) 2017, Houston, TX

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# 3 dimensions of “risk”

1) Who has the disease

    Neurologist defined CS with high RoPE Score

2) Who has the disease and has a high risk of recurrence

    Controversial predictors

3) Who is likely to benefit from treatment

    RESPECTable patients

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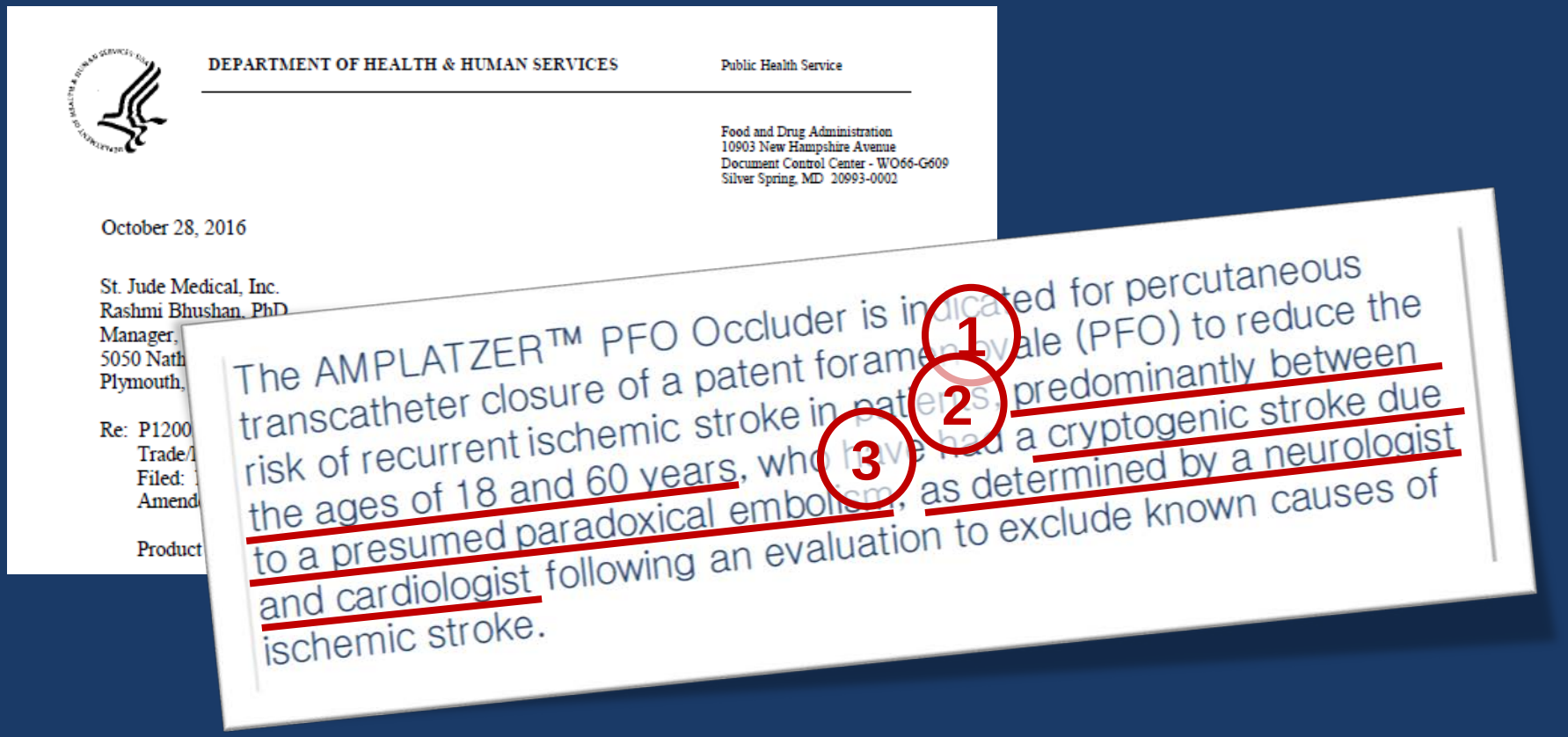
# What is certain?

- PFO is related to cryptogenic stroke
- Not all PFOs are pathogenic
- Recurrence risk of PFO-related stroke is about 1%/yr
- Predictors of recurrence include prior stroke, hypermobile septum, and small (??) shunt
- Devices are LOW risk (but *not* NO risk)
- RoPE Scores can identify likelihood of PFO relatedness
- PFO closure is associated with fewer recurrent strokes than medical Rx



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Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager,
5050 Nath
Plymouth,

Re: P1200
Trade/
Filed:
Amend

Product

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

1

2

3

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# It may never come to this...


Slide courtesy of Vincent Thijs, MD

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# RESPECT Trial Steering Committee

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# A guide to patient selection for PFO closure


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# Suggestions

1. Neurologists and cardiologists must collaborate
2. Involve neurologists in the diagnosis of stroke
3. Exclude other common “cryptogenic” causes: PAF, aortic atheroma, lacunes, dissection
4. Continue aggressive risk factor modification after closure
5. Continue antithrombotic medication after closure
6. Involve patients in the decision making
7. Intersociety position statements

# A (partial) list of outstanding issues

- Device-specific risk/benefits?
- Patient-centered outcomes
- Patients >60y
- PFO + PE
- Pregnancy, OCP, HRT
- Silent brain infarcts
- Activity advice to patients
- Patients with short life expectancy and high venous thrombosis burden
- Right atrial wires
- Transplanted PFOs
- SCUBA divers, astronauts

Thank you.

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