

**Q: Does the Presence of Atrial Septal Aneurysm and/or a Large Degree of Shunting Identify Patients Most Likely to Benefit?**

**A: No!**

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# Disclosure Statement of Financial Interest

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

## Affiliation/Financial Relationship

## Company

- Grant/Research Support
- **Consulting Fees/Honoraria**
- Major Stock Shareholder/Equity
- Royalty Income
- Ownership/Founder
- Intellectual Property Rights
- Other

**Steering Committee,  
RESPECT Trial, Abbott**



Food and Drug Administration  
10903 New Hampshire Avenue  
Document Control Center - W066-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

Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1,  
2014, February 27, 2015, September 17, 2015, October 8, 2015

Product Code: MLV

# What does the FDA label say about subgroups?

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.

**Tufts** Medical  
Center

See important safety information referenced within.



***If PFO characteristics are important, then it would make sense for echo findings to differ in patients with high vs. low RoPE scores***

## Transesophageal Echocardiography in Cryptogenic Stroke and Patent Foramen Ovale

### Analysis of Putative High-Risk Features From the Risk of Paradoxical Embolism Database

Benjamin S. Wessler, MD; David E. Thaler, MD, PhD; Robin Ruthazer, MPH;  
 Christian Weimar, MD; Marco R. Di Tullio, MD; Mitchell S.V. Elkind, MD, MS;  
 Shunichi Homma, MD; Jennifer S. Lutz, MS; Jean-Louis Mas, MD; Heinrich P. Mattle, MD;  
 Bernhard Meier, MD; Krassen Nedeltchev, MD; Federica Papetti, MD;  
 Emanuele Di Angelantonio, MD, MSc, PhD; Mark Reisman, MD; Joaquín Serena, MD, PhD;  
 David M. Kent, MD, CM, MSc

**Table 3. Putative High-Risk TEE Features Across High and Low RoPE Score Strata**

TEE Findings	All PFO Patients With At Least Some TEE Data (n=1294)	RoPE Score >6 (n=637)	RoPE Score ≤6 (n=657)	P Value*
Large no. of bubbles vs not large	64.4% (695/1079)	67.4% (347/515)	61.7% (348/564)	0.5286
Shunt at rest vs no shunt	69.6% (484/695)	67.6% (238/352)	71.7% (246/343)	0.4474
Hypermobility septum vs not	25.3% (320/1265)	23.0% (144/626)	27.5% (176/639)	0.1063

PFO indicates patent foramen ovale; RoPE, Risk of Paradoxical Embolism; and TEE, transesophageal echocardiography.

\*P values from generalized mixed models (TEE variables only) after adjusting for random site effect.

from **Circ Cardiovasc Imaging** 2014 7:125-131

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

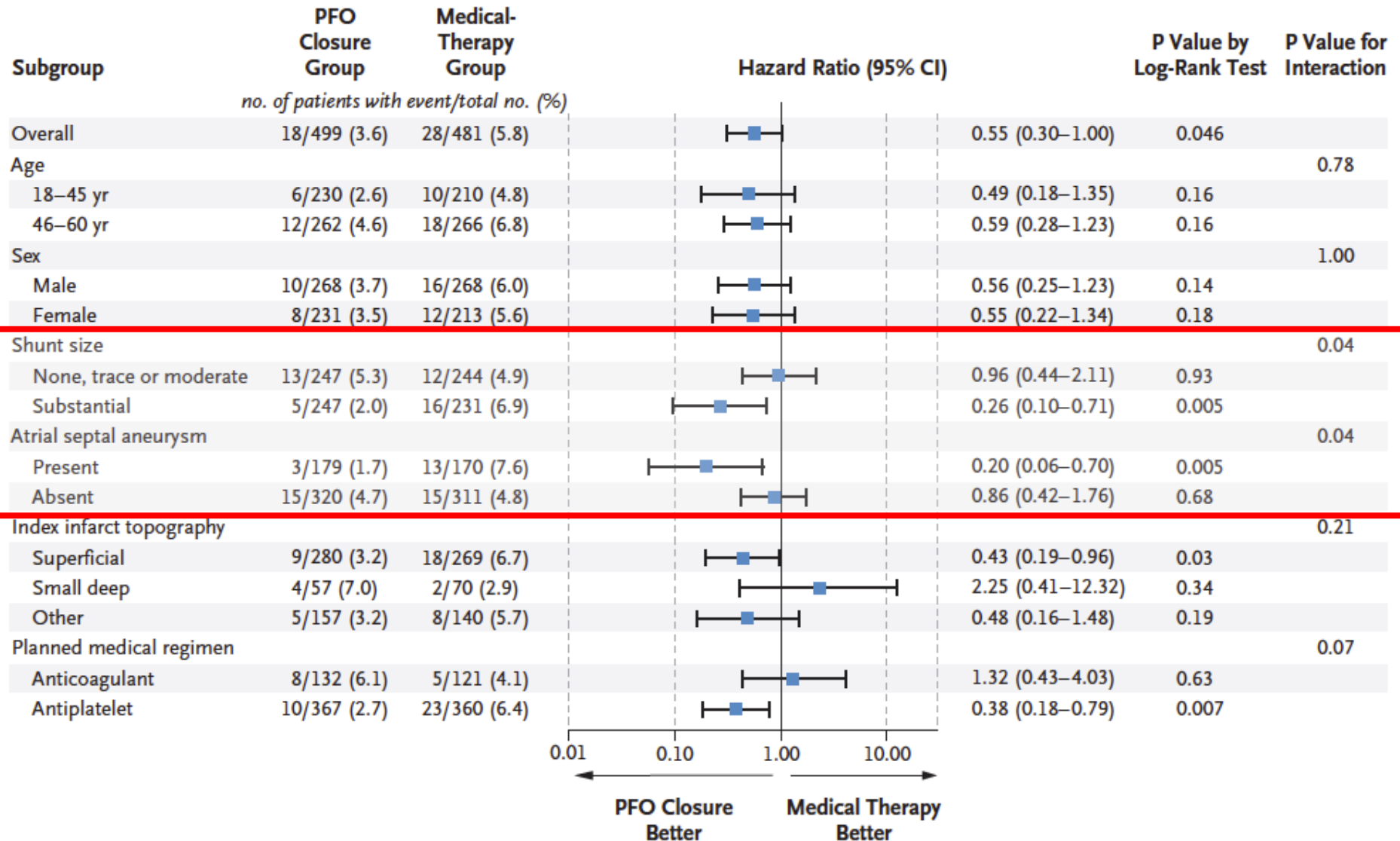
Variable	Adjusted hazard ratio (95% confidence interval)		Interaction p value <sup>a</sup>
	Point score ≤6 (raw event rate: 87/677 = 13%)	Point score >6 (raw event rate: 35/647 = 5%)	
Age (linear), hazard ratio per 10-y increase	1.47 (1.18-1.83) <sup>b</sup>	0.83 (0.57-1.20)	0.0083
Treated with antiplatelets	1.69 (1.05-2.74) <sup>b</sup>	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) <sup>b</sup>	0.0911
Small shunt	1.29 (0.82-2.03)	3.26 (1.59-6.67) <sup>b</sup>	0.0306
Hypermobility interatrial septum	0.83 (0.49-1.42)	2.31 (1.05-5.05) <sup>b</sup>	0.0350
All subjects (raw event rate: 122/1,324 [9%])			
Incident TIA (vs stroke)	1.69 (1.05-2.74) <sup>b</sup>		

Hazard ratio >1 indicates positive association with outcome.

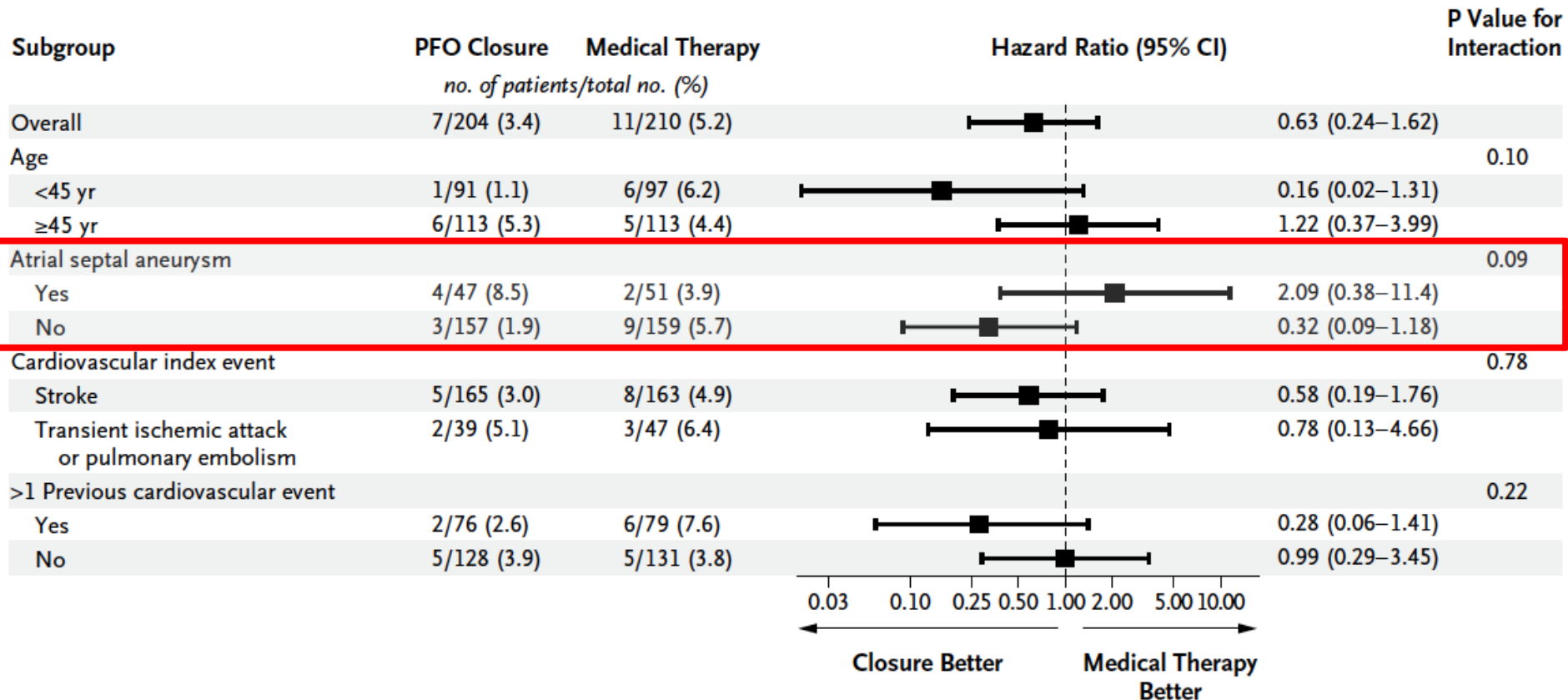
<sup>a</sup>If the p value of the variable or the interaction with the categorized point score (≤6, >6) was ≤0.10, then the interaction term was left in the model and hazard ratios were estimated separately for the point score subgroups. If the interaction p value was ≥0.10, then the interaction term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

<sup>b</sup>95% Confidence interval for hazard ratio is above or below 1 (with a corresponding p value of ≤0.05).

# Subpopulation Differential Treatment Effect: RESPECT



# Subpopulation Differential Treatment Effect: PC Trial

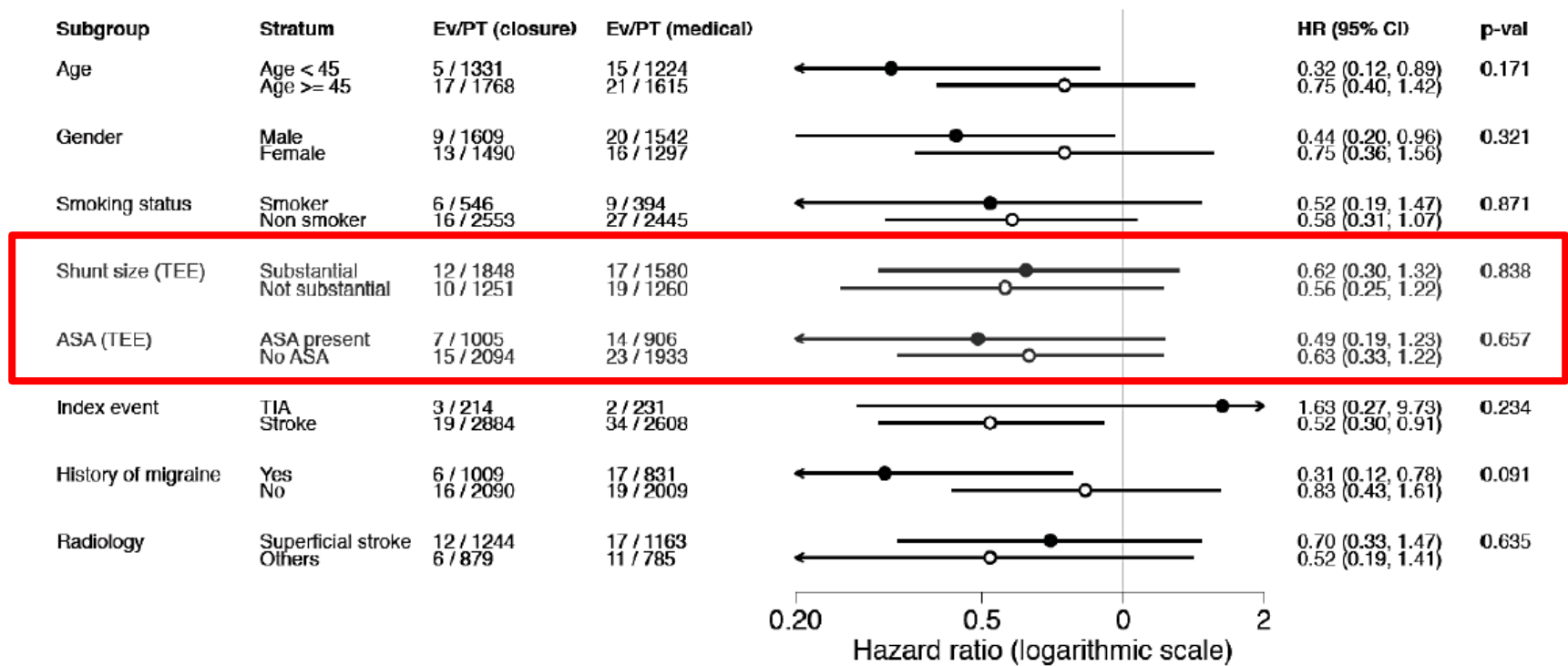




# Subpopulation Differential Treatment Effect: IPDMA

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

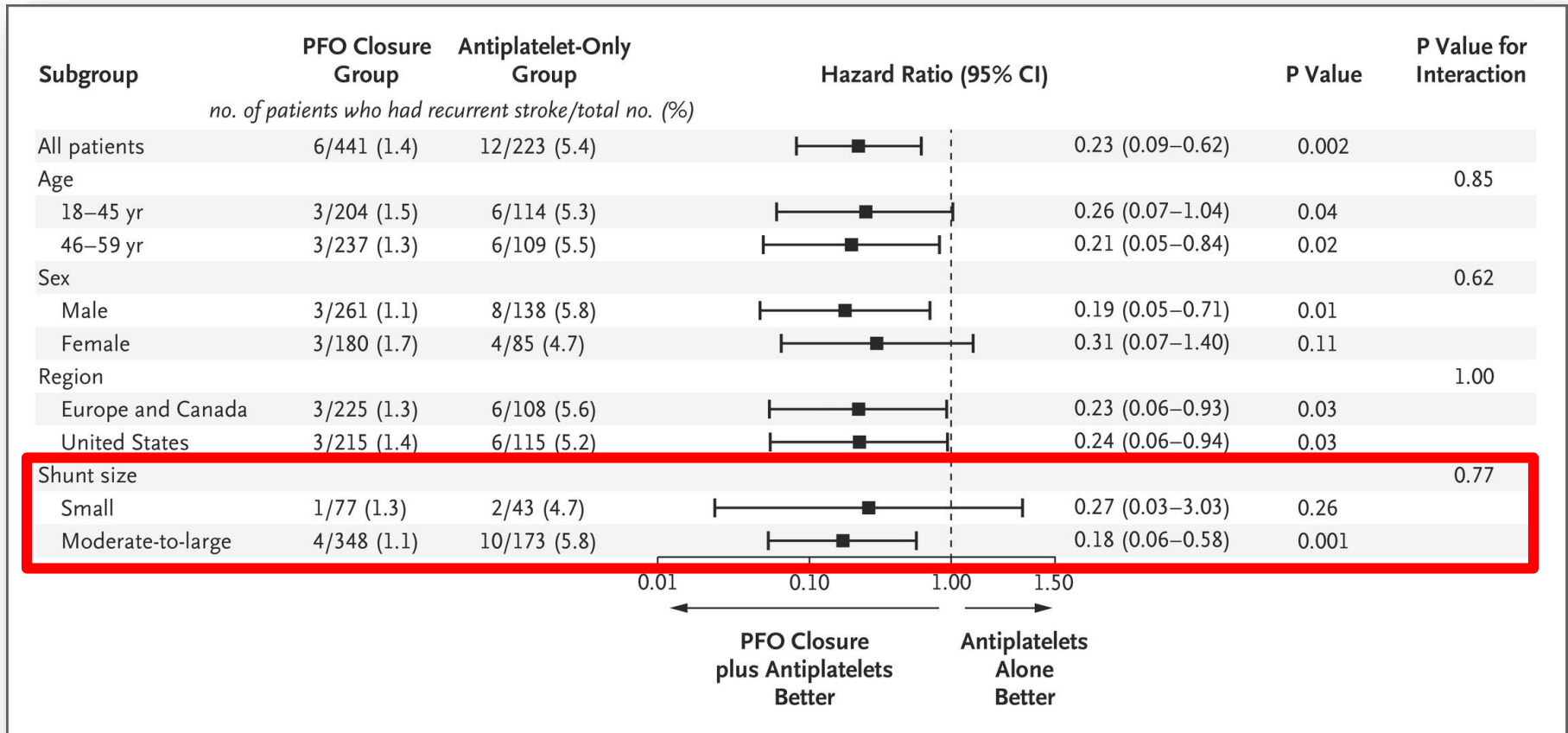
Appendix Figure 1. Subgroup analysis for recurrent ischemic stroke (intention-to-treat analyses)



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

# REDUCE TRIAL

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



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

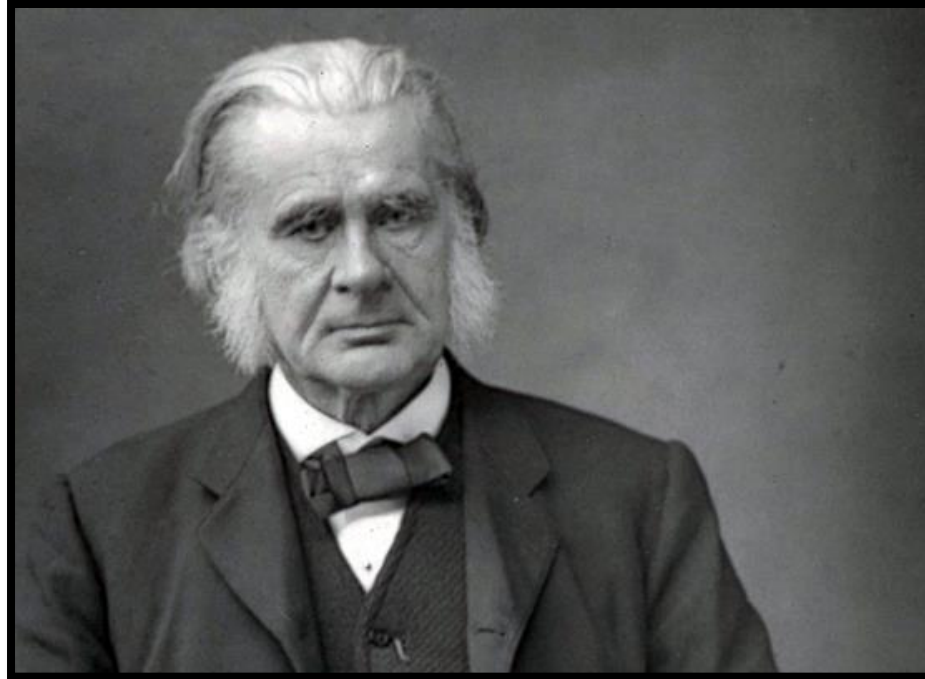
# There are always two sides of a coin



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



# Thomas Henry Huxley, “Darwin’s Bulldog”



***“The great tragedy of Science —  
the slaying of a beautiful hypothesis by an ugly fact.”***

Presidential Address at the British Association, "[Biogenesis and abiogenesis](#)" (1870);  
later published in *Collected Essays*, Vol. 8, p. 229.

# Donald Rumsfeld on PFO closure



*“As we know, there are **known knowns**; there are things we know we know.”*

~ PFO closure is associated with fewer recurrent strokes than medical Rx alone

*“We also know there are **known unknowns**; that is to say we know there are some things we do not know.”*

~ Heterogeneity (subgroups) not established

*“But there are also **unknown unknowns**—the ones we don’t know we don’t know.”*

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~ Preferential benefit in ... pets? Left handers?

# Conclusion

- PFO closure is associated with a lower risk of recurrent stroke
- Heterogeneity of treatment effect has NOT been established based on PFO characteristics
- Be aware that by arguing for treatment of *purported* high risk PFOs you are by necessity arguing for *withholding* treatment from some patients who may benefit
- A repeat IPDMA with new RCT data is needed (and being planned!)