Are the Feds Going to Finally Let Us Treat These Patients: What Patients with PFO Can Have Closure?

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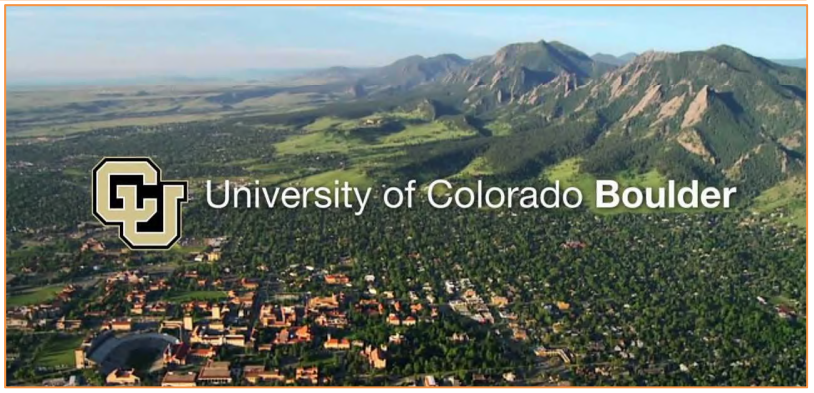
Professor of Medicine
Director of Interventional Cardiology
University of Colorado

One of America's top 20 heart hospitals by *US News and World Report in 2017*



Disclosure

- **John Carroll has been a member of the Steering Committee of the RESPECT Clinical Study since 2003 and has received compensation for services related to that role from the study sponsors (AGA Medical, St. Jude Medical, and Abbott Vascular)**

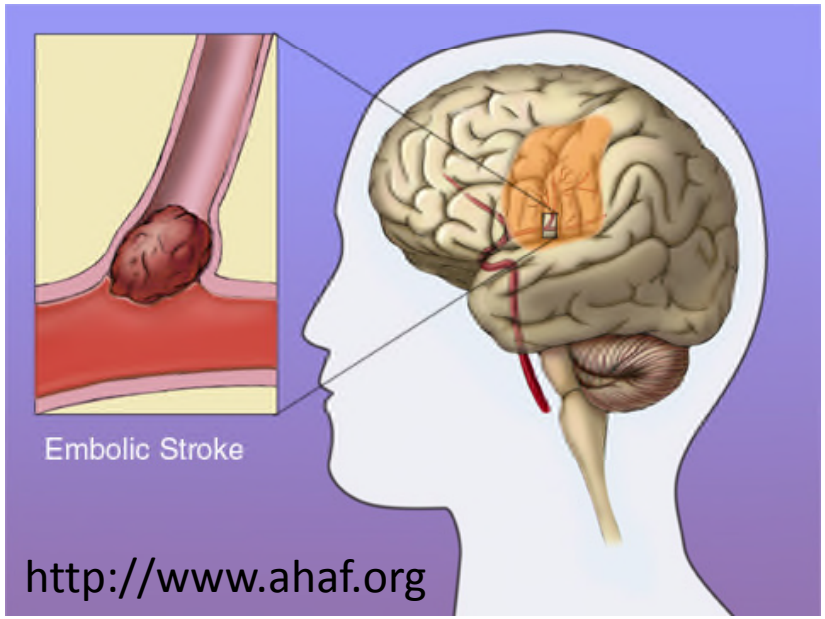
Case Presentation

- A 62 year old woman suffered an episode of left hand weakness 1 year ago. This episode lasted for 3 hours. She saw a neurologist who thought this was a TIA with an MRI revealing no evidence of a stroke. A week prior to visiting you, the patient had a transient visual field loss that was very concerning to her and lasted approximately one and one-half hours. The TEE reveals a large PFO with a septal aneurysm and a very positive bubble test.

The Central Hypothesis

A PFO enables right-to-left intracardiac shunting. In so doing it compromises a function of the pulmonary circulation:

Filtering of debris including small (1-3mm) emboli

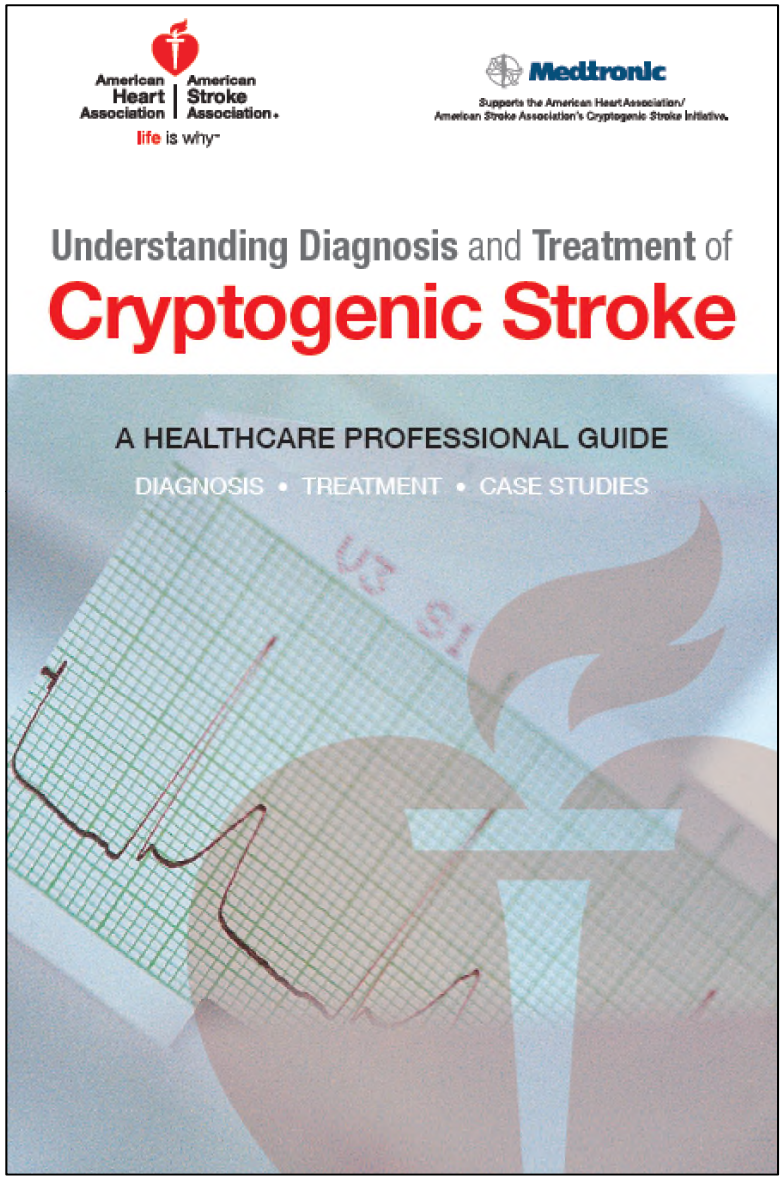


"A Device to Avert Strokes Lacks Proof That It Works"

The New York Times

"**Given a choice** of treatments to reduce his risk of stroke, David Dansereau elected an implanted device over daily drugs."

http://www.nytimes.com/2009/01/14/health/research/14heart.html?_r=1&ref=todayspaper



2015

Key Points

- Approximately 200,000 cryptogenic strokes annually in the U.S.
- Cryptogenic stroke is a brain infarction not clearly attributable to a definite mechanism despite extensive investigation.
- *The ability to more clearly define the etiology of cryptogenic stroke has profound implications for subsequent treatment and risk for recurrent events*.
- Most patients with cryptogenic stroke are treated with a combination of antiplatelet therapy and stroke risk factor reduction— treatments that are not highly effective in preventing recurrent strokes of cardioembolic origin.

Background

- The role of transcatheter PFO closure to prevent recurrent ischemic strokes has been ***very controversial*** for over 15 years.
- Many clinicians accepted observational data as adequate proof of efficacy.
- In the U.S. “off-label” closure of PFOs using devices approved for other indications became widespread.
  - Produced difficulty for RCT enrollment and retention of patients
- Other countries approved PFO closure devices without RCT proof
  - Italy has 11 “approved” PFO closure devices

Migliore, A., et al., *Implantable devices for the closure of patent foramen ovale in adults: an Italian rapid health technology assessment.* Expert Rev Med Devices, 2014. **11**(2): p. 151-61.

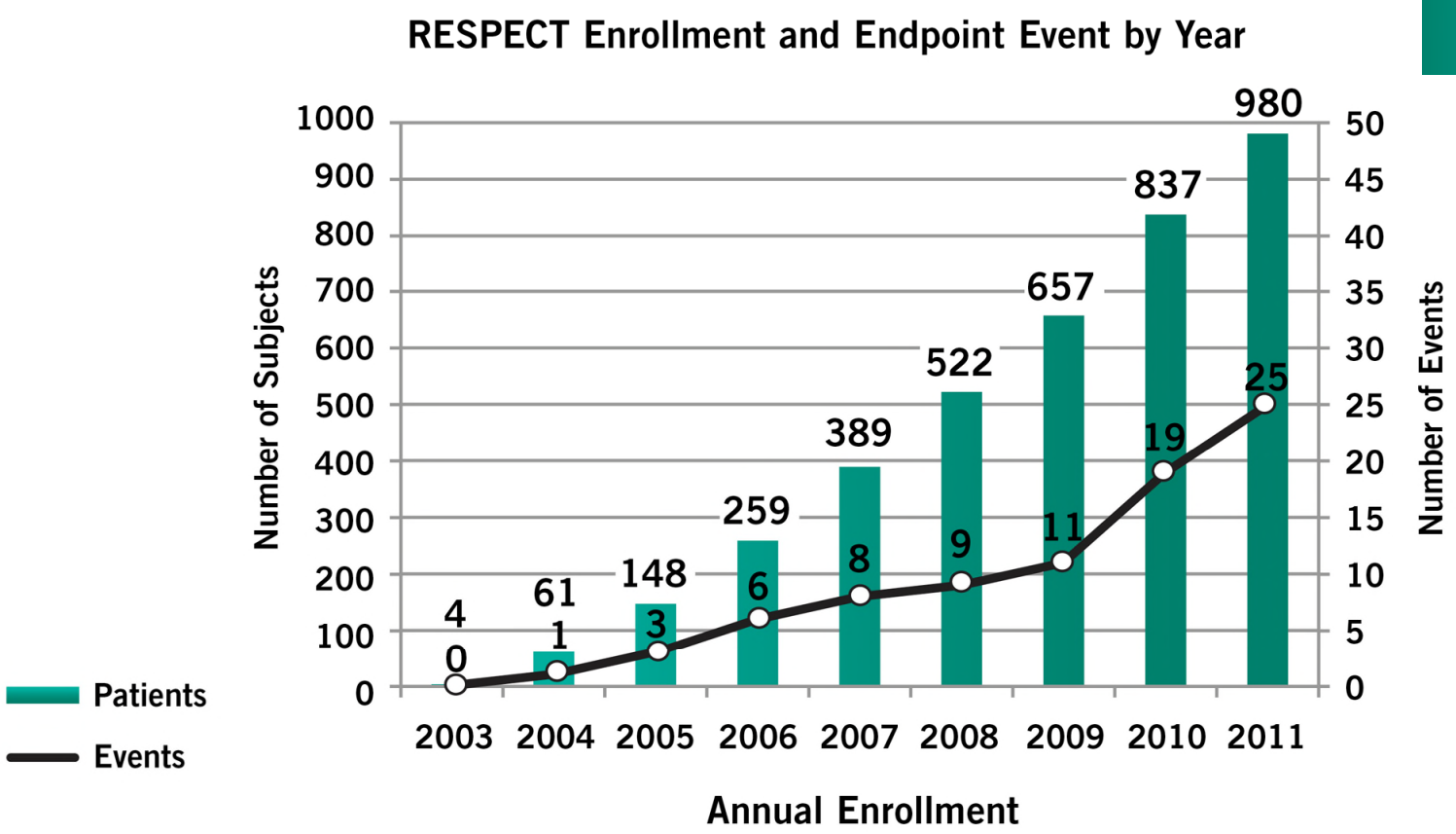
Additional Challenges in Clinical Trial Design

- PFO is considered an **innocent remnant of the fetal circulation** in the vast majority of the approximately 25% of adults having a PFO.
  - PFO is present in 40-50% of patients with cryptogenic strokes suggesting a possible mechanism for their strokes
  - But an association does not prove causality
  - How to distinguish an incidental PFO from a pathogenic PFO?
- A stroke occurs when a presumed embolus passes thru a PFO and occludes a cerebral vessel resulting in an ischemic stroke.
  - But rarely is a thrombus found in a systemic vein
  - And it only takes 2-3 mm thrombus, that becomes an paradoxical embolus, to occlude a middle cerebral artery causing a devastating stroke

Eight Years of Enrolling Patients Finished in 2011

RESPECT: Initial Results Ready to Report!

- The 25 adjudicated endpoint events
  - All primary endpoints were recurrent ischemic strokes. No study related deaths
  - Analytic data set: observational period from the beginning of the trial to the date when the 25th primary endpoint event was adjudicated



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

N Engl JMed 2012;**366**:991–999.

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*

N Engl J Med, 2013;**368**:1083-91.

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

N Engl J Med, 2013;**368**:1092-100.

Level of Evidence for PFO Closure

Prior to 2014

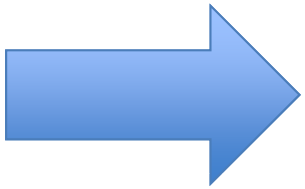
CLASS IIb

Benefit ≥ Risk

Additional studies with broad objectives needed; additional registry data would be helpful

Procedure/Treatment **MAY BE CONSIDERED**

- Recommendation's usefulness/efficacy less well established
- Greater conflicting evidence from single randomized trial or nonrandomized studies



2014-2016

CLASS III *No Benefit* or **CLASS III** *Harm*

	Procedure/ Test	Treatment
COR III: No benefit	Not Helpful	No Proven Benefit
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

“Negative” Trials, But We Learned

- Low yearly event rates necessitate long-term follow-up that may then prove PFO closure is superior to medical management.
- The Intention-To-Treat population for a device trial is imperfect and the tyranny of $p<0.05$ is painful.
  - 3 patients in device arm with recurrent ischemic strokes did not have a device in place!
- DO NOT GIVE UP PREMATURELY! PERSIST for our patients sake!

RESPECT Long-Term

- Early and medium-term results in RESPECT showed point estimates in favor of closure but did not reach statistical significance (0.089) for the intention to treat population.
  - As treated and per protocol populations demonstrated statistically significant reduction of recurrent strokes with PFO closure
  - Carroll et al. NEJM 2013:368(12); 1092–1100
- RESPECT protocol pre-specified follow-up until an FDA regulatory decision
- Following FDA Advisory Panel in May 2016, the FDA requested an analysis of long-term outcomes using updated data – these final analyses (data lock, May 2016) of RESPECT are presented today

RESPECT Trial

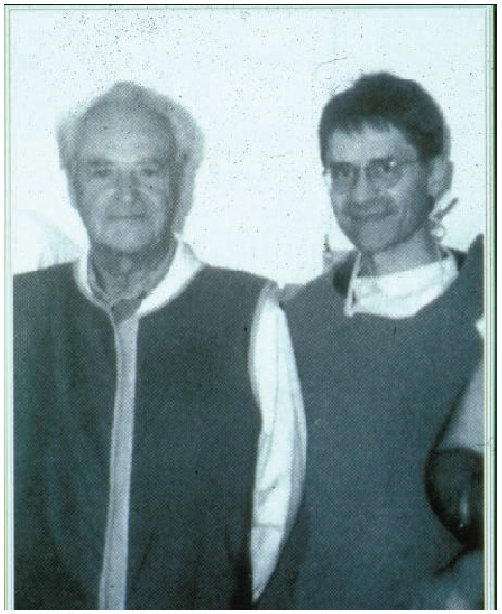
- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada

AMPLATZER™ PFO Occluder

A Physician Designed Medical Device

The Pioneers:

Drs. Kurt Amplatz (left) and Bernhard Meier (right) on the occasion of the world's first closure of a patent foramen ovale using an Amplatzer PFO Occluder (insert) on September 10, 1997, in Switzerland.



Enrollment Criteria

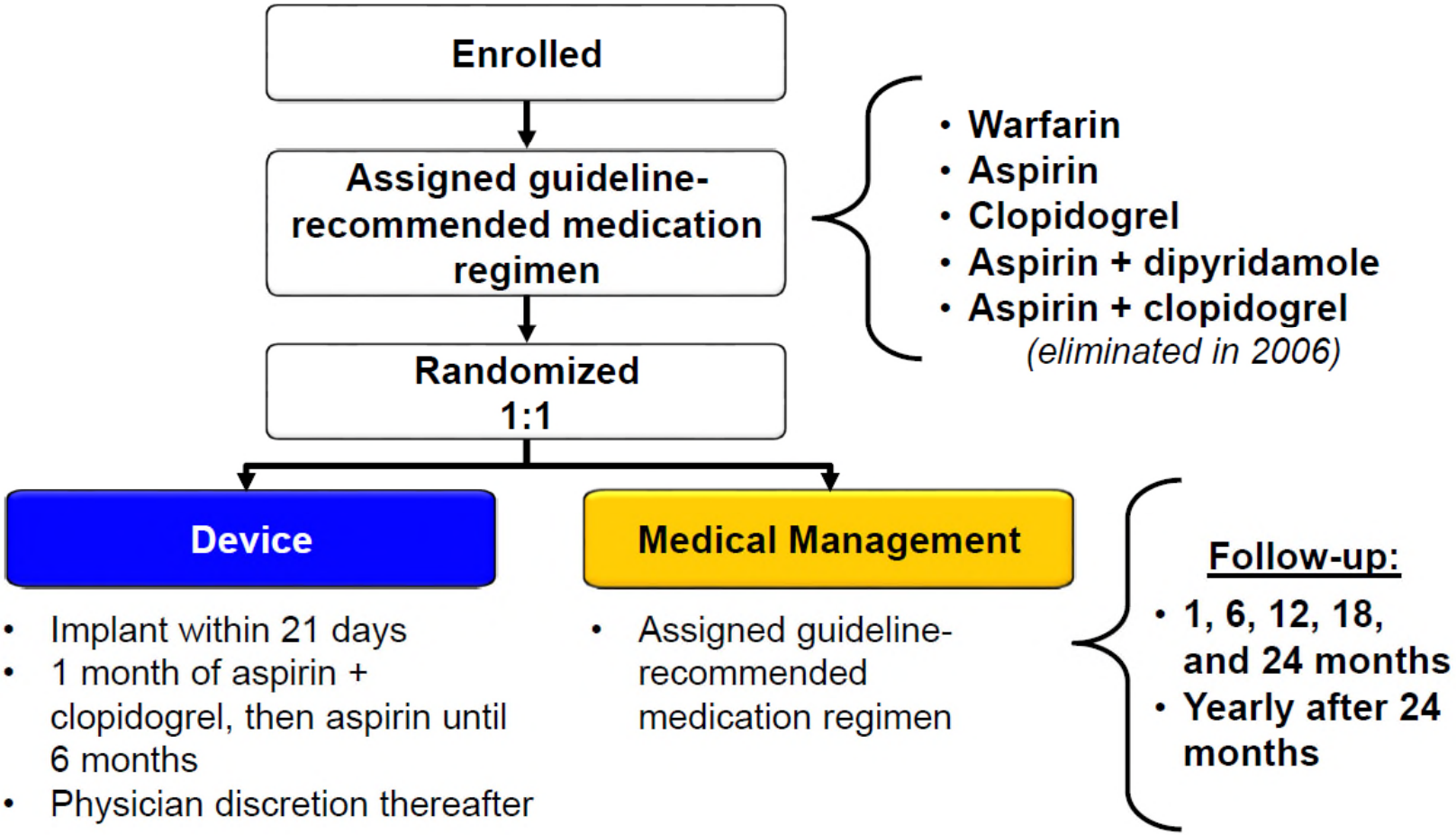
Key Inclusion Criteria

- Cryptogenic stroke within last 9 months
- TEE-confirmed PFO
- 18-60 years

Key Exclusion Criteria

- Stroke due to identified cause such as:
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- Inability to discontinue anticoagulation

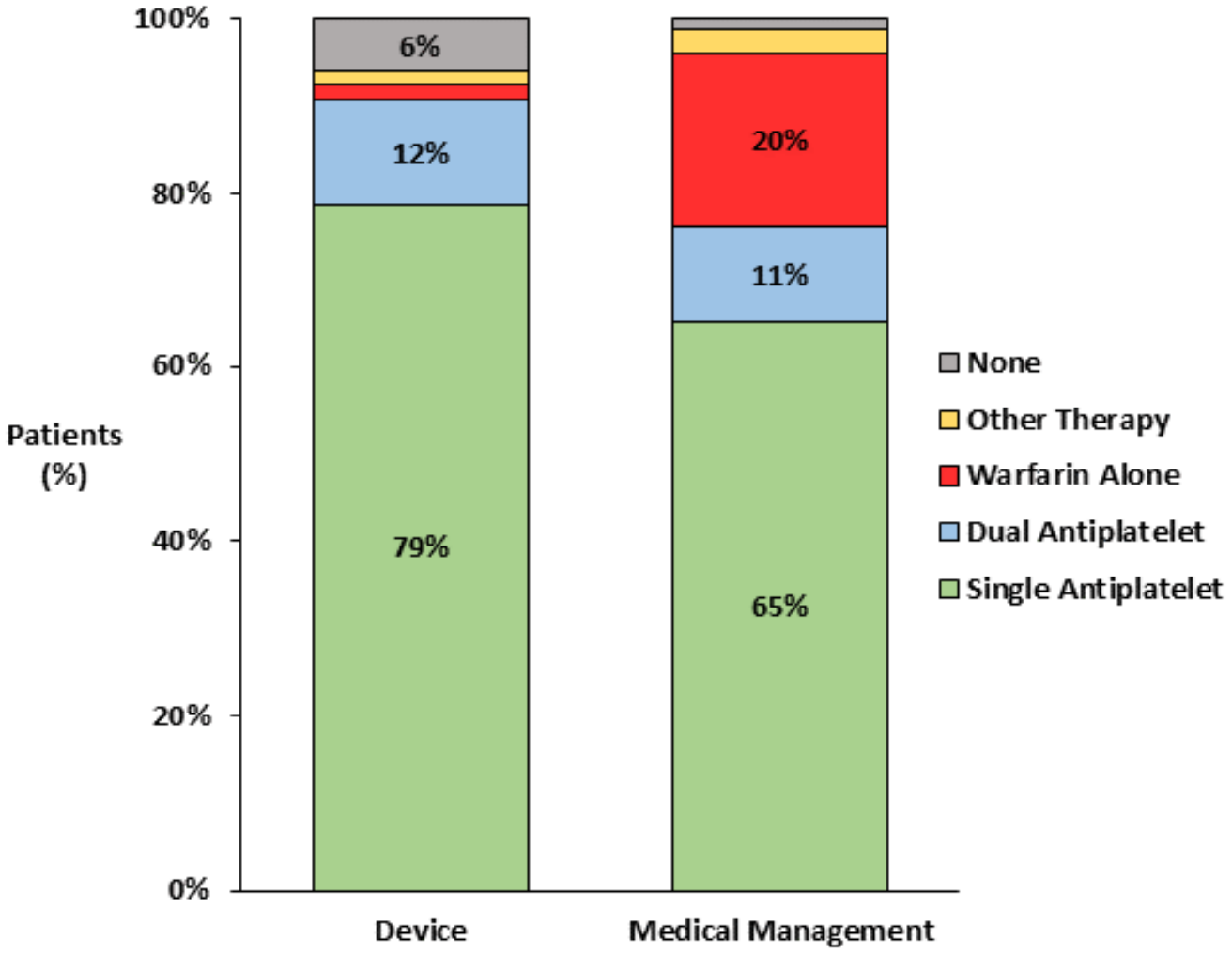
Patient Flow



Baseline Characteristics Balanced Between Groups

Characteristic	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	48 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	41%
Family h/o CAD	33%	33%
Hypertension	32%	32%
COPD	0.8%	1.5%
Congestive heart failure	0.6%	0%
History of DVT	4.0%	3.1%
Atrial septal aneurysm	36%	35%
Substantial shunt	50%	48%

Antithrombotic Medication Use During Follow-up



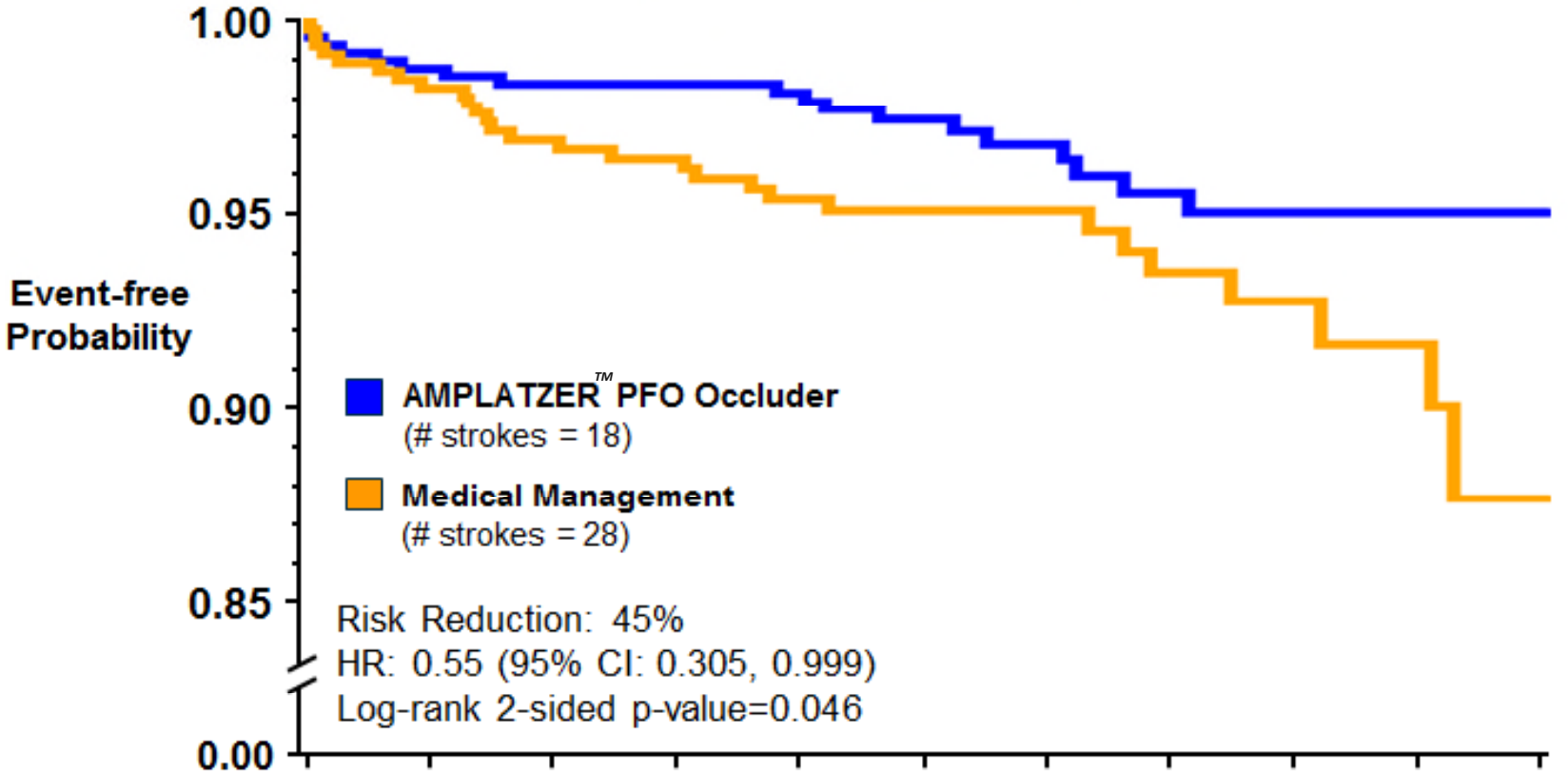
Procedural Results and Follow-up

- Technical Success* 99.1%
- Procedural Success** 96.1%
- Mean Follow-up: 5.9 years (0-12 years)
  - Device
    - Mean 6.3 years; Total 3141 patient-years
  - Medical Management
    - Mean 5.5 years; Total 2669 patient-years

*Delivery and release of the device

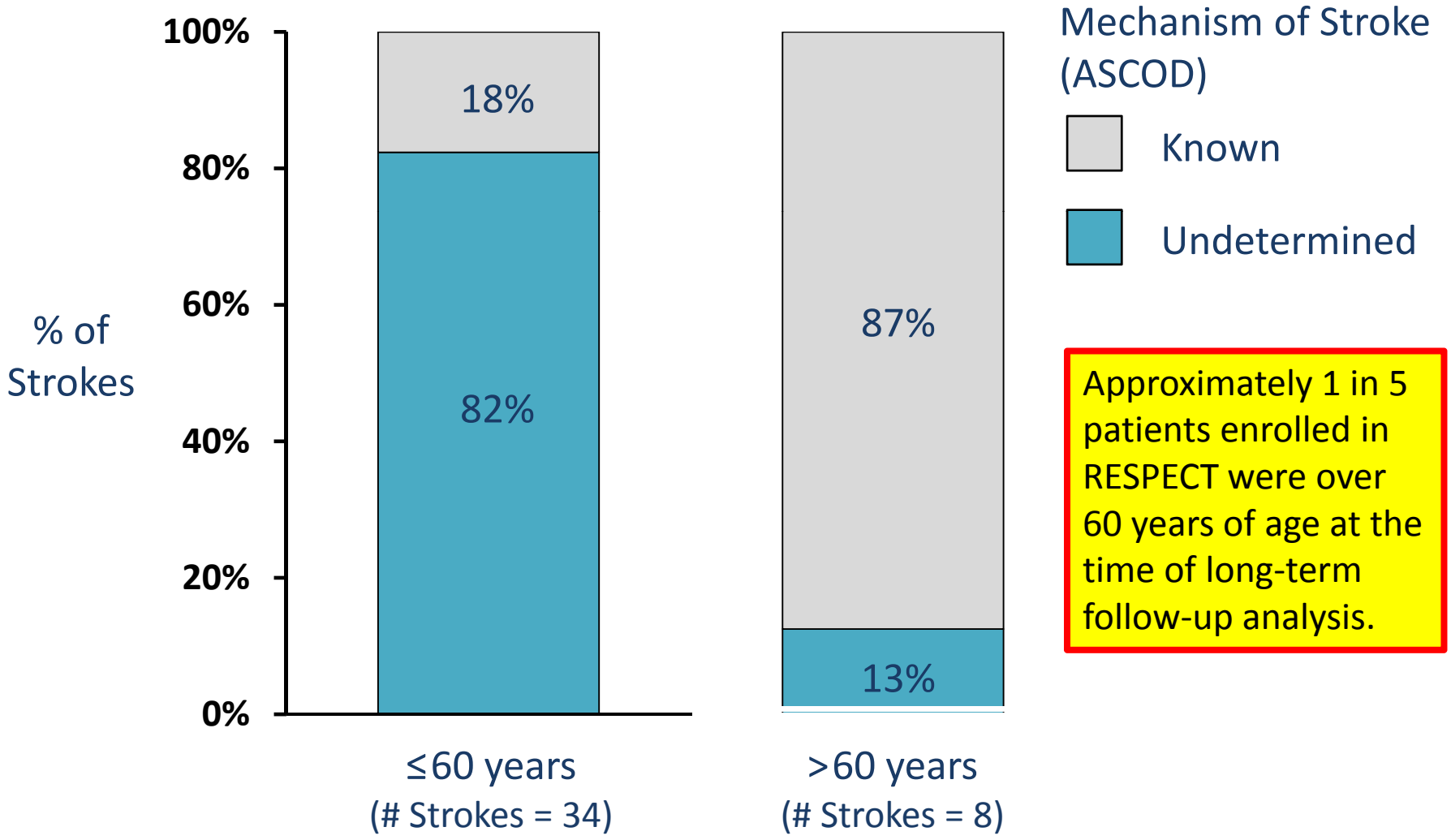
**Implantation without in-hospital SAE

Freedom from Recurrent Ischemic Stroke (Intention to Treat)



# at Risk (KM Estimates)										
AMPLATZER	499 (0%)	476 (1.4%)	464 (1.6%)	447 (1.6%)	421 (1.9%)	352 (2.6%)	262 (3.3%)	197 (4.5%)	128 (5.0%)	77 (5.0%)	41 (5.0%)
MM	481 (0%)	433 (1.8%)	394 (3.2%)	380 (3.7%)	354 (4.7%)	282 (5.0%)	218 (5.0%)	150 (6.6%)	104 (7.3%)	59 (8.5%)	31 (12.5%)

The Mechanisms of Recurrent Strokes Through Long-Term Follow-Up



Approximately 1 in 5 patients enrolled in RESPECT were over 60 years of age at the time of long-term follow-up analysis.

Interpretation

- These analyses support the hypothesis that PFO closure is preventing PFO-related recurrent strokes
- PFO-closure cannot prevent strokes from non-PFO related causes

Intentional to Treat Population	HR (95% CI)	Relative Risk Reduction	P-value
All Ischemic strokes	0.55 (0.305-0.999)	45%	0.046
Strokes without known mechanism	0.38 (0.18-0.79)	62%	0.007
Age-censored analysis: All ischemic strokes in patients <60 years old	0.42 (0.21-0.83)	58%	0.01

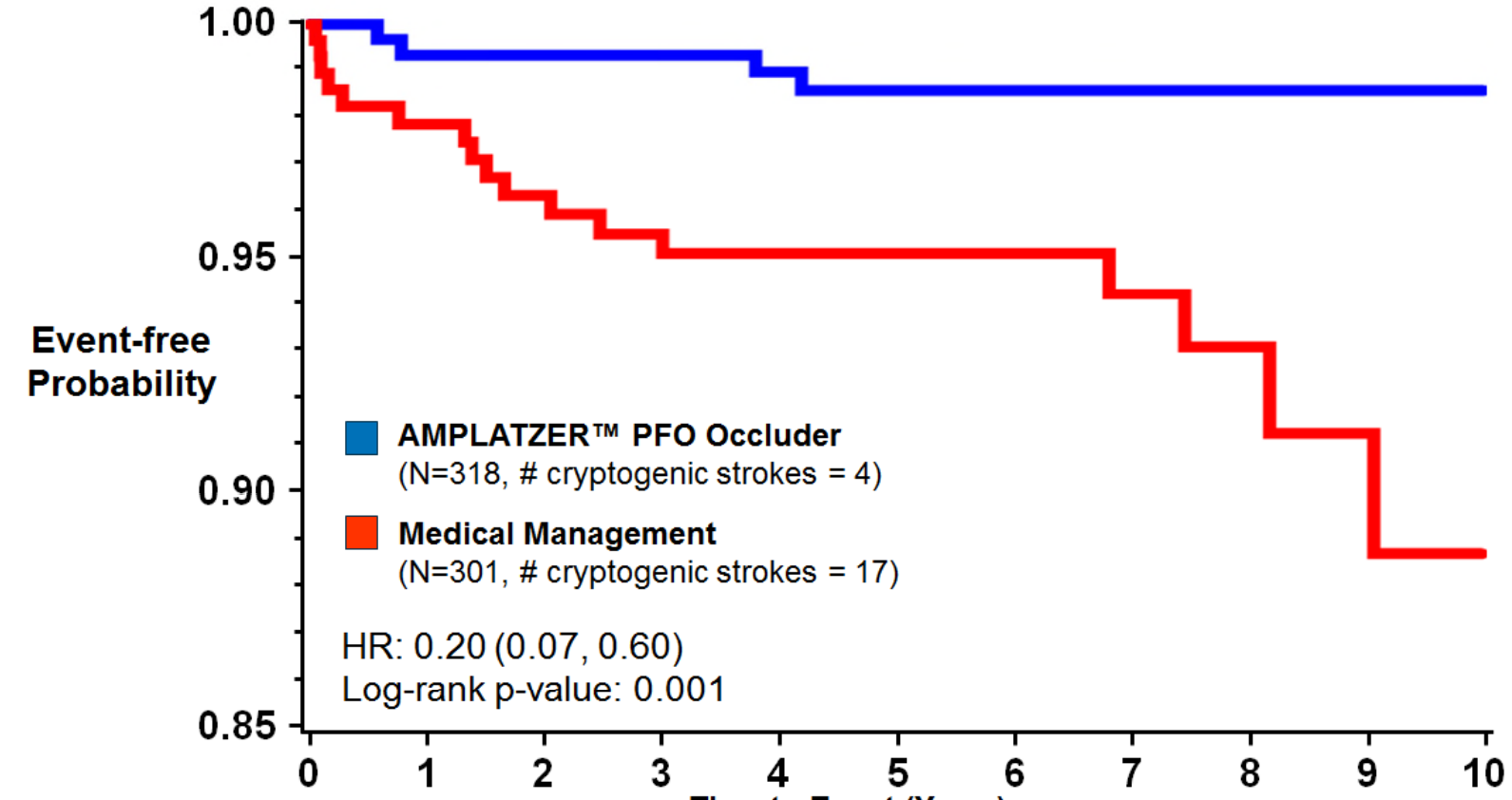
Did The Characteristics of PFO Impact on the Benefit of PFO Closure in the RESPECT Trial?

Atrial septal aneurysm: > 10 mm excursion

Large shunt: >20 microbubbles immediately in left atrium

Greater Benefit in Substantial Shunt or ASA Subgroup

80% Relative Risk Reduction in Recurrent Cryptogenic Stroke in ITT Population



 # at Risk (KM Estimates)

AMPLATZER	**318** (0%)	**299** (0.6%)	**270** (1.0%)	**165** (1.4%)	**78** (1.4%)	**23** (1.4%)
MM	**301** (0%)	**243** (3.6%)	**219** (4.8%)	**130** (4.8%)	**69** (6.8%)	**20** (11.2%)

Key Points in Understanding Treatment Benefit of PFO Closure

- The absolute yearly rate of ischemic strokes is low in both groups but lower with PFO closure
  - Event rate of 0.58 vs. 1.07 per 100 patient years
- The treatment effect continues to accrue with time.
  - Important if you are 40 years old!
- Patients with high-risk PFO characteristics of ASA or large shunt have a large relative risk reduction from PFO closure
  - At ten years the expected frequency of recurrent stroke would be reduced from 12.90% to 2.94% from PFO closure with a calculated number needed to treat of only 10!

SAFETY RESULTS

DSMB Adjudicated
Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion

2.4% of Device Patients Had a Procedure-related SAE (n=12)

Event Type	n (%)
Pericardial tamponade *(required pericardiocentesis)*	2 (0.4%)
Cardiac perforation *(no treatment required)*	1 (0.2%)
Pericardial effusion *(no treatment required)*	1 (0.2%)
Access site bleeding *(1 required a stitch, 1 required transfusion, 1 required no treatment)*	3 (0.6%)
Right atrial thrombus *(detected during procedure – no device implanted and procedure abandoned)*	1 (0.2%)
Deep vein thrombosis	1 (0.2%)
Atrial fibrillation *(successfully cardioverted)*	1 (0.2%)
Other (*allergic drug reaction, vasovagal response*)	2 (0.4%)

No SAEs of acute ischemic stroke due to air or thromboemboli or device embolization

BS9

2.0% of Device Patients Had a Device-related SAE (n=10)

Event Type	n (%)
Ischemic stroke *(primary endpoint)* *One 7 days post-procedure and one 3 months post-procedure adjudicated as device-related since within the 6 month post-procedure period. Neither with atrial fib nor thrombus on device.*	2 (0.4%)
Pulmonary embolism	2 (0.4%)
Explant/surgical intervention (*sinus venosus atrial septal defect, endocarditis at ~2 yrs*)	2 (0.4%)
Atrial fibrillation *(cardioverted medically)*	1 (0.2%)
Residual shunt *(requiring closure with septal occluder device)*	1 (0.2%)
Other *(chest tightness, atrial flutter, non-sustained VT, sepsis)*	4 (0.8%)

No SAEs of thrombus on device or device erosion

Slide 30

BS9 The Pulmonary Embolism was hidden - I've rearranged to show these events

Barathi, 2/20/2017

Rate of Atrial Fibrillation: Both Serious and Non-Serious as Adjudicated by DSMB

Adverse Event	AMPLATZER PFO Occluder (N=499)			Medical Management (N=481)		
	# Patients	# Events	Rate Per 100 PYs	# Patients	# Events	Rate Per 100 PYs
Atrial fibrillation	**22**	**25**	**0.80**	**9**	**12**	**0.45**
Peri-procedural	**7**	**7**	**0.22**	**N/A**	**N/A**	**N/A**
Post-procedural*	**15**	**18**	**0.57**	**9**	**12**	**0.45**

- All 7 peri-procedural AF events in Device arm resolved prior to discharge with no reoccurrence.
- No significance difference in post-procedure atrial fib versus medical management arm: *p=0.51 based on normal approximation of Poisson rates
- 1 AF-related stroke in Device arm, 3 in MM arm

Higher Rate of Venous Thromboembolic Events (VTE) in Device Arm over 9-Year Follow-up

Event	AMPLATZER PFO Occluder (N=499)			Medical Management (N=481)		
	# Patients	# Events	Rate Per 100 PYs	# Patients	# Events	Rate Per 100 PYs
All VTEs*	**20**	**27**	**0.86**	**4**	**6**	**0.22**
DVT	**14**	**14**	**0.45**	**3**	**3**	**0.11**
PE	**12**	**13**	**0.41**	**3**	**3**	**0.11**

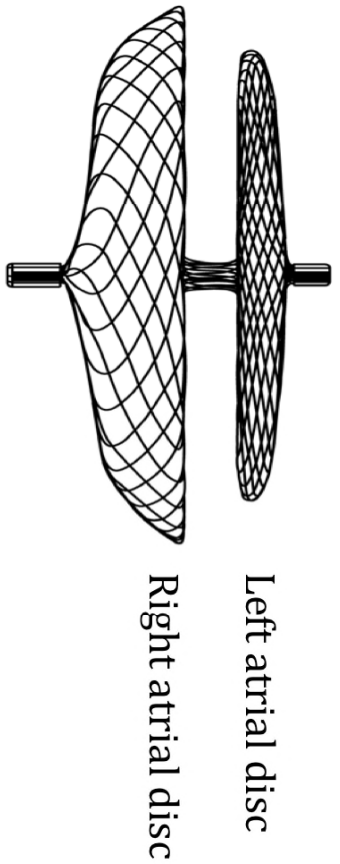
- Not found to be associated with device thrombus and most occurred years after procedure
- History of DVT was major predictor
- Protocol-driven imbalance of warfarin therapy offers one likely explanation for imbalance in VTEs

***p=0.0008 based on normal approximation of Poisson rates**

Conclusions

- In the RESPECT Long-Term trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone to reduce the risk of recurrent stroke
- The risks of the procedure and device are relatively low with most complications treatable with no sequelae
- The AMPLATZER™ PFO Occluder is only FDA approved device in the U.S.

Table 1. FDA Approval of PMA Application for AMPLATZER™ PFO Occluder on October 28, 2016

Indications and Usage	
"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."	
FDA Documents Approval letter: http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120021a.pdf Approval announcement: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm527096.htm Summary of safety and effectiveness data: http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120021b.pdf	

RESPECT Long-Term Is Not The Only Positive Trial

REDUCE

&

CLOSE

ORIGINAL ARTICLE

Long-Term Outcomes of PFO Closure or Medical Therapy after Stroke

Saver, JL., Carroll, JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL, for the RESPECT Investigators.

Presented at TCT, October 2016.

N Engl J Med 2017; 377: 1022-32.

Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke.

Søndergaard L, Kasner SE, Rhodes JF, et al. for the REDUCE Investigators.

Presented at European Stroke Organization Conference, May 2017.

N Engl J Med 2017; 377: 1033-42.

Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke.

Mas J-L, Derumeaux G, Guillon B, et al. for the CLOSE Investigators.

Presented at European Stroke Organization Conference, May 2017.

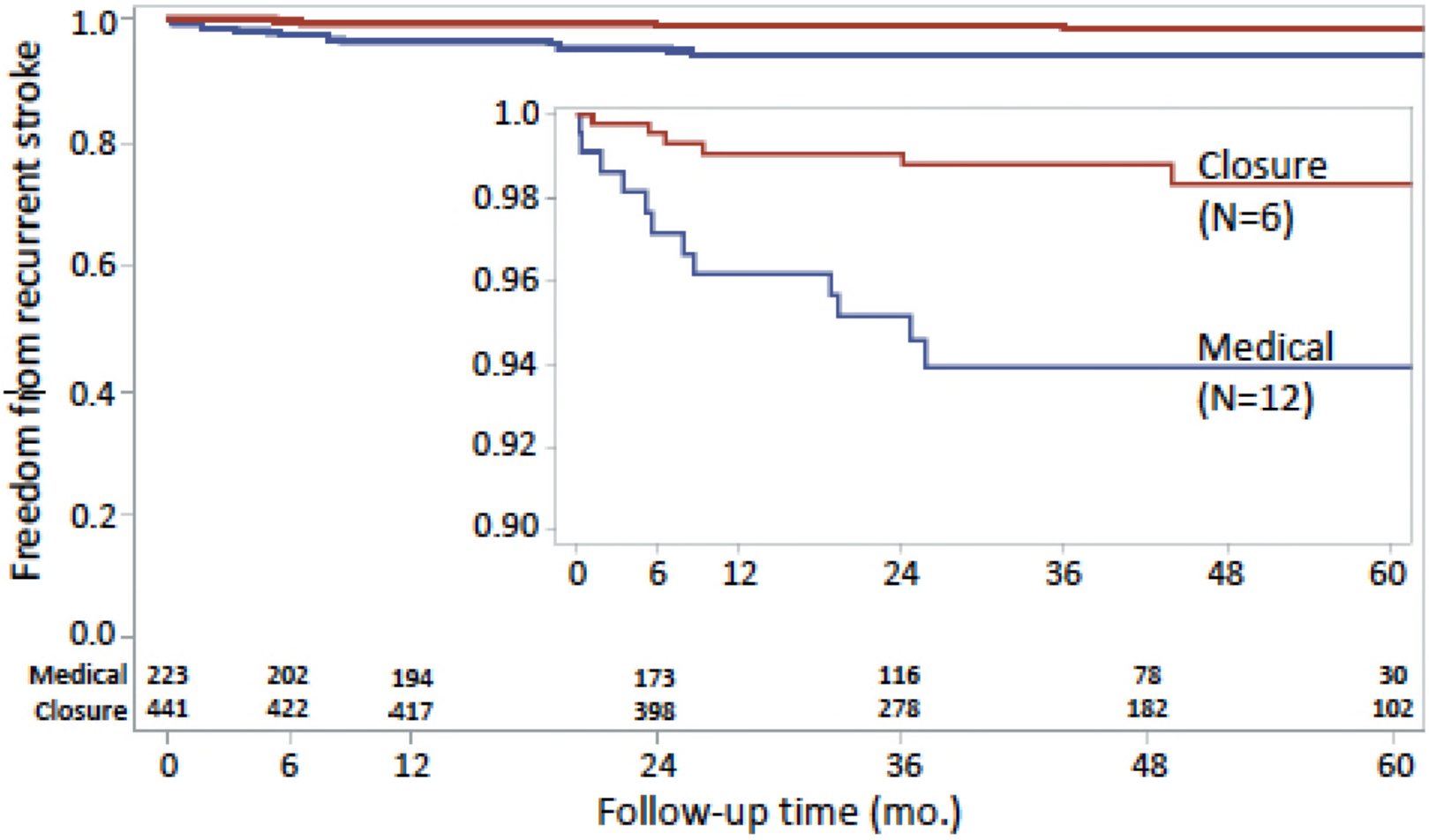
N Engl J Med 2017; 377: 1011-21.

REDUCE: Study Design

- Aim: establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct
- Randomized, controlled, open-label trial
- MRI pre and post
- 664 subjects randomized in a 2:1 ratio to:
  - Closure: PFO closure with GORE® HELEX® Septal Occluder or GORE® CARDIOFORM Septal Occluder plus antiplatelet therapy
  - Medical therapy: antiplatelet therapy alone
- 63 sites in 7 countries
- Canada, Denmark, Finland, Norway, Sweden, UK, US

Recurrent Clinical Stroke in IIT Population:

77% Risk Reduction from PFO Closure



Hazard ratio 0.23: 95% CI 0.09-0.62, Log-rank p = 0.001

The CLOSE Trial

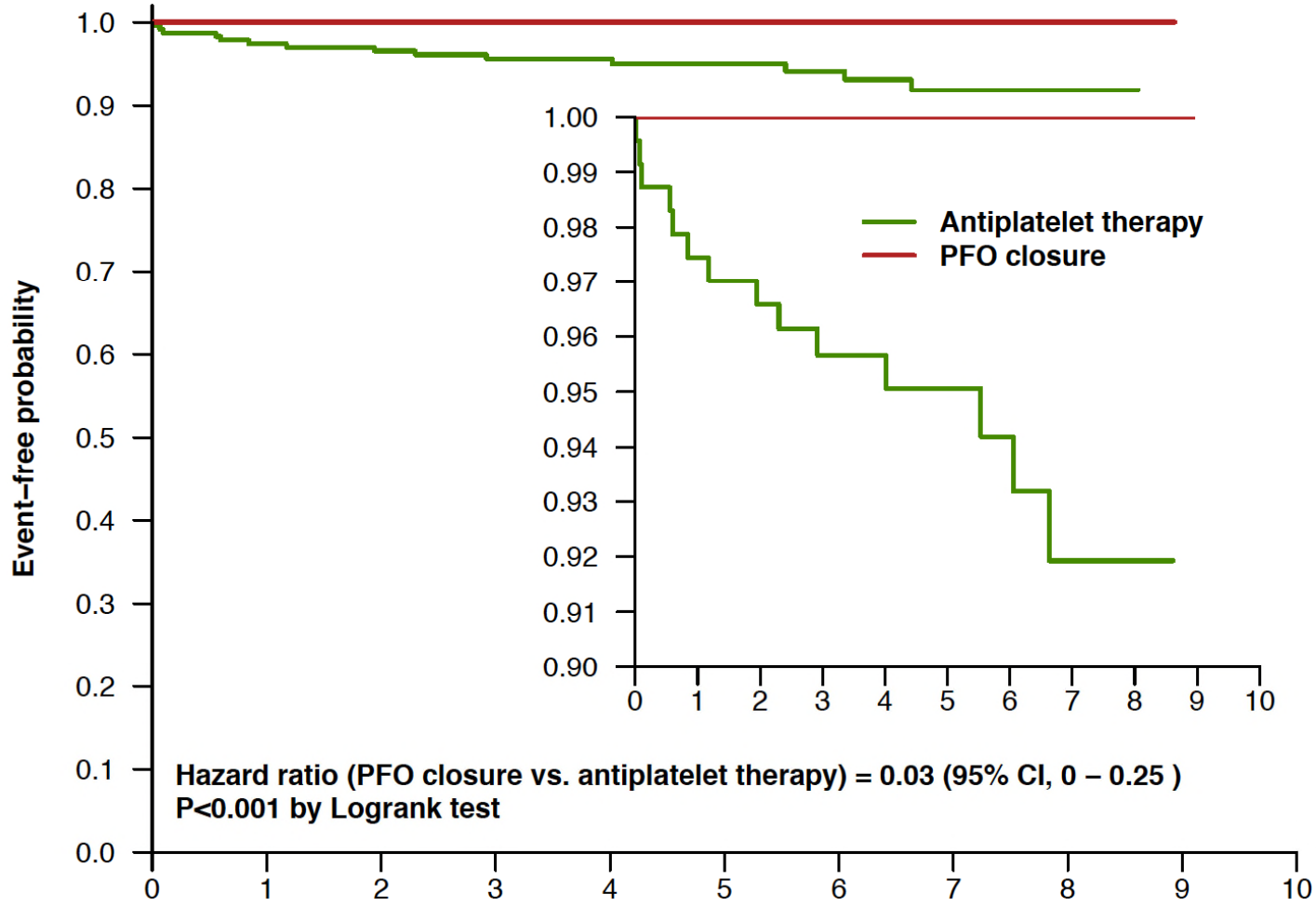
- Objectives: To assess whether PFO closure with device plus antiplatelet therapy on one hand and oral anticoagulants on the other hand, are superior to antiplatelet therapy for secondary stroke prevention in patients 18-60 years old with cryptogenic stroke and *PFO with atrial septal aneurysm or PFO with large shunt.*
- Randomization: Three groups

CLOSE: Device versus Antiplatelet Arm

Recurrent Strokes:

Device = 0 versus APL = 14

Recurrent Ischemic Strokes



Antiplatelet therapy	235	229	223	198	160	130	96	55	19	0	0
PFO closure	238	238	232	200	179	141	99	64	20	0	0

Three Trial Comparisons

- **Efficacy data are consistent**
  - All three trials demonstrated superiority of PFO closure compared to only medical therapy
    - RESPECT largest trial with longest follow-up
    - REDUCE unequivocal efficacy results
    - CLOSURE even greater treatment effect if treating only patients with “high-risk” PFO characteristics
- **Safety data are similar**
  - All three trials showed a relatively low rate of procedure and device complications and most were transient and treatable

What Else Have We Learned?

- PFO closure is a targeted therapy: it does not “cure” patients from having other types of strokes. After PFO closure long-term low dose aspirin and vigorous modification of any vascular risk factor are needed.
- PFO closure in highly selected patients is key to maximizing benefit and avoiding closing incidental PFO’s
- Aspirin in the medical arm was key to demonstrating device tx superior.
  - Warfarin and DOACs not adequately studied in this patient population but what 40 year old wants to take them for the next four decades!

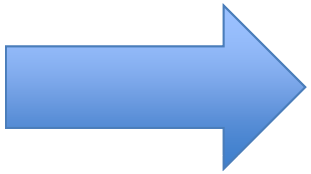
Classification of Recommendations and Level of Evidence for PFO Closure

2014-2016

CLASS III *No Benefit*
or **CLASS III** *Harm*

	Procedure/ Test	Treatment
COR III: No benefit	Not Helpful	No Proven Benefit
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses



2018?

CLASS I

Benefit >>> Risk

Procedure/Treatment **SHOULD** be performed/ administered

- Recommendation that procedure or treatment is useful/effective
- Sufficient evidence from multiple randomized trials or meta-analyses

“…. it seems reasonable that the presence of a PFO and a sizable interatrial shunt should …. no longer result in the categorization of a stroke as cryptogenic.”

EDITORIAL

n engl j med 377;11:1093-1094.

Tipping Point for Patent Foramen Ovale Closure

Allan H. Ropper, M.D.

Conclusions

- PFO closure, with long-term antiplatelet therapy, has conclusive evidence that it reduces the rate of recurrent ischemic strokes versus medical therapy alone.
- The risks of the procedure and the device are relatively low and most are transient.
- The clinical trials stress the importance of careful patient selection, multidisciplinary approach, and meticulous attention to procedure performance with the goal of no complications.

Case Presentation

- A **62** year old woman suffered an episode of left hand weakness 1 year ago. This episode lasted for 3 hours. She saw a neurologist who thought this was a **TIA** with an MRI revealing no evidence of a stroke. A week prior to visiting you, the patient had a transient visual field loss that was very concerning to her and lasted approximately one and one-half hours. The TEE reveals a large PFO with a **septal aneurysm and a very positive bubble test**.

Case Discussion

- My additional questions:
  - Did she have occult PAF excluded with 30 days of monitoring?
  - What other stroke risk factors does she have?
  - Did a neurologist classify her as having a cryptogenic TIA and was the w/u complete?
- RCT's had upper age limit of 60 for good reasons.
  - Recurrent strokes in >60 mostly from non-PFO reasons
- RCT's did not enroll TIA patients for good reasons.
  - No evidence of cortical stroke reduces strength of evidence that she has had paradoxical embolism x2.
- Her PFO has high risk features.
- Was she on aspirin at the time of the TIA's?
- Recommendation: Discuss PFO closure with the patient about the uncertainties of her case, the safety of PFO closure, and the need for aggressive risk factor modification.

Thank You!

Questions and Comments