AMPLATZER™ PFO Occluder for the Prevention of Recurrent Ischemic Stroke

May 24, 2016

St. Jude Medical, Inc.

Circulatory System Device Panel

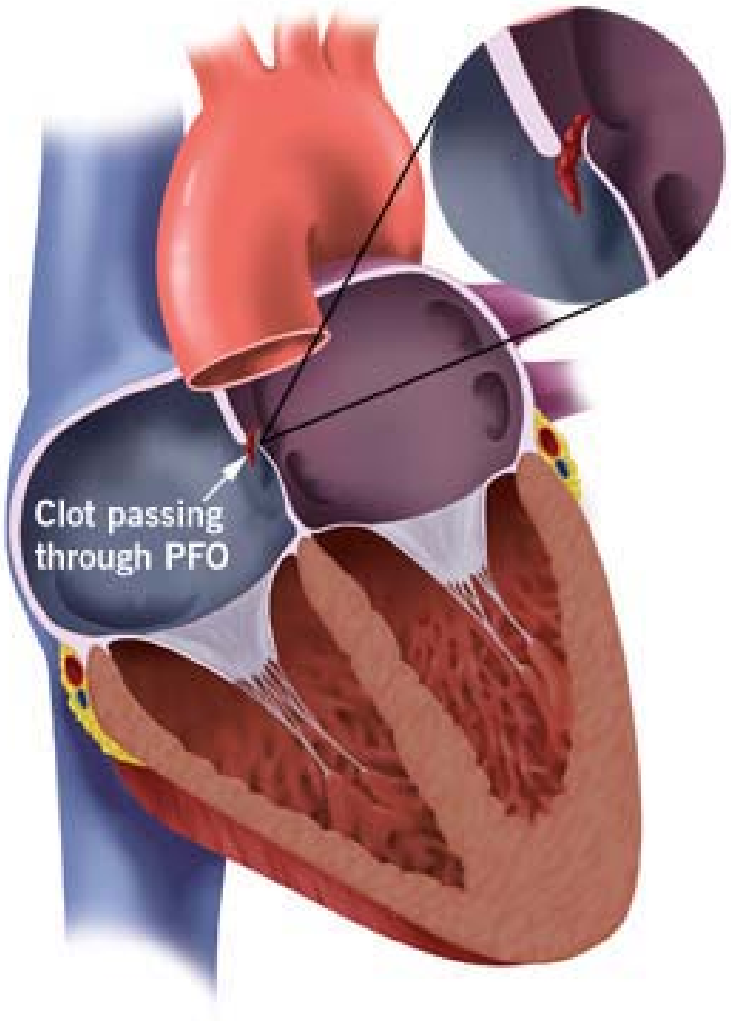
Introduction

Mark D. Carlson, M.D.

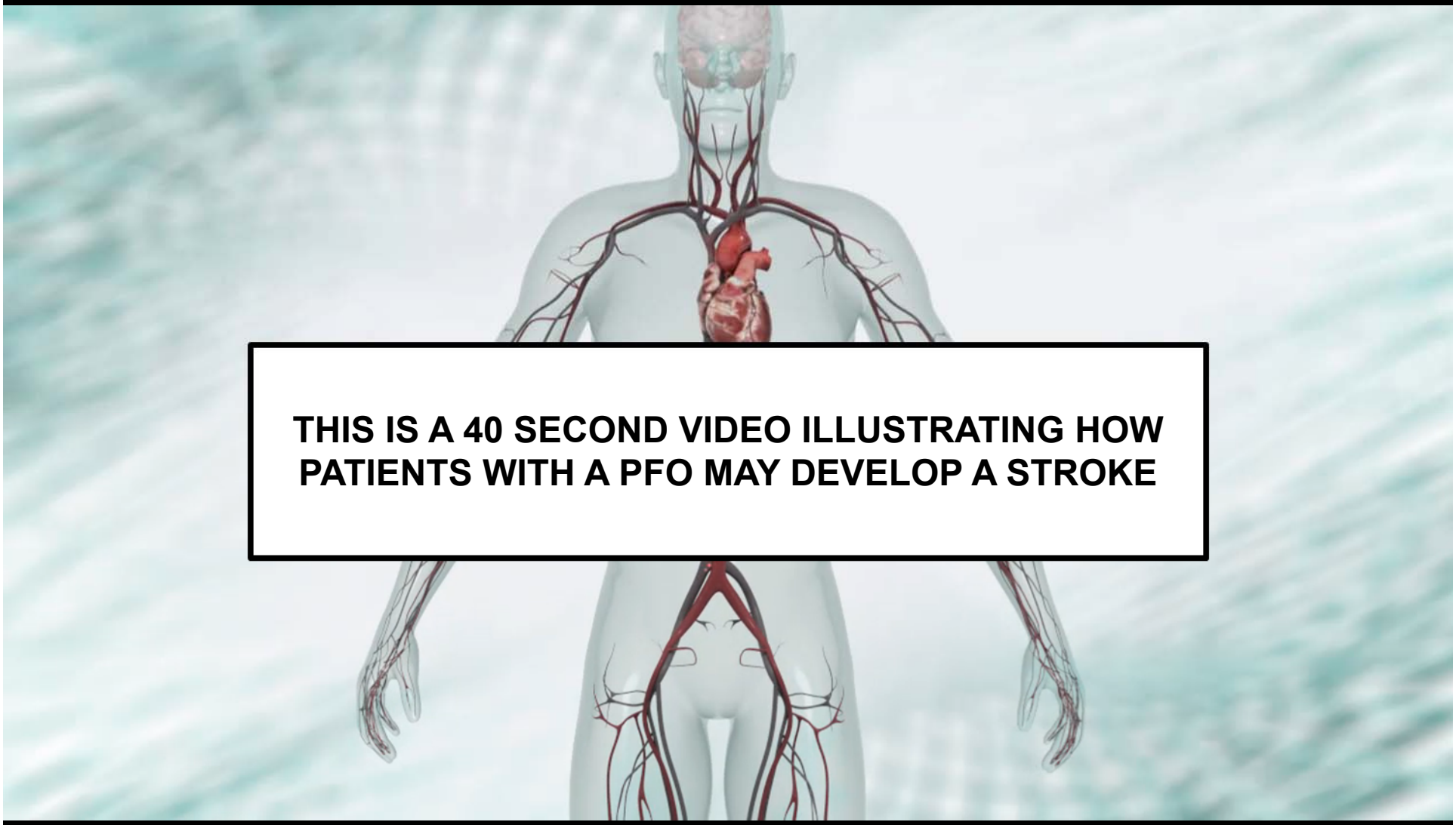
Chief Medical Officer and Global Clinical Vice President

St. Jude Medical, Inc.

PFO: A Hole in the Heart that Usually Closes After Birth

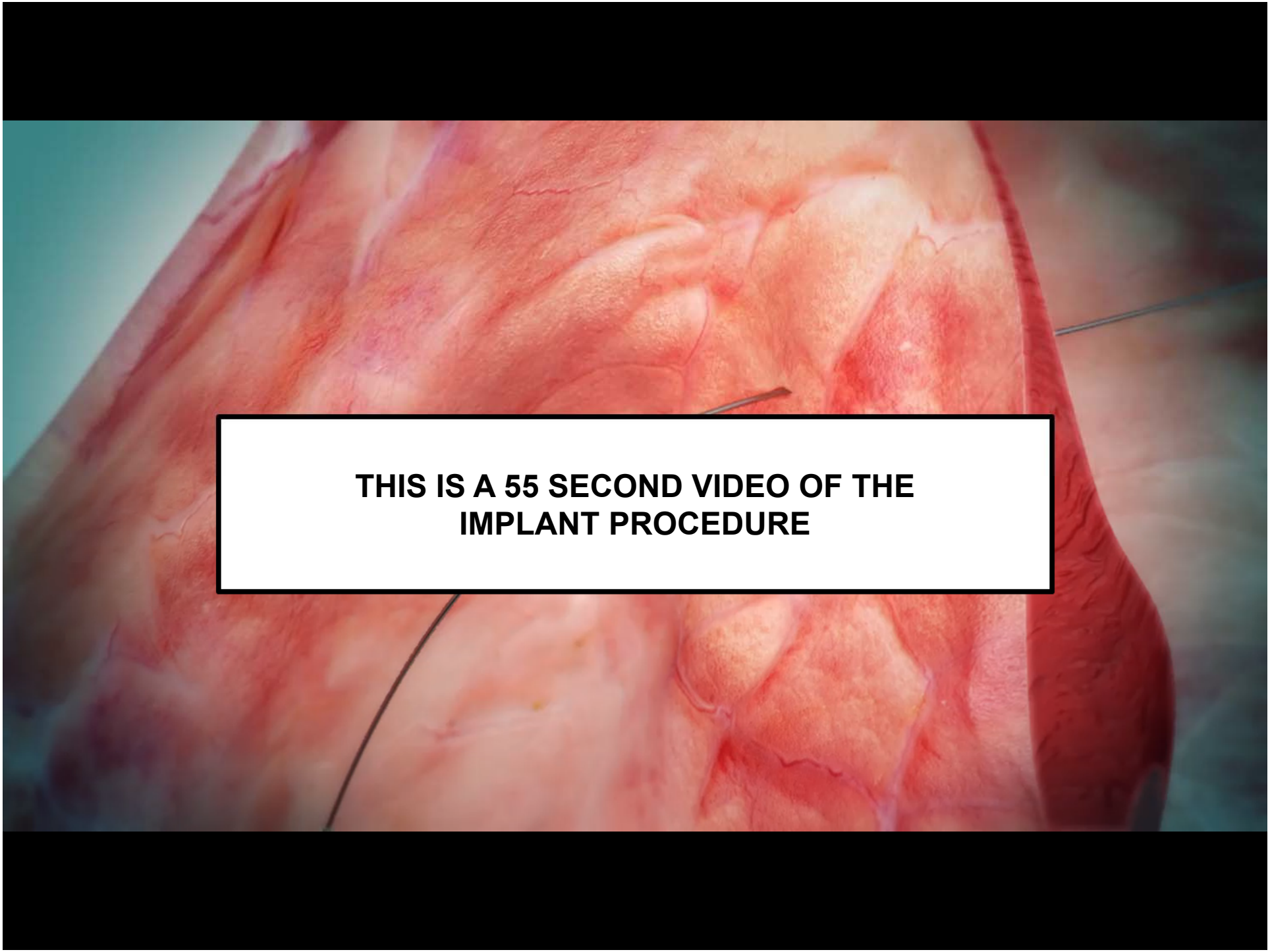


- Some patients with PFO experience stroke at young age
- PFO can allow clots to go from right side of heart to left, travel to brain, cause stroke
- Mechanism is paradoxical embolism
  - Venous thrombus occludes systemic artery


THIS IS A 40 SECOND VIDEO ILLUSTRATING HOW
PATIENTS WITH A PFO MAY DEVELOP A STROKE

AMPLATZER PFO Occluder is a Minimally-invasive PFO Closure Device

- Self-expandable device
- Nitinol wire mesh
- Shape memory and super-elasticity
- 2 discs linked by short connecting waist
- Contains thin polyester fabric to inhibit blood flow


THIS IS A 55 SECOND VIDEO OF THE
IMPLANT PROCEDURE

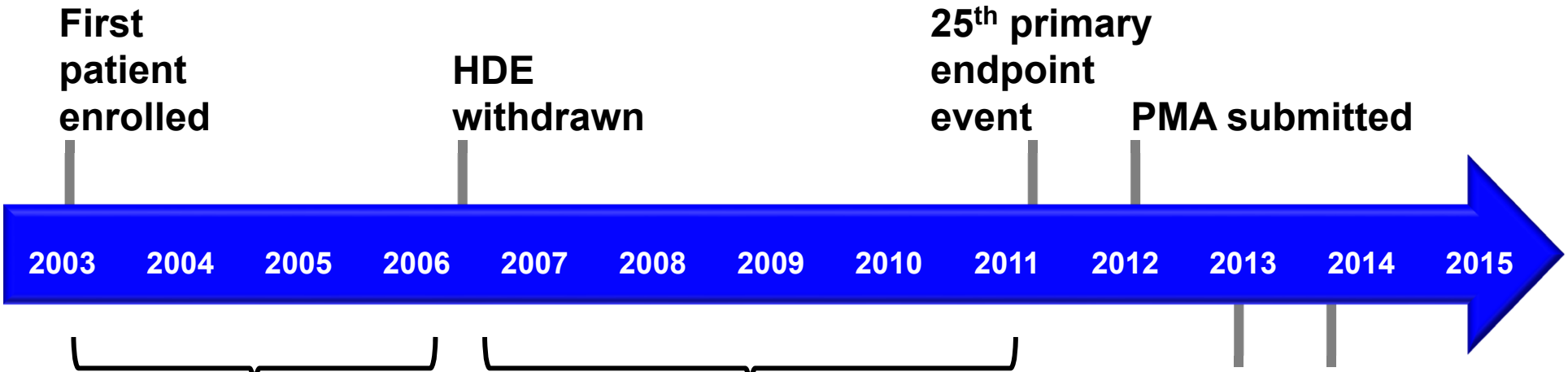
AMPLATZER PFO Occluder is Targeted Therapy for Specific Mechanism of Stroke

- Designed to prevent recurrent stroke due to paradoxical embolism
- PFO closure will not prevent strokes due to other mechanisms

RESPECT Designed to Show Superiority Over Medical Management Alone

- Randomized, event-driven superiority trial
- Patients with cryptogenic stroke and PFO
- Expected event rates based on observational studies

RESPECT Studied Stroke Prevention in Cryptogenic Stroke Patients with PFO



- 259 RESPECT patients enrolled (Avg 78 per year)
- 721 RESPECT patients enrolled (Avg 144 per year)
- 9,700 AMPLATZER PFO Occluders shipped under HDE

Event rate was 50% lower than expected

Key Issues Addressed in Deficiency Letters

- Sensitivity analyses related to patient accountability / populations
- Testing to assess exclusion of other potential causes of index stroke
- Clinical evaluations conducted at time of recurrent stroke
- Questions / meetings related to the indication

RESPECT is Largest Randomized Clinical Trial of PFO Closure Device

- 980 patients enrolled
- At primary assessment
  - > 2,700 patient-years of follow-up
  - > 2 years median follow-up

RESPECT Published Primary Results in *NEJM* in 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

Carroll et al. *NEJM* 2013;368:1092-110.

Primary Endpoint Results Support Clinical Effectiveness of AMPLATZER PFO Occluder

Analysis Population	Relative Risk Reduction	P-value
ITT (Primary Analysis Population)	**50%**	**0.089**
Per-Protocol	**63%**	**0.034**
As-Treated	**72%**	**0.008**
Device-in-Place	**70%**	**0.007**

Proposed AMPLATZER PFO Occluder Indication

The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a PFO to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Agenda

Unmet Need and RESPECT Trial Design	**Jeffrey L. Saver, M.D.** Professor, SA Vice Chair of Neurology Director, Comprehensive Stroke Center David Geffen School of Medicine, UCLA
Effectiveness Results	**David E. Thaler, M.D., Ph.D.** Chairman, Department of Neurology Tufts University School of Medicine
Safety Results	**John D. Carroll, M.D.** Professor of Medicine-Cardiology University of Colorado School of Medicine
Post-approval Plans	**Mark D. Carlson, M.D.**
Clinical Perspectives and Benefit-risk Assessment	**John D. Carroll, M.D.**

Additional Experts

Cardiology	**Richard Smalling, M.D., Ph.D.** Director, Interventional Cardiovascular Medicine University of Texas Health Science Center at Houston
Statistics	**Christopher Mullin, M.S.** Director, Product Development Strategy North American Science Associates
Neurology	**Irfan Altafullah, M.D.** Clinical Professor of Neurology, University of Minnesota
Hematology	**Ken Bauer, M.D.** Professor of Medicine, Harvard Medical School
Neuroradiology	**Brian Larkin, M.D.** North Memorial Medical Center, Minneapolis Radiology Associates Ltd.
RESPECT trial	**Barathi Sethuraman, Ph.D.** Vice President, Clinical Science St. Jude Medical, Inc.
Pre-clinical	**Mike Meyer, B.M.E.** Senior Manager, Research & Development St. Jude Medical, Inc.

Unmet Need for Preventing Recurrent Cryptogenic Strokes in Patients with a PFO

Jeffrey L. Saver, M.D.

Professor and SA Vice Chair of Neurology

Director, Comprehensive Stroke Center

David Geffen School of Medicine

UCLA

Cryptogenic Ischemic Strokes are Strokes of Unknown Cause

Cryptogenic Strokes

- Ischemic strokes without identified cause after thorough evaluation
- ~25% of all ischemic strokes[1]
- 34-46% of ischemic strokes in young and middle-aged (18-60 years)[2,3]
- Often not associated with traditional risk factors
  - Hypertension, diabetes, high cholesterol, smoking

1. Hart et al. *Lancet Neurology* 2014;13:429-436.
2. Putaala et al. *Stroke* 2009;40:1195-1203.
3. Wolf et al. *Cerebrovascular Dis* 2015;40:129-135.

PFOs Related to Cryptogenic Strokes

- PFO present in:
  - 25.4% of U.S. adults[1]
  - 40-50% of cryptogenic stroke patients[2,3]
- Annual burden in the U.S. of young and middle-aged cryptogenic stroke patients with PFO is ~16,000 per year[4-7]

1. Hagen et al. *Mayo Clinic Proceedings* 1984;59:17-20.
2. Lechat et al. *NEJM* 1988;318:1148-1152.
3. Webster et al. *Lancet* 1988;332:11-12.
4. Mozaffarian et al. *Circulation* 2015;131:e29-322.
5. Fonarow et al. *Circ* 2010;121:879-91.
6. Hart et al. *Lancet Neurol* 2014;13:429-38.
7. Handke et al. *NEJM* 2007;357:2262-8.

Consequences of Cryptogenic Stroke

- Extended, lifetime risk of recurrent stroke during most productive years
  - 10-20% by 10 years[1-3]
  - Recurrent stroke most commonly cryptogenic[2]
- Substantial morbidity and mortality[4]
  - At 2 years:
    - 85% have persisting neurologic deficits
    - 55% are disabled (e.g., can't work, drive)
    - 15% died or need daily assistance

1. Arauz et al. *Int J Stroke* 2012;7:631-634.
2. Oxford Vascular Study. *Lancet Neurol* 2015;14:903-913.
3. Cerrato et al. *Neurol Sci* 2006;26:411-418.
4. Redfors et al. *Acta Neurol Scand* 2012;126:329-335.

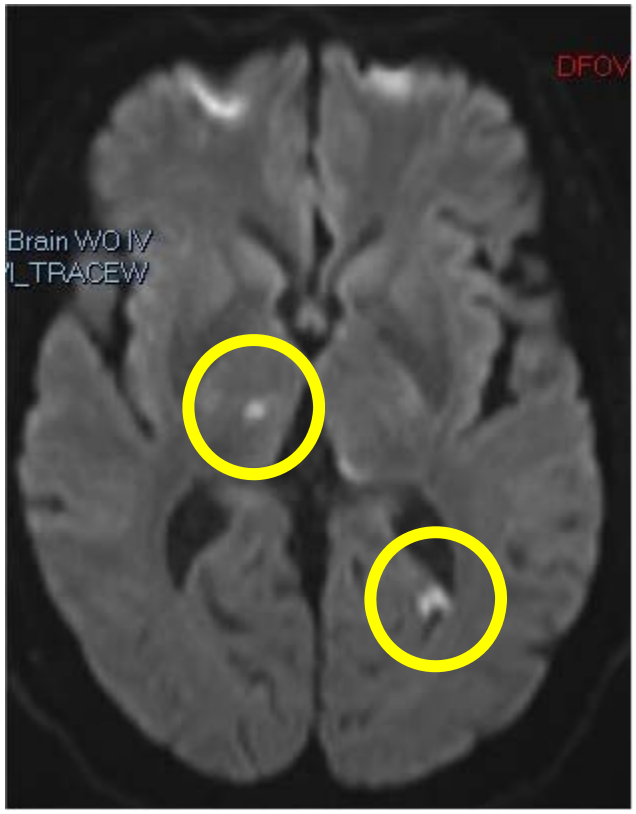
Potential Treatment Options for Secondary Prevention of Cryptogenic Stroke

- Guideline-directed medication regimen
  - Insufficient data on anticoagulant vs. antiplatelet therapy[1]
  - Concerns for long-term antithrombotic therapy
    - Physical labor, sports, pregnancy, etc.
    - 35-50% non-compliance at 1-2 years post-stroke [2,3]
  - Every year, 1-2% rate of recurrence[4,5]
- Surgical PFO closure
  - Small series, some with high complication rates[6]
- Transcatheter PFO closure
  - Must be done using devices off-label that are not intended for PFO closure

1. AHA/ASA Guidelines. *Stroke* 2014;45:2160-2236.
2. Bushnell et al. *Neurol* 2011;77:1182-90.
3. Glader et al. *Stroke* 2010;41:397-401.
4. Mas et al. *NEJM* 2001;345:1740-1746.
5. Arauz et al. *Int J Stroke* 2012;7:631-634.
6. Gasiavelis et al. *Scand Cardiovasc J* 2004;38:375-379.

Patient With PFO Suffering Cryptogenic Strokes

- 54 year-old male, first stroke in 2010
  - No conventional cause
  - PFO and ASA present
- Aspirin initiated as preventative therapy
- Second stroke in 2016
  - Basilar artery occluded



Summary of Unmet Need

- PFOs permit venous clots to paradoxically embolize and travel to the brain
- PFO-related cryptogenic strokes can be devastating
  - Can occur in otherwise healthy people with few, if any, traditional risk factors
  - Medical management does not eliminate risk
- Transcatheter PFO closure could be an important additional treatment option for patients

RESPECT Trial Design and Baseline Characteristics

RESPECT Designed to Show Superiority Over Medical Management Alone

- Superiority trial: AMPLATZER PFO Occluder vs. guideline-directed medical management (MM)
- Design: randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1
  - 69 sites in U.S. and Canada
  - Enrolled from 2003 to 2011
  - Patients continue to be followed

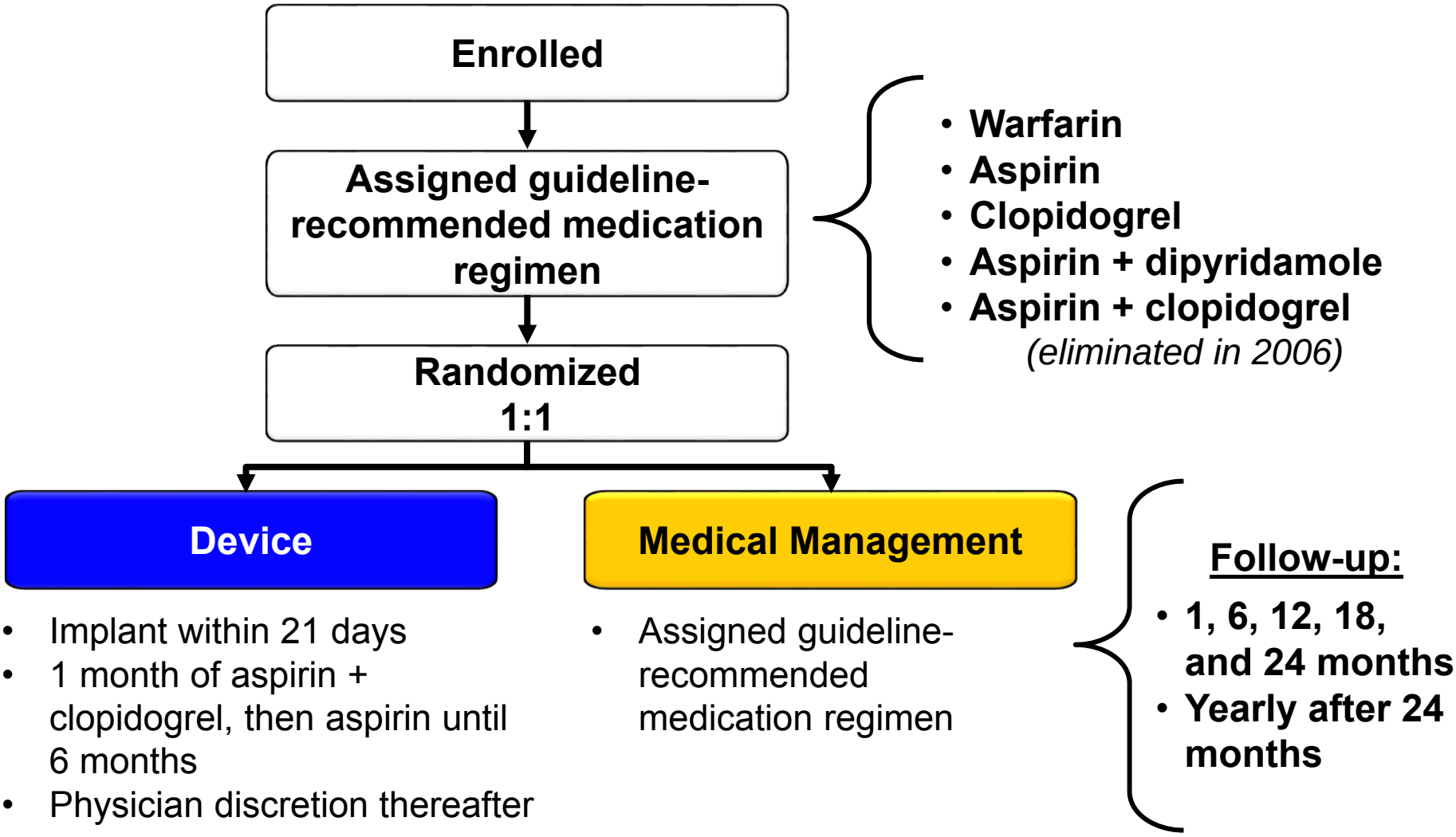
Key Inclusion Criteria

- Cryptogenic stroke within last 9 months
  - Stroke = acute focal neurological deficit + new cerebral infarct or ≥ 24 hr symptoms
- Presence of PFO by TEE
- Between 18 and 60 years
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

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
- Unable to discontinue anticoagulants

Trial Design



Primary Endpoint

- Primary endpoint is a composite of:
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Post-randomization death (within 45 days)
- Stroke defined as acute focal neurological deficit with new cerebral infarct or symptoms at least 24 hours

Ascertainment of Primary Endpoint Events

- Unscheduled clinic visits
- Hospitalizations
- Neurologic General Symptoms Interview[1] at all scheduled follow-up visits
  - Weakness, dizziness, problems with speaking, vision, or sensation

1. ACAS TIA/Stroke methodology

Adjudication of Primary Endpoint Events

- Stroke adjudication by independent Clinical Events Committee
- Blinded to treatment arm

Trial Assumed 75% Relative Risk Reduction Based on Observational Data

- 2-year rates based on published observational studies:
  - 4.3% for medically managed patients[1-3]
  - 1.0% for patients receiving AMPLATZER or other PFO occluders[4-9]

1. Mas & Zuber *Am Heart J* 1995;130:1082-8.
2. Bogousslavsky et al. *Neurol* 1996;46:1301-5.
3. DeCastro et al. *Stroke* 2000;31:2407-13.
4. Onorato et al. *J Interv Cardiol* 2003;16:43.
5. Sievert et al. *J Interv Cardiol* 2001;14:261.
6. Butera et al. *Ital H J* 2001;2:115-8.
7. Brandt et al. *J Am S Echocardiog* 2002;15:1094-8.
8. Martin et al. *Circulation* 2002;106:1121-6.
9. Beitzke et al. *Zeitschrift Für Kardiologie* 2002;91:693-700.

Statistical Methods

- Powered at 80% at 0.05 two-sided significance level
  - Event-based trial
  - Designed to enroll patients until 25 primary endpoint events were adjudicated
- Statistical analysis
  - Raw count analysis, Fisher's exact test
  - Kaplan-Meier analysis with log-rank test, Cox models to estimate hazard ratios

Key Defining Features of Analysis Populations

Analysis Population	Patients Included	Analysis Groups
ITT	All randomized	Randomization arm
Per-Protocol	Adherent to protocol requirements	Randomization arm
As-Treated	Adherent to protocol requirements	Treatment actually received
Device-in-Place	All randomized	Treatment actually received

Demographics and Stroke Risk Factors Balanced Between Arms

Characteristic	AMPLATZER PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	46 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	40%
Family history of heart disease	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%

Planned Medication Regimen if Randomized to MM Arm

	AMPLATZER PFO Occluder (N=499)	Medical Management (N=481)
Warfarin	26%	25%
Aspirin	50%	47%
Clopidogrel	12%	14%
Aspirin + dipyridamole	5%	8%
Aspirin + clopidogrel[1]	7%	6%

1. Eliminated as a treatment option in 2006

99.6% Successful Implant Rate

	N
Patients randomized to device (ITT)	**499**
No attempt (patient decision)	17
No attempt (intra-procedural exclusion)	15
Device implant attempted	**467**
Failure to implant	2
Successful implant	**465* (99.6%)**

* 463 devices implanted on the first attempt

Evaluation of Closure Status at 6 Months

- Echo Core Lab assessed closure status of shunt via TEE
- Successful assessment required classification both *at rest* and *valsalva*

Disposition of 6-month TEE	N (%)
Total patients with successful implant	**465 (100%)**
TEE completed	**440 (95%)**
Technically adequate per Echo Core Lab	**349 (75%)**
Not fully technically adequate per Echo Core Lab	**91 (20%)**

PFO Closure in the RESPECT Device Arm at 6 Months

Closure	Definition	n/N (%)
Complete	0 microbubbles at rest and at Valsalva	249/349 (71%)
Effective	0-9 microbubbles at rest and at Valsalva	323/343 (94%)

- Effective closure
  - Many will progress to complete closure[1-3]
  - Technical efficacy endpoint in CLOSURE and PC trials[4,5]

1. von Bardeleben et al. *Int J Cardiol* 2009;134:33–41.
2. Hammerstingl et al. *Eur J Med Res* 2011;16: 13–19.
3. Matsumura et al. *Cath Cardiovasc Interv* 2014;84:455–463.
4. Furlan et al. *NEJM* 2012;366:991-9.
5. Meier et al. *NEJM* 2013;368:1083-91.

Patient Disposition at Time of Primary Assessment

Disposition	AMPLATZER PFO Occluder (N=499)	Medical Management (N=481)
Withdrawal[1]	50 (10%)	84 (17%)
Withdrawal of consent	23 (5%)	50 (10%)
Lost to follow-up	21 (4%)	27 (6%)
Other (includes death)	6 (1%)	7 (1%)

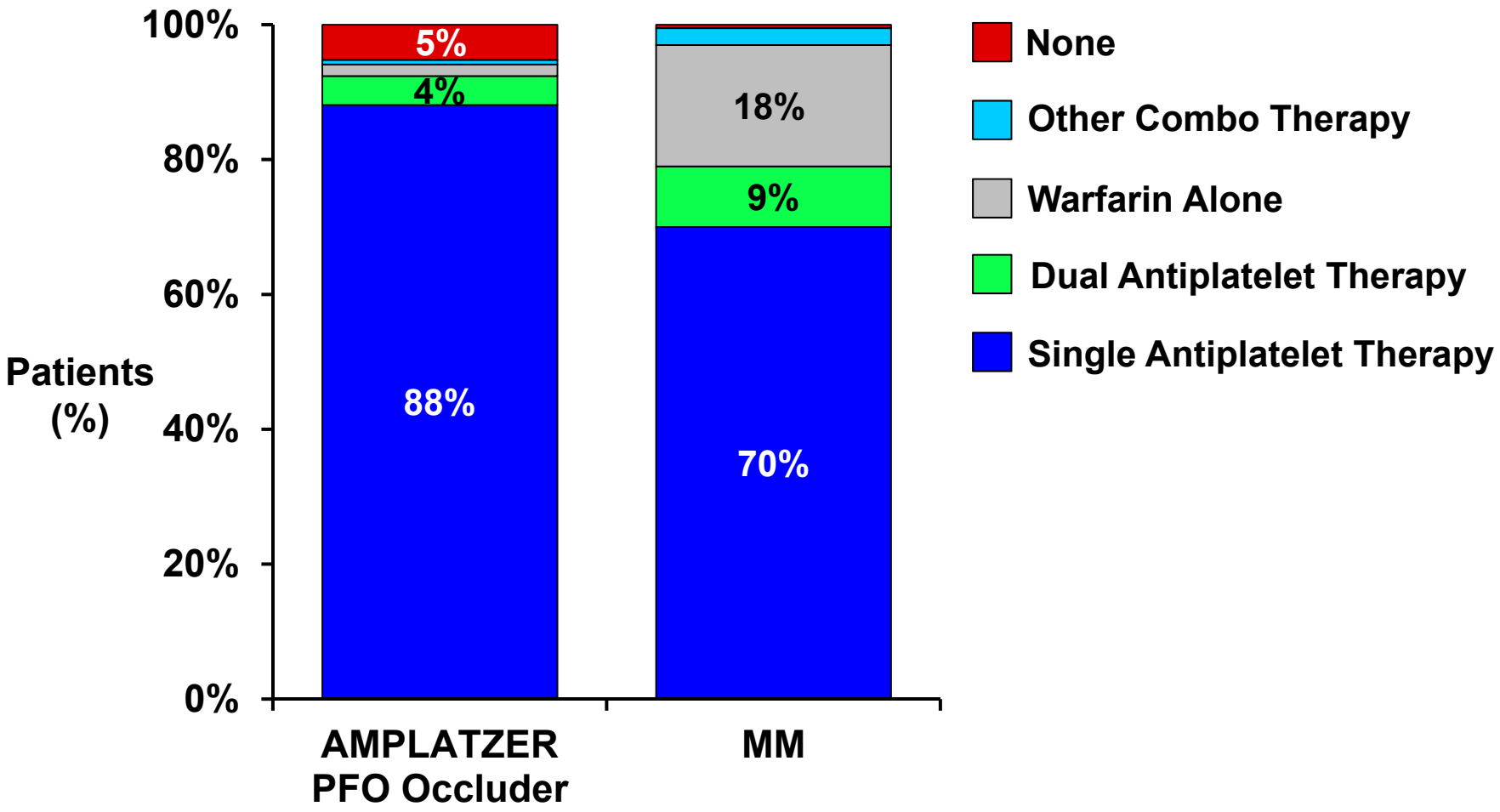
- MM withdrawal of consent includes 28 patients unhappy with randomization or stated they intended to seek PFO closure outside the trial

1. Before primary endpoint event

Follow-up Duration at Time of Primary Assessment

	AMPLATZER PFO Occluder (N=499)	Medical Management (N=481)
Mean (years)	**3.0**	**2.7**
Median (years)	**2.9**	**2.1**
Total (patient-years)	**1,476**	**1,284**

Antithrombotic Medication Use at 2 Year Follow-up



RESPECT Effectiveness Results

David E. Thaler, M.D., Ph.D.
Chairman, Department of Neurology
Tufts University School of Medicine
Tufts Medical Center

Outline for Effectiveness Results

Primary Endpoint Analysis in ITT and PP Populations

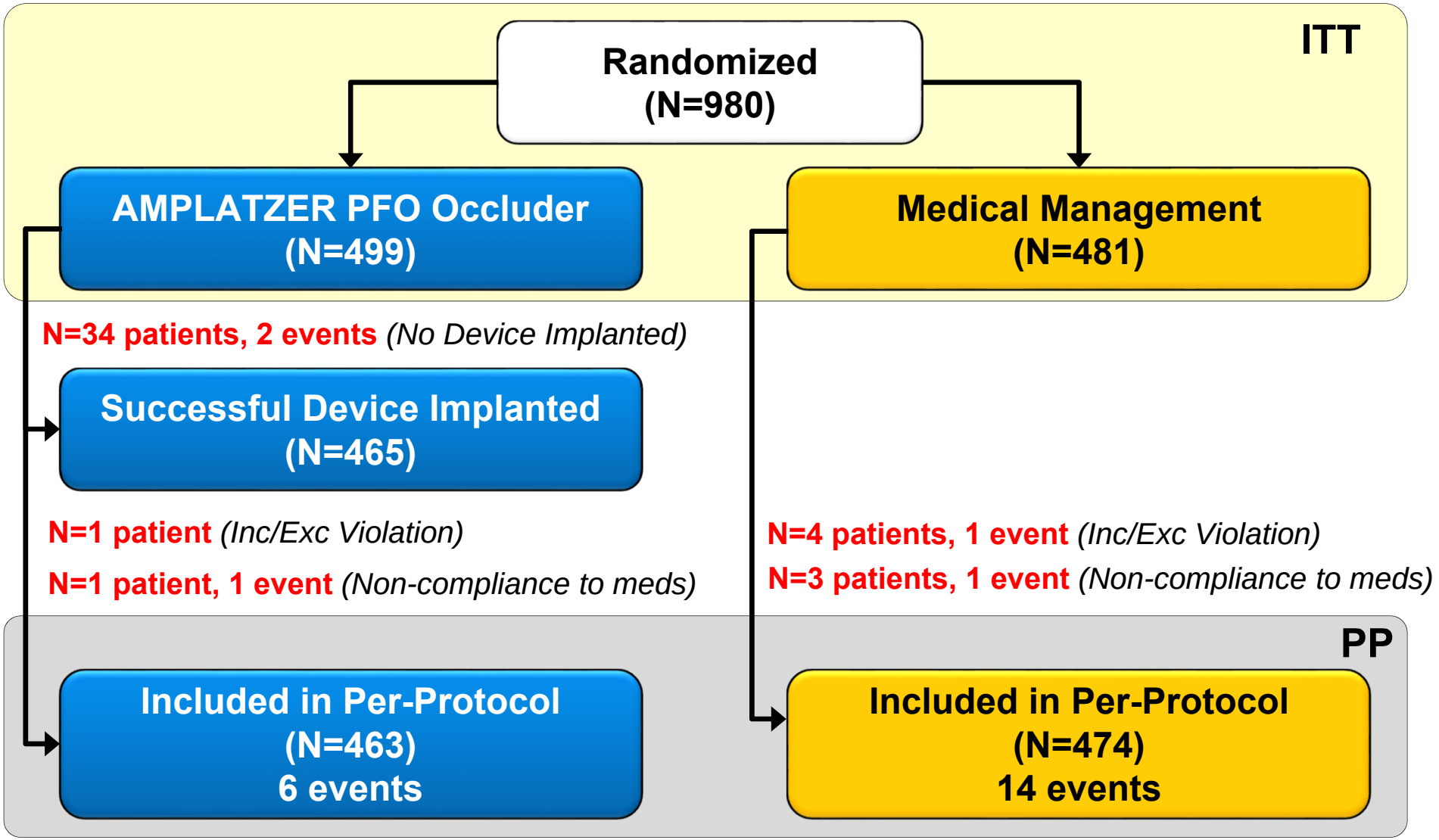
Sensitivity Analysis for Missing Data

Primary Endpoint Analysis in As-Treated and Device-in-Place Populations

Primary Endpoint Analysis in the Extended Follow-up Period

Patient-Level Meta-Analysis

Disposition for Intention to Treat (ITT) and Per-Protocol Populations (PP)

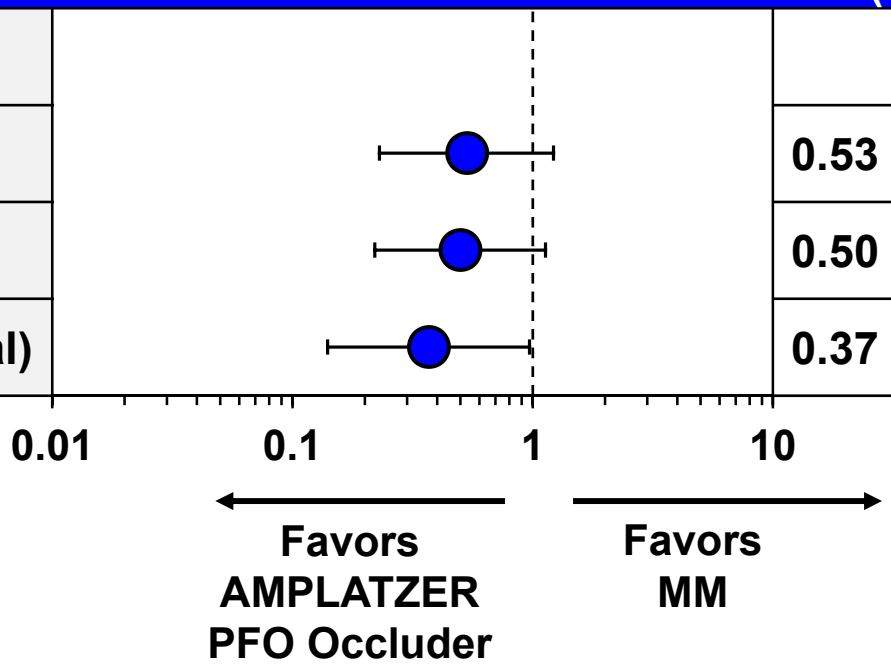


All Primary Endpoint Events That Occurred in RESPECT Were Recurrent Nonfatal Strokes

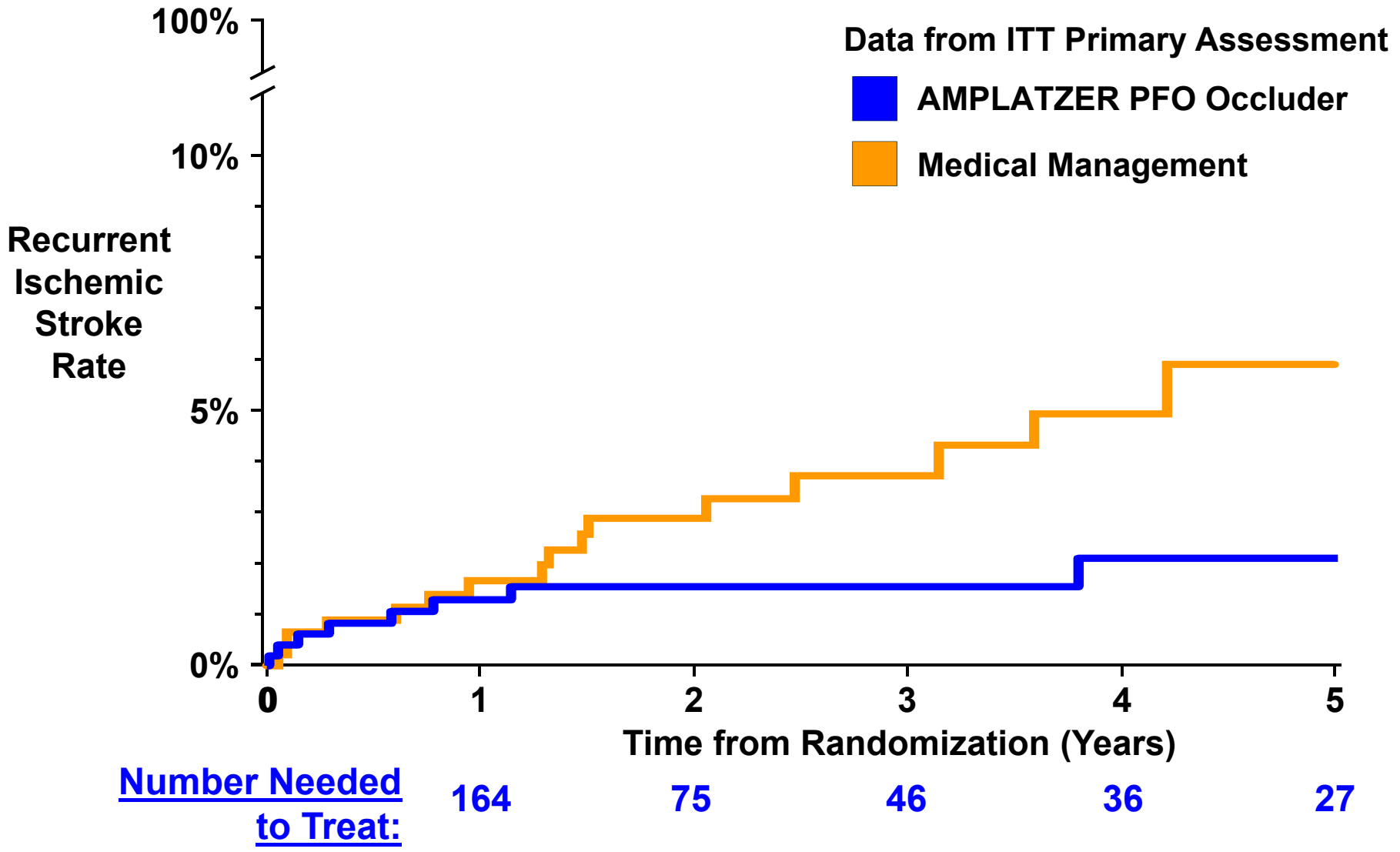
- Composite endpoint
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Post-randomization death (within 45 days)
- Deaths: 3 Device arm and 6 MM arm
- **All primary outcome events were recurrent nonfatal ischemic strokes**

Pre-specified Analyses of Primary Endpoint

Population (Analysis)	Hazard Ratio or Odds Ratio (95% CI)	P-Value
Pre-specified Analyses		
ITT (Raw Count)	0.53 (0.23, 1.22)	0.16
ITT (Survival)	0.50 (0.22, 1.13)	0.089
Per-Protocol (Survival)	0.37 (0.14, 0.97)	0.034



Number Needed To Treat for PFO Closure Declines Over Time



Outline for Effectiveness Results

Primary Endpoint Analysis in ITT and PP Populations

Sensitivity Analysis for Missing Data

Primary Endpoint Analysis in As-Treated and Device-in-Place Populations

Primary Endpoint Analysis in the Extended Follow-up Period

Patient-Level Meta-Analysis

Patients Who Withdrew Had Higher Prevalence of Stroke Risk Factors

- 50 Device and 84 MM patients withdrew without experiencing a primary endpoint event
- Risk factors for stroke were more common among patients who withdrew than those who remained in the trial:
  - Stroke prior to qualifying cryptogenic stroke (16% vs. 10%)
  - Current smoker (18% vs. 12%)
  - Former smoker (34% vs. 27%)

Device Arm Stroke Rate Would Need to be 10 Times Higher to Tip Per-Protocol Analysis

	AMPLATZER PFO Occluder	Medical Management
N events	6	14
Observed event rates	0.4% per year	1.2% per year
Missing follow-up	90 PYs	321 PYs

- Tipping point analysis assumed the same stroke rate in missing MM data as observed MM data (1.2% per year)
  - 4 strokes imputed
- Added device strokes until analysis "tipped" to insignificance
  - Required 4 additional strokes (4.4% per year) to tip the per-protocol analysis
  - Would need to assume stroke rate in missing device data was ***10 times greater*** than that observed in trial

Outline for Effectiveness Results

Primary Endpoint Analysis in ITT and PP Populations

Sensitivity Analysis for Missing Data

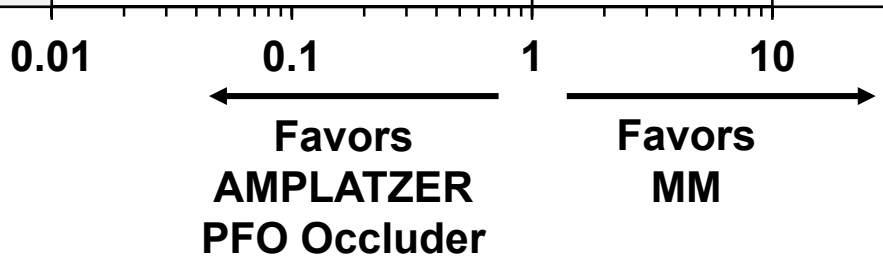
Primary Endpoint Analysis in As-Treated and Device-in-Place Populations

Primary Endpoint Analysis in the Extended Follow-up Period

Patient-Level Meta-Analysis

Primary Endpoint Results in All Analysis Populations

Endpoint	Hazard Ratio (95% CI)
Pre-specified Analyses	
ITT (Raw Count)	0.53 (0.23, 1.22)
ITT (Survival)	0.50 (0.22, 1.13)
Per-Protocol (Survival)	0.37 (0.14, 0.97)
Exploratory Analyses	
As-Treated (Survival)	0.28 (0.10, 0.77)
Device-in-Place (Survival)	0.30 (0.12, 0.76)



Outline for Effectiveness Results

Primary Endpoint Analysis in ITT and PP Populations

Sensitivity Analysis for Missing Data

Primary Endpoint Analysis in As-Treated and Device-in-Place Populations

Primary Endpoint Analysis in the Extended Follow-up Period

Patient-Level Meta-Analysis

Considerations Regarding Extended Follow-Up Period

- Post-hoc analysis to address FDA request for updated safety and effectiveness data
- Differential drop-out persisted
- Key assumption of RESPECT: recurrent strokes mostly due to paradoxical embolism
  - Less valid assumption in extended follow-up
    - 1 in 5 patients had aged > 60 years old
    - Aging population at increasing risk for competing, non-PFO related strokes

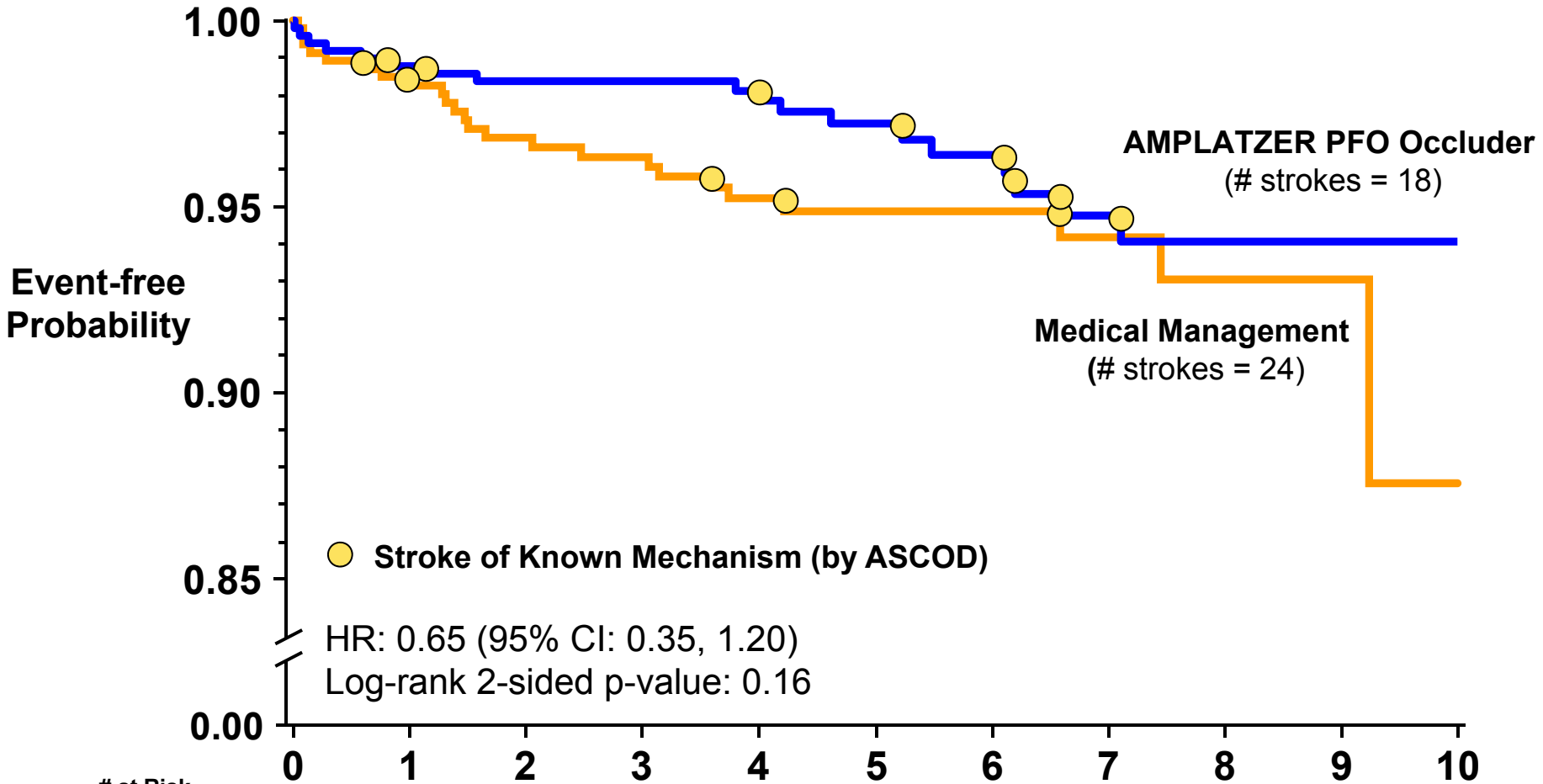
Nearly 1/3 of Recurrent Strokes Through Extended Follow-up Are of Known Mechanism (ITT)

	AMPLATZER PFO Occluder	Medical Management
Strokes Through Extended Follow-Up	**18**	**24**
Strokes of Known Mechanism	**8**	**5**
Atherosclerosis	1	0
Small Vessel Disease	4	2
Cardioembolic	2	3
Other	1	0
Dissection	0	0
Strokes of Undetermined Mechanism	**10**	**19**

Amarenco et al. *Cerebrovasc Dis* 2013;36:1-5.

Phenotyping by ASCOD

All Recurrent Strokes Through Extended Follow-up (ITT)

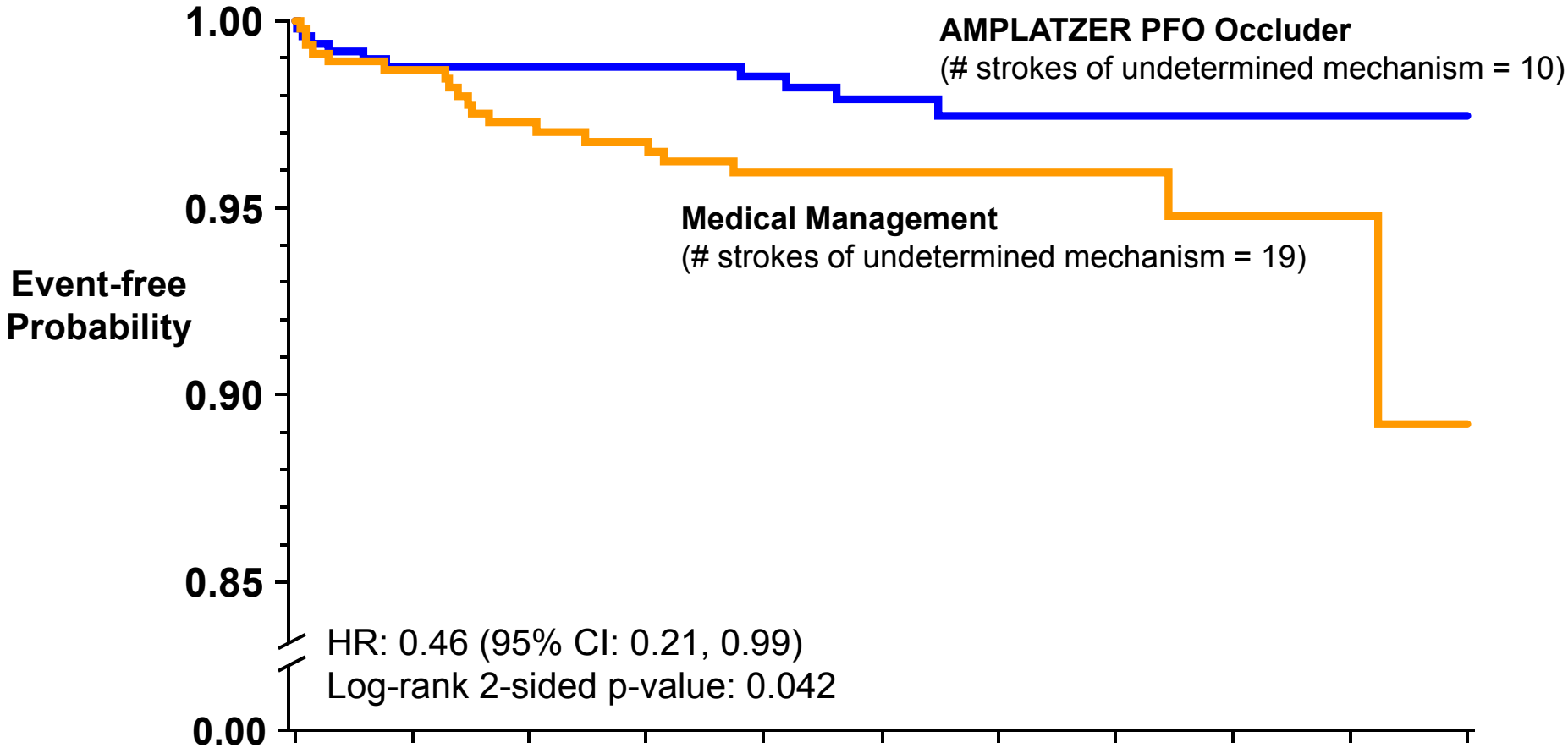


# at Risk (KM Estimates)										
AMPLATZER	**499** (0%)	**476** (1.4%)	**463** (1.6%)	**434** (1.6%)	**369** (1.9%)	**282** (2.8%)	**212** (3.6%)	**151** (5.2%)	**86** (6.0%)	**44** (6.0%)	**20** (6.0%)
MM	**481** (0%)	**432** (1.8%)	**394** (3.2%)	**367** (3.7%)	**307** (4.8%)	**238** (5.1%)	**168** (5.1%)	**113** (5.8%)	**71** (7.0%)	**34** (7.0%)	**10** (12.4%)

Amarenco et al. *Cerebrovasc Dis* 2013;36:1-5.

54% Relative Risk Reduction for Recurrent Stroke of Undetermined Mechanism (ITT)

Phenotyping by ASCOD



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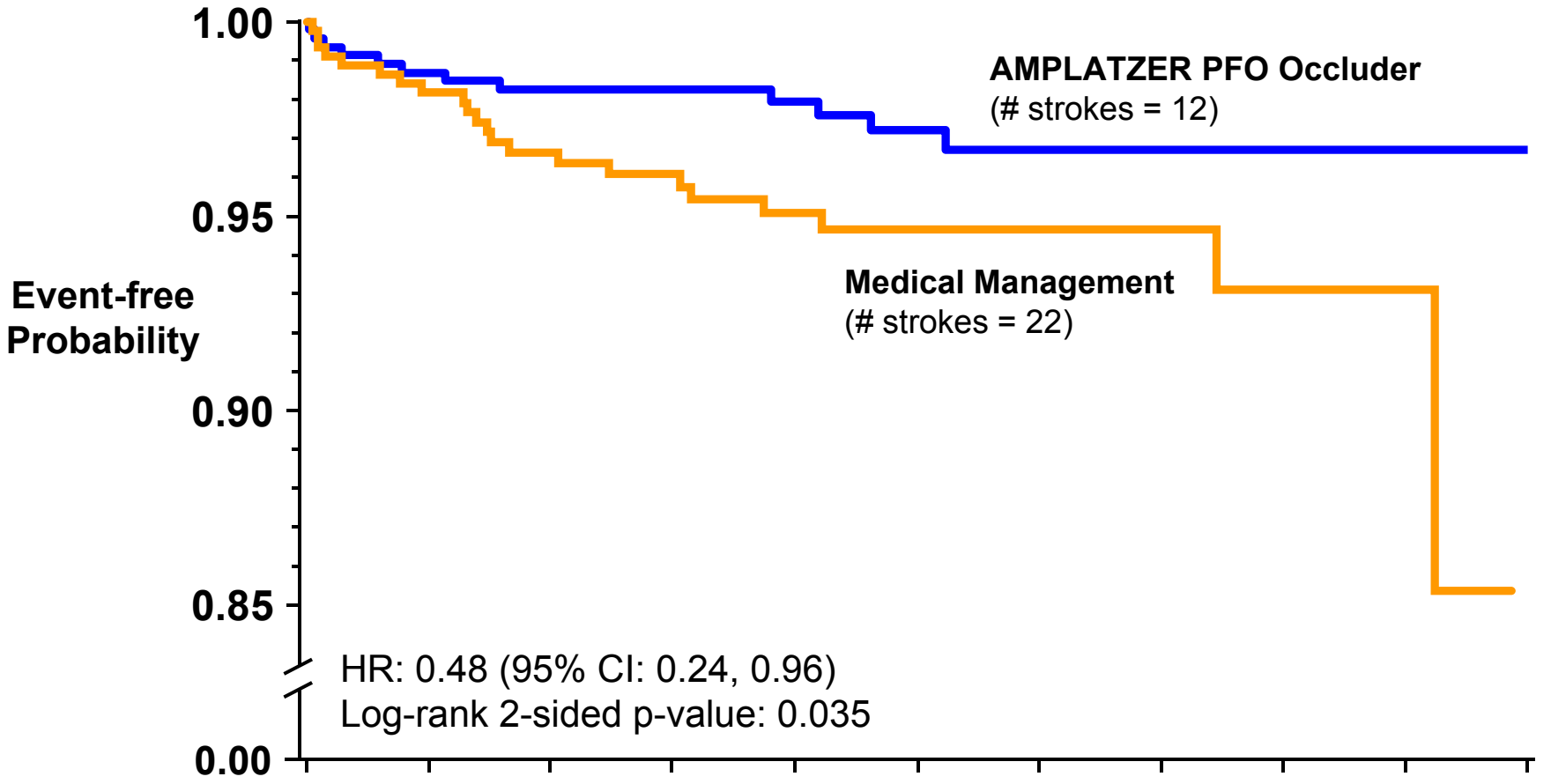
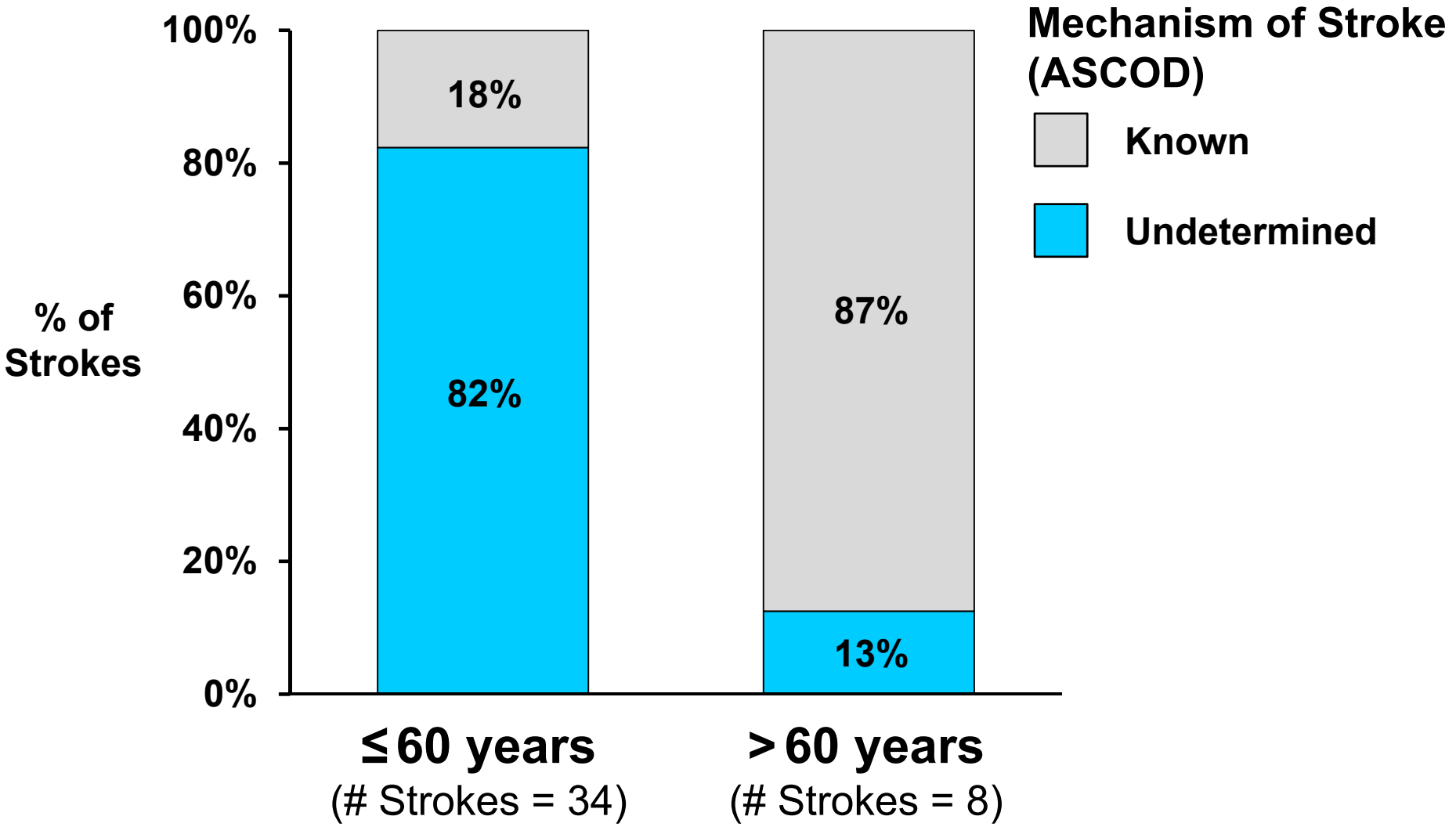
52% Relative Risk Reduction for Recurrent Stroke in Patients < 60 Years (ITT)



# at Risk (KM Estimates)										
AMPLATZER	**475** (0%)	**443** (1.3%)	**417** (1.8%)	**375** (1.8%)	**308** (2.1%)	**230** (2.8%)	**166** (3.3%)	**117** (3.3%)	**69** (3.3%)	**33** (3.3%)	**15** (3.3%)
MM	**463** (0%)	**401** (1.8%)	**353** (3.4%)	**313** (4.0%)	**254** (4.9%)	**189** (5.4%)	**124** (5.4%)	**86** (5.4%)	**51** (6.9%)	**26** (6.9%)	**9** (14.7%)

Nearly All Strokes Through Extended Follow-Up for Patients > 60 Due to Known Mechanism



Outline for Effectiveness Results

Primary Endpoint Analysis in ITT and PP Populations

Sensitivity Analysis for Missing Data

Primary Endpoint Analysis in As-Treated and Device-in-Place Populations

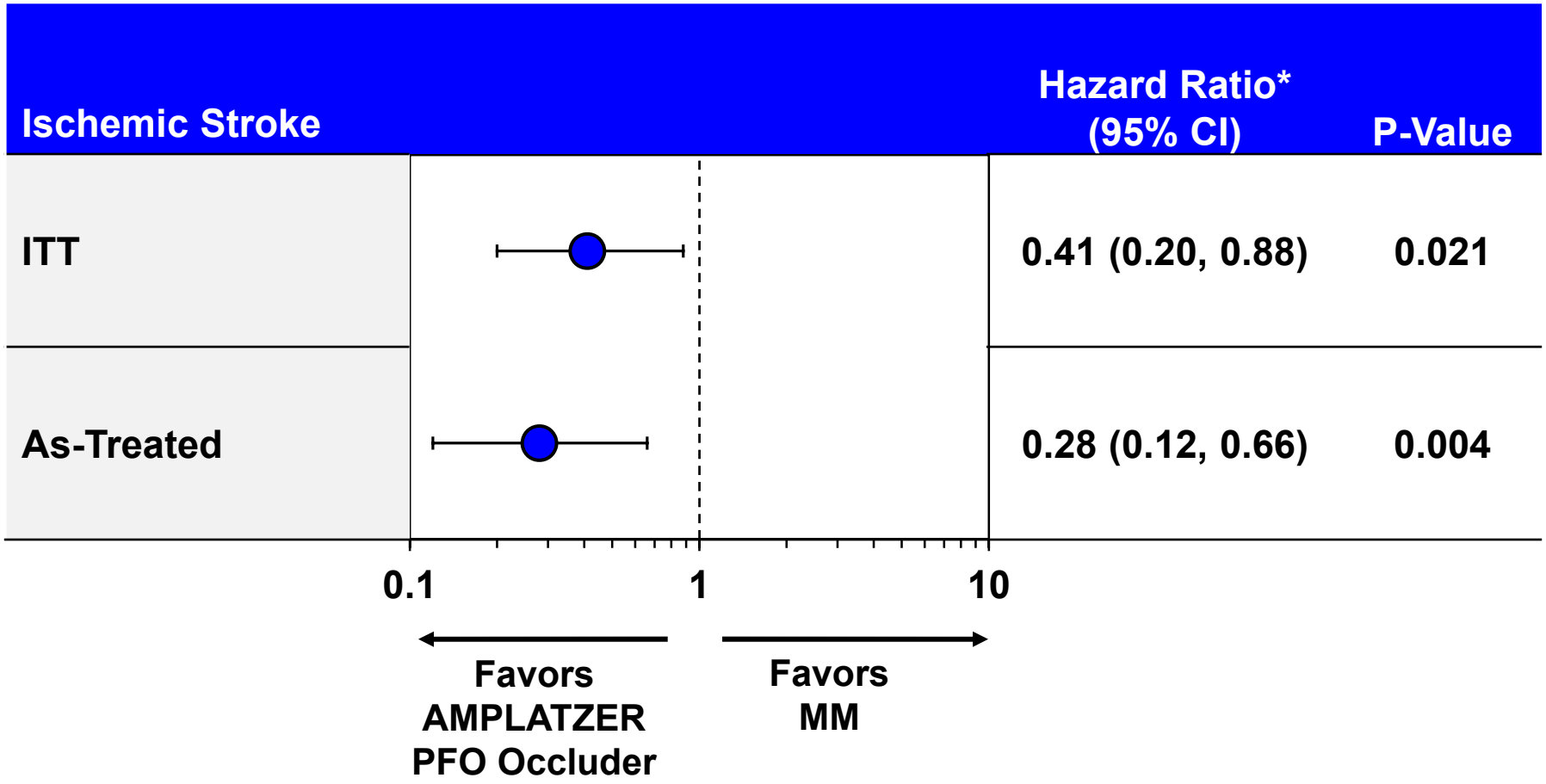
Primary Endpoint Analysis in the Extended Follow-up Period

Patient-Level Meta-Analysis

Design of RESPECT and PC Trials

	RESPECT	PC
Device	AMPLATZER PFO Occluder	
Geography	U.S. and Canada	Canada, Europe, Brazil, Australia
Randomization	1:1 (Device:MM)	
Trial enrollment dates	2003 – 2011	2000 – 2009
Total patients	980	414

Significant Relative Risk Reduction for Recurrent Ischemic Stroke in Meta-Analysis



*Models adjusted for: age, sex, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, ASA, shunt size

Kent et al. *J Am Coll Cardiol* 2016;67:907-17.

Summary of Effectiveness Findings

- RESPECT primary endpoint not met in ITT analysis population
  - 50% relative risk reduction (p=0.089)
- Additional analysis populations support device effect
- Through extended follow-up, persistent benefit for recurrent cryptogenic strokes
- Significant reduction in recurrent ischemic stroke in meta-analysis of AMPLATZER PFO Occluder trials
  - 59% relative risk reduction (p=0.021)

RESPECT Safety Findings

John D. Carroll, M.D.
Professor of Medicine – Cardiology
University of Colorado School of Medicine
University of Colorado Hospital

Similar SAE Profile Between Arms Through Extended Follow-up

SAE Type	AMPLATZER PFO Occluder (N=499)		Medical Management (N=481)	
	n (%)	Rate per 100 PYs	n (%)	Rate per 100 PYs
Any SAE	189 (37.9%)	13.9	168 (34.9%)	12.5
Unanticipated adverse device effect	0 (0%)	0	--	--
Deaths related to procedure or device	0 (0%)	0	--	--
SAE related to procedure	12 (2.4%)	0.4	--	--
SAE related to device	10 (2.0%)	0.5	--	--

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 - 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

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

Event Type	n (%)
Ischemic stroke *(primary endpoint)*	2 (0.4%)
Pulmonary embolism	2 (0.4%)
Thrombus in right atrium *(not attached to device)*	1 (0.2%)
Explant/surgical intervention	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

Rate of Atrial Fibrillation Similar Between Arms after Accounting for Peri-procedural Events

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	20	23	0.83	9	12	0.51
Peri-procedural	7	7	0.25	-	-	-
Post-procedural	13	16	0.58	-	-	-

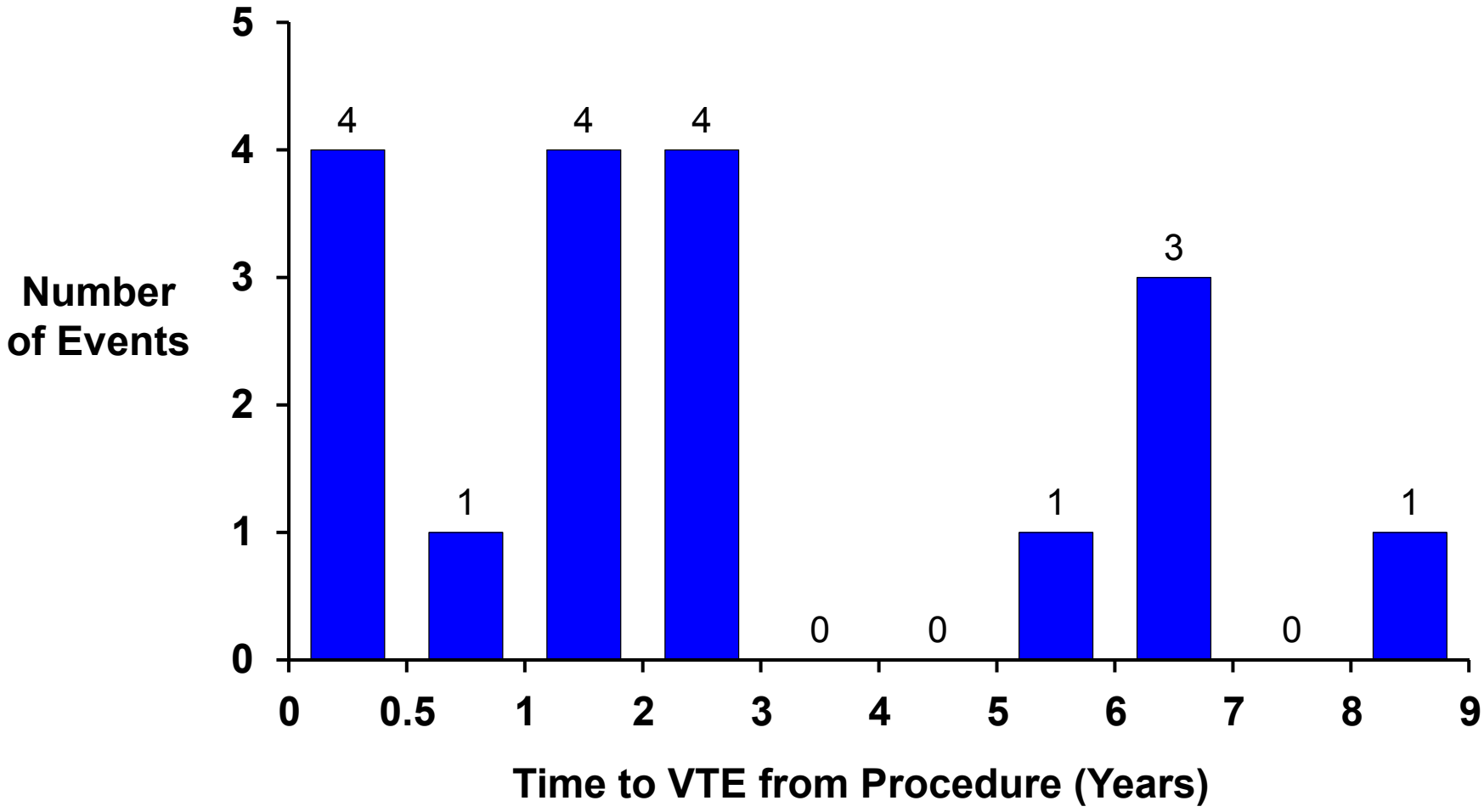
- Includes both serious and non-serious events
- All 7 peri-procedural AF events in Device arm resolved prior to discharge
- 1 AF-related stroke in Device arm, 3 in MM arm

Higher Rate of Venous Thromboembolic Events (VTE) in Device Arm

Event	AMPLATZER PFO Occluder (N=499)			Medical Management (N=481)		
	# Patients	# Events	Rate Per 100 PYs	# Patients	# Events	Rate Per 100 PYs
All VTEs	18	24	0.87	3	5	0.21
DVT	11	11	0.40	3	3	0.13
PE	12	13	0.47	2	2	0.08

- Cryptogenic stroke patients are likely at high risk for thromboembolic events
- Device prevents paradoxical embolism, but does not prevent clots from forming in the first place

Most VTEs in Device Arm Occurred > 1 Year After Implant Procedure



Extended Follow-up

Protocol-driven Differences in Medical Therapy is a Likely Explanation for Imbalance in VTE

- History of DVT impacts underlying risk
  - 12 times more likely to have VTE during trial
- Protocol-driven imbalance of warfarin therapy offers likely explanation for imbalance in VTEs
  - MM patients 9 times as likely as Device patients to be on warfarin during follow-up
  - Device patients discontinued warfarin upon device implant
    - No device patient with DVT history was on warfarin at time of VTE

Current Evidence Does Not Suggest VTE Imbalance is Due to Device

- Most events occurred after device would likely have been endothelialized
- No thrombus on device at 6 months
- No thrombus on device on any other echo
- No physiologic rationale for device causing DVT
  - Of the 18 Device patients with VTEs:
    - 11 had DVTs (with or without PE)
    - 7 had isolated PEs

Summary of Safety Findings

- Overall SAE rates were similar in the two arms
- 4.2% rate of serious device- or procedure-related complications
  - 0.4% rate of cardiac tamponade
  - No intra-procedure strokes or device embolizations
  - No thrombus on device or device erosions
- Peri-procedural AF was transient; post-procedural AF rate was comparable to AF rate in MM arm
- VTE events more common in Device arm
  - Anticoagulation recommended for patients with history of DVT

Post-approval Plans

Mark D. Carlson, M.D.

Chief Medical Officer and Global Clinical Vice President

St. Jude Medical, Inc.

AMPLATZER PFO Occluder Physician Training Program

- Patient selection
- Implanting physician qualification
- Implant and post-procedural training

Multidisciplinary Team Approach To Ensure Appropriate Patient Selection

- AHA/ASA Guide for work-up and diagnosis of cryptogenic stroke
- SJM will promote multidisciplinary team approach
  - Neurologist and interventionalist
  - Comprehensive work-up for suspected cryptogenic stroke
  - Neurologist confirmation of diagnosis and recommendation for PFO closure

Training Program for Implanting Physicians Tailored to Experience

- Only physicians qualified for left atrial procedures via the right atrium will be trained
- Mandatory training components of physician didactic training include:
  - Patient selection
  - Device overview
  - Clinical trial data
  - Procedure
  - Post-procedural care
- Proctoring will be tailored to physician experience

Post-approval Studies

St. Jude Medical Plans to Conduct Two Post-approval Studies

- PAS-1: continue to follow current RESPECT patients through their 5-year follow-up visit
- PAS-2: newly implanted patients
  - 806 patients
  - Patients followed through 5 years

PAS-2 Endpoints

- Safety: Composite of device/procedure-related SAEs through 5 years, including
  - New onset atrial fibrillation
  - Pulmonary embolism
  - Device thrombus
  - Device erosion/embolization
  - Major bleeding requiring transfusion
  - Vascular access site complications requiring surgery
  - Device- or procedure-related SAE leading to death
- Effectiveness: Recurrent ischemic stroke through 5 years

Clinical Perspectives and Benefit-Risk Assessment

John Carroll, M.D.

Professor of Medicine – Cardiology

University of Colorado School of Medicine

University of Colorado Hospital

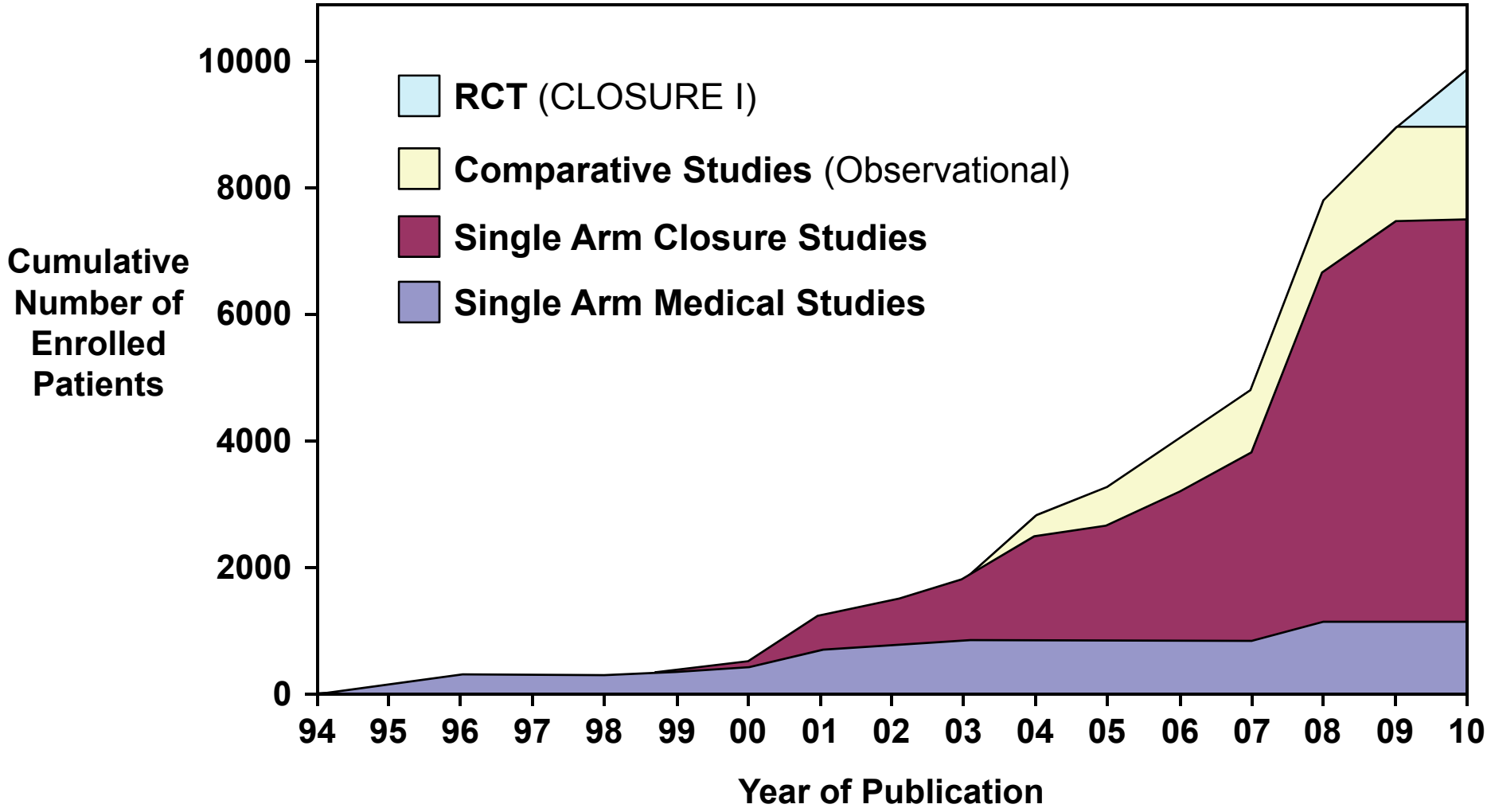
PFO Closure is Mechanistic Therapy for the Prevention of Paradoxical Embolism

- Targeted therapy for carefully selected patients
- Surgical/device closure is standard of care for managing many congenital heart diseases
- Closing the PFO does not prevent:
  - Venothromboembolic disease
  - Strokes due to known risk factors
- Strokes related to other causes highlights need for comprehensive risk factor modification

Challenging Environment to Answer Straightforward Clinical Question

- ***Can we lower the risk of recurrent stroke by mechanically closing the PFO?***
- Many clinicians did not have equipoise to conduct a RCT
- Difficult to enroll and retain patients in randomized PFO closure trials
  - Hampered by off-label PFO closure

Patients Reported in PFO Closure Publications from 1994 to 2010



Kitsios et al. *Stroke* 2011;43:422-31.

Importance of Need for Randomized Evidence Recognized in Cardiology and Neurology

COMMENTARY

JAMA 2005;294:366-9.

Patent Foramen Ovale Closure Devices

Moving Beyond Equipoise

William H. Maisel, MD, MPH
Warren K. Laskey, MD

Treatment Options for Patients With PFO and Cryptogenic Stroke

Treatment options for patients with cryptogenic stroke and

JACC 2009;53:2014-8.

Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention

A Call for Completion of Randomized Clinical Trials

A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation

The American Academy of Neurology affirms the value of this science advisory.

Patrick T. O'Gara, MD, FAHA, FACC, Chair; Steven R. Messe, MD, FAHA; E. Murat Tuzcu, MD, FAHA, FACC; Gloria Catha, BA; John C. Ring, MD, FACC

AMPLATZER PFO Occluder Provides Reasonable Assurance of Effectiveness and Safety

Effectiveness

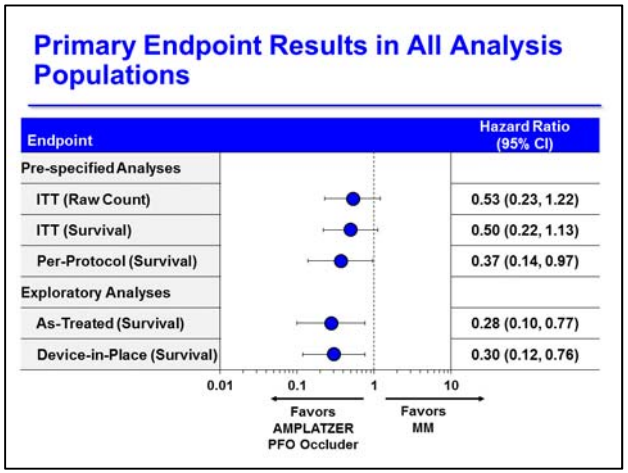
- Medical therapy provides only partial protection from recurrent stroke
- PFO closure further reduces risk in select patients

Safety

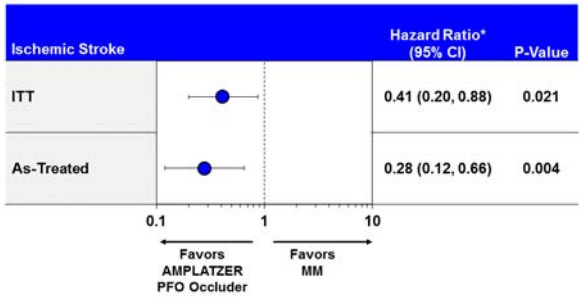
- Closing the PFO with AMPLATZER PFO Occluder has acceptable risk profile

AMPLATZER PFO Data Demonstrate Clinically Meaningful Reductions in Risk for Recurrent Stroke

Primary Endpoint Results in All Analysis Populations



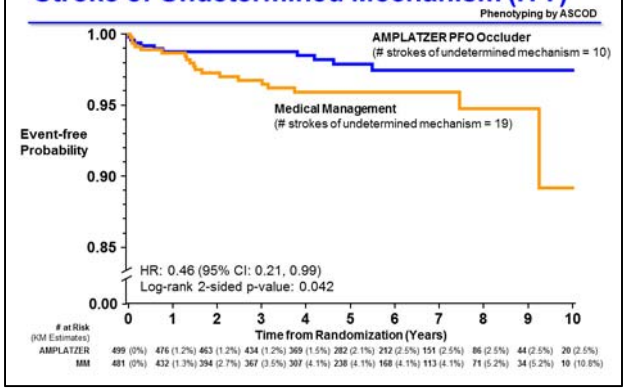
Significant Relative Risk Reduction for Recurrent Ischemic Stroke in Meta-Analysis



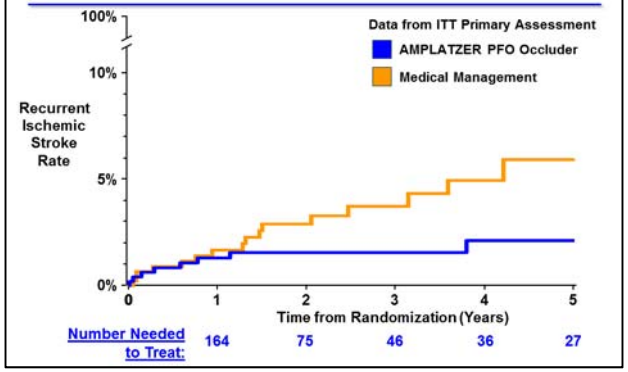
* Models adjusted for: age, sex, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, ASA, shunt size

Kent et al. *J Am Coll Cardiol* 2016;67:907-17.

54% Relative Risk Reduction for Recurrent Stroke of Undetermined Mechanism (ITT)



Number Needed To Treat for PFO Closure Declines Over Time



Acceptable Risk Profile

- Overall SAE rates were similar
- 4.2% device/procedure-related complication rate
  - No known long-term sequelae
- Higher incidence of VTEs with Device
  - Appears largely due to differential use of warfarin
  - Guidelines recommend consideration of extended anticoagulation for patients with history of unprovoked VTE[1]

1. Kearon et al. *Chest* 2016;149:315-352.

AMPLATZER PFO Occluder is a Needed Therapeutic Option

- Approval of AMPLATZER PFO Occluder would replace off-label closure with regulated device that is designed specifically for PFO anatomy
  - Reasonable assurance of safety and effectiveness from RCTs
- SJM would provide clinical community with rational dispersion of first-in-class therapy:
  - Proper physician training
  - Appropriate patient selection
  - Post-market surveillance

AMPLATZER PFO Occluder is an Important, Effective, Safe Option

- Needed treatment option for prevention of recurrent stroke due to paradoxical embolism
- AMPLATZER PFO Occluder reduces risk compared to medical management alone
- Procedure is safe; risk for VTE should be addressed with guideline-directed anticoagulation
- Benefits of reduction in stroke risk outweighs risks among carefully selected patients

AMPLATZER™ PFO Occluder for the Prevention of Recurrent Ischemic Stroke

May 24, 2016

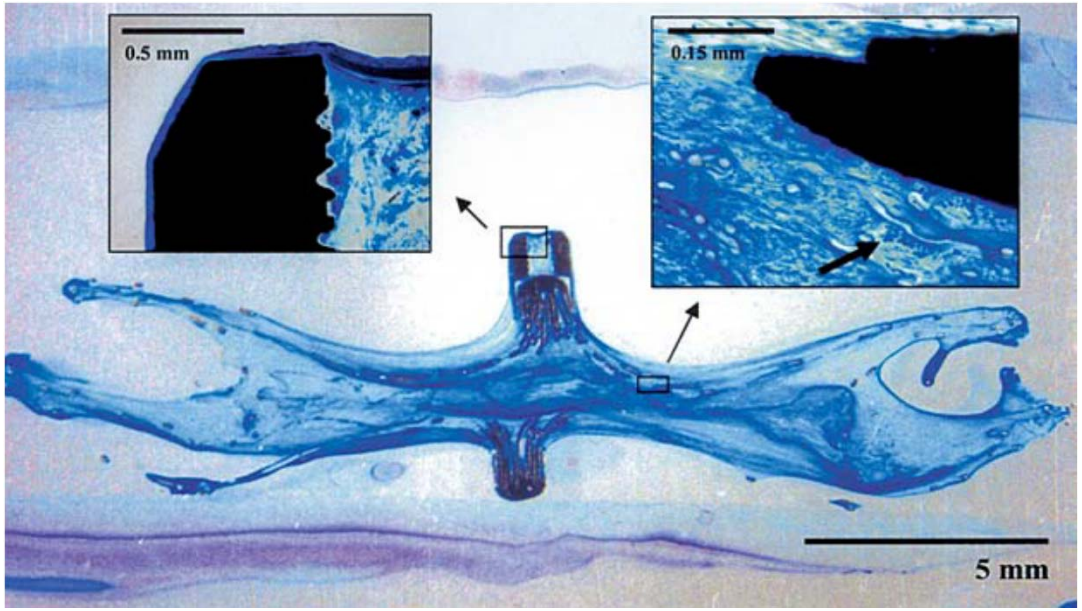
St. Jude Medical, Inc.

Circulatory System Device Panel

Q&A Slides

15 Month Human Autopsy Shows Tissue Coverage Over the Screw in an AMPLATZER Septal Occluder

- At 15 months, tissue coverage of the device including the screw is seen indicating a lower risk of thrombus due to the device over time.



Human Explant at 15 Months

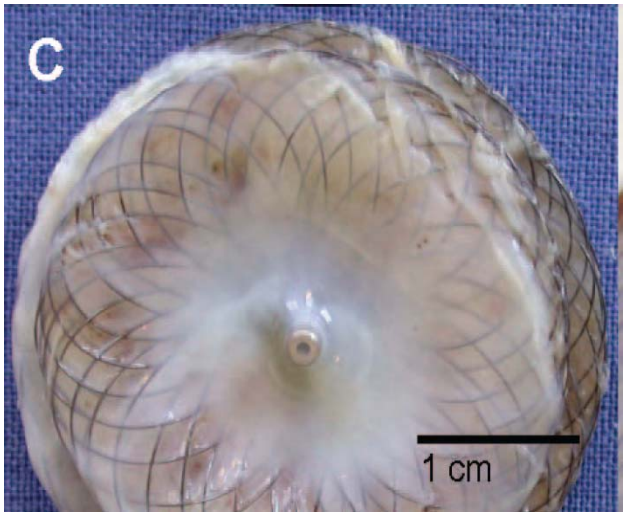


Table 31: Demographics and Baseline Characteristics of Patients in the PFO ACCESS Registry

Variable	Device (N=640)
Age (years), mean ± SD	59.5 ± 13.4
Sex, male, n (%)	391 (61.1%)
Congestive heart failure, n (%)	18 (2.8%)
Coronary artery disease, n (%)	118 (18.4%)
Deep vein thrombosis, n (%)	48 (7.5%)
Pulmonary embolus, n (%)	19 (3%)
Previous myocardial infarction, n (%)	43 (6.7%)
Hypertension, n (%)	411 (64.2%)

Major Bleeding Rates Were Similar in Device and MM Patients

- Major Bleeding Rates were similar in Device (0.61 events/100 patient years) and MM patients (0.59 events/100 patient years)
- Definition - Intracranial hemorrhage or bleeding that led to hemodynamic compromise requiring intervention (e.g., pericardiocentesis, blood transfusion) or death

	Device (N = 499)		Medical Management (N = 481)	
Adverse Event	Patients with Events n/N (%)	# of Events	Patients with Events n/N (%)	# of Events
Gastrointestinal Bleeding	5 (1.0%)	5	3 (0.6%)	3
Hematoma	1 (0.2%)	3	2 (0.4%)	2
Intracranial Bleeding	2 (0.4%)	2	5 (1.0%)	5
Menorrhagia	1 (0.2%)	1	2 (0.4%)	2
Pericardial Effusion /Tamponade	3 (0.6%)	3	1 (0.2%)	1
Bleeding	3 (0.6%)	3	1 (0.2%)	1
Total	13 (2.6%)	17 (0.61 per PY)	14 (2.9%)	14 (0.59 per PY)

Extended follow-up

Table 8: Patient Disposition

	Device (N=499)	Medical Management (N=481)
Discontinued	50 (10.0%)	84 (17.5%)
Withdrawal of consent	23 (4.6%)	50 (10.4%)
Lost to Follow-up	21 (4.2%)	27 (5.6%)
Other	6 (1.2%)	7 (1.5%)

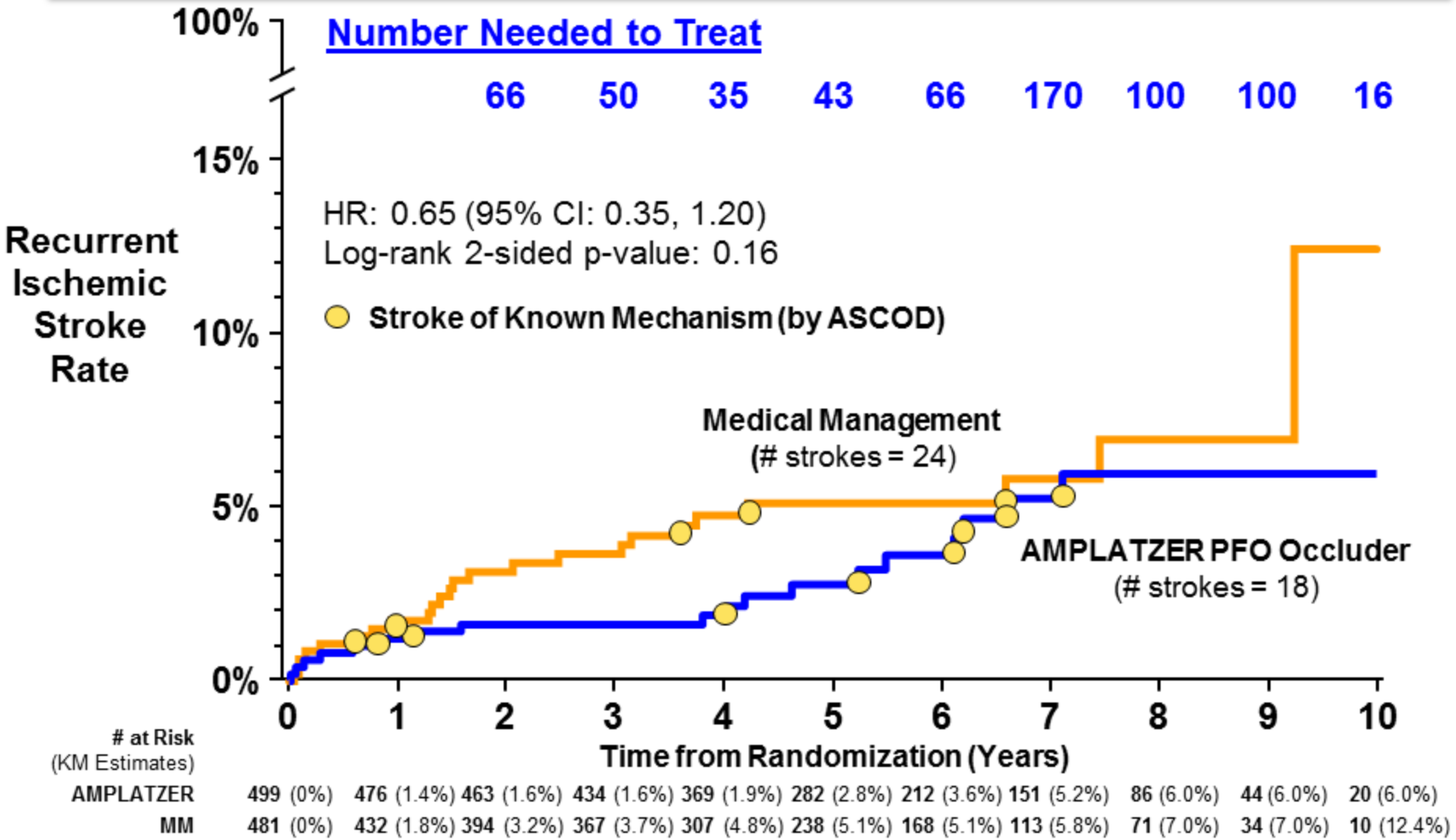
[1] Disposition is shown only for patients who did not experience a primary endpoint event

Patients with Recurrent Stroke After Device Implant with Complete PFO Closure per TEE

Patient ID	Lesion Size at Baseline	Time from Random-ization	Baseline Stroke Risk Factors	Age at Recurrent Stroke	Medications at Time of Recurrent Stroke	ASCOD Recurrent Stroke
(b)(6)	**Massive (> 6.0 cm)**	**7.0 Months**	• Deep vein thrombosis • Hypertension	**50**	**Clopidogrel**	**Unknown Cause**
(b)(6)	**Small (<0.5 cm)**	**9.4 Months**	• Palpitations • Previous transient ischemic attack • Current Smoker • Hypercholesterolemia • Hypertension	**51**	**Aspirin**	**Unknown Cause**
(b)(6)	**Moderate (1.6-3.0 cm)**	**1.1 Years**	• Palpitations • Stroke prior to qualifying cryptogenic stroke • Current Smoker • Hypercholesterolemia	**44**	**Aspirin**	**Grade 1** (Radiation arteriopathy)
(b)(6)	**Intermediate (0.5-1.5 cm)**	**5.2 Years**	• Sinus tachycardia • Family history of ischemic heart disease • Family history of stroke • Former smoker	**32**	**Arixtra**	**Grade 1** (Small vessel, lupus)

Primary Assessment

All Recurrent Strokes Through Extended Follow-up (ITT)

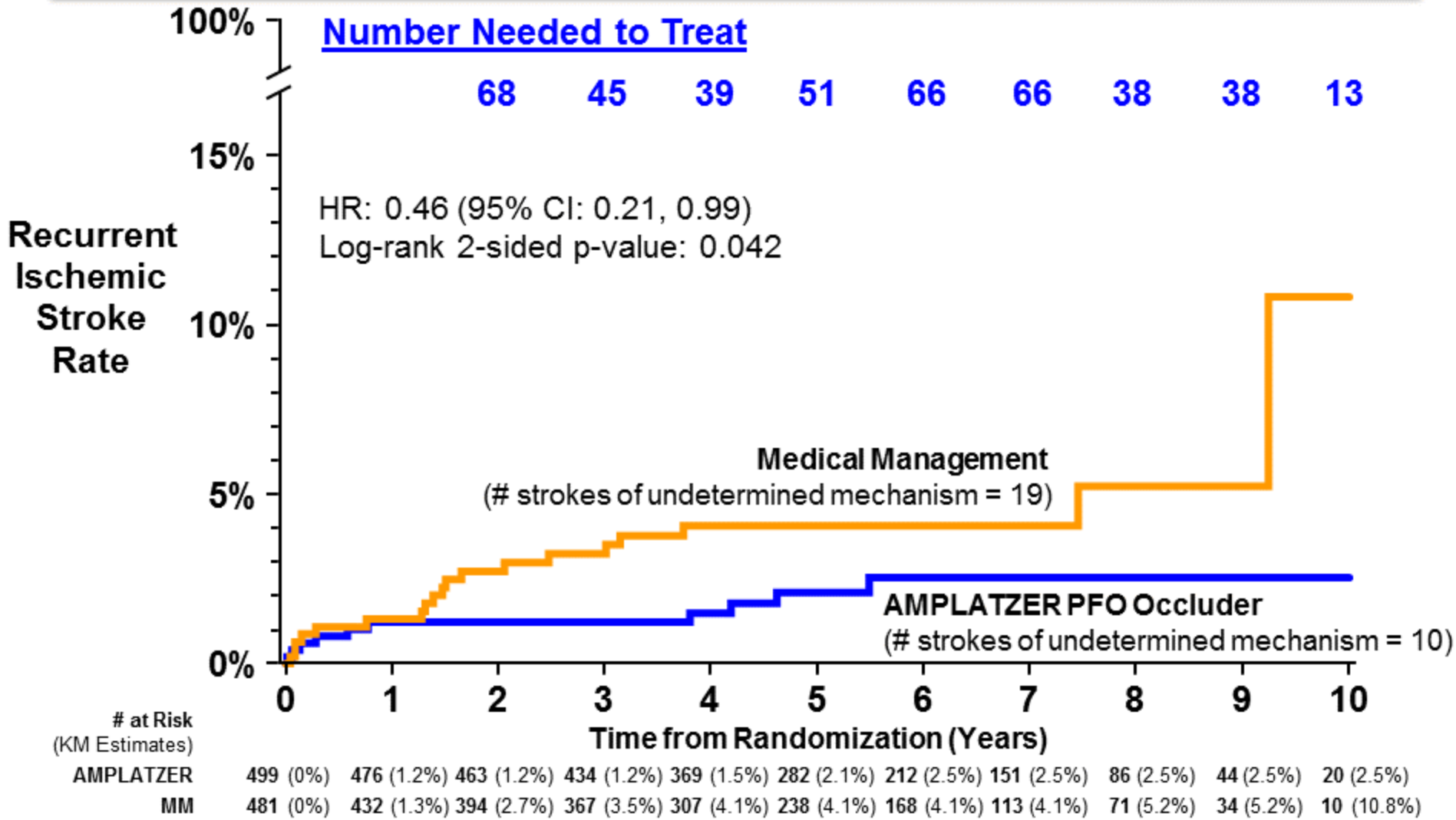


# at Risk (KM Estimates)										
AMPLATZER	499 (0%)	476 (1.4%)	463 (1.6%)	434 (1.6%)	369 (1.9%)	282 (2.8%)	212 (3.6%)	151 (5.2%)	86 (6.0%)	44 (6.0%)	20 (6.0%)
MM	481 (0%)	432 (1.8%)	394 (3.2%)	367 (3.7%)	307 (4.8%)	238 (5.1%)	168 (5.1%)	113 (5.8%)	71 (7.0%)	34 (7.0%)	10 (12.4%)

Amarenco et al. *Cerebrovasc Dis* 2013;36:1-5.

54% Relative Risk Reduction for Recurrent Stroke of Undetermined Mechanism (ITT)

Phenotyping by ASCOD



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MM	481 (0%)	432 (1.3%)	394 (2.7%)	367 (3.5%)	307 (4.1%)	238 (4.1%)	168 (4.1%)	113 (4.1%)	71 (5.2%)	34 (5.2%)	10 (10.8%)

Patients with a History of DVT who Develop a VTE

	Baseline History of DVT	Subjects with VTE During Extended Follow-up
Device (N=499)	20	5 / 20 (25%)
MM (N=481)	15	0 / 15 (0%)

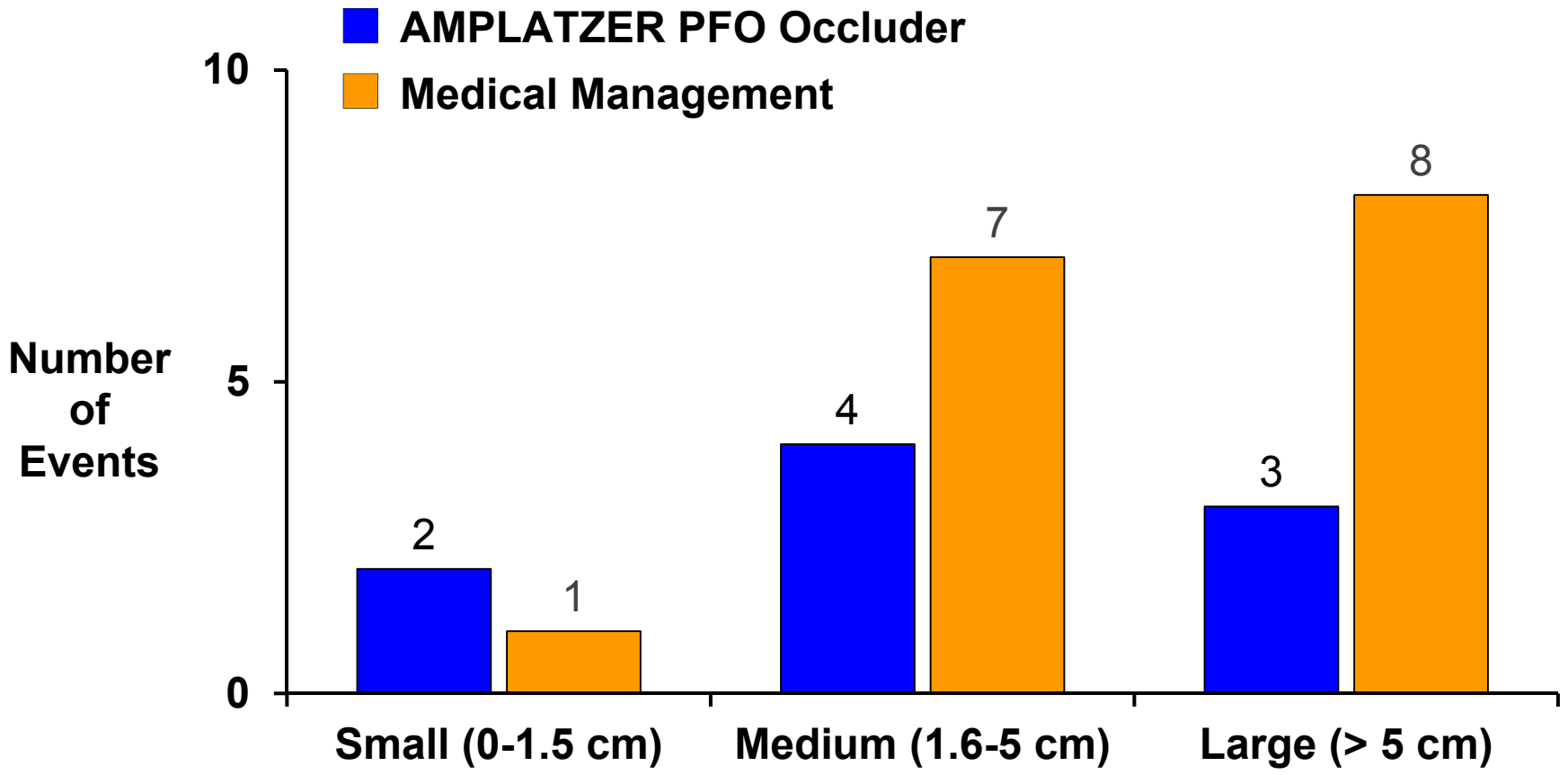
Patients with Recurrent Stroke (MM)

Patient ID	ASCOD Recurrent Stroke	Time from Rando-mization	Medications at Time of Recurrent Stroke	Age at Recurrent Stroke	Comment
(b)(6) [redacted]	Grade 1 (AF)	7.2 Months	Warfarin	38	History of a single episode A Fib at baseline not deemed exclusionary
(b)(6) [redacted]	Grade 1 (Small vessel)	11.3 Months	Aspirin	53	--
(b)(6) [redacted]	Unknown Cause	1.5 Years	Unknown	59	Primary brain hemorrhage (ischemic infarct 5 days later)
(b)(6) [redacted]	Grade 1 (AF)	3.6 Years	Aspirin/extended -release dipyridamole	62	--
(b)(6) [redacted]	Grade 1 (AF)	4.2 Years	aspirin	59	--

Sponsor Actions to Mitigate Patient Withdrawal

- Allowed transfer of patients between investigational sites for patients that moved
- Reimbursement for patient travel expenses was added to reimbursement agreement
- Sponsor provided funding for required tests in the case of financial hardship
- Allowed phone visits at 3 years and beyond
- Sites were required to make at least two phone calls and send a certified letter prior to considering a patient lost to follow-up

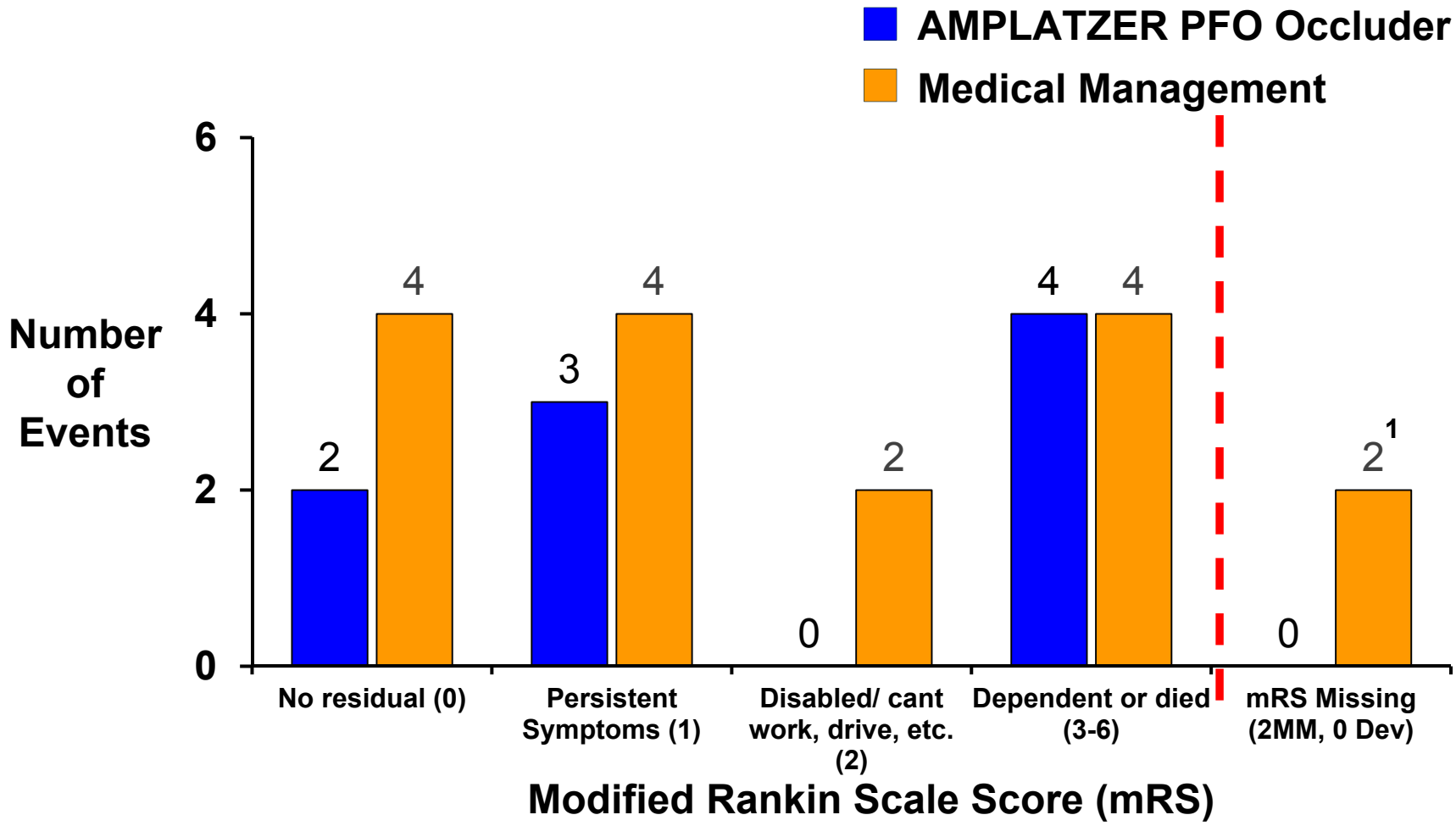
Infarct Size of Recurrent Ischemic Stroke



Infarct size measured by longest lesion

Primary Assessment

Functional Outcome After Recurrent Ischemic Stroke



mRS score obtained an average of 86 days post-stroke

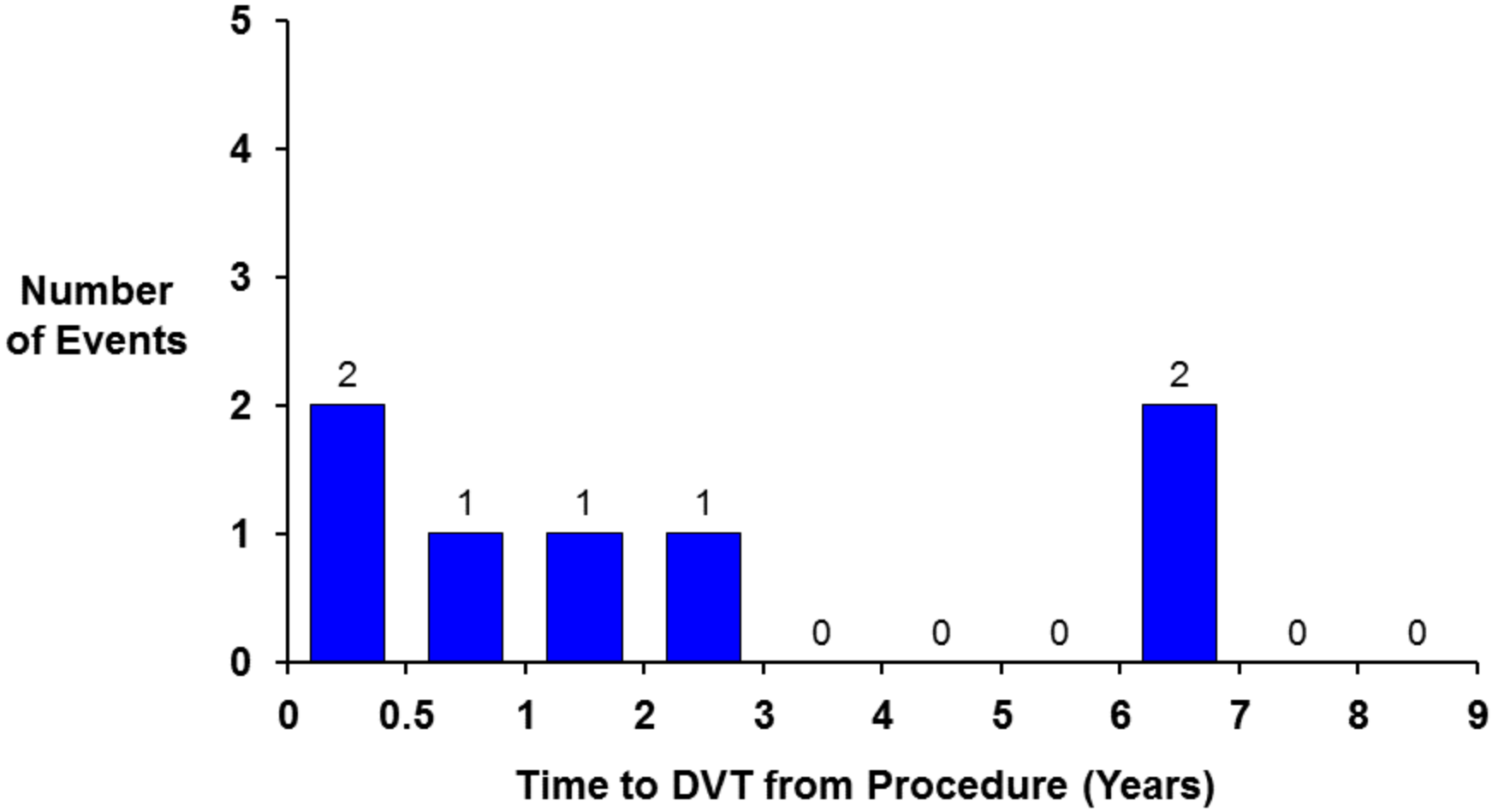
[1](1) Patient withdrew due to severity of stroke: NIHSS 23; (2) Patient had no residual effects noted post stroke

Primary Assessment

No Relationship Noted Between DVT Location and Implant Procedure Access Site

- 6 device patients experienced only a DVT
  - 4 were ipsilateral
  - 2 were contralateral
- 11 device patients experienced a DVT alone or a DVT in conjunction with a PE
  - 8 were ipsilateral side
  - 3 were contralateral side
- 1 device patient experienced a DVT in the arm

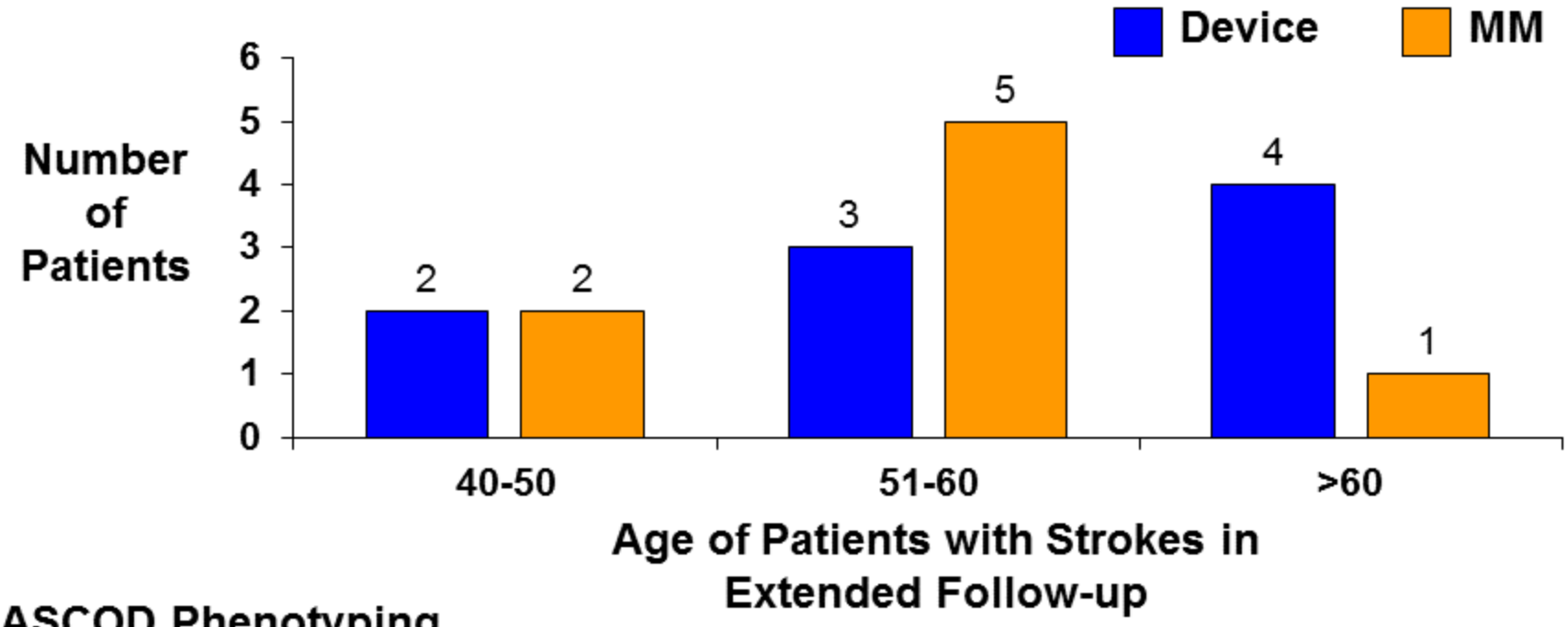
Patients with DVT Alone



Extended Follow-up

Nearly All Strokes Through Extended Follow-Up for Patients > 60 Due to Known Mechanism

- 1 in 5 RESPECT patients age > 60 years old
- 8 strokes in extended follow-up in patients > 60 years old, 87% were of known mechanism



ASCOD Phenotyping

Mortality risk for device arm patients who experienced a pulmonary embolism event

- Risk stratification based on CT findings
- One patient death was categorized as a high-risk pulmonary embolism event
- The remaining 12 PE's were either intermediate (n=4) or low risk (n=8)

Pulmonary embolism risk stratification	Device Pulmonary Embolism events N=13	MM Pulmonary Embolism events N=2
High Risk (15% mortality)	1/13	0/2
Intermediate risk (3-15% mortality)	4/13	1/2
Low risk (<1% mortality)	8/13	1/2

Outcomes and Resolution of VTE Events

Device (N=24)	No further symptoms	Ongoing symptoms	Death
PE	9	3	1

Extended follow-up

Strengths of ASCOD for Assessing Stroke Phenotypes

	ASCOD
Published	2013
Categories	Athero / Small vessel / Cardiac / Other / Dissection
Handling of multiple causes	Identifies all
Incorporates modern imaging*	Yes
Informative after targeted repeat work-up (typical in recurrent ischemic stroke)	Yes

*ASCOD explicitly incorporates CTA, MRA, DWI MR, FAT-SAT MR, and other modern techniques that are not formally considered in the TOAST algorithm

Antithrombotic Medication Within 1 Week Prior to Recurrent Stroke

Medication	AMPLATZER PFO Occluder (N=18)	MM (N=24)
Aspirin alone	11	12
Aspirin and Warfarin	0	1
Aspirin and Clopidogrel	1	1
Aspirin/extended-release dipyridamole	0	2
Warfarin alone	0	1
Clopidogrel alone	1	1
Fondaparinux sodium	1	0
None/missed doses	4	5
Unknown	0	1