The Final Results with Primary End Point Analyses

RESPECT

CLINICAL TRIAL

RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

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FOR THE RESPECT INVESTIGATORS

Disclosure Statement of Financial Interest

- Within the past 12 months, John Carroll and the University of Colorado (his employer) have had a financial interest/arrangement or affiliation with the organization listed below:

Affiliation/Financial Relationship	Company
Research Support to Perform Clinical Trials (RESPECT and ACP)[1]	AGA Medical/ St. Jude Medical
Consulting Fees for Steering Committee Work with RESPECT[1]	AGA Medical/ St. Jude Medical

1. Paid to University Physician Inc. of the University of Colorado School of Medicine

Background: Cryptogenic Stroke and PFO

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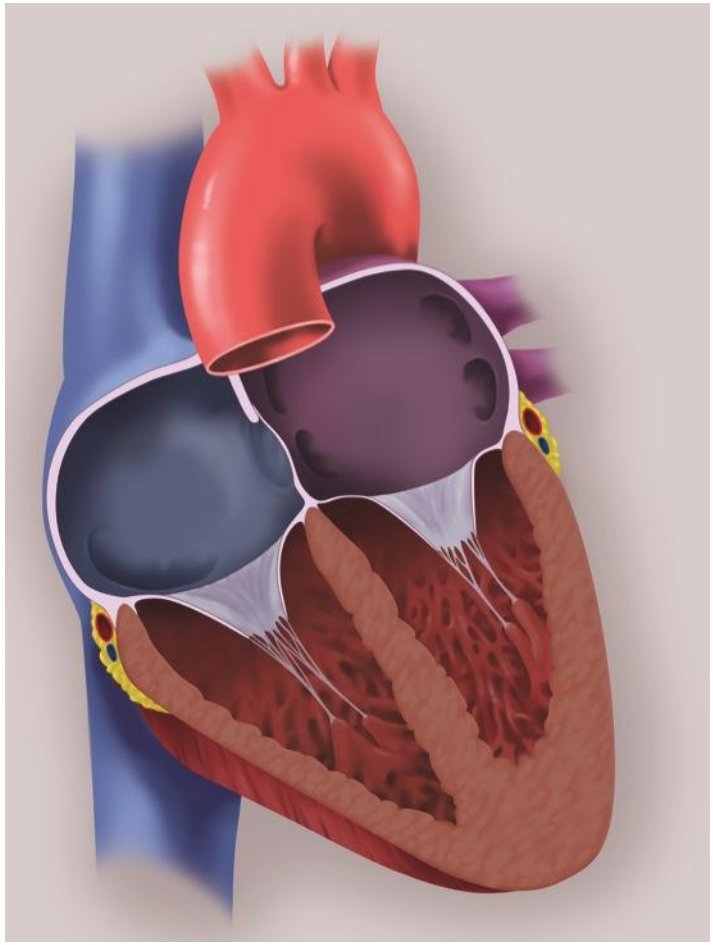
- Cryptogenic stroke remains a major challenge
  - PFO-related strokes, i.e. due to paradoxical embolism, have been strongly implicated as a possible cause
  - Patients age 20-54 are now a larger percentage of all stroke patients and among first ever strokes in the younger population there is growth in ischemic strokes[1]
  - Cost of stroke is significant, with over $94B[2,3] spent each year in the US and EU alone – cost implications with young patients are immense, based on the loss of productivity and long-term care
- The results of PFO closure trials have included positive observational studies and one negative randomized trial
- The RESPECT trial was designed with a well-defined stroke population, a statistical design appropriate for expected low recurrent event rates, and used a device with an excellent safety record

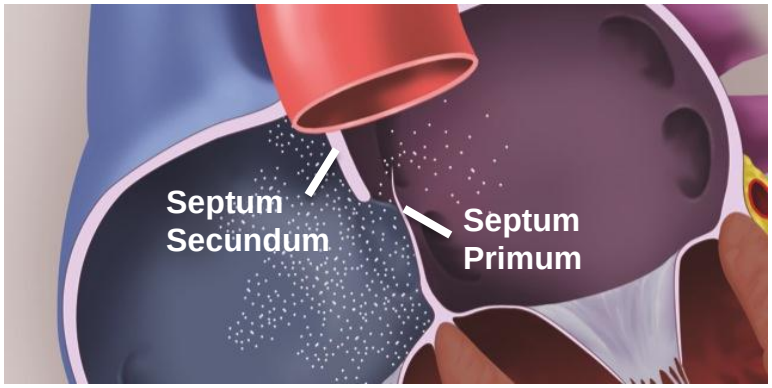
1. Kissela, BM, Khoury, JC, Alwell, K,et al. Age at stroke Temporal trends in stroke incidence in a large, biracial population. *Neurology* 2012;79:1781-1787
2. Roger, V, Go, A, Lloyd-Jones, D, et. Al. Heart Disease and Stroke Statistics – 2012 Update: A Report from the American Heart Association. *Circulation*. 2012; 125:e2-e220
3. Allender,S, Scarborough, P, Peto, V, et al European cardiovascular disease statistics 2008

Pathophysiology of PFO and Paradoxical Embolism

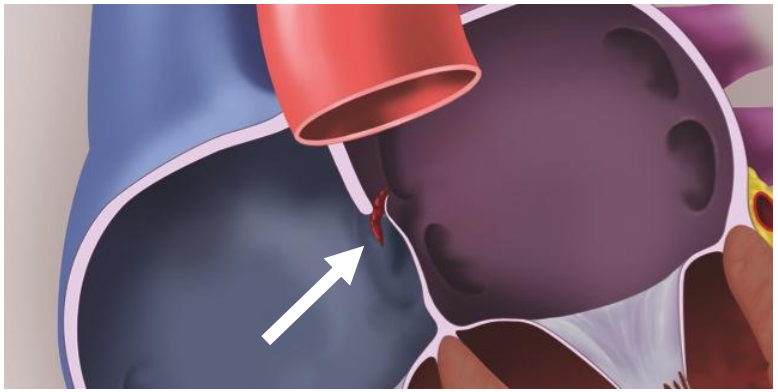
Normal appearing atrial septum



Agitated saline study demonstrating right to left shunting through the PFO



Blood clot passing through the PFO becoming a paradoxical embolism



Trial Design

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Design	▪ Multicenter: 69 Sites (62 US, 7 Canada)
	▪ Prospective, 1:1 Randomized stratified by site and atrial septal aneurysm
	  ▪ Device Group (Test):
	  ▪ Closure with the AMPLATZER™ PFO Occluder plus medical therapy
	  ▪ Medical Group (Control): 5 Medical Treatment Regimens:
	  ▪ Aspirin
	  ▪ Warfarin
	  ▪ Clopidogrel
	  ▪ Aspirin with dipyridamole
	  ▪ Aspirin with clopidogrel[1]
	  ▪ Sample Size: Event-driven – continued enrollment until 25th endpoint

Primary Analyses	Four protocol-specified analyses with raw count primary analysis
Trial Status	Trial was conducted under an Investigational Device Exemption (IDE)
Sponsor	St. Jude Medical, St. Paul, MN *Study initiated under AGA Medical, Plymouth, MN

1. Aspirin with clopidogrel was removed from the protocol in 2006 based on changes to the AHA/ASA treatment guidelines

Study Governance and Organization

Executive Steering Committee	▪ John D. Carroll, MD, University of Colorado/University of Colorado Hospital, Department of Medicine (Cardiology) ▪ Jeffrey L. Saver, MD, University of California, Los Angeles, Department of Neurology ▪ Richard W. Smalling, MD, PhD, University of Texas/Memorial Hermann Heart and Vascular Institute, Division of Cardiology ▪ David E. Thaler, MD, PhD, Tufts University/ Tufts Medical Center, Department of Neurology

Independent Review	▪ Independent Clinical Events Committee (CEC)
	▪ Independent Data Safety and Monitoring Board (DSMB)
	▪ Independent Neurological Executive Committee
	▪ Core Laboratories:
	  ▪ Hematology (Quintiles)
	  ▪ Echocardiography (CVR Consulting, PC)

Statistical Oversight	▪ Independent Biostatistician: Berry Consultants

AMPLATZER PFO Occluder

AMPLATZER PFO Occluder*

- Percutaneous, transcatheter device
- Self-expanding, double-disc design
- Nitinol wire mesh with polyester fabric/thread
- Radiopaque marker bands
- Sizes: 18, 25, 35 mm
- Recapturable and repositionable

*CAUTION: Investigational device in the United States. Limited by Federal (or U.S.) law to investigational use. Not available for sale in the U.S.

Inclusion/Exclusion Criteria

- **Inclusion Criteria:**
  - Patients (ages 18 to 60) with PFO who have had a cryptogenic stroke within 270 days
    - Stroke defined as acute focal neurological deficit, presumed to be due to focal ischemia, and either symptoms persisting 1) ≥ 24 hours, or 2) < 24 hours with MR or CT confirmed new, neuroanatomically relevant, cerebral infarct
    - PFO defined as TEE visualization of micro-bubbles in the left atrium within 3 cardiac cycles of their appearance in the right atrium at rest and/or during Valsalva release
- **Key Exclusion Criteria:**
  - Cerebral, cardiovascular, and systemic conditions that suggest other mechanisms for stroke. Examples:
    - Carotid disease, atrial fibrillation, cardiomyopathy, etc
    - Arterial hypercoagulable states
    - Uncontrolled diabetes mellitus or hypertension
    - Other sources of right to left shunt
  - Contraindications:
    - To aspirin or clopidogrel
    - Anatomical to device placement
  - Any other reason to expect limited life expectancy, inability to attend follow-up visits, or inability to provide informed consent

Primary and Secondary Endpoints

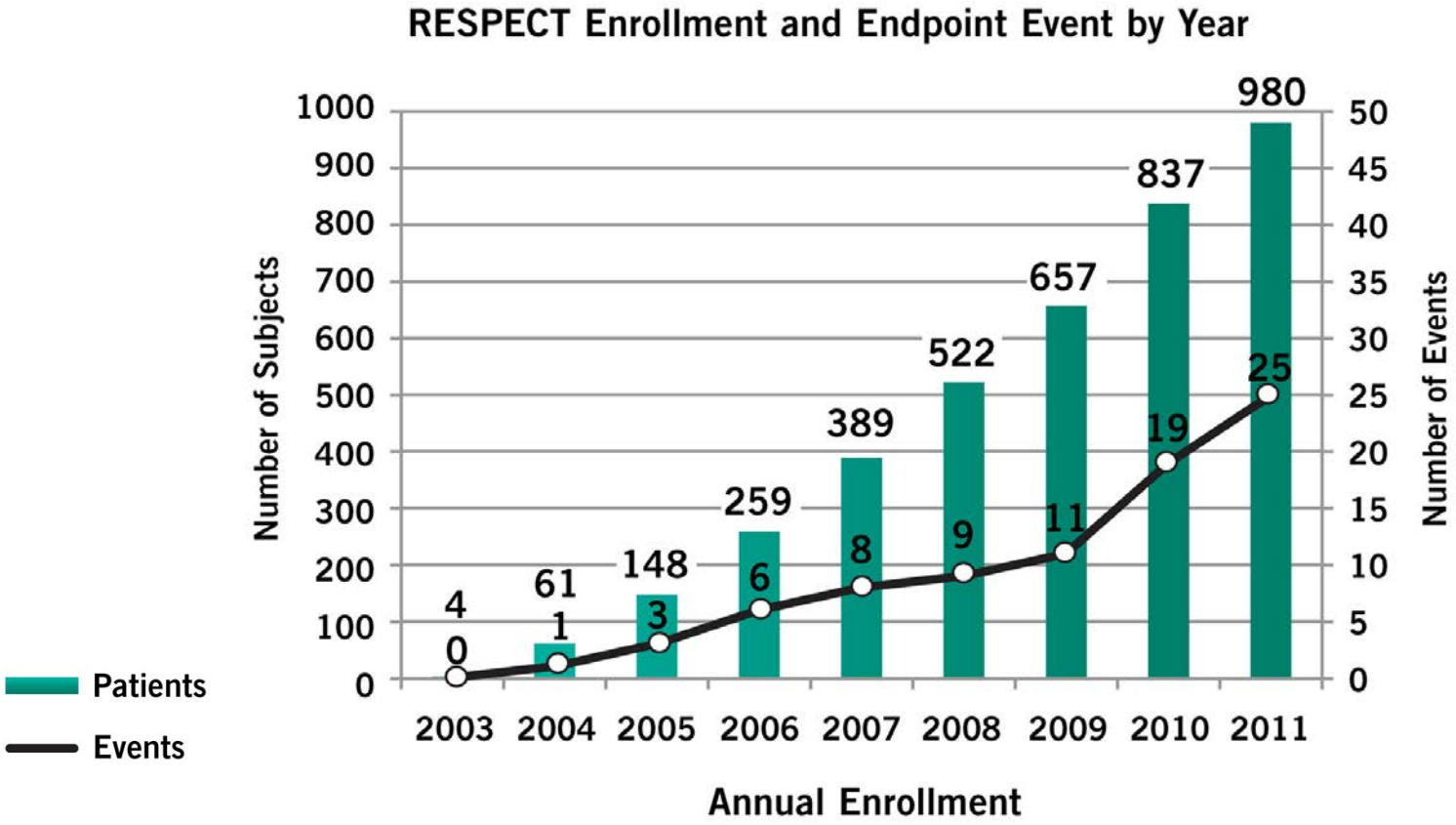
- **Primary Endpoints**
  - Recurrence of a nonfatal ischemic stroke *or*
  - Fatal ischemic stroke *or*
  - Early post-randomization death defined as all-cause mortality
    - Device group – within 30 days after implant or 45 days after randomization, whichever occurs latest
    - Medical group – within 45 days after randomization
- **Secondary Endpoints**
  - Complete closure of the defect demonstrated by transesophageal echocardiography (TEE) and bubble study at the 6-month follow-up (Device Group)
  - Absence of recurrent symptomatic cryptogenic nonfatal stroke or cardiovascular death
  - Absence of transient ischemic attack (TIA)

Power Analysis and Event Driven Design

- Estimated rate of primary efficacy events at 2 years was 4.3% in the medical group and 1.05% in the device group
- An event driven trial design was employed since event rates were estimated to be low
  - Decision rules for trial stopping & power were based on event raw counts and assumed equal follow-up in both study groups
  - Enrollment was stopped December 29, 2011 when the decision rule of 25 primary endpoint events was reached which led to this presentation of results

Primary Endpoint Analyses Population

- 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



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Trial Results

Subject Distribution

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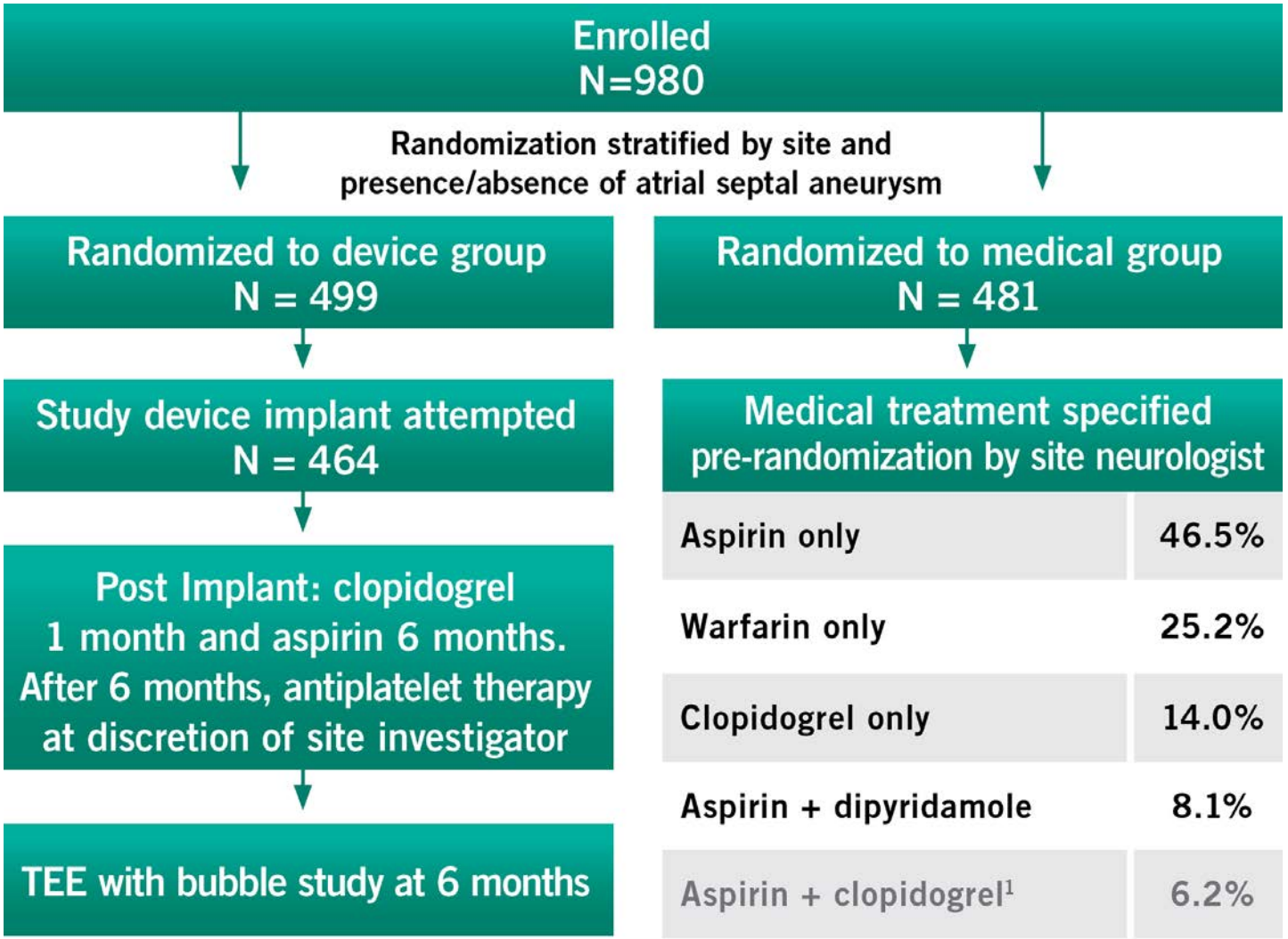

Medical treatment specified pre-randomization by site neurologist	
Aspirin only	46.5%
Warfarin only	25.2%
Clopidogrel only	14.0%
Aspirin + dipyridamole	8.1%
Aspirin + clopidogrel[1]	6.2%

1. Aspirin + clopidogrel was removed from the protocol in 2006 based on changes to the AHA/ASA treatment guidelines

Baseline Characteristics

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	Device Group[1] (N=499)	Medical Group[1] (N=481)	P-value[2]
Age (years)[3]	45.7 (9.7)	46.2 (10.0)	0.491
Gender male (%)	53.7	55.7	0.564
Days from qualifying stroke to randomization	130 (70)	130 (69)	0.891
Atrial septal aneurysm (%)	36.1	35.1	0.790
Maximal baseline shunt Grade II - III (%)[3,4]	77.9	74.1	0.176
Qualifying Stroke Size			
Smaller infarct ≤ 1.5 cm	50.6	51.8	0.714
Larger infarct > 1.5 cm	49.4	48.2	

1. Statistics are represented as either mean (standard deviation) or percentages
2. Based on a 2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized), and Fisher's Exact test (sex)
3. Numbers vary by site; Age N=968; Shunt N=969
4.

Right to left shunt grading scale (at rest or post-Valsalva)			
Grade 0	No bubbles	Grade II	10 - 20 bubbles
Grade I	1 - 9 bubbles	Grade III	≥ 20 bubbles

Baseline Medical Characteristics

No differences between the two groups

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Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value[2]
Diabetes mellitus	33 (6.6%)	40 (8.3%)	0.332
Systemic hypertension	158 (31.7%)	150 (31.2%)	0.891
Current smoker	75 (15%)	55 (11.4%)	0.109
Hypercholesterolemia	194 (38.9%)	193 (40.1%)	0.696
Coronary artery disease (CAD)	19 (3.8%)	9 (1.9%)	0.084
Peripheral vascular disease (PVD)	5 (1%)	1 (0.2%)	0.218
Previous transient ischemic attack (TIA)	58 (11.6%)	61 (12.7%)	0.626
Previous stroke[1]	53 (10.6%)	51 (10.6%)	1
History of migraine	195 (39.1%)	185 (38.5%)	0.844
History of deep vein thrombosis (DVT)	20 (4%)	15 (3.1%)	0.494

1. For Device Group N=498
2. P-value calculated using Fisher's Exact test

Serious Adverse Events Adjudicated as Related to Procedure, Device, or Study

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Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value[7]
Thrombus on device	0 (0%)	N/A	N/A
Device embolization	0 (0%)	N/A	N/A
Atrial fibrillation[1]	3 (0.6%)	3 (0.6%)	1
Transient ischemic attack (TIA)	3 (0.6%)	3 (0.6%)	1
Major bleeding	8 (1.6%)	9 (1.9%)	0.810
Pericardial tamponade (procedure related)[2]	2 (0.4%)	N/A	N/A
Major vascular complications	4 (0.8%)	0 (0%)	0.124
Pulmonary embolism[3]	1 (0.2%)	0 (0%)	1
Cardiac thrombus[4]	2 (0.4%)	0 (0%)	0.500
Ischemic stroke[5]	2 (0.4%)	N/A	N/A
Death[6]	0 (0%)	0 (0%)	N/A

1. For all AE's, atrial fibrillation occurred in 3.0% versus 1.5% in the device and medical groups respectively, p=0.13
2. Pericardial tamponade is a subset of major bleeds, and thus counted in the major bleed category as well
3. For all SAEs, pulmonary embolism occurred in 1.2% and 0.2% in device and medical groups, respectively, p=0.124
4. 1 case of right atrial thrombus resulted in abandonment of device implant procedure (no device received); 1 case of right atrial thrombus (located inferiorly) not attached to device detected in patient with DVT and PE 4 months after procedure
5. 1 ischemic stroke one week post implant; 1 five months post implant with finding of severe shunting related to previously undiagnosed sinus venosus defect, requiring surgical closure
6. For all SAEs, there were 3 device group deaths (0.6%) and 6 medical group deaths (1.2%) all of which were not study related, p= 0.334
7. P-values are calculated using Fisher's Exact test

Device Performance

Procedural Outcomes	n/N (%)
Technical success[1]	460 / 464 (99.1%)
Procedural success[2]	444 / 462 (96.1%)
Effective closure[3]	244 / 261 (93.5%)

Maximum Residual Shunting at Rest and Valsalva at 6 Months
Grade 0: 72.7%
Grade 1: 20.8%
Grade 2-3: 6.5%

1. Defined as successful delivery and release of the device for subjects in whom the delivery system was introduced into the body
2. Defined as successful implantation with no reported in-hospital serious adverse events
3. Defined as complete obliteration or trivial residual shunting (Grade 0 or I at rest and Valsalva) at 6 months, adjudicated by echo core lab

Treatment Exposure and Follow-up

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	Device Group (N=499)	Medical Group (N=481)	All Subjects N=980	P-value[1]
Mean (SD), years	2.8 (2.0)	2.5 (1.9)	2.6 (2.0)	
Median, years	2.2	2.1	2.1	
Range, years	0 - 8.1	0 - 8.1	0 - 8.1	
Total exposure, patient-years	1,375	1,184	2,559	0.009

- Total population with greater than 2,550 years of follow-up
- Device group had greater follow-up (fewer drop-outs)
  - 48 drop-outs in the device group versus 90 in the medical group

1. P-value calculated using Wilcoxon-Mann-Whitney test

Primary End Point Analysis – Intent to Treat (ITT) Raw Count Cohort

Subjects N total (nD / nM)	Events N total (nD / nM)	Relative Risk (RR) [D vs M][1] RR (95% CI)	Risk Reduction (1 – RR)	P value[2]
980 (499 / 481)	25 (9 / 16)	0.534 (0.234, 1.220)	46.6%	0.157

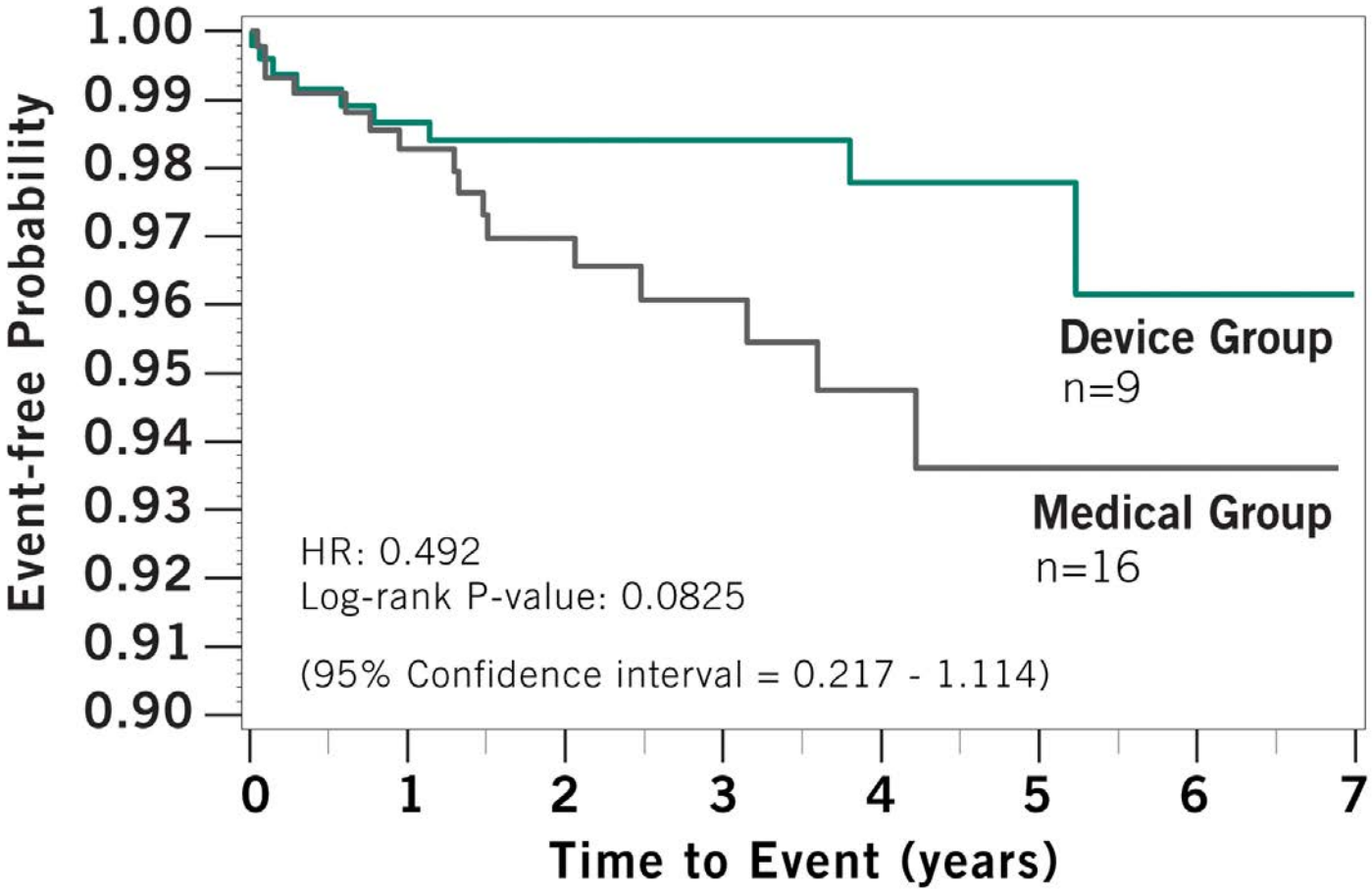
Abbreviations: D = Device group; M= Medical group

- The primary analysis using the raw count of the ITT cohort was deemed invalid because the exposure to the two treatment options was unequal due to a greater drop-out rate in the medical group
- The protocol specified that, if unequal drop-out occurred, then survival functions for the time-to-endpoint event for each treatment group would be used to provide an exposure-stratified comparison
  - Survival analysis methods would then be used at a two-sided 0.05 level using the log-rank statistic. Hazard ratios were calculated using a Cox proportional-hazards model

1. Relative risk is represented by the Mantel-Haenszel odds ratio
2. P-value is 2-sided and calculated using Fisher's Exact test

Primary Endpoint Analysis – ITT Cohort

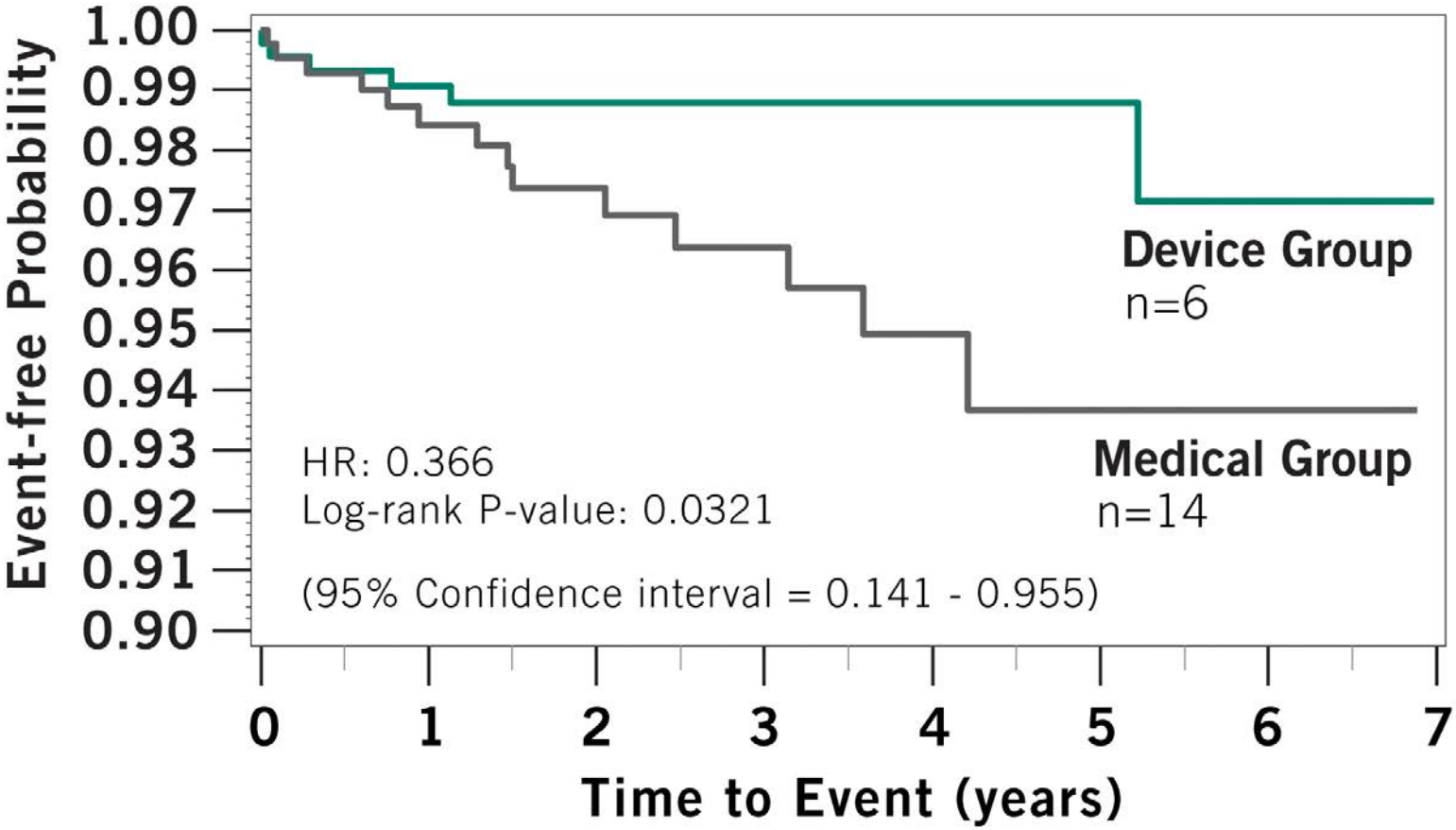
50.8% risk reduction of stroke in favor of device



- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

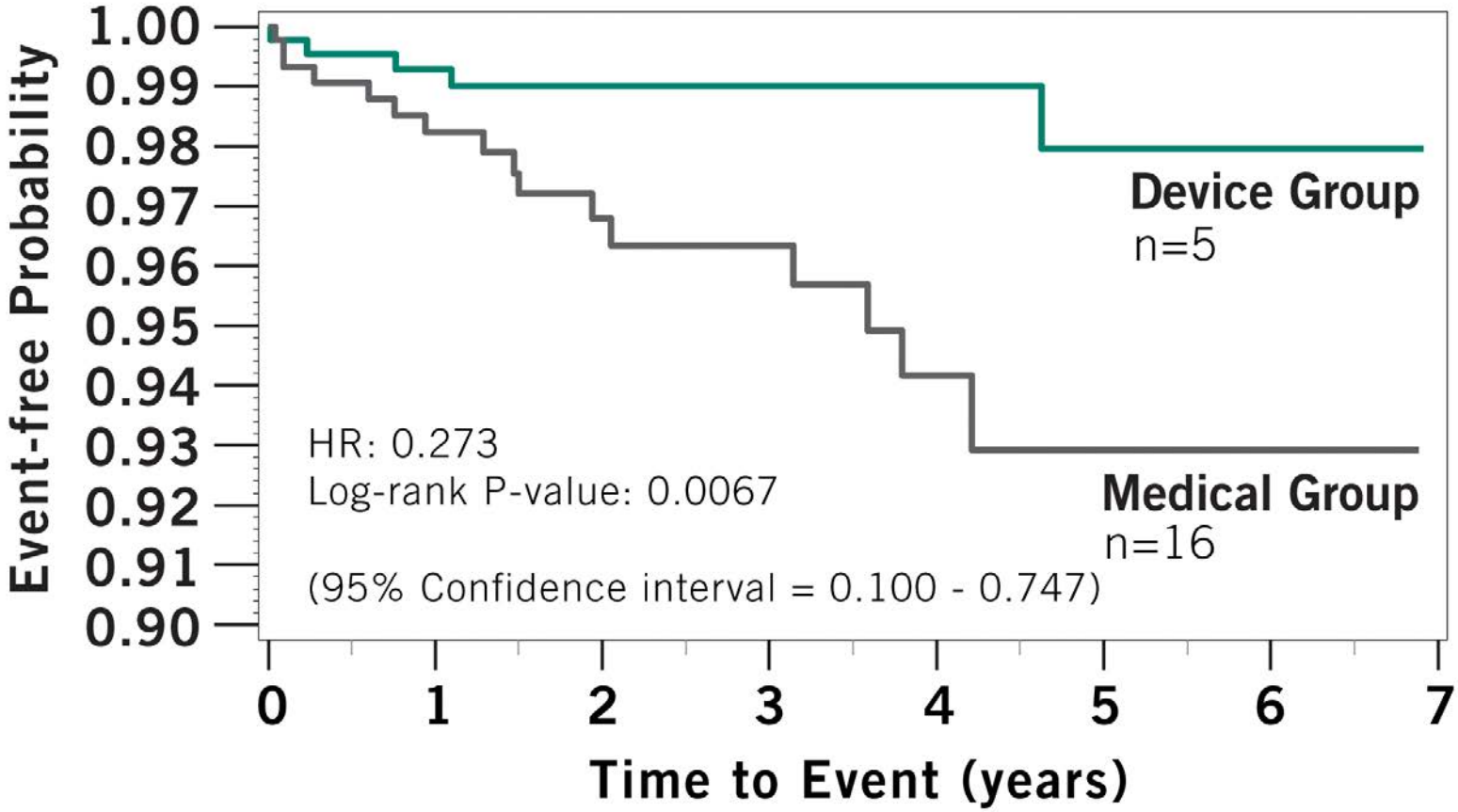
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

1. Cox model used for analysis

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Totality of Evidence and NNT

46.6%-72.7% risk reduction of stroke in favor of device

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Totality of Evidence

Analysis	Risk Reduction	P-Value[1]
Intent to Treat Raw Count	46.6%	0.157
Intent to Treat KM	50.8%	0.083
Per Protocol KM	63.4%	0.032
As Treated KM	72.7%	0.007

Number Needed to Treat (NNT)

	NNT[2]	Device Group Event Rate[3]	Medical Group Event Rate[3]
1 Year	250	1.33%	1.73%
2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

1. P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
2. The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
3. Calculated using the Kaplan-Meier estimated event rates for each treatment group

Subpopulation Differential Treatment Effect

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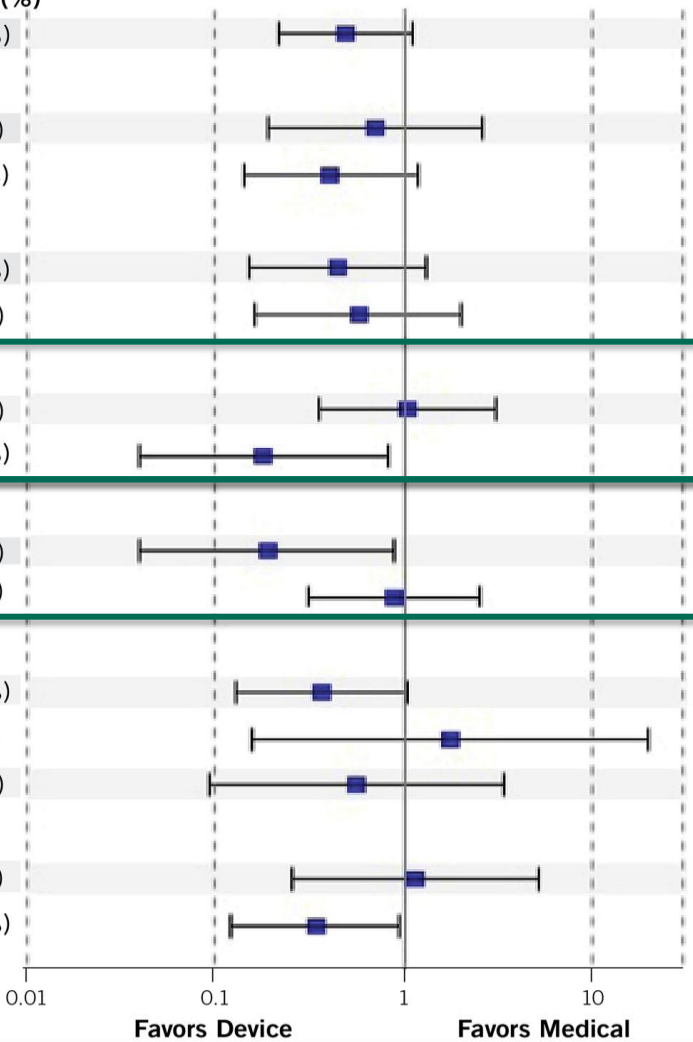
Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI		Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)					
Overall	9/499 (1.8%)	16/481 (3.3%)		0.492 (0.217, 1.114)	0.0825	
Age						0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)		0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)		0.405 (0.140, 1.165)	0.0828	
Sex						0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)		0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)		0.571 (0.161, 2.024)	0.3789	
Shunt Size						0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)		1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)		0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm						0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)		0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)		0.889 (0.312, 2.535)	0.8259	
Index infarct topography						0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)		0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)		1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)		0.558 (0.093, 3.340)	0.5167	
Planned medical regimen						0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)		1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)		0.336 (0.120, 0.944)	0.0299	



Recurrent Cerebral Infarct Size[1]

Methods pre-specified; analysis post-hoc

Event	Device Group n/N (%)	Medical Group n/N (%)	P-value[2]
Larger infarct >1.5cm	1/7 (14%)	9/13 (69%)	P=0.0573
Smaller infarct ≤ 1.5cm	6/7 (86%)	4/13 (31%)	

- This exploratory analysis of site-reported recurrent cerebral infarct size is provocative in suggesting that recurrent ischemic strokes in the medical versus device group are not only more frequent but also larger

1. Recurrent infarct size reported on primary endpoint population
2. P-value based on Fisher's Exact test

Limitations

- Differential drop-out rate
  - Some medical group patients left study and underwent off-label closure
- ITT Results
  - Raw count analysis invalid due to differential treatment exposure
  - Borderline p-value for ITT-KM cohort
    - Even though 3/9 device patients with recurrent ischemic stroke did not have device in place when stroke occurred
  - PP and AT cohorts are relevant to assessing treatment
  - Totality of evidence must be considered
- Sub-group analysis with only 25 events is exploratory in nature
  - Clinically, the atrial septal aneurysm and shunt size findings are relevant and support mechanism of action
- RESPECT took over 8 years to complete
  - Yet, this produced longer term outcomes than any other study particularly important for young stroke patients who face a risk of recurrent stroke for decades
  - Benefit became especially prominent 2-5 years after device placement

Conclusion

- For carefully selected patients with history of cryptogenic stroke and PFO, the RESPECT Trial provides evidence of benefit in stroke risk reduction from closure with the AMPLATZER PFO Occluder over medical management alone
  - Primary analysis of ITT cohort was not statistically significant but trended towards superiority while secondary analyses suggested superiority
  - Stroke risk reduction was observed across the totality of analyses with rates ranging from 46.6% - 72.7%
- PFO closure with the AMPLATZER PFO Occluder exposes patients to a very low risk of device- or procedure-related complications
- Results of the RESPECT Trial have substantial import for the treatment of patients with a history of cryptogenic stroke and PFO
- Follow-up of patients is on-going and will continue to provide additional longer term information regarding benefits, risks, and differential treatment effects in sub-populations

Study Sites and Principal Investigators

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Study Site	Principal Investigator
Swedish Medical Center/ South Denver Cardiology/ Blue Sky Neurology	Lee MacDonald, MD
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Tufts University/Tufts Medical Center	David Thaler, MD, PhD
University of Washington	David Tirschwell, MD, MSc Steven Goldberg, MD
University of Texas/Memorial Hermann Heart and Vascular Institute	Richard Smalling, MD PhD
Duke University Medical Center	Larry Goldstein, MD
OSF St. Francis Medical Center	David Wang, DO Douglas Schneider, MD
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UCLA	Jeffrey Saver, MD
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Oregon Health and Science University	Helmi Lutsep, MD
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Study Site	Principal Investigator
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Charleston Area Medical Center	Stephen Lewis, MD
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St. Vincent's Medical Center	Samer Garas, MD
Sentara General Hospital	Deepak Talreja, MD
University of Minnesota	Fareed Suri, MD Gareth J Parry, MD
The Board of Trustees of the University of Alabama for University of Alabama at Birmingham	Andrei Alexandrov, MD
Lancaster General Hospital	Venkatachalam Mangeshkumar, MD
Summit Medical Center	John Chiu, MD Robert E. Gwynn, MD
LAC-USC Medical Center	Anilkumar Mehra, MD

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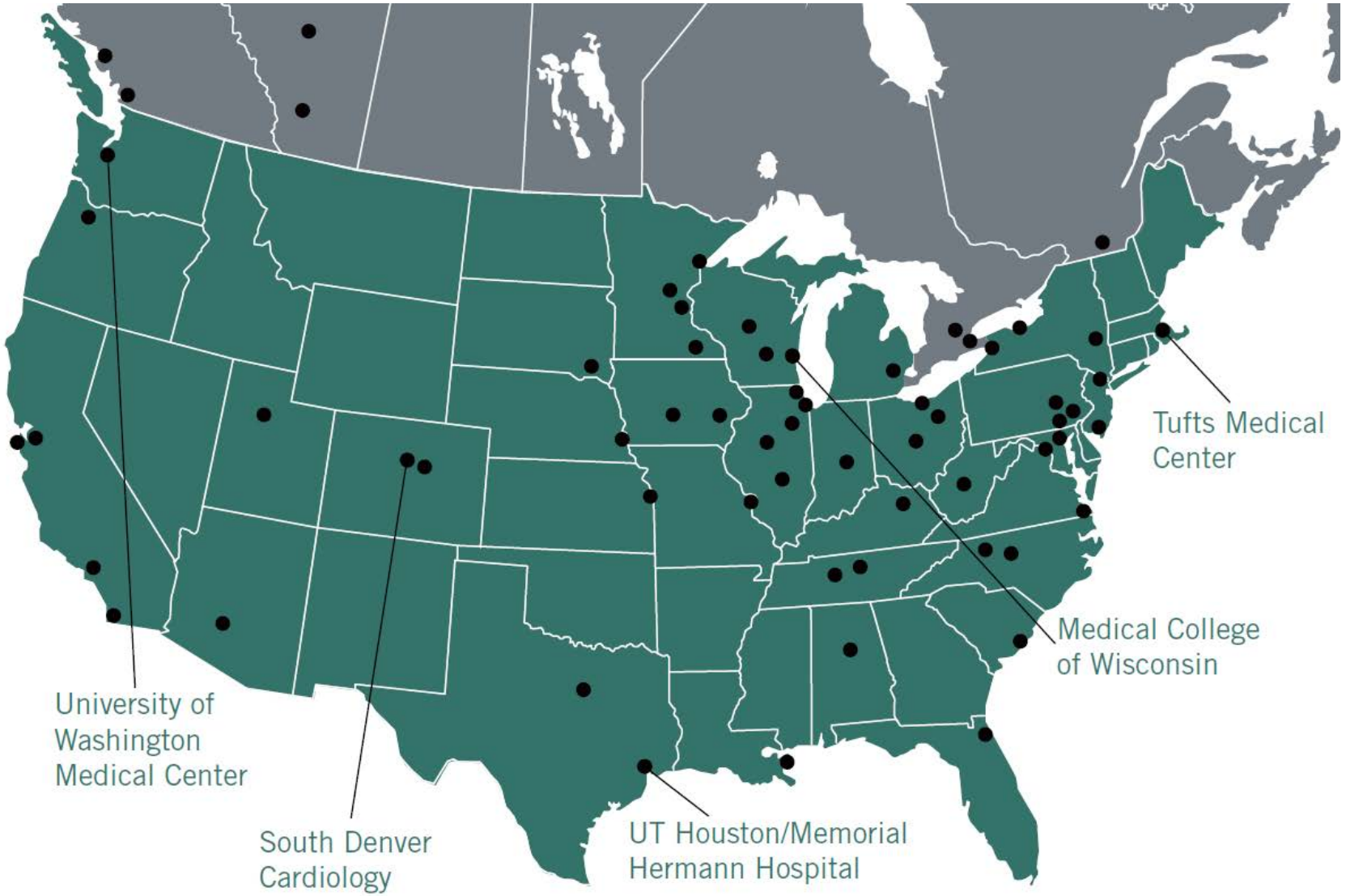
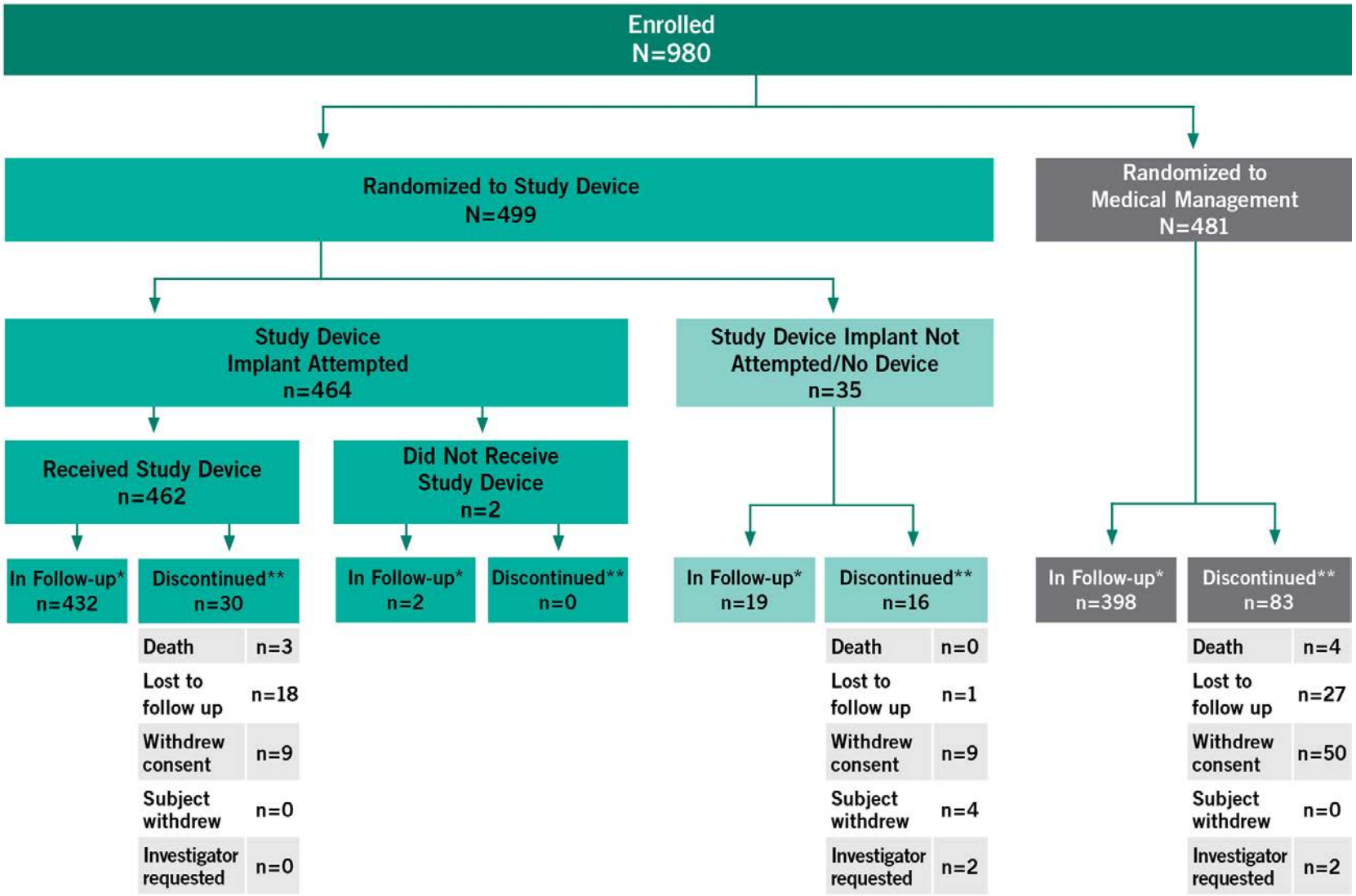
Southern Illinois University	Sushant Punjaram Kale, MD Zeng Yu Wang, MD, PhD Joni Clark, MD
Medical Center of the Rockies	John Bradley Oldemeyer, MD
Marshfield Clinic	Milind Shah, MD
North Central Heart Institute	J. Michael Bacharach, MD
Methodist Hospital/Park Medical Center	Nicollet Jay Simonson, MD Carmelo Panetta, MD
Albany Medical Center	Gary Bernardini, MD, PhD
Intermountain Stroke Center	Nancy Futrell, MD
St. Francis Hospital/Indiana Heart Physicians	Saeed Shaikh, MD
University of Chicago	Atman Shah, MD Neeraj Jolly, MD
Advocate Healthcare	Franco Campanella, MD
University of Medicine and Dentistry of New Jersey	Marc Klapholz, MD
George Washington University	Jonathan Reiner, MD
St. Joseph's/MidAtlantic Cardiovascular Associates	Michael Drossner, MD
Sharp Memorial Hospital	Raghava Gollapudi, MD
Royal Columbian Hospital	Albert Chan, MD
Mayo Clinic Rochester	Guy Reeder, MD Donald Hagler, MD
Lourdes Medical Center	Manoj Khandelwal, MD
Toronto General Hospital	Eric Horlick, MD
University of Calgary	Michael D Hill, MD

Trial Sites

Top 5 enrollers noted



Patient Disposition:
Randomization and Follow-Up



* Completed primary endpoint follow-up
** Discontinued prior to primary endpoint