PFOs – Are There Holes in the Arugment? To Close or Not

Walter N. Kernan, MD
Professor of Medicine
Yale School of Medicine
October, 2017

Presenter Disclosure Information
Walter N. Kernan, MD

Topic

PFO Closure

Conflict of Interest

None

Unlabeled Use

None

Five Considerations
In The Decision to Close or Not

1. The evidence on the closure procedure
   - ❖ Efficacy
   - ❖ Safety
2. Alternative therapies
3. The patient's values and preferences

Given the evidence, some patients will choose closure, others will not. How we present this evidence will influence their decisions.

Three Open-label Trials of PFO Closure In patients ~16-60 with cryptogenic IS*

Study	N	Mean F/U (years)	Stroke Rate			
			Closure	Anti-Platelet	RD†	HR (95% CI)
REDUCE	664	3.2	1.4%	5.4%	4.0%	0.23 (0.09-0.62)
RESPECT	980	5.9	3.4%	6.3%	2.9%	0.55 (0.31-0.99)
CLOSE	473	5.3	0.0%	5.0%	5.0%	0.03 (0.00-0.26)*

*closure vs. antiplatelet only group
†estimated at the mean follow-up

Adverse Events

		Patients with Adverse event Closure Group/Medical Group		
Study	N	Patients with procedure or device-related complication†	Afib Requiring Rx	DVT/PE
REDUCE	664	3.8%/NA	NS	1%/1%
RESPECT	980	4.2%/NA	13%/10%	3%/1%
CLOSE	473	5.9%/NA	5%/1%	0%/0%

†Includes cardiac perforation, cardiac thrombus, stroke, pericardial tamponade, PE, bleeding, infective endocarditis. Gore did not list arrhythmias as a procedure complication, but RESPECT and CLOSE did.

How Reliable is the Evidence for PFO Closure?

B+

1. All three trials were open label
2. 2/3 trials reported substantial losses
3. None required prolonged rhythm monitoring
4. None report f/u beyond median 5 years

Primary Outcomes

		# Primary Outcomes by Group	
Trial	Total N	Closure	Antiplatelet
Reduce	664	6	12
Respect	980	18	28
Close	473	0	14
TOTAL		24	54

REDUCE
Evidence for Surveillance Bias

End Point	PFO Closure Group	AP-Only Group	Effect Size	P-Value
	No. of patients/total no. (%)			
Clinical Ischemic Stroke	6/441 (1.4)	12/223 (5.4)	0.23 (0.09-0.62)	0.002
New Brain Infarction	22/383 (5.7)	20/177 (11.3)	0.51 (0.29-0.91)	0.04
Clinically apparent	5/383 (1.3)	12/177 (6.8)	0.19 (0.07-0.54)	0.005
Silent	17/383 (4.4)	8/177 (4.5)	0.98 (0.43-2.23)	0.97

L Sondergaard. NEJM 2017;377:1033-42

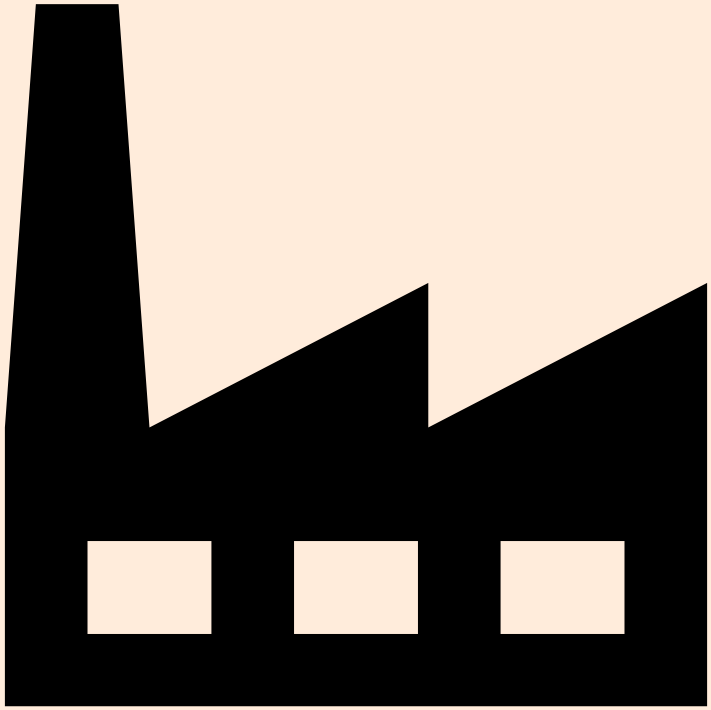
Losses in 2017 PFO trials

		Losses	
Trial	Total N	Closure	Antiplatelet
REDUCE	664	9%	15%
RESPECT	980	21%	33%
CLOSE	473*	0%	<1%

*PFO closure vs antiplatelet arm only

Europeans stay connected.

Did The 2017 Trials Ask The Correct Question?



(This symbolizes industry.)

CLOSE Results
Oral Anticoagulation vs. Antiplatelet Therapy

	# Outcomes			
Outcome	OAC N=187	AP N=174	HR	95% CI
Any Stroke	3	7	0.44	0.11-1.48
Disabling	1	1	0.96	0.08-11.85
Death	1	0	2.84	0.15-414.86

J-L Mas NEJM 2017;377:1011

Informed Consent to Promote Patient-Centered Care*

Background
You have a hole in your heart . . .

Procedure
PFO closure involves . . .

Potential Benefits

Potential Risks

Other Treatments

Experience of Your Team

*HM Krumholz. JAMA 2010;303:1190

Informed Consent to Promote Patient-Centered Care*

Potential Benefits

"What we know about PFO closure is based on five studies that included about 2000 patients who had the closure procedure. The studies followed patients for up to 8 years. Based on the results of these studies, PFO closure is likely to reduce your risk of stroke: Among 100 patients who have their PFO closed, 2 will have another stroke within 5 years. Among 100 patients who take aspirin instead, 6 will have a stroke within 5 years."

*HM Krumholz. JAMA 2010;303:1190

Communicating PFO Closure Benefit At 5 Years

Informed Consent to Promote Patient-Centered Care*

Potential Risks

If you choose to have your PFO closed, there are risks related to the procedure and the device. These include:

- An irregular heart beat called atrial fibrillation. During the closure procedure, some patients will develop atrial fibrillation. For most patients, this will resolve within a month and will not require further treatment. However, for every 1000 patients who have their PFO closed, about 40 will develop atrial fibrillation that will last for more than a month. By comparison, about 10 patients who receive medical therapy will develop atrial fibrillation lasting more than a month. Atrial fibrillation is important because it can cause recurrent stroke and often requires use of a blood thinning medication.

*HM Krumholz. JAMA 2010;303:1190

Informed Consent to Promote Patient-Centered Care*

Potential Risks (continued)

- A Serious Complication During the Procedure. During closure of the PFO, serious problems can occur. These include atrial fibrillation, bleeding from the skin puncture side, bleeding around the heart, stroke, heart perforation, and blood clots in the heart or lung. These complications can usually be treated without long-term consequences. Among 1000 patients who have a PFO closed, about 40 will have one of these or other complications.

*HM Krumholz. JAMA 2010;303:1190

Informed Consent to Promote Patient-Centered Care*

Background
You have a hole in your heart . . .

Procedure
PFO closure involves . . .

Potential Benefits

Potential Risks

Other Treatments

Experience of Your Team

*HM Krumholz. JAMA 2010;303:1190

Summary

In circumstances of:

- Imperfect evidence
- A small absolute risk reduction
- Uncertain long-term effects
- Unexamined alternative therapy

High quality shared making is critically important

END

Thank You

PFOs – Are there holes in the argument: To Close or Not?

David Thaler, MD, PhD, FAHA

***Director emeritus*, The Comprehensive Stroke Center at Tufts Medical Center**
***Professor of Neurology*, Tufts University School of Medicine**
***Chairman*, Department of Neurology, Tufts University School of Medicine**

October 26, 2017

Disclosure Statement of Financial Interest

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

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

I believe that closing a hole that’s causing trouble makes sense. But I know…

… that belief without facts, is not knowledge.

2011, 2013: Trial data arrive

And 2015 and 2016

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CLOSURE I, RESPECT, PC-Trial

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*

ABSTRACT

BACKGROUND

The prevalence of patent foramen ovale among patients with cryptogenic higher than that in the general population. Closure with a percutaneous often recommended in such patients, but it is not known whether this in reduces the risk of recurrent stroke.

METHODS

We conducted a multicenter, randomized, open-label trial of closure taneous device, as compared with medical therapy alone, in patients be 60 years of age who presented with a cryptogenic stroke or transient is (TIA) and had a patent foramen ovale. The primary end point was a stroke or transient ischemic attack during 2 years of follow-up, d cause during the first 30 days, or death from neurologic causes b and 2 years.

RESULTS

A total of 909 patients were enrolled in the trial. The cumulative in Meier estimate) of the primary end point was 5.5% in the closure g as compared with 6.8% in the medical-therapy group (462 patient ratio, 0.78; 95% confidence interval, 0.45 to 1.35; P=0.37). The re 2.9% and 3.1% for stroke (P=0.79) and 3.1% and 4.1% for TIA (occurred by 30 days in either group, and there were no deat causes during the 2-year follow-up period. A cause other than p was usually apparent in patients with recurrent neurologic ev

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent with a device did not offer a greater benefit than medical prevention of recurrent stroke or TIA. (Funded by NMT Me number, NCT00201461.)

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 David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale is effective in the prevention of ischemic stroke in patients who have had a cryptogenic stroke is unknow ducted a trial to evaluate whether closure is superior to medical thera preventing recurrent ischemic stroke or early death in patients 18 to 60

METHODS

In this prospective, multicenter, randomized, event-driven trial, we signed patients, in a 1:1 ratio, to medical therapy alone or closure foramen ovale. The primary results of the trial were analyzed when 25 primary end-point events had been observed and adjudicated.

RESULTS

We enrolled 980 patients (mean age, 45.9 years) at 69 sites. The group received one or more antiplatelet medications (74.8%) or Treatment exposure between the two groups was unequal (1375 closure group vs. 1184 patient-years in the medical-therapy group), a higher dropout rate in the medical-therapy group. In the intent 9 patients in the closure group and 16 in the medical-therapy rence of stroke (hazard ratio with closure, 0.49; 95% confiden to 1.11; P=0.08). The between-group difference in the rate of significant in the prespecified per-protocol cohort (6 events in 14 events in the medical-therapy group; hazard ratio, 0.37; P=0.03) and in the as-treated cohort (5 events vs. 16 events; CI, 0.10 to 0.75; P=0.007). Serious adverse events occurred in the closure group and in 21.6% in the medical-therapy dure-related or device-related serious adverse events occur in the closure group (4.2%), but the rate of atrial fibrillatio not increased.

CONCLUSIONS

In the primary intention-to-treat analysis, there was no s with closure of a patent foramen ovale in adults who h mic stroke. However, closure was superior to medic specified per-protocol and as-treated analyses, with (Funded by St. Jude Medical; RESPECT ClinicalTrials

From the University of Colorado Denver/University of Colorado Hospital, Aurora (J.D.C.); University of California Los Angeles, Los Angeles (J.L.S.); Tufts University/Tufts Medical Center, Boston (D.E.T.); University of Texas/Memorial Hermann Heart and Vascular Institute, Houston (R.W.S.); Barry Consultants, Austin, TX (S.B.); South Denver Cardiology/Swedish Medical Center, Littleton, CO (L.A.M.); Medical College of Wisconsin Milwaukee, Milwaukee (D.S.M.); and the University of Washington, Seattle (D.L.T.). Address reprint requests to Dr. Carroll at the University of Colorado Denver, Anschutz Medical Campus, Leprino Bldg., 12401 East 17th Ave., Mail Stop 8132, Aurora, CO 80045, or at john.carroll@ucdenver.edu.

*The investigators, institutions, and other organizations participating in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) are listed in the Supplementary Appendix, available at NEJM.org.

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Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

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ABSTRACT

BACKGROUND

The options for secondary prevention of cryptogenic embolism in patients with patent foramen ovale are administration of antithrombotic medications or percutaneous closure of the patent foramen ovale. We investigated whether closure is superior to medical therapy.

METHODS

We performed a multicenter, superiority trial in 29 centers in Europe, Canada, Brazil, and Australia in which the assessors of end points were unaware of the study-group assignments. Patients with a patent foramen ovale and ischemic stroke, transient ischemic attack (TIA), or a peripheral thromboembolic event were randomly assigned to undergo closure of the patent foramen ovale with the Amplatzer PFO Occluder or to receive medical therapy. The primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. Analysis was performed on data for the intention-to-treat population.

RESULTS

The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical-therapy group. The primary end point occurred in 7 of the 204 patients (3.4%) in the closure group and in 11 of the 210 patients (5.2%) in the medical-therapy group (hazard ratio for closure vs. medical therapy, 0.63; 95% confidence interval [CI], 0.24 to 1.62; P=0.34). Nonfatal stroke occurred in 1 patient (0.5%) in the closure group and 5 patients (2.4%) in the medical-therapy group (hazard ratio, 0.20; 95% CI, 0.02 to 1.72; P=0.14), and TIA occurred in 5 patients (2.5%) and 7 patients (3.3%), respectively (hazard ratio, 0.71; 95% CI, 0.23 to 2.24; P=0.56).

CONCLUSIONS

Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT00166257.)

From the Departments of Cardiology (R.M., B.K., A.A.K., A.W., S.W.) and Neurology (H.P.M.), Bern University Hospital, and the Institute of Social and Preventive Medicine (B.K., P.J.) and Clinical Trials Unit (B.K., P.J.), University of Bern — both in Bern, Switzerland; Brighton and Sussex University Hospitals, Brighton, United Kingdom (D.H.-S.); University Hospital, Jagiellonian University Medical College, Krakow, Poland (D.D.); Aarhus University Hospital, Aarhus, Denmark (G.A.); University of Montreal, Montreal (R.I.); Herzzentrum Leipzig, Leipzig, Germany (G.S.); and Allied Hospital, Melbourne, VIC, Australia (A.S.W.). Address reprint requests to Dr. Meier at the Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland, or at bernhard.meier@insel.ch.

*Investigators in the Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (PC Trial) are listed in the Supplementary Appendix, available at NEJM.org.

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Forbes / Pharma & Healthcare

Controversial PFO Closure Trials Published In NEJM

Two controversial trials testing PFO closure with the Amplatzer PFO Occluder (St. Jude Medical) in patients with cryptogenic stroke, first presented last fall at the TCT meeting, have now been published in the *New England Journal of Medicine*. Both trials missed their primary endpoints but contained suggestions of possible benefit. The results appear unlikely to resolve the ongoing controversy over the value, or lack of value, of this procedure, but, as an accompanying editorial states, both advocates and critics of PFO closure will find source material for their arguments in these papers.

Amplatzer PFO Occluder with Medical Treatm... an ischemic stroke, TIA, or a peripheral throu... Occluder.

After 4.1 years of followup in the closure ... primary endpoint (the composite of dea...

- Primary endpoint: 3.4% in the closure ...
- Nonfatal stroke: 0.5% versus 2.4...
- TIA: 2.5% versus 3.3% (HR 0.7...

The RESPECT trial similarly ... dropped out during the coun... after 25 primary endpoint ... randomization), but presp...

- Primary ...
- Recurrent st...
- Recurrent stroke (as-treated ...

In the accompanying editorial, Steven ... due to widespread off-label use of atrial septal ... the field. CLOSURE 1, did not show significant benefi... benefit.

They conclude:

> ...we are left for the moment to make decisions under conditions of uncertainty. In such circ... makers — patients, clinicians, authors of practice guidelines, and regulatory authorities — depending ... also on the potential consequences of their decisions. Some of them may interpret the data as supporting ... therapeutic option, even while conceding the failure of trials to show the superiority of closure over medical therapy ... foramen ovale in the general population, the enormous potential for overuse of percutaneous closure of a patent foramen ... risk of stroke in patients who are treated medically, the routine use of this therapy seems unwise without a clearer view of who, if ... benefit.... Randomized studies of closure may come to an end, however, if the Amplatzer device is approved. Thus, all eyes will be on the ...

Larry Husten
CONTRIBUTOR

FULL BIO >

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Heart-Plug Benefit Questioned

Doctors Debate Whether Device Can Help Young Stroke Patients

By JOSEPH WALKER
March 11, 2013 6:54 p.m. ET

Mending a young person's broken heart may be good in love stories, but is it a way to prevent strokes? That's a question the Food and Drug Administration will consider later this year when it evaluates a heart plug made by St. Jude Medical Inc.

At issue is whether a heart-plug procedure to repair a birth defect that is common in about a quarter of the U.S. population can prevent strokes in young people. Some of the country's leading cardiologists are debating the procedure, which can provide ...

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RESPECT

CLINICAL TRIAL

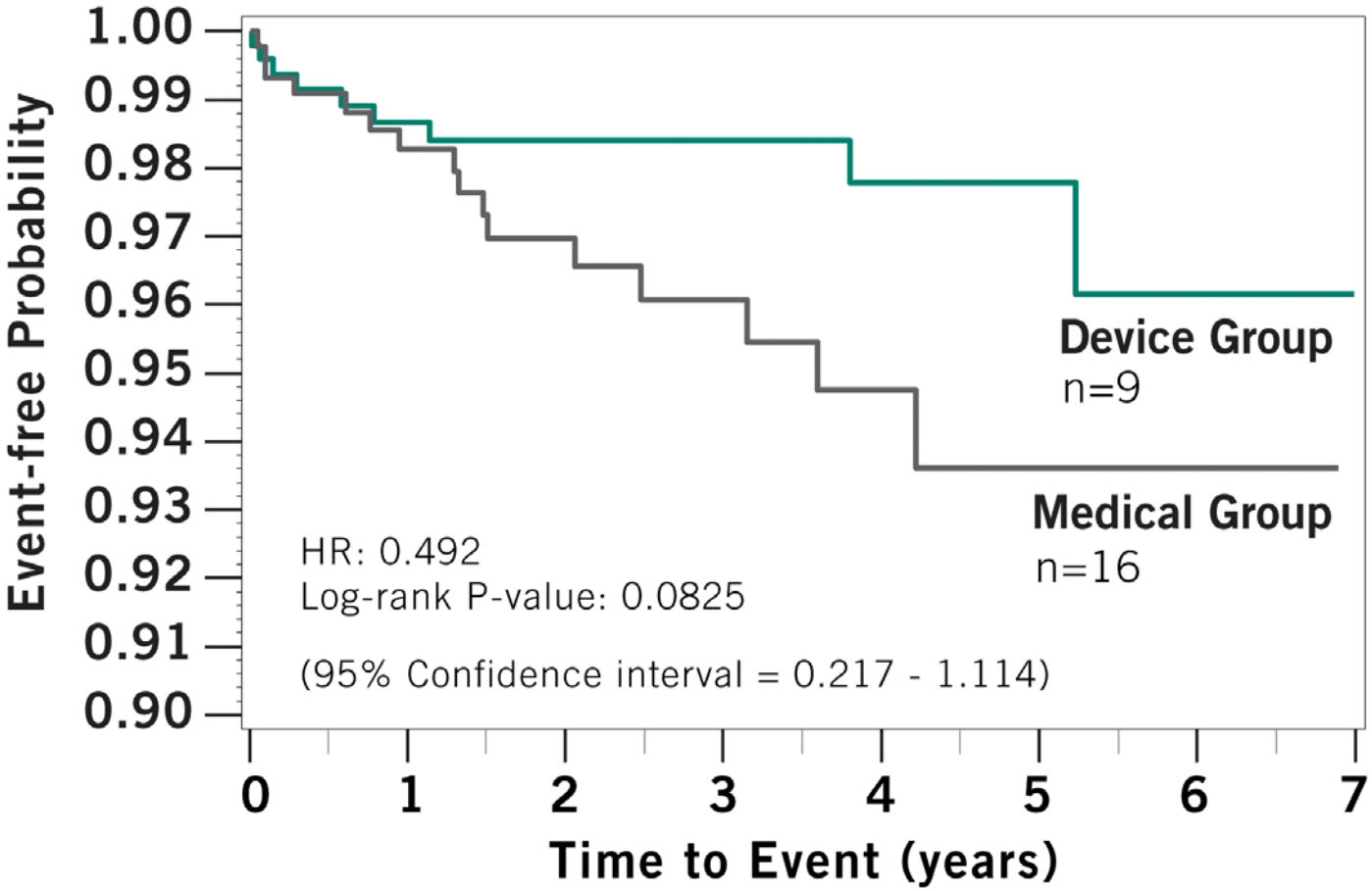
RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

JOHN D. CARROLL, MD, JEFFREY L. SAVER, MD, DAVID E. THALER, MD, PHD, RICHARD W. SMALLING, MD, PHD, SCOTT BERRY, PHD, LEE A. MACDONALD, MD, DAVID S. MARKS, MD, MBA, DAVID L. TIRSCHWELL, MD
FOR THE RESPECT INVESTIGATORS

TCT2012

CARDIOVASCULAR RESEARCH FOUNDATION
a passion for innovation

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

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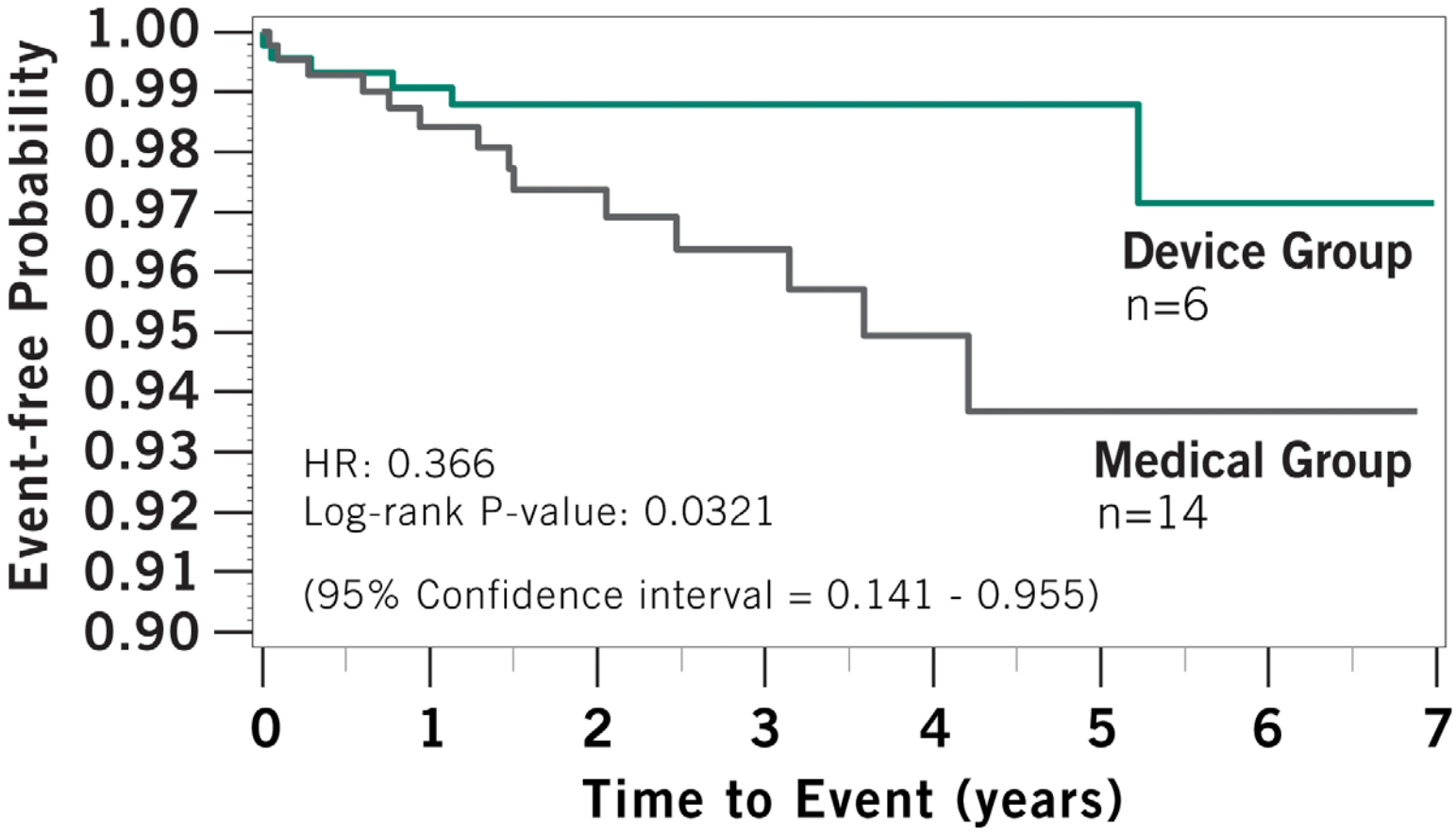
1. Cox model used for analysis

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

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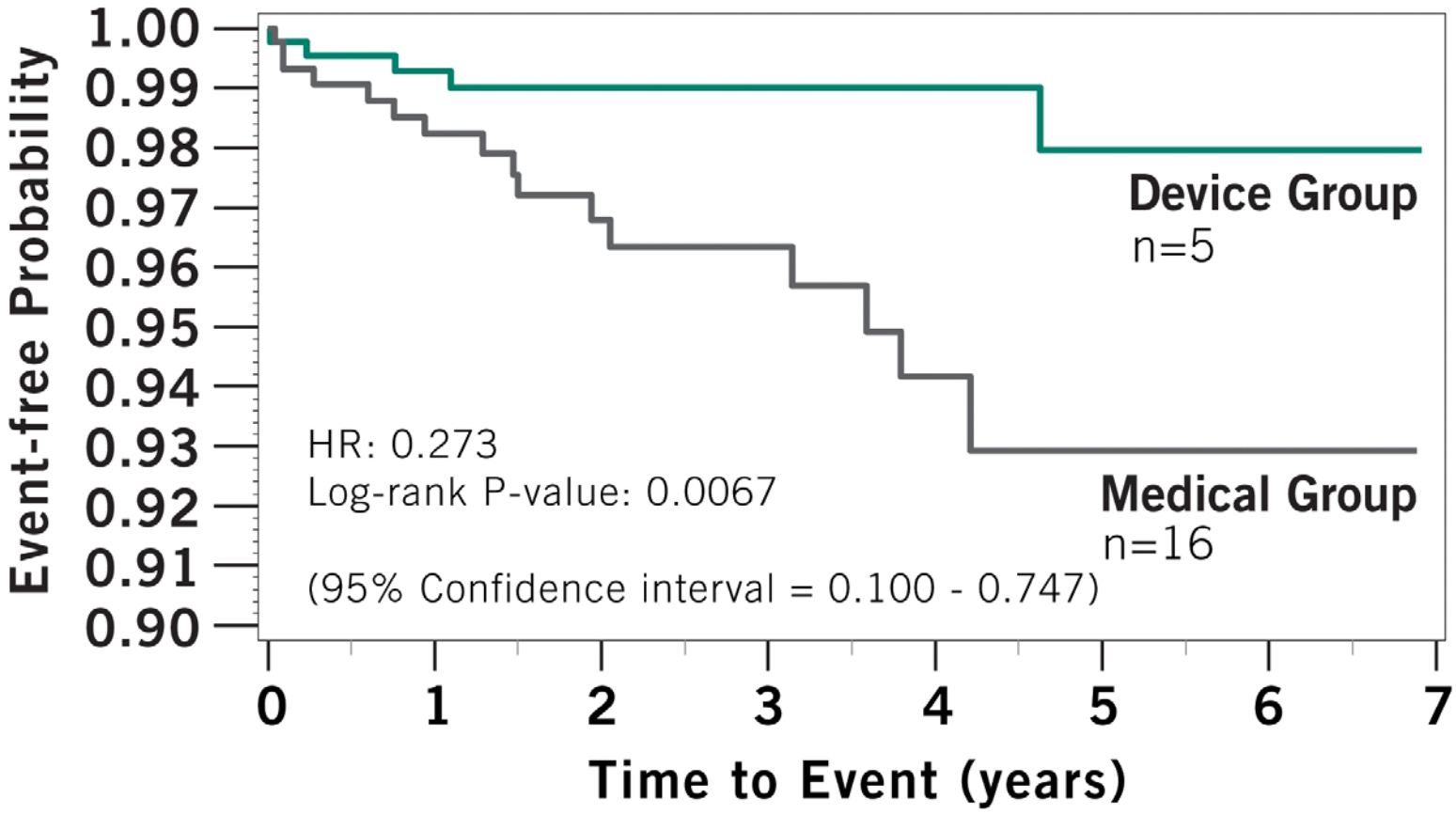
1. Cox model used for analysis

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

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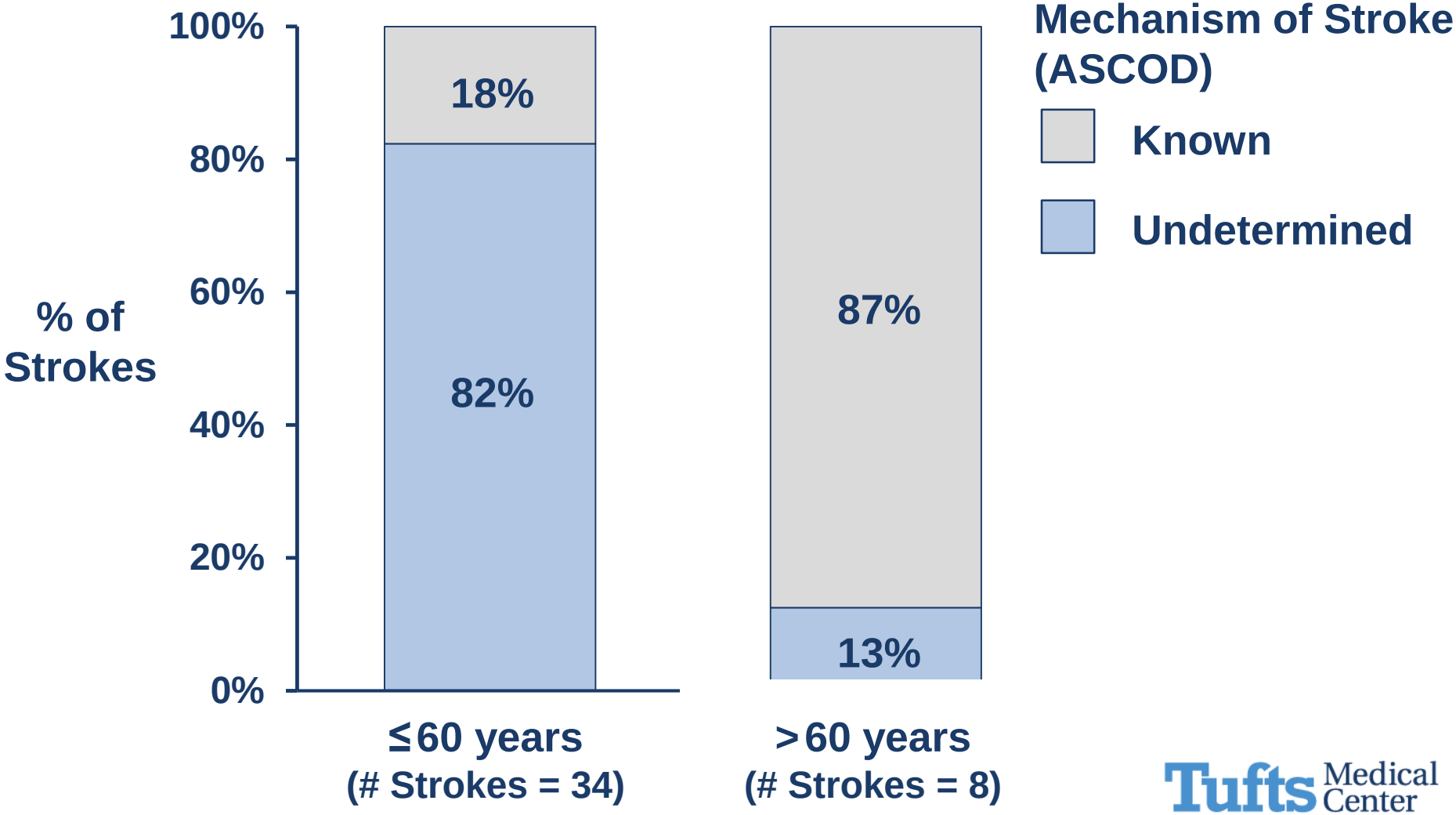
1. Cox model used for analysis

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



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Device Closure of Patent Foramen Ovale After Stroke

Pooled Analysis of Completed Randomized Trials

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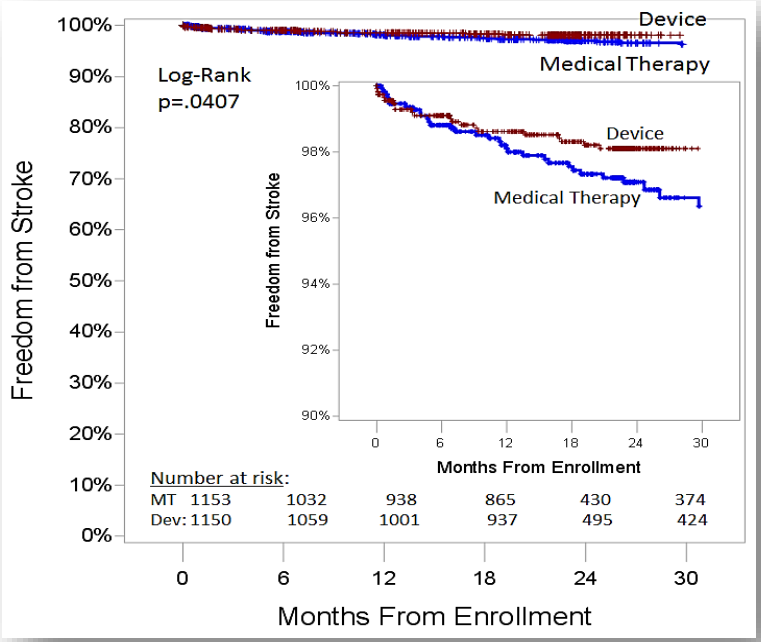
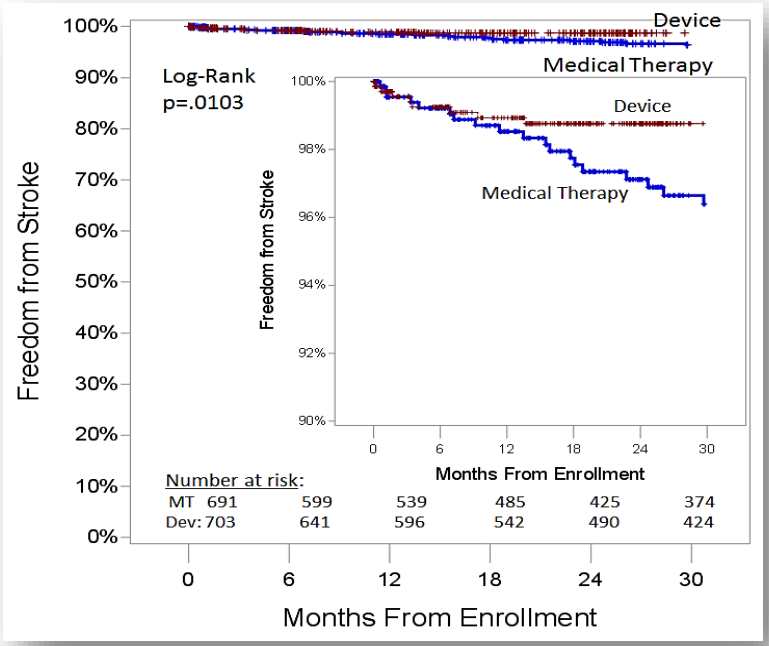
Pooled Data – **All 3** Trials: STROKE OUTCOME



Analysis	Annualized Outcome Rates		Cox PH Model	Covariate-adjusted Cox PH model*
	Device Closure Percent per person year (event/person years)	Medical Therapy Percent per person year (event/person years)	Hazard Ratio ++ (95% CI); p-value	Hazard Ratio ++ (95% CI); p-value
Pooled Data (n=2303)				
Composite	1.5%(45/3057)	2.3% (63/2792)	0·69 (0·47 to 1·01) p=0·0531	0·68 (0·46 to 1·00) p=0·0491
Recurrent Stroke	0·7% (22/3099)	1·3% (36/2839)	0·58 (0·34 to 0·98); p=0·0433	0·58 (0·34 to 0·99) p=0·0443

++ Adjusted Hazard ratios estimated using Cox proportional hazard model combined from ten multiply imputed datasets. For pooled results, the study was included in the model as a stratification term * Adjusted for: age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking

Pooled Data – Amplatzer Trials: STROKE OUTCOME



Analysis	Annualized Outcome Rates		Cox PH Model	Covariate-adjusted Cox PH model*
	Device Closure Percent per person year (event/person years)	Medical Therapy Percent per person year (event/person years)	Hazard Ratio ++ (95% CI); p-value	Hazard Ratio ++ (95% CI); p-value
Pooled Amplatzer Data (n=1394) *				
Composite	1.0% (22/2274)	1.6%(32/2021)	0·63 (0·36 to 1·08) p=0·0914	0.64 (0·37 to 1·11) p=0·1150
Recurrent Stroke	0·4% (10/2301)	1·1% (23/2044)	0·39 (0·19 to 0·82) p=0·0133	0·41 (0·20 to 0·88) p=0·0213

++ Adjusted Hazard ratios estimated using Cox proportional hazard model combined from ten multiply imputed datasets. For pooled results, the study was included in the model as a stratification term * Adjusted for: age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Still No Closure on the Question of PFO Closure

Steven R. Messé, M.D., and David M. Kent, M.D.

In approximately 30% of young survivors of stroke, no clear cause is identified despite a thorough evaluation.[1] Patent foramen ovale is found on transesophageal echocardiography in about half of these patients, as compared with approximately 25% of the general population. Clinicians, then, often assume that the patent foramen ovale was the cause of the stroke, although it may be incidental in some patients.[2-4] The most effective strategy for the prevention of stroke recurrence in such patients is uncertain, and some experts recommend closure of the patent foramen ovale to prevent future embolic events, although high-level data have been lacking.

In this issue of the *Journal*, the long-awaited results of the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT)[5]

randomization and were follow
rate of the primary end point o
ischemic attack, or systemic e
significantly lower in patients
closure with the use of the S
(NMT Medical) than in patients
medical therapy (5.5% and 6.8%
P=0.37); the rate of the secondar
stroke alone was also not significa
the closure group (2.9% with closure a
with medical therapy, P=0.79).[9]

Like CLOSURE I, neither RESPECT
PC Trial showed a significantly lower rate
primary end points with closure than with
ical therapy in their intention-to-treat anal
The PC Trial investigators randomly assig
414 patients to closure or to medical ther
and followed them for an average of appro

who, if anyone, is likely to benefit. To that end, it is excellent news that the RESPECT investigators are continuing to accrue data on the patients they enrolled and that other studies of closure of patent foramen ovale are ongoing. Randomized studies of closure may come to an end, however, if the Amplatzer device is approved. Thus, all eyes will be on the regulatory agencies to see how they will interpret these results in light of their own evidentiary standards.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Hospital of the University of Pennsylvania, Philadelphia (S.R.M.); and Tufts University, Boston (D.M.K.).

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Extended f/u presented at TCT LBCT session (#2)

Extended Follow-up Provides Considerable New Data

	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Mean Follow-up (years)		
Initial Analysis	3.0	2.7
Extended Follow-up	5.5	4.9
Total Patient-Years of Follow-up		
Initial Analysis	1476	1284
Extended Follow-up	2769	2376

tct2015

CRF CARDIOVASCULAR RESEARCH FOUNDATION

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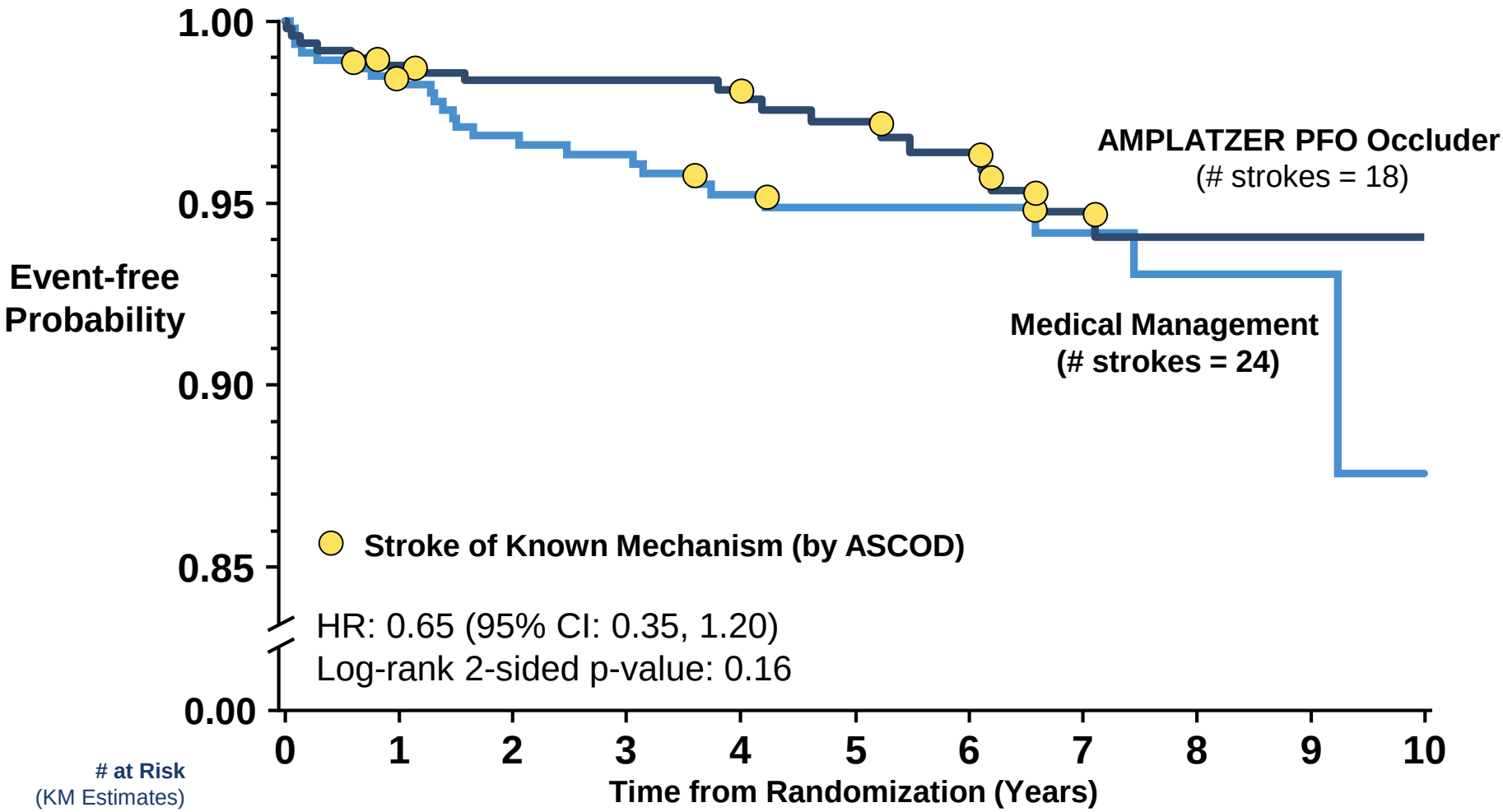
All Recurrent Strokes Through Extended Follow-up (ITT)

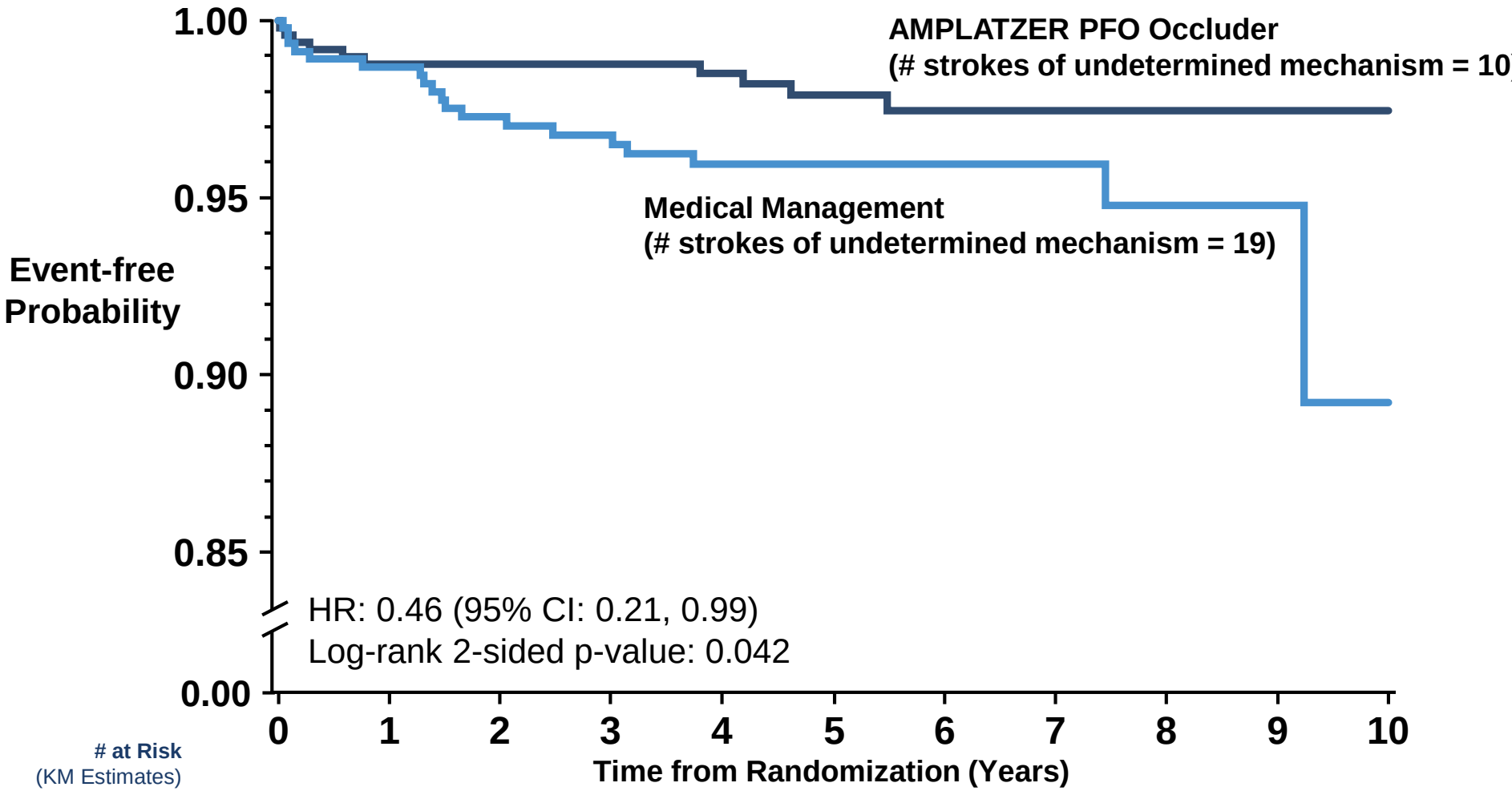


# at Risk (KM Estimates)										
AMPLATZER	**499** (0%)	**476** (1.4%)	**463** (1.6%)	**434** (1.6%)	**369** (1.9%)	**282** (2.8%)	**212** (3.6%)	**151** (5.2%)	**86** (6.0%)	**44** (6.0%)	**20** (6.0%)
MM	**481** (0%)	**432** (1.8%)	**394** (3.2%)	**367** (3.7%)	**307** (4.8%)	**238** (5.1%)	**168**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

Phenotyping by ASCOD



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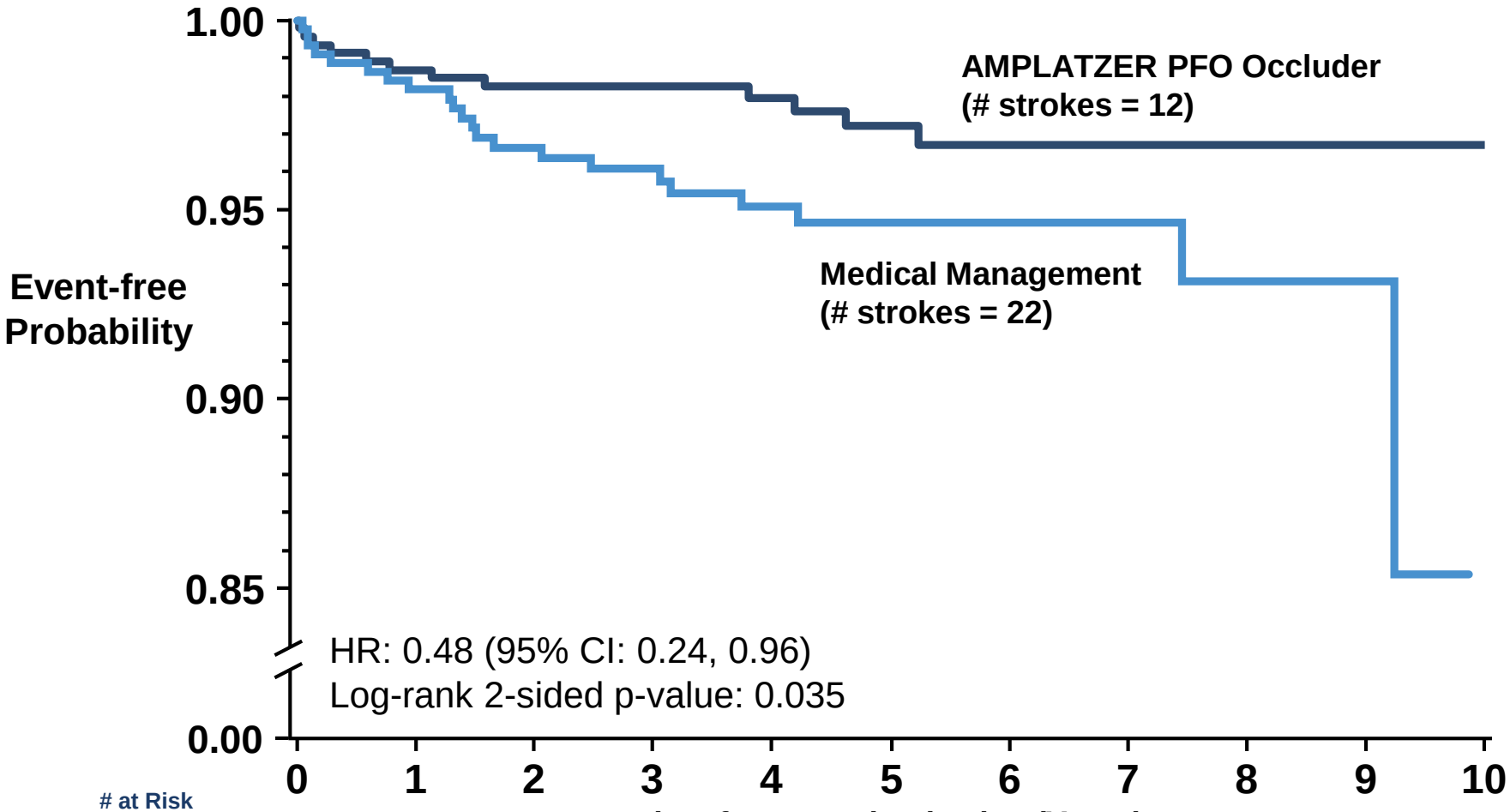
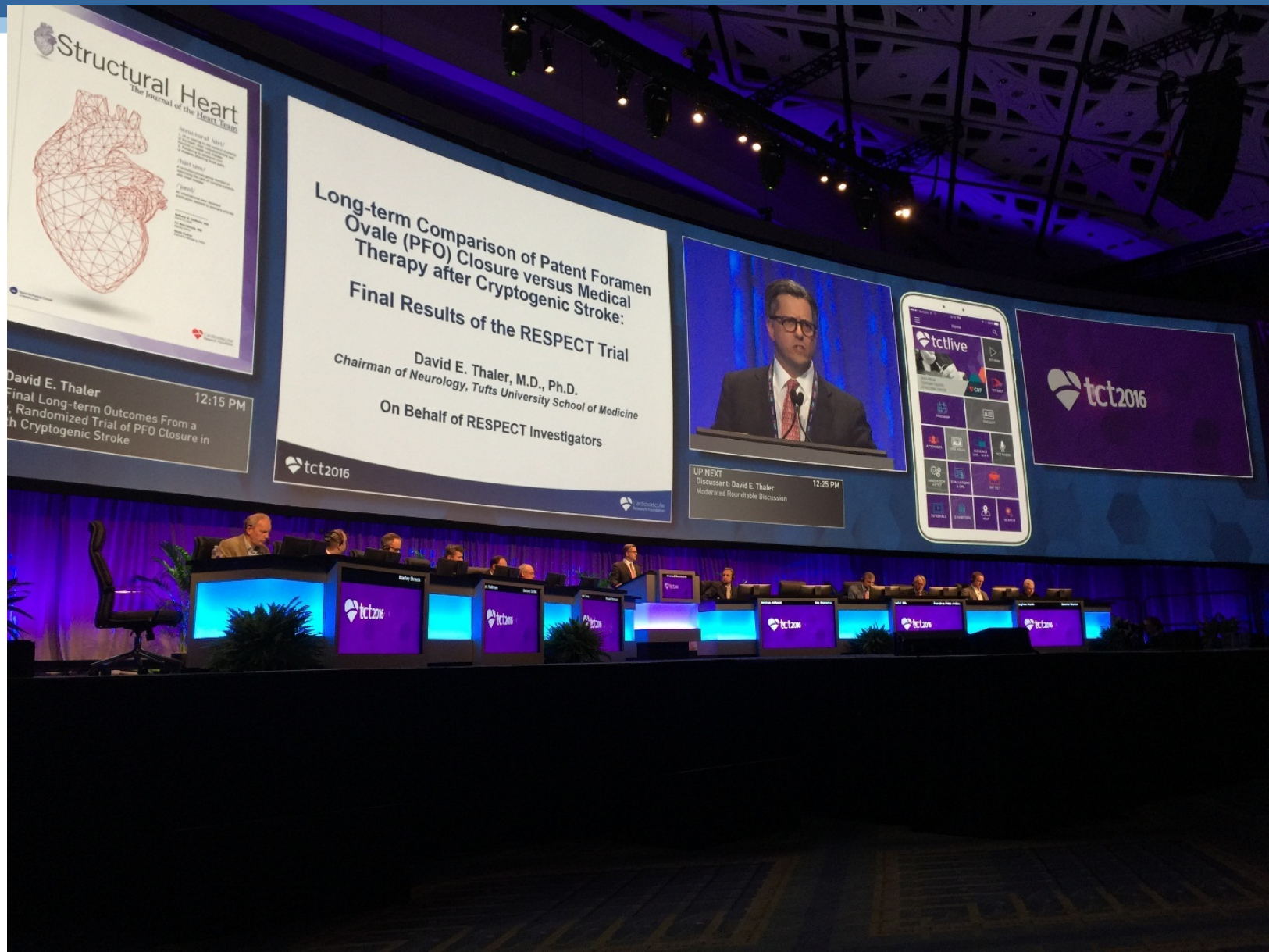
52% Relative Risk Reduction for Recurrent Stroke in Patients < 60 Years



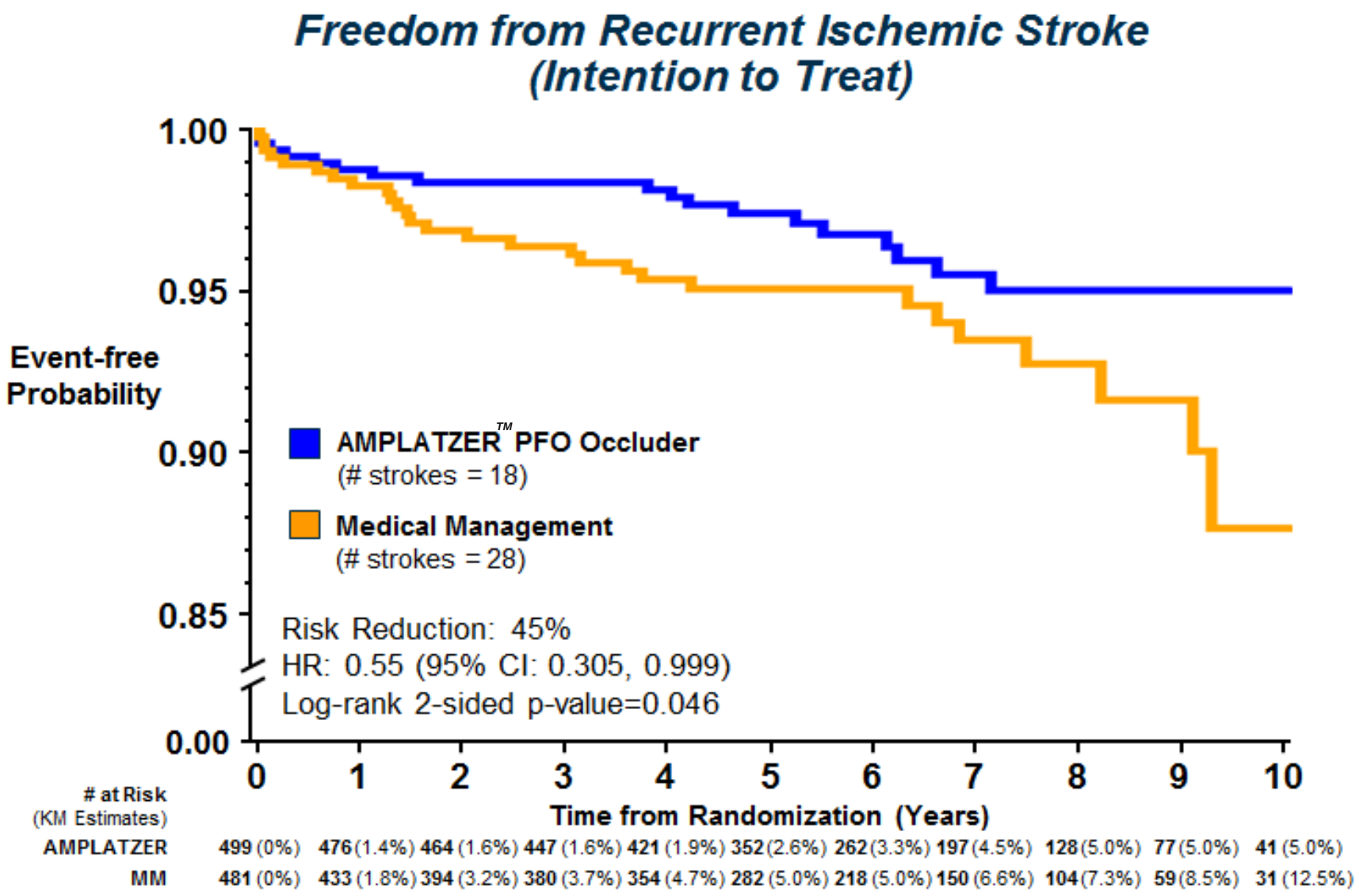
# at Risk (KM Estimates)											
AMPLATZER	475 (0%)	443 (1.3%)	417 (1.8%)	375 (1.8%)	308 (2.1%)	230 (2.8%)	166 (3.3%)	117 (3.3%)	69 (3.3%)	33 (3.3%)	15 (3.3%)
MM	463 (0%)	401 (1.8%)	353 (3.4%)	313 (4.0%)	254 (4.9%)	189 (5.4%)	124 (5.4%)	86 (5.4%)	51 (6.9%)	26 (6.9%)	9 (14.7%)

- Food and Drug Administration (FDA) Advisory Panel in May 2016 (data lock, August 2015)
- Following panel meeting, FDA requested an analysis of long-term outcomes using updated data
- Final analyses (data lock, May 2016) of RESPECT presented at TCT, Washington DC, Nov 2016

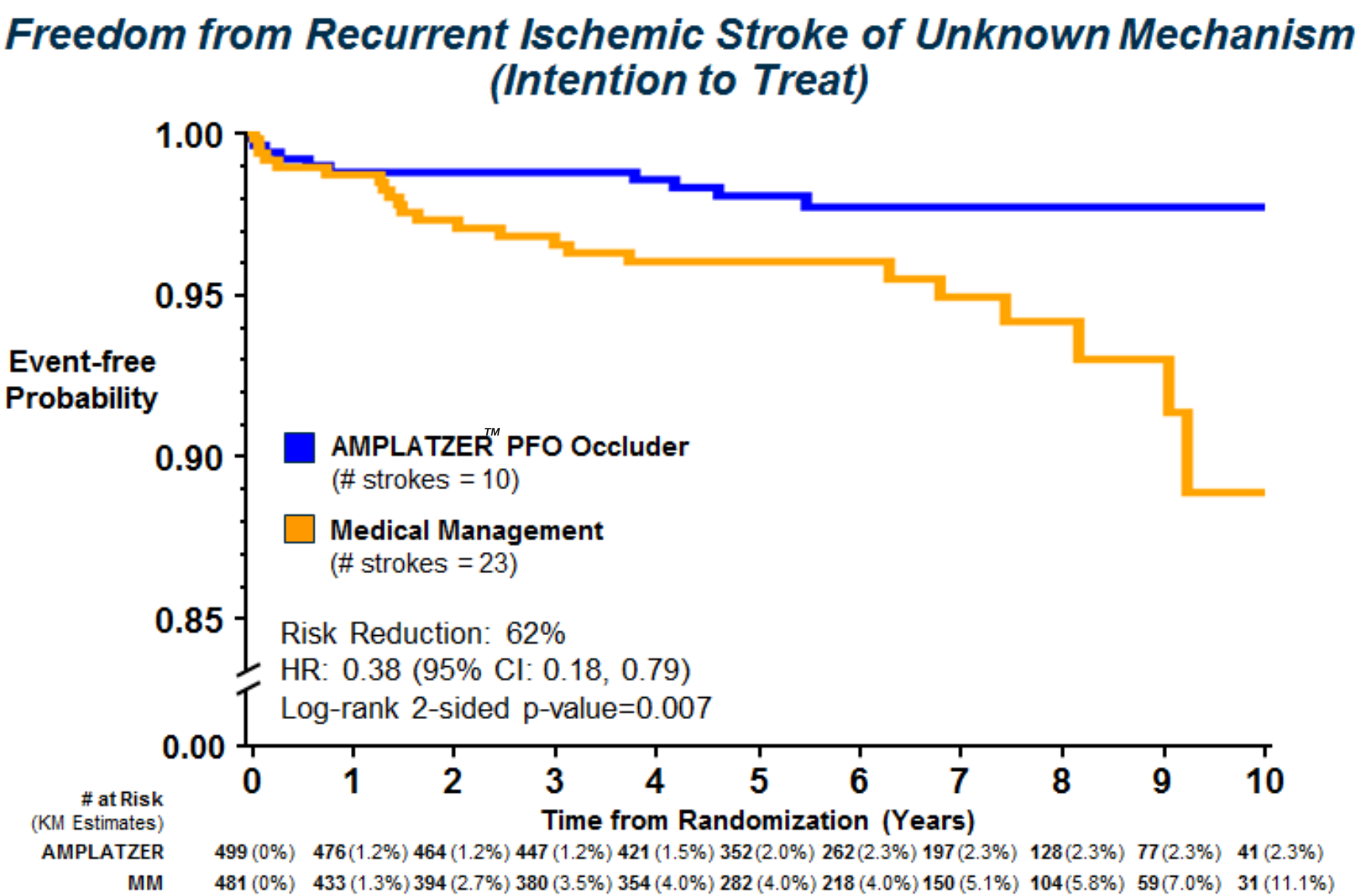
TCT Conference – Nov 2016 (LBCT #3!)
RESPECT Trial - final results



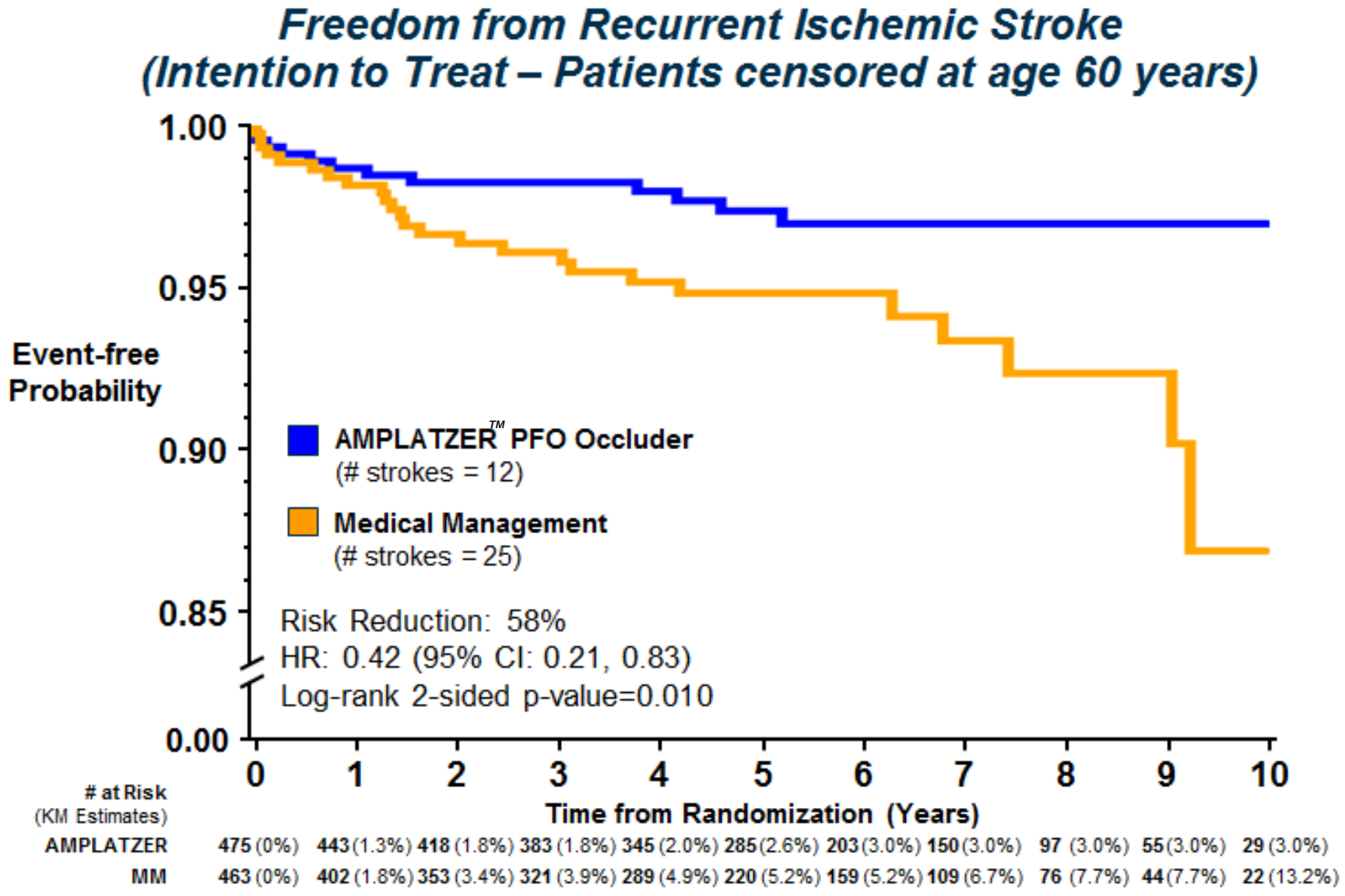
RESPECT Final Results



RESPECT Final Results – Only CS recurrence



RESPECT Final Results – Censored >60yr



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**

	HR (95% CI)	Relative Risk Reduction	P-value
Ischemic stroke	0.55 (0.305-0.999)	45%	0.046
Stroke without known mechanism	0.38 (0.18-0.79)	62%	0.007
Age-censored analysis (<60y)	0.42 (0.21-0.83)	58%	0.01

But aren’t there risks from PFO closure?

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DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)

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DSMB-adjudicated SAEs of Interest

Event Type	AMPLATZER™ PFO Occluder (N=499) [3141 Pt-Yrs]		Medical Management (N=481) [2669 Pt-Yrs]		P-value**
	Events	Rate*	Events	Rate*	
Atrial fibrillation	8	0.25	4	0.15	0.37
Major bleeding	18	0.57	15	0.56	0.96
Death from any cause	7	0.22	11	0.41	0.21
DVT/PE	18	0.57	4	0.15	0.006

* Rate expressed as number of events per 100 patient-years
**Based on the normal approximation to a difference in Poisson rates

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Apples and oranges

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WHO Global Burden of Disease

Circ Res 2016: **118:1340-7**

Strokes have longer more significant consequences than venous thrombombolism (VTE)

	VTE (per 10,000)	Stroke (per 10,000)
Disability-Adjusted Life Year	<1	22-136
Mortality	<10	42

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OK, it might be statistically,
but not clinically, significant

(absolute risk reduction << relative risk reduction)

… but risk of recurrence seems to hold steady at

~1% each year

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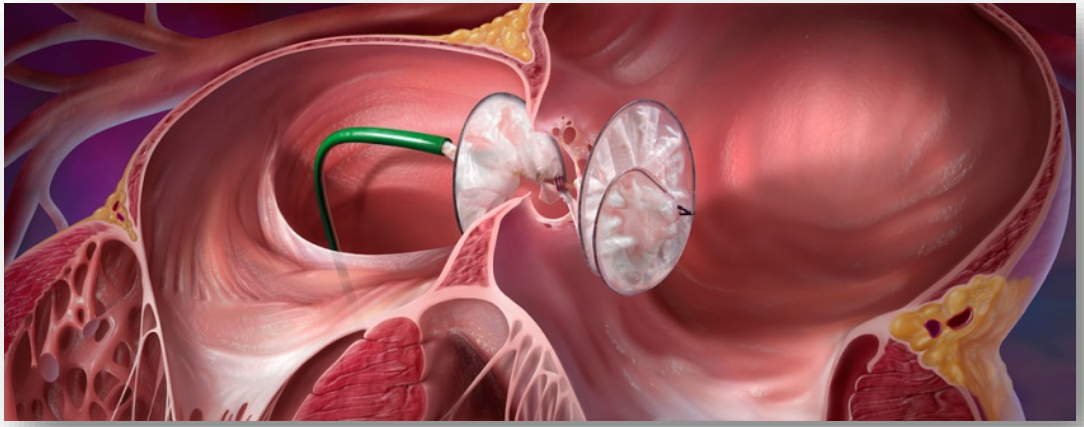
Confirmatory trials (presented May 2017)

- **REDUCE**: www.clinical.goremedical.com/REDUCE



- **Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)**
  - Closure vs Anticoagulation vs Antiplatelet
  - JL Mas, Paris

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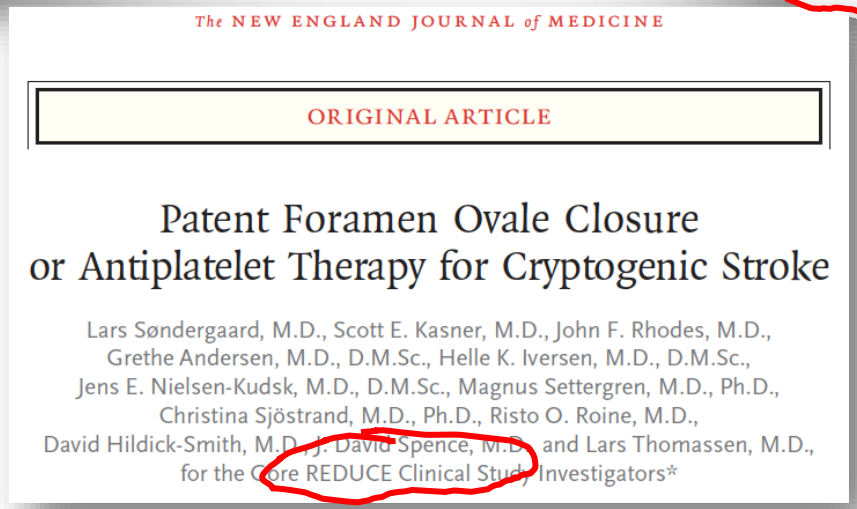
September 2017 – RESPECT, REDUCE, CLOSE



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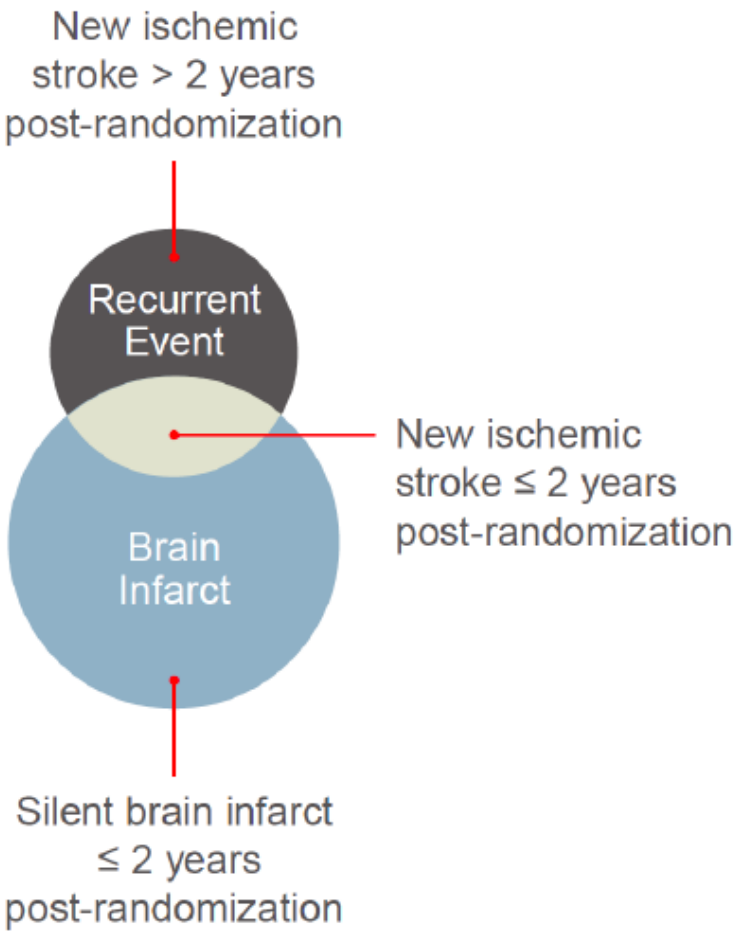
Co-Primary Endpoints

- Freedom from **recurrent clinical ischemic stroke** through at least 24 months

- Incidence of **new brain infarct** (defined as clinical ischemic stroke or silent brain infarct*) through 24 months



*New T2 hyperintense MRI lesion with diameter ≥3 mm; adjudicated by MRI core lab

GORE
REDUCE
CLINICAL STUDY

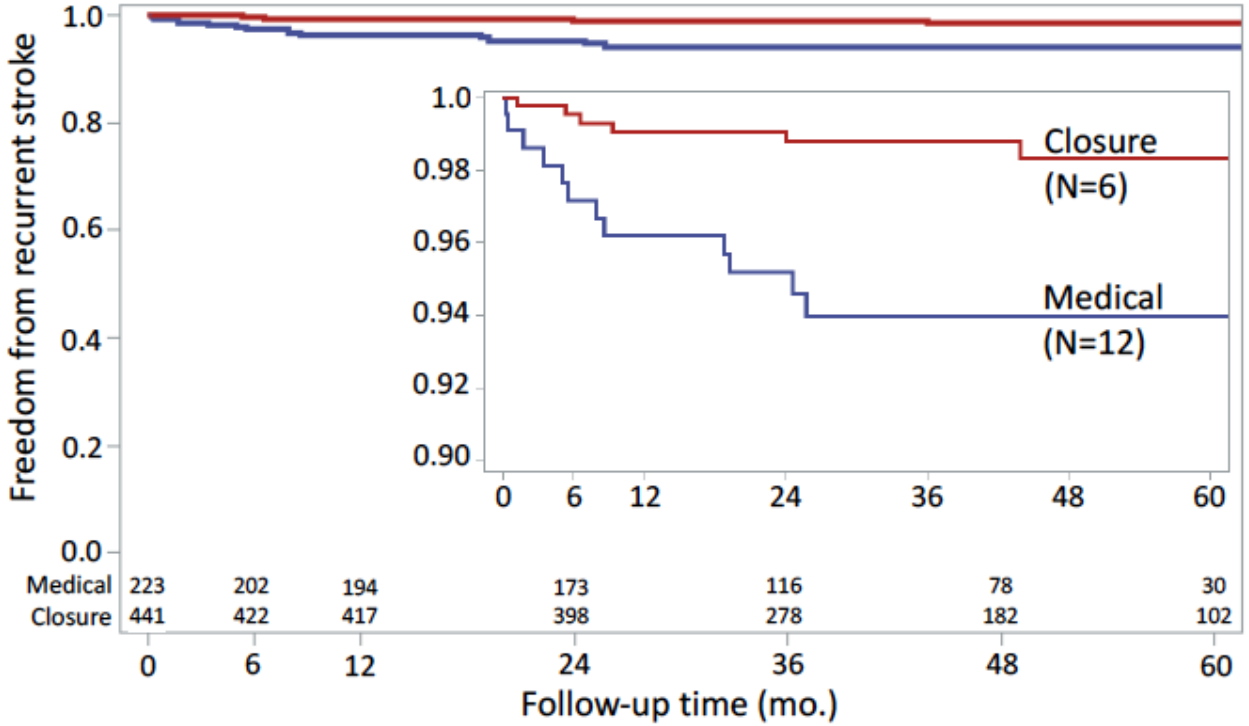
Safety

- Bleeding similar
- Atrial fibrillation (AF) / flutter rate higher in the closure group
  - non-serious (63%)
  - onset in 1st month (79%)
  - resolved within 2 weeks (59%)
  - 1/29 with AF after closure had a stroke
- Rate of device events was low and generally occurred around implant procedure
  - 1/2 with device thrombosis had a recurrent stroke
- DVT and PE similar

All Enrolled Subjects (N=664)	Closure (n=441)	Medical (n=223)	p-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**0.57**
Procedure-related	4 (0.9%)	-	0.31
Other	4 (0.9%)	6 (2.7%)	0.09
Any AF/ flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**<0.001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	<0.001
Serious device adverse events	**6 (1.4%)**	**-**	**-**
Device dislocation	3 (0.7%)	-	-
Device thrombosis	2 (0.5%)	-	-
Aortic dissection	1 (0.2%)	-	-
Any DVT or PE adverse events	**3 (0.7%)**	**2 (0.9%)**	**1.0**

GORE
REDUCE
CLINICAL STUDY

First co-primary endpoint: clinical stroke, intention-to-treat
77% reduction in risk with closure



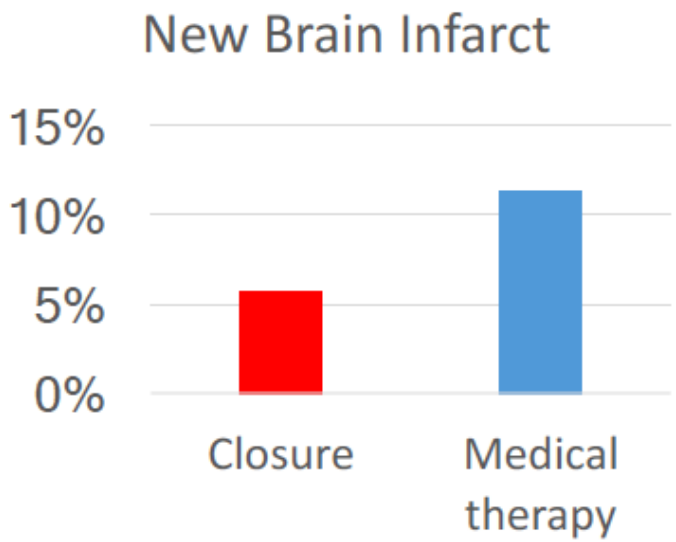
Hazard ratio, 0.23
95% CI, 0.09-0.62
Log-rank p=0.001
Adjusted for multiple testing

Annualized event rates
Closure: 0.39 per 100 person-years
Medical: 1.70 per 100 person-years

REDUCE
CLINICAL STUDY

Second co-primary endpoint: new brain infarct, intention-to-treat

	Closure (N=441)	Medical (N=223)
Subjects without Evaluation	58	46
Brain Infarct Evaluable	383	177
Brain Infarct Present	**22 (5.7%)**	**20 (11.3%)**
Recurrent Stroke Only	3	6
Both	2	6
Silent Brain Infarct Only	17	8
Brain Infarct Absent	361 (94.3%)	157 (88.7%)



- **Difference in incidence of new brain infarct of 5.6%**
- **Relative risk 0.51; 95% CI: 0.29 to 0.91**
- **p=0.024** after adjustment for multiple testing
- silent infarcts about twice as common as clinical stroke

GORE
REDUCE
CLINICAL STUDY

CLOSE
Methods

Key inclusion criteria

- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE,TEE) confirmed by echo core lab before randomization

Key exclusion criteria

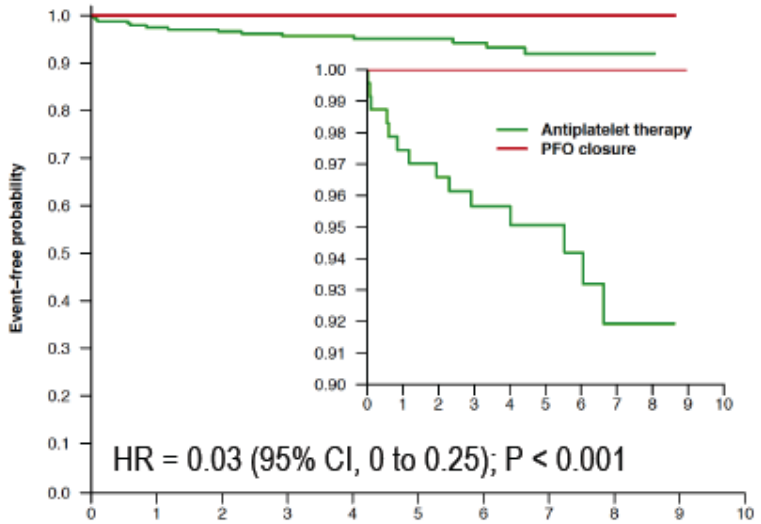
- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

Outcomes

- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications

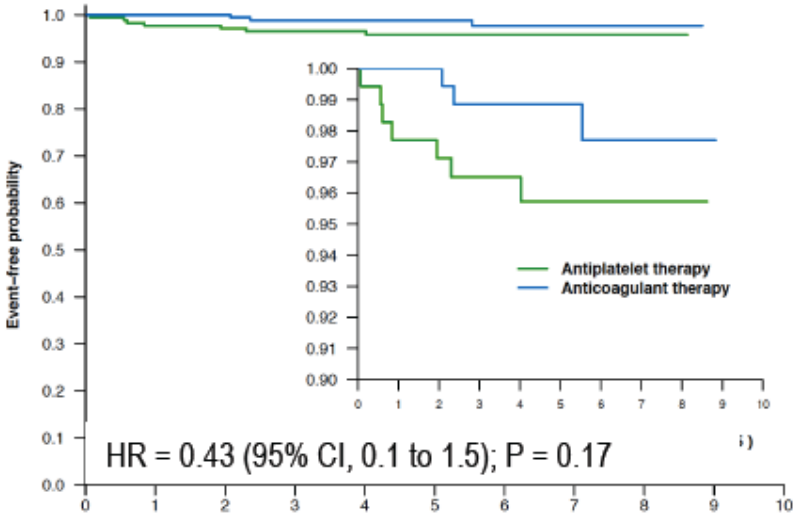
CLOSE

PFO closure vs. Antiplatelet therapy



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

Oral anticoagulants vs. Antiplatelet therapy



Antiplatelet therapy	174	170	167	151	121	99	73	45	15	0	0
Oral anticoagulants	187	187	183	154	139	110	78	49	22	0	0

Trial	RESPECT-LT		REDUCE		CLOSE	
Arm of Study	Device	Medical	Device	Medical	Device	Medical
# with Events / # Randomized	18/499	28/481	6/441	12/223	0/238	14/235
Recurrent Stroke Risk Reduction	45%		77%		97%	
HR 95% CI, p value	0.55 (0.31-0.999) p = 0.046		0.23 (0.09-0.62) p = 0.001		0.03 (0-0.25) p < 0.001	
Recurrent Stroke Rate at 5 Years	2.6%	5.0%	1.4%	5.4%	0%	5.0%
Number Needed to Treat in 5 years	42		25		20	

Adapted with thanks from John Carroll, MD

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A (partial) list of outstanding issues

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

PFOs – Now do we have enough evidence to change practice?

PFOs – Now do we have enough evidence to change practice?

I think we do.

Thank you!

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THALER REBUTTAL SLIDES

Clinical Trial Assumption: #1

- Subjects in the trial had PFO-related index events

BUT

- Mean RoPE Score is ~7
- PFO attributable fraction ~72%

Clinical Trial Assumption: #2

- Pts with PFO-related index strokes will have PFO related recurrences

BUT

- ~1/3 of recurrences have known cause

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- ***Stroke is not a disease***
  - but the endpoint of many others

- ***PFO closure SHOULD ONLY BE EXPECTED to prevent PFO-related recurrences***