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Where Are We with PFO Closure? Long-Term Outcome from Randomized Trials

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No Disclosures

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3 Questions in Life….

- What is worth living for?
- What is worth dying for?
- Is PFO closure superior to medical therapy in preventing recurrent cryptogenic stroke?

PFO Device Approval -Roller Coaster

HDE Approval → ***"Overuse"*** → ***2006 - Removal of HDE***

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Randomized Trials of PFO Closure vs Medical Therapy

- Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale – CLOSURE I

- Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism - PC Trial

- Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment – RESPECT

- Gore HELEX/Gore Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale - REDUCE

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CLOSURE I

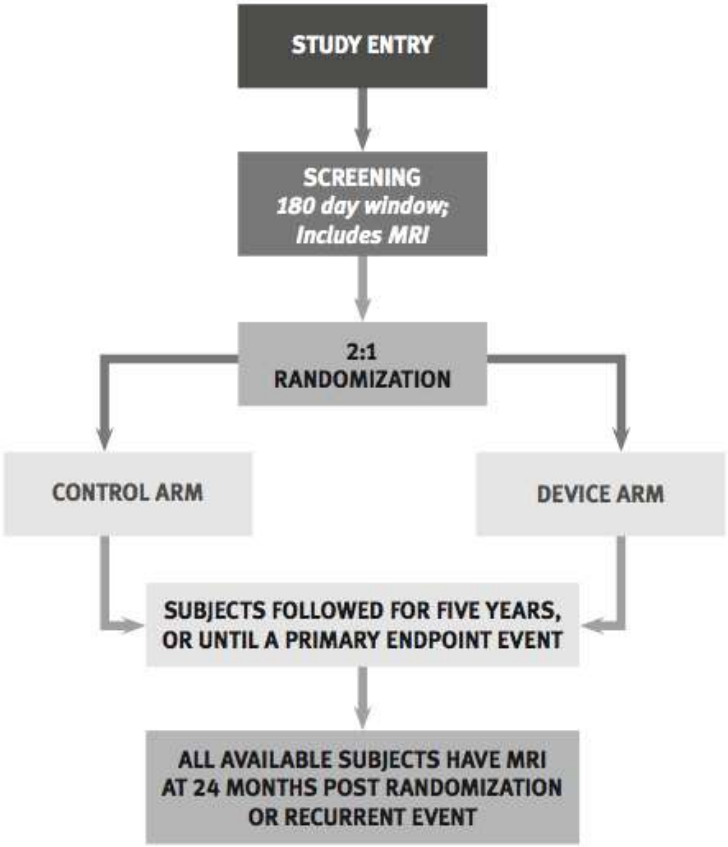
- Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale
- 2-year superiority trial
- 909 patients from 87 sites over 5 years
- Patients with well-defined and independently adjudicated TIA were randomized.

- No benefit vs device closure – Effective Closure 86%. Thrombus 1.1%.
- Limitations: Device; Study Design

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

REDUCE

- 65 investigational sites in the US, Canada, UK, Denmark, Norway, Sweden, and Finland
- 664 subjects
- Enrolment complete Feb ‘15
- Minimum of two years of follow-up evaluations before analysis of the study endpoints.



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REDUCE

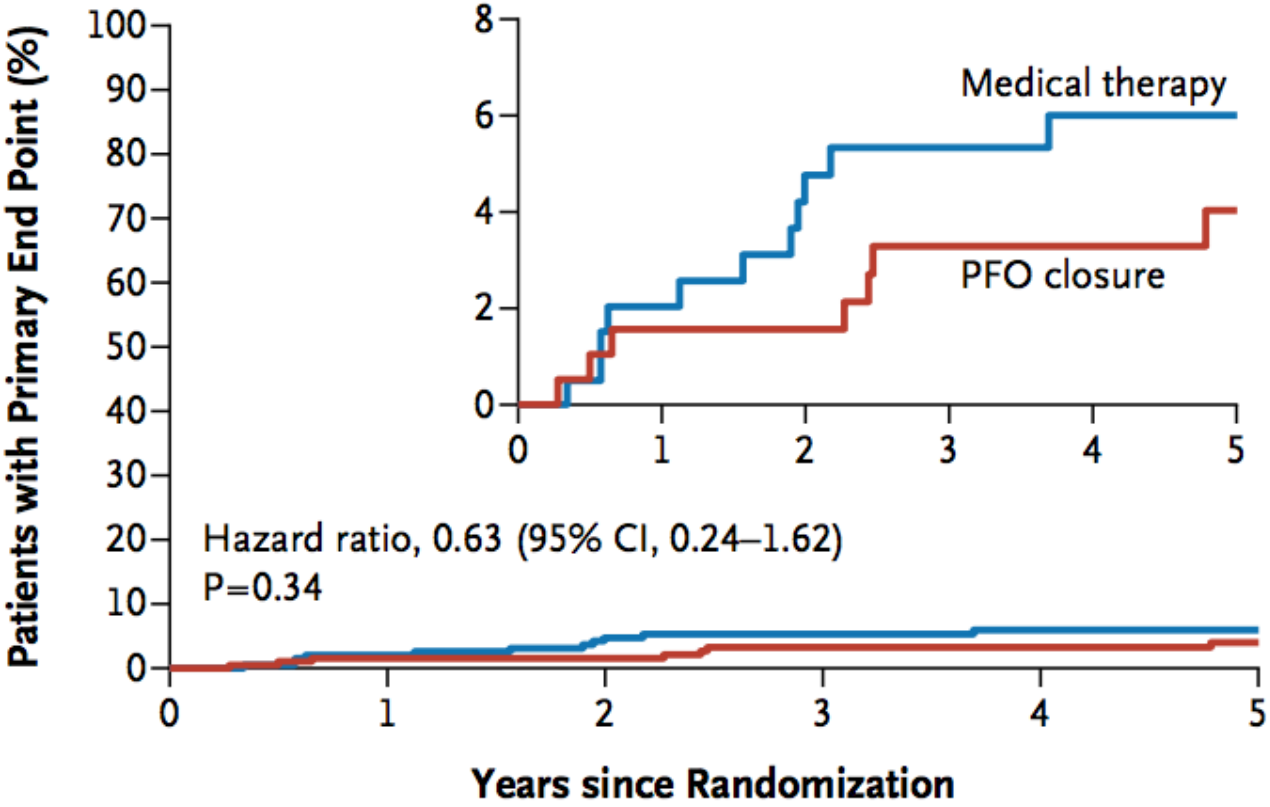
- Both test and control arms for the study are prescribed the same medical therapy (antiplatelets)
  - Avoids confounding effect on study endpoints
- Subjects are followed for a minimum of two years and up to five years after randomization
  - Strokes occurring between years two and five will be included in the primary endpoint analysis
- Neuroimaging is conducted on every subject at two years following treatment
  - An assessment of these silent infarcts across treatment arms may further support the proof of concept of device closure

Longer-Term Follow-Up Studies

PC Trial

- Multicenter, superiority trial in 29 centers in Europe, Canada, Brazil, and Australia
- Intention-to-treat
- <60 years – PFO and Stroke/TIA with neuroradiologically verified cerebral ischaemic lesion
- 414 patients over 9 years (mean age 44 years)
- Mean follow-up 4 years
  - Potential Primary Endpoints: n=9 (closure); n=18 (medical)
  - Stroke n=1 (closure); n=5 (medical)
  - Contemporary stroke definition (RESPECT): n=1 (closure); n=7 (medical) ***P=0.07***

Primary End Point Analysis



No. at Risk

Medical therapy	210	185	170	159	131	90
PFO closure	204	186	181	163	142	110

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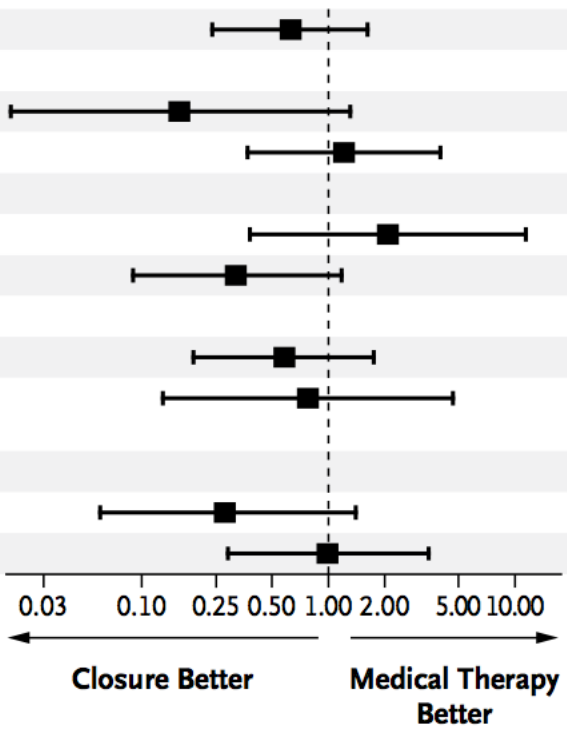
Subgroup Analyses of Primary End Point

Subgroup	PFO Closure	Medical Therapy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no. (%)			
Overall	7/204 (3.4)	11/210 (5.2)	0.63 (0.24–1.62)	
Age				0.10
<45 yr	1/91 (1.1)	6/97 (6.2)	0.16 (0.02–1.31)	
≥45 yr	6/113 (5.3)	5/113 (4.4)	1.22 (0.37–3.99)	
Atrial septal aneurysm				0.09
Yes	4/47 (8.5)	2/51 (3.9)	2.09 (0.38–11.4)	
No	3/157 (1.9)	9/159 (5.7)	0.32 (0.09–1.18)	
Cardiovascular index event				0.78
Stroke	5/165 (3.0)	8/163 (4.9)	0.58 (0.19–1.76)	
Transient ischemic attack or pulmonary embolism	2/39 (5.1)	3/47 (6.4)	0.78 (0.13–4.66)	
>1 Previous cardiovascular event				0.22
Yes	2/76 (2.6)	6/79 (7.6)	0.28 (0.06–1.41)	
No	5/128 (3.9)	5/131 (3.8)	0.99 (0.29–3.45)	



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Key Aspects of RESPECT Trial

- Device trial for secondary prevention
- Superiority trial: PFO closure vs. guideline-directed medications
- Largest randomized PFO trial: 980 patients
  - 499 AMPLATZER™ PFO Occluder; 481 MM
- Assumptions
  - Paradoxical embolism was cause of initial stroke
  - Recurrent strokes would be due to recurrent paradoxical embolism

RESPECT Trial Population

- **Included:**
  - **Subjects with a PFO who have had a cryptogenic stroke within the last 270 days**
- **Excluded:**
  - **Subjects aged <18 years or >60 years**
  - **Subjects with identified stroke etiology**
  - **Subjects who are unable to discontinue anticoagulants**

RESPECT Primary Endpoint Results

- **Enrollment ended when 25 ischemic stroke events occurred - results were reported in NEJM**

Analysis Population	Relative Risk Reduction	P-Value
Intention-to-Treat	50%	0.089
Per-Protocol	58%	0.048
As Treated	67%	0.013

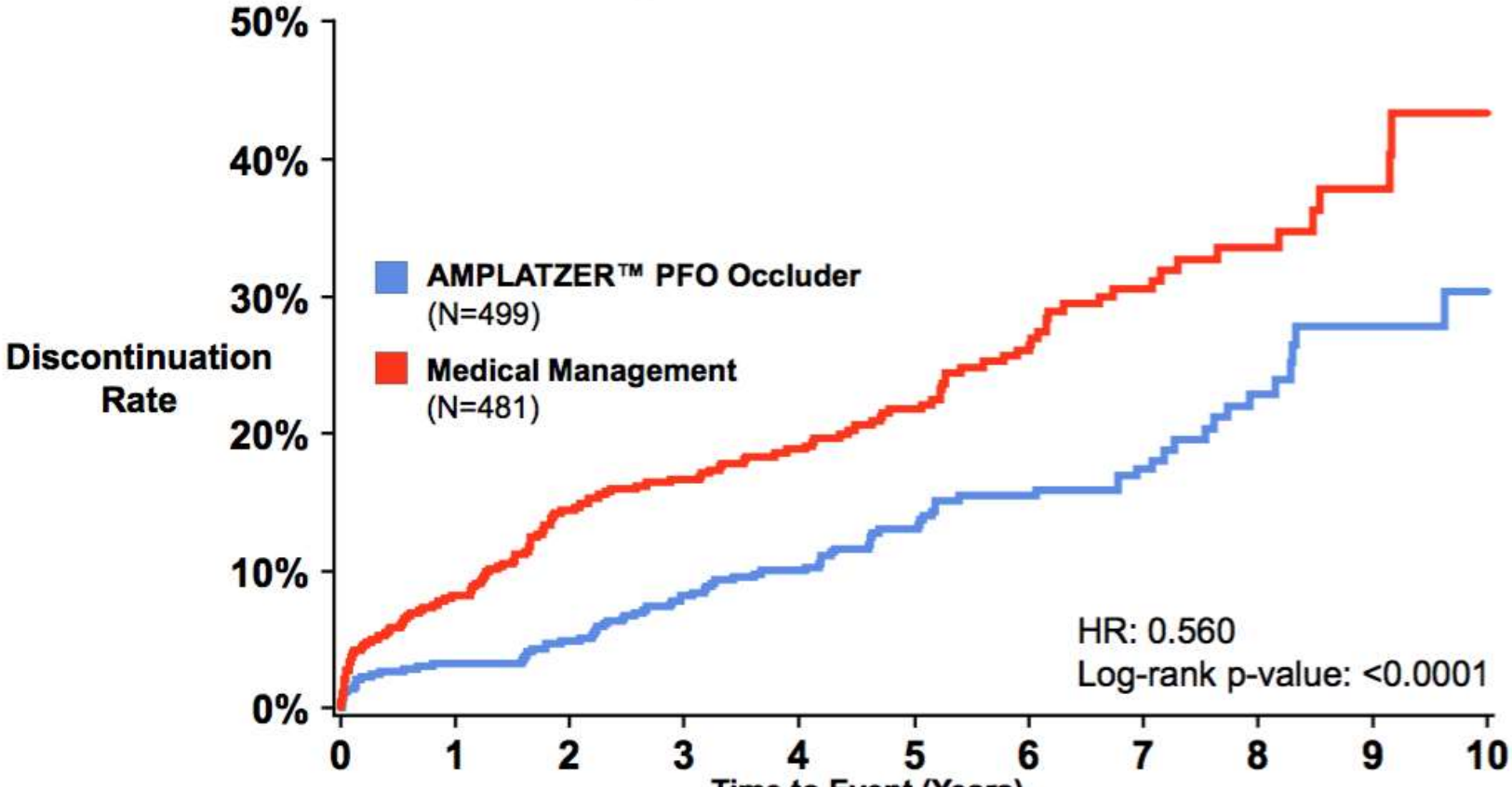
N Engl J Med. 2013 Mar 21;368(12):1092-100.

Extended Follow-Up

	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

Higher Discontinuation Rate in MM Arm

11% of MM Subjects: Off-Label PFO Closure



 # at Risk (Discontinuation Rate)

AMPLATZER	**499** (0%)	**463** (4.9%)	**369** (10.0%)	**212** (15.4%)	**86** (22.8%)	**20** (30.3%)
MM	**481** (0%)	**394** (14.4%)	**307** (18.8%)	**168** (26.5%)	**71** (33.5%)	**10** (43.3%)

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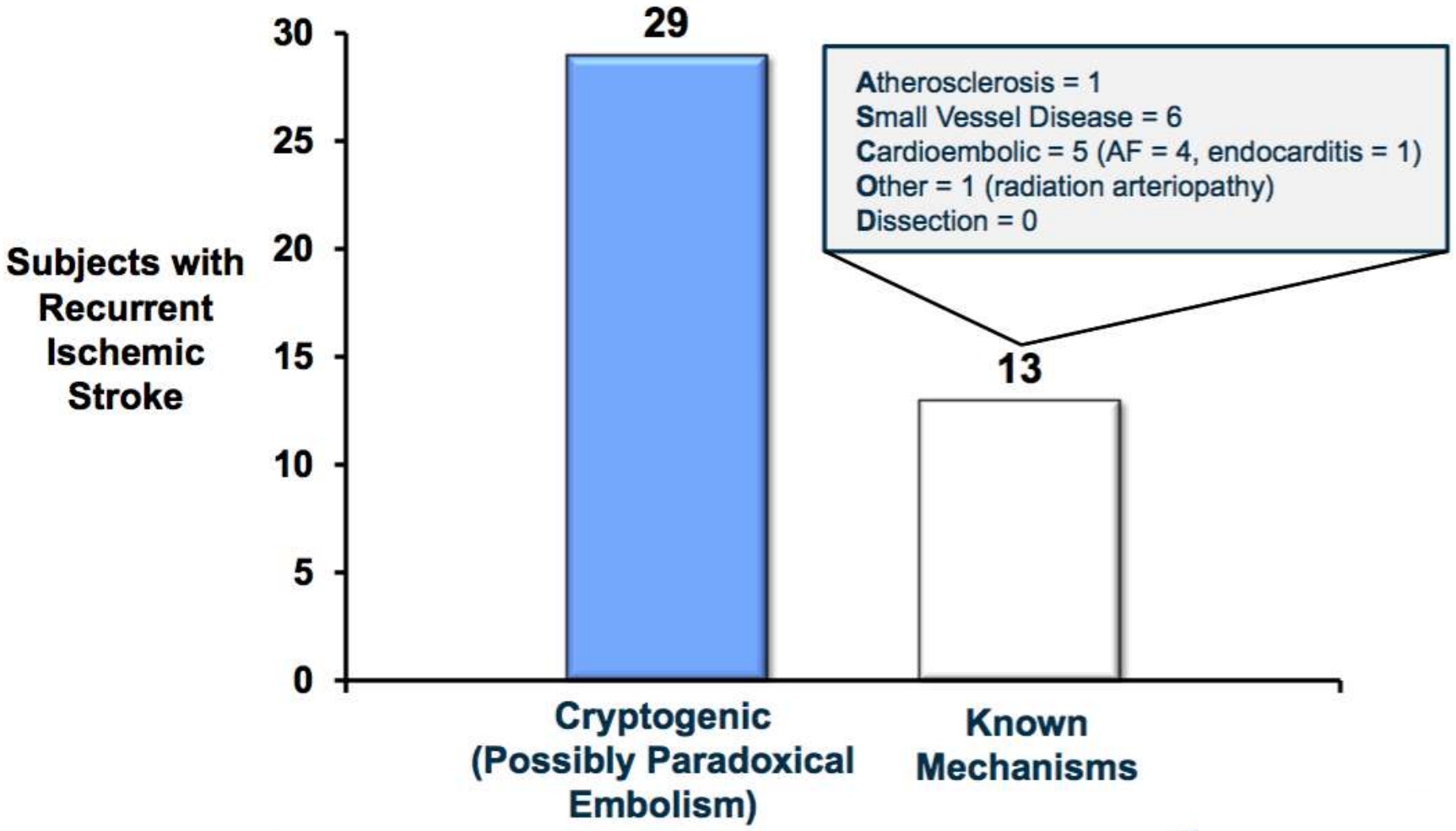
1 out of 5 Patients Were >60 Years in Extended Follow-up Analysis

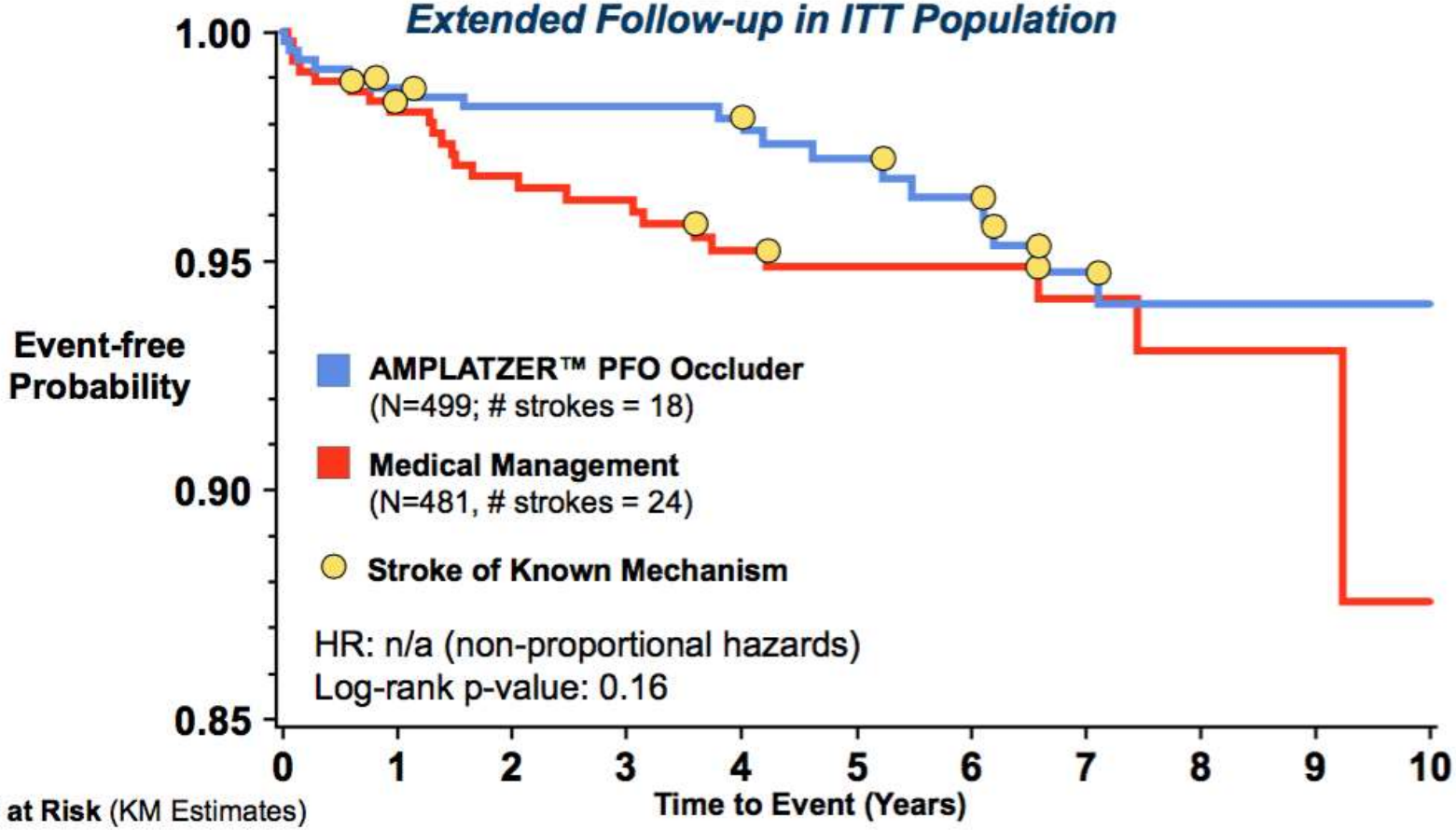
- As patients age, increase in non-cryptogenic strokes expected
- PFO closure can only reduce risk for recurrent strokes mediated by paradoxical embolism
  - Appropriate clinical interpretation of trials requires adjudication for stroke mechanism

Nearly 1/3 of Recurrent Strokes in Extended Follow-up Are of Known Mechanism



1 out of 3 Recurrent Strokes Had Mechanism That PFO Closure Cannot Prevent

Extended Follow-up in ITT Population

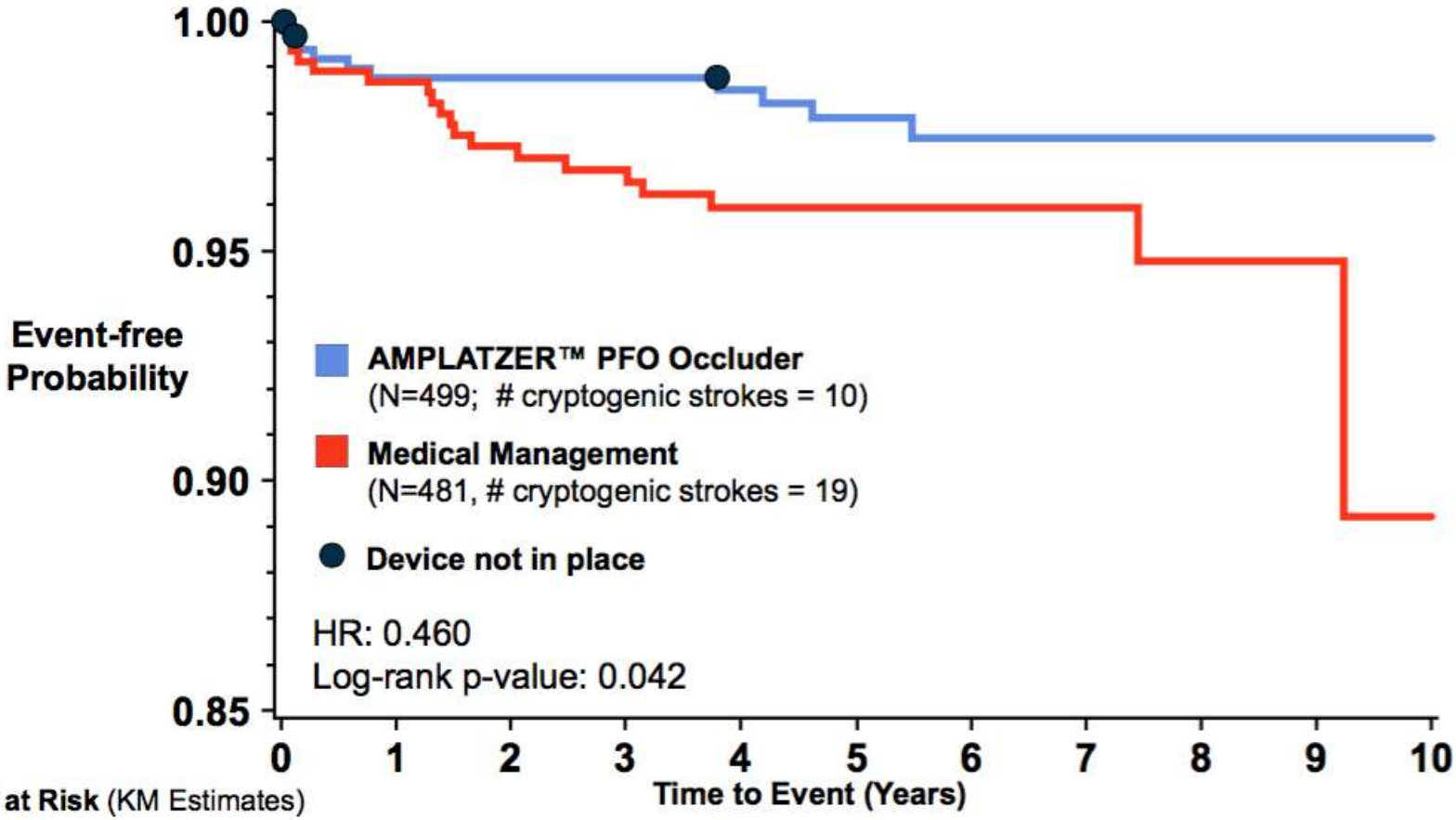


 # at Risk (KM Estimates)

AMPLATZER	**499** (0%)	**463** (1.6%)	**369** (1.9%)	**212** (3.6%)	**86** (6.0%)	**20** (6.0%)
MM	**481** (0%)	**394** (3.2%)	**307** (4.8%)	**168** (5.1%)	**71** (7.0%)	**10** (12.4%)

Significant Reduction in Recurrent Cryptogenic Stroke

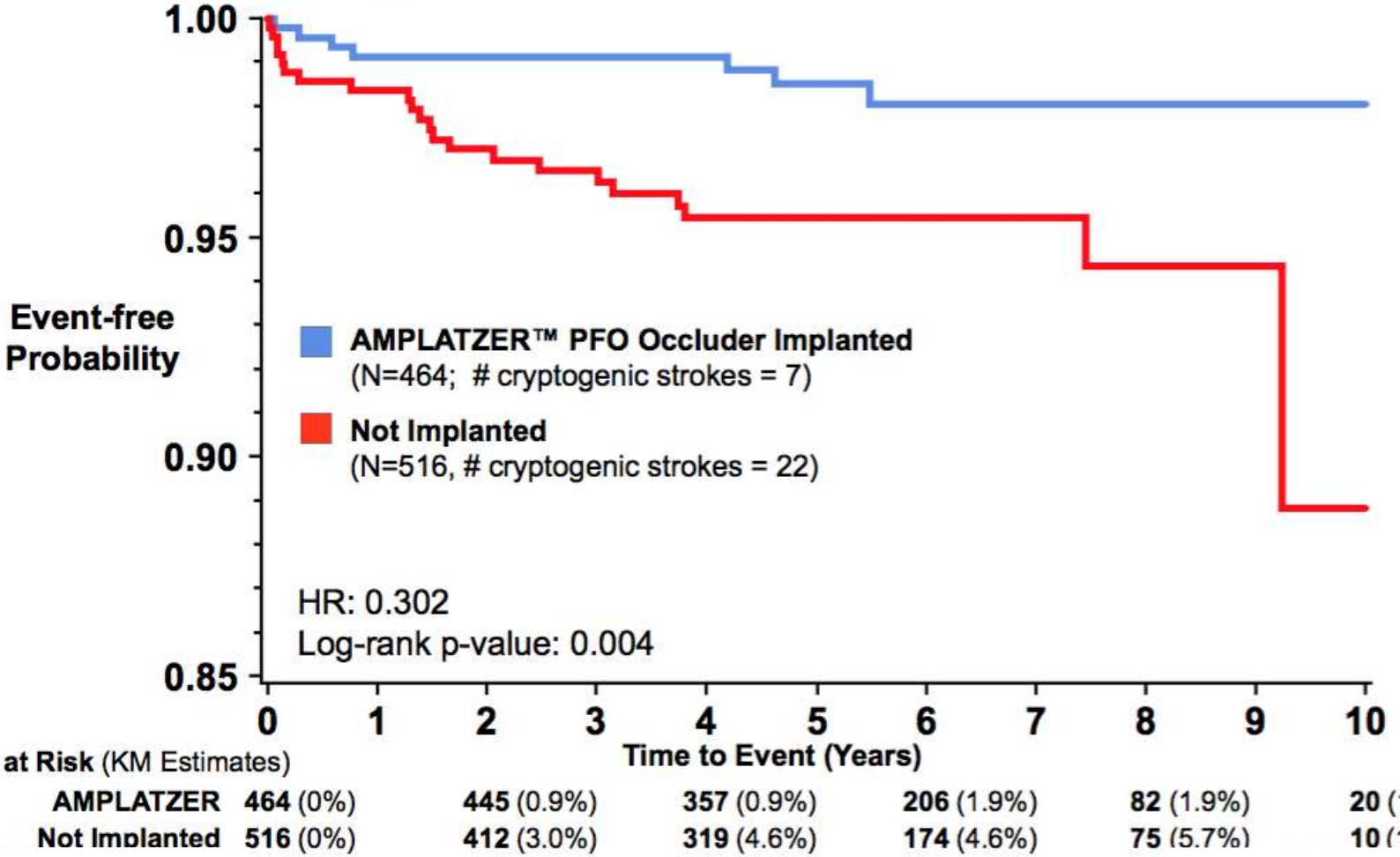
54% Relative Risk Reduction in ITT Population



 # at Risk (KM Estimates)

AMPLATZER	**499** (0%)	**463** (1.2%)	**369** (1.5%)	**212** (2.5%)	**86** (2.5%)	**20** (2.5%)
MM	**481** (0%)	**394** (2.7%)	**307** (4.1%)	**168** (4.1%)	**71** (5.2%)	**10** (10.8%)

70% Relative Risk Reduction in Recurrent Cryptogenic Stroke With Device In Place



 # at Risk (KM Estimates)

AMPLATZER	**464** (0%)	**445** (0.9%)	**357** (0.9%)	**206** (1.9%)	**82** (1.9%)	**20** (1.9%)
Not Implanted	**516** (0%)	**412** (3.0%)	**319** (4.6%)	**174** (4.6%)	**75** (5.7%)	**10** (11.2%)

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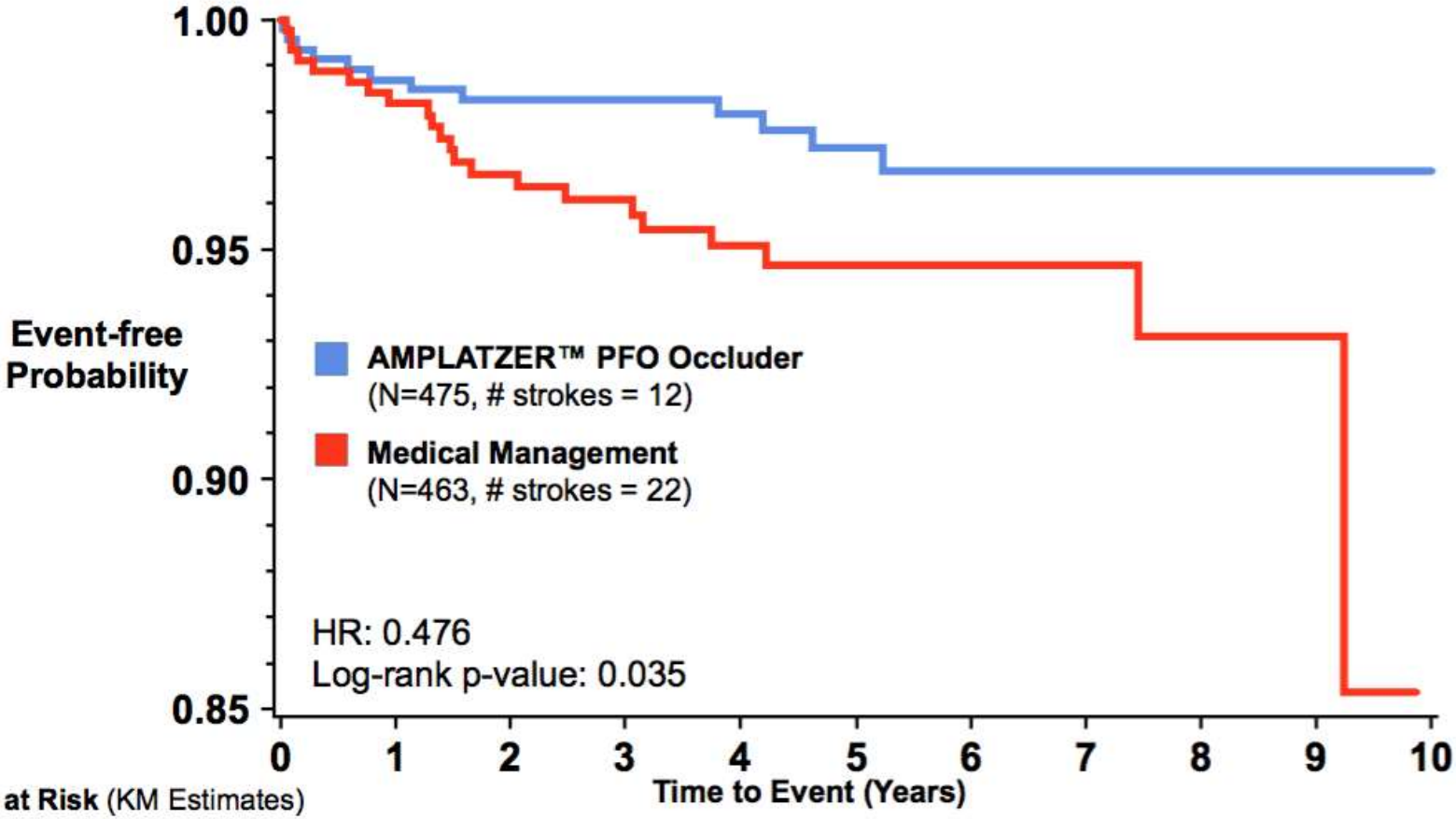
Freedom from Recurrent Stroke of Any Mechanism: <60 Yrs

52% Relative Risk Reduction in ITT Sensitivity Analysis



 # at Risk (KM Estimates)

AMPLATZER	**475** (0%)	**417** (1.8%)	**308** (2.1%)	**166** (3.3%)	**69** (3.3%)	**15** (3.3%)
MM	**463** (0%)	**353** (3.4%)	**254** (4.9%)	**124** (5.4%)	**51** (6.9%)	**9** (14.7%)

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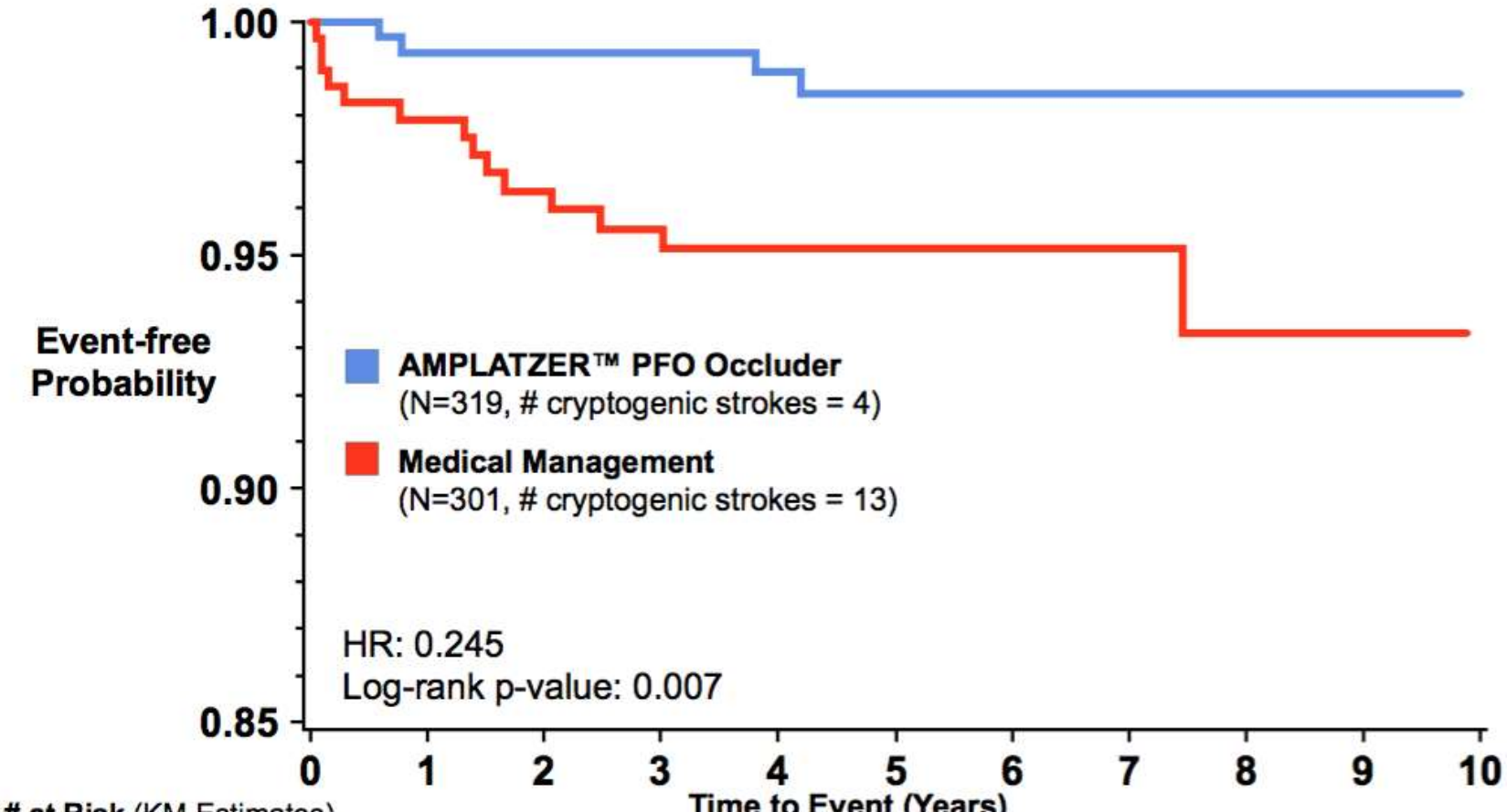
Greater Benefit in Substantial Shunt or ASA Subgroup

75% Relative Risk Reduction in Recurrent Cryptogenic Stroke in ITT Population



# at Risk (KM Estimates)						
AMPLATZER	319 (0%)	299 (0.6%)	229 (1.0%)	134 (1.5%)	52 (1.5%)	11 (1.5%)
MM	301 (0%)	243 (3.6%)	186 (4.8%)	105 (4.8%)	45 (6.6%)	7 (6.6%)

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Summary - RESPECT

Analysis Population (Endpoint)	Relative Risk Reduction	P-Value	Analysis Conclusion
ITT (All-Cause Stroke)	**n/a***	0.16	Confounded by strokes of known mechanism
ITT (Cryptogenic Stroke)	**54%**	0.042	Efficacy for cryptogenic stroke prevention
Device In Place (Cryptogenic Stroke)	**70%**	0.004	Accounting for device placement increases efficacy
ITT: <60 years old (All-Cause Stroke)	**52%**	0.035	Supportive sensitivity analysis
ITT: ASA/SS Subgroup (Cryptogenic Stroke)	**75%**	0.007	Additional benefit in patients with ASA or SS

non-proportional hazards (not appropriate to estimate)

Adjudicated SAEs of Interest

Favorable SAE Profile for AMPLATZER™ PFO Occluder

Event Type	AMPLATZER™ PFO Occluder (N=499) [2769 Pt-Yrs]		Medical Management (N=481) [2376 Pt-Yrs]	
	Events	Rate*	Events	Rate*
Atrial fibrillation	7	0.25	4	0.17
Major bleeding	17	0.61	14	0.59
Death from any cause	6	0.22	10	0.42
DVT/PE	17	0.61	3	0.12

* Rate expressed as number of events per 100 patient-years

- DVT/PE rate of unclear significance
  - Not associated with procedure/access site, thrombophilia evaluation not done in trial, and warfarin was allowed in MM group