

# Katetrizační uzávěr PFO

## RESPECT studie – prodloužené sledování

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# Key Aspects of RESPECT Trial

- **Superiority trial of PFO closure vs. guideline-directed medications for secondary prevention after cryptogenic stroke**
- **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

Carroll et al. *NEJM* 2012;368:1092-100.

# 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

Carroll et al. *NEJM* 2012;368:1092-100.

Note: Per Protocol and As Treated analysis modified from NEJM analysis in response to FDA questions.

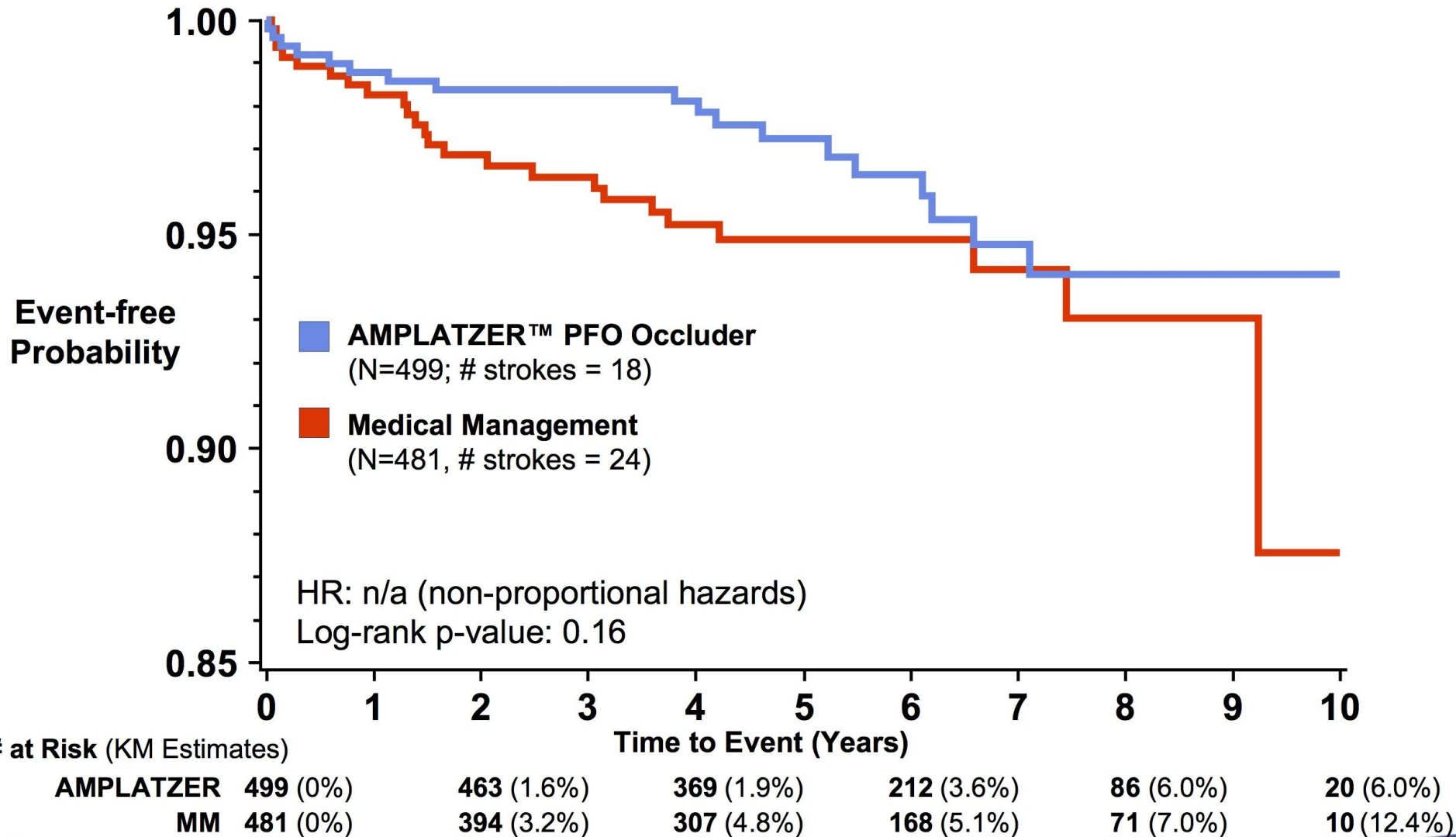
# Extended Follow-up Provides Considerable New Data

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

\*11% of MM pts crossed over to PFO closure or withdrew because of intended XO

# Freedom from All-cause Stroke

## Extended Follow-up in ITT Population

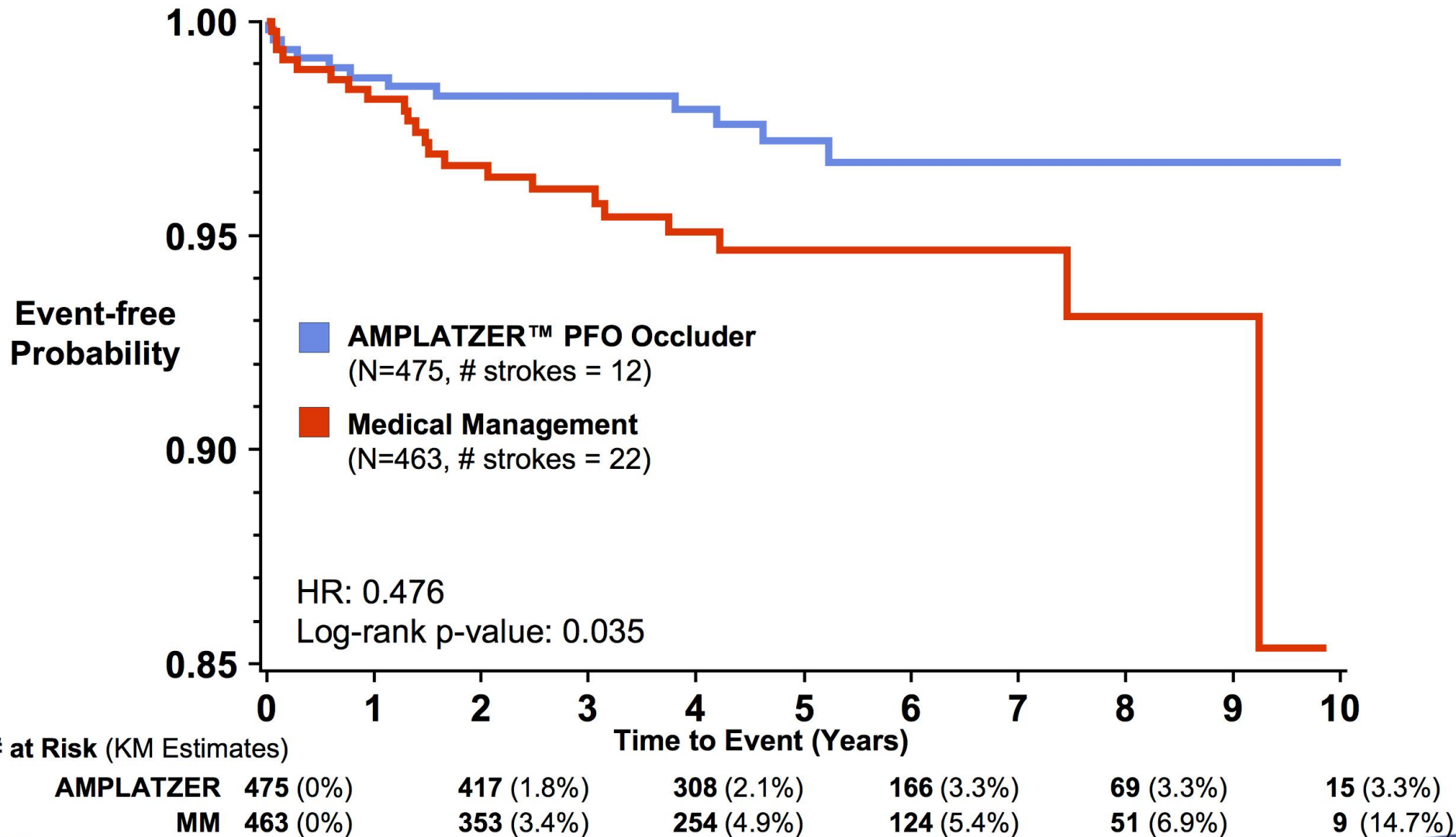


# 1 out of 5 Patients Were >60 Years in Extended Follow-up Analysis

- 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

# Freedom from Recurrent Stroke of Any Mechanism: <60 Yrs

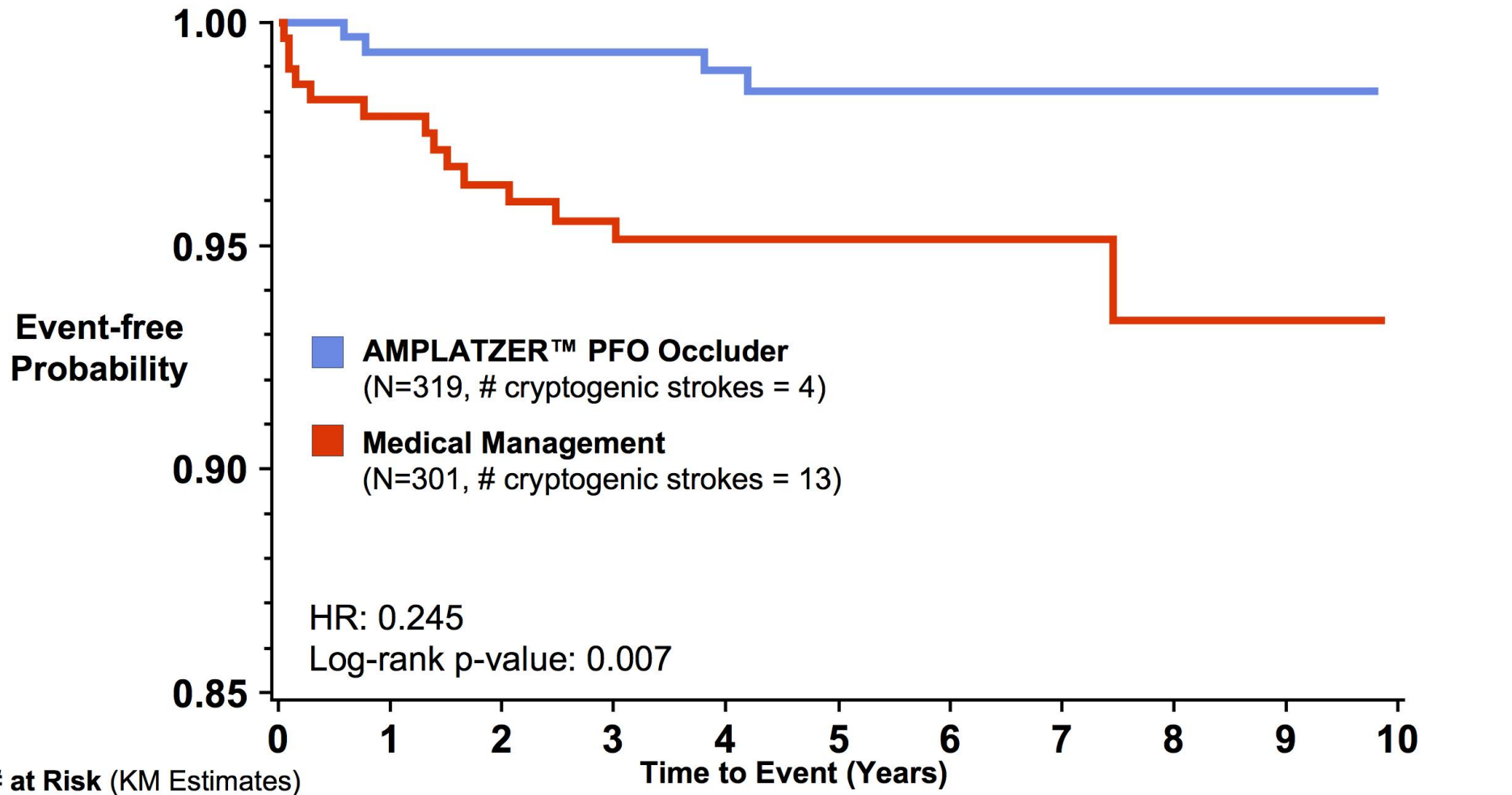
## 52% Relative Risk Reduction in ITT Sensitivity Analysis





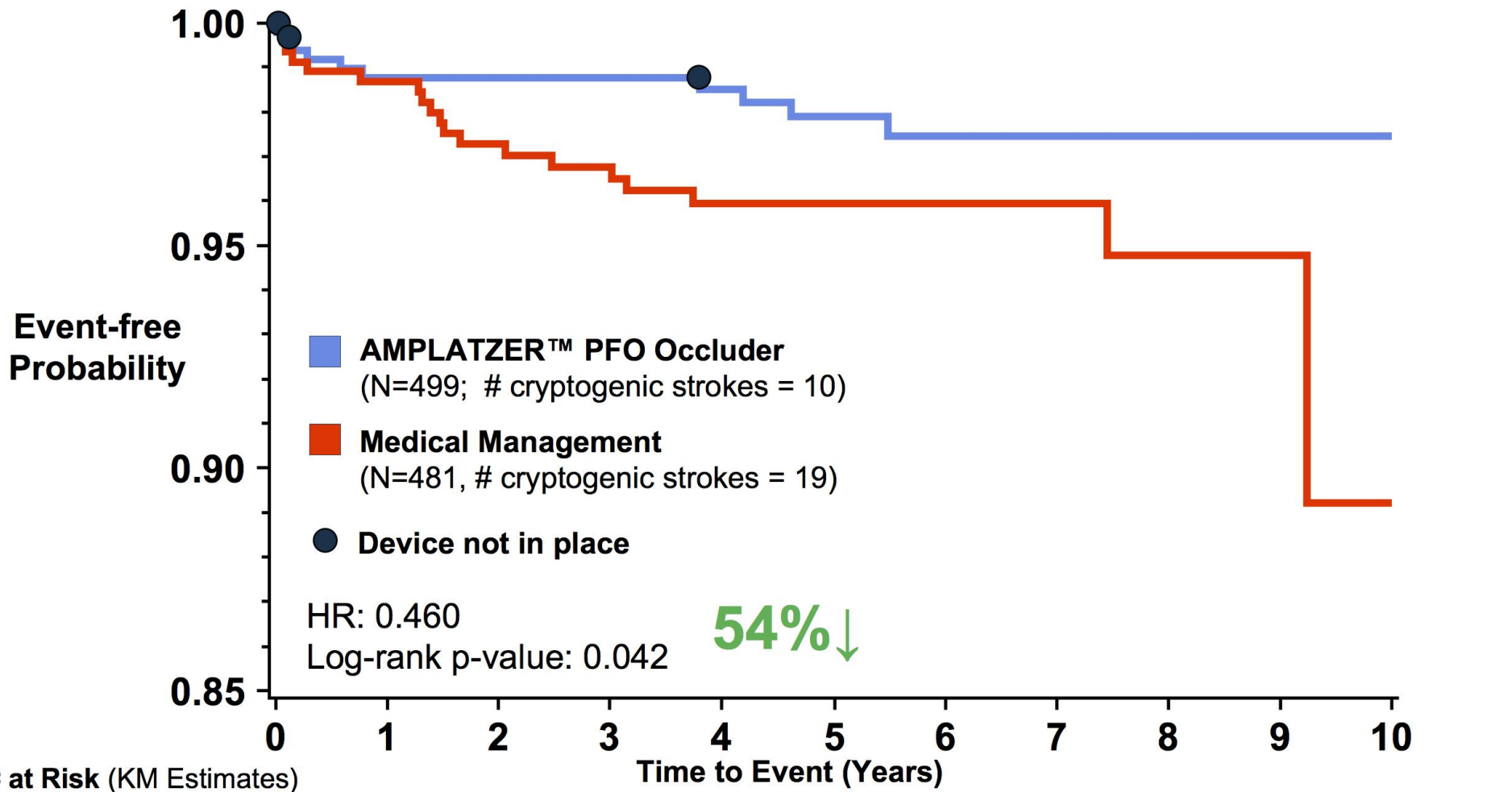
# Greater Benefit in Substantial Shunt or ASA Subgroup

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



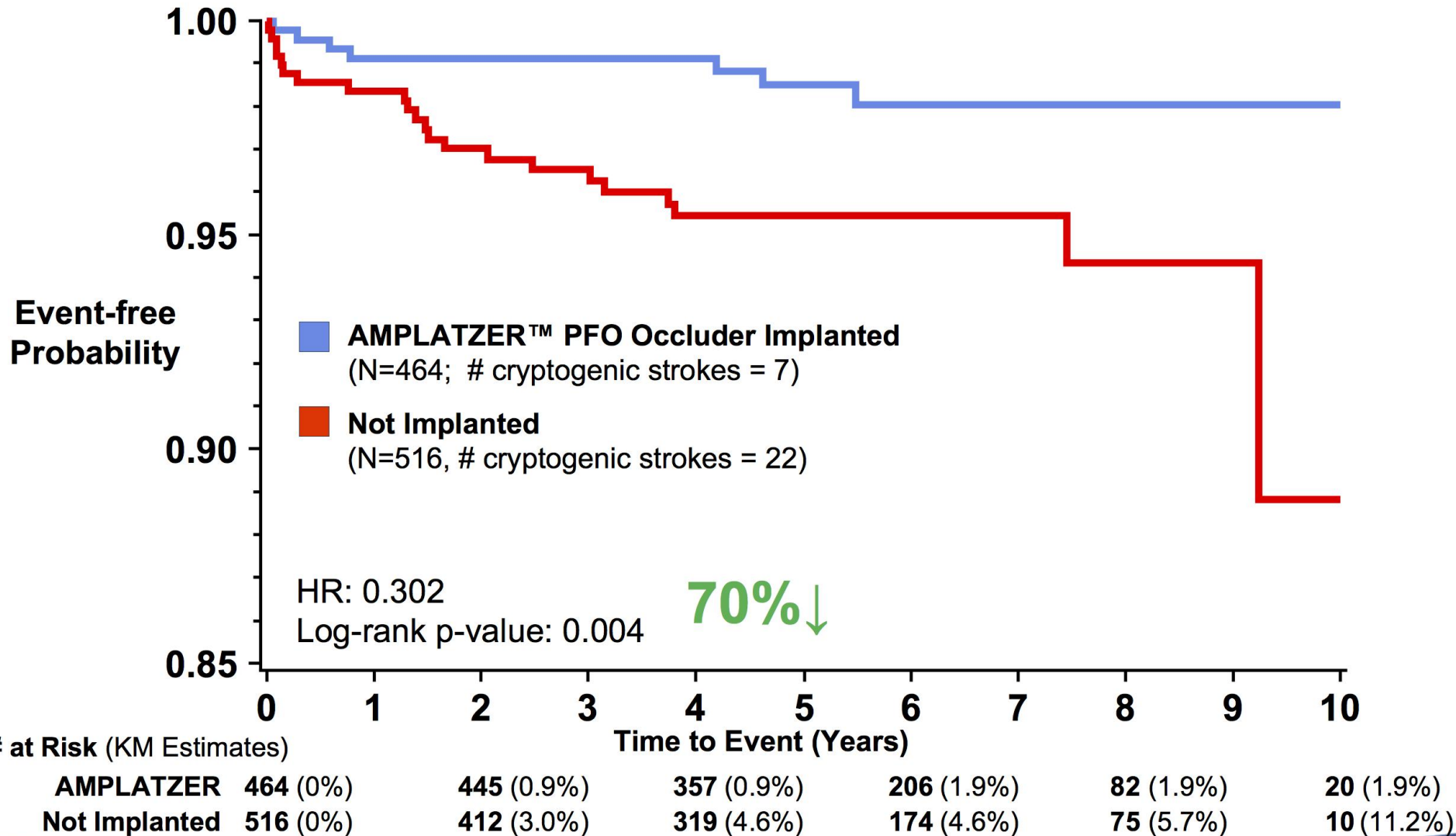
	0	1	2	3	4	5	6	7	8	9	10
<b>AMPLATZER</b>	319 (0%)	299 (0.6%)	229 (1.0%)	134 (1.5%)	52 (1.5%)	11 (1.5%)					
<b>MM</b>	301 (0%)	243 (3.6%)	186 (4.8%)	105 (4.8%)	45 (6.6%)	7 (6.6%)					

# Freedom from Recurrent Cryptogenic Stroke (ITT)



	0	1	2	3	4	5	6	7	8	9	10
<b>AMPLATZER</b>	499 (0%)	463 (1.2%)	369 (1.5%)	212 (2.5%)	86 (2.5%)	20 (2.5%)					
<b>MM</b>	481 (0%)	394 (2.7%)	307 (4.1%)	168 (4.1%)	71 (5.2%)	10 (10.8%)					

# Freedom from Recurrent Cryptogenic Stroke With Device In Place



# Summary of Efficacy Findings in Extended Follow-up

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)

# Procedure or Device Related SAEs

## *SAEs Adjudicated by DSMB*

- **No intra-procedure strokes**
- **No device embolizations**
- **No device thromboses**
- **No device erosions**
- **Very low rate of major vascular complications (0.9%) and device explants (0.4%)**

# 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

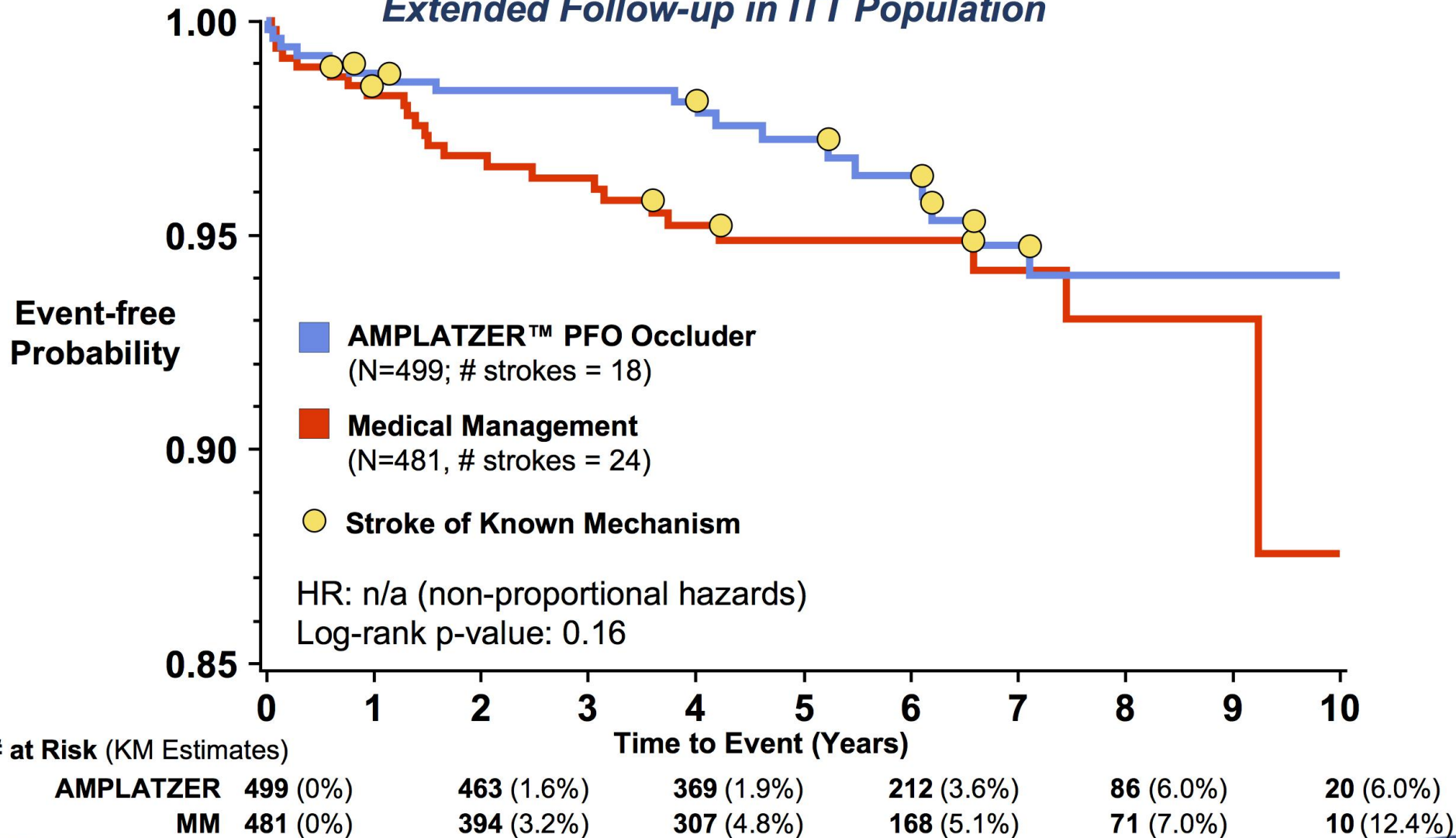
- DVT/PE rate of unclear significance
  - Not associated with procedure/access site, thrombophilia evaluation not done in trial, and warfarin was allowed in MM group

# Conclusions

- **AMPLATZER™ PFO Occluder is superior to medical management in reducing recurrent cryptogenic ischemic stroke**
  - Treatment effect is fully manifest in types of strokes for which closure is intended
  - Superiority is substantial and sustained
- **Procedure and device are safe**
- **RESPECT reinforces need for comprehensive risk factor modification**

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

*Extended Follow-up in ITT Population*





# Questions after RESPECT LATE

1. Is RESPECT a positive or negative trial?
2. In the types of pts enrolled in RESPECT, does PFO closure reduce 'stroke'?
  - All-cause stroke?
  - Cryptogenic stroke, but not all-cause?
  - Only in patients with ASA/large shunt?
  - Only in young pts?
3. Should PFO closure be approved to prevent cryptogenic stroke? If so, "write the label".