

PFO Closure for Prevention of Cryptogenic Stroke: What Is the Final Word?

Extended Follow-up of the RESPECT Trial

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The RESPECT Trial

- Superiority trial of PFO closure vs. guideline directed therapy for secondary prevention of cryptogenic stroke
- 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

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Patient Population

- 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

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Primary Endpoint Results

Enrollment ended when 25 ischemic stroke events occurred

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

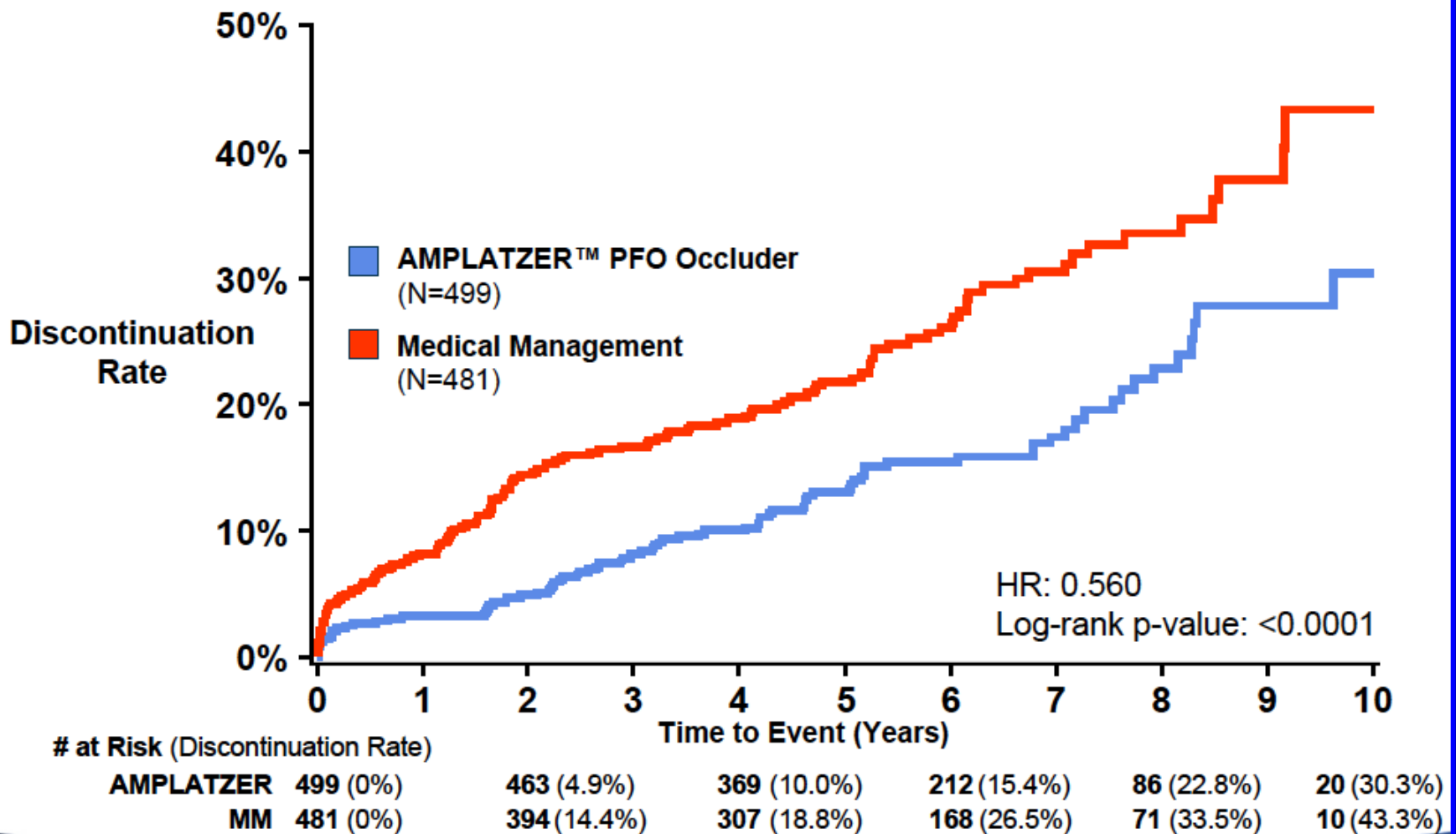
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Extended Follow-Up

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

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11% of MM Subjects: Off label PFO closure



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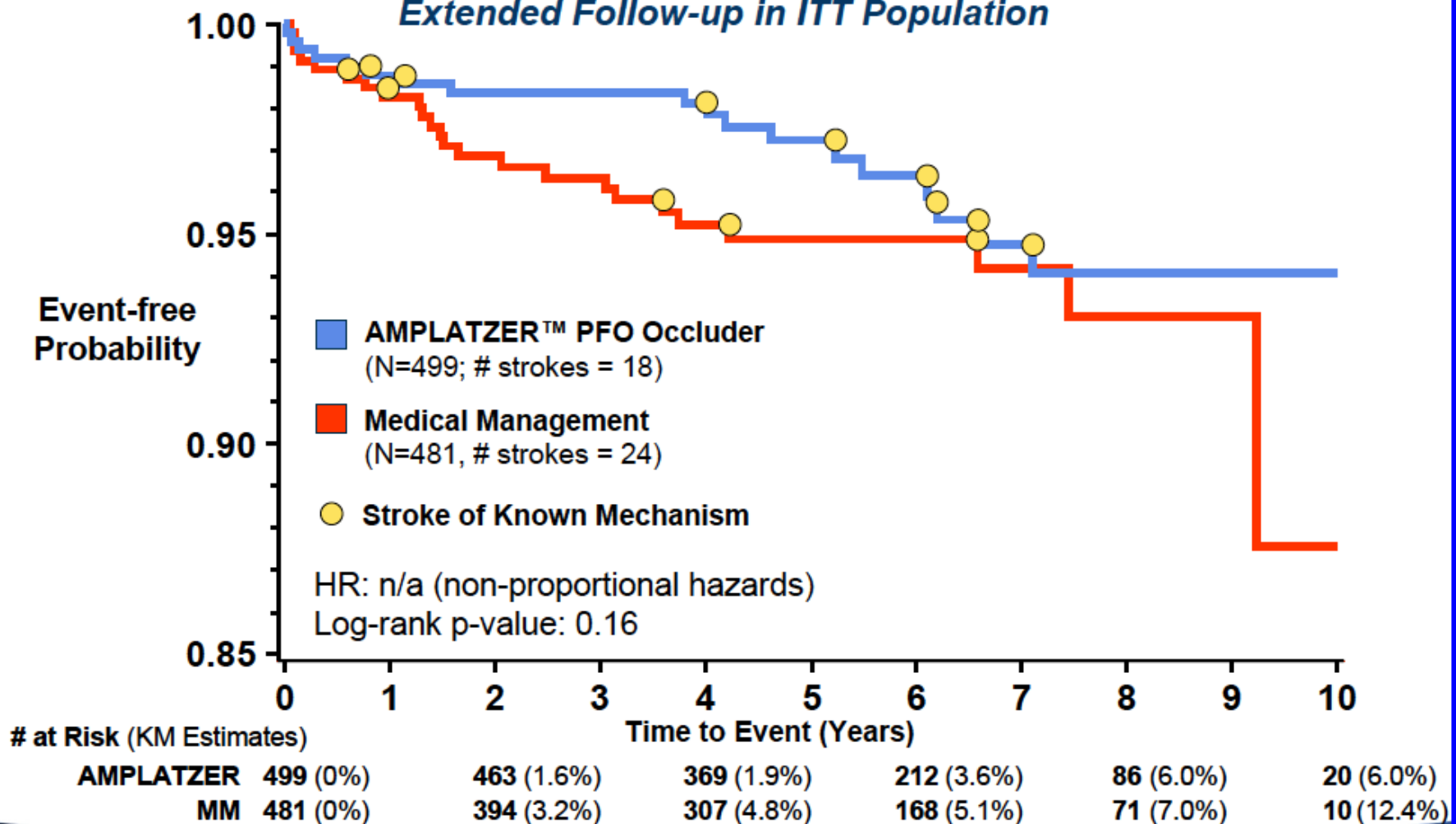
Impact of Extended FU on Patient Risk Profile and Stroke Type

- 1 out of 5 patients became >60 yrs. of age
- As a patient ages, non cryptogenic stroke risk increases
- 1/3 of strokes in extended FU were of unknown mechanism
- Appropriate clinical interpretation of PFO closure trials
requires adjudication of stroke mechanism

**How Do Recurrent Strokes
from Known Mechanisms
Confound Interpretation of
RESPECT?**

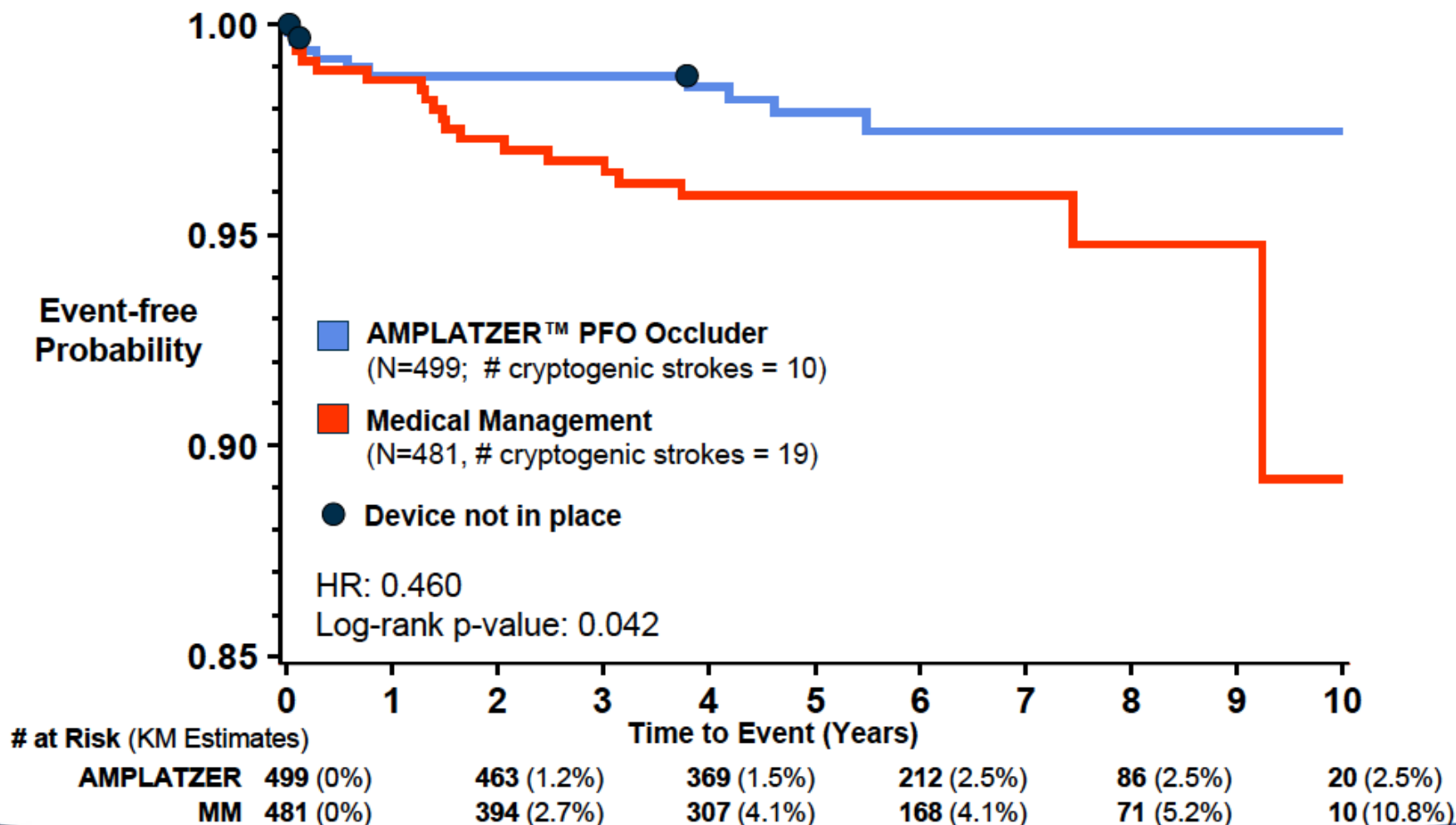
1 out of 3 Recurrent Strokes Had Mechanism That PFO Closure Cannot Prevent

Extended Follow-up in ITT Population

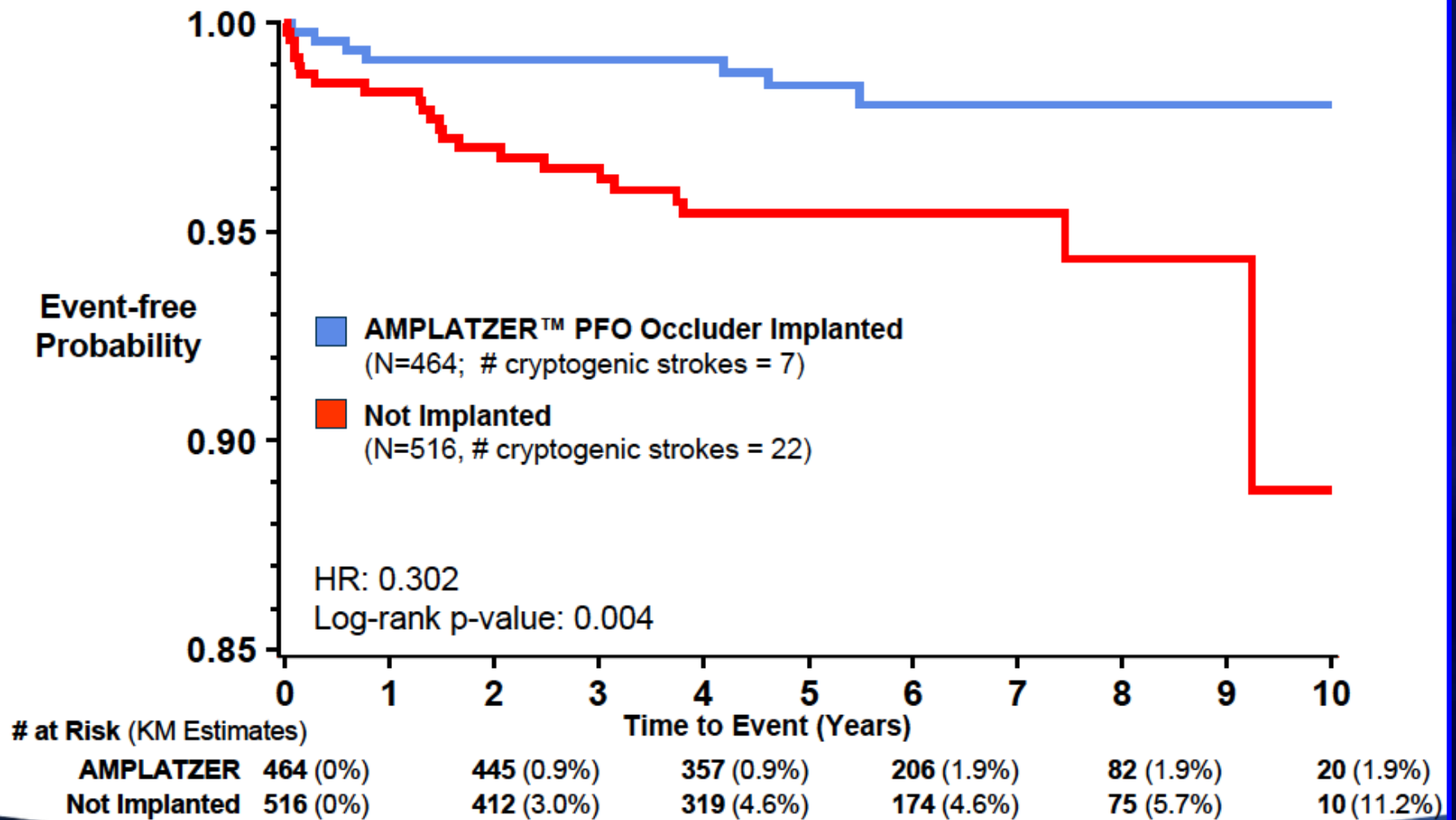


Significant Reduction in Recurrent Cryptogenic Stroke

54% Relative Risk Reduction in ITT Population



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

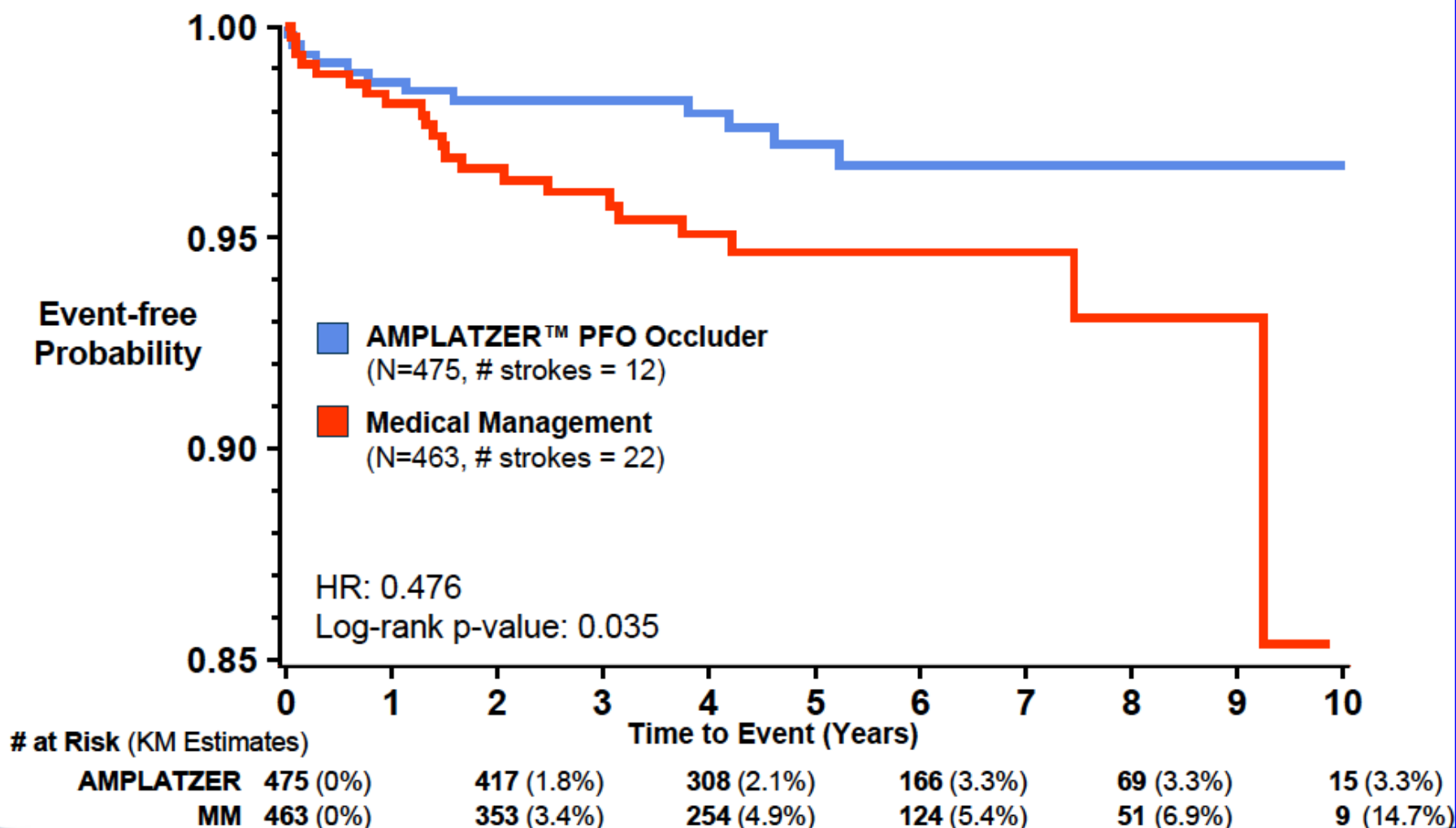


Is the superiority of PFO Closure more clearly seen in younger patients?

Analysis not dependent on stroke etiology phenotyping

Freedom from Recurrent Stroke of Any Mechanism: <60 Yrs

52% Relative Risk Reduction in ITT Sensitivity Analysis

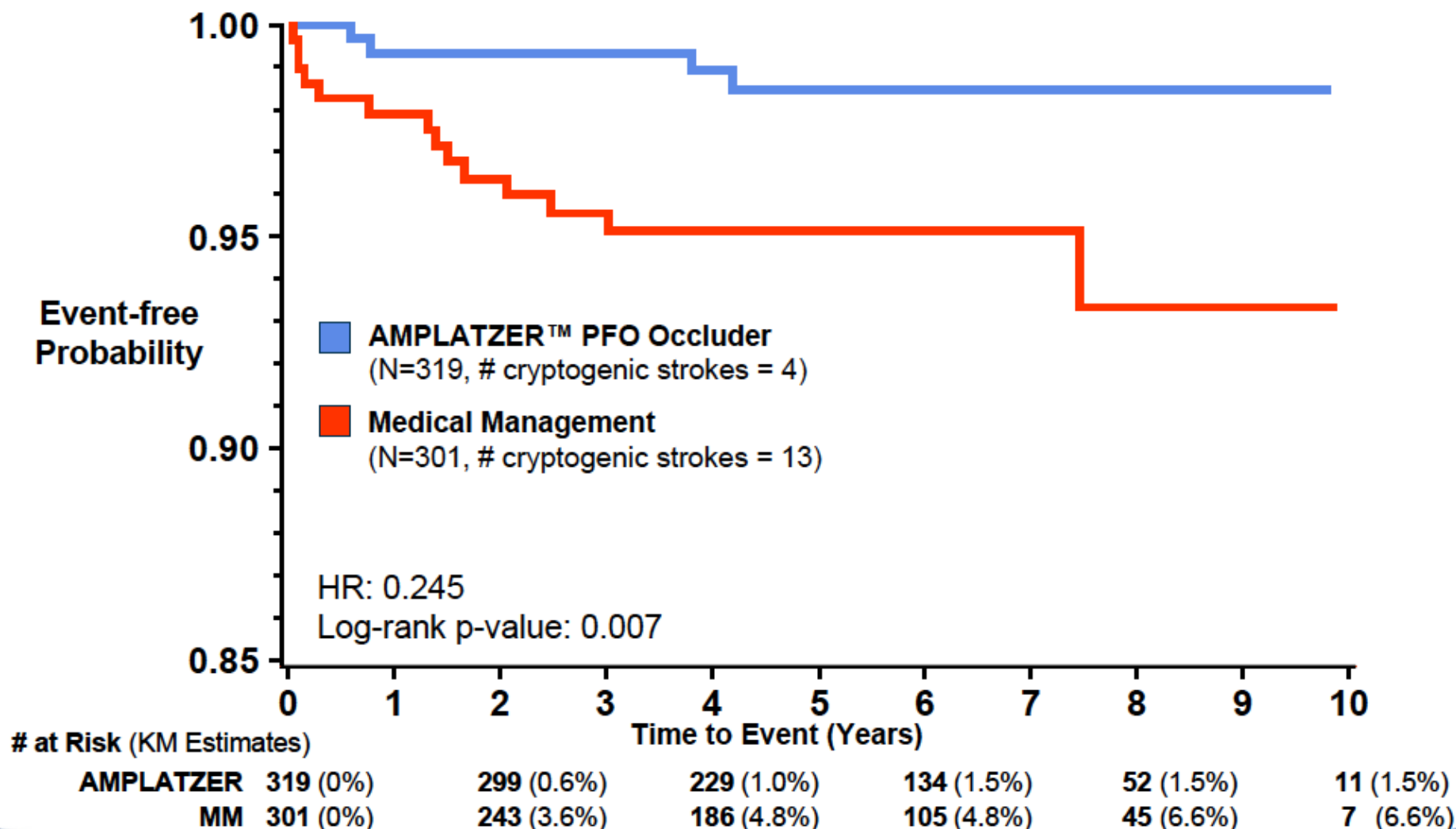


**Does anatomy and physiology
of PFO matter in terms of
treatment effect?**

***Atrial septal aneurysm (ASA) and
substantial right-to-left shunts are
used by clinicians to identify PFOs
that may not be incidental***

Greater Benefit in Substantial Shunt or ASA Subgroup

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



The RESPECT Trial

Efficacy Findings in Extended FU

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

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Procedure or Device Related SAEs

- No intra-procedure strokes
- No device embolization
- No device thrombosis
- No device erosion
- Very low rate of major vascular complications (0.9%) and device explants (0.4%)

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Adjudicated SAEs

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

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Strengths and Limitations

Strengths

- High procedural success and effective closure rates
- Longest follow-up of PFO closure RCTs
- Adjudication of stroke mechanism

Limitations

- Powered to detect overly optimistic treatment effect
- Differential dropout rate could lead to bias
- Significant rate of off-label PFO closure (11%)

The RESPECT Trial

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