

# Structural Heart Interventions for prevention of stroke



Ruby Satpathy, MD, FACC, FSCAI,  
Director, Structural Heart Program,  
Baptist Medical Center

*I have no financial disclosure pertaining to this presentation.*



*Excellence in Patient Care*

Afib and associated stroke risk

Limitations and risks of OAC

Minimally invasive approach for LAA closure to reduce stroke risk

Review recent clinical evidence

PFO and associated cryptogenic stroke risk

Review medical management and percutaneous closure of PFO

Review recent clinical evidence



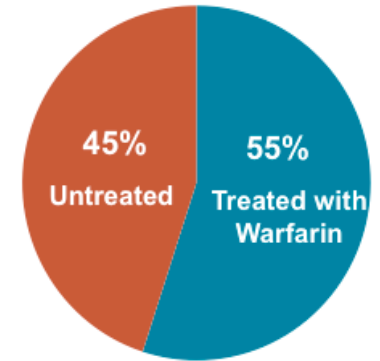
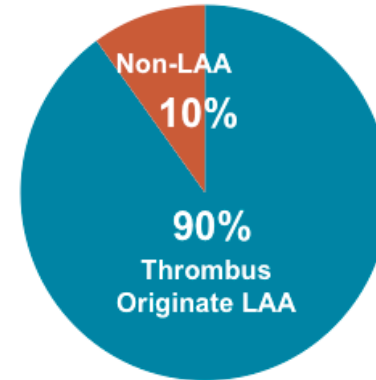
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AF is the most common cardiac arrhythmia

AF increases risk of stroke

Blood clots form in the left atrial appendage

Many patients are unprotected



**> 33M**  
people with AF Worldwide<sup>1</sup>

**5x**  
greater risk of stroke with AF<sup>2</sup>

**>90%**  
of stroke-causing clots that come from the left atrium in non-valvular AF are formed in the LAA<sup>3</sup>

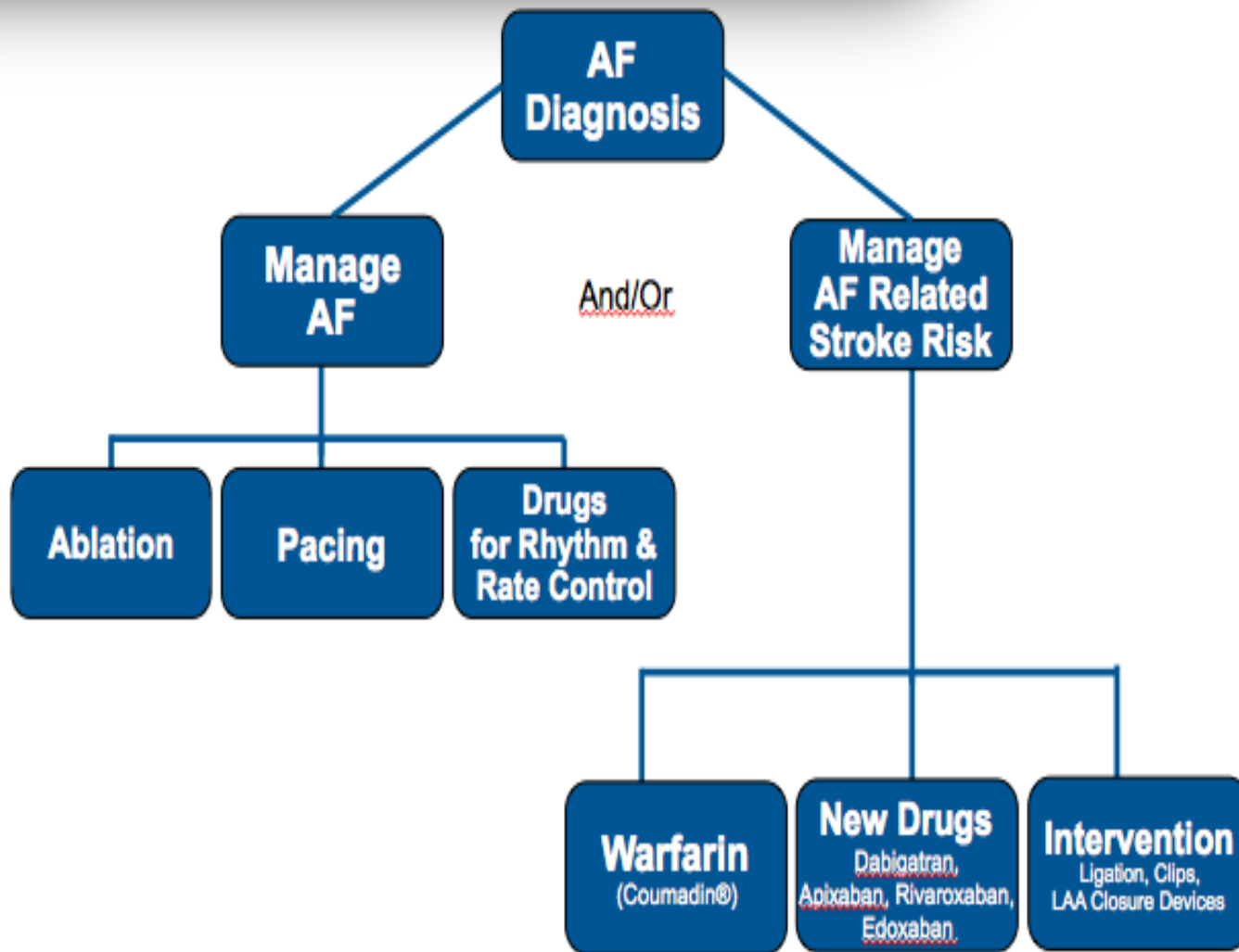
**~45%**  
of patients eligible for warfarin are untreated (tolerance/adherence)<sup>4</sup>

- Assess stroke risk with CHA<sub>2</sub>DS<sub>2</sub>-VASc score
  - Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  - Score ≥2: Annual stroke risk 2%-15%, oral anticoagulants are recommended
- Higher CHADS<sub>2</sub> score predicts worse outcomes (stroke, major bleeding & vascular mortality)<sup>1</sup>
- Balance benefit vs. bleeding risk



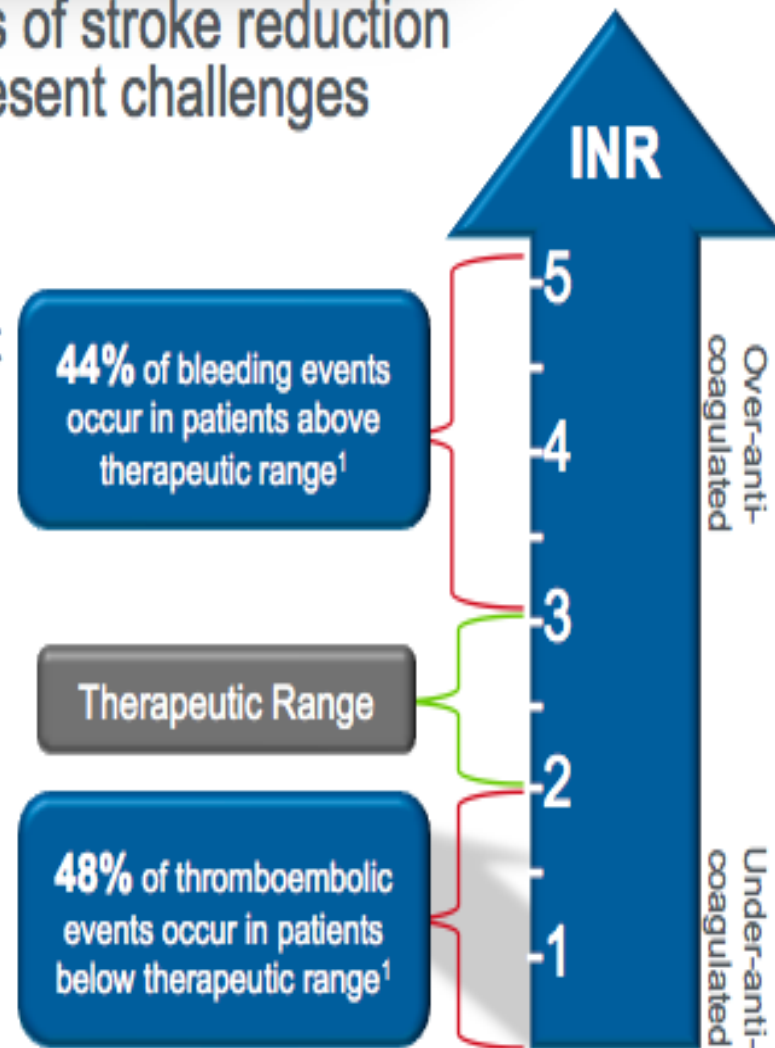
2014 AHA/ACC/HRS Guideline for the Management of Patients with AF





## Warfarin is an effective means of stroke reduction in patients with AF but can present challenges

- Many patients spend a significant amount of time outside of the therapeutic range.
- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans<sup>2</sup>



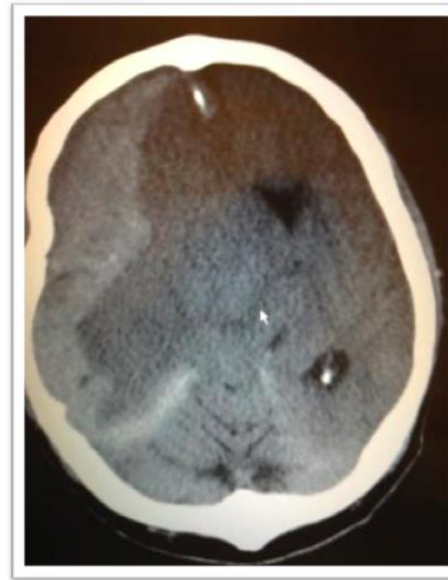
Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)
Rivaroxaban <sup>1</sup>	24%	3.6%
Apixaban <sup>2</sup>	25%	2.1%
Dabigatran <sup>3</sup> (150 mg)	21%	3.3%
Edoxaban <sup>4</sup> (60 mg / 30 mg)	33 % / 34%	2.8% / 1.6%
Warfarin <sup>1-4</sup>	17 – 28%	3.1 – 3.6%

**There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs**



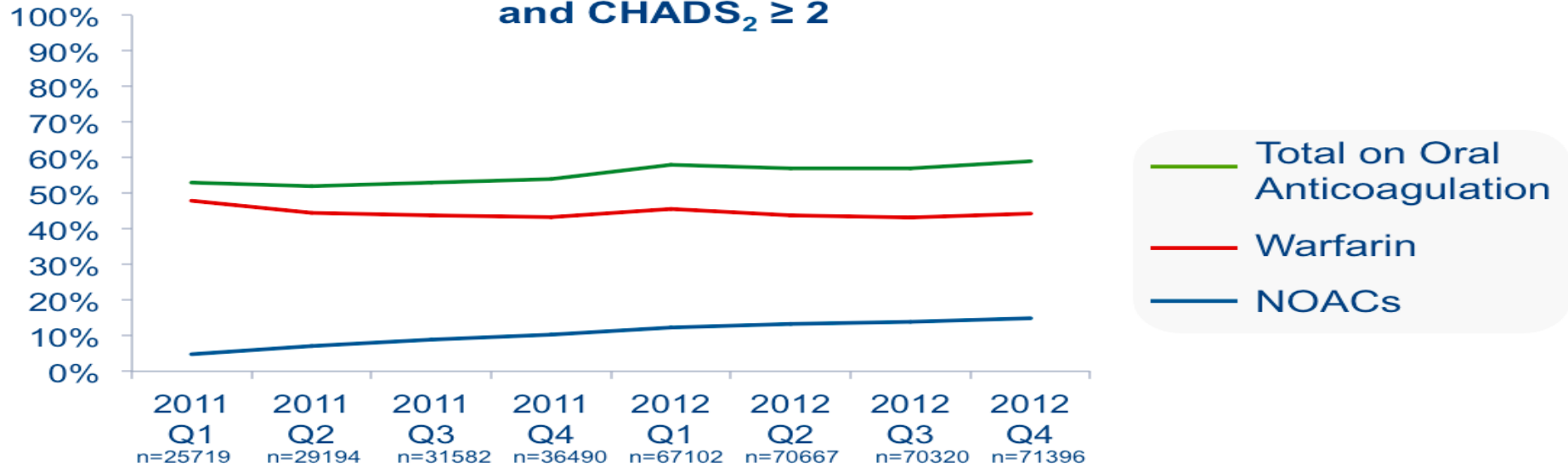


Spontaneous intra-parenchymal bleed



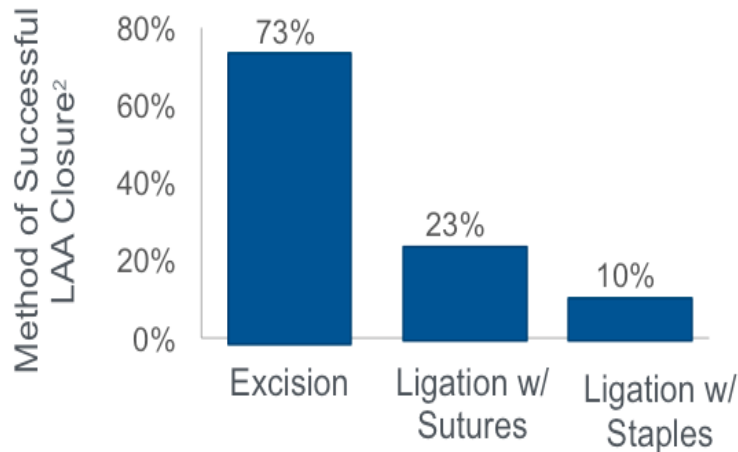
Hemorrhagic transformation

### Anticoagulant Use in Patients with NVAF and CHADS<sub>2</sub> ≥ 2



Results from the NCDR PINNACLE Registry<sup>1</sup>

- Surgical approaches to thromboembolic prophylaxis have been explored since the 1940s
- LAA closure or obliteration has most often been considered as an adjunct to other cardiac procedures such as mitral valvotomy or cardiac bypass surgery
- Studies on patients undergoing LAA closure have shown a trend toward reduction in embolic events



- A review of the literature on LAA closure prior to 2010 found closure rates of 10%-73%<sup>1</sup>

A need exists for a less invasive approach that can consistently close the LAA

# LAA Closure (LAAC) Devices



- First LAAC device (2001)
- Device no longer available

**PLAATO**



**WATCHMAN™  
Device**

- Only LAAC device with 2 Randomized Controlled Trials
- FDA approved with specific indication to reduce the risk of thromboembolism

ClinicalTrials.gov identifiers:  
NCT00129545 (PROTECT AF)  
NCT01182441 (PREVAIL)



**ACP**

- US Trial halted in 2013
- AMPLATZER™ Cardiac Plug Clinical Trial

ClinicalTrials.gov identifier:  
NCT01118299

## LAA Clip

**EXCLUDE** Trial (completed)

- AtriClip Device was FDA approved in 2010 for LAA closure
  - No specific indication for Stroke Reduction

ClinicalTrials.gov identifier: NCT00779857



## Surgical Ligation

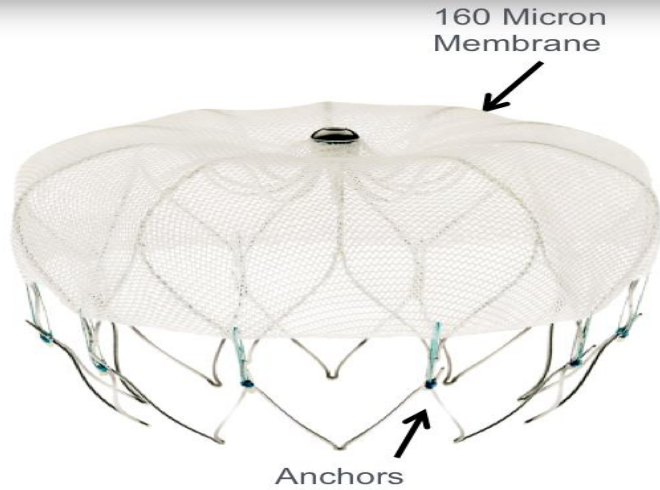
**“Safety and Efficacy of Left Atrial Appendage Occlusion Devices”**

Observational Study (retrospective)

- To compare LARIAT® vs. WATCHMAN™
- LARIAT currently does not have a specific indication for LAA Closure or Stroke Reduction

ClinicalTrials.gov identifier: NCT01695564





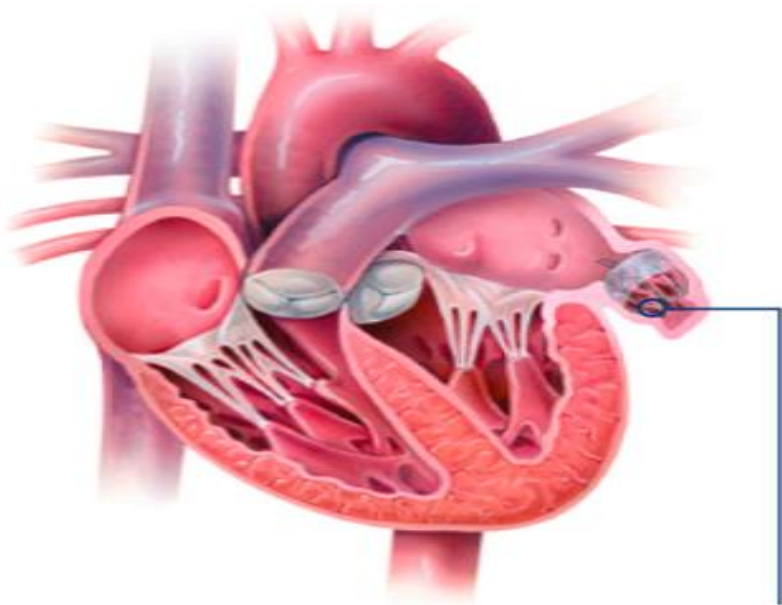
*Designed specifically for the left atrial appendage*

### Nitinol Frame

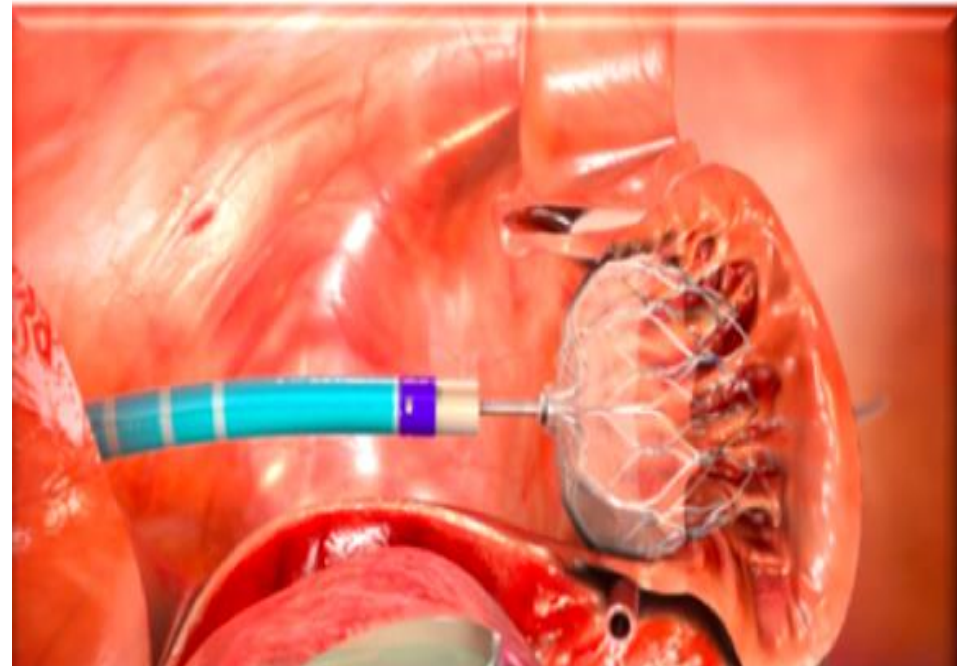
- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention
- Features an intra-LAA design to avoid contact with Left Atrial wall

### 160 Micron Membrane

- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA

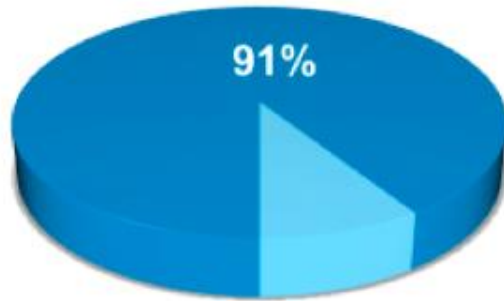


**Left Atrial Appendage**  
with WATCHMAN™ device implanted

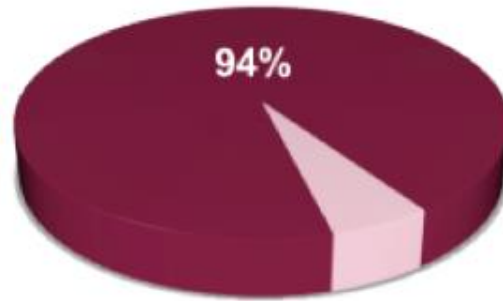


	PROTECT AF	CAP Registry	PREVAIL	CAP2 Registry	Totals
<b>Enrollment</b>	2005-2008	2008-2010	2010-2012	2012-2014	
<b>Enrolled</b>	800	566	461	579	<b>2406</b>
<b>Randomized</b>	707	---	407	---	<b>1114</b>
WATCHMAN: warfarin (2:1)	463 : 244	566	269 :138	579	1877: 382
<b>Mean Follow-up (years)</b>	4.0	3.7	2.2	0.58	N/A
<b>Patient-years</b>	2717	2022	860	332	<b>5931</b>

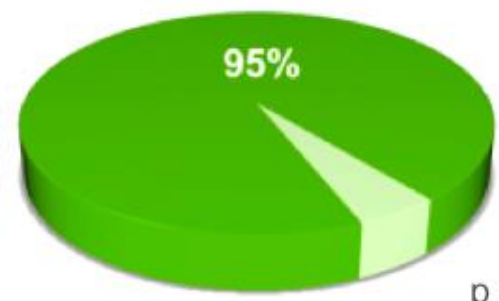
**PROTECT AF**  
Implant success



**CAP**  
Implant success



**PREVAIL**  
Implant success

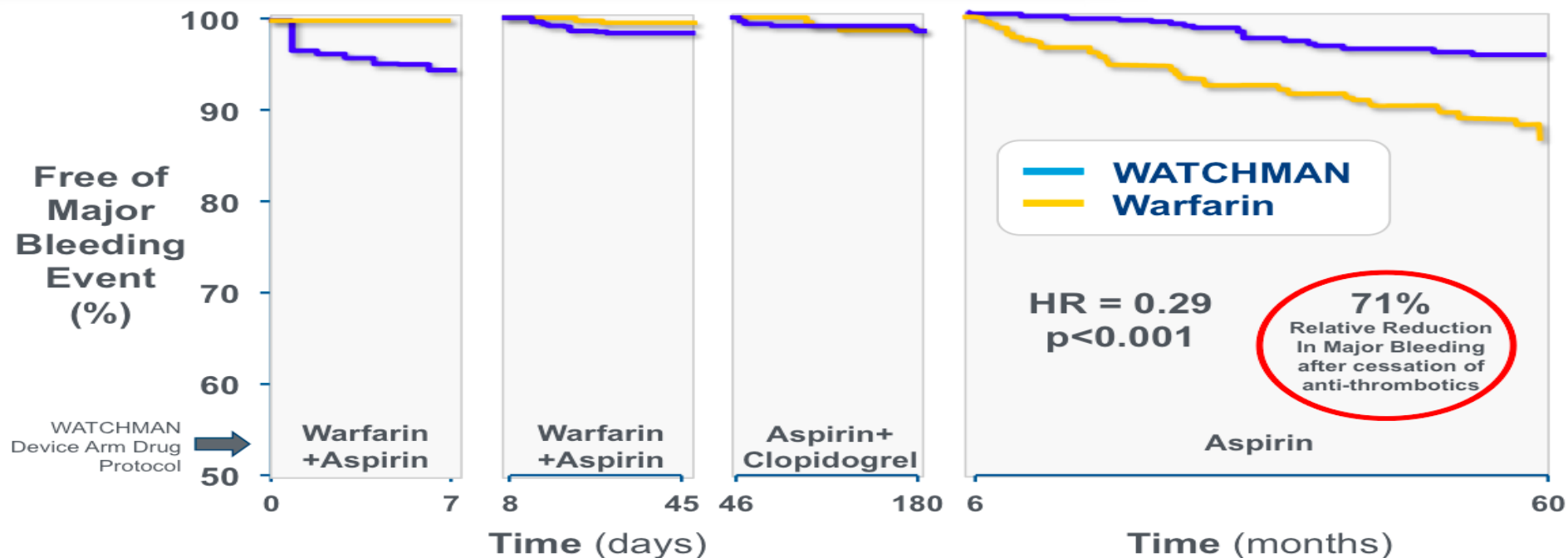
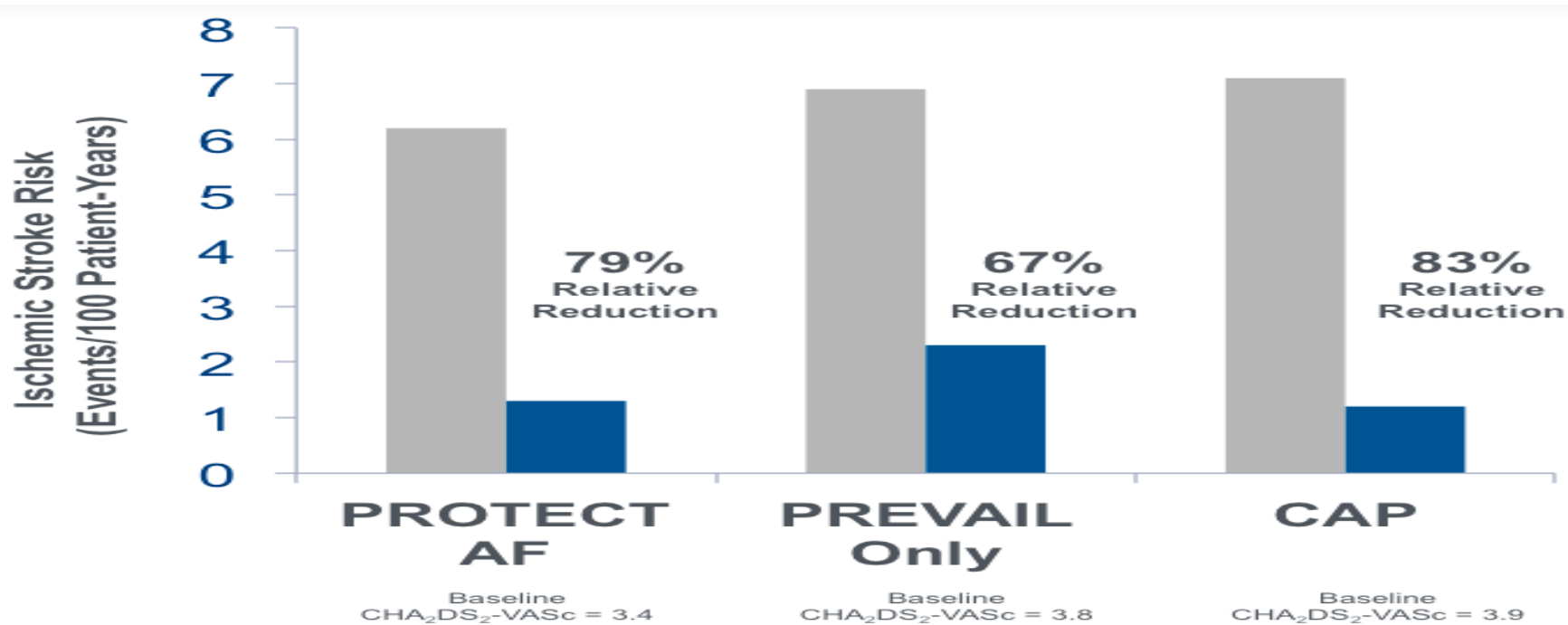


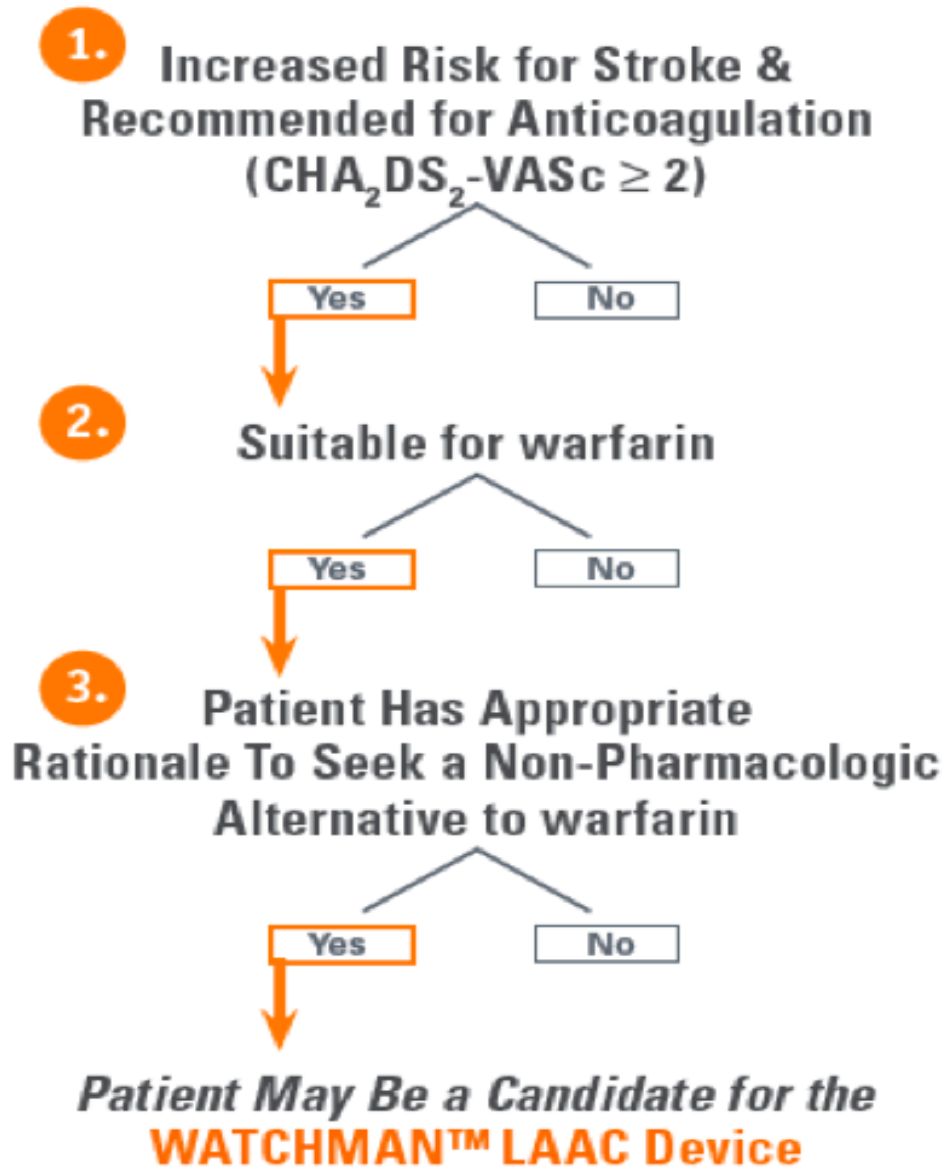
$p = 0.04$

Implant success defined as deployment and release of the device into the left atrial appendage

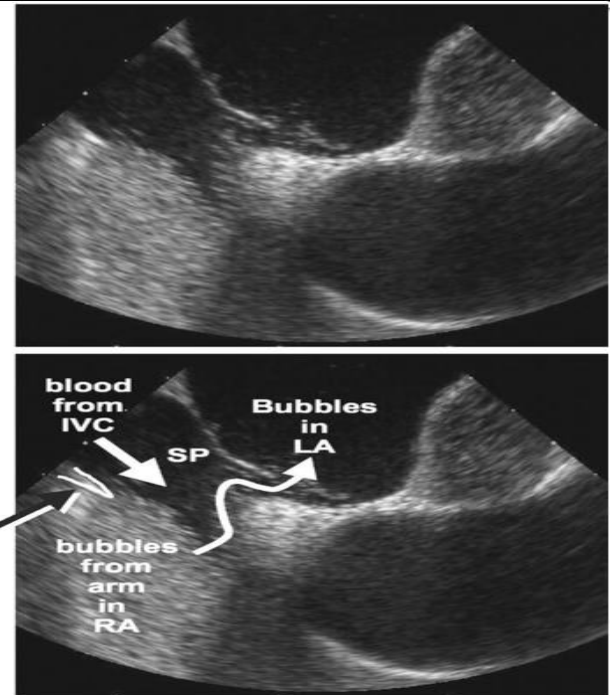
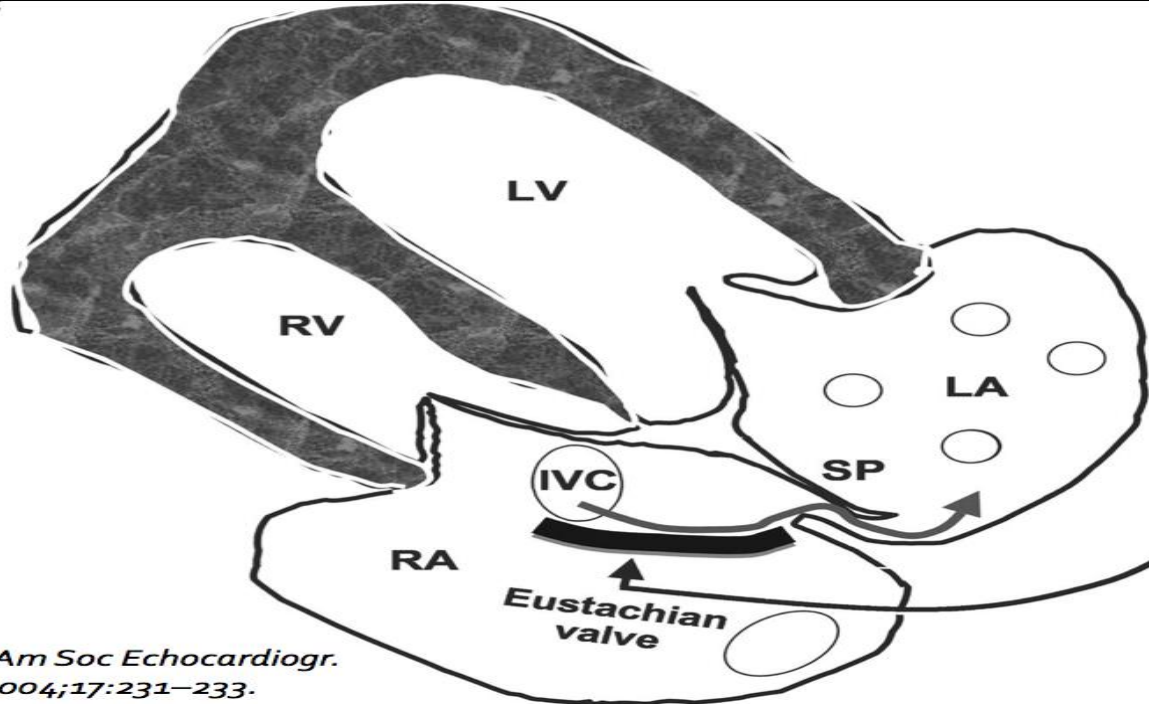
## Warfarin Cessation

Study	45-day	12-month
<b>PROTECT AF</b>	<b>87%</b>	<b>&gt;93%</b>
<b>CAP</b>	<b>96%</b>	<b>&gt;96%</b>
<b>PREVAIL</b>	<b>92%</b>	<b>&gt;99%</b>



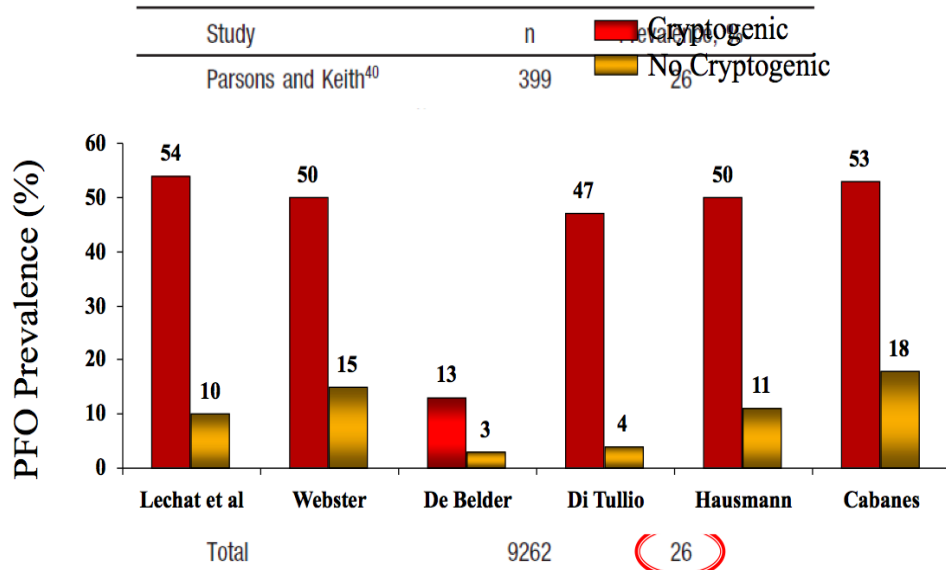






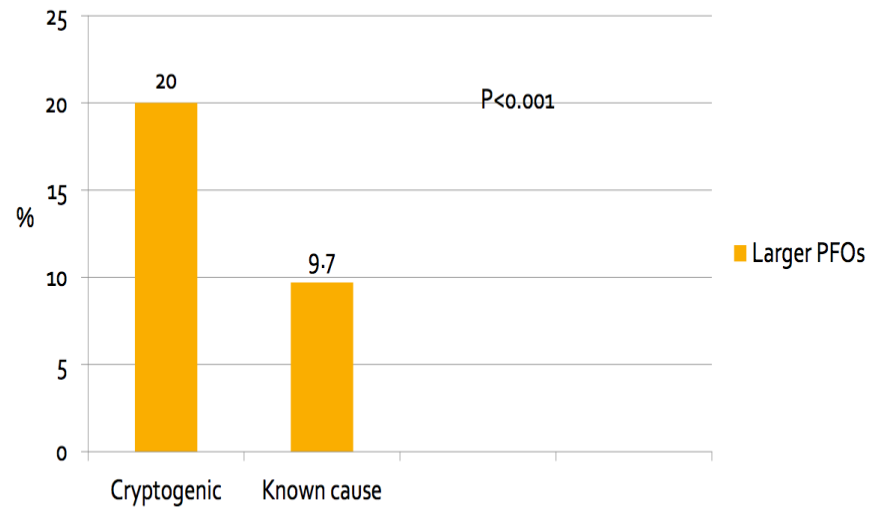
*J Am Soc Echocardiogr.*  
2004;17:231-233.

TABLE 3. Autopsy Prevalence of PFO



AUTHOR - STUDY  
*Circulation* 2005;112:1063-1072

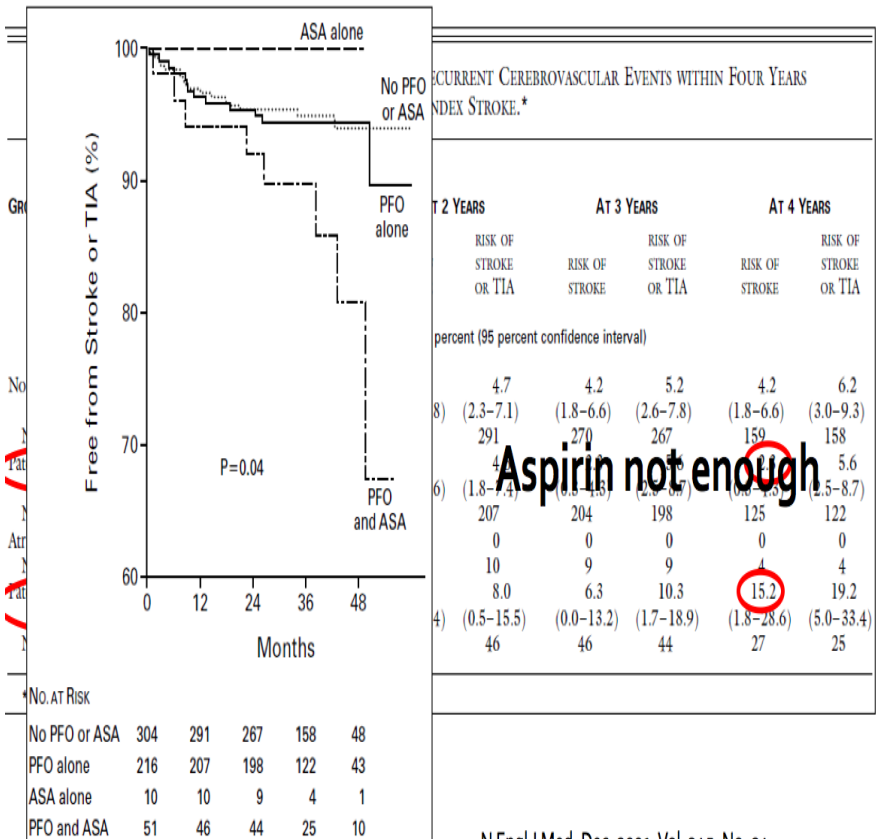
Larger PFOs



Homma S, et al. PICSS trial. *Circulation* 2002;105:2625-2631

# RECURRENT CEREBROVASCULAR EVENTS ASSOCIATED WITH PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM, OR BOTH

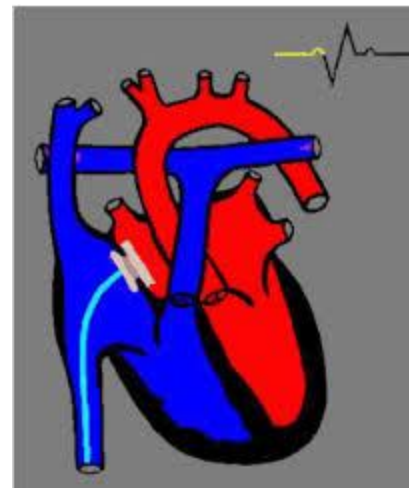
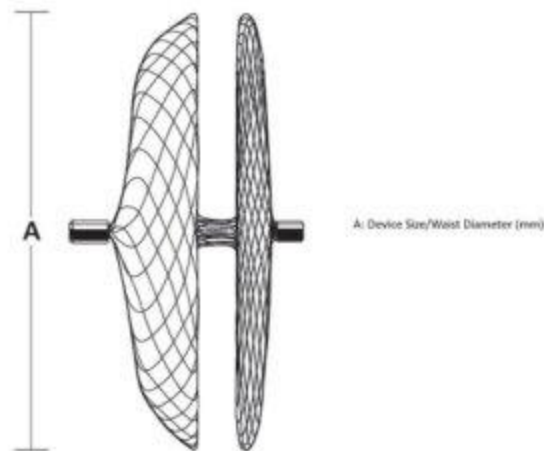
JEAN-LOUIS MAS, M.D., CAROLINE AROUZAN, M.D., CATHERINE LAMY, M.D., MATHIEU ZUBER, M.D., LAURE CABANES, PH.D., GENEVIÈVE DERUMEUX, M.D., AND JOËL COSTE, PH.D., FOR THE PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM STUDY GROUP\*



## Conclusion:

- Aspirin therapy may be adequate for secondary prevention in young patients with isolated PFO and cryptogenic stroke
- Patients with cryptogenic stroke and the presence of both PFO & atrial septal aneurysm constitute a high risk subset And preventive strategies other than aspirin should be considered

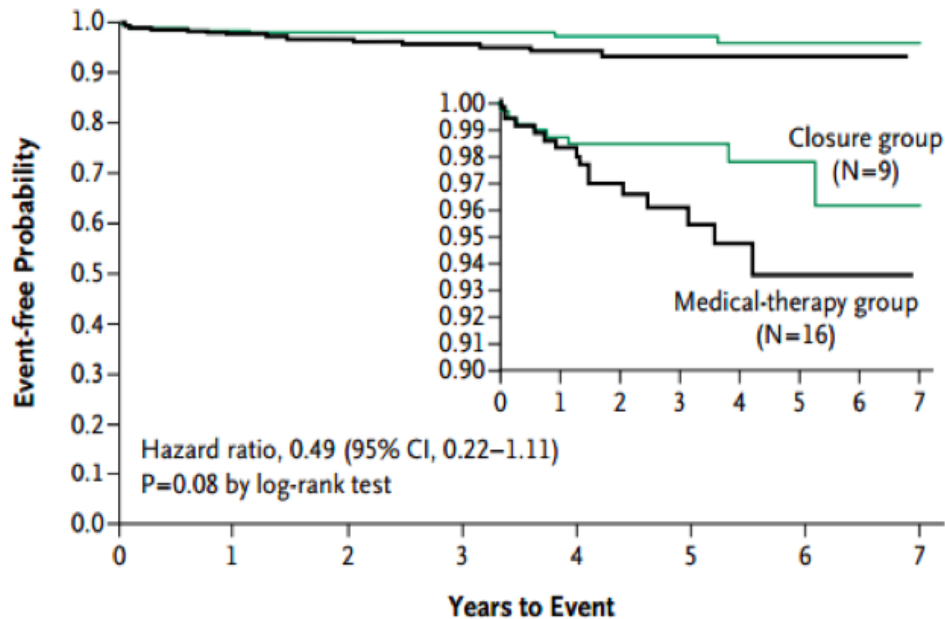
Author	Study acronym	Enrolment	Country	Number of patients	Mean follow-up (months)	Lost to F/U	Intervention group	Medical therapy group	Study conclusions
Carroll <i>et al.</i>	RESPECT	2003–11 multicentre, randomized	USA and Canada	980	31	Medical group 17.2% 83/481 Device group 9.2% 46/499	Amplatzer PFO occluder + aspirin and clopidogrel for 1 month followed by aspirin for at least 5 months	Aspirin 46.5% Coumadin 25.2% Clopidogrel 14% Aspirin + dipyridamole 8.1% Aspirin + clopidogrel 6.2%	No significant benefit of PFO closure for recurrent stroke prevention
Meier <i>et al.</i>	PC	2000–09 multicentre randomization by web-based system	29 Centres in Europe, Canada, Brazil, and Australia	414	49	Medical group 15% 31/210 Device group 12% 24/204	Amplatzer PFO occluder + aspirin (5–6 months) and ticlopidine OR clopidogrel	Antiplatelet OR, AND coumadin (left at the discretion of treating physician)	No significant reduction in the risk of recurrent embolic events or death in the closure group, as compared with the medical therapy group
Furlan <i>et al.</i>	CLOSURE I	2003–08 multicentre, randomized	USA and Canada	909	44	Medical group 17% 77/462 Device group 5%, 24/447	STARFlex + aspirin (2 years) and clopidogrel (6 months)	Aspirin, coumadin OR aspirin and coumadin (left at the discretion of treating physician)	No significant difference between closure with a percutaneous device plus antiplatelet therapy and medical therapy alone with respect to the prevention of recurrent stroke or TIA



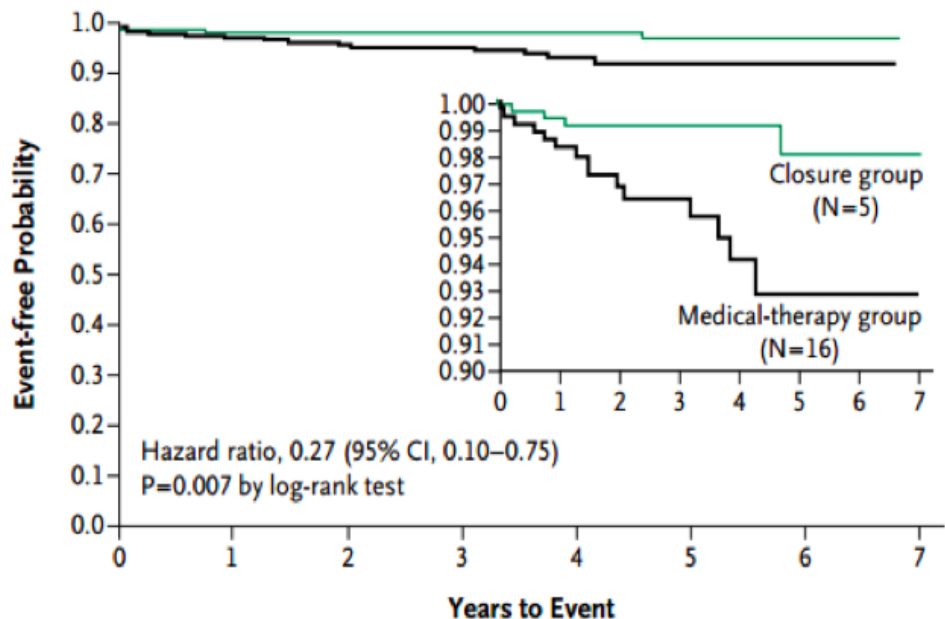
# RESPECT Trial Population

- 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

## A Intention-to-Treat Cohort



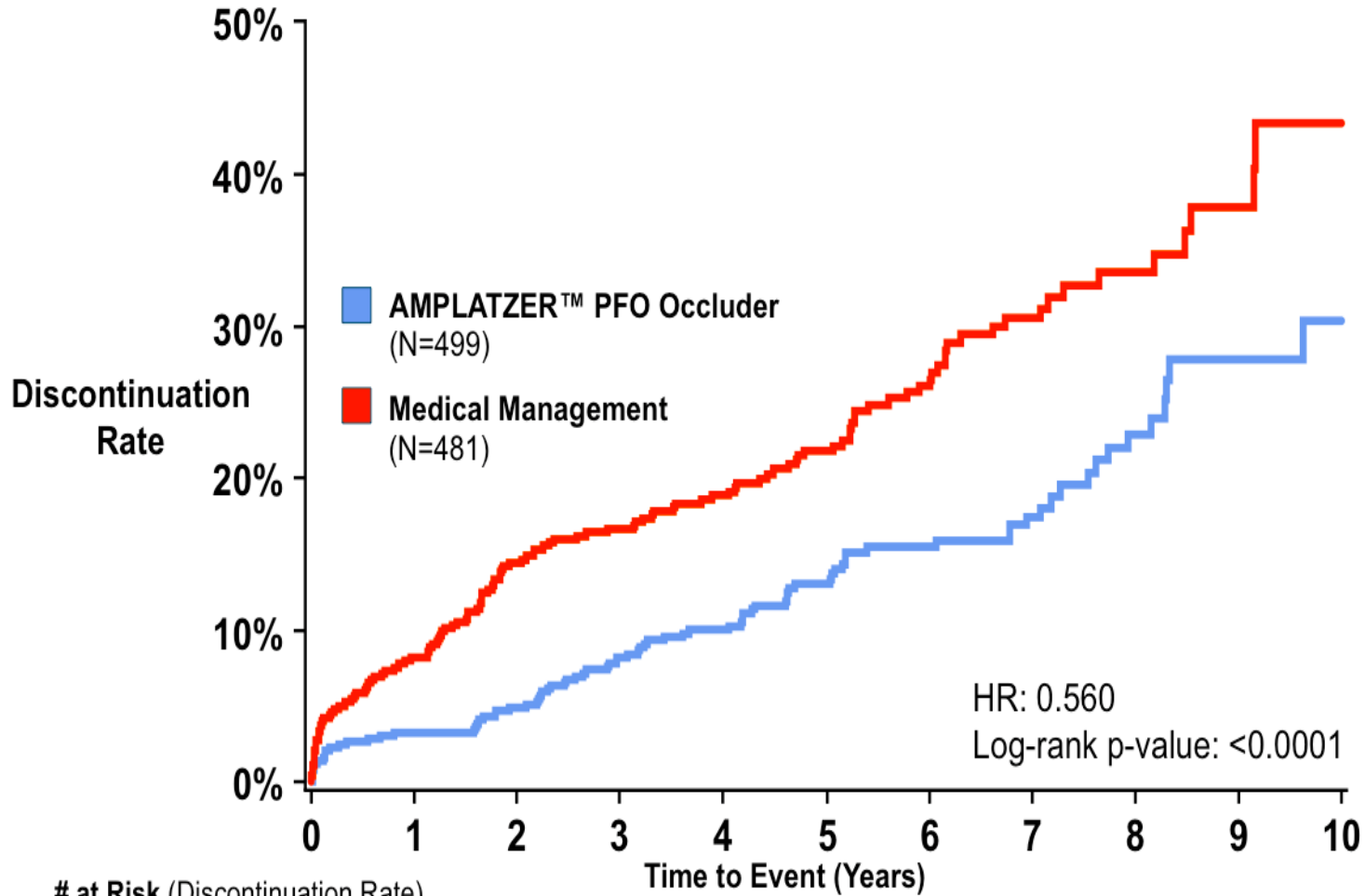
## B As-Treated Cohort



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

	<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 Subjects: Off-Label PFO Closure



# at Risk (Discontinuation Rate)

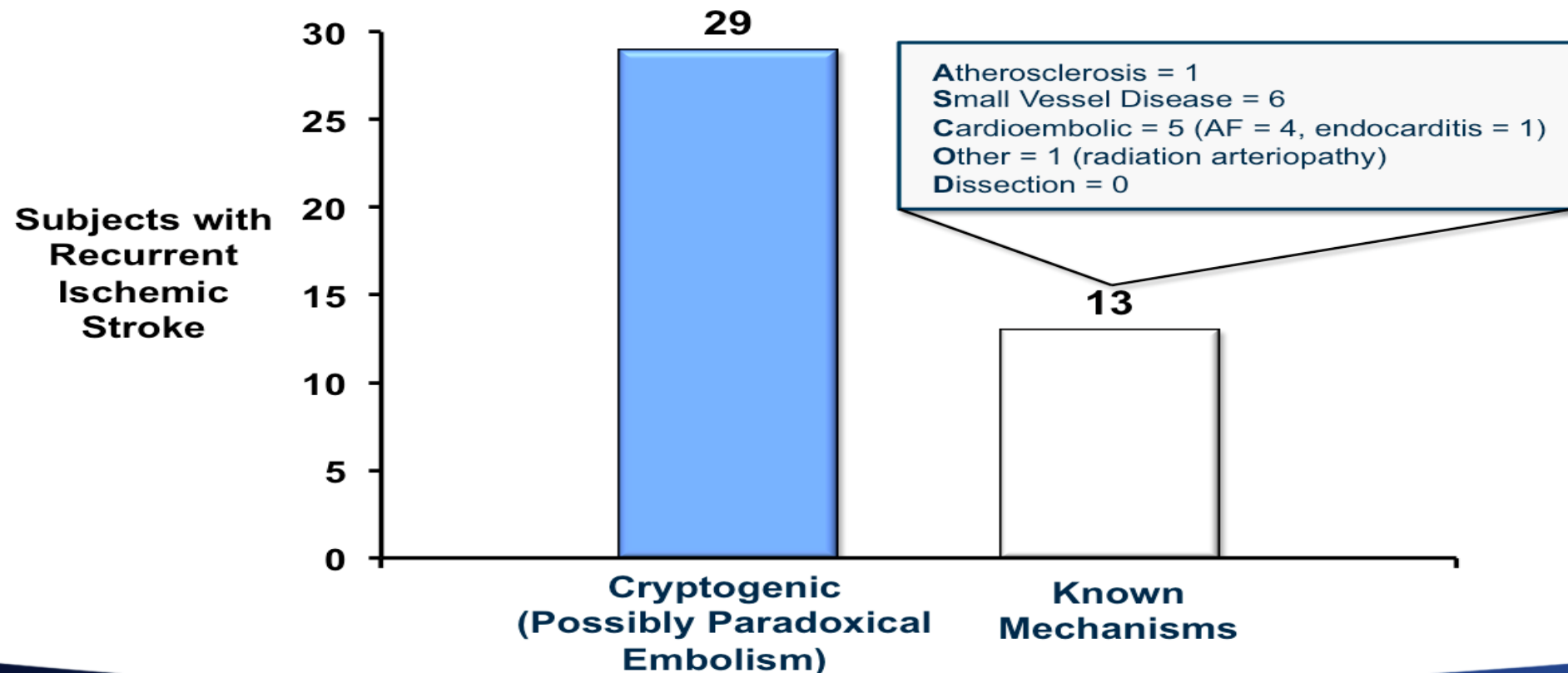
	0	1	2	3	4	5	6	7	8	9	10
<b>AMPLATZER</b>	499 (0%)	463 (4.9%)	369 (10.0%)	212 (15.4%)	86 (22.8%)	20 (30.3%)					
<b>MM</b>	481 (0%)	394 (14.4%)	307 (18.8%)	168 (26.5%)	71 (33.5%)	10 (43.3%)					

1. Differentiate true cryptogenic stroke from other mechanisms
2. As treated analysis (comparing the arm who got devices vs who did not)
3. Does age matter?
4. Does size of shunt and Aneurysmal IAS matter?

## Blinded Adjudication of Stroke Cause Using ASCOD Phenotyping

- ASCOD coding captures presence of possible stroke etiologies, and assigns a probability of relatedness (post-hoc)
- Five phenotypes:
  - A = atherosclerosis
  - S = small vessel disease
  - C = cardiac pathology
  - O = other cause
  - D = dissection
- Recurrent strokes classified as either cryptogenic or of known cause

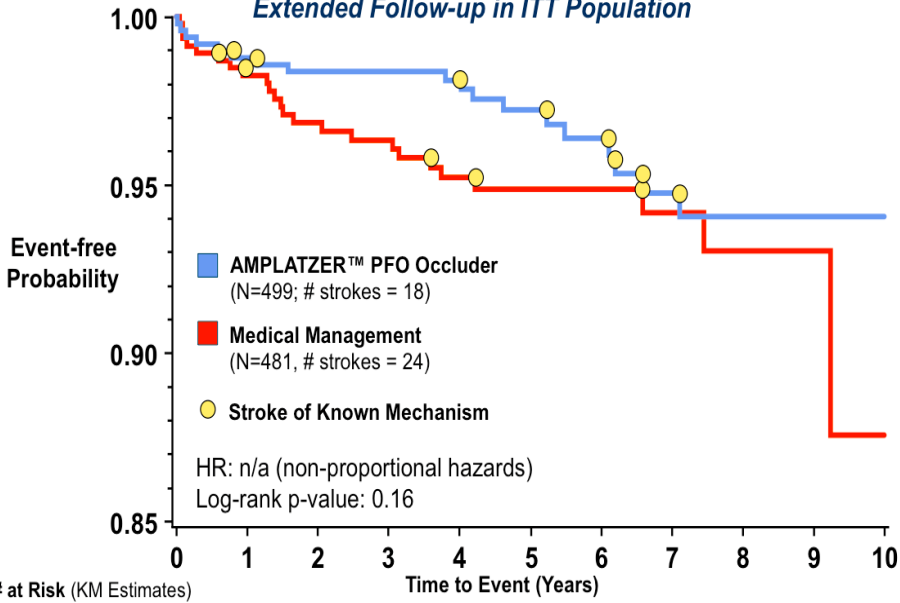
Amarenco et al. *Cerebrovasc Dis* 2013;36:1-5





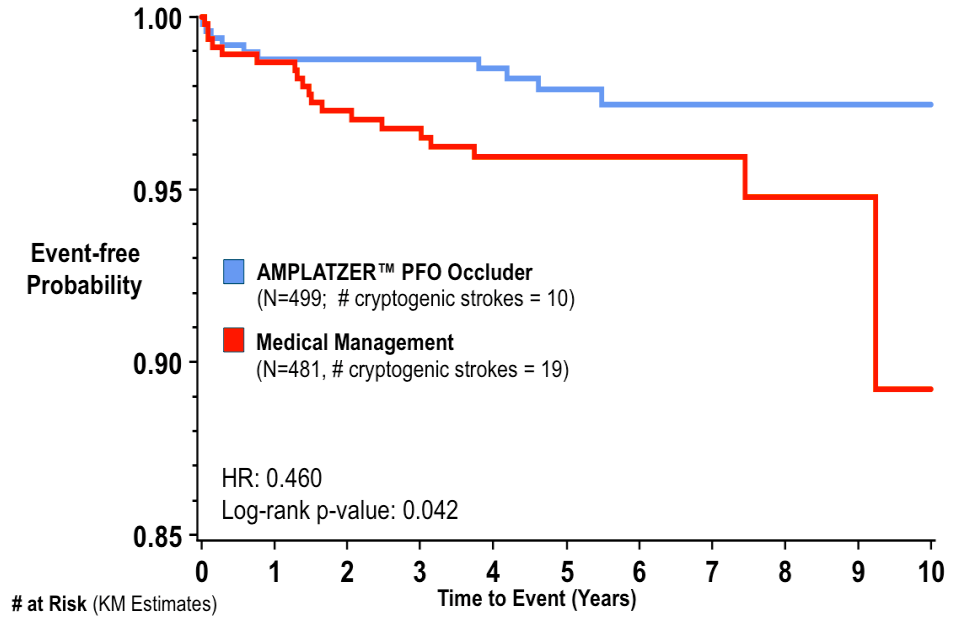
## 1 out of 3 Recurrent Strokes Had Mechanism That PFO Closure Cannot Prevent

*Extended Follow-up in ITT Population*



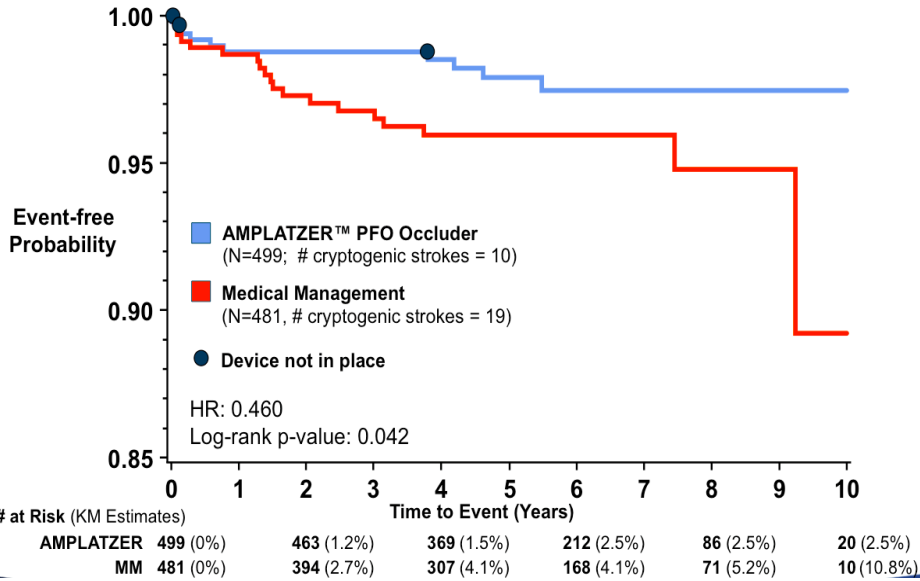
## Significant Reduction in Recurrent Cryptogenic Stroke

*54% Relative Risk Reduction in ITT Population*

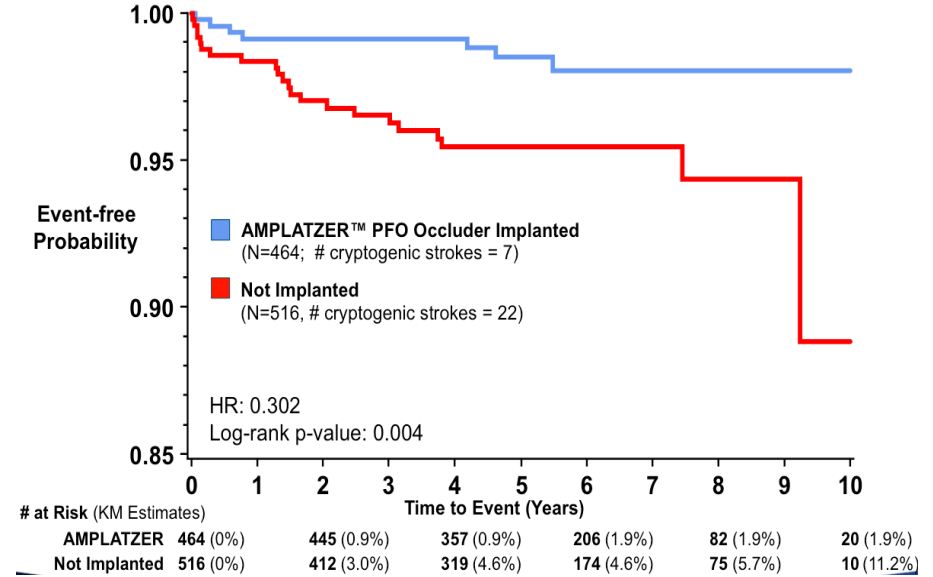


## Significant Reduction in Recurrent Cryptogenic Stroke

54% Relative Risk Reduction in ITT Population

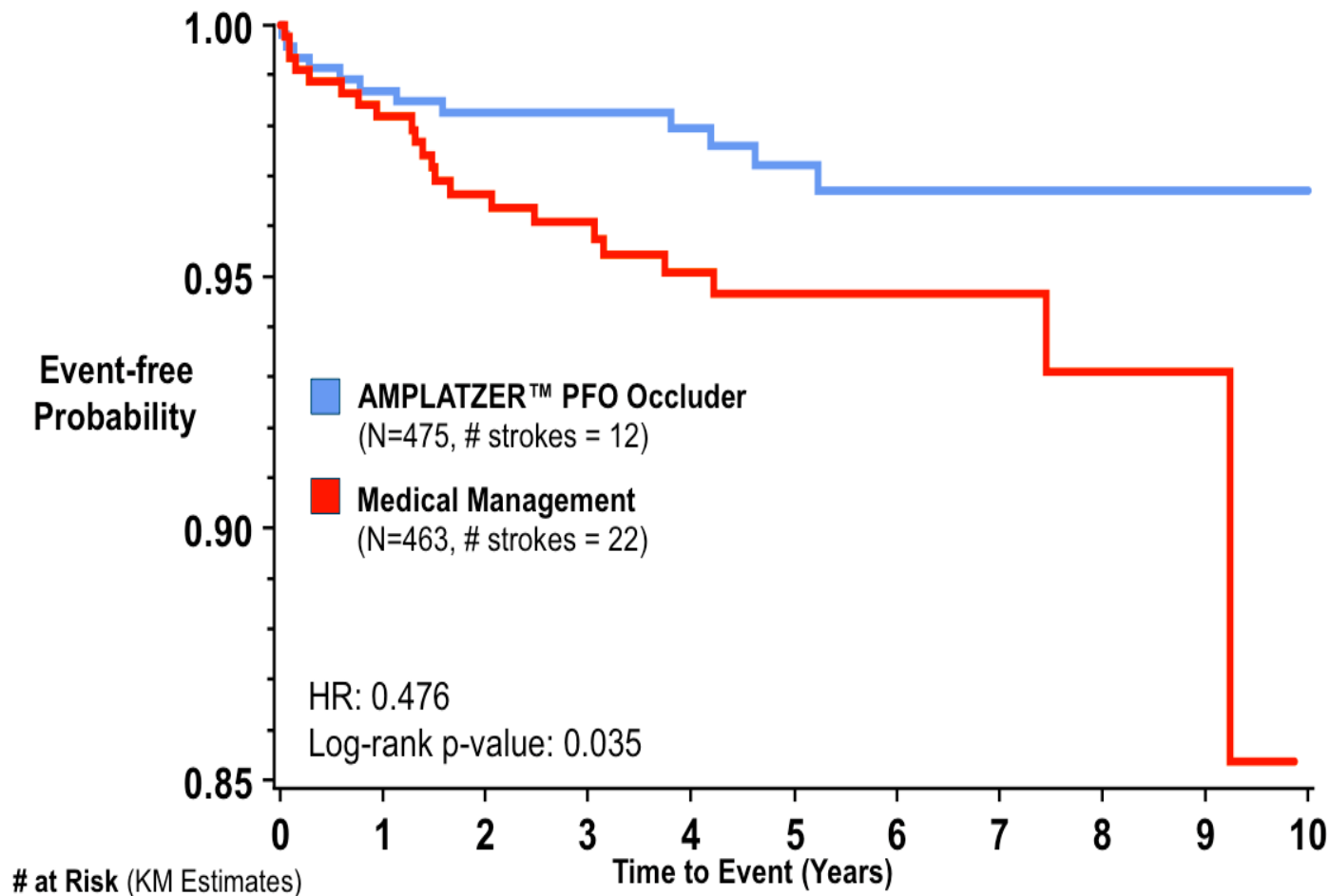


## 70% Relative Risk Reduction in Recurrent Cryptogenic Stroke With Device In Place



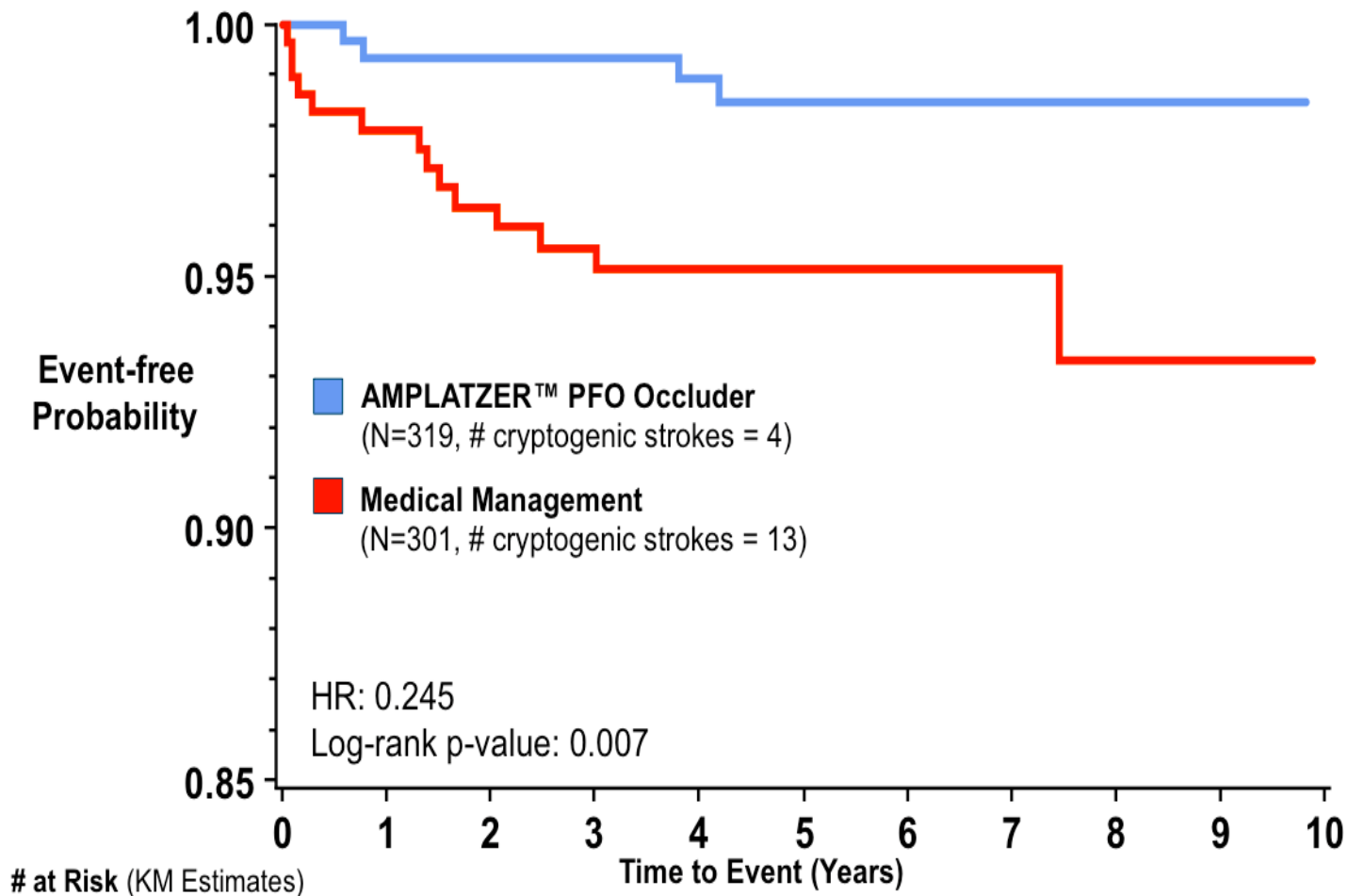
# Freedom from Recurrent Stroke of Any Mechanism: <60 Yrs

*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*



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

PFO closure is superior to medical management in reducing recurrent Cryptogenic Ischemic stroke especially in young patients who has large Shunts and aneurysmal IAS.





Let no one ever come to you without leaving better and happier. Be the living expression of God's kindness: kindness in your face, kindness in your eyes, kindness in your smile.

(Mother Teresa)