Contemporaneous approach of the left atrial appendage and patent oval foramen: when intervention is indicated

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Disclosure

- Carlos AC Pedra, MD, PhD, FACC, FSCAI
  - Proctor for the Amplatzer Cardiac Plug (St Jude Medical) in LATAM
  - Proctor for the Melody Valve (Medtronic) in LATAM

Contemporaneous approach of the LAA: when intervention is indicated

Treatment options: Oral Anti-Coagulation Coumadin

1. Multiple Randomized Trials have established the efficacy of Oral Anticoagulation (64% strokes risk reduction)
2. Contraindicated for 14-47% of patients (who are at risk for stroke)
3. Limitations Include:
    1. Narrow Therapeutic Window
    2. Need for close monitoring and pharmacological interactions
    3. Intracranial Hemorrhage 1.8% of patients per year age 75 and older
    4. Delays on other urgent procedure
4. Discontinuation rate is estimated to be 38% per year

Interventional treatments for stroke prevention Mobius-Winkler et al.

Stroke Treatment Option:
Novel Oral Anticoagulants (NOACs)

Boston Scientific

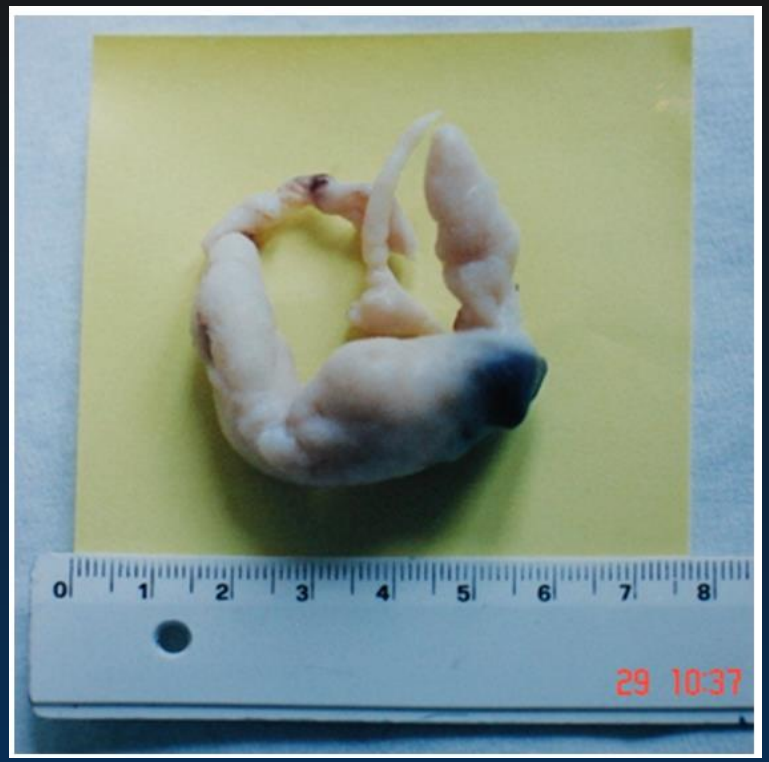
Study	Treatment	Major Bleeding	Hemorrhagic Stroke
RE-LY[1]	Dabigatran (110 mg)	2.71%	0.12%
	Dabigatran (150 mg)	3.11%	0.10%
	Warfarin	3.36%	0.38%
ROCKET-AF[2]	Rivaroxaban	3.6%	0.5%
	Warfarin	3.4%	0.7%
ARISTOTLE[3]	Apixaban	2.13%	0.24%
	Warfarin	3.09%	0.47%

This chart is not based on a head-to-head trial and is not intended to suggest head-to-head comparisons of the separate trials or the therapies under study

1 Connelly SJ et al, *NEJM* 2009;361:1139–51; 2 Patel MR et al, *NEJM* 2011;365:883–91; 3 Granger J. et al, *NEJM* 2011;365:981–92

SH-230609-AA APR2014

Rationale for local therapy: LAA is the source of embolization!



Setting	No. of Patients	Thrombus Location (n, %) LA Appendage	LA Cavity	Total
TEE†	317	66 (20.8)	1 (0.3)	67 (21.1)
TEE	233	34 (14.6)	1 (0.4)	35 (15.0)
Autopsy	506	35 (6.9)	12 (2.4)	47 (9.3)
TEE	52	2 (3.8)	2 (3.8)	4 (7.7)
TEE	48	12 (25.0)	1 (2.1)	13 (27.1)
TEE and operation	171	8 (4.7)	3 (1.8)	11 (6.4)
ACUTE	549	67 (12.2)	9 (1.6)	76 (13.8)
TEE	272	19 (7.0)	0 (0)	19 (7.0)
TEE	60	6 (10.0)	0 (0)	6 (10.0)
Total	2208	249 (11.3)	29 (1.3)	278 (12.6)

> 90% of thrombi located in the LAA

Onalan O; Stroke 2007

WATCHMAN Device

- Nitinol frame
- 160 micron PET membrane
- row of fixation barbs around the mid perimeter
- 21, 24, 27, 30 mm

Randomized trial has finished enrolment

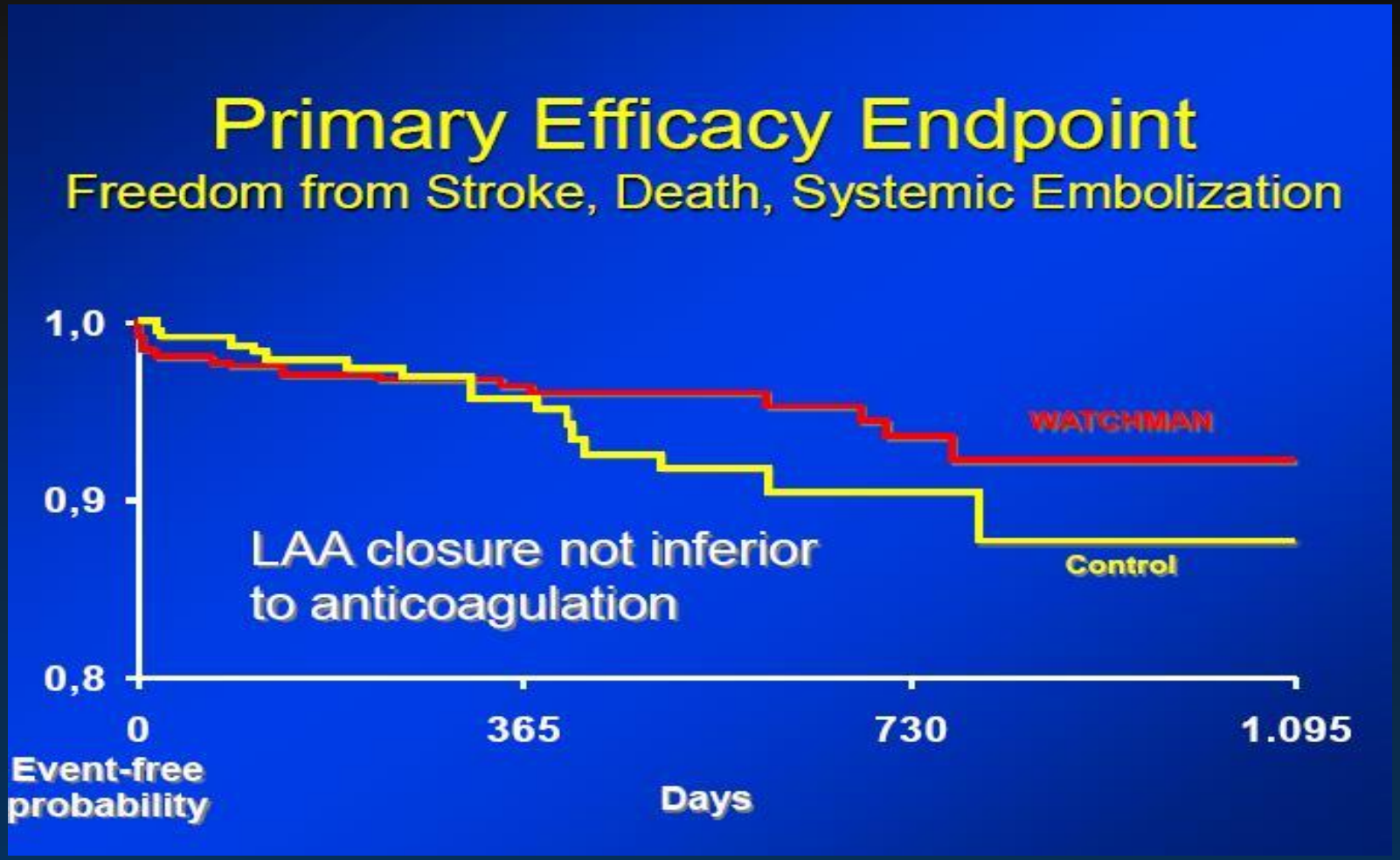
WATCHMAN™ Clinical Leadership

WATCHMAN™

Pilot	Early feasibility with >6 years of follow-up	n=66
PROTECT-AF	WATCHMAN primary efficacy, CV death, and all-cause mortality superior to warfarin at 4 years[1]	n=800
CAP Registry	Significantly improved safety results[2]	n=566
ASAP	Expected rate of stroke reduced by 77% in patients contraindicated to warfarin[3]	n=150
PREVAIL	Improved implant success procedure safety confirmed with new and experienced operators[4]	n=453
CAP2	Currently enrolling up to 1500 patients at ~ 60 sites	n= 505[5]

1. Reddy, VY et al. HRS 2013; 2. Reddy, VY et al. Circulation. 2011;123:417-424; 3. Reddy, et al. JACC 2013; 61(25):2551–6; 4 Holmes, DR et al., CIT 2013;
5. Reflects current enrollment as of 2/24/14

PROTECT - AF



Holmes D; Lancet 2009

Safety

Freedom from device embolization, pericardial effusion, Severe bleeding

Holmes D; Lancet 2009

PROTECT – AF. Continued Access Registry
Modified Risk Score for Death or Disabling Sequela

Table 5. Functional Impact of Safety Events

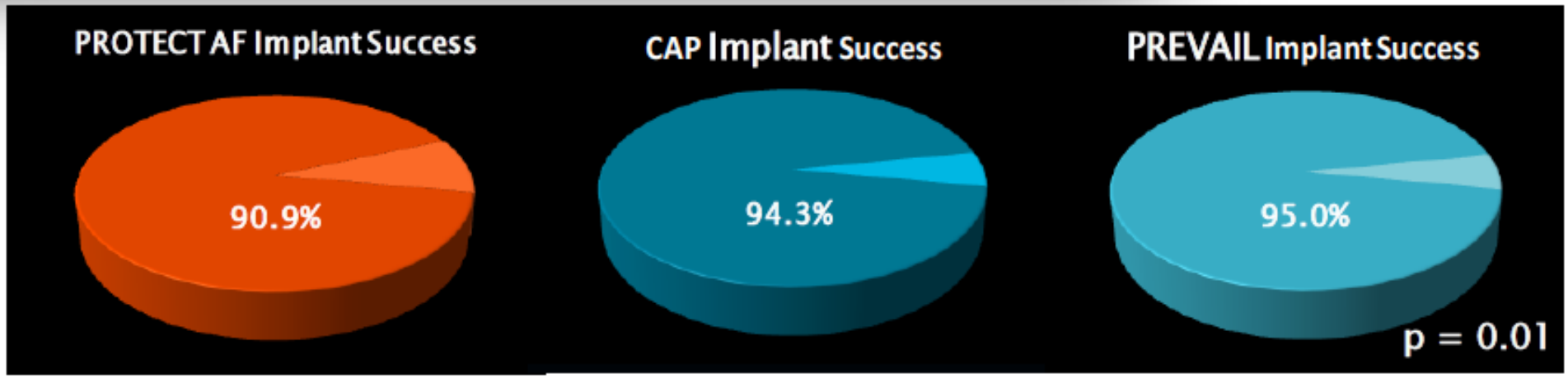
	Watchman Group Event Rate, % (n per 100 Patient-y)	Warfarin Group Event Rate, % (n per 100 Patient-y)	Relative Risk (95% CI)
MRS increase ≥1 or death	1.8 (19/1042.2)	4.3 (24/559.5)	0.43 (0.24–0.82)
MRS increase ≥2 or death	1.5 (16/1047.1)	3.7 (21/563.9)	0.41 (0.22–0.82)
MRS increase ≥3 or death	1.4 (15/1048.5)	3.3 (19/567.5)	0.43 (0.22–0.88)

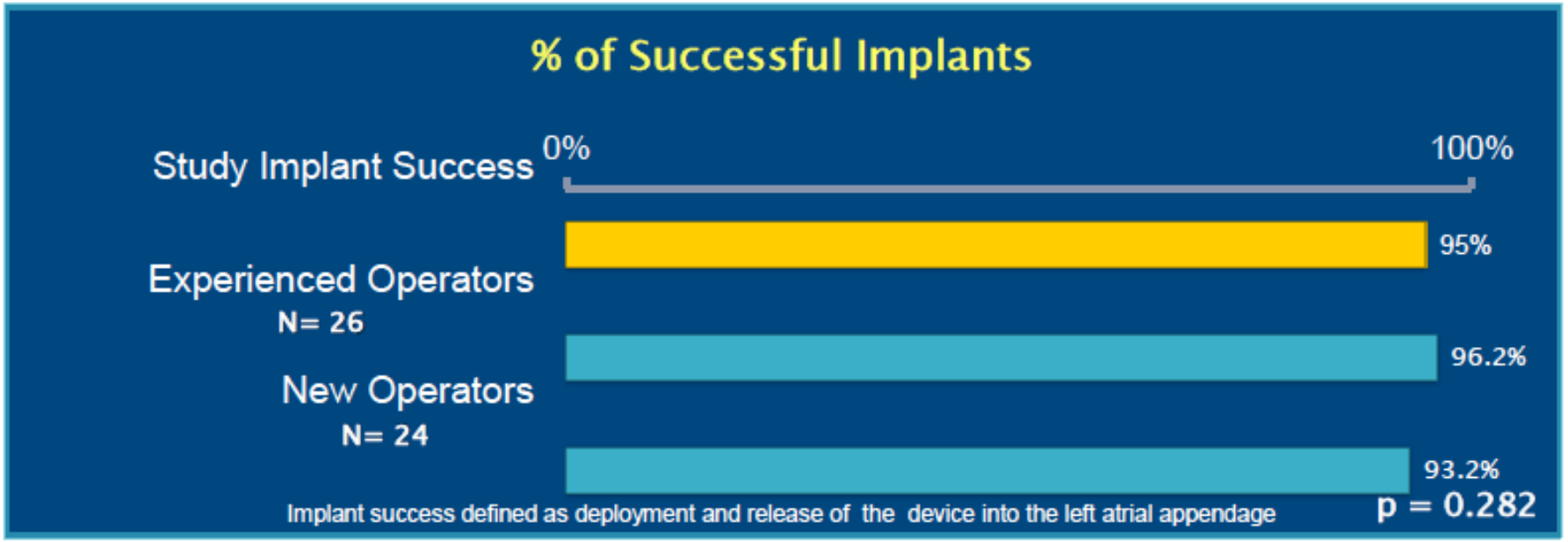
CI indicates confidence interval.

Reddy VY et al. Circulation 2011

WATCHMAN™ Device Implant Success Rates

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE



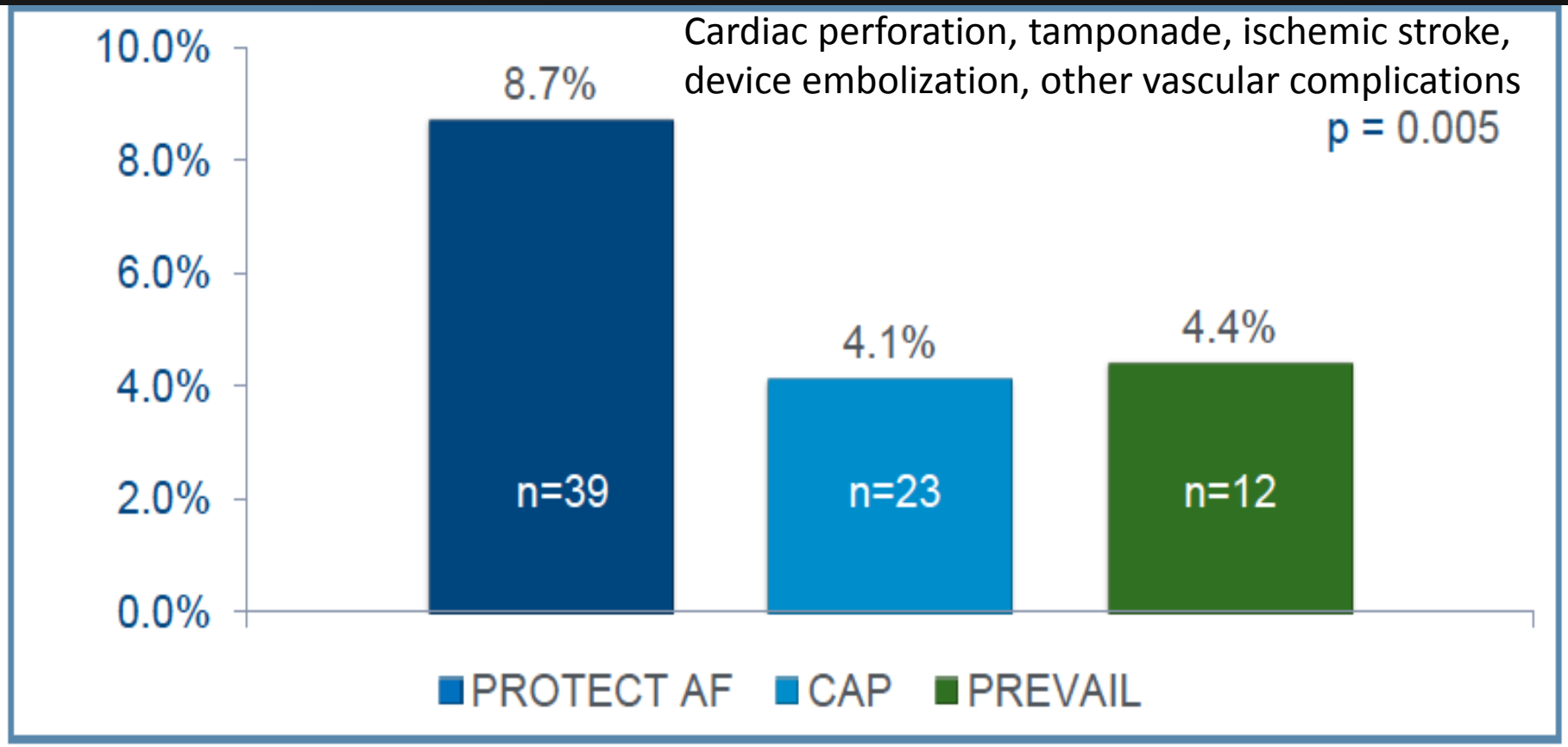


PROTECT AF and CAP data from Reddy, VY et al. *Circulation*. 2011;123:417-424. PREVAIL Results from Holmes, DR et al. CIT 2013

Vascular Complications

7 Day Serious Procedure/Device Related

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE



Cardiac perforation, tamponade, ischemic stroke, device embolization, other vascular complications

p = 0.005

No procedure-related deaths reported in any of the trials

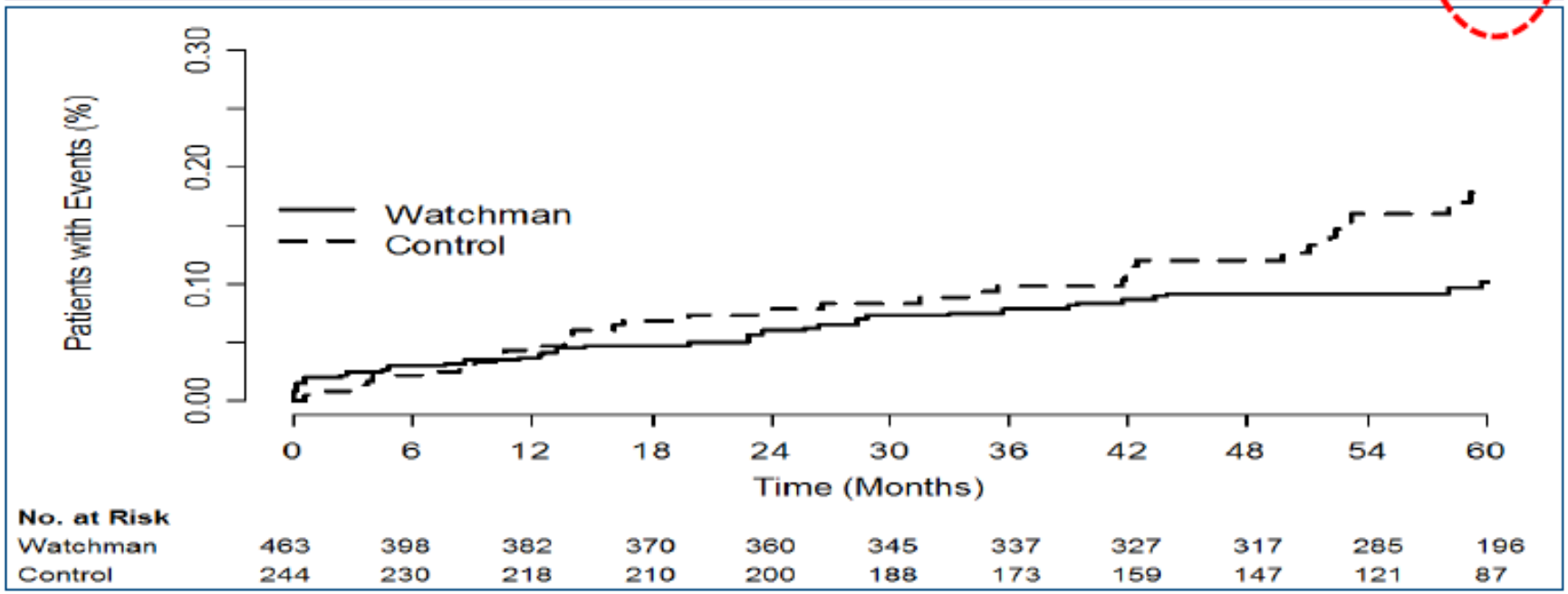
1 Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

Sources: PROTECT AF and CAP data from Reddy, VY et al. *Circulation*. 2011;123:417-424. PREVAIL Results from Holmes, DR et al. CIT 2013

PROTECT AF Long Term (4 Year) Follow-up
Primary Efficacy

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960



40% Reduction in Primary Efficacy events vs. warfarin – **Superior**

Reddy, V et al. HRS LBCT 2013

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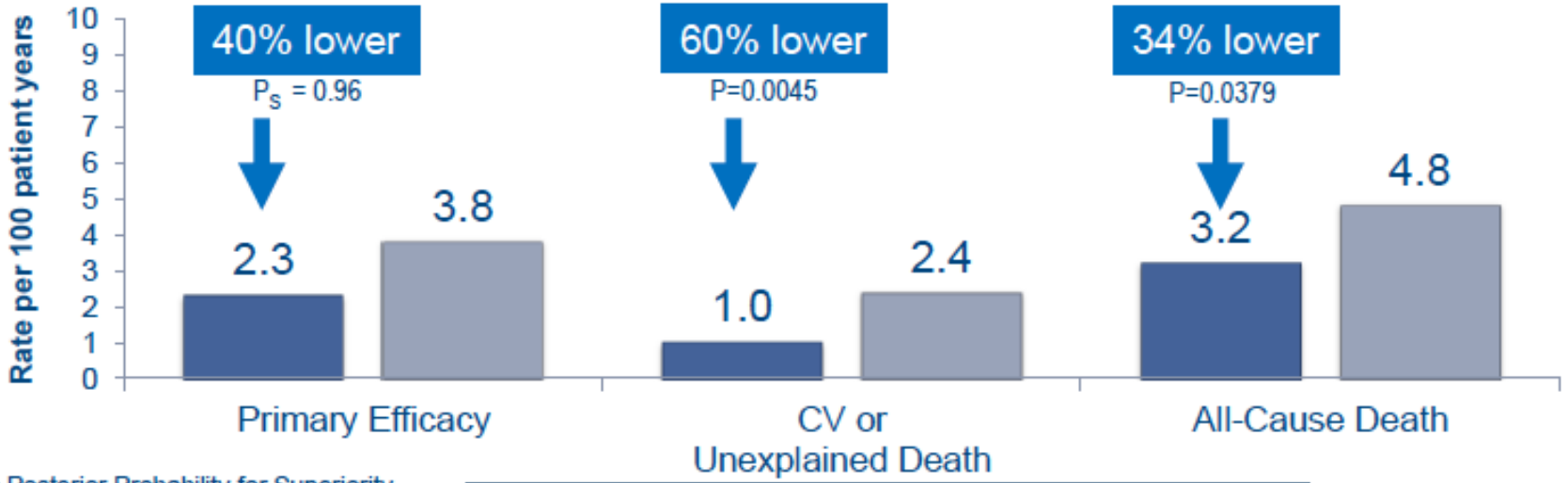
PROTECT AF Long Term (4 Year) Follow-up
Statistical Superiority

WATCHMAN™
LEFT ATRIAL APPENDAGE CLOSURE DEVICE

	WATCHMAN Observed Rate per 100 pt-yrs	Warfarin Observed Rate per 100 pt-yrs	% Reduction (vs Warfarin)	
Primary Efficacy Endpoint	2.3	3.8	40%	Superior
CV Death	1.0	2.4	60%	Statistically Superior
All-cause Death	3.2	4.8	34%	Statistically Superior

Events in PROTECT AF trial at 2,621 patient years



Ps = Posterior Probability for Superiority

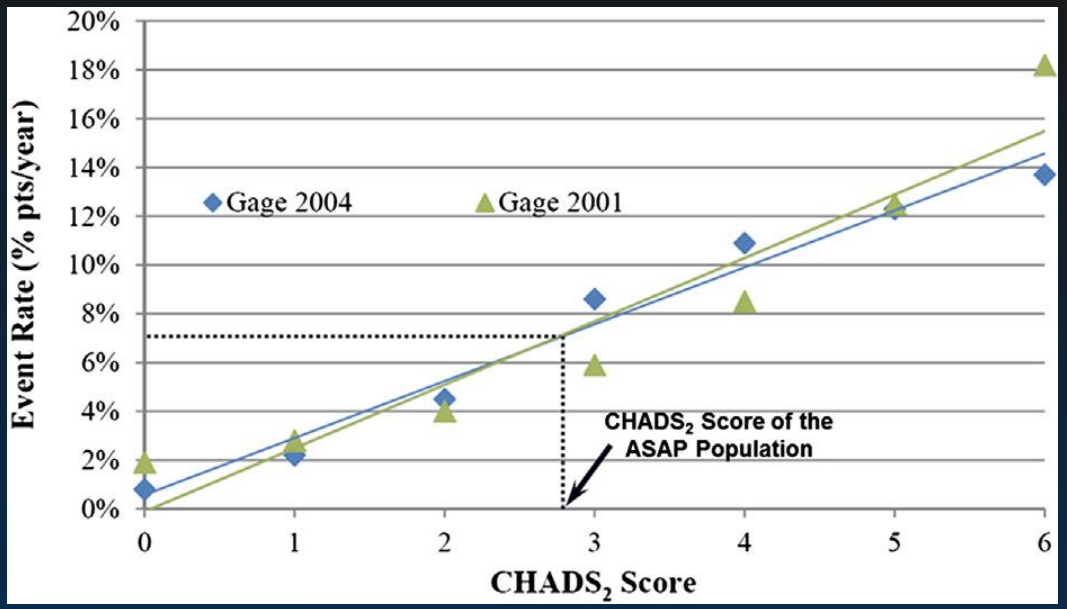
Reddy, et al., HRS LBCT May 2013

SH-230609-AA APR2014

ASAP study. Contra indication for oral warfarin

Expected vs observed annual rate of stroke based on CHADS2 score

Expected



Observed

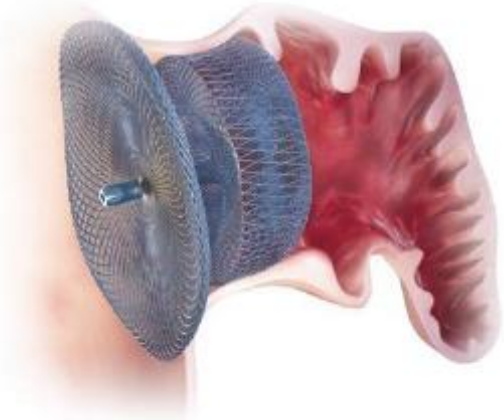
Table 4 Clinical Outcomes

	Entire Cohort Events/Patient-Years*
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

77% fewer events

Clopidogrel: 32% reduction rate which would decrease the expected rate to 5%
Even so, “local”protection would confer a 64% reduction in the ischemic stroke rate

Amplatzer Cardiac Plug
EU Prospective Observational Study



- Sample size:
  - 204 pts with non-valvular AF
- Objectives:
  - Evaluate device performance and assess AEs
- Follow up visits:
  - Baseline, Procedure, Discharge, 1 & 6 months post procedure
- Rigorously executed with high level of data quality and integrity:
  - 100% of reported data has been monitored
  - Independent committee adjudicates all AEs
- Status:
  - Enrollment completed September 2011
  - 15 participating centers from Germany, Spain, UK, Ireland and Czech Republic
  - Final report on 204 pts, 1214 patient follow-up months

Device/Procedure Related Safety Events

	≤7 Days Post Procedure	>7 days Post Procedure	Total
Peri-procedural Stroke / TIA*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious Pericardial Effusion	3 (1.5%)	0 (0.0%)	3 (1.5%)
Device Embolization	3 (1.5%)	0 (0.0%)	3 (1.5%)
Device Related Thrombus	0 (0.0%)	5 (2.4%)	5 (2.4%)
Total Safety Events	**6 (2.9%)**	**5 (2.4%)**	**11 (5.4%)**

* The stroke/TIA is reference to device or procedure related strokes as adjudicated by the AE Review Committee.

N=204

Amplatzer Cardiac Plug. Efficacy

	Total Patients	Total Patient years	$CHADS_2$ Score	Estimated Stroke Rate per $CHADS_2$	Actual annual stroke rate (number of events)
ACP EU Observational	204	101 yrs	2.6	5.6%*	1.98% (N=2)

- 65% reduction in stroke risk from estimated stroke rate

The ACP® is an investigational device not for sale in the USA

ESC Guidelines for the management of AF

Recommendations for LAA closure/occlusion/excision

Recommendations	Class[a]	Level[b]	Ref[c]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B	115, 118

Key point

- Interventional percutaneous occlusion/closure of the LAA has a role in patients with thromboembolic risk who cannot be managed in the long-term using any form of OAC.

Camm A. et al Eur Heart J 2012

Conclusions for LAA closure

- Percutaneous closure of the LAA with the Watchman device is a safe and effective treatment modality to prevent stroke in patients with non-valvular AF
- ACP seems to have similar performance
- It ~~May~~ Should be considered in patients with CHADS score $\geq$ 2 and contra-indications to OAC, difficult OAC or adverse events in OAC.

Contemporaneous approach of the PFO: when intervention is indicated

AVC e FOP

AVC criptogênico *versus* Causa conhecida (~ pop geral)

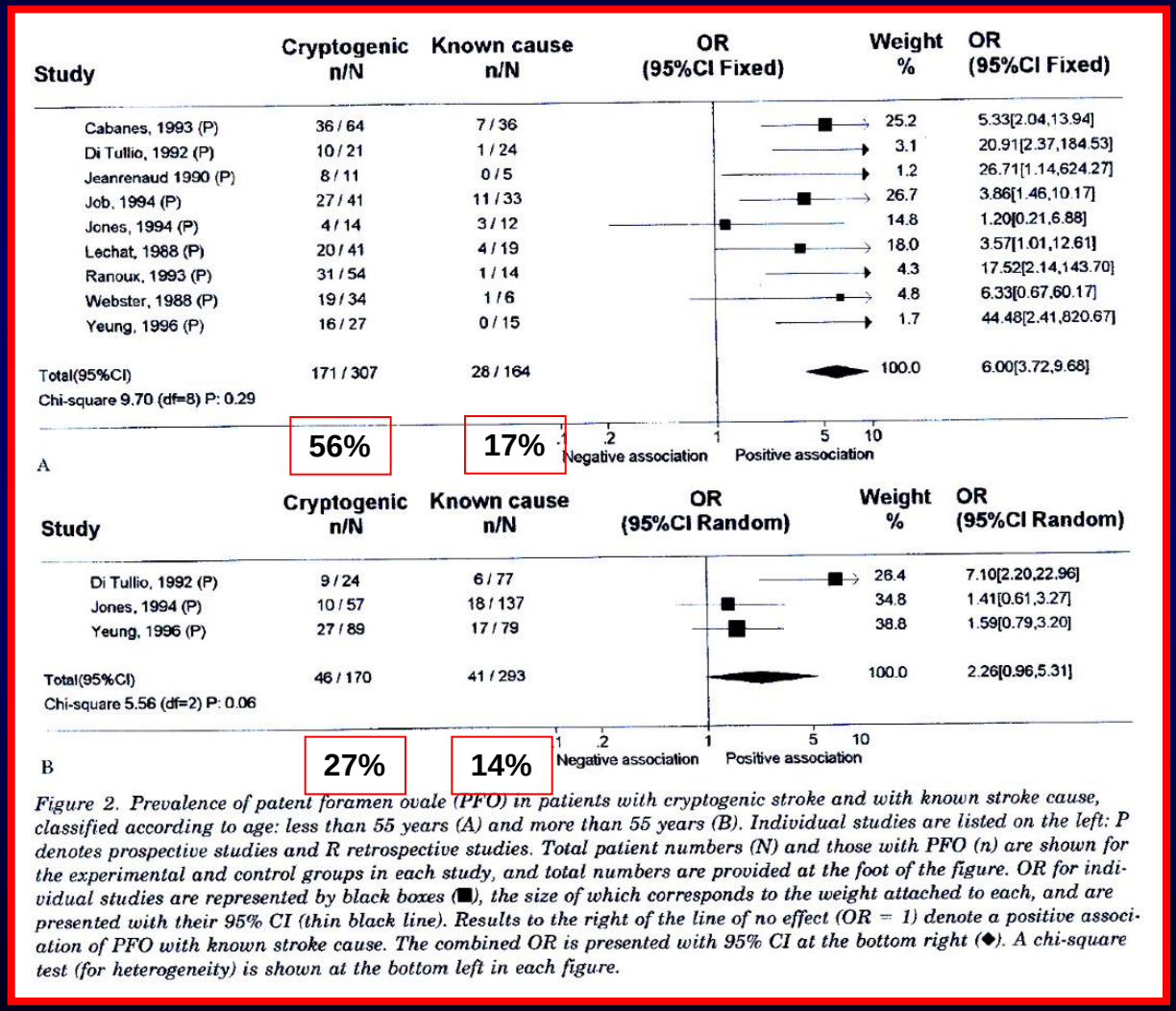


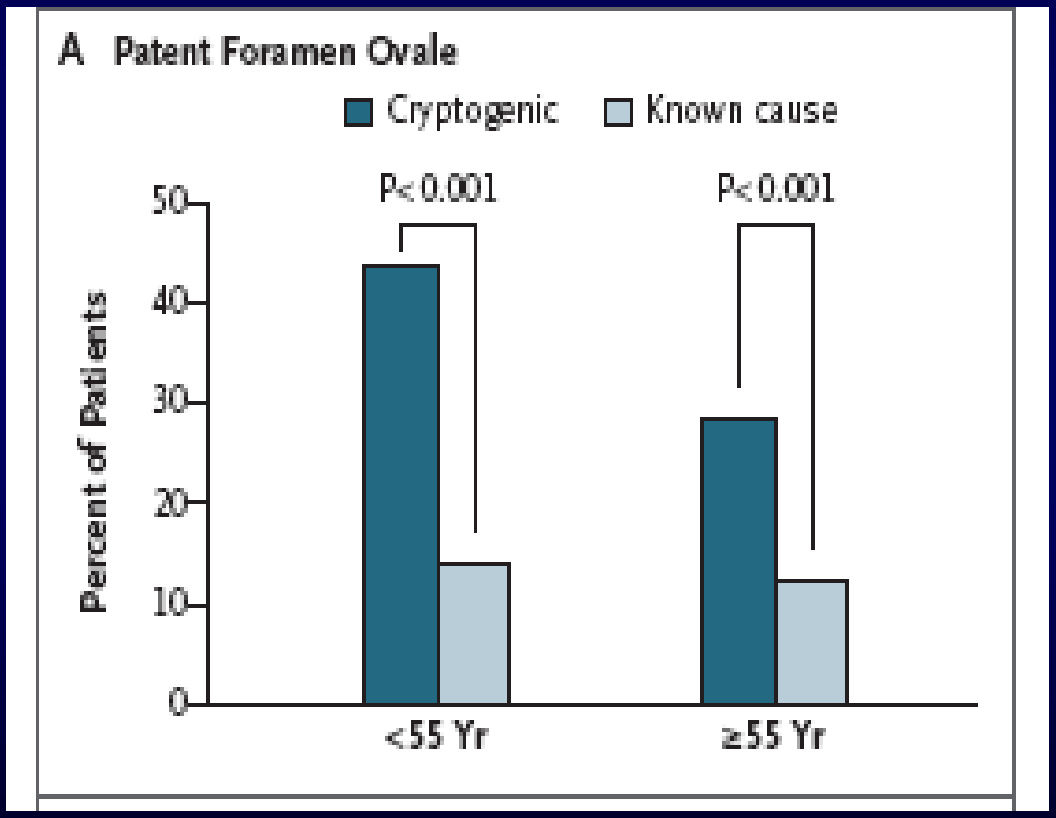
Figure 2. Prevalence of patent foramen ovale (PFO) in patients with cryptogenic stroke and with known stroke cause, classified according to age: less than 55 years (A) and more than 55 years (B). Individual studies are listed on the left: P denotes prospective studies and R retrospective studies. Total patient numbers (N) and those with PFO (n) are shown for the experimental and control groups in each study, and total numbers are provided at the foot of the figure. OR for individual studies are represented by black boxes (■), the size of which corresponds to the weight attached to each, and are presented with their 95% CI (thin black line). Results to the right of the line of no effect (OR = 1) denote a positive association of PFO with known stroke cause. The combined OR is presented with 95% CI at the bottom right (◆). A chi-square test (for heterogeneity) is shown at the bottom left in each figure.

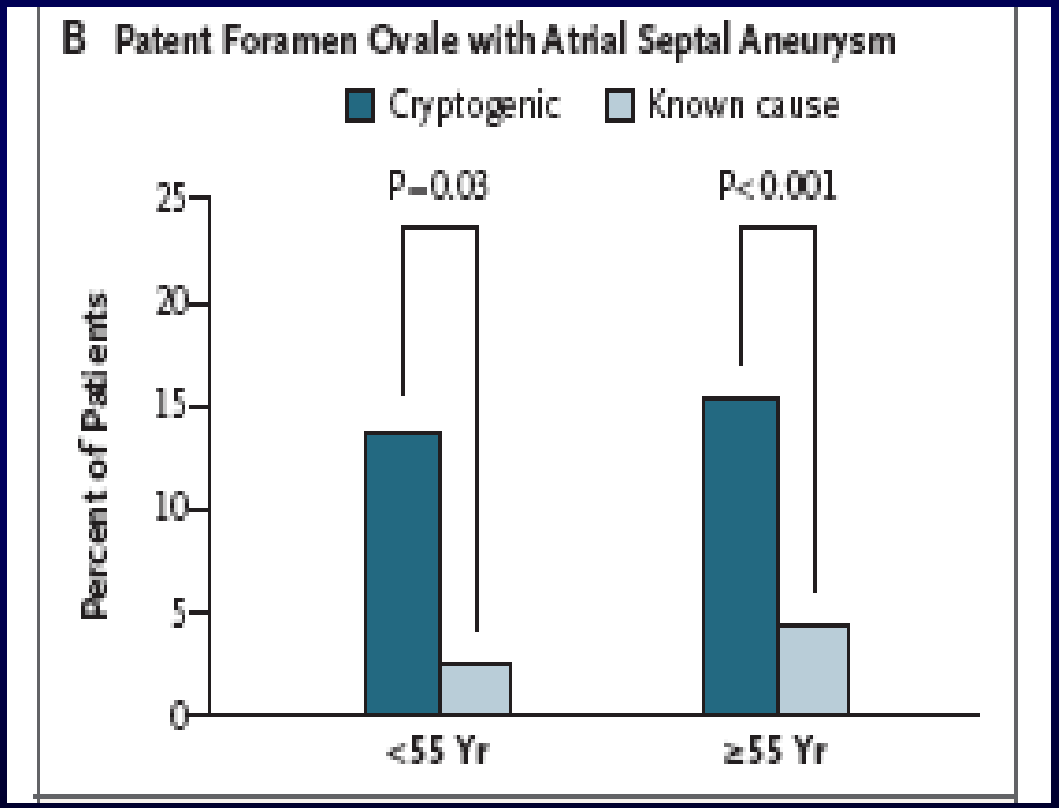
< 55 anos

> 55 anos

Overell JR et al. Neurology, 2000

Associação entre as anormalidade do SAI e AVC em pacientes com idade > 55 anos





Andke NEJM 2007

Distribuição do RoPE Score e FOP

POINT SCORE	A. Cryptogenic Stroke (N=3023)		
	Number of Patients	Prevalence of Patients with a PFO % (95% CI*)	PFO-Attributable Fraction % (95% CI*)
0-3	613	23% (19% to 26%)	0% (0% to 4%)
4	511	35% (31% to 39%)	38% (25% to 48%)
5	516	34% (30% to 38%)	34% (21% to 45%)
6	482	47% (42% to 51%)	62% (54% to 68%)
7	434	54% (49% to 59%)	72% (66% to 76%)
8	287	67% (62% to 73%)	84% (79% to 87%)
9-10	180	73% (66% to 79%)	88% (83% to 91%)

Thaler D et al; Trials 2013

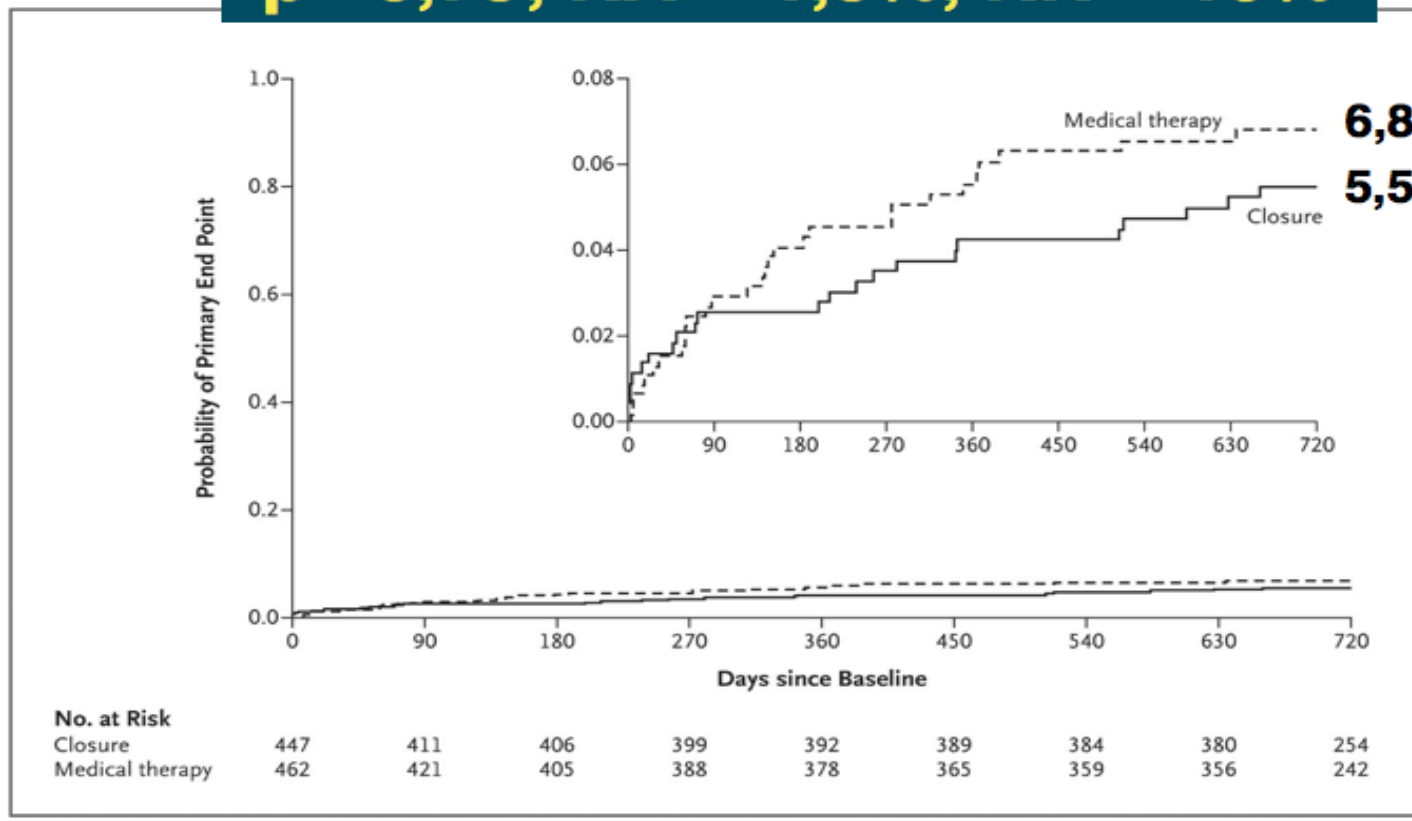
Diretrizes para AVC cripto e FOP

For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.	Class changed from IIa to I
For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A)*. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C)*.	New recommendations
For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure *(Class III; Level of Evidence A)*.	Class changed from IIb to III
In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C)*.	New recommendation

Stroke; May 2014

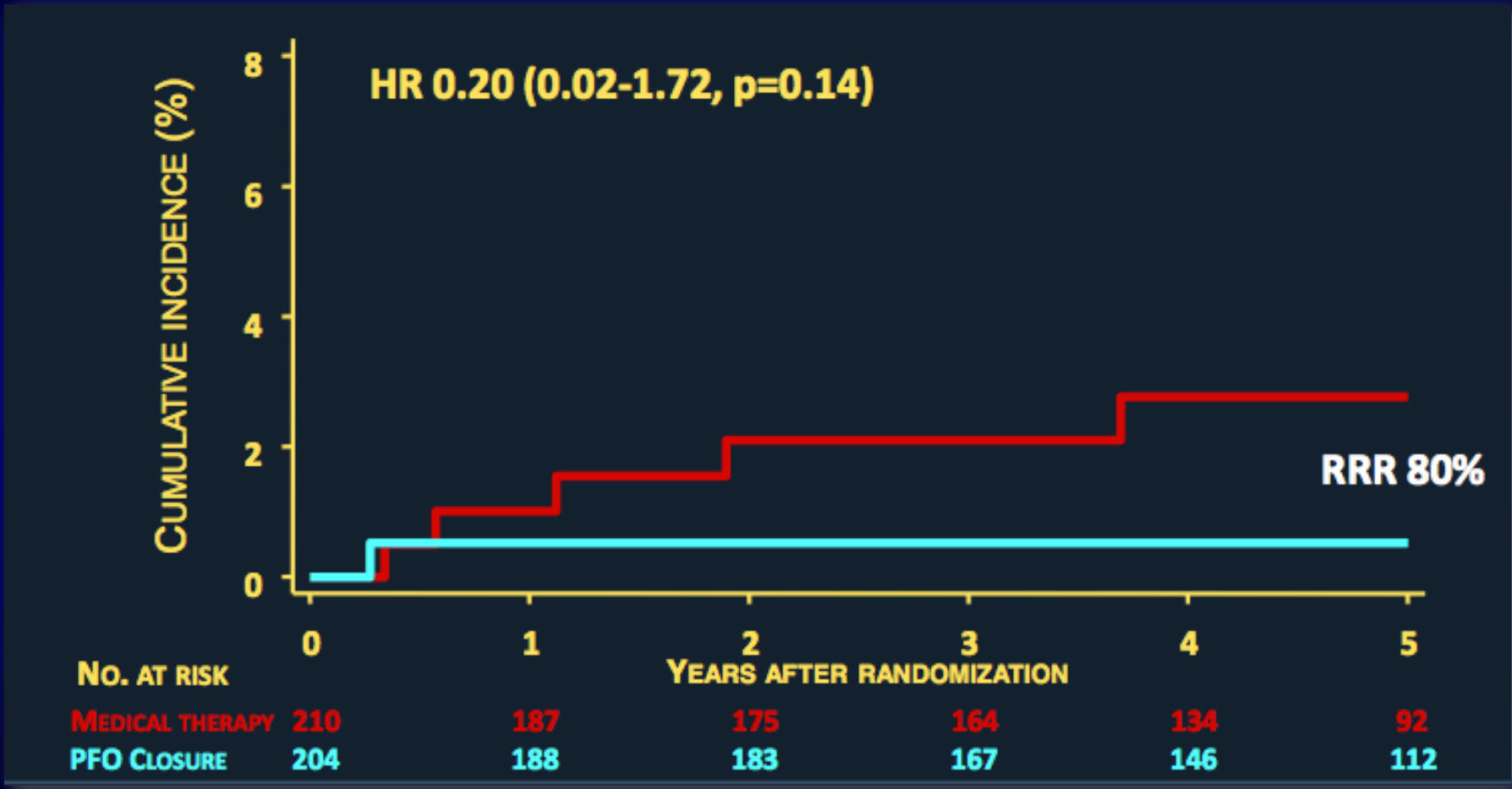
CLOSURE I - Desfecho primário AVC, AIT ou Morte

p= 0,73; RA= -1,3%, RR= -19%



Furlan AJ et al. N Engl J Med 2012;366:991-999

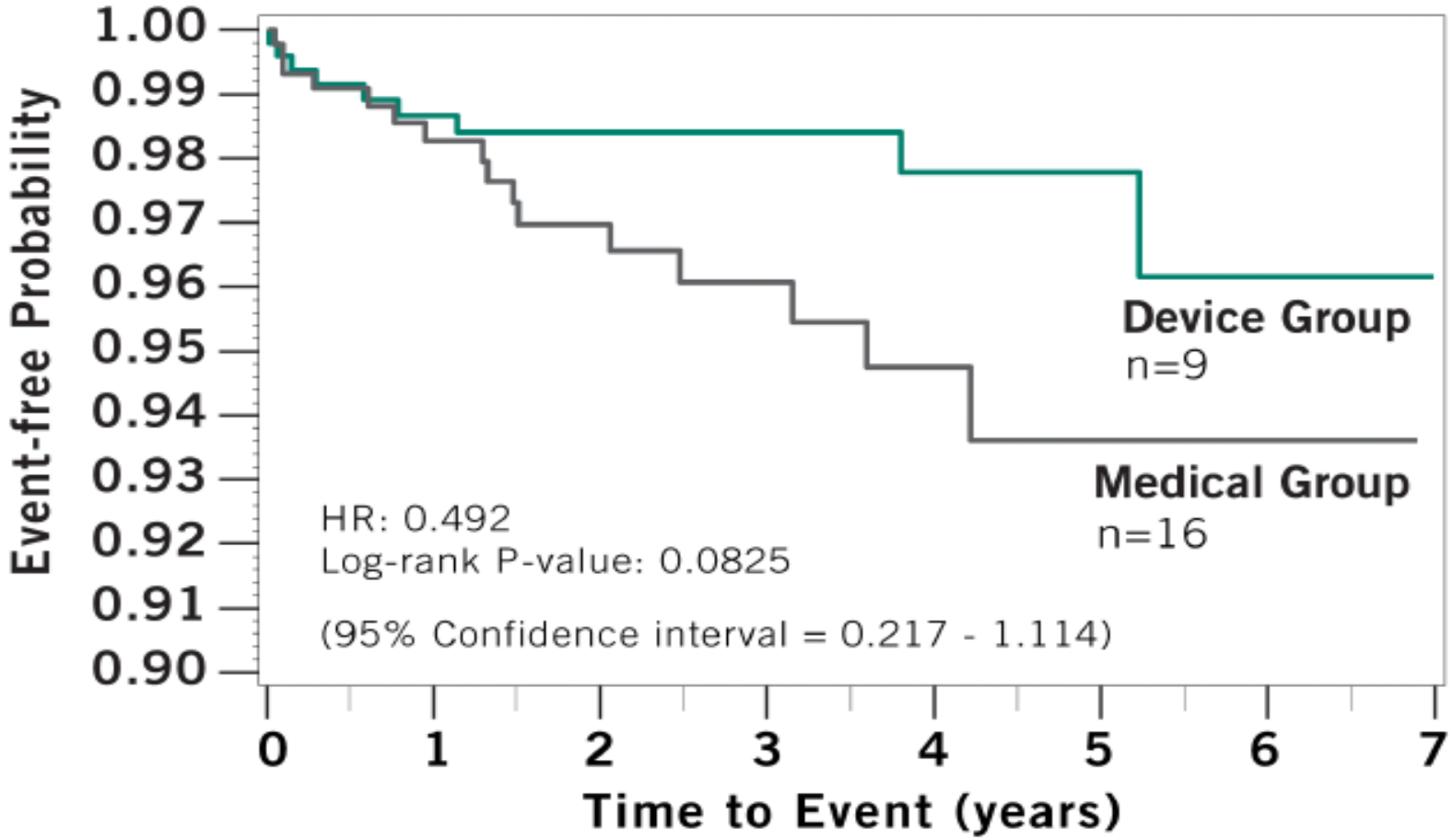
PC trial: Stroke incidence



Widecker S et al. NEJM 2013

Primary Endpoint Analysis – ITT Cohort

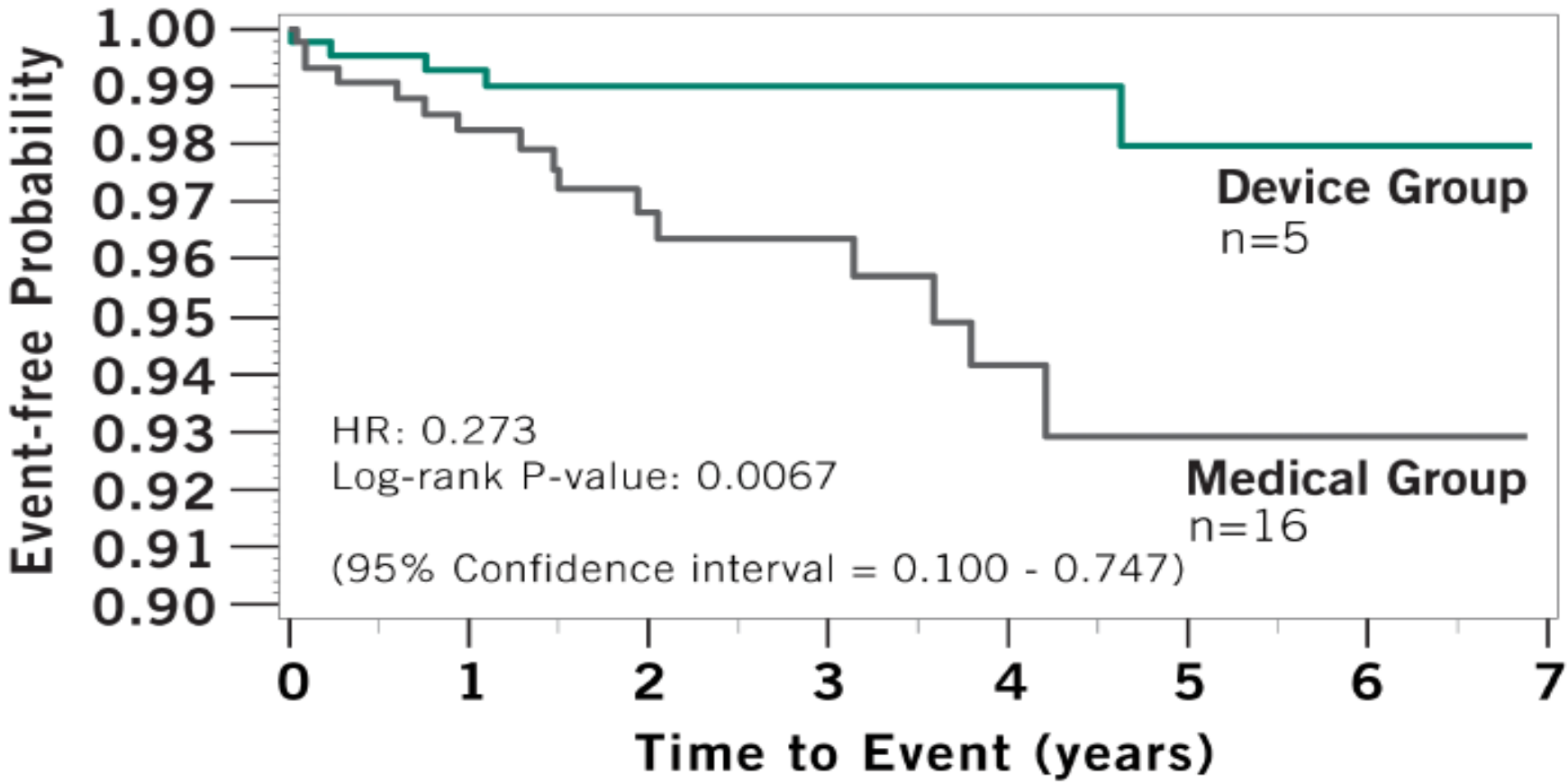
50.8% risk reduction of stroke in favor of device



- **3/9** device group patients did not have a device at time of endpoint stroke

1. Cox model used for analysis

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



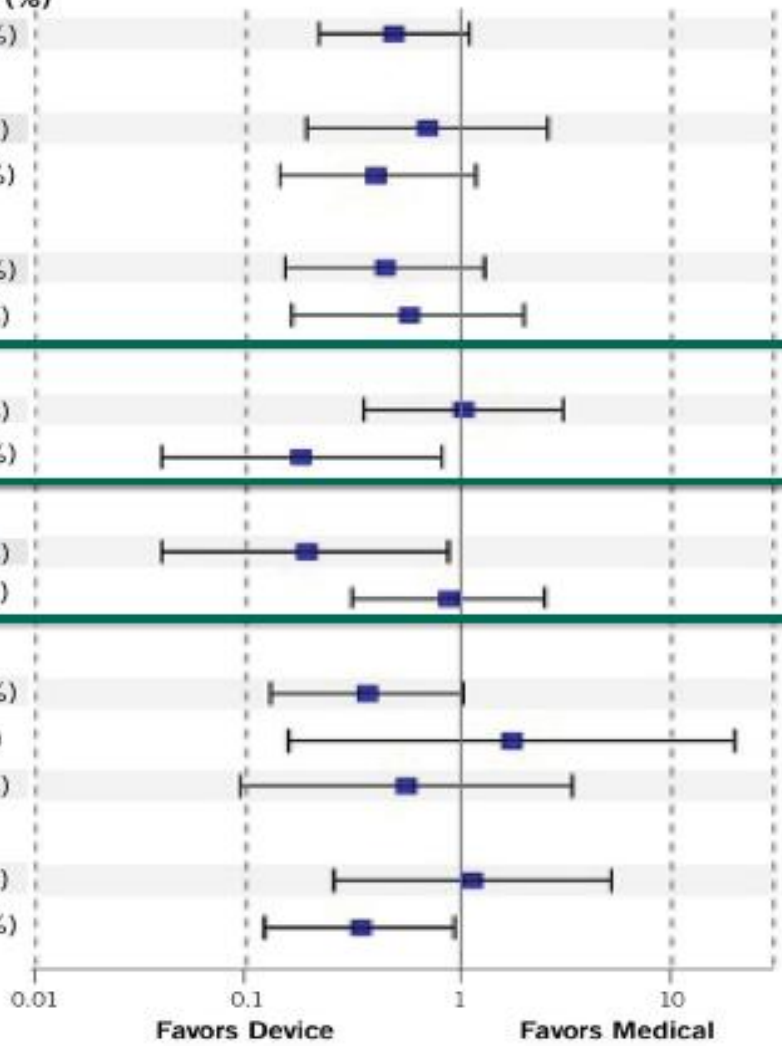
- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

1. Cox model used for analysis

Subpopulation Differential Treatment Effect

RESPECT CLINICAL TRIAL

Subgroup	Device Group	Medical Group	Hazard Ratio and 95% CI		Pvalue (Log Rank)	Interaction Pvalue
	no. of patients/total number (%)					
Overall	9/499 (1.8%)	16/481 (3.3%)		0.492 (0.217, 1.114)	0.0825	
Age						0.5156
- 18-45	4/230 (1.7%)	5/210 (2.4%)		0.698 (0.187, 2.601)	0.5901	
- 46-60	5/262 (1.9%)	11/266 (4.1%)		0.405 (0.140, 1.165)	0.0828	
Sex						0.7312
- Male	5/268 (1.9%)	10/268 (3.7%)		0.448 (0.153, 1.311)	0.1321	
- Female	4/231 (1.7%)	6/213 (2.8%)		0.571 (0.161, 2.024)	0.3789	
Shunt Size						0.0667
- None, trace or moderate	7/247 (2.8%)	6/244 (2.5%)		1.034 (0.347, 3.081)	0.9527	
- Substantial	2/247 (0.8%)	10/231 (4.3%)		0.178 (0.039, 0.813)	0.0119	
Atrial septal aneurysm						0.1016
- Present	2/180 (1.1%)	9/169 (5.3%)		0.187 (0.040, 0.867)	0.0163	
- Absent	7/319 (2.2%)	7/312 (2.2%)		0.889 (0.312, 2.535)	0.8259	
Index infarct topography						0.3916
- Superficial	5/280 (1.8%)	12/269 (4.5%)		0.366 (0.129, 1.038)	0.0487	
- Small Deep	2/57 (3.5%)	1/70 (1.4%)		1.762 (0.156, 19.93)	0.6429	
- Other	2/157 (1.3%)	3/139 (2.2%)		0.558 (0.093, 3.340)	0.5167	
Planned medical regimen						0.1966
- Anticoagulant	4/132 (3.0%)	3/121 (2.5%)		1.141 (0.255, 5.098)	0.8628	
- Antiplatelet	5/367 (1.4%)	13/359 (3.6%)		0.336 (0.120, 0.944)	0.0299	



Metanálise 3 ECR. Intenção de tratar

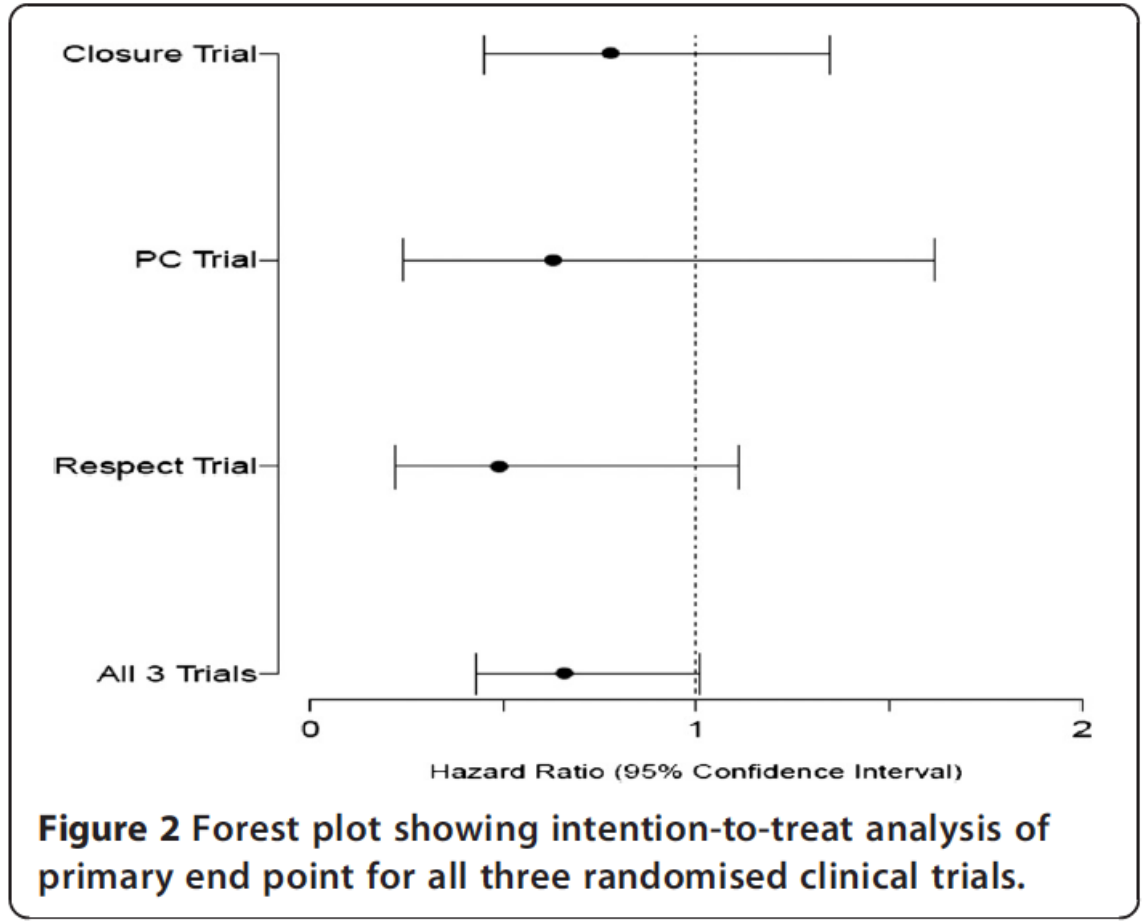


Figure 2 Forest plot showing intention-to-treat analysis of primary end point for all three randomised clinical trials.

Riaz et al. BMC Cardiovascular Disorders 2013, 13:116

Metanálise 3 ECR. Pelo Protocolo

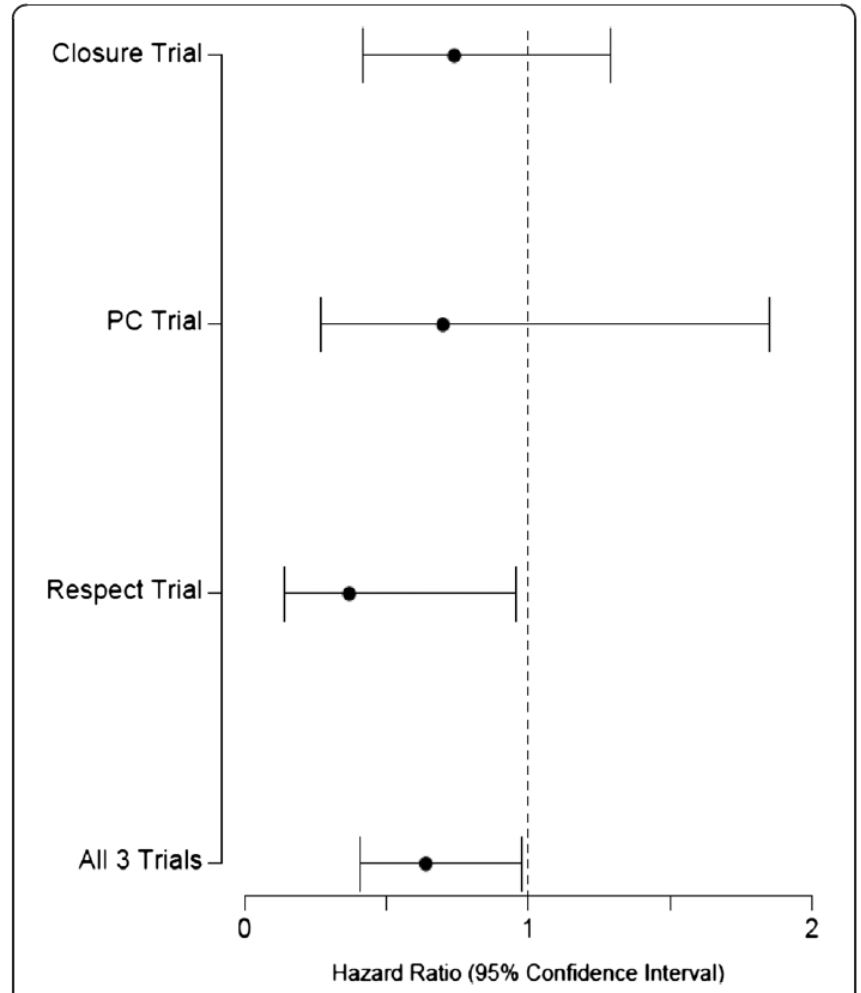


Figure 3 Forest Plot showing per-protocol analysis of primary end points for all three randomised clinical trials.

Riaz et al. BMC Cardiovascular Disorders 2013, 13:116

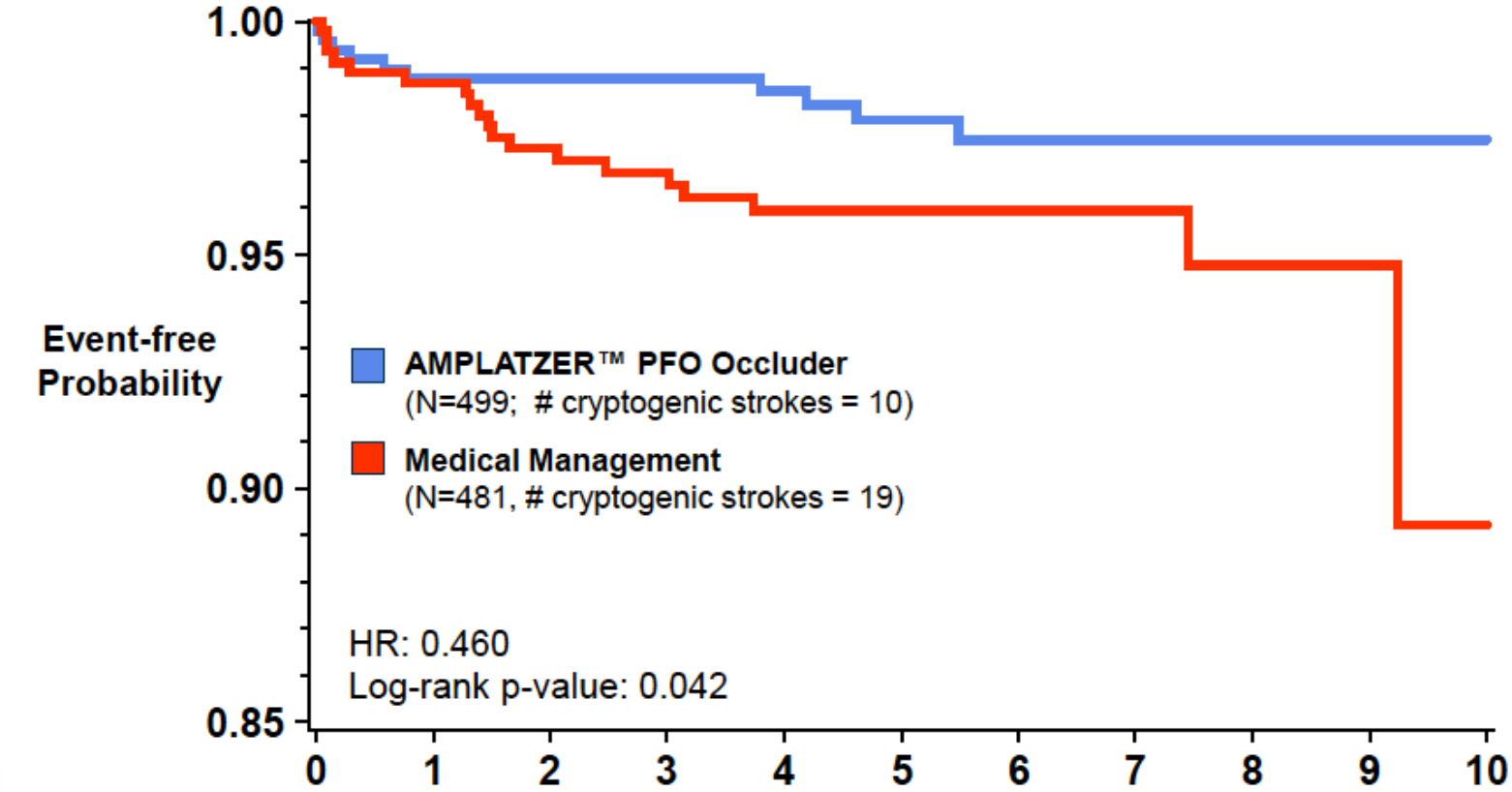
RESPECT Trial: Extended Follow-Up

- **Included:**
  - **Subjects with a PFO who have had a cryptogenic stroke within the last 270 days**
- **Excluded:**
  - **Subjects aged <18 years or >60 years**
- **Design:**
  - **980 subjects randomized:**
    - **499 AMPLATZER™ PFO Occluder versus**
    - **481 Guideline-directed medications**
- **Results at TCT 2015:**
  - **The longest follow-up ever conducted in the largest randomized trial: Mean > 5 years with trial duration over 10 years.**

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

Significant Reduction in Recurrent Cryptogenic Stroke

54% Relative Risk Reduction in ITT Population

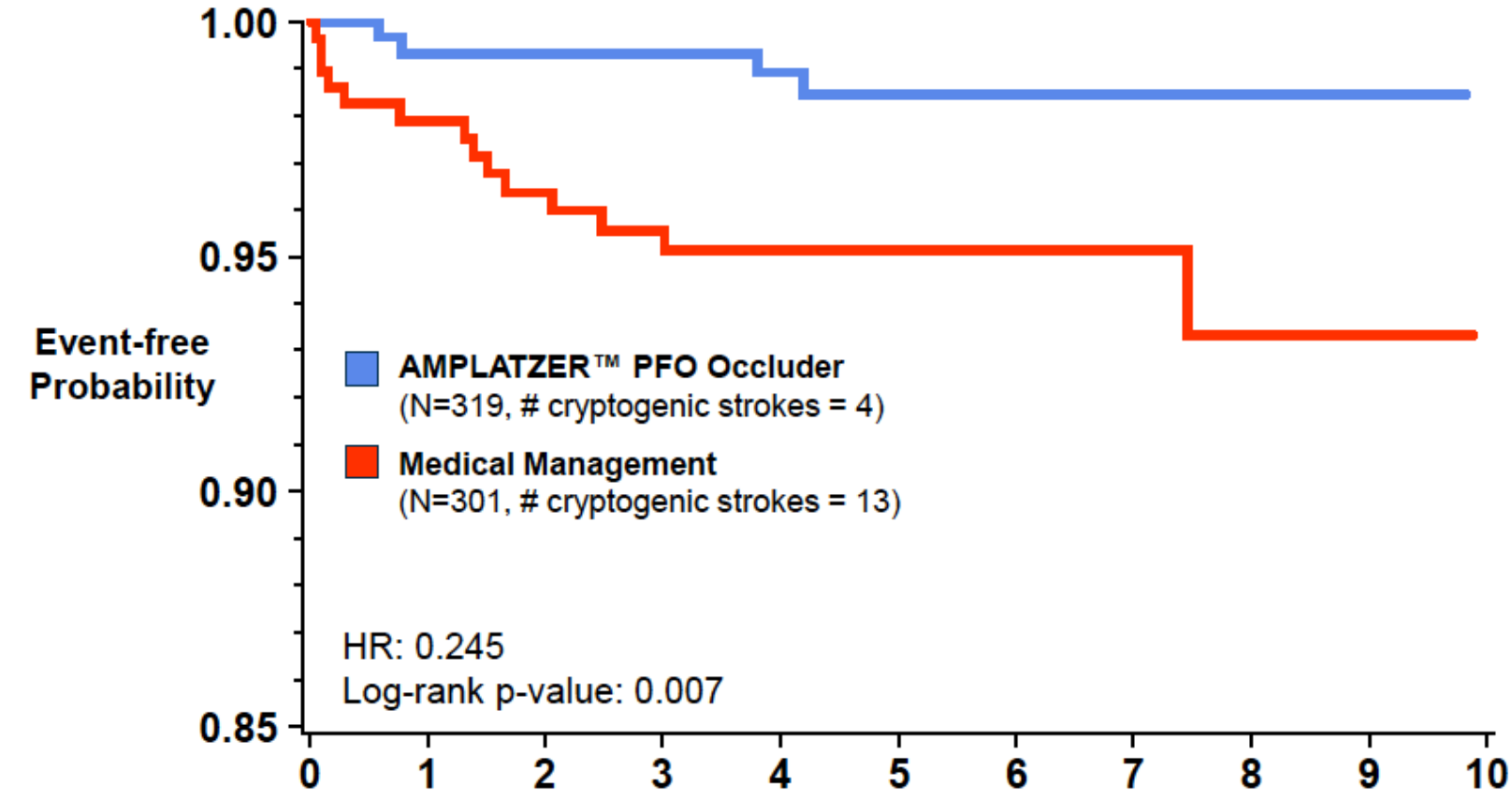


 # at Risk (KM Estimates)

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%)

Additional 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%)

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

No intra-procedure strokes

No device embolization

No device thrombosis

No device erosion

FDA Panel Meeting

Brief Summary of the Circulatory System Devices Panel Meeting – May 24, 2016

Vote:
The panel voted on the safety, effectiveness, and risk benefit ratio of the AMPLATZER™ PFO Occluder.

On Question 1, the panel voted 15-1 that the data show a reasonable assurance that the AMPLATZER™ PFO Occluder is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 9-7 that there is reasonable assurance that the AMPLATZER™ PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 11-5 that the benefits of the AMPLATZER™ PFO Occluder outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Several panelists noted that their positive vote reflected their belief that the PFO Occluder should be available for selected patients with a PFO and cryptogenic stroke with a recommendation that the final labeling help identify patients who could potentially benefit from the device.

Conclusions for PFO closure

- Based on the current available evidence it seems that transcatheter closure of the PFO should be indicated to prevent recurrent ischemic strokes in patients in whom the PFO is the most likely “culprit”, especially in the younger population (< 55-60 years of age), with no or few other risk factors.
- Patients with substantial shunt across the defect and/or with ASA association are the most benefited from the procedure.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Thank you !!


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