18th ANGIOPLASTY SUMMIT-TCTAP 2013
Seoul, Korea, April 23-26, 2013

Clinical Trials for PFO Closure: Lessons Learnt and Future Perspectives

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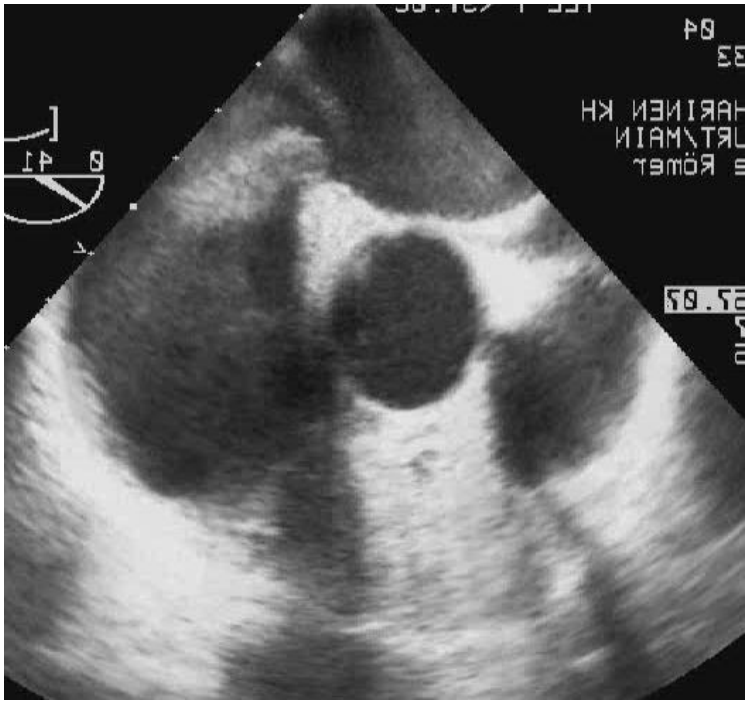
Frankfurt, Germany

We know

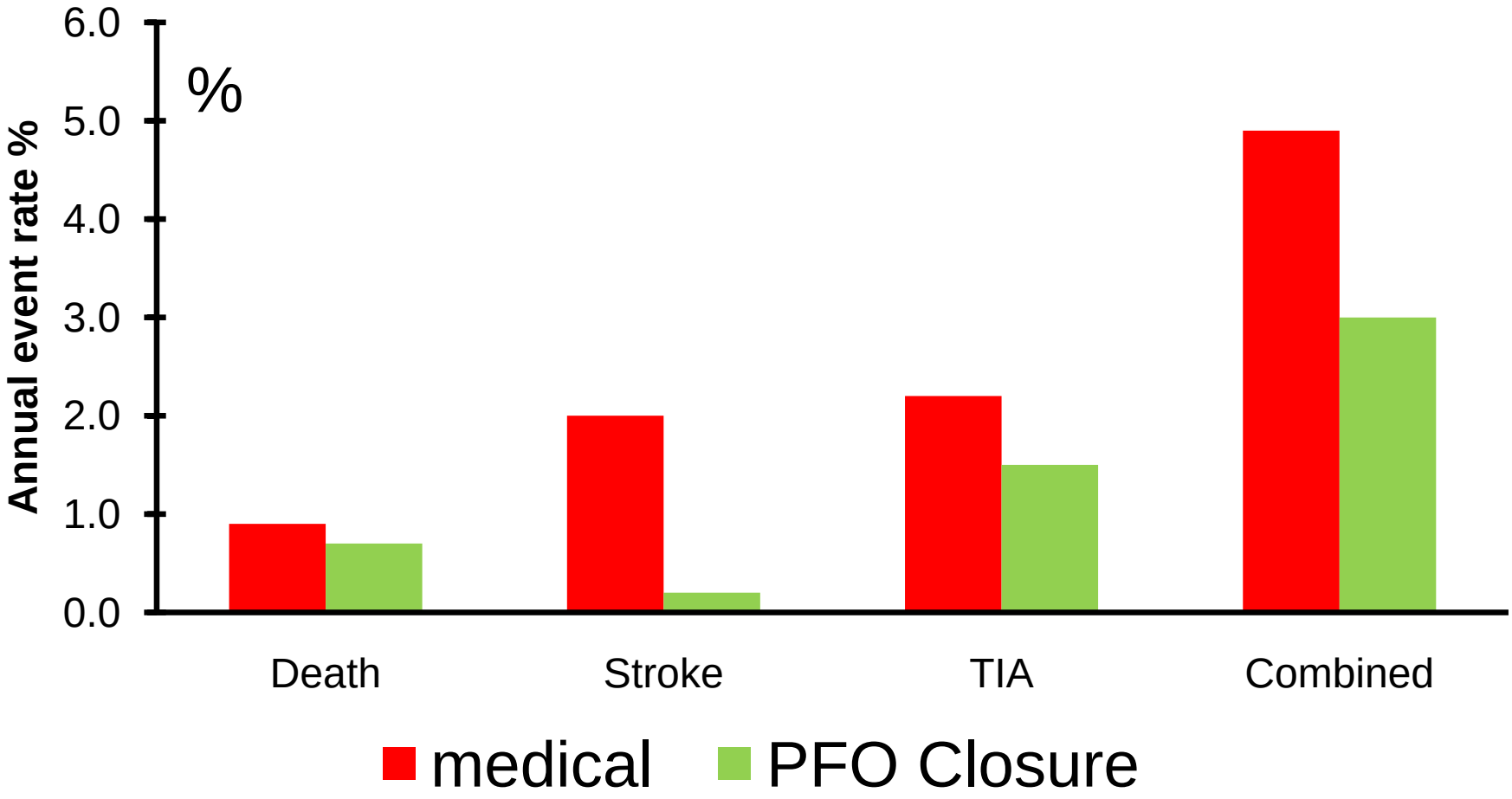
- … that a PFO can cause stroke
- … that this is due to paradoxical embolism



- Do we have enough evidence to close PFOs?

Meta-analysis of Event Rates in Patients with Cryptogenic Stroke

- 12 studies with 943 medically treated cryptogenic stroke pts (mean age 45 years, mean F/U 34 mos)
- 12 studies with 1,430 stroke pts after PFO closure (mean age 46 years, mean F/U 18 mos)



Homma S et al. Circulation 2005

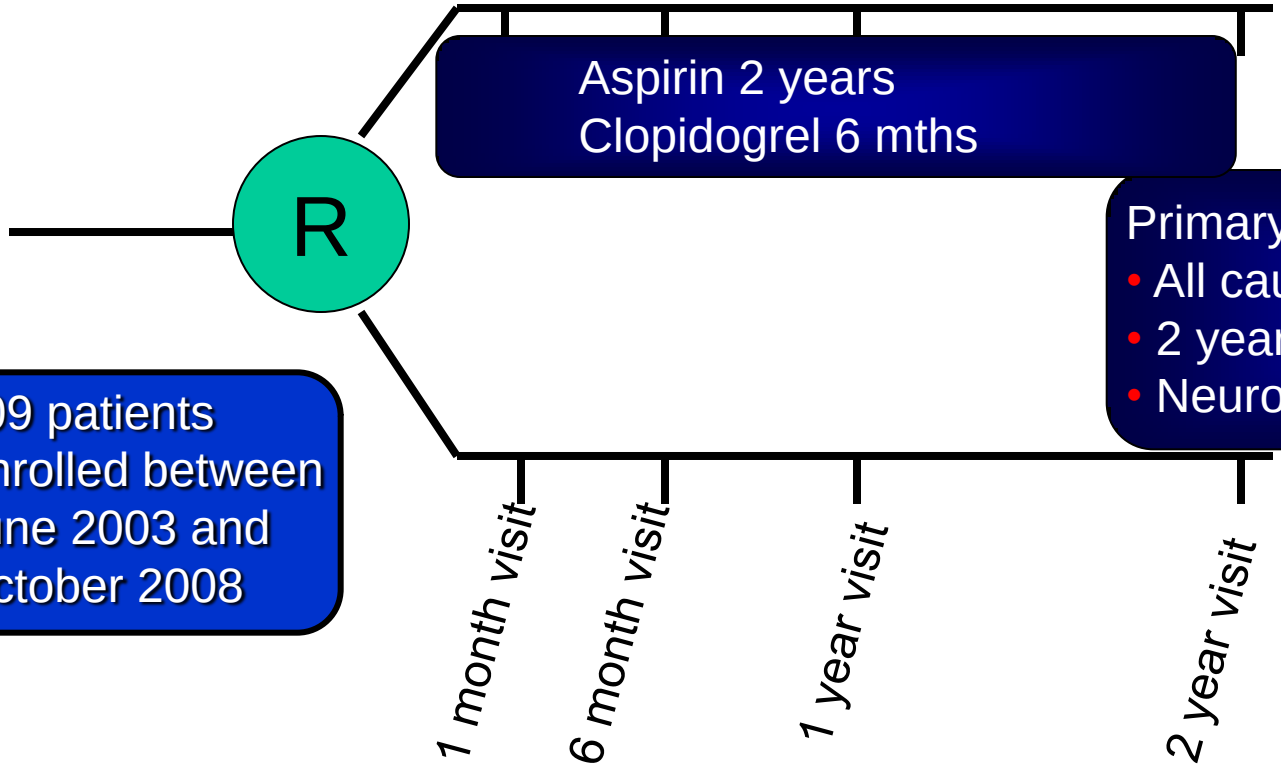
And Randomized Trials?

CLOSURE I

Inclusion
- Age 18-60 yrs
- Cryptogenic stroke or TIA

Exclusion
- DVT
- Hypercoagulopathy

Device Group: Starflex Occuder and Aspirin



Primary End points
- All cause death at 30 days
- 2 year Stroke or TIA
- Neurological death >30 days

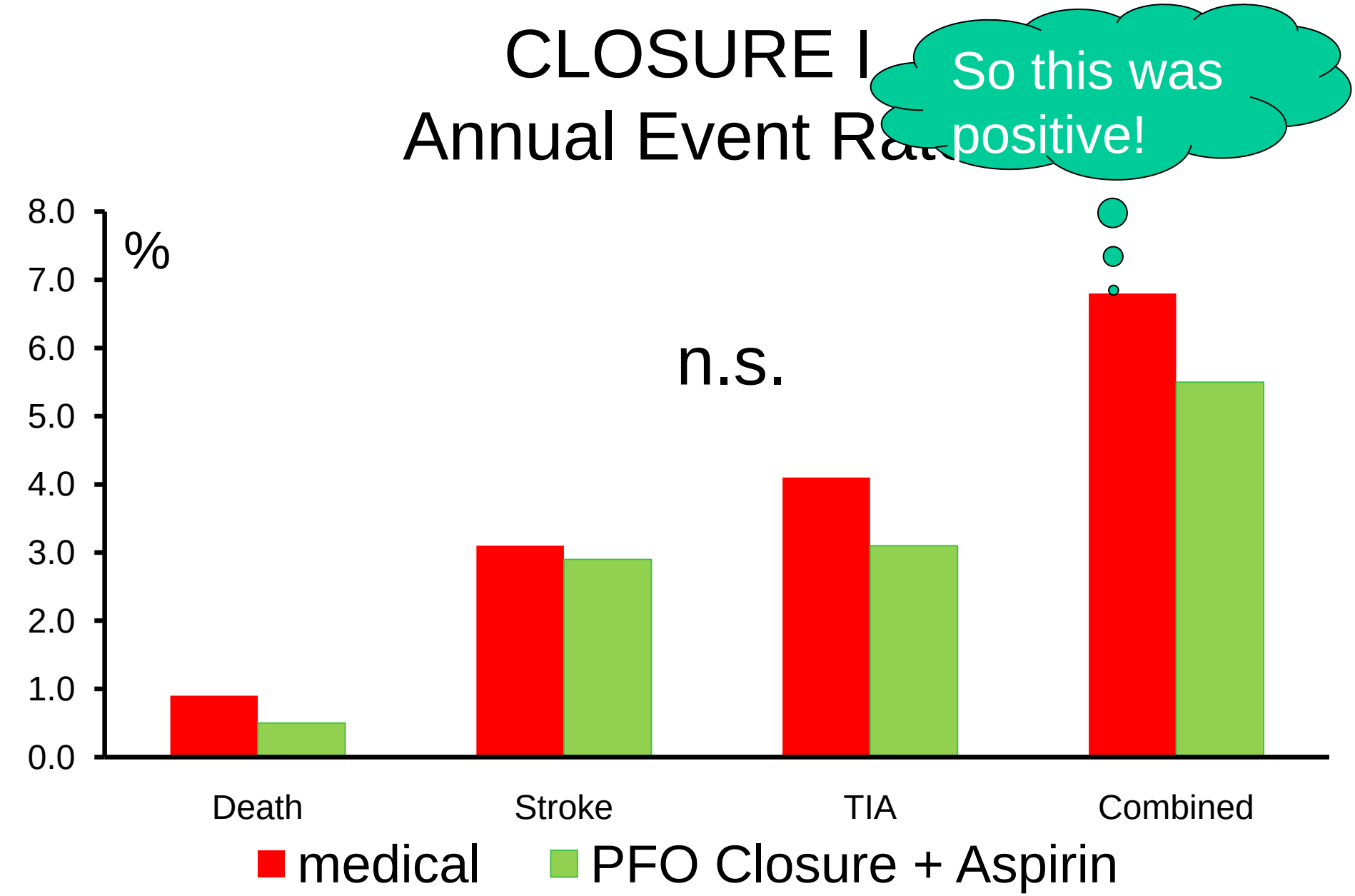
909 patients Enrolled between June 2003 and October 2008

Control Group: Aspirin and/or Coumadin 2 years

Superiority Study

J. Furlan, AHA 2010

CLOSURE I
Annual Event Rat



AJ Furlan, AHA 2010

How about safety?

CLOSURE I
Investigating the PFO Stroke Connection

Safety
Adverse Events

	STARFlex N=402	Medical N=458	P value
Major vascular complications*	3.2% (n =13)	0.0%	<0.001
Atrial fibrillation	5.7% (n= 14/23 periprocedural)	0.7% (n=3)	<0.001
Major bleeding	2.6% (n=10)	1.1% (n=4)	0.11
Deaths (all non endpoint)	0.5% (n=2)	0.7% (n=3)	ns
Nervous system disorders	3.2% (n=12)	5.3% (n=20)	0.15
Any SAE	16.9% (n=68)	16.6% (n=76)	ns

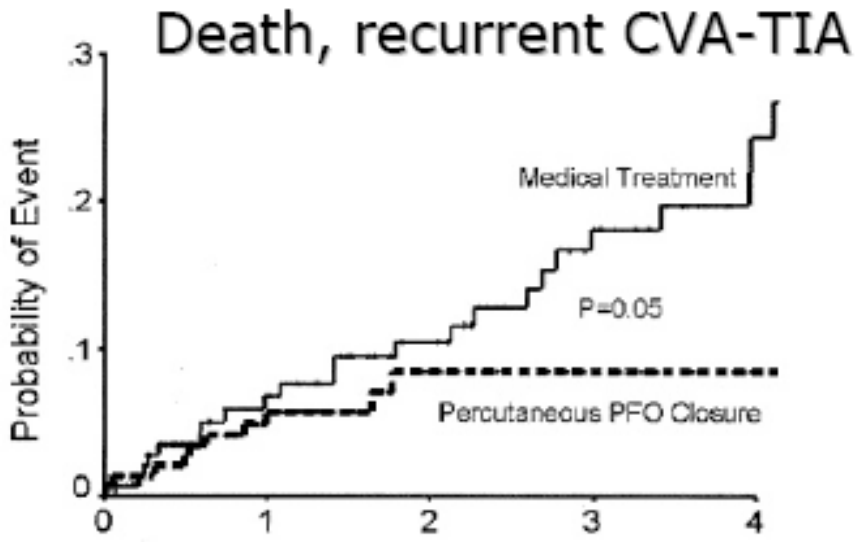
*Perforation LA (1); hematoma >5cm at access site (4); vascular surgical repair (1); peripheral nerve injury (1); procedural related transfusion (3);retroperitoneal bleed (3)

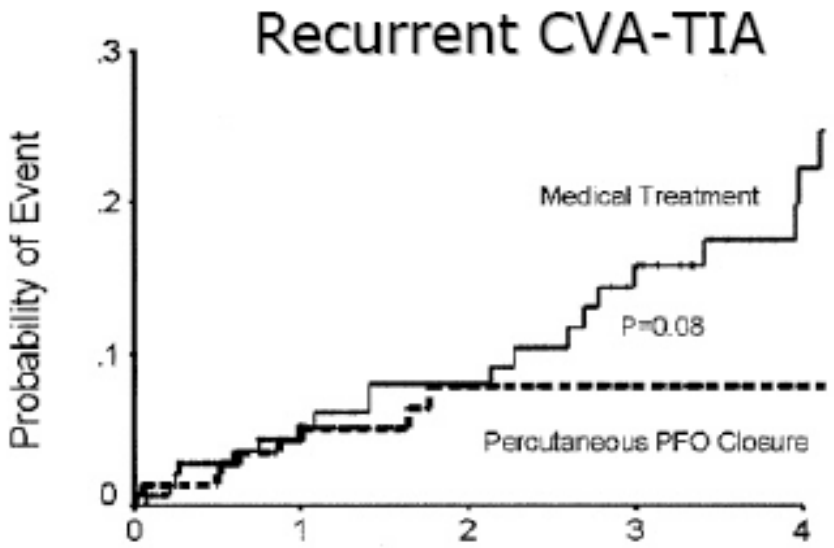
"CLOSURE I was negative"

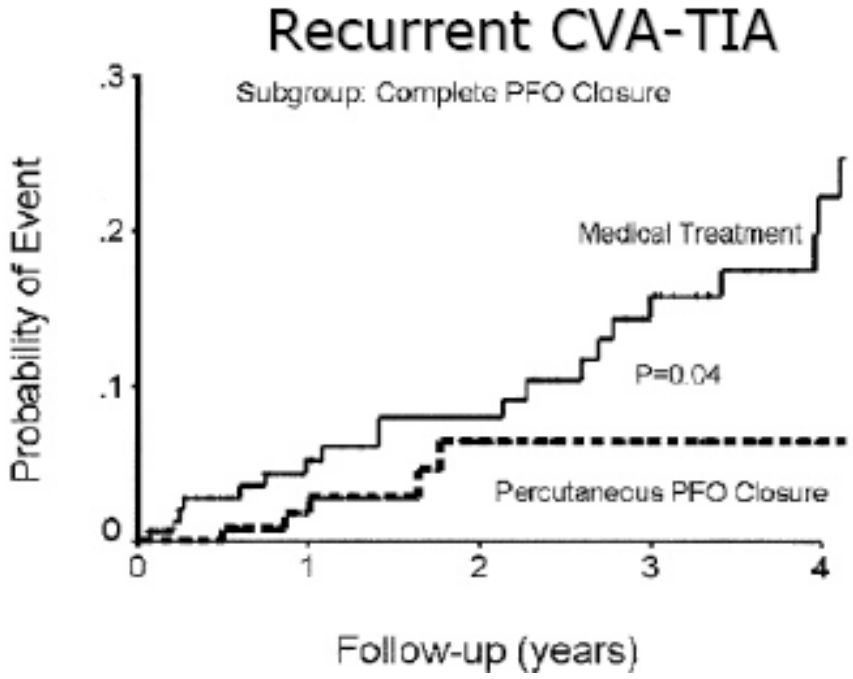
What went wrong?

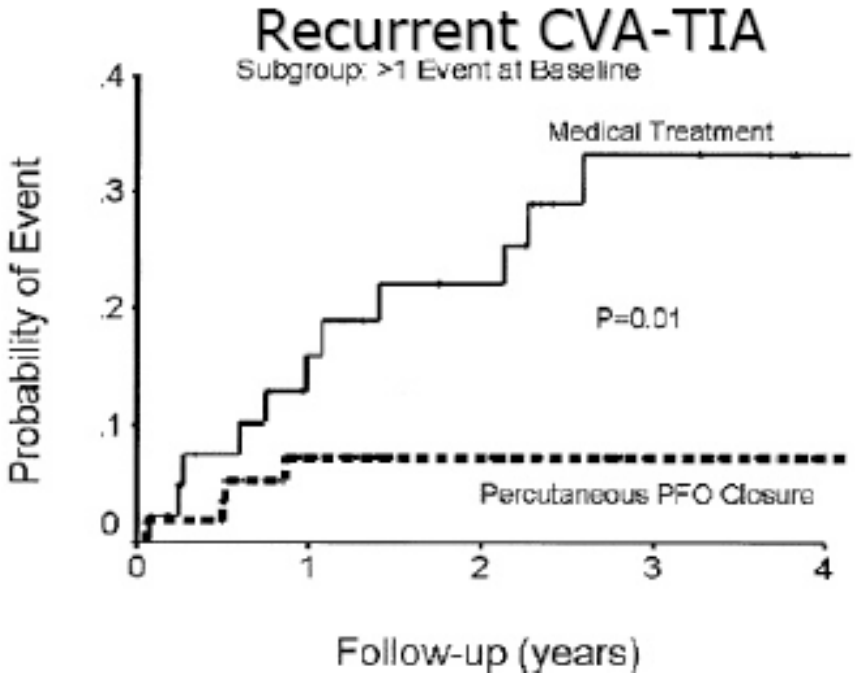
Reasons why CLOSURE I failed

1. Superiority study design was more than what was needed
2. To exclude DVT and hypercoagulopathy from PFO closure was a mistake
   - These patients would benefit most
4. Very slow enrolment
   - only 2 patients/year/center
   - There must have been a selection bias
5. Patient number too small
   - Assumptions (6% vs 2 % event rate) too optimistic
6. Follow-up too short
   - Patients go for PFO closure because they want to avoid 30 yrs of anticoagulation









Windecker, JACC 2004

Randomized trial parachute vs control group

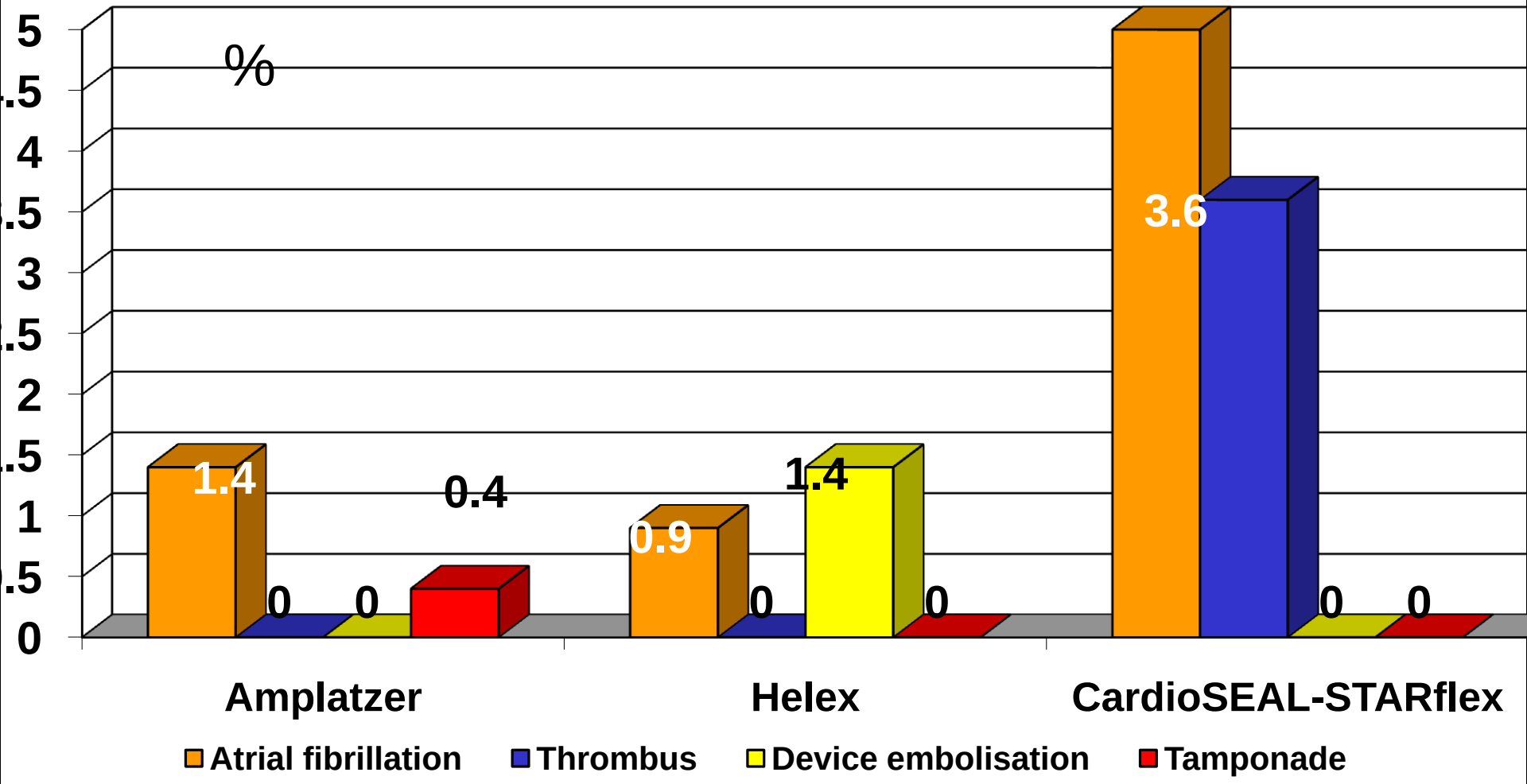
- Stopped after 500 m of free fall
- No significant difference between parachute and control
- Conclusion: parachutes are not effective

Reasons why CLOSURE I failed

7. Some strange findings in the control group
   - Higher event rate in small PFOs
   - Higher event rate in PFOs without septal aneurysm
8. Some operators had been at the beginning of their learning curve
9. Technology outdated
   - We know from many trials that Cardioseal has a higher rate of afib and clot formation than other devices

30 Day Outcome of PFO Closure

660 PFO-Patients, Randomized to 3 Devices



Am J Cardiol. 2008;101:1353-8

Reasons why CLOSURE I failed

10. Long-term anticoagulation therapy in general does not work
    - Stopping rate for warfarin is >70% after only 5 years
11. Very high complication and event rate in the device group compared to the literature

Any good from CLOSURE I?

- There was a trend towards less events after PFO closure compared to medical therapy after only 2 yrs
- Despite the high complication rate PFO closure was as safe as medical therapy
- Medical therapy is approved – so PFO closure should also be approved ...
  - ... and it is in most countries!

The Final Results with Primary End Point Analyses

RESPECT

CLINICAL TRIAL

RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

JOHN D. CARROLL, MD, JEFFREY L. SAVER, MD, DAVID E. THALER, MD, PHD, RICHARD W. SMALLING, MD, PHD, SCOTT BERRY, PHD, LEE A. MACDONALD, MD, DAVID S. MARKS, MD, MBA, DAVID L. TIRSCHWELL, MD

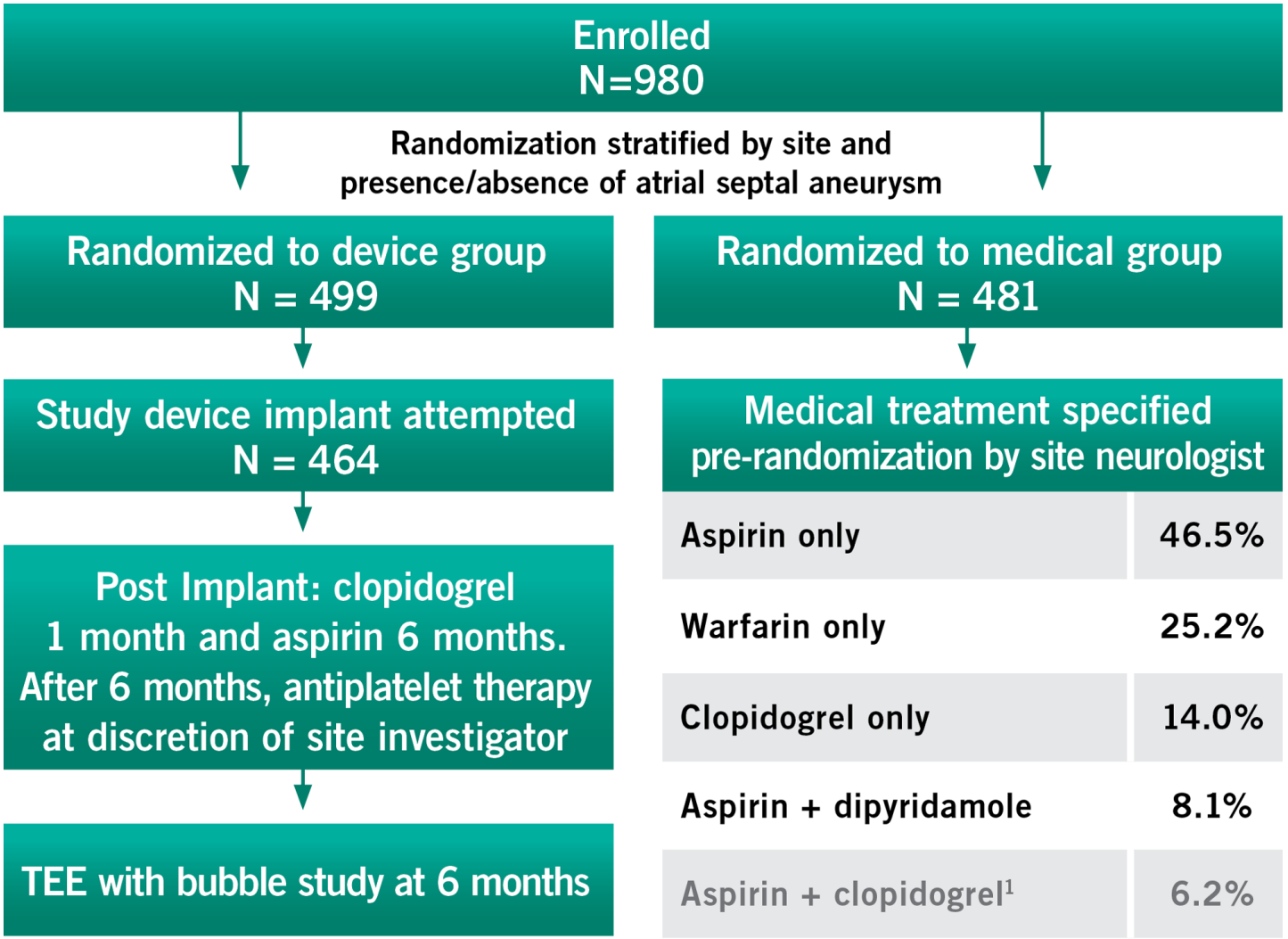
FOR THE RESPECT INVESTIGATORS

- Primary Endpoints
  - ischemic stroke
  - death within 45 days
- Estimated rate of primary efficacy events at 2 years was 4.3% in the medical group and 1.05% in the device group
- Study duration: stop after 25 primary endpoint events

AMPLATZER PFO Occluder

Subject Distribution

RESPECT CLINICAL TRIAL



Medical treatment specified pre-randomization by site neurologist	
Aspirin only	46.5%
Warfarin only	25.2%
Clopidogrel only	14.0%
Aspirin + dipyridamole	8.1%
Aspirin + clopidogrel[1]	6.2%

1. Aspirin + clopidogrel was removed from the protocol in 2006 based on changes to the AHA/ASA treatment guidelines

Serious Adverse Events Adjudicated as Related to Procedure, Device, or Study

RESPECT CLINICAL TRIAL

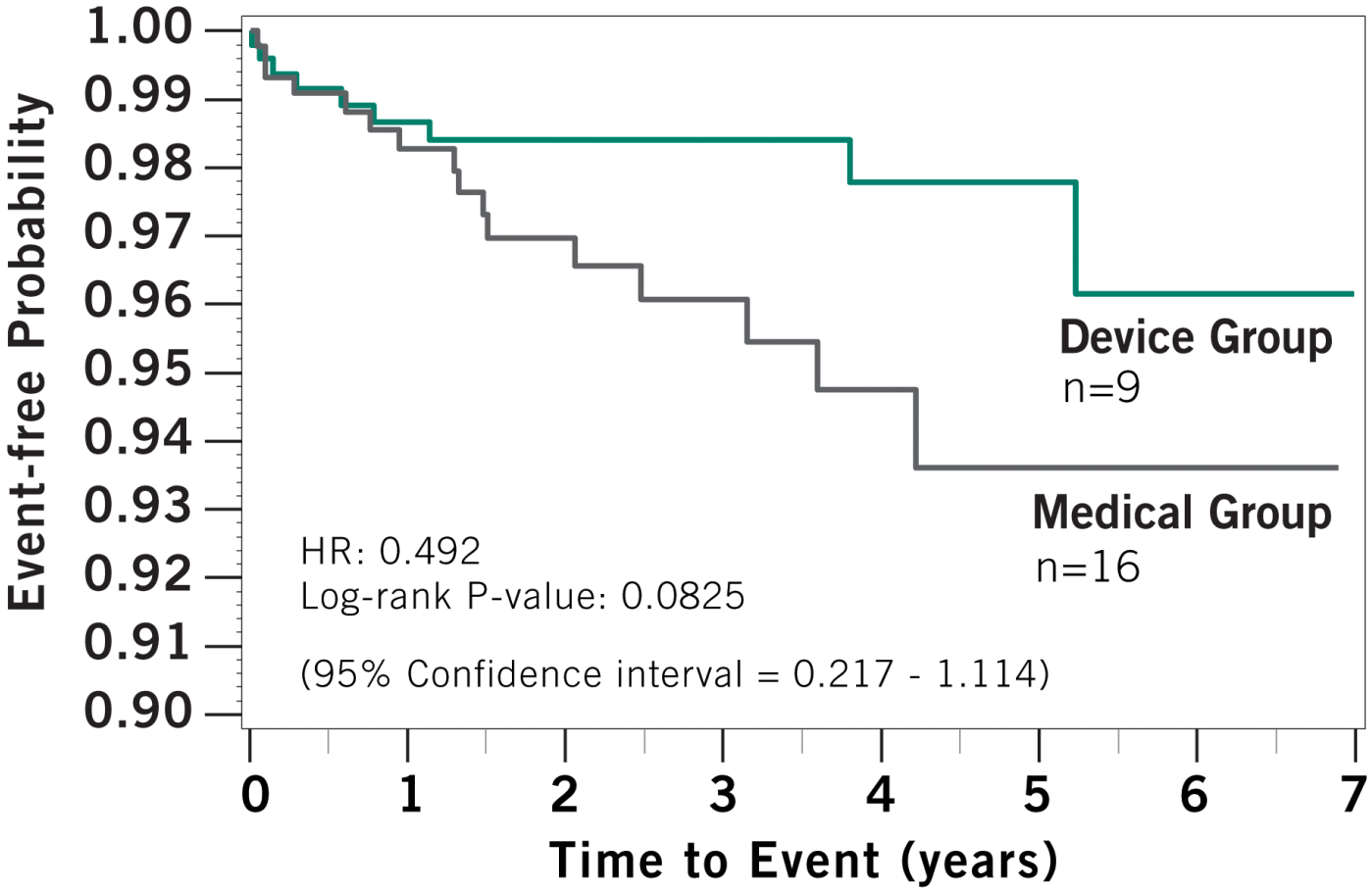
Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value[7]
Thrombus on device	0 (0%)	N/A	N/A
Device embolization	0 (0%)	N/A	N/A
Atrial fibrillation[1]	3 (0.6%)	3 (0.6%)	1
Transient ischemic attack (TIA)	3 (0.6%)	3 (0.6%)	1
Major bleeding	8 (1.6%)	9 (1.9%)	0.810
Pericardial tamponade (procedure related)[2]	2 (0.4%)	N/A	N/A
Major vascular complications	4 (0.8%)	0 (0%)	0.124
Pulmonary embolism[3]	1 (0.2%)	0 (0%)	1
Cardiac thrombus[4]	2 (0.4%)	0 (0%)	0.500
Ischemic stroke[5]	2 (0.4%)	N/A	N/A
Death[6]	0 (0%)	0 (0%)	N/A

1. For all AE's, atrial fibrillation occurred in 3.0% versus 1.5% in the device and medical groups respectively, p=0.13
2. Pericardial
3. For all SAE
4. 1 case of r
   detected ir
5. 1 ischemic
6. For all SAEs, there were 3 device group deaths (0.6%) and 6 medical group deaths (1.2%) all of which were not study related, p= 0.334
7. P-values are calculated using Fisher's Exact test

PFO closure is as safe as medical therapy

Primary Endpoint Analysis – ITT Cohort

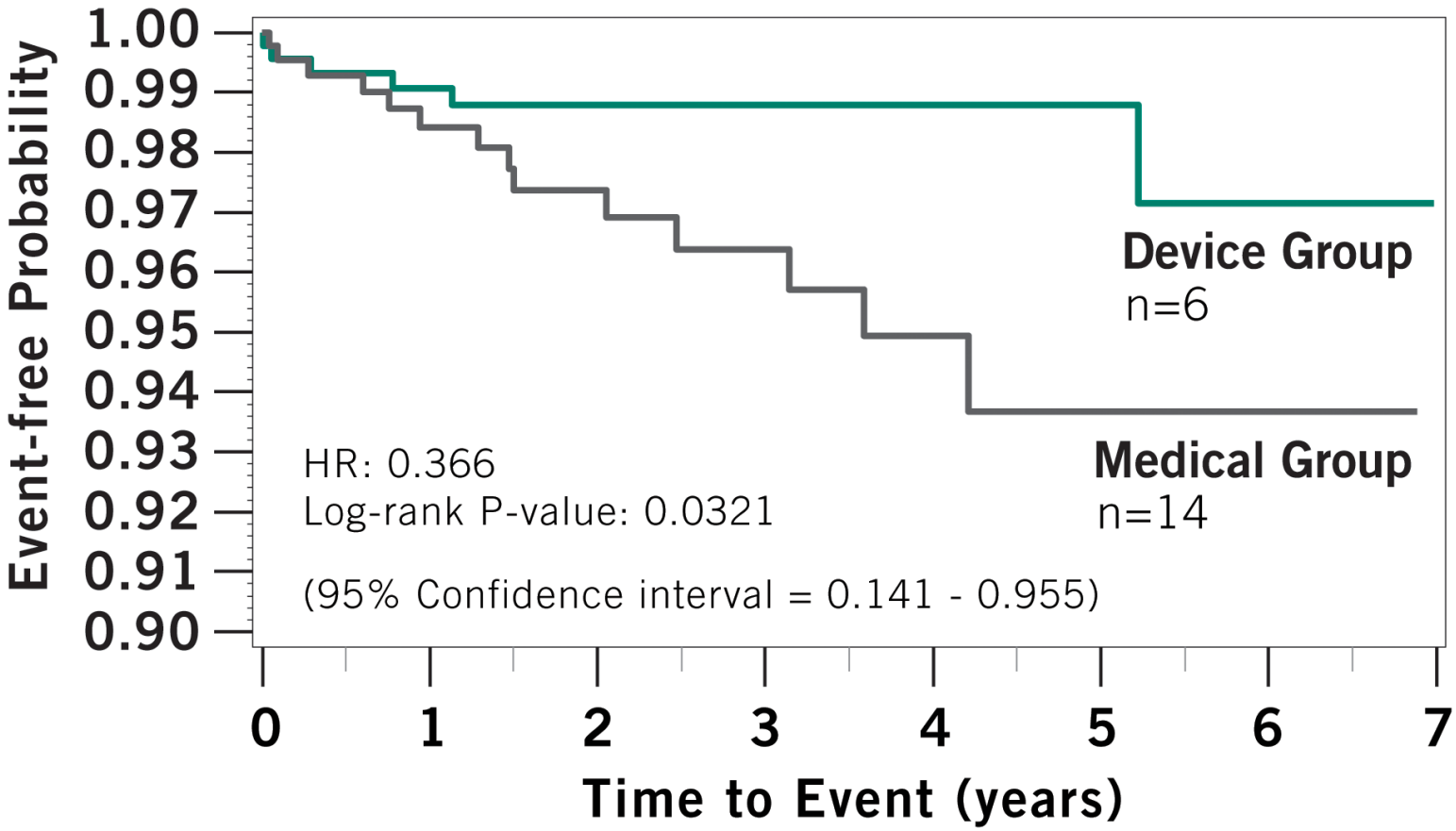
50.8% risk reduction of stroke in favor of device



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

1. Cox model used for analysis

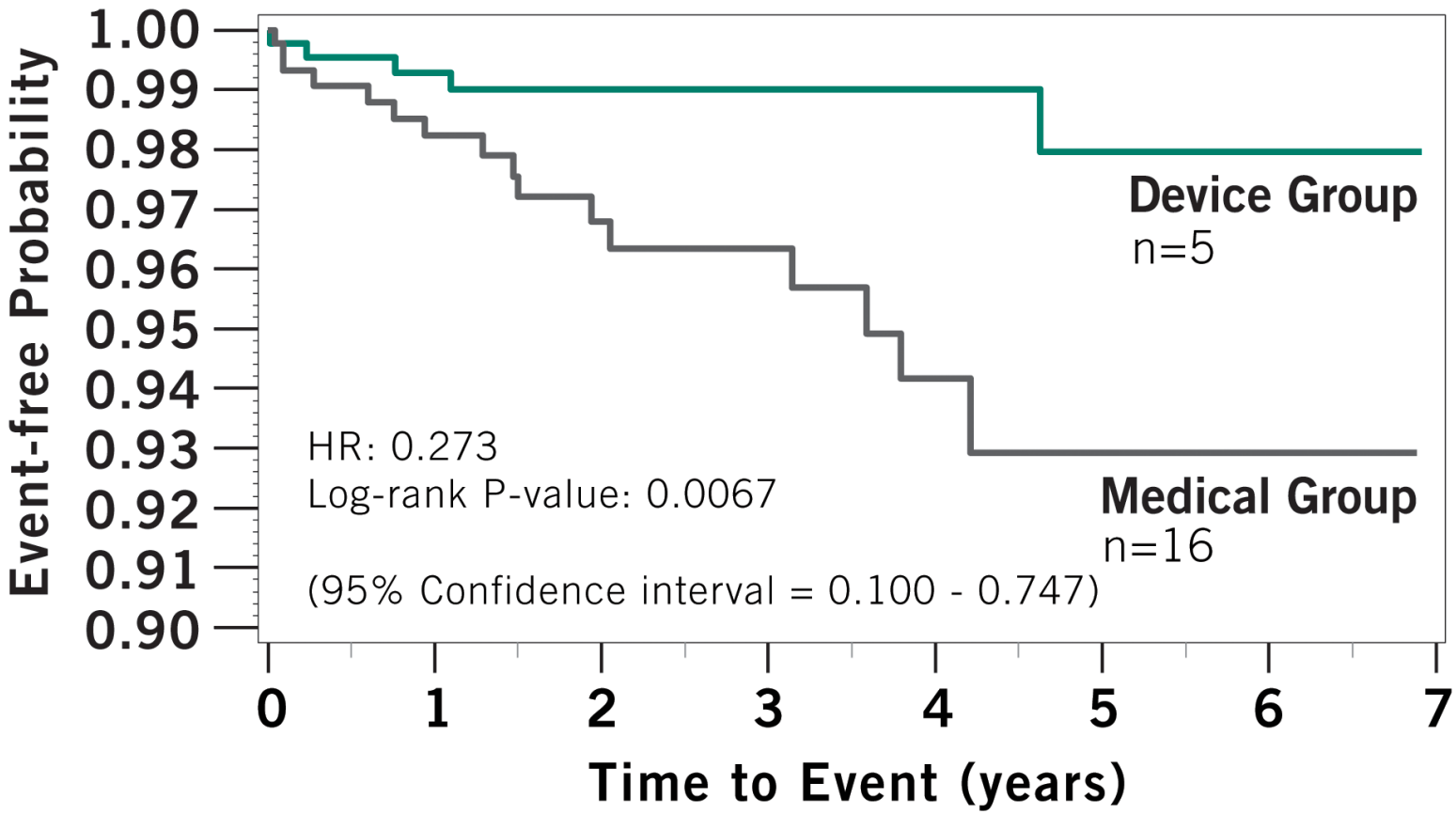
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- The Per Protocol (PP) cohort includes patients who adhered to the requirements of the study protocol

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

Totality of Evidence and NNT

46.6%-72.7% risk reduction of stroke in favor of device

RESPECT CLINICAL TRIAL

Totality of Evidence

Analysis	Risk Reduction	P-Value[1]
Intent to Treat Raw Count	46.6%	0.157
Intent to Treat KM	50.8%	0.083
Per Protocol KM	63.4%	0.032
As Treated KM	72.7%	0.007

Number Needed to Treat (NNT)

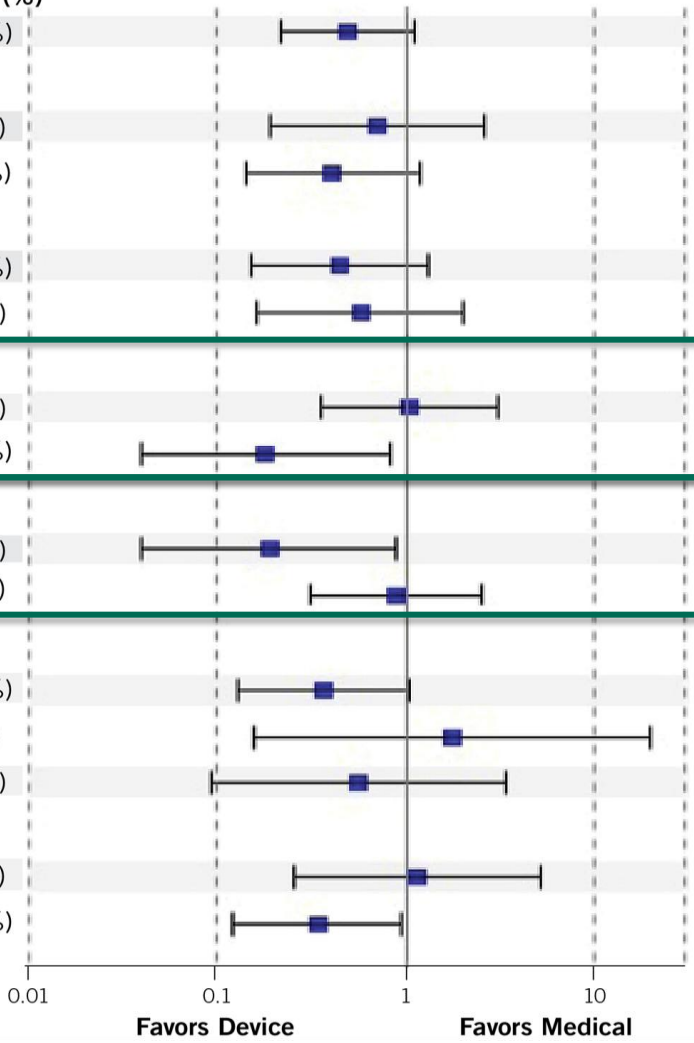
	NNT[2]	Device Group Event Rate[3]	Medical Group Event Rate[3]
1 Year	250	1.33%	1.73%
2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

1. P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
2. The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
3. Calculated using the Kaplan-Meier estimated event rates for each treatment group

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	



Recurrent Cerebral Infarct Size[1]

Methods pre-specified; analysis post-hoc

Event	Device Group n/N (%)	Medical Group n/N (%)	P-value[2]
Larger infarct >1.5cm	1/7 (14%)	9/13 (69%)	P=0.0573
Smaller infarct ≤ 1.5cm	6/7 (86%)	4/13 (31%)	

- This exploratory analysis of site-reported recurrent cerebral infarct size is provocative in suggesting that recurrent ischemic strokes in the medical versus device group are not only more frequent but also larger

1. Recurrent infarct size reported on primary endpoint population
2. P-value based on Fisher's Exact test

RESPECT Conclusions

- Primary analysis of ITT cohort was not statistically significant but trended towards superiority while secondary analyses suggested superiority
- Stroke risk reduction was observed across the totality of analyses with rates ranging from 46.6% - 72.7%
- Risk of PFO closure is extremely low
- Follow-up is ongoing

What went wrong?

What went wrong in RESPECT?

1. Superiority study design was more than what was needed
   - Because medical therapy has never been studied in a randomized trial
2. Very slow enrolment
   - only 1.8 patients/year/center
   - There must have been a selection bias
3. Patient number too small
   - Assumptions (2% vs 0.5 % event rate/yr) too optimistic
4. Follow-up too short
   - Patients go for PFO closure because they want to avoid 30 yrs of anticoagulation

Percutaneous Closure of Patent Foramen Ovale versus Medical Treatment in Patients with Cryptogenic Embolism:

The PC Trial

NCT00166257

Bernhard Meier, Bindu Kalesan, Ahmed A. Khattab, David Hildick-Smith, Dariusz Dudek, Grethe Andersen, Reda Ibrahim, Gerhard Schuler, Antony S. Walton, Andreas Wahl, Stephan Windecker, Heinrich P. Mattle, and Peter Jüni

Procedures

Percutaneous PFO Closure

Amplatzer PFO Occluder

Acetylsalicylic acid (100-325mg qd)

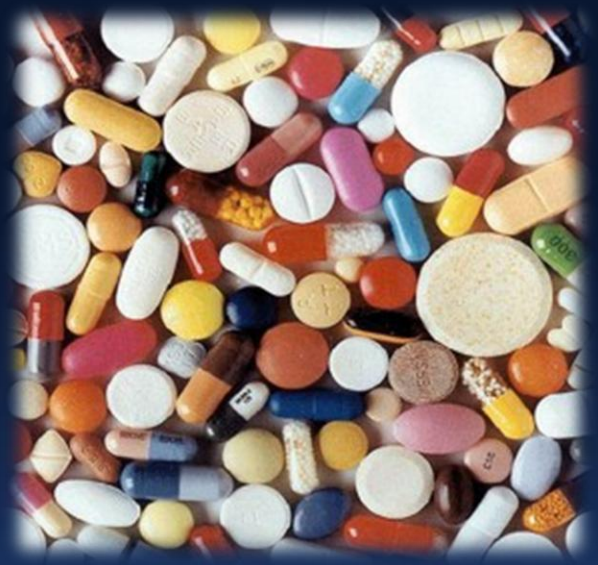
and ticlopidine (250-500mg qd)

or clopidogrel (75mg qd)

for 6 months

1:1

RCT



Medical Treatment

Oral anticoagulation or

Antiplatelet therapy

at the discretion of the neurologist

Patient Population
Main Inclusion Criteria

- Age < 60 years
- ischemic stroke or TIA with documented corresponding ischemic lesion or
- extracranial peripheral thromboembolism

Windecker, TCT 2012, modified

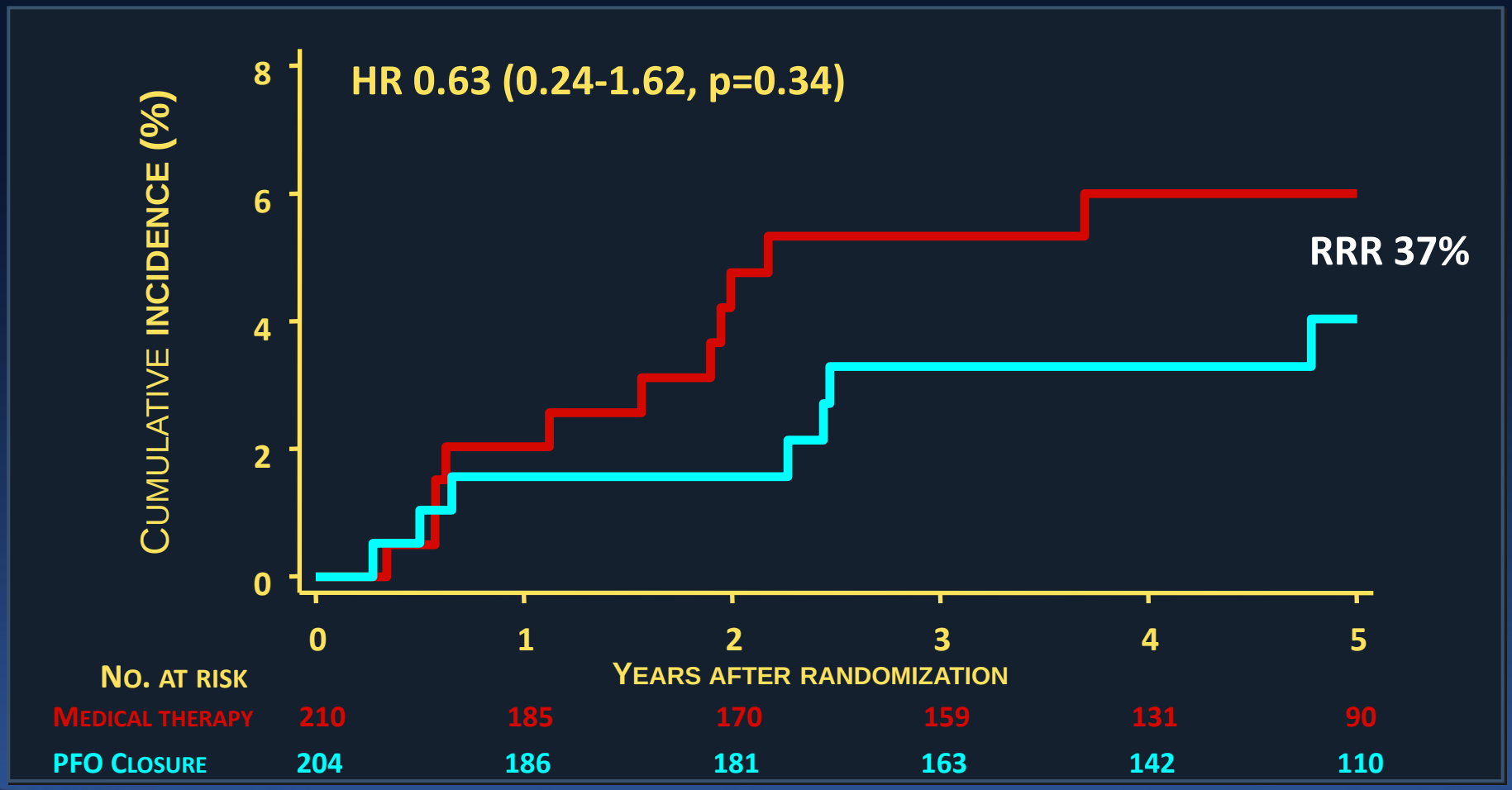
Patient Population

Exclusion Criteria

- **Cause for thromboembolic event other than PFO**
  - Cardiac (mural thrombus, DCM, Afib, prosthetic heart valves)
  - Cerebral (significant intracranial disease, relevant atherosclerosis, dissection of intra- or extracranial arteries)
  - Vascular (arteritis, vasculitis, collagen vascular disease)
  - Hematological (hyperviscosity syndrome, hypercoagulable state)
- **Contraindication for chronic antithrombotic Rx**
- **Clinical indication other than PFO for chronic antithrombotic Rx**
- **Previous surgical or percutaneous PFO closure**
- **Central nervous system disease**
  - seizure disorder, disability from previous stroke, etc.

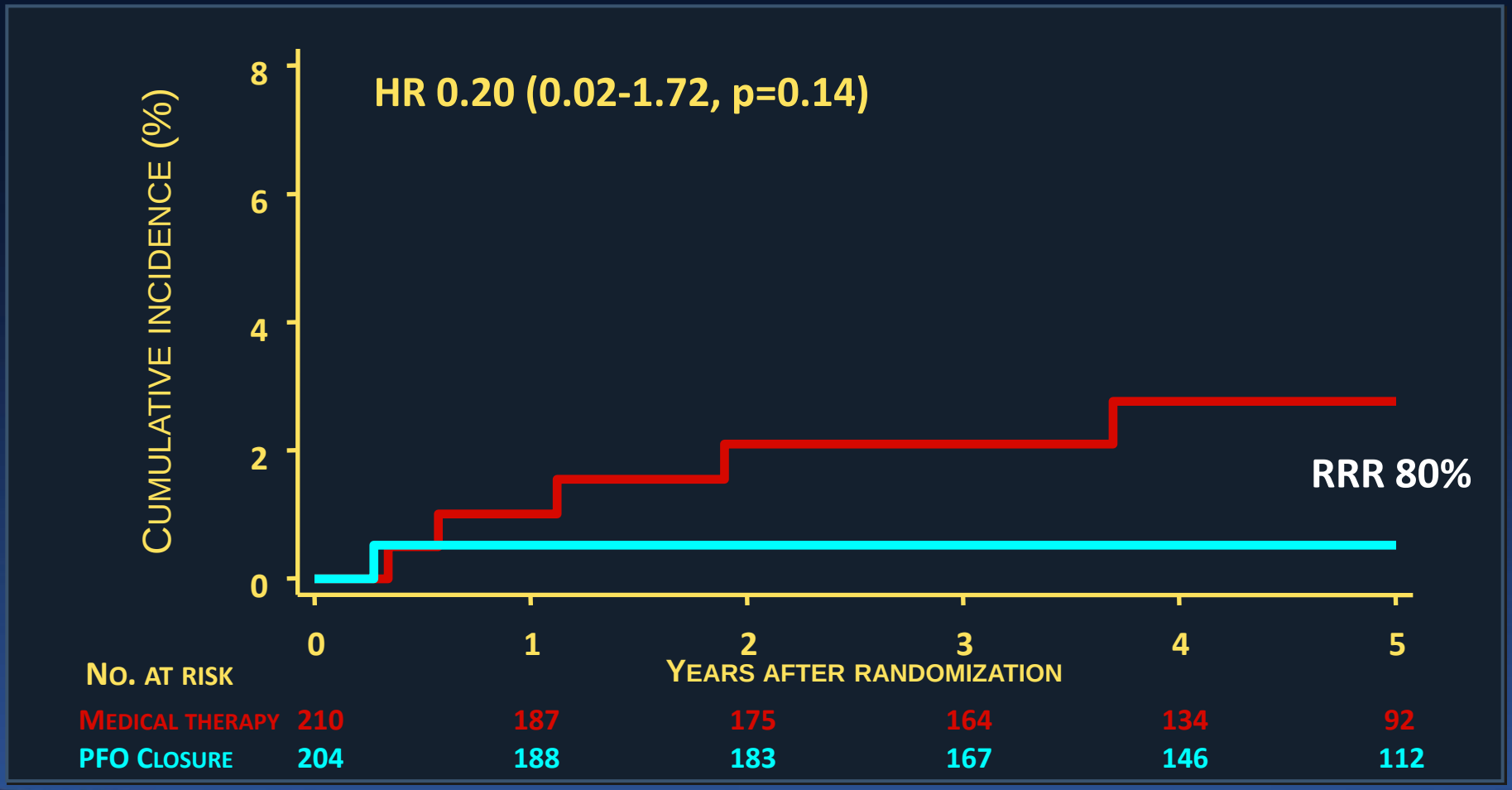
Primary Composite Endpoint

Death from any cause, non-fatal Stroke, TIA and peripheral Embolism



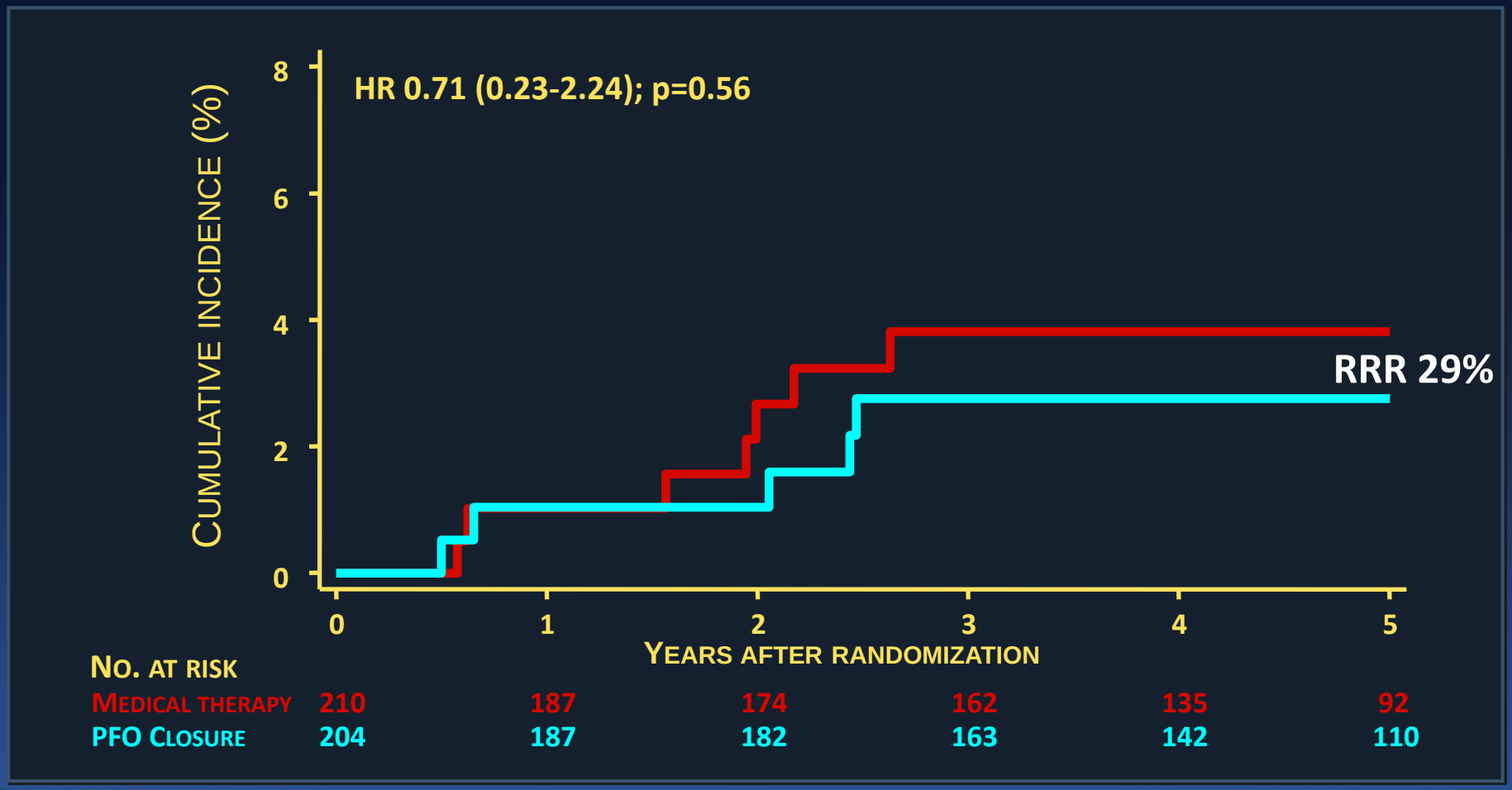
Secondary Endpoint

Stroke



Secondary Endpoint

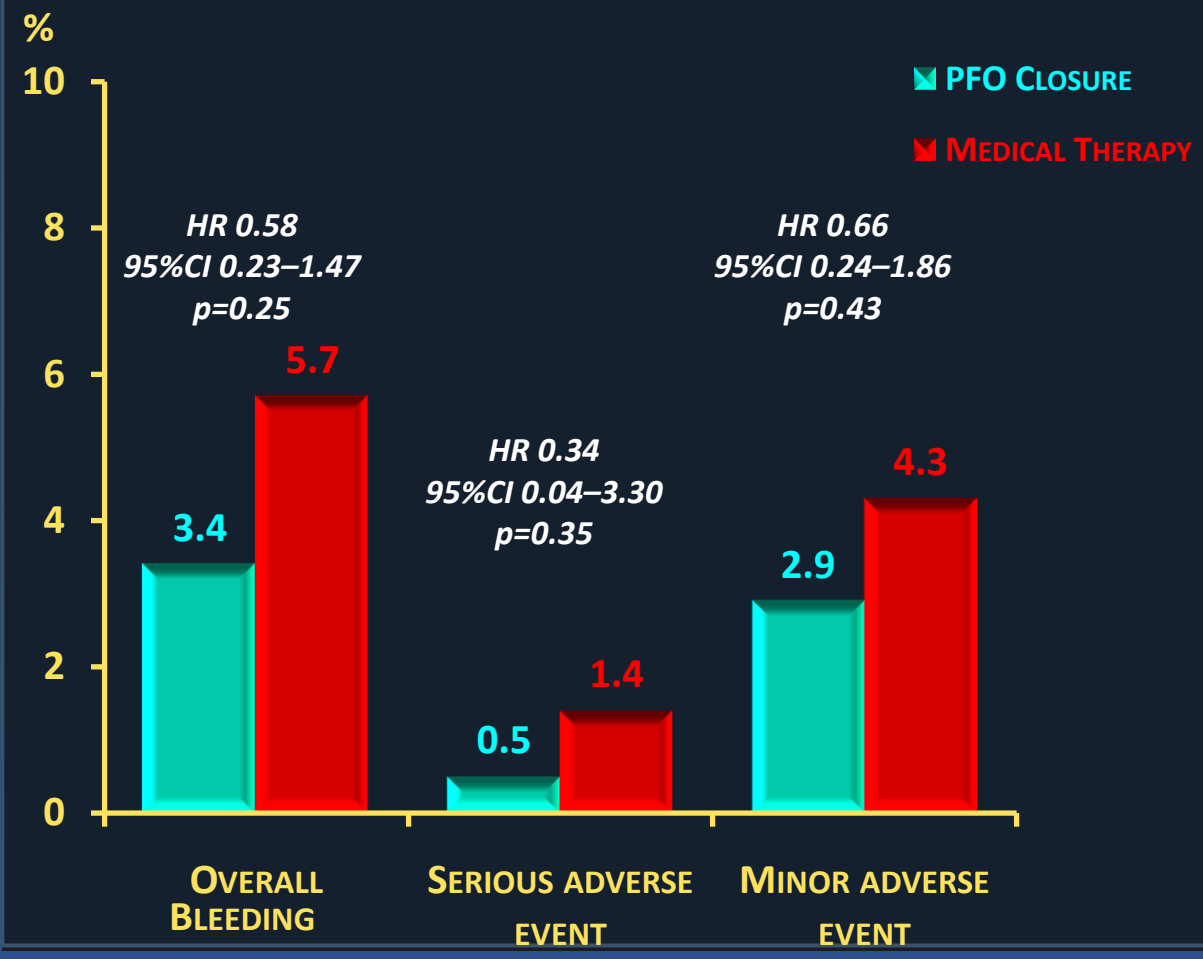
Transient Ischemic Attack



Bleeding and Atrial Fibrillation

Bleeding

Atrial fibrillation



Conclusions

- PFO closure showed no significant reduction in ischemic and bleeding events compared with medical treatment
- However, the observed difference in stroke (80% relative risk reduction, NNT=40) may be clinically relevant if confirmed in further studies

Windecker, TCT 2012 (modified)

What went wrong in PC?

1. Superiority study design was too much
2. Very slow enrolment
   - only 1.6 patients/year/center
   - There must have been a selection bias
3. Patient number too small
   - Assumptions too optimistic (event rate in the medical arm lower than expected)
4. Follow-up too short
   - Patients go for PFO closure because they want to avoid 30 yrs of anticoagulation

Stroke reduction in randomized trials

	n	**Follow-up (yrs)**	**Risk ratio**
CLOSURE I	909	2	0.9
RESPECT	980	2.6	0.49
PC	414	4.1	0.2
	2303	**2.6**	**0.56**

These randomized trials have confirmed the results of prior trials …

… but they had been under-powered

So are these negative trials?

They give you all options

PHARMA & HEALTHCARE | 10/25/2012 @ 3:41下午 | 882 views

TCT: Two PFO Closure Trials Miss Primary Endpoints

Two trials presented today at the TCT meeting in Miami testing the benefits of PFO closure in patients with cryptogenic stroke have failed to convincingly demonstrate any significant benefit for the controversial procedure.

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial randomized 980 patients to PFO closure with the Amplatzer PFO Occluder device or medical therapy. According to the lead investigator John Carroll, the rate of recurrent stroke was low in both arms of the trial: 1.6% in the closure group and 3% in the medical group.

This difference vetween the groups did not achieve significance in the intention-to-treat (ITT) analyses:

FAIL ☹?

Science News

... from universities, journals, and other research organizations

PFO Closure May Be Superior to Medical Therapy in Preventing Stroke

ScienceDaily (Oct. 25, 2012) — Results of a large-scale, randomized clinical trial called RESPECT revealed that patent foramen ovale (PFO) closure may be superior to medical therapy in preventing recurrent stroke, according to a presentation of findings today at the Transcatheter Cardiovascular Therapeutics (TCT) conference in Miami.

See Also:

Health & Medicine
- Heart Disease
- Stroke Prevention

"In contrast to a previously reported randomized trial for the treatment of cryptogenic stroke, the RESPECT trial enrolled only patients with documented cryptogenic embolic strokes and excluded patients with other potential causes of stroke and/or TIA. The period of follow-up approached nine years and was not restricted to only events within the initial two years of follow-up," said Richard Smalling, M.D., Ph.D., James D. Wood Distinguished Chair in Cardiovascular Medicine at The University of Texas Health Science Center at Houston (UTHealth), who

Related Stories

Study Suggests a Relationship Between Migraine Headaches in Children and a Commo

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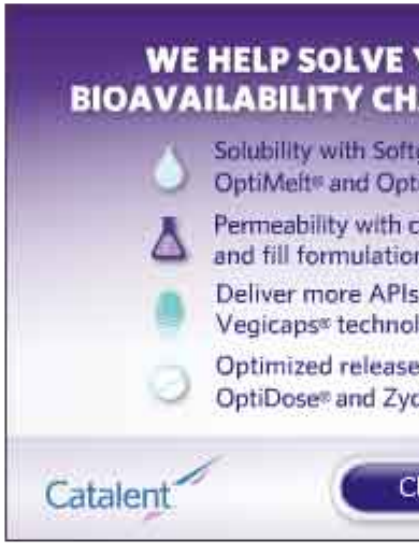
more brea



MAY BE?

St. Jude Medical RESPECT Trial for PFO Closure Provides Clinical Evidence of Risk Reduction in Prevention of Recurrent Cryptogenic Stroke

Results offer compelling evidence for closure with the AMPLATZER PFO Occluder over conventional medical management alone

BusinessWire

Press Release: St. Jude Medical, Inc. – Thu, Oct 25, 2012 11:16 AM EDT

RELATED QUOTES

Symbol	Price	Change
STJ	38.29	+0.02

ST. PAUL, Minn.--(BUSINESS WIRE)--

St. Jude Medical, Inc. (STJ), a medical device company, today

GREAT ☺?

… and if you believe that the trials had been negative

What to do then in a patient who had a stroke due to a PFO?

Stroke due to a PFO

- Nothing?
  - No evidence
  - Against guidelines
  - Difficult to explain
- Surgical closure?
  - 30 day mortality 0.5-1%
  - Periprocedural stroke rate 1-2%
- Medical therapy?
  - Not better than PFO closure (CLOSURE I, RESPECT, PC)
  - Has to be given life-long
    - annual bleeding risk 0.5% - 3% per year
  - Not safer than PFO closure (CLOSURE I, RESPECT, PC)
- PFO closure
  - In 30 min problem solved without additional risk

Future perspectives

Ongoing Randomized Trials

- RESPECT – extended FU
- PC Trial – extended FU
- REDUCE

- Will PFO closure be dead if they are negative?

Regardless of clinical trials results, it will be like with PCI or carotid stenting

- No trials ever showed convincing evidence that this is superior to alternative treatments
- Nevertheless since > 30 yrs patients prefer these non-invasive techniques over surgery or doing nothing
- Numbers went up and down but procedures never disappeared

We will continue to get referals like this:

-------- Original Message --------

Dear Professor Sievert,

I am the chief of neurology of an academic teaching hospital. The 25 yr. old daughter of our major is my patient. She had suffered from a stroke due to a PFO. According to the guidelines of the Society of Neurology aspirin is recommended. However, in this particular case, also because the parents are very much concerned, I think the PFO should be closed

.....

PFO closure will stay

- At least for
  - Daughters of majors
  - Sons of colleagues
  - Wives of neurologists
  - Any other daughters, sons and wives
  - and also for those patients whose parents are very much concerned