

19th CardioVascular Summit-TCTAP 2014
Seoul, Korea, April 22-25, 2014

Should PFOs Be Closed?

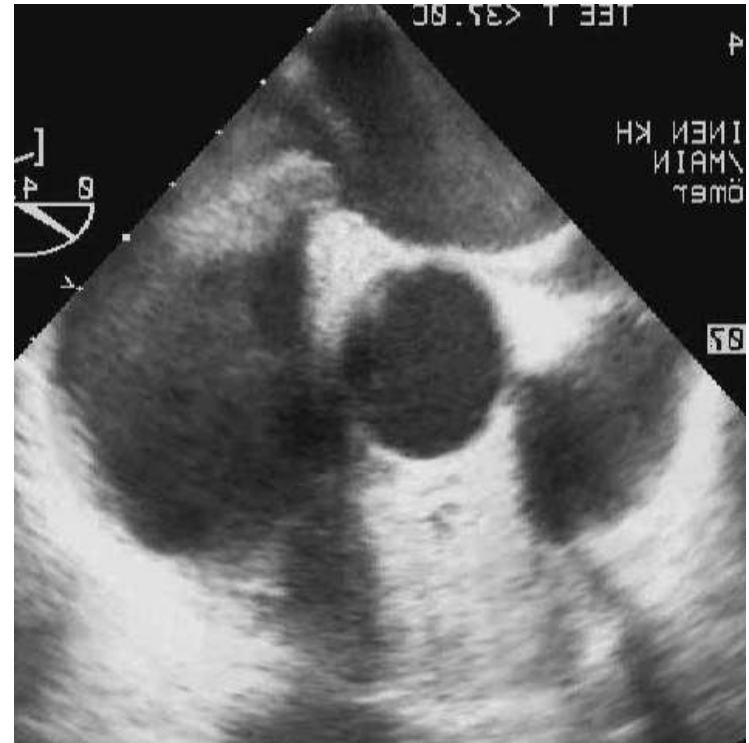
Horst Sievert,
Sameer Gafoor, Stefan Bertog,
Ilona Hofmann, Laura Vaskelyte,
Predrag Matić, Markus Reinartz
CardioVascular Center Frankfurt CVC
Frankfurt, Germany

Should PFOs Be Closed?

Yes, they should be closed if they can cause stroke

Can PFO cause stroke?

Yes, they can!



No need for a randomized trial

I am not a big fan
of guidelines

But for PFOs the guidelines are
not as bad as you may think

So what is in the Guidelines?

Stroke

American Stroke
AssociationSM

A Division of American
Heart Association



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Recommendations

1. For patients with an ischemic stroke or TIA and PFO, antiplatelet therapy is recommended (Class IIa; Level of Evidence B).
2. There are insufficient data to determine if oral anticoagulation is equivalent or superior to antiplatelet therapy for secondary stroke prevention in patients with PFO (Class IIb; Level of Evidence B). (New recommendation)
3. There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO (Class IIb; Level of Evidence C) (Table 10).

So they just don't know!

A green thought bubble with a black outline, containing the text "So they just don't know!". The bubble is positioned over the third recommendation in the list.



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SOURCE

Facilitating Learning and Change in Clinical Care

Antithrombotic Therapy and Prevention of Thrombosis



9th Edition of Chest Physicians Clinical Practice Guidelines: **Patients With PFO and Atrial Septal Aneurysm**

PATIENT POPULATION	INTERVENTION RECOMMENDATION	GRADE
Patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm	Suggest against antithrombotic therapy	2C
Patients with cryptogenic stroke and PFO or atrial septal aneurysm	Recommend aspirin (50-100 mg/d) over no aspirin	1A
Patients with cryptogenic stroke and PFO or atrial septal aneurysm who experience recurrent events despite aspirin therapy	Suggest treatment with VKA therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy	2C
Patients with cryptogenic stroke and PFO with evidence of DVT	Recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0)	1B
	Consideration of device closure over no VKA therapy or aspirin therapy	2C



AMERICAN ACADEMY OF
NEUROLOGY®

Recurrent Stroke in Patients with Patent Foramen Ovale and Atrial Septal Aneurysm

April 2004

Current guideline. Reaffirmed on July 21, 2013. Guideline Projects in Process

In patients with a cryptogenic stroke and an atrial septal abnormality, warfarin or aspirin is superior in preventing recurrent stroke or death compared with aspirin. There is insufficient evidence to evaluate the efficacy of aspirin compared with warfarin.

The AAN is currently developing guidelines on the following topics (as of November 2013):

- ▼ **RECURRENT STROKE WITH PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM (UPDATE)**
 - › What is the risk of recurrent stroke in patients with patent foramen ovale (PFO) and/or atrial septal aneurysm (ASA)?
 - › What is the optimal management to prevent recurrent stroke in patients with PFO and/or ASA: medical therapy (antiplatelets or anticoagulation) or endovascular closure plus medical therapy?

What is in the Guidelines?

- Most guidelines are not against PFO closure
 - "Not enough evidence to evaluate ..."
 - "PFO closure can be considered "
- All guidelines are older than the recent randomized trials
- What is the evidence in view of 20 years of experience with PFO closure and the recent randomized trials?

Prospective Registries

Meta-analyses

Metaanalysis of non randomized trials PFO Closure vs Medical Therapy

10 Transcatheter Closure Studies

1355 Patients

6 Medical Management Studies

895 Patients

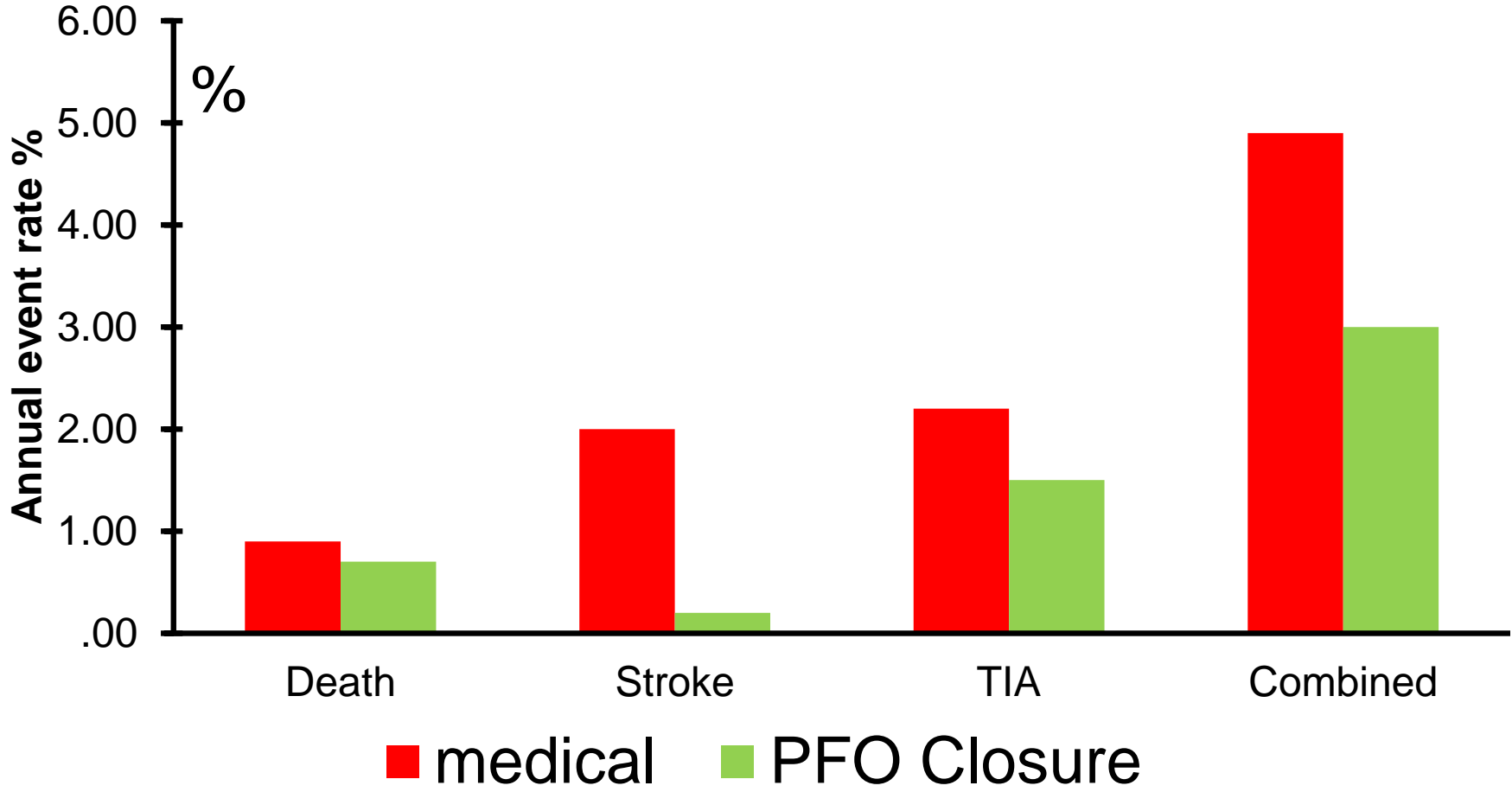
Recurrent event @ 1 Yr

0 - 4.9%

3.8% - 12%

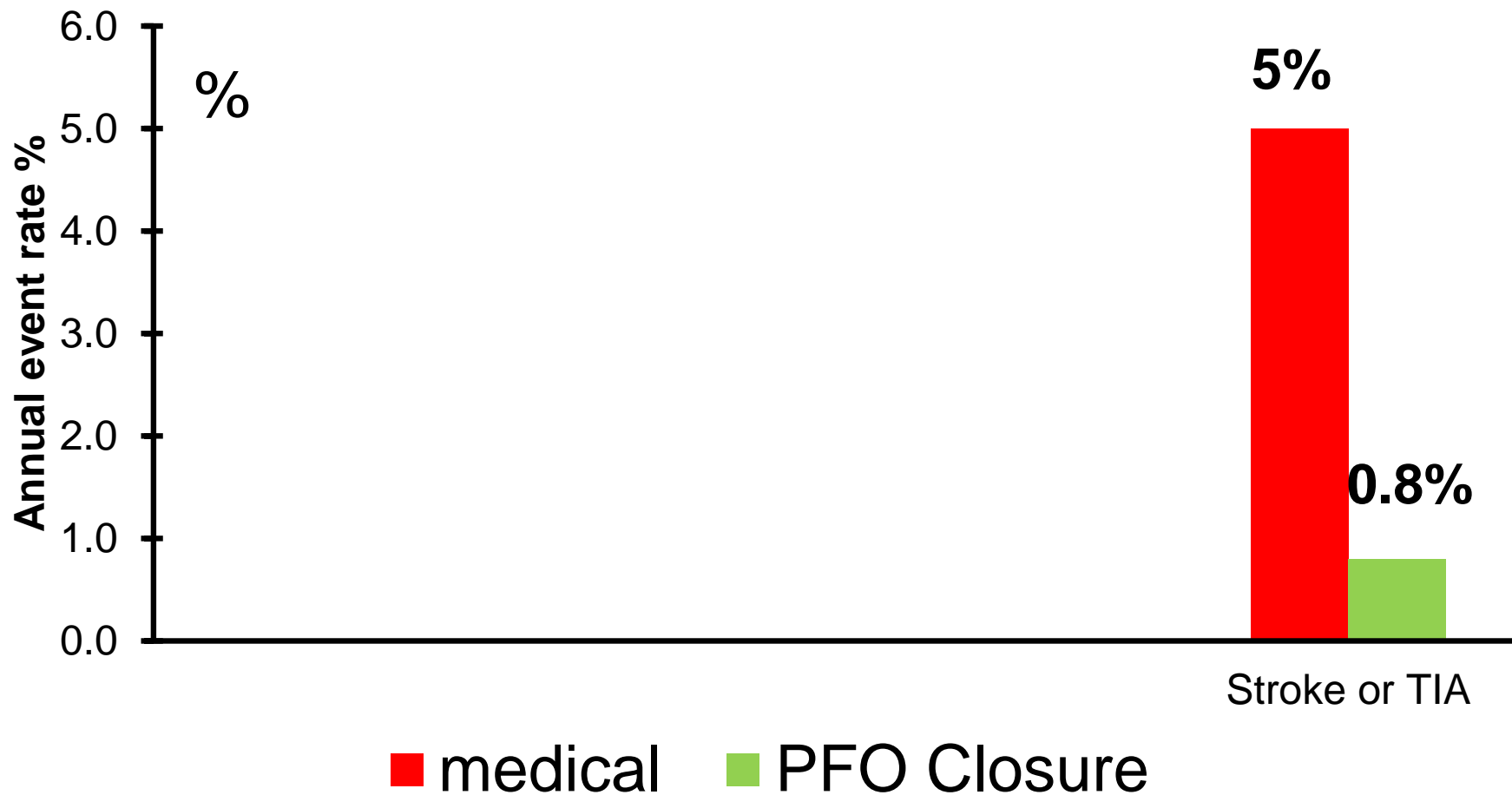
Meta-analysis of Event Rates in Patients with Cryptogenic Stroke

- **9 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)



Meta-analysis of Transcatheter Closure vs Medical Therapy

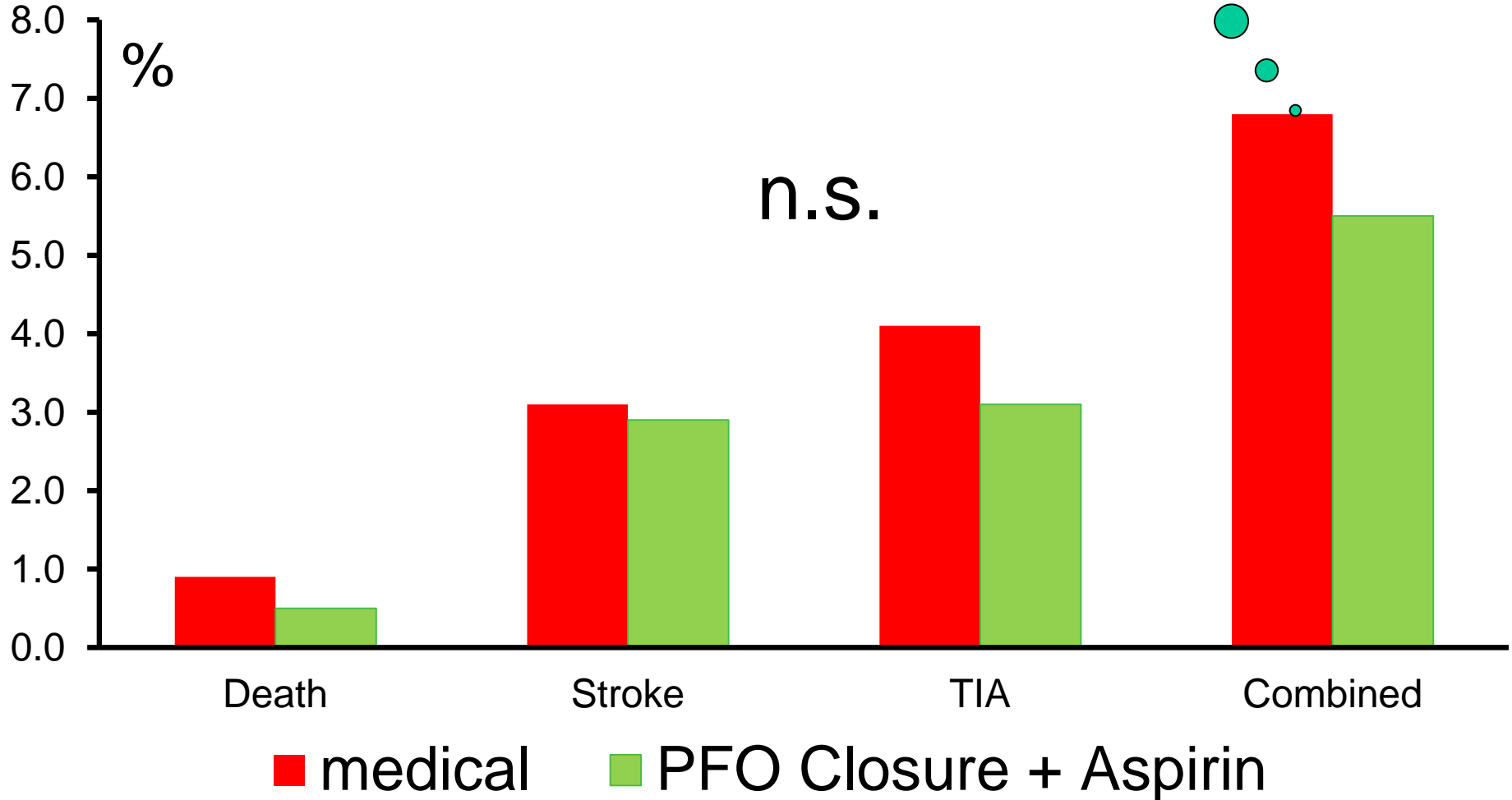
48 studies 2001-2011



And
Randomized
Trials?

CLOSURE Annual Event

So this trial was
positive!



CLOSURE I: PFO Closure is safe

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)

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
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
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

The good news 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

The Final Results with Primary End Point Analyses



RESPECT

CLINICAL TRIAL



**RANDOMIZED EEVALUATION OF RECURRENT STROKE
COMPARING PPFO CLOSURE TO ESTABLISHED CCURRENT
STANDARD OF CARE TTREATMENT**

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

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

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 in

5. 1 ischemic

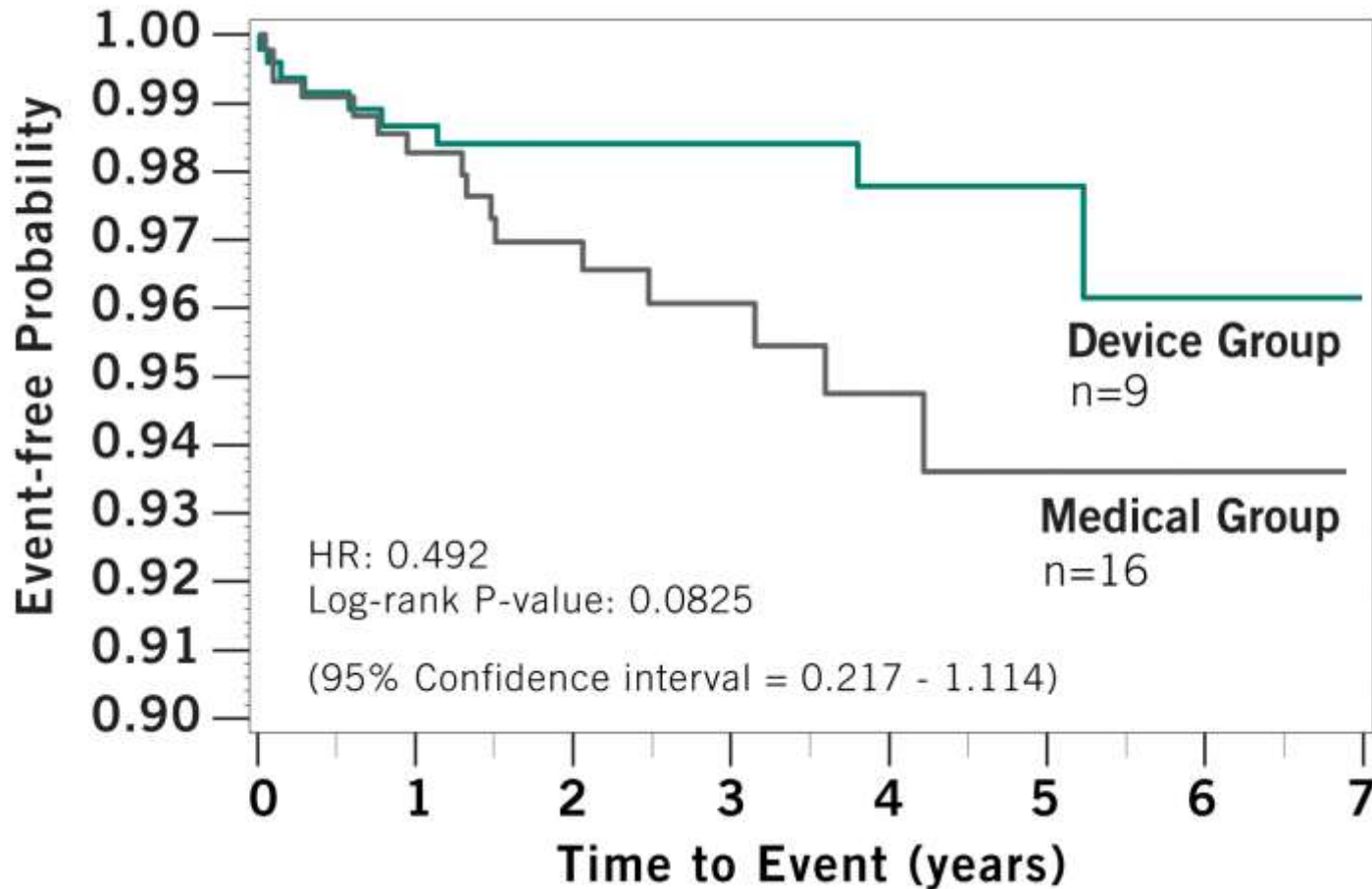
6. For all SAEs, there were 3 device group deaths (0.6%) and 6 medical group deaths (1.2%) all of which were not study related, p= 0.334

7. P-values are calculated using Fisher's Exact test

PFO closure is as safe as medical therapy

Primary Endpoint Analysis – ITT Cohort

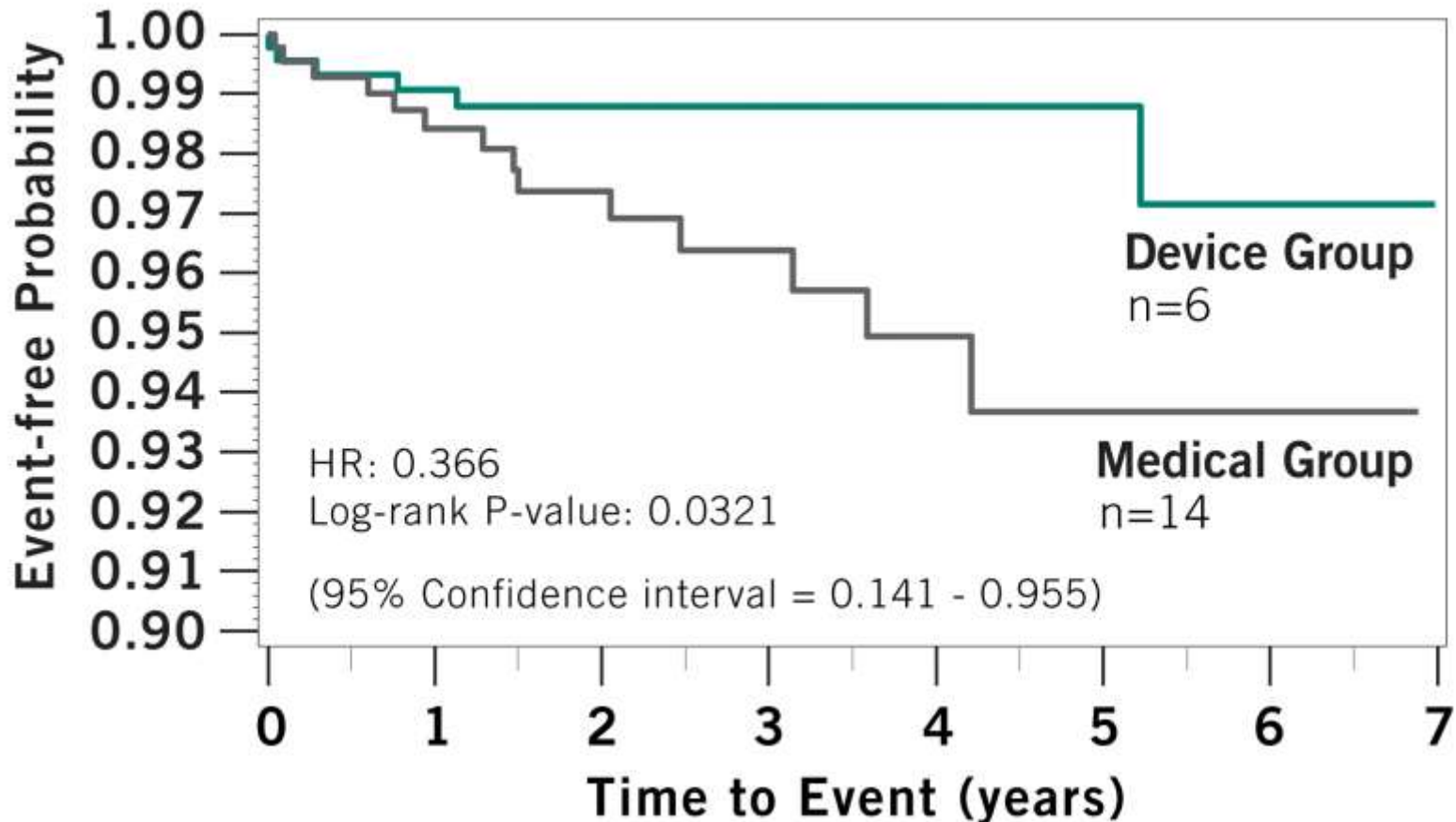
50.8% risk reduction of stroke in favor of device



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

Primary Endpoint Analysis – Per Protocol Cohort

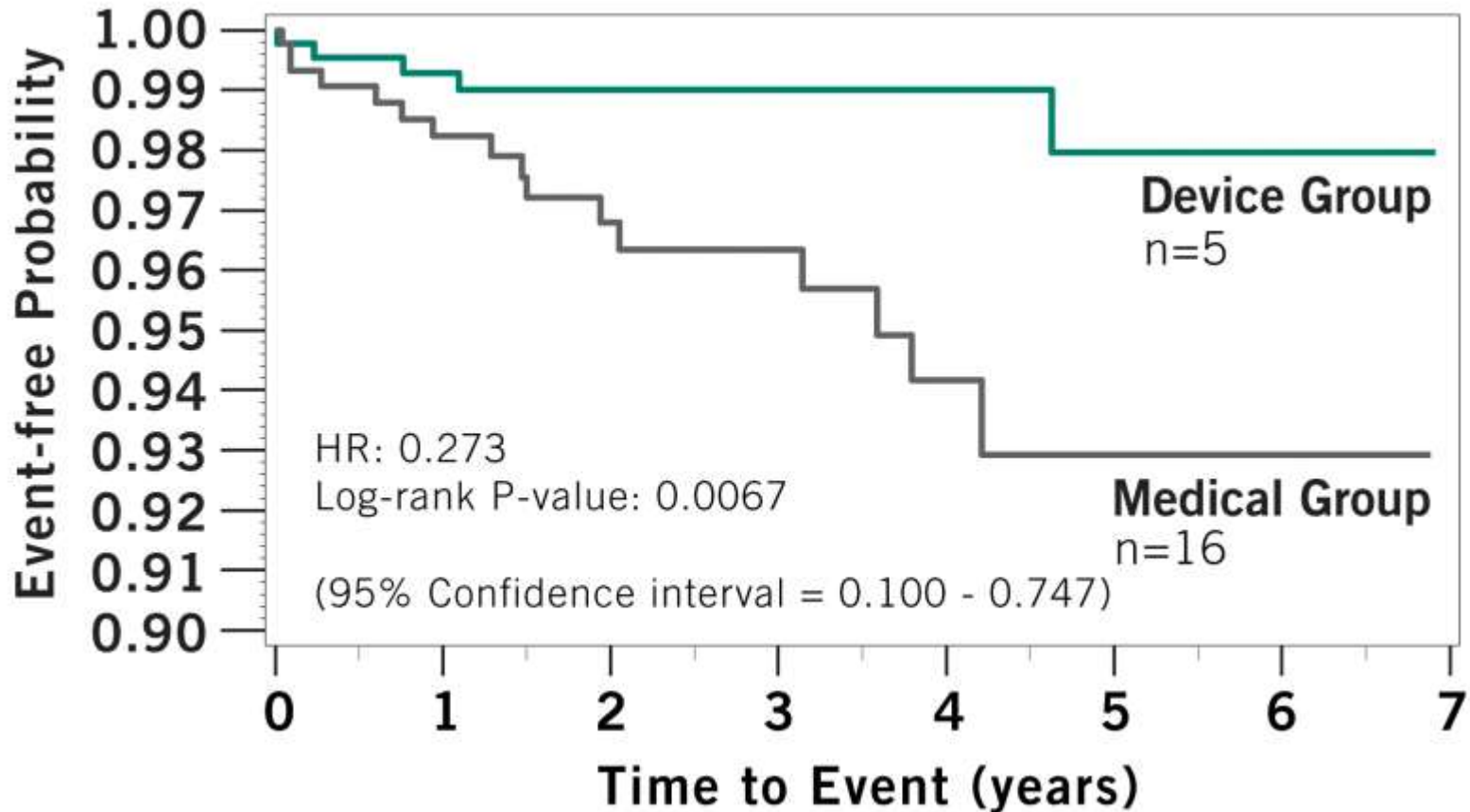
63.4% risk reduction of stroke in favor of device



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

Primary Endpoint Analysis – As Treated Cohort

72.7% risk reduction of stroke in favor of device



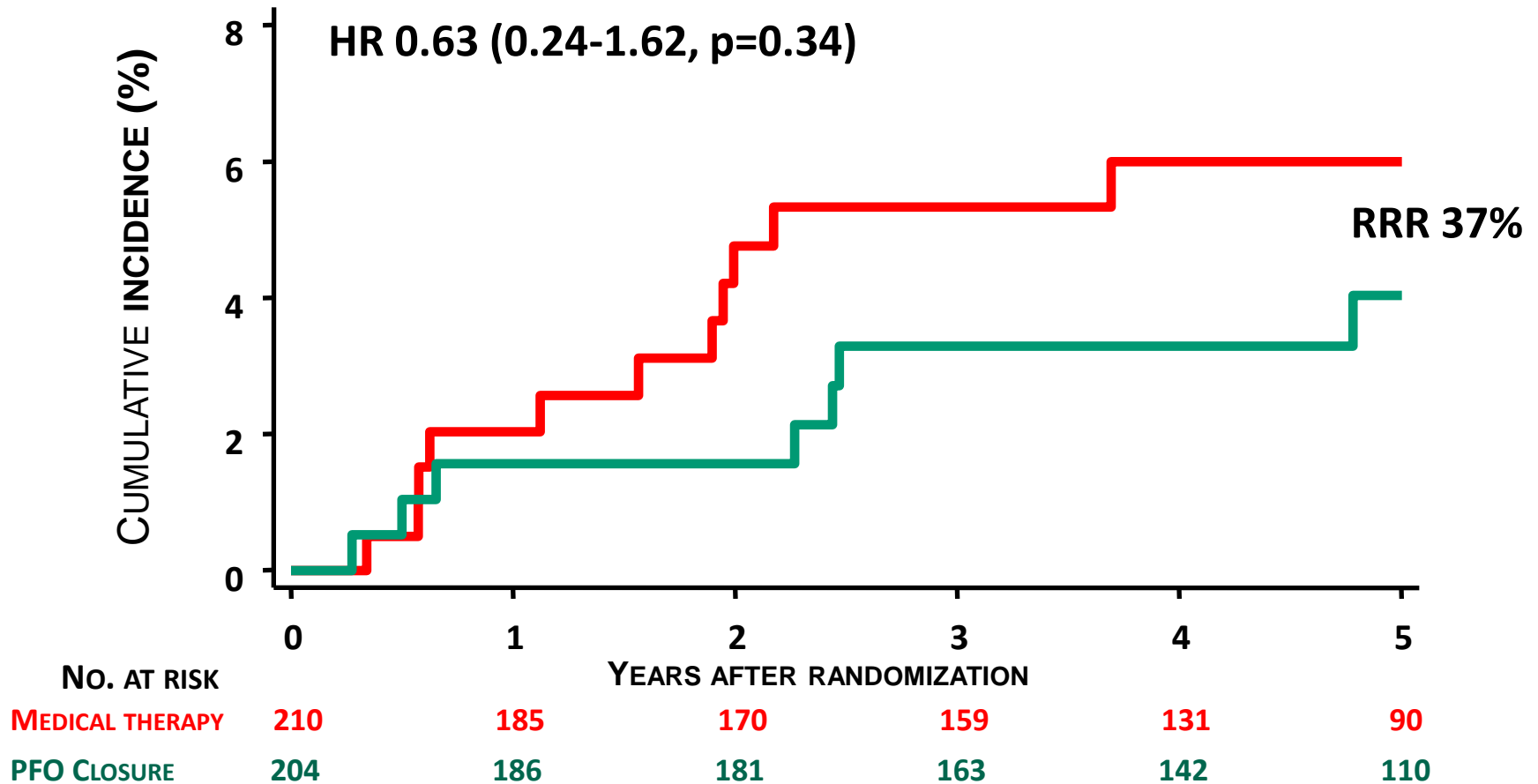
- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

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

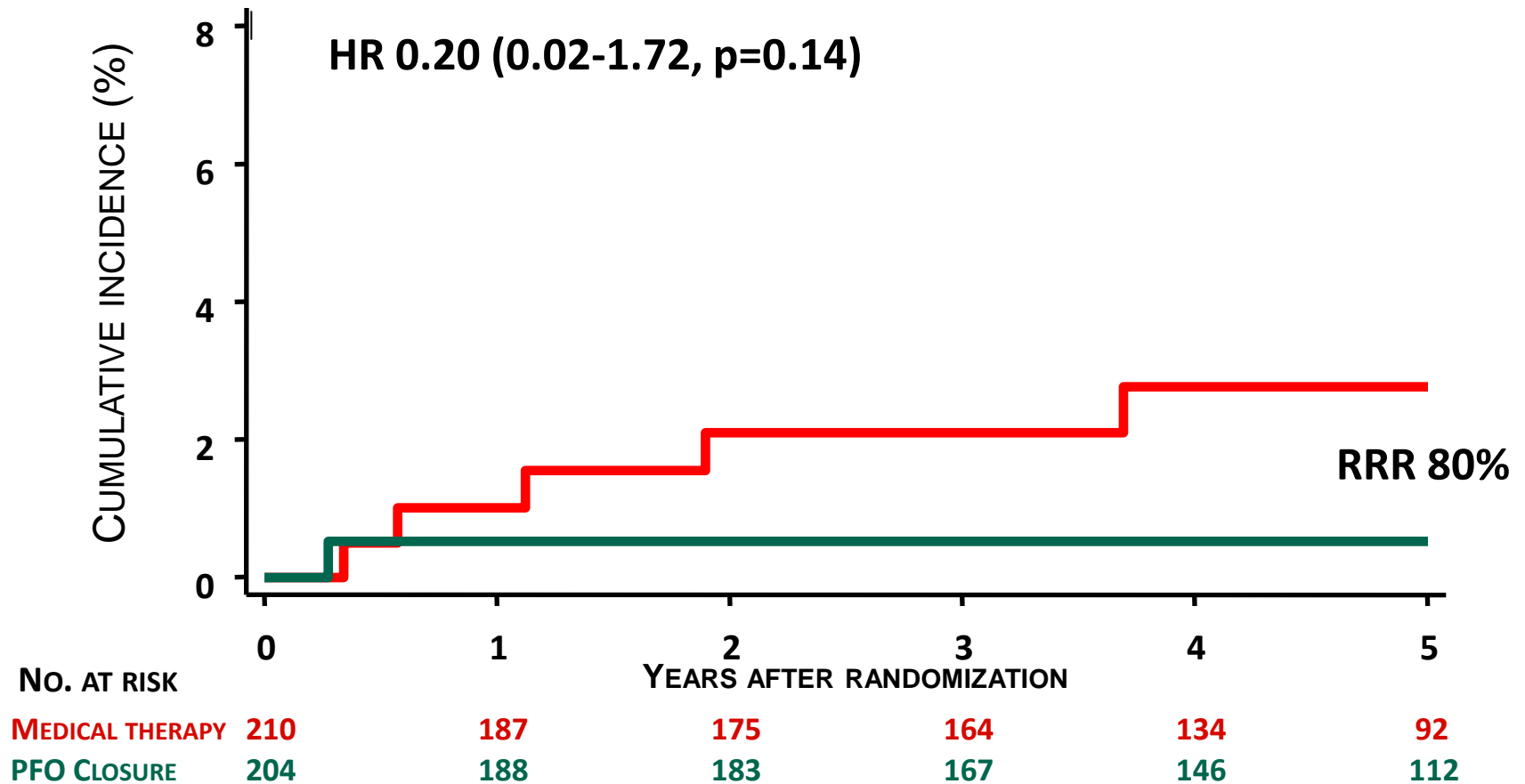
PC TRIAL: PRIMARY COMPOSITE ENDPOINT

*DEATH FROM ANY CAUSE, NON-FATAL STROKE,
TIA AND PERIPHERAL EMBOLISM*



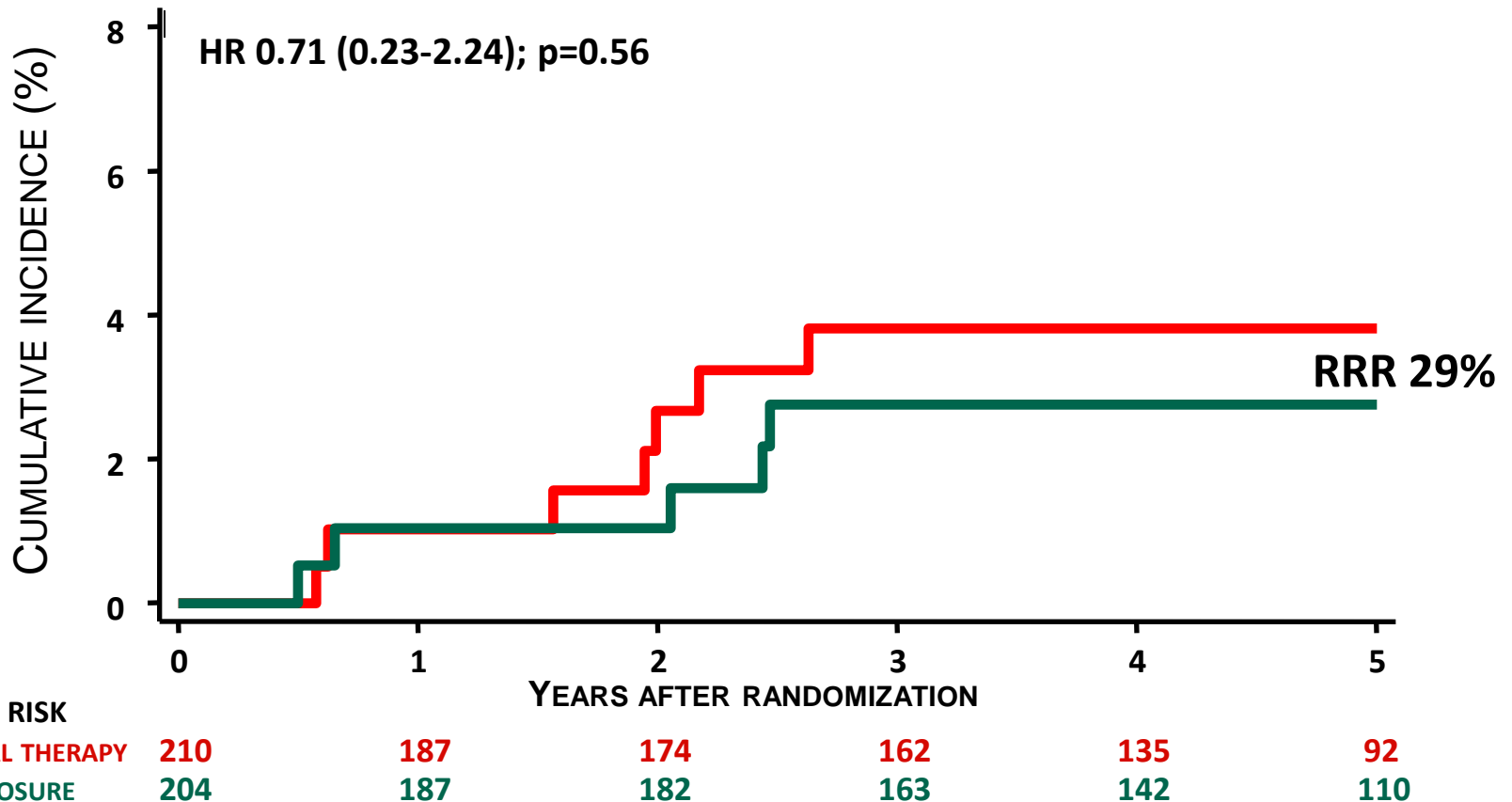
PC TRIAL: SECONDARY ENDPOINT

STROKE



PC TRIAL: SECONDARY ENDPOINT

TRANSIENT ISCHEMIC ATTACK



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 non-randomized trials ...

... but they had been under-powered

So are these
negative trials?

They give you
all options

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TCT: Two PFO Closure Trials Miss Primary Endpoints

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

FAIL 😞?



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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.

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"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

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Ask a Doctor Online Now — A Doctor Will Answer in Minutes! Questions Answered Every 9 Seconds. ... > Erectile-Dysfunction.JustAnswer.com

Tinnitus Behandlung Hilfe — Selbsttherapie - EarNoiseEliminator Patentierte CH-Technologie ... > www.EarNoiseEliminator.ch

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[Finance Search](#)
Sun, Oct 28, 2012, 7:01AM EDT - US Markets are closed

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



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

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RELATED QUOTES

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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

How about Metaanalyses of
the randomized trials?



Safety and efficacy of device closure for

J·Stroke·Cerebrovasc·Dis. 2014·Feb·1. pii: S1052-3057(13)00428-X. doi: 10.1016/j.jstrokecerebrovasdis.2013.10.018. [Epub ahead of print]

Review

Safety and efficacy of device closure for patent secondary prevention of neurological events: C systematic review at Int J Cardiol. 2013·Oct

Abdul Hakeem^a, Konstantino: 28. Massoud Leesar^c, Steven R.

Risk of Stroke in Patients with Patent Foramen Ovale: An Updated Meta-analysis of Observational Studies.

DEQ...



Stroke Prevention by Percutaneous Closure of Patent Foramen Ovale

A Systematic Review and Meta-analysis

Mathias Wolfrum, Georg M Froehlich, Guido Knapp, Leanne K Casaubon, James J DiNicolantonio, Alexandra J Lansky, Pascal Meier | Heart. 2014;100(5):389-395.

Patent Foramen Ovale cryptogenic stroke: a systematic review and meta-analysis.

Trials.

[Khan AR](#)¹, [Bin Abdulhak AA](#)², [Sheikh MA](#)¹, [Khan S](#)¹, [Erwin PJ](#)³, [Tlevjeh I](#)⁴, [Khuder S](#)⁵, [tian F. Witzke](#)¹, [Eltahawy EA](#)⁶.

[Pandit A](#)¹, [Arval MR](#)², [Pandit AA](#)³, [Jalota L](#)⁴, [Kantharajpur S](#)⁴, [Hakim FA](#)³, [Lee HR](#)³.

patients with cryptogenic stroke and patent foramen ovale

Metaanalyses

- Most did find a strong trend in favour of PFO closure
- Others did find a significant benefit of PFO closure
 - Mostly those who focussed on the Amplatzer device

Not one single study ever
showed a trend towards
better results with medical
therapy compared to PFO
closure

Future perspectives

Ongoing Randomized Trials

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

- Will PFOs not be closed anymore 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
referrals 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
.....

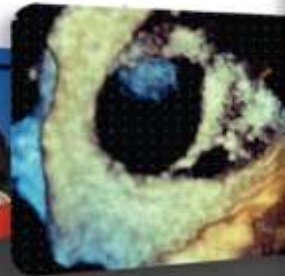
PFO closure will stay

- 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

Yes, you should
close PFOs

There is nothing else
you can do with them

Thank you!



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