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

Review Year and Future
To Closure or Not to Close
(LAA Closure & PFO Closure)

Horst Sievert

CardioVascular Center Frankfurt - CVC

Frankfurt, Germany

Obviously,
holes should be closed ...

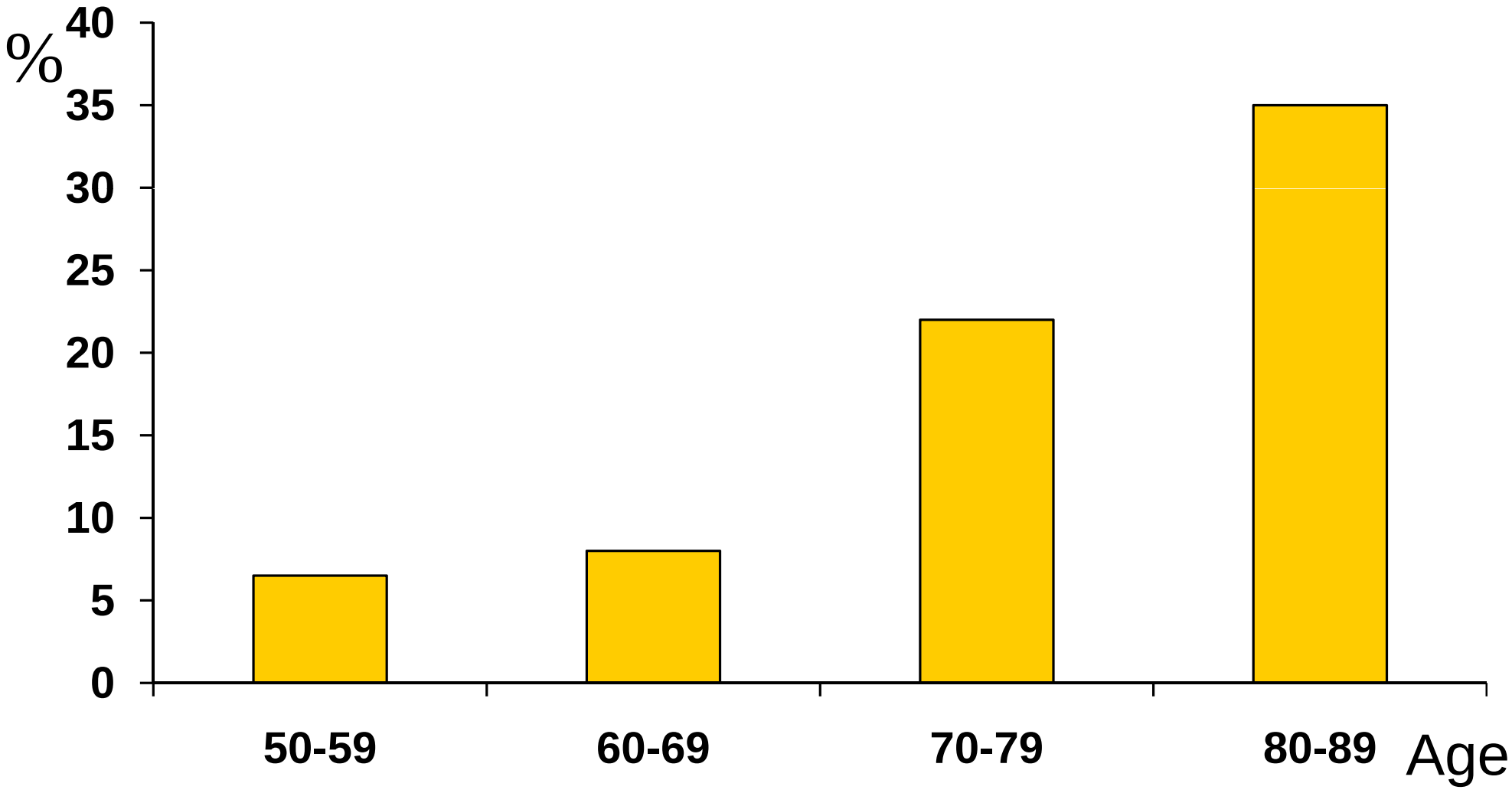
... because
they are there!

Tasks

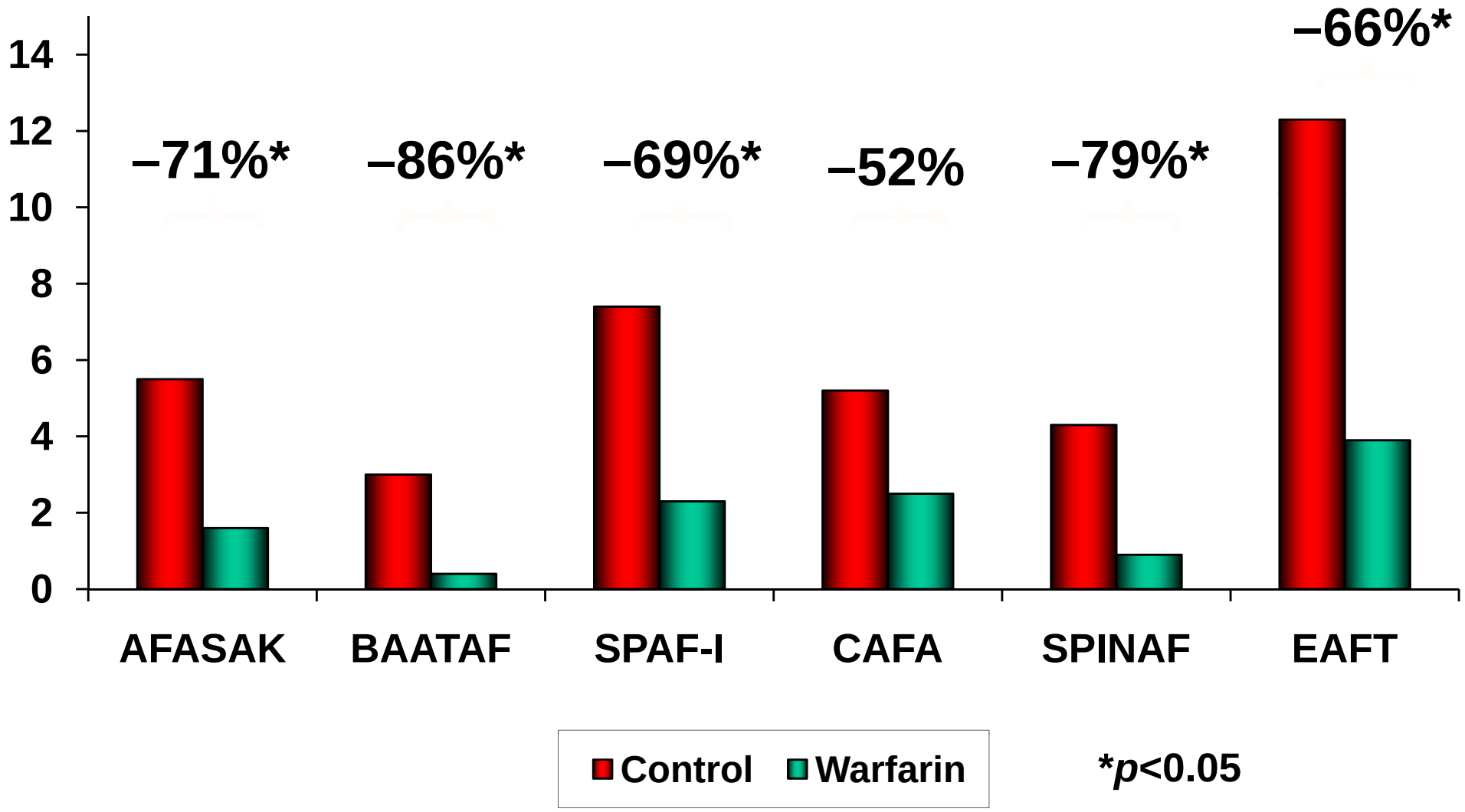
- I will give you some additional reasons to closed them ...
- ... and also draw your attention to some concerns which exist and which have to be taken seriously

Atrial fibrillation is one of the most important stroke causes, especially in the elderly

Framingham Study, Wolf, 1991



Anticoagulation in AF
Randomised Trials



Anticoagulation is effective, …

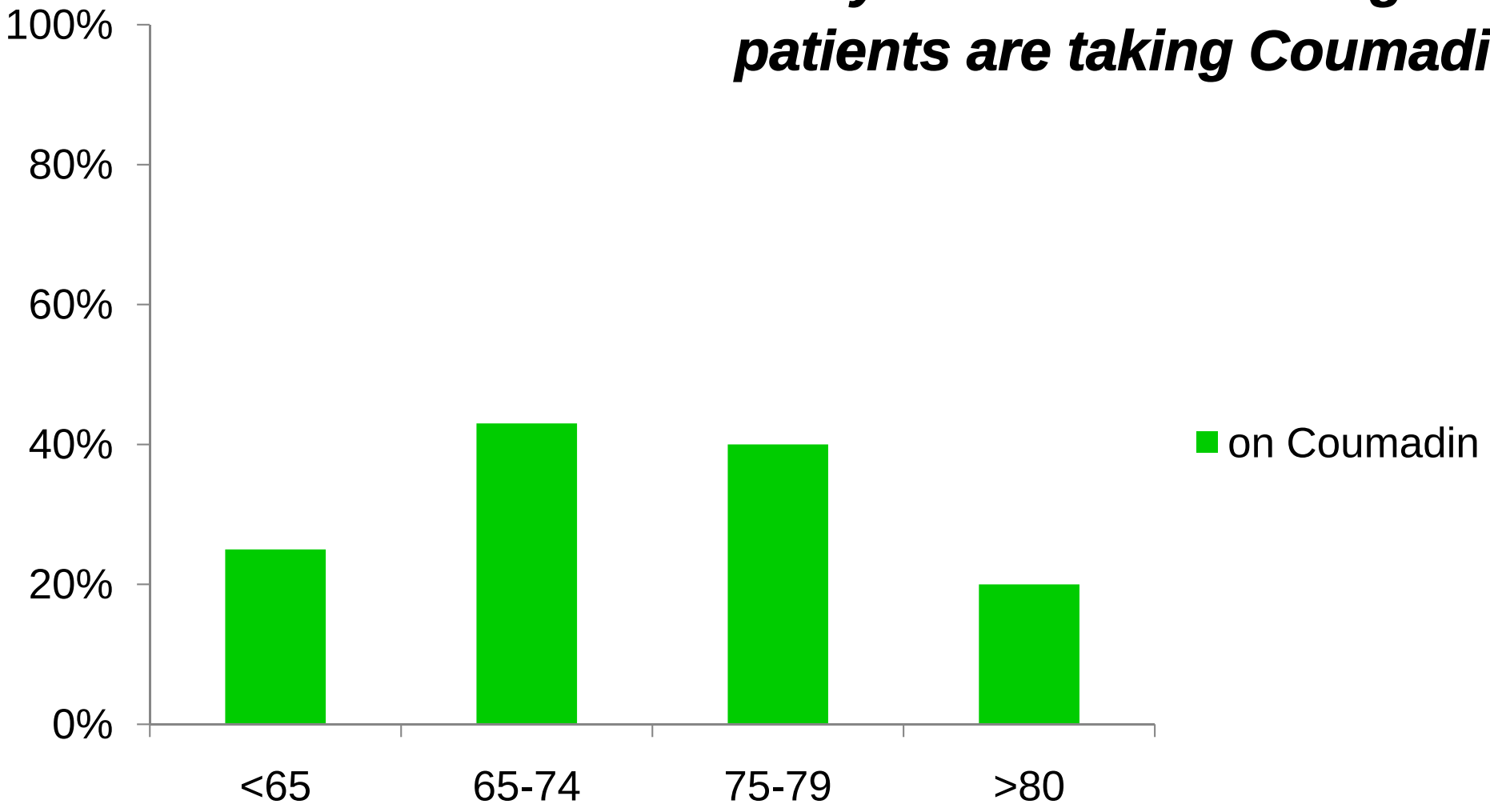
… but unfortunately it does not work in clinical practice…

… not with coumadin and not with newer drugs

- Any localized or general physical condition in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Any personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation
- Pregnancy
- Hemorrhagic tendencies
- Blood dyscrasias.
- Recent or contemplated surgery of central nervous system
- Recent or contemplated surgery of the eye
- Recent or contemplated traumatic surgery resulting in large open surfaces
- Gastrointestinal bleeding
- Genitourinary tract bleeding
- Respiratory tract bleeding
- Cerebrovascular hemorrhage
- Cerebral aneurysms
- Dissecting aorta
- Pericarditis
- Pericardial effusions
- Bacterial endocarditis
- Threatened abortion
- Eclampsia
- Preeclampsia
- Inadequate laboratory facilities
- Unsupervised patients
- Senility
- Alcoholism
- Psychosis
- Lack of patient cooperation
- Spinal puncture
- Other diagnostic procedures with potential for uncontrollable bleeding
- Therapeutic procedures with potential for uncontrollable bleeding
- Major regional anesthesia
- Lumbar block anesthesia
- Malignant hypertension

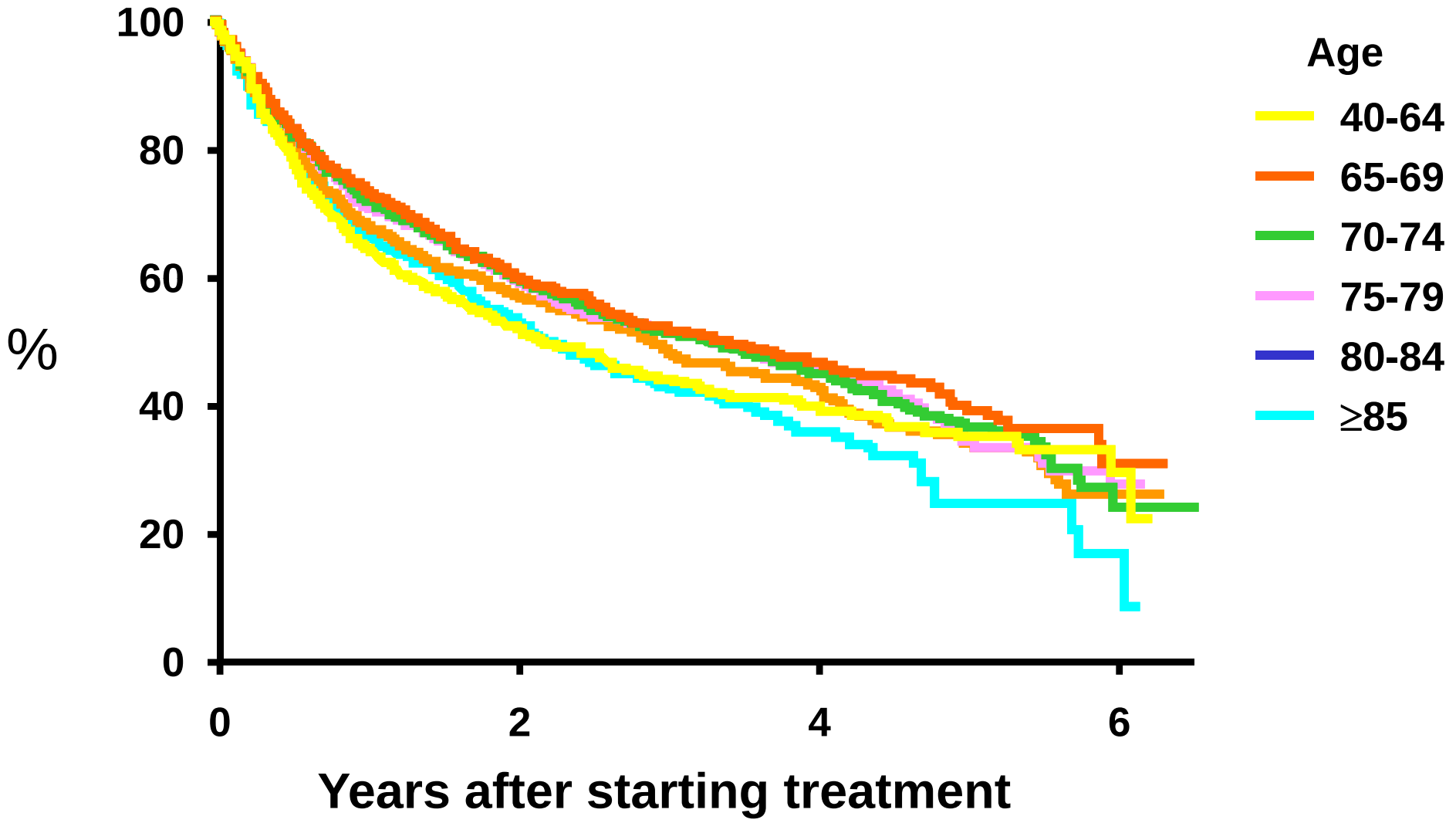
Lone Atrial Fibrillation

Only about 1/3 of all eligible patients are taking Coumadin



Stafford and Singer, Arch Int Med, 1996

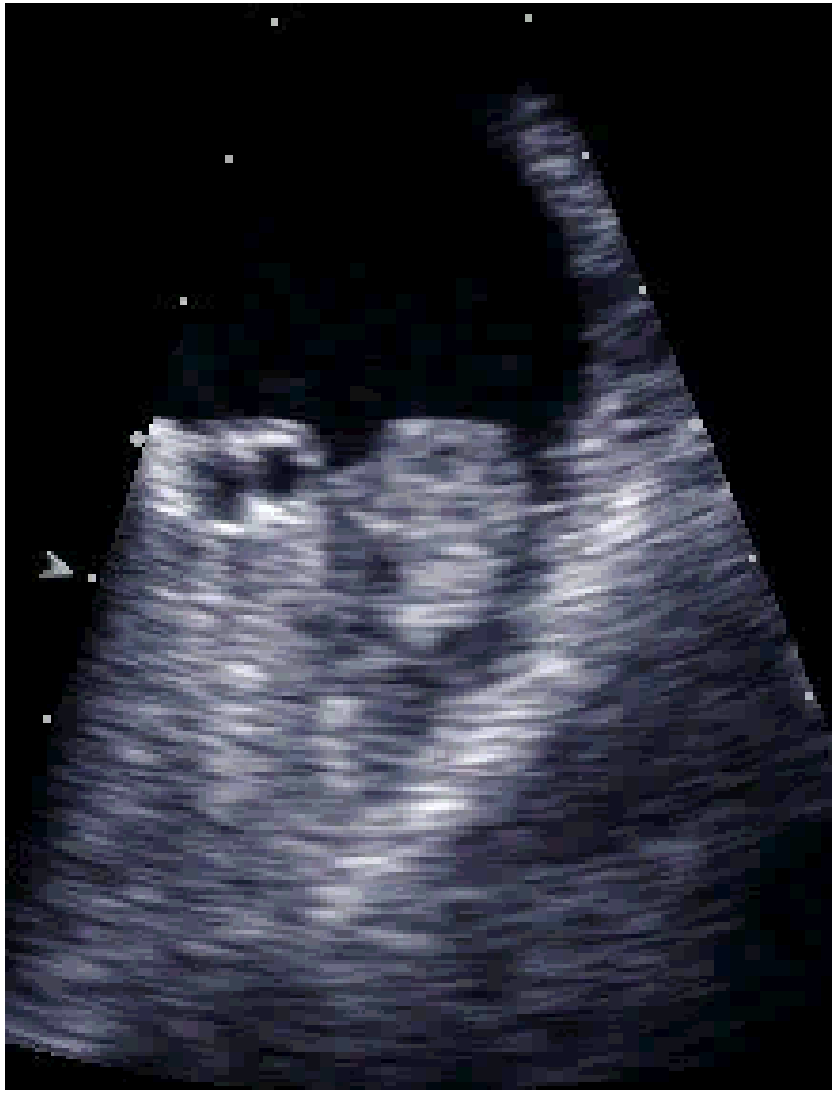
Warfarin Use in General Practice
Discontinuation



Gallagher AM et al: J Thromb Haemost 6:1500, 2008

But we know that thrombi arise in the LAA!

Not all of them but 90 %



Therefore it is logical to close the LAA

LAA closure
is a causal therapy

Where is the evidence?

Protect AF

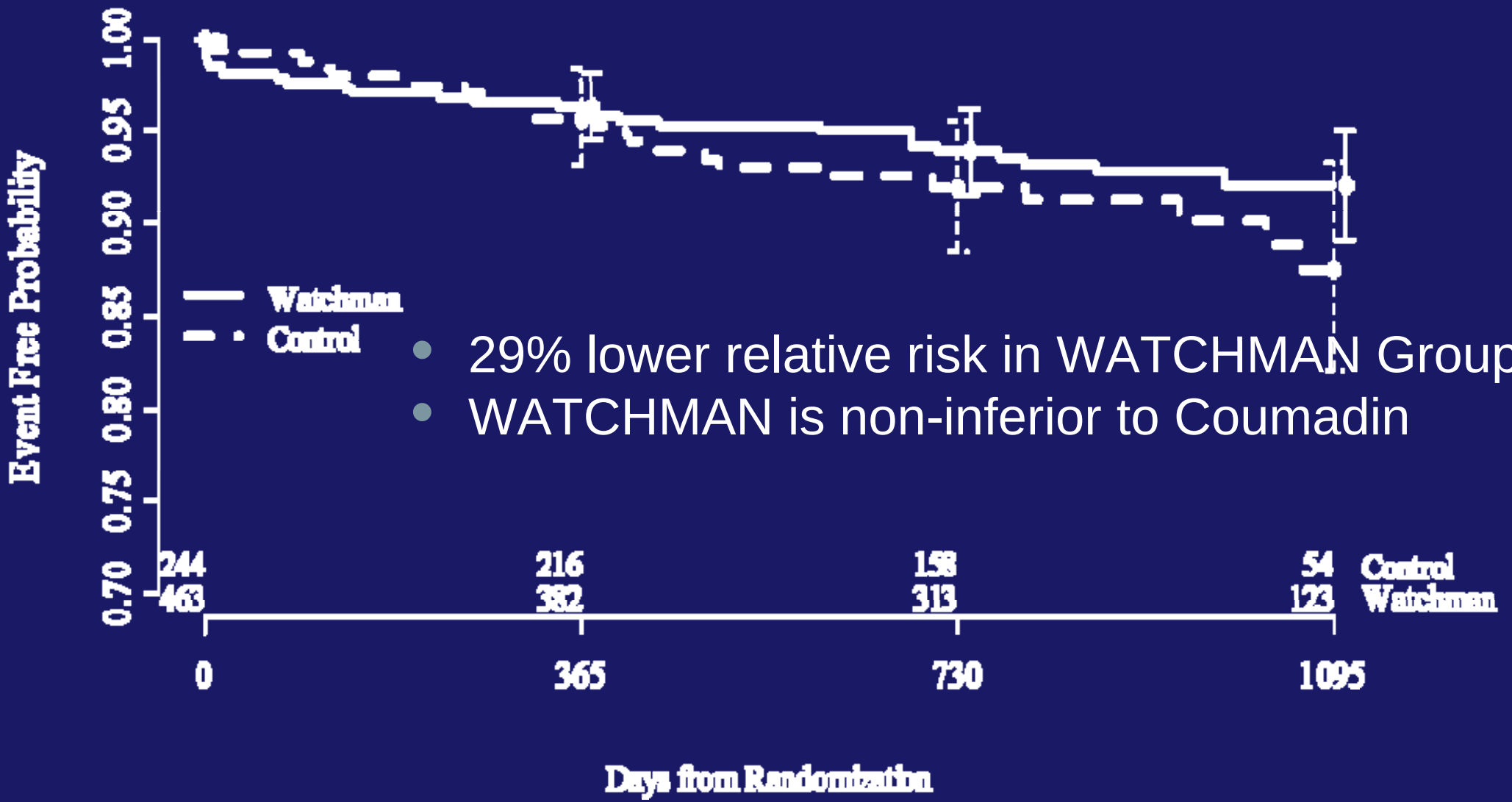
(System for Embolic **PROTECT**ion
in Patients with **A**trial **F**ibrillation)

- Multicenter
- Prospective randomized, FDA controled
- WATCHMAN gen 2 vs coumadin 2:1
- Non-inferiority trial
- 800 pts
- 1500 patient-years

Holmes D, et al Lancet 2009

Primary Efficacy Endpoint

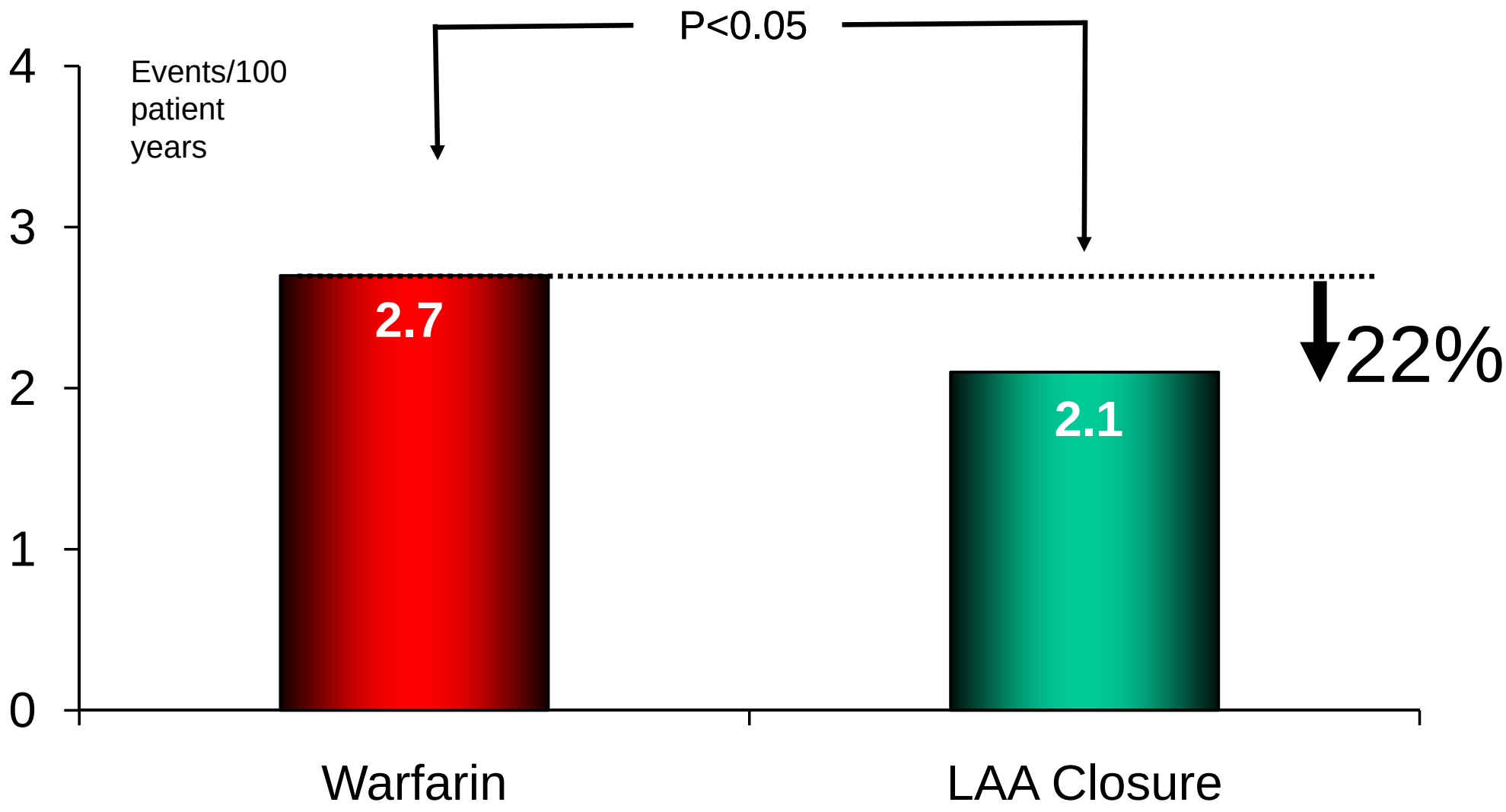
Freedom from Stroke, Death, Systemic Embolization



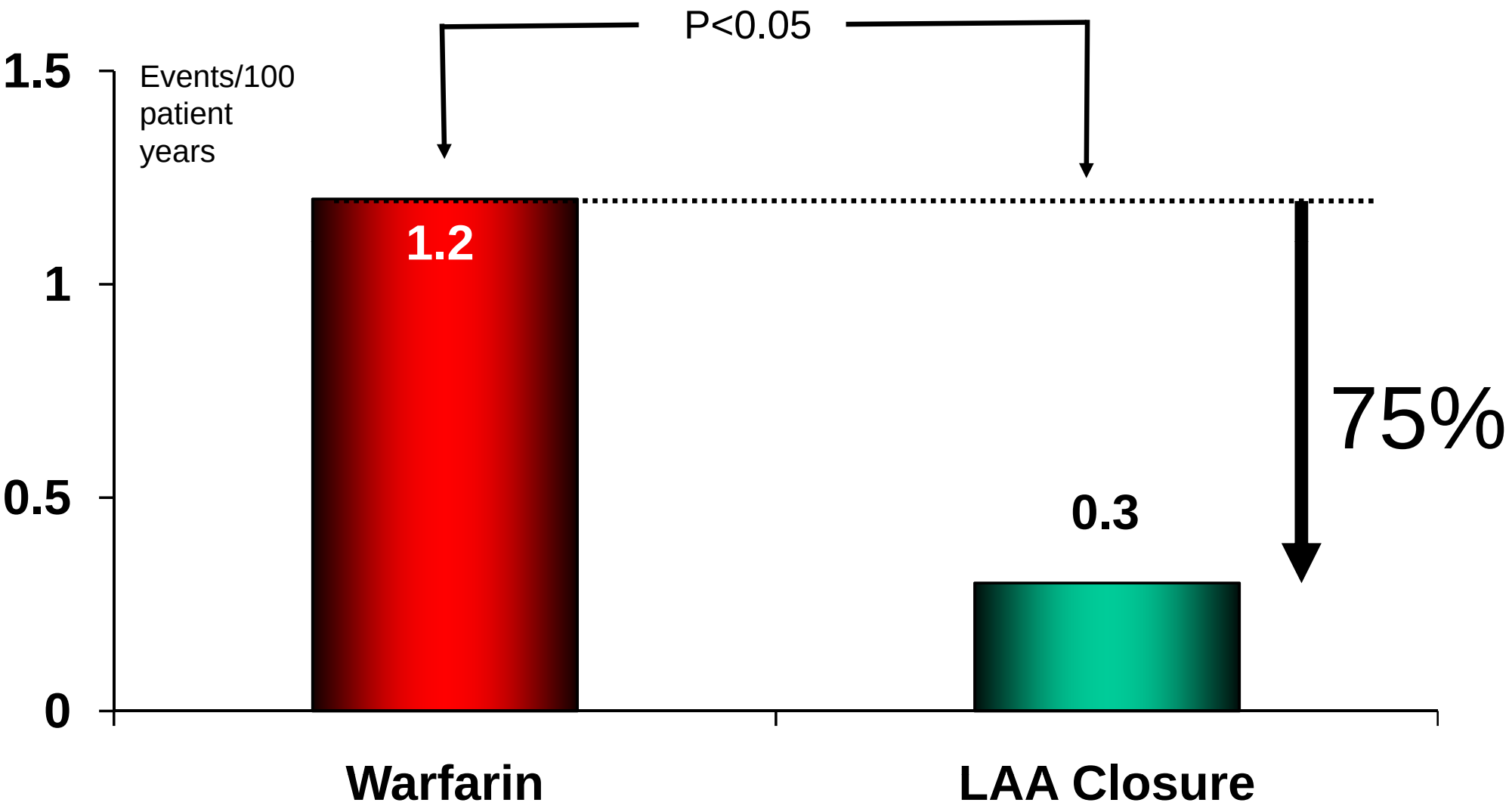
- 29% lower relative risk in WATCHMAN Group
- WATCHMAN is non-inferior to Coumadin

Other significant findings

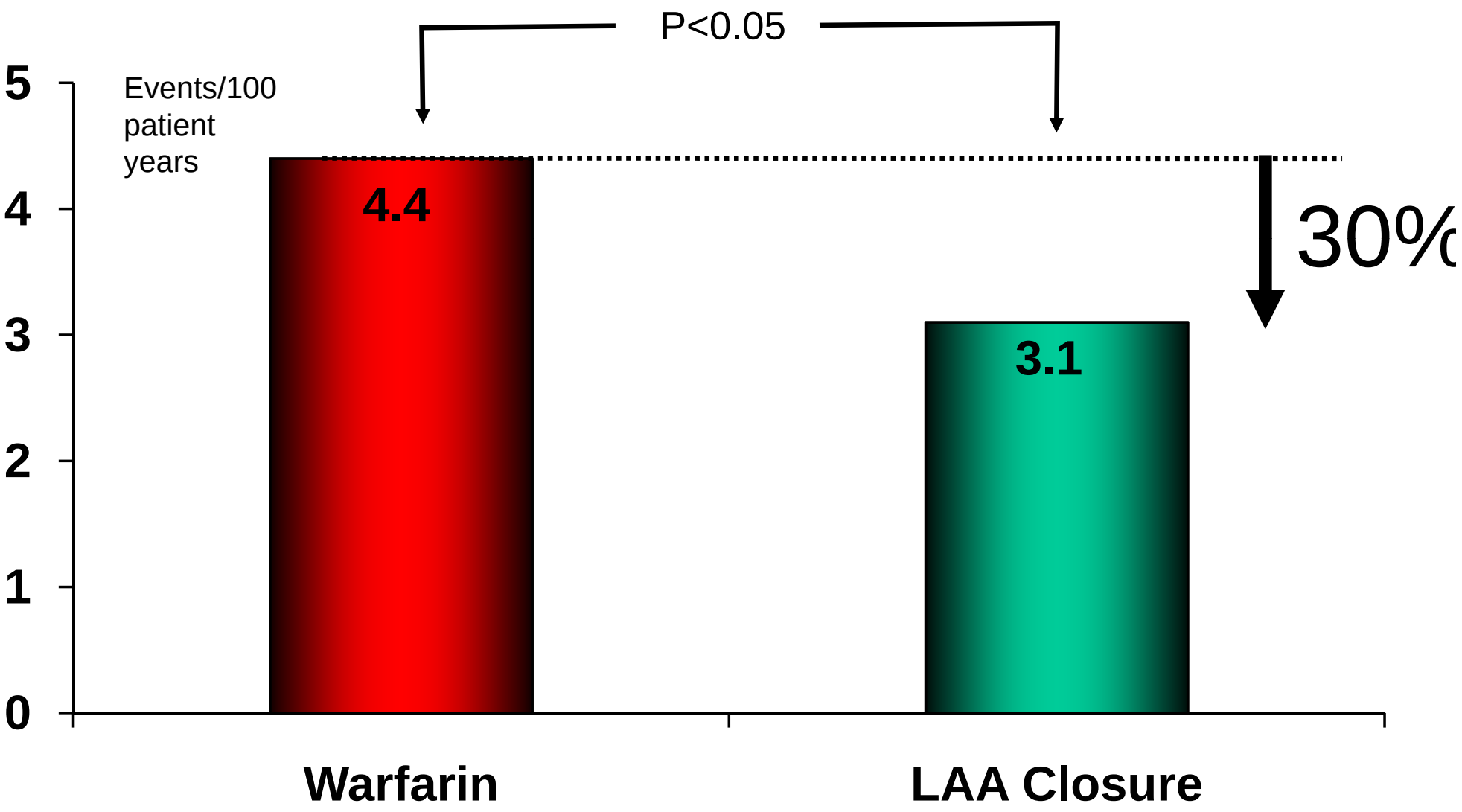
All Stroke


P<0.05
Events/100 patient years
4
3
2
1
0
2.7
2.1
22%
Warfarin
LAA Closure

Hemorrhagic Stroke

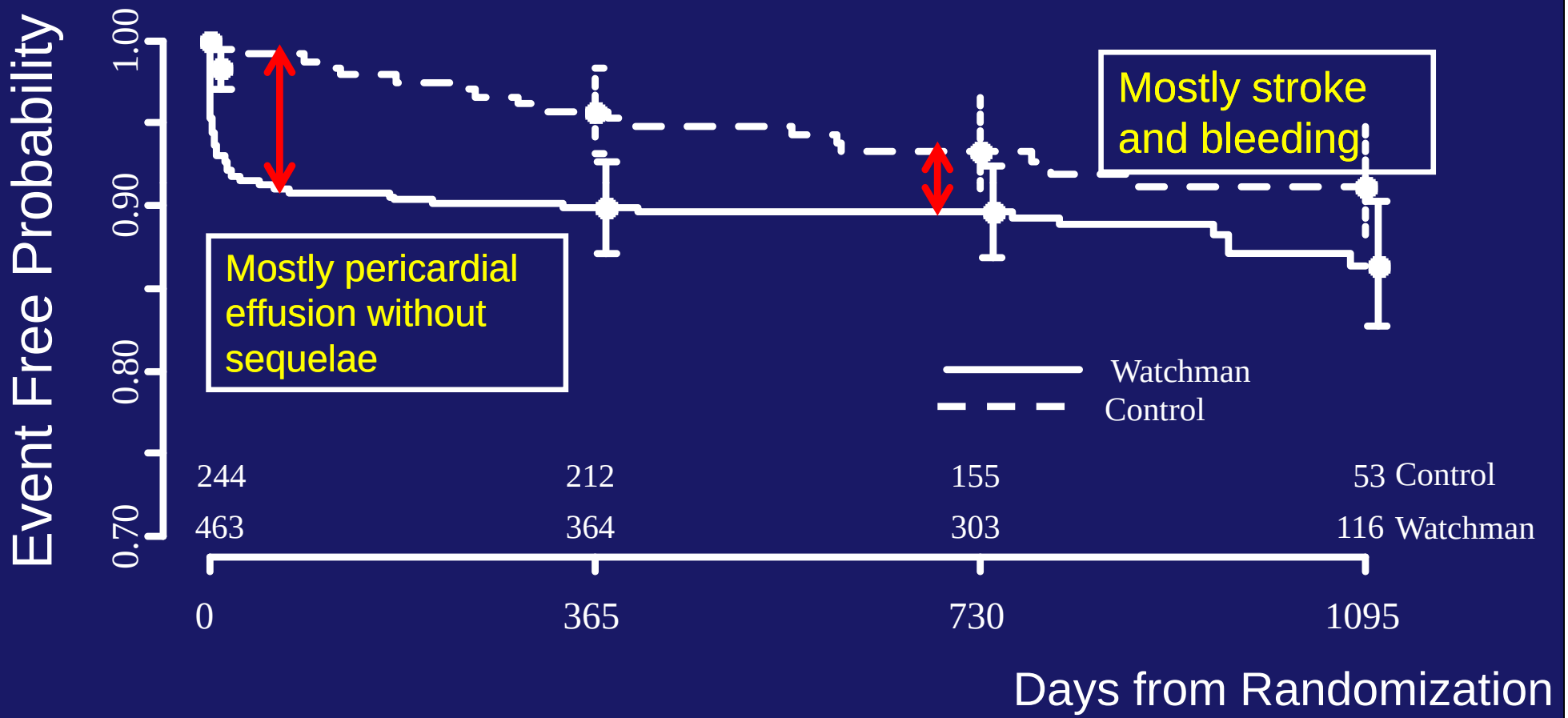


Mortality


P<0.05
Events/100 patient years
5
4
3
2
1
0
4.4
3.1
30%
Warfarin
LAA Closure

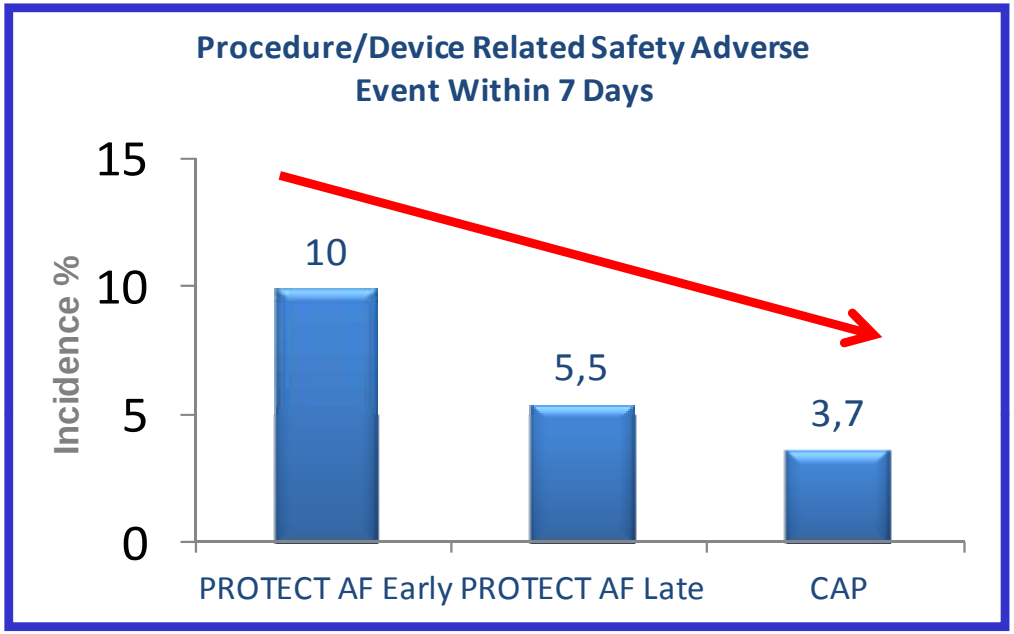
Safety

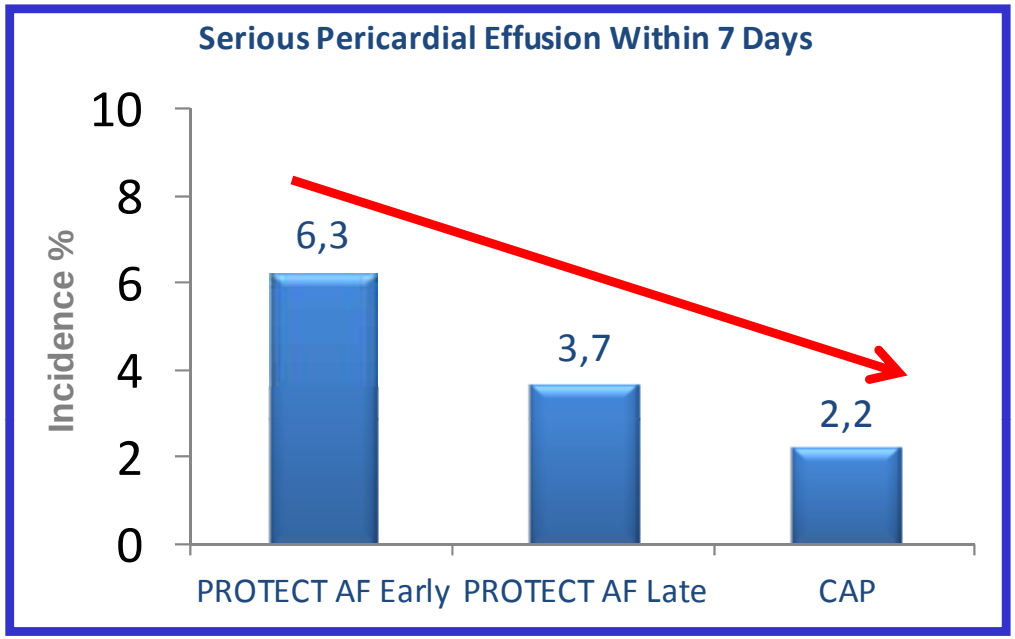
Freedom from device embolization, pericardial effusion, severe bleeding

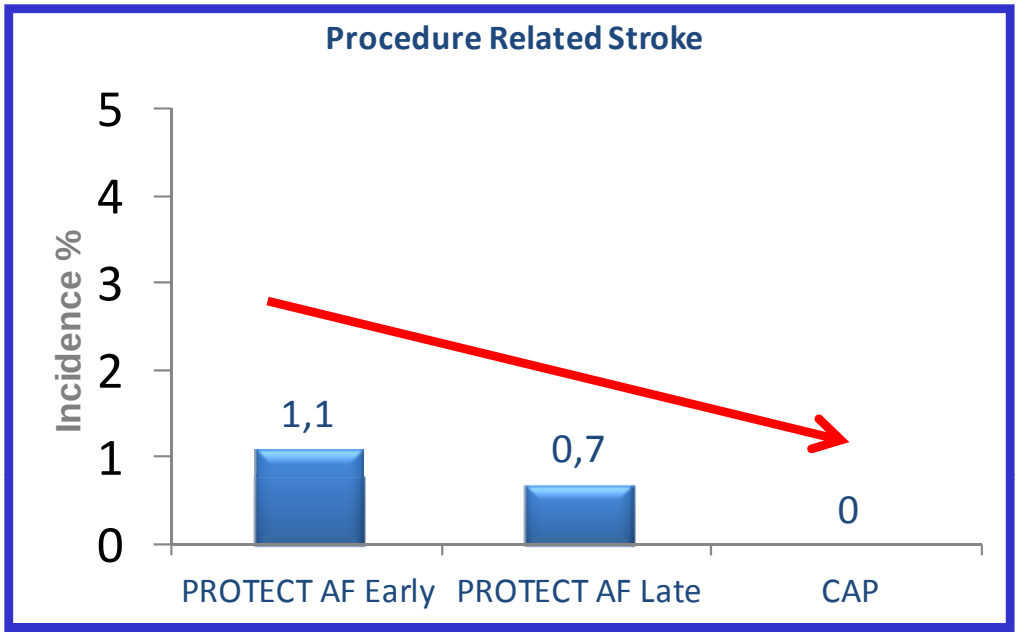


Performance – Learning Curve Effect

PROTECT-AF vs. CAP







With increased operator experience, the procedure related adverse events and serious pericardial effusions were reduced significantly. Peri-procedural strokes were eliminated

Nevertheless, LAA closure is not a trivial procedure

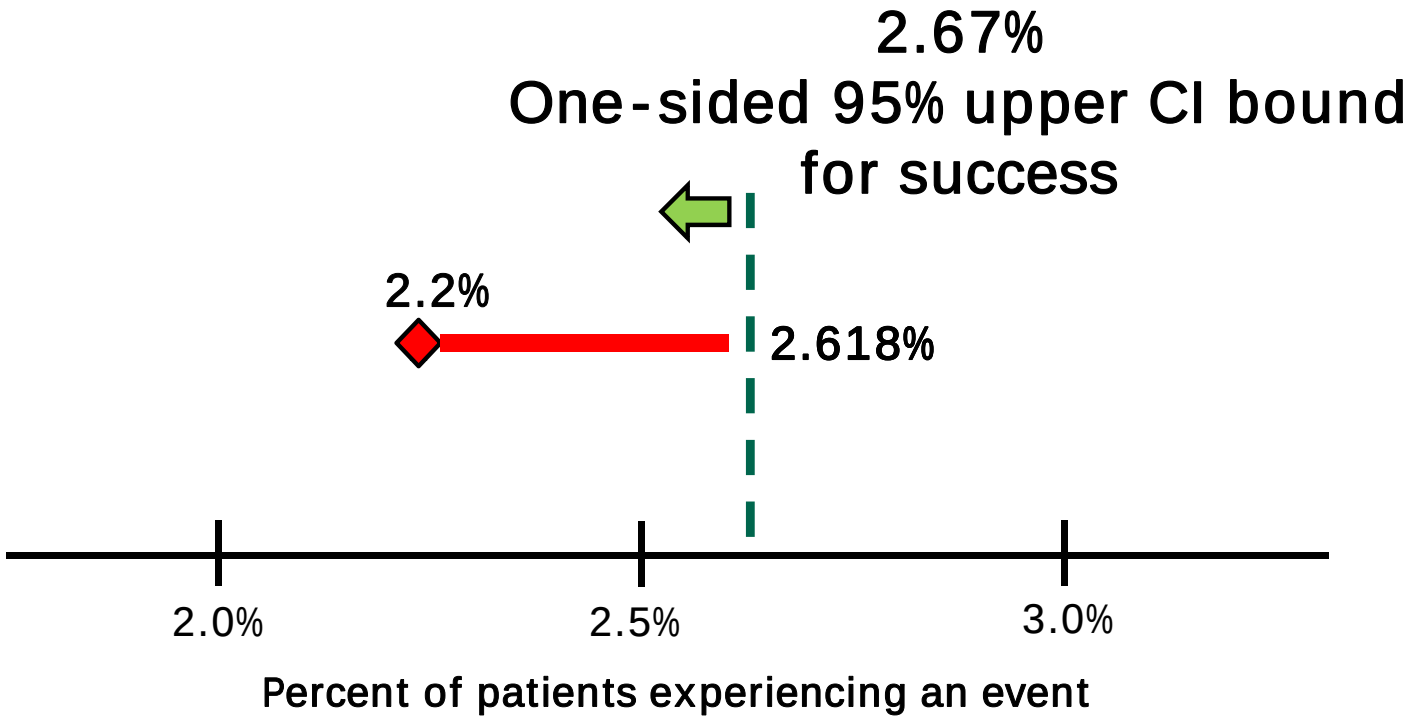
So there is a risk that with wide spread use complications become more frequent

PREVAIL

- Similar design to PROTECT AF:
  - prospective randomized 2:1 (device: control)
- 407 randomized patients
- Purpose
  - Confirm the results of PROTECT AF
  - Demonstrate improved safety profile
  - Inclusion of new operators to show enhancements to the training program are effective

First Primary Endpoint

Acute (7-day) Procedural Safety (compared to PROTECT AF)



- Significant less complications compared to PROTECT AF (95% Upper confidence bound < 2.67%)
  - 95% CI = 2.618%

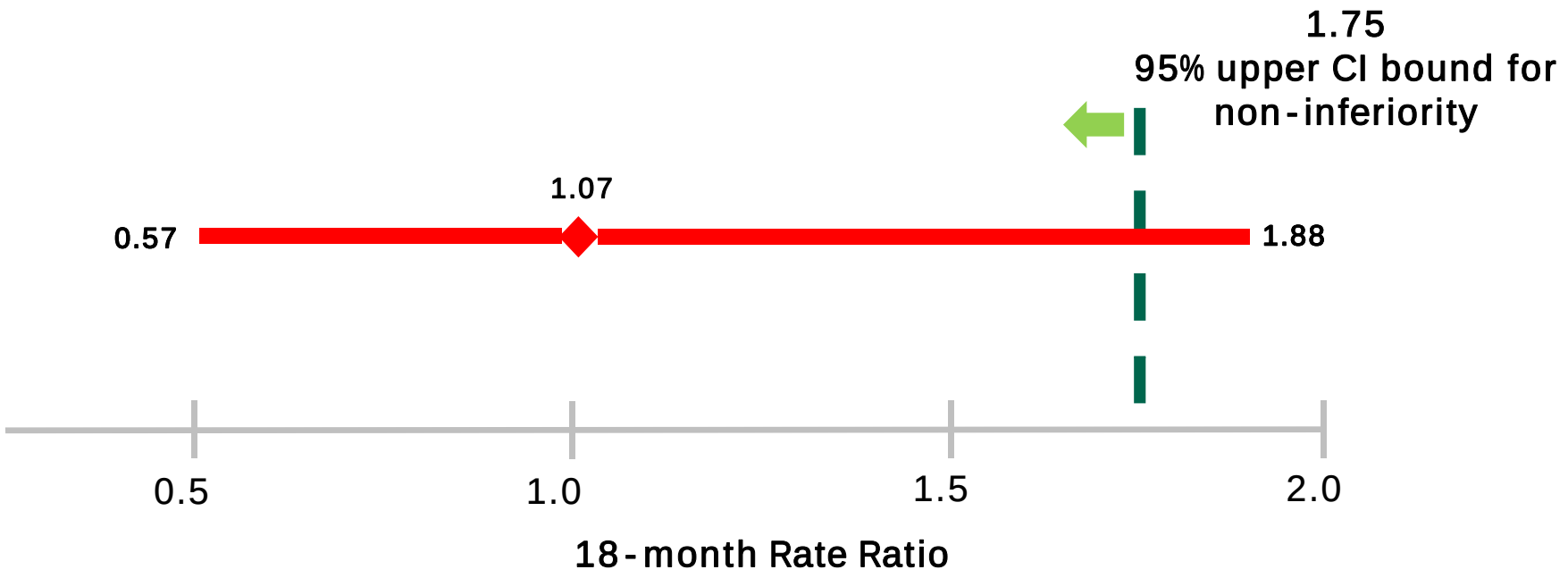
Results are preliminary; final validation not yet complete

PREVAIL
Technical Success and Complications

- Higher success rate p=0.04
- Less vascular complications p=0.004
- Less procedural stroke p=0.007
- Less tamponade needing surgery p=0.027
- Comparable results in experienced vs inexperienced operators

Second Primary Endpoint

18-month stroke, systemic embolism, and cardiovascular death

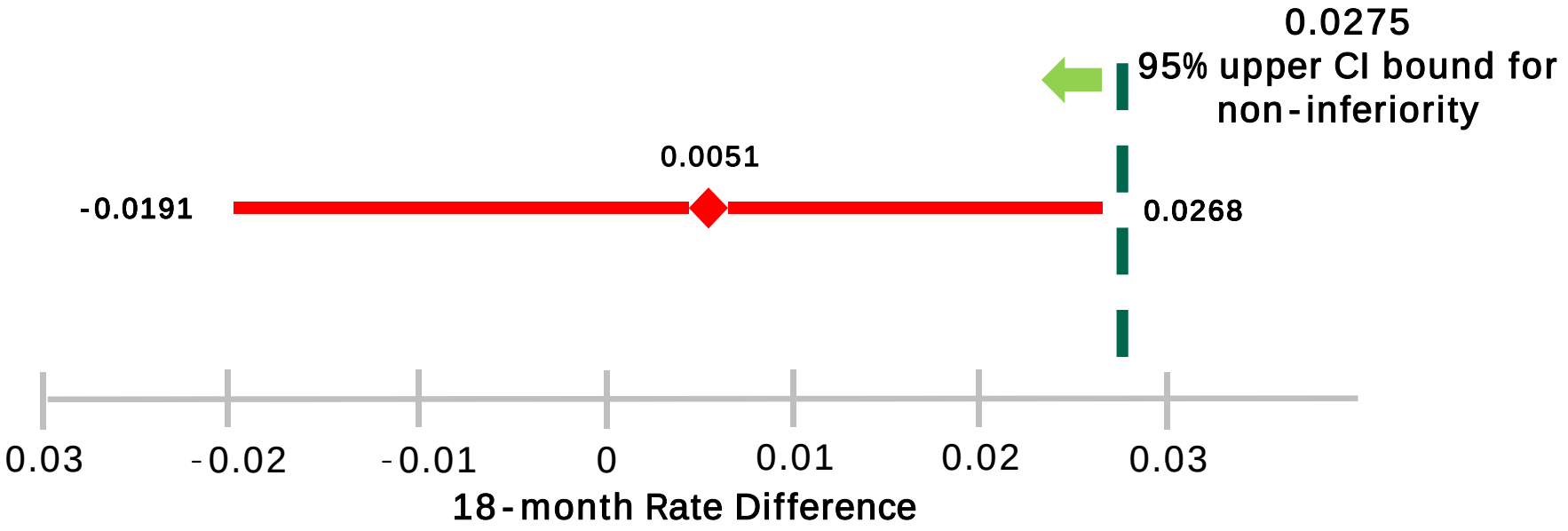


- Similar 18-month event rates in both control and device groups = 0.064
- Upper 95% CI bound slightly higher than allowed to meet success criterion (<1.75)
  - Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)

Results are preliminary; final validation not yet complete

Third Primary Endpoint

18-month Thromboembolic Events (beyond 7 days)



- LAA closure non-inferior to anticoagulation (95% CI Upper Bound < 0.0275%)

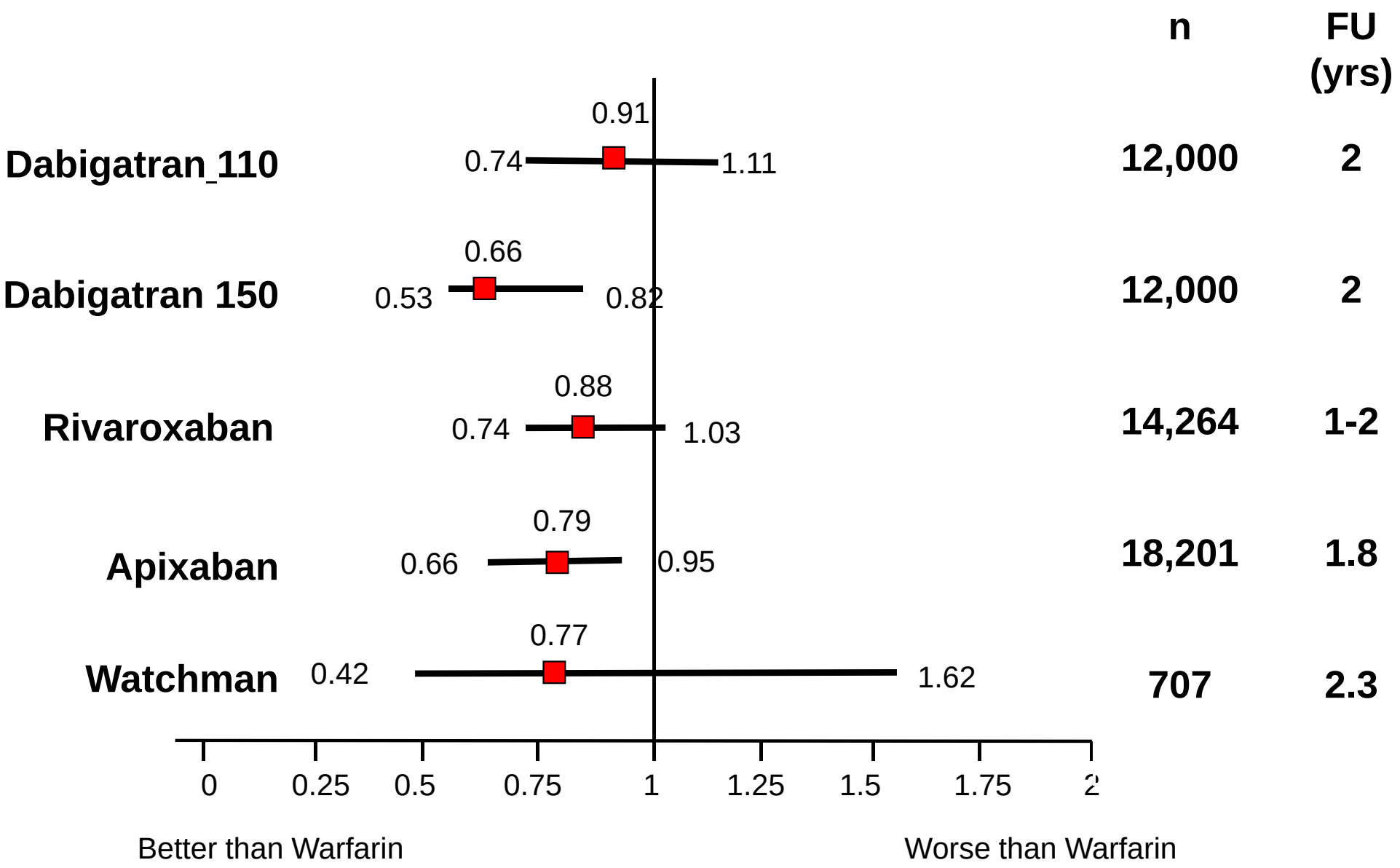
Results are preliminary; final validation not yet complete

PREVAIL did confirm the results of PROTECT AF

- Significant less procedural complications than in PROTECT AF
  - Despite including new operators
- 18 months stroke, embolism, death rate almost non-inferior to anticoagulation
  - Not significant yet due to small patient number and low event rate
- 18 months stroke/embolism rate non inferior to anticoagulation

New anticoagulants

New anticoagulants are better than warfarin



LAA closure has to be tested against new anticoagulants?

Or new anticoagulants against LAA closure?

And all new anticoagulants against each other?

New anticoagulants

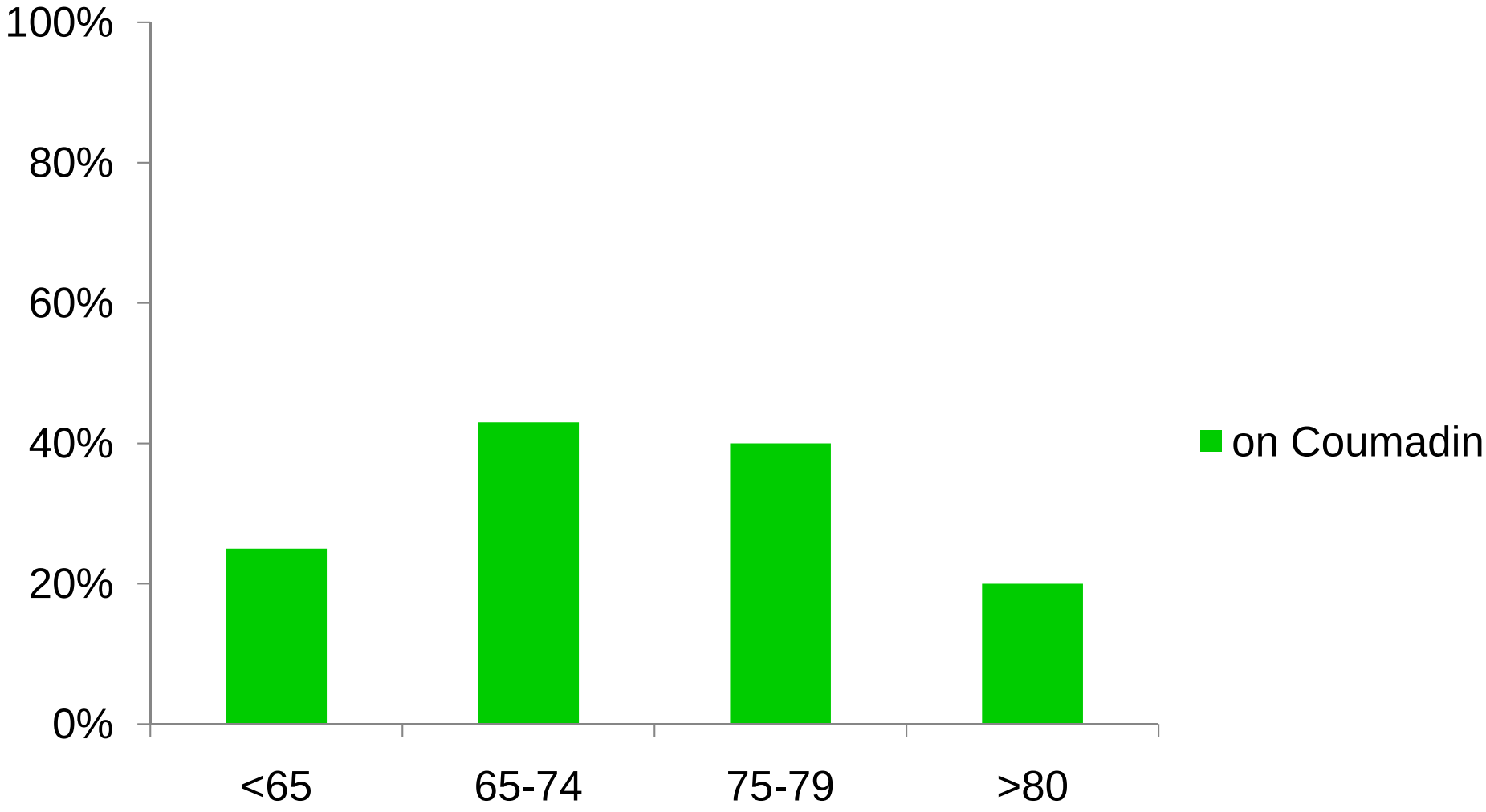
- Are easier to take, but
  - contraindicated in patients with risk of bleeding
  - not better tolerated than coumadin

All Anticoagulants

- Per definition
  - have to be given lifelong
  - have a bleeding risk
- Bleeding risk increases with age
- At some point during life anticoagulants will have to be stopped

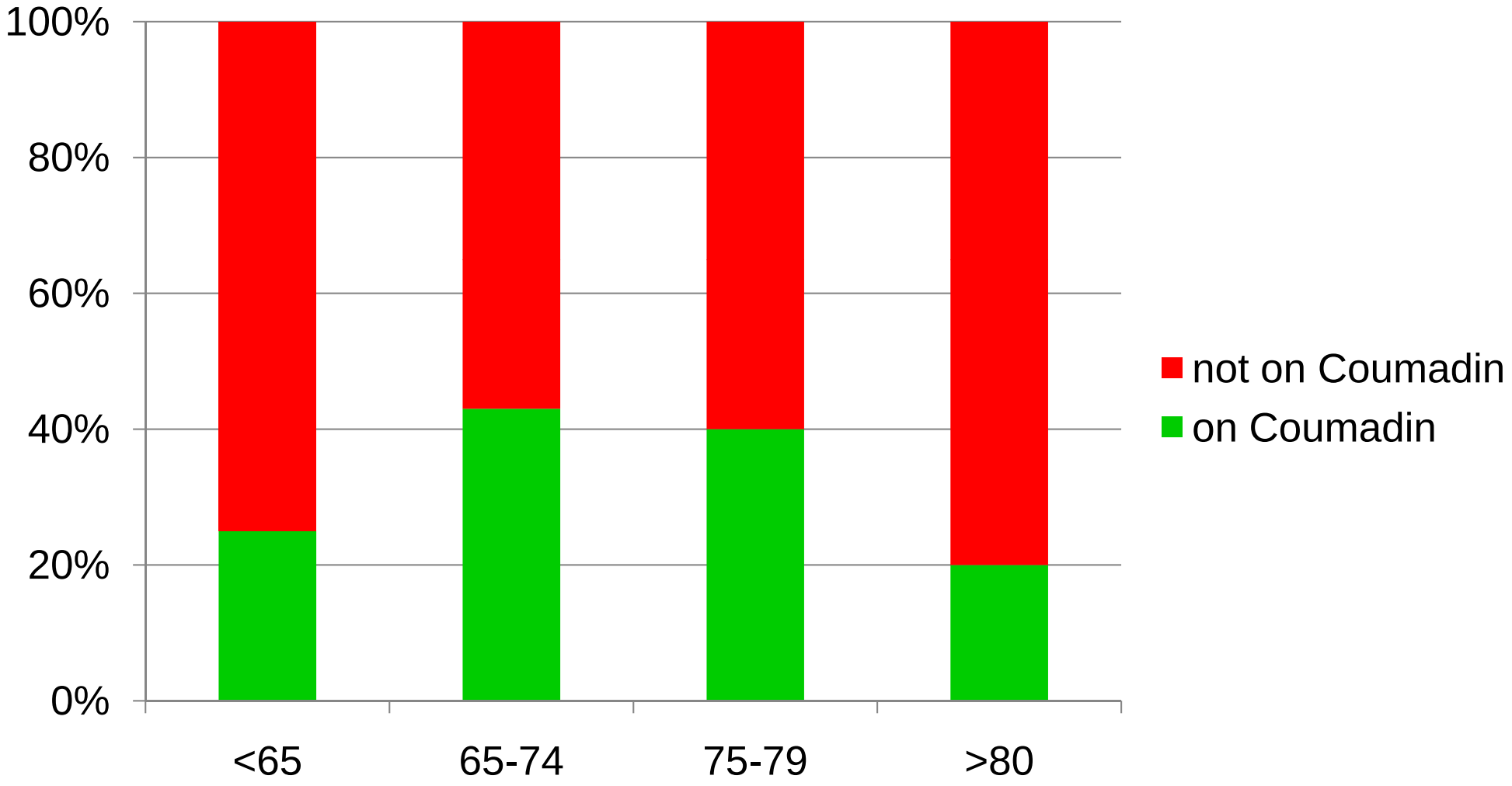
In how many of your patients with Afib should you consider LAA closure?

Lone Atrial Fibrillation



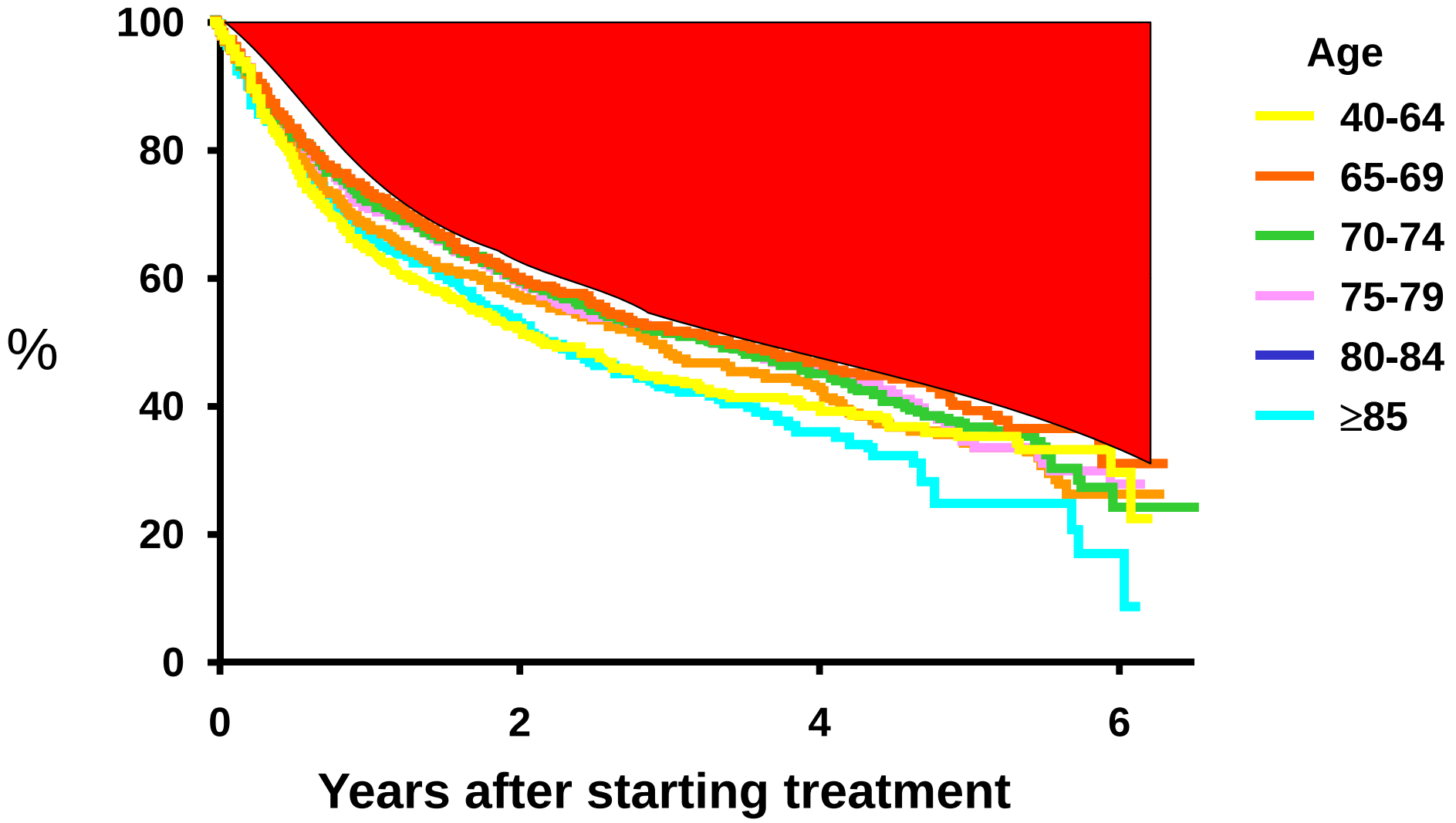
Stafford and Singer, Arch Int Med, 1996

Lone Atrial Fibrillation



Stafford and Singer, Arch Int Med, 1996

Warfarin Use in General Practice
Discontinuation



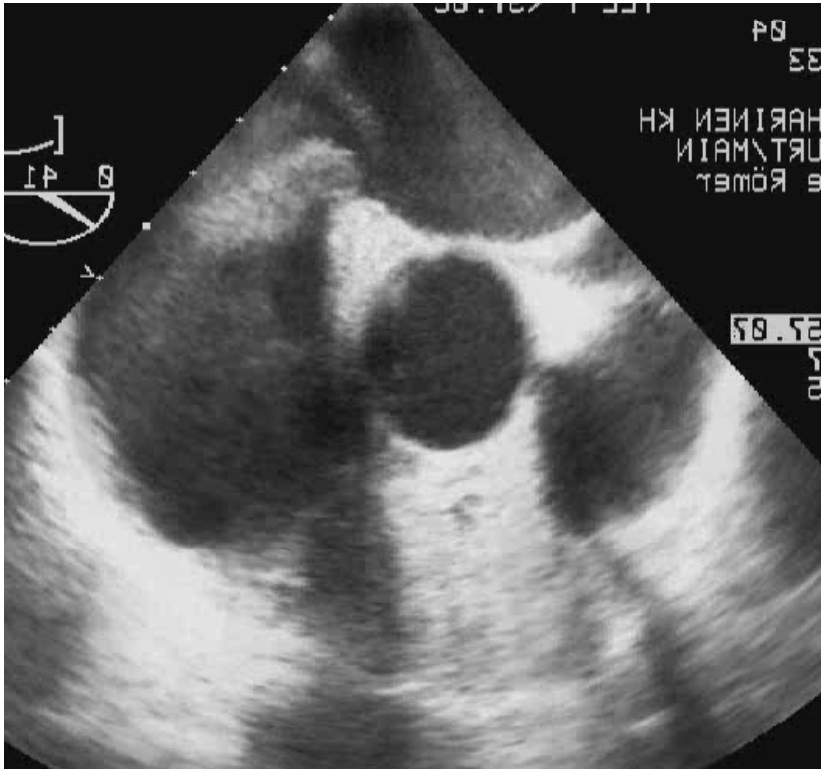
Gallagher AM et al: J Thromb Haemost 6:1500, 2008

PFO closure is different

- More common sense
- Patients feel more need
- Easier to do
- Less evidence

We know

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



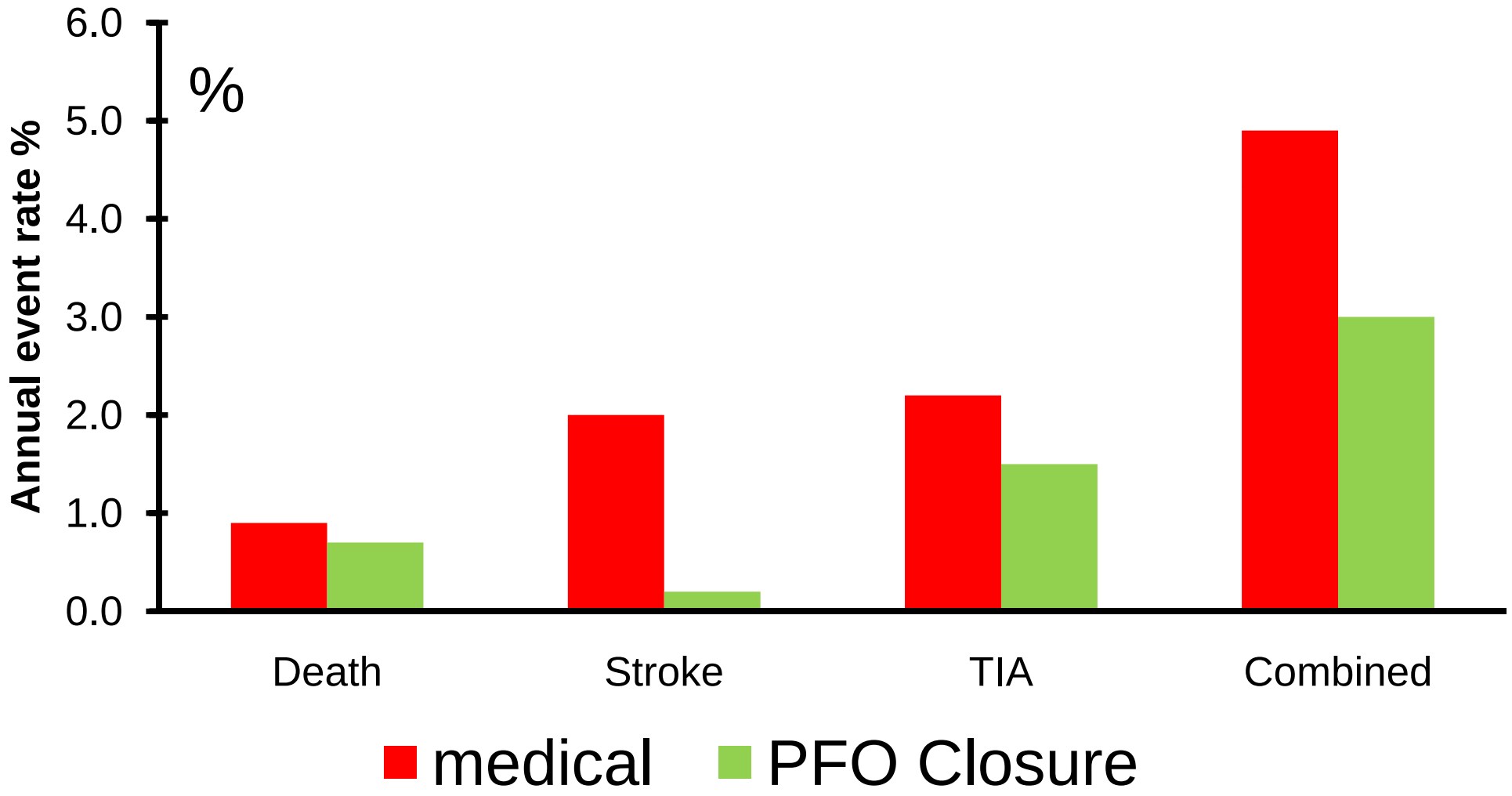
- "And you want me to wait for a second stroke??"

Today in the slide preview center:

- Jung Lim Won (Student of physiology): “What is a PFO?”
- Horst Sievert: “A small hole in the heart. A clot can go through and cause stroke”
- Student: “So it is the most important thing!”

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?

My Prediction:

- Trials will be negative
  - Some centers/operators did not have enough experience when they started the trial
  - Patient numbers are too small
  - Follow-up is too short
  - Technology outdated

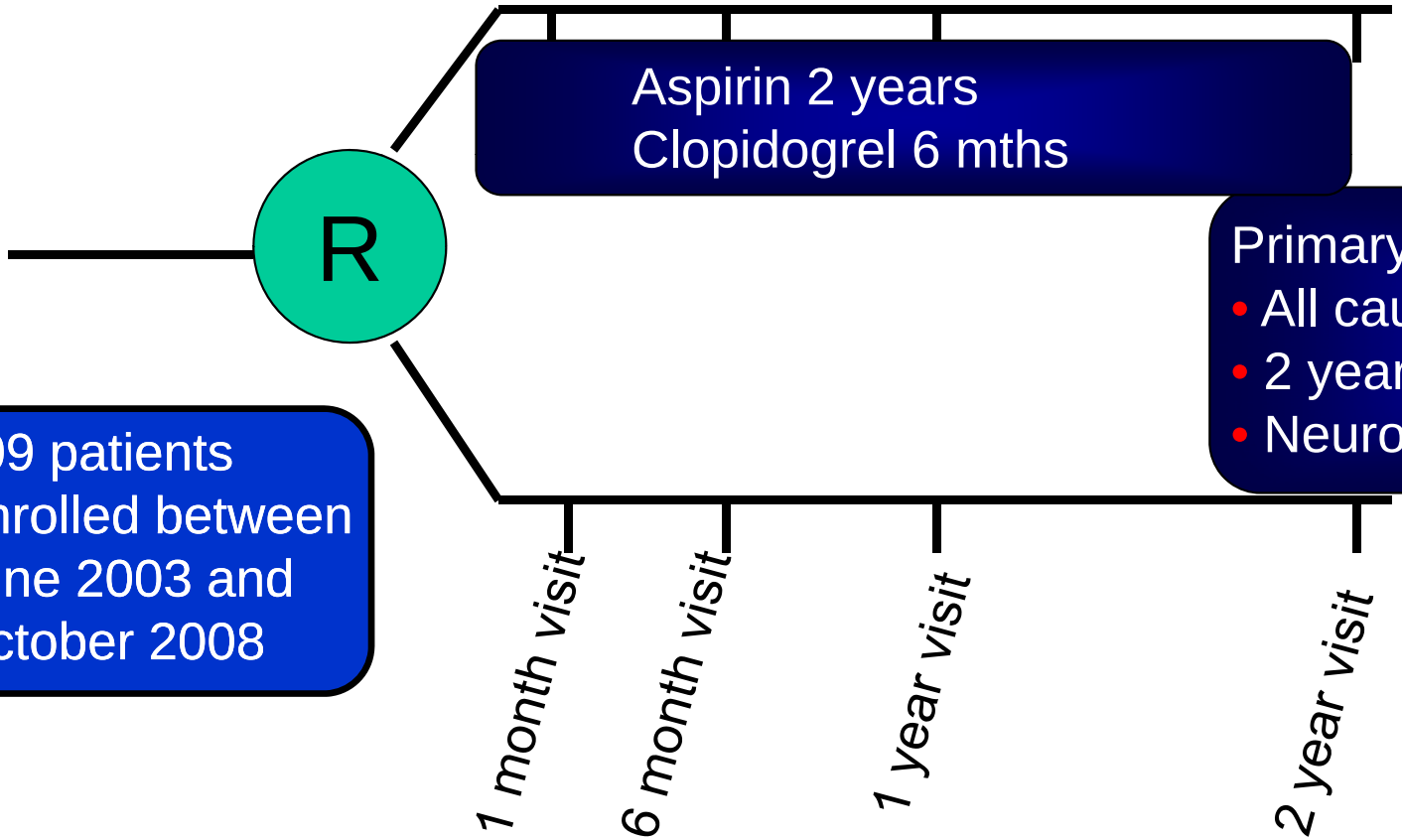
Horst Sievert, PCR 2007

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

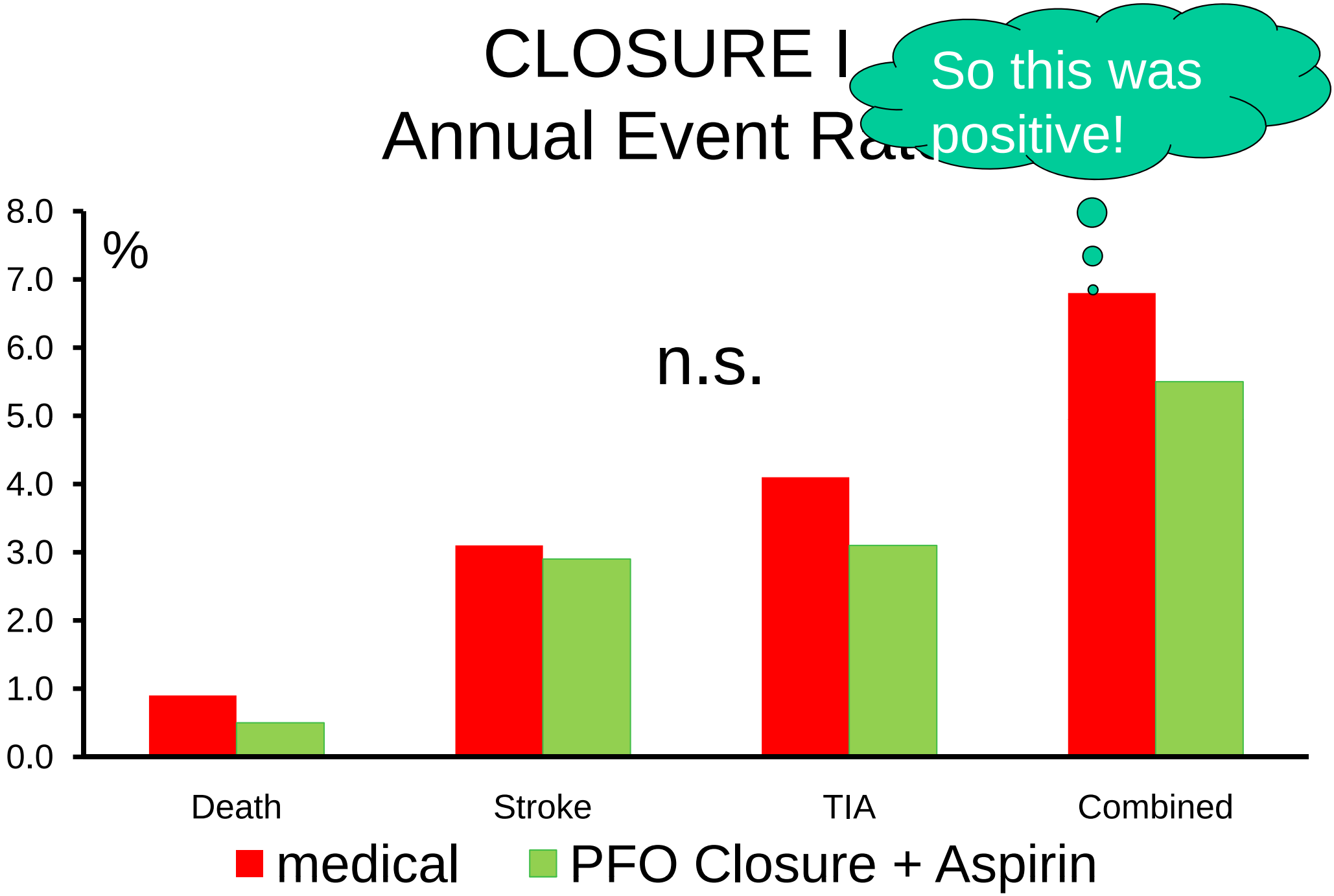
909 patients Enrolled between June 2003 and October 2008

Control Group:
Aspirin and/or Coumadin 2 years

Superiority Study

J. Furlan, AHA 2010

CLOSURE I
Annual Event Rat



AJ Furlan, AHA 2010

"CLOSURE I Issues"

- Study design
- Device
- Exclusion- inclusion criteria
- Pt number and follow-up
- Procedural complications
- Residual shunts

Any 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 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

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

RESPECT CLINICAL TRIAL

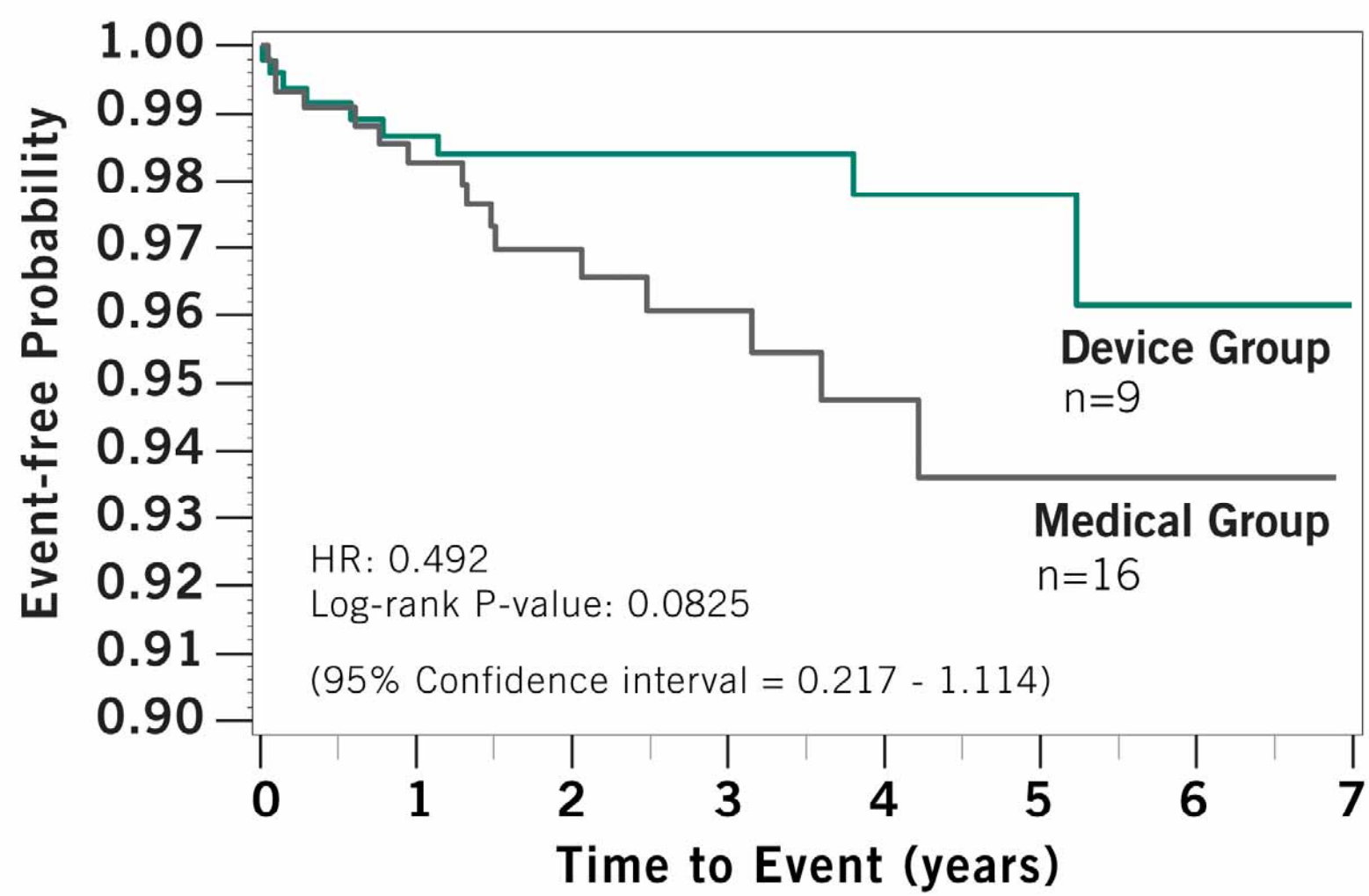
Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value[7]
Thrombus on device	0 (0%)	N/A	N/A
Device embolization	0 (0%)	N/A	N/A
Atrial fibrillation[1]	3 (0.6%)	3 (0.6%)	1
Transient ischemic attack (TIA)	3 (0.6%)	3 (0.6%)	1
Major bleeding	8 (1.6%)	9 (1.9%)	0.810
Pericardial tamponade (procedure 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 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

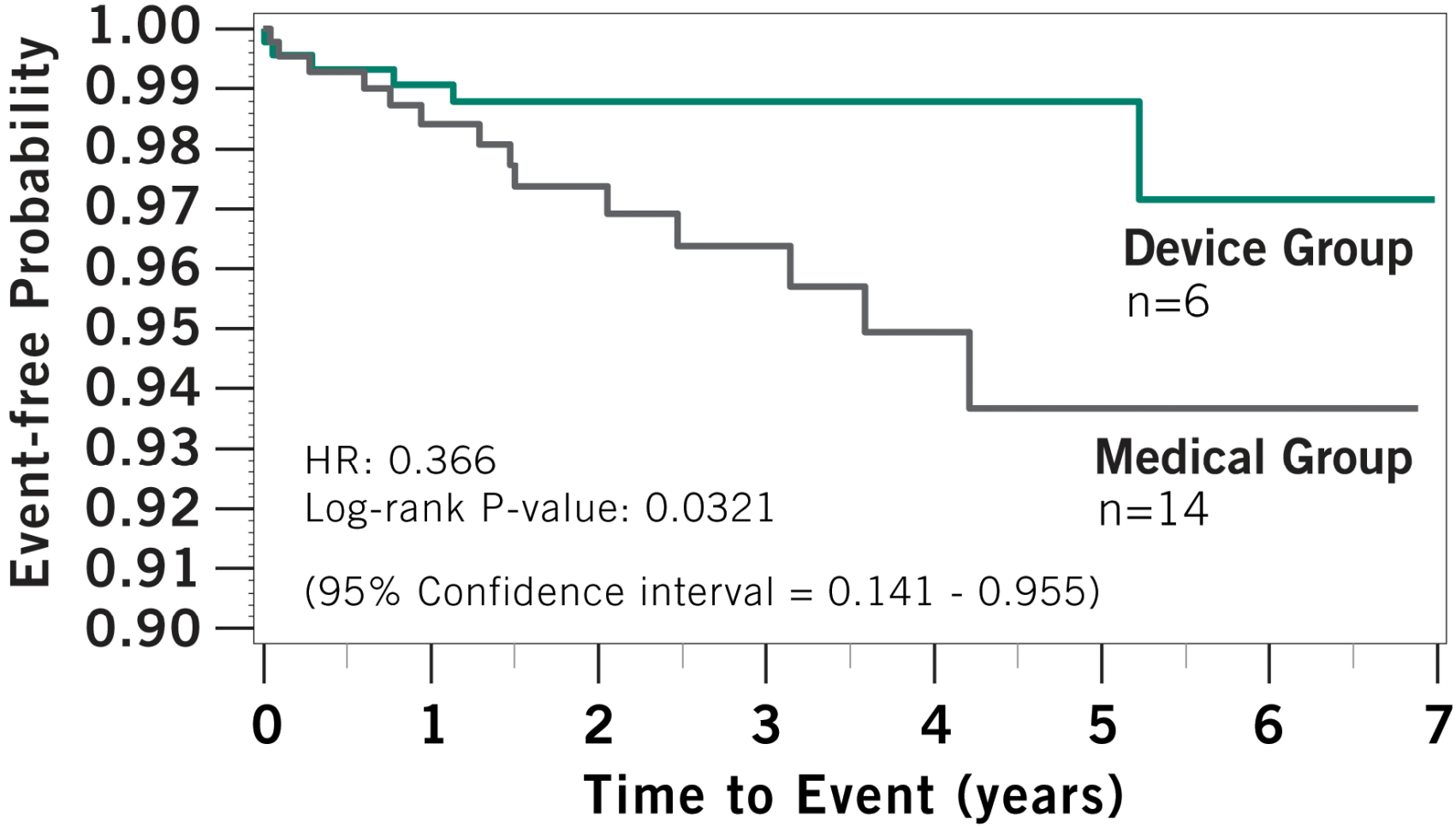
50.8% risk reduction of stroke in favor of device



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

1. Cox model used for analysis

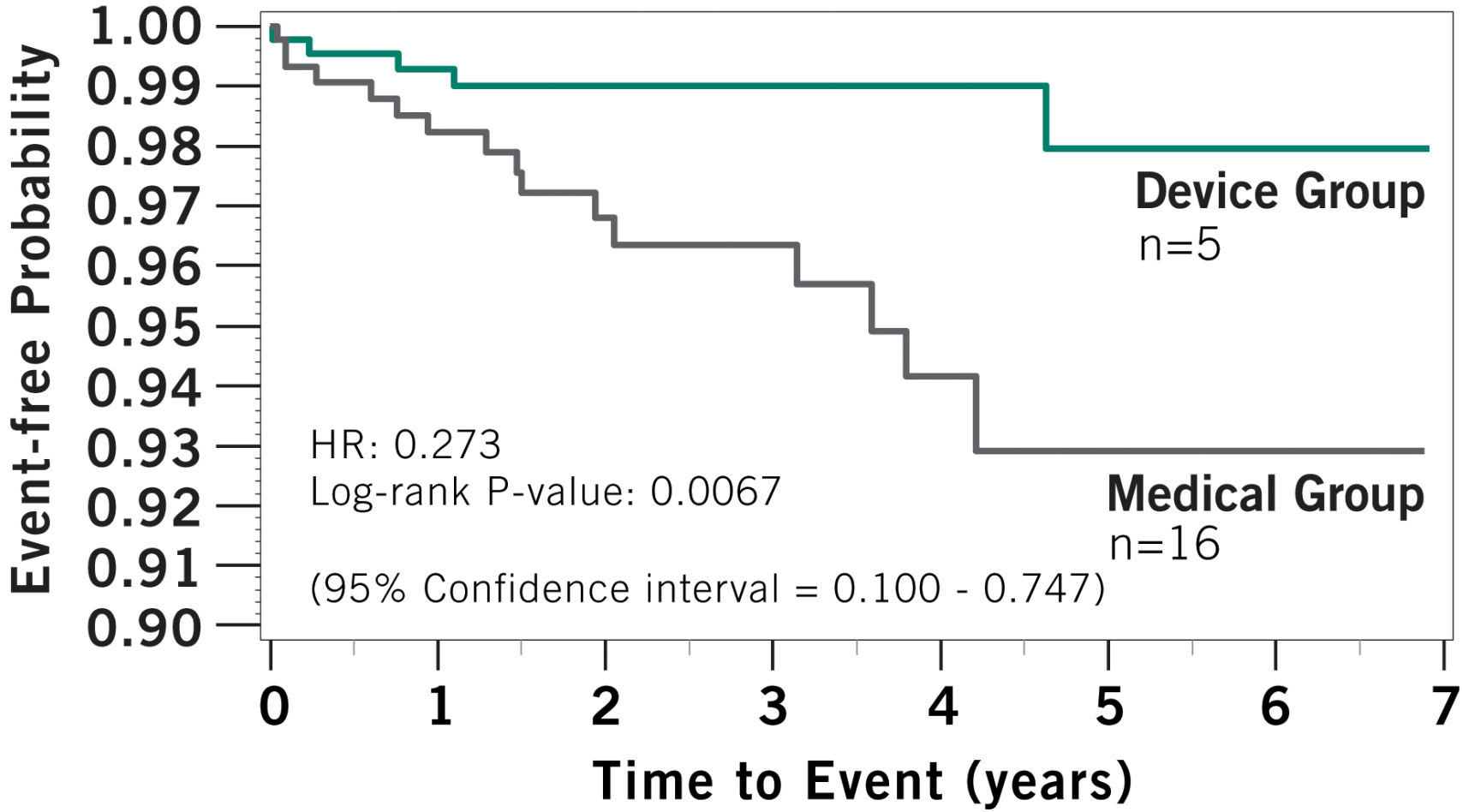
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



- 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

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

The PC Trial

NCT00166257

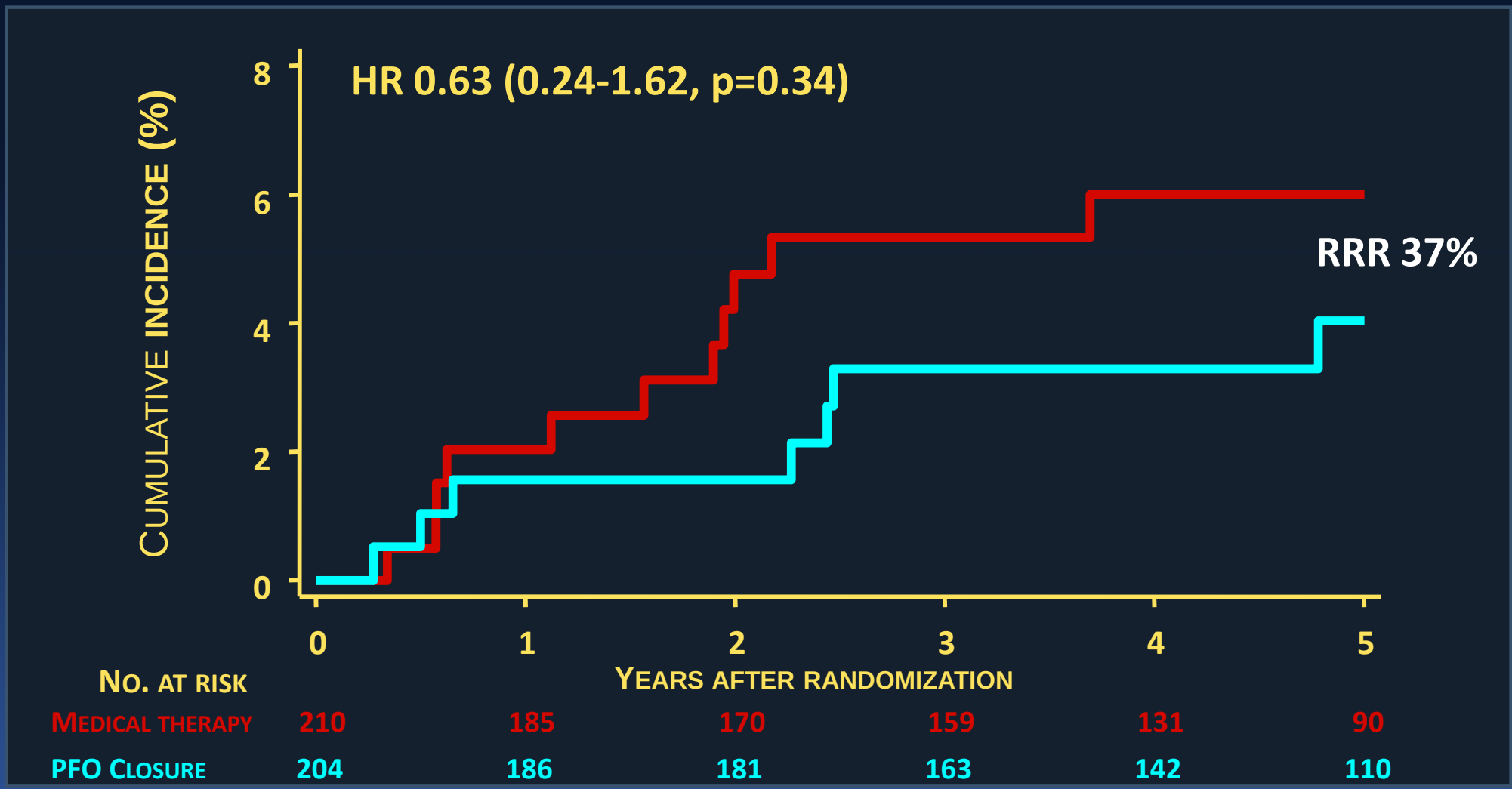
Bernhard Meier, Bindu Kalesan, Ahmed A. Khattab, David Hildick-Smith, Dariusz Dudek, Grethe Andersen, Reda Ibrahim, Gerhard Schuler, Antony S. Walton, Andreas Wahl, Stephan Windecker, Heinrich P. Mattle, and Peter Jüni

TCT2012

CARDIOVASCULAR RESEARCH FOUNDATION
a passion for innovation

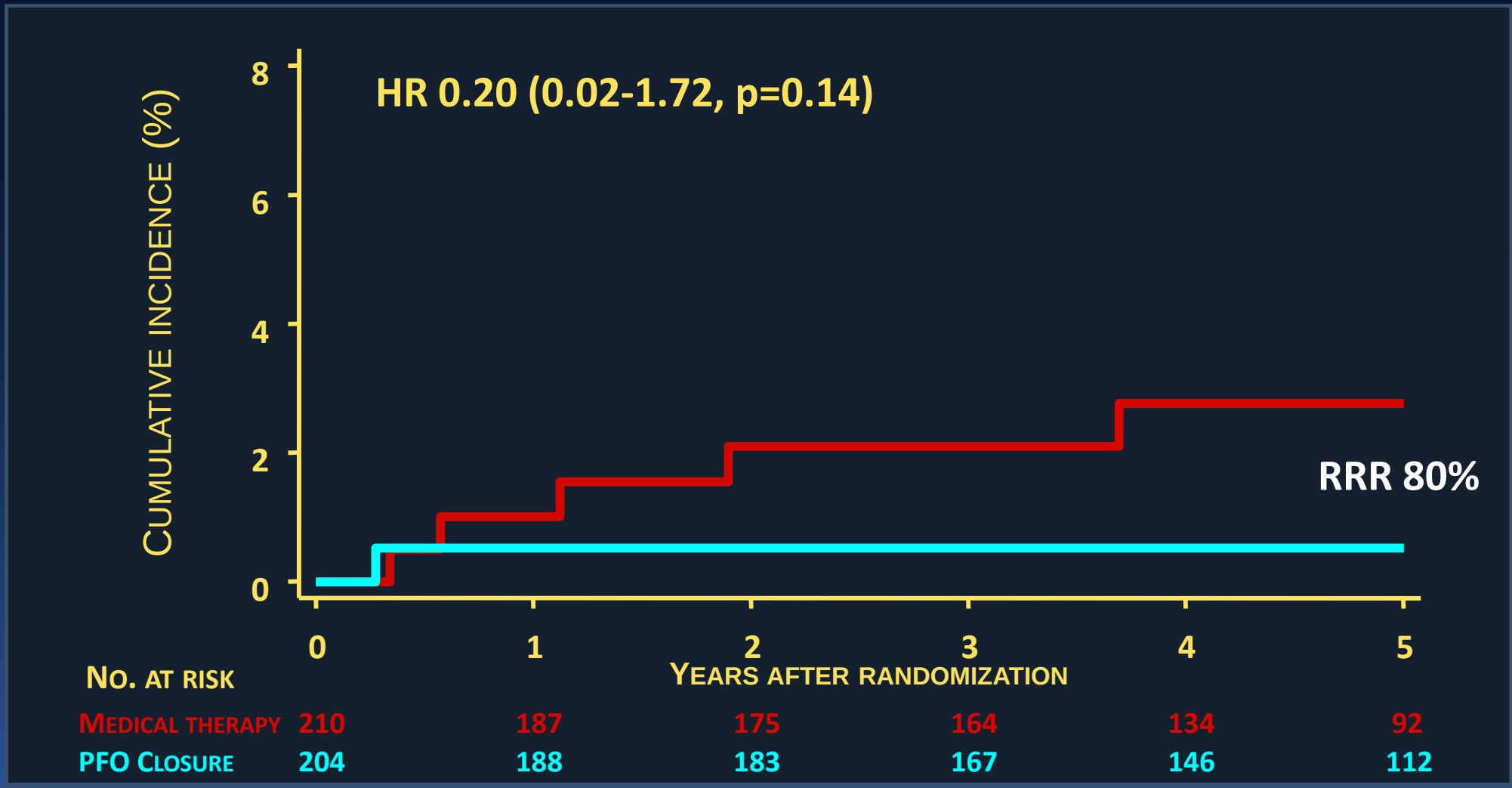
Primary Composite Endpoint

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



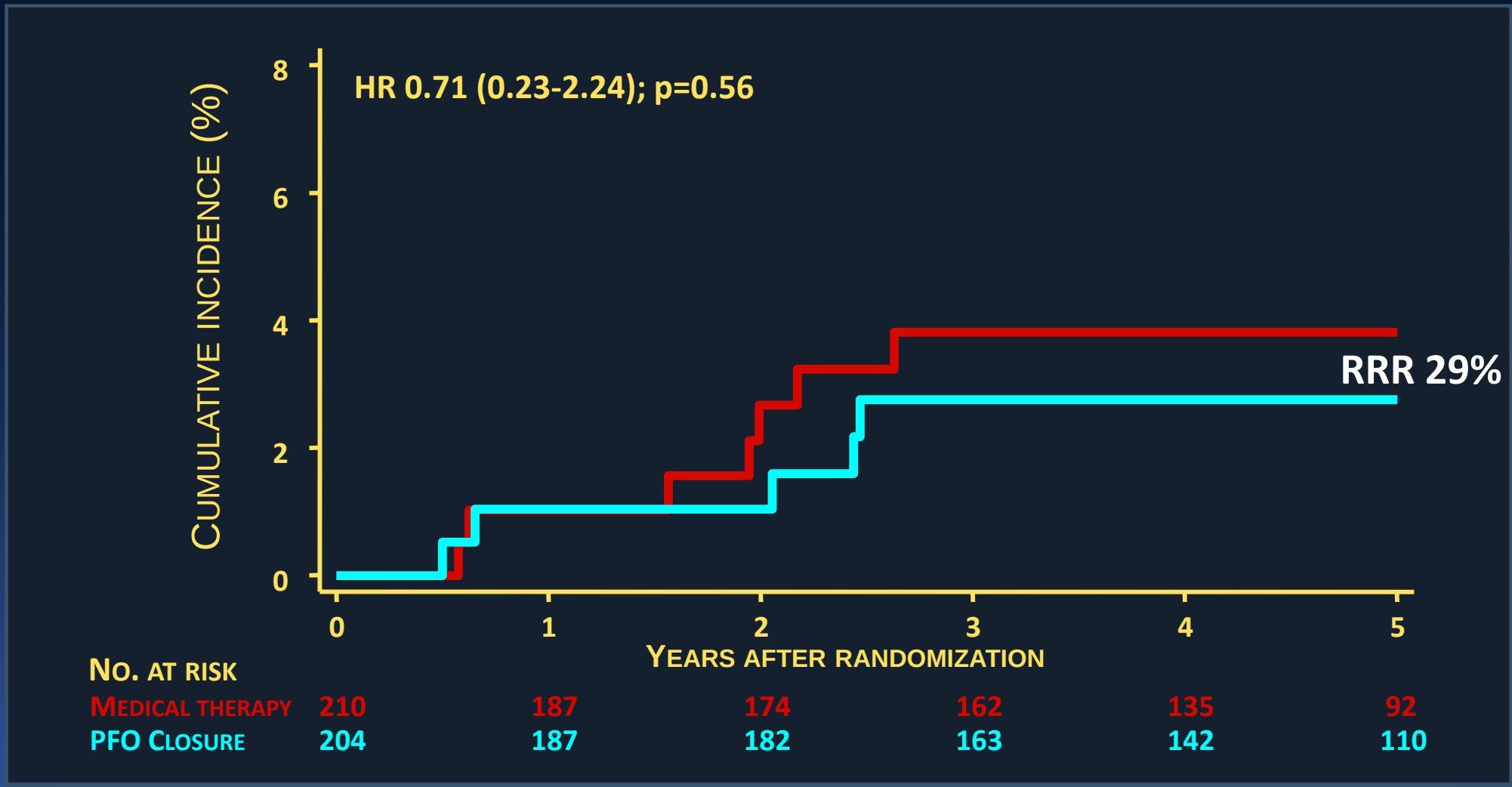
SECONDARY ENDPOINT

STROKE



Secondary Endpoint

Transient Ischemic Attack



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

Stroke reduction in randomized trials

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

These randomized trials have confirmed the results of prior non-randomized trials …

… but they had been under-powered

So if you believe only in randomized trials …

… you should not close PFOs

So what if these trials are …

- Positive, i.e. PFO closure is better than medical therapy
  - Neurologist will not believe it
- Negative, i.e. medical therapy is better than PFO closure
  - Cardiologists will not believe it
- Patients will prefer PFO closure anyway

Horst Sievert, AHA 2005