No More Device, Lack of Evidence

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Evanston Hospital

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Disclosure Information

The following relationships exist:

Grant support: Abbott, BSC,
Edwards, St Jude, WL Gore
Consultant: Abbott, BSC, Coherex, Edwards, Intervalve,
Diiachi Sankyo-Lilly, WL Gore
Speaker: Boston Scientific

Off label use of products and investigational devices will be discussed in this presentation

Evidence Base for PFO Closure

- Observational
- Retrospective
- Meta-analysis
- Prospective RCT

Paradoxical Embolism

The condition known as *crossed* or *paradoxical embolism* is defined.

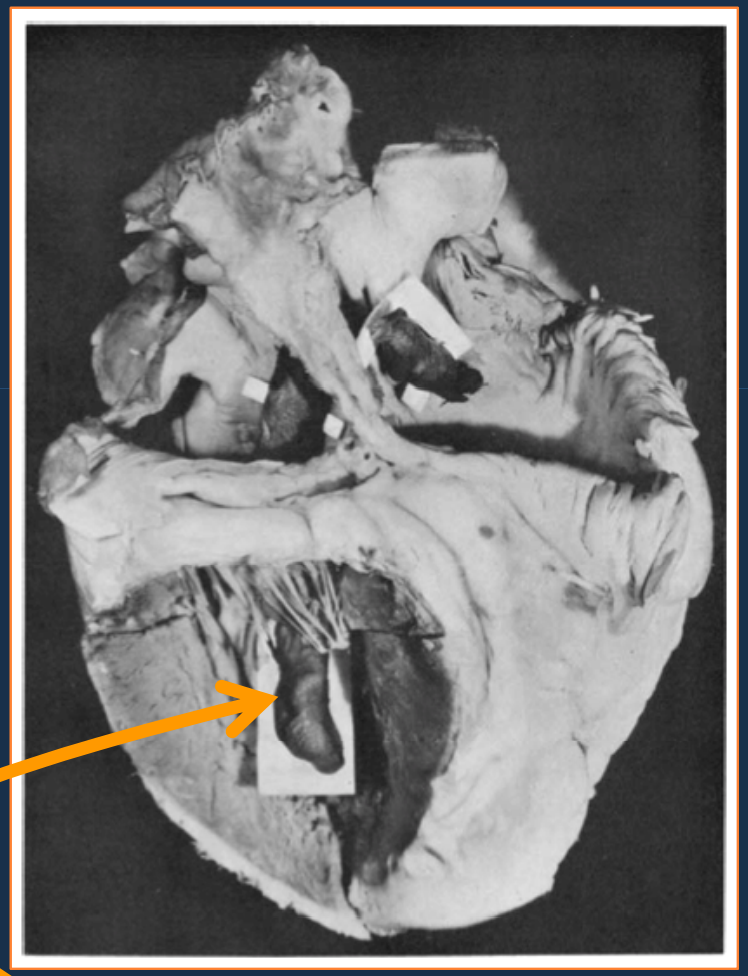


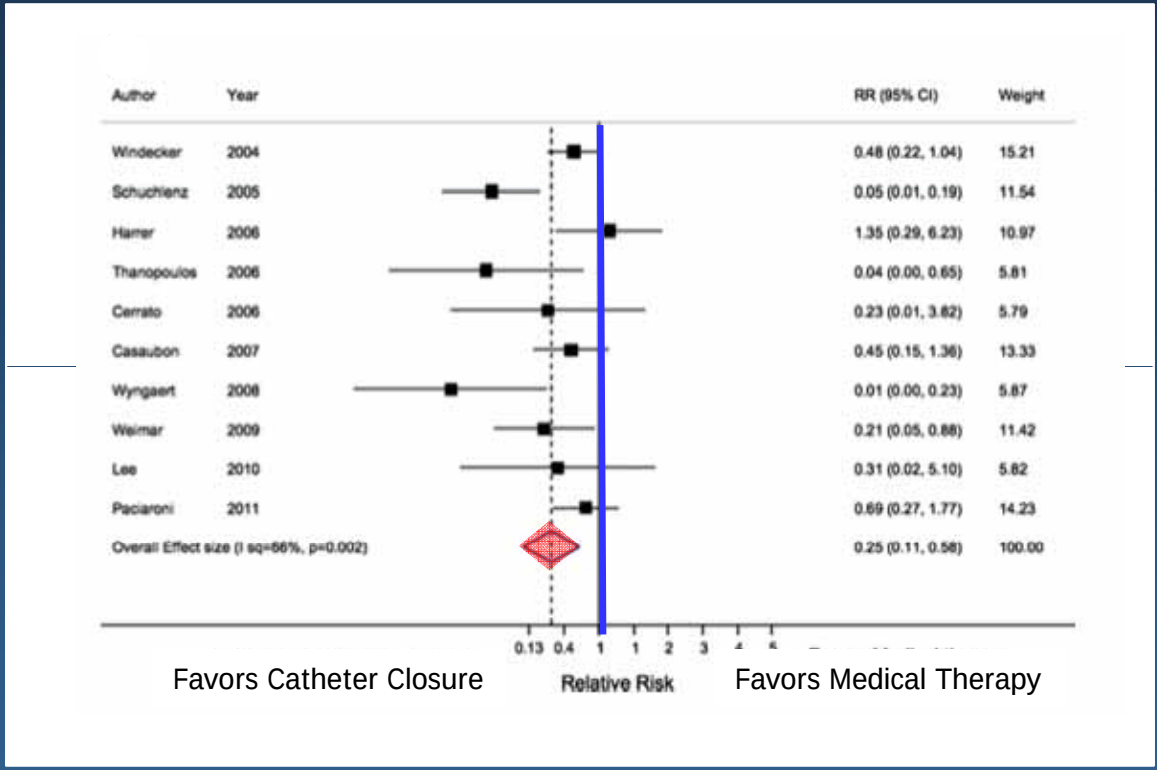
FIG. 2. Showing the heart in Mr. Ferguson Wilson's case. The auricles and left ventricle are viewed from behind. The embolus extends from the right auricle to the apex of the left ventricle and is seen passing through a patent foramen ovale into the left auricle and finally through the mitral valve into the left ventricle.

Thompson T, Evans W Quarterly Journal of Medicine 1930 23:135

It is clear that paradoxical embolism can cause stroke- does that mean that PFO should always be closed when associated with stroke?

Meta-Analysis of Transcatheter Closure Versus Medical Therapy for PFO After Presumed Paradoxical Embolism

Rate of recurrent neurological events



a meta-analysis of observational studies was performed to compare the rate of recurrent neurological events of patients with cryptogenic stroke/TIA and PFO

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J Am Coll Cardiol Intv 2012;5:777–89

a meta-analysis of observational studies was performed to compare the rate of recurrent neurological events of patients with cryptogenic stroke/TIA and PFO

- Stroke
- TIA
- Migraine
- Anxiety
- Other…

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Criteria for judgment of causal associations

- **Temporal sequence:** Did exposure precede outcome?
- **Strength of association:** How strong is the effect, measured as relative risk or odds ratio?
- **Consistency of association:** Has effect been seen by others?
- **Biological gradient (dose-response relation):** Does increased exposure result in more of the outcome?
- **Specificity of association:** Does exposure lead only to outcome?
- **Biological plausibility:** Does the association make sense?
- **Coherence with existing knowledge:** Is the association consistent with available evidence?
- **Experimental evidence:** Has a randomised controlled trial been done?
- **Analogy:** Is the association similar to others?

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Grimes DA: Lancet 359; 2002: 248-252

CLOSURE I
Investigating the PFO Stroke Connection

Randomization

Randomization
1 : 1
N = 909

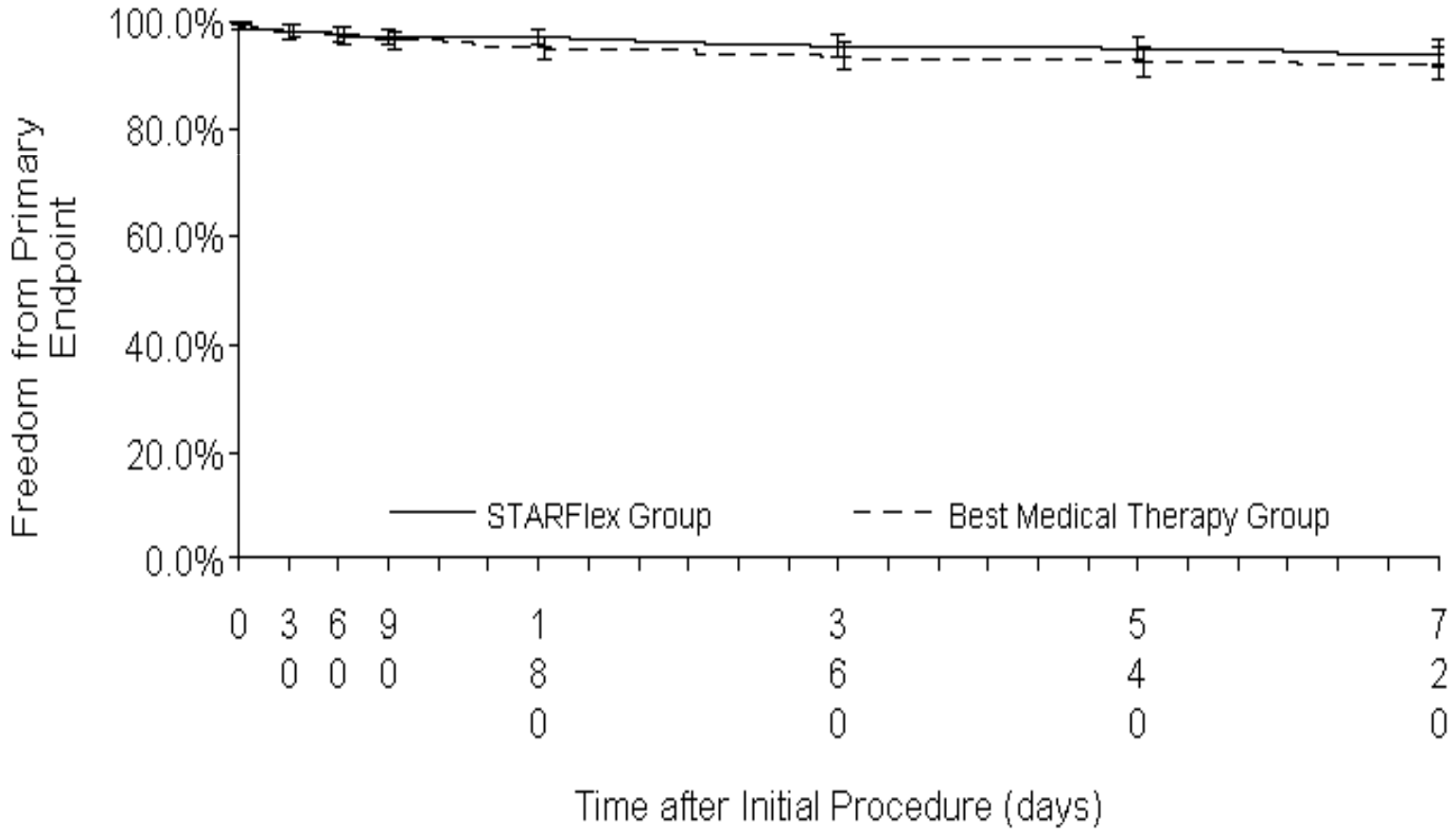
N=447
STARFlex®
Closure (within 30 Days)
6 Months Aspirin and Clopidigrel
followed by 18 Months Aspirin

N=462
Best Medical Therapy
24 Months Aspirin Or Warfarin
Or Combination

Between June 2003 and October 2008, 909 patients randomized at 87 sites in the US and Canada.
Block randomization with stratification by study site and by the presence or absence of an ASA viewed by TEE.

CLOSURE I
Investigating the PFO Stroke Connection

Kaplan-Meier for Primary Endpoint ITT



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

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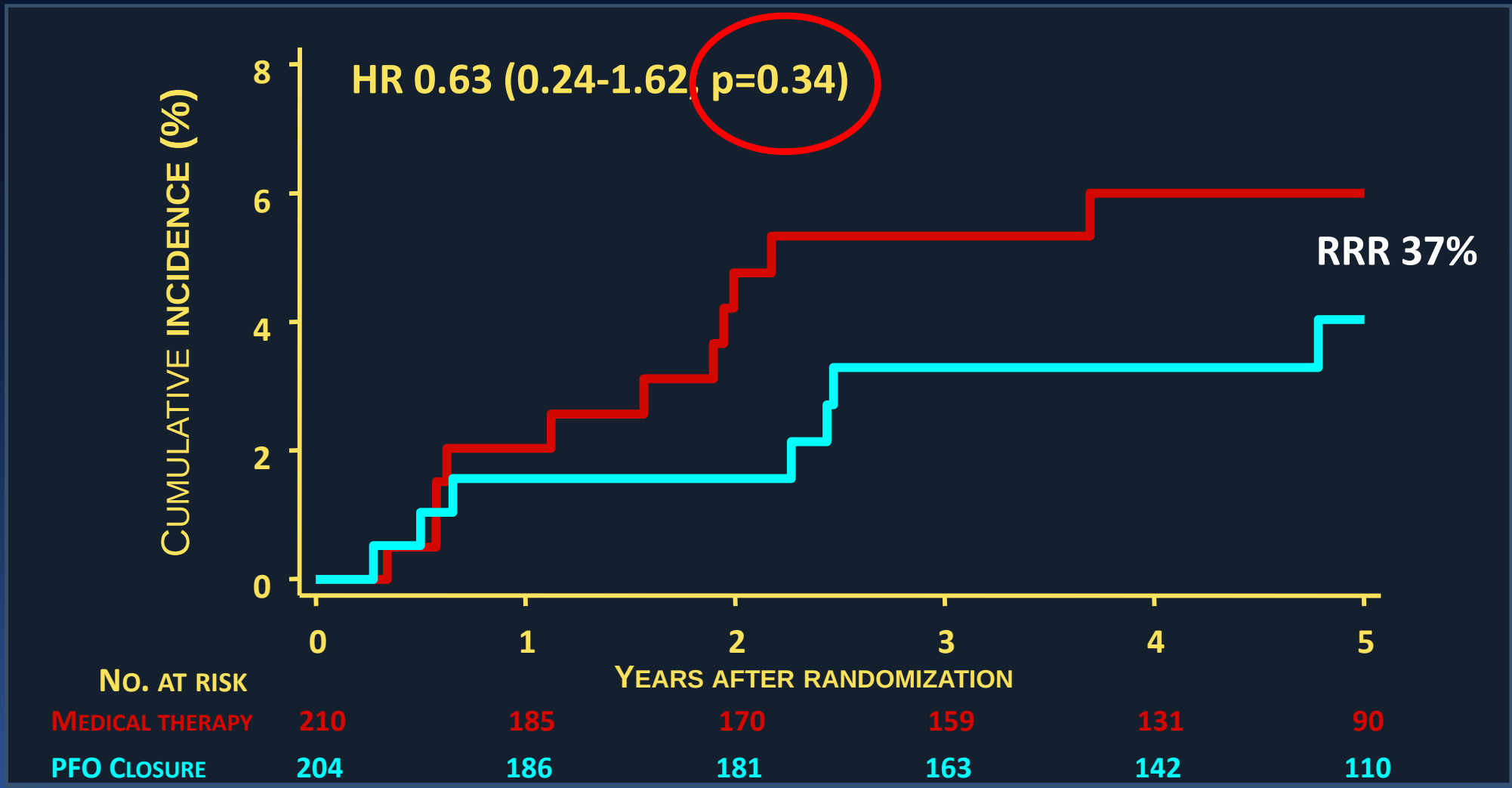
Primary Composite Endpoint

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



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

The NEGATIVE 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*

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The Final Results with Primary End Point Analyses

RESPECT

CLINICAL TRIAL

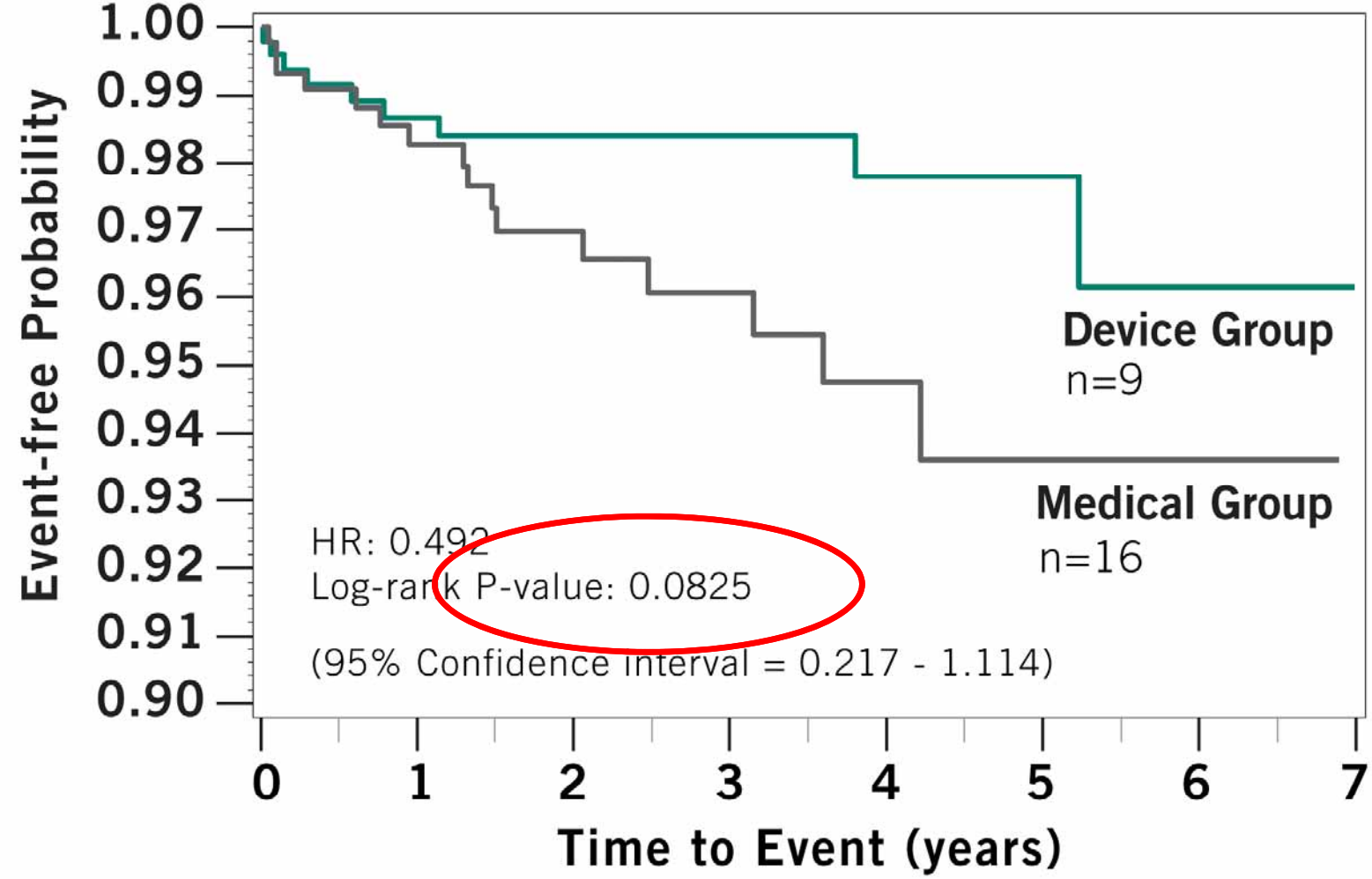
RANDOMIZED EVALUATION OF RECURRENT STROKE COMPARING PFO CLOSURE TO ESTABLISHED CURRENT STANDARD OF CARE TREATMENT

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 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

3 Negative Randomized Trials

EDITORIAL

Still No Closure on the Question of PFO Closure

- failure of trials to show superiority of closure over medical therapy
- enormous potential for overuse of percutaneous closure
- low risk of stroke in patients who are treated medically
- routine use of this therapy seems unwise without a clearer view of who, if anyone, is likely to benefit

NEJM 368;12; 2013

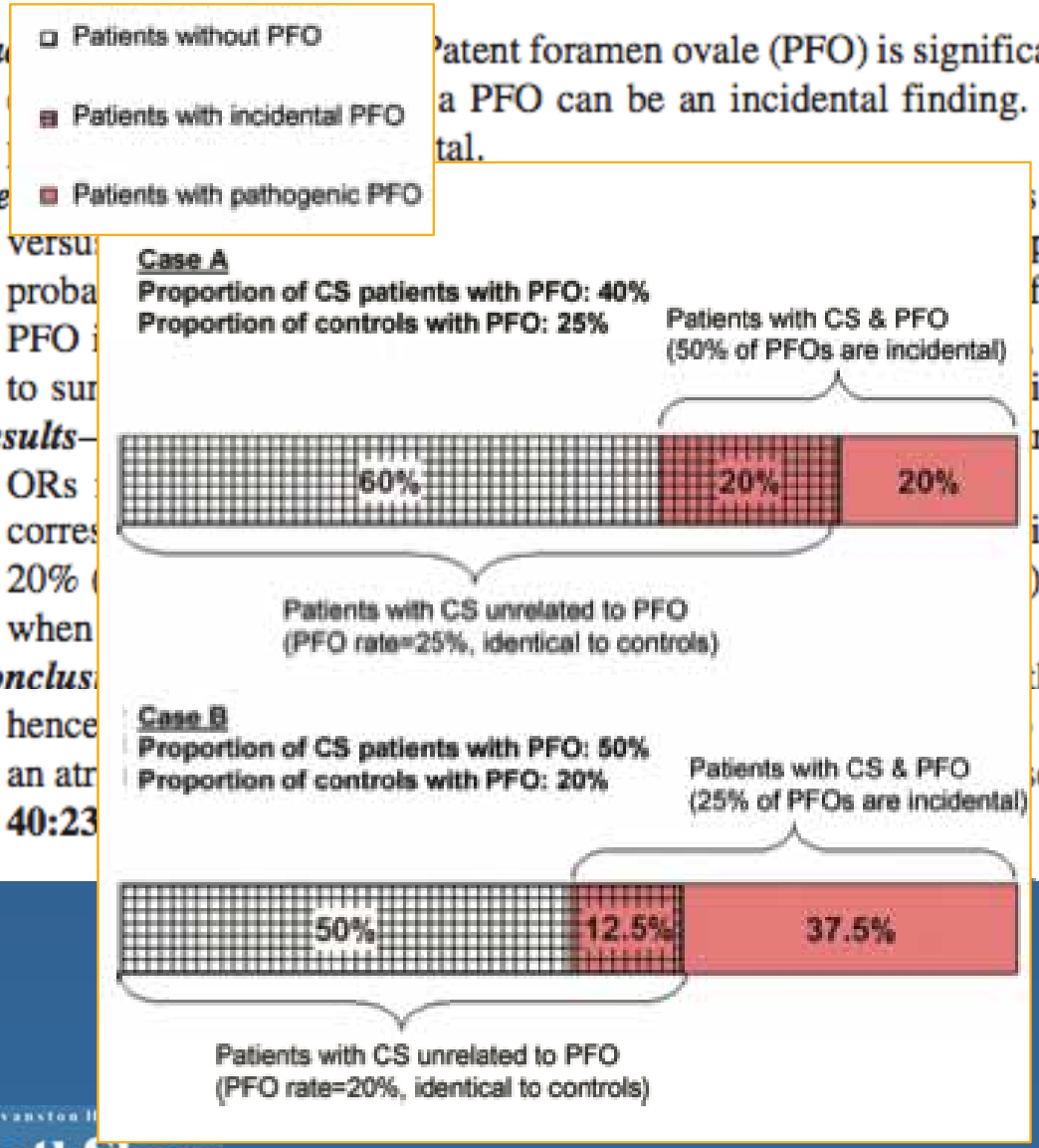
PFO in Cryptogenic Stroke
Incidental or Pathogenic?

Ba *Patent foramen ovale (PFO) is significantly associated with cryptogenic stroke (CS). However, a PFO can be an incidental finding. We sought to estimate the probability that a PFO in a tal.*

Me *examining the prevalence of PFO in patients with CS ple assumptions and Bayes' theorem, we calculated the ffects meta-analyses estimated the odds ratio (OR) of a with or without atrial septal aneurysms, and were used is incidental.*

Results– *rol subjects was 2.9 (CI, 2.1 to 4.0). The corresponding (3.3 to 7.8) and 2.0 (>1.0 to 3.7), respectively. The idental were 33% (28% to 39%) in age-inclusive studies,) in older patients. These probabilities were much lower*

Conclus *hird of discovered PFOs are likely to be incidental and patient characteristics such as age and the presence of election in therapeutic decision-making.* ***(Stroke. 2009; 40:23***



approximately one third of PFOs are likely to be incidental and hence not benefit from closure

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Stroke. 2009; 40:2349-2355

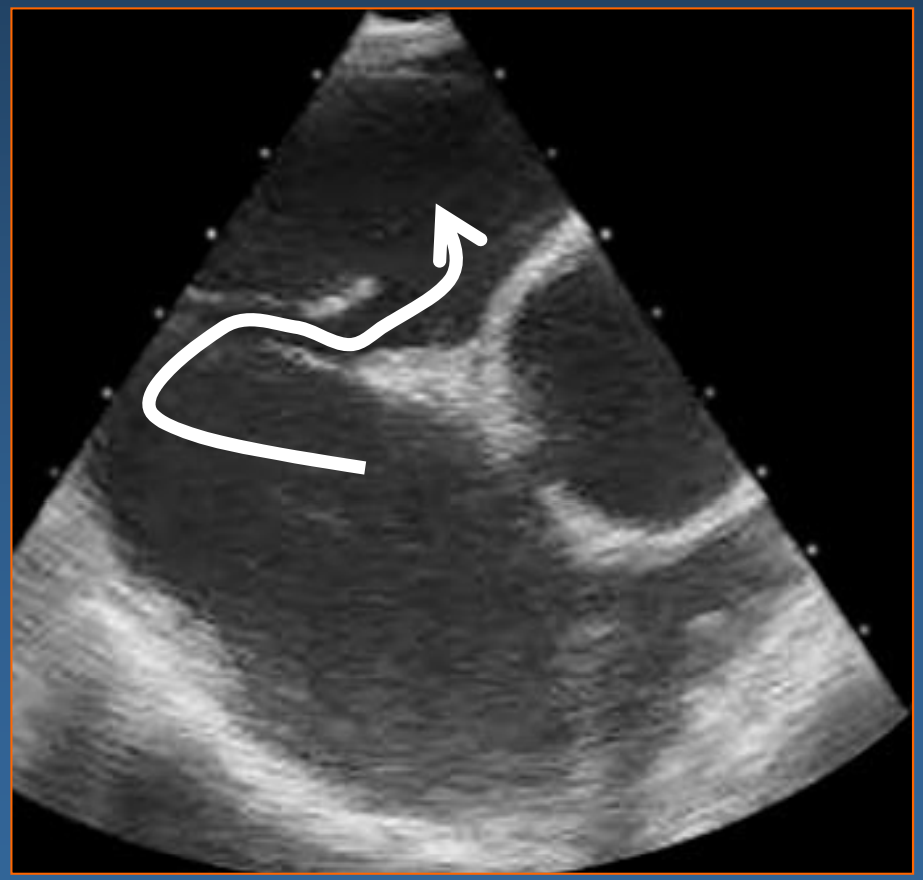
The GORE REDUCE Clinical Study

- Patient has presence of cryptogenic, ischemic stroke or transient ischemic attack (TIA) with MRI (or CT) evidence of a presumably embolic infarction verified by a neurologist within 180 days prior to randomization
- 2:1 randomization
- Antiplatelet regimens for **all subjects**:
  - Aspirin alone or
  - Aggrenox or generic equivalent (aspirin and dipyridamole) or
  - Clopidogrel (Plavix®)
- Warfarin NOT allowed after randomization

GORE REDUCE CLINICAL STUDY

World's Most Accurate Chart

The way to a man's head is through his heart.



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