Recent PFO Trials and Future Perspectives

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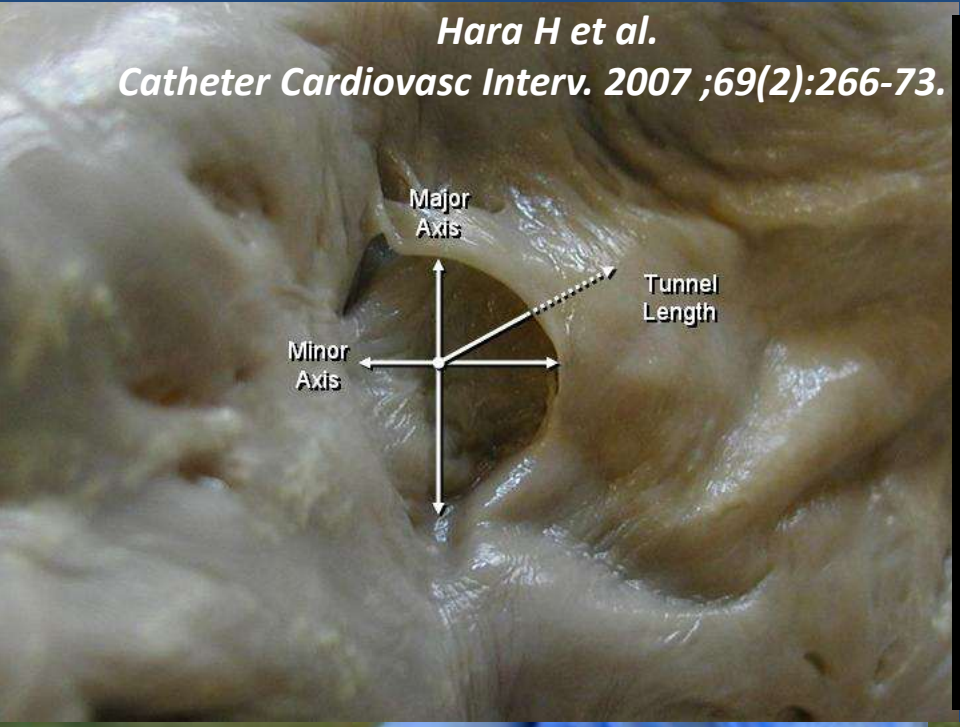
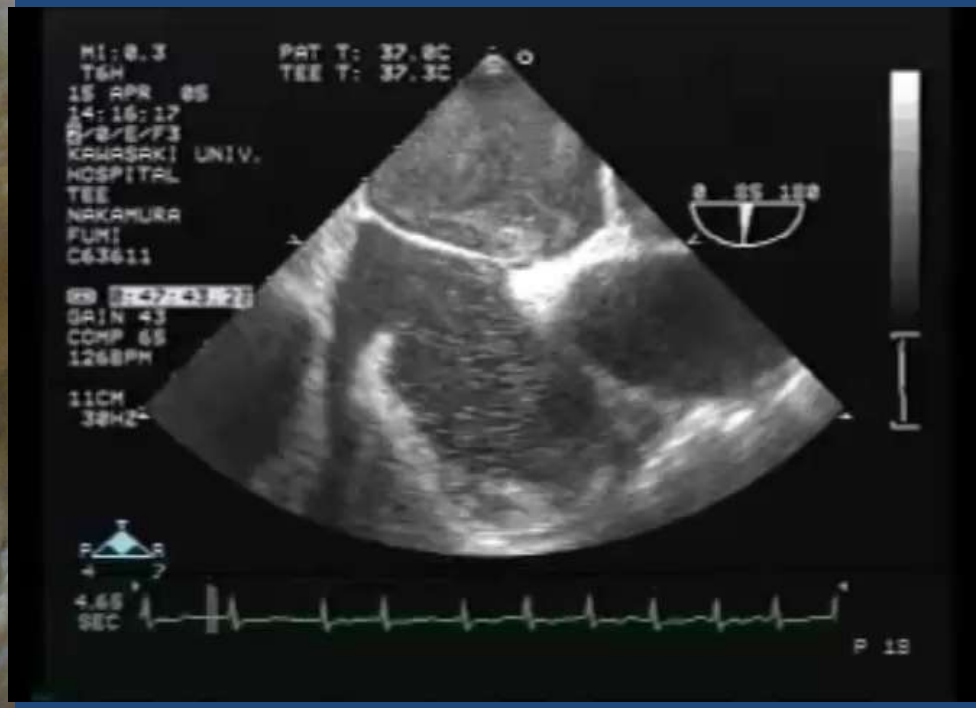
CARDIOVASCULAR SUMMIT
TCTAP 2015

I have nothing to disclose.

Hara H et al.
Catheter Cardiovasc Interv. 2007 ;69(2):266-73.





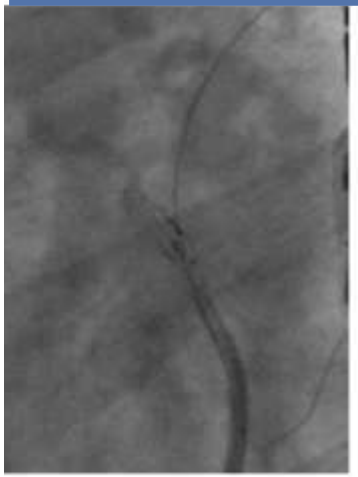
- ✓ We saw many case reports that described clots crossing PFOs
- ✓ Prior PFO closure certainly can prevent this event
- ✓ If we use *Common sense,* to perform PFO closure must be better for the patients with paradoxic stroke instead of life-long anticoagulation

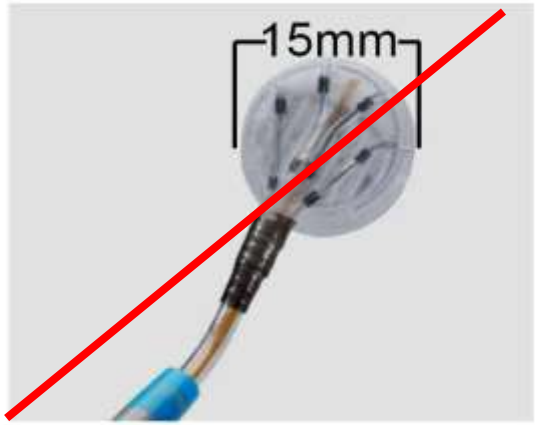
10 year ago, many devices

Plenty of companies had been working for PFO devices

- Permanent implant
- Arrythmias
- Thrombus risk
- Device erosion
- Device embolization

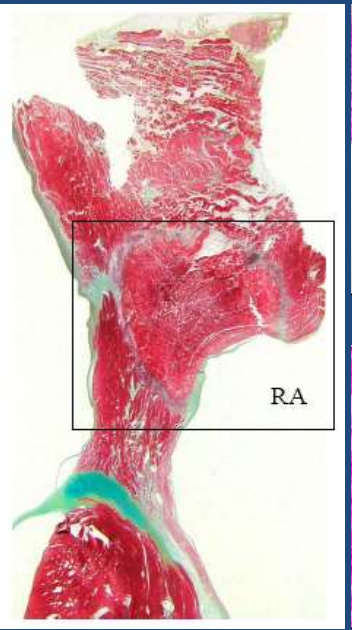
The Cierra PFx™ System

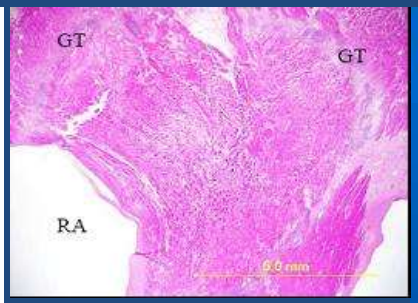


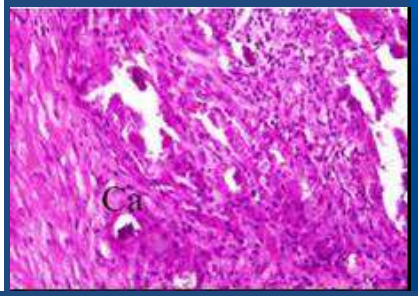


PFx - 15

Sievert H et al. Circulation 2007 116: 1701





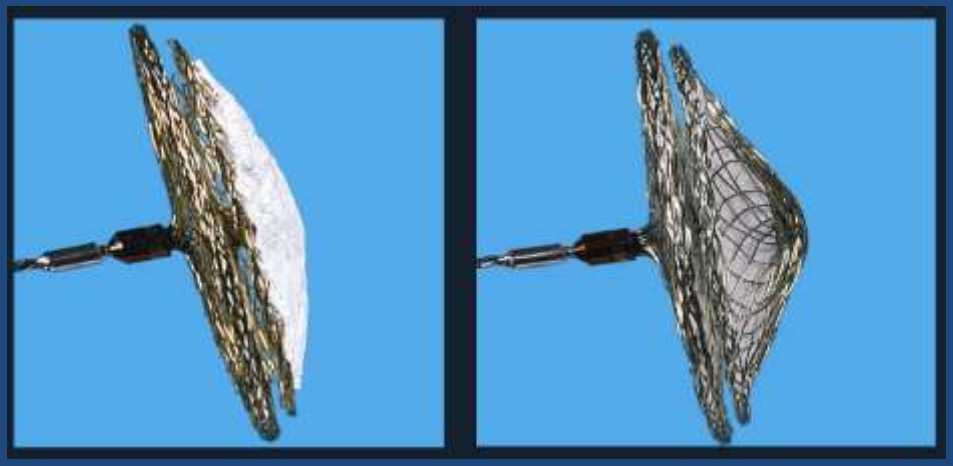


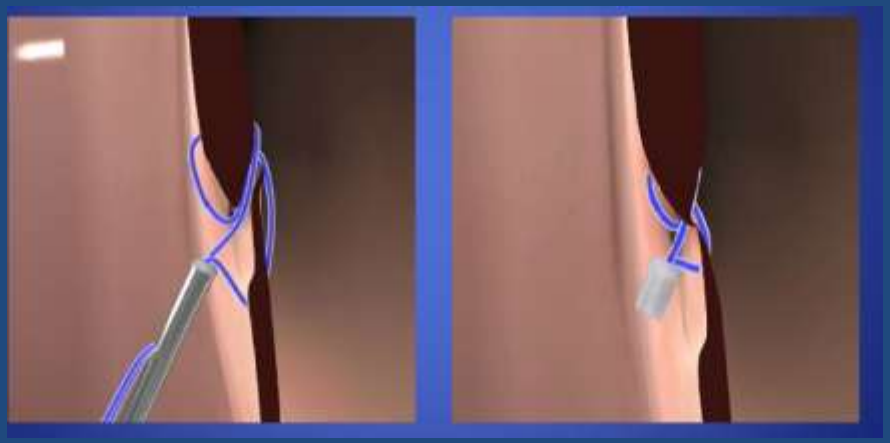
CoAptus™ PFO Closure System

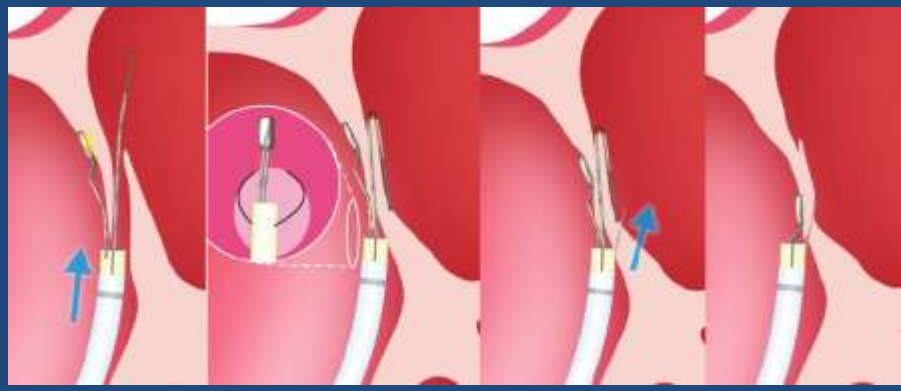
Investigational medical device in E.U.
Not available in U.S.

Hara H et al. Circulation. 2007 ;116(6):648-53

Other devices coming







CLOSURE I
Investigating the PFO Stroke Connection

Randomization

Randomization
1 : 1
N = 909

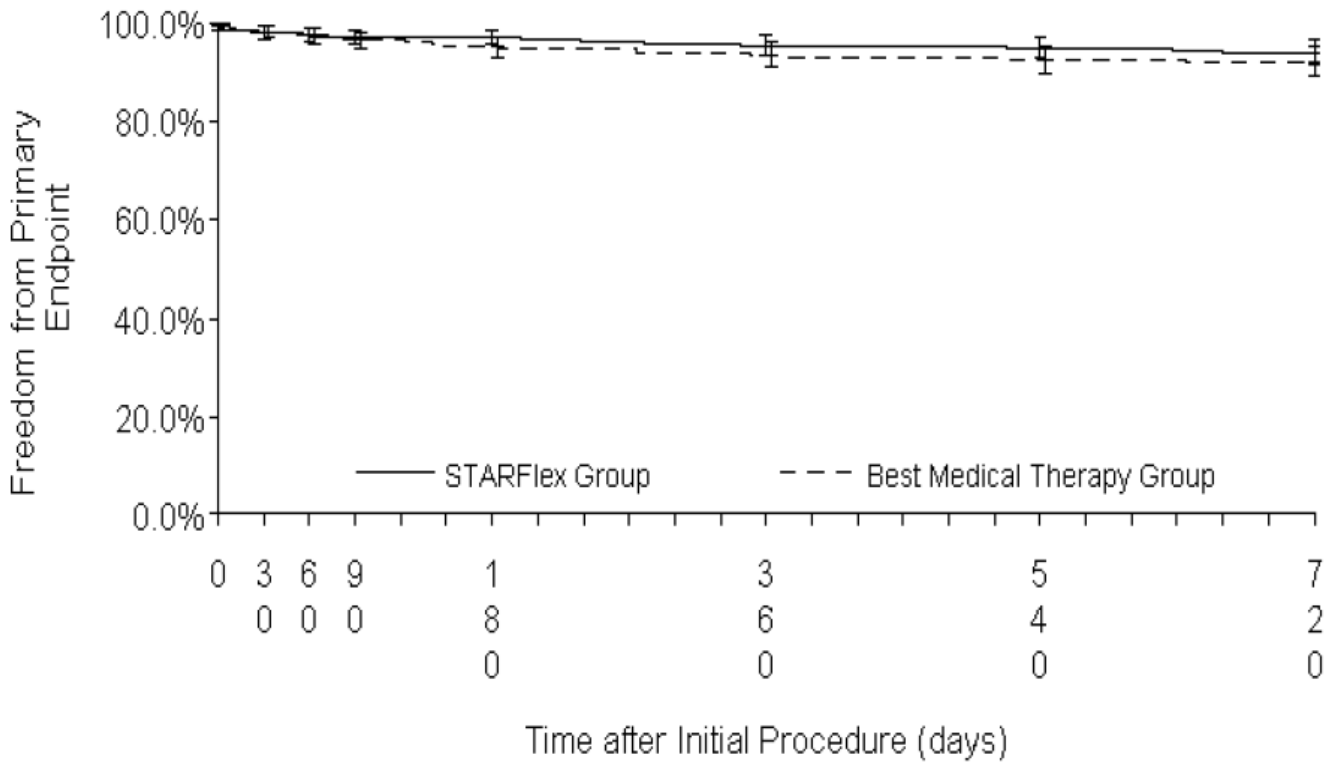
N=447
STARFlex®
Closure (within 30 Days)
6 Months Aspirin and Clopidigrel
followed by 18 Months Aspirin

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

TCT2012

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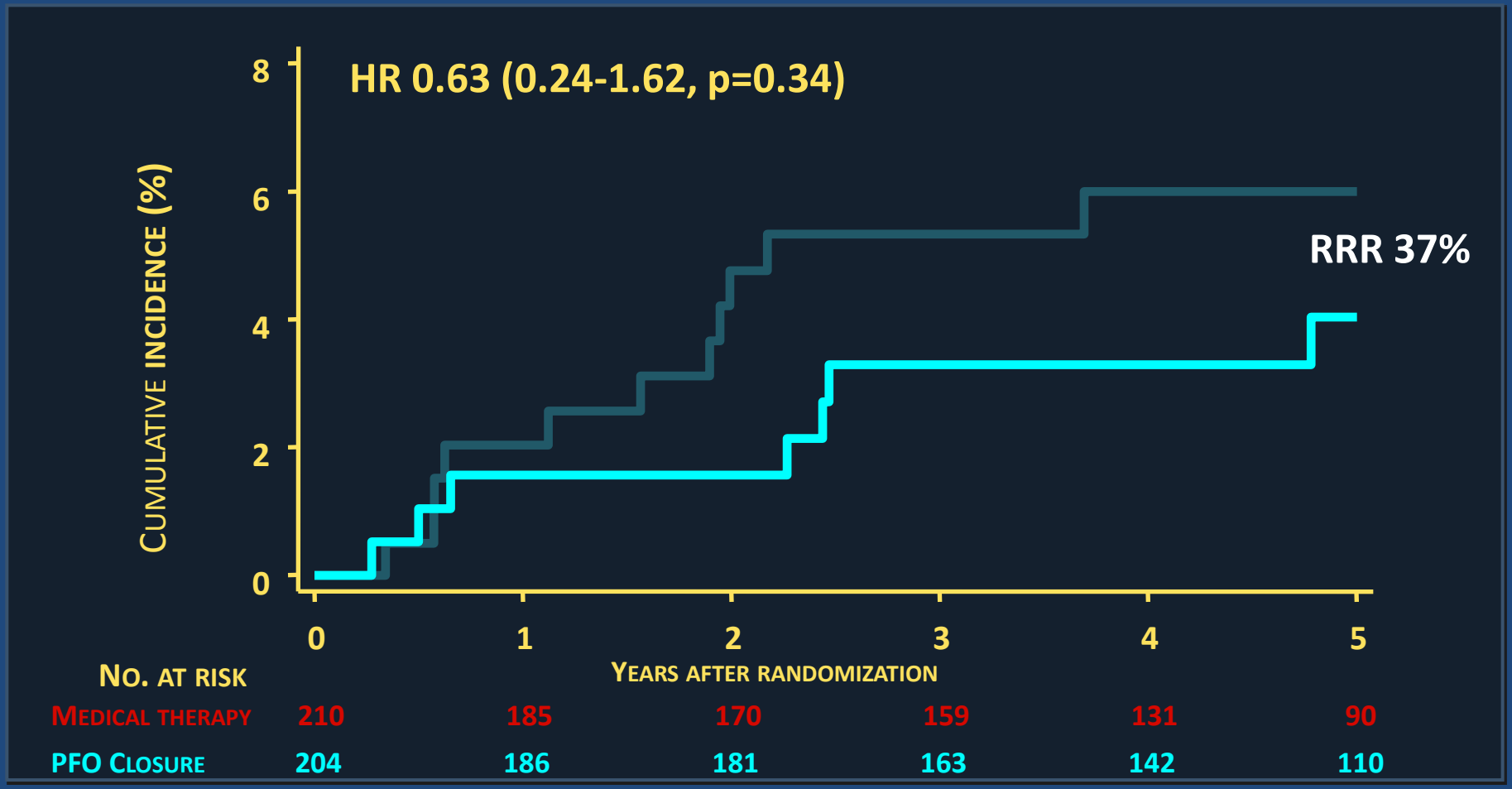
a passion for innovation

PC Primary Composite Endpoint

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



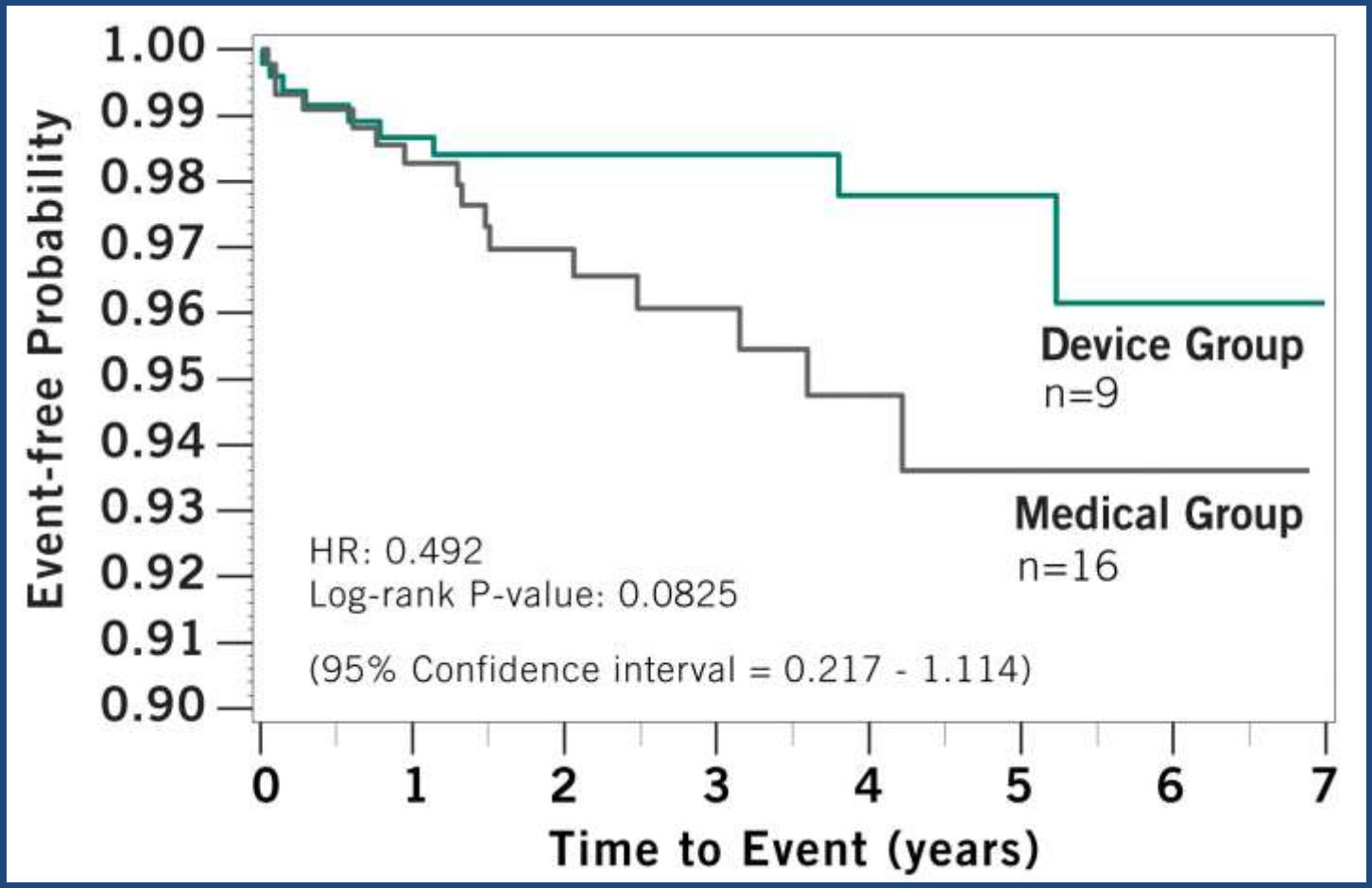
RESPECT

CLINICAL TRIAL

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

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

There are **3 Negative Randomized Trials** published in high ranking journal

The NEW ENGLAND JOURNAL of MEDICINE

That is why many people or many doctors believe PFO closure is no sense !

Or PFO closure is nearly dead….

What are the issues in *CLOSURE* / ?

✓ Superiority study design may not be appropriate

- Because medical therapy has never been studied in a randomized trial
- The device does not need to beat the medication. If the result of device is just as good as that of medication, we can choose both treatments.
- Non-inferiority designed trial will work

What are the issues in *CLOSURE* / ?

- ✓ To exclude DVT and hypercoagulopathy from PFO closure might have been a mistake
- These patients would benefit most
- ✓ Very slow enrolment
- only 2 patients/year/center
- There must have been a selection bias
- ✓ Follow-up too short
- Patients go for PFO closure because they want to avoid 30 yrs of anticoagulation
- ✓ Some operators had been at the beginning of their learning curve
- ✓ Technology outdated
- We know from many trials that STARFlex has a higher rate of afib and clot formation than other devices have.

So, we should talk about other device for PFO closure issues

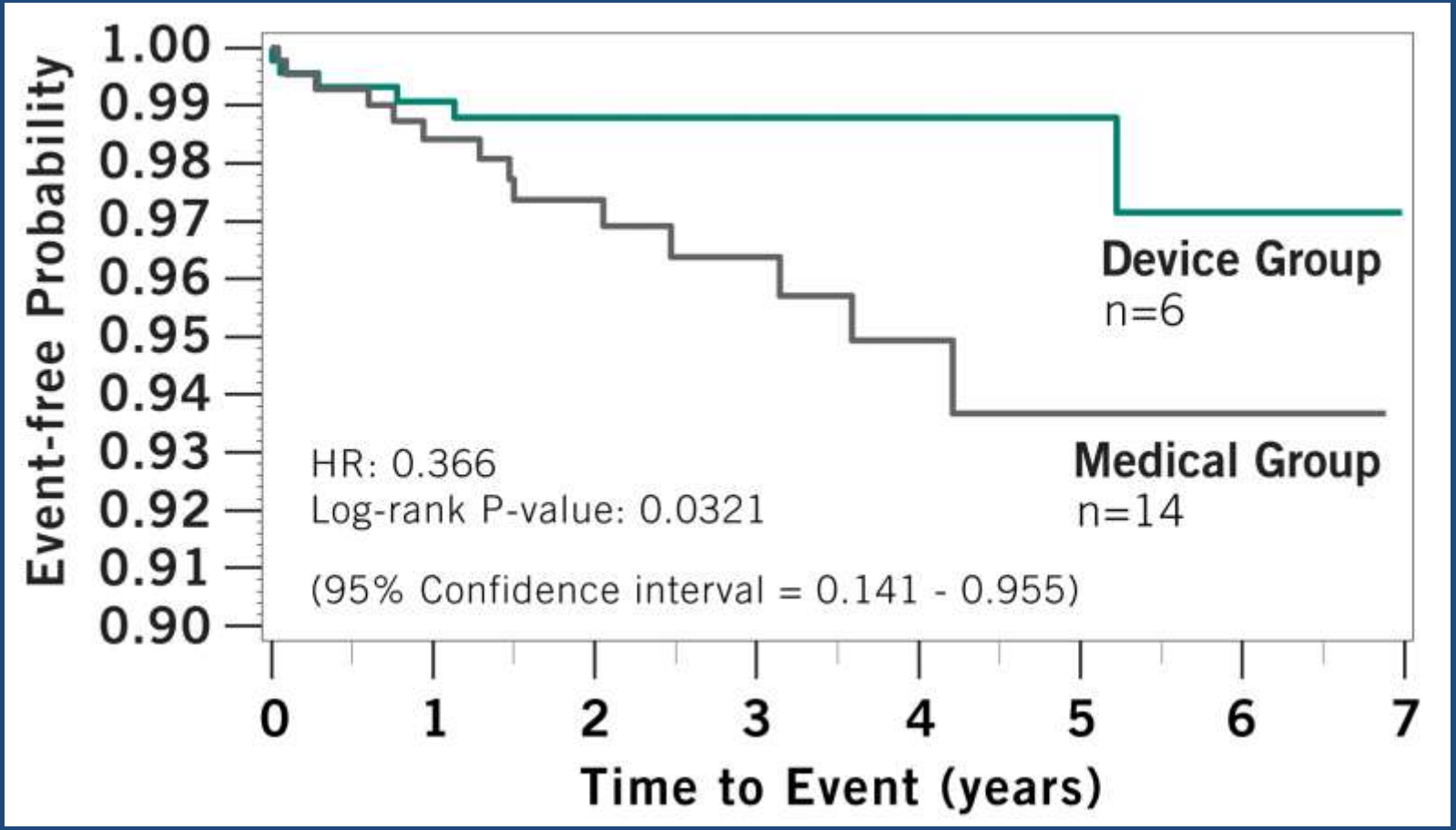
AMPLATZER PFO Occluder

AMPLATZER PFO Occluder*

- Percutaneous, transcatheter device
- Self-expanding, double-disc design
- Nitinol wire mesh with polyester fabric/thread
- Radiopaque marker bands
- Sizes: 18, 25, 35 mm
- Recapturable and repositionable

*CAUTION: Investigational device in the United States. Limited by Federal (or U.S.) law to investigational use. Not available for sale in the U.S.

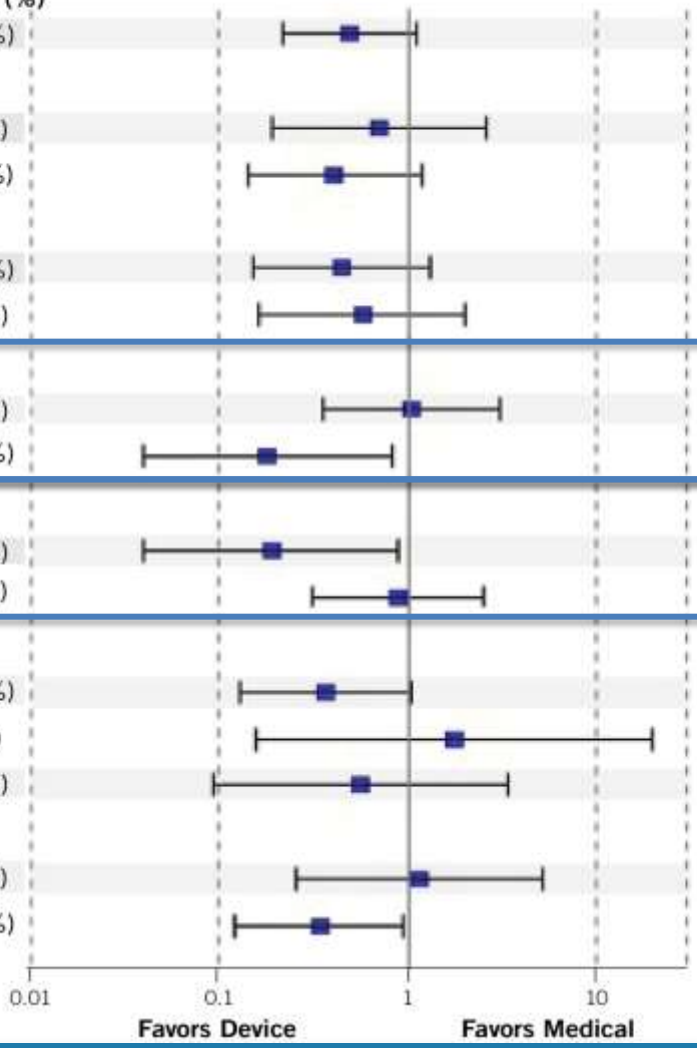
Primary Endpoint Analysis – Per Protocol Cohort
63.4% risk reduction of stroke in favor of device



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

Subpopulation Differential Treatment Effect

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	



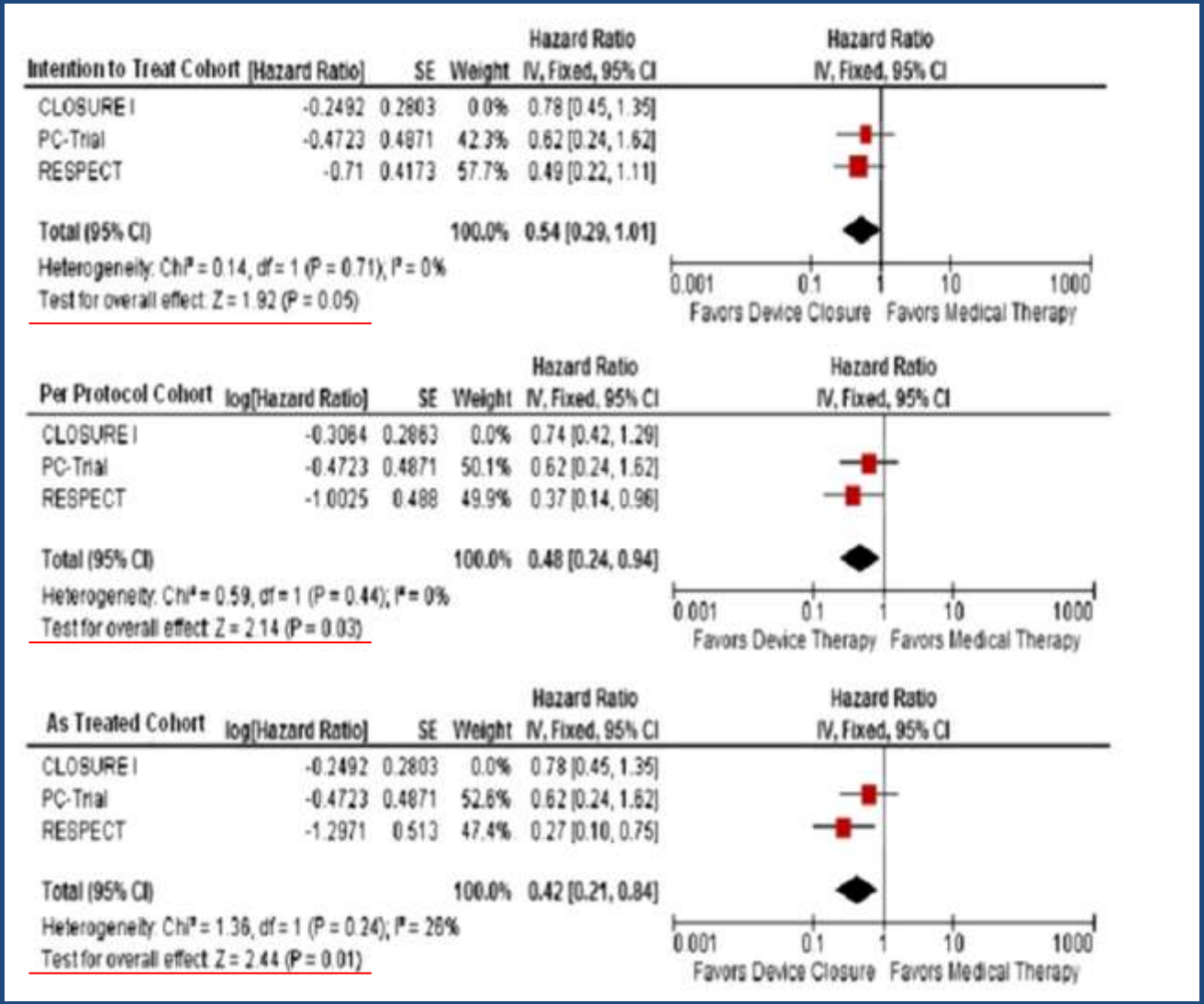
Results of meta-analyses

- Wolfrum M, et al. Heart: Borderline significant risk reduction in stroke in PFO TC closure (3RCT + 2non-RCT) HR=0.58 (0.33-0.99), p=0.047

- Rengifo-Moreno P, et al. Eur Heart J: Significant risk reduction in TIA/Stroke in PFO TC closure (3RCT) HR=0.59 (0.36-0.97), p=0.04

- Pineda AM, et al. CCI: Trend in favor of PFO TC closure (3RCT), OR=0.7 (0.47-1.05) ,p=0.08 in the composite endpoint

PFO closure is beneficial as compared to medical therapy in the prevention of recurrent neurological events



J Am Coll Cardiol Intv 2013;6:1316–23

How about the Association between PFO closure and Migraine

Observational Studies

Effect of PFO closure on migraine

Study	Prevalence # migraine / # closed (%)	% migraine improved or cured	Length of follow up (months)
Wilmshurst 2000	21/37 (57%)	86%	up to 30
Morandi 2003	17/62 (27%)	88%	6
Schwerzmann 2004	48/215 (22%)	81%	12
Post 2004	26/66 (39%)	65% cured	6
Reisman 2005	57/162 (35%)	70%	12
Azarbal, Tobis 2005	37/89 (42%)	76%	mean 18

Total: 206/631 (33%) 78%

MIST Results

1. Migraine with Aura: 135 pts randomized.
2. Primary Endpoint: complete cessation of MHA:

   3 pts in Device group and 3 in Control group

   (significant placebo effect in migraine studies)
3. Secondary Endpoint: 50% reduction of MHA days

   Device: 42% of pts.

   Control: 23% of pts. } p<0.04
4. PFO closure effectiveness data: controversial (5-35%)
   Important to know if residual shunt with Starflex accounts for persistent migraines. If so, the data would support the underlying hypothesis.

OR: pts with severe MHA are different than CS pts + MHA

Circulation March 2008

Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura

PRIMA

David Hildick-Smith, Heinrich P. Mattle, Stefan Evers, Werner J. Becker, Helmut Baumgartner, Jeremy Chataway, Marek Gawel, Hartmut Göbel, Axel Heinze, Eric Horlick, Iqbal Malik, Adam Zermansky, Simon Ray, Oliver Findling, Stephan Windecker, Bernhard Meier.

On Behalf of the PRIMA Investigators

PRIMA

- Design
  - Multicenter: 20 sites
    - Canada, Germany, Switzerland, United Kingdom
  - Prospective, Randomized, “Open label”
  - Closure Group
    - Amplatzer PFO Occluder implantation
    - 3 months clopidogrel; 6 months aspirin
  - Medical Group
    - Continuation of current medication
    - 3 months clopidogrel; 6 months aspirin

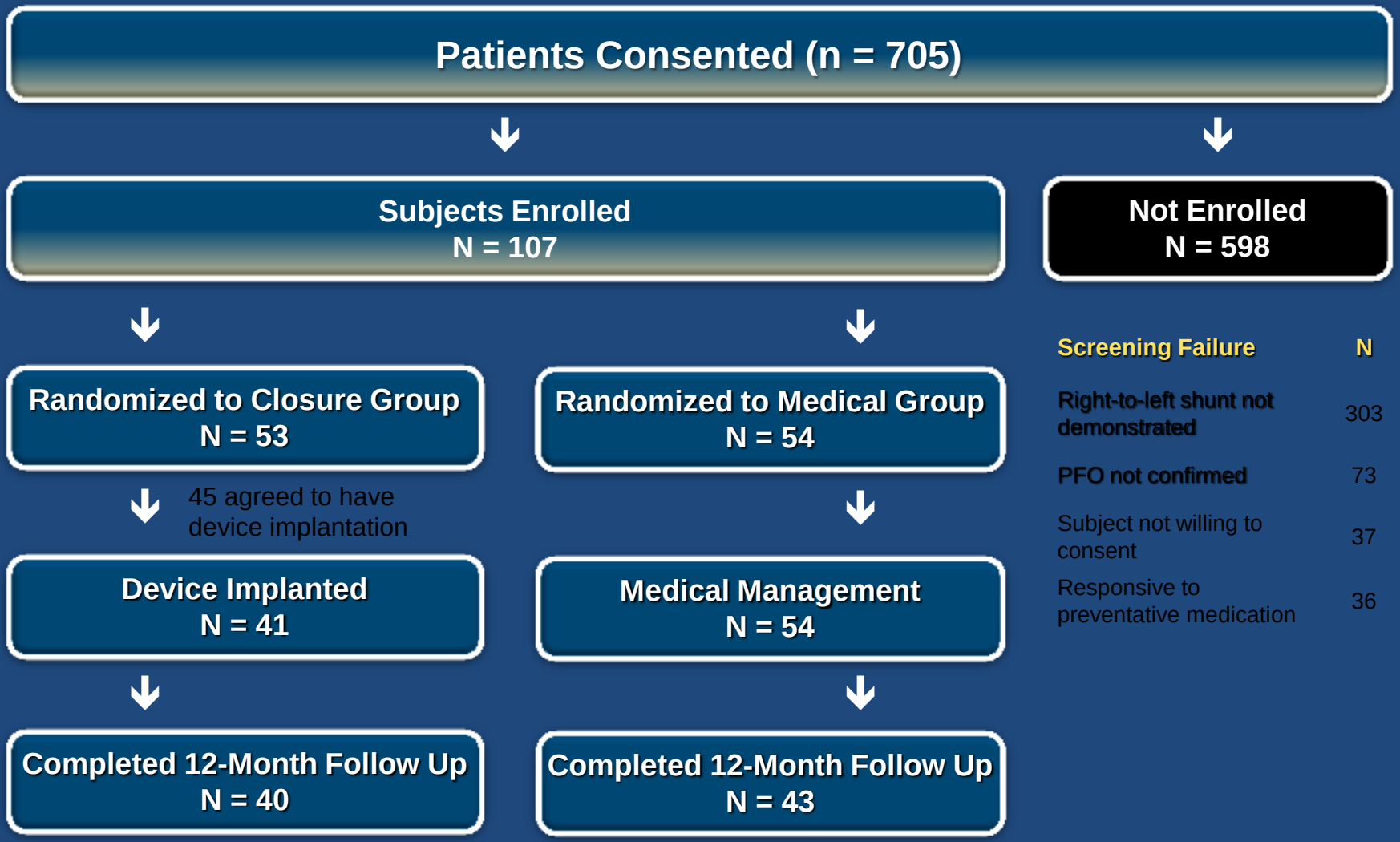
Study endpoints

- Primary Endpoint
  - Reduction in migraine days 1 year after randomization
    - Mean number of migraine days in months 10-12, subtracted from…
    - Mean number of migraine days in months “-3” to 0 (3 months roll-in)

Study endpoints

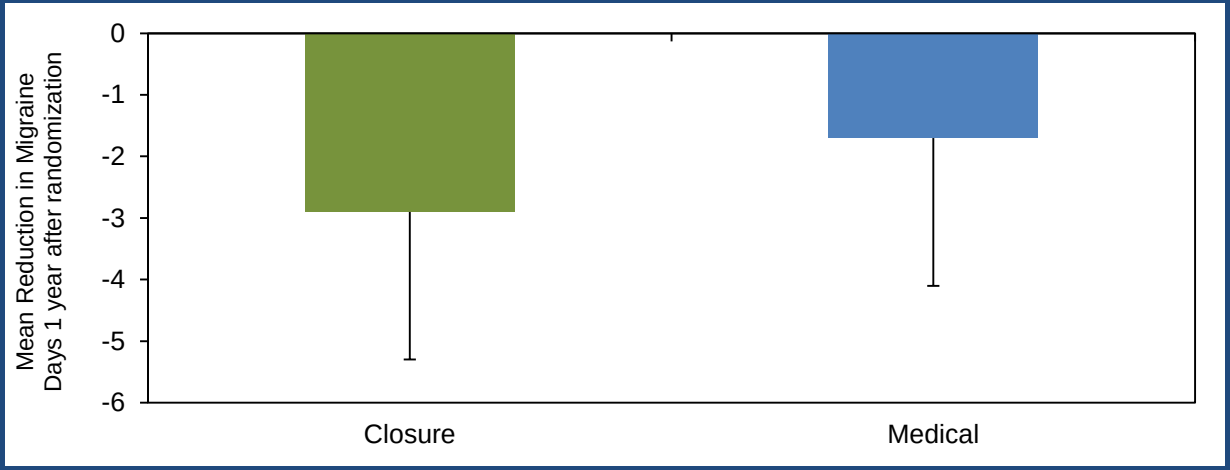
- Secondary Endpoints
  - Change in responder rate
    - (≥50% reduction in number of migraine days)
  - Change in the number of monthly migraine attacks
  - Change in use of acute migraine medications
  - Change in MIDAS score
  - Quality of life measures
  - Beck Depression Inventory Score
  - Effects of antiplatelet medication during study
  - Completeness of PFO closure at 12 months

Patient Flow



Primary Endpoint
Reduction in Migraine Days

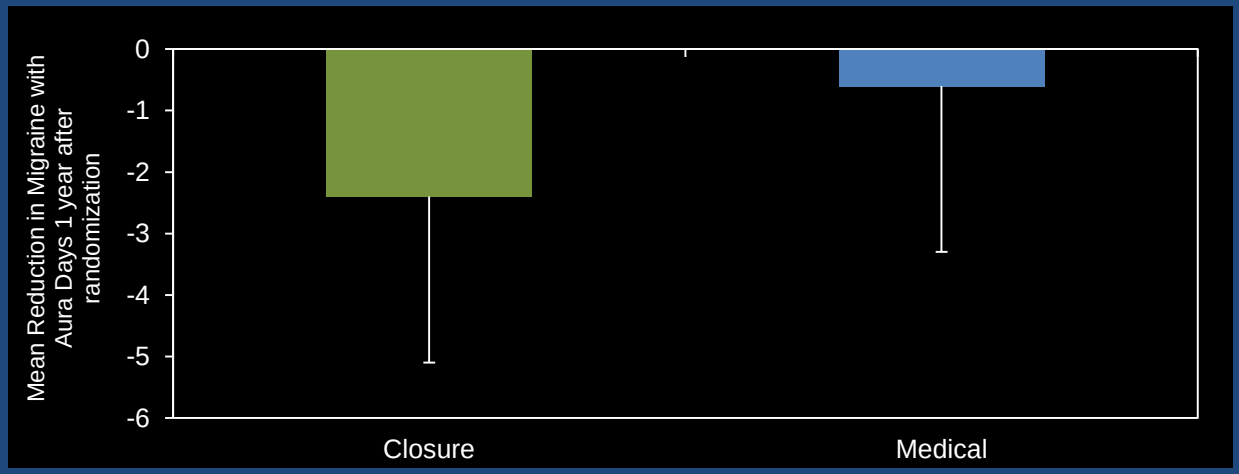
	N	Mean Days at Baseline	Mean Days at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	8.0	5.1	-2.9	4.7 (-11.7, 9.0)	0.17
Medical	41	8.3	6.5	-1.7	2.4 (-6.3, 3.5)	



Secondary Endpoint

Reduction in Migraine with Aura Days

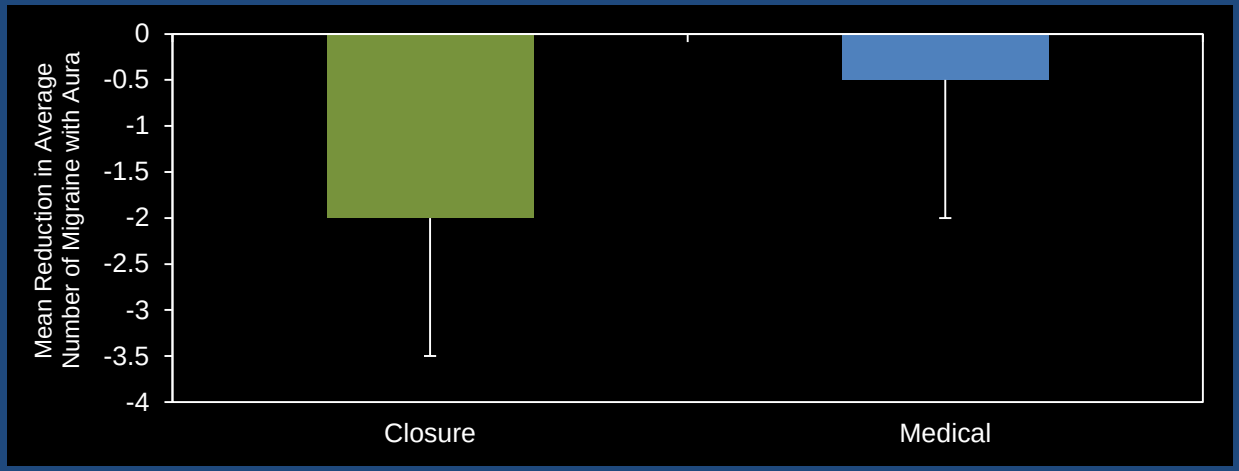
	N	Mean at Baseline	Mean at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	4.1	1.7	-2.4	3.6 (-9.7, 7.3)	**0.01**
Medical	40	4.0	3.4	-0.6	2.7 (-9.1, 5.5)	



Secondary Endpoint

Reduction in Migraine with Aura Attacks

	N	Mean at Baseline	Mean at Months 10-12	Mean Reduction	Std Deviation (Min, Max)	P-Value
Closure	40	3.0	1.0	-2.0	2.0 (-7.16, 1.00)	< 0.01
Medical	40	2.8	2.3	-0.5	1.5 (-3.3, 3.4)	



CONCLUSIONS of PRIMA

- Interventional studies in migraine/aura patients are difficult to do
- 40% of patients in PRIMA had a R to L shunt
- PFO closure is safe in these patients
- PFO closure did not reduce total migraine days significantly compared to medical therapy

Future perspective

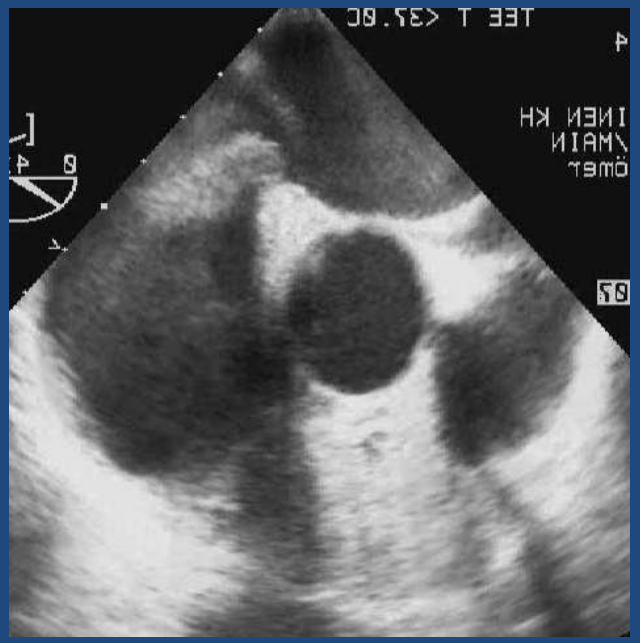
Acronym	Place	Device	Patients	Status
CLOSE	France	Multiple	???/900	?
REDUCE**	global	HELEX	???/664	?
PREMIUM	US	AMPLATZER		?
DEFENCE	Korea	AMPLATZER		?

Long term follow-up of RESPECT

After 10 years of research …

… all randomized trials have been negative

But all of them are pointing into the direction of closure



So the questions are:

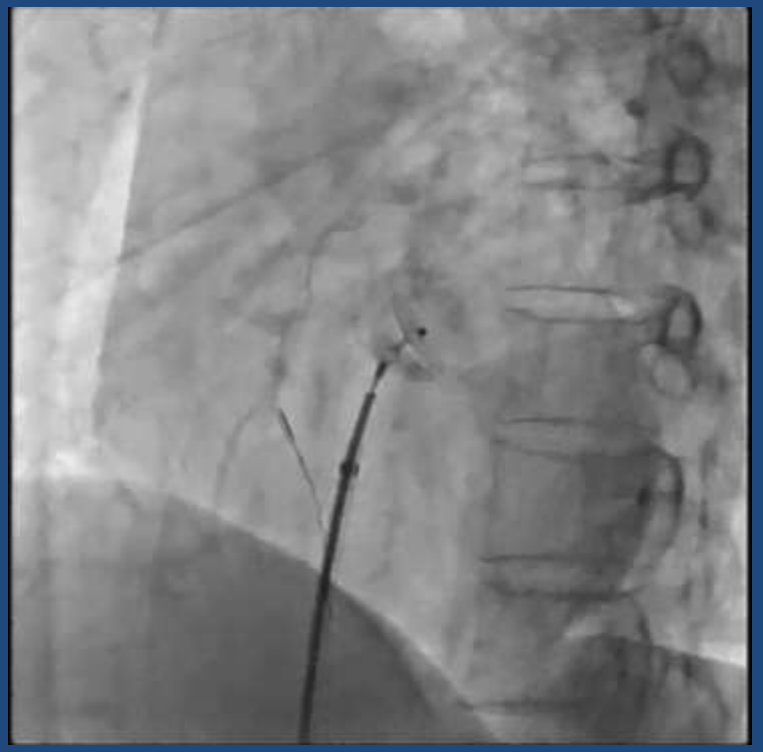
Should we believe more in randomized trials or in common sense?

And at this time, do we need more randomized trials or more common sense?

Courtesy of H Sievert

Take Home Message

- ✓There are certain patients who will definitely receive benefit from PFO closure
- ✓To prove the all the mechanism of PFO-stroke association is still major challenge
- ✓ We should participate and contribute this field



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