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

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support

Company

- Abbott
- Biosensors
- Biotronik
- Boston Scientific
- Cordis
- Medtronic
- St. Jude Medical

Background

- A cause-effect relationship between the presence of a PFO and risk of stroke of unknown origin is supported by
  - Consistency of the association
  - Biologic plausibility
  - Dose-response relationship
  - Proven paradoxical embolism

Background

- A cause-effect relationship between the presence of a PFO and risk of stroke of unknown origin is supported by
  - Consistency of the association
  - Biologic plausibility
  - Dose-response relationship
  - Proven paradoxical embolism
- **Percutaneous PFO closure is a safe and effective minimal-invasive procedure to eliminate the atrial right-to-left shunt**

Background

- **Whether percutaneous PFO closure is superior to medical treatment among patients with stroke of unknow origin remains controversial**
  - Observational studies suggest a lower risk of recurrence with PFO closure compared with medical treatment
  - CLOSURE I failed to show superiority of PFO closure over medical treatment
  - Outcomes may be influenced by device-type in terms of closure success and thrombus formation

Study Hypothesis

Among patients with cryptogenic stroke and peripheral embolism percutaneous closure of patent foramen ovale (PFO) using the Amplatzer PFO Occluder is superior to medical treatment with antiplatelet agents or Vitamin K antagonists for secondary prevention of thromboembolism.

PROCEDURES

PERCUTANEOUS PFO CLOSURE

Amplatzer PFO Occluder

Acetylsalicylic acid (100-325mg qd)

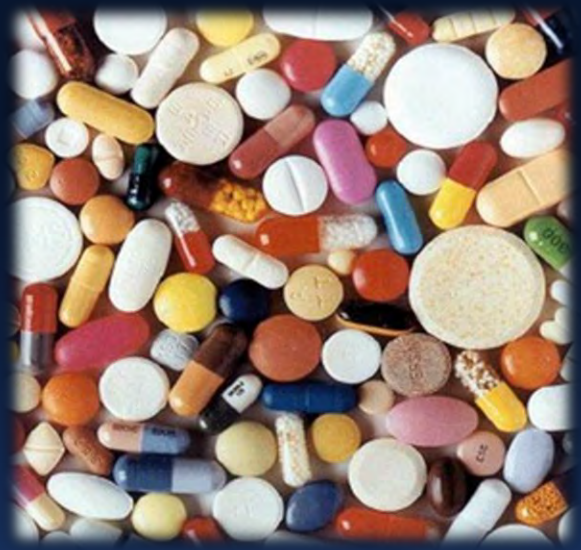
and ticlopidine (250-500mg qd)

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

Inclusion Criteria

- Age < 60 years
- Presence of PFO (with or without ASA)
- Clinically and neuro-radiologically verified ischemic stroke or transient ischemic attack (TIA) with documented corresponding intracranial ischemic lesion or
- Clinically and radiologically verified extracranial peripheral thromboembolism
- Sufficient recovery from the thomboembolic index event to allow independent daily activities

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.

Endpoints and Sample Size

Primary Composite Endpoint

- Composite of death from any cause, non-fatal stroke, TIA, and peripheral embolism
- 205 patients per group provide 80% power to detect a reduction in the primary composite endpoint from 3% to 1% at a mean follow-up of 4.5 years and an α-level of 0.0492

Secondary Endpoints

- Myocardial infarction
- New arrhythmia (atrial fibrillation)
- Re-hospitalization related to PFO or its treatment
- Device – related problems (dislodgement, structural failure, infection, thrombosis)

Endpoint Definitions

- **Death**
  - Fatal stroke
  - Cardiovascular death
  - Non-cardiovascular death
- **Stroke**
  - Acute focal neurological deficit lasting >24 hours with MRI or CT evidence of new intracranial lesion
- **Peripheral embolism**
  - End-organ ischemia other than in the brain documented by Duplex, CT, MRI, or angiography
- **TIA**
  - Acute neurologic deficit lasting <24 hours with complete resolution

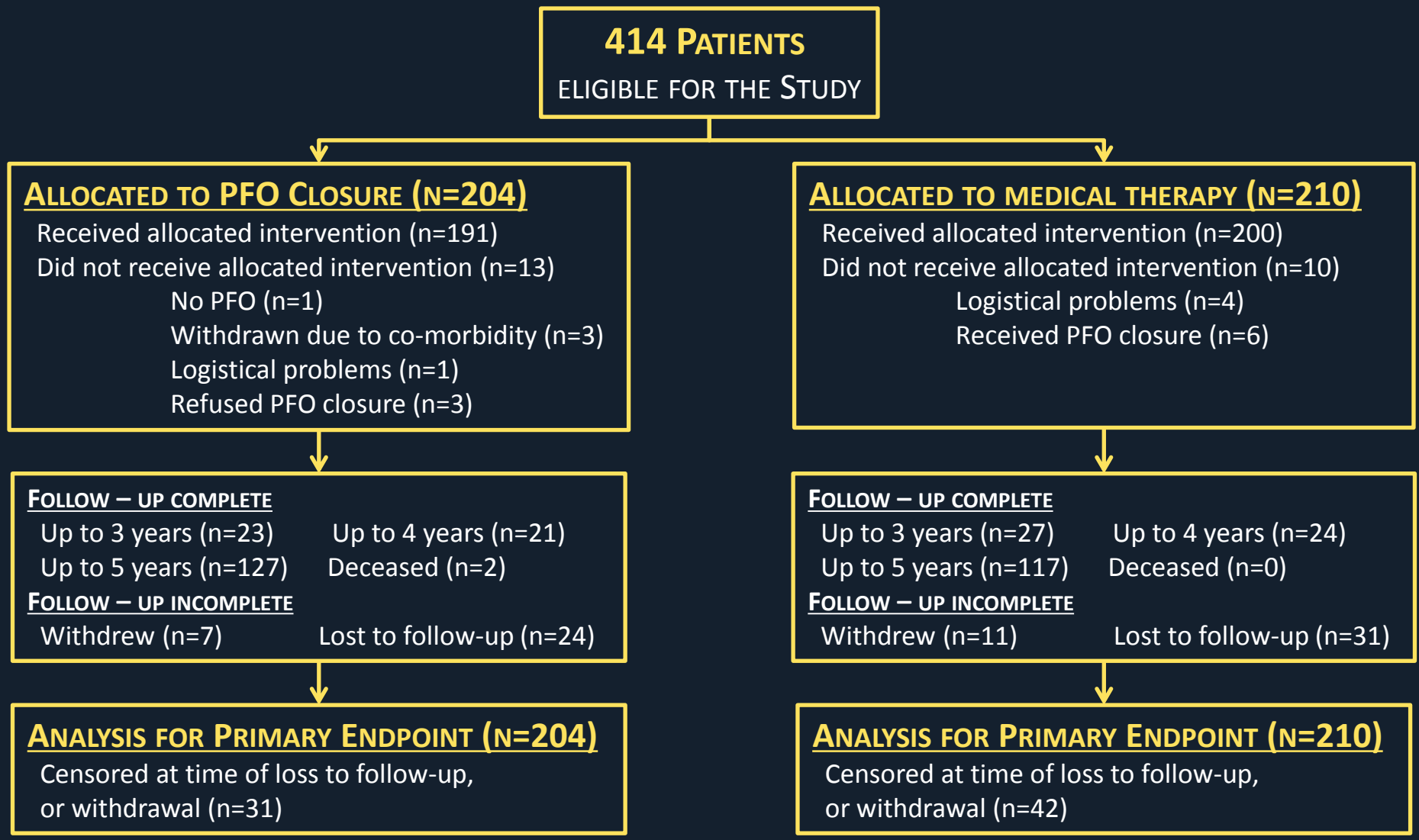
Study Centers and Investigators

Australia		
Monash Medical Center, Melbourne	S. Menahem, S. Bower, R. Harper	
Sir Charles Gairdner Hospital, Nedlands	B.E.F. Hocking, W.Carroll	
Epworth Hospital, Prahran	T.Walton	
Alfred Hospital, Prahran	J. Frayne, M. Butler, L. Iles, E. Ivens, J.Hare, E. Kotschet	
Austria		
Uni-Klinik Innere Med II, AKH Vienna	P. Probst, W. Lalouschek, H. Baumgartner, R. Rosenhek	
Belgium		
A.Z. Sint-Jan AV, Brugge	G. Vanhoorem, L. Muyldermans	
Brazil		
Hospital Sao Paulo, Sao Paulo	A.C.C. Carvalho, M.M. Fukujima C.M.C. Silva	
Canada		
Montreal Heart Institute, Montreal	S. Lanthier, R. Ibrahim	
Queen Elizabeth II Health Sciences Centre, Halifax	S. Philipps, J. Howelett	
Denmark		
Aalborg Sygehus, Aalborg	B. Kristensen, R. Nielsen	
Aarhus Universitetshospital, Aarhus	G. Andersen, T.S. Jensen K. Emmersten	
Germany		
Klinik d. J.W.Goethe Universität Frankfurt	V. Schächinger, T. Trepels	
Universitätsklinikum Giessen, Giessen	W. Waas, M. Jauss	
Herz- und Diabeteszentrum NRW, Minden	W.Scholtz, D. Fassbender	
Johannes Wesling Klinikum Minden, Minden	J. Glahn, H. Wuttig	
Herzzentrum Leipzig GmbH, Leipzig	G. Schuler, G. Marcus, M. Sandri	
Brüderkrankenhaus Trier, Trier	K.E. Hauptmann, T. Gehrig	
Städtisches Klinikum Fulda, Fulda	M. Conze, M. Emir, J.M. Klotz	
Klinikum d. Philipps-Universität Marburg, Marburg	B. Maisch, R. Funck	
Germany		
Universitätskliniken des Saarlands, Homburg/Saar	M.Böhm, B. Scheller	
Medizinische Universitätsklinik Würzburg, Würzburg	P. Schänzenbächer, W. Müllges	
Leopoldina KH der Stadt Schweinfurt GmbH, Schweinfurt	J. Mühler, K. Dötter	
Lukaskrankenhaus Neuss, Neuss	M. Haude, H. Degen	
Poland		
Medikal University of Gdansk, Gdansk	J. Erecinski, Chojnicki, R. Sabiniewicz	
Card. Dept.Institute of Cardiology, Krakow	D. Dudek, A. Szczudlik, P. Szermer, S. Bartus, D. Sorysz, B. Chyrchel	
Slovakia		
Slovak Institute of Cardiovascular Disease	V. Fridrich	
Switzerland		
Bern University Hospital / Inselspital	B. Meier, H. Mattle, S. Windecker, A. Wahl	
United Kingdom		
Sussex Cardiac Centre, Brighton	D. Hildick-Smith, P. Kumar	
Western General Hospital, Edinburgh	B. Weller, M. Dennis, D. Northridge	
Royal Surrey County Hospital, Guilford	E.W. Leatham	
St. George´s Hosp. Med. School, London	H. Markus, M. Punter	
Clarence Wing – St. Mary's Hospital NHS Trust, London	I. Mallik	
New Cross Hospital, Wolverhampton	S.S. Khogali, L. Evans, A. Smallwood	

Study Organisation

Grant support	St. Jude Medical, Plymouth, Minnesota, USA
Principal investigators	Bernhard Meier, Heinrich P. Mattle
Study monitoring	E&E CRO, Clinical Research Organization, Vienna, Austria
Data management	Academic Research Organisation InterCorNet, Zurich Heart House, Zurich, Switzerland
Statistical analysis	CTU Bern (Bindu Kalesan, Peter Jüni)
DSMB	R. Stables, P. Sandercock, T. Gasser
CEC	B. Martin (Chairman), R. Baumgartner, F. Eberli

Patient Flow



Baseline Clinical Characteristics

	Percutaneous PFO Closure n = 204	Medical Treatment n = 210
Age ≥ 45 years	113 (55.4)	113 (53.8)
Male gender	92 (45.1)	114 (54.3)
Family history of cerebrovascular accidents	53 (26.0)	40 (19.1)
Currently smoking	52 (25.5)	47 (22.4)
Arterial hypertension	49 (24.0)	58 (27.6)
Diabetes mellitus	5 (2.5)	6 (2.9)
Hypercholesterolemia	50 (24.5)	62 (29.5)
Peripheral vascular disease	3 (1.5)	2 (1.0)

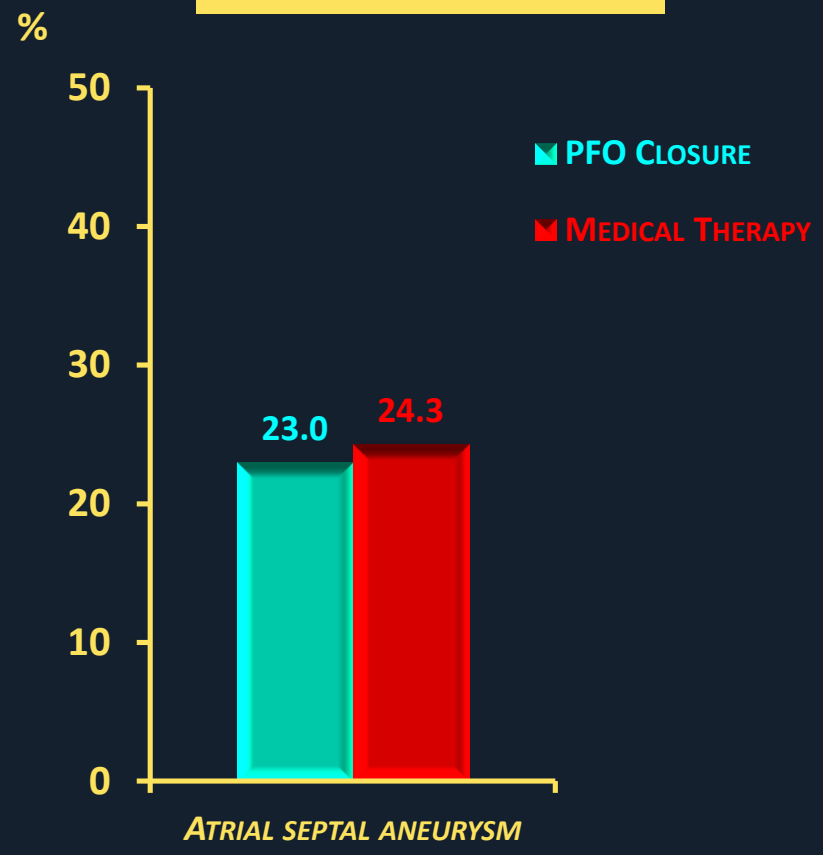
Baseline Clinical Characteristics

	Percutaneous PFO Closure n = 204	Medical Treatment n = 210
Coronary artery disease	4 (2.0)	4 (1.9)
History of myocardial infarction	3 (1.5)	1 (0.5)
Migraine	47 (23.0)	38 (18.1)
Cerebrovascular index event		
Stroke	165 (80.9)	163 (77.6)
Transient ischemic attack	33 (16.2)	42 (20.0)
Peripheral embolism	6 (2.9)	5 (2.4)
> 1 previous cerebrovascular event	76 (37.3)	79 (37.6)

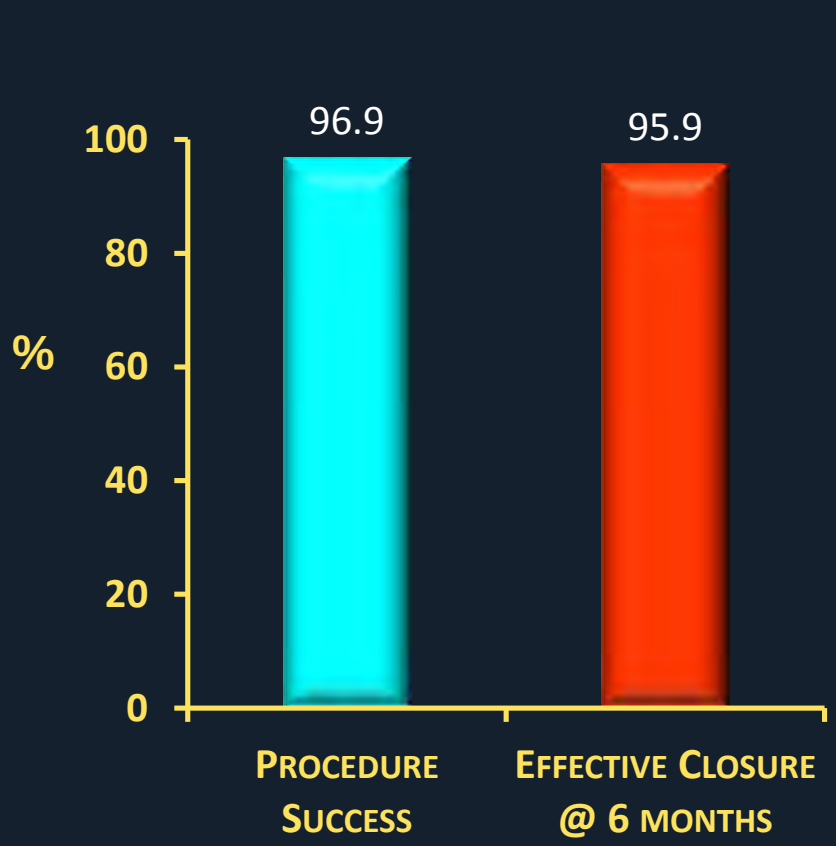
Atrial Septal Anatomy

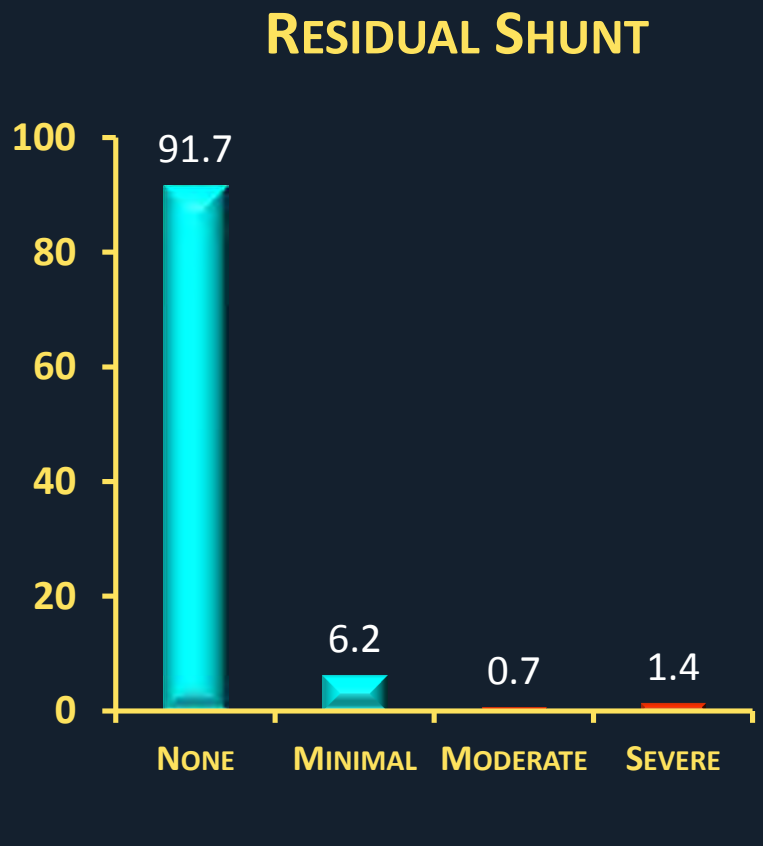
Atrial Septal Aneurysm

Inter-Atrial Right to Left Shunt



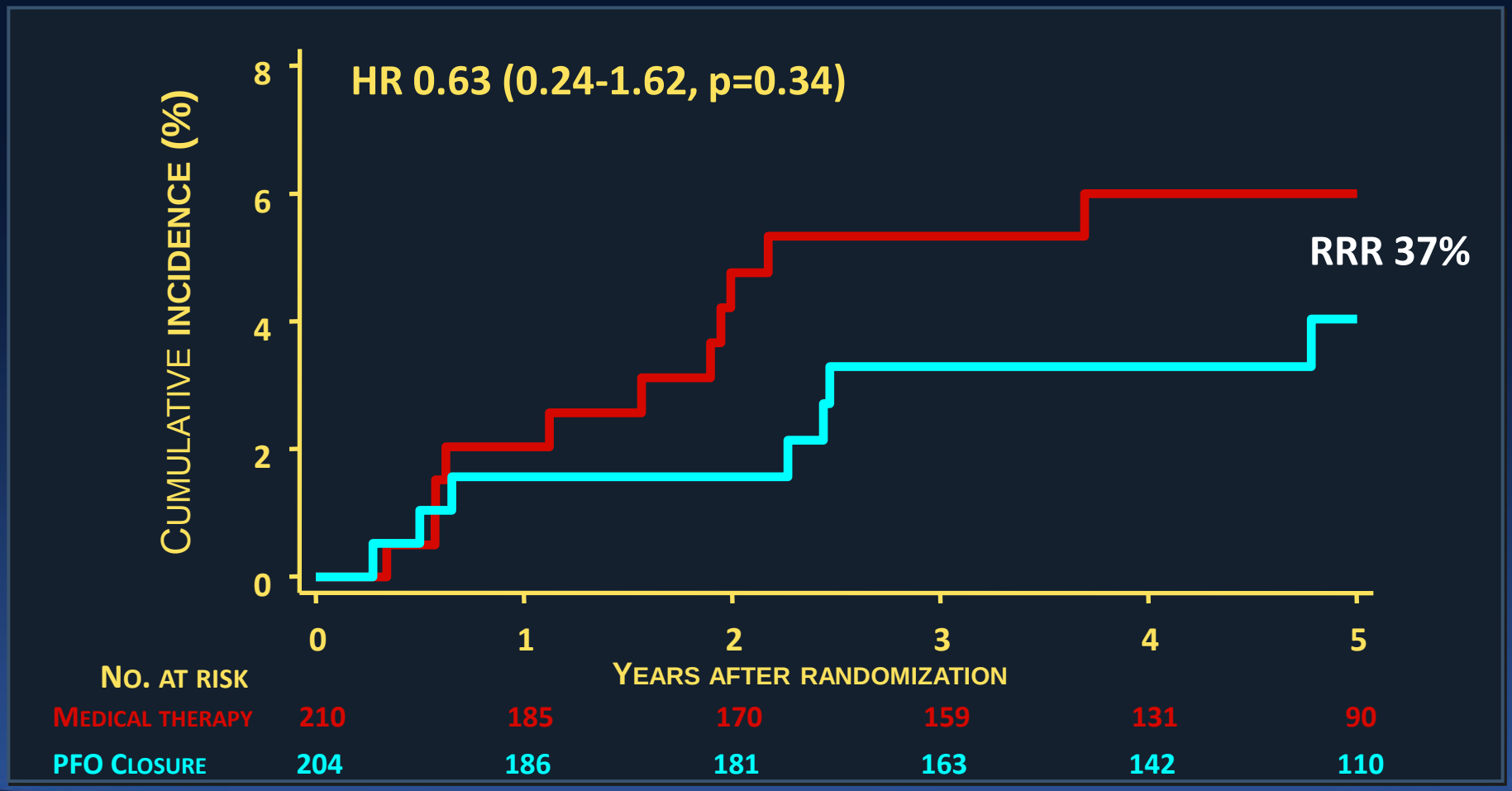
Procedure Success and Closure Rate





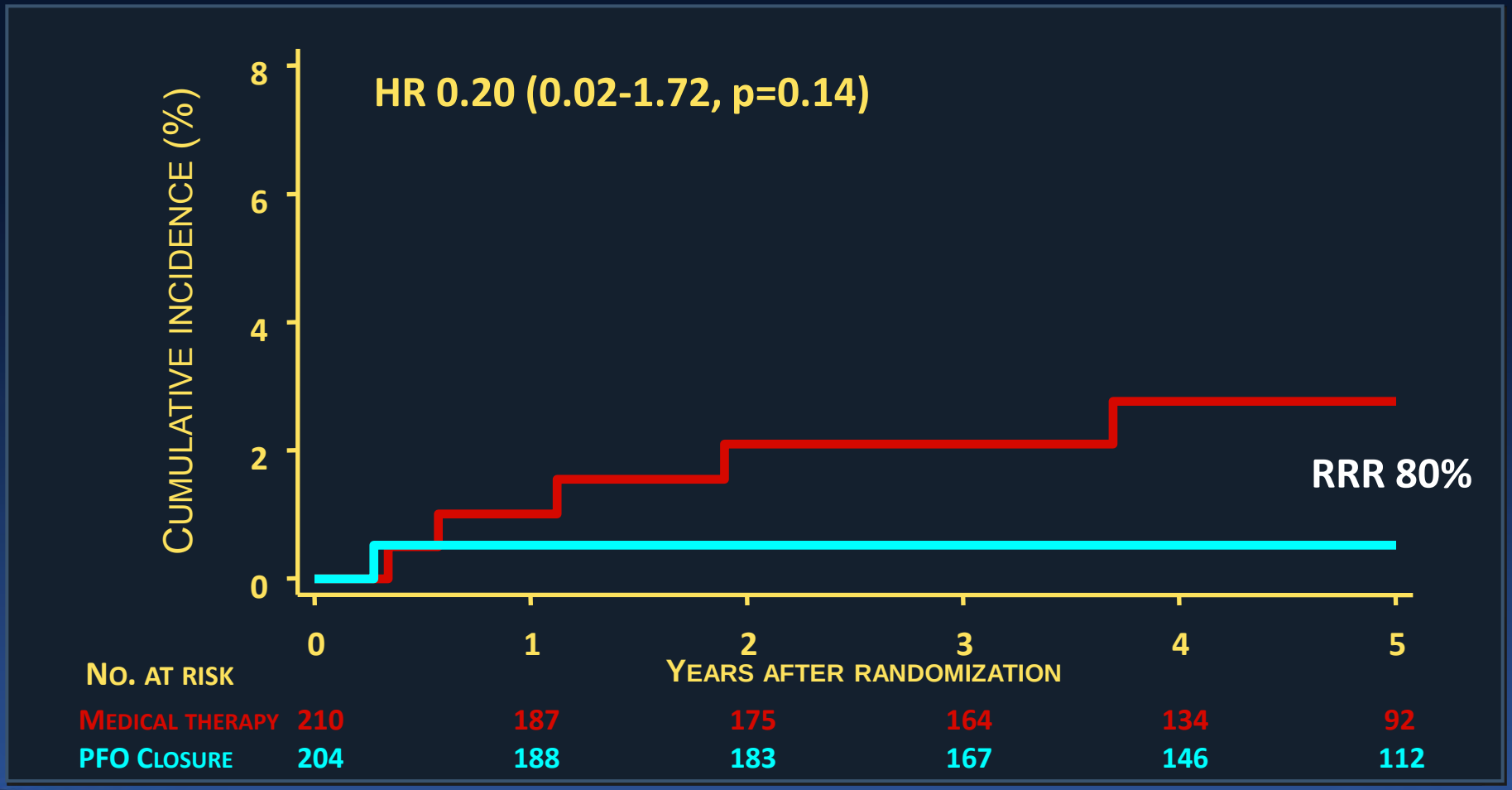
Primary Composite Endpoint

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



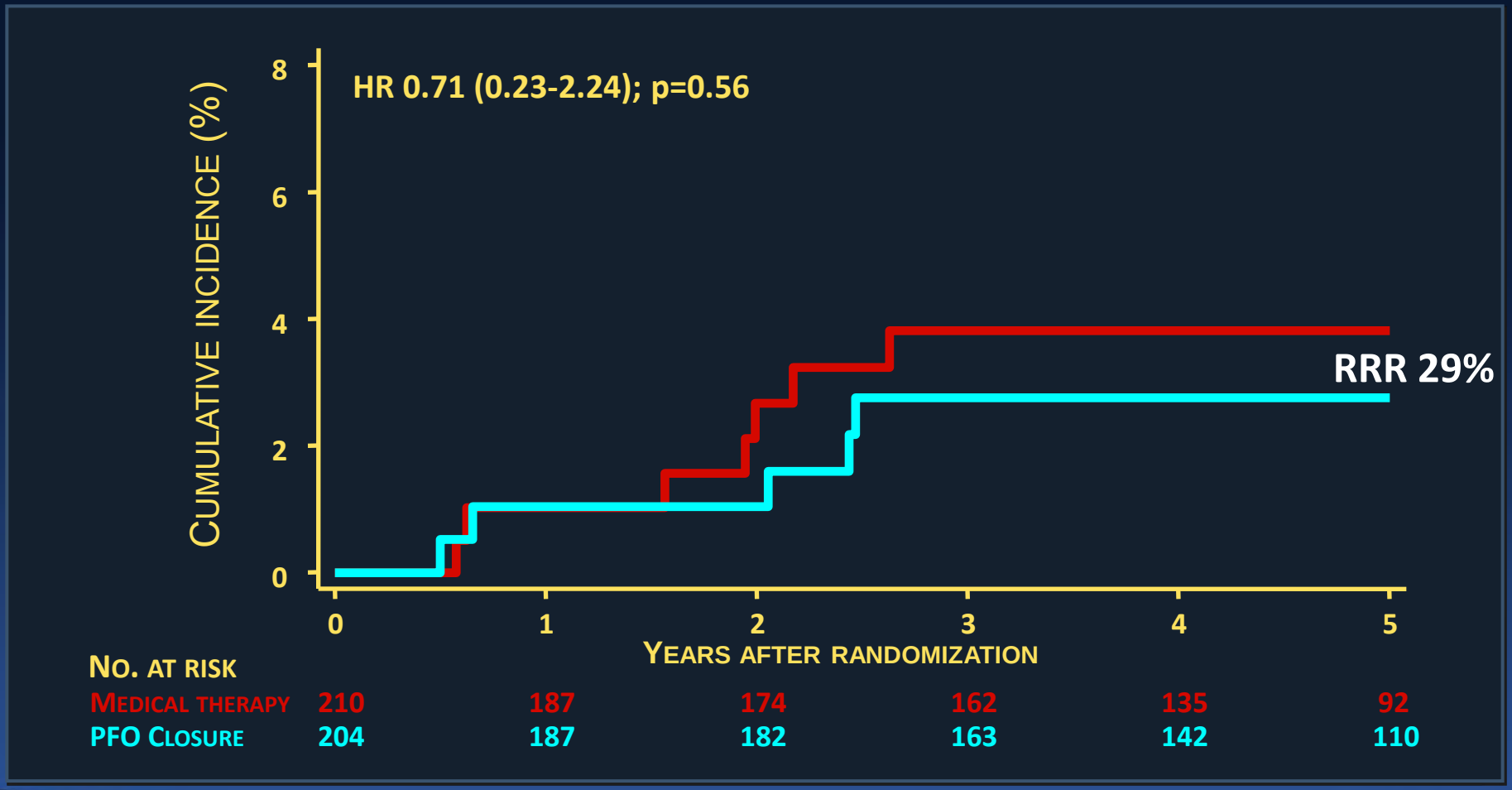
Secondary Endpoint

Stroke

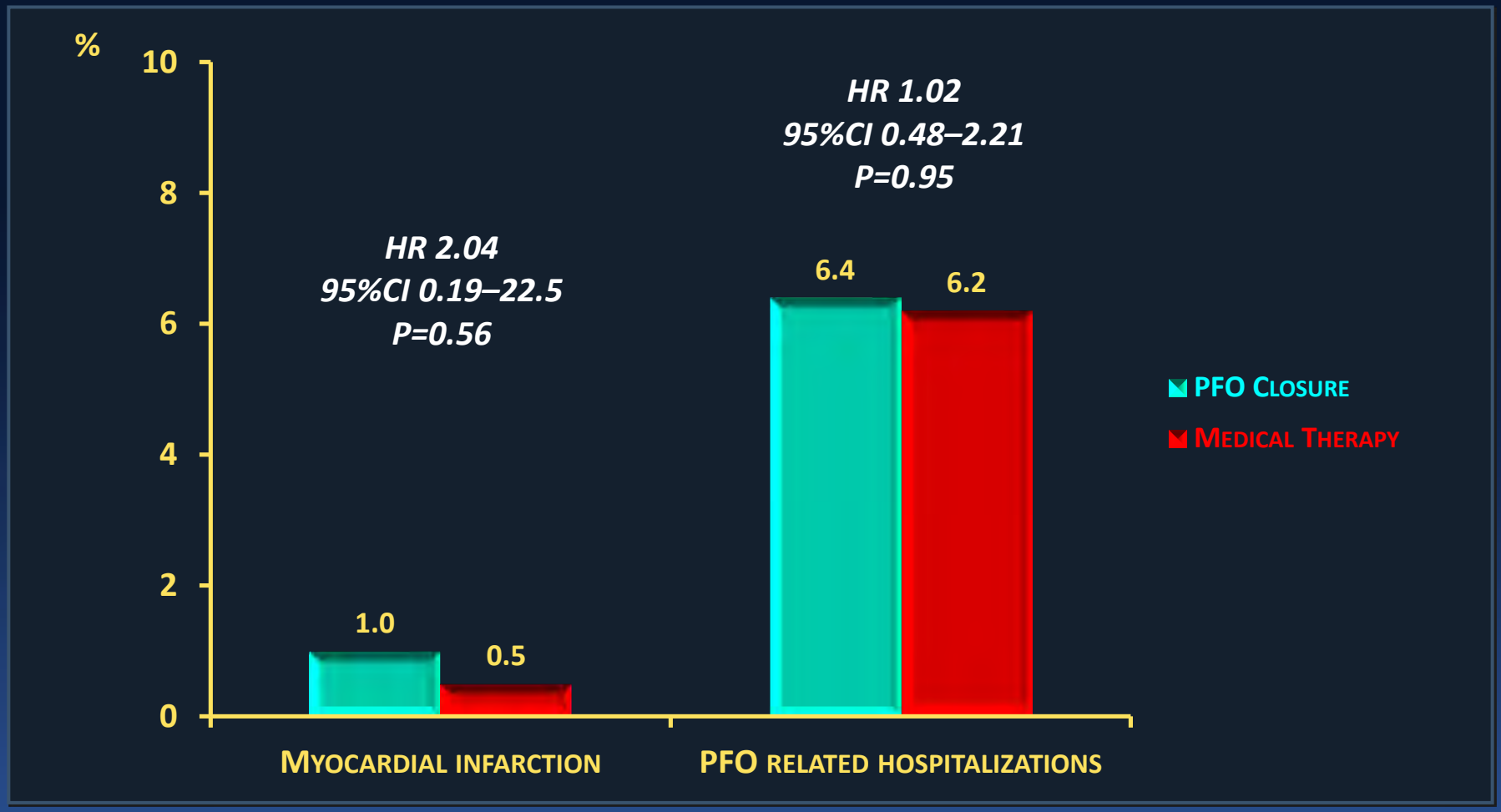


Secondary Endpoint

Transient Ischemic Attack



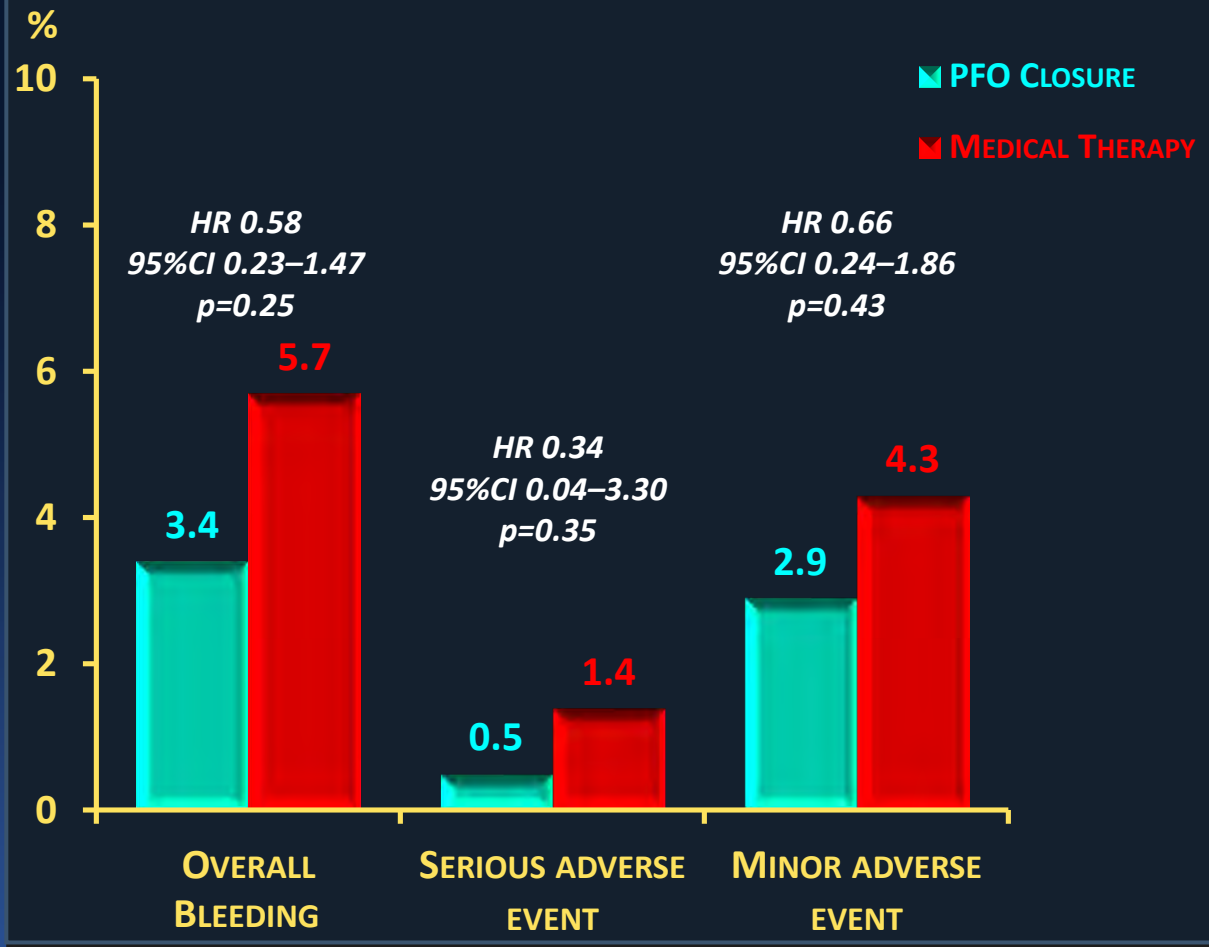
SECONDARY ENDPOINTS



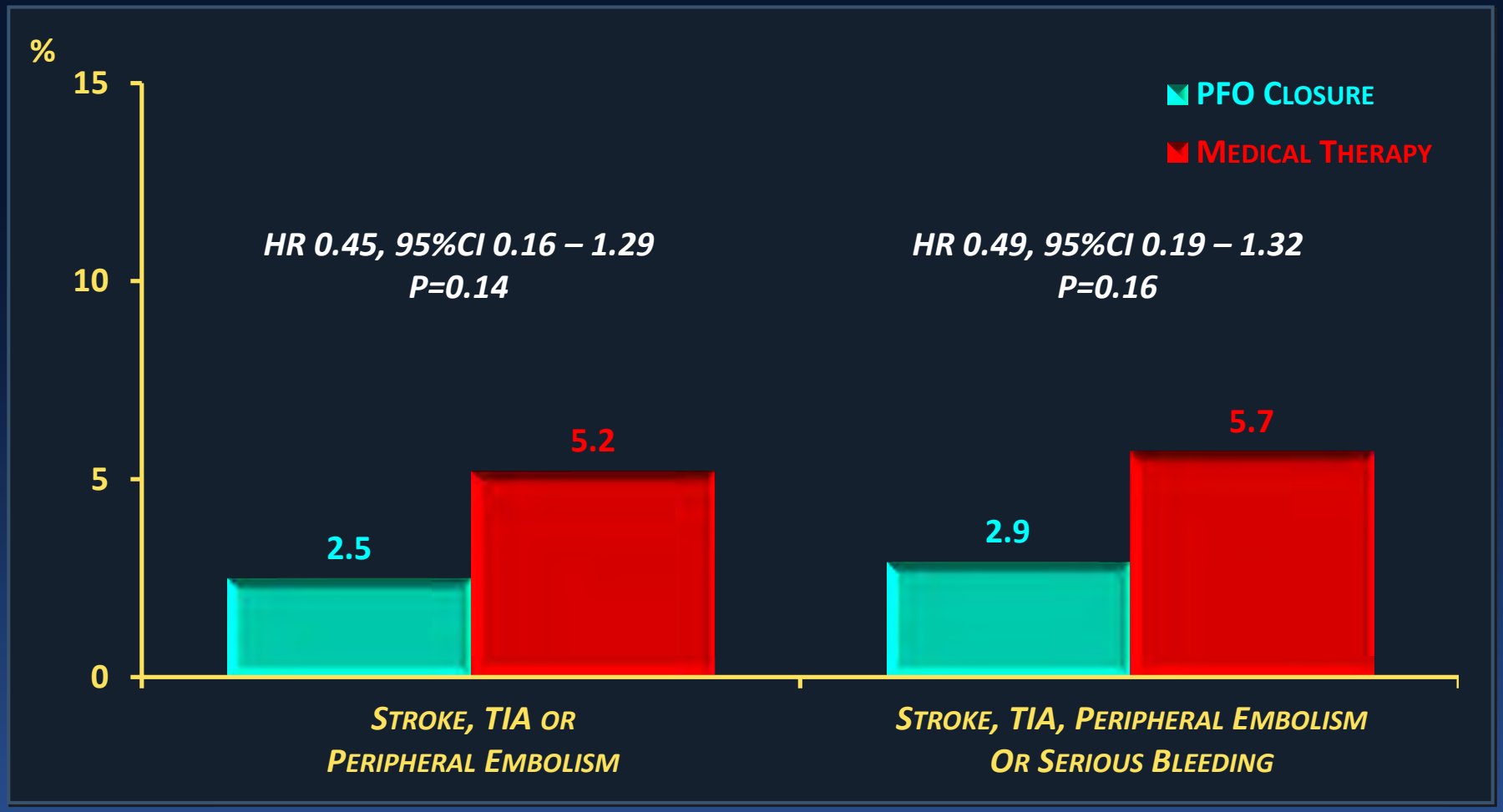
Bleeding and Atrial Fibrillation

Bleeding

Atrial fibrillation

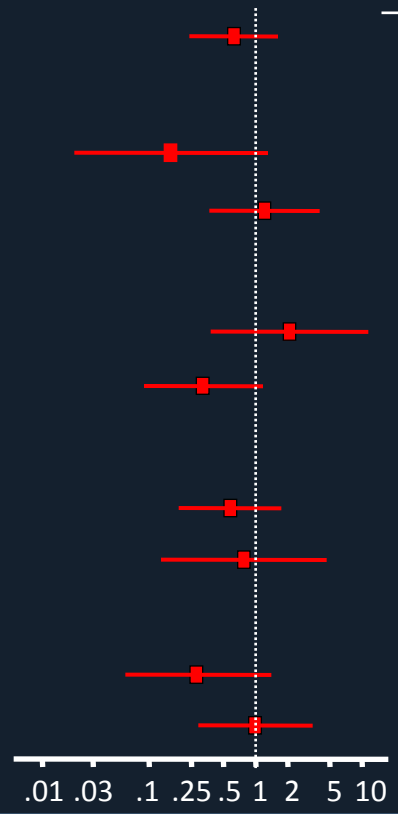


Thromboembolic and Bleeding Events



Stratified Analysis of the Primary Endpoint

	PFO Closure	Medical Therapy	HR (95% CI)	P-Interaction
Overall	7 (3.4)	11 (5.2)	0.63 (0.24-1.62)	
Age				0.10
<45 years	1 (1.1)	6 (6.2)	0.16 (0.02-1.31)	
≥45 years	6 (5.3)	5 (4.4)	1.22 (0.37-3.99)	
Atrial septal aneurysm				0.09
Yes	4 (8.5)	2 (3.9)	2.09 (0.38-11.4)	
No	3 (1.9)	9 (6.0)	0.32 (0.09-1.18)	
CV Index event				0.78
Stroke	5 (3.1)	8 (4.9)	0.58 (0.19-1.76)	
TIA or PE	2 (5.1)	3 (6.4)	0.78 (0.13-4.66)	
More than 1 CV event				0.22
Yes	2 (2.6)	6 (7.6)	0.28 (0.06-1.41)	
No	5 (3.9)	5 (3.8)	0.99 (0.29-3.45)	



LIMITATIONS

- **Study power and sample size**
  - Observed event rate in medical Rx group (5.2%) lower than anticipated (12%) at a mean follow-up of 4 years
  - Power to detect hypothesized 66% relative risk reduction less than 40%
- **Composite primary endpoint**
  - Death – non-specific
  - TIA – soft endpoint
  - Historical stroke endpoint definition
- **Long recruitment duration**
- **Attrition rate**

Conclusions

- Percutaneous PFO closure with the Amplatzer PFO Occluder for secondary prevention of thromboembolism showed no significant reduction in ischemic and bleeding events compared with medical treatment in this trial
- However, the observed difference in stroke (80% relative risk reduction, NNT=40) may be clinically relevant if confirmed in further studies