Patent Foramen Ovale Closure: Long-term Results

Paolo Scacciatella,
Ilaria Meynet, Lorenza Biava, Pierluigi Omedè, Fulvio Orzan

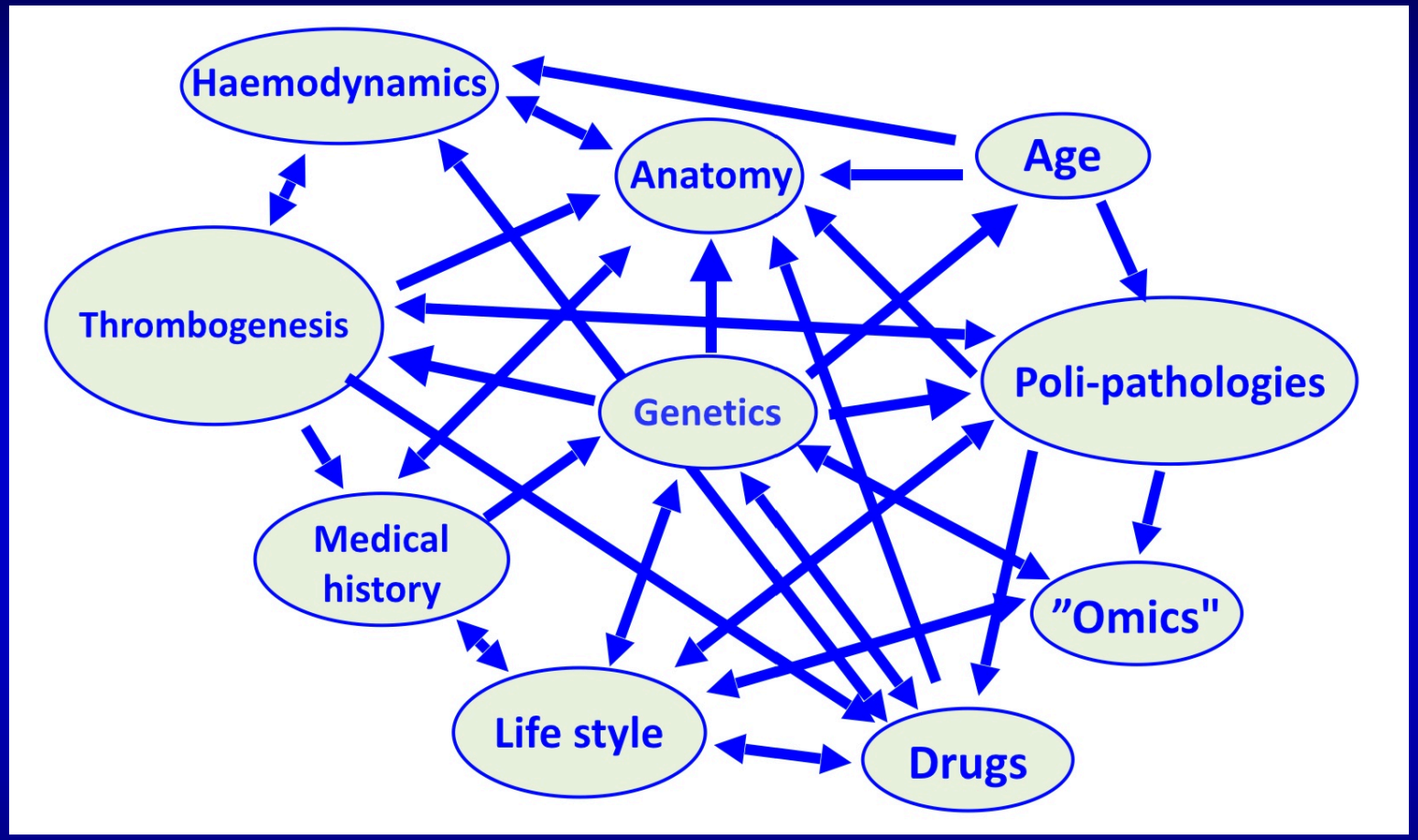
Cardiologia Universitaria
Città della Salute e della Scienza
di Torino

INTRODUCTION

The causal involvement of PFO in several diseases has been well-documented.

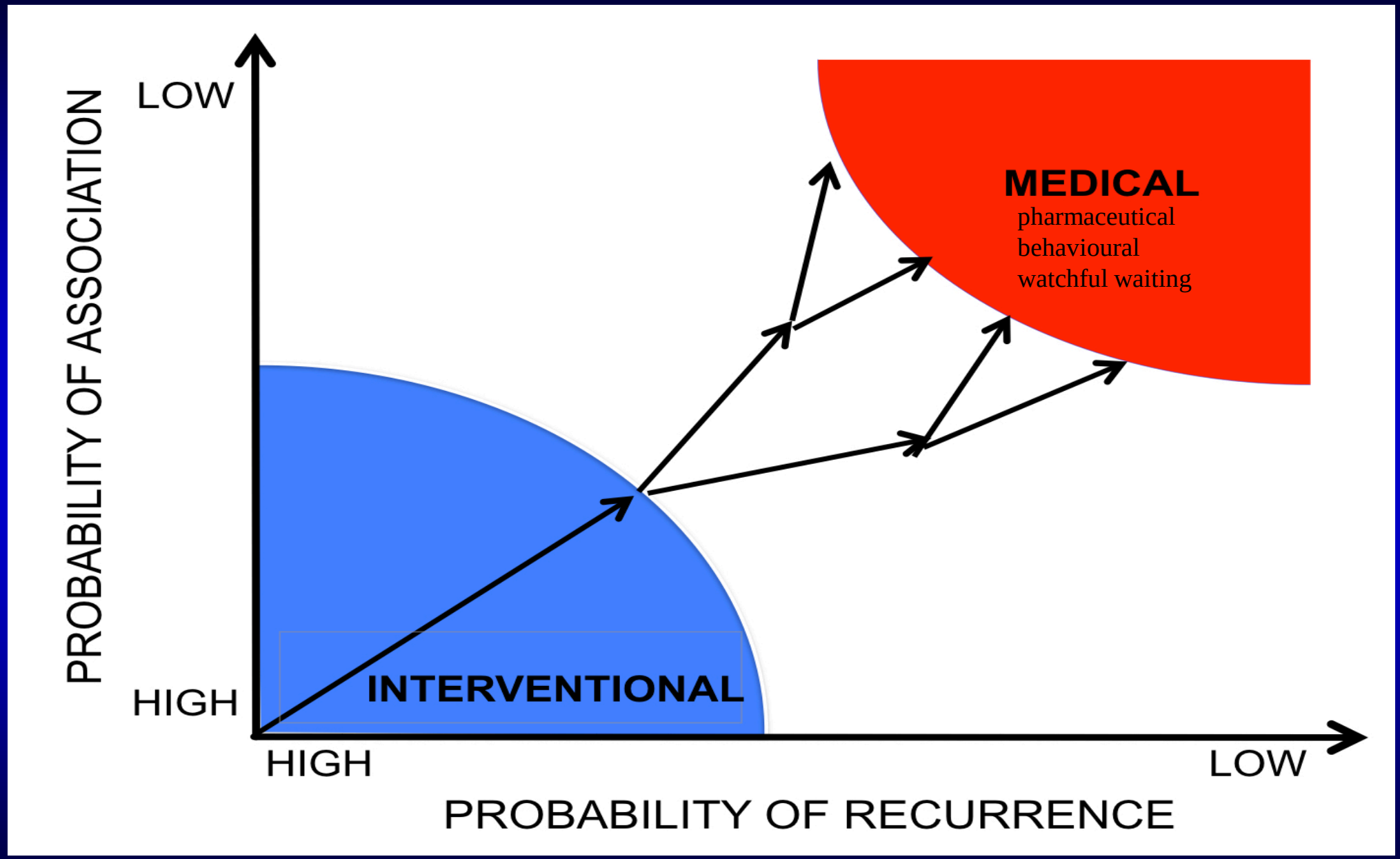
However, the role of PFO in most causal mechanisms remains elusive because:

1) a **high prevalence of PFO in the general population** produces a "statistical noise";
2) the **anatomic PFO phenotypes are various** and are even multiplied by their temporal variation;
3) the causal role of PFO is often **momentary**;
4) the diagnostic accuracy of PFO tests is not always optimal.



COMPLEX SYSTEM

PRECISION MEDICINE


LOW
PROBABILITY OF ASSOCIATION
HIGH
MEDICAL
pharmaceutical
behavioural
watchful waiting
INTERVENTIONAL
HIGH
LOW
PROBABILITY OF RECURRENCE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

N ENGL J MED 368;12 NEJM.ORG MARCH 21, 2013

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 8, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2015.12.023

Device Closure of Patent Foramen Ovale After Stroke

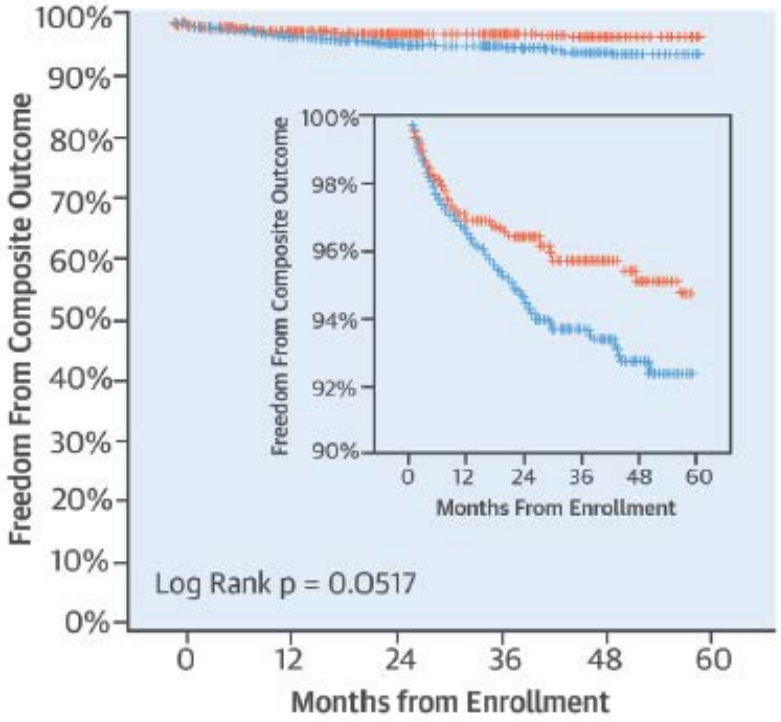
Pooled Analysis of Completed Randomized Trials

David M. Kent, MD,[a,b] Issa J. Dahabreh, MD,[a,c,d,e] Robin Ruthazer, MPH,[a] Anthony J. Furlan, MD,[f] Mark Reisman, MD,[g] John D. Carroll, MD,[h] Jeffrey L. Saver, MD,[i] Richard W. Smalling, MD, PHD,[j] Peter Jüni, MD,[k,l] Heinrich P. Mattle, MD,[m] Bernhard Meier, MD,[n] David E. Thaler, MD[b]

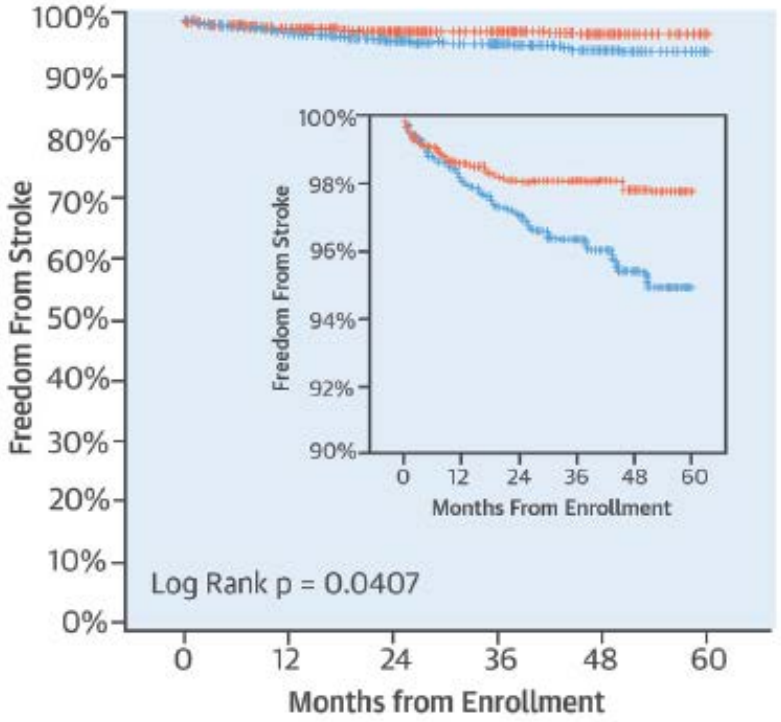
From the [a]Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center/Tufts University School of Medicine, Boston, Massachusetts; [b]Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, Boston, Massachusetts; [c]Center for Evidence-based Medicine, School of Public Health, Brown University, Providence, Rhode Island; [d]Department of Health Services, Policy & Practice, School of Public Health, Brown University, Providence, Rhode Island; [e]Department of Epidemiology, School of Public Health, Brown University, Providence, Rhode Island; [f]Department of Neurology, Case Western Reserve University, Cleveland, Ohio; [g]Division of Cardiology, University of Washington Medical Center, Seattle, Washington; [h]Division of Cardiology, Department of Medicine, University of Colorado Denver, Aurora, Colorado; [i]Comprehensive Stroke Center and Department of Neurology, David Geffen School of Medicine/University of California Los Angeles, Los Angeles, California; [j]Division of Cardiology, Department of Medicine, The University of Texas Medical School at Houston, Houston, Texas; [k]Institute of Primary Health Care and Clinical Trials Unit Bern, University of Bern, Switzerland; [l]Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Ontario, Canada; [m]Department of Neurology, Bern University Hospital, Bern, Switzerland; and the [n]Department of Cardiology, Bern University Hospital, Bern, Switzerland. This study was supported by the National Institutes of Health (R01 NS062153, R21 NS079826), Patient-Centered Outcomes Research Institute (ME-1306-03758), and PACE Center Funds,

ALL TRIALS

A. Composite Outcome (Ischemic Stroke/TIA/Death)



B. Recurrent Ischemic Stroke Outcome



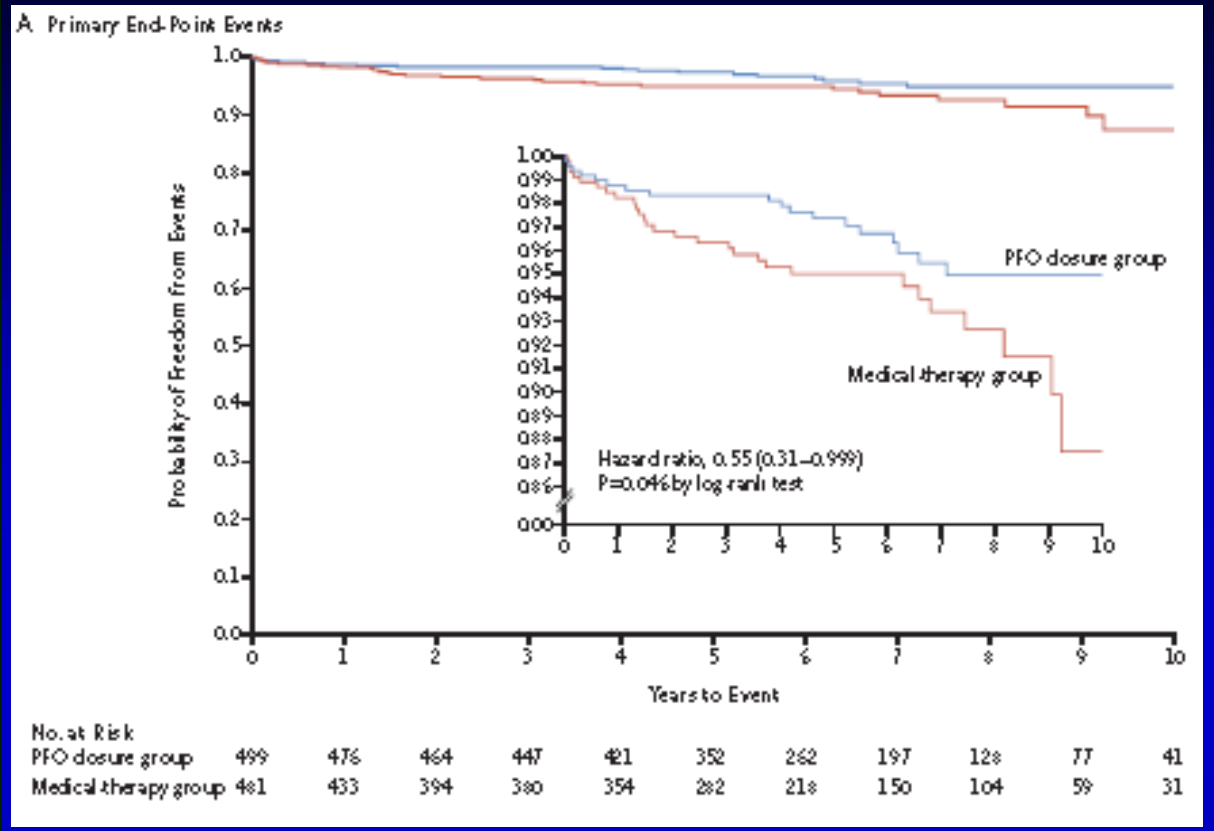
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 377;11 NEJM.ORG SEPTEMBER 14, 2017

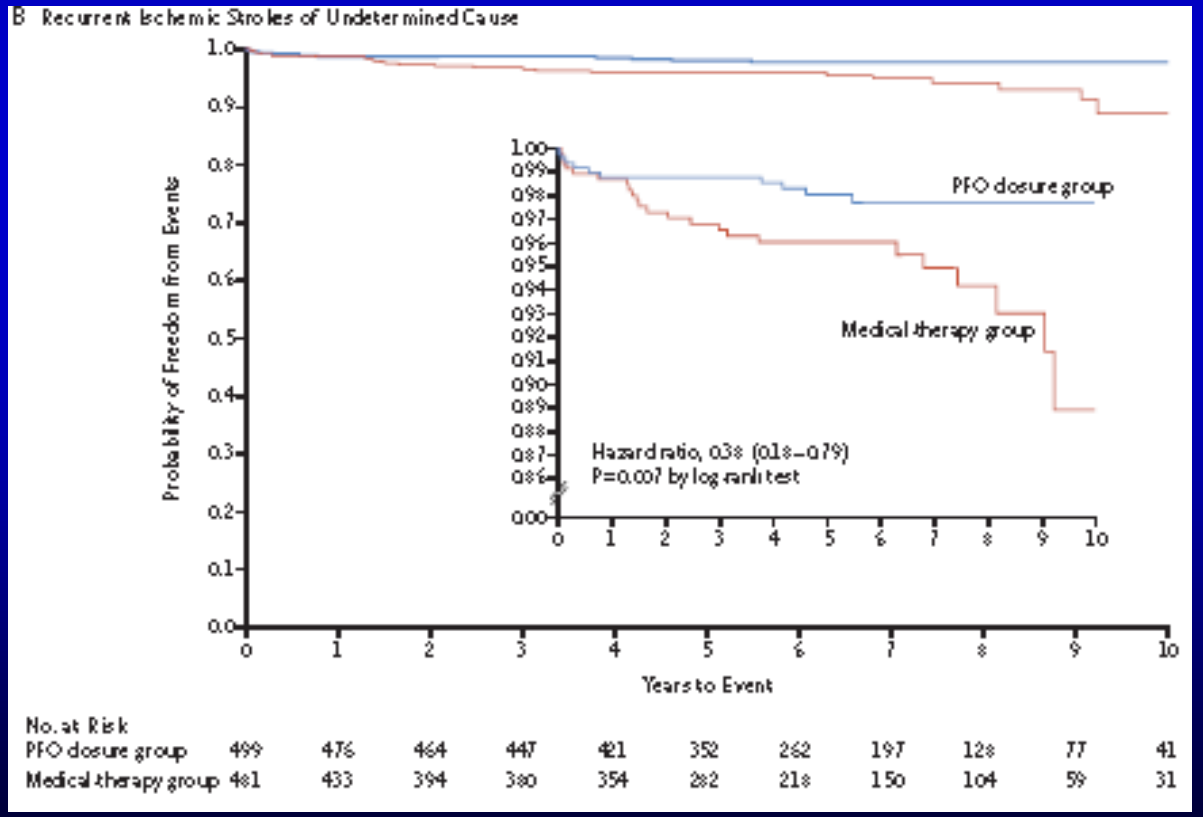
ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

ABSTRACT


A Primary End-Point Events
Probability of Freedom from Events
Years to Event
PFO closure group
Medical therapy group
Hazard ratio, 0.55 (0.31–0.999)
P=0.046 by log-rank test
No. at Risk
PFO closure group 499 476 464 447 421 352 262 197 128 77 41
Medical therapy group 481 433 394 380 354 282 218 150 104 59 31


B Recurrent Ischemic Strokes of Undetermined Cause
Probability of Freedom from Events
Years to Event
PFO closure group
Medical therapy group
Hazard ratio, 0.38 (0.18–0.79)
P=0.007 by log-rank test
No. at Risk
PFO closure group 499 476 464 447 421 352 262 197 128 77 41
Medical therapy group 481 433 394 380 354 282 218 150 104 59 31

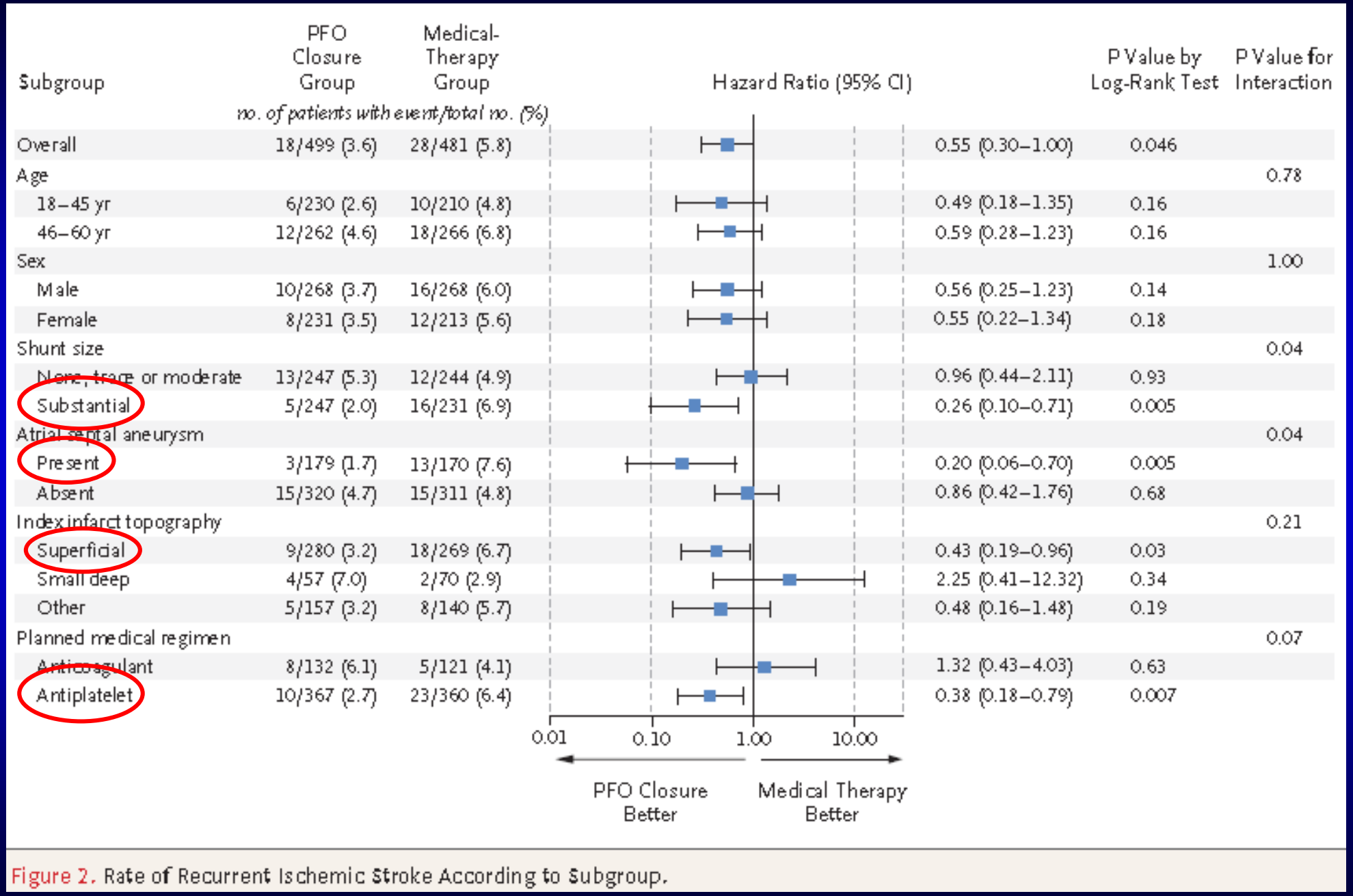


Figure 2. Rate of Recurrent Ischemic Stroke According to Subgroup.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*

CLOSE
Methods

Key inclusion criteria

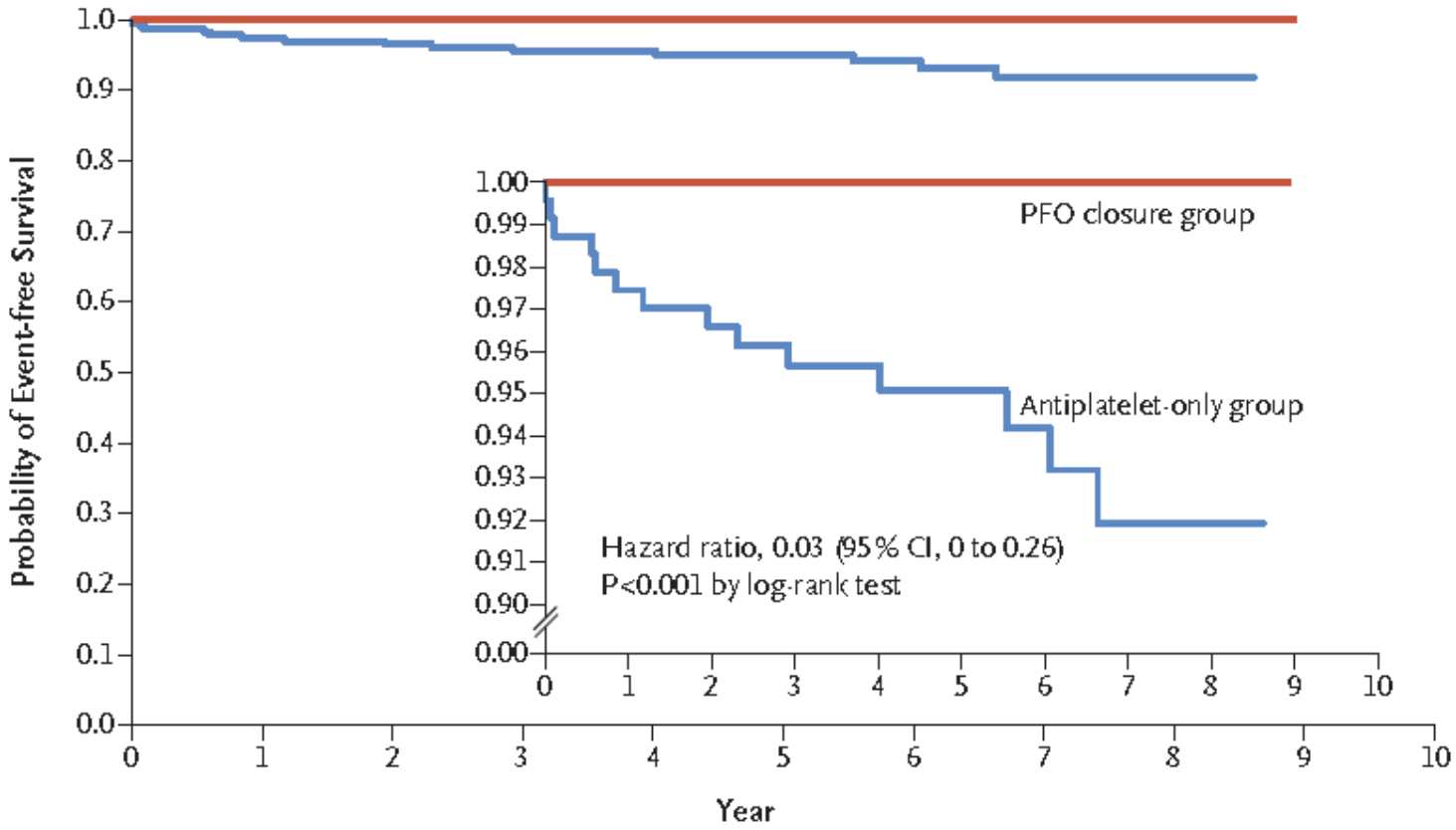
- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE,TEE) confirmed by echo core lab before randomization

Key exclusion criteria

- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

Outcomes

- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications



No. at Risk											
PFO closure group	238	238	232	200	179	141	99	64	20	0	0
Antiplatelet-only group	235	229	223	198	160	130	96	55	19	0	0

Figure 2. Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.

The analysis was performed in the intention-to-treat cohort, which included all patients who were randomly assigned to a treatment. The inset shows the same data on an enlarged y axis.

Table 3. Procedural Complications and Serious Adverse Events.*

Complication or Event	Randomization Groups 1 and 2			Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	P Value	Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	P Value
	no. of patients (%)			*no. of patients (%)*		
Major or fatal device-related or procedure-related complication†	14 (5.9)	NA	NA	NA	NA	NA
Major or fatal bleeding complication	2 (0.8)	5 (2.1)	0.28	10 (5.3)	4 (2.3)	0.18
Atrial fibrillation or flutter‡	11 (4.6)§	2 (0.9)	0.02	0	2 (1.1)	0.23
Death	0	0	NA	1 (0.5)¶	0	0.65
At least one serious adverse event	85 (35.7)	78 (33.2)	0.56	62 (33.2)	59 (33.9)	0.88

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

Inclusion and exclusion criteria

- Age 18–59 years
- Cryptogenic ischemic stroke within 180 days
  - Ischemic stroke = clinical symptoms ≥ 24 hours or with MRI evidence of infarction
  - Cryptogenic
    - No stenosis > 50 percent or ulcerated plaque in relevant intra- or extra-cranial vessels
    - No atrial fibrillation or high risk source of cardioembolism
    - Non-lacunar (based on syndrome and / or size)
    - No evidence of hypercoagulable disorder
    - No other known cause of stroke
- PFO
  - Confirmed by transesophageal echocardiography (TEE / TOE) with bubble study demonstrating right-to-left shunt at rest or during Valsalva maneuver
- No indication for anticoagulation
- No uncontrolled diabetes mellitus, hypertension, autoimmune disease, alcohol or drug abuse

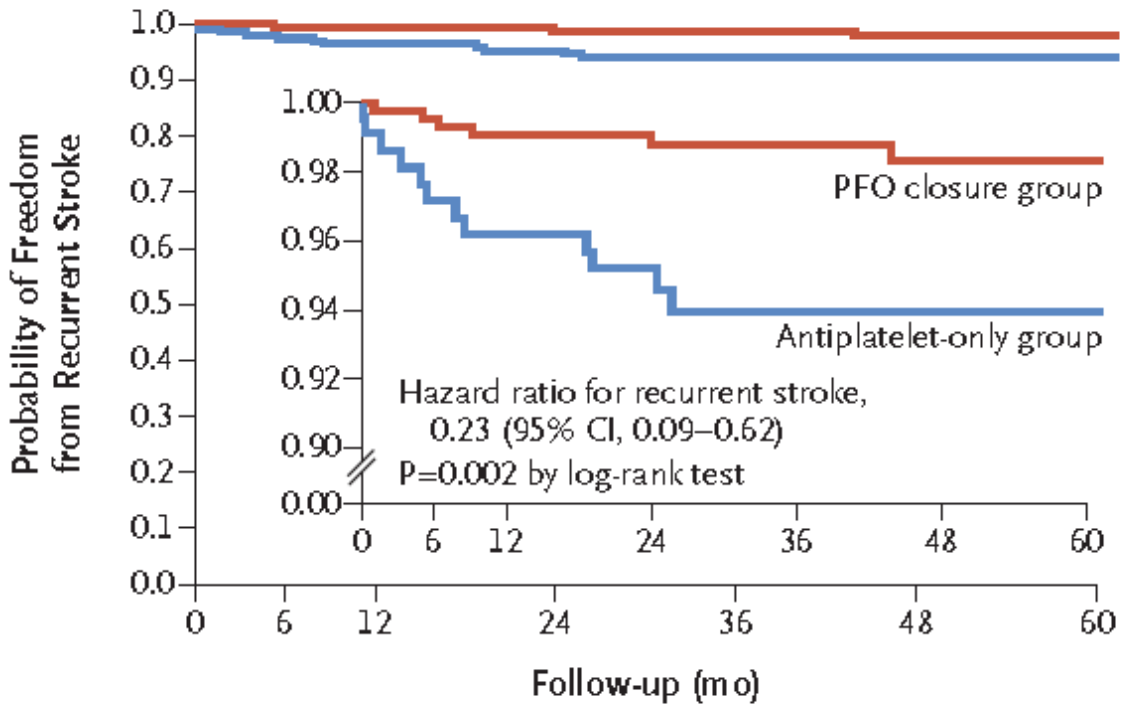


Figure 1. Probability of Freedom from Clinica
Stroke.

Table 2. Coprimary End Points of Freedom from Clinical Ischemic Stroke and Incidence of New Brain Infarction.*

End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	no. of patients/total no. (%)			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)‖	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)‖	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)‖	0.97**

Table 3. Adverse Events.

Adverse Event	PFO Closure Group (N = 441)	Antiplatelet-Only Group (N = 223)	P Value*
	no. of patients (%)		
Any serious adverse event	102 (23.1)	62 (27.8)	0.22
Device related	6 (1.4)	NA	NA
Procedure related	11 (2.5)	NA	NA
Death†	2 (0.5)	0	0.55
Serious bleeding adverse event	8 (1.8)	6 (2.7)	0.57
Procedure associated‡	4 (0.9)	NA	NA
Other§	4 (0.9)	6 (2.7)	0.09
Any atrial fibrillation or flutter	29 (6.6)	1 (0.4)	<0.001
Serious atrial fibrillation or flutter¶	10 (2.3)	1 (0.4)	0.11
Serious device-related adverse event‖	6 (1.4)	NA	NA
Device dislocation	3 (0.7)		
Device-related thrombosis	2 (0.5)		
Aortic dissection	1 (0.2)		
Any deep-vein thrombosis or pulmonary embolism	3 (0.7)	2 (0.9)	1.00

PATIENTS SELECTION

FOLLOW UP DURATION

UNRESOLVED ISSUES

1) REPRODUCIBILITY OF THE RANDOM TRIALS

2) OLDER PATIENTS

3) ATRIAL FIBRILLATION

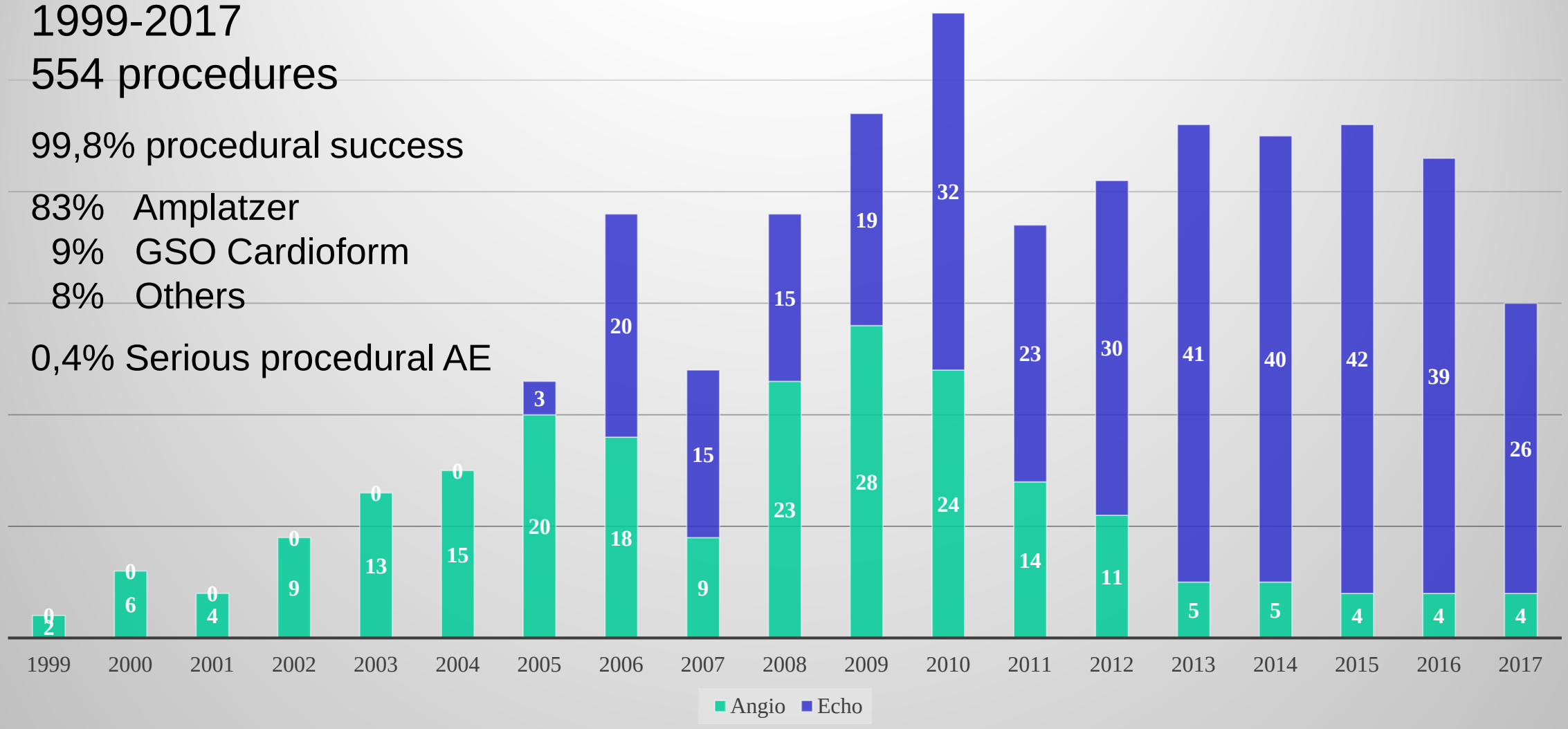
PFO closure at Città della Salute e della Scienza di Torino

1999-2017
554 procedures

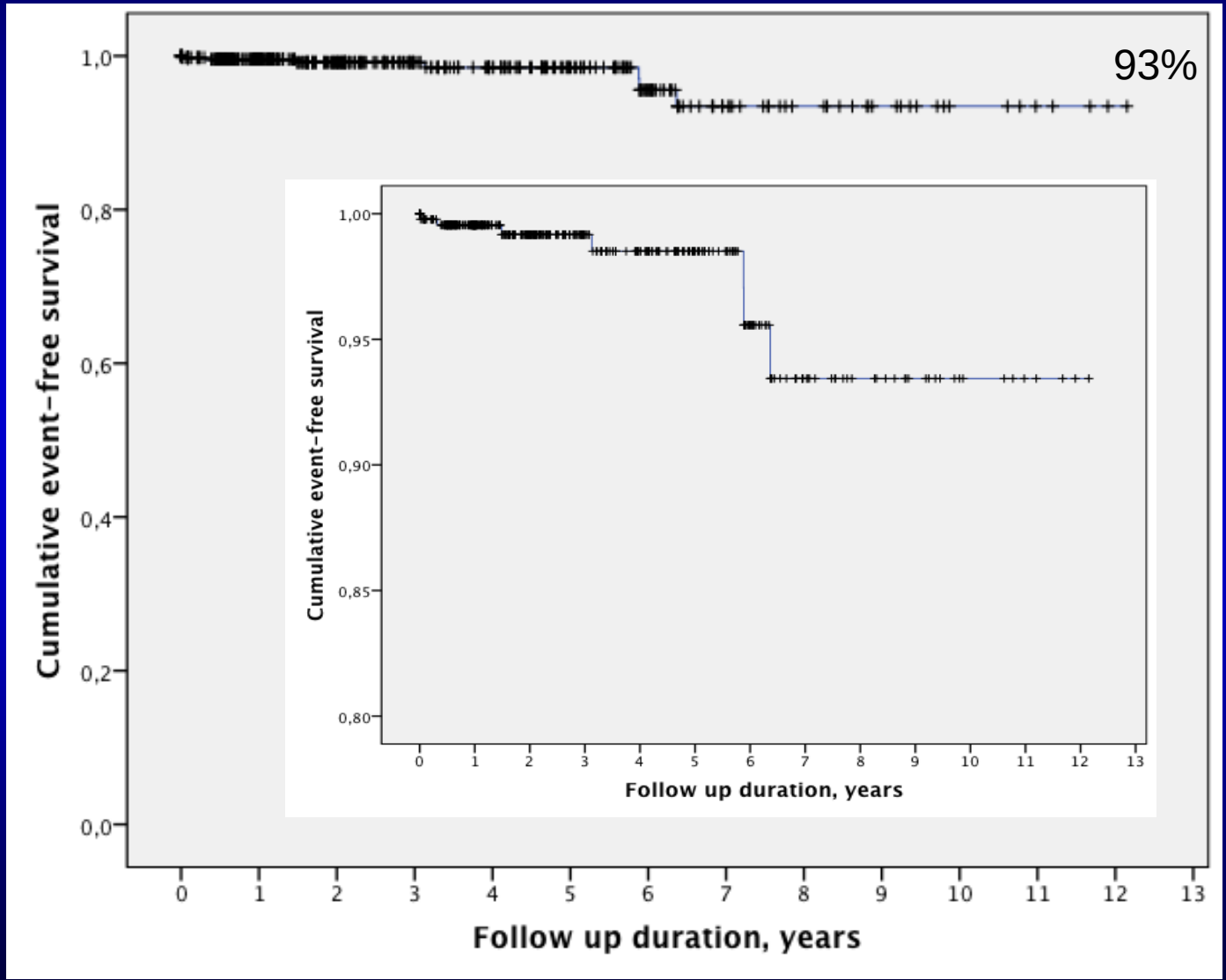
99,8% procedural success

83% Amplatzer
9% GSO Cardioform
8% Others

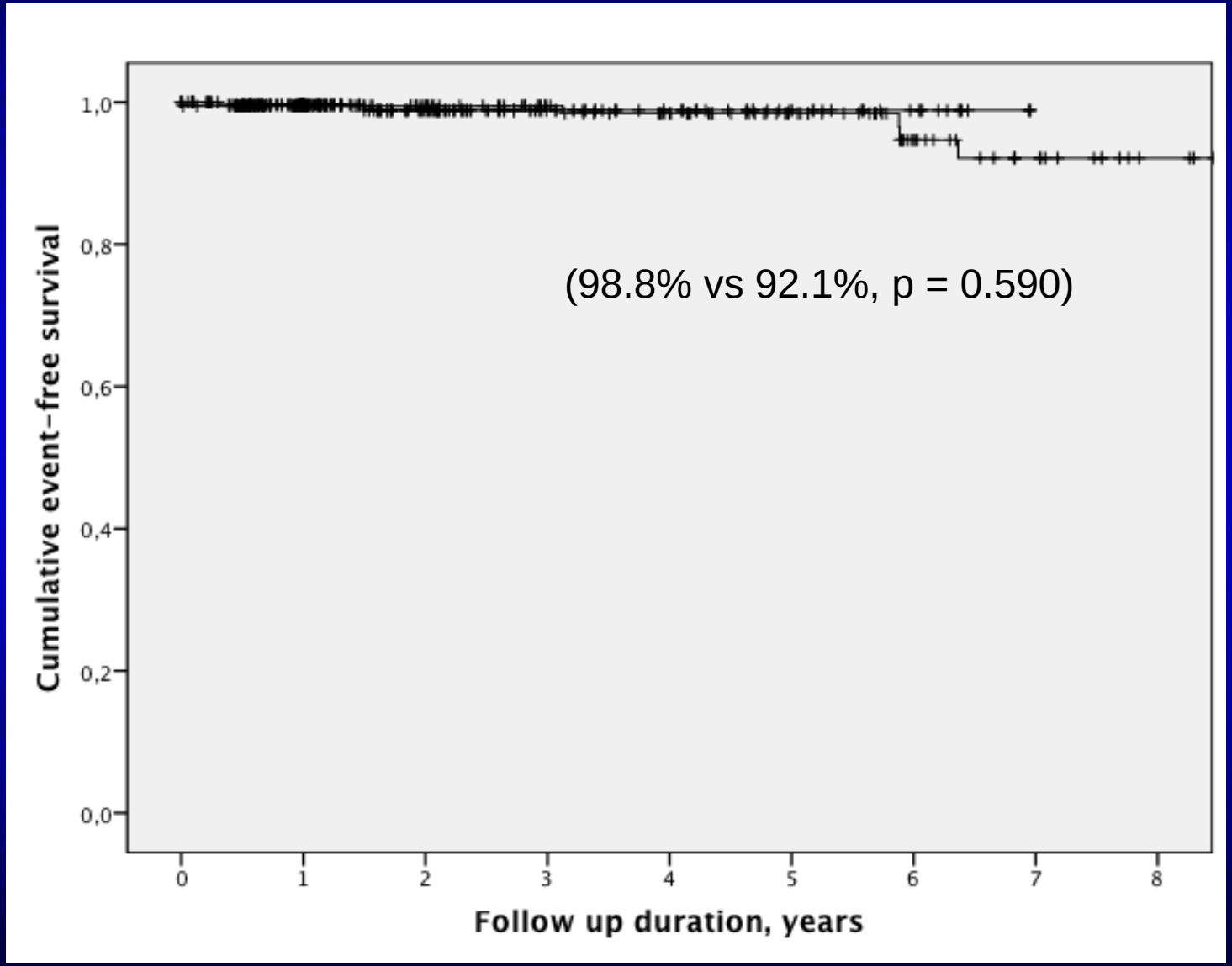
0,4% Serious procedural AE



PFO closure ay Città della Salute e della Scienza di Torino
Total recurrence free-survival



PFO closure ay Città della Salute e della Scienza di Torino
Total recurrence free-survival echo vs angio



Original Studies

Catheterization and Cardiovascular Interventions 87:508–514 (2016)

Recurrent Cerebral Ischemia After Patent Foramen Ovale Percutaneous Closure In Older Patients: A Two-Center Registry Study

Paolo Scacciatella,[1*] MD, Ilaria Meynet,[1] MD, Patrizia Presbitero,[2] MD, Mauro Giorgi,[1] MD, Carla Lucarelli,[2] MD, Dennis Zavalloni Parenti,[2] MD, Lorenza Michela Biava,[1] MD, and Sebastiano Marra,[1] MD

TABLE IV. Long-Term Results

	Age ≥55 years (151 patients)	Age <55 years (307 patients)	*P*-value
Recurrent cerebral ischemia	6 (4.0%)	1 (0.3%)	0.002
TIA	4 (2.6%)	1 (0.3%)	0.02
Stroke	2 (1.4%)	0	0.04
All cause death	1 (0.7%)	2 (0.7%)	0.98
Cardiovascular death	0	0	
Device-related complications	0	1 (0.3%)	0.48
AF onset	5 (3.3%)	6 (2.0%)	0.37
Redo of PFO closure	2 (1.4%)	8 (2.6%)	0.37

Abbreviations: TIA, transient ischemic attack.

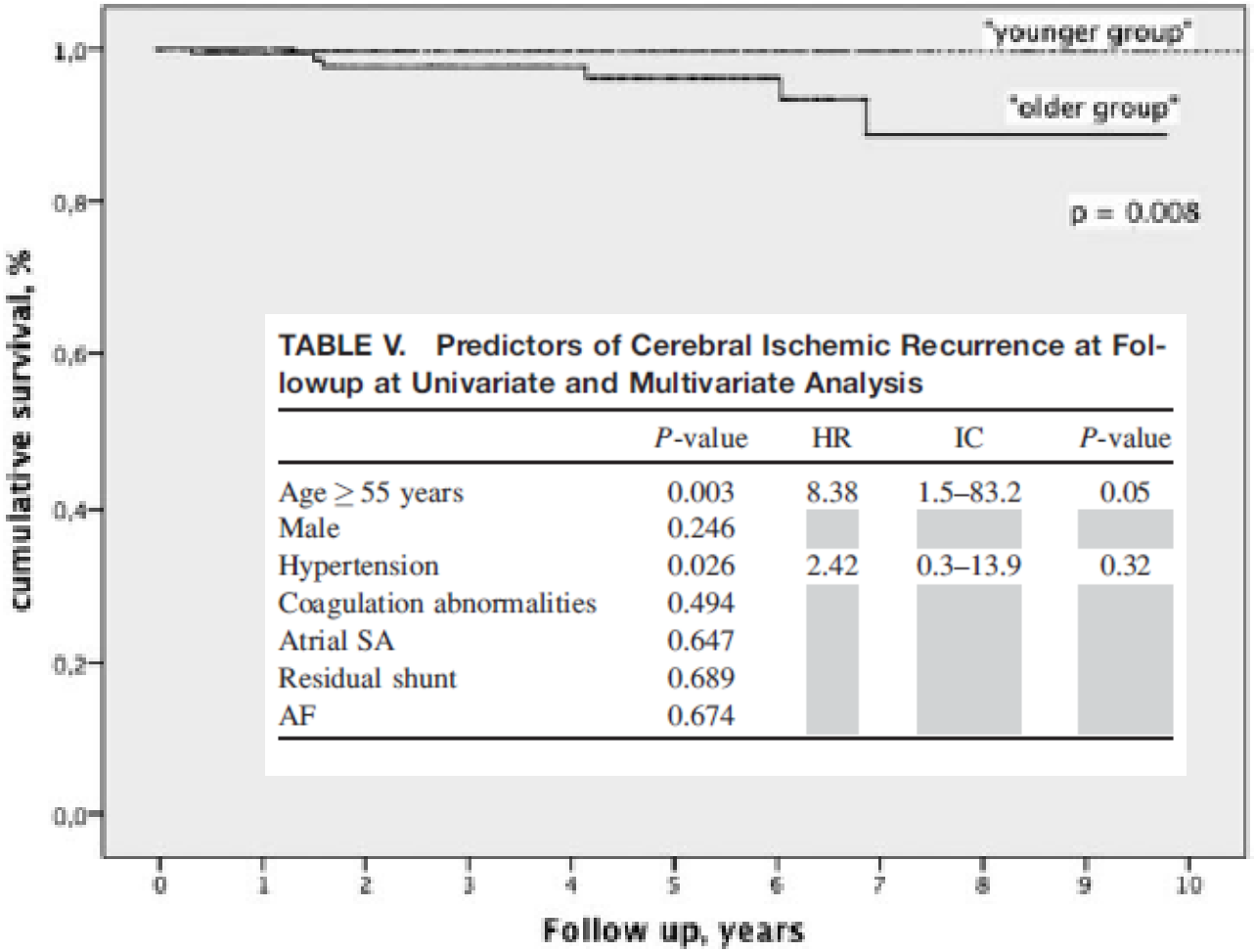


TABLE V. Predictors of Cerebral Ischemic Recurrence at Followup at Univariate and Multivariate Analysis

	P-value	HR	IC	*P*-value
Age ≥ 55 years	0.003	8.38	1.5–83.2	0.05
Male	0.246			
Hypertension	0.026	2.42	0.3–13.9	0.32
Coagulation abnormalities	0.494			
Atrial SA	0.647			
Residual shunt	0.689			
AF	0.674			

Fig. 1. Event-free survival at the end of the followup in the two subgroups. The Kaplan–Meier curve shows a significatively higher event-free survival at the end of the followup in the younger group ($P = 0.008$).

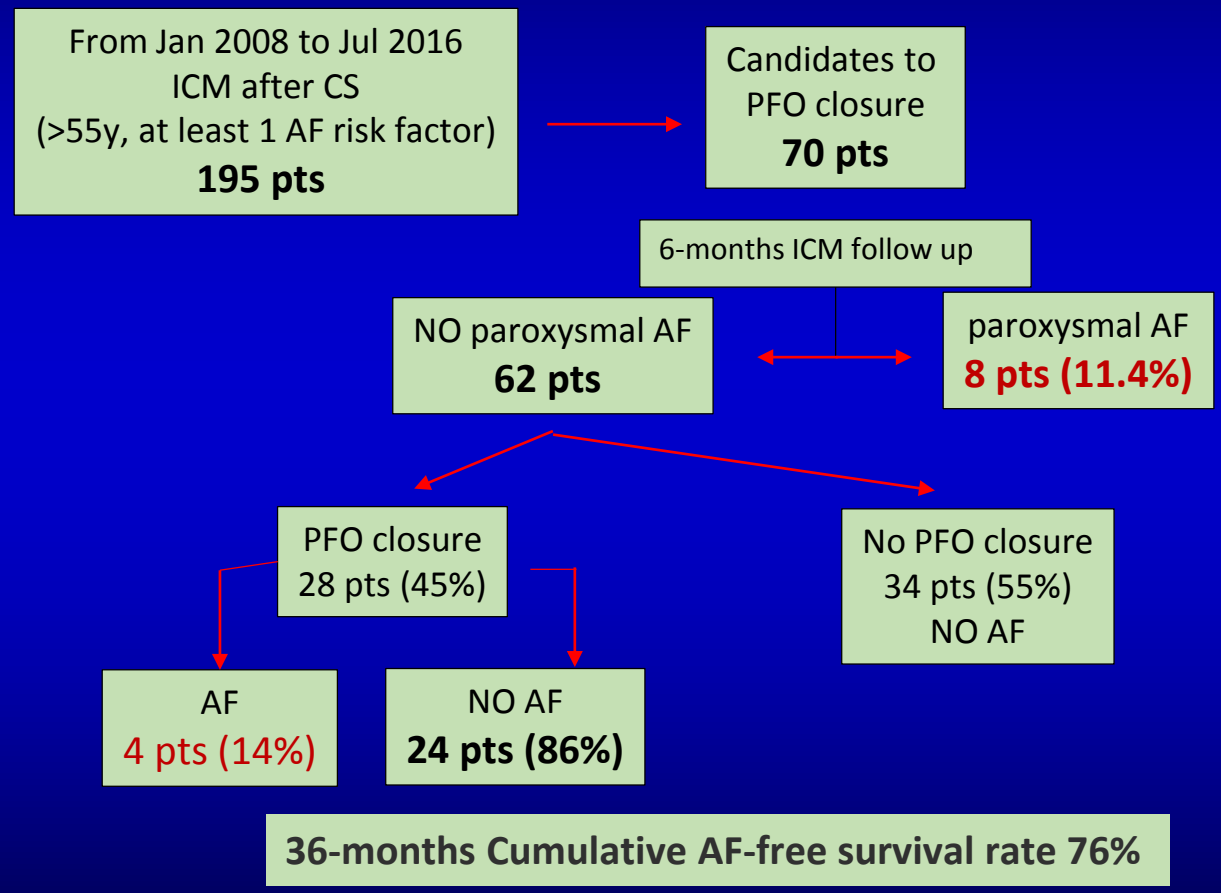
INSERTABLE CARDIAC MONITOR IN OLDER PATIENTS CANDIDATES TO PERCUTANEOUS PFO CLOSURE.

PRELIMINARY RESULTS OF A PERSPECTIVE REGISTRY STUDY

Candidates to PFO closure. Presence of significant right-to-left shunt and one or more of the following high-risk features: **permanent right-to-left shunt**, **atrial septal aneurysm**, **prominent Eustachian valve**, **recurrent brain ischemia**, **previous deep vein thrombosis**, **thrombophilia**.

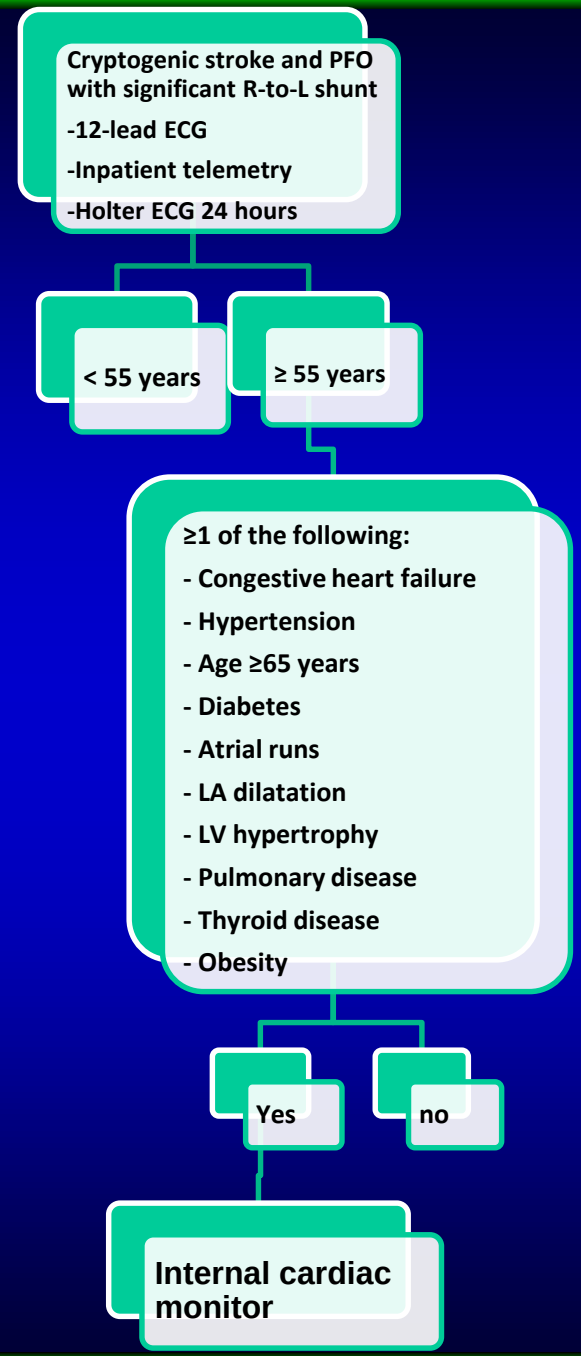
ICM Inclusion criteria. A cryptogenic stroke (CS), **more than 55y** and one or more of the following AF risk factors: **heart failure**, **hypertension**, **age ≥65 years**, **diabetes**, **atrial runs**, **left atrium dilatation**, **left ventricle hypertrophy**, **pulmonary disease**, **thyroid disease**, **obesity**.

ICM-detected AF threshold. An AF duration of **more than 5 minutes** was considered clinically meaningful, indicating oral anticoagulation and excluding a percutaneous treatment.



ESC Congress, Barcelona 2017
Stroke, under review

“AF rule-out” flow chart for left circulation cryptogenic embolism



FUTURE RESEARCHES

1) CLINICAL RELEVANCE OF RESIDUAL SHUNT

2) CLOSURE vs NAO

3) «ONE FIT ALL» vs «TAYLORED APPROACH»

4) DEVICE vs SUTURE CLOSURE

Cath LAB
Paolo Scacciatella, Fulvio Orzan, Pierluigi Omedè

Echo LAB
Mauro Giorgi and echo LAB medical staff

Stroke Unit
Paolo Cerrato

ICM monitoring
Carlo Budano, Davide Castagno, Marcella Jorfida, Lucia Garberoglio, Carla Giustetto

Data Bases and Statistical Analysis
Ilaria Meynet, Lorenza Michela Biava, Sara Santacesarea, Fabrizio D'Ascenzo

Nurse Staff
Anella Rizzo on behalf of nurses staff

pscacciatella@cittadellasalute.to.it
paolo.scacciatella@tin.it

GRAZIE DELL'ATTENZIONE