



The S. Giovanni Battista “Molinette” Hospital Experience with Patent Foramen Ovale Transcatheter Closure

Paolo Scacciarella, MD

Fulvio Orzan, MD

Dipartimento Cardiovascolare e Toracico



**Azienda Ospedaliera
Città della Salute e
della Scienza di Torino**

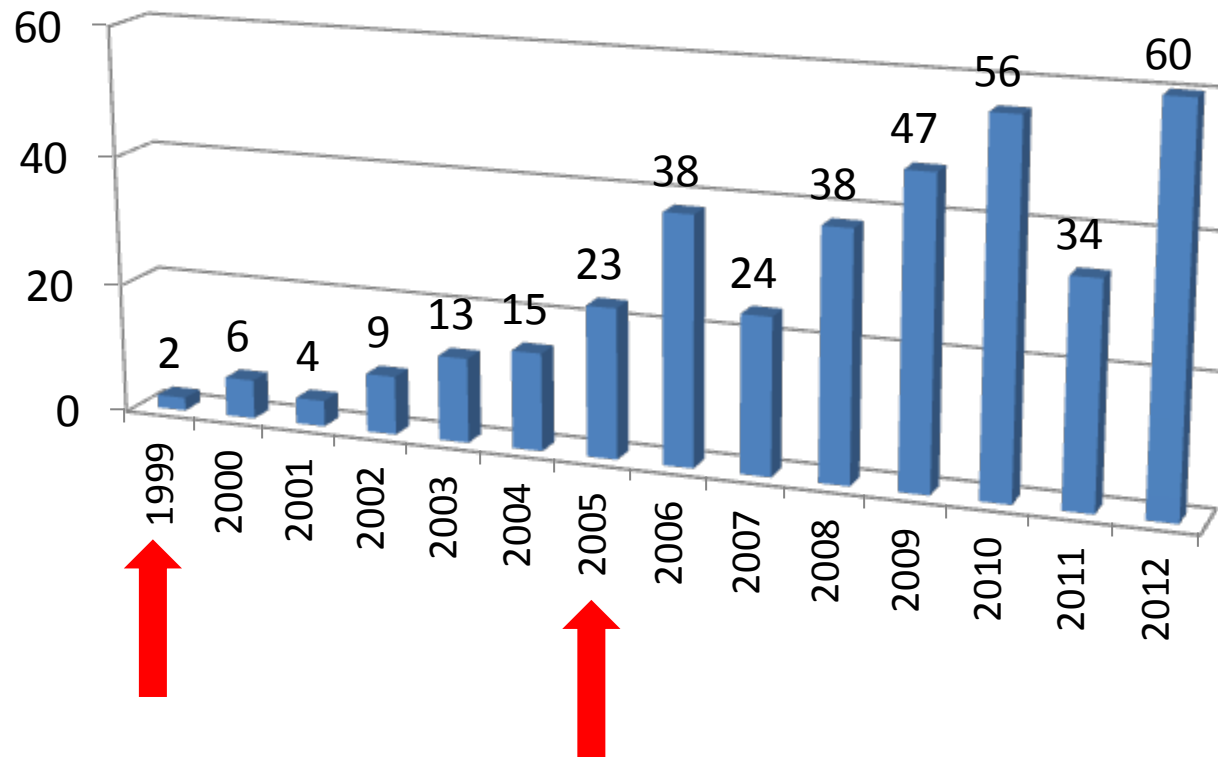


**Università degli Studi
di Torino**

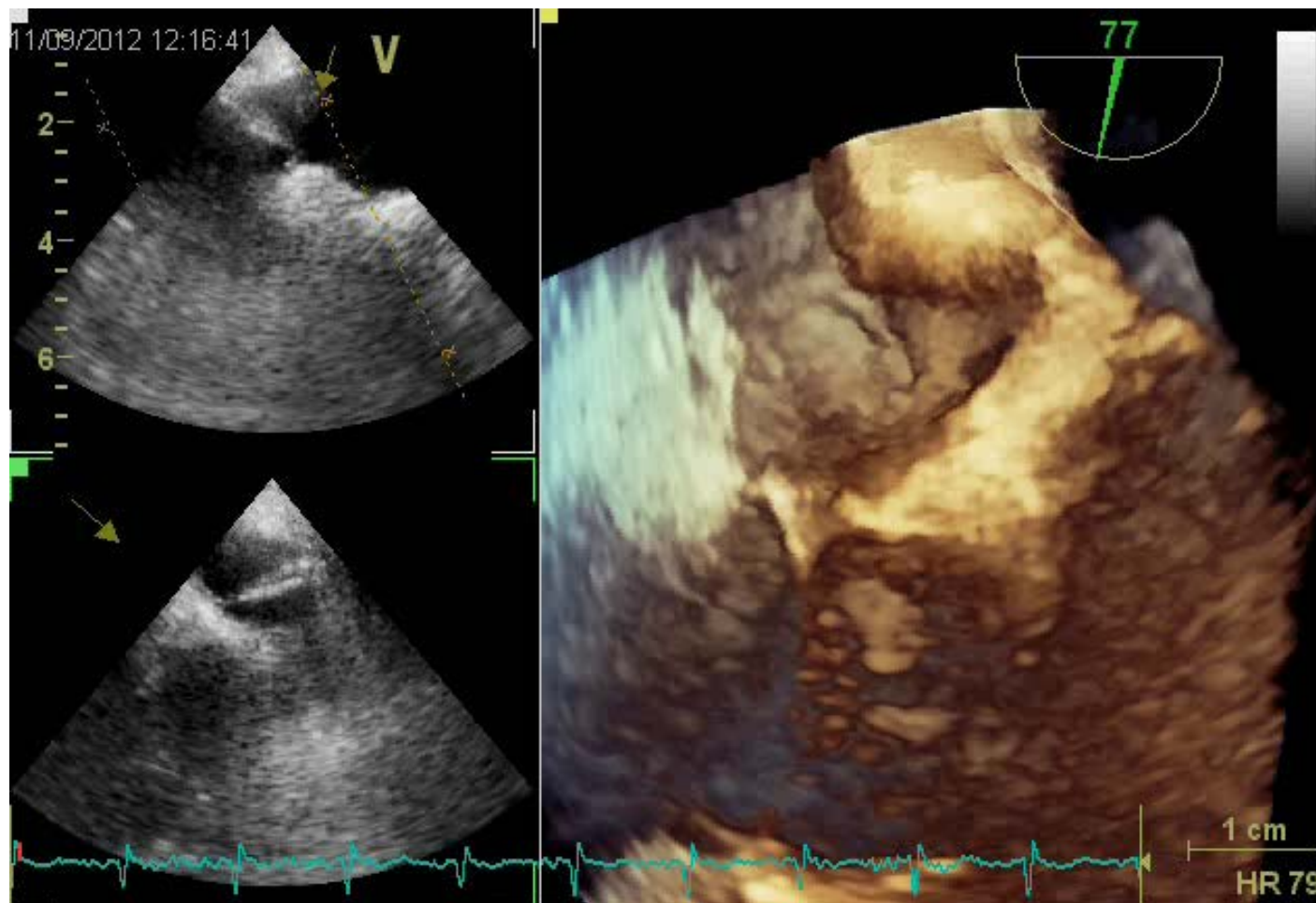


PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

Procedure/anno



RIGHT to LEFT SHUNT as a basis of a Clinical Event





CLINICAL EVENT = INDICATION

Pathophysiology

Desaturation

Paradoxical Embolism

Pathology

Platypnea Orthodeoxya
Sleep Apnea

Stroke, TIA

Peripheral Arterial Embolism
Decompression Illness
Migraine (with aura)

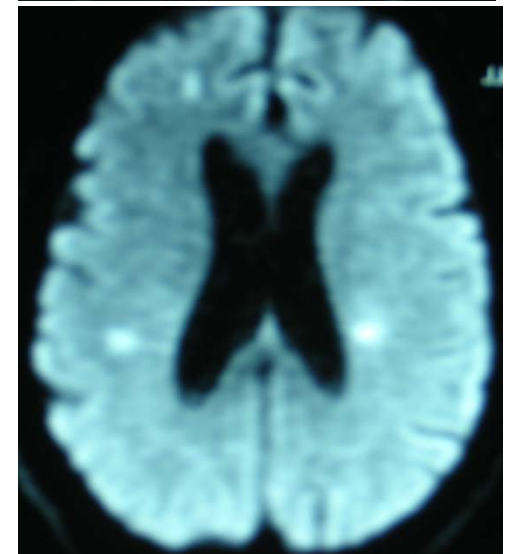


Cryptogenic Stroke

WARSS-Study 40% of all strokes !
Mohr et al. NEJM. 2001; 345:1444-1451

Diagnosis of cryptogenic stroke:

- | | |
|--------------|--------------------------------------|
| Exclusion of | Atrial Fibrillation (ECG, 3 Holter) |
| | Carotid artery disease (Ultrasound) |
| | Intracerebral tenosis (TCD, CT, MRT) |
| | Aortic plaques (TEE) |
| | Valvular vegetation (TEE) |
| | Atrial thrombus (TEE) |





CAUSE-EFFECT RELATIONSHIP



“...First publication to mention the possible relationship of a cerebrovascular event with the presence of PFO was reported in 1877 by Julius Cohnheim, a German pathologist who reported a case of a young woman died of a stroke. He hypothesized that the clot passed through the PFO...”



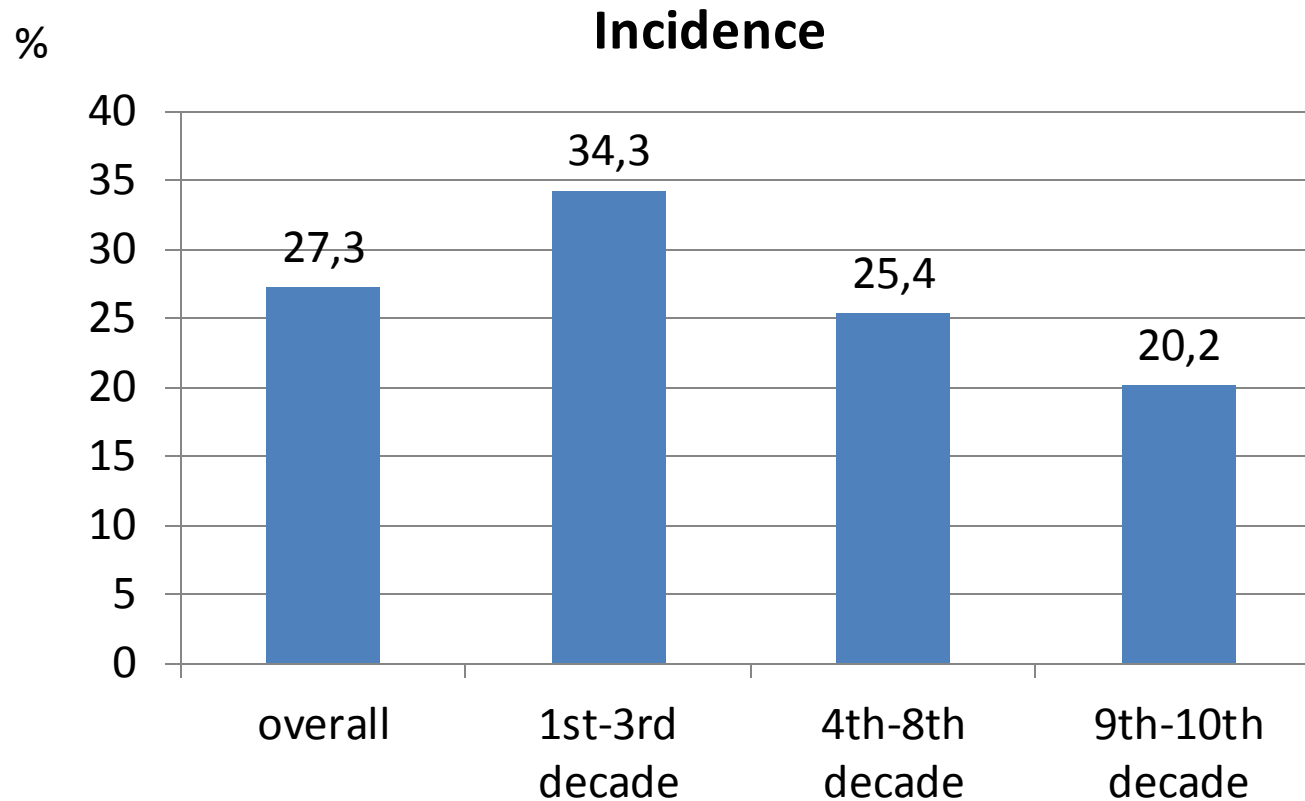
*Hagen PT, Scholz DG, Edwards WD
Mayo Clin Proceed 1984; 59 (1): 17-20*

965 autopsy specimens

263 exhibited patency

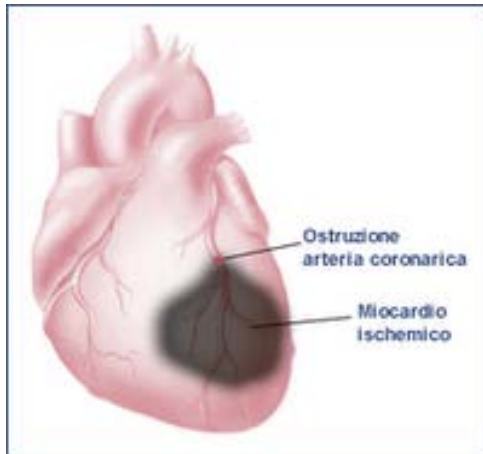
1-10 mm diameter

The size tended to increase with increasing age



Problem of cause-effect relationship

Direct
e.g. myocardial infarction



Local
Istantaneous
Static
Curative

Indirect
PFO - Stroke



Remote
Sequential
Dynamic
Preventive



Association by chance or cause-effect relationship?

CRITERIA in FAVOR of a CAUSE-EFFECT RELATIONSHIP

- I. Strength and consistency of association
- II. Biologic plausibility
- III. Risk of recurrence
- IV. Biological gradient

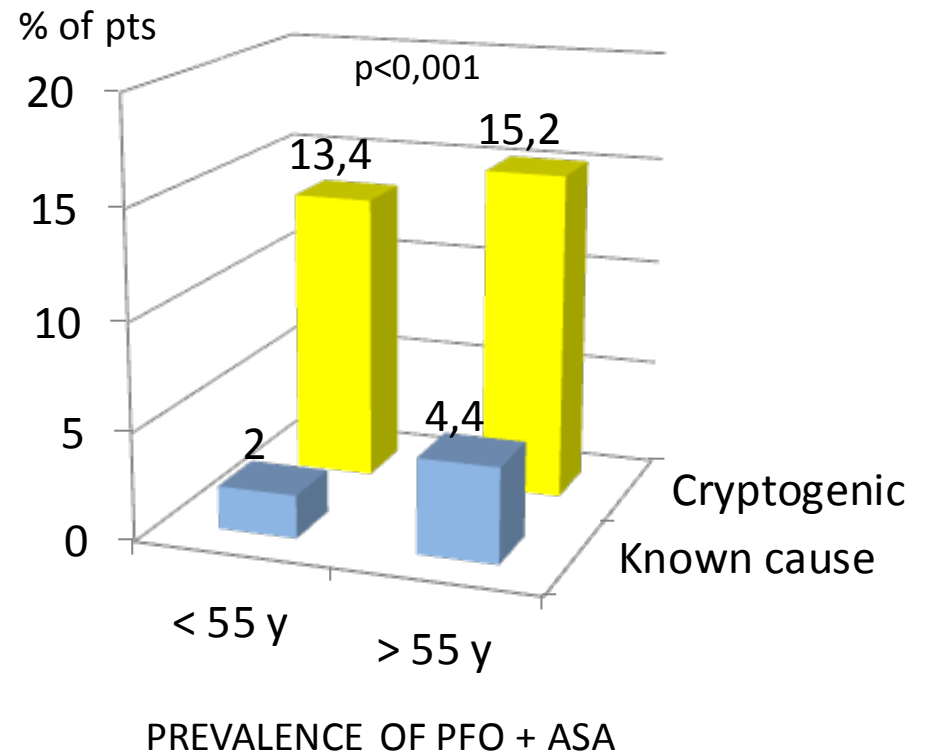
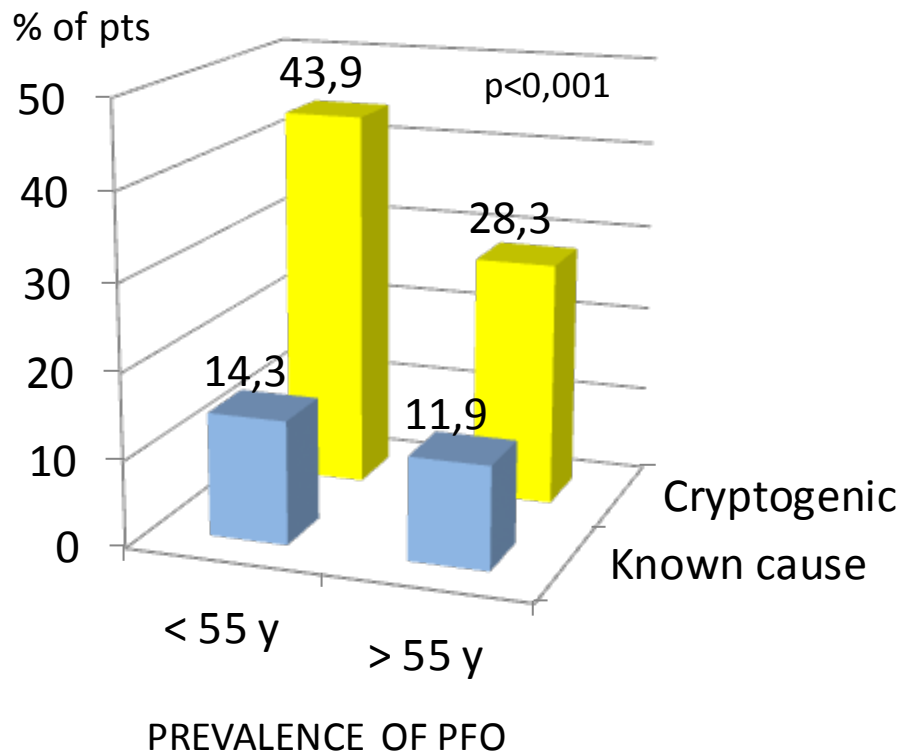
Bias and Causal Associations in Observational Research



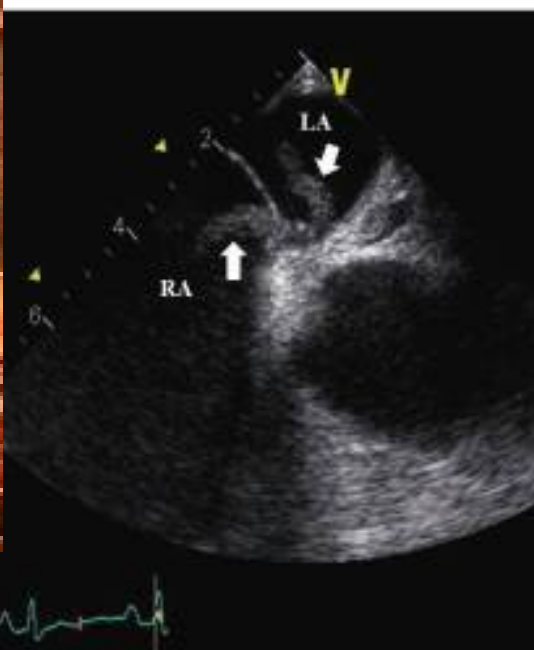
Strength and consistency of association

PFO and CRYPTOGENIC STROKE are HIGHLY CORRELATED

Handke et al. N Engl J Med 2007; 357: 2262



Biologic plausibility



Risk of recurrence

Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale[☆]

Herwig Walter Schuchlenz^{a,*}, Wolfgang Weihs^a, Andrea Berghold^b,
Anita Lechner^c, Reinhold Schmidt^c

International Journal of Cardiology 101 (2005) 77–82

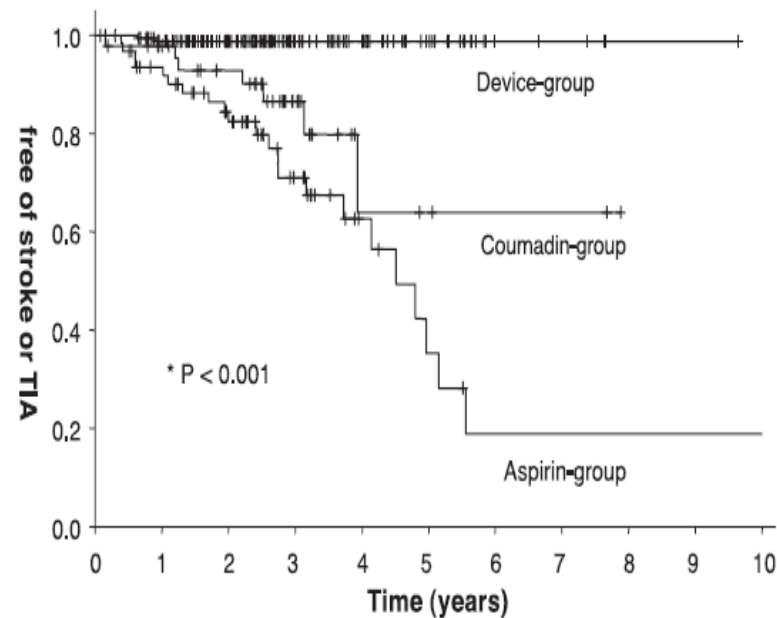


Fig. 1. Kaplan–Meier event free survival curves (stroke and transient ischemic attack [TIA]) of patients with cryptogenic cerebrovascular events and a patent foramen ovale according to different treatment strategies. *The log-rank test was used to calculate the *P* value.

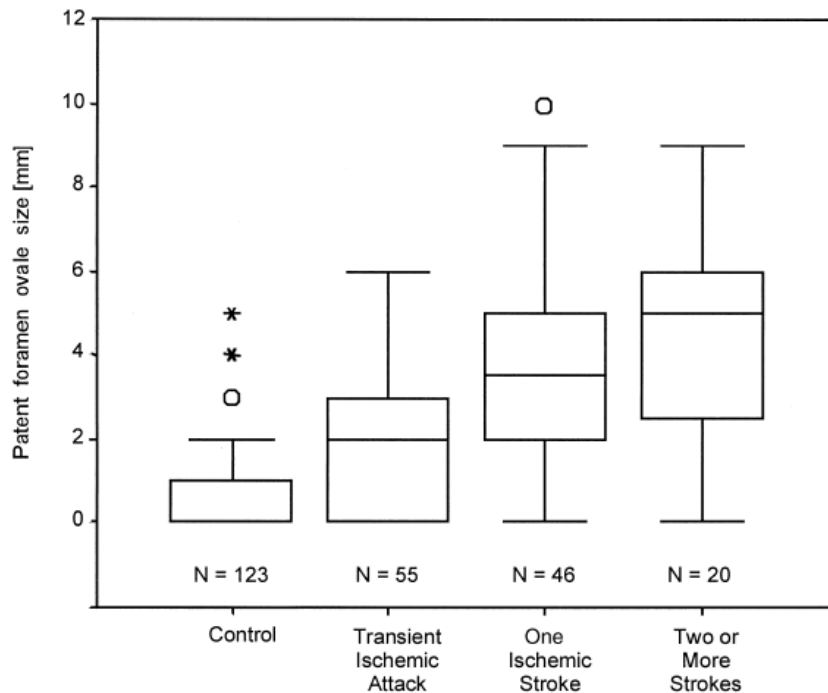


Biological gradient

The Association between the Diameter of a Patent Foramen Ovale and the Risk of Embolic Cerebrovascular Events

Herwig W. Schuchlenz, MD, Wolfgang Weihs, MD, Susanne Horner, MD, Franz Quehenberger, PhD

Am J Med. 2000;109:456–462.



Permanent Right-to-Left Shunt Is the Key Factor in Managing Patent Foramen Ovale

Gianluca Rigatelli, MD, PhD,* Fabio Dell'Avvocata, MD,* Paolo Cardaioli, MD,* Massimo Giordan, MD,* Gabriele Braggion, MD,* Silvio Aggio, MD,* Mauro Chinaglia, MD,† Sangeeta Mandapaka, MD,‡ John Kuruvilla, MD,‡ Jack P. Chen, MD,*§ Aravinda Nanjundappa, MD‡
Rovigo, Italy; Charleston, West Virginia; and Atlanta, Georgia

(*J Am Coll Cardiol* 2011;58: 2257–61)

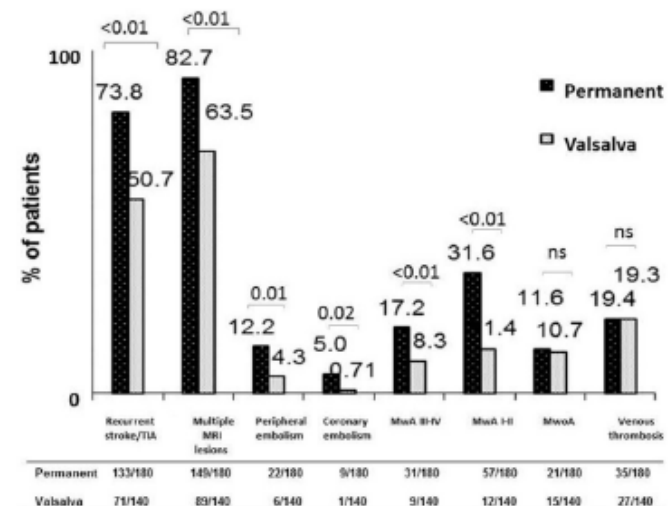


Figure 1 Clinical Profile Comparison Between Permanent and Valsalva Shunt Patients

Histogram representation of the comparison of clinical history between patients with permanent shunt and Valsalva-induced shunt. (Bottom) The nominal number of patients for each group. MRI = magnetic resonance imaging; MWA = migraine with aura; MWAo = migraine without aura.

SECONDARY PREVENTION TREATMENT





EVIDENCE BASED MEDICINE

- ✓ Single-center series
- ✓ Case-control studies
- ✓ Meta-Analysis
- ✓ 2 prospective randomized clinical endpoint trial
(CLOSURE I, RESPECT)
- ✓ More prospective randomized clinical endpoint trials
in progress (PC, REDUCE, ...)

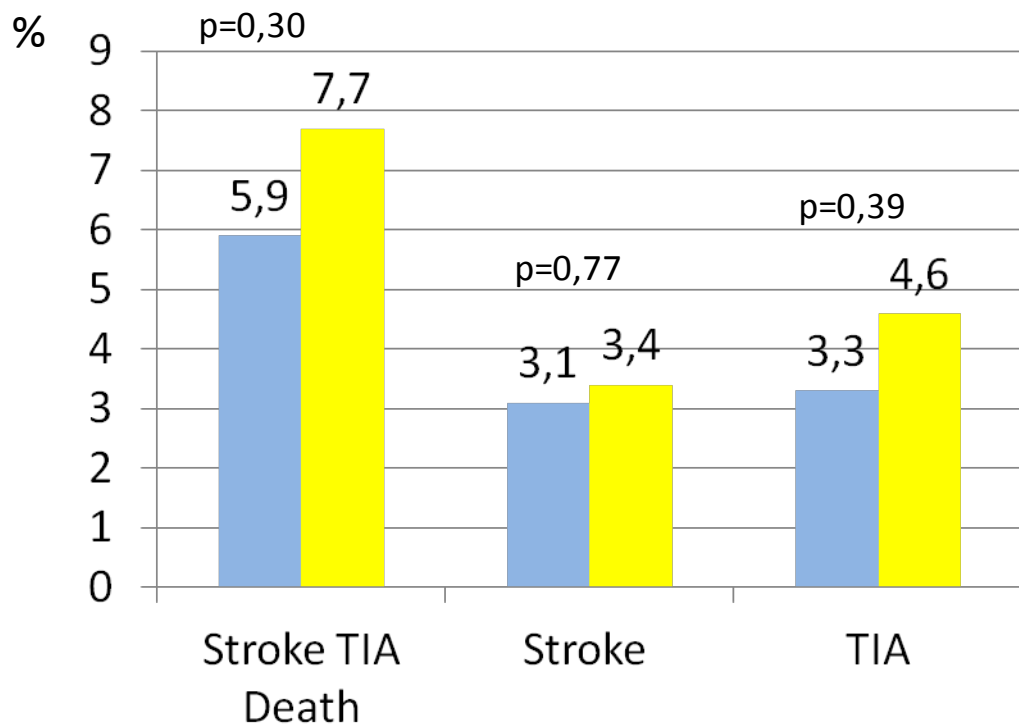


A Prospective, Multicenter, Randomized Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex® Septal Closure System Versus Best Medical Therapy in Patients with a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale

Anthony J Furlan MD
Gilbert Humphrey Professor
Chairman Department of Neurology
Co-Director Neurological Institute
University Hospitals Case Medical Center
Case Western Reserve University School of Medicine

For the CLOSURE I Investigators

Trial Sponsor: NMT Medical Boston



Clinical end point at 2 years

■ Device
■ Medical



**A Prospective, Multicenter, Randomized Controlled Trial to
Evaluate the Safety and Efficacy of the STARFlex® Septal Closure
System Versus Best Medical Therapy in Patients with a Stroke or
Transient Ischemic Attack due to Presumed Paradoxical
Embolism through a Patent Foramen Ovale**

Anthony J Furlan MD
Gilbert Humphrey Professor
Chairman Department of Neurology
Co-Director Neurological Institute
University Hospitals Case Medical Center
Case Western Reserve University School of Medicine

For the CLOSURE I Investigators

Trial Sponsor: NMT Medical Boston

1. Follow up interval too short
2. Devices issues
3. Selection bias (enrollement 2 pts/center/year)
4. Exclusion of DVT and thrombophilia

Meta-Analysis of Transcatheter Closure Versus Medical Therapy for Patent Foramen Ovale in Prevention of Recurrent Neurological Events After Presumed Paradoxical Embolism

Shikhar Agarwal, MD, MPH, CPH,* Navkaranbir Singh Bajaj, MD,†
 Dharam J. Kumbhani, MD, SM,‡ E. Murat Tuzcu, MD,* Samir R. Kapadia, MD*

Cleveland, Ohio; and Boston, Massachusetts

JACC: CARDIOVASCULAR INTERVENTIONS

VOL. 5, NO. 7, 2012

© 2012 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

ISSN 1936-8798/\$36.00

PUBLISHED BY ELSEVIER INC.

<http://dx.doi.org/10.1016/j.jcin.2012.02.021>

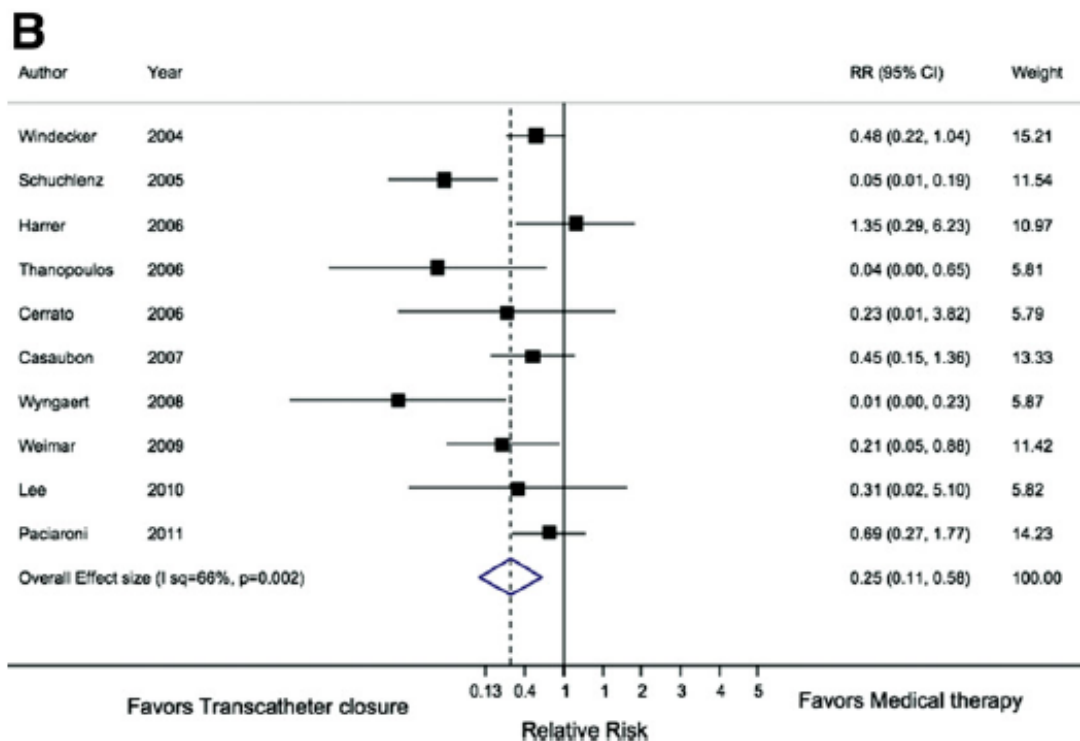


Figure 2. Incidence of Recurrent Neurological Events in the 2 Study Groups



Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on Patent Foramen Ovale Closure Devices

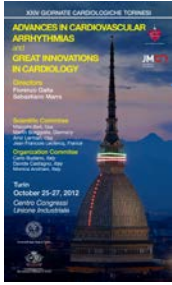
Tina L. Pinto Slottow, Daniel H. Steinberg and Ron Waksman

Circulation. 2007;116:677-682

TABLE 2. Summary of Guidelines

Association	Recommendations
American College of Chest Physicians ¹⁵	<p>Antiplatelet therapy after cryptogenic stroke should include 1 of the following: (1) aspirin 50 to 325 mg daily; (2) aspirin 25 mg and extended-release dipyridamole 200 mg twice daily; or (3) clopidogrel 75 mg daily. Antiplatelet agents are recommended instead of oral anticoagulation unless a patient has a well-documented prothrombotic disorder.</p> <p>After cryptogenic ischemic stroke, in the presence of a PFO, antiplatelet therapy is recommended instead of warfarin unless a patient has evidence of deep venous thrombosis.</p>
American Academy of Neurology ⁴	<p>After cryptogenic stroke, evidence indicates the risk of recurrent stroke or death does not vary between patients with and without PFOs who are treated medically.</p> <p>There is insufficient evidence to determine the superiority of antiplatelet agents vs warfarin.</p> <p>There is insufficient evidence regarding the effectiveness of PFO closure.</p>
AHA/American Stroke Association ¹⁶	<p>After noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (class I, level of evidence A).</p> <p>Aspirin (50 to 325 mg/d), aspirin and extended-release dipyridamole in combination, and clopidogrel are all acceptable options for initial therapy (class IIa, level of evidence A).</p> <p>After ischemic stroke or TIA in patients with a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (class IIa, level of evidence B).</p> <p>Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation, such as underlying hypercoagulable state or evidence of venous thrombosis (class IIa, level of evidence C).</p> <p>Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIb, level of evidence C).</p>

TIA indicates transient ischemic attack.



PFO CLOSURE in
CARDIOVASCULAR DEPARTMENT
CITTA' della SALUTE e della SCIENZA di TORINO
1999 - 2012

The “Dangerous PFO”

Probability of ASSOCIATION - RECURRENCE

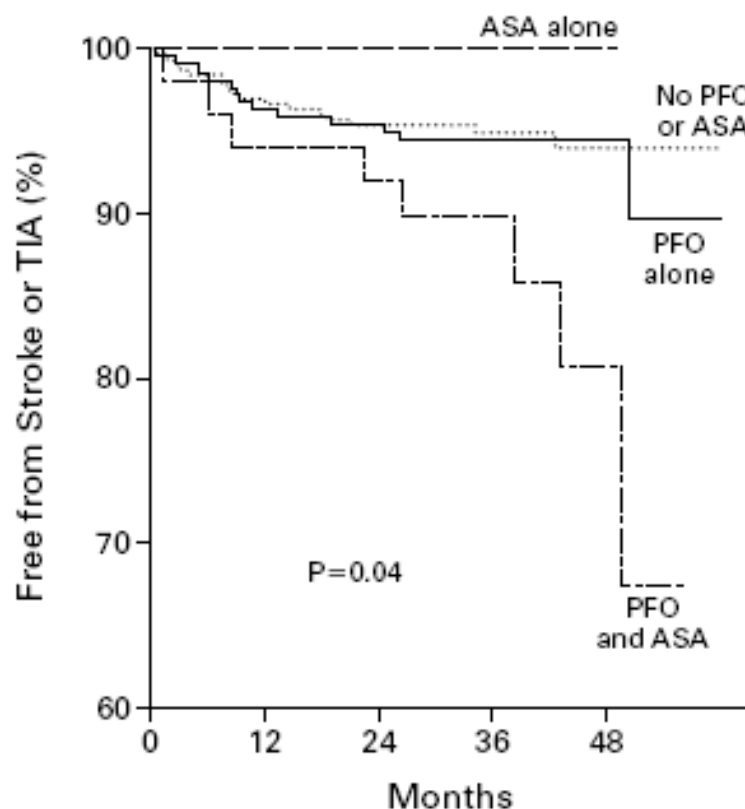
- ✓ Young (conventional cut-off 55 y)
- ✓ Deep vein thrombosis
- ✓ Pulmonary Embolism
- ✓ Thrombophylic disorders
- ✓ Multiple Ischemic events
- ✓ Recurrency despite OMT
- ✓ Atrial septal aneurysm
- ✓ Prominent Eustachian valve
- ✓ Severe basal shunt
- ✓ Wide tunnel



RECURRENT CEREBROVASCULAR EVENTS ASSOCIATED WITH PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM, OR BOTH

JEAN-LOUIS MAS, M.D., CAROLINE ARQUIZAN, M.D., CATHERINE LAMY, M.D., MATHIEU ZUBER, M.D.,
LAURE CABANES, PH.D., GENEVIÈVE DERUMEUX, M.D., AND JOËL COSTE, PH.D.,
FOR THE PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM STUDY GROUP*

N Engl J Med, Vol. 345, No. 24 · December 13, 2001



GROUP

AT 4 YEARS

RISK OF
STROKE

RISK OF
STROKE
OR TIA

No atrial septal abnormality

4.2
(1.8-6.6)

6.2
(3.0-9.3)

No. at risk

159

158

Patent foramen ovale alone

2.3
(0.3-4.3)

5.6
(2.5-8.7)

No. at risk

125

122

Atrial septal aneurysm alone

0

0

No. at risk

4

4

Patent foramen ovale and atrial
septal aneurysm

15.2
(1.8-28.6)

19.2
(5.0-33.4)

No. at risk

27

25



Persistent Venous Valves Correlate With Increased Shunt and Multiple Preceding Cryptogenic Embolic Events in Patients With Patent Foramen Ovale: An Intracardiac Echocardiographic Study

Gianluca Rigatelli,^{1*} MD, Fabio Dell'Avvocata,¹ MD, Gabriele Braggion,¹ MD, Massimo Giordan,¹ MD, Mauro Chinaglia,² MD, and Paolo Cardaioli,¹ MD

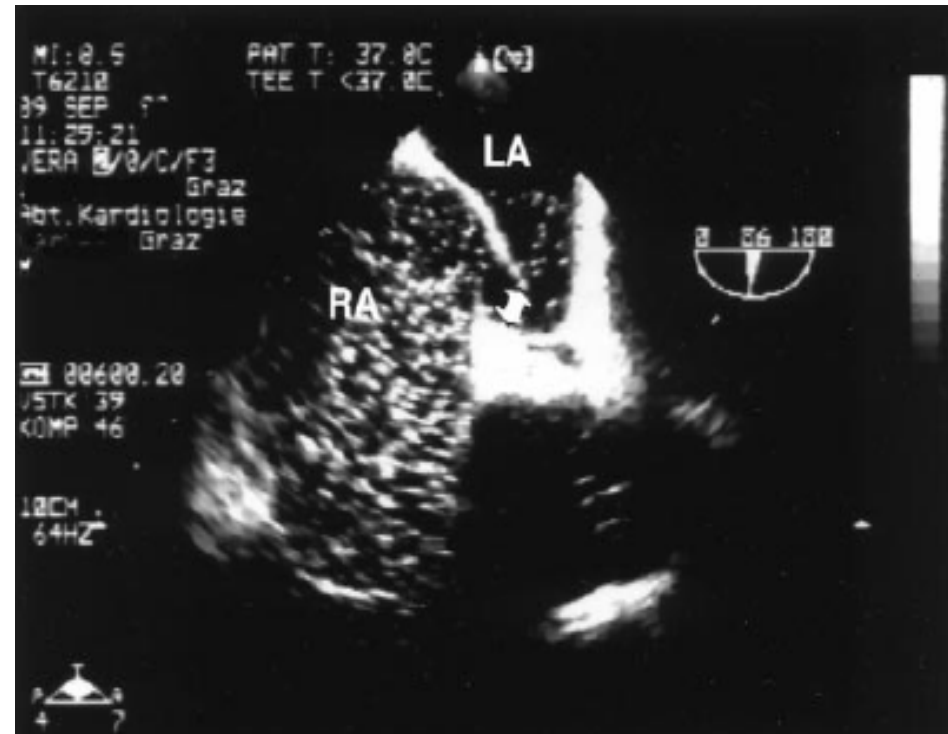
Catheterization and Cardiovascular Interventions 72:973–976 (2008)

TABLE II. Comparison of Clinical and Functional Parameters Between Patients With and Without EV/CN

	Prominent EV/CN	No prominent EV/CN	<i>P</i>
Curtain pattern on TC-D	41/72 (56.9%)	2/35 (5.7%)	<0.001
Large shunt on TEE	50/72 (69.4%)	3/35 (8.6%)	<0.001
≥2 ischemic strokes and/or >2 ischemic foci on MRI	40/72 (55.5%)	8/35 (22.8)	0.0014

MRI, magnetic resonance imaging; TC-D, transcranial Doppler ultrasound; TEE, transesophageal echocardiography.

Am J Med. 2000;109:456–462.



Gianluca Rigatelli, MD, PhD,* Fabio Dell'Avvocata, MD,* Paolo Cardaioli, MD,*
Massimo Giordan, MD,* Gabriele Braggion, MD,* Silvio Aggio, MD,* Mauro Chinaglia, MD,†
Sangeeta Mandapaka, MD,‡ John Kuruvilla, MD,‡ Jack P. Chen, MD,*§ Aravinda Nanjundappa, MD‡
Rovigo, Italy; Charleston, West Virginia; and Atlanta, Georgia

Outcome	Permanent (%)	Valsalva (%)	P-value
Recurrent stroke/TIA	73.8	50.7	<0.01
Multiple MRI lesions	82.7	63.5	<0.01
Peripheral embolism	12.2	4.3	0.01
Coronary embolism	5.0	0.7	0.02
MWO B-I-V	17.2	8.3	<0.01
MWO B-I	31.6	1.4	<0.01
MWO A	11.6	10.7	ns
Venous thrombosis	19.4	19.3	ns

(Bottom) The nominal number of patients for each group. MRI = magnetic resonance imaging; MwA = migraine with aura; MwoA = migraine without aura.



PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

Treated

369
patients

Clinical Indication

340
EMBOLIC
EVENTS

29
MIGRAINE
MR -

Clinical presentation

334
BRAIN

6
PERIPHERAL

133
TIA

195
STROKE

5
MIGRAINE
RM+

1
ASYMPTOM
ATICRM+

101
Single

32
Multiple

165
Single

30
Multiple



PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

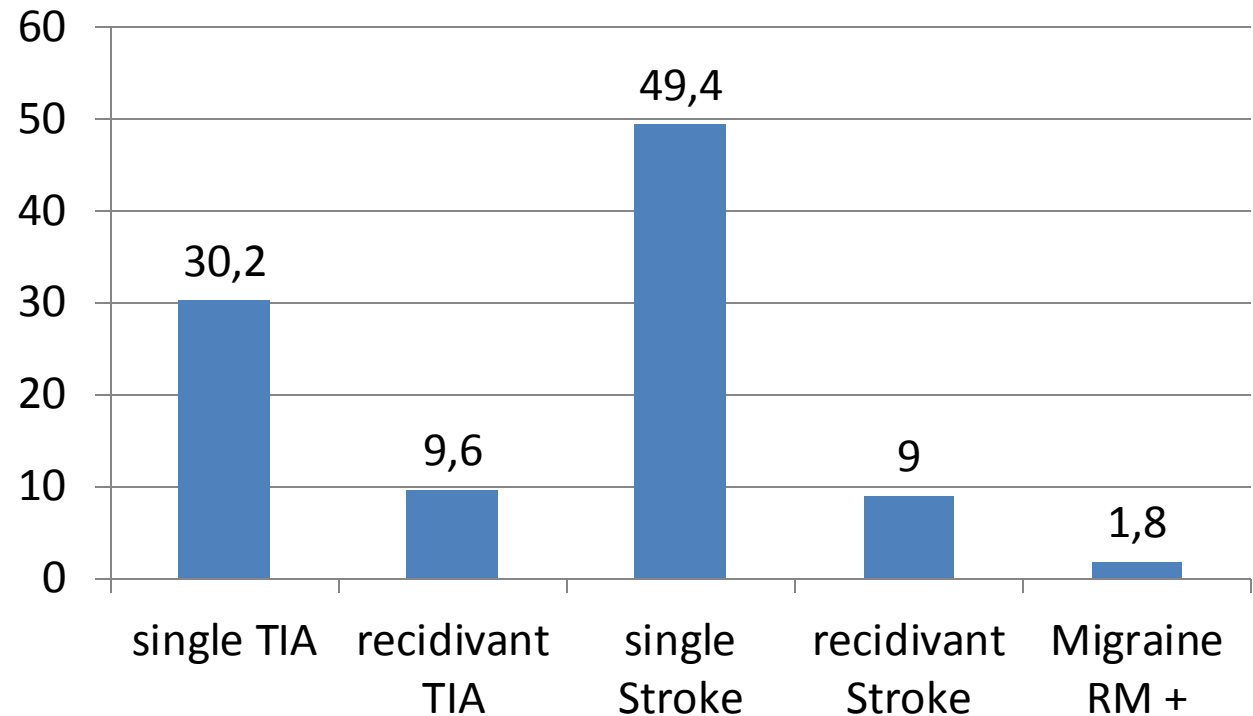
Age
 50 ± 14 y
M
45,2%

Atrial septum
Aneurysm
51,8%

Coag. Disorders
19,5%

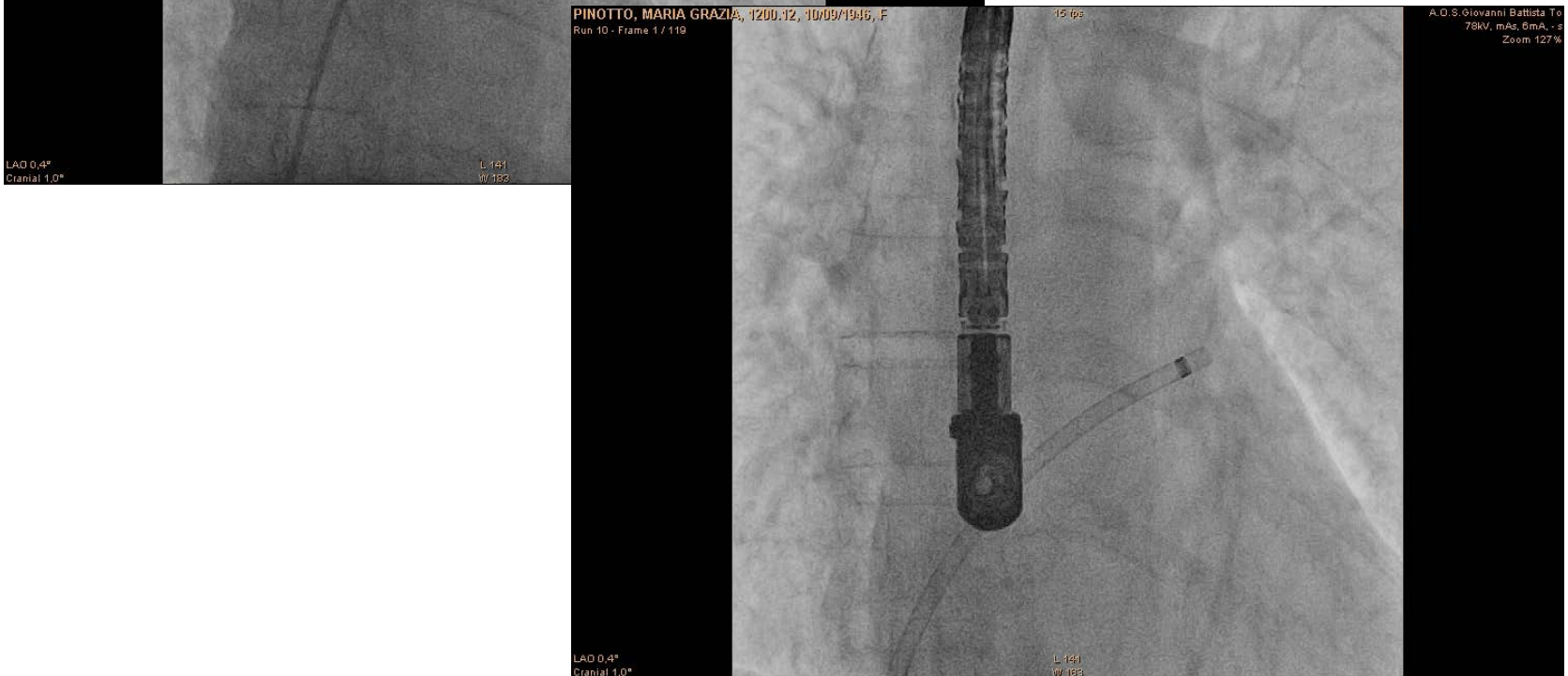
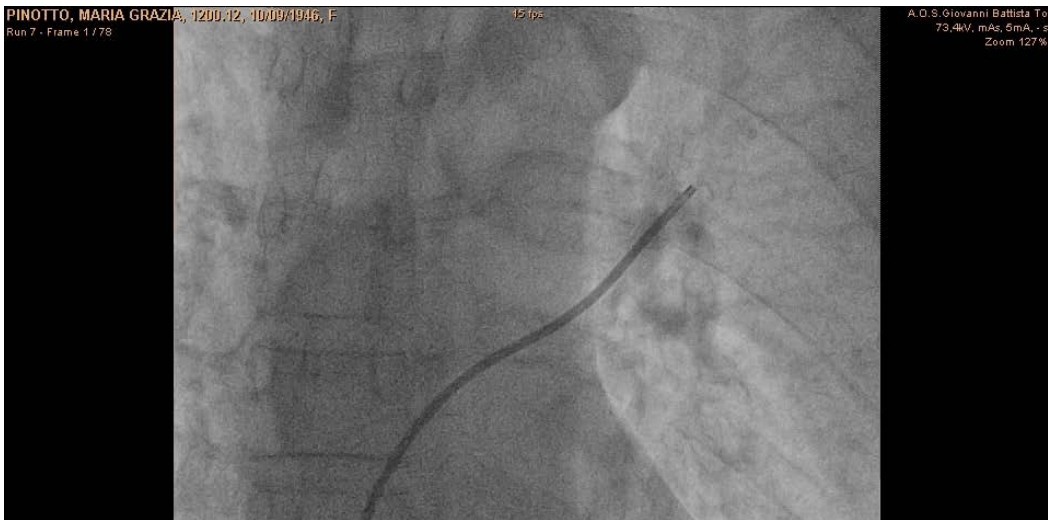
DVT/PE
11,7%

Clinical presentation % 334 pts



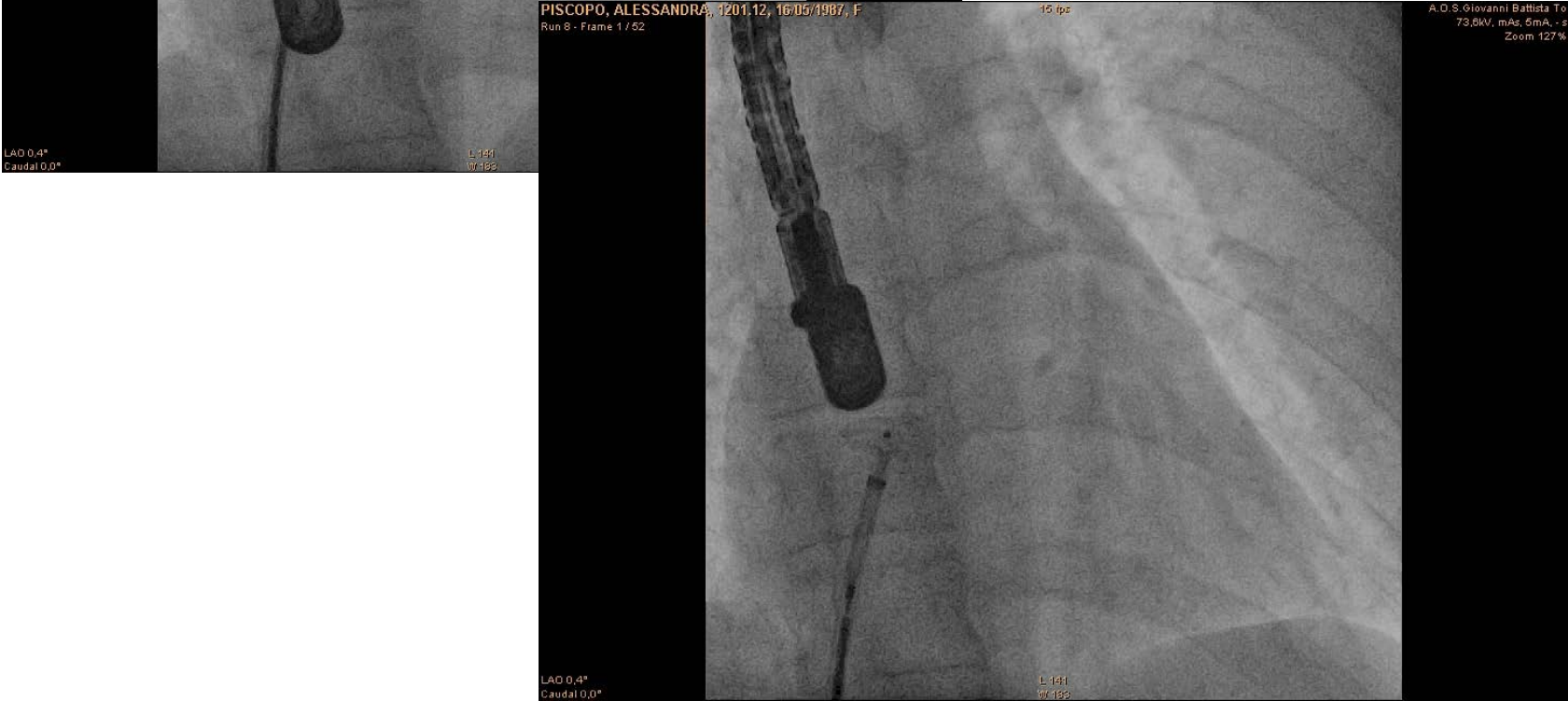
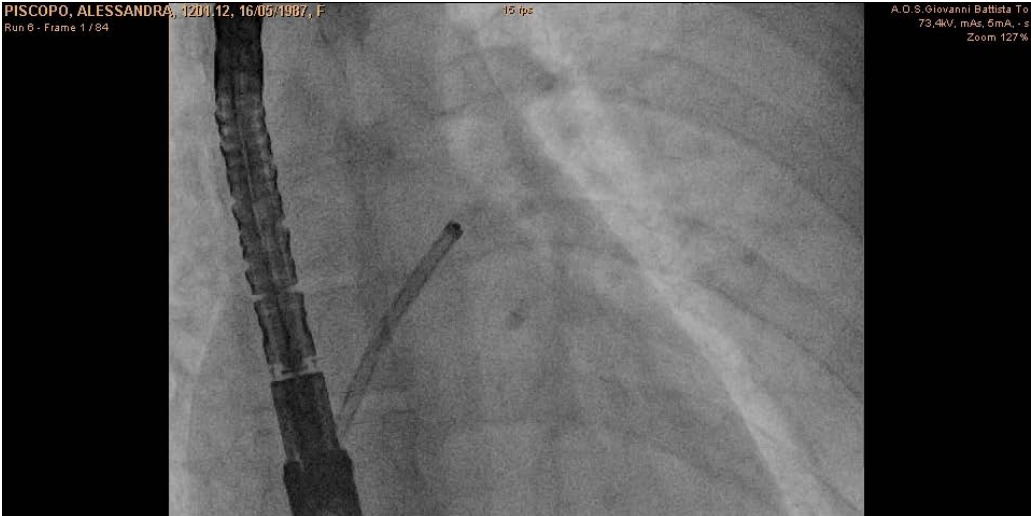


Patent Foramen Ovale Transcatheter Closure - Paolo Scacciarella, MD





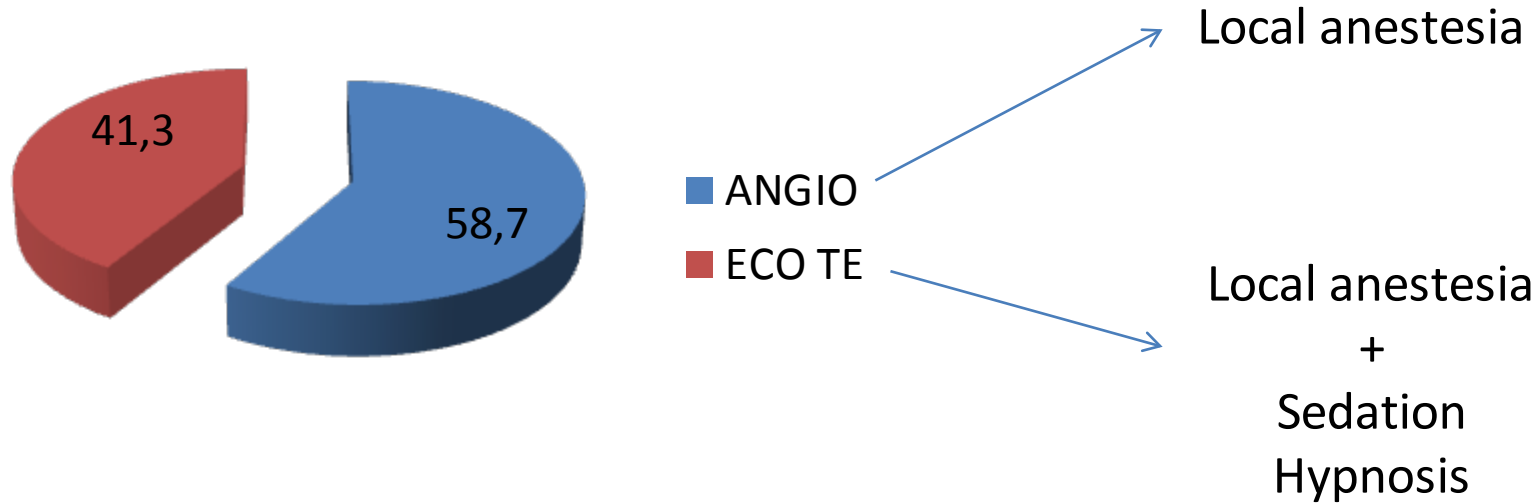
Patent Foramen Ovale Transcatheter Closure - Paolo Scacciarella, MD





PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

Procedural imaging



PROCEDURAL SUCCESS

99,7%



Patent Foramen Ovale Transcatheter Closure - Paolo Scaciatella, MD

CUFFARO, PASQUALE, 1309 GAITA, 30/11/1953, M

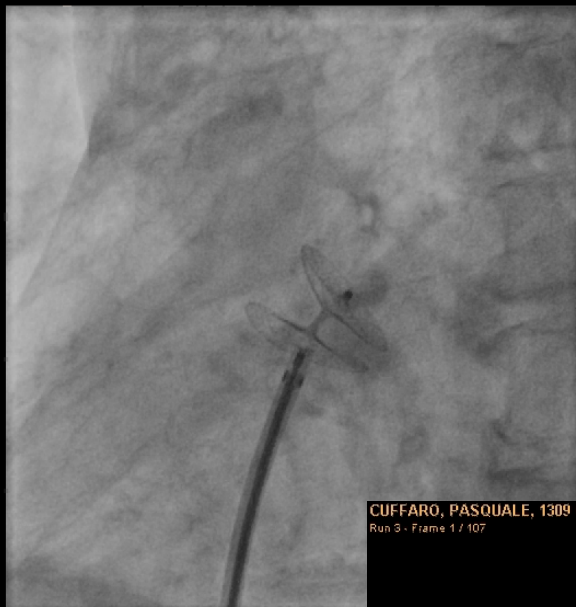
Run 2 - Frame 1 / 34

15 fps

A.O.S. Giovanni Battista To

74.7kV, mAs, 814mA, 6s

Zoom 127%



LAD 49.6°
Caudal -0.3°

L 138
W 190

CUFFARO, PASQUALE, 1309 GAITA, 30/11/1953, M

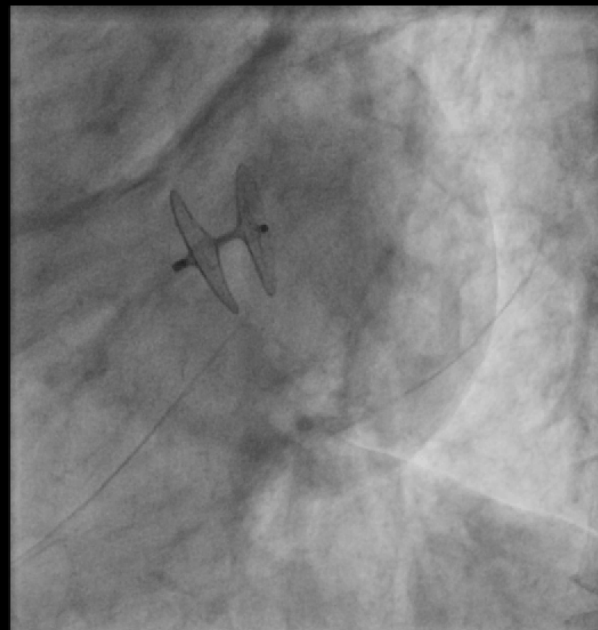
Run 3 - Frame 1 / 107

15 fps

A.O.S. Giovanni Battista To

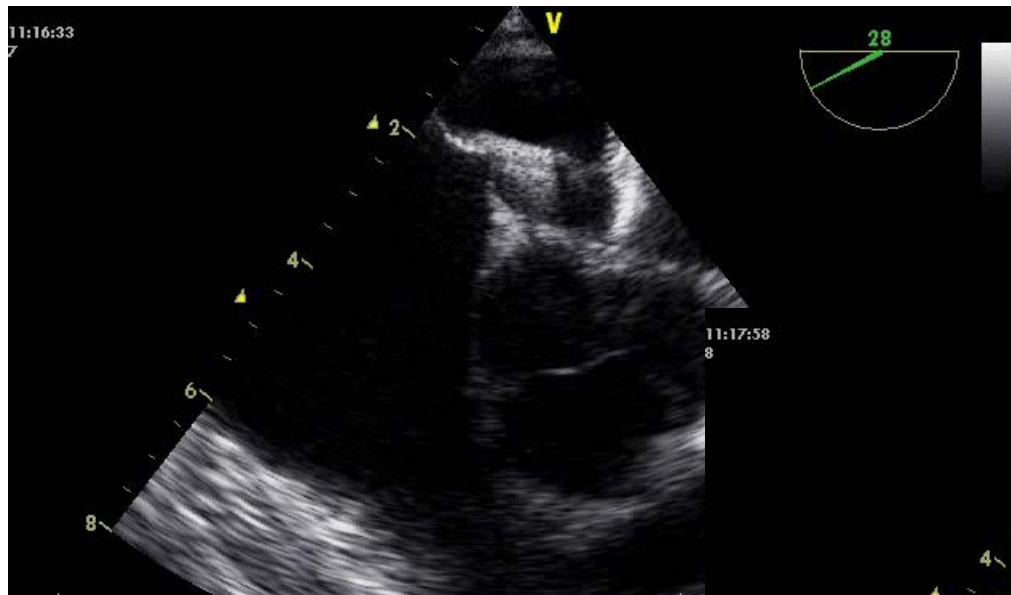
70.8kV, mAs, 529mA, 5s

Zoom 127%

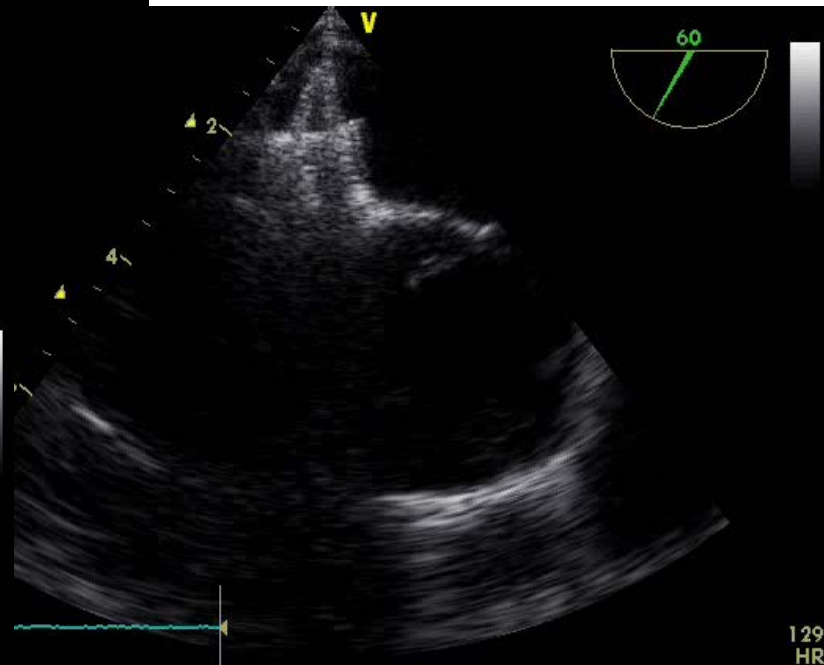


LAD 63.1°
Caudal -0.4°

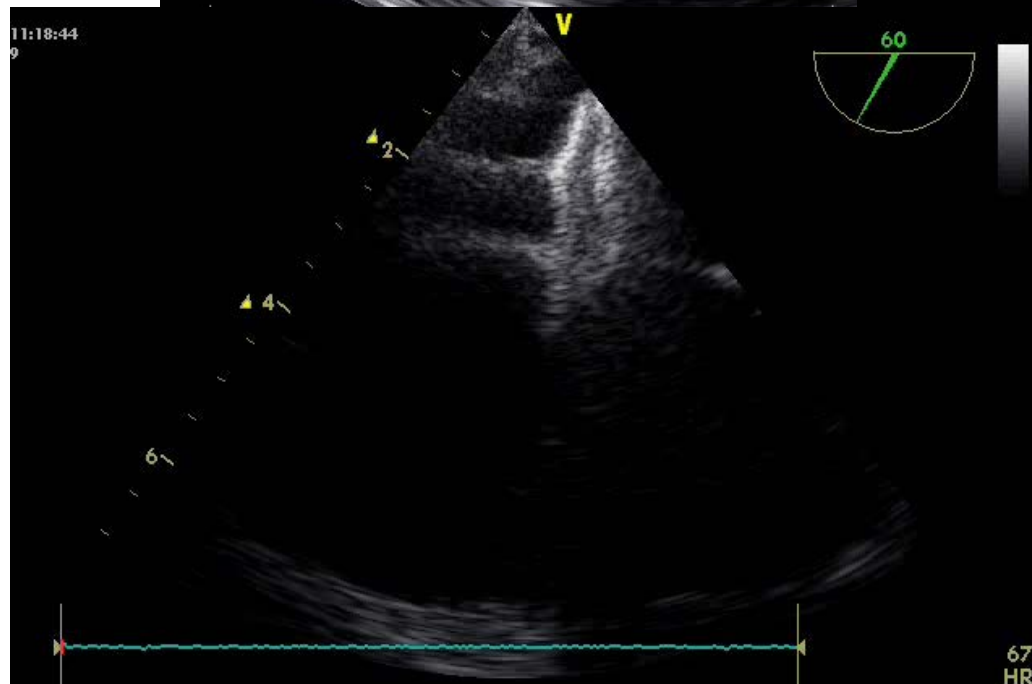
L 138
W 190



11:17:58
 8



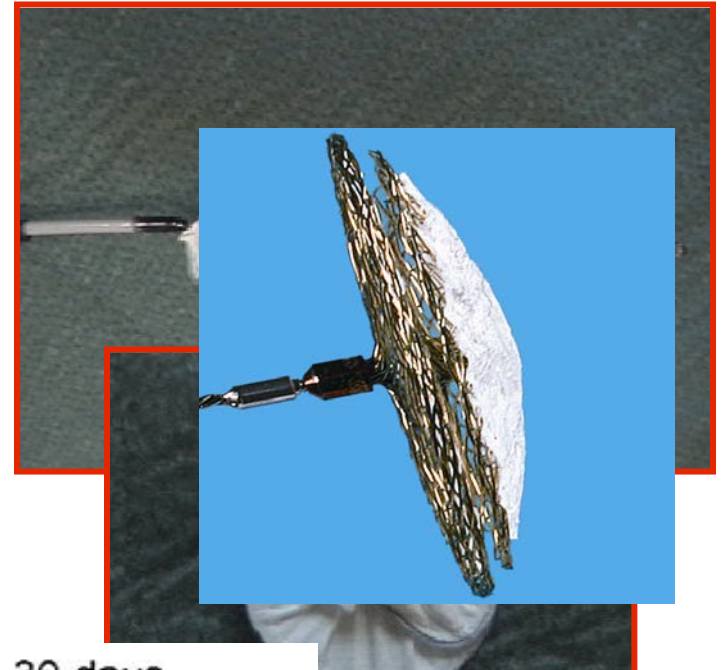
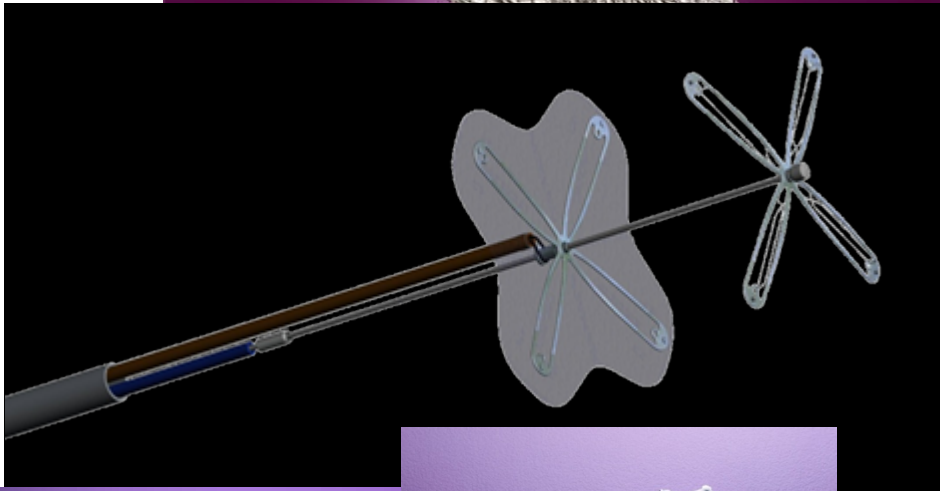
129
 HR



67
 HR



Patent Foramen Ovale Transcatheter Closure - Paolo Scacciatella, MD



30 days

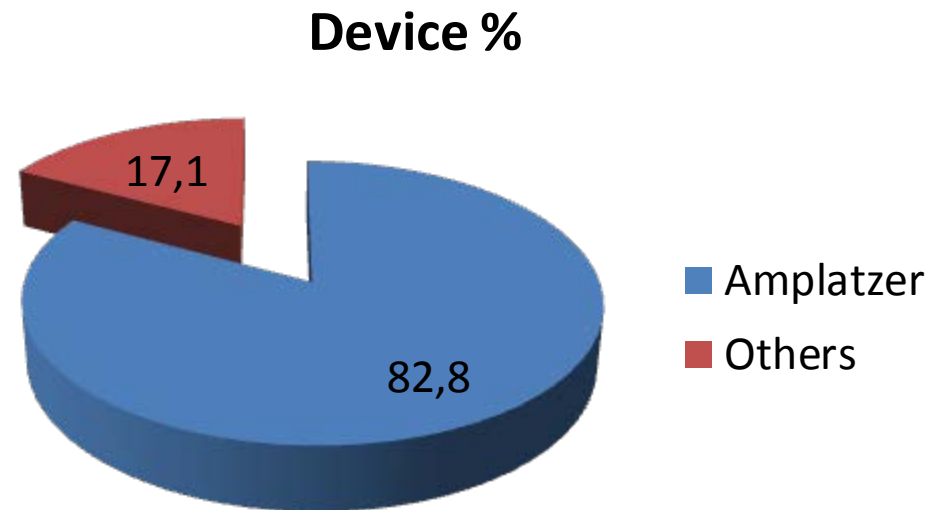




PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

The "KISS" rule

Keep
It
Simple
for Safe



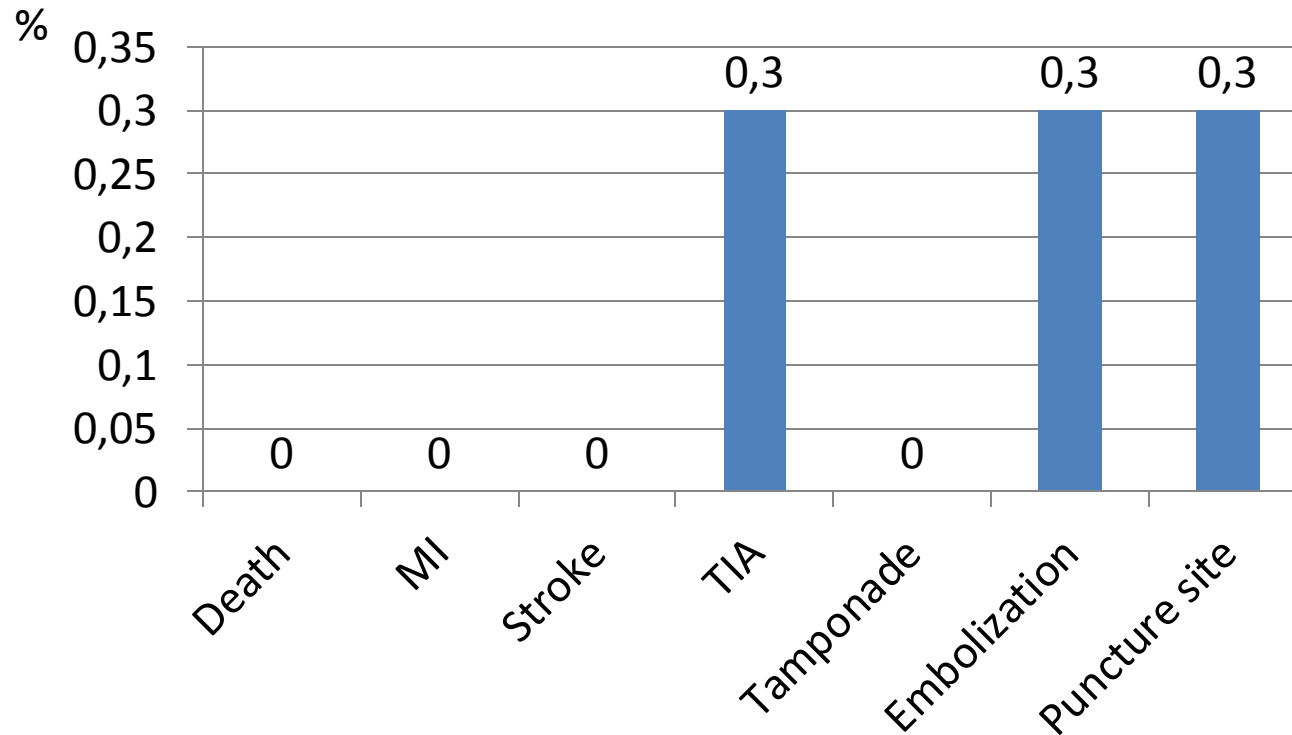
One of the most predictable and easy-to-deploy device

*Ease-of-use translate to fewer mistakes, shorter procedures,
and fewer complications*



PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

Procedural Adverse Event

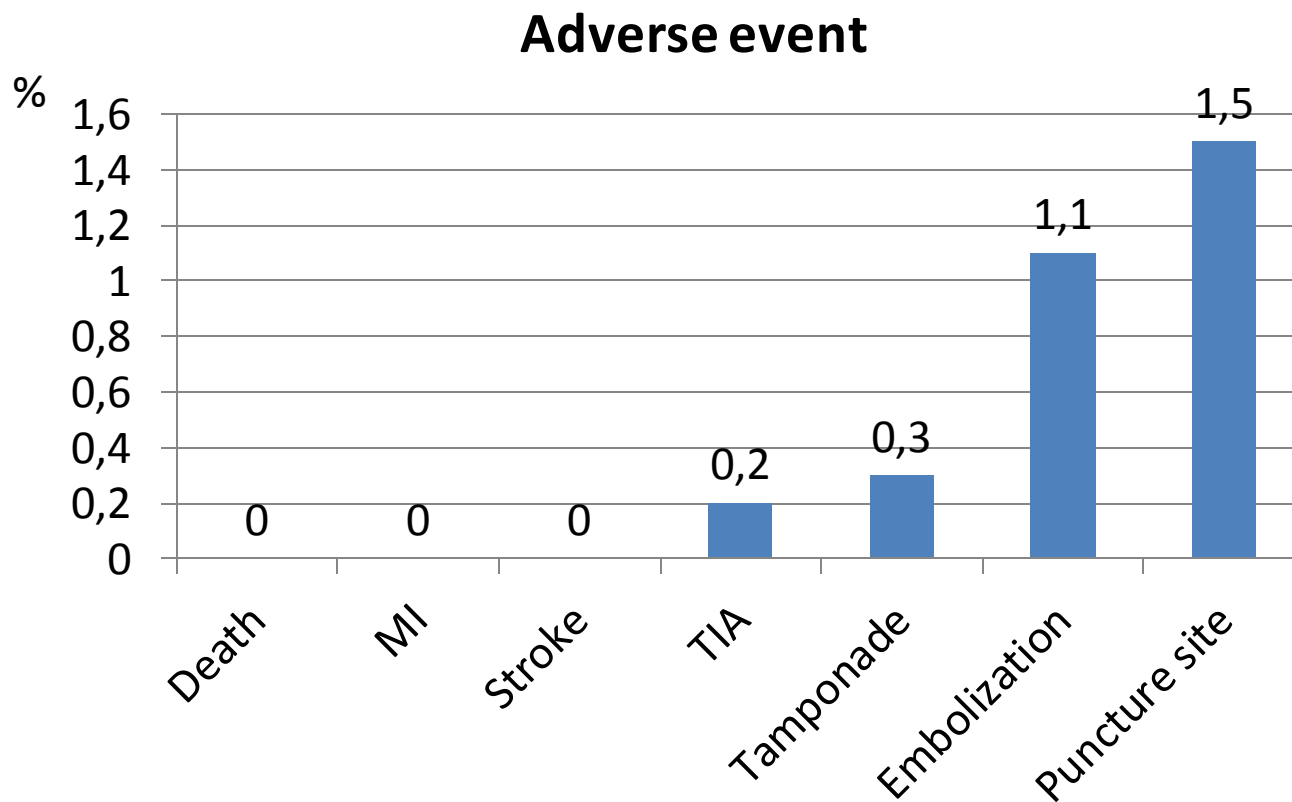




Procedural Complication of Percutaneous PFO Closure

Whorle J. Lancet 2006; 368: 35

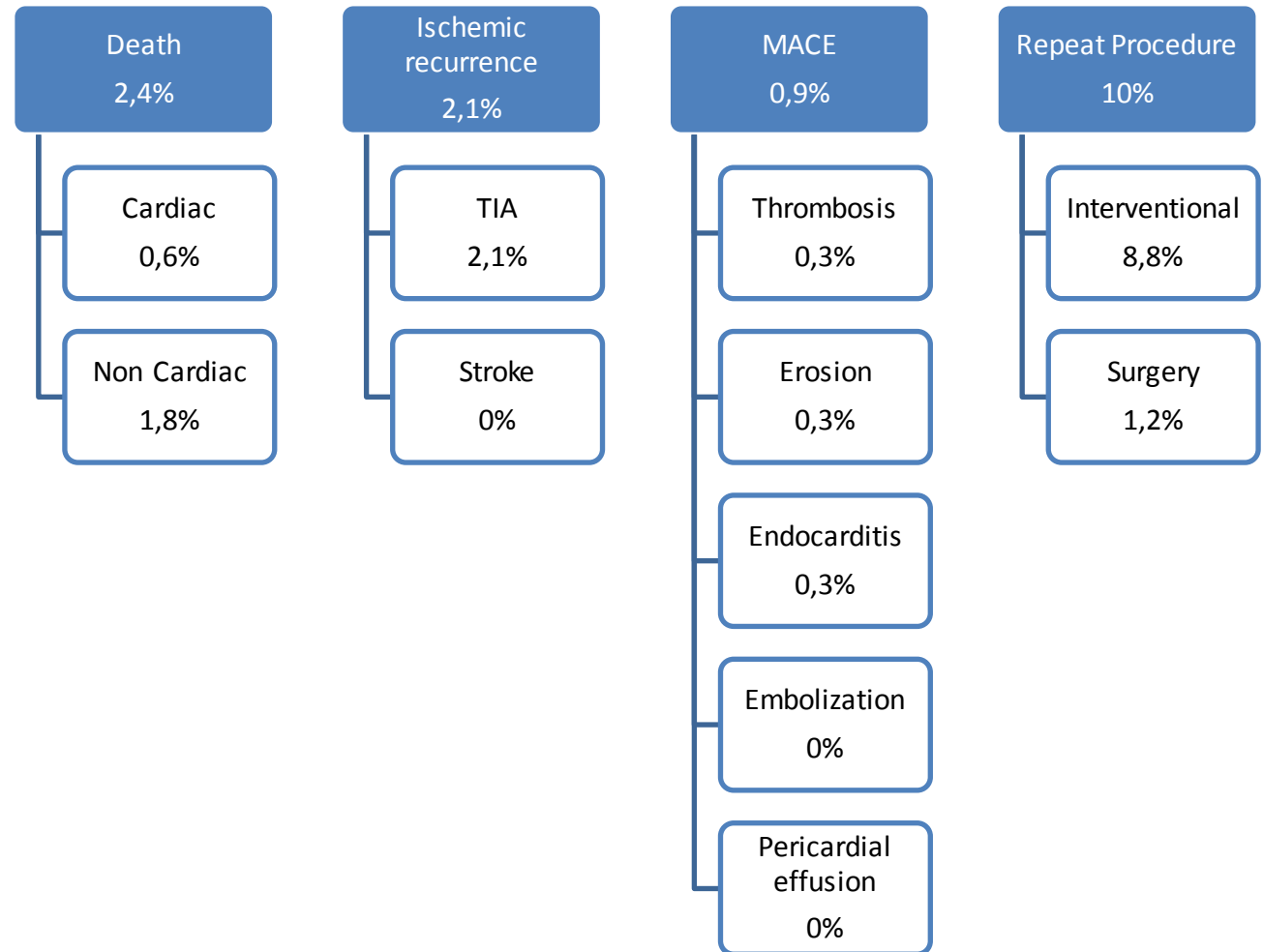
11 studies, 1970 patients





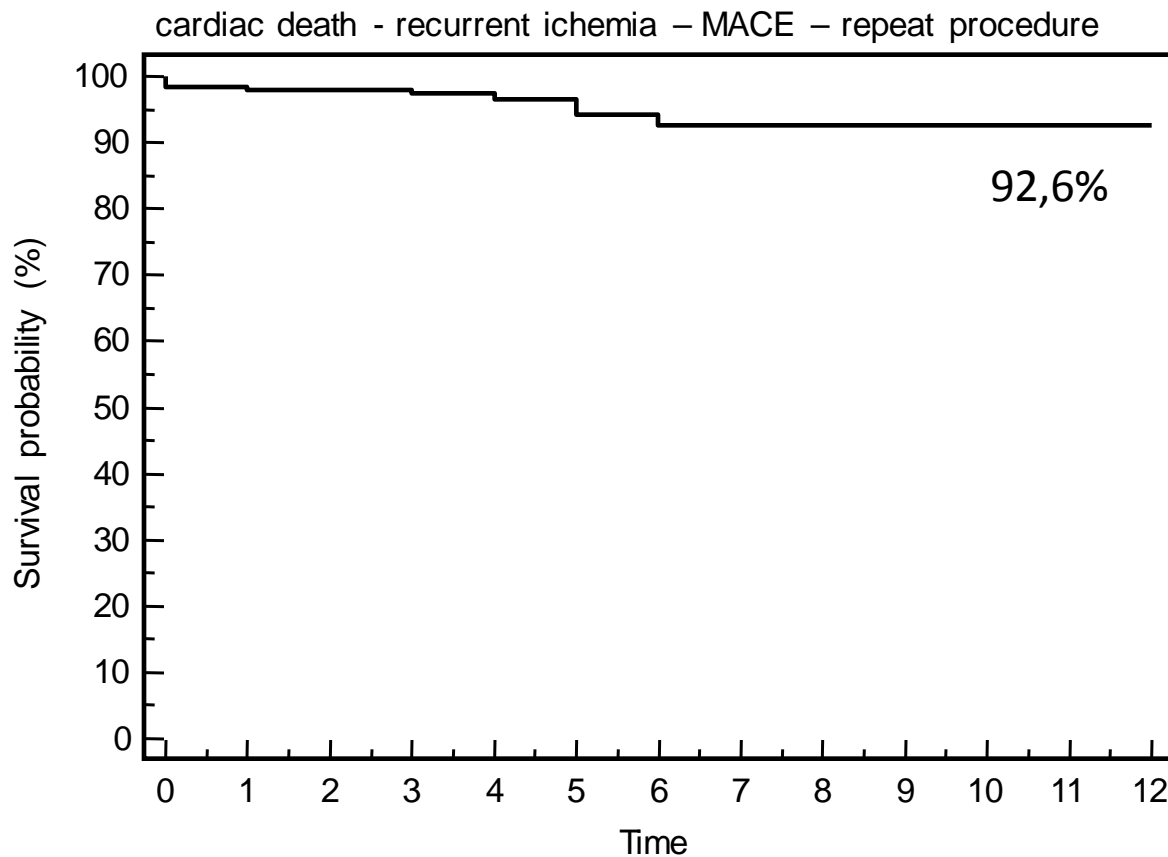
PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

FOLLOW UP
6 months – 12 years
mean 37 ± 31 months





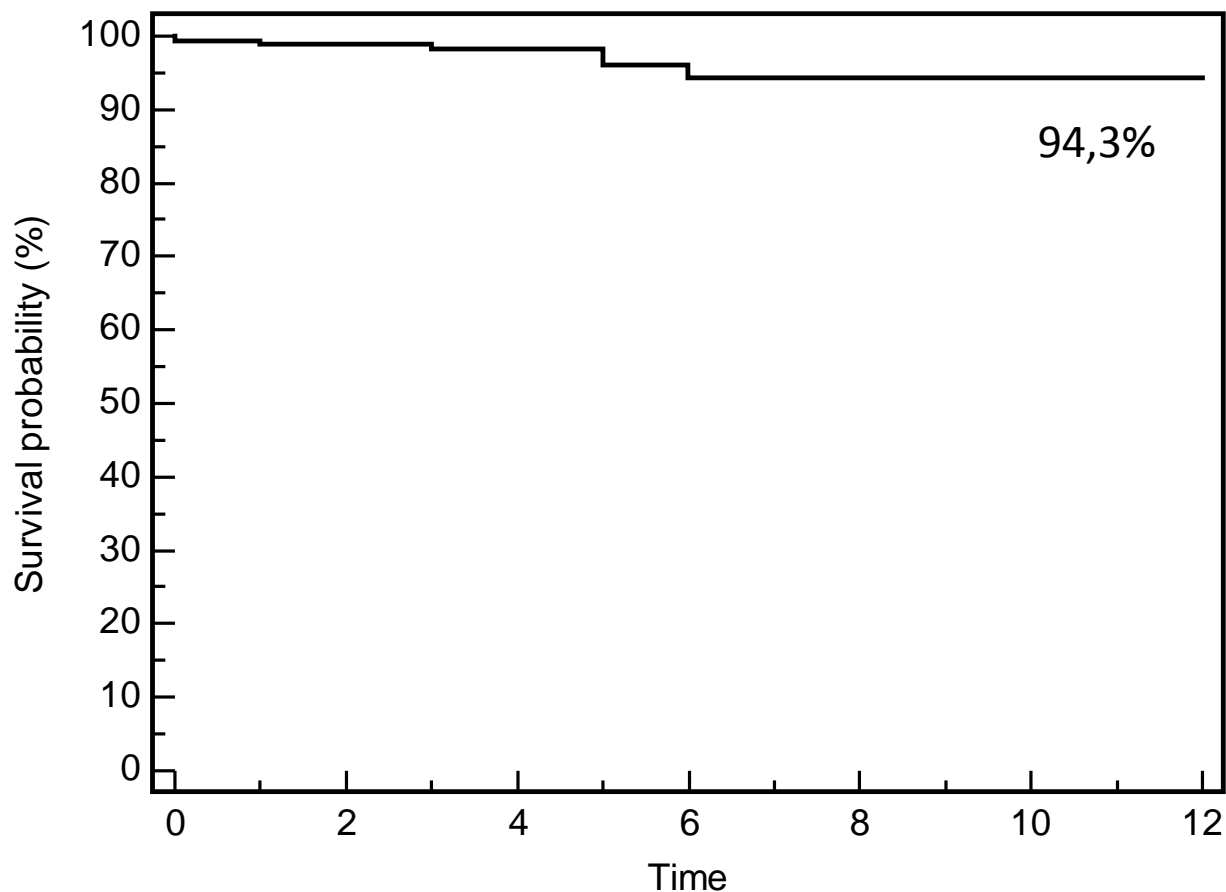
PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012





PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

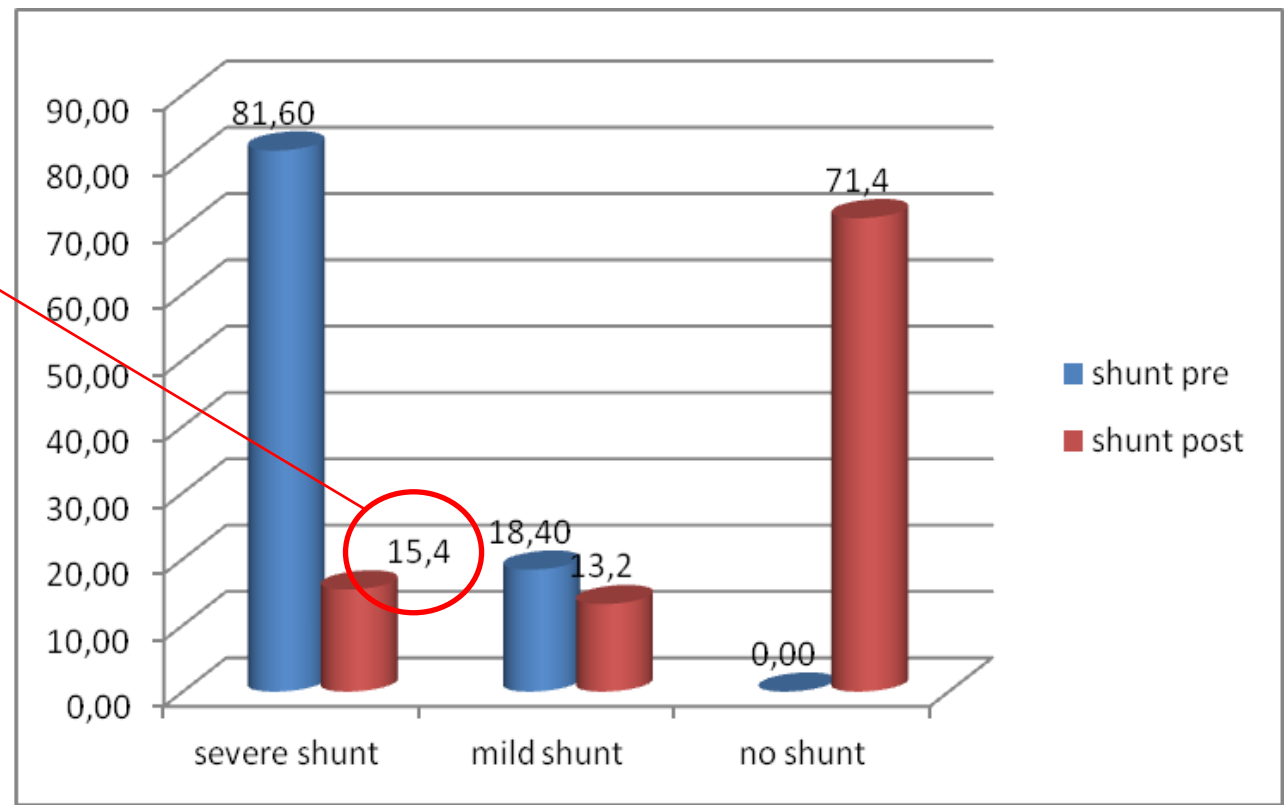
Recurrent ischemia (stroke, TIA)





PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

6 months RESIDUAL SHUNT



REINTERVENTION
72%
(success 41%)

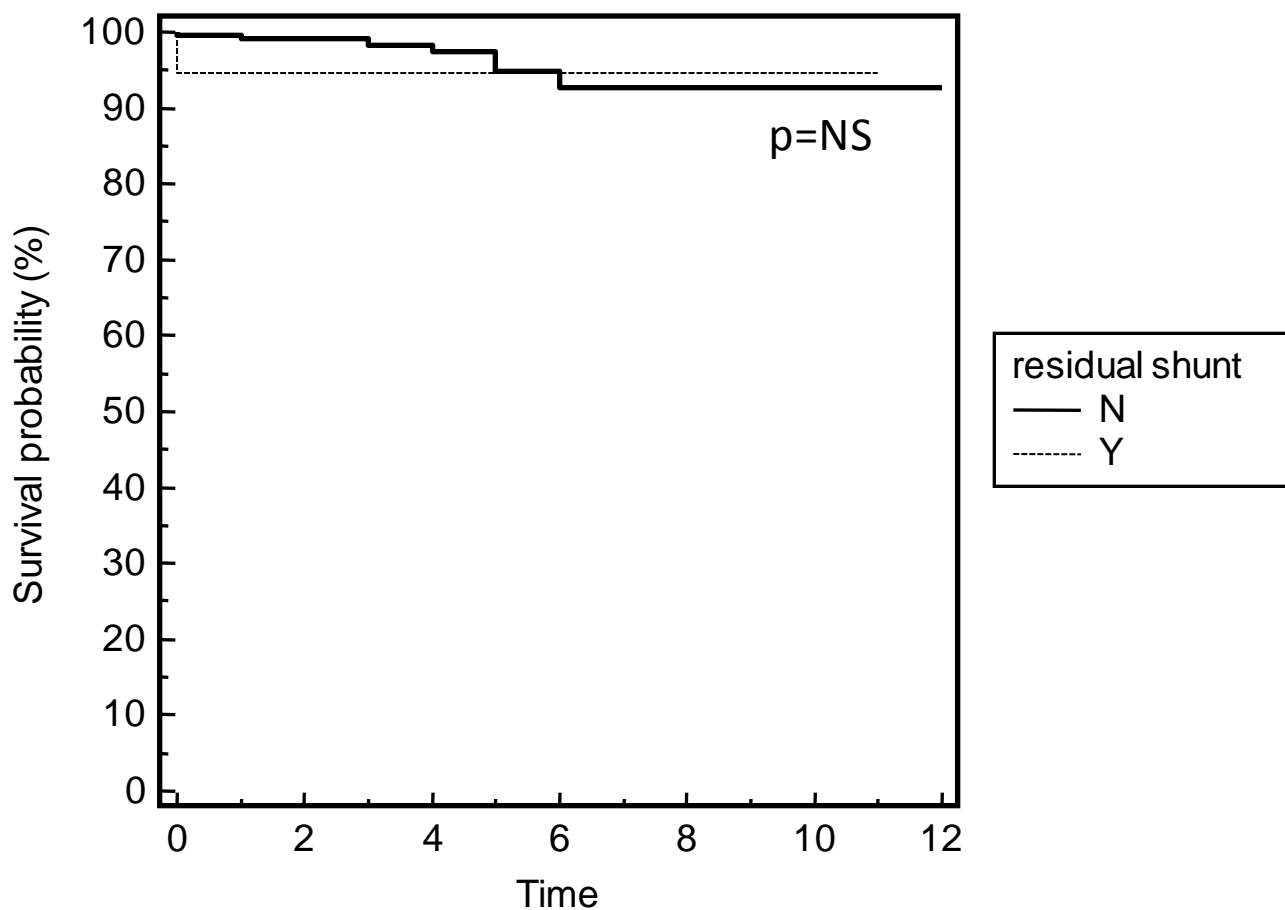
CARDIAC SURGERY
2,5%

MEDICAL TREATMENT
25,5%



PFO CLOSURE in CARDIOVASCULAR DEPARTMENT CITTA' della SALUTE e della SCIENZA di TORINO 1999 - 2012

cardiac death - recurrent ischemia - MACE - repeat procedure





- Transcatheter PFO Closure is safe and effective in prevention of recurrence in patients with cryptogenic stroke
- It requires specific skills and clinical competence
- Procedural complication are rare and must be avoided
- Wide clinical indication to closure are expected in the next years on the basis of RCT results



TCT Congress 2012

- 19 Lectures on PFO topics
- 6 Lectures on RESPECT trial

TCT Late breaking trials (tonight)

RESPECT Trial

- Event driven
- 85% basal shunt
- 36% atrial septum aneurysm
- 8 y data collection and follow up
- Results in favour to transcatheter closure are expected



Transcatheter PFO Treatment Program

Head Interventional PFO Treatment Program

Paolo Scacciatella Fulvio Orzan

Head Stroke Unit

Paolo Cerrato

Catheterization LAB

Mauro Pennone Pierluigi Omedè
Filippo Sciuto

Head ECHO LAB

Mauro Giorgi Mara Morello

Clinical Follow up

Gaetana Ferraro Anna Laura Fanelli
Matteo Marchetti Elisa Pelloni
Luigi Biasco

Data Base Managent and Statistical analysis

Ilaria Meynet