



Conoscere e Curare il Cuore 2016

LA CHIUSURA DEL PFO. QUANDO LE METANALISI RENDONO GIUSTIZIA

Achille Gaspardone

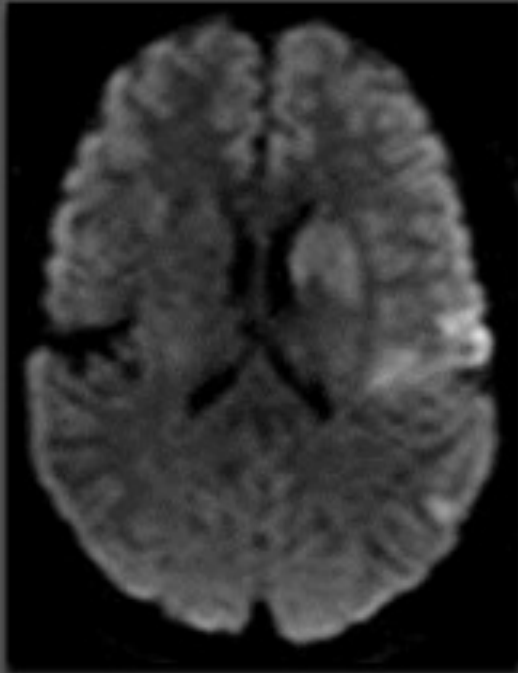
*Unità Operativa Complessa di Cardiologia
Ospedale S. Eugenio, Roma*



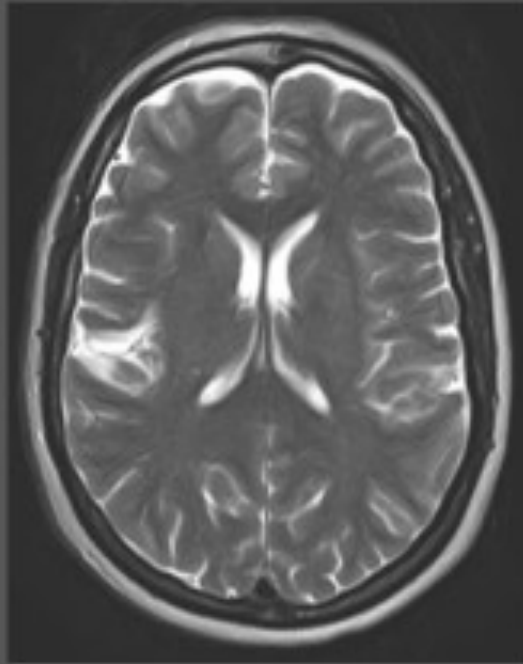
A Clinical Case

- 48 yrs old woman (profession: teacher)
- Two children (19 and 13 yrs old)
- No risk factor for CVD
- No previous symptom and healthy life
- No drug
- No history of DVT
- **1 Oct 2015**: 07:20 sudden episode of right hemiparesis associated with dysarthria immediately after difficult evacuation

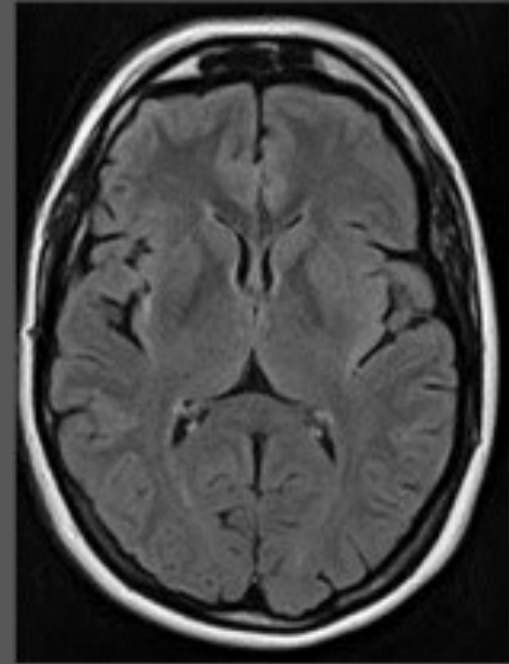
Diffusion 1-10-15



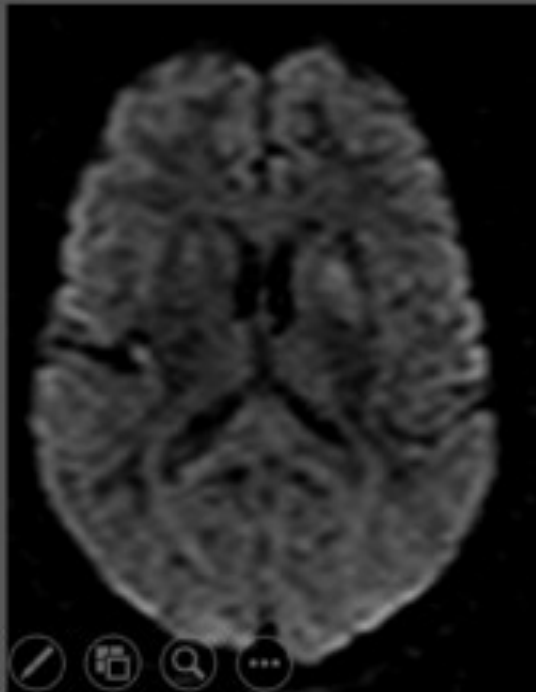
T2 1-10-15



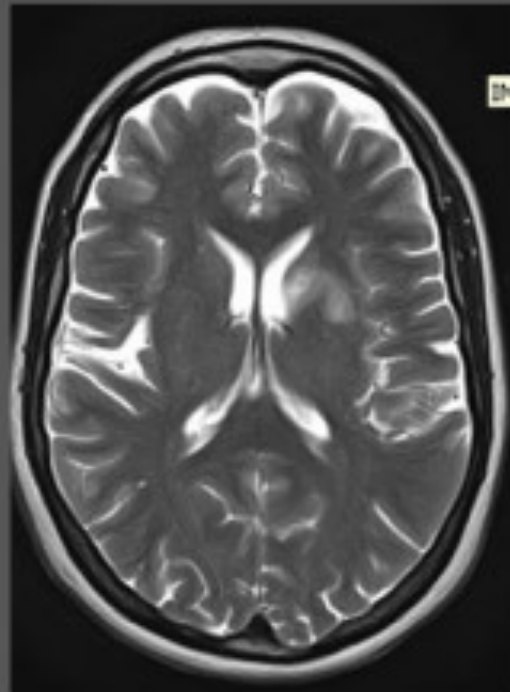
Flair 1-10-15



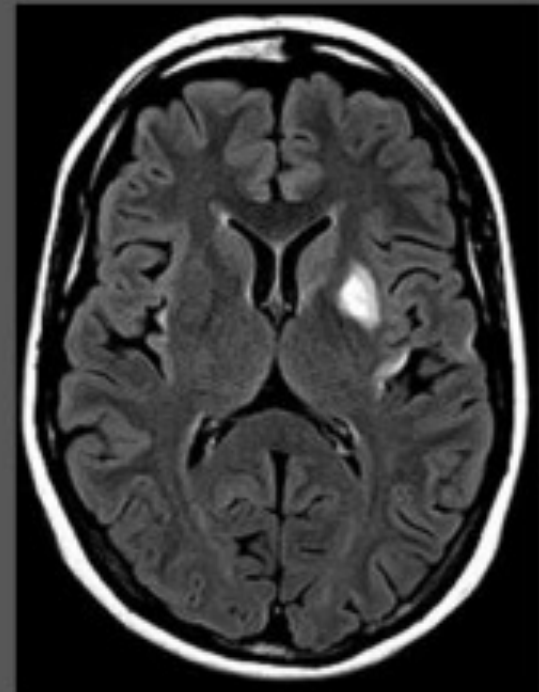
Diffusion 21-10-15



T2 21-10-15



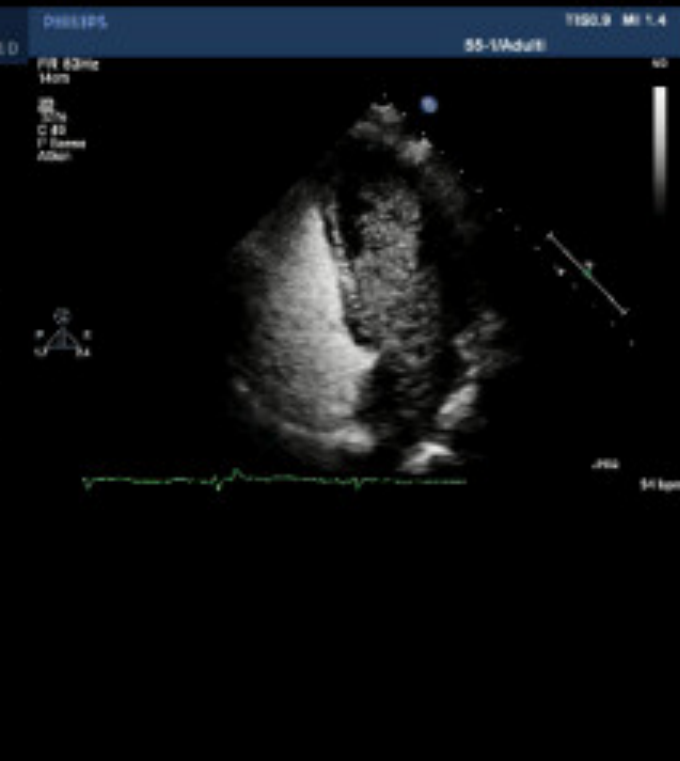
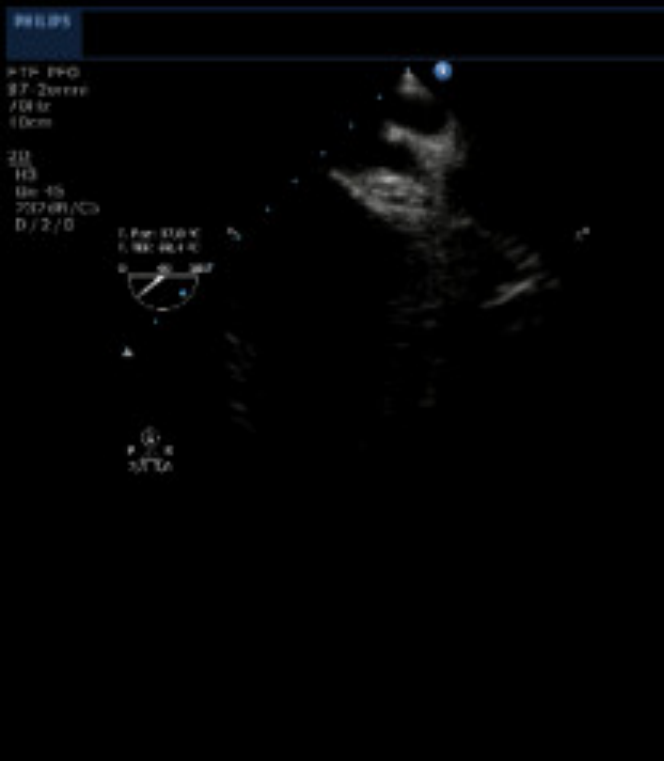
Flair 21-10-15



Diagnostic Protocol



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Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Walter N. Kernan, Bruce Ovbiagele, Henry R. Black, Dawn M. Bravata, Marc I. Chimowitz, Michael D. Ezekowitz, Margaret C. Fang, Marc Fisher, Karen L. Furie, Donald V. Heck, S. Claiborne (Clay) Johnston, Scott E. Kasner, Steven J. Kittner, Pamela H. Mitchell, Michael W. Rich, DeJuran Richardson, Lee H. Schwamm and John A. Wilson

- | | |
|---|-------------------------------|
| For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended (<i>Class I; Level of Evidence B</i>). | Class changed from IIa to I |
| For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (<i>Class I; Level of Evidence A</i>). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (<i>Class IIa; Level of Evidence C</i>). | New recommendations |
| For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (<i>Class III; Level of Evidence A</i>). | Class changed from IIb to III |
| In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (<i>Class IIb; Level of Evidence C</i>). | New recommendation |

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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Class changed from IIa to I

For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (*Class I; Level of Evidence A*). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (*Class IIa; Level of Evidence C*).

New recommendations

For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (*Class III; Level of Evidence A*).

Class changed from IIb to III
Downgrading

In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (*Class IIb; Level of Evidence C*).

New recommendation

The Evidence-Based Medicine

The Tsunami of Meta-Analyses of PFO

**3 Randomized Controlled Trials
and 24 Meta-Analyses!**

Same Numbers Same Patients

The *Tsunami* of Meta-Analysis of PFO Closure vs Medical since 2012

Medical Rx ± better (10)

Udell JA et al. Can J Cardiol 2014
Spencer FA et al. BMJ 2014
Ma B et al. J Stroke Cerebrovasc Dis 2014
Nagaraja V et al. Int J Cardiol 2014
Dentali F et al. Thromb Haemost 2014
Zhang B et al. Int J Cardiol 2013
Nagaraja V et al. Heart Lung Circ 2013
Wolfrum M et al. Heart 2014
Kwong JS et al. Int J Cardiol 2013
Kitios GD et al. Stroke 2012

Closure ± better (12)

Pickett CA et al. Tex Heart Inst J 2014
Storecky S et al. Eur Heart J 2015
Hernandez J et al. World J Cardiol 2014
Pandit A et al. Heart Lung Circ 2014
Riaz IB et al. BMC Card Dis 2013
Capodanno D et al. EuroIntervention 2014
Khan AR et al. JACC Cardiovasc Int 2013
Hakeem A et al. Cardiovasc Rev Med 2013
Ntaios G et al Int J Cardiol 2013
Rengifo-Moreno P et al. Eur Heart J 2013
Pineda AM et al. Cath Cardiovasc Int 2013
Kent DM et al JACC 2016

Kent DM et al. Eur Heart J 2015
Patti G et al. Am J Cardiol 2015

Randomized Controlled Trials on PFO

The “Evidence Based Medicine”

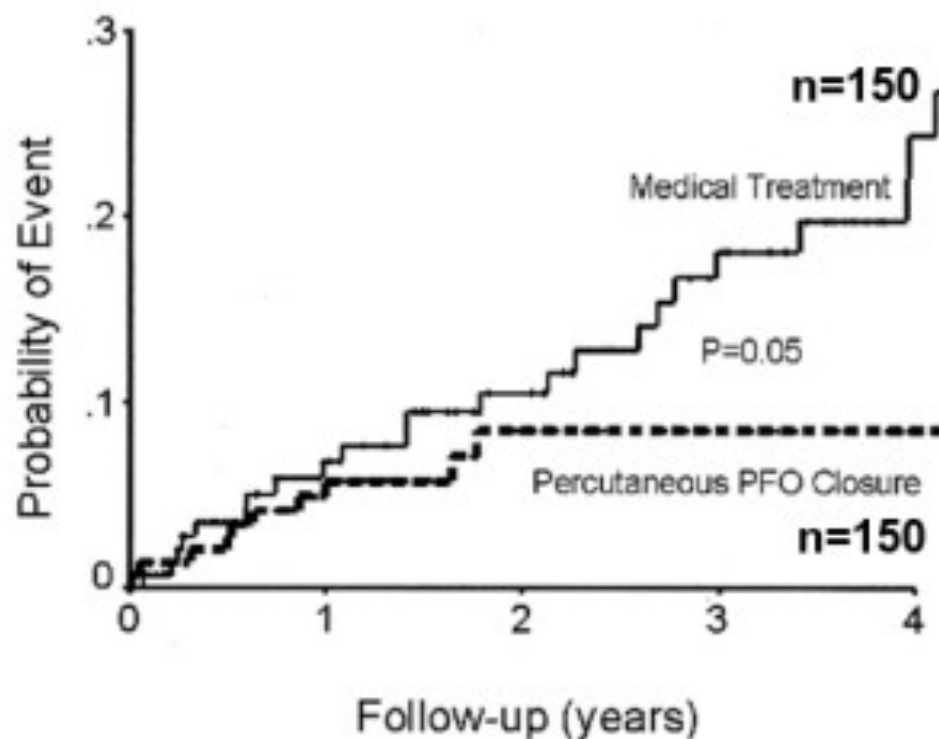
TRIAL*	Pts	Device	Event	No° Centers	Recruitment Time (ysr)	Recruitment Rate (pts/center/yr)	Follow Up Time
CLOSURE I *	909	Starflex	Stroke TIA	87	5 (2003-2008)	2.08**	2.0
PC-TRIAL *§	414	Amplatzer	Stroke TIA PE	29	9 (2000-2009)	1.58	4.1
RESPECT *§	980	Amplatzer	Stroke	69	8 (2003-2011)	1,77	2.6
Mean/total	2303			185 (61,66)	7,33	1,69	2,9

* “All-comers studies”; ** 10% of centers did not enroll patients

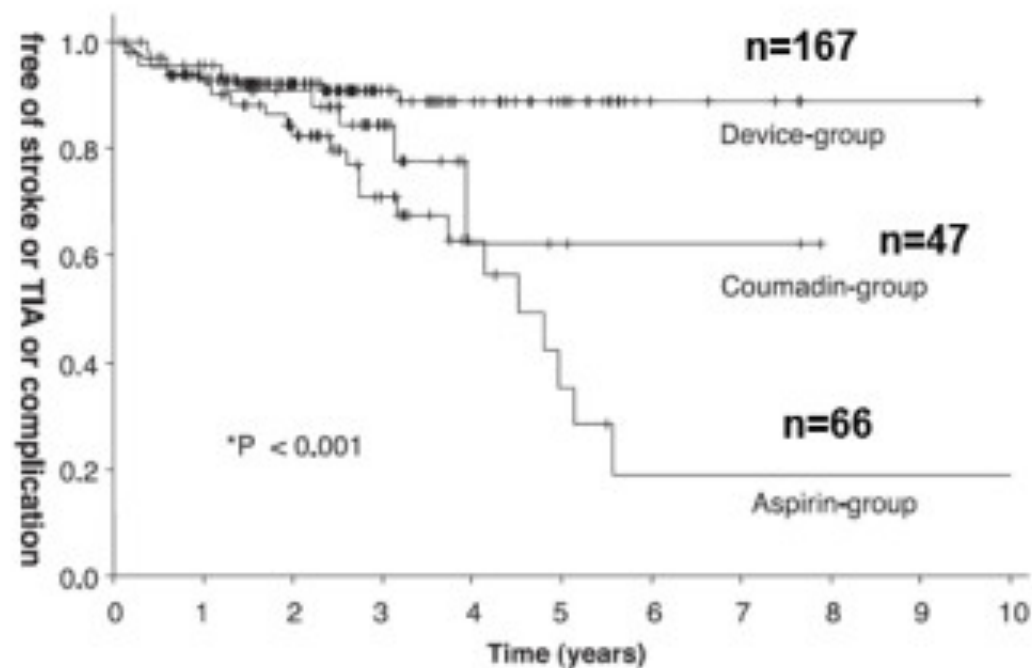
§ In PC-Trial and RESPECT the definition of Stroke and TIA different

On-going RCTs: CLOSE (2017), Gore REDUCE (2017)

Probability of recurrent stroke & TIA stratified for medical treatment and percutaneous PFO closure

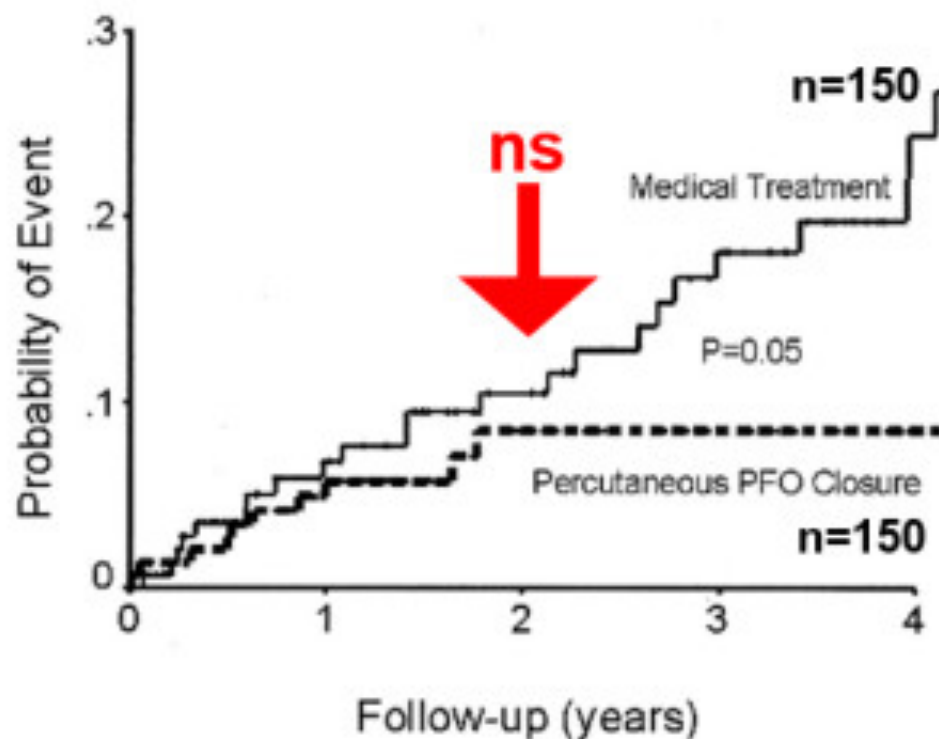


Windecker, S. et al. J Am Coll Cardiol 2004;44:750-758

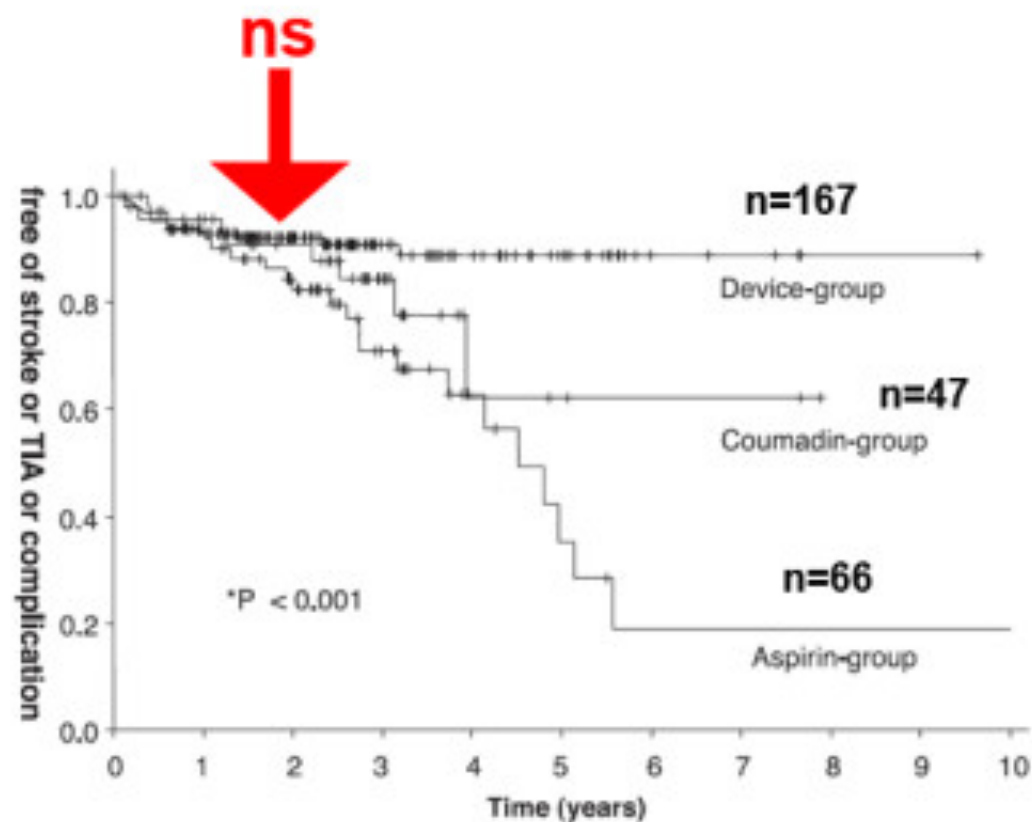


Schuchlenz HW et al. Int J Cardiol 2005;101:77-82

Probability of recurrent stroke & TIA stratified for medical treatment and percutaneous PFO closure

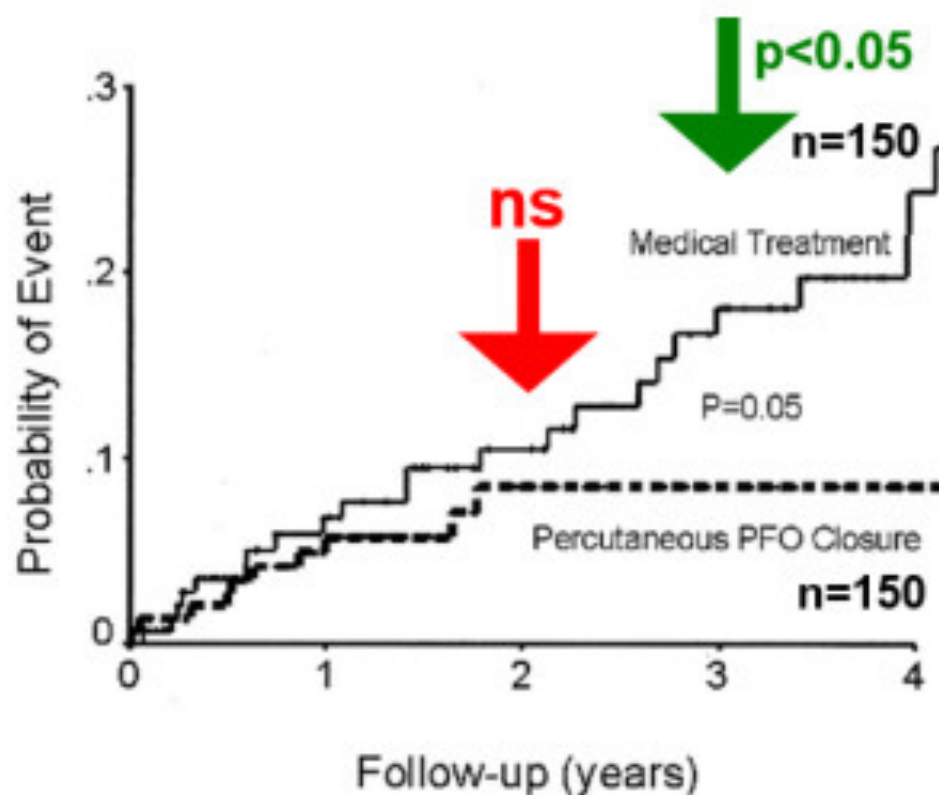


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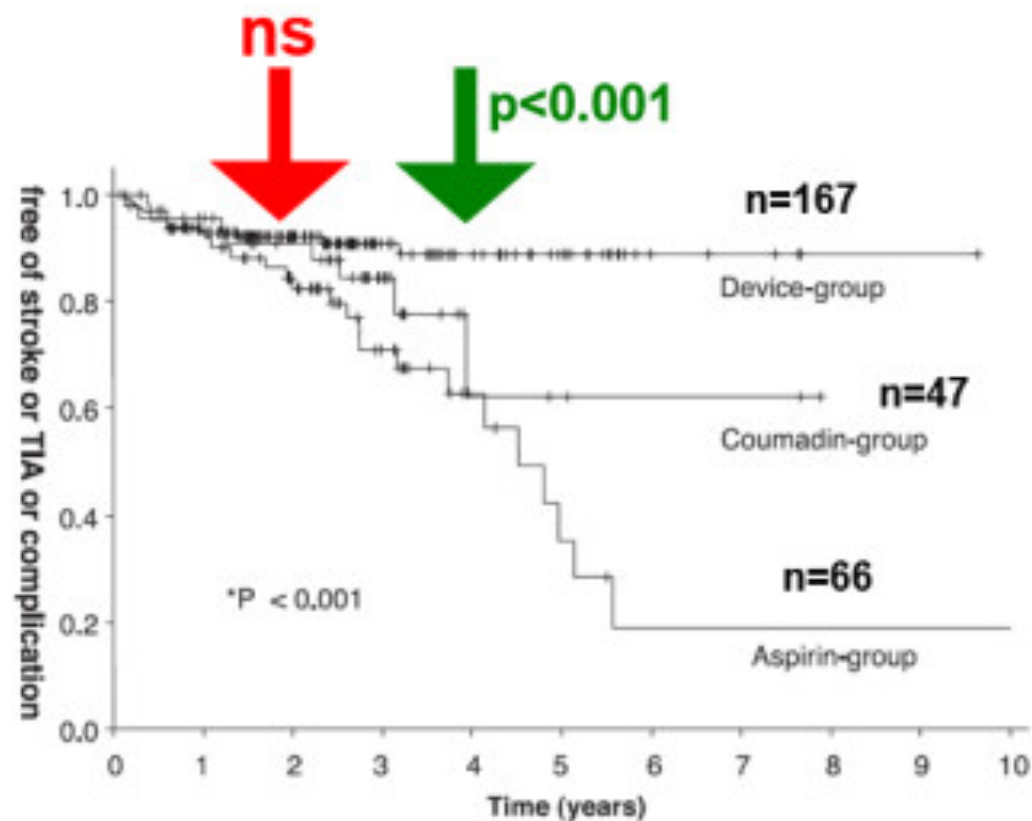


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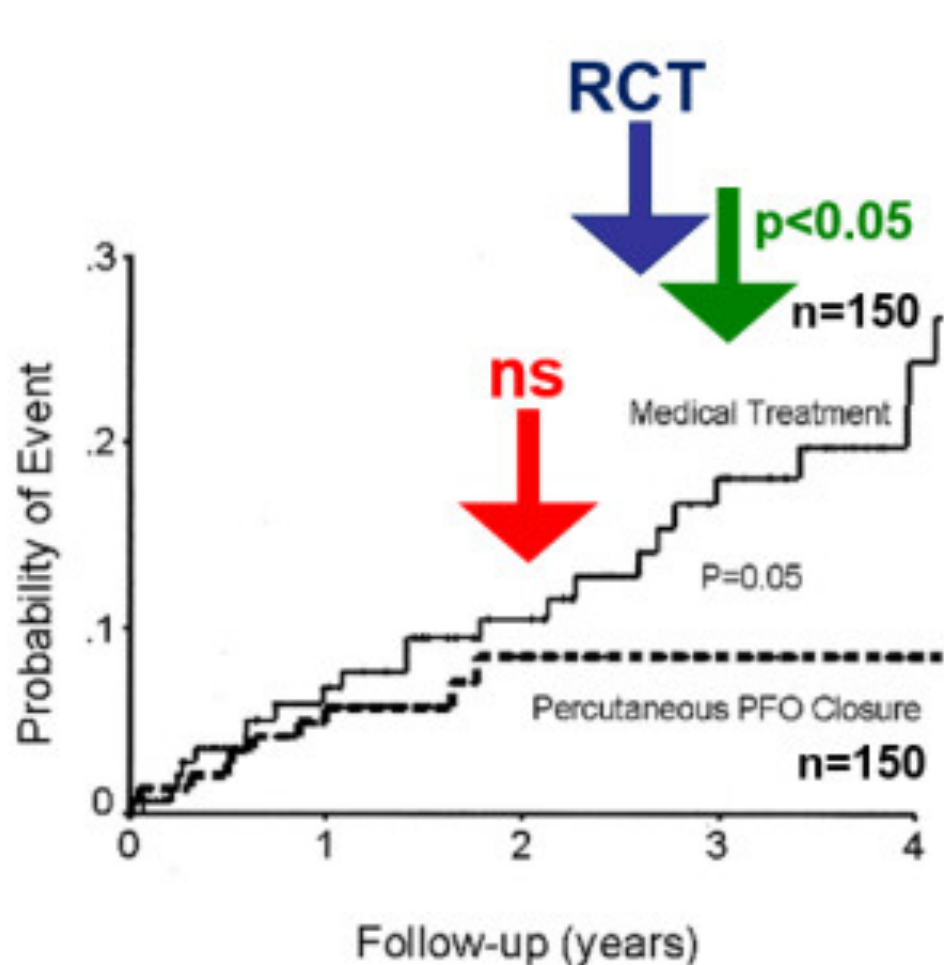


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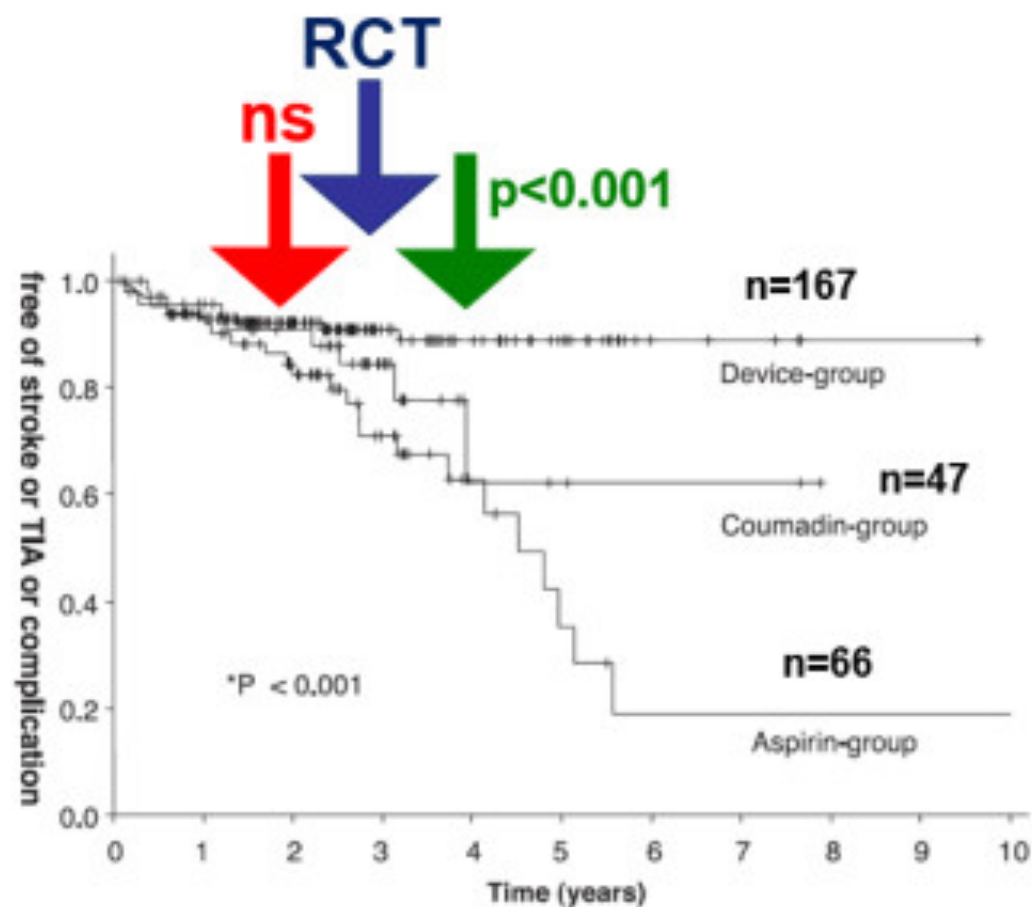


Schuchlenz HW et al. Int J Cardiol 2005;101:77-82

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Windecker, S. et al. J Am Coll Cardiol 2004;44:750-758



Schuchlenz HW et al. Int J Cardiol 2005;101:77-82

RESPECT

Extended Follow-up Results

John D. Carroll, M.D.

Acknowledgements

Jeffrey L. Saver, M.D.

David E. Thaler, M.D., Ph.D.

Richard Smalling, M.D., Ph.D.

Lee A. MacDonald, M.D.

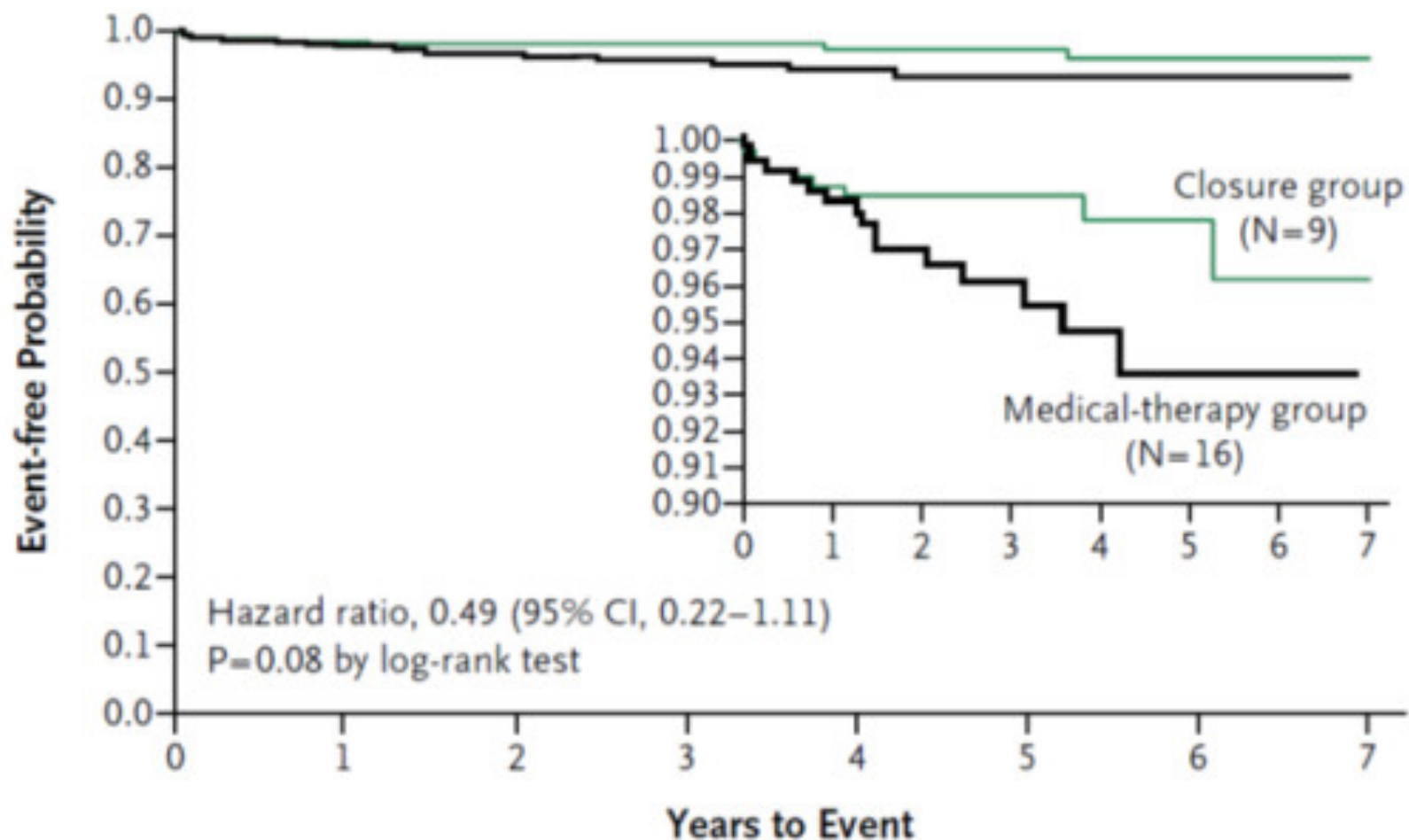
David S. Marks, M.D.

David L. Tirschwell, M.D.

for the RESPECT Investigators

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

A Intention-to-Treat Cohort

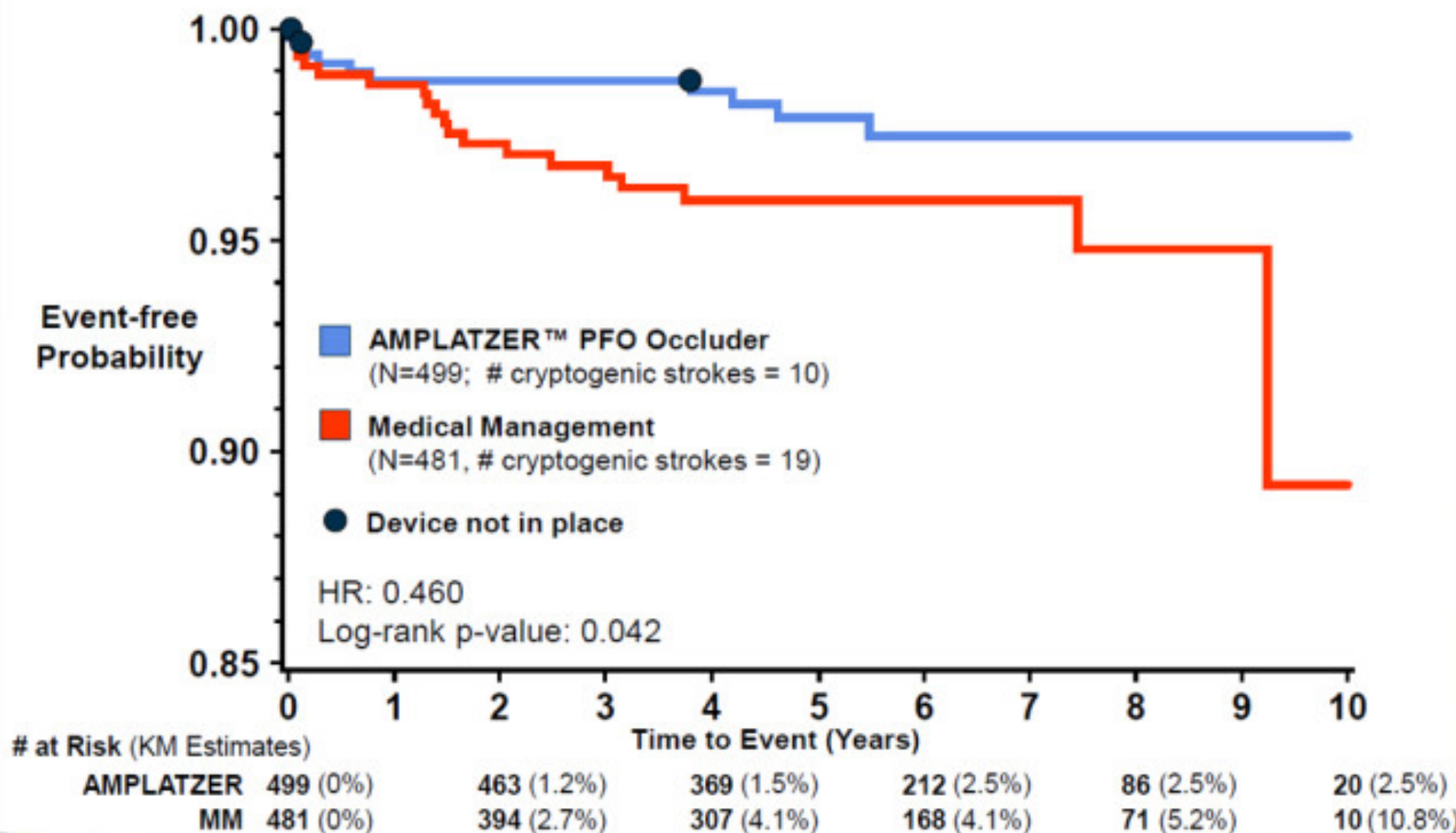


Extended Follow-up Provides Considerable New Data

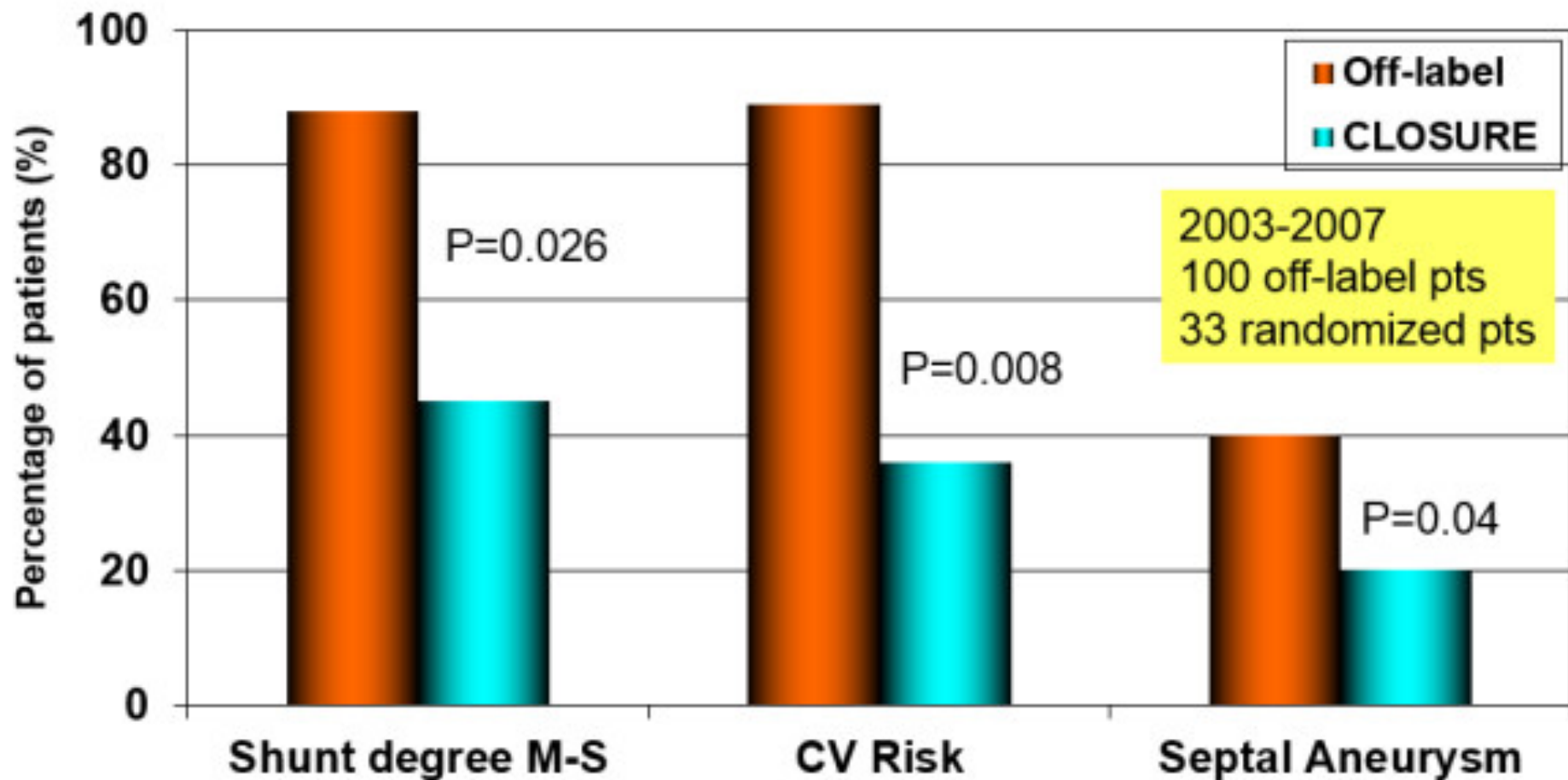
	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Mean Follow-up (years)		
Initial Analysis	3.0	2.7
Extended Follow-up	5.5	4.9
Total Patient-Years of Follow-up		
Initial Analysis	1476	1284
Extended Follow-up	2769	2376

Significant Reduction in Recurrent Cryptogenic Stroke

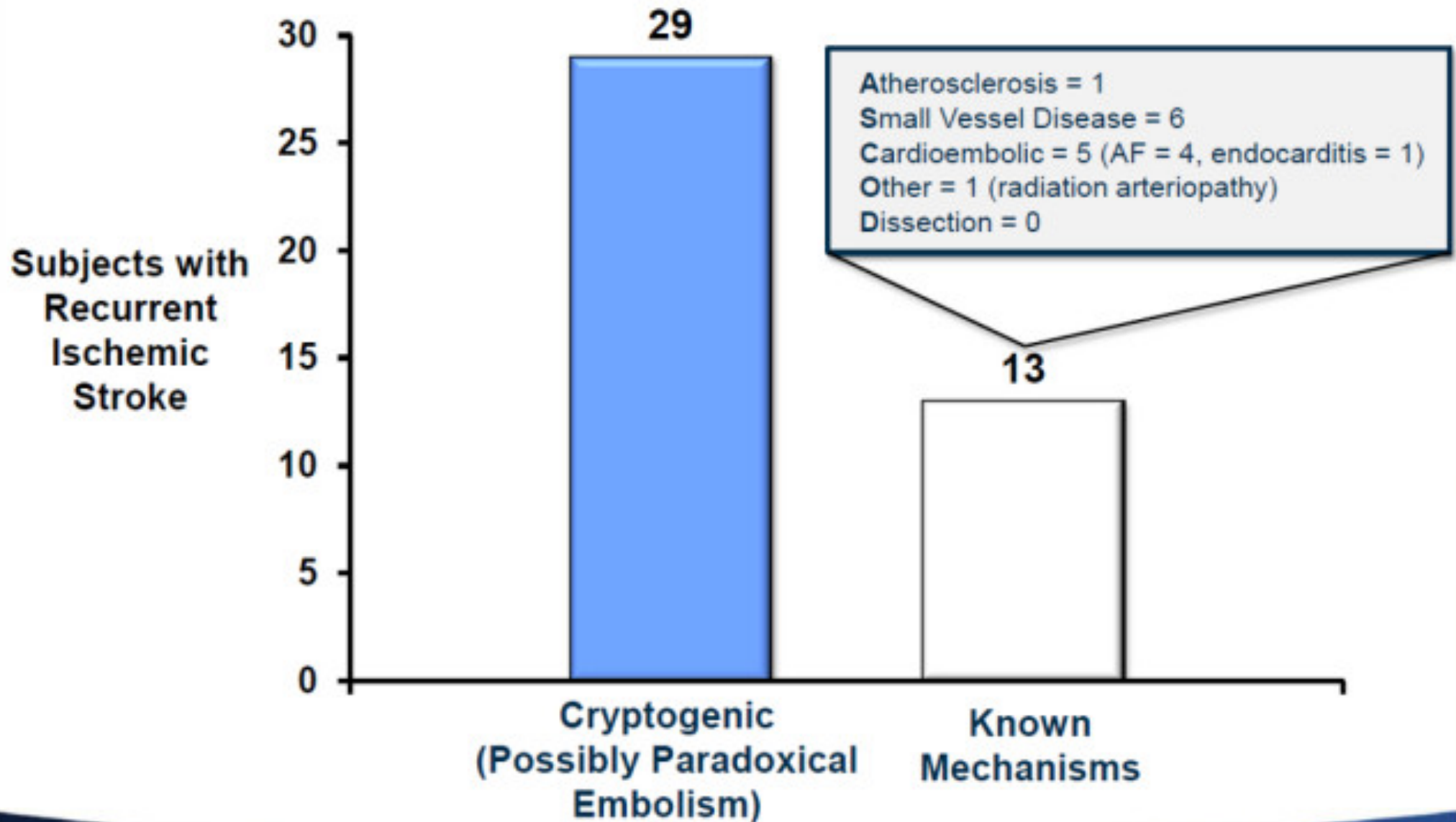
54% Relative Risk Reduction in ITT Population



Off-Label Closure during CLOSURE I (at Cleveland Clinic)

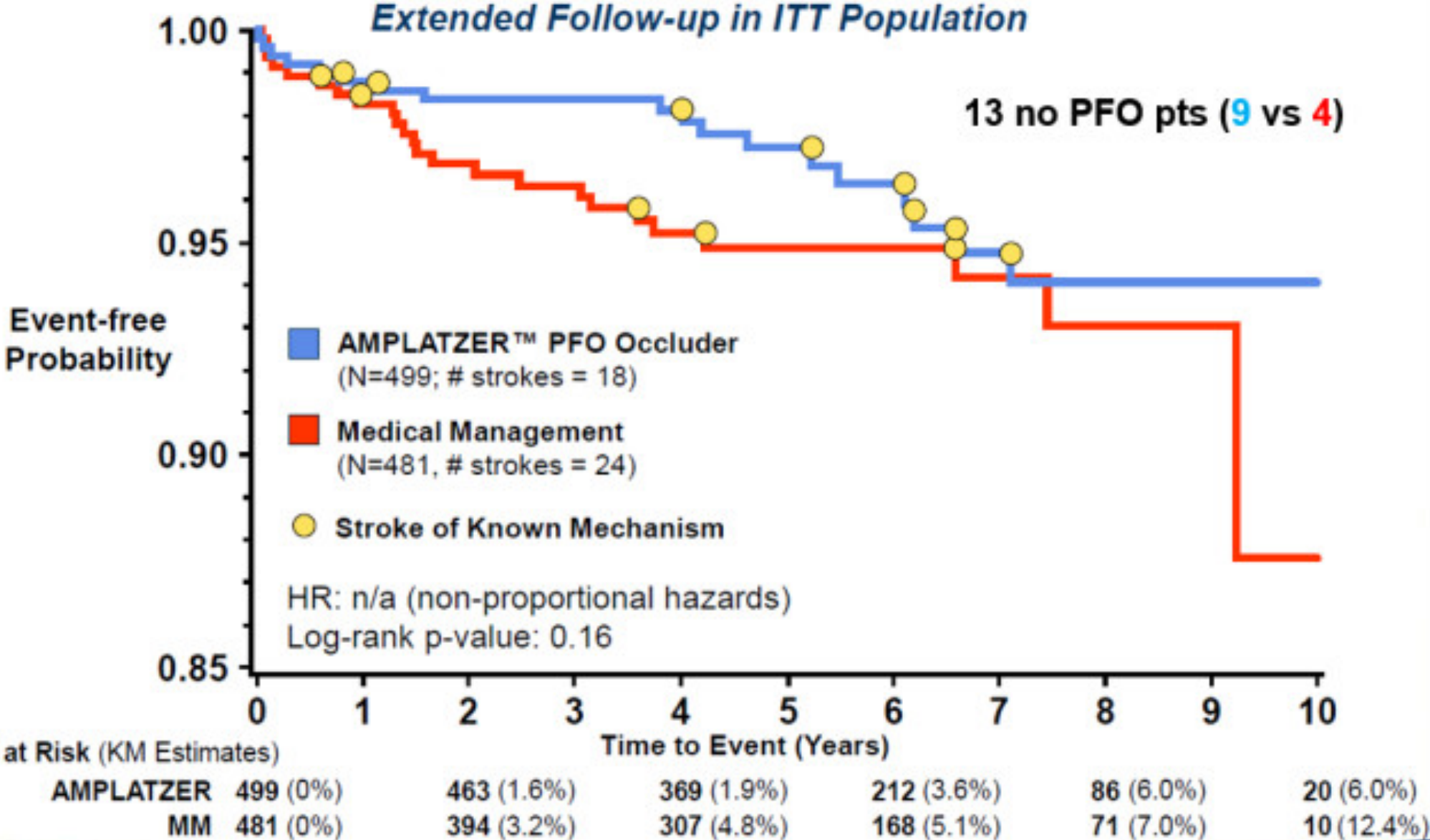


Nearly 1/3 of Recurrent Strokes in Extended Follow-up Are of Known Mechanism



1 out of 3 Recurrent Strokes Had Mechanism That PFO Closure Cannot Prevent

Extended Follow-up in ITT Population



Cosa fareste quindi ?

PHILIPS

TIS0.9 MI 1.4

S5-1/Adulti

FR 53Hz
14cm

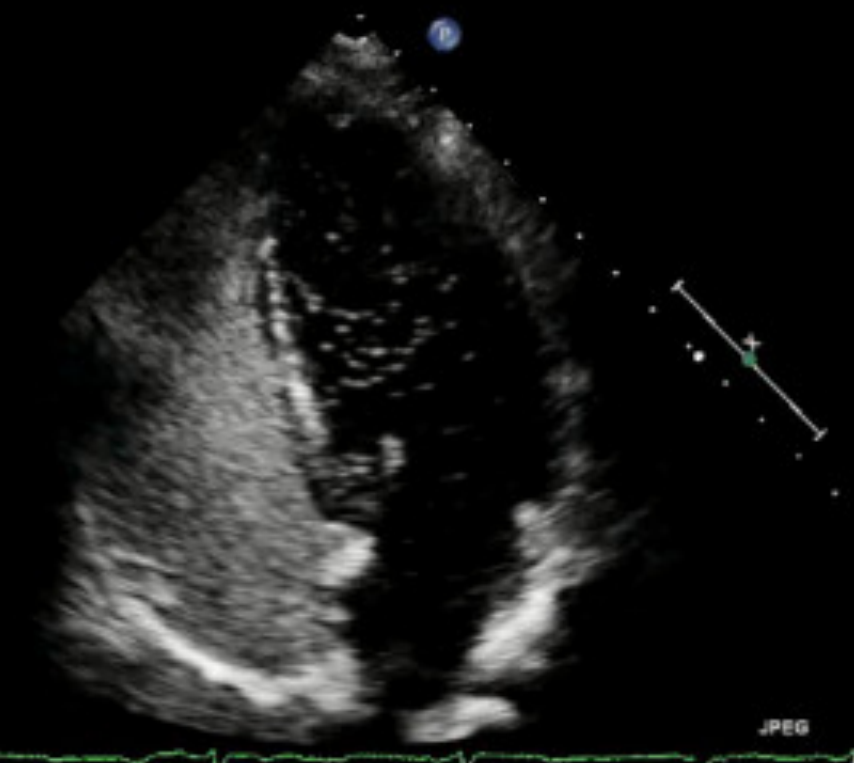
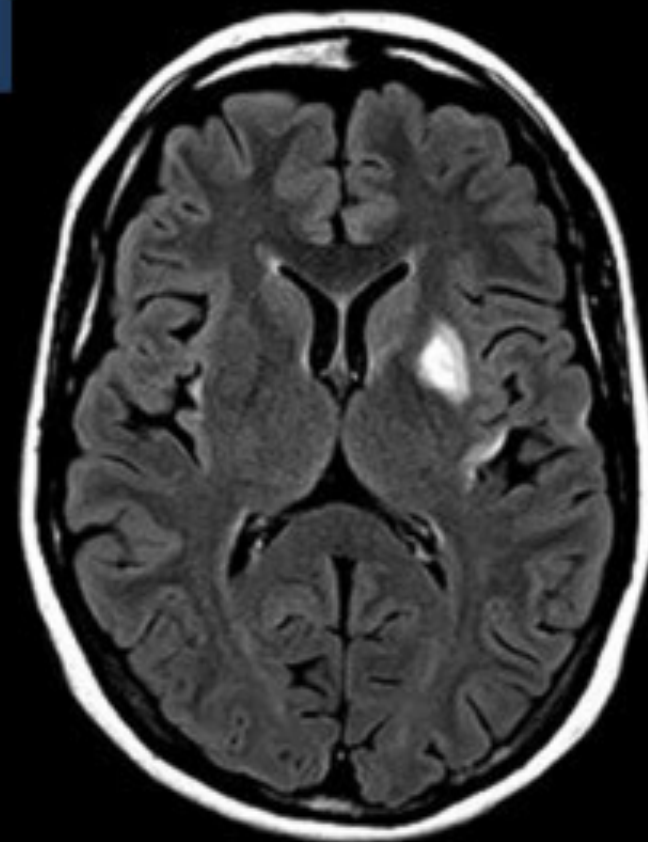
2D
53%
C 49
P Bassa
AGen

M3

Ⓞ
P R
1.7 3.4

JPEG

54 bpm



PFO Recommendations



1. There are insufficient data to establish whether anti-coagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (*Class IIb; Level of Evidence B*).
2. For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended (*Class I; Level of Evidence B*). (Revised recommendation)
3. For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (*Class I; Level of Evidence A*). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (*Class IIa; Level of Evidence C*). (New recommendation)
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Stroke



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Stroke, published online May 1, 2014.

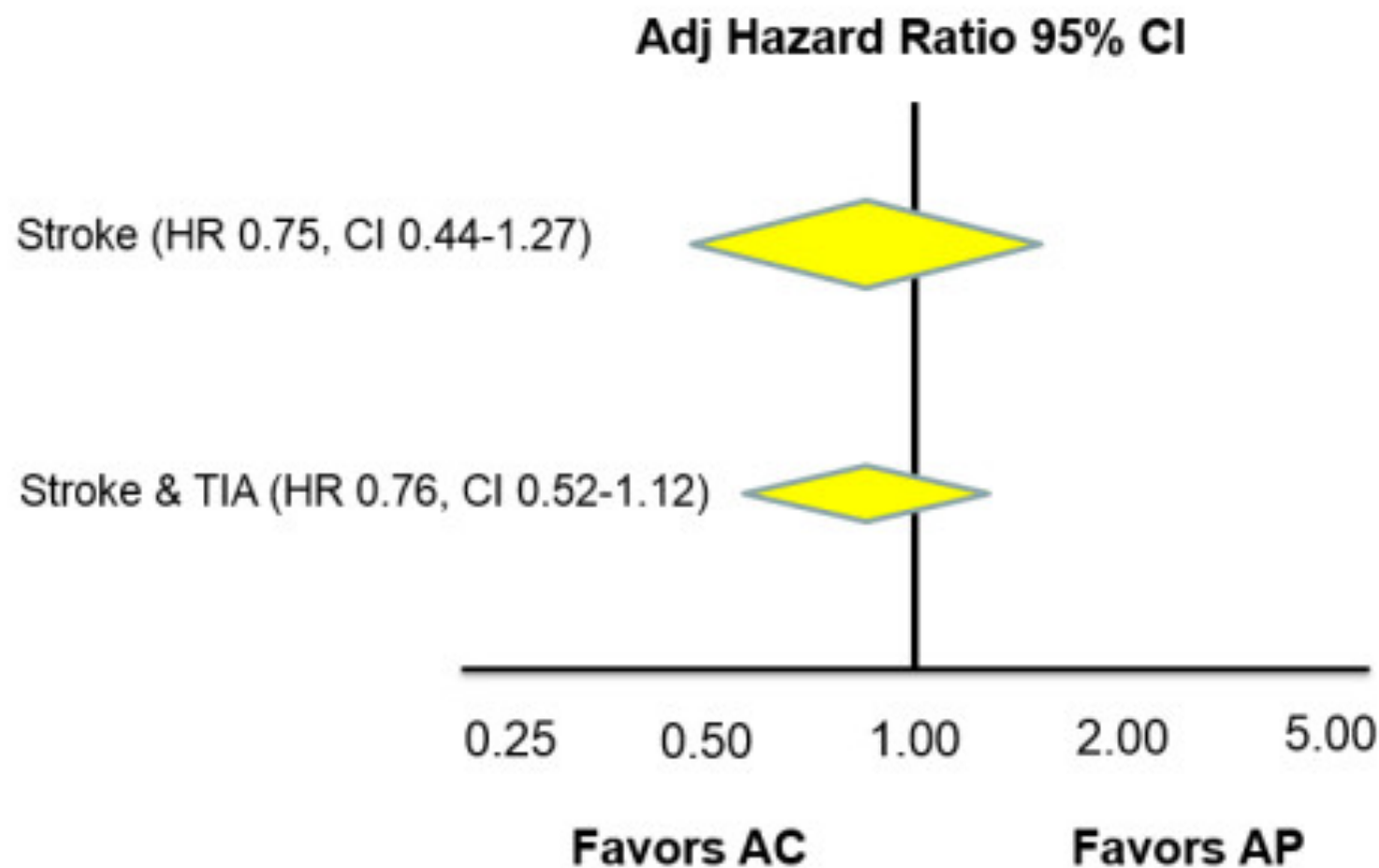
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Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis



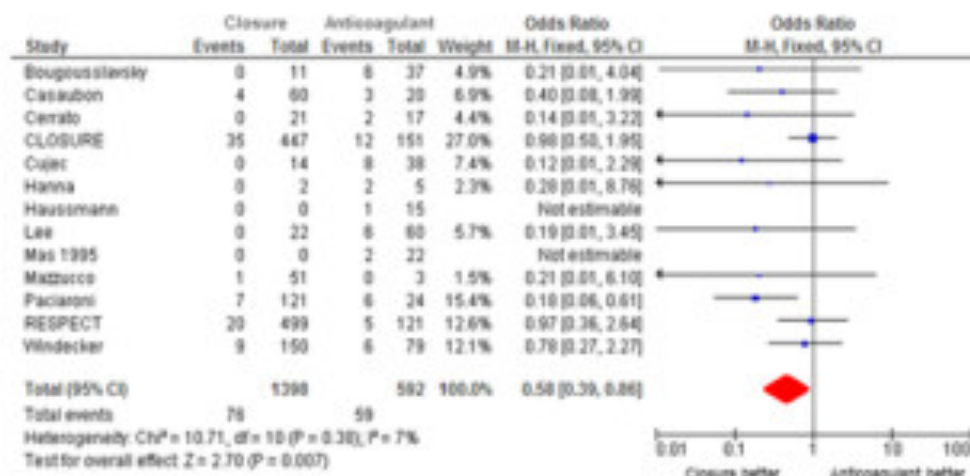


Ariel Sharon 1928-2014

It was the evening of 18 Decembre 2005. Ariel Sharon, prime minister of Israel, was on his way home, when he suddenly had difficulties articulating. He was diagnosed with TIA and recovered quickly. **The plausible reason for his TIA was identified: a PFO.** He was slated to undergo percutaneous PFO closure after the holidays on 5 January 2006. Until the procedure the PM was treated with LMWH. The day before the scheduled procedure he had a haemorrhagic stroke and never recovered remaining in coma for 8 years until his death in January 2014.

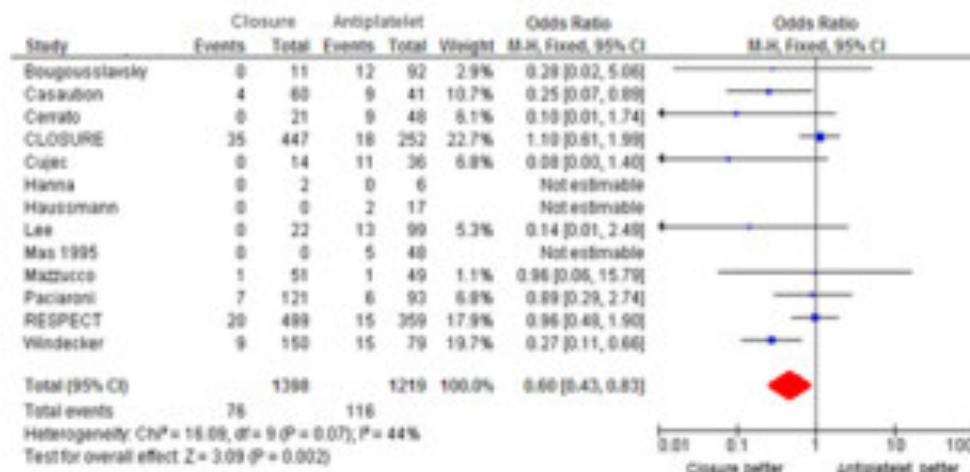
PFO closure vs anticoagulant/antiplatelet therapy in patients with cryptogenic stroke: **Net Clinical Benefit**

ANTICOAGULANT
OR for net clinical
benefit (recurrent
stroke/TIA and **bleeding**)



-42%

ANTIPLATELET
OR for net clinical
benefit (recurrent
stroke/TIA and **bleeding**)



-40%

Quando le Meta-analisi rendono «In-Giustizia»: Messaggi Conclusivi

- Lo tsunami delle meta-analisi sulla miglior strategia terapeutica del PFO hanno prodotto risultati contrastanti, non conclusivi e non hanno reso giustizia in quanto i 3 RCT finora pubblicati presentano importanti limiti metodologici che ne inficiano i risultati
- Non esiste attualmente una BMT per i pazienti con PFO ma solo (per quieto vivere) consuetudini terapeutiche potenzialmente pericolose (durata a vita e rischio di sanguinamento)
- Al momento, la miglior strategia terapeutica deve scaturire da una valutazione personalizzata delle possibili cause dell'evento ischemico.

“Cryptogenic” Stroke/TIA/Embolism & PFO with R-L Shunt

First Event
without anatomical/clinical
risk factors

First Event
with ≥ 1 anatomical/clinical
risk factors

Recurrent event
on anti-platelet and/or TAO
medical therapy



Medical therapy

Cath PFO closure

Cath PFO closure

Anatomical risk factors

- Atrial septal aneurysm
- Large PFO (>4 mm)
- Basal R-L shunt
- Eustachian valve >10 mm
- Chiari network
- Long PFO tunnel

Clinical risk factors

- Young age and Multiple ischemic lesions on CT/MR
- History of DVT/PE and/or Thrombophilia
- Valsalva-associated (diving) embolic event
- Ischemic event on arousal (OSAS)
- Long travel/immobilization associated event
- Stroke/TIA & simultaneous systemic/pulmonary embolism