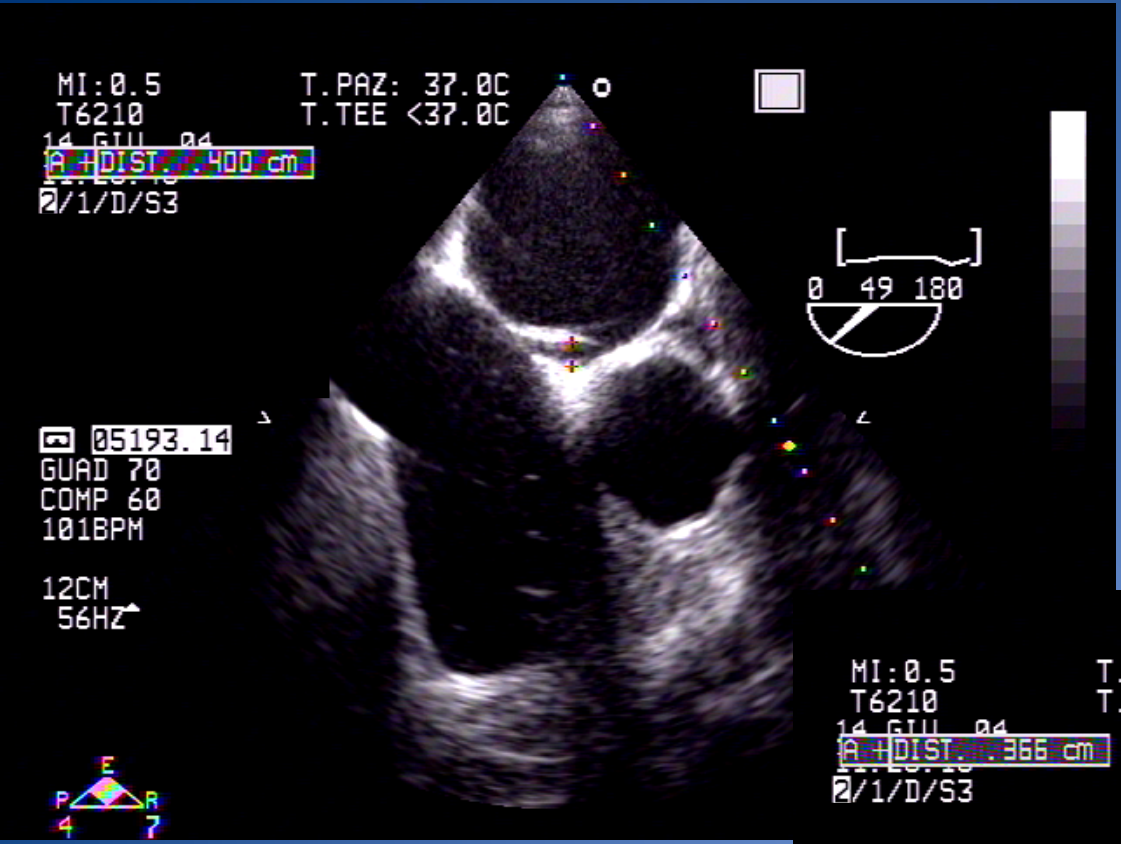
IL PFO: CLINICA ED IMAGING PER INDICAZIONI E GUIDA ALLA (NON) CHIUSURA

P. Faggiano
U.O. Cardiologia - Spedali Civili, Brescia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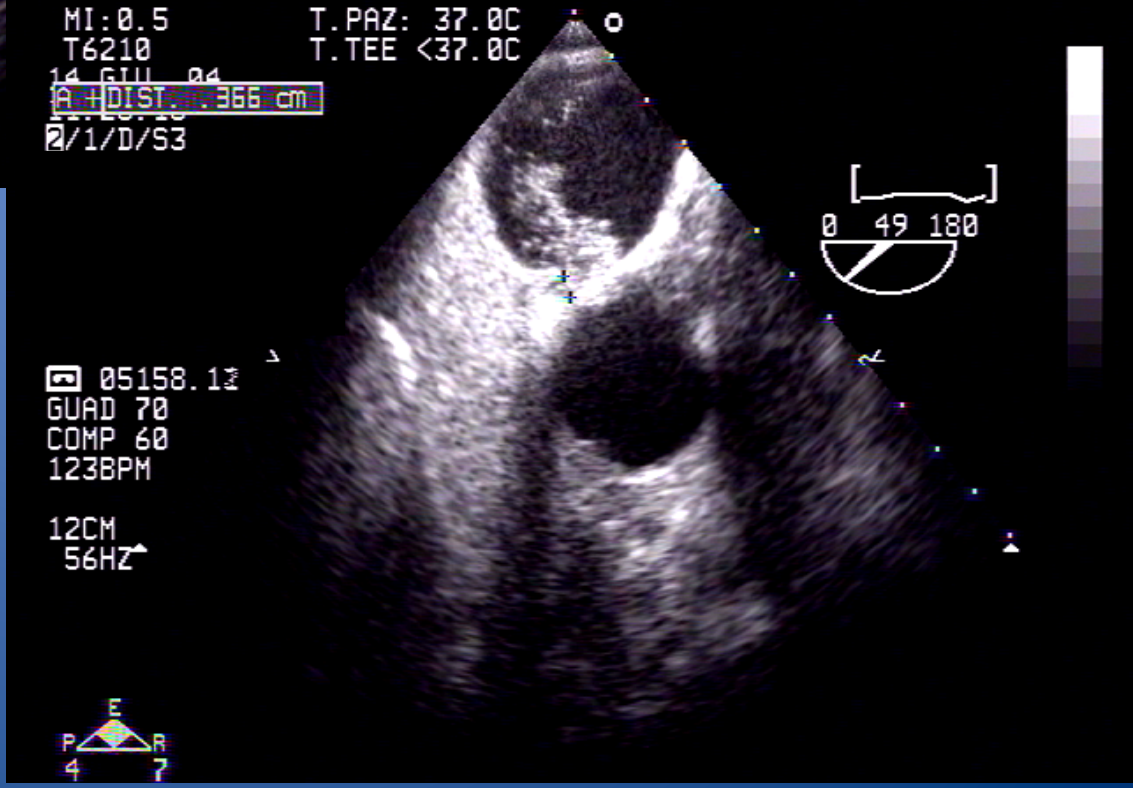
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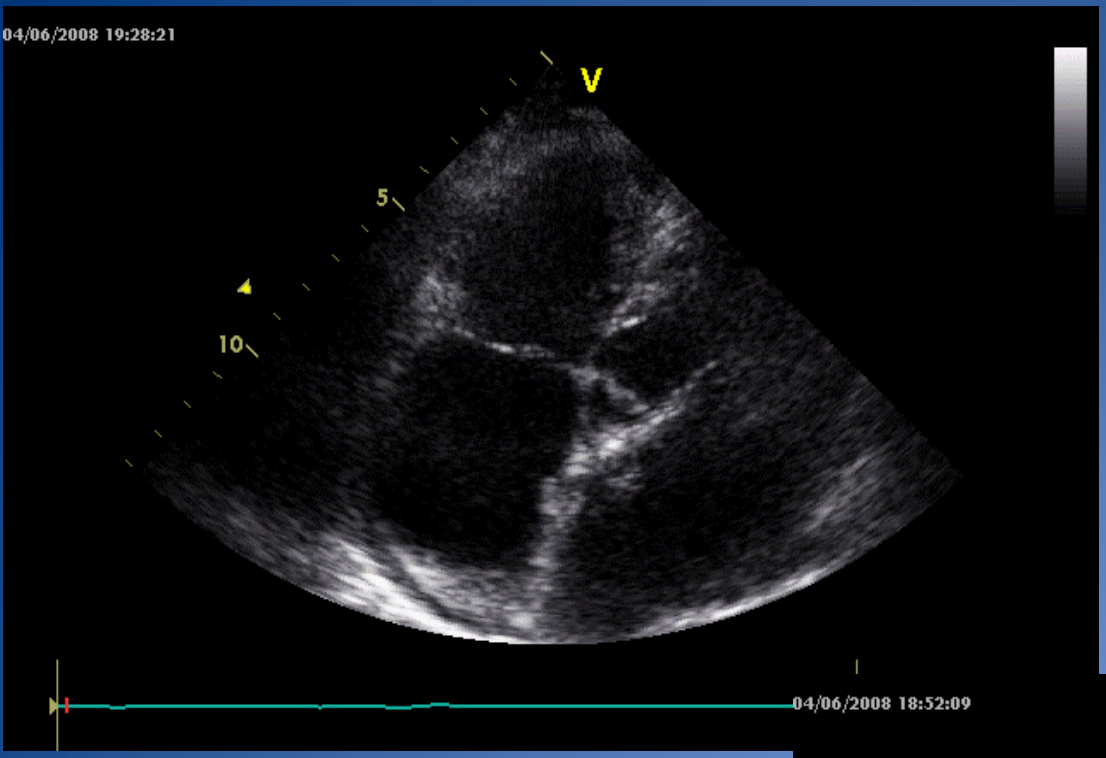
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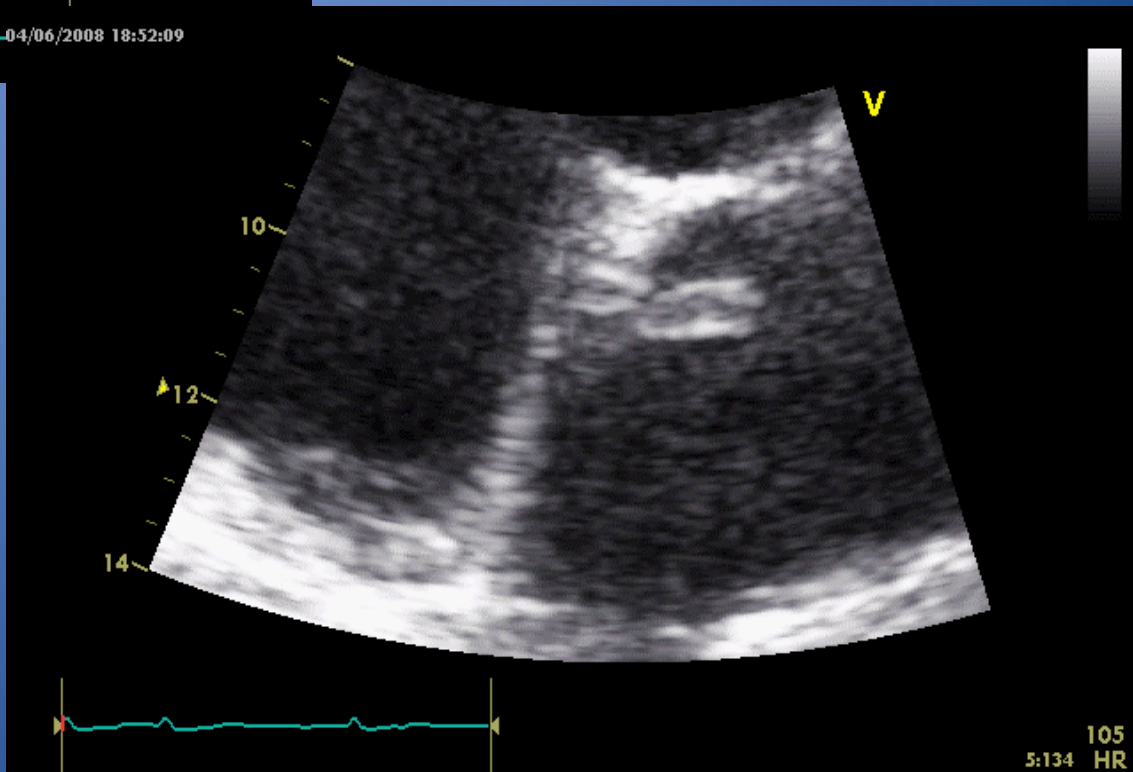
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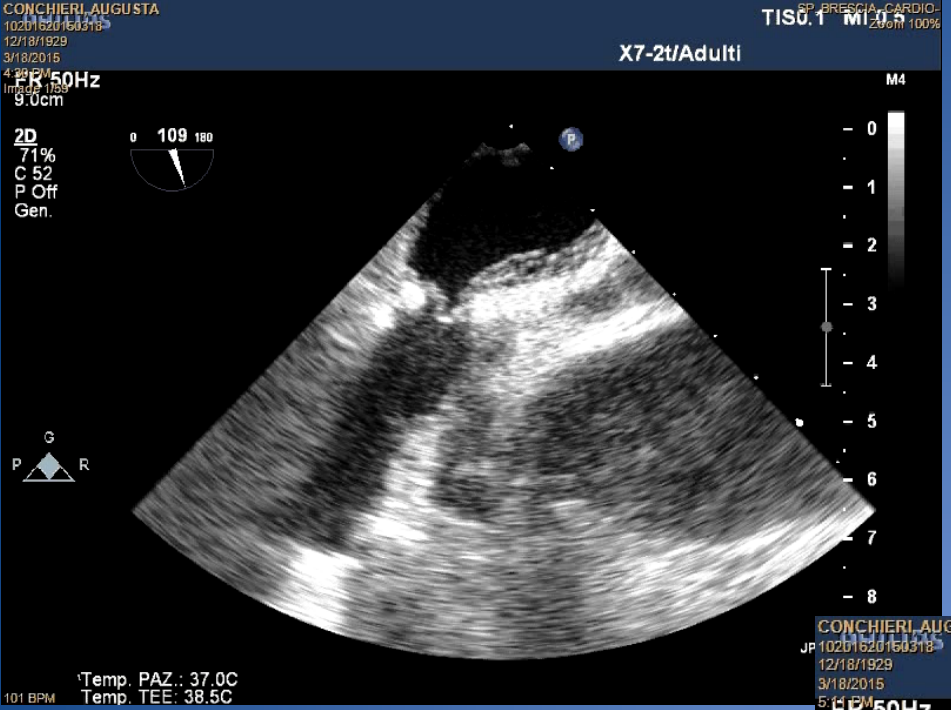
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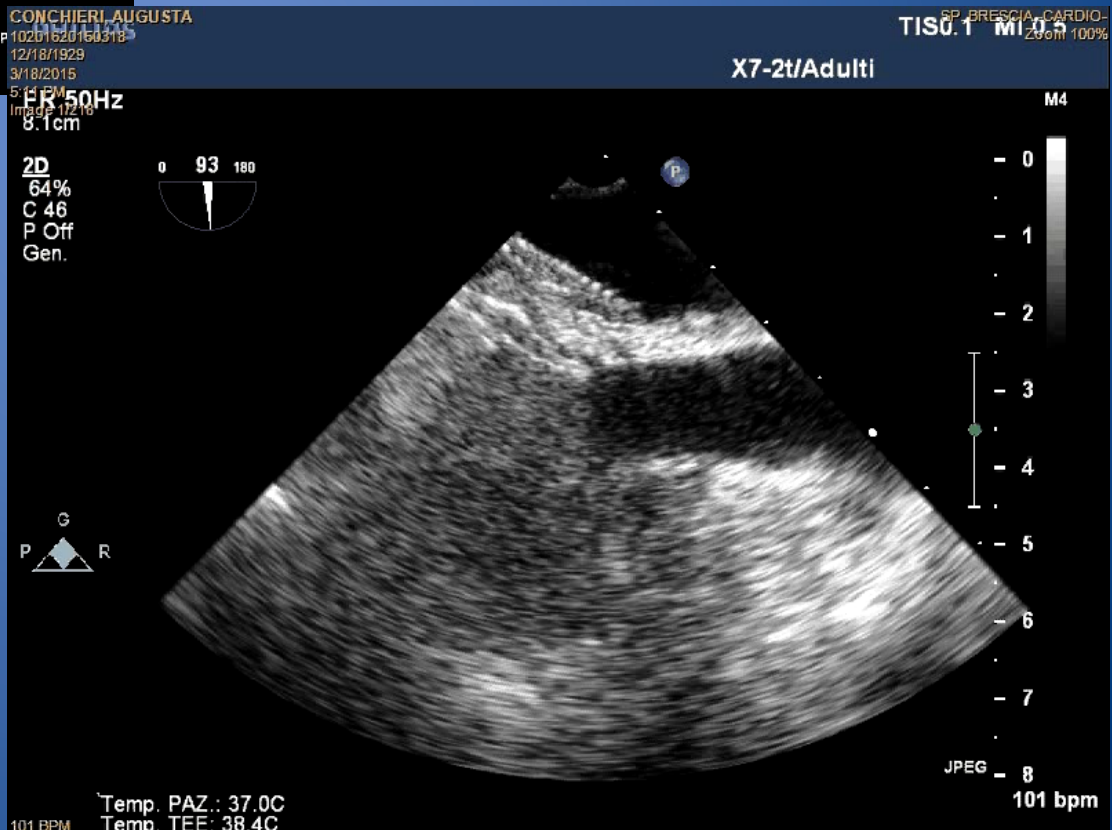
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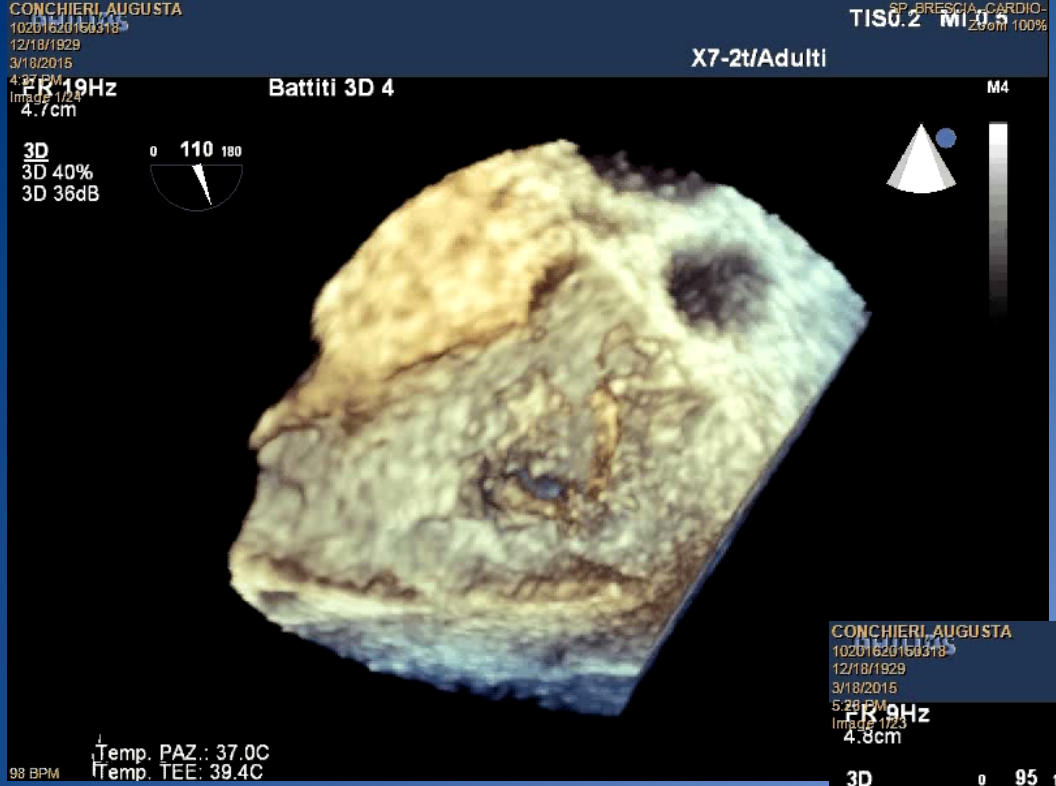
Temp. TEE: 38.4C
101 BPM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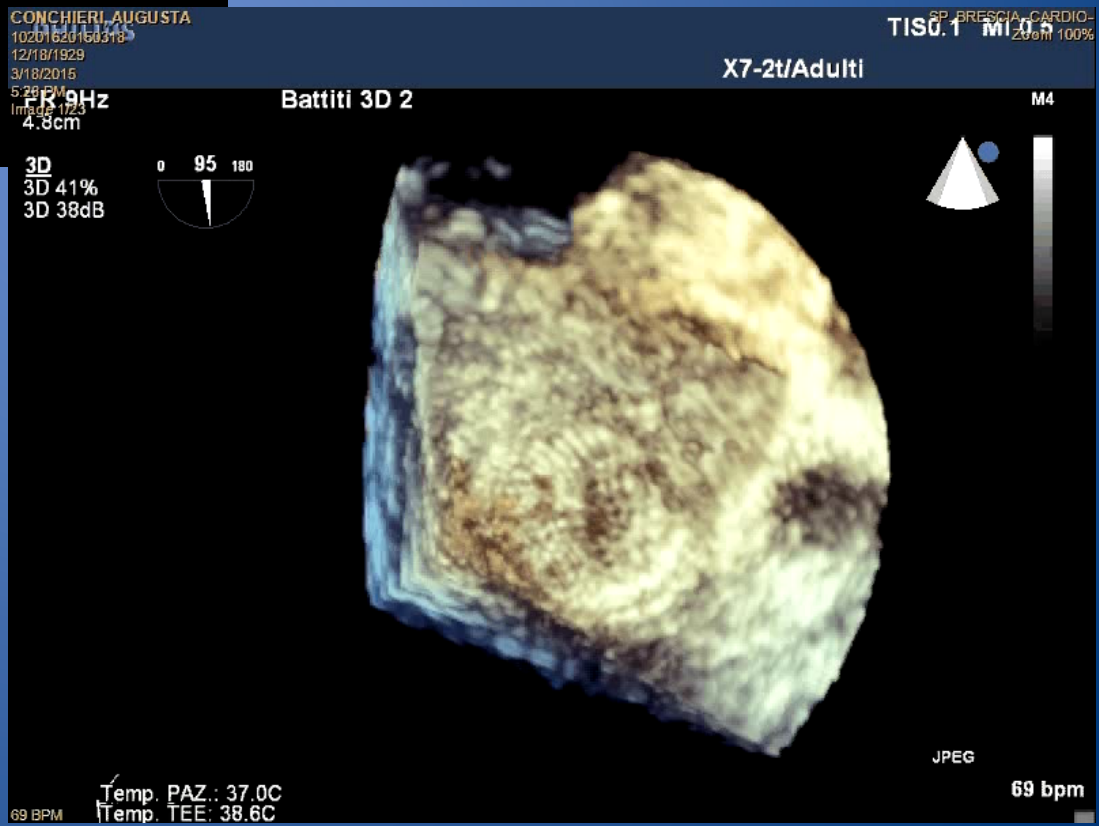
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Image 1/23
SP_BRESCIA_CARDIO-
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X7-2t/Adulti
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Battiti 3D 2
4.8cm
M4
3D
3D 41%
3D 38dB
0 95 180
JPEG
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Temp. TEE: 38.6C
69 BPM

Ma siamo proprio sicuri ?

PFO e stroke criptogenetico

Associazione statistica documentata

- **Studi caso-controllo:**

maggiore prevalenza PFO nei pz con stroke (40% vs 10-20%)

Lechat P et al. **N Engl J Med 1988; 318: 1148-52**

Webster MW et al. **Lancet 1988; 2:11-2**

Di Tullio M et al. **Ann Intern Med 1992;117:461-5**

Overell JR et al. Meta-analysis**. Neurology 2000;55:1172-9**

- **PICCS study (**studio prospettico**):**

maggiore prevalenza del PFO nello stroke criptogenetico vs stroke ad eziologia nota

Homma S et al. **Circulation 2002; 105:2625-31**

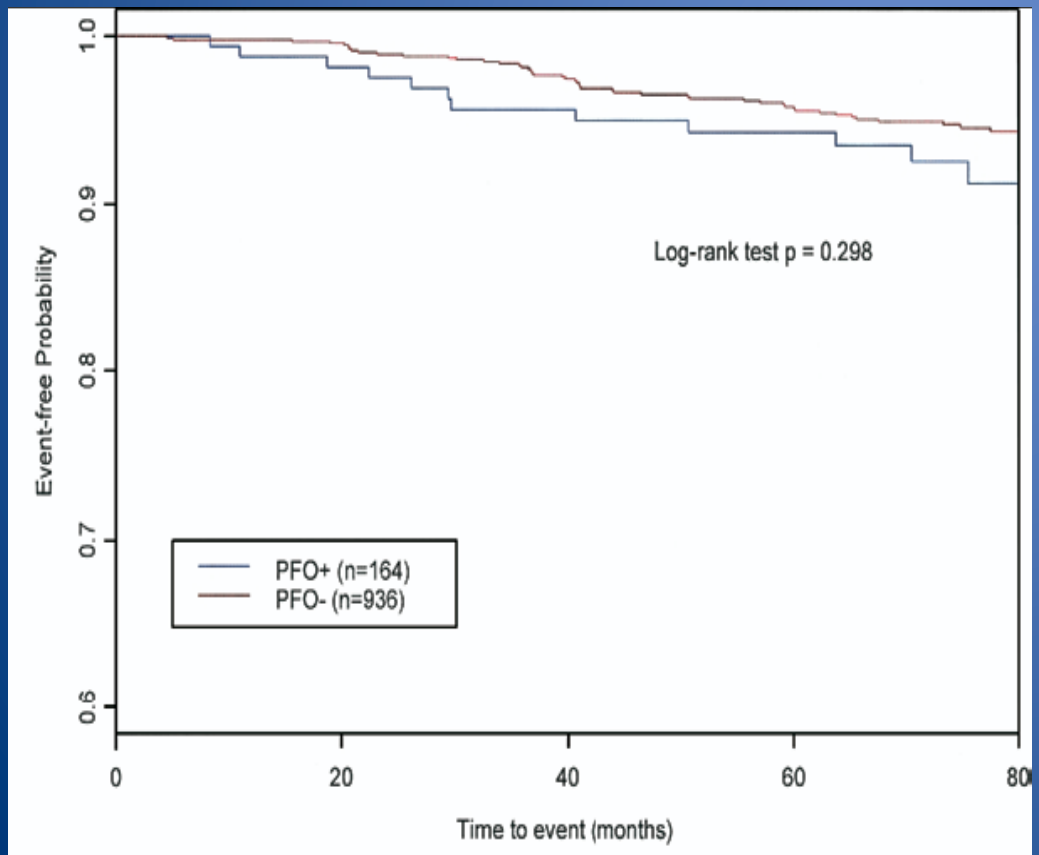
Patent Foramen Ovale and the Risk of Ischemic Stroke in a Multiethnic Population

Marco R. Di Tullio, MD,* Ralph L. Sacco, MD,†‡ Robert R. Sciacca, ENGSCD,* Zhezhen Jin, PHD,§ Shunichi Homma, MD, FACC*

New York, New York

J Am Coll Cardiol 2007;49:797–802

1100 soggetti (> 39 aa); Follow –up medio 79.7 mesi (range 43–135)
PFO in 164 (14.9%) ; ASA in 27 (2.5%); PFO + ASA in 19 (1.7%)



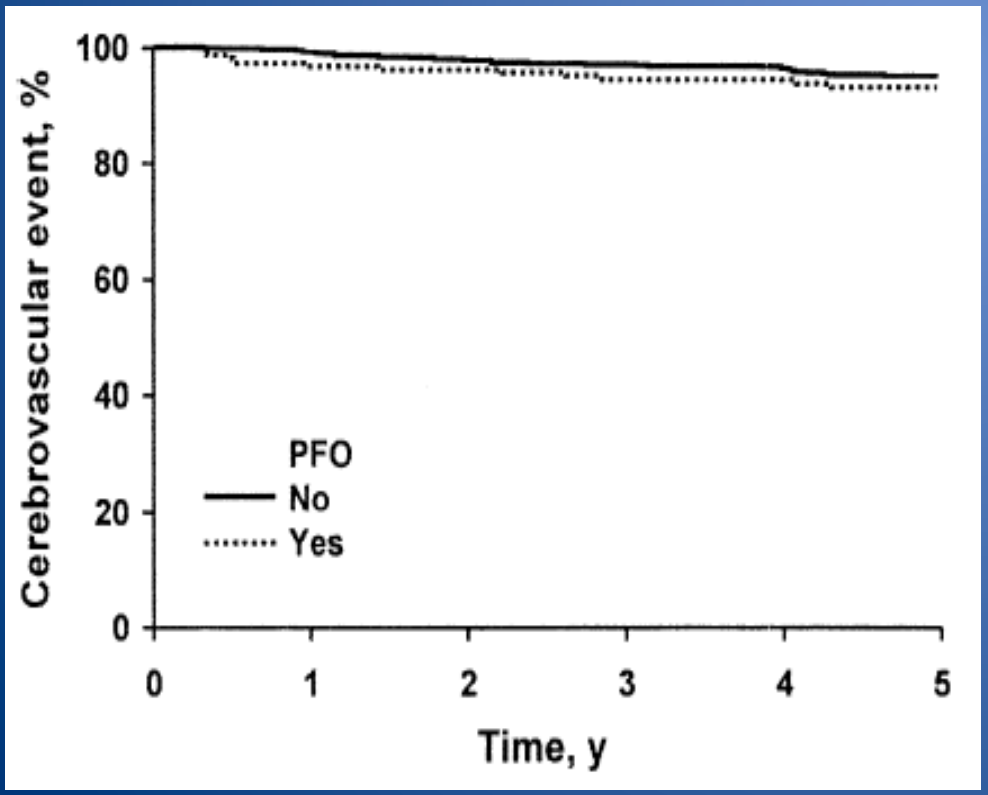
"Il PFO, da solo o associato ad ASA, non è associato ad un aumentato rischio di stroke nella popolazione generale"

Patent Foramen Ovale: Innocent or Guilty?

Evidence From a Prospective Population-Based Study

Irene Meissner, MD,*‖ Bijoy K. Khandheria, MD,† John A. Heit, MD,* George W. Petty, MD,* Sheldon G. Sheps, MD,‡ Gary L. Schwartz, MD,‡ Jack P. Whisnant, MD,§ David O. Wiebers, MD,*‖ Jody L. Covalt,¶ Tanya M. Petterson,‖ Teresa J. H. Christianson,‖ Yoram Agmon, MD*

585 soggetti (> 45 aa); PFO in 140 soggetti (24.3%); ASA in 11 (1.9%) .
Eventi cerebrovascolari in 41 soggetti durante un follow-up di 5 anni



PFO non è un predittore indipendente di stroke.

Il rischio di eventi cerebrovascolari nei soggetti con ASA (2/41 eventi) è stato 4 vv > che in quelli senza ASA

J Am Coll Cardiol 2006; 47: 440 –5

EDITORIAL COMMENT

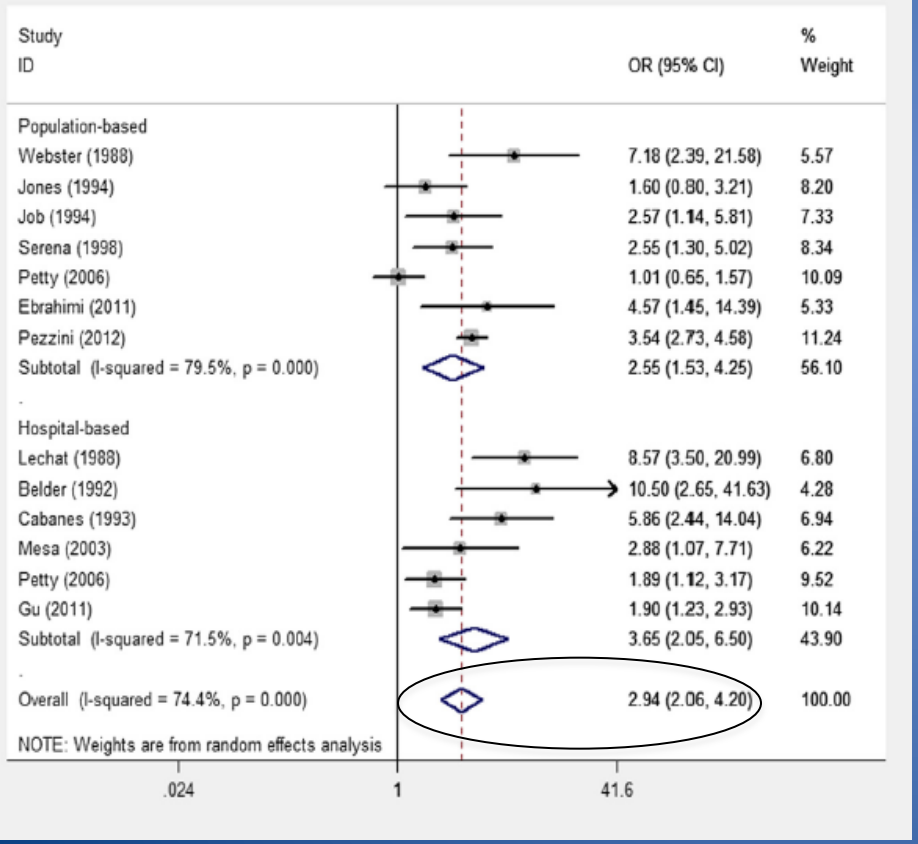
Patent Foramen Ovale, Guilty But Only as a Gang Member and for a Lesser Crime*

Bernhard Meier, MD, FACC, FESC

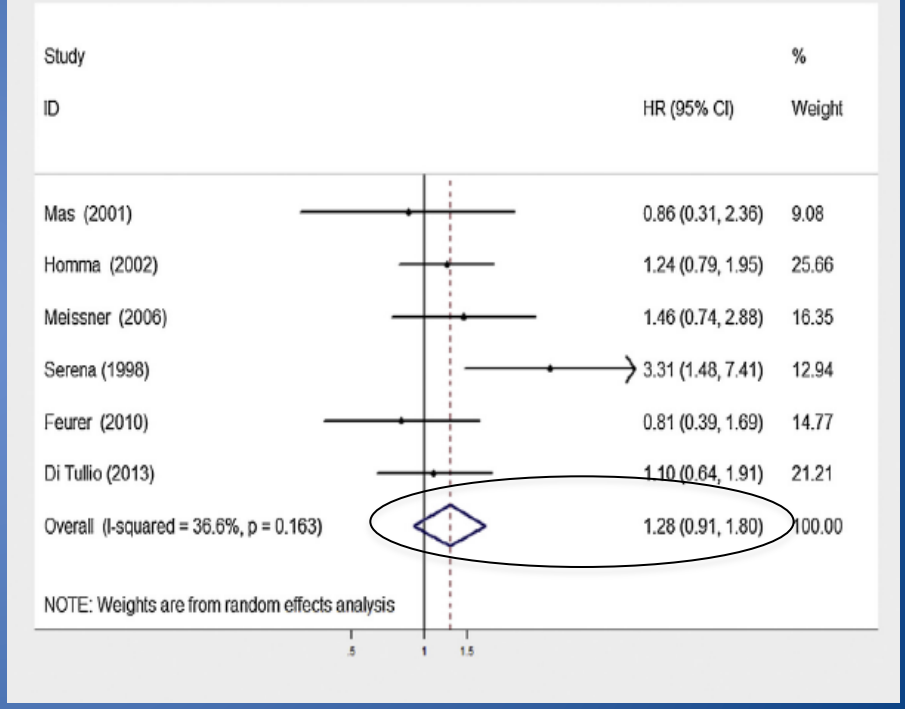
Risk of Stroke in Patients with Patent Foramen Ovale: An Updated Meta-analysis of Observational Studies

Journal of Stroke and Cerebrovascular Diseases, Vol. 23, No. 5 (May-June), 2014

Case-control series



Cohort studies



"Further data are needed to confirm the effect of PFO on Stroke"

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

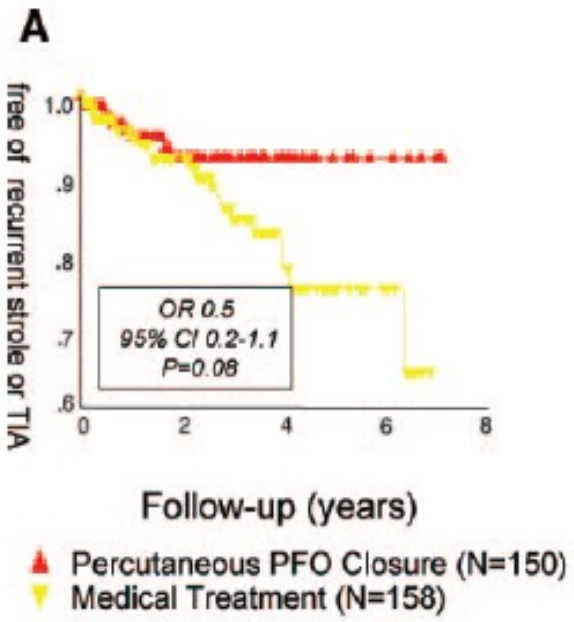
Is closure recommended for patent foramen ovale and cryptogenic stroke?

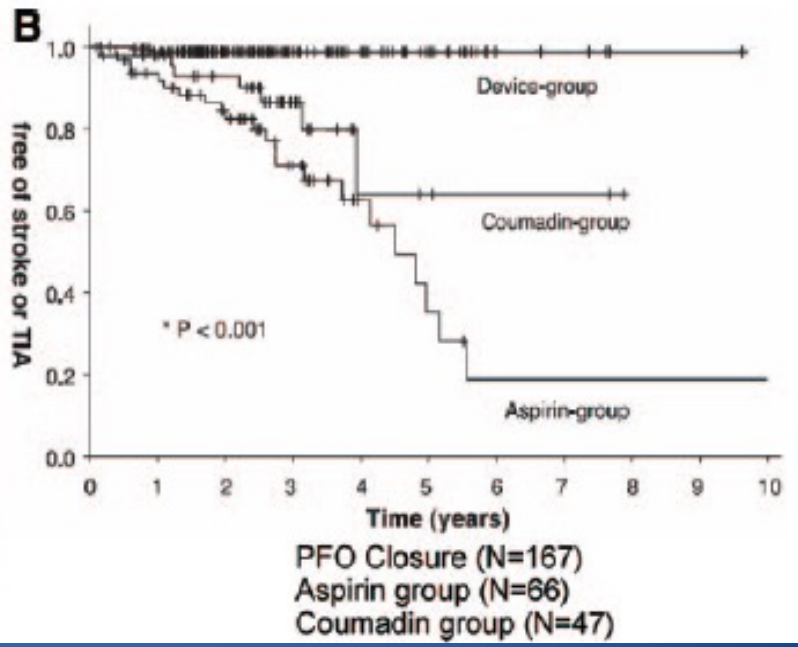
Patent Foramen Ovale and Cryptogenic Stroke: To Close or Not to Close?

Closure: What Else!

Stephan Windecker, MD; Bernhard Meier, MD

Follow-up medio 4 anni





Circulation 2008

Patent Foramen Ovale May Be Causal for the First Stroke but Unrelated to Subsequent Ischemic Events

- 308 pz con PFO e stroke criptogenetico, età media 50 anni:
  - 158 pz in tp medica (48% ASA, 2% Clopidogrel, 50% TAO)
  - 150 pz con chiusura PFO

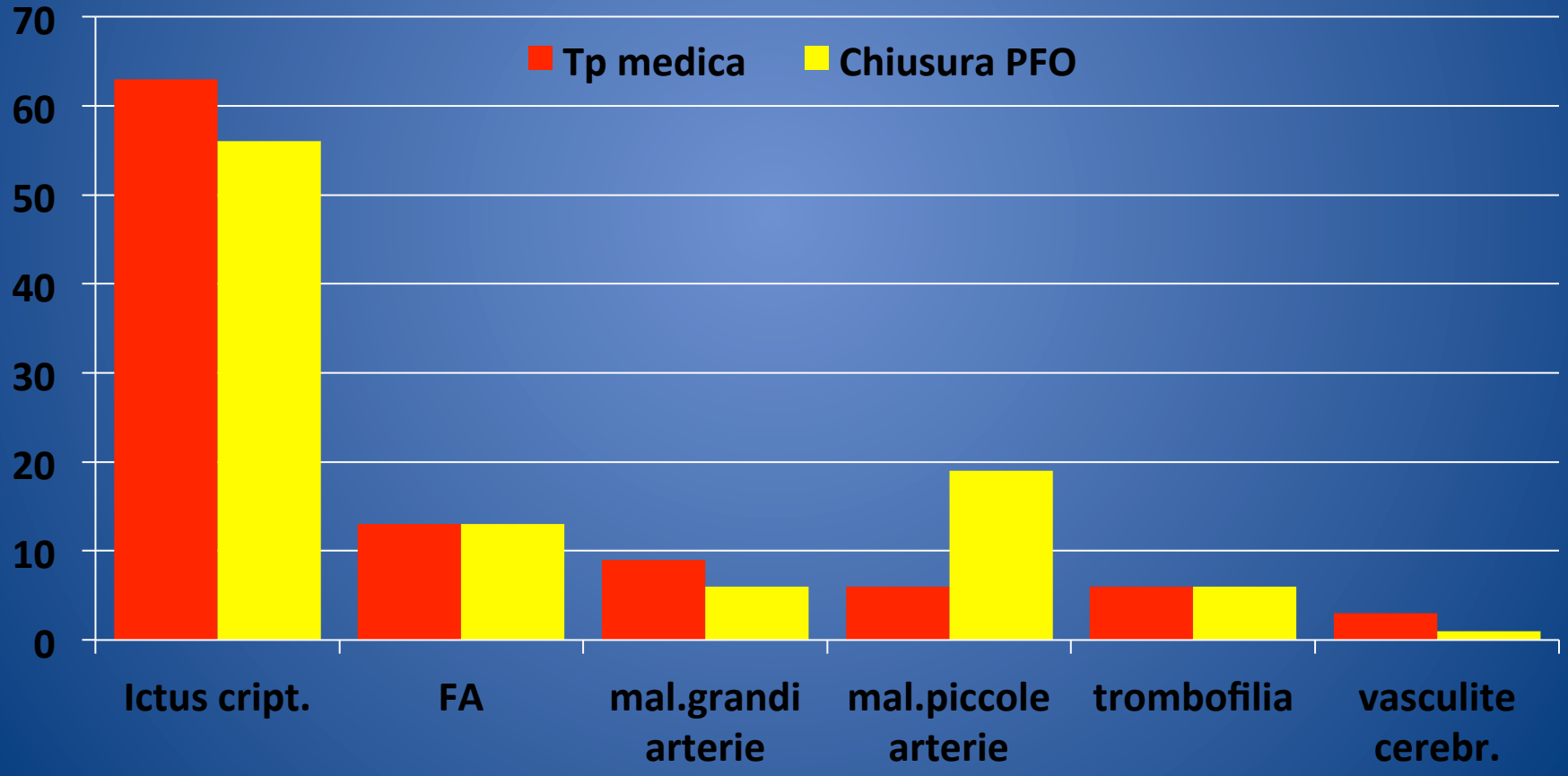
- **Follow-up: 8.7 ± 4 anni**

- Eventi ischemici cerebrali nel follow-up:
  - 32 nel gruppo in tp medica (13 ictus ; 19 TIA)
  - 16 nel gruppo sottoposto a chiusura PFO (8 ictus; 8 TIA)

(*Stroke*. 2011;42:00-00.)

Eventi cerebrovascolari nel follow-up: Eziologia

Una causa più probabile del PFO è stata individuata nel 38% (almeno) e nel 44% dei casi, rispettivamente nel gruppo in terapia medica e nel gruppo sottoposto a chiusura del PFO



(*Stroke*. 2011;42:00-00.)

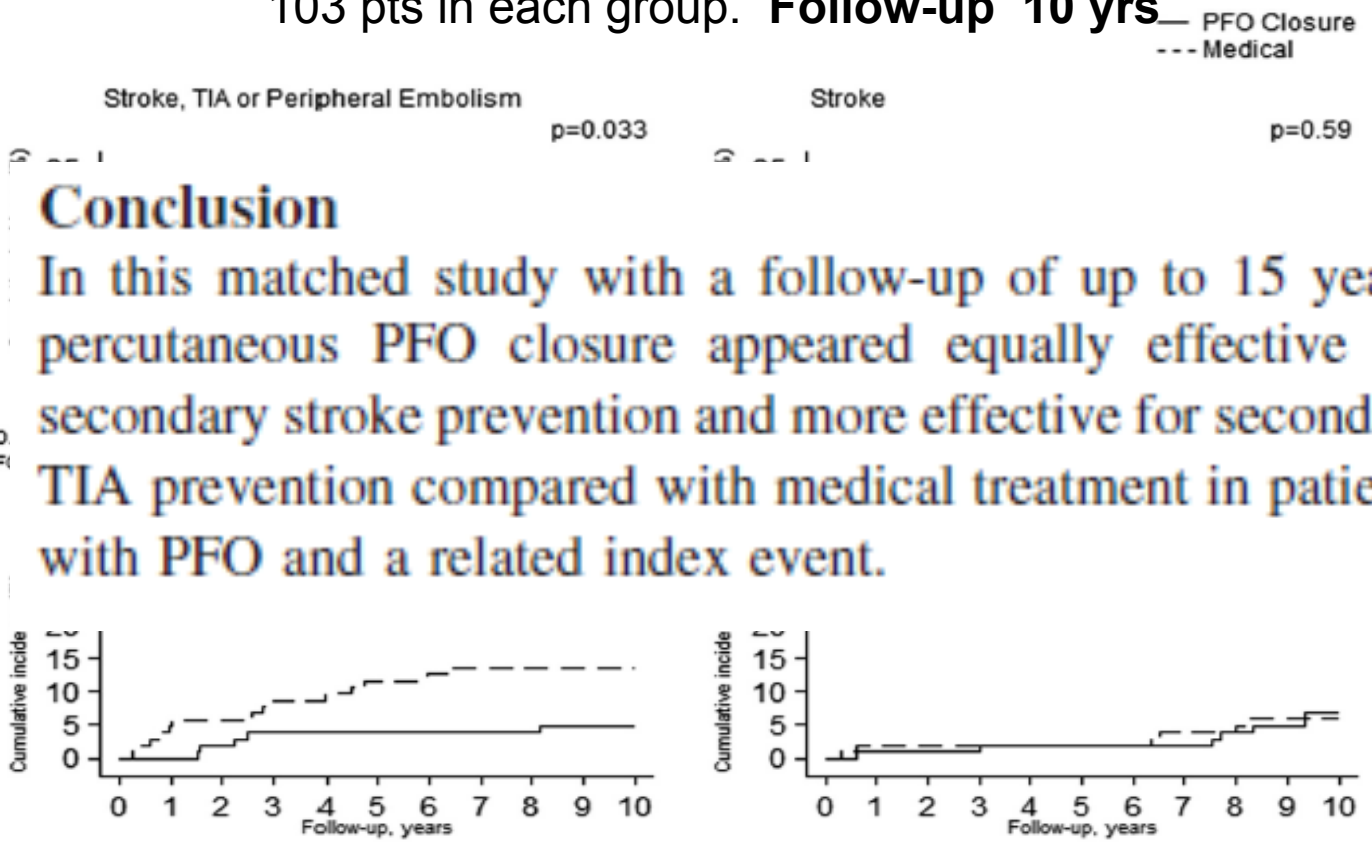
Conclusions

"Concurrent etiologies are identified for more than one third of recurrent ischemic events in patients with cryptogenic stroke, casting ***doubt on the sole causal role of PFO*** *in the case of stroke recurrence and indicating that* ***secondary prevention*** *in patients with cryptogenic stroke and PFO* ***should not be focused on PFO closure alone****"*

(*Stroke*. 2011;42:00-00.)

Long-Term Propensity Score–Matched Comparison of Percutaneous Closure of Patent Foramen Ovale With Medical Treatment After Paradoxical Embolism

103 pts in each group. **Follow-up 10 yrs**



Conclusion

In this matched study with a follow-up of up to 15 years, percutaneous PFO closure appeared equally effective for secondary stroke prevention and more effective for secondary TIA prevention compared with medical treatment in patients with PFO and a related index event.

Meier, Circulation 2013

Patent Foramen Ovale in Cryptogenic Stroke
Incidental or Pathogenic?

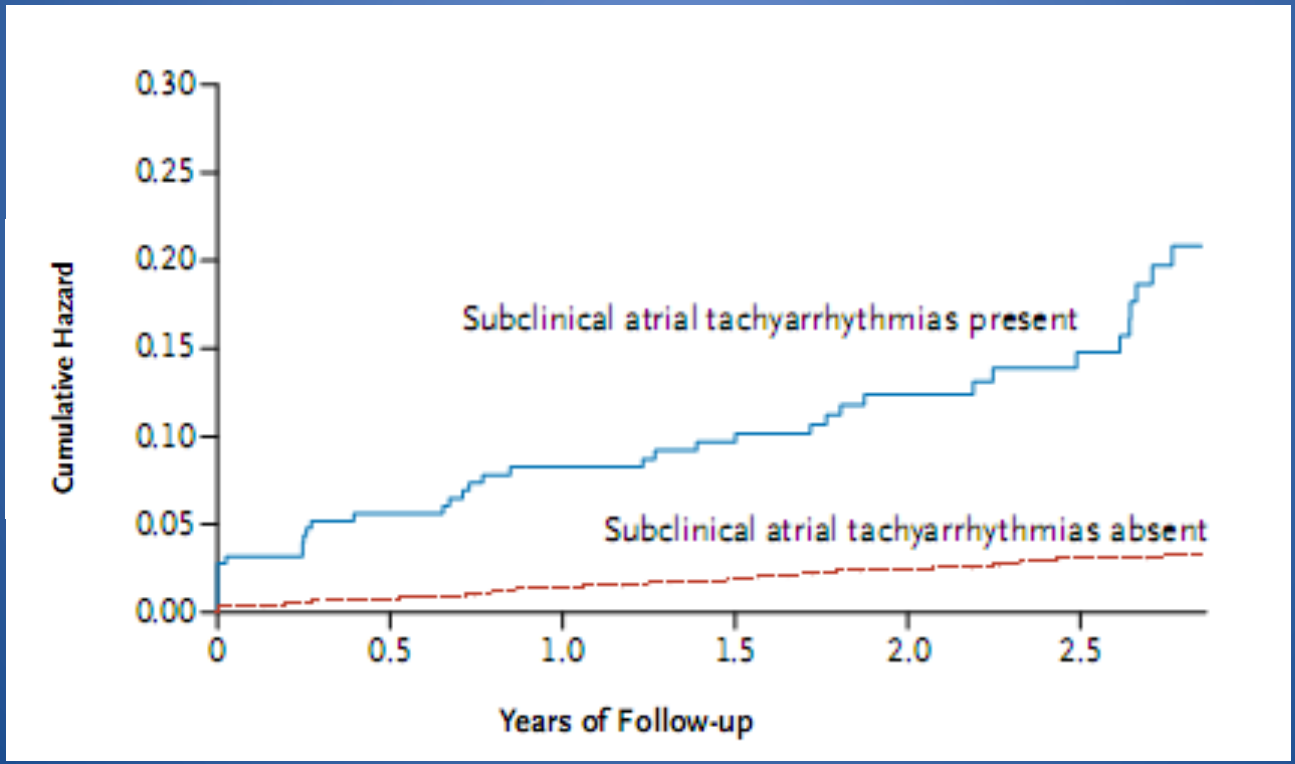
A.A. Alsheikh-Ali, D.E. Thaler and D.M. Kent. *Stroke 2009, 40:2349-2355*

"In patients with otherwise CS, approximately one third of discovered PFOs are likely to be incidental and hence not benefit from closure."

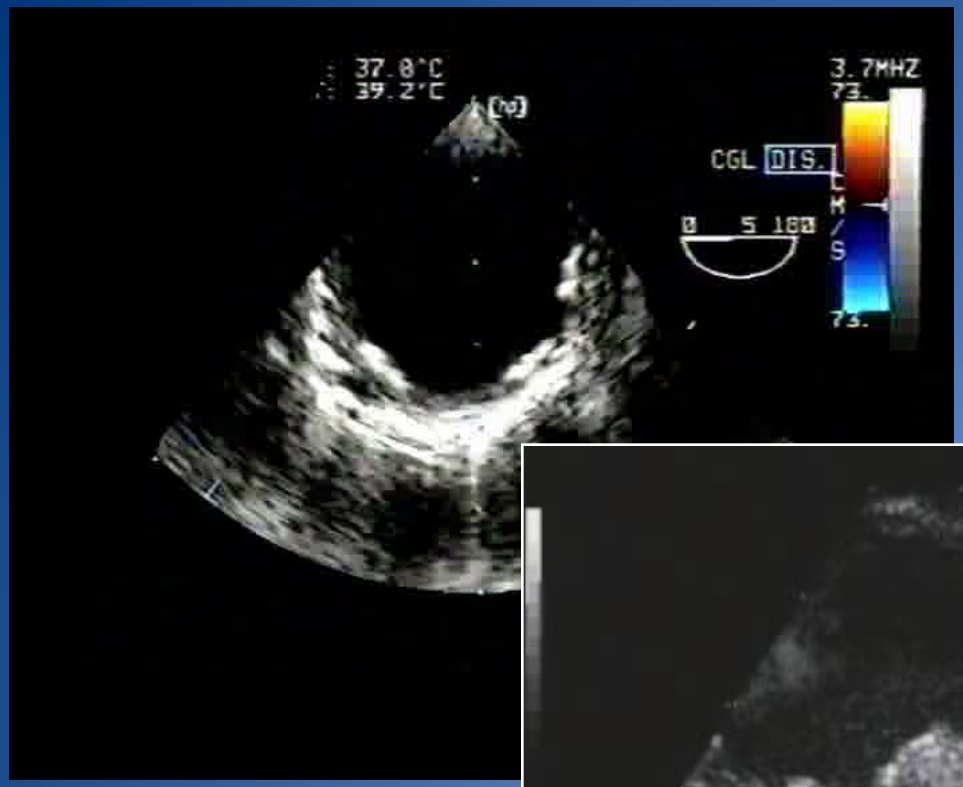
Subclinical Atrial Fibrillation and the Risk of Stroke

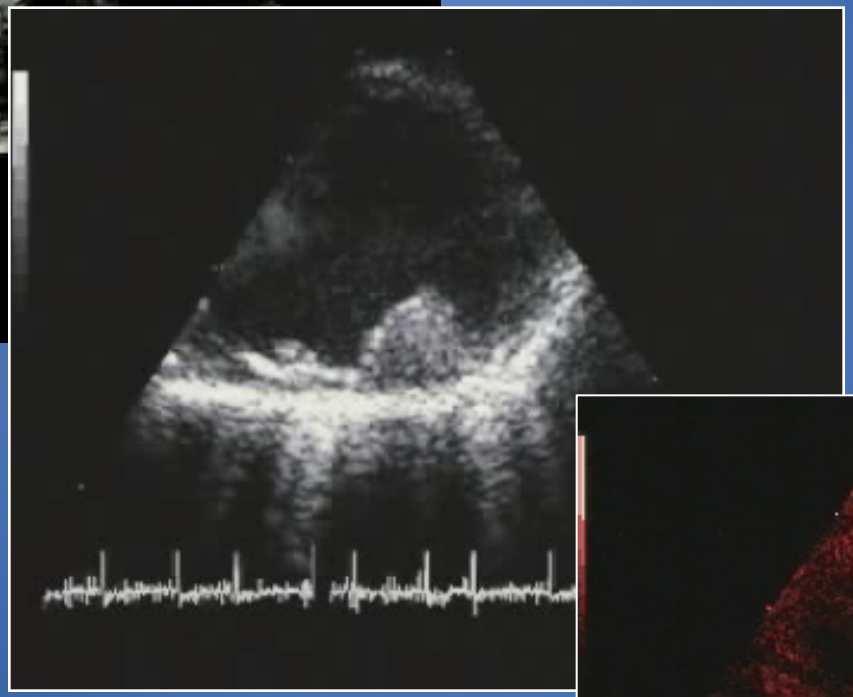
JS Healey, S J. Connolly et al N Engl J Med 2012

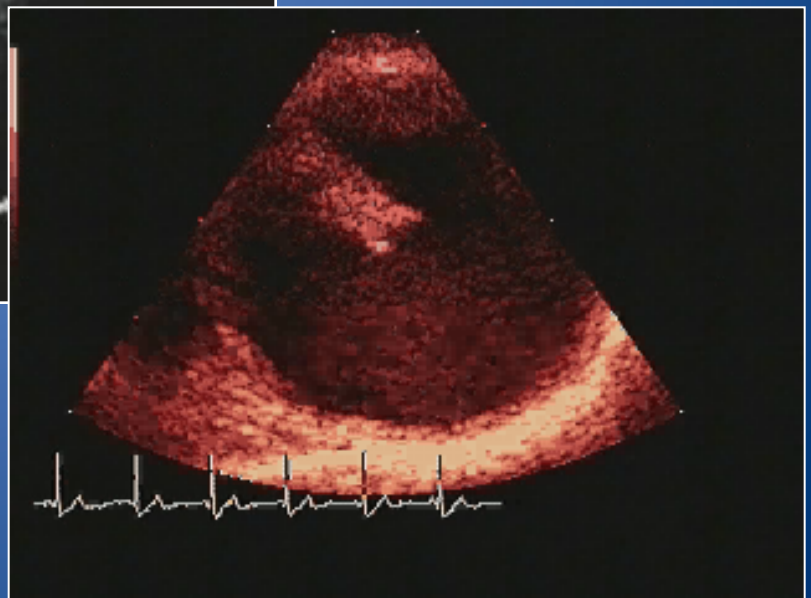
2451 patients with a newly implanted pacemaker
followed for a mean of 2.5 years (subclinical atrial tachyarrhythmias > 6 min)



Ateromasia Aortica







Contents lists available at ScienceDirect

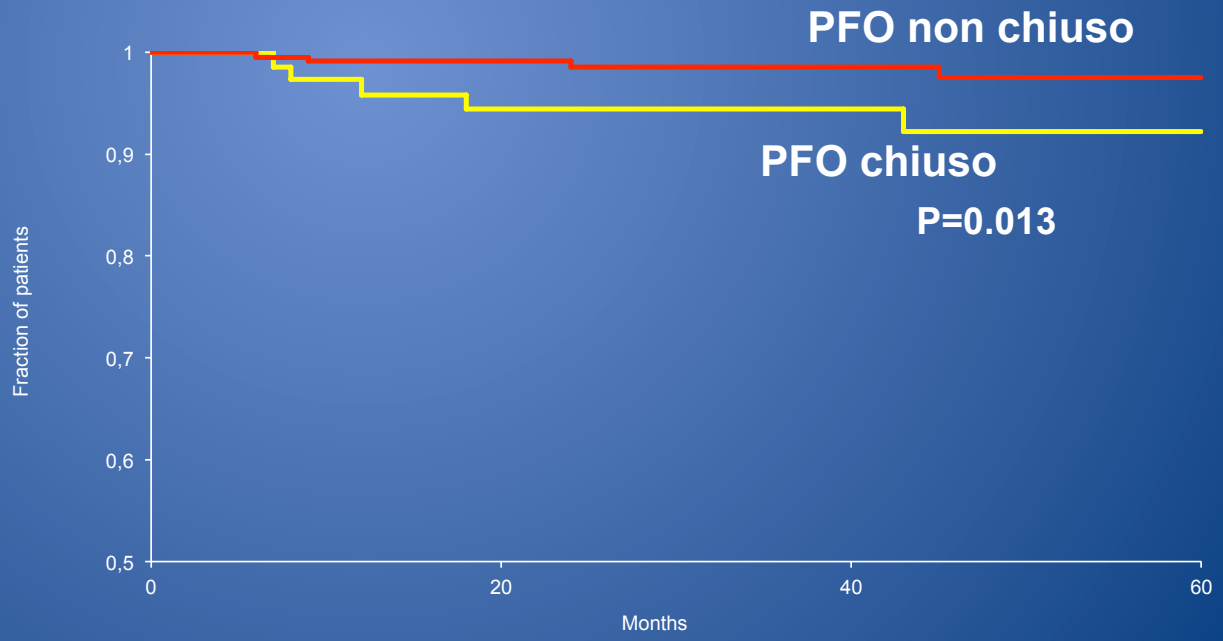
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Low cerebrovascular event rate in subjects with patent foramen ovale and different clinical presentations
Results from a prospective non randomized study on a population including patients with and without patent foramen ovale closure

Pompilio Faggiano [a,*,1], Silvia Frattini [a,1], Piergiuseppe Piovesana [b], Roberto Lorusso [c], Ermanna Chiari [a], Francesco Scolari [d], Alessandro Padovani [e], Livio Dei Cas [a]

Incidenza di nuovi eventi (stroke/TIA) pari al 2.7% in più di 4 anni → incidenza annuale di stroke e TIA pari a 0.2% e 0.4% rispettivamente.



PFO chiuso	99	95	95	94
PFO non chiuso	347	345	344	343

PFO and cryptogenic stroke: the guidelines

American Heart Association/ American Stroke Association

1. For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable (Class IIa; Level of Evidence B).

2. There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (Class IIb; Level of Evidence B).

3. There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO (Class IIb; Level of Evidence C)

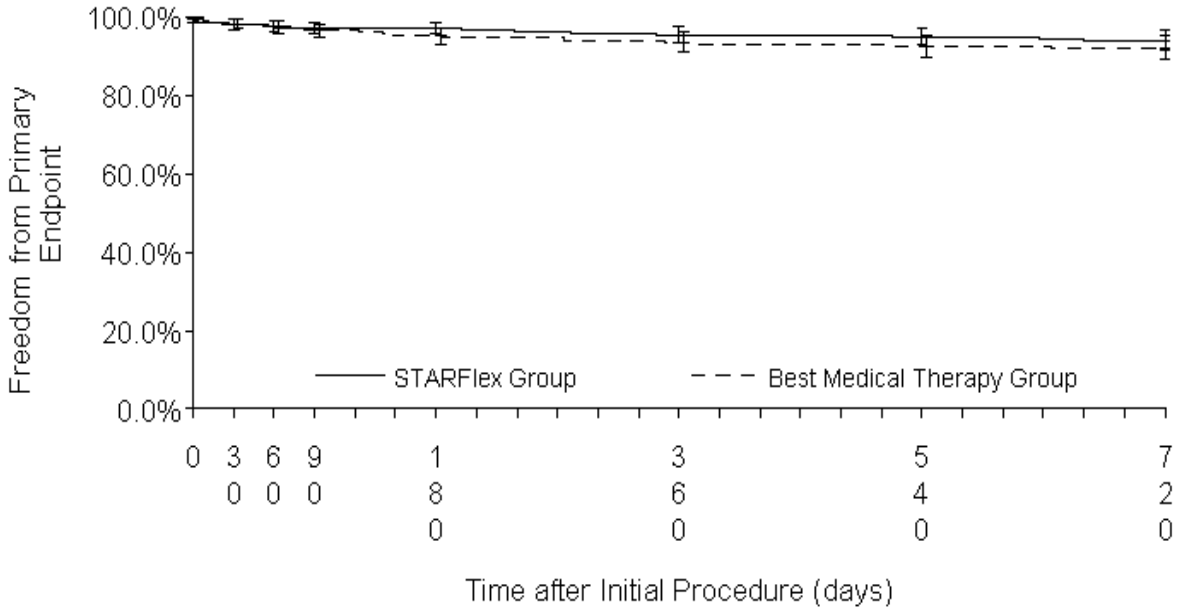
Furie KL (2011) Stroke 42:227-276

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

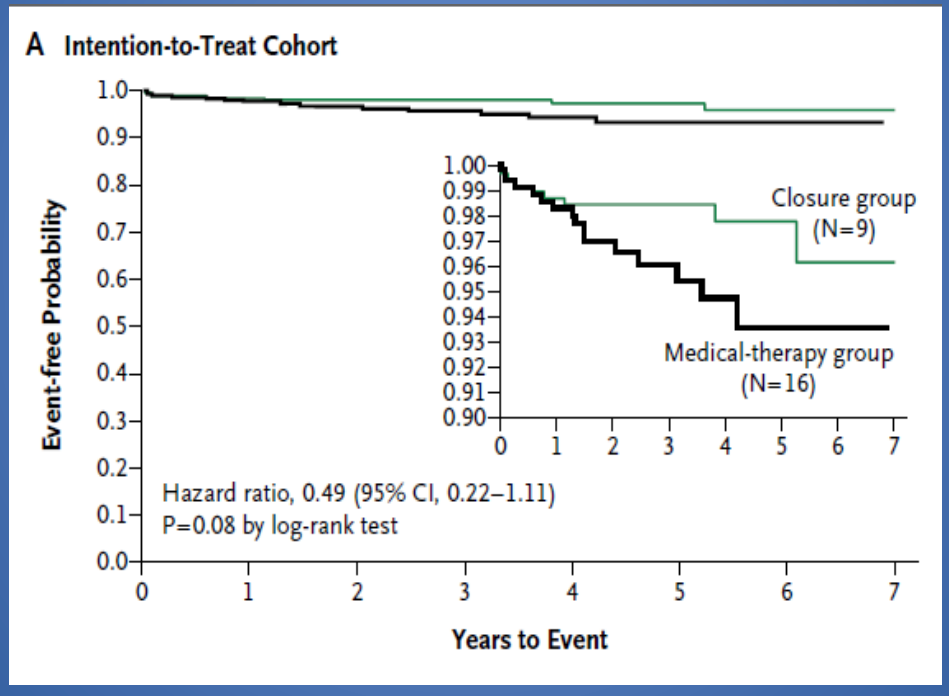
Anthony J. Furlan, M.D., Mark Reisman, M.D., Joseph Massaro, Ph.D., Laura Mauri, M.D., Harold Adams, M.D., Gregory W. Albers, M.D., Robert Felberg, M.D., Howard Herrmann, M.D., Saibal Kar, M.D., Michael Landzberg, M.D., Albert Raizner, M.D., and Lawrence Wechsler, M.D., for the CLOSURE I Investigators*



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

Respect Trial

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke



CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 21, 2013 VOL. 368 NO. 12

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

100 (%)

8

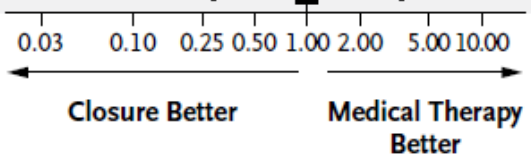
Subgroup | PFO Closure | Medical Therapy | Hazard Ratio (95% CI) | Interaction

no. of patients/total no. (%)

CONCLUSIONS

Closure of a patent foramen ovale for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT00166257.)

>1 Previous cardiovascular event				0.22
Yes	2/76 (2.6)	6/79 (7.6)	0.28 (0.06–1.41)	
No	5/128 (3.9)	5/131 (3.8)	0.99 (0.29–3.45)	



CLOSURE I trial limitations

1. Sluggish recruitment

2. Off-label occlusion

3. Inclusion of TIA causing heterogeneity of patient population

4. Device associated with higher rate of periprocedural complication (in particular AF) than that of current devices

PFO and cryptogenic stroke: Reactions post RCTs

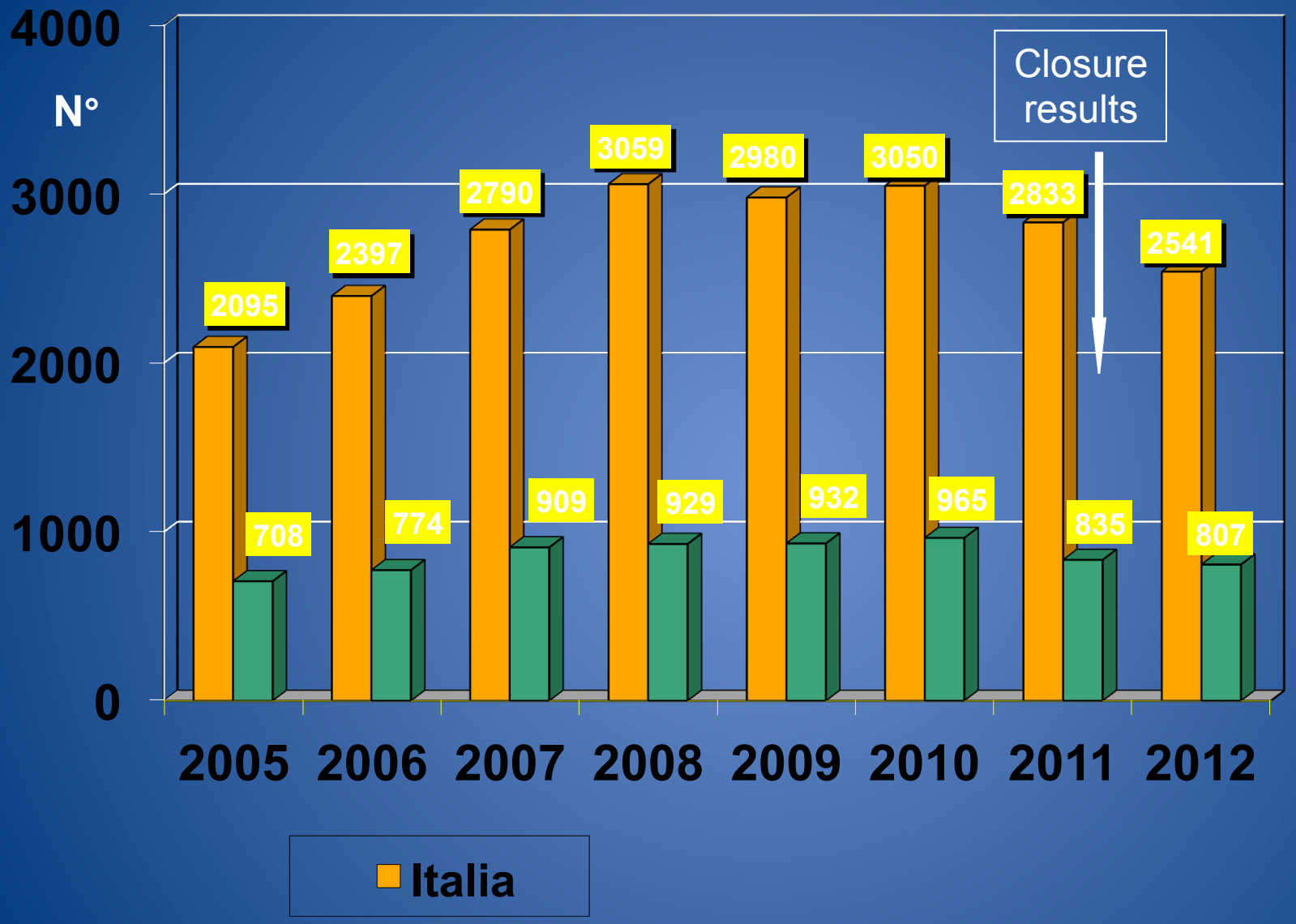
Patent foramen ovale closure--closing the door except for trials.
Johnson SC (2012) NEJM 366 (11):1048-50

Still no closure on the question of PFO closure.
Messe SR (2013) NEJM 368 (12):1152-3

Closure of the Patent Foramen Ovale. Because we can, should We? And in Whom?
Piana RN (2013) JACC Intv 6(11):1184-1185

PFO Closure: Trying the Trials.
Butman S. (2013) Catheter Cardiovasc Interv. 82(6):976.

Dati GISE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2095
708
2397
774
2790
909
3059
929
2980
932
3050
965
2833
835
2541
807
Closure results
2005
2006
2007
2008
2009
2010
2011
2012
Italia

PFO and cryptogenic stroke: the guidelines

- SICI-GISE/ ISA-AIS/ SNO/ANMCO/SICP/ SIEC, SISET.

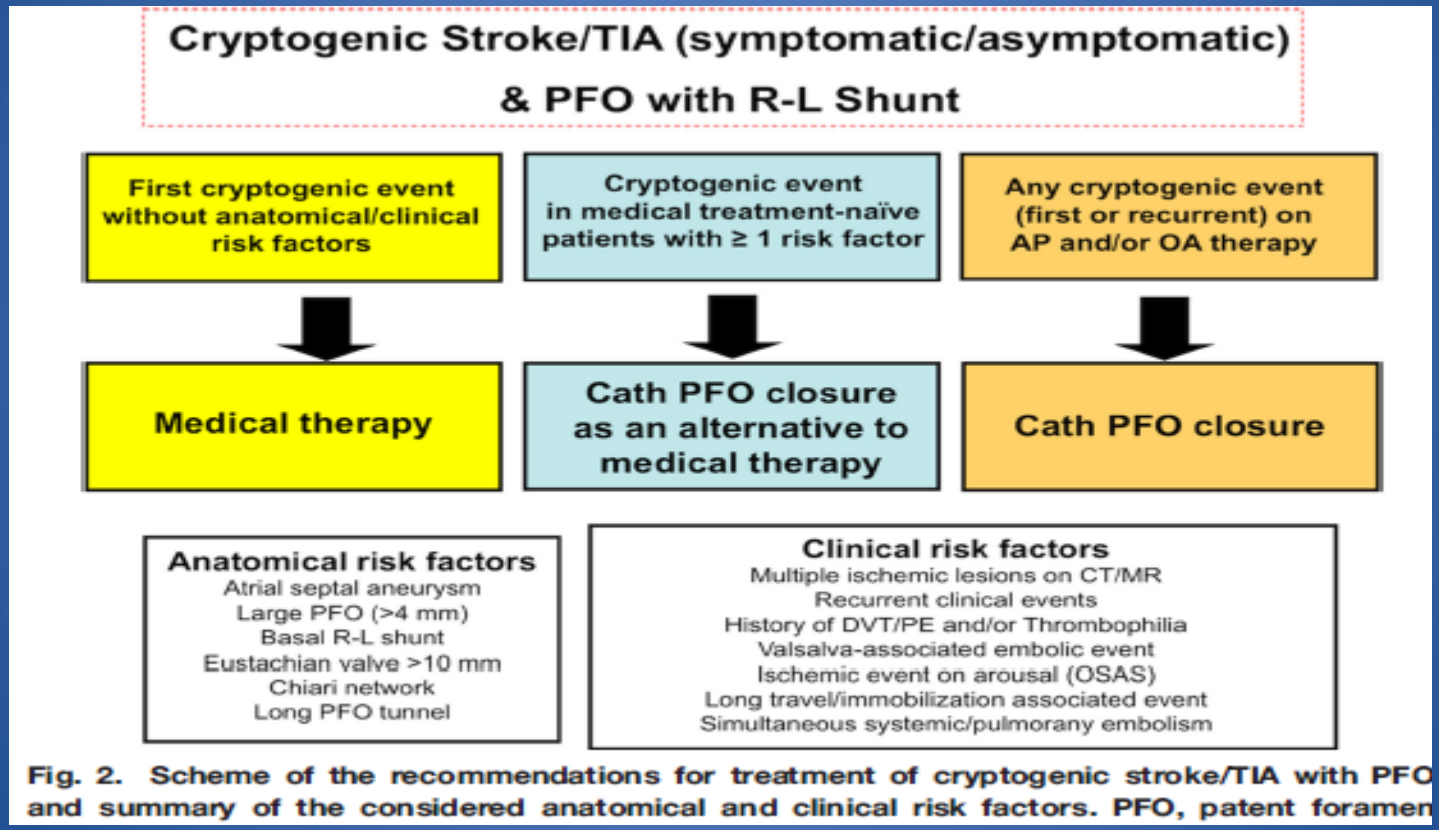


Fig. 2. Scheme of the recommendations for treatment of cryptogenic stroke/TIA with PFO and summary of the considered anatomical and clinical risk factors. PFO, patent foramen

Published after CLOSURE I, but prior to RESPECT and PC pubblication

Pristipino C et al. (2013) Catheter Cardiovasc Interv. 82(1):E38-51

Transesophageal Echocardiography in Cryptogenic Stroke and PFO: The Analysis of Putative High Risk Features from the Risk of Paradoxical Embolism (RoPE) Database

Circ Cardiovasc Imaging. 2014 January 1; 7(1): 125–131

Methods and Results—We used a recently derived score based on clinical and neuroimaging features to stratify patients with PFO and CS by the probability that their stroke is PFO-attributable. We examined whether high risk TEE features are seen more frequently in patients more likely to have had a PFO-attributable stroke (n = 637) compared to those less likely to have a PFO attributable stroke (n = 657). Large physiologic shunt size was not more frequently seen among those with probable PFO-attributable strokes (OR=0.92; p = 0.53). Neither the presence of a hypermobile septum nor a right-to-left shunt at rest were detected more often in those with a probable

Conclusions—We found no evidence that the proposed TEE risk markers of large PFO size, hypermobile septum, and presence of right-to-left shunt at rest are associated with clinical features suggesting that a CS is PFO-attributable. Additional tools to describe PFOs may be useful in helping to determine whether an observed PFO is incidental or pathogenically related to CS.

PFO and cryptogenic stroke: Meta-analysis 2013-2014 (may)

Against PFO closure

- Henderson RA el (2013) BMJ 347: f6193
- Kwong JSW et al (2013) Int J Cardiol 168:4132-38
- Zhang B et al (2013) Int J Cardiol 169:e106-e108
- Chen L et al. (2013) J Neurol Science ePub
- Hakeem A et al (2013) Cardiovasc Revasc Med14(6):349-55.
- Wolfrum M et al (2013) Heart ePub
- Calvet D et al (2014) Curr Opin Neurol 27:13-19
- Spencer FA et al (2014) BMJ

In favour of PFO closure

- Pineda AM et al (2013) Catheter Cardiovasc Interv. 82(6):968-75
- Moreno-Rengifo P et al. (2013) Eur Heart J 34:3342-3352
- Ntaios G et al (2013) Int J Cardiol 169:101-105
- Riaz IB et al. (2013) BMC cardiovasc disorders 13:116
- Capodanno D et al. (2013) EuroIntervention. ePub
- Pena JM et al (2013) Curr Atheroscler Rep 15:338
- Khan AR et Al. (2013) JACC Intv

The tsunami of meta-analyses of patent foramen ovale closure for secondary prevention of cryptogenic stroke

Michael Tzu Min Wang[1]*; Tom Kai Ming Wang[2], MBCHB

Despite pooling identical cohorts of patients (total n=2,303) from trials with similar conclusions, there was a diverse range of results, interpretations and conclusions across these 13 meta-analyses.

……there was no consensus in the interpretation of these findings. Nine studies said that there was no benefit for PFO closure, although five mentioned potential signals of benefit either in certain subgroups or with borderline non-significant p-values. The other four studies concluded that PFO closure is potentially beneficial

Further trials such as CLOSE, Gore-REDUCE and DEFENSE-PFO are nearing completion, but it remains to be seen whether they will help answer the question, or if the controversy will be further clouded by another flurry of meta-analyses.

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke.

Kent DM al. Neurology 2013;81:619 – 625

Table 2. Patent foramen ovale prevalence, attributable fraction, and estimated 2-year risk of stroke/TIA by Risk of Paradoxical Embolism point score strata (using control rate of 25% in general population)

	Cryptogenic stroke ($n = 3023$)			CS with PFO ($n = 1324$)
RoPE Score	Number of patients	Prevalence of patients with a PFO (95% CI)	PFO-attributable fraction (95% CI)	Estimated 2-y stroke/TIA recurrence rate (95% CI)
0–3	613	23% (19–26)	0% (0–4)	20% (12–28)
4	511	35% (31–39)	38% (25–48)	12% (6–18)
5	516	34% (30–38)	34% (21–45)	7% (3–11)
6	482	47% (42–51)	62% (54–68)	8% (4–12)
7	434	54% (49–59)	72% (66–76)	6% (2–10)
8	287	67% (62–73)	84% (79–87)	6% (2–10)
9	180	73% (66–79)	88% (83–91)	2% (0–4)
Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)				0

Editorial

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Is patent foramen ovale closure an option in patients with cryptogenic stroke? An Italian multicentre registry proposal

Pompilio Faggiano[a], Danilo Toni[b], Stefano Strano[c] and Fulvia Seccareccia[d]

J Cardiovascular Medicine 2014

MEETING DI AGGIORNAMENTO SCIENTIFICO
LA RETE DELLE NEUROCARDIOLOGIE ITALIANE PER LA PREVENZIONE SECONDARIA DELL'ICTUS CARDIOEMBOLICO
ROMA, 31 Gennaio 2015
Circolo Ufficiali dell'Aeronautica Militare "Casa dell'Aviatore"

Lo Studio OPTION

Studio Osservazionale per la valutazione comParaTiva di effIcacia della chiusura endovascolare del fOrame ovale pervio vs il trattamento medico, in pazienti con stroke criptogeNetico

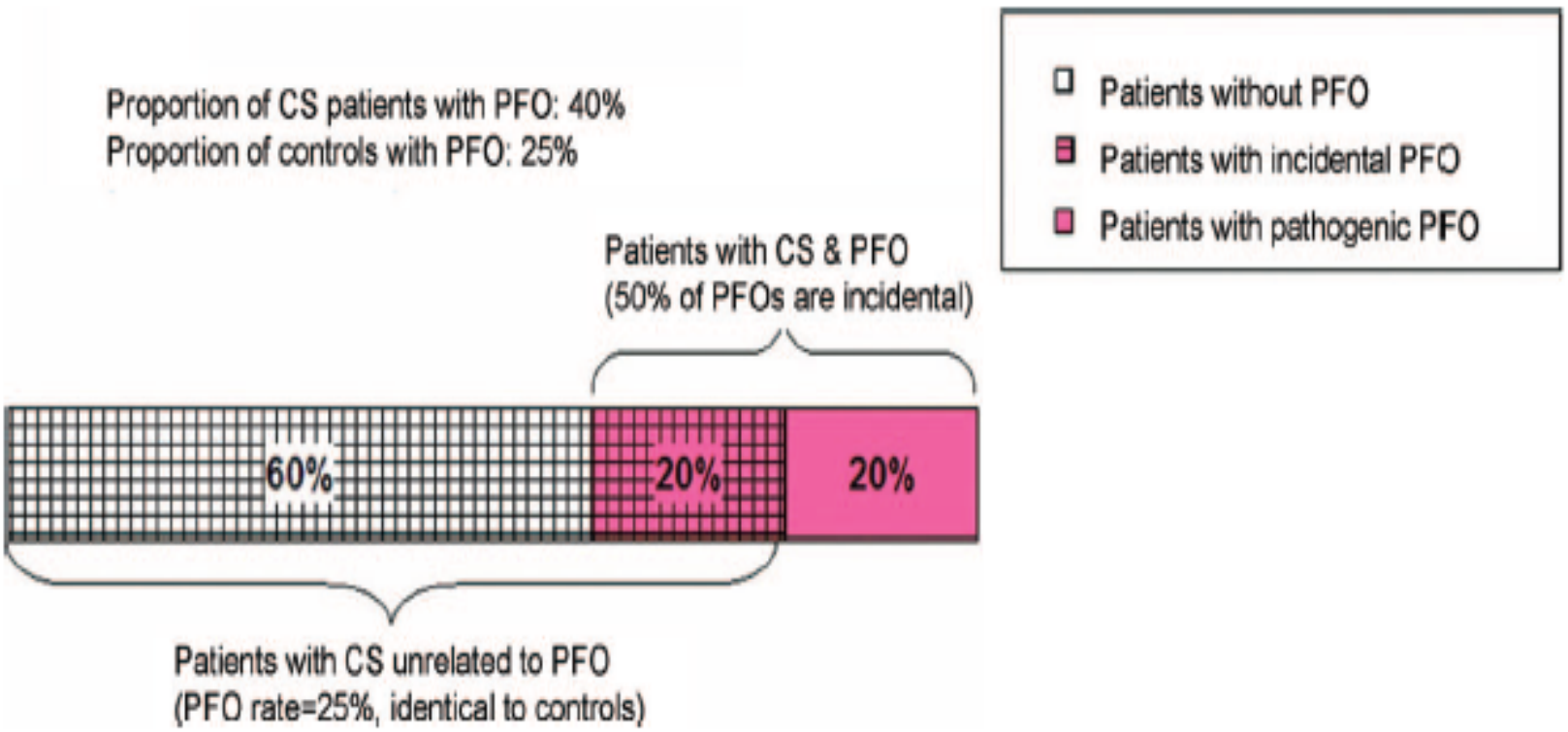
Obiettivi specifici dello studio OPTION

- Valutare e confrontare gli outcome a medio e lungo termine nei pazienti con CS e PFO sottoposti a chiusura endovascolare o chirurgica del PFO vs il solo trattamento medico
- Verificare appropriatezza d'uso della chiusura endovascolare o chirurgica del PFO negli ospedali Italiani

Waiting for an OPTION…

Grazie per l’attenzione

Proportion of pts with CS and PFO with incidental PFO



When the prevalence of PFO in the CS population is 40% and the prevalence of PFO in the control group is 25%, then 50% of PFOs discovered in CS patients would be incidental.

This is based on the assumption that CS patients who have strokes from causes unrelated to PFO will have the same PFO prevalence as the control group (in this case, 25%)

Steering Committee dello studio OPTION

- Fulvia Seccareccia, Paola D'Errigo, Nicola Vanacore - *Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute – Istituto Superiore di Sanità*
- Danilo Toni - *Dipartimento di Neurologia e Psichiatria – Università La Sapienza di Roma.*
- Stefano Strano - *Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche – Università La Sapienza di Roma.*
- Pompilio Faggiano - *Divisione di Cardiologia - Spedali Civili di Brescia e Università di Brescia*
- Domenico Inzitari - *Dipartimento di Scienze Neurologiche e Psichiatriche, Università di Firenze*
- Maurizio Paciaroni - *Stroke Unit e Divisione di Medicina cardiovascolare, Università di Perugia*
- Gennaro Santoro - *Dipartimento Cardiologico e dei vasi, Ospedale di Careggi, Firenze.*

Disegno dello studio OPTION

- Studio di coorte prospettico osservazionale multicentrico.

  Avendo l'obiettivo di osservare e registrare quanto accade nella pratica clinica quando un paziente con CS e PFO viene ricoverato in una Unità Neurovascolare, lo studio non interferirà in nessun modo con i processi decisionali locali relativi al trattamento.

- Nelle Unità Neurovascolari che aderiscono allo studio viene avviata un'indagine prospettica che, per ogni paziente con CS e PFO prevede:
  - La raccolta sistematica da parte degli operatori dei centri di un set minimo di informazioni cliniche, anatomiche e terapeutiche standardizzate, utili a definire il profilo di rischio del paziente e le caratteristiche del trattamento (medico o interventistico) impiegato.
  - La raccolta degli outcome e delle variabili cliniche e strumentali a 6, 12, 24 e 36 mesi dal trattamento (medico o interventistico) per ciascun paziente arruolato *(Follow-up clinico e amministrativo)*

Metodi (2)

Popolazione dello studio

- La coorte sarà costituita da tutti i pazienti di età 15-65 anni afferenti ad una Unità Neurovascolare (Stroke Unit) italiana con una diagnosi di CS e successivo riscontro di PFO all'ecocardiografia transtoracica o transesofagea associato o meno ad aneurisma del setto interatriale.
- Si definisce Stroke Criptogenetico uno stroke per il quale siano state escluse cause cardiache ad alto rischio cardioembolico (Fibrillazione atriale, Flutter atriale, Sick sinus syndrome, aneurisma del VS, cardiomiopatie dilatative, tumori del cuore, vegetazioni, stenosi mitralica, protesi valvolari meccaniche), a medio incerto rischio cardioembolico (ecocontrasto spontaneo in AS, Prolasso della mitrale, calcificazioni dell'anulus mitralico, stenosi aortica), aortiche, carotidee o intracraniche [Doufekias E et al: JACC; 2008; 51: 1049]
- Nel periodo di arruolamento ciascuna Unità Neurovascolare partecipante allo studio deve arruolare consecutivamente tutti i pazienti che soddisfano le condizioni elencate sopra.

Metodi (4)

End-point e Follow-up

- L' endpoint primario è un endpoint combinato costituito da stroke fatale e non fatale, ischemico o emorragico, validato attraverso neuroimmagini, che si verifica a 24 e 36 mesi dal ricovero in Unità Neurovascolare.

Metodi (5)

Gli Endpoint secondari

- Incidenza a 6 e 12 mesi di stroke fatale e non fatale, ischemico o emorragico (validato attraverso neuroimmagini)
- incidenza a 6, 12, 24 e 36 mesi di
  - mortalità per tutte le cause (dati amministrativi; linkage SDO-Anagrafe tributaria trasmessa da Agenas)
  - incidenza di eventi cardio e cerebrovascolari maggiori intraospedalieri (MACCE)
  - sanguinamenti intracranici fatali e non fatali
  - sanguinamenti maggiori da anticoagulanti o da antiaggreganti
  - embolie sistemiche
  - complicanze tardive correlate al device
  - qualsiasi evento avverso periprocedurale l'impianto del device
- percentuale di pazienti con shunt residuo a 6 mesi diagnosticato con ecocardiografia transtoracica o transesofagea

Metodi (7)

Ipotesi statistica

- I dati riportati in letteratura, documentano una incidenza di Stroke in pazienti con CS e PFO trattati con terapia medica di circa il 6% in tre anni vs una incidenza di 1.6% in pazienti con CS e PFO trattati con chiusura endovascolare/chirurgica + terapia medica, e un RR dei pazienti trattati con chiusura endovascolare/chirurgica + terapia medica vs pazienti trattati solo con terapia medica di 0.27 (Rapid HTA Report 2013).
- Per verificare questa ipotesi, considerando un rapporto trattati/non trattati = 1 a 2, potenza = 80% e alfa = 0.05, **sarà necessario arruolare consecutivamente nei centri partecipanti almeno 274 pazienti trattati con chiusura endovascolare/chirurgica del PFO e 548 trattati farmacologicamente.**

Metodi (1)

Periodo dello studio

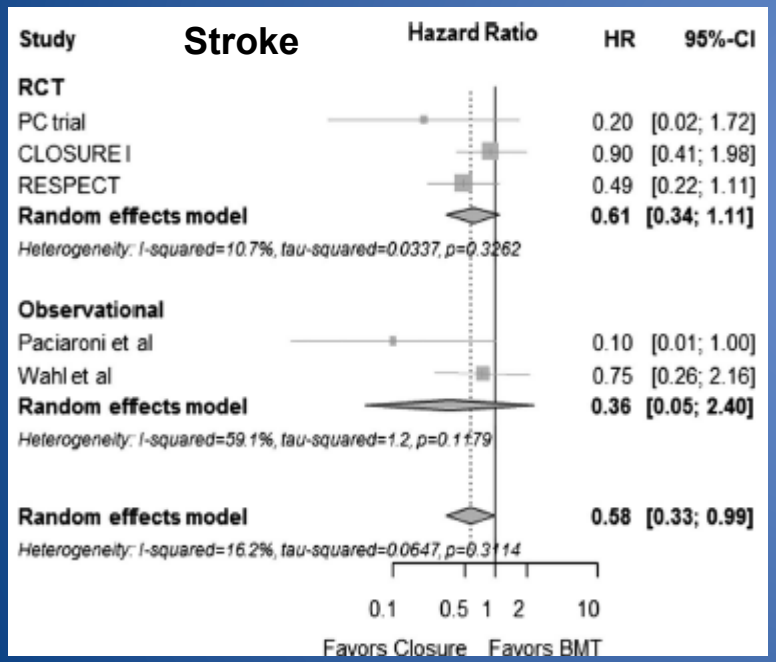
- Lo studio inizia ufficialmente in …….. 2015; ciascun centro avrà la possibilità di aderire allo studio non oltre il 30 luglio 2014.
- Per ciascun centro il periodo di arruolamento dei casi dovrà essere di almeno 12 mesi a partire dalla data di inizio dell'arruolamento stesso.

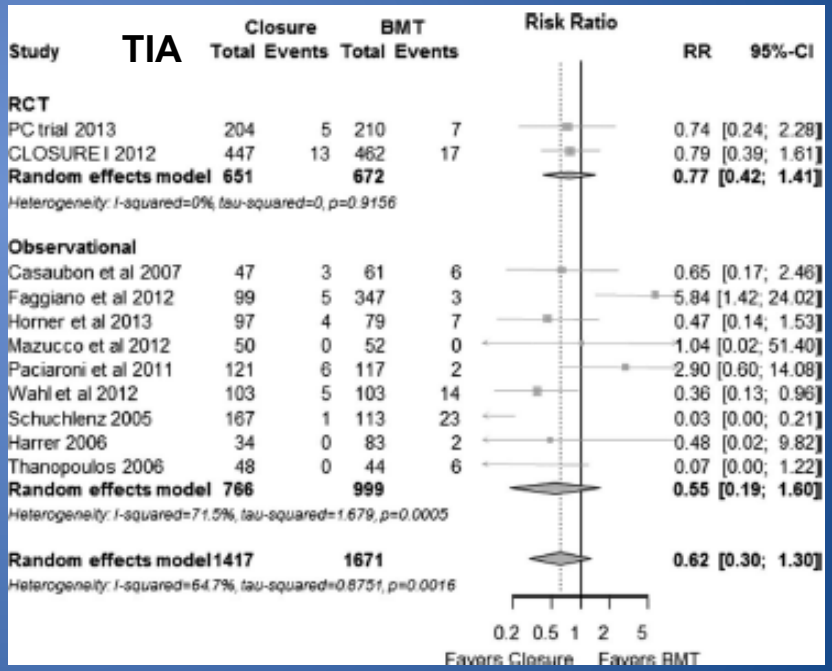
Principali risultati attesi e impatto

- Confronto di esiti (RNE) a 24 e 36 mesi dei trattamenti considerati (chiusura endovascolare del PFO vs terapia medica) nei pazienti con CS e PFO, controllando per i fattori di selezione delle due procedure e per i fattori di rischio dei pazienti.
- Individuazione di categorie di pazienti con CS e PFO che beneficiano del trattamento endovascolare con conseguente riduzione di recidive e miglioramento della qualità della vita
- Individuazione di categorie di pazienti con CS e PFO che non beneficiano del trattamento endovascolare con conseguente riduzione di interventi inutili e risparmio di risorse
- Elaborazione di criteri di indirizzo per una corretta selezione dei pazienti con CS e PFO da inviare ad uno dei due trattamenti in esame (chiusura endovascolare del PFO e terapia medica)
- Possibilità di osservare tutti i device utilizzati, compresi quelli di nuova generazione e introdotti nel SSN durante lo svolgimento dello studio; descrizione della casistica degli interventi endovascolari in termini di tipologia di device ed eventuale valutazione comparativa di efficacia tra diverse tipologie
- Impianto di un sistema di follow-up amministrativo per l'identificazione di RNE nel corso di ricoveri successivi alla procedura in esame

PFO and cryptogenic stroke: Meta-analysis

N= 4335 pts. 11 non RCTs and 3 RCTs
End points: recurrent strokes, TIA, peripheral embolisms, PE, AF, death.
No significant effect of PFO closure among RCTs





Wolfrum M et al (2013) Heart ePub ahed of printing

PFO and cryptogenic stroke: Meta-analysis

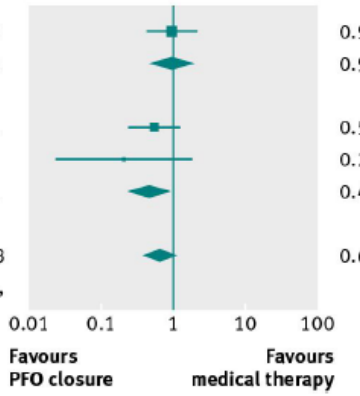
N= 2303 pts. 3 RCTs

Primary end point: stroke

Study or subgroup	Events/total: PFO closure	Events/total: Medical therapy	Risk ratio (95% CI)	Risk ratio (95% CI)
Starflex device				
Closure 1	12/447	13/462		0.95 (0.44 to 2.07)
Subtotal	12/447	13/462		0.95 (0.44 to 2.07)
Amplatzer PFO occluder				
RESPECT	9/499	16/481		0.54 (0.24 to 1.22)
PC Trial	1/204	5/210		0.21 (0.02 to 1.75)
Subtotal	10/703	21/691		0.48 (0.23 to 1.02)
Total	22/1150	34/1153		0.66 (0.37 to 1.19)

Test for heterogeneity: $\tau^2=0.03$, $\chi^2=2.25$, df=2, P=0.32, $I^2=11\%$

Test for overall effect: z=1.37, P=0.17

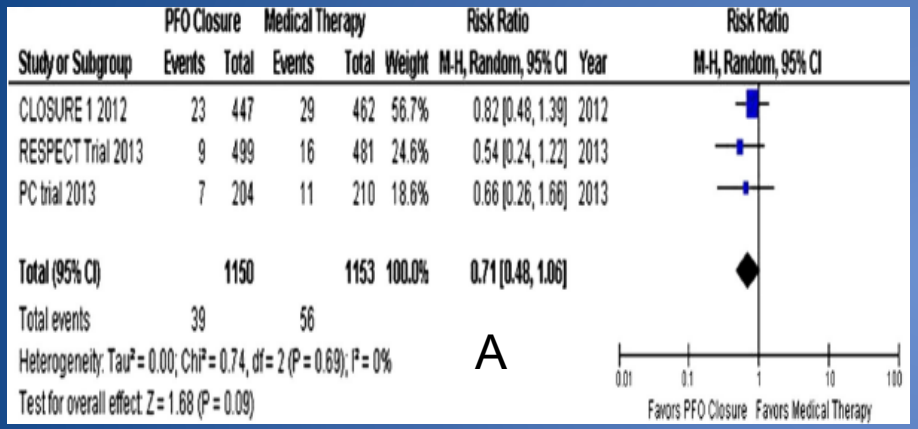


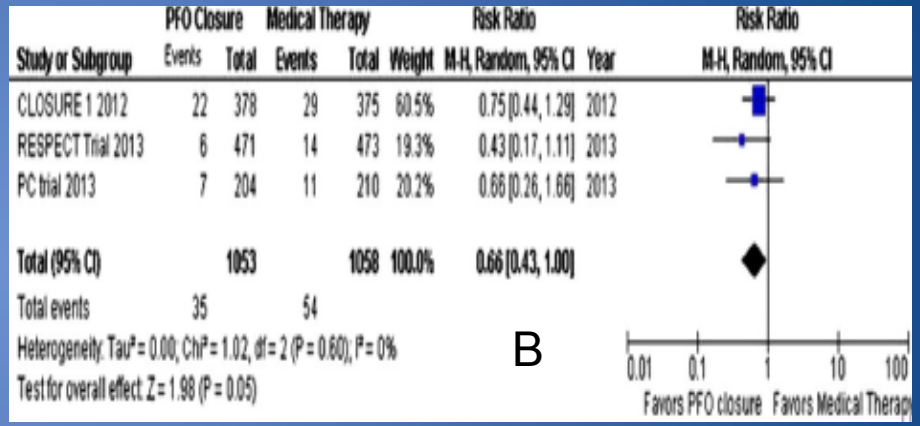
Forest plot of three trials of patent foramen ovale (PFO) closure versus medical therapy for the endpoint of stroke, stratified by closure device (Starflex or Amplatzer PFO occluder). Overall there is no evidence of benefit from closure, but in the subgroup who underwent closure with the Amplatzer PFO occluder there is a reduction in the rate of stroke of borderline statistical significance

Henderson RA et al. (2013) BMJ BMJ 347: f6193

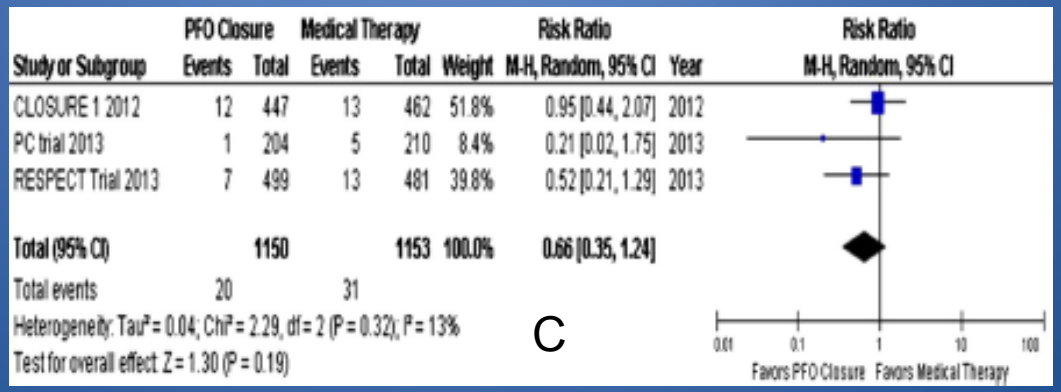
PFO and cryptogenic stroke: Meta-analysis

N= 2303 pts. 3 RCTs
Intention to treat analysis and per protocol analysis
Primary end point: composite of death, stroke, recurrent embolic events





A: Primary endpoint
B: Per protocol primary endpoint
C: Incidence of stroke



Hakeem A et al. (2013) Cardiovasc Revasc Med14(6):349.

PFO and cryptogenic stroke: Meta-analysis

N= 2303 pts. 3 RCTs
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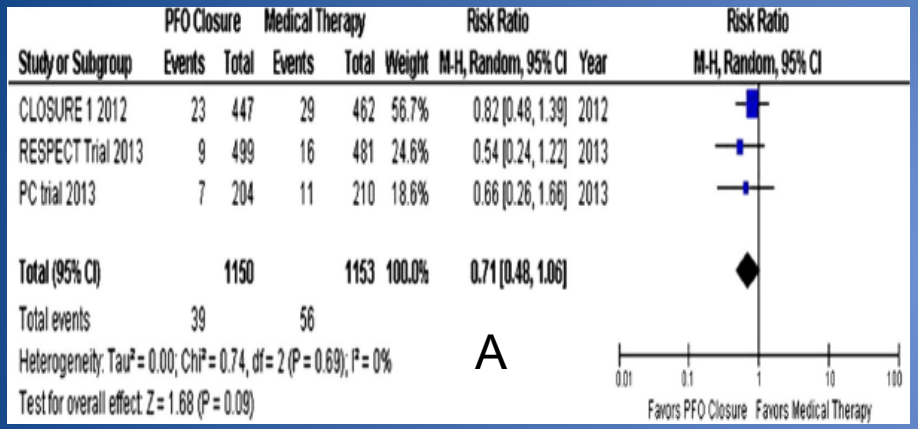

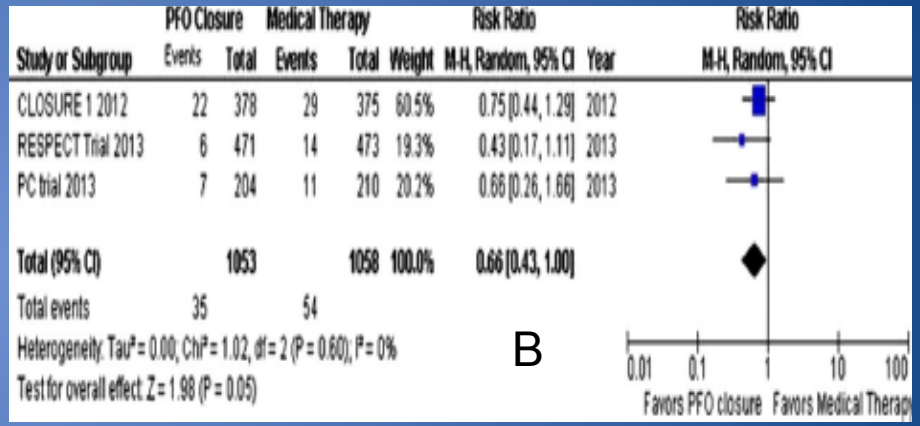

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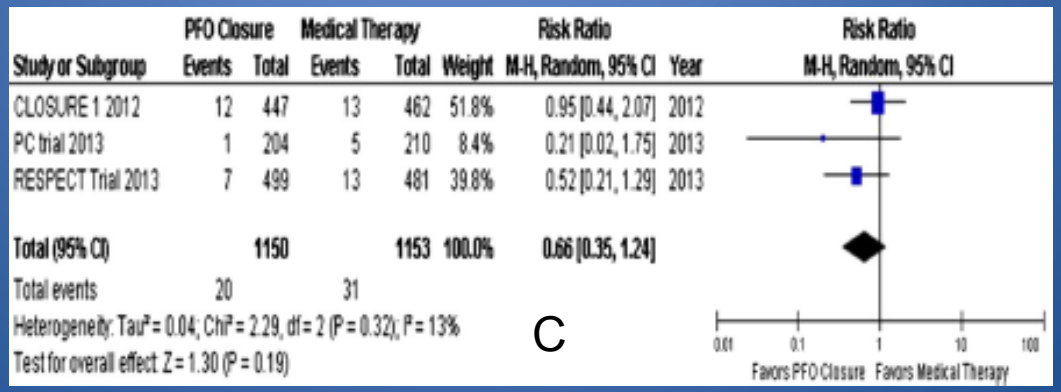


Hakeem A et al. (2013) Cardiovasc Revasc Med14(6):349.

PFO and cryptogenic stroke: Meta-analysis

3 RCTs (CLOSURE I, RESPECT and PC)
Intention to treat analysis and per protocol analysis
Primary end point: composite of death, stroke, recurrent embolic events

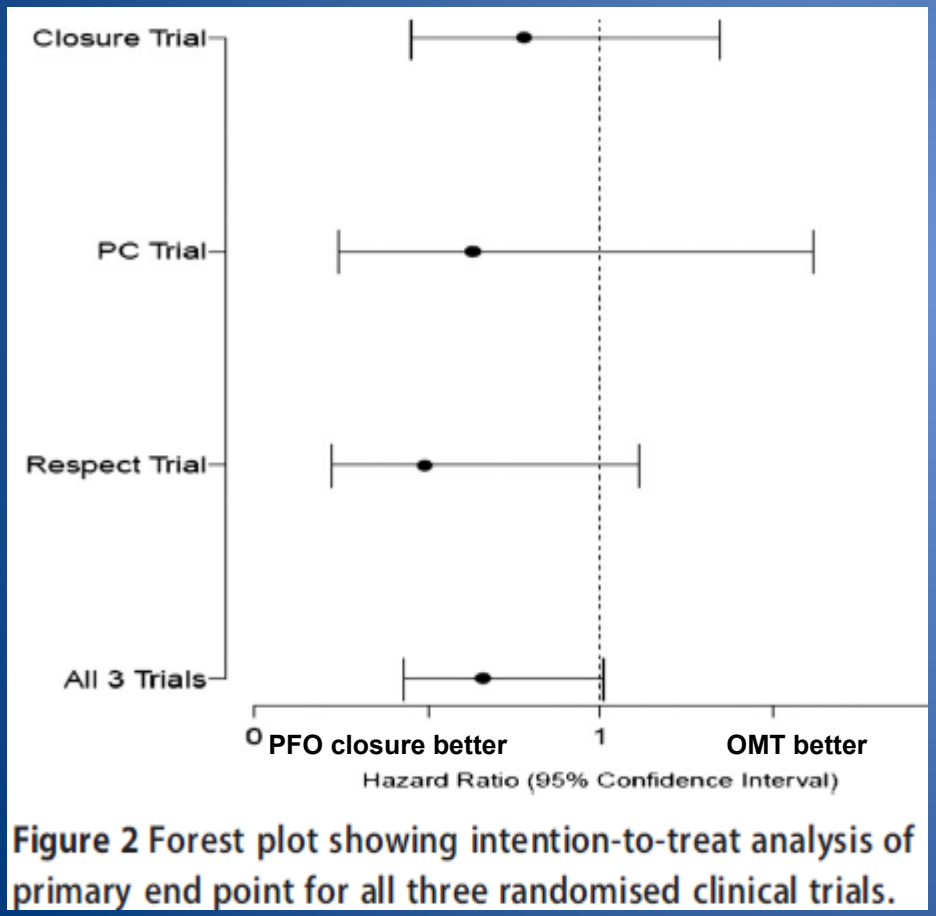


Figure 2 Forest plot showing intention-to-treat analysis of primary end point for all three randomised clinical trials.

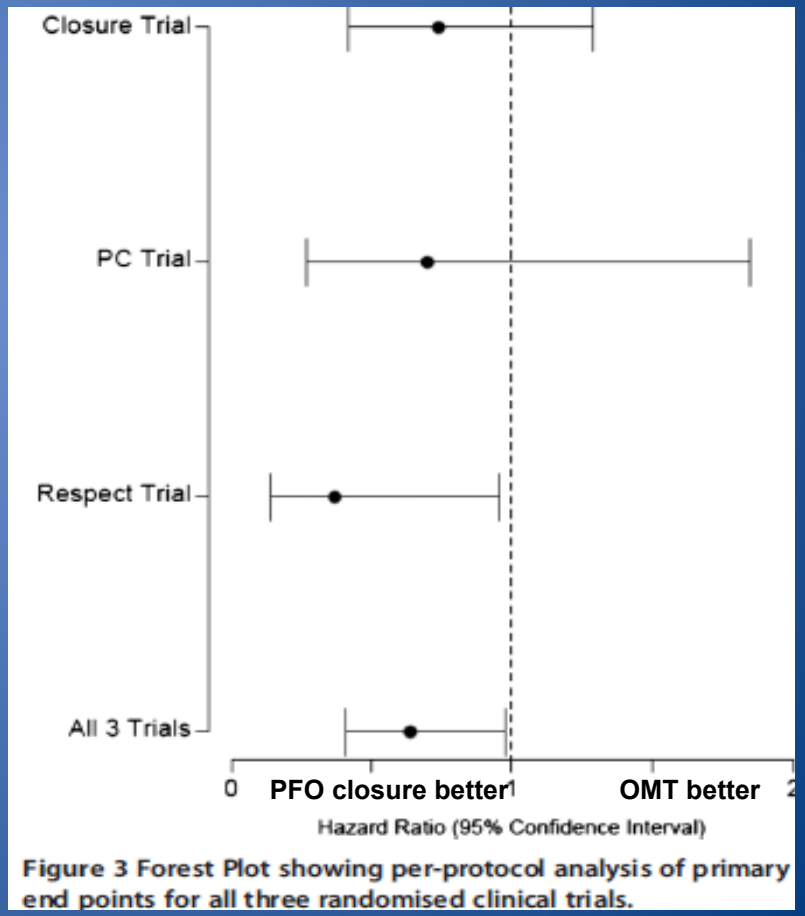


Figure 3 Forest Plot showing per-protocol analysis of primary end points for all three randomised clinical trials.

Riaz IB et al. (2013) BMC cardiovasc disorders 13:116

CONCLUSIONS

- PFO is an extremely common cardiac abnormalitiy among general population
- PFO is not associated with a significantly increased risk of stroke in general pupulation and its detection is not warrented in primary prevention
- Different studies have shown a correlation with cryptogenic stroke, however the underlying pathophysioly is not fully understood.

CONCLUSIONS

- Despite a trend towards a protective role of PFO percutaneous closure, no RCTs has proved its superiority and therefore it should not be routinely performed in secondary prevention (as stated by international guidelines)

- However RCTs were limited by different factors and the ongoing trial may help overcoming this limitation

CONCLUSIONS

- When should we close it?
- When should we look for PFO?

Hardly ever!

Hardly ever!

PFO and cryptogenic stroke: a therapeutic dilemma

N= 446. Mean age 50 ± 14 years.
Mean follow up: 54 ± 20 mesi (12-96)

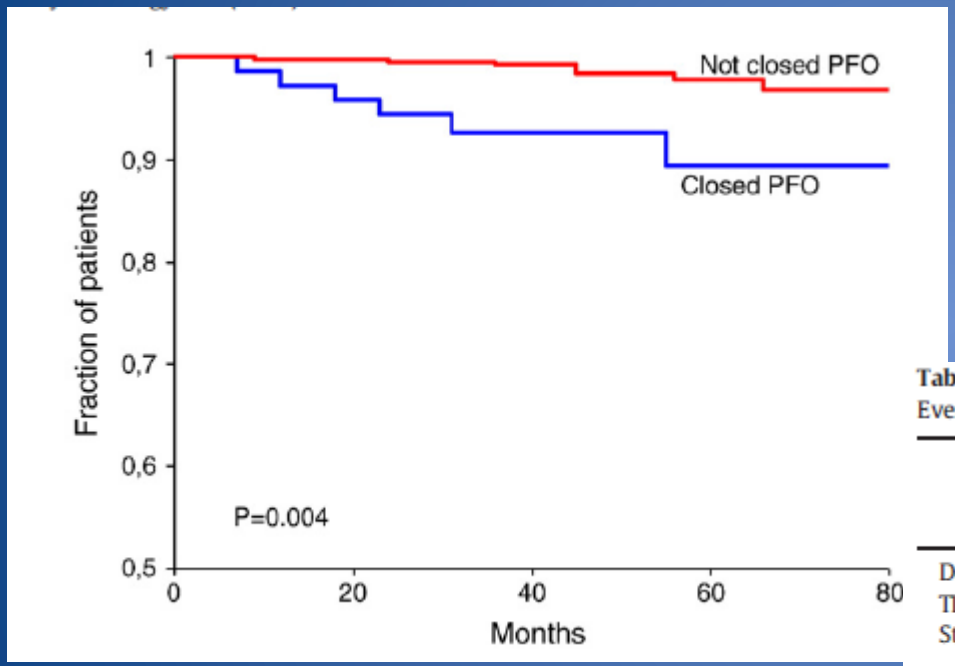


Table 3
Events during follow-up. See text for details.

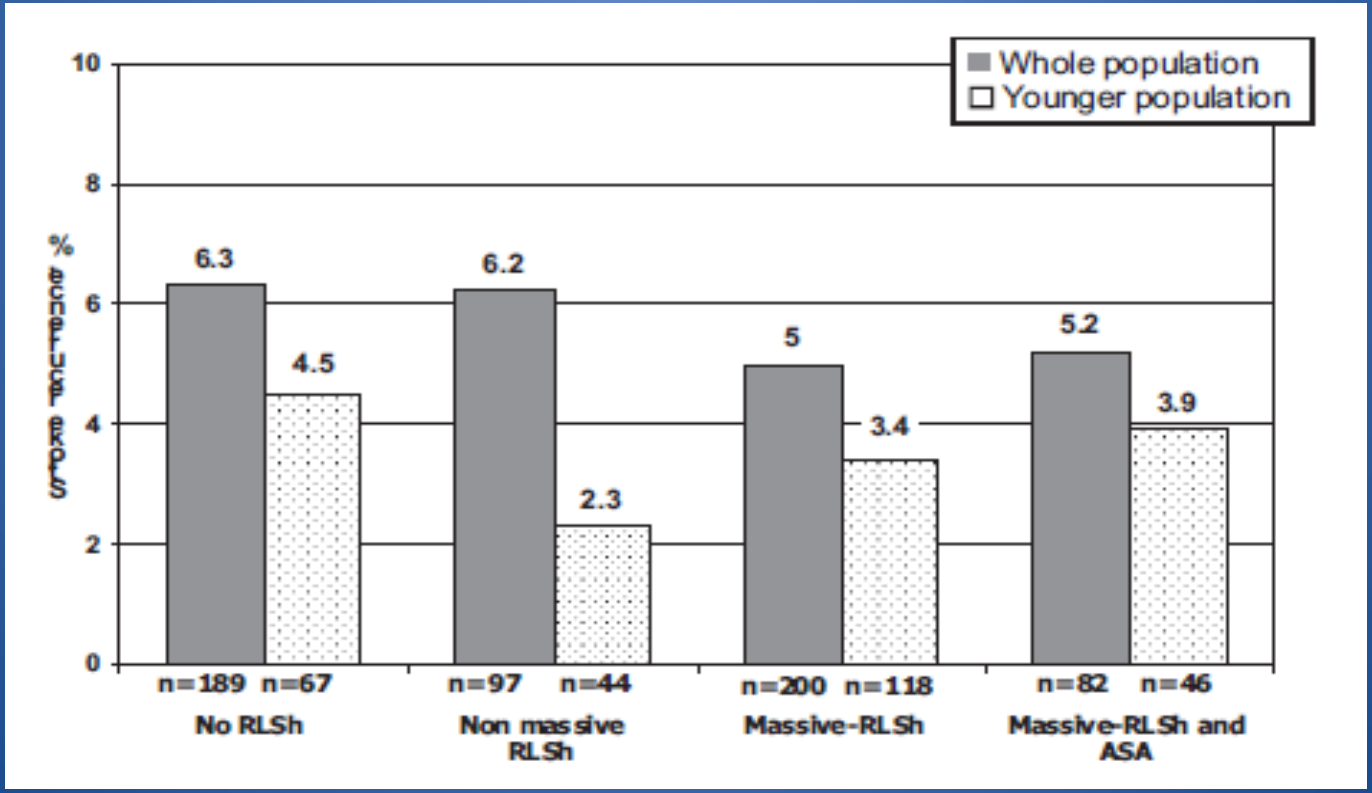
	All pts $n=446$	Group 1 (closed PFO) $n=99$	Group 2 (unclosed PFO) $n=347$	p
Death	10 (2.2%)	1 (1%)	9 (2.6%)	0.58
TIA	8 (1.8%)	5 (5%)	3 (0.8%)	0.02
Stroke	4 (0.9%)	1 (1%)	3 (0.86%)	0.63
Fatal Stroke	1 (0.2%)	1 (1%)	0	0.50
Non fatal Stroke	3 (0.6%)	0	3 (0.8%)	0.81
Endocarditis	1 (0.22%)	1 (1%)	0	0.50
Peripheral embolism	1 (0.22%)	1 (1%)	0	0.50
Pulmonary embolism	1 (0.22%)	0	1 (0.28%)	0.50
Aspecific neurological symptoms	7 (1.5%)	5 (5%)	2 (0.5%)	0.007

Faggiano P et al (2012) Int J Cardiol 156 47–52

Recurrent Stroke and Massive Right-to-Left Shunt

Results From the Prospective Spanish Multicenter (CODICIA) Study

- **Il rischio di recidiva di stroke in pazienti con PFO è basso,**
- **Non ci sono differenze tra soggetti con o senza shunt dx-sx e in quelli con shunt dx-sx e concomitante aneurisma del setto interatriale**



Stroke 2008;39;3131-3136

PFO mar iologists

Steven R. M
Jeanie Luci

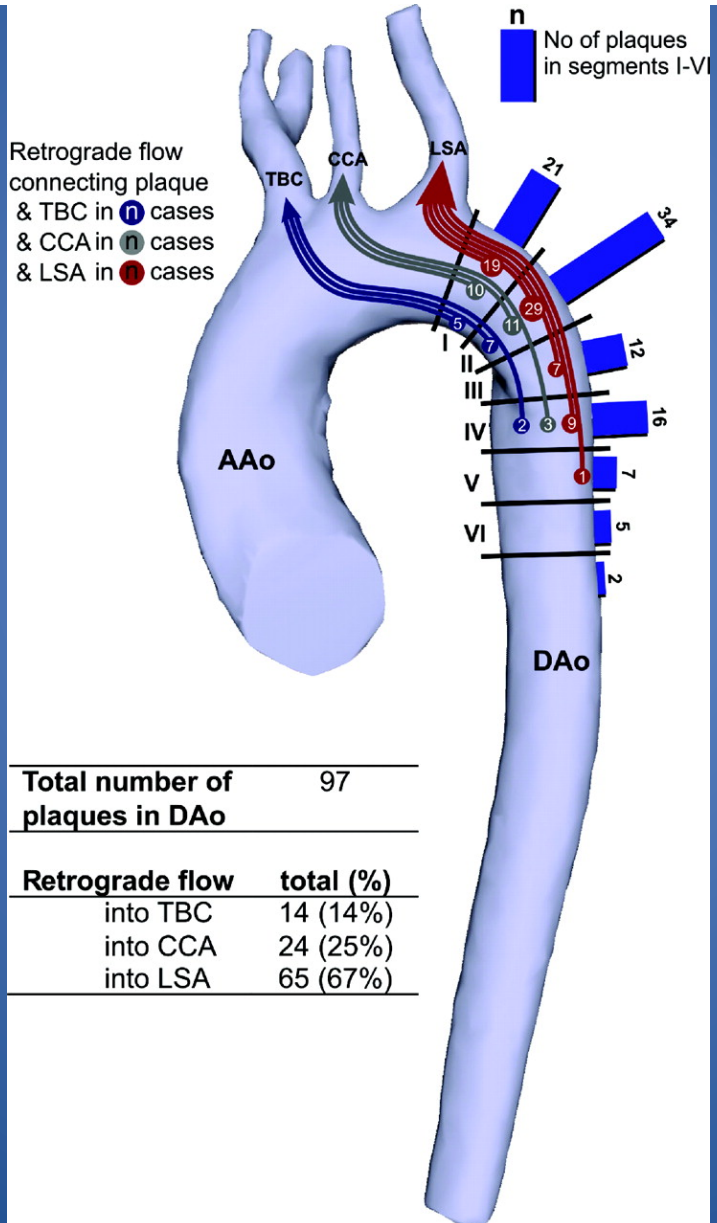
Neurology 2005

Table *Diagnostic and treatment strategies for patent foramen ovale (PFO) by specialty*

	Neurologists, n = 47	Cardiologists, n = 46	*p*
Initial study to rule out cardioembolic source			
Transesophageal echocardiogram	34	37	
Transthoracic echocardiogram	62	63	0.25
Transcranial Doppler	4	0	
Distribution of treatments*			
Antiplatelet agents	49 ± 33	26 ± 26	0.0003
Warfarin	28 ± 26	17 ± 22	0.04
Surgical closure	2.3 ± 9	0.2 ± 0.8	0.05
Endovascular closure	20 ± 21	55 ± 34	0.0001
Have recommended PFO closure in an asymptomatic patient	2	9	0.2
Have recommended PFO closure for SCUBA diving	6	24	0.02
Have recommended PFO closure for migraines	0	14	0.01

Complex Plaques in the Proximal Descending Aorta

An Underestimated Embolic Source of Stroke



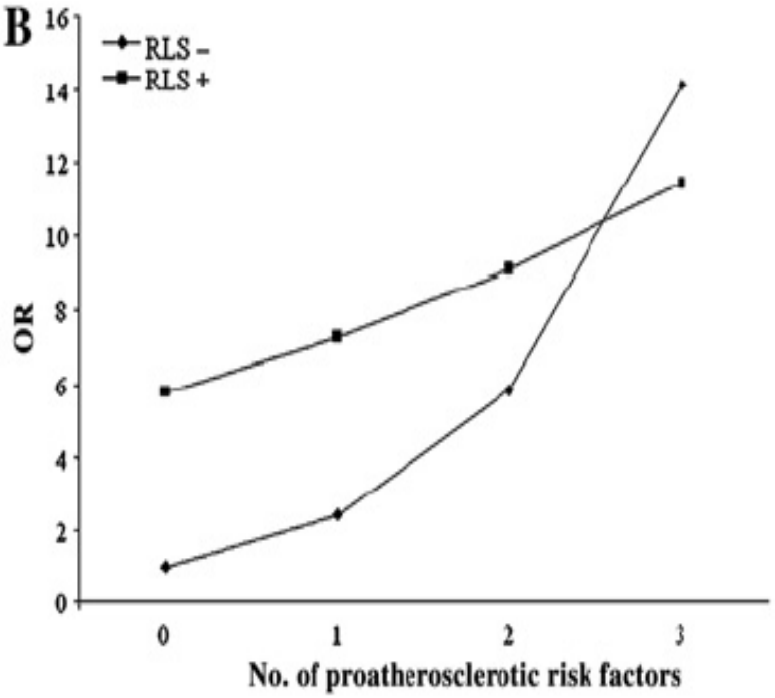
Total number of plaques in DAo	97
Retrograde flow	**total (%)**
into TBC	14 (14%)
into CCA	24 (25%)
into LSA	65 (67%)

Harloff et Al.
Stroke 2010

Interaction between proatherosclerotic factors and right-to-left shunt on the risk of cryptogenic stroke: the Italian Project on Stroke in Young Adults

Table 1 Demographic characteristics of patients with cryptogenic stroke and control subjects

Characteristic	Cryptogenic stroke (n=588)	Control Subject (n=585)	p Value
Age (years), mean ± SD	35.3±7.5	34.0±8.0	0.003
Sex, women	302 (51.4)	310 (53.0)	0.576
Hypertension	110 (18.7)	27 (4.6)	<0.001
Diabetes mellitus	16 (2.7)	14 (2.4)	0.722
Current smokers	216 (36.7)	152 (26.0)	<0.001
Hypercholesterolaemia	141 (24.1)	68 (11.6)	<0.001
Proatherosclerotic score			<0.001
0	242 (41.3)	361 (61.7)	
1	235 (40.1)	190 (32.5)	
2	82 (14.0)	31 (5.3)	
3	25 (4.3)	3 (0.5)	
4	2 (0.3)	0 (0.0)	
Right-to-left shunt	279 (47.5)	119 (20.3)	<0.001



Conclusions The influence of RLS on the risk of CS decreases with increasing number of atherosclerotic factors, and is highest when such factors are absent. Individual proatherosclerotic profiles may help to identify patients with CS whose patent foramen ovale is probably pathogenic.

Pezzini et Al. Heart 2012

RESPECT trial limitations

1. Different dropout rate between groups ⟶ possible off-label procedures

2. High-risk patients preferentially treated outside the trial

3. Results of the PP and AT analyses to be interpreted with caution

4. Sub-group analysis with only 25 events is exploratory in nature

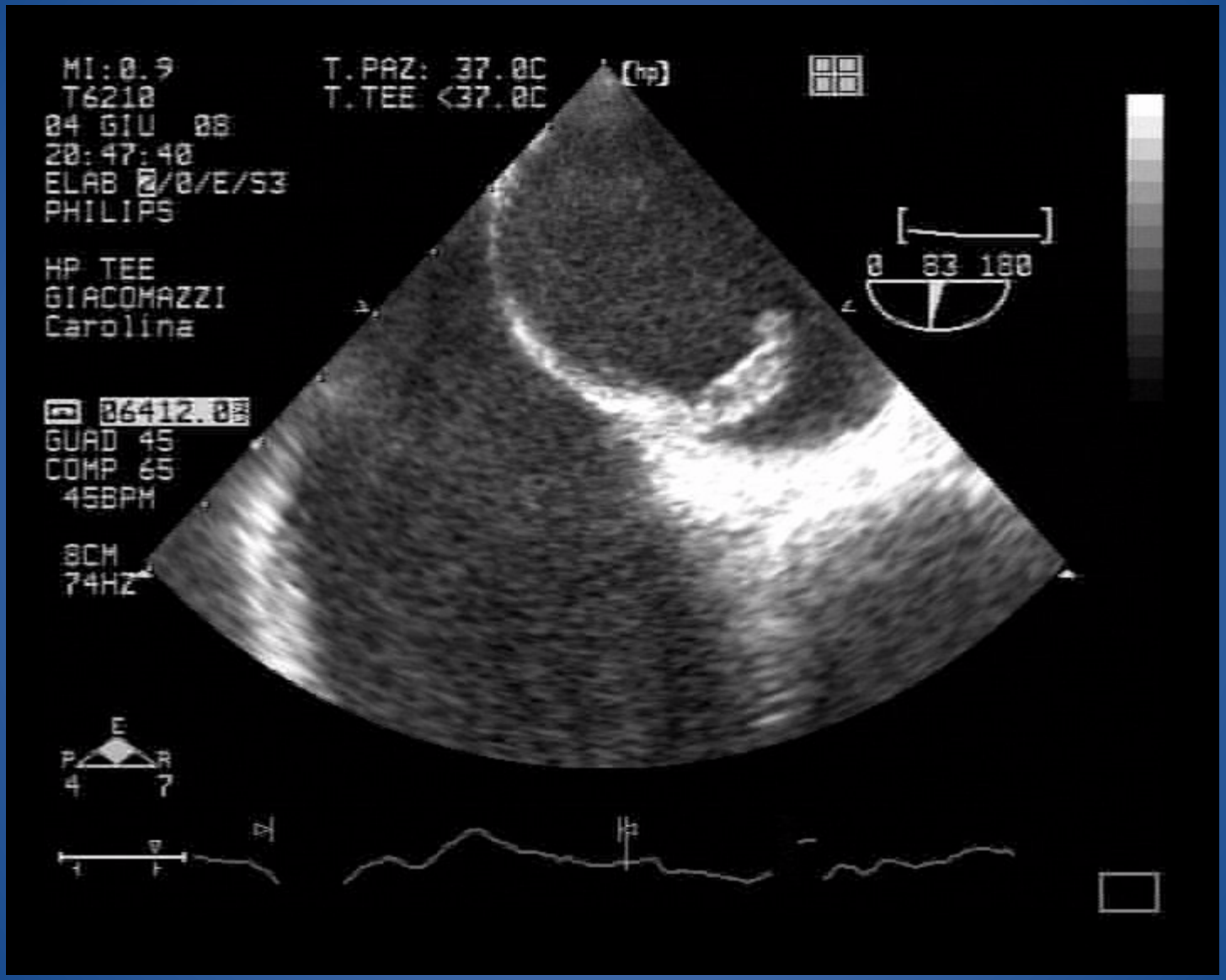
PC trial limitations

1. Primary composite end point problematic
a. Death is not specific to the studied condition
b. TIA is a less clearcut end point than stroke
    - Different definitons of index and of recurrent TIA (n.d.a)

2. Difficulty recruiting patients:
a. unusually long recruitment period
b. selected patient population (possible limited generalizability of results)

3. Patient retention lower than expected: possible attrition bias that could distort the results in either direction

4. The clinical-events committee discounted potential primary end-point events more often in the medical-therapy group than in the closure group.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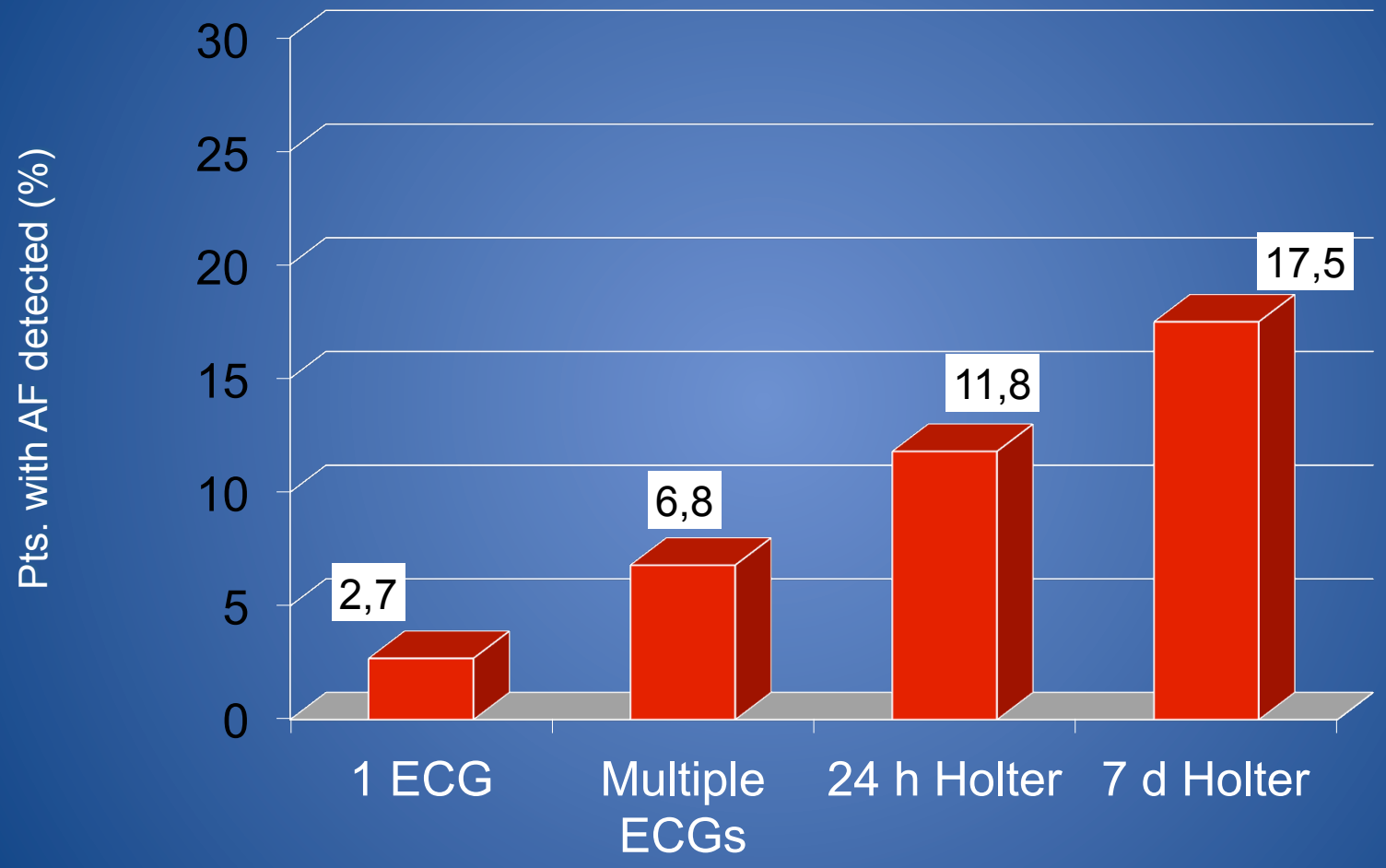
AF monitoring after cryptogenic stroke



D. Jabaudon. Stroke 2004; 35: 1647-1651

FDA Circulatory System Devices Panel Recommendations

- Randomized controlled trials of PFO closure to prevent recurrent stroke are required
- A "proof of principle" trial with pooled data demonstrating that PFO closure does prevent recurrent stroke could allow this question to be answered in a timely fashion, if sponsors are amenable to cooperating and sharing data. "Proof of device" trials demonstrating that an individual device effectively closes a PFO could be done separately
- "Off-label" closure should be discouraged. Enrollment in ongoing trials should be encouraged
- Patients and physicians should be educated about the lack of evidence of benefit of closure and the need for completion of trials.

Slottow TLP. Circulation. 2007;116:677-682

Meta-Analysis of Net Long-Term Benefit of Different Therapeutic Strategies in Patients With Cryptogenic Stroke and Patent Foramen Ovale

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(1)use of anticoagulant therapy is more effective than antiplatelet therapy for preventing recurrent stroke and/or TIA, but at the price of increased risk of major bleeding complications

(2)percutaneous PFO closure is associated with significant net clinical benefit versus both antiplatelet and anticoagulant therapy; such benefit is driven by lower incidence of recurrent stroke and/or TIA versus antiplatelet therapy and by decrease of major bleeding versus anticoagulant therapy.

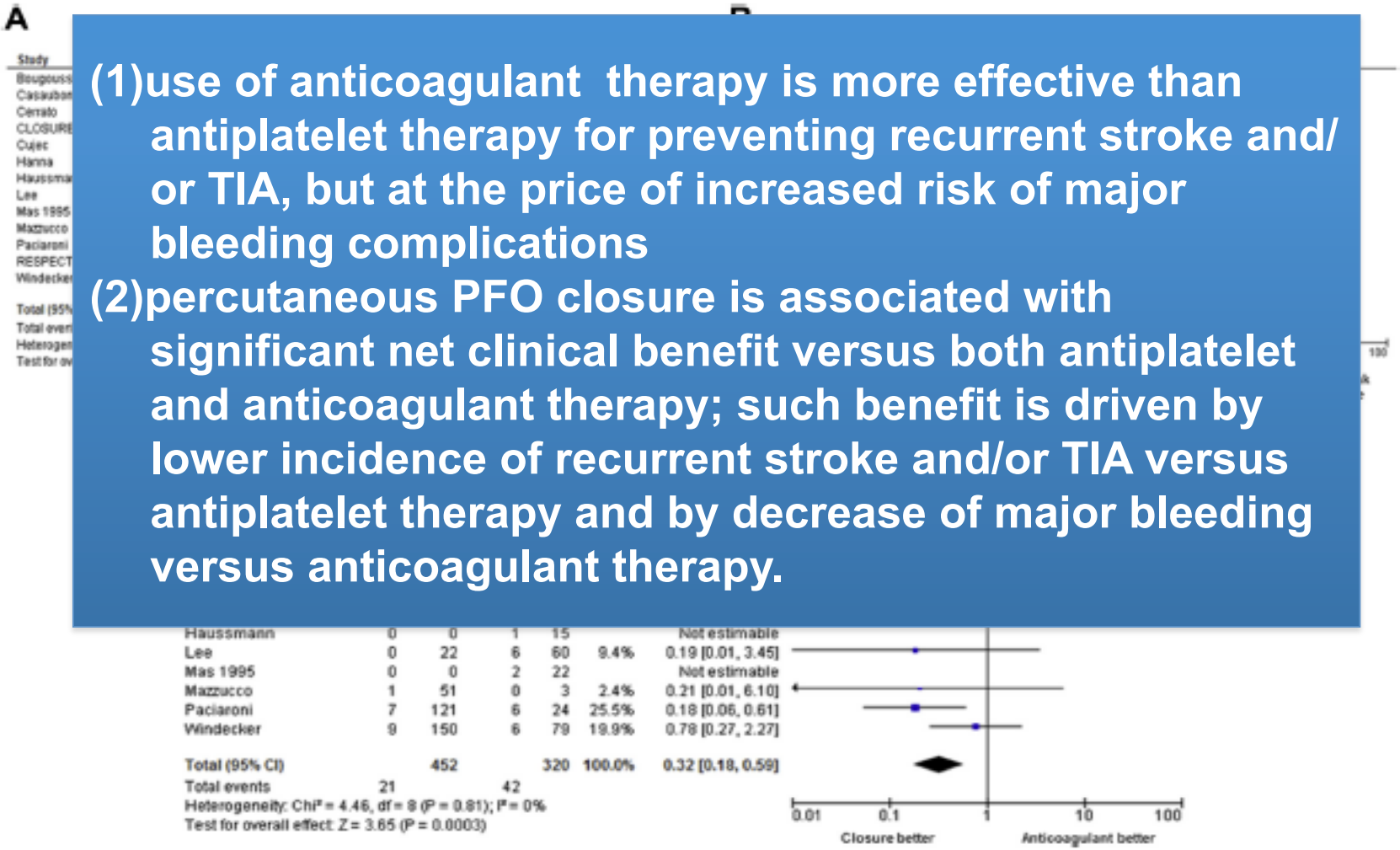

Figure 4. Odds ratios (with 95% confidence interval) of recurrent stroke and/or TIA (*panel A*), major bleeding (*panel B*), and cumulative incidence of recurrent stroke and/or TIA or major bleeding (*panel C*) in patients undergoing percutaneous PFO closure or receiving anticoagulant therapy.