



Congresso
Novas Fronteiras em Cardiologia
8 a 10 fevereiro.2013
Hotel Vila Galé Ericeira

ENCERRAMENTO DE FORAMEN OVALE PATENTE.

COMO AGIR PERANTE AS EVIDENCIAS MAIS RECENTES ?

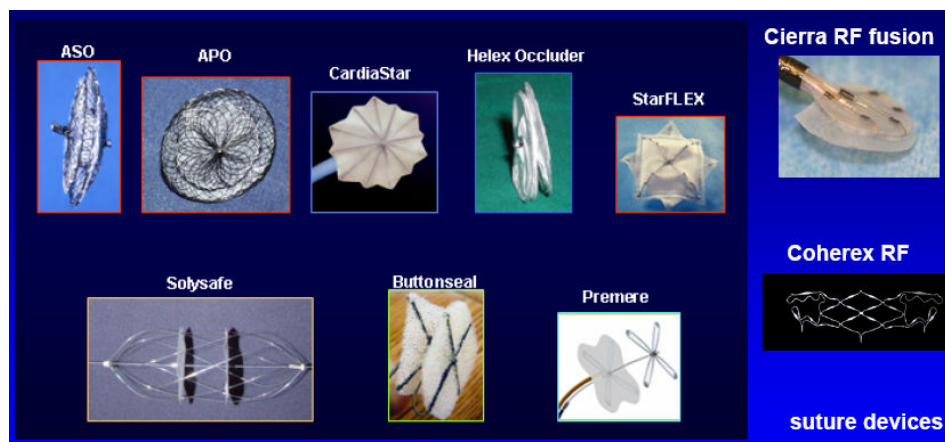
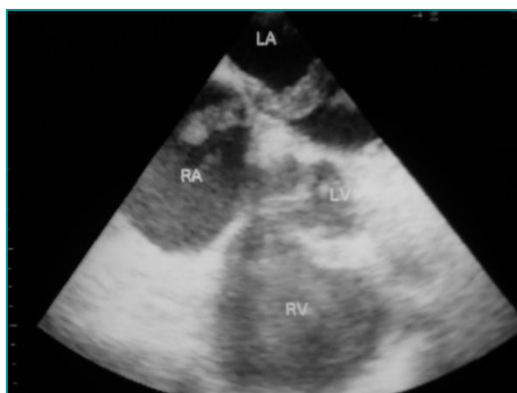
Lídia de Sousa





Oclusão Percutânea de FOP – onde estamos?

- AVC causa maior de mortalidade e morbilidade
- Cerca de 40% sem etiologia identificável → criptogénico
- 25% dos casos de AVC são eventos recorrentes → prevenção 2ª
- EUA 795 000 AVC isquémicos / ano
- Custo \$ 94 biliões dólares / ano
- Encerramento percutâneo do FOP: mercado potencial FOP/AVC \$2 biliões dólares / ano





French PFO-ASA Study

Recurrent Cerebrovascular Events Associated With PFO, ASA or Both

Mas JL et al. *NEJM* 2001;345:1740

581 patients

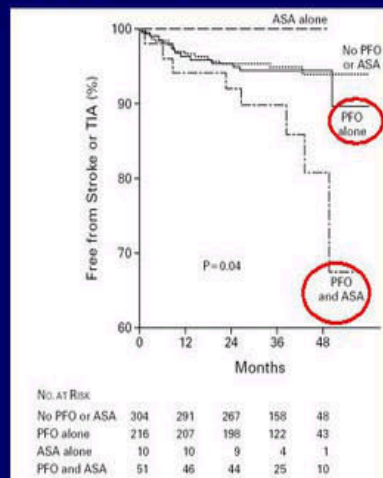
- age 18-55
- cryptogenic stroke patients

TEE

- no septal abnormality: n=304
- PFO alone: n=216
- ASA alone: n=10
- PFO and ASA: n=51

Treatment

- Aspirin 300 mg qd



PICCS

Ischemic Stroke Recurrence Prevention

PICSS (PFO In Cryptogenic Stroke Study)

substudy of WARSS (Warfarin Aspirin Recurrent Stroke Study)

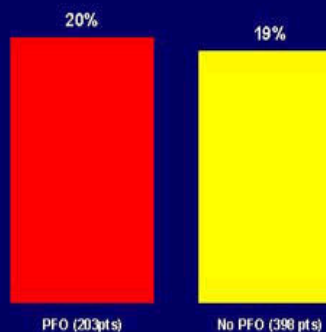
- 620 patients randomized and analyzed (29% of WARSS)
- Mean age 59 (30 - 85) years
- Follow-up: mean 13 months
- Cryptogenic stroke: 42%

- PFO 203 pts 48% cryptogenic
- No PFO 398 pts 38% cryptogenic

- Warfarin (312 pts) **P=0.02**
 - INR
 - target 1.4 - 2.8
 - mean 2.0
 - median 1.9
- Aspirin 325 mg / day (318 pts)

- Minor (major) bleedings (p<0.001)
 - Warfarin 23% (1.8%) / year
 - Aspirin 9% (1.9%) / year

Entire Population
Death / Stroke / TIA at 2 Years



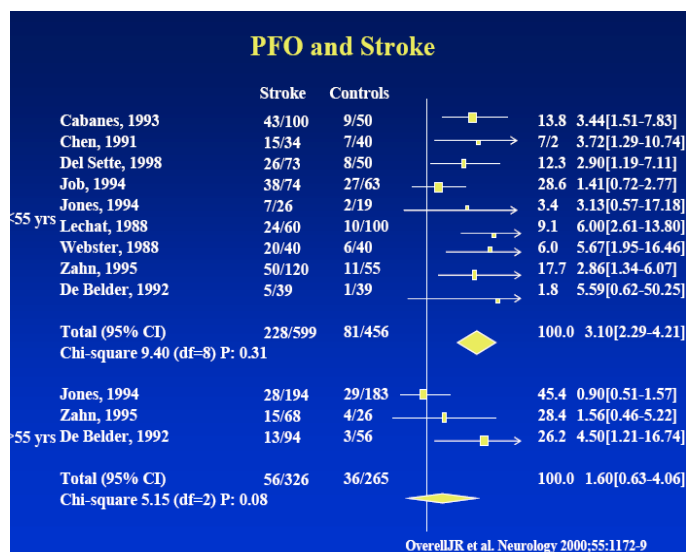
P=NS

Homma S et al. *Circulation* 105:2625, 2002



Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies

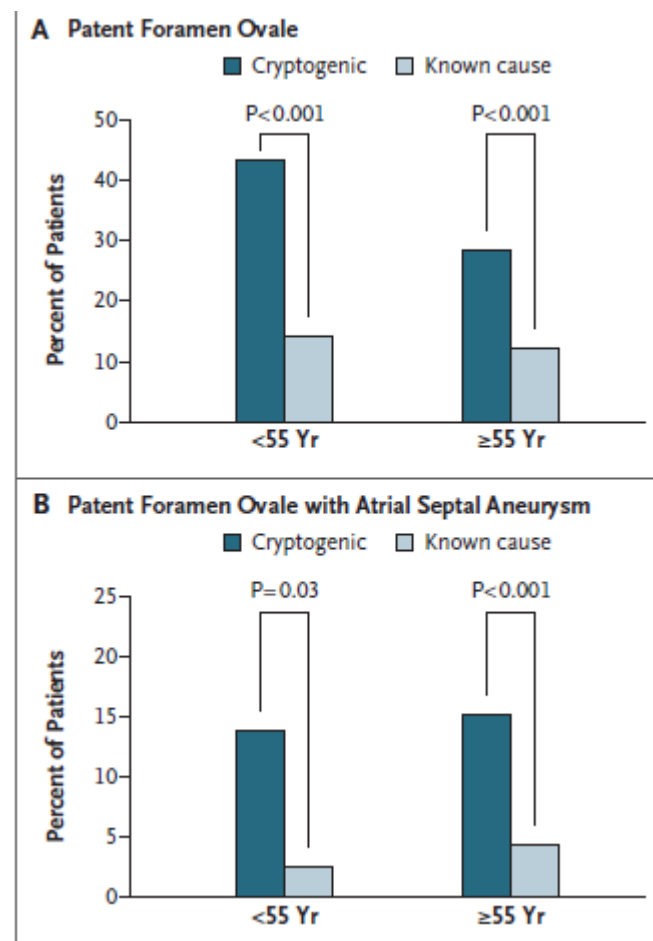
PFO and ASA are significantly associated with ischemic stroke in patients younger than 55 years



Overell I. Neurology.2000;55: 1172

Patent Foramen Ovale and Cryptogenic Stroke in Older Patients

Michael Handke, M.D., Andreas Harloff, M.D., Manfred Olschewski, M.Sc.,
Andreas Hetzel, M.D., and Annette Geibel, M.D.



NEJM 2007; 357:22



Estudos Prospectivos Populacionais

NOMAS

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

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

Conclusions

Patent foramen ovale, alone or together with ASA, was not associated with an increased stroke risk in this multi-ethnic cohort. The independent role of ASA needs further assessment in appositely designed and powered studies. (J Am Coll Cardiol 2007;49:797-802) © 2007 by the American College of Cardiology Foundation

SPARC

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*

CONCLUSIONS

These prospective population-based data suggest that, after correction for age and comorbidity, PFO is not an independent risk factor for future cerebrovascular events in the general population. A larger study is required to test the putative stroke risk associated with ASA. (J Am Coll Cardiol 2006;47:440-5) © 2006 by the American College of Cardiology Foundation



FOP E RISCO DE RECORRENCIA

Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis.

CONCLUSIONS: In medically treated patients with prior cryptogenic stroke, while the absolute rate of recurrent events is variable, available evidence does not support an increased relative risk of recurrent ischemic events in those with vs without a patent foramen ovale. Patent foramen ovale closure in these patients cannot be recommended until the results of ongoing clinical trials are reported.

Almekhalfi MA. Neurology 2009; 73: 89

Recurrent stroke and massive right-to-left shunt: results from the prospective Spanish multicenter (CODICIA) study.

CONCLUSIONS: These results suggest that neither massive RLSH nor massive RLSH with concurrent atrial septal aneurysm is an independent risk factor for recurrent stroke, in either the general or younger stroke populations.

Serena J. Stroke 2008;39:3131



Encerrar um FOP “incidental”

- **Não diminui o risco de recorrência
(outros mecanismos de AVC que não a embolia paradoxal)**
- **Acréscimo de risco – procedimento / dispositivo**
- **Dispositivos não resolvem (agravam??) vulnerabilidade auricular e risco arritmico**
- **Risco possivelmente aumentado por terapêutica médica “inadequada” pós-encerramento**



Guidelines / Recomendações

Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke

Practice Parameter:

Recurrent Stroke With Patent Foramen Ovale and Atrial Septal Aneurysm

Report of the Quality Standards Subcommittee of the American Academy of Neurology*

Issue date: January 2005

*National Institute for
Clinical Excellence*

**Percutaneous closure of patent
foramen ovale for the prevention of
cerebral embolic stroke**

**CONSENSUS SUR LES INDICATIONS DE LA FERMETURE ENDOVASCULAIRE
DU FORAMEN OVALE PERMEABLE APRES UN ACCIDENT ISCHEMIQUE CEREBRAL
SOCIETE FRANÇAISE NEURO-VASCULAIRE SOCIETE FRANÇAISE DE CARDIOLOGIE**



CLOSURE I Trial

Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

CONCLUSIONS

In patients with cryptogenic stroke or TIA who had a patent foramen ovale, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. (Funded by NMT Medical; ClinicalTrials.gov number, NCT00201461.)

Furlan AJ.NEJM 2012; 366: 991



Limitações do CLOSURE I

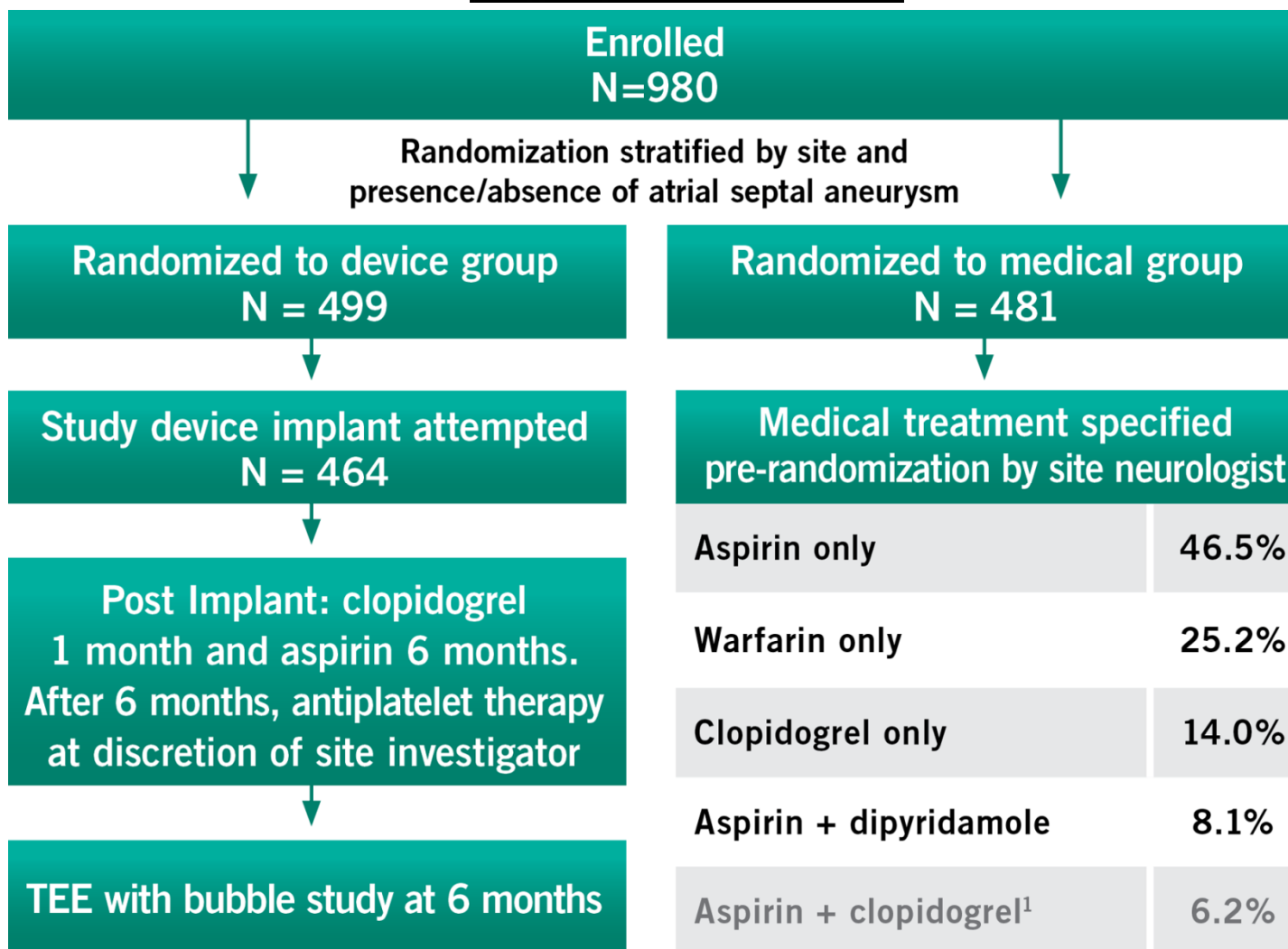
- **Subdimensionado para detectar diferenças com significado estatístico dada a redução da população em relação ao projectado inicialmente (1600 para 900 doentes)**
- **Estudo prévio da etiologia do AVC muito incompleto**
- **Análise de endpoint incluiu AIT sem tradução na RM**
- **Problemas relacionados com o dispositivo (STARFlex): quase 50% dos AVC foram relacionados com os dispositivo e um quarto ocorreram nos primeiros 30 dias pos-procedimento**
- **Fibrilhação auricular frequente**
- **Follow-up aos 2 anos demasiado curto para evidenciar benefício**



PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism

- 414 patients randomized to PFO closure or medical therapy
- nonsignificant 37% relative reduction in the primary end point of death from any cause, nonfatal stroke, transient ischemic attack, and peripheral embolism
- baixa taxa de eventos neurológicos recorrentes – estudo subdimensionado
- validade da análise de sub-grupos questionável

Meier B, TCT 2012





RESPECT Trial

Limitações



- **Recrutamento demorou 8 anos...**
- **Problemas na análise estatística:**
 - **alguns doentes do grupo da terapêutica médica abandonaram o estudo e foram submetidos a oclusão *off-label***
 - **no grupo randomizado para o dispositivo, 3 dos 9 doentes do grupo que tiveram eventos sofreram AVC antes de ser ocluído o FOP**
- **No desenho inicial do estudo já eram previstos vários tipos de análise se houvesse diferenças na terapêutica prevista e efectuada (*intention to treat, per protocol*)**
- **A baixa incidência de eventos é limitativa para a análise de sub-grupos**



Totality of Evidence

Analysis	Risk Reduction	P-Value ¹
Intent to Treat Raw Count	46.6%	0.157
Intent to Treat KM	50.8%	0.083
Per Protocol KM	63.4%	0.032
As Treated KM	72.7%	0.007

46.6%-72.7% risk reduction of stroke in favor of device

Number Needed to Treat (NNT)

	NNT ²	Device Group Event Rate ³	Medical Group Event Rate ³
1 Year	250	1.33%	1.73%
2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

Benefit became especially prominent 2-5 years after device placement



RESPECT Trial Conclusões

- **For carefully selected patients with history of cryptogenic stroke and PFO, the RESPECT Trial provides evidence of benefit in stroke risk reduction from closure with the AMPLATZER PFO Occluder over medical management alone**
 - **Primary analysis of ITT cohort was not statistically significant but trended towards superiority while secondary analyses suggested superiority**
 - **Stroke risk reduction was observed across the totality of analyses with rates ranging from 46.6% - 72.7%**
- **PFO closure with the AMPLATZER PFO Occluder exposes patients to a very low risk of device- or procedure-related complications**
- **Follow-up of patients is on-going and will continue to provide additional longer term information regarding benefits, risks, and differential treatment effects in sub-populations**



Oclusão Percutâneo de FOP

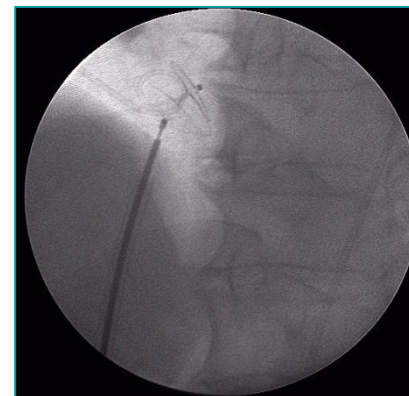
H. Santa Marta

RECORRÊNCIA DE EVENTOS EMBÓLICOS EM DOENTES SUBMETIDOS A ENCERRAMENTO PERCUTÂNEO DE FORAMEN OVAL PATENTE

260 doentes (idade média 44 anos) com follow-up médio 36 meses submetidos a oclusão entre 2000-2010

- **mortalidade 1,2% (3 dts: 1 TEP, 1 AVC hemorrágico, 1 suicídio)**
- **recorrência de eventos isquémicos cerebrais 4 dts (1 AVC, 3 AIT – um FA “de novo”)**
- **taxa de recorrência anual de 1,3%**

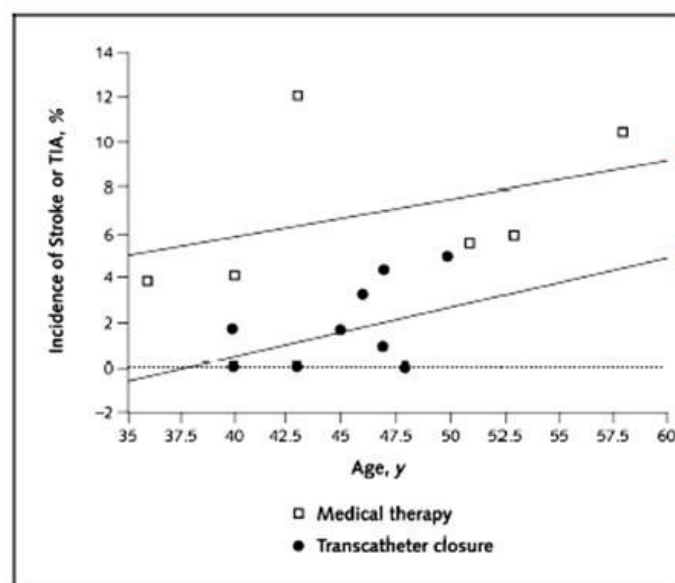
Ferreira F., CPC 2012





Meta Analysis Comparison of Recurrent Neurologic Event Rates

Figure 2. Incidence of recurrent events by patient age per study for medical therapy and transcatheter closure of patent foramen ovale.



Solid lines are regression lines; the dotted line marks the zero level. TIA = transient ischemic attack.

Medical Therapy

895 pts

Transcatheter Closure

1355 pts

Khaly P et al. Ann Intern Med.
2003;139:753-760



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

Conclusions Rates of RNE with transcatheter closure and medical therapy in patients presenting with cryptogenic stroke or TIA were estimated at 0.8 and 5.0 events/100 PY. Further randomized controlled trials are needed to conclusively compare these 2 management strategies. (J Am Coll Cardiol Interv 2012;5:777–89) © 2012 by the American College of Cardiology Foundation

Agarwal S. JACC Cardiovasc Interv 2012; 5:777



Neuroimaging Findings in Cryptogenic Stroke Patients With and Without Patent Foramen Ovale

Conclusions—This is the largest study to report the radiological characteristics of patients with cryptogenic stroke and known PFO status. Strokes that were large, radiologically apparent, superficially located, or unassociated with prior radiological infarcts were more likely to be PFO-associated than were unapparent, smaller, or deep strokes, and those accompanied by chronic infarcts. There was no association between PFO and multiple acute strokes nor between specific echocardiographic PFO features with neuroimaging findings.

Thaler DE. Stroke 2013; published online before print January 22 2013



Paradoxical embolism as a cause of silent brain infarctions in healthy subjects: the ICONS study (Identification of the Cause of Silent Cerebral Infarction in Healthy Subjects)

- **RESULTS:**

Amongst 1103 consecutive healthy adults who underwent MRI, 347 (31%) had one or more SBIs located outside the perforating artery territory, suggesting embolism. Amongst them, 253 subjects underwent agitated saline TCD monitoring and 128 (51%) had right-to-left shunts (RLS). The prevalence of RLS was similar to cryptogenic embolic stroke (62.0%, $P = 0.056$), but higher than in patients with other stroke subtypes (36.2%, $P = 0.021$). Amongst subjects with silent brain infarctions, absence of microangiopathy leukoaraiosis was the only factor associated with RLS (OR 1.78; 95% CI 1.01-3.14; $P = 0.046$).

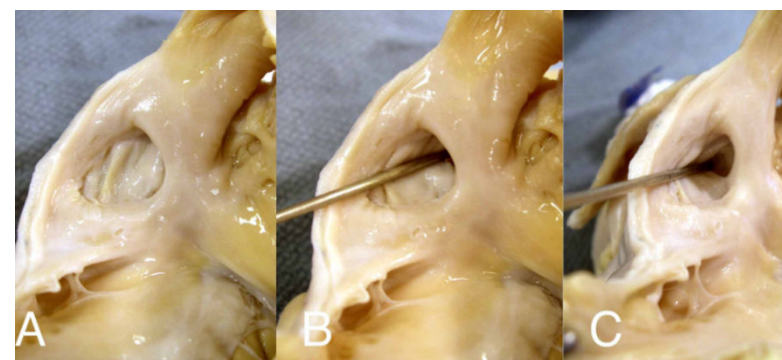
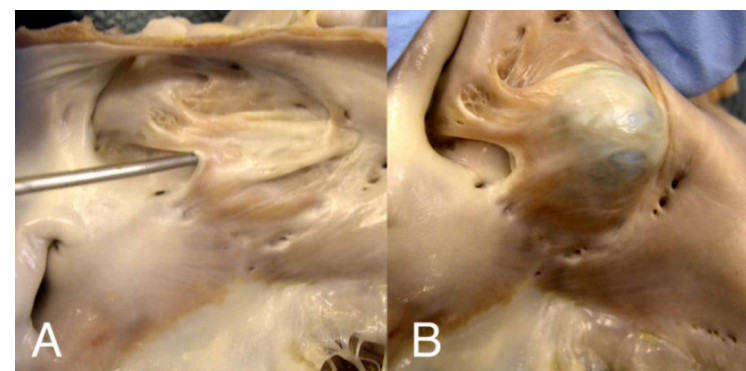
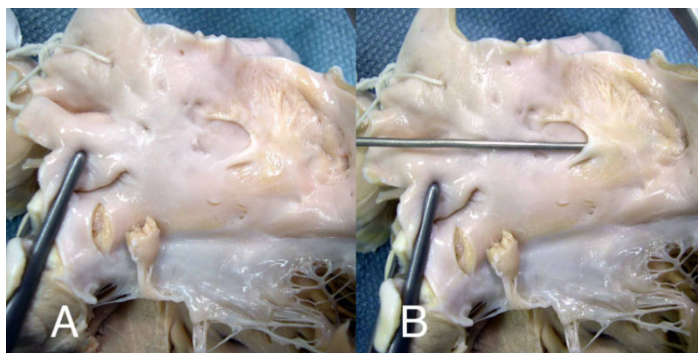
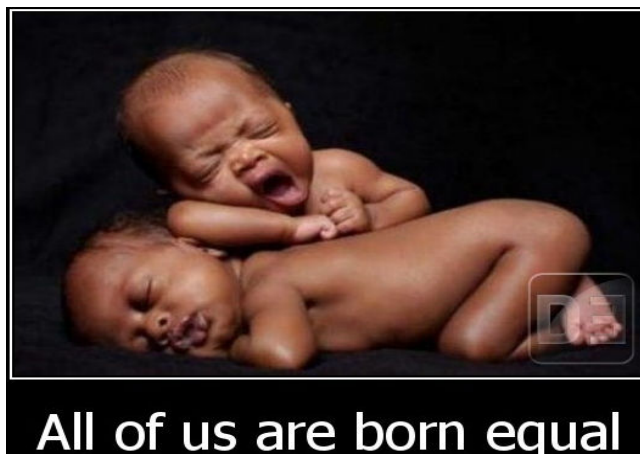
- **CONCLUSION:**

Our results suggest that paradoxical embolism may play an important role in the development of silent brain infarctions outside the perforating artery territory in apparently healthy adults.



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Bass, JL, CSI Frankfurt 2007



É mesmo um AVC criptogénico?



- « cryptogenic » stroke is the most difficult diagnosis
- Consider PFO + ASA as a potential cause only if you are confident with your negative work-up

Theoretically required:

« Cardiac source »

Clinical and neuroimaging features

No other cause

Complete evaluation

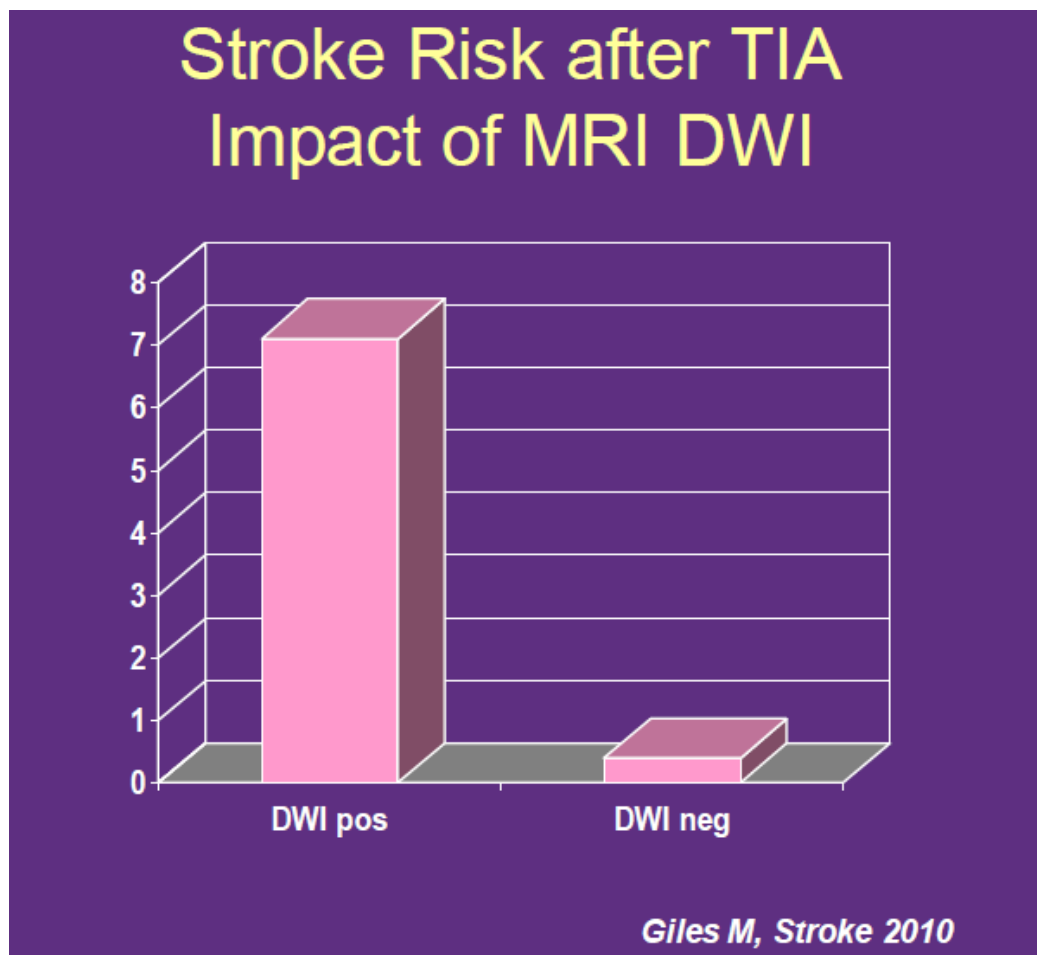
Real world:

- Sources uncertain
- Nonspecific syndrome, imaging sometimes normal (TIAs)
- 15-25% with coexisting causes
- Often incomplete

FA paroxística oculta / dc aterosclerótica aortica subclínica, ...



As implicações dos eventos ...





Long-term results of a comparison

“Ideal” PFO Device

- Soft enough not to damage cardiac structures, but stiff enough not to embolize
- Narrow enough for a tunnel, but able to fill the potential defect of a redundant PFO flap
- Cover the entire fossa ovalis
- Flattens the “aneurysm” of the atrial septum
- Small inventory
- No fractures, no erosions

of FU



O que dizer aos doentes?

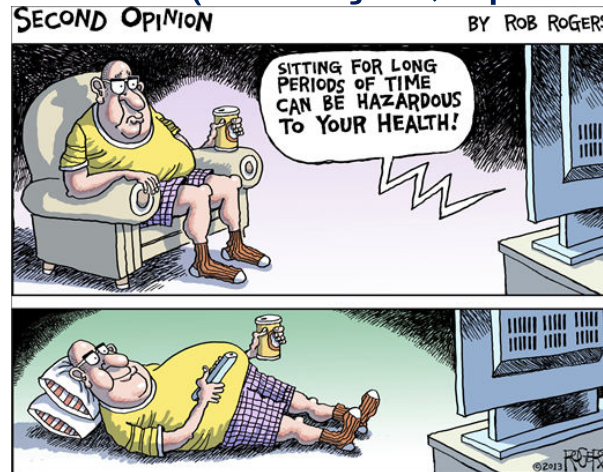
- It's a probability discussion. You can't tell anyone that you're going to prevent their next stroke. You can tell them the likelihood that you're going to reduce their risk over a period of years.“

Ted Feldman

Probabilidade



características do doente, do FOP, do AVC
aspectos técnicos (avaliação, operadores, centro)





Encerramento Percutâneo do FOP COMO AGIR PERANTE AS EVIDENCIAS MAIS RECENTES ?

- **Nunca em doentes assintomáticos !**
- **Encerramento em alguns doentes com AVC criptogénico**
- **Melhor selecção dos doentes criptogénico (estudo completo do AVC) e identificação de características de risco**
- **Discussão benefício / risco individualizada**
- **Aguardar novos estudos e resultados de follow-up mais longo dos já existentes**
- **Novos dispositivos (*endotelizáveis* / biodegradáveis)**



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“For those who believe, no explanation is necessary; for those who don't, no explanation is possible.”

Joseph Dunninger