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Novas Fronteiras
em Cardiologia

AVC Criptogénico: Está na altura de alterar as guidelines?

Claudia Jorge
University Hospital of Santa Maria

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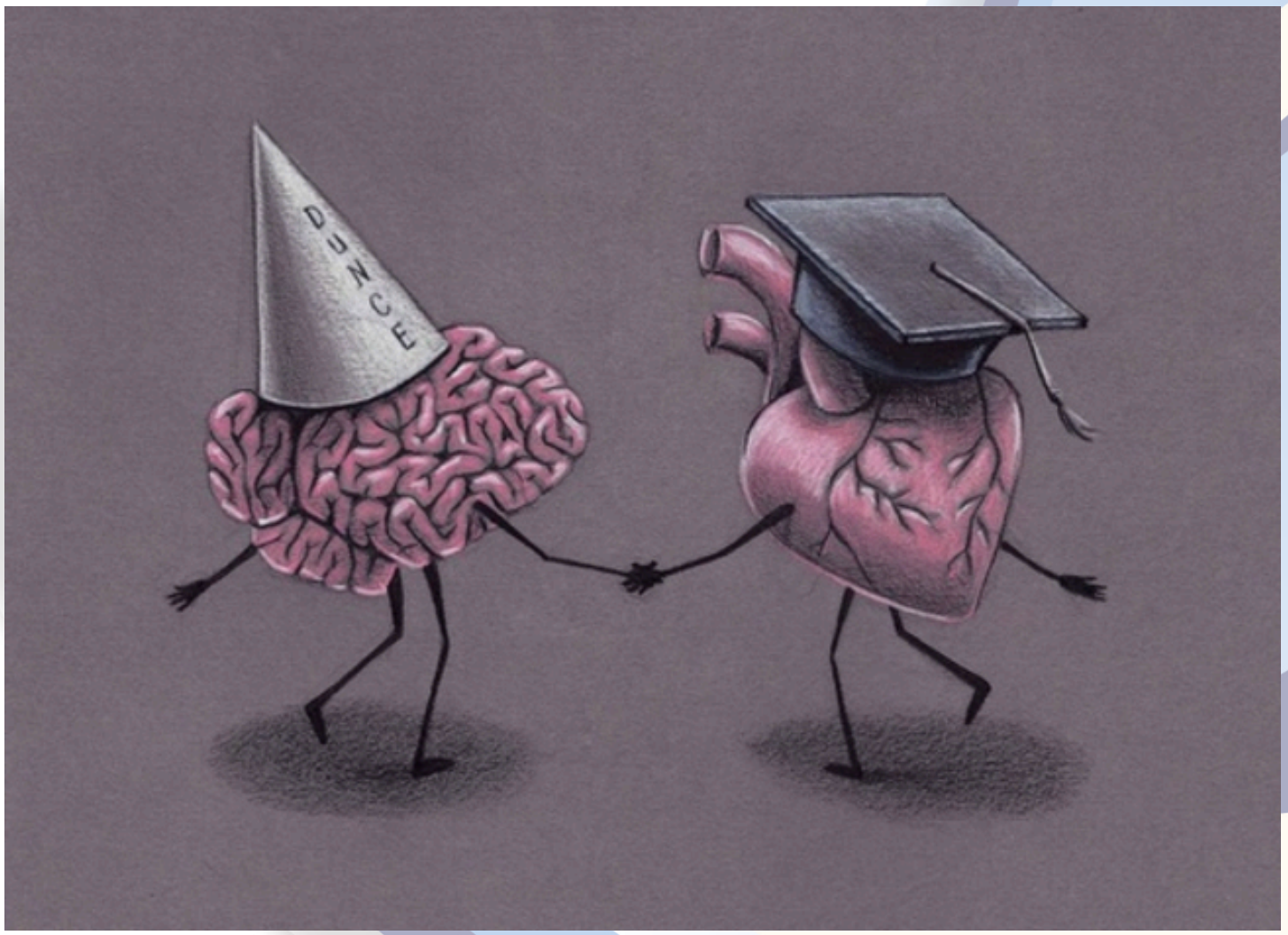

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- ~25% of all ischemic strokes are "cryptogenic"[1]
- 34-46% of ischemic strokes occur between 18-60 years [2]
- PFO present in 40-50% of cryptogenic stroke patients [3]
- Young and middle aged patients have continued exposure to PFO-related recurrence risk

Cryptogenic stroke remains a major challenge

- PFO-related strokes, i.e. due to paradoxical embolism, have been strongly implicated as a possible cause

1-Hart et al. Lancet Neurology 2014
2-Wolf et al. Cerebrovascular Dis 2015
3-Lechat et al. NEJM 1988
4-Kissela, et al, *Neurology* 2012

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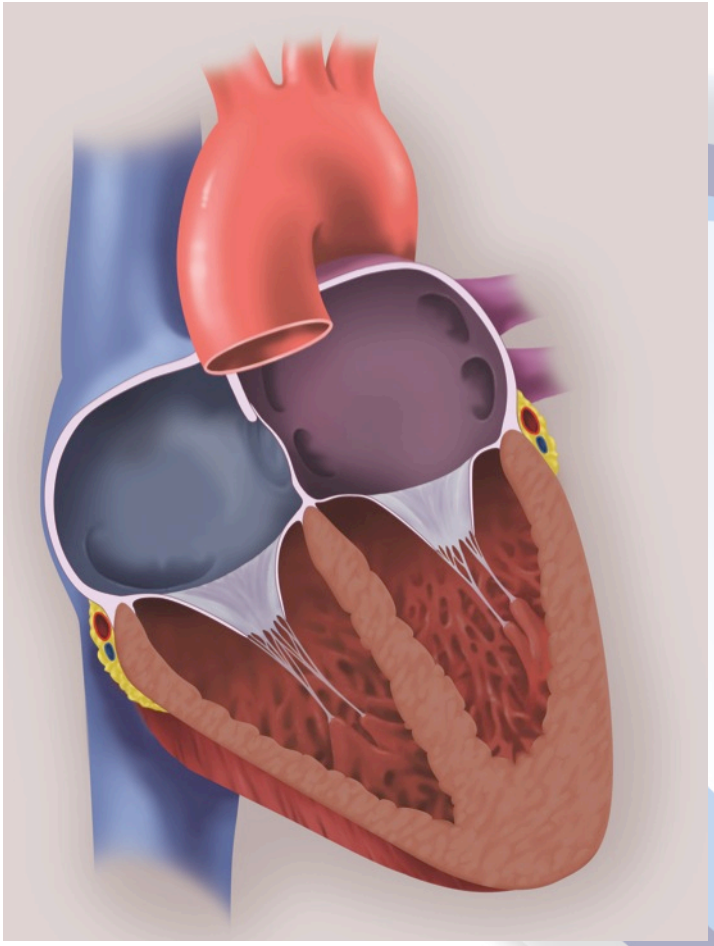
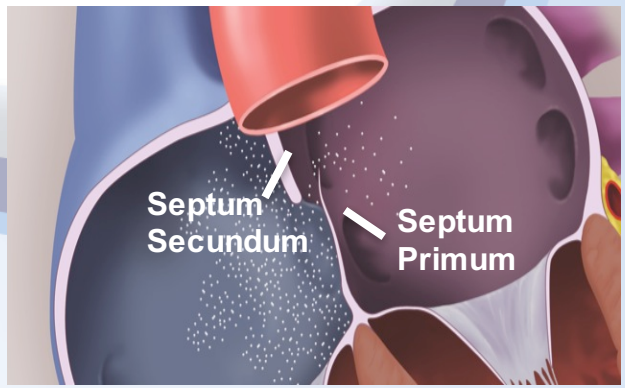
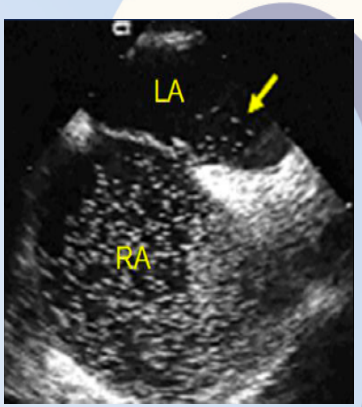
Normal appearing atrial septum

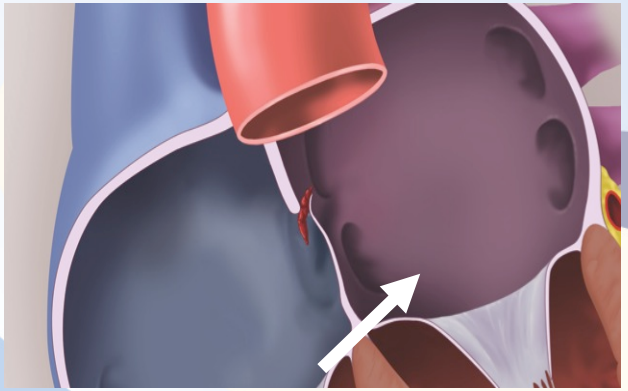


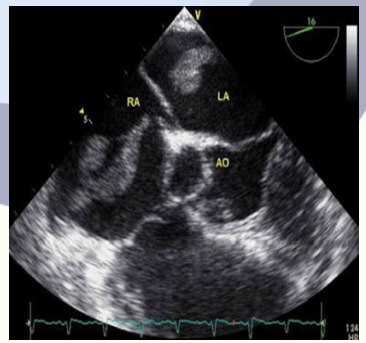
Agitated saline study demonstrating right to left shunting through the PFO





Blood clot passing through the PFO becoming a paradoxical embolism





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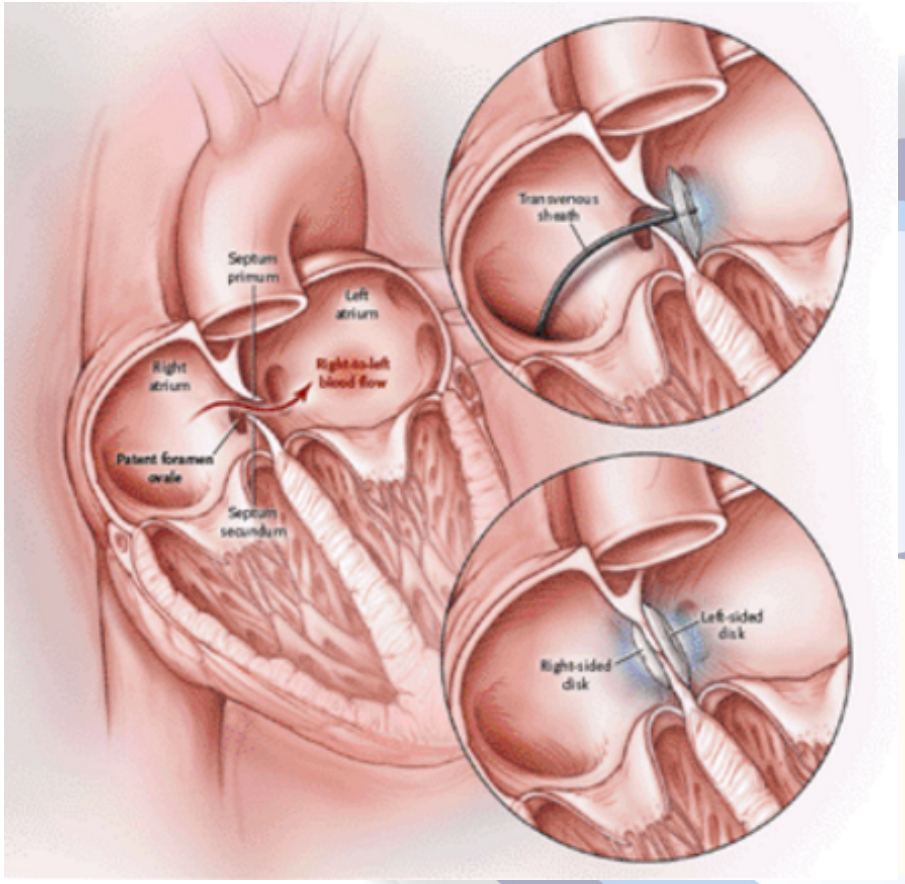

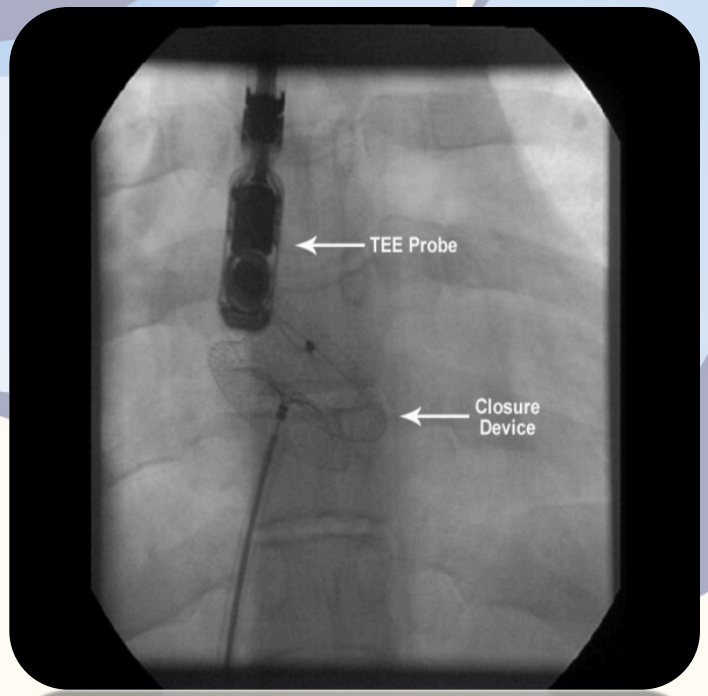

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CLOSURE Trial 2012

PC Trial 2013

RESPECT trial 2013

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Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale

Multicenter, randomized, open-label

Starflex device (NMT Medical, Boston, MA) 2 years follow-up

PFO percutaneous closure (C)(n=4

Medical therapy (MT) (

86% eff

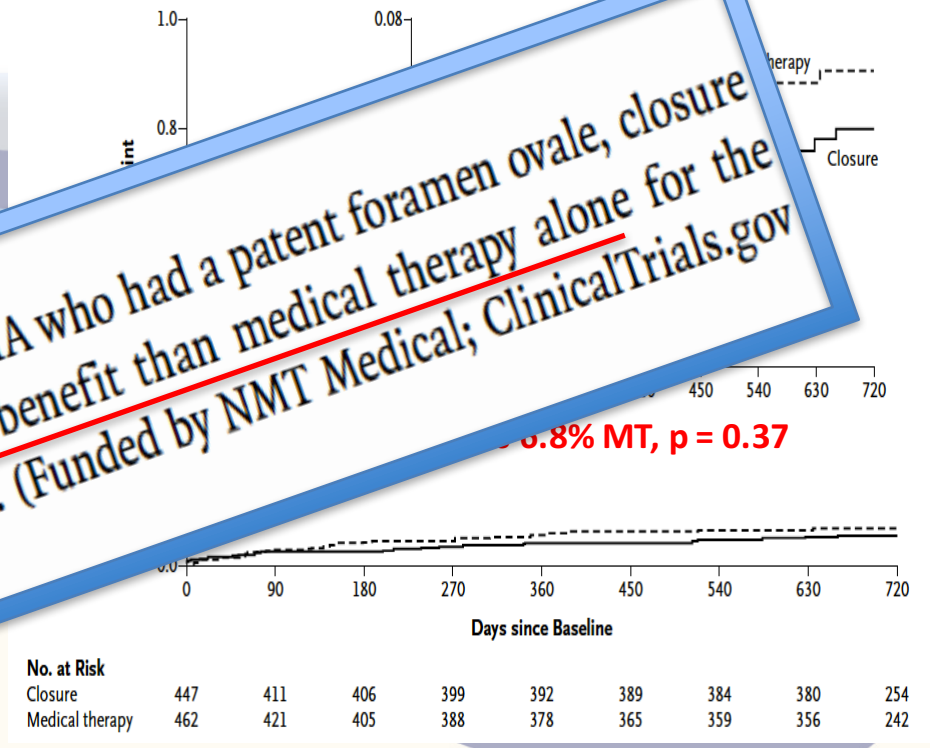
3.2% ma

AF: 5.7% PF p<0.001

Recurrent stroke: 2.9% closure vs 3.1% MT, risk difference – 0.13%

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.)



Primary end point

stroke or TIA (2 years)

death from any cause (first 30 days)

death from neurologic causes (31 days and 2 years)

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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

Multicenter, randomized, open-label

AMPLATZER PFO (St. Jude Medical,Inc, St. Paul, MN)

PFO percutaneou

Medi

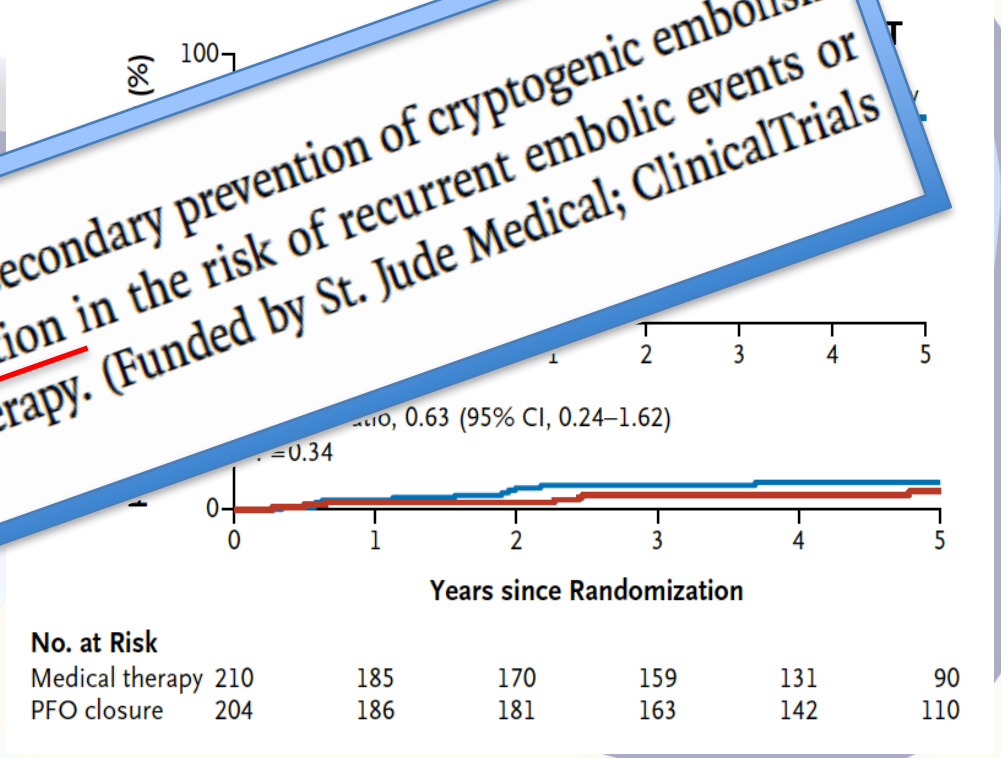
4 yea

Bleedi , p=0.4

AF: 2.9% MT, p=0.16

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.)



Recurrent stroke:
0.5% closure vs 2.4% MT, p=0.14

Primary end point

Composite of death from any cause

non-fatal stroke, TIA

peripheral embolism

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Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

Multicenter, randomized, open-label

AMPLATZER PFO (St. Jude Medical,Inc, St. Paul, MN)

2.5 years follow-up

PFO percuta

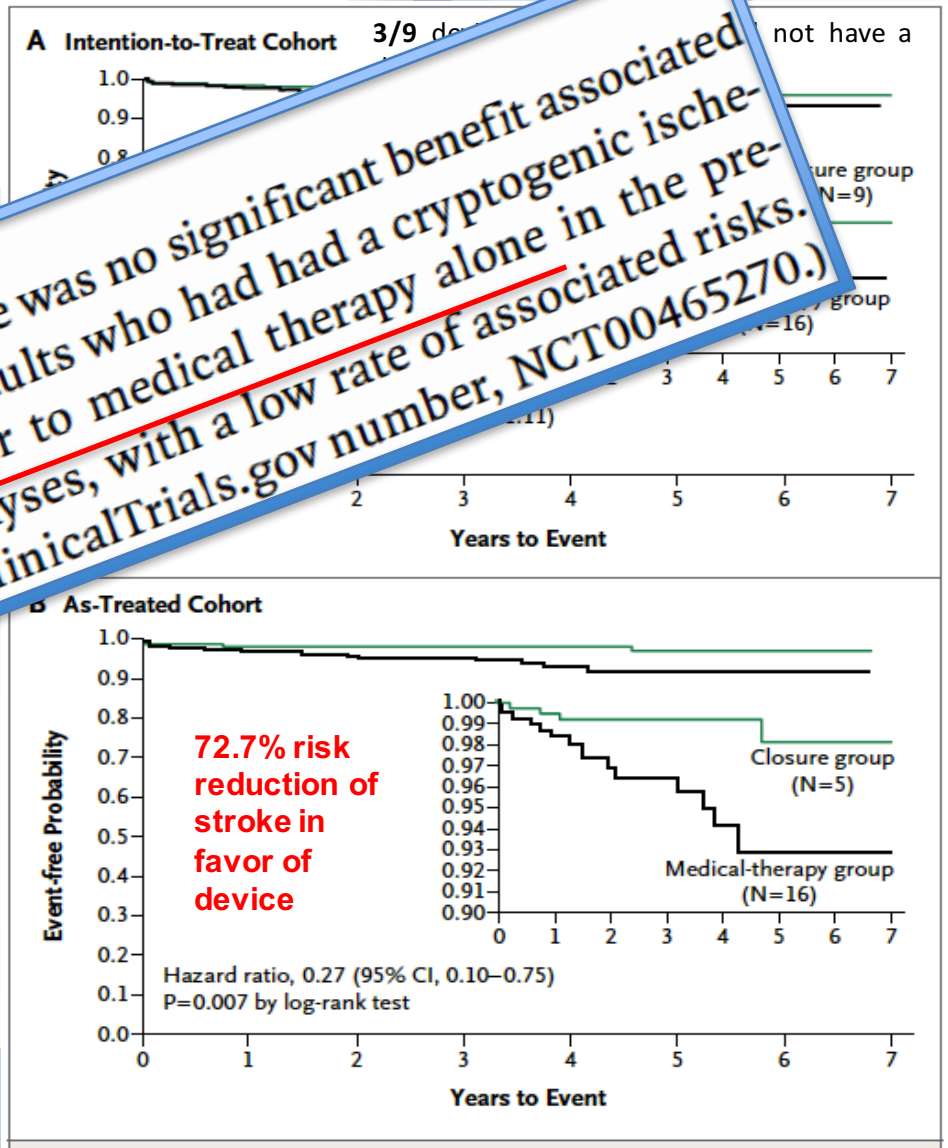
M

L .9% MT, p=0.8

AF: % PFO C vs 1.5% MT, p=0.13

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. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)



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guidelines?

Published Ahead of Print on July 27, 2016 as 10.1212/WNL.0000000000002961

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter)

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Steven R. Messé, MD
Gary Gronseth, MD
David M. Kent, MD, MSc
Jorge R. Kizer, MD, MSc
Shunichi Homma, MD
Lee Rosterman, DO
Scott E. Kasner, MD, MSCE

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To update the 2004 American Academy of Neurology guideline for patients with stroke and patent foramen ovale (PFO) by addressing whether (1) percutaneous closure of PFO is superior to medical therapy alone and (2) anticoagulation is superior to antiplatelet therapy for the prevention of recurrent stroke.

Methods: Systematic review of the literature and structured formulation of recommendations.

Conclusions: Percutaneous PFO closure with the STARFlex device possibly does not provide a benefit in preventing stroke vs medical therapy alone (risk difference [RD] 0.13%, 95% confidence interval [CI] −2.2% to 2.0%). Percutaneous PFO closure with the AMPLATZER PFO Occluder possibly decreases the risk of recurrent stroke (RD −1.68%, 95% CI −3.18% to −0.19%), possibly increases the risk of new-onset atrial fibrillation (AF) (RD 1.64%, 95% CI 0.07%–3.2%), and is highly likely to be associated with a procedural complication risk of 3.4% (95% CI 2.3%–5%). There is insufficient evidence to determine the efficacy of anticoagulation compared with antiplatelet therapy in preventing recurrent stroke (RD 2%, 95% CI −21% to 25%).

Recommendations: Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C). In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO (Level C). **Neurology® 2016;87:1–7**

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse event; **AF** = atrial fibrillation; **CI** = confidence interval; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HR** = hazard ratio; **INR** = international normalized ratio; **NNT** = number needed to treat; **PFO** = patent foramen ovale; **RCT** = randomized controlled trial; **RD** = risk difference; **RESPECT** = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

In 2004, the American Academy of Neurology (AAN) published a practice guideline addressing secondary stroke in patients with patent foramen ovale (PFO). The guideline concluded that the optimal therapy for secondary stroke prevention in this population was unknown.[1] Since that time, additional studies necessitated that we update our prior guideline, addressing the following therapeutic questions:

1. In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone?
2. In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does anticoagulation reduce the risk of stroke recurrence compared with antiplatelet medication?

This practice advisory is not intended to be a comprehensive guideline for the management of other stroke risk factors or causes. The primary audiences are neurologists, cardiologists, and other clinicians caring for patients with cryptogenic ischemic stroke and PFO.

DESCRIPTION OF THE ANALYTIC PROCESS This practice advisory follows the methodologies outlined in the 2011 edition of the AAN's guideline development

Supplemental data at Neurology.org

From the Department of Neurology (S.R.M., S.E.K.), University of Pennsylvania School of Medicine, Philadelphia; Department of Neurology (G.G., L.R.), University of Kansas Medical Center, Kansas City; Institute for Clinical Research and Health Policy Studies (D.M.K.), Tufts University School of Medicine, Boston, MA; Department of Medicine (Cardiology) and Epidemiology and Population Health (J.R.K.), Albert Einstein College of Medicine, Bronx; and Division of Cardiology (S.H.), Columbia University Medical Center, New York, NY.

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on April 22, 2015; by the Practice Committee on August 25, 2015; and by the AAN Institute Board of Directors on June 2, 2016.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter)

Conclusions. For patie … and PFO, percutaneo … STARFlex device:

1. Possibly does not pro… ing stroke in place o… 0.13%, 95% CI -2.2… the risk of new-onset … 8% (1 Class I study, … for risk of bias relativ…
2. Probably is associate… al complication risk … (1 Class I study).

1. Clinicians must counsel patients considering percutaneous PFO closure that having a PFO is common; it occurs in about 1 in 4 people; it is impossible to determine with certainty whether their PFOs caused their strokes or TIAs; the effectiveness of the procedure for reducing stroke risk remains uncertain; and the procedure is associated with relatively uncommon, yet potentially serious, complications (Level A).

… cryptogenic stroke … closure with the …

… f recurrent stroke— … 8% to −0.19%; … new-onset AF—RD … % (2 Class I studies; *w* for risk of bias rel- … und imprecision); … ed with a procedural … 5% CI 2.3%–5% (2 …

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Published Ahead of Print on July 27, 2016 as 10.1212/WNL.0000000000002961

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Methods: Systematic review of the literature and ...

Conclusions: Percutaneous PFO clo... in preventing stroke vs m... [CI] −2.2% to ...

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...ternal; **GRADE** = Grading of ... International normalized ratio; **NNT** = ...ntrolled trial; **RD** = risk difference; **RESPECT** = ...o Established Current Standard of Care Treatment.

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RESPECT protocol required follow-up until Food and Drug Administration (FDA) regulatory decision (data lock, August 2015)

FDA Advisory Panel in May 2016 requested a final analysis of long-term outcomes using updated data (data lock, May 2016)

In the ITT population, early and medium-term results in in RESPECT showed point estimates in favor of closure but did not reach statistical significance

Low event rates increase importance of longer follow-up

RESPECT Primary Endpoint Results

- Enrollment ended when 25 ischemic stroke events occurred - results were reported in NEJM

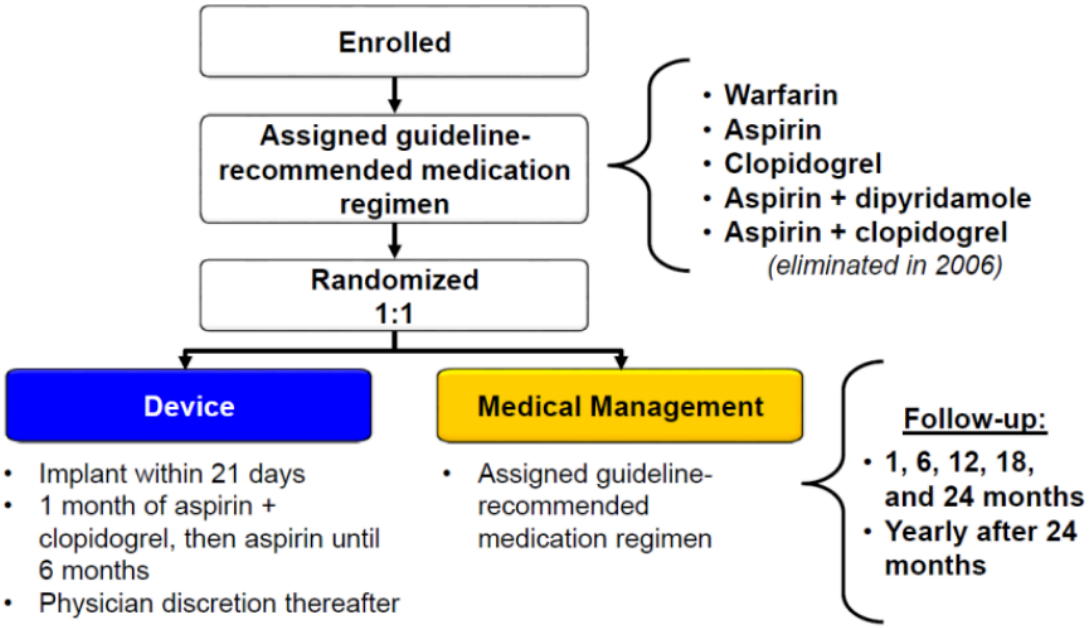
Analysis Population	Relative Risk Reduction	P-Value
Intention-to-Treat	50%	0.089
Per-Protocol	58%	0.048
As Treated	67%	0.013

Carroll et al. *NEJM* 2012;368:1092-100.
Note: Per Protocol and As Treated analysis modified from NEJM analysis in response to FDA questions.

tct2015 CRF

RESPECT
CLINICAL TRIAL

Patient Flow



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Primary Endpoint

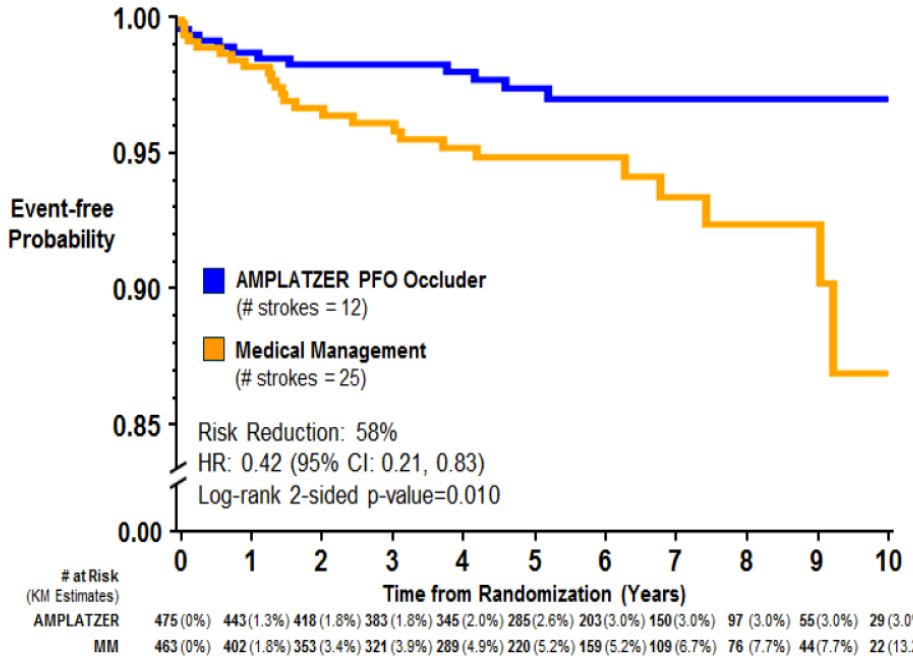
- **Composite of:**
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)
- **Stroke definition:**
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuroanatomically relevant infarct on imaging

      or
    - Symptoms >24 hours

RESPECT
CLINICAL TRIAL

RESPECT Final Results

Freedom from Recurrent Ischemic Stroke
(Intention to Treat – Patients censored at age 60 years)



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RESPECT
CLINICAL TRIAL

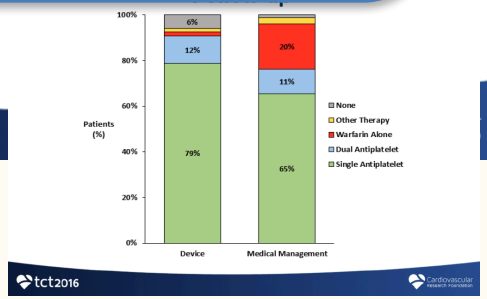
DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
-
-
-
-

Adjudicated SAEs of Interest

	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)	

In the RESPECT trial, for patients with cryptogenic stroke and PFO, closure with the AMPLATZER PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke, with very low risk



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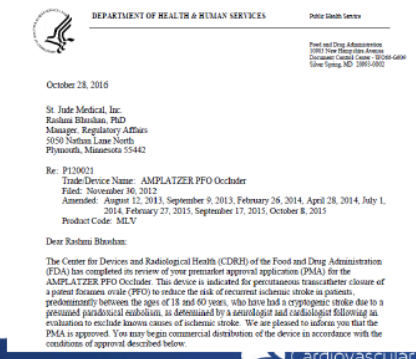
FDA Approval 10/28/16

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

CE-Mark in 1998; currently available in > 80 countries worldwide



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager, Regulatory Affairs
5050 Nathan Lane North
Plymouth, Minnesota 55442

Re: P120021
Trade/Device Name: AMPLATZER PFO Occluder
Filed: November 30, 2012
Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1, 2014, February 27, 2015, September 17, 2015, October 8, 2015
Product Code: MLV

Dear Rashmi Bhushan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AMPLATZER PFO Occluder. This device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

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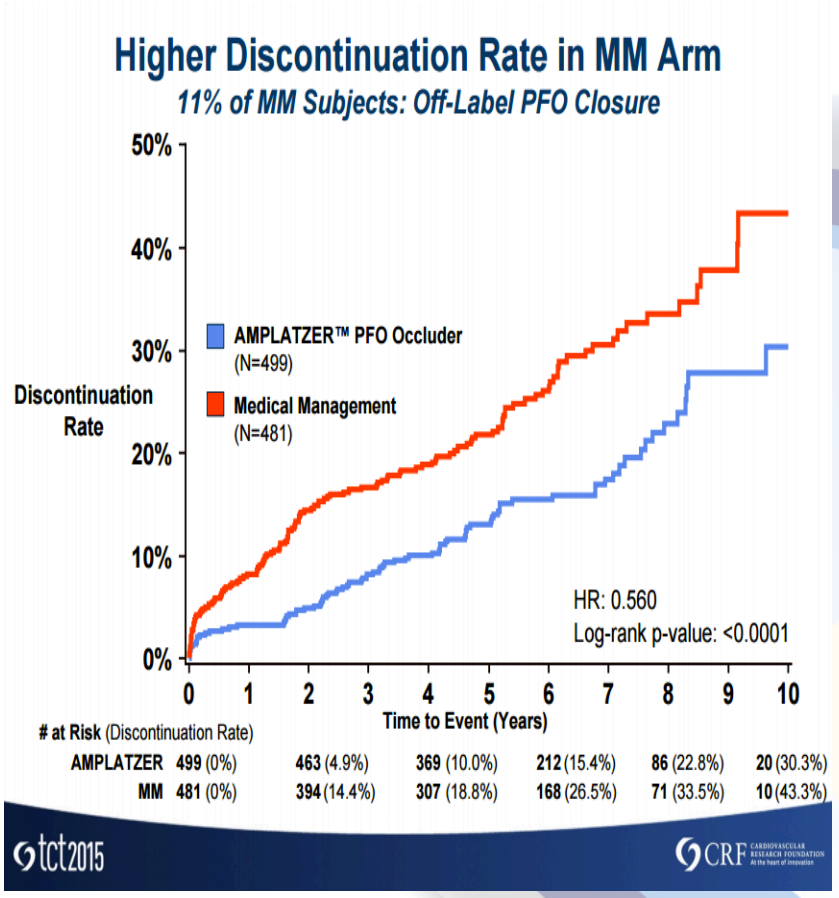

RESPECT TRIAL August 14, 2015,

Primary events
18 PFO Closure *vs* 24 MT events

Dropout rate
18.2% PFO Closure *vs* 30.1% MT

Atrial fibrillation
4.2% PFO Closure vs 1.9% MT

DVT or pulmonary embolism
18 PFO Closure *vs* 3 MT

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GORE® HELEX® Septal Occluder / GORE® Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients - The Gore REDUCE Clinical Study (HLX 06-03)

This study is ongoing, but not recruiting participants.

Sponsor:
W.L.Gore & Associates

Information provided by (Responsible Party):
W.L.Gore & Associates

ClinicalTrials.gov Identifier:
NCT00738894

First received: August 19, 2008
Last updated: April 21, 2016
Last verified: April 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

GORE® HELEX® Septal Occluder / GORE® Septal Occluder + antiplatelet medical *vs* antiplatelet medical management alone

Population: PFO and cryptogenic stroke or imaging-confirmed TIA

https://clinicaltrials.gov/ct2/show/NCT00738894

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Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)

This study has been completed.

Sponsor:
Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):
Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:
NCT00562289

First received: November 21, 2007
Last updated: February 2, 2017
Last verified: January 2017
History of Changes

Primary objective

assess whether chronic anticoagulation on the one hand and endovascular treatment on the other hand are superior to chronic antiplatelet therapy

https://clinicaltrials.gov/ct2/show/NCT00562289?term=close+pfo&rank=2

"For those who believe, no explanation is necessary; for those who don't, no explanation is possible."
Joseph Dunninger

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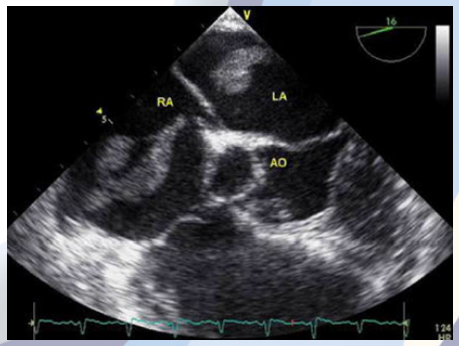
Está na altura de **voltar** a alterar as guidelines!

Claudia Jorge, Hospital de Santa Maria


Obrigada!
c_jorge@sapo.pt

- Nunca em doentes assintom.ticos !
- • Encerramento em alguns doentes com AVC criptog.nico
- • Melhor selec..o dos doentes criptog.nico (estudo completo do AVC) e
- identifica..o de caracter.sticas de risco
- • Discuss.o benef.cio / risco individualizada
- • Aguardar novos estudos e resultados de follow-up mais longo dos j.
- existentes
- • Novos dispositivos (endotelizáveis / biodegrad.veis)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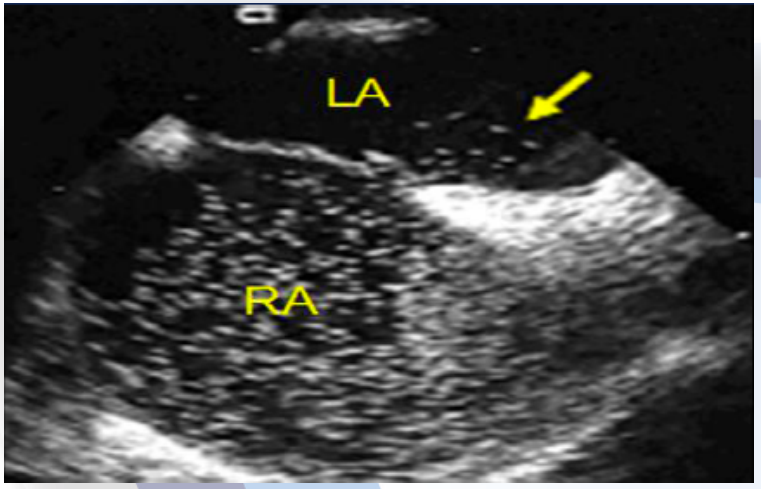
AO


LA
RA