



Il Paziente Fragile in cardiologia

CARDIOLOGI E MEDICI  
DI MEDICINA GENERALE  
"IN RETE"

La costruzione di percorsi condivisi

**SABATO 9 NOVEMBRE 2019**

Aula Carlo Ravetti  
Ospedale San Giovanni Bosco

# **Razionale ed indicazioni alla chiusura percutanea dell'auricola sinistra**

**Giacomo Boccuzzi, MD, FESC**

S.C Cardiologia  
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In 1955 Belcher *et al* suggested that the LAA could be amputated at mitral valvotomy as a means of prophylaxis of thromboembolism



ELSEVIER

European Journal of Cardio-thoracic Surgery 17 (2000) 711–722

## The left atrial appendage: our most lethal human attachment! Surgical implications

W. Dudley Johnson<sup>a,\*</sup>, A.K. Ganjoo<sup>b</sup>, Christopher D. Stone<sup>c</sup>, Ramahalli C. Srivyas<sup>a</sup>,  
Mary Howard<sup>a,d</sup>

turner tumours in the head itself. The prognosis is therefore uncertain and further resection may be required.

Another lesson to be learnt from this case is that focal neurological disturbances may result from hypoglycaemia. This was shown by focal pareses in the early history, focal twitchings in the later fits, and predominantly unilateral E.E.G. abnormality, corresponding to these manifestations. Black *et al.* (1954) reported a case developing a hemiplegia, and it seems that vascular insufficiency may be superimposed on the more diffuse pathological changes of hypoglycaemia described by Lawrence *et al.* (1952), and resembling the findings in cerebral anoxia.

In obscure cases of epilepsy of late onset when investigations have failed to reveal a cerebral neoplasm, the diagnosis of cortical atrophy or cerebral arteriosclerosis is sometimes too easily accepted. Even if the fits are of focal type the possibility of hyperinsulinism should always be explored. A single normal early morning blood sugar should not, however, be considered to exclude the diagnosis, and complete starvation for at least twelve hours may be essential to produce the characteristic clinical picture and abnormal

1000 OCT. 22, 1955

ADENOMATOSIS OF ISLETS OF LANGERHANS

BRITISH  
MEDICAL JOURNAL

reportedly fulfilled Whipple's diagnostic criteria—(a) neurological disturbances occurring while fasting, (b) blood sugar below 50 mg. per 100 ml., and (c) rapid relief on the administration of glucose.

In all the previously reported cases of adenomatosis of the islets the condition has been discovered either at necropsy or after subtotal resection of the pancreas occasioned by relapse of symptoms following previous removal of single adenomata. Many authors, including Black *et al.* (1954) recently, stress the dark red or plum-coloured appearance of these neoplasms, and their firm consistency as compared with normal pancreatic tissue.

Our case illustrates, however, that a state of adenomatosis may exist without any visible or palpable abnormality in the

Subtotal resection of an apparently entirely normal pancreas revealed the very rare condition of adenomatosis of the islets of Langerhans.

This patient was originally referred to one of us (E. R. B.) by Mr. J. M. Small. We wish to thank Mr. S. G. Smith, of the Biochemistry Department at Dudley Road Hospital, for carrying out the blood-sugar estimations, and Dr. W. Whitelaw, Director of Pathology, Dudley Road Hospital, for his advice and encouragement.

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EUROPEAN JOURNAL OF  
CARDIO-THORACIC  
SURGERY

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## EMBOLISM AND LEFT THROMBOSIS IN MITRAL VALVOTOMY

BY

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AND

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Department of Cardiology, the  
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themic embolism in rheumatic  
complicated before the introduc-

tion of surgery in the treatment of mitral valve disease. Some of the recent papers, such as those of Jordan, Scheiffley, and Edwards (1951), and of Wallach, Lukash, and Angrist (1953), were based on necropsy findings and must have included a number of cases which would have been too advanced or too complicated for surgery.

The incidence of embolism and auricular thrombosis may well be different in the fatal and in the operable cases. Apart from Wood (1954), few authors have referred in any detail to embolism in the latter group. We have therefore reviewed our cases in order to ascertain: (1) the clinical features of patients with systemic embolism before operation; (2) whether it is possible to diagnose left auricular thrombosis before operation; (3) the significance of previous embolism and of left auricular clot in relation to operative and post-operative embolism; (4) the influence of valvotomy on the incidence of late embolism.

## REVIEW

## Left atrial appendage structure, function, and role in thromboembolism

N M Al-Saady, G A Obel, A J Camm

- Remnant of the original embryonic LA developing during the 4th week of gestation
- 30% of ANP production
- Modulates relationships between pressure and volume

The most effective current prophylaxis of stroke in atrial fibrillation is warfarin. Warfarin is contraindicated in many patients, particularly in the elderly in whom the risk of stroke is highest. Alternative treatments are needed, and obliteration of the LAA is one such option. However, this is technically challenging and may result in unfavourable haemodynamic and hormonal effects, which could be particularly important in patients with left ventricular failure and valvar heart disease. Direct or thoracoscopic obliteration are possibilities, but technical aspects of the thoracoscopic procedure must be developed before it can be offered as an alternative.

Nel **90%** dei pazienti con FA non valvolare i trombi si formano in auricola sx

CURRENT REVIEWS

## Appendage Obliteration to Reduce Stroke in Cardiac Surgical Patients With Atrial Fibrillation

Joseph L. Blackshear, MD, and John A. Odell, FRCS(Ed)

Division of Cardiovascular Diseases, Mayo Clinic Jacksonville, Jacksonville, Florida and Division of Cardiovascular Surgery, Mayo Clinic, Rochester, Minnesota

**Background.** Left atrial appendage obliteration was historically ineffective for the prevention of postoperative stroke in patients with rheumatic atrial fibrillation who underwent operative mitral valvotomy. It is, however, a routine part of modern "curative" operations for nonrheumatic atrial fibrillation, such as the maze and corridor procedures.

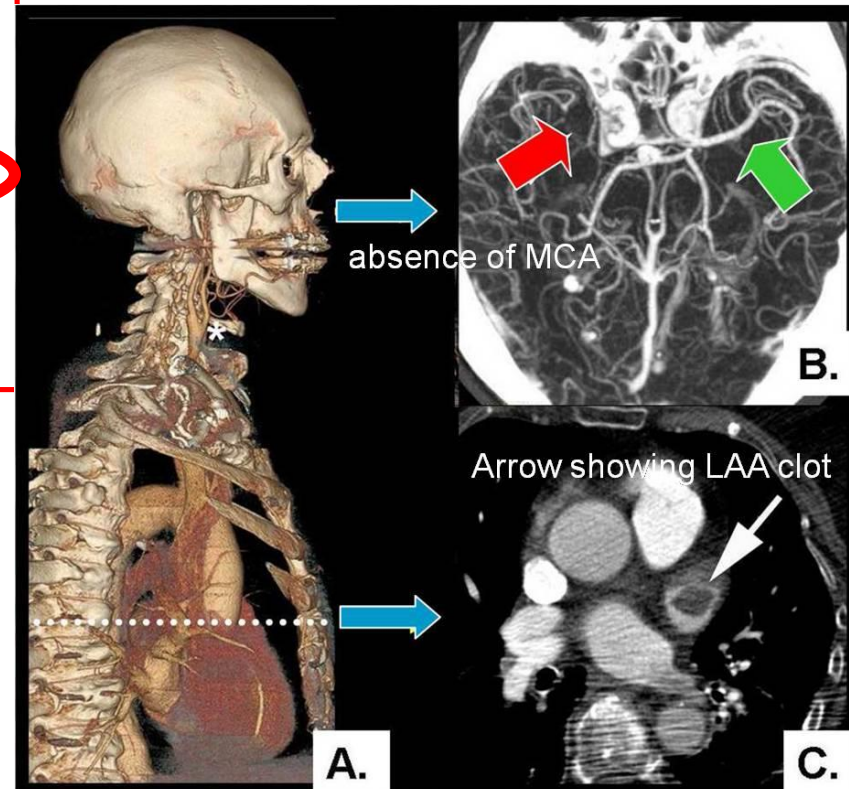
**Methods.** To assess the potential of left atrial appendage obliteration to prevent stroke in nonrheumatic atrial fibrillation patients, we reviewed previous reports that identified the etiology of atrial fibrillation and evaluated the presence and location of left atrial thrombus by transesophageal echocardiography, autopsy, or operation.

**Results.** Twenty-three separate studies were reviewed,

and 446 of 3,504 (13%) rheumatic atrial fibrillation patients, and 222 of 1,288 (17%) nonrheumatic atrial fibrillation patients had a documented left atrial thrombus. Anticoagulation status was variable and not controlled for. Thrombi were found to be present in the left atrial appendage and extended into the left atrial cavity in 254 of 446 (57%) of patients with rheumatic atrial fibrillation. In contrast, 201 of 222 (91%) of nonrheumatic atrial fibrillation-related left atrial thrombi were isolated to, or originated in the left atrial appendage ( $p < 0.0001$ ).

**Conclusions.** These data suggest that left atrial appendage obliteration is a strategy of potential value for stroke prophylaxis in nonrheumatic atrial fibrillation.

(Ann Thorac Surg 1996;61:755-9)

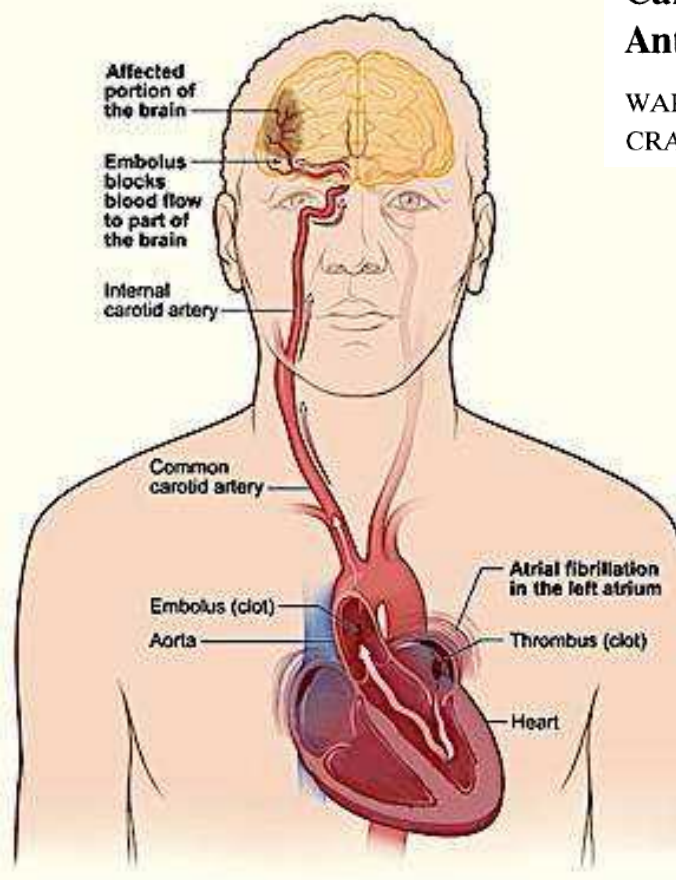




## Transesophageal Echocardiographically Facilitated Early Cardioversion From Atrial Fibrillation Using Short-Term Anticoagulation: Final Results of a Prospective 4.5-Year Study

WARREN J. MANNING, MD, FACC, DAVID I. SILVERMAN, MD, FACC,\*

CRAIG S. KEIGHLEY, MB, BS, PETER OETTGEN, MD, FACC, PAMELA S. DOUGLAS, MD, FACC



Setting	No. of Patients	Thrombus Location (n, %)		
		LA Appendage	LA Cavity	Total
TEE†	317	66 (20.8)	1 (0.3)	67 (21.1)
TEE	233	34 (14.6)	1 (0.4)	35 (15.0)
Autopsy	506	35 (6.9)	12 (2.4)	47 (9.3)
TEE	52	2 (3.8)	2 (3.8)	4 (7.7)
TEE	48	12 (25.0)	1 (2.1)	13 (27.1)
TEE and operation	171	8 (4.7)	3 (1.8)	11 (6.4)
ACUTE	549	67 (12.2)	9 (1.6)	76 (13.8)
TEE	272	19 (7.0)	0 (0)	19 (7.0)
TEE	60	6 (10.0)	0 (0)	6 (10.0)
<b>Total</b>	<b>2208</b>	<b>209 (11.3)</b>	<b>29 (1.3)</b>	<b>278 (12.6)</b>

Orhan Onalan and Eugene Crystal, *Stroke* 2007;38:624-630

# Changes in LAA in AF patients

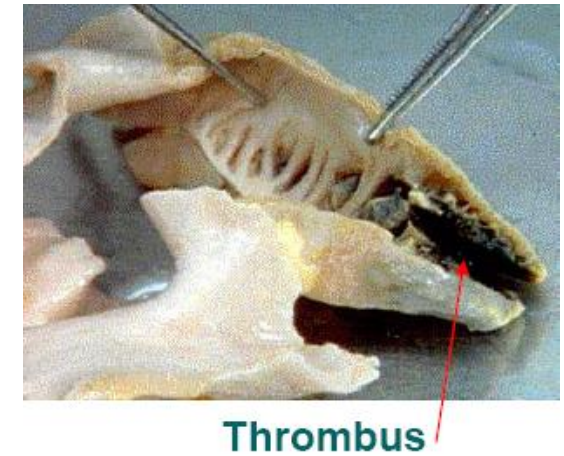
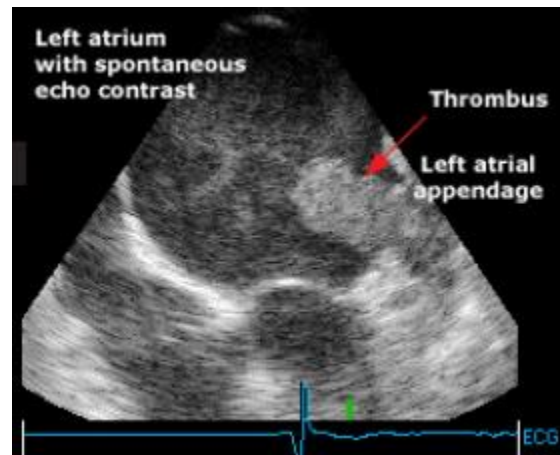
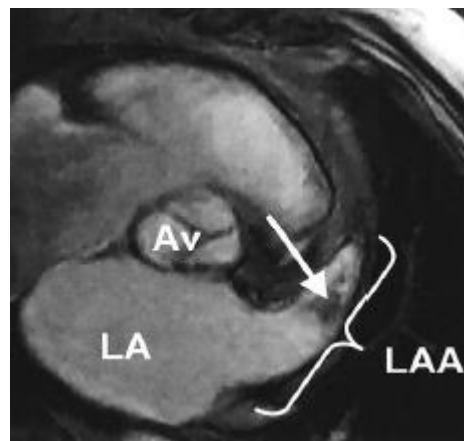
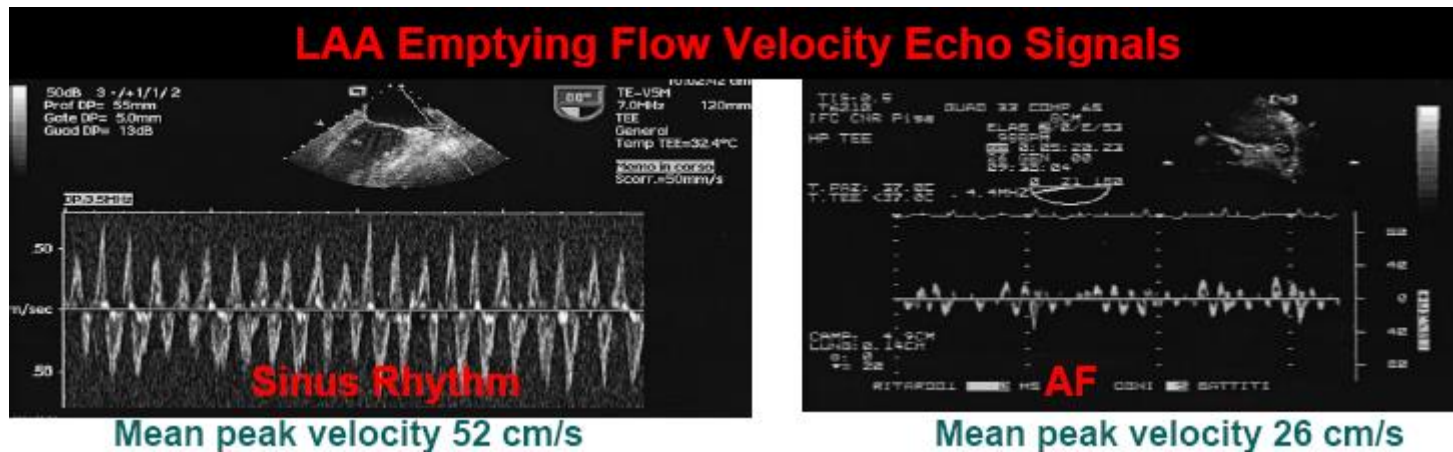
Decrease in LAA contractility and function

Dilation of the LAA

IREVIEWS  
STATE-OF-THE-ART PAPERS

The Left Atrial Appendage:  
Anatomy, Function, and  
Noninvasive Evaluation

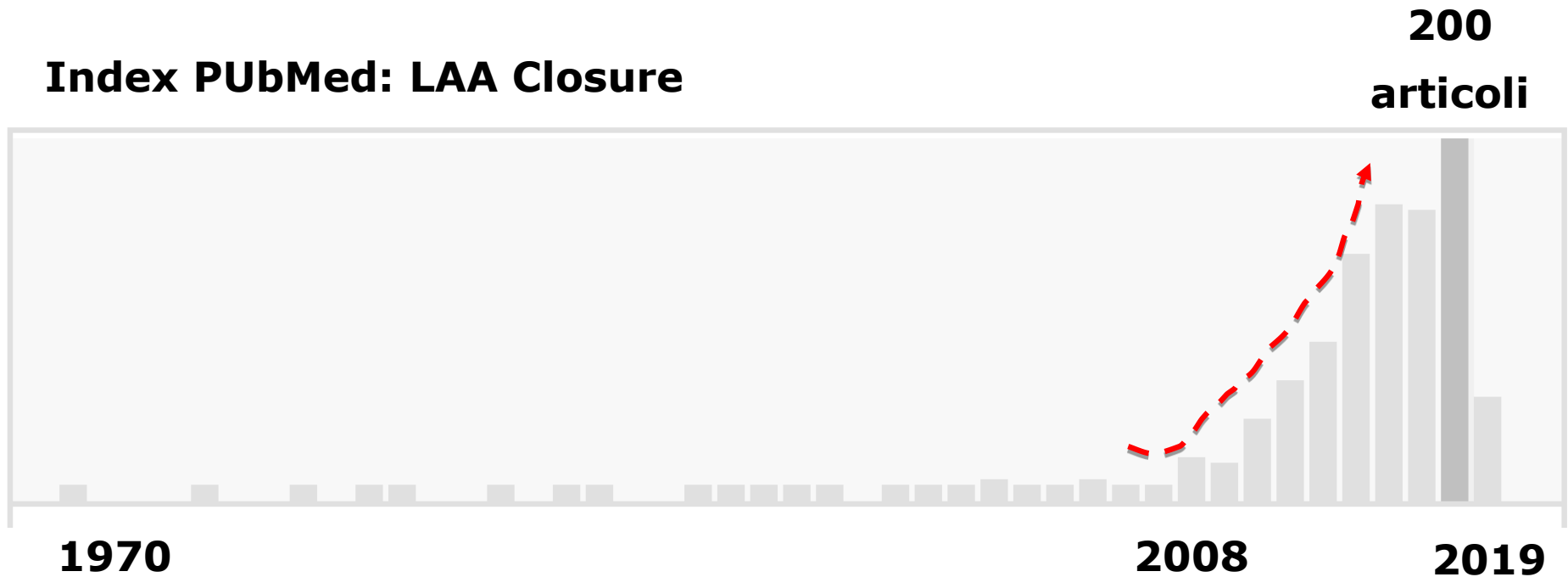
Roy Beigel, MD,\*; Nina C. Wunderlich, MD,; Siew Yen Ho, MD,; Reza Arsanjani, MD,\* Robert J. Siegel, MD\*



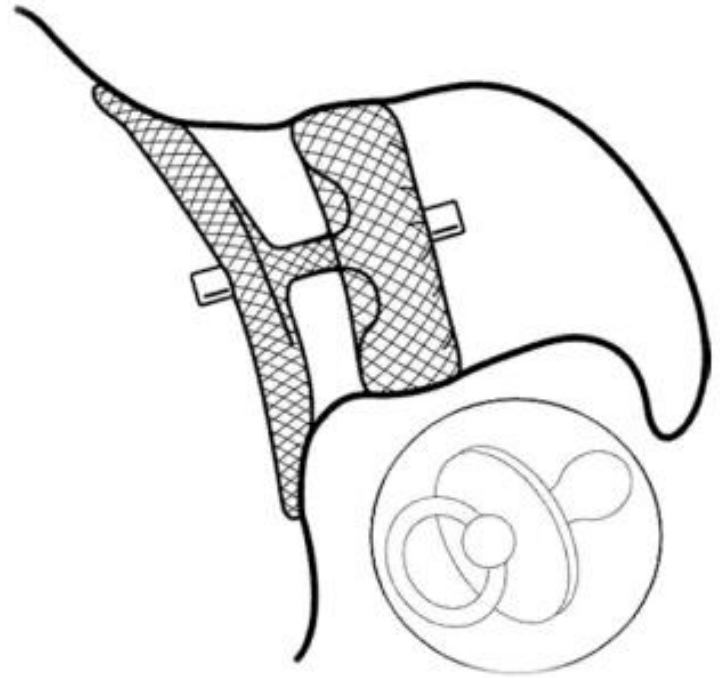
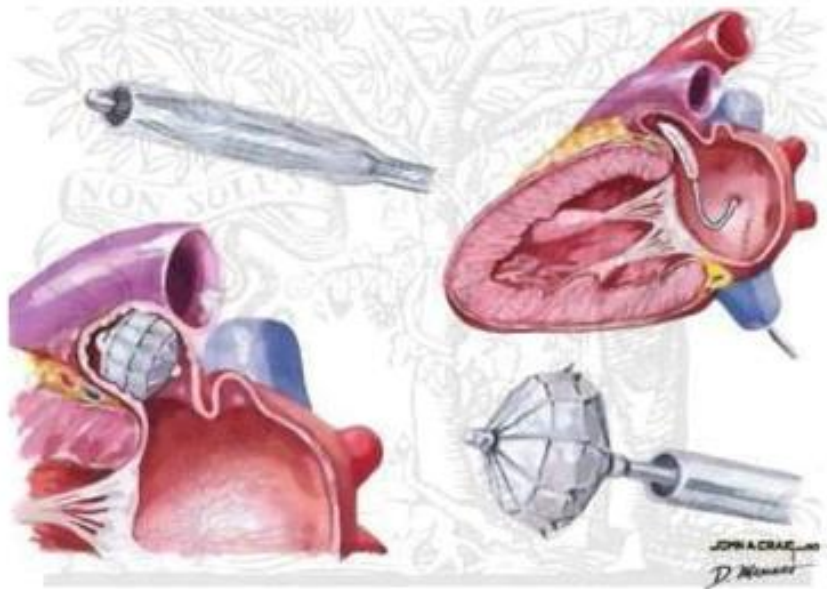
The remodeling process associated with AF causes the LAA to function as a static pouch, predisposing to stagnation and thrombosis

# Interesse della comunità scientifica

**Index PubMed: LAA Closure**

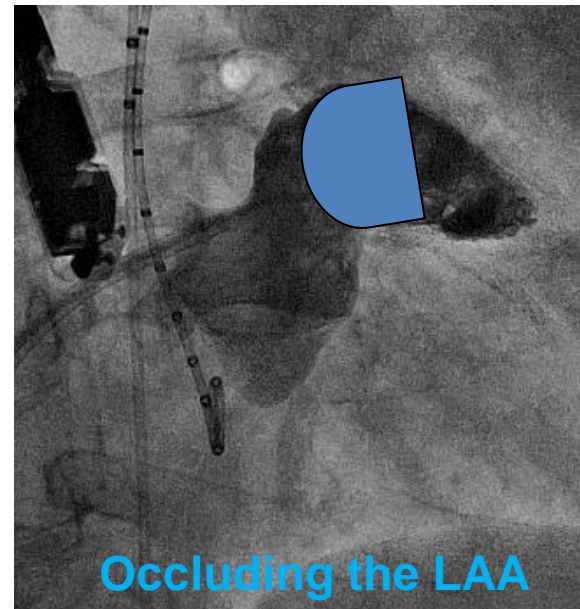
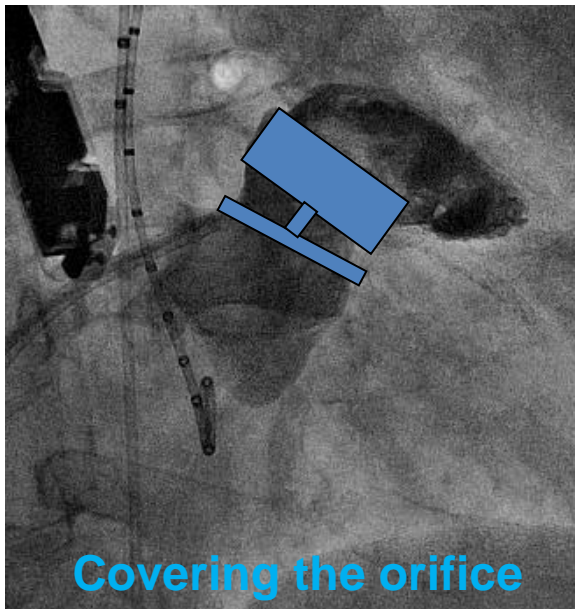
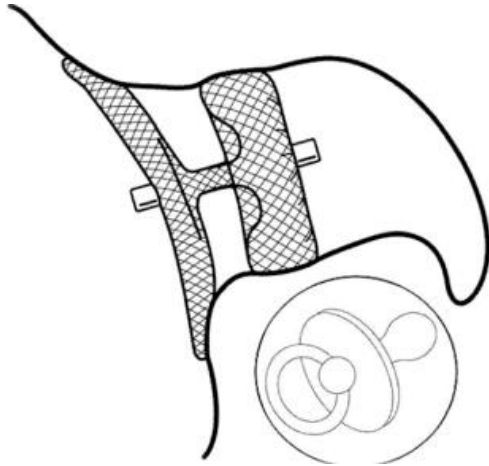


# Cos'è la chiusura percutanea dell'auricola sinistra?

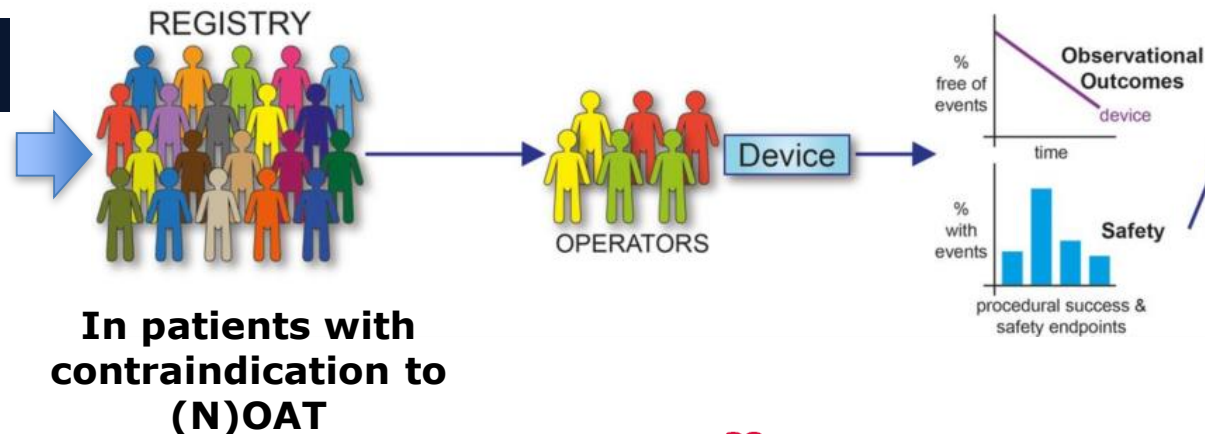
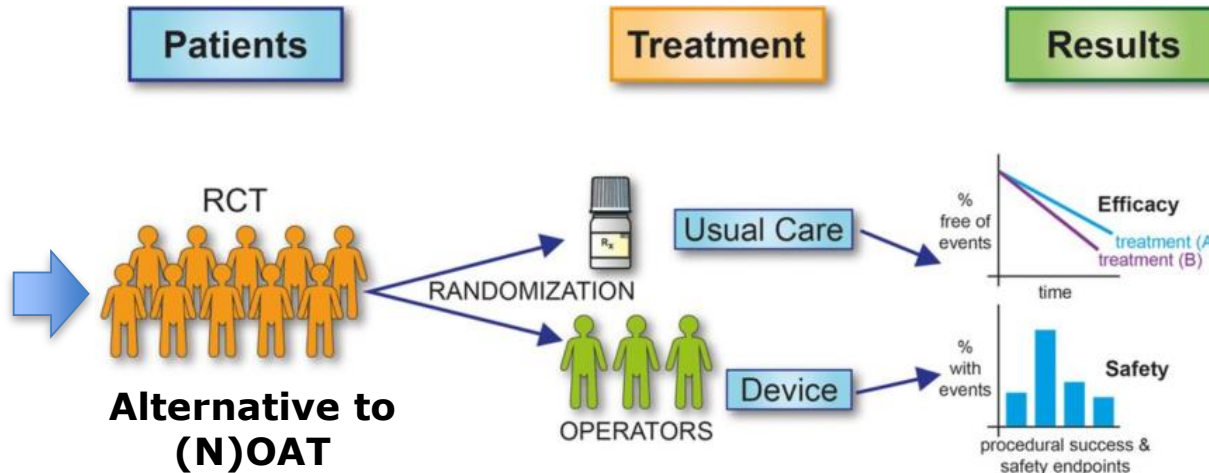




# ACP/Amulet vs. Watchman



# Evidenze scientifiche



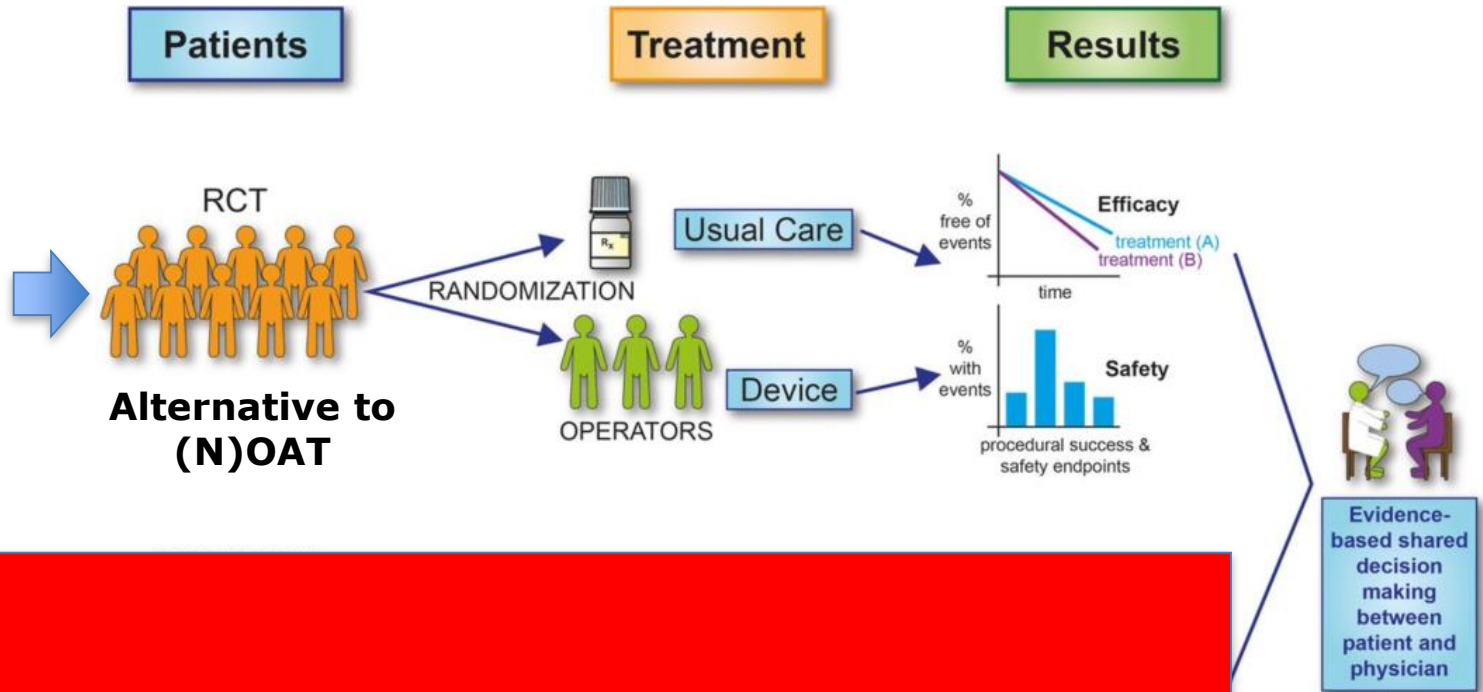
European Heart Journal (2016) 37, 2475–2477  
doi:10.1093/eurheartj/ehw041

**EDITORIAL**

**The evolution of left atrial appendage occlusion: EWOLUTION and the WATCHMAN in practice**

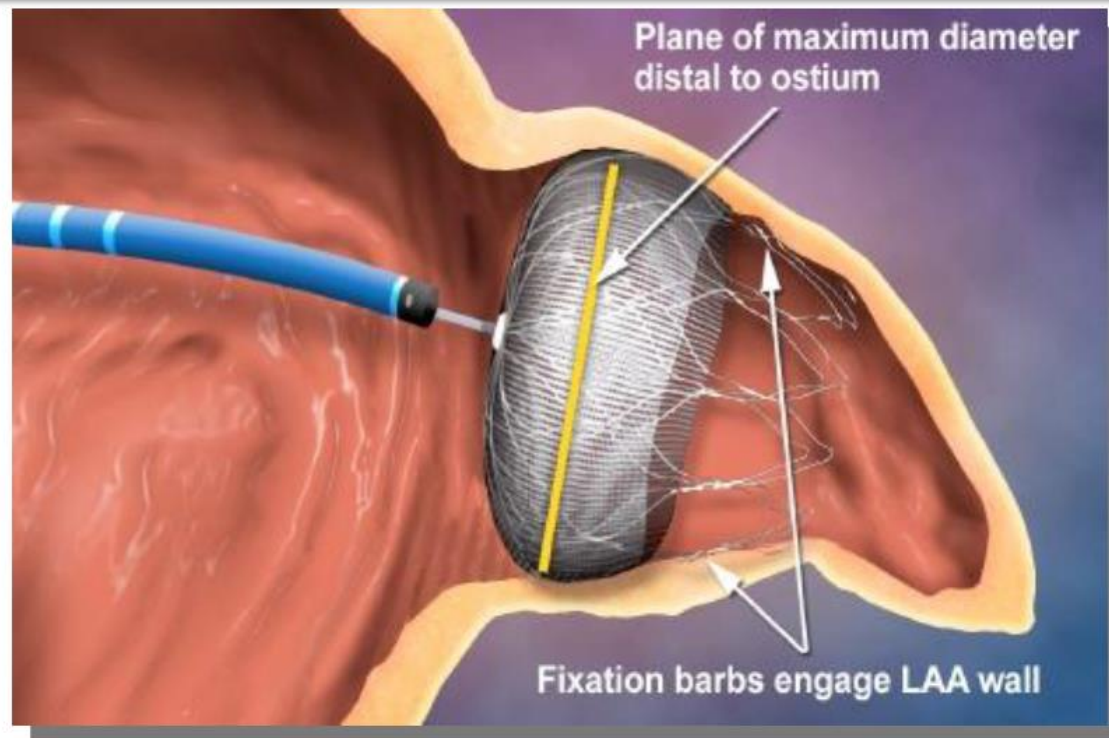
Frederick A. Masoudi<sup>1,2\*</sup>

# Alternative to (N)OAT



# Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators\*



Lancet 2009; 374: 534–42



- Prospective RCT, WATCHMAN vs warfarin (2:1 ratio) (707 patients randomly assigned, 93 roll-in)
- Patients with NVAF **eligible** for warfarin,  $\text{CHADS}_2 \geq 1$
- Noninferiority and superiority bayesian sequential design (analysis at 600 pt-y and every 150 pt-y thereafter till 1500 pt-y; follow-up to 5 y)
- 59 centers in Europe and United States, Feb 2005 to June 2008
- Exclusion criteria:
  - **Contraindications to warfarin**
  - Comorbidities requiring chronic warfarin use
  - LAA thrombus
  - PFO with atrial septal aneurysm + R-L shunt
  - Mobile aortic atheroma
  - Symptomatic carotid disease
  - $\text{LVEF} < 30\%$

### Anticoagulation Regimen

Implant to 6 wk

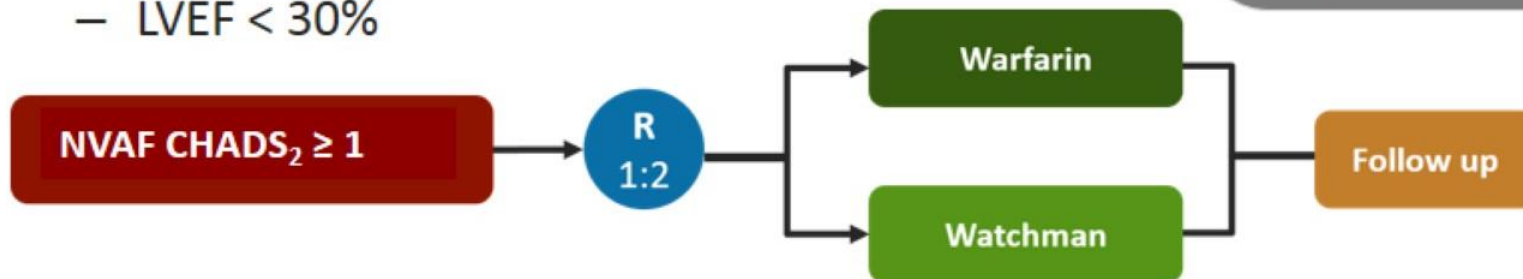
- Warfarin (INR 2 to 3) for 6 wk
- Aspirin (81 to 325 mg)

6 wk to 6 mo

- Clopidogrel (75 mg)
- Aspirin (81 to 325 mg)

After 6 mo

- Aspirin (81 to 325 mg)



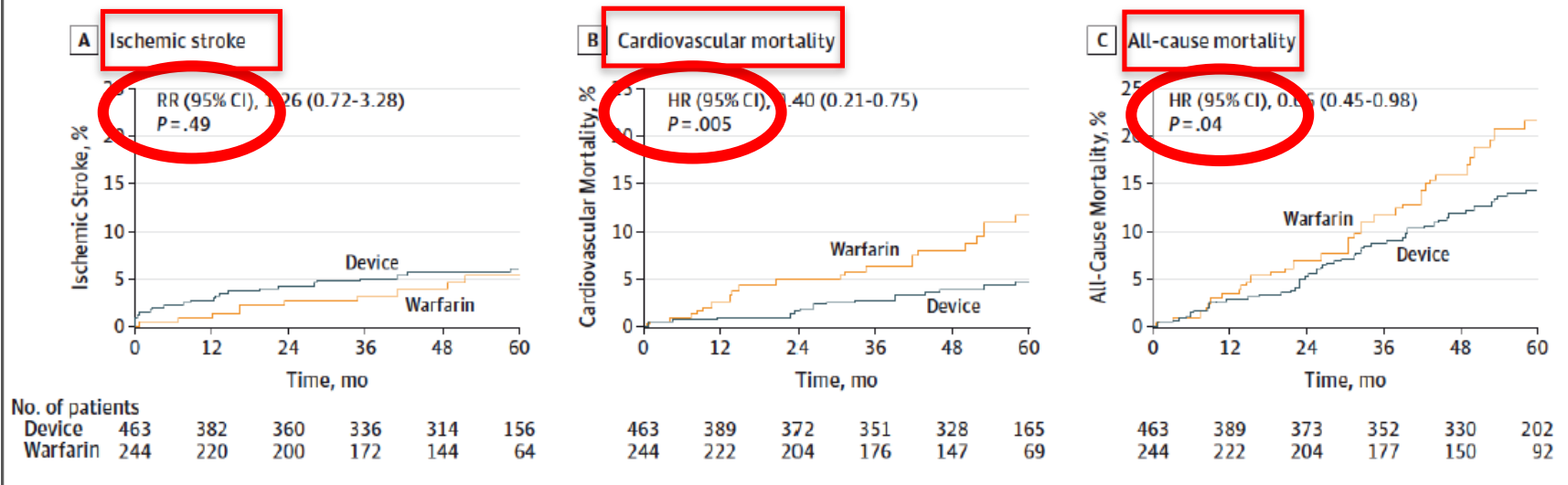
# PROTECT AF : 4 years follow up

## Original Investigation

### Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation A Randomized Clinical Trial

Vivek Y. Reddy, MD; Horst Sievert, MD; Jonathan Halperin, MD; Shephal K. Doshi, MD; Maurice Buchbinder, MD; Petr Neuzil, MD, PhD; Kenneth Huber, MD; Brian Whisenant, MD; Saibal Kar, MD; Vijay Swarup, MD; Nicole Gordon, BSEE; David Holmes, MD; for the PROTECT AF Steering Committee and Investigators

Figure 3. Kaplan-Meier Curves for Ischemic Stroke, Cardiovascular Mortality, and All-Cause Mortality



HR indicates hazard ratio; RR, rate ratio.

# WATCHMAN clinical Program

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## Post-FDA Approval US Experience (n = 3822)

Trial	Description	N
Pilot	Early feasibility, > 6 y follow-up	66
PROTECT AF	Primary efficacy, CV death, all-cause death superior to warfarin at 4 y	800

# WATCHMAN clinical Program

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# WATCHMAN clinical Program

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ASAP	Expected stroke rate reduced by 77%, patients contraindicated to warfarin	150
PREVAIL	Improved implant success and procedural study (new and experienced operators)	461

# WATCHMAN clinical Program

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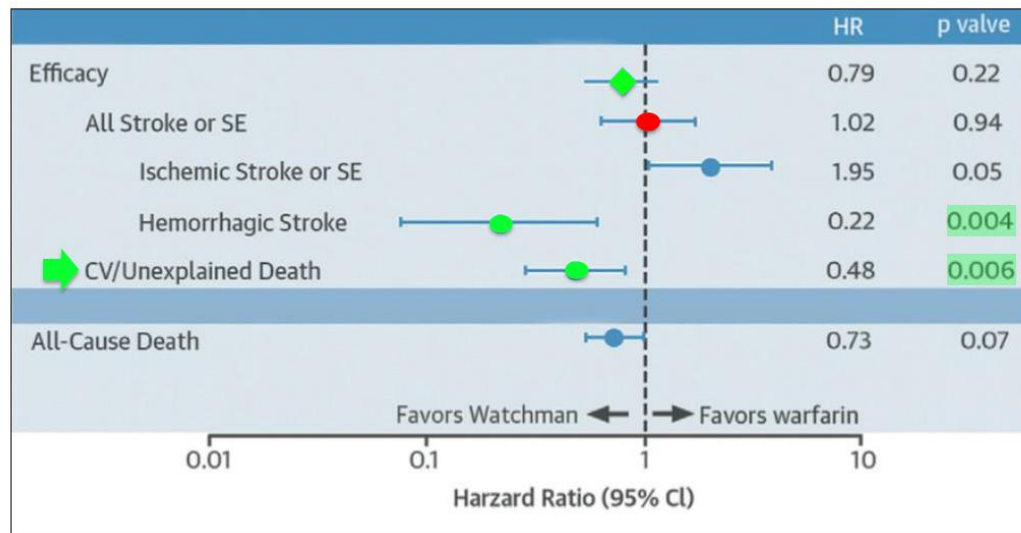
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**2015 : FDA Approval**

# Meta analysis Watchman studies

## Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation

A Patient-Level Meta-Analysis

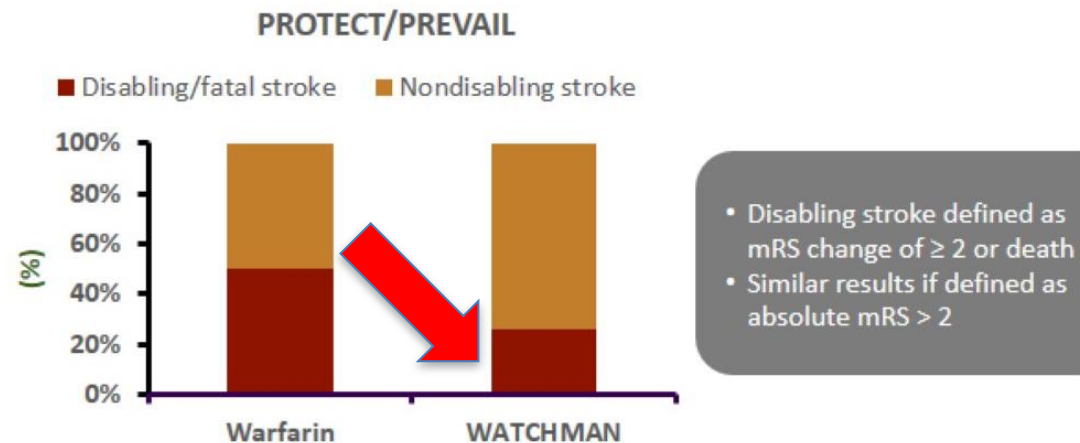


- WATCHMAN is indicated to reduce the risk for thromboembolism from the LAA in patients with NVAF who are at increased risk for stroke and SE based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores
- Patients who are deemed by their physicians to be suitable for warfarin and have an appropriate rationale to seek a nonpharmacologic alternative to warfarin

**FDA Approval**

# Gravità dello Stroke/TIA in base al trattamento

	LAA Closure	Warfarin	NOACs
Stroke Outcomes			
Nondisabling stroke (MRS 0 to 2), %	75.8	24.0	44.0
Moderately disabling (MRS 3), %	3.0	29.0	21.4
Severely disabling (MRS 4 to 5), %	15.2	35.0	25.8
Fatal stroke (MRS 6), %	6.1	12.0	8.8





# Contraindication to (N)OAT

Patients

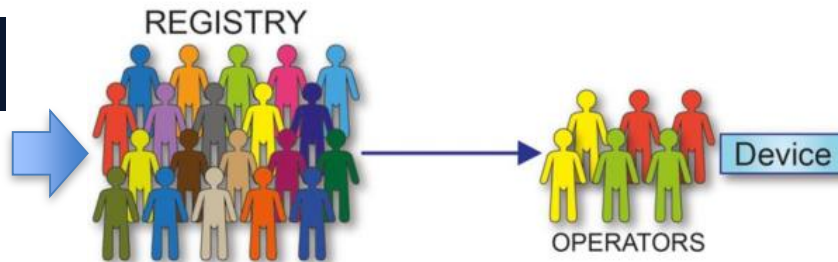
Treatment

Results

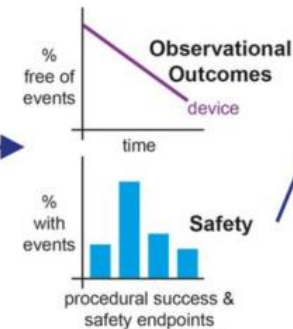


Evidence-based shared decision making between patient and physician

EUROPE



**In patients with  
contraindication to  
(N)OAT**



# In patients with contraindication to (N) OAT

## Results of the Amplatzer Cardiac Plug European Multicenter Observational Study

Jai-Wun Park, MD

- Multi-center, n=204 pts
- Procedural success 96.6%
- Major complication 2.9%
- Ischemic stroke 1.98%/yr (↓ **65%\***)

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### CLINICAL RESEARCH

### Mini-Focus: Left Atrial Closure in Atrial Fibrillation

#### Percutaneous Left Atrial Appendage Closure With the AMPLATZER Cardiac Plug Device in Patients With Nonvalvular Atrial Fibrillation and Contraindications to Anticoagulation Therapy

Marina Urena, MD,\* Josep Rodés-Cabau, MD,\* Xavier Freixa, MD,† Jacqueline Saw, MD,‡  
John G. Webb, MD,§ Melanie Freeman, MD,§ Eric Horlick, MD,|| Mark Osten, MD,||  
Albert Chan, MD,¶ Jean-Francois Marquis, MD,¶ Jean Champagne, MD,\* Réda Ibrahim, MD†  
Quebec City, Quebec; Montreal, Quebec; Vancouver, British Columbia; Toronto, Ontario; and  
Ottawa, Ontario, Canada

- Single-center, n=52 pts
- Procedural success 98.1%
- Major complication 5.8%
- Ischemic stroke 2.3%/yr (↓ **68%\***)

\*Compared to estimate stroke rate

# Left atrial appendage occlusion for stroke prevention in atrial fibrillation

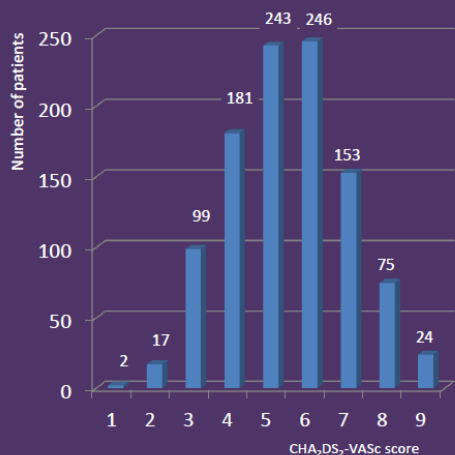
## Multicenter experience with the Amplatzer Cardiac Plug

**In patients with contraindication to (N) OAT**

1053 consecutive patients from 22 clinical sites in Europe and Canada, treated between December 2008 and November 2013.

### Stroke Risk Assessment

CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

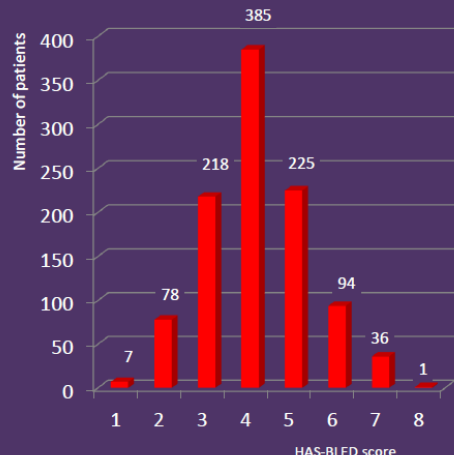


Mean  $4.5 \pm 1.6$

N=1047

### Bleeding Risk Assessment

HAS-BLED Score

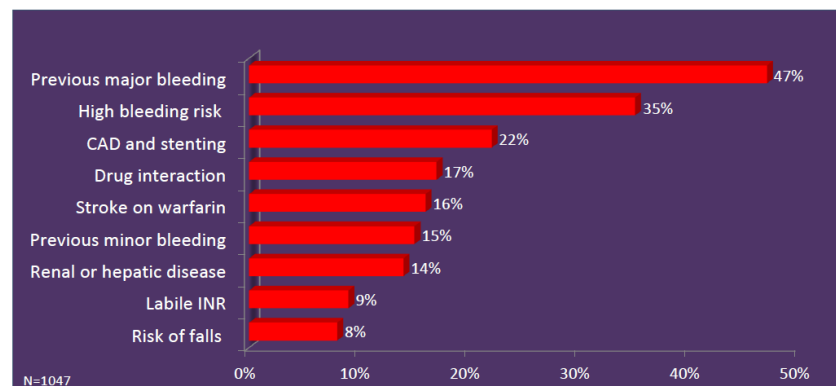


Mean  $3.1 \pm 1.2$

N=1047

■ euro  
PCR  
2014

### Indications for LAAO

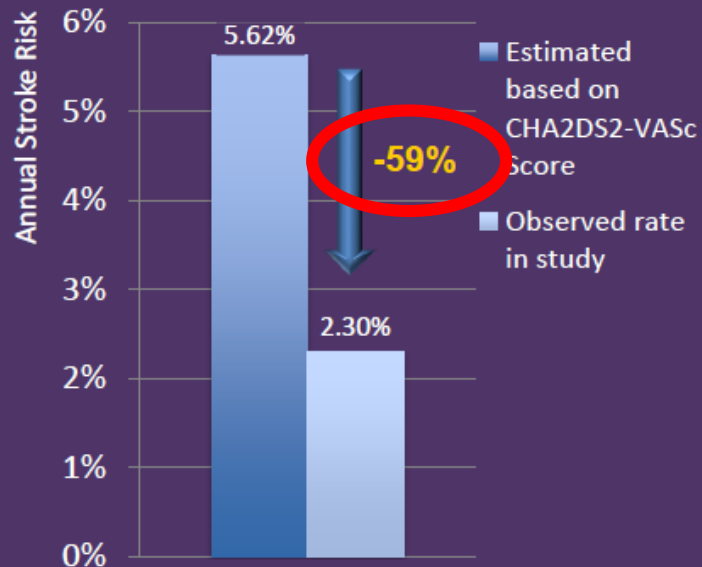


N=1047

Death	8	0.76%
Pericardial tamponade	13	1.24%
Major bleeding	13	1.24%
Stroke	9	0.86%
Device embolization	1	0.10%
MI	1	0.10%
<b>Total</b>	<b>45</b>	<b>4.30%</b>

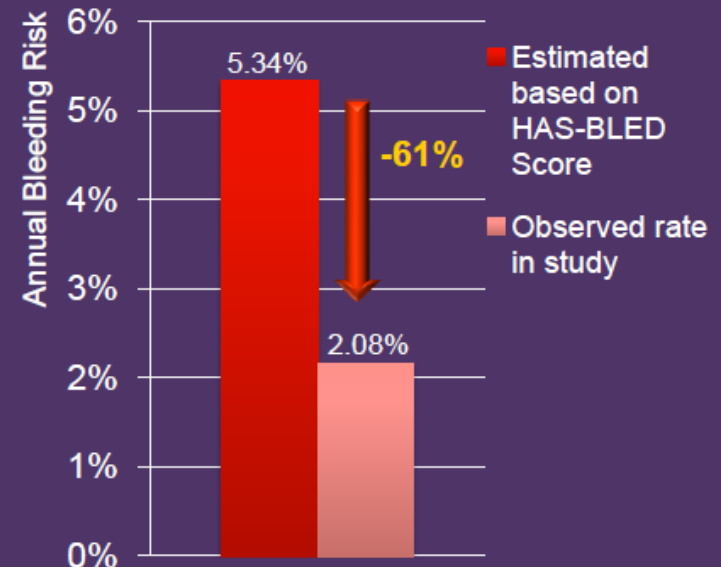
## In patients with contraindication to (N) OAT

### Effectiveness in Stroke Reduction vs Estimated



Total Patients	Total Patient Years	CHA <sub>2</sub> DS <sub>2</sub> -VASc Score
1001	1349	4.43
Estimated Stroke Rate per CHA <sub>2</sub> DS <sub>2</sub> -VASc		Actual Annual Stroke Rate (N strokes + TIA)
5.62%		2.30% (31)

### Effectiveness in Bleeding Reduction vs Estimated

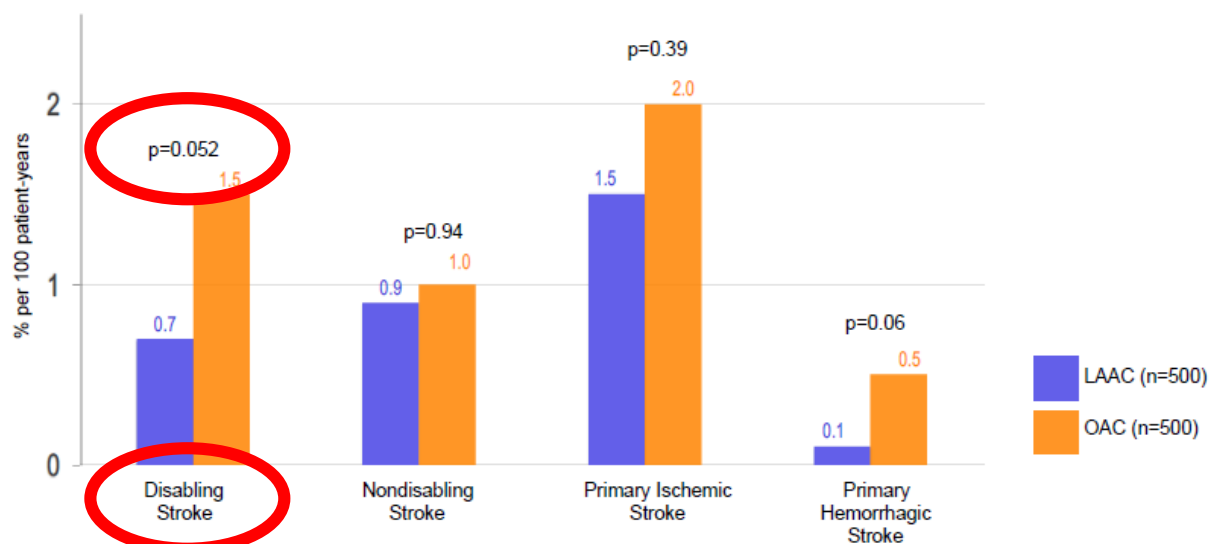


Total Patients	Total Patient Years	HAS-BLED Score
1001	1349	3.12
Estimated Bleeding Rate per HAS-BLED		Actual Annual Bleeding Rate (N major bleeds)
5.34%		2.08% (28)

Percutaneous left atrial appendage closure vs. oral anticoagulation:  
A propensity score matched study of 1000 patients with  
atrial fibrillation

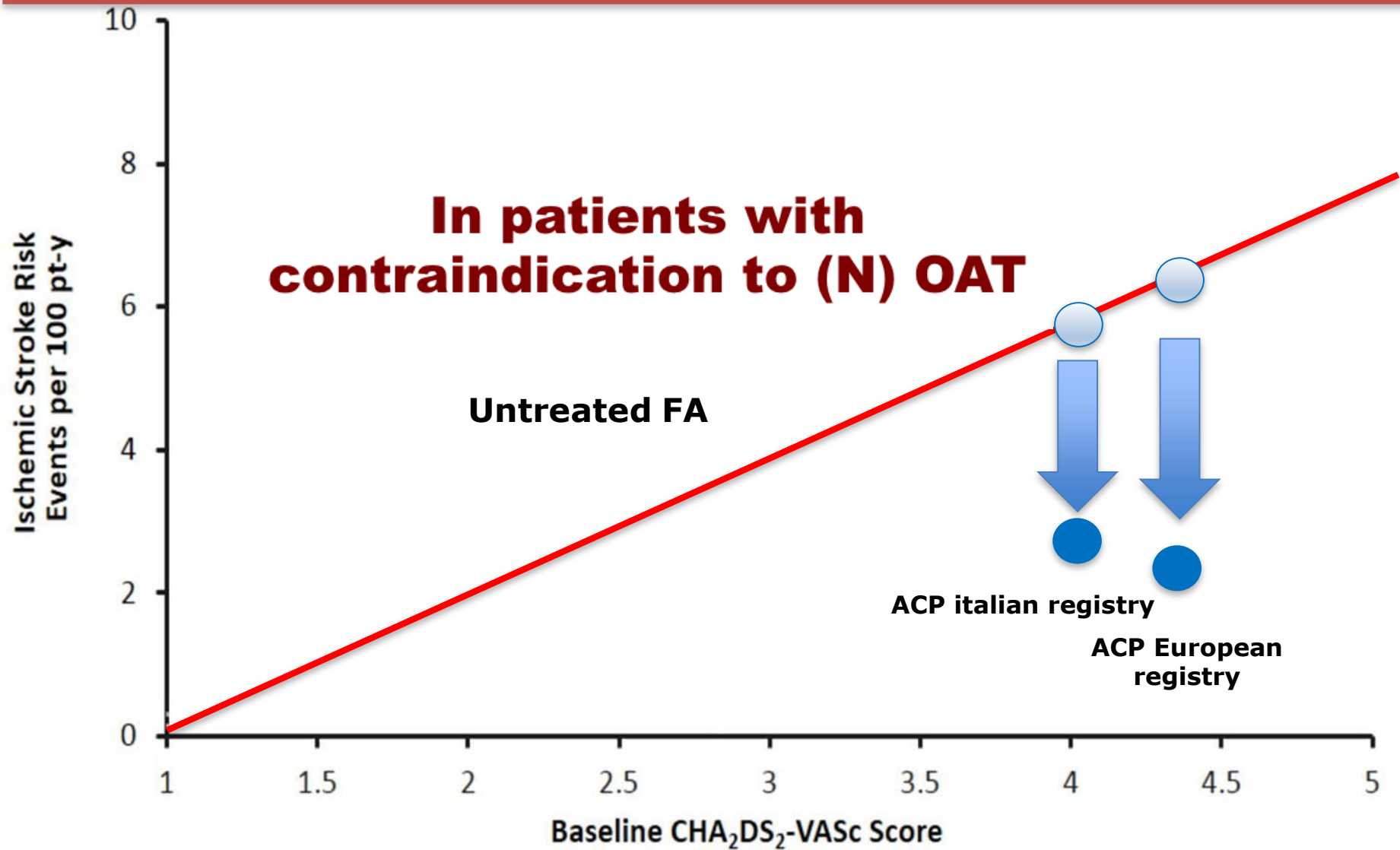
## STROKE TYPES

PERCUTANEOUS LEFT ATRIAL APPENDAGE CLOSURE  
vs.  
ORAL ANTICOAGULATION



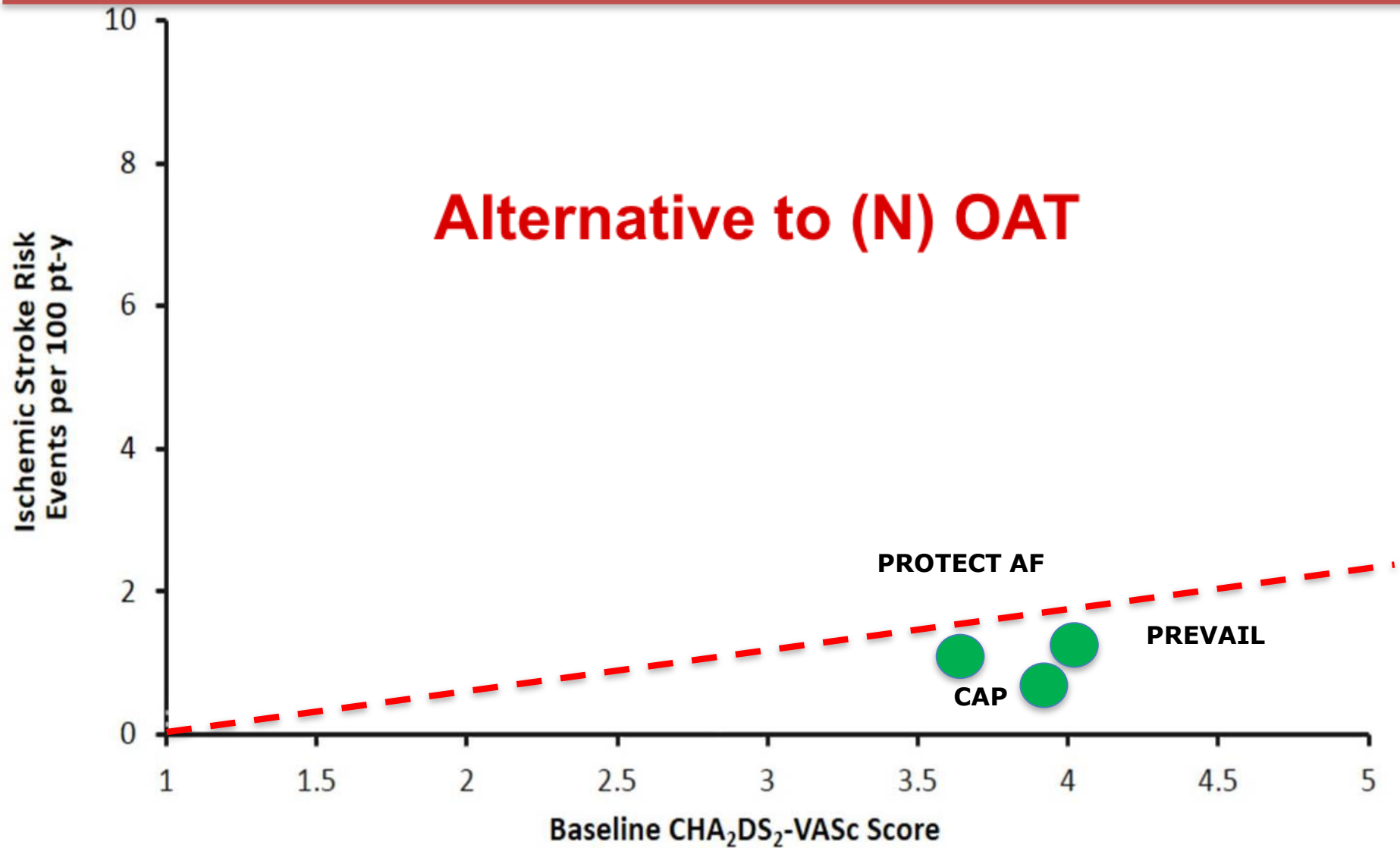


# EFFICACIA

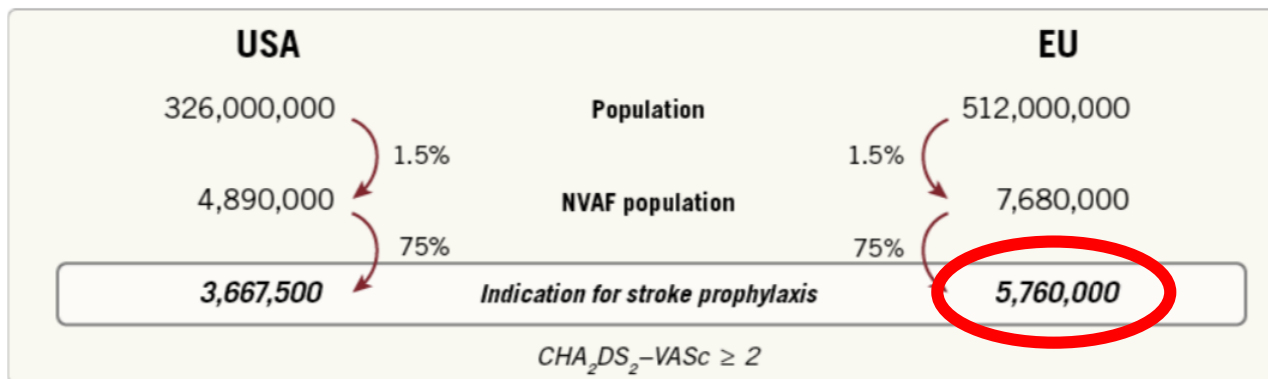


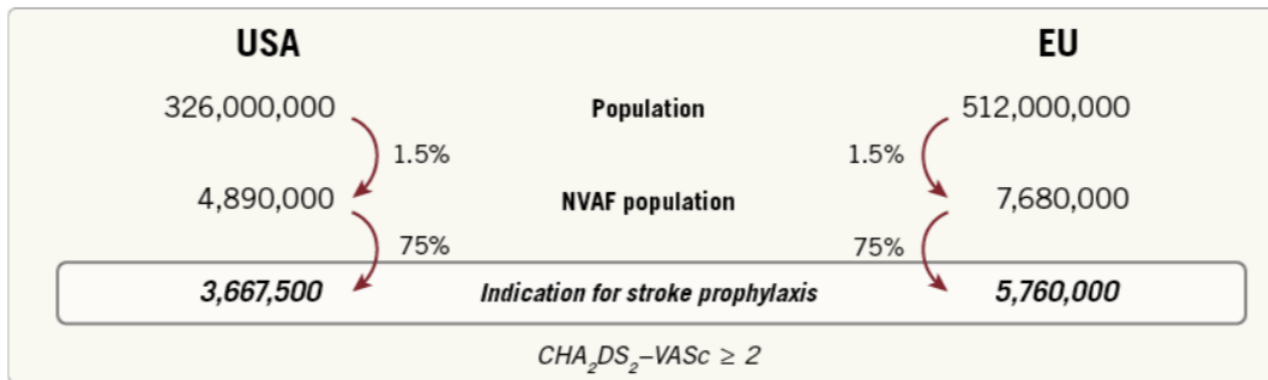
Friberg L, et al. *Eur Heart J*. 2012;33:1500-1510; Lopes R, et al. *Lancet*. 2012;380:1749-1758; Granger CB, et al. *N Engl J Med*. 2011;365:981-992.

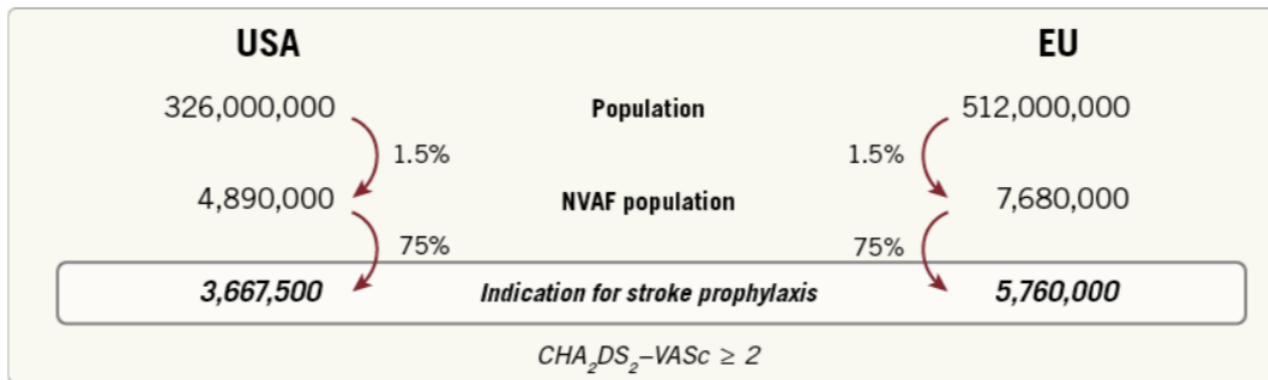
# EFFICACIA



Friberg L, et al. *Eur Heart J*. 2012;33:1500-1510; Lopes R, et al. *Lancet*. 2012;380:1749-1758; Granger CB, et al. *N Engl J Med*. 2011;365:981-992.

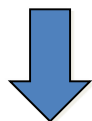




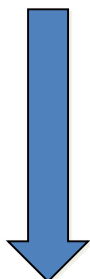




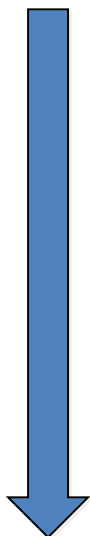
**Pazienti con  
CHADVASC2  $\geq 2$   
HASBLEED  $\geq 3$   
che **devono iniziare TAO/NAO****



**CONTROINDICAZIONE  
ALLA TERAPIA  
ANTICOAGULANTE**



**NON VOGLIONO  
ASSUMERE LA  
TERAPIA  
ANTICOAGULANTE**



**“TROPPO MALATI”**



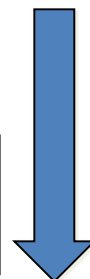
**IN ALTERNATIVA**

**CHIUSURA AURICOLA  
SINISTRA**

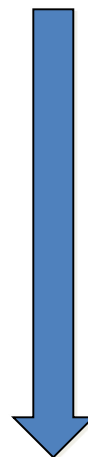
**Pazienti con CHADVASC2  $\geq 2$   
HASBLEED  $\geq 3$   
che **hanno avuto una failure con  
TAO/NAO****



**SANGUINAMENTI  
RICORRENTI  
(CEREBRALI O G.E)**



**STROKE/TIA IN TERAPIA  
CON TAO/NAO**



**SCARSA COMPLIANCE**

**CHIUSURA AURICOLA  
SINISTRA**

# Documento di consenso aziendale



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# **MIE CONCLUSIONI**

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**LA CHIUSURA PERCUTANEA DELL'AURICOLA SINISTRA E' SICURA**

**LA CHIUSURA PERCUTANEA DELL'AURICOLA SINISTRA E' EFFICACE**

**LA CHIUSURA PERCUTANEA DELL'AURICOLA SINISTRA E' STATA  
ESEGUITA AD OGGI IN 90.000 PAZIENTI**

**ESISTE UNA POPOLAZIONE DI PAZIENTI CHE MERITEREBBERO IL  
TRATTAMENTO MA CHE NON VENGONO INVIATI**

A nighttime photograph of the Mole Antonelliana in Turin, Italy. The dome is illuminated with a warm light, and a vertical line of red lights runs up its side. The spire is also lit. In the background, the snow-capped peaks of the Alps are visible under a dark blue sky. The city of Turin is visible in the foreground, with its lights reflecting on the water in the foreground.

# Grazie