



ADVANCES IN CARDIOVASCULAR ARRHYTHMIAS AND GREAT INNOVATIONS IN CARDIOLOGY
XXIV GIORNATE CARDIOLOGICHE TORINESI – Turin, October 20-22, 2011

FOCUS ON LEFT ATRIAL APPENDAGE CLOSURE IN PATIENTS WITH ATRIAL FIBRILLATION

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DIPARTIMENTO DEL CUORE E DEI VASI. AZIENDA OSPEDALIERO-UNIVERSITARIA CAREGGI.
FIRENZE.

Background

Epidemiology of AF

- AF is the most common sustained cardiac arrhythmia
 - Affects more than 6 million individuals in Europe
 - Its prevalence will double by 2050
- Lifetime risk of developing AF in men and women >40 yo is 1 in 4
- Patients with AF have a 5-fold higher risk of stroke
 - One in five of all strokes is attributed to AF
 - Annual stroke rate 2-20% (age and risk factors)
- Stroke is the #1 cause of long-term disability and the third leading cause of death in patients with AF


ESC Guidelines for the management of atrial fibrillation.
Eu Heart Journal 2010; 31, 2369-2429



Table 9 Approach to thromboprophylaxis in patients with AF

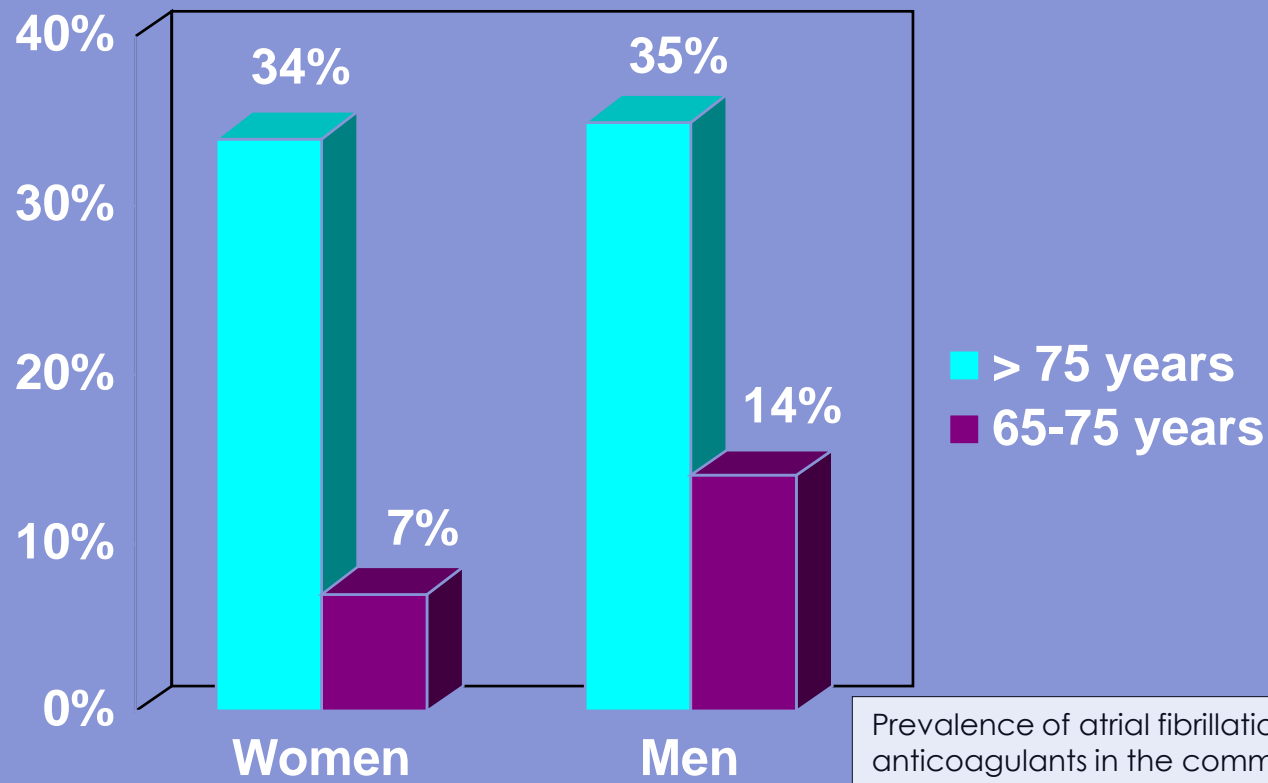
Risk category	CHA ₂ DS ₂ -VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC ^a
One 'clinically relevant non-major' risk factor	1	Either OAC ^a or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Major limitations of warfarin therapy

- Absolute and relative contraindications
 - Compliance (long life therapy)
 - Narrow therapeutic range
 - Interactions with other drugs
 - Frequent monitoring required (>cerebral)
- 
- DABIGATRAN**
Rivaroxaban
Apixaban

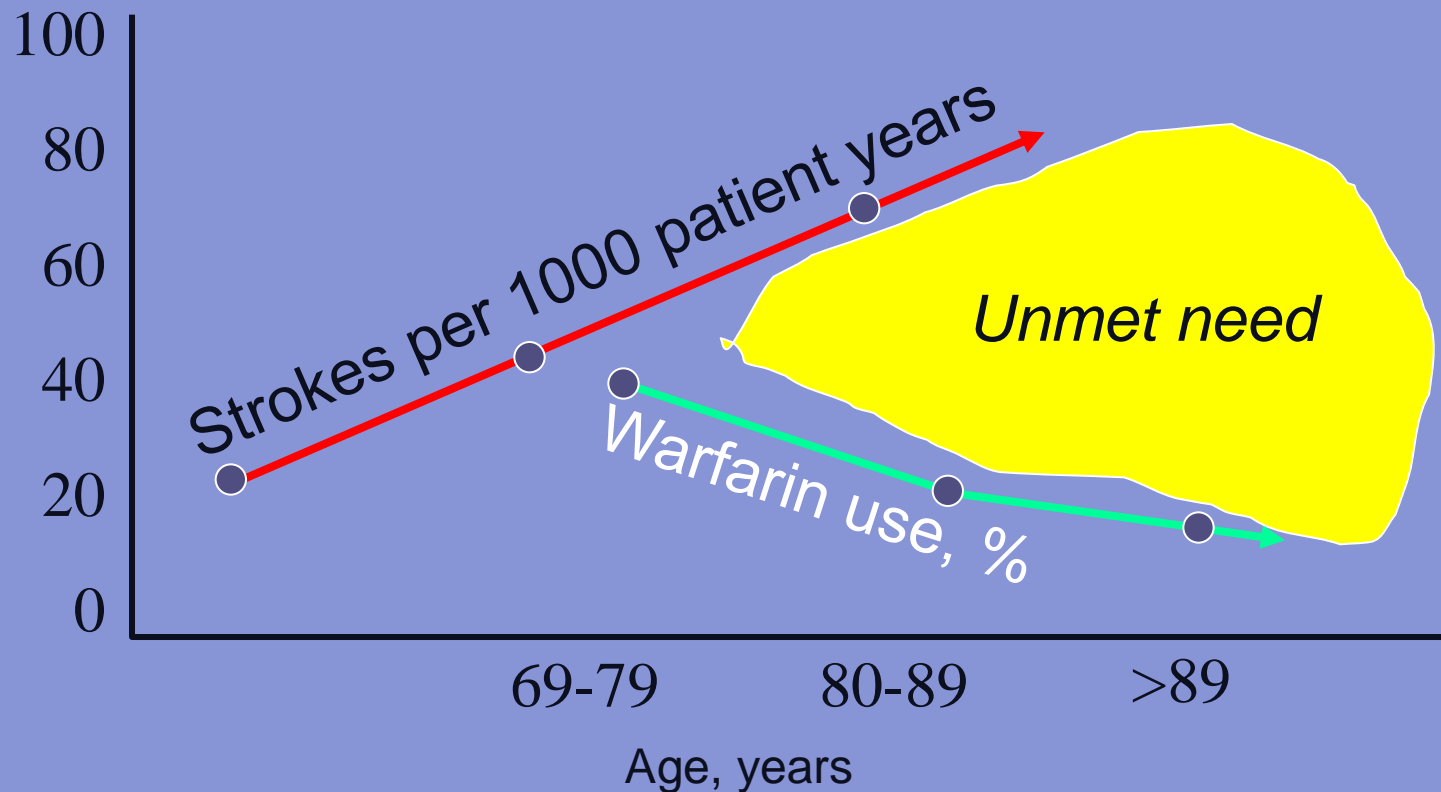
Prevalence of irreversible contraindication* to OAC in general AF population depending on age and gender

* SPAF III study: Major bleeding previous 6 months, frequent falls, inability to comply to treatment, excessive alcohol consumption, (uncontrolled hypertension, daily use of NSAIDs)



Prevalence of atrial fibrillation and eligibility for anticoagulants in the community
Sudlow M et al. The Lancet 1998

Age-related trends in AF



Wolf PA, Arch Intern Med 1987; 147:1561-4
White RH, Am J Med 1999; 106:165-71

Why to close the LAA?



Table 1. . Review of Published Reports Detailing the Frequency and Site of Thrombus Location in Patients With Nonrheumatic Atrial Fibrillation

Setting	No. of Patients	Thrombus Location		Reference No.
		LA Appendage	LA Cavity	
TEE ^a	317	66	1	40
TEE	233	34	1	25
Autopsy	506	35	12	39
TEE	52	2	2	28
TEE	48	12	1	41
TEE and Operation	171	8	3	24
SPAF III TEE Study	359	19	1	42
TEE	272	19	0	26
TEE	60	6	0	43
Total	1,288	201	21	

90% of clots form in the LAA

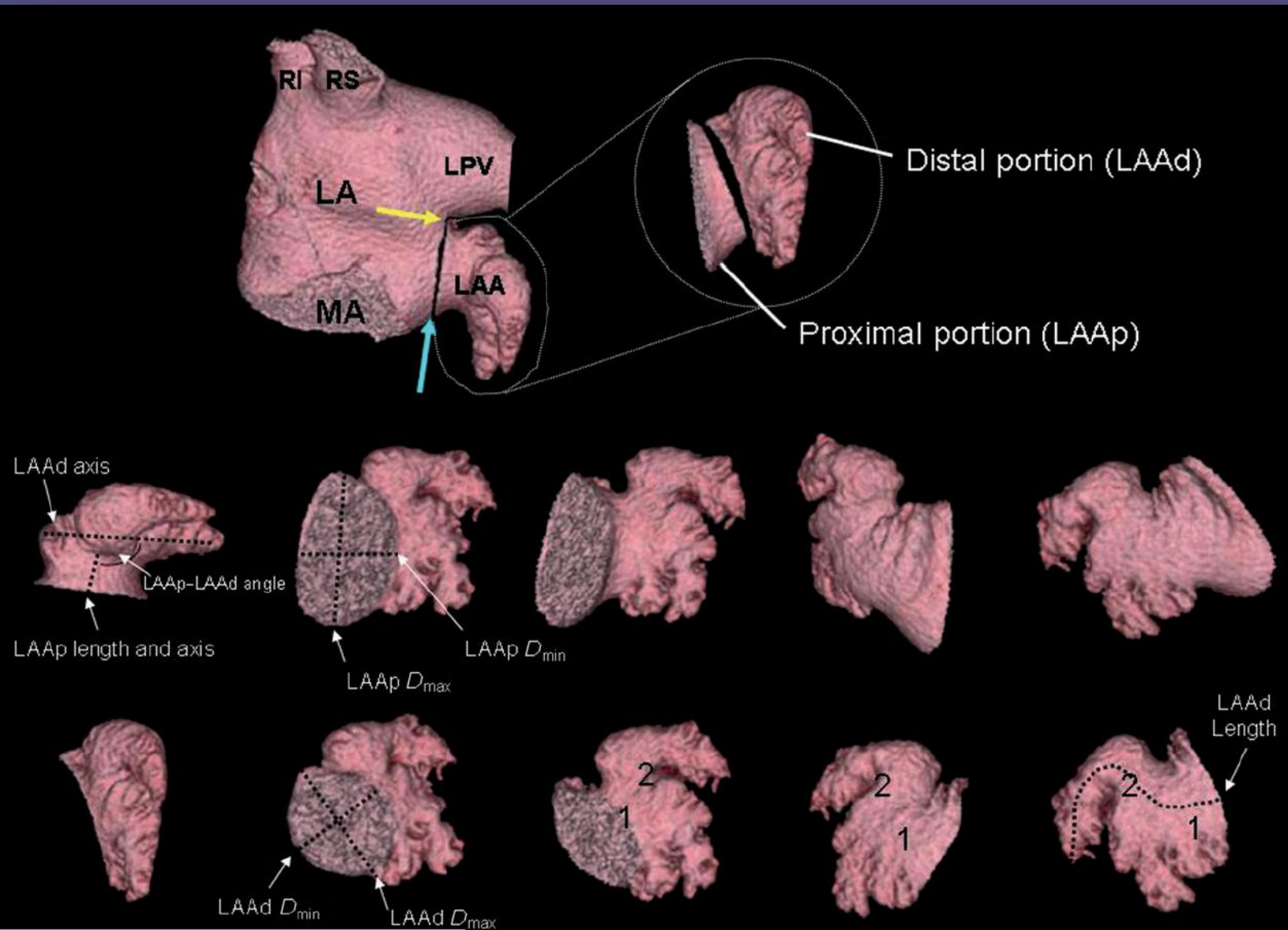
^a 5% of this cohort had mitral stenosis or a prosthetic mitral valve.

LA = left atrium; SPAF III = Stroke Prevention in Atrial Fibrillation Trial; TEE = transesophageal echocardiography.



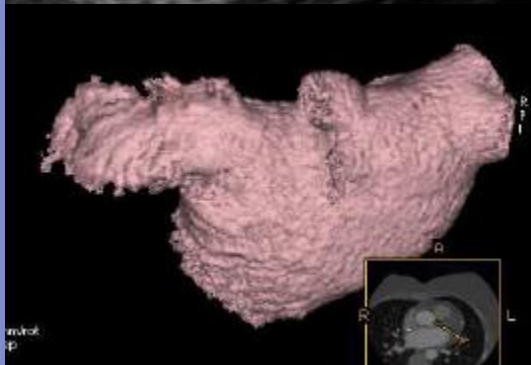
How to close the LAA

Complexity of LAA anatomy



LAA Common Morphologies

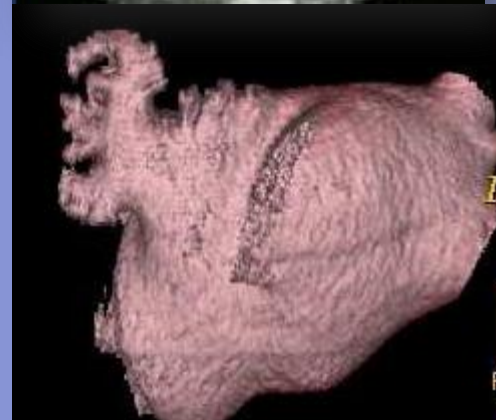
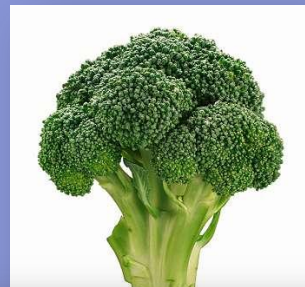
The Wind Sock Type



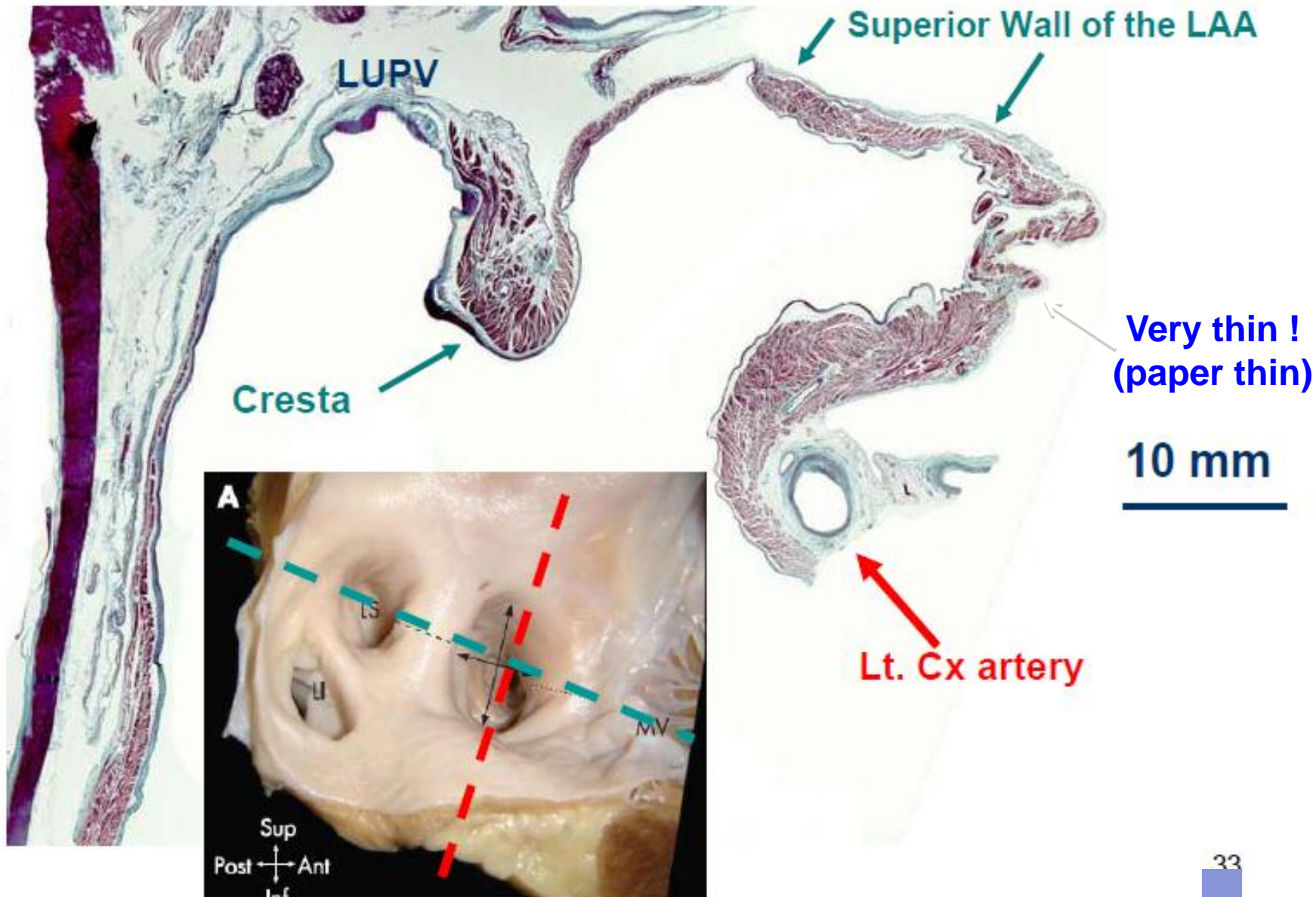
The Chicken Wing Type



The Broccoli Type



Aorta



Courtesy of Dr. Lopez-Mingues, Spain

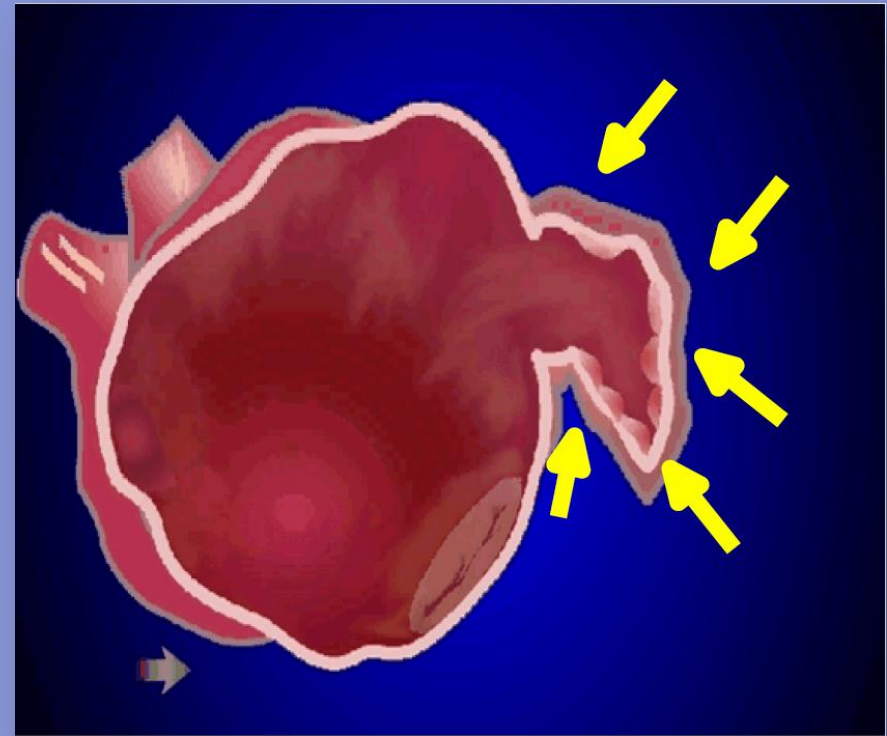
33

Different approaches to occlude the LAA

Endocardial



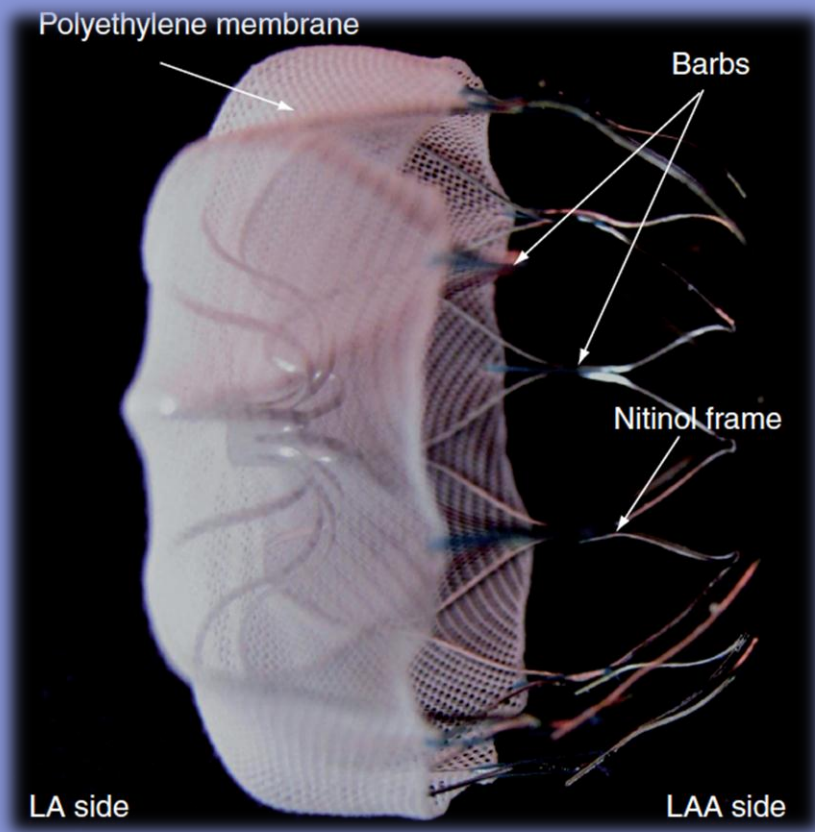
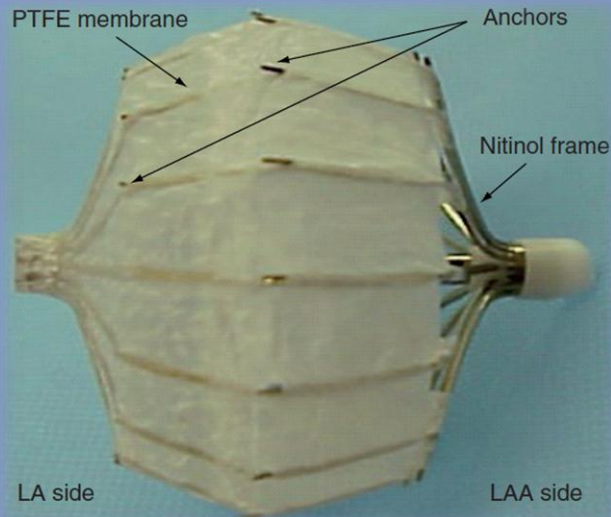
Epicardial



Endocardial

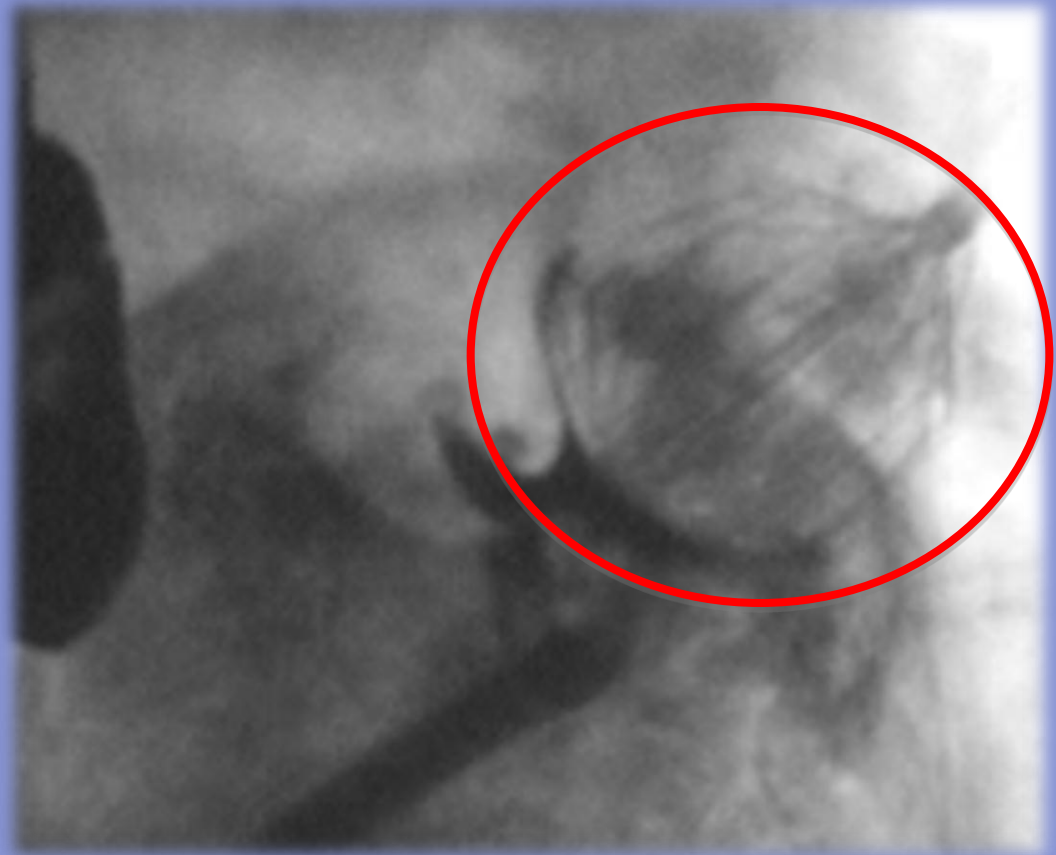
- Atritech-4^o generation device
- AGA -ACP device
- Occlutech
- Coherex
- Custom Medical Devices (Sideris Patch)
- Gore
-

Devices for percutaneous occlusion of LAA



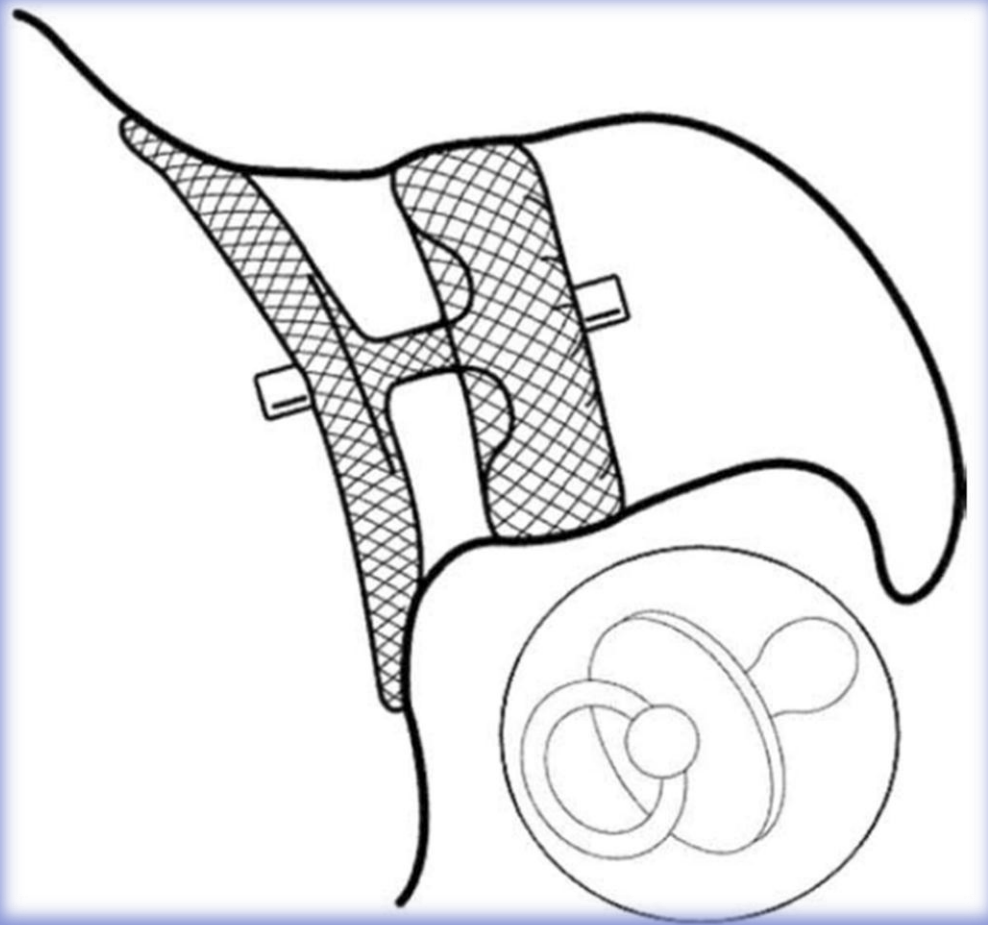
Concept of PLAATO and Watchman

**To Close the
LAA like with a ball**



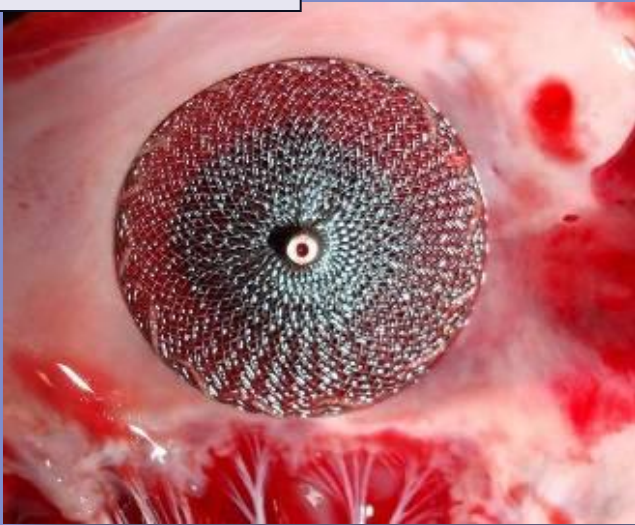
Concept of ACP

**To Close the
LAA like a
pacifier**



Necropsy Photo

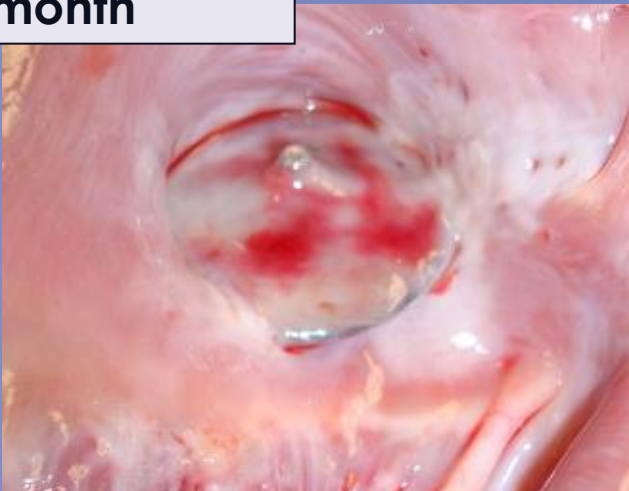
Acute



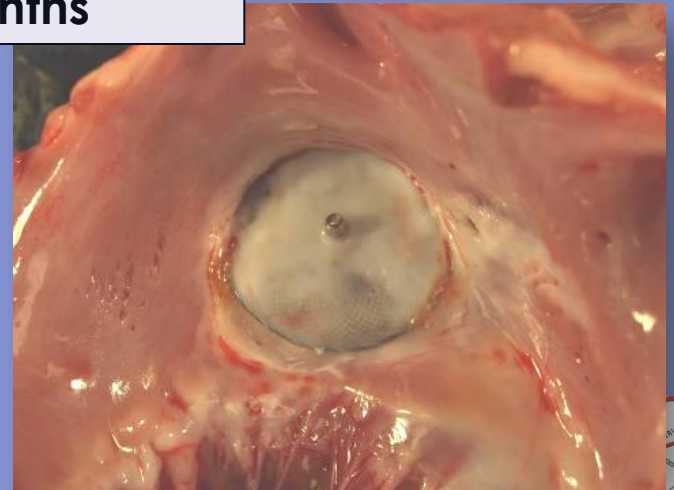
2 days



1 month



3 months



Main steps of the procedure

- *Right venous femoral access*
- *TEE monitoring (deep sedation often required)*
- *Trans-septal catheterization*
- *Pig Tail inside LAA*
- *LAA dimensions, choice of the device size*
- *Extra-stiff wire in left atrium/ LAA*
- *Sheath inside the LAA*
- *Implantation of the device*
- *Release of the device (after gentle “tug” testing)*
- *ASA + Plavix 4 weeks after implantation*



Image size: 512 x 512
View size: 1126 x 1124
WL: 120 WW: 255

P45574_95.y_95.y
Coro 15 -15 - unnamed
7131

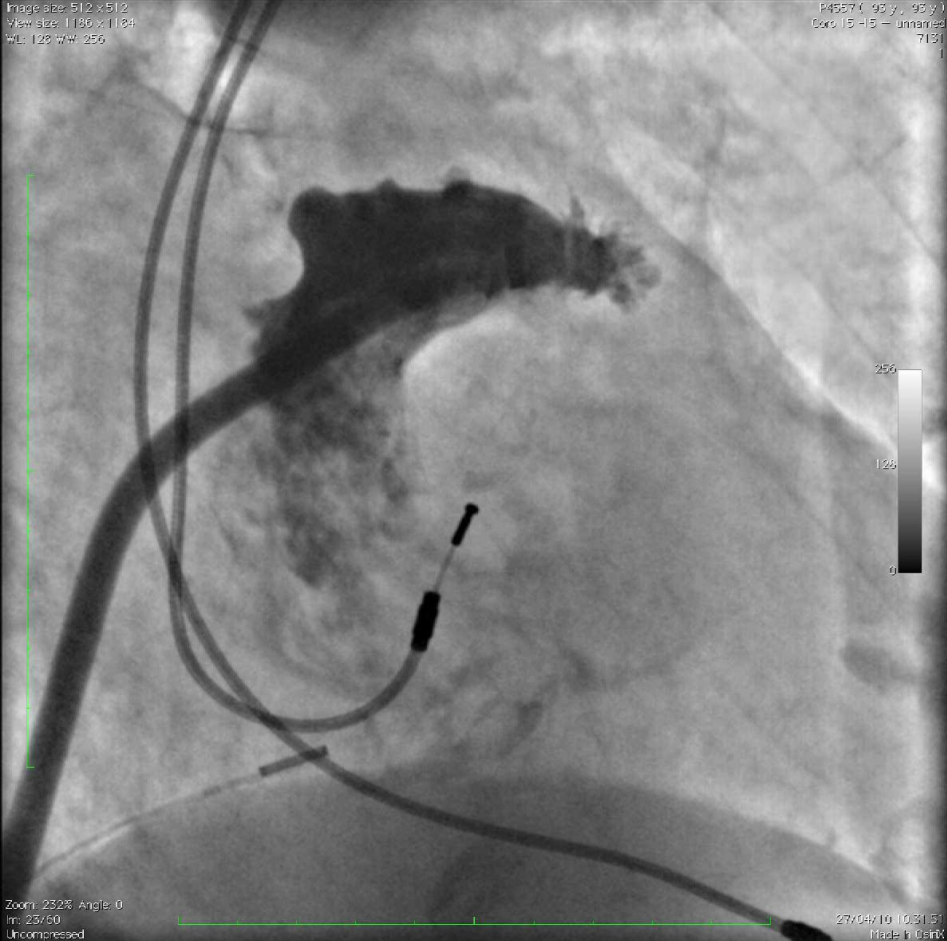
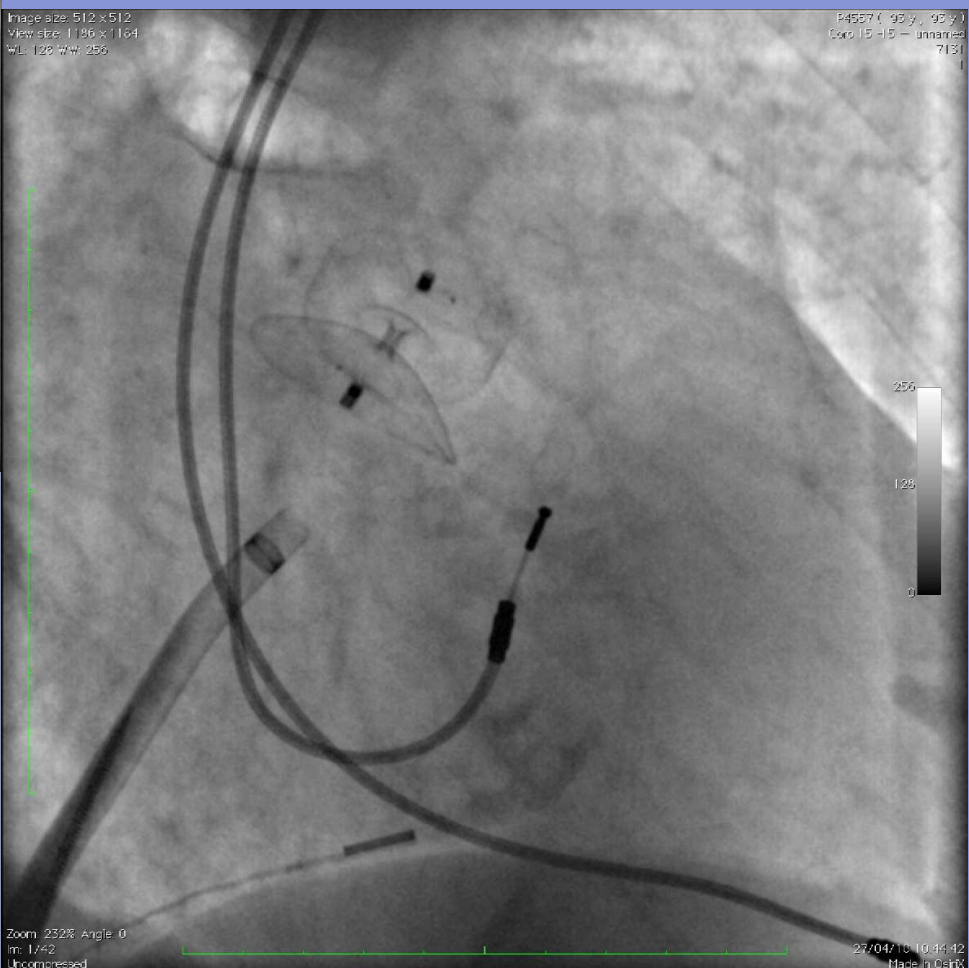


Image size: 512 x 512
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WL: 120 WW: 255

P45574_95.y_95.y
Coro 15 -15 - unnamed
7131

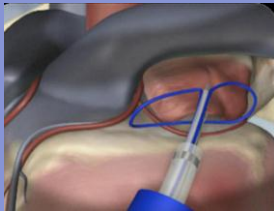


Different approaches to occlude the LAA

- AtriCure



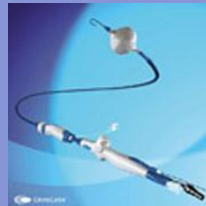
- Epitek



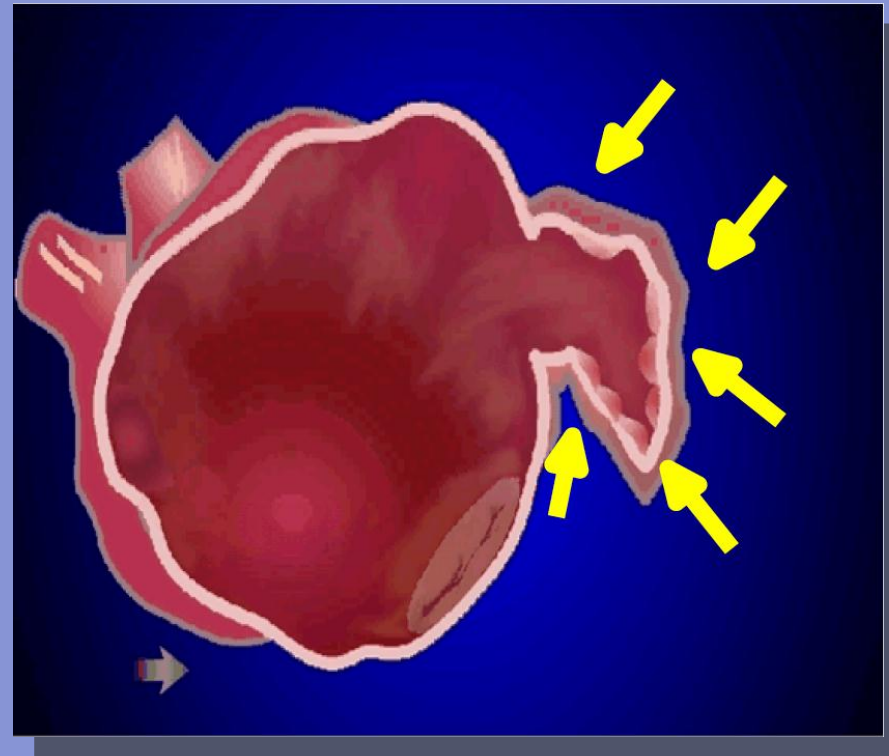
- Medtronic



- SentreHeart

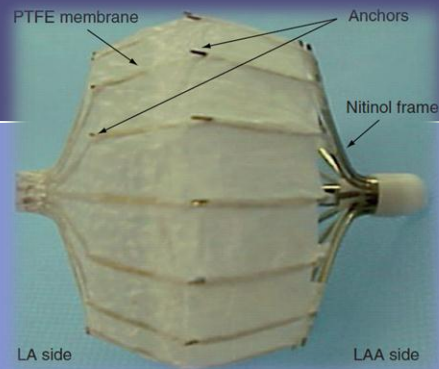


Epicardial



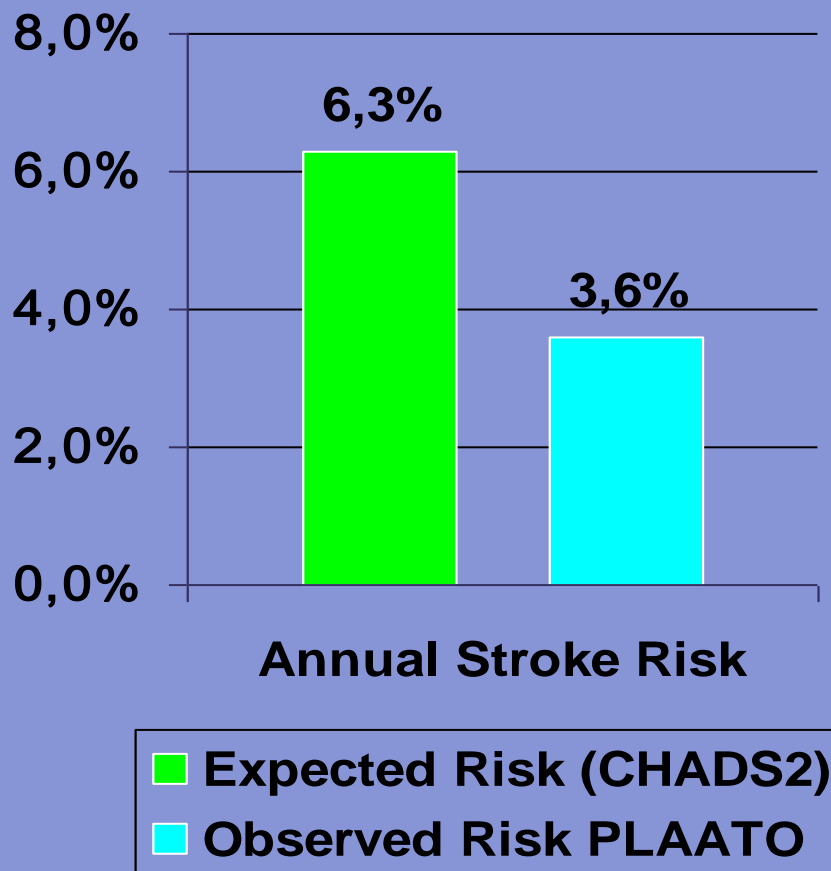
Results of percutaneous closure

PLAATO



Results – Estimated Stroke Reduction

Estimated 43% reduction in stroke risk

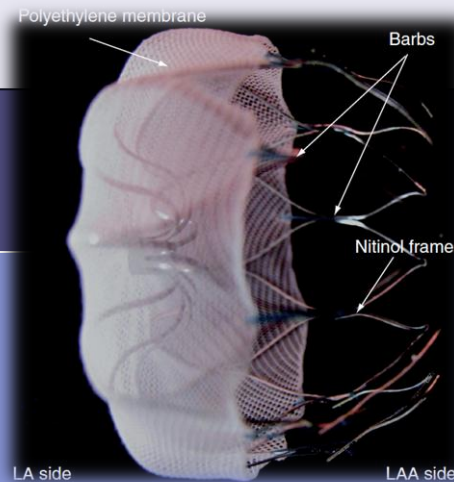


- Observed incidence of stroke to date:
 - 6 strokes/168 patient years of follow-up:
 - 3.6% annual rate
- Expected risk of stroke based on patients' baseline adjusted CHADS₂ score distribution:
 - 6.3% annual rate

JACC INTV 2009;2;594-600



WATCHMAN

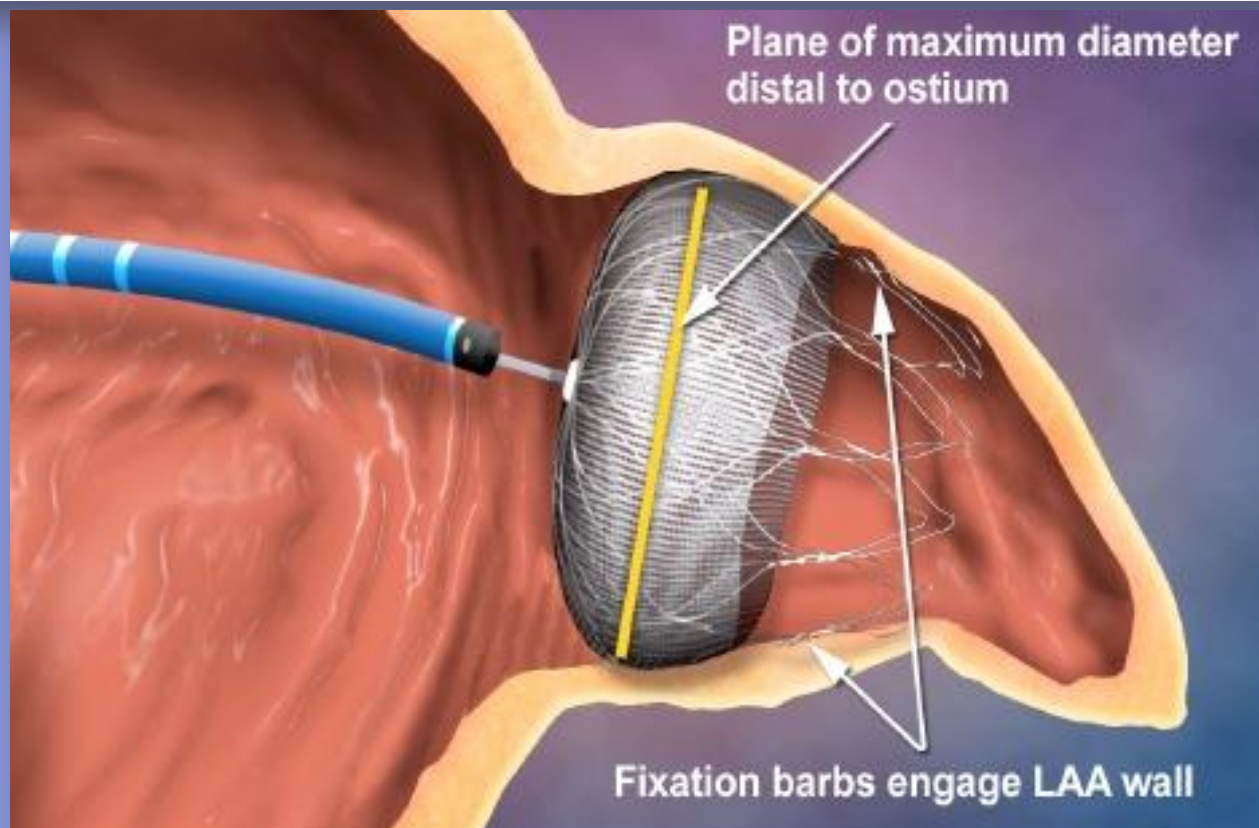


WATCHMAN Clinical Studies

STUDY	PATIENTS	SITES	COMMENTS
PILOT	66	8	<ul style="list-style-type: none"> • 318 patient years of follow-up • 30 patients with 5+ years of follow-up
PROTECT AF	800	59	<ul style="list-style-type: none"> • 1.500 patient years of follow-up • 27 months average follow-up per patient
Continued Access Registry (CAP)	567	26	<ul style="list-style-type: none"> • Significantly improved safety results
ASAP	83	4	<ul style="list-style-type: none"> • Treat patients contra-indicated for warfarin
EVOLVE	22	3	<ul style="list-style-type: none"> • Evaluate next generation WATCHMAN
Total	1.538		
PREVAIL	≤400	≤50	<ul style="list-style-type: none"> • Same endpoints as PROTECT AF • Revised inclusion/exclusion criteria • Initiate enrollment October 2010

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**



PROTECT AF Clinical Trial Design

- Prospective, randomized study of WATCHMAN LAA Device vs. Long-term Warfarin Therapy
- 2:1 allocation ratio device to control
- Non-inferiority comparison
- 800 Patients enrolled from Feb 2005 to Jun 2008-707 randomized
- 59 Enrolling Centers (U.S. & Europe)
- Follow-up Requirements
 - TEE follow-up at 45 days, 6 months and 1 year
 - Clinical follow-up biannually up to 5 years
 - Regular INR monitoring while taking warfarin
- Enrollment continues in Continued Access Registry



PROTECT AF Trial Endpoints

Primary Efficacy Endpoint

- All stroke: ischemic or hemorrhagic
 - deficit with symptoms persisting more than 24 hours or
 - symptoms less than 24 hours confirmed by CT or MRI
- Cardiovascular and unexplained death: includes sudden death, MI, CVA, cardiac arrhythmia and heart failure
- Systemic embolization

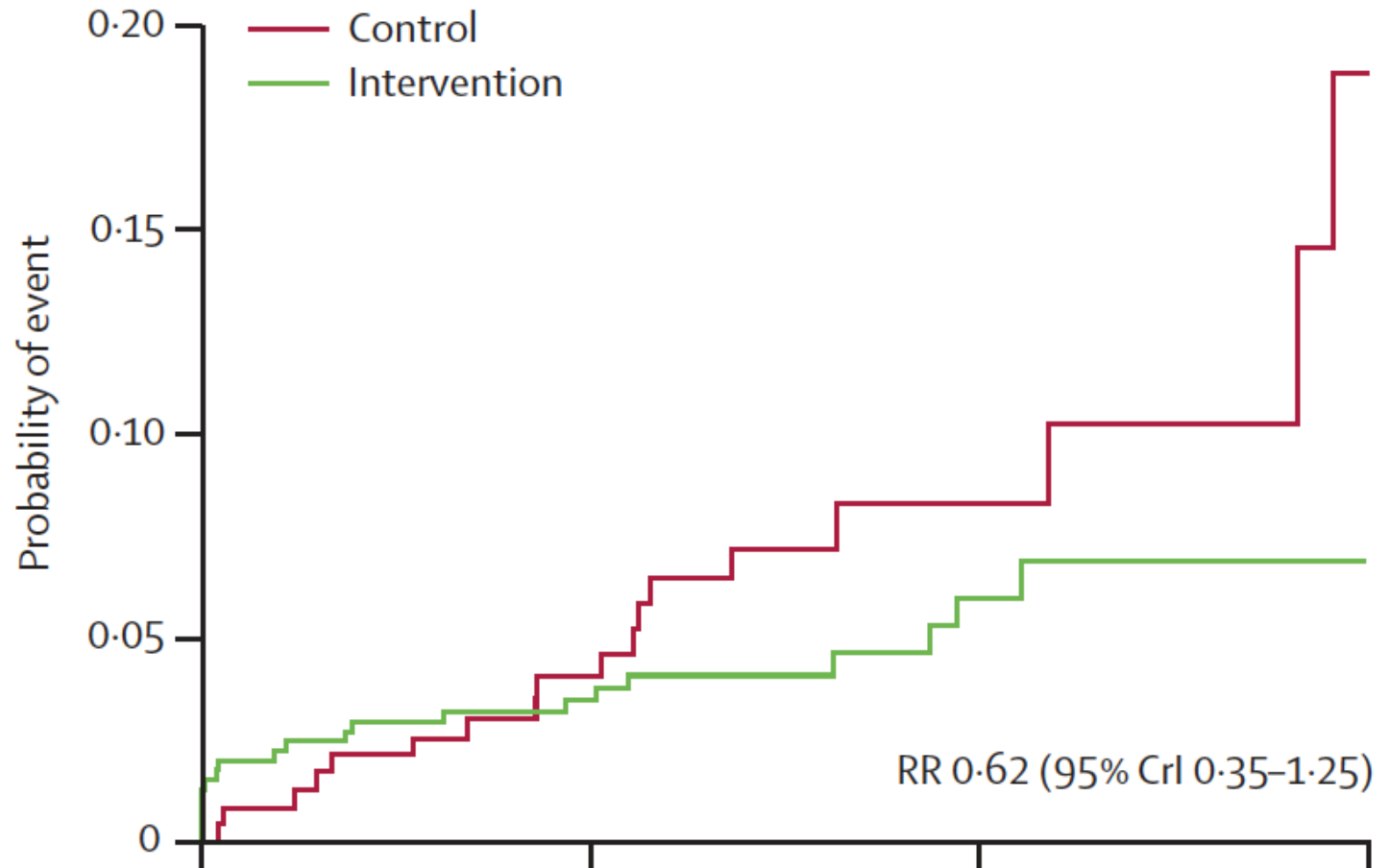
Primary Safety Endpoint

- Device embolization requiring retrieval
- Pericardial effusion requiring intervention
- Cranial bleeds and gastrointestinal bleeds
- Any bleed that requires ≥ 2 uPRBC

NB: Primary effectiveness endpoint contains safety events

	Intervention group (n=463)	Control group (n=244)
Characteristics		
Age (years)	71·7(8·8;46·0-95·0)	72·7(9·2;41·0-95·0)
Male	326 (70·4%)	171 (70·1%)
Race/ethnicity		
Asian	4 (0·9%)	1 (0·4%)
Black/African-American	6 (1·3%)	5 (2·0%)
White	425 (91·8%)	222 (91·0%)
Hispanic/Latin American	25 (5·4%)	15 (6·1%)
Hawaiian/Pacific Islander	1 (0·2%)	1 (0·4%)
Other	2 (0·4%)	0
Risk factors		
CHADS ₂ score*		
1	157 (33·9%)	66 (27·0%)
2	158 (34·1%)	88 (36·1%)
3	88 (19·0%)	51 (20·9%)
4	37 (8·0%)	24 (9·8%)
5	19 (4·1%)	10 (4·1%)
6	4 (0·9%)	5 (2·0%)

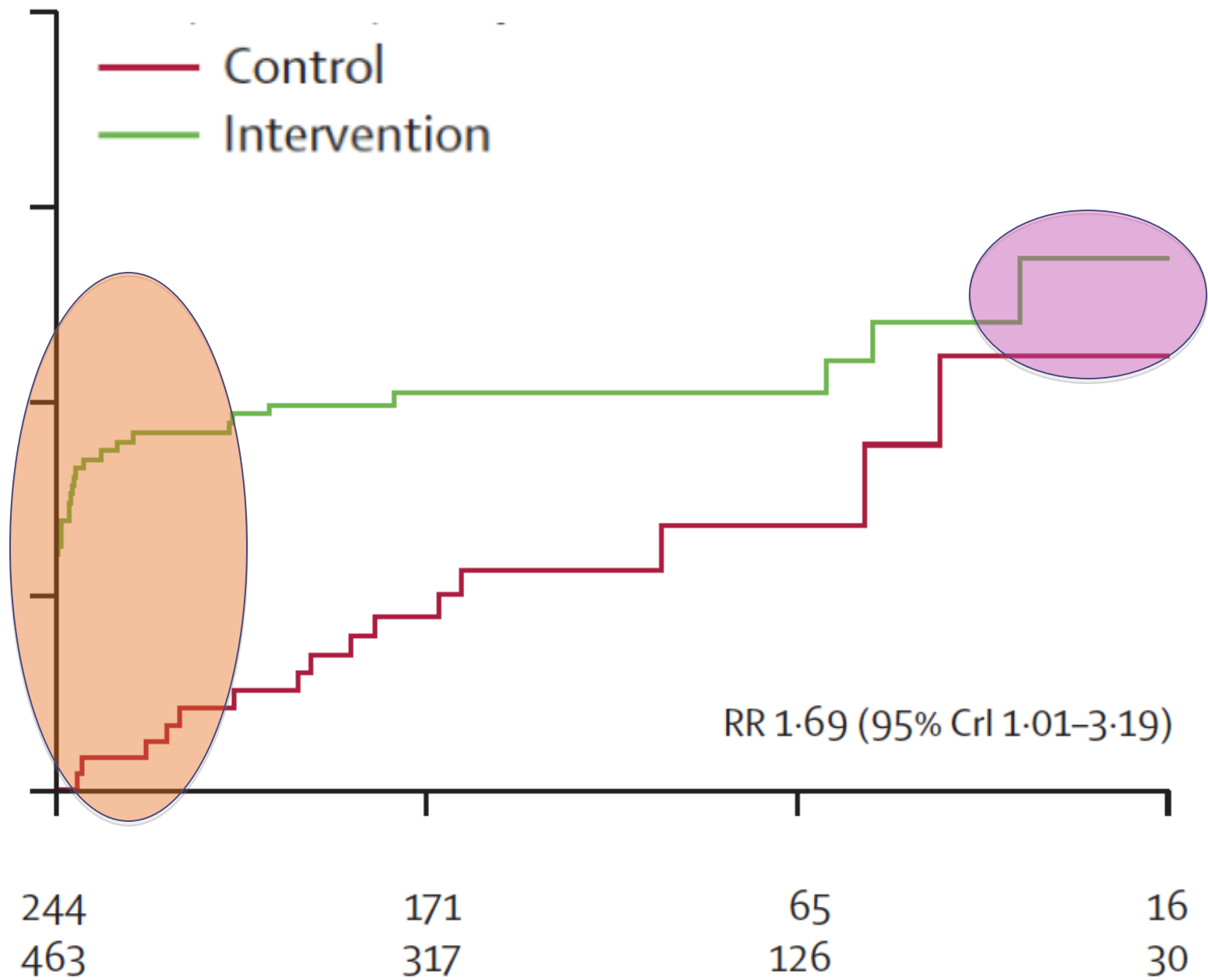
A Primary efficacy endpoint



Number at risk

Control	244	174	67	17
Intervention	463	332	132	34

B Primary safety endpoint



PROTECT AF Procedural Complications

- 12,3%
- Pericardial effusion requiring drainage 4,8%
 - reduction 50% > 3 cases- none disabling
- Periprocedure ischemic stroke 1,1%
 - air or thromboemboli
- Device removal
 - embolization or sepsis n=4
- Thrombus on device in 3,7%
 - clopidogrel x 6 months
- Learning curve effect substantial



PROTECT AF & CAP Registry: Safety Events

420 *Circulation* February 1, 2011

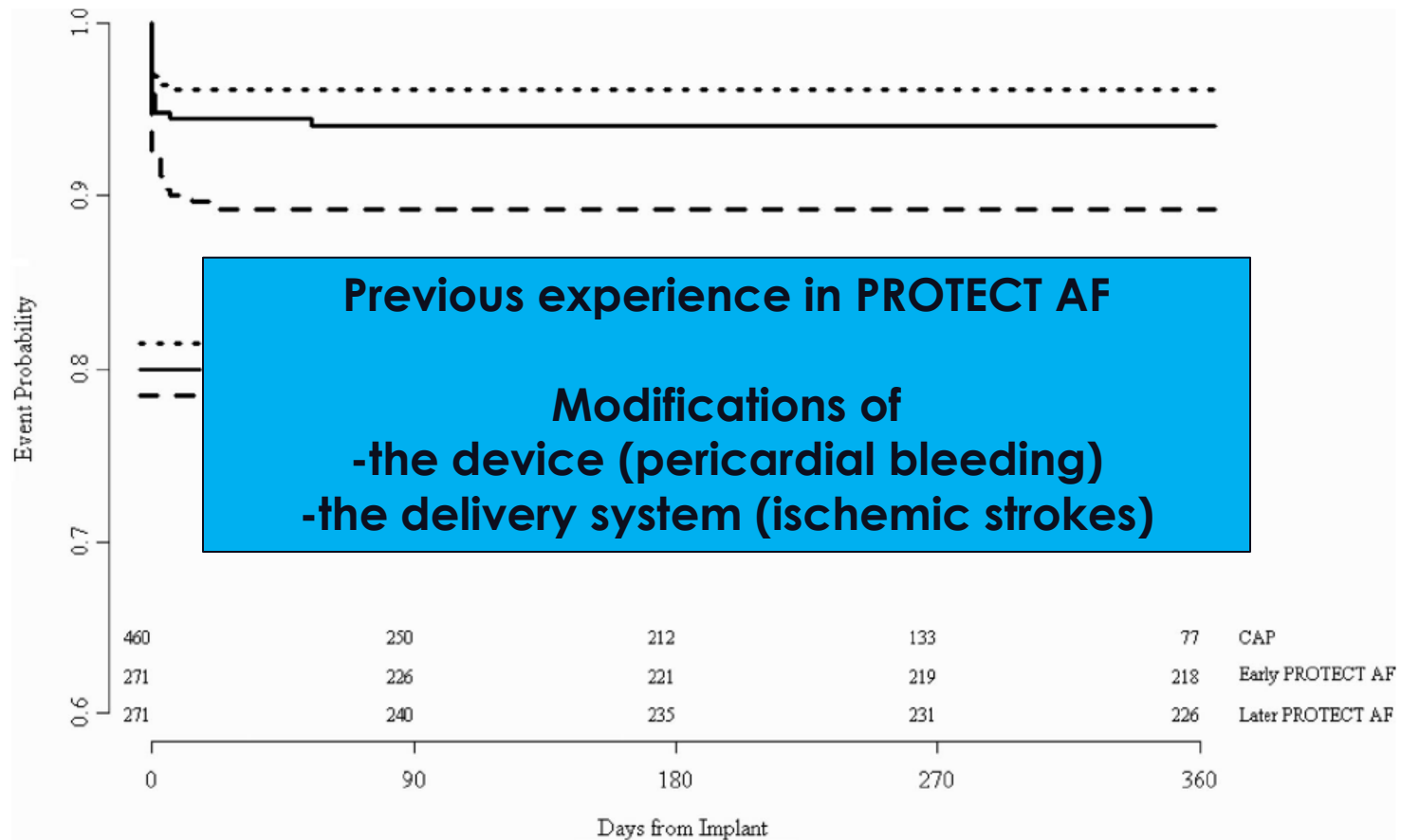


Figure. Kaplan-Meier curve of the incidence of procedure- or device-related safety events for PROTECT AF and CAP Registry device patients. The early and late PROTECT AF patient cohorts represent those patients enrolled in the first and second halves of the study, respectively.



PROTECT AF Critique

- Sample size – too small
- Statistical analysis plan – too complex
- Enrollment criteria – too low risk
- Control group anticoagulation – not enough
- Device group anticoagulation – too much
- Learning curve – too long
- Complication rate – too high
- Duration of follow-up – too short



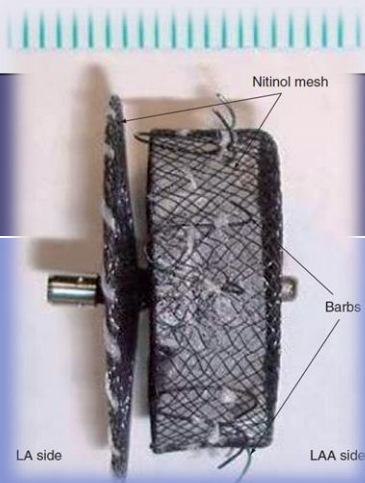
NEW RCT requested by FDA

PREVAIL trial

- Watchman vs Coumadin as PROTECT AF
- Actual device and delivery system
- **FDA request: the study will only involve participating centers that were not part of PROTECT AF**
- **same end-point as PROTECT AF**
- **will randomize 475 pts (2:1)**
- **CHADS2 ≥ 2**
- **first patient enrolled in October 2010**
- **first results expected for the end of 2012**
- **FDA approval awaited for April 2013**



ACP



LEFT ATRIAL APPENDAGE CLOSURE WITH AMPLATZER CARDIAC PLUG FOR PREVENTION OF STROKE IN ATRIAL FIBRILLATION – INITIAL EUROPEAN EXPERIENCE –

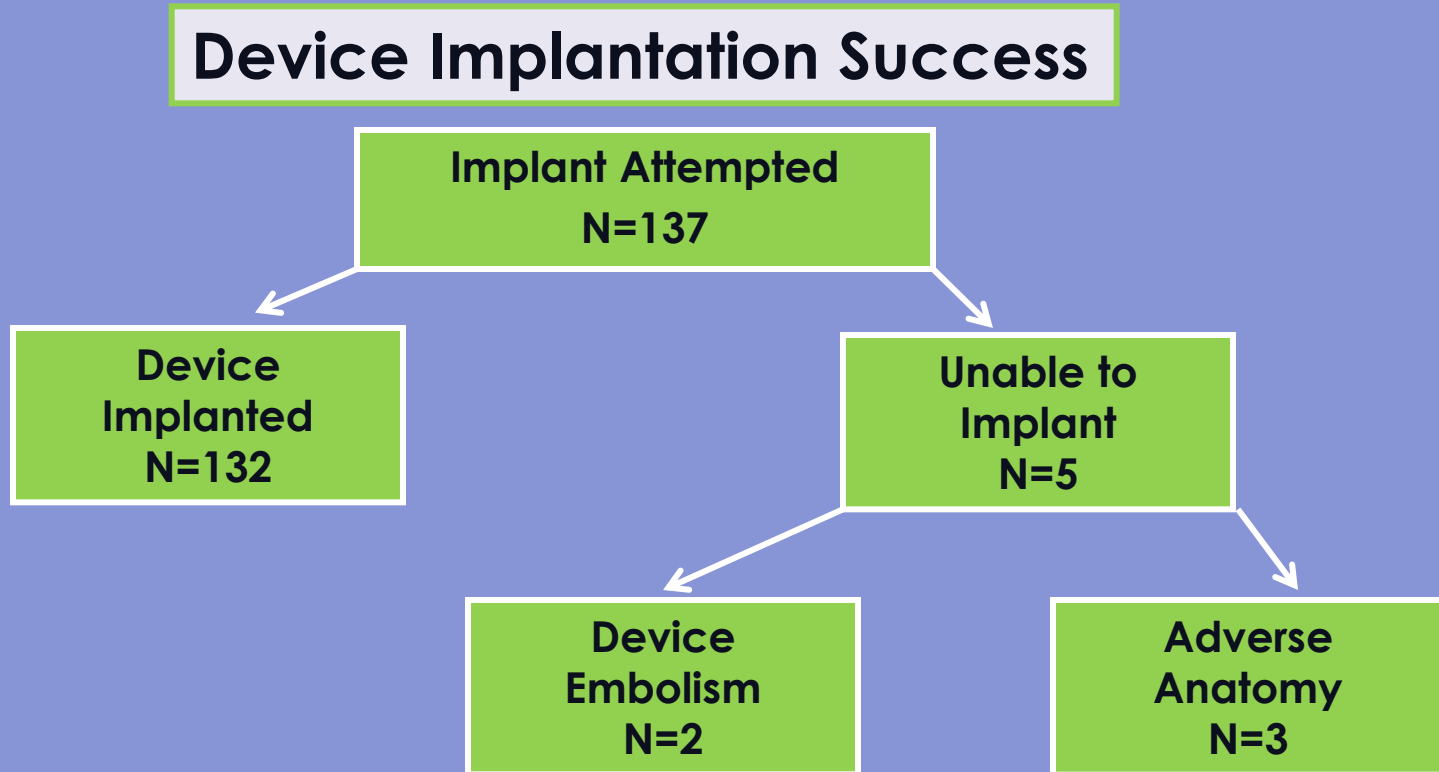
Jai-Wun Park¹, MD, Armando Bethencour², MD, Horst Sievert³, MD, Gennaro Santoro⁴, MD, Bernhard Meier⁵, MD, Kevin Walsh⁶, MD, Jose Ramon Lopez-Minquez⁷, MD, David Meerkin⁸, MD, Mariano Valdés⁹, MD, Oliver Ormerod¹⁰, MD, Boris Leithäuser¹, MD

¹Asklepios Klinik Harburg, Hamburg, Germany; ²Hospital Universitario Son Dureta, Palma de Mallorca, Spain; ³Cardiovascular Center Sankt Katharinen, Frankfurt, Germany; ⁴Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; ⁵Universitätsklinikum Bern, Switzerland; ⁶Mater Public Hospital, Dublin, Republic of Ireland; ⁷Hospital Universitario Infanta Cristina, Badajoz, Spain; ⁸Shaare Zedek Medical Center, Jerusalem, Israel; ⁹Arrixaca University Hospital, Murcia, Spain; ¹⁰John Radcliffe Hospital, Oxford, United Kingdom

Catheterization and Cardiovascular Interventions 77:700-706 (2011)



Initial ACP European Experience



**Implant Successful in 96.4%
(132/137) of Attempts**

24-h Procedure Related Serious Complications

	WATCHMAN PROTECT AF N=463	ACP Pre-Registry N=143
Serious Pericardial Effusion	N=22 (4.8%)	N=5 (3.5%)*
Device Embolization	N=1 (0.2%)	N=2 (1.4%)
Ischemic Stroke (Air Emboli?)	N=5 (1.1%)	N=3 (2.1%)
Total	N=28 (6.0%)	N=10 (7.0%)

***1 tamponade due to pulmonary artery puncture**

ACP Results Across Series*

	ACP Initial European Registry ¹ N = 143	ACP Italian registry ² N = 100	Dual Center experience ³ N = 131	ACP Post Market Registry N = 145
Enrollment period	December 2008 - November 2009	December 2008 – November 2010	2010 - 2011	August 2009- May 2011 (interim)
Serious Pericardial Effusion	N = 5 (3.5%)	N = 2 (2.0 %)	N = 0	N = 3
Device Embolization	N = 2 (1.4%)	N = 0 (0%)	N = 0	N = 2
Ischemic Stroke	N = 3 (2.1%)	N = 0 (0%)	N = 0	N = 0
Total reported safety events	N = 10 (7%)	N = 2 (2%)	N = 0 (0%)	N = 5 (3.4%)

* Hospital discharge or ≤ 24 hrs.

1. Park, J.-W. et al. (2011), Left atrial appendage closure with Amplatzer Cardiac Plug in Atrial Fibrillation: Initial European experience. *Catheterization and Cardiovascular Interventions*, 77: 700–706. doi: 10.1002/ccd.22764
2. G. Santoro (presented at the Progress In Clinical Pacing Congress in Rome) December 2010.
3. Park, J.W., Leithauser, B., Schmid, M., Khattab, A., Gloeckler, S., Sperl, T., Kasch, F. and Meier, B. (2011) Dual Center Experience with Different Strategies of Left Atrial Appendage Closure with Amplatzer Cardiac Plug for Prevention of Stroke in Atrial Fibrillation. Presented at UHK_Mayo Clinic Asia cardiovascular summit. 26-7 March (Hong Kong).



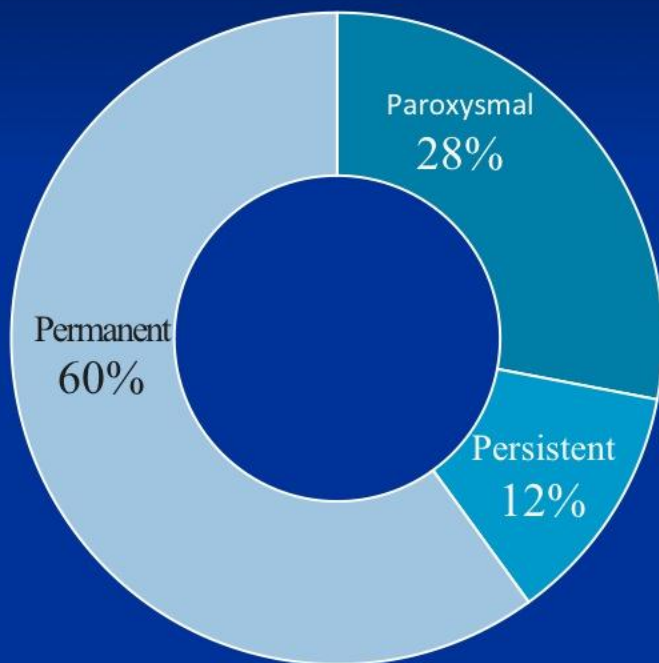
Learning curve

- **Transseptal**
- **Working inside the left atrium**
- **Working inside the left atrial appendage**
- **Device placement**

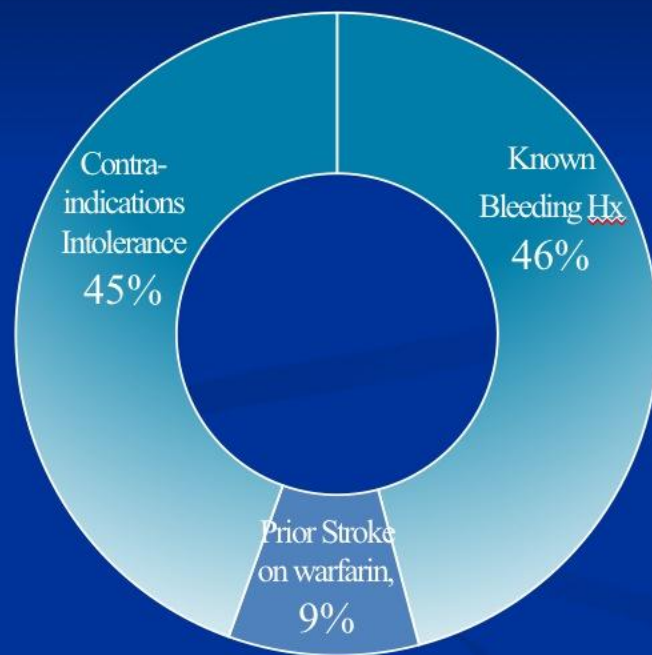


Baseline Demographics Cont'd

History of Atrial Fibrillation



Indication for LAA Closure



- Only 3.3% of patients with active anticoagulation therapy at time of enrollment

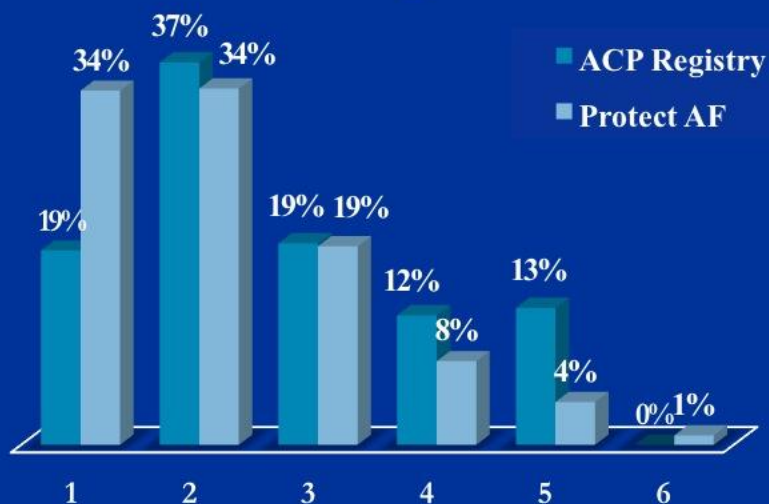
N= 148

Comparison Patient of Populations

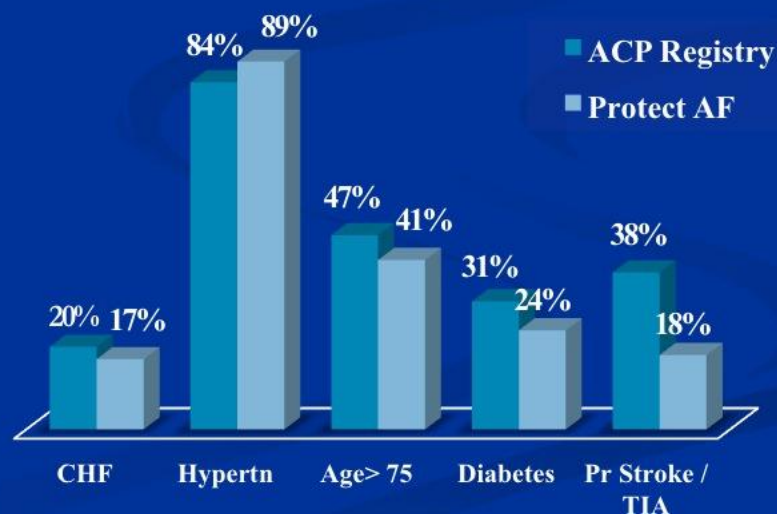
Demographics	<i>Protect AF¹</i>	<i>ACP registry</i>
CHADS ₂	2.2 ± 1.2	2.6 ± 1.3
Age (yrs)	71.7 ± 8.8	73.6 ± 8.9
Prior Stroke/TIA	17.7 %	38%
On anti-coagulants	100%	3.3%

AF Pattern	<i>Protect AF¹</i>	<i>ACP registry</i>
Paroxysmal	43%	28%
Persistent	21%	12%
Permanent	35%	60%

CHADS₂ score



Risk Factors



1. Holmes, et al., (2009) Percutaneous Closure of the Left Atrial Appendage versus Warfarin Therapy for the Prevention of Stroke in patients with : A randomized non-inferiority Trial. *The Lancet*. 374: 534-42.

No long-term data !!

A prospective study is planned



Are you or is someone you know at risk for stroke due to atrial fibrillation?

Help find an alternative to warfarin to prevent stroke in patients with atrial fibrillation

U.S. Clinical Trial

- Initiated June 2010
- Feasibility – 45 pts randomized 2:1
- Pivotal – 400-2,000 pts; up to 90 centers; adaptive bayesian design with multiple interim analyses

Conclusions

Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

“ Current evidence suggests that percutaneous occlusion of the left atrial appendage is efficacious in reducing the risk of thromboembolic complications associated with non valvular atrial fibrillation ”

Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism

“Percutaneous occlusion of the LAA is a technically challenging procedure which should only be carried out by clinicians with **specific training** and appropriate experience in the procedure”

Patients selection in our centre

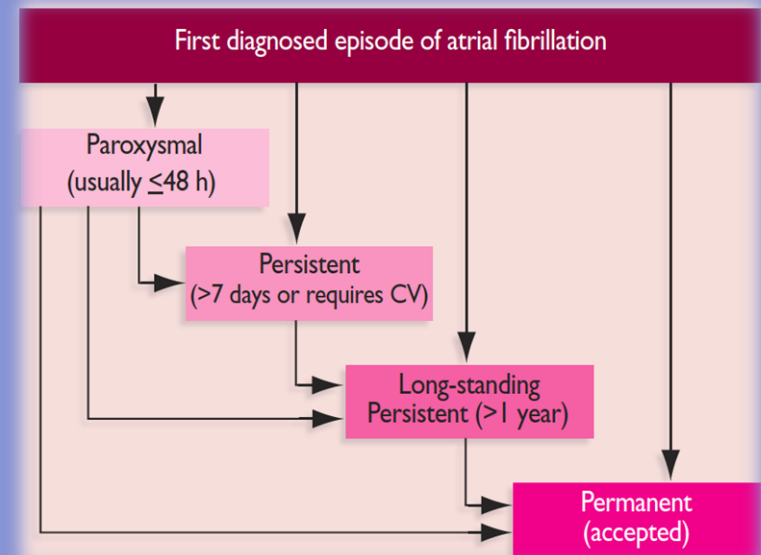
ATRIAL FIBRILLATION



$CHA_2DS_2-VASc \geq 2$



- **Contraindication to OAC**
- **High risk of bleeding with OAC**
- **Difficult to maintain INR within the therapeutic range**
- **Poor compliance**
- **Difficulty to manage the patient because of logistic problems**



Conclusions -2-

LAA occlusion is feasible and is emerging as a preferred alternative in many situations

If successful implant → RR 0.40

Safety of the procedure needs to be stressed:

if you have a $\text{CHA}_2\text{DS}_2\text{-VASc}$ risk of stroke of 2,2% your LAA procedure must be safer!!!

The learning curve with actual devices does exist and must be approached with adequate training and proctoring



Neurologist

TEAMWORK

**Clinical
Cardiologist**

**Echo
Team**

**Interventional
Cardiologist**

Electrophysiologist

**Thank you for your
attention**

