



Occlusione dell'Auricola Sinistra nel Fibrillante Anziano ad Alto Rischio Emorragico

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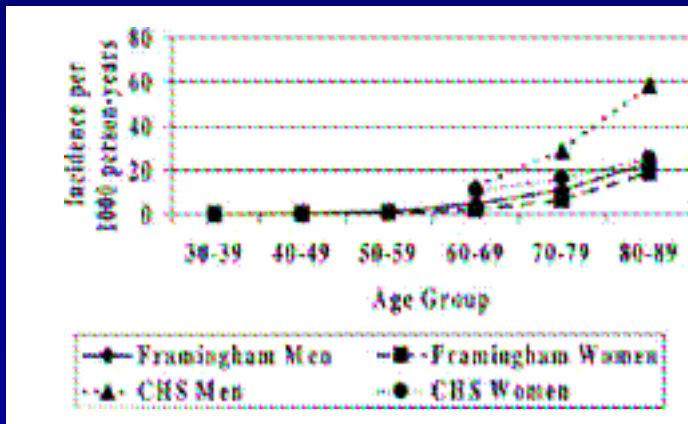
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**55° Congresso Nazionale della Società
Italiana di Gerontologia e Geriatria
Firenze
30 novembre - 4 dicembre 2010**

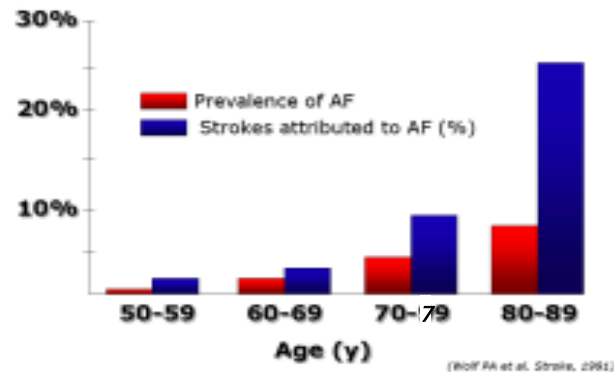
Facts About Atrial Fibrillation (AF)

- AF is the most common cardiac arrhythmia
 - *Affects more than 3 million in the US and 4.5 million in the EU*
 - *Projected to increase to 16 million in the US by 2050*
- AF Incidence increases with age
- AF is responsible for 15-20% of ischemic strokes

Incidence of AF with aging



Relationship of AF and stroke



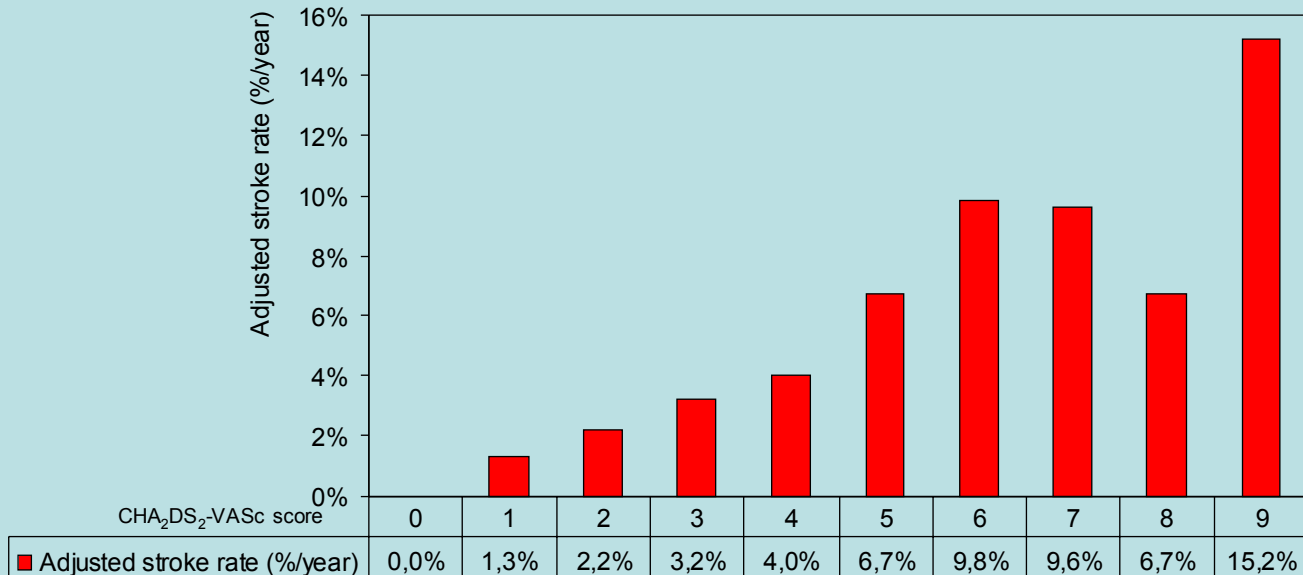
Stroke Risk Assessment

CHA₂DS₂-VASc Score

Letter	Risk factor	Points awarded
C	- Congestive heart failure/LV dysfunction	1
H	- Hypertension	1
A	- Age >75	2
D	- Diabetes mellitus	1
S	- Stroke/TIA/thrombo-embolism	2
V	- Vascular disease	1
A	- Age 65–74	1
Sc	- Sex-category (i.e. female sex)	1
	Maximum score	9

CHA₂DS₂-VASc Score and Stroke Rate

Adjusted Stroke Rate according to CHA₂DS₂-VASc score



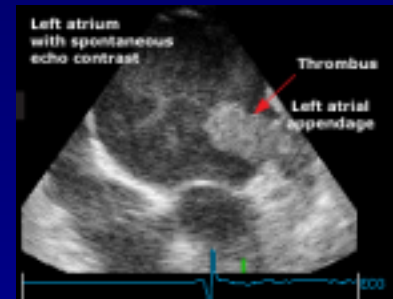
Thrombus Location in Non-Valvular AF

90% (201/222) of Left Atrial Thrombus Localized in the LAA

Setting	N	LAA	%	LA Body	%	Reference
TEE	317	66	21	1	0.3	Stoddard; JACC, 1995
TEE	233	34	15	1	0.4	Manning; Circ, 1994
Autopsy	506	35	7	12	2.4	Aberg; Acta Med Scan, 1969
TEE	52	2	4	2	3.8	Tsai; JFMA, 1990
TEE	48	12	25	1	2.1	Klein; Int J Card Image, 1993
TEE & Operation	171	8	5	3	1.8	Manning; Circ, 1994
SPAF III TEE	359	19	5	1	0.3	Klein; Circ, 1994
TEE	272	19	7	0	0.0	Leung; JACC, 1994
TEE	60	6	10	0	0.0	Hart; Stroke, 1994
Total Thrombus		201		21		


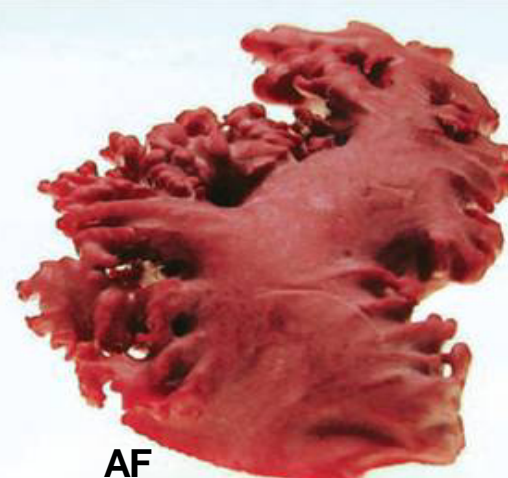
Sinus Rhythm

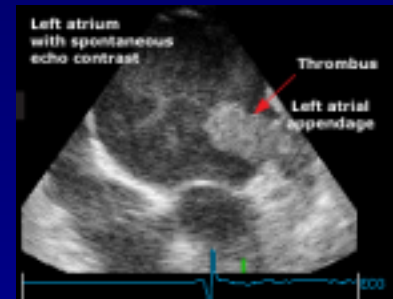
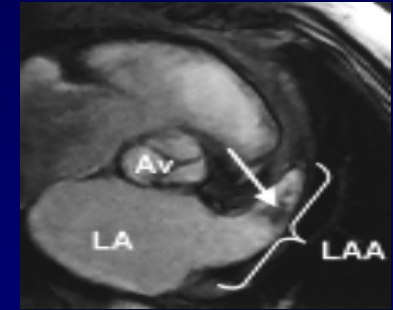
AF



Thrombus Location in Non-Valvular AF

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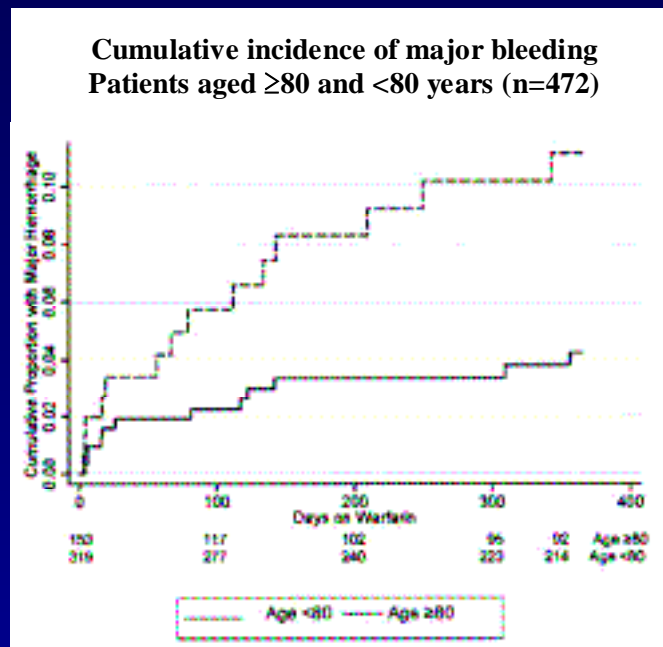
Non-Valvular AF

Challenges in Treating AF

- Coumadin is the cornerstone of therapy
 - *60-70% risk reduction vs. no treatment, 30-40% risk reduction vs. aspirin*
- However coumadin is not always well-tolerated
 - *Narrow therapeutic range (INR between 2.0 – 3.0)*
 - *Need close monitoring/dose adjustment and has food/drug interactions*
 - *Risk of bleeding particularly in elderly patients (IH 1.8%/yr in ≥ 78 yrs)*
 - *Discontinuation rate estimated to be 38%/yr*
- Less than 50% of patients eligible are being treated with coumadin due to intolerance or non-compliance issues
- SPORTIF trials: only 60% of treated patients are within a therapeutic INR range, while 29% have INR levels < 2.0 and 15% have levels > 3.0

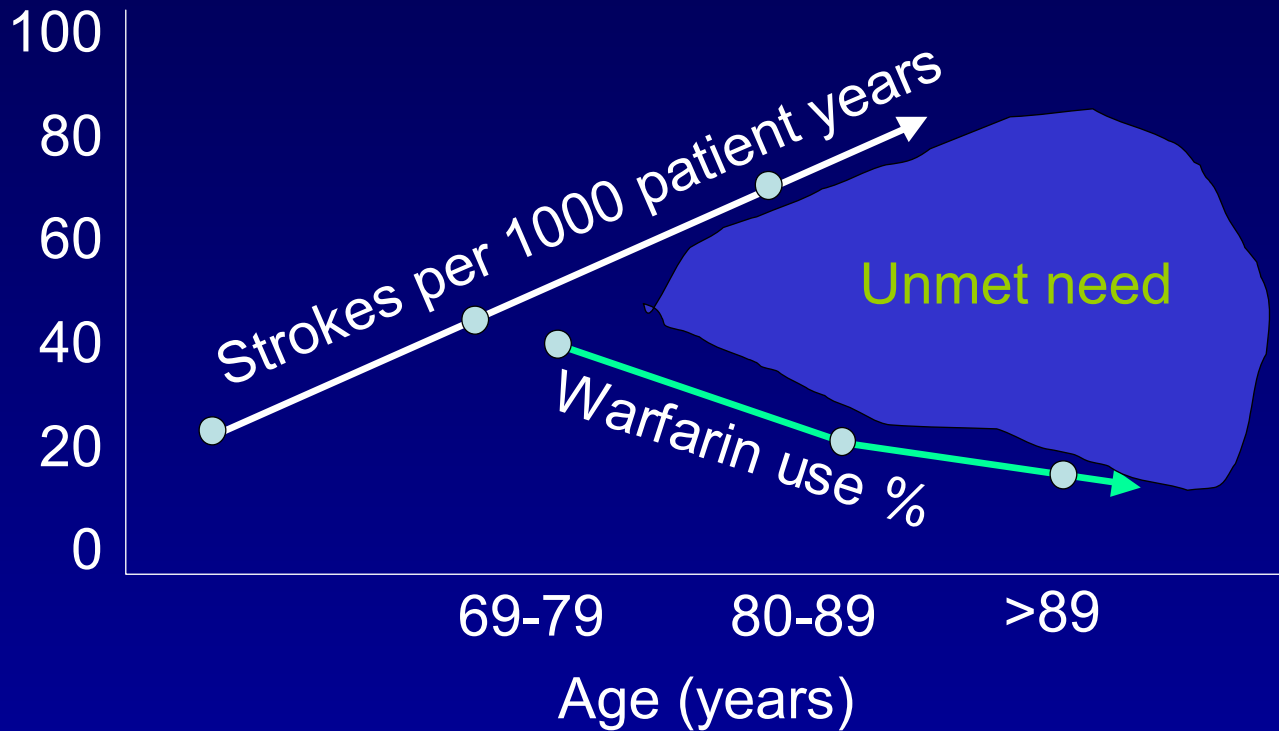
Major Hemorrhage on Warfarin

- Stroke prevention among elderly patients with atrial fibrillation remains challenging
- Aggregate hemorrhage rate 7.2% per 100 person/yr
 - 4.75% pts <80 yrs
 - 13.1% for pts ≥80 yrs
 - First 90 days associated with 3-fold increased risk
- 26% pts ≥80 yrs taken off warfarin
 - 81% due to safety concerns



Hylek et al. Major Hemorrhage and Tolerability of warfarin in the 1st Year of Therapy Among Elderly Patients with AF. *Circulation* 2007;115:2689-2696.

Age-related Trends in AF



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

Stroke Prevention in Non-Valvular AF

Currently Available Management Options



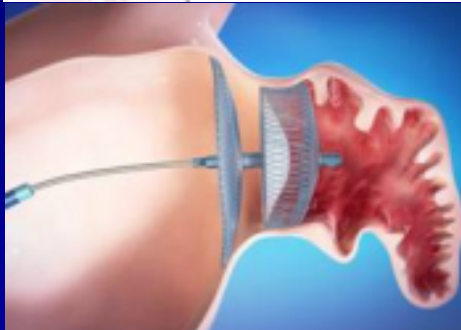
Medical Management: Coumadin

- Effective: 67% stroke risk reduction
- Narrow therapeutic window for proper dose
- Contraindicated in 14-47% of patients at risk of stroke
- Major complication: bleeding



Surgical Excision (Appendectomy)

- High invasiveness (not a stand-alone procedure)
- Residual shunt 10%
- Inconsistent outcomes due to incomplete exclusion
- Can create pouch with stagnant blood flow



Transcatheter Device Closure

- LAA percutaneous closure for prevention of clot embolization that may form in the LAA
- Minimally invasive
- Intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation

PLAATO - The FIM Feasibility Study Proof of Concept Launched a New Field

Percutaneous Left Atrial Appendage Transcatheter Occlusion to Prevent Stroke in High-Risk Patients With Atrial Fibrillation Early Clinical Experience

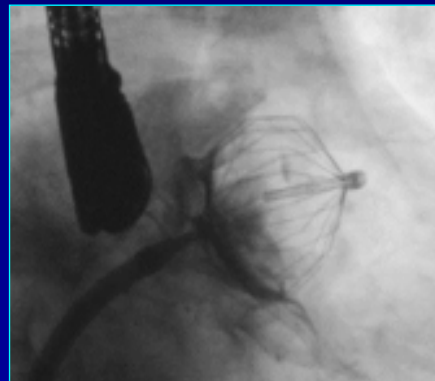
Horst Sievert, MD; Michael D. Lesch, MD; Thomas Trepels; Heydyer Otman, MD; Antonio Bartorelli, MD; Paola Della Bella, MD; Toshiko Nishii, MD; Mark Reisman, MD; Carlo DiMario, MD; Peter Block, MD; Paul Kramer, MD; Dirk Fleschenberg; Ulrike Krumsdorf; Detlef Scherer, MD

Background—Thromboembolism due to atrial fibrillation (AF) is a frequent cause of stroke. More than 90% of thrombi in AF form in the left atrial appendage (LAA). Obliteration of the appendage may prevent embolic complications.

Methods and Results—We evaluated the feasibility and safety of implanting a novel device for percutaneous left atrial appendage transcatheter occlusion (PLAATO). LAA occlusion using the PLAATO system was attempted in 15 patients with chronic AF at high risk for stroke, who are poor candidates for long-term warfarin therapy. The implant consists of a self-expanding nitinol cage covered with a polymeric membrane (ePTFE). The LAA was successfully occluded in 15/15 patients (100%). Angiography and transesophageal echocardiography (TEE) during the procedure showed that the device was well-seated in all patients and that there was no evidence of perforation, device embolization, or interference with surrounding structures. In 1 patient, the first procedure was complicated by a hemopericardium, which occurred during LAA access. A second attempt 30 days later was successful with no untoward sequelae. No other complications occurred. At 1-month follow-up, chest fluoroscopy and TEE revealed continued stable implant position with smooth atrial-facing surface and no evidence of thrombus.

Conclusions—Thus, transcatheter closure of the LAA is feasible in humans. This novel implant technology may be appropriate for patients with AF who are not suitable candidates for anticoagulation therapy. Further trials are needed to show the long-term safety and its efficacy in reducing stroke. (*Circulation*. 2004;109:1887-1889.)

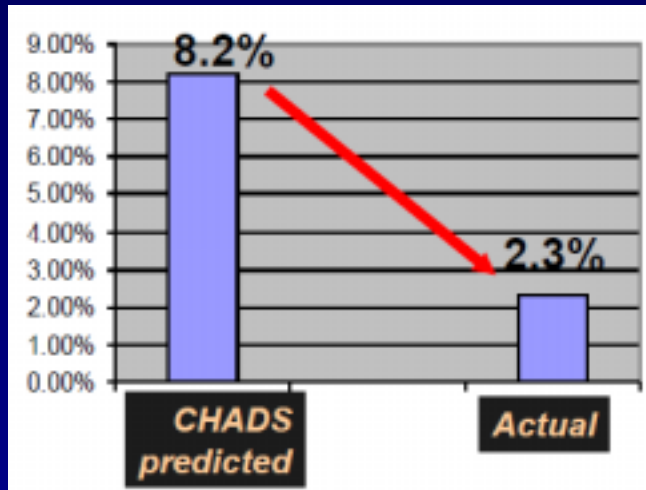
Key Words: atrial flutter ■ embolism ■ stroke ■ thrombus ■ atrium



PLAATO F/U DATA

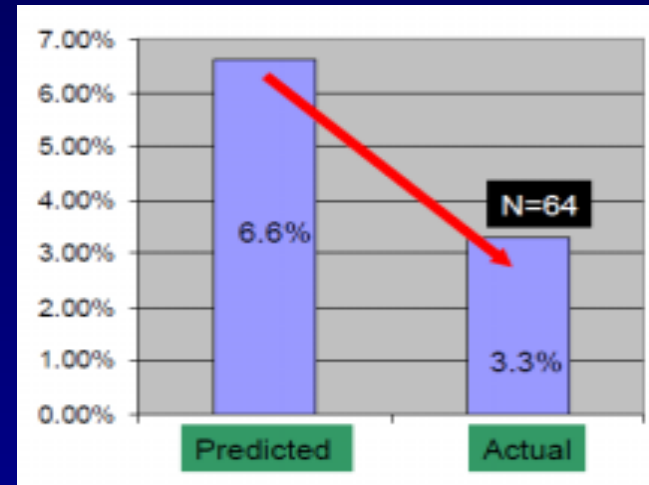
Estimated Stroke Reduction

European Registry



72% stroke reduction

US 5-year F/U



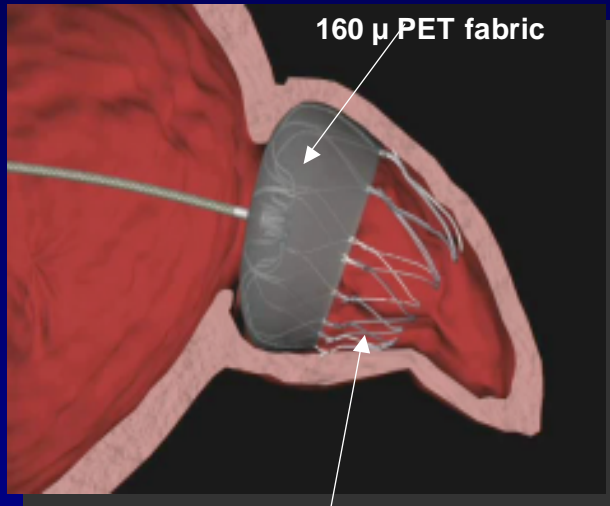
50% stroke reduction

Expected risk of stroke based on patients' baseline adjusted CHADS₂ score

Block PC TCT 2009

What Next ?

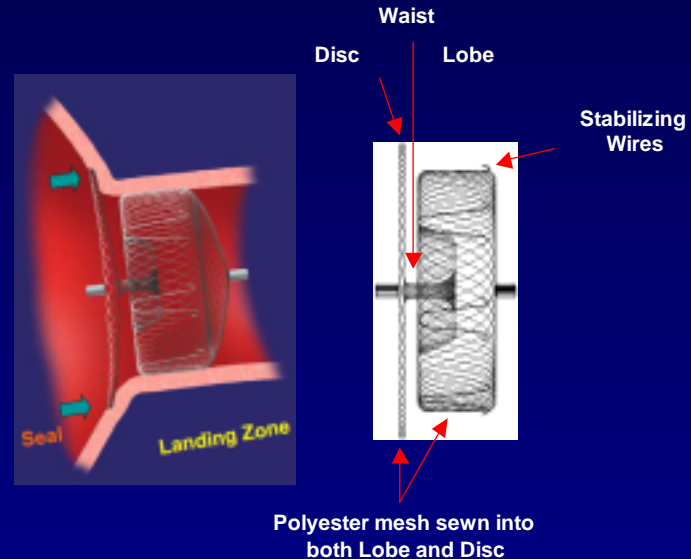
Watchman® System (Atritech)



Fixation barbs engage
LAA wall

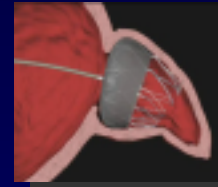
- Designed to “fill” and filter the LAA
- Coumadin indicated for 45 days (permeable polyester membrane)
- PROTECT AF trial completed

Amplatzer® Cardiac Plug (AGA)



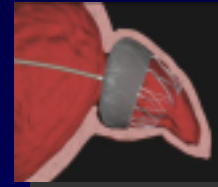
- Designed to occlude (versus “filter”) the LAA
- The disc covers LAA orifice independent of LAA shape rather than attempting to “fill” the LAA
- The waist provides positional flexibility enabling the disc to self-orient to cover the LAA orifice
- Phase I and II trial approval awaited

PROTECT AF Clinical Trial



- Prospective, randomized study of WATCHMAN LAA device vs. long-term coumadin therapy
- 2:1 allocation ratio device to control
- 800 patients enrolled from Feb 2005 to Jun 2008
 - 93 Roll-in; 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
 - INR monitoring every 2 weeks for 6 months and monthly thereafter

PROTECT AF Clinical Trial

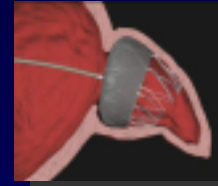


Intent-to-Treat: Primary Efficacy Results

Cohort	WATCHMAN		Control		Rel. Risk (95% CI)		Posterior Probabilities	
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)			Non-inferiority	Superiority
600 pt-yrs	4.4	2.6, 6.7	5.8	3.0, 9.1	0.76	0.39, 1.67	0.992	0.734
900 pt-yrs	3.4	2.1, 5.2	5.0	2.8, 7.6	0.68	0.37, 1.41	0.998	0.837
1065 pt-yrs	3.0	1.9, 4.5	4.9	2.8, 7.1	0.62	0.35, 1.25	>0.999	0.900

- Non-inferiority criteria met
- 38% lower relative risk in WATCHMAN Group

PROTECT AF Clinical Trial



Per-Protocol: Primary Efficacy Results

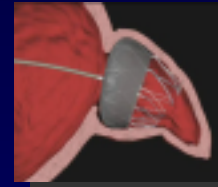
- Assess only those successfully treated with randomized therapy
- Includes only patients who received their assigned therapy
- Helps to isolate sole device effect

Cohort	WATCHMAN		Control		Rel. Risk (95% CI)		Posterior Probabilities*	
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)			Non-Inferiority	Superiority
600 pt-yrs	2.5	1.1, 4.8	5.4	2.7, 8.6	0.47	0.19, 1.21	0.999	0.938
900 pt-yrs	2.1	1.0, 3.7	4.7	2.6, 7.2	0.44	0.20, 1.03	>0.999	0.971
1065 pt-yrs	1.9	1.0, 3.2	4.6	2.6, 6.8	0.40	0.19, 0.91	>0.999	0.986

*No adjustment made for multiple comparisons

- 60% lower relative risk in WATCHMAN Group

PROTECT AF Clinical Trial

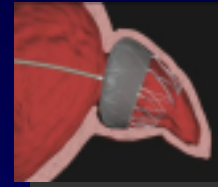


Primary Safety Endpoint – Up Front Risk

Timeframe	Event Description	WATCHMAN N (% of 463)		Control N (% of 244)
Events Within 7 Days of Procedure	Pericardial Effusion	21	4.5%	N/A
	Ischemic Stroke	5	1.1%	N/A
	Device Embolization	1	0.2%	N/A
	Major Bleeding	5	1.1%	N/A
	Other	2	0.4%	N/A
Total		34	7.3%	N/A

- Highest rate of safety events in WATCHMAN Group occur on the day of the procedure

PROTECT AF Clinical Trial

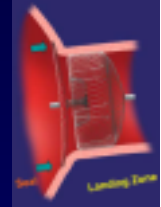


Primary Safety Endpoint – Continuous Risk

Timeframe	Event Description	WATCHMAN N (% of 463)		Control N (% of 244)	
		N	%	N	%
Events After 7 Days	Pericardial Effusion	1	0.2%	N/A	
	Device Embolization	2	0.4%	N/A	
	Hemorrhagic Stroke	1	0.2%	6	2.5%
	Major Bleeding	11	2.4%	10	4.1%
Total		15	3.2%	16	6.6%

- After peri-procedural period, event rate in WATCHMAN Group is lower than the Control Group

Initial ACP European Experience



Implant successful in 96.4% (132/137) of attempts

24-h Procedure Related Complications

Serious complications

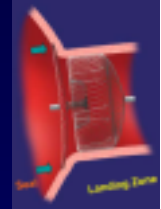
Serious pericardial effusion*	N=5 (3.5%)
Device embolization	N=2 (1.4%)
Ischemic stroke (embol. of air or thrombus?)	N=3 (2.1%)

Minor complications

Trivial pericardial effusion	N=4 (2.8%)
Transient myocardial ischemia (air embolism)	N=2 (1.4%)
Device snared from femoral vein (implant remained at the right side)	N=1 (0.7%)

* 1 tamponade due to pulmonary artery puncture

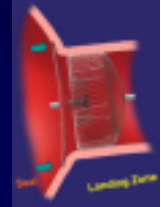
Initial ACP European Experience



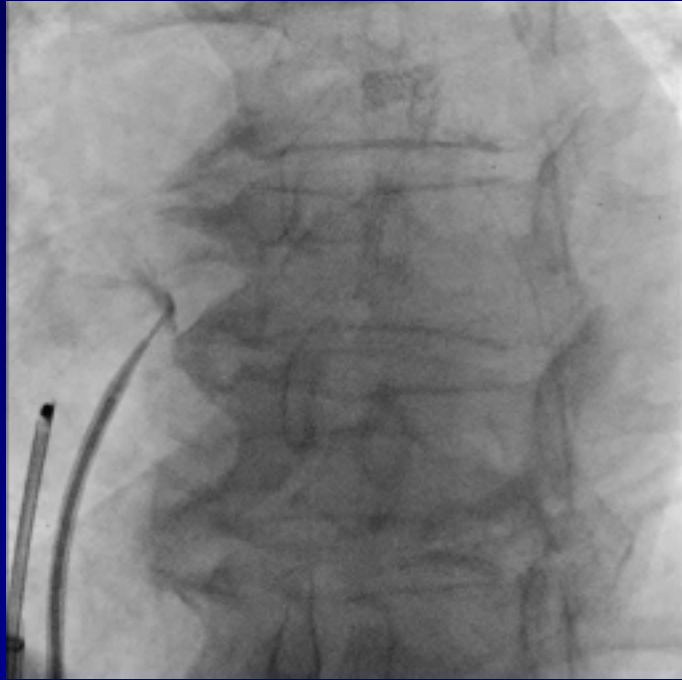
FOLLOW-UP Up to 9 Months

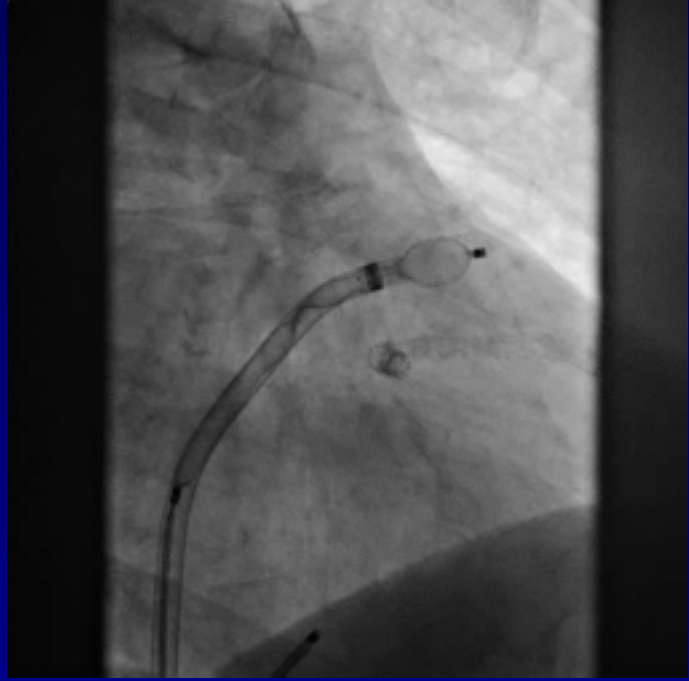
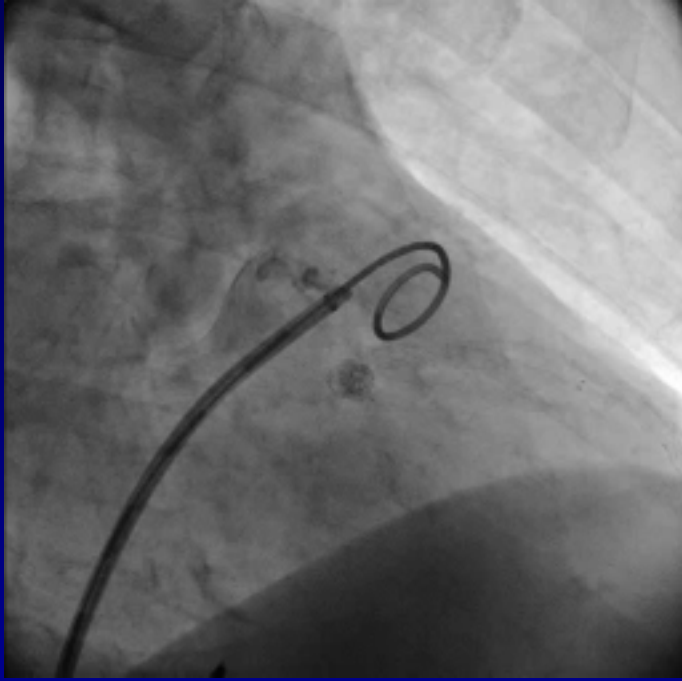
■ TIA	0
■ STROKE	0
■ Device Embolization	0
■ Thrombus on the device	0
■ Residual flow	0

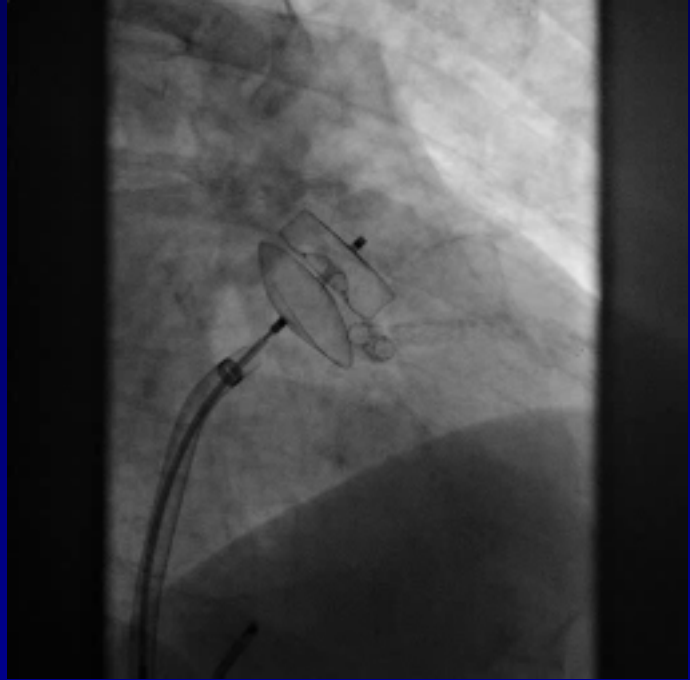
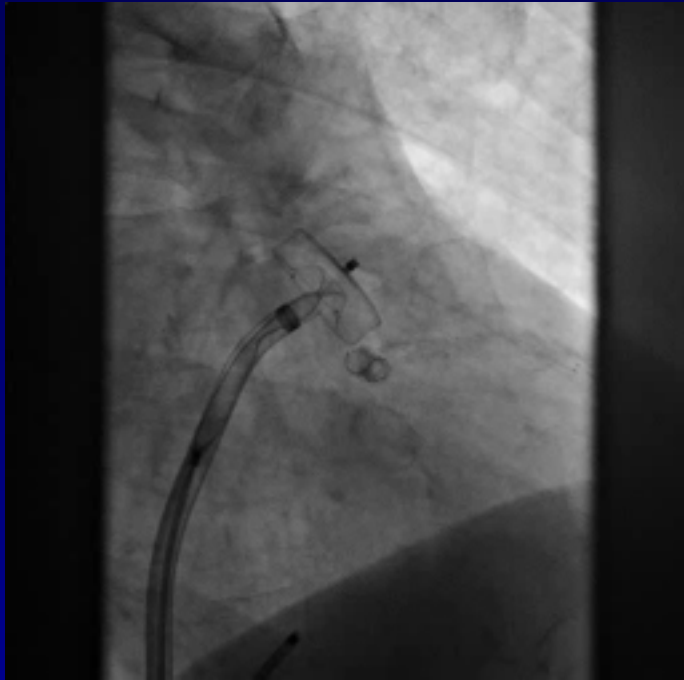
Amplatzer Closure Plug Case

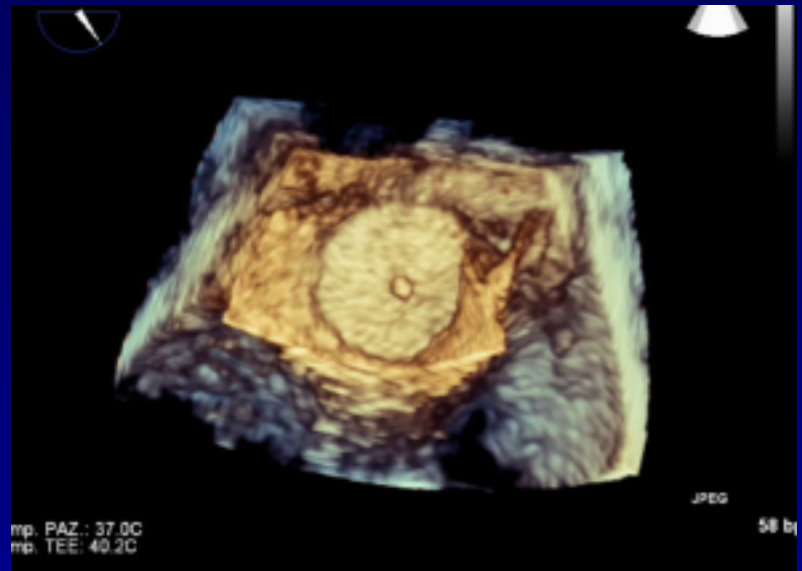
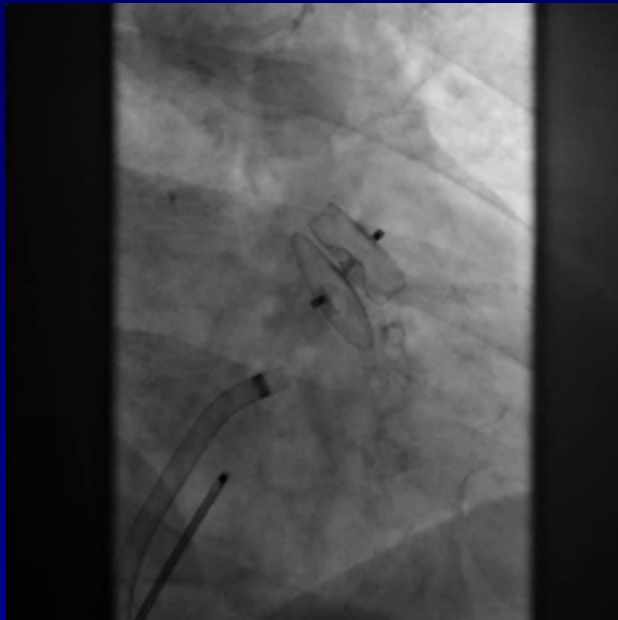


- 80-year-old man
- Prior PCI x 2 for 2VD
- Prior PTA x 2 of both legs + surgical AAA treatment
- Chronic AF since 2006
- Three previous cardioembolic events on coumadin: right leg + left arm (treated with Fogarty catheter) and retina (right eye blindness)
- **CHA₂DS₂-VASc Score: 5**









Conclusions (I)

- Nonvalvular AF is common in the general population
- AF and stroke have a strong relationship and the risk of both conditions increase with ageing
- Anticoagulation is a valid option but has several limitations, particularly in elderly patients
- Despite improvements of OAT (Dabigatran) the benefits of anticoagulation do not come without the risk of bleeding
- Stroke prevention among elderly patients with AF remains a challenging and pressing health concern

Conclusions (II)

- The vast majority (>90%) of all cardiac thrombi in patients with AF form in the left atrial appendage (LAA)
- Thus, excluding the LAA percutaneously seems a rationale approach
- PLAATO was the proof of concept that launched a new therapeutic strategy
- Protect AF demonstrated that LAA occlusion may offer an effective alternative in pts with non-valvular AF at risk for stroke who are not eligible for coumadin
- LAA percutaneous occlusion is feasible but technically challenging and should performed by physicians with specific training and appropriate experience