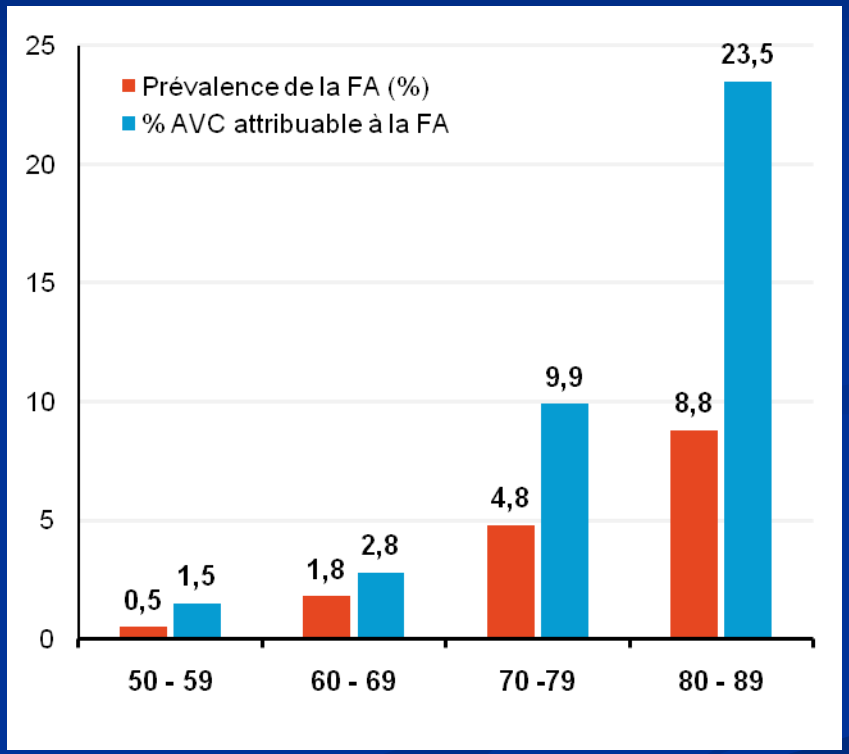
Left atrial appendage occlusion: where are we now?

Nicolas Lellouche
Fédération de Cardiologie
Hôpital Henri Mondor
Créteil

Atrial Fibrillation is a major cause of Stroke : (1,2)

- **AF is associated with a 5 fold increase risk of stroke** (2)
- **AF is responsable for 20 % of stroke** (3)
  - % of stroke due to AF increase with age (1,3,4)
- **In France, every 20 minutes 1 stroke due to AF***

Prévalence de la FA en fonction de l'âge et % d'AVC attribuable à la FA (7)



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2. Marini C *et al.* Contribution of Atrial Fibrillation to Incidence and Outcome of Ischaemic Stroke : Results From a Population-Based Study. Stroke 2005 ; 36 : 1115-1199.
3. Guidelines for the management of atrial fibrillation. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010 ; 31 : 2369-2449..
4. Kannel WB *et al.* Prevalence, Incidence, Prognosis, and Predisposing Conditions for Atrial Fibrillation: Population-Based Estimates.Am J Cardiol 1998 ; 82 : 2N-9N.
5. Ministère de la santé et des sports. La prévention et la prise en charge des accidents vasculaires cérébraux en France : Rapport à Madame la ministre de la santé et dessports présenté par la Docteure Elisabeth Fery-Lemonnier. Juin 2009. www.sante.gouv.fr
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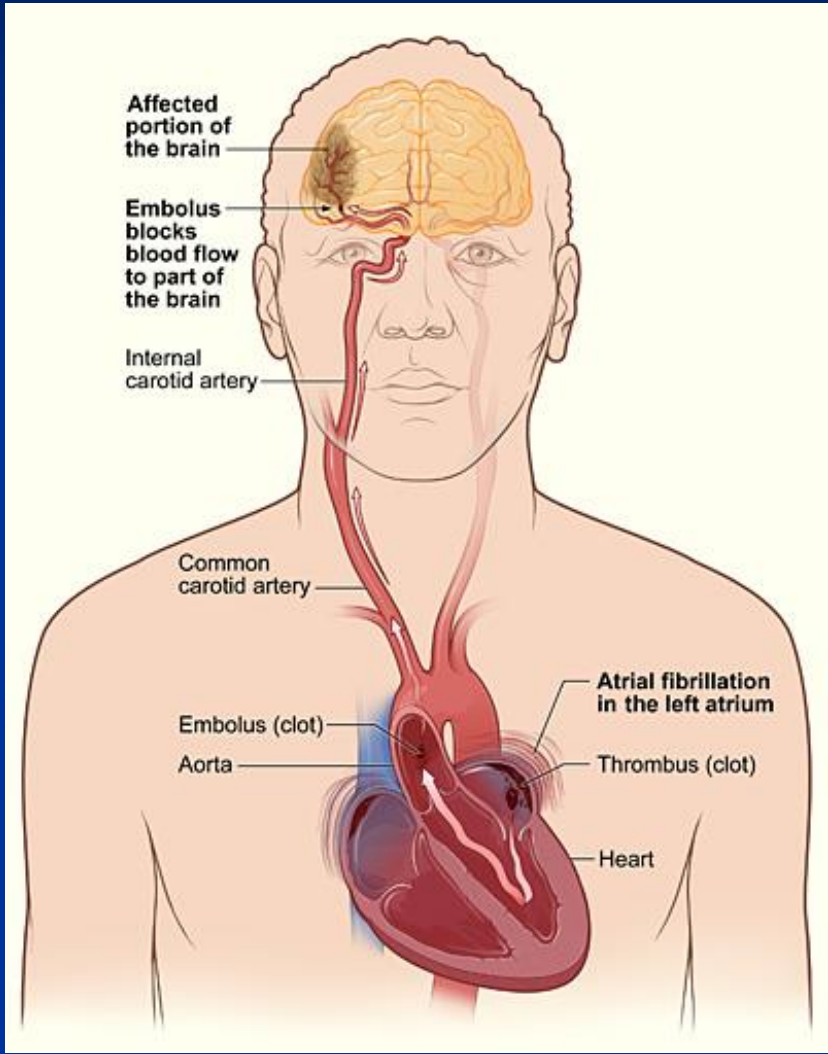
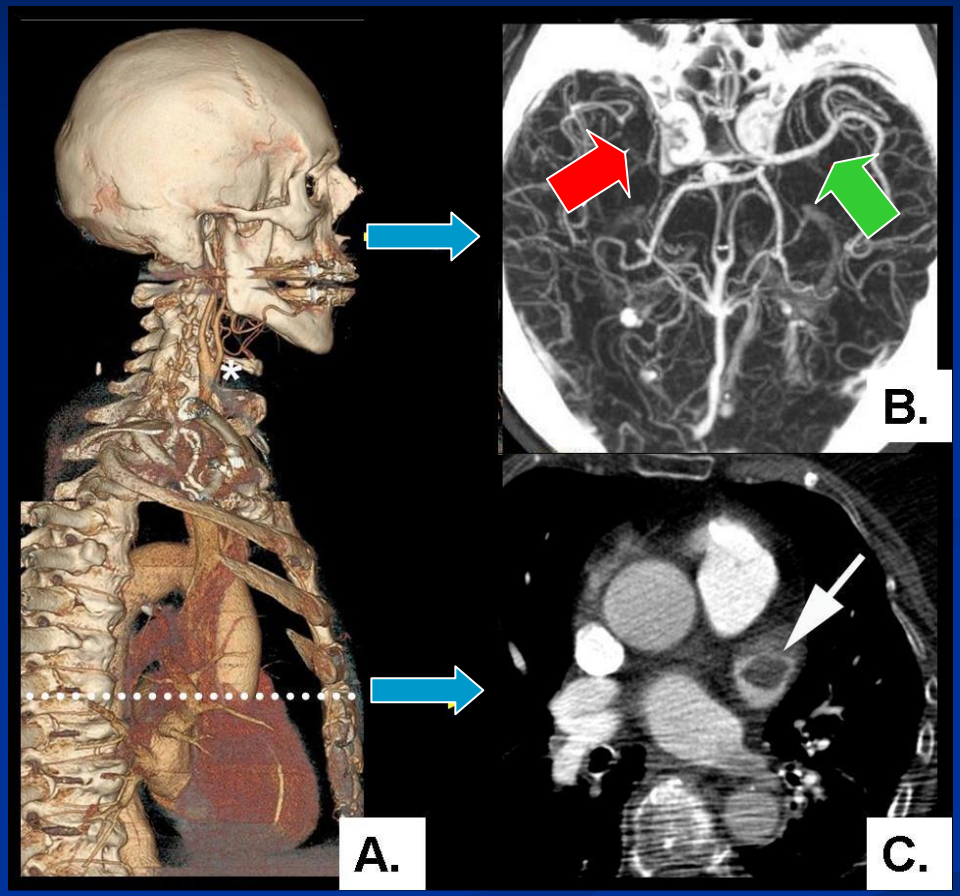
Association between AF and Stroke

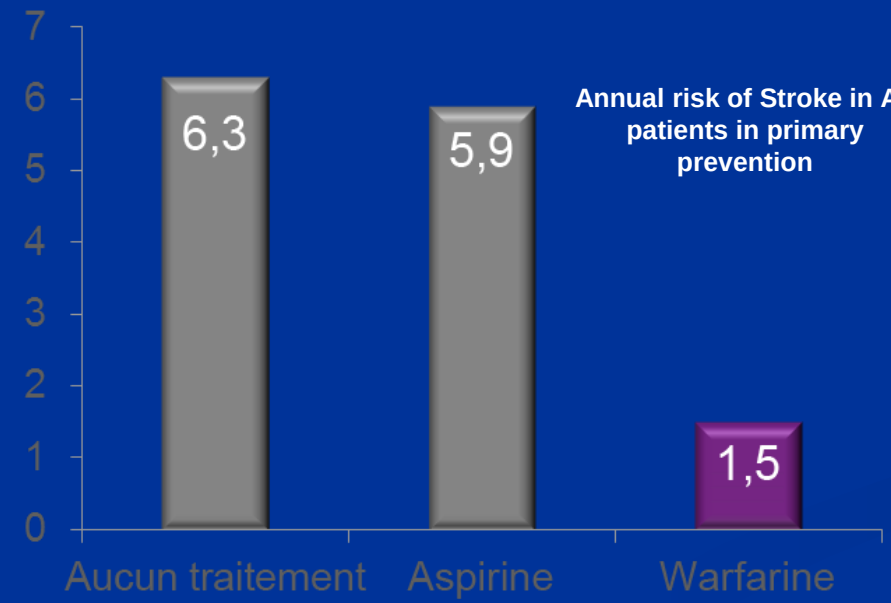


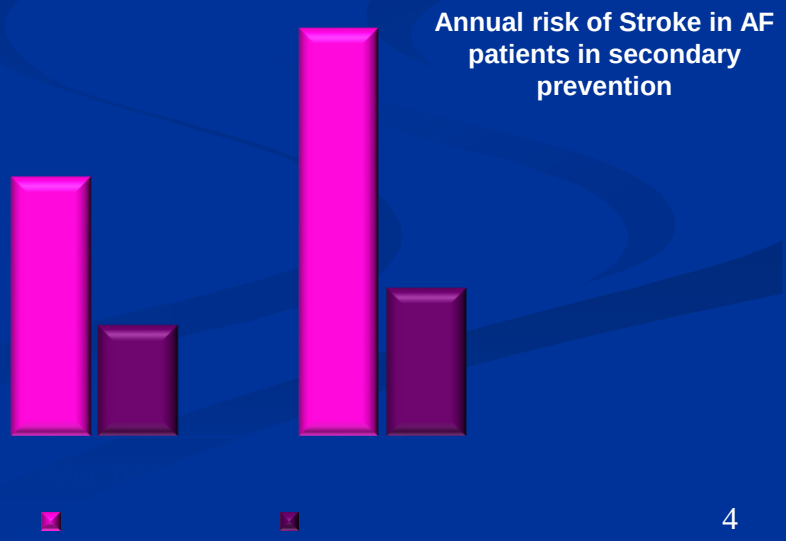


A: 3-D CT
B: Angio: ⇨ - normal MCA
⇨ - absence of MCA
C: CAT scan: Arrow showing LAA clot

Stroke Prevention during AF

- Oral anticoagulation (VKA) reduces the risk of stroke during AF :
  - 60% reduction of stroke
  - 25% reduction of overall mortality

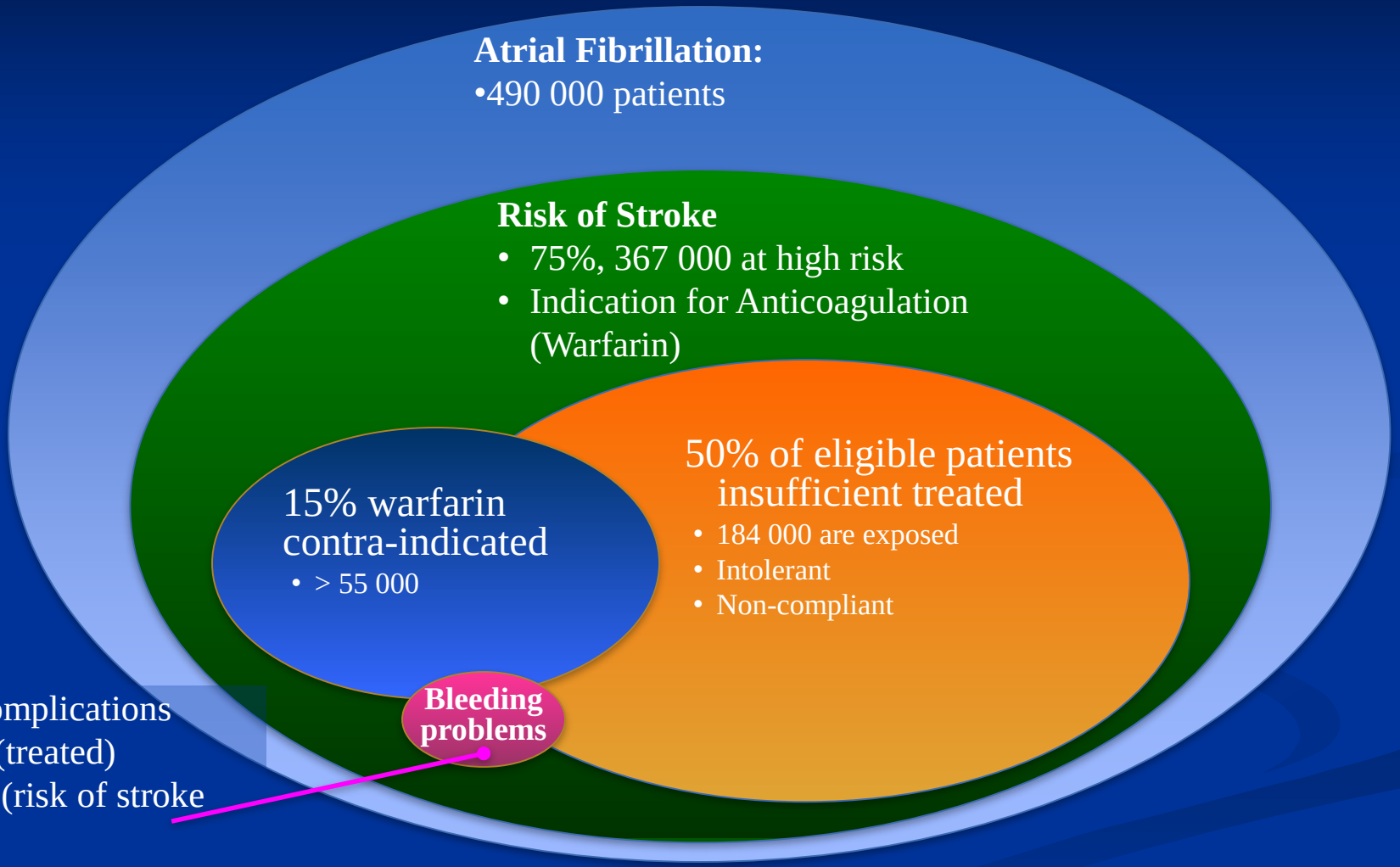




Even with new oral anticoagulant agent: hemorragic risk still persist

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin	
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr
Major bleeding	322	2.71	375	3.11	397	3.36
Life threatening	145	1.22	175	1.45	212	1.80
Non–life threatening	198	1.66	226	1.88	208	1.76

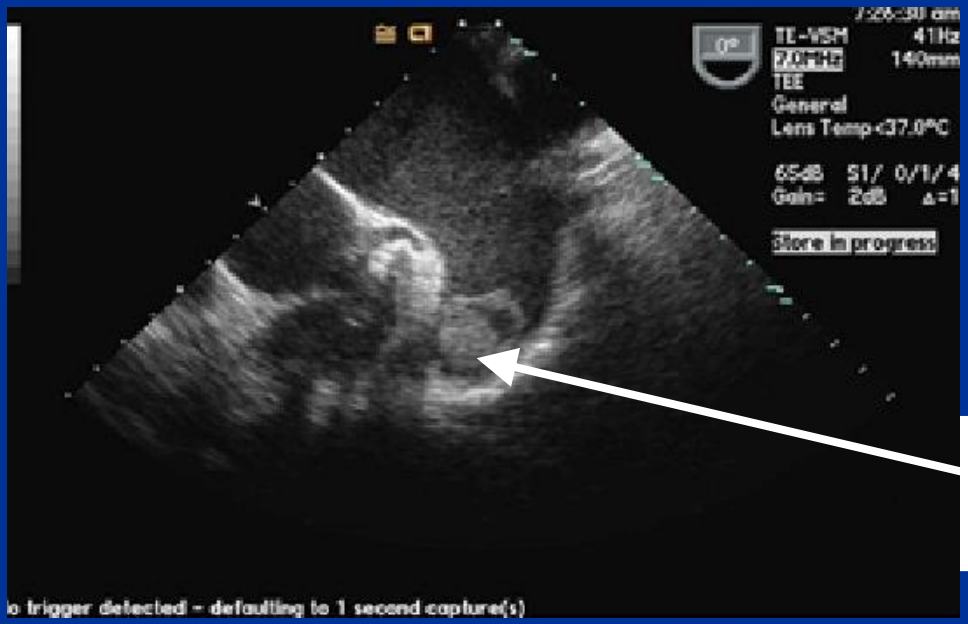
Patient Population *France*



Bleeding Complications
- 5 500 /yr (treated)
- 11 000/yr (risk of stroke group)

AF and thrombo-embolism risk

- In 90% of cases thrombus is coming from LAA during AF

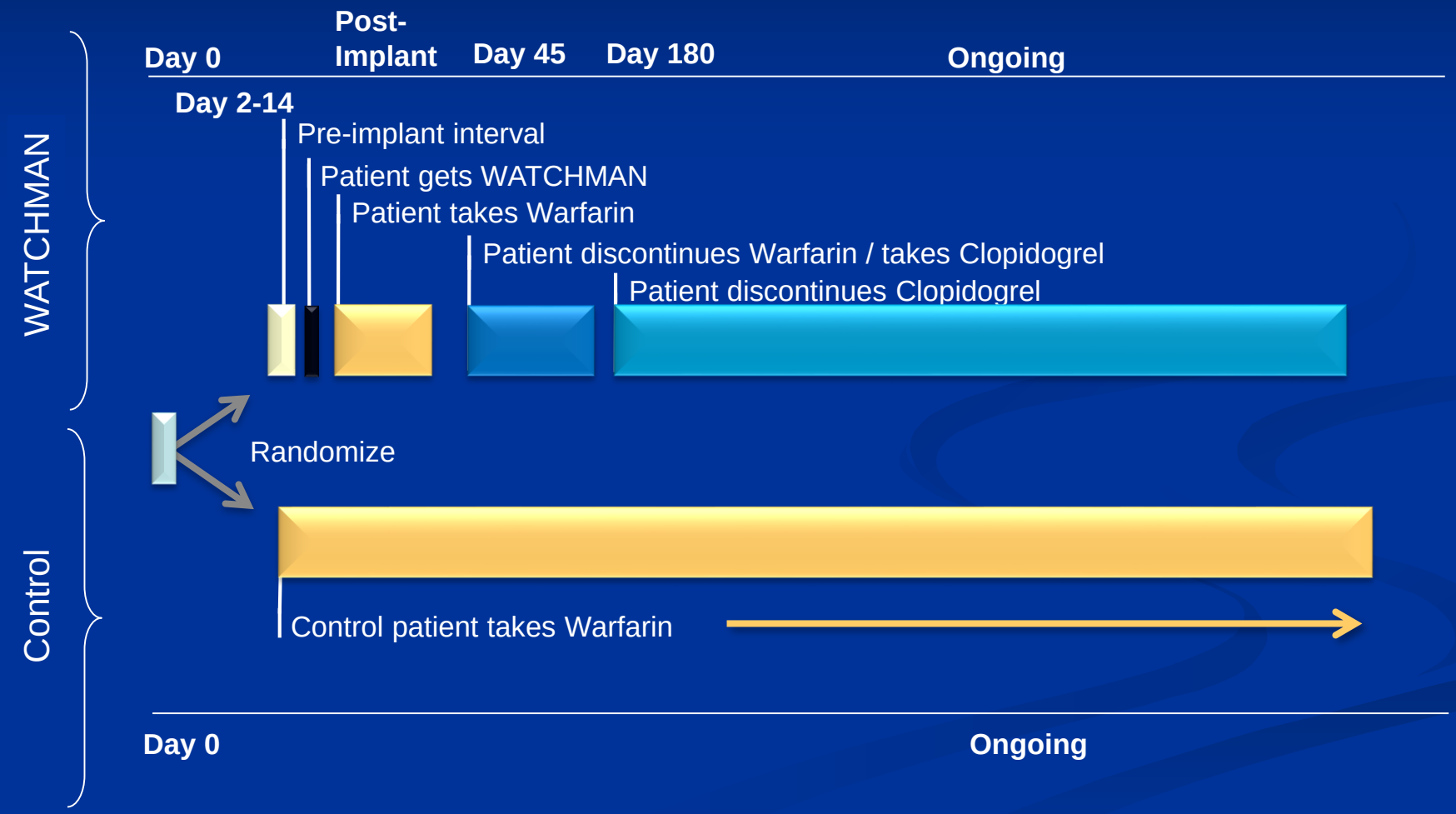


LAA Thrombus

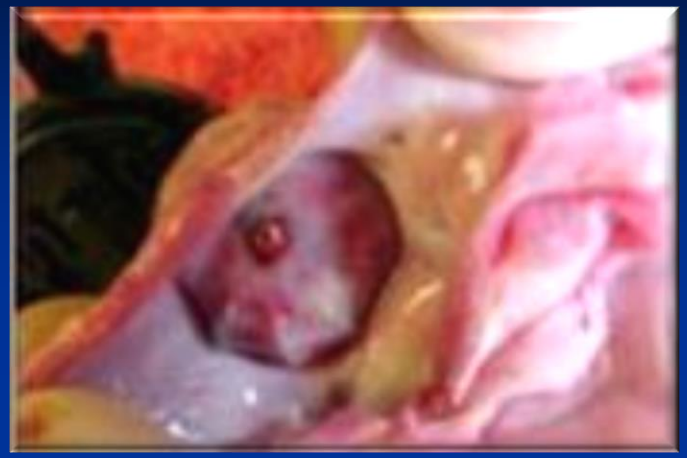
PROTECT AF

Study Objective:	Evaluate the efficacy and safety of the WATCHMAN LAA Closure Device as compared to long-term warfarin therapy in patients with non-valvular atrial fibrillation and $CHADS_2$ score $\geq$ 1
Study Design:	Prospective, randomized (2 Device: 1 Control), non-inferiority study of the Watchman device compared to long-term warfarin therapy
Primary Endpoint:	Non-inferiority of the WATCHMAN device to warfarin therapy for the composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death
Additional Endpoints:	Life-threatening events including device embolization requiring retrieval, pericardial effusion requiring intervention, cranial and GI bleeding, and bleeding requiring transfusion $\geq$ 2 units PRBCs
Patient Population:	WATCHMAN n=463 Control n=244 Roll-in n=93
Number of Sites:	59 (55 U.S., 4 EU)

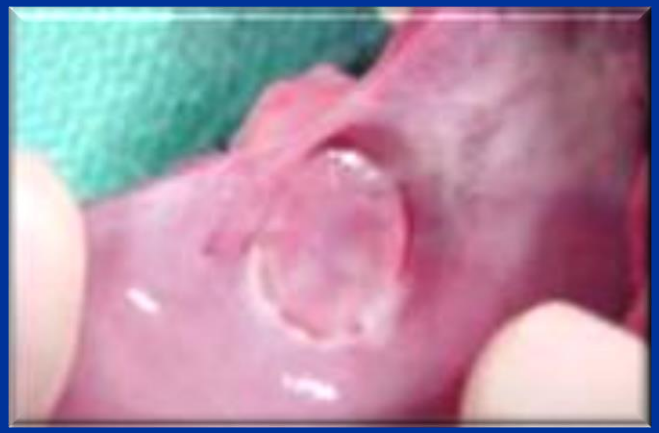
Design de l'étude



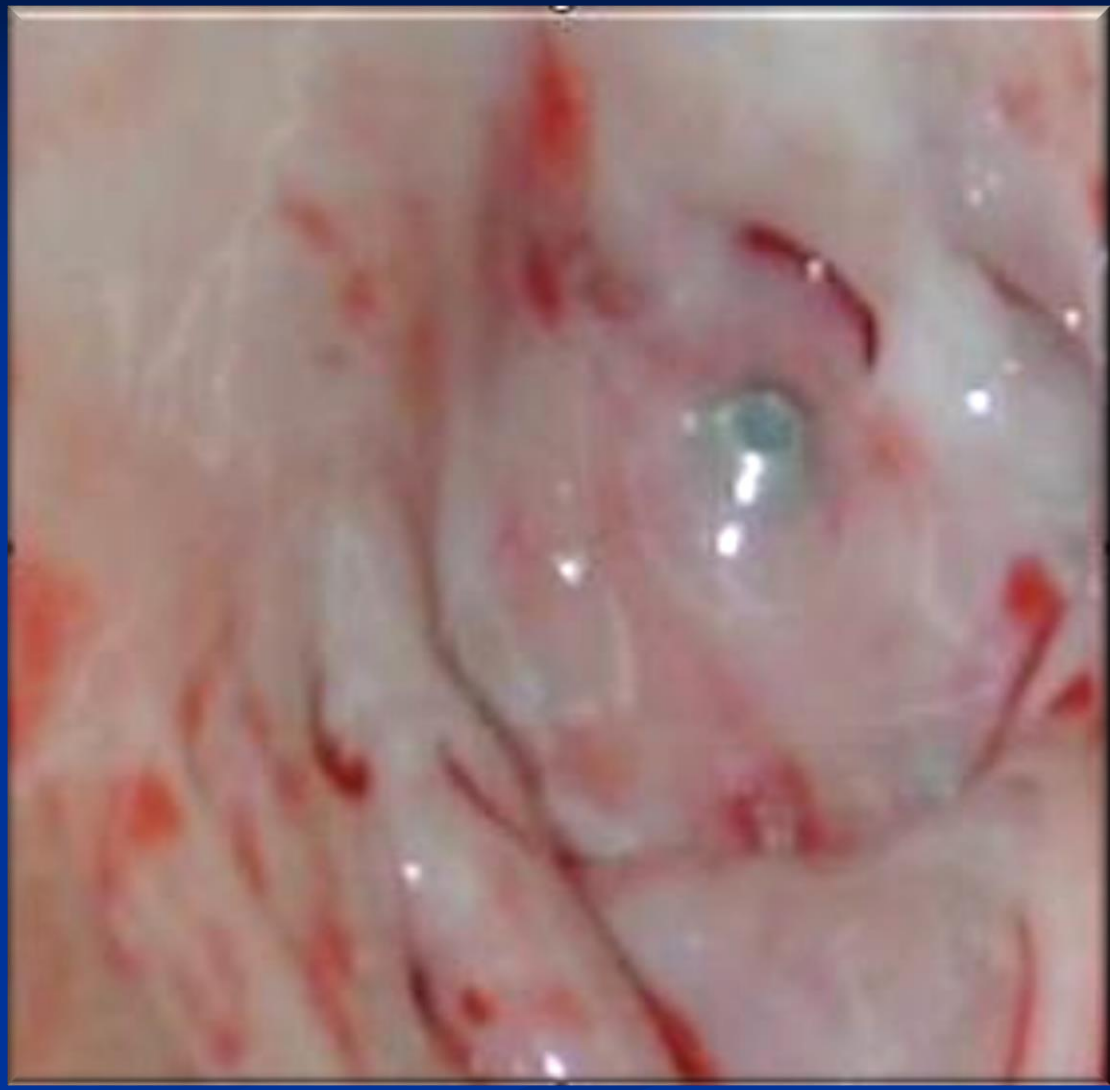
WATCHMAN: Device endothelialization



Canine Model – 30 Day

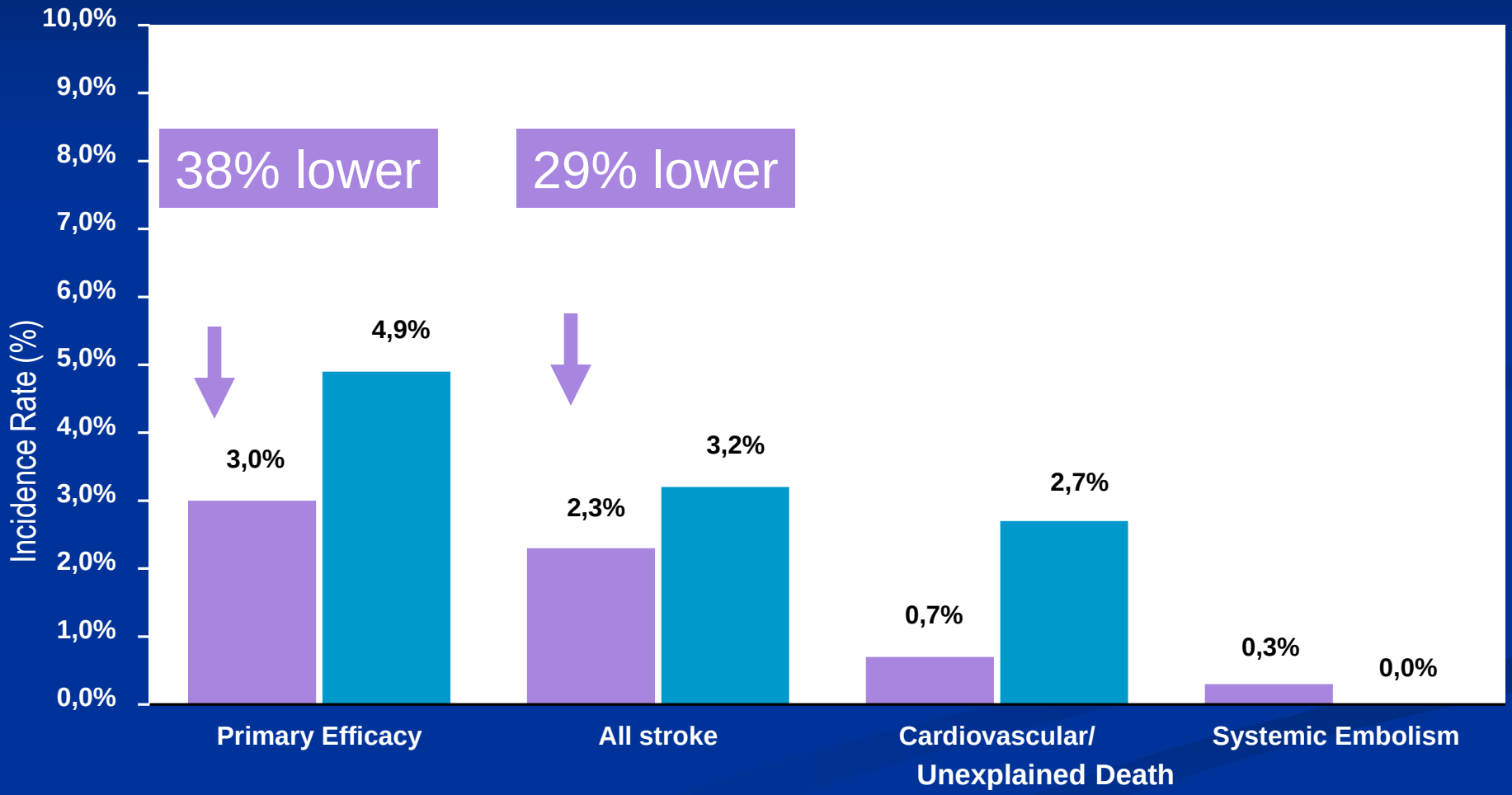


Canine Model – 45 Day



Human Pathology – 9 Months Post-implant
(Non-device related death)

PROTECT AF – Primary Efficacy Endpoint



Suivi à long terme de Protect AF

Importance While effective in preventing stroke in patients with atrial fibrillation (AF), warfarin is limited by a narrow therapeutic profile, a need for lifelong coagulation monitoring, and multiple drug and diet interactions.

Objective To determine whether a local strategy of mechanical left atrial appendage (LAA) closure was noninferior to warfarin.

Design, Setting, and Participants PROTECT AF was a multicenter, randomized (2:1), unblinded, Bayesian-designed study conducted at 59 hospitals of 707 patients with nonvalvular AF and at least 1 additional stroke risk factor ($CHADS_2$ score ≥1). Enrollment occurred between February 2005 and June 2008 and included 4-year follow-up through October 2012. Noninferiority required a posterior probability greater than 97.5% and superiority a probability of 95% or greater; the noninferiority margin was a rate ratio of 2.0 comparing event rates between treatment groups.

Interventions Left atrial appendage closure with the device (n = 463) or warfarin (n = 244; target international normalized ratio, 2-3).

Main Outcomes and Measures A composite efficacy end point including stroke, systemic embolism, and cardiovascular/unexplained death, analyzed by intention-to-treat.

Results At a mean (SD) follow-up of 3.8 (1.7) years (2621 patient-years), there were 39 events among 463 patients (8.4%) in the device group for a primary event rate of 2.3 events per 100 patient-years, compared with 34 events among 244 patients (13.9%) for a primary event rate of 3.8 events per 100 patient-years with warfarin (rate ratio, 0.60; 95% credible interval, 0.41-1.05), meeting prespecified criteria for both noninferiority (posterior probability, >99.9%) and superiority (posterior probability, 96.0%). Patients in the device group demonstrated lower rates of both cardiovascular mortality (1.0 events per 100 patient-years for the device group [17/463 patients, 3.7%] vs 2.4 events per 100 patient-years with warfarin [22/244 patients, 9.0%]; hazard ratio [HR], 0.40; 95% CI, 0.21-0.75; *P* = .005) and all-cause mortality (3.2 events per 100 patient-years for the device group [57/466 patients, 12.3%] vs 4.8 events per 100 patient-years with warfarin [44/244 patients, 18.0%]; HR, 0.66; 95% CI, 0.45-0.98; *P* = .04).

Conclusions and Relevance After 3.8 years of follow-up among patients with nonvalvular AF at elevated risk for stroke, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.

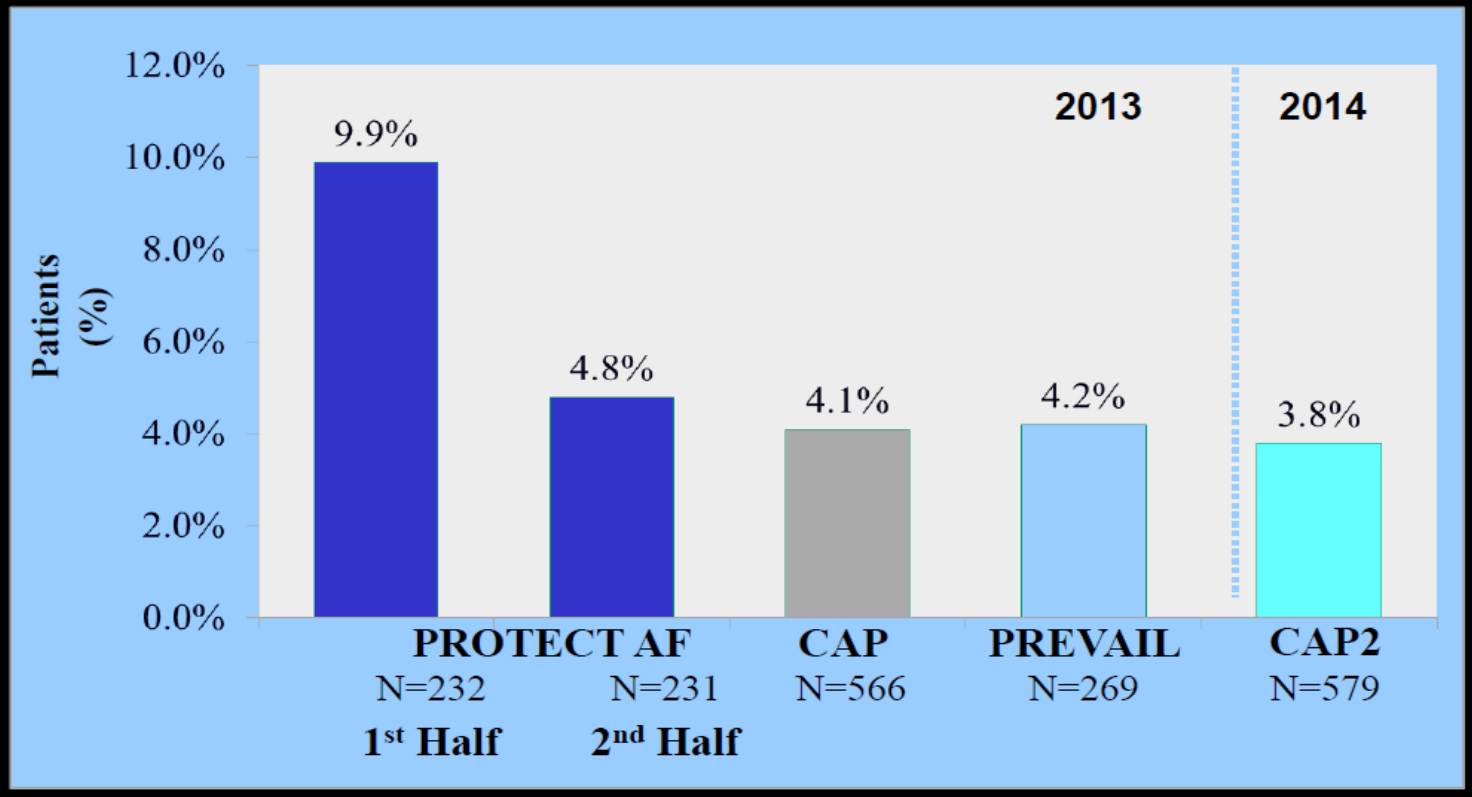
Left Atrial Appendage Closure with the Watchman Device in Patients with a Contraindication for Oral Anticoagulation: ASA Plavix Feasibility Study with Watchman
Left Atrial Appendage Closure Technology (ASAP Study)

Objectives: To assess the safety and efficacy of left atrial appendage closure (LAA) in nonvalvular atrial fibrillation (AF) patients ineligible for warfarin therapy.
Background: The PROTECT AF trial demonstrated that LAA closure with the Watchman device was non-inferior to warfarin therapy. However, PROTECT AF only included patients that were candidates for warfarin, and even patients randomized to the LAA closure arm received concomitant warfarin for 6 weeks after Watchman implantation.
Methods: Multi-center, prospective, non-randomized study of LAA closure with the Watchman device in 150 patients with non-valvular AF and CHADS2 ≥1, who were considered ineligible for warfarin. The primary efficacy endpoint was the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular/unexplained death.
Results: The mean CHADS2 and CHA2DS2-VASc scores were 2.8 ± 1.2 and 4.4±1.7, respectively. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Mean duration of follow-up was 14.4 ± 8.6 months. Serious procedureor device-related safety events occurred in 8.7% of patients (13/150 patients). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year); ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). This ischemic stroke rate was less than that expected (7.3% per year) based on the CHADS2 scores of the patient cohort.
Conclusions: LAA closure with the Watchman device can be safely performed without a warfarin transition, and is a reasonable alternative to consider for patients at high risk for stroke but with contraindications to systemic oral anticoagulation.

Learning curve confirmed

	Initial European Registry[1]	**EU Prospective Observational Study**
Number of patients (Follow-up period)	N = 143 (Discharge or < 24 hrs)	N = 204 (< 7 days)
Enrollment Period	December 2008 – December 2009	August 2009 – September 2011
Stroke	N = 3 (2.1%)	N = 0 (0.0%)
Serious Pericardial Effusion	N = 5 (3.5%)	N = 3 (1.5%)
Device Embolization	N = 2 (1.4%)	N = 3 (1.5%)
Device Related Thrombus	N= 0 (0.0%)	N = 0 (0.0%)
Total reported Safety Events	**N = 10 (7%)**	**N = 6 (2.9%)**

Consistent Safety Profile Since Second Half of PROTECT AF



EWOLUTION registry

- International prospective Registry (**1025 patients**, 47center, 13 countries)
- Inclusion : patients with WATCHMAN prosthesis implanted according to national ou international guidelines
- **62% of patients** (only) considered as contre-indicated for oral anticoagulation
- Characteristics of the population

High stroke risk : **CHA_2DS_2-VASc :** 4.5 ± 1.6
moderate haemorragic risk : **HAS-BLED** : 2.3 ± 1.2

Boersma L; Eur Heart J. 2016

Serious complications at D30

Serious adverse events	Device-/procedure-related SAEs ($N = 34$)	Unrelated SAEs ($N = 50$)
Major bleeding requiring transfusion	8	11
Other bleeding complications (haematoma, haemoptysis, haematuria, and anaemia requiring transfusion)	2	4
Pericardial effusion	3	2
Cardiac tamponade	2	0
Strokes	1	2
Suspected TIA	0	2
Pulmonary embolism	0	1
Air embolism	3	0
Device embolization	2	0
Adverse reaction to anaesthesia	2	0
Reintervention due to incomplete seal	2	0
Vascular damage at puncture site	5	0
Hypotension	1	0

Boersma L; Eur Heart J. 2016

Mortality rate at D 30 in EWOLUTION registry

- **Mortality rate at D 30** : 0,7%
  - **1 death due to** gaz embolism
  - **3 death due to heart or respiratory failure non related to the procedure** (occuring from D0 to D6)
  - 3 death from other causes (2 hémorragae)

➡ Limited complication rate

Boersma L; Eur Heart J. 2016

French Registry for Left Atrial Appendage Closure (FLAAC)

Registry
From September 2013- End 2015

Rang	Hôpital	Nombre inclus centre
1	CHU BORDEAUX	82
2	CHU GRENOBLE	61
3	Henri Mondor	51
4	CHU Sud AMIENS	50
5	Nouvelles Cliniques NANTaisES	44
6	CHRU LILLE	42
7	Bichat	41
8	CHU MONTPELLIER	36
9	CHU Louis Pradel LYON	36
10	Centre Cardiologique du Nord	32
11	CHU TOULOUSE Rangueil	31
12	Institut Hosp Jacques Cartier MASSY	31
13	Marie Lannelongue	29
14	CHU TOURS	26
15	HEGP	22
16	Hôpital Européen de MARSEILLE	20
17	Cl. du Tonkin (LYON)	19
18	CHU ROUEN	18
19	IMM	17
20	Hôpital de la Timone de MARSEILLE	16
21	CHU NIMES	15
22	Cl. Du Millénaire MONTPELLIER	14
23	Polyclinique Les Fleurs	12
24	Hôpital Saint Joseph MARSEILLE	11
25	Cl. Pasteur -TOULOUSE	9
26	CHU NANTES Hopital Laennec	9
27	Centre Hospitalier d'ANNECY	9
28	Cl. Ambroise Paré NEUILLY	9
29	hôpital privé Beauregard MARSEILLE	9
30	CHU BESANCON	8
31	CHU de NANCY	7
32	CHPG MONACO	6
33	Polyclinique du bois LIILLE	6
34	CHU STRASBOURG	5
35	CHU CLERMONT FERRAND	4
36	Pôle Santé Oréliance (SARAN)	2

- **41 French centers, 36 including patients**
- **Indépendant of the implanted prosthesis**

Inclusion Criteria:

- Patients with any **prosthesis implanted** according national ou international

839 patients included during september 2013 and september 2015

First analysis with 436 patients and 1 year follow-up
Mean Follow-up : 12.7 months
Exhaustivity of the follow-up at one year: 99.8%

Patient Characteristics

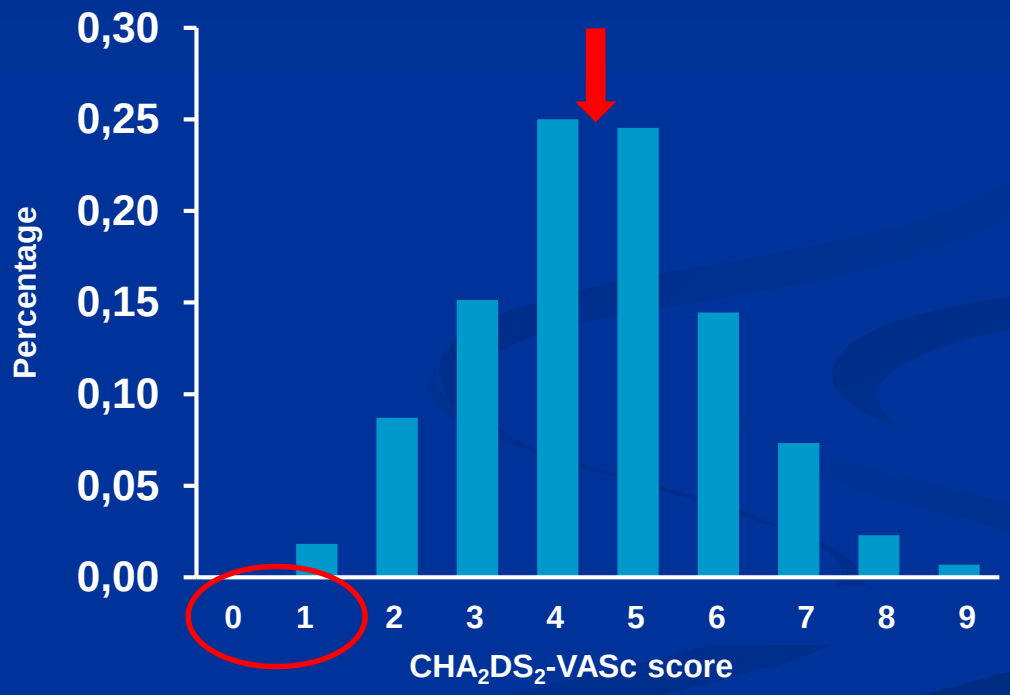
Patients characteristics	n (%)
Age	75,5±0,4
Age > 75 years	58,3%
Male	62,2%
Comorbidities	
Heart failure	26%
Previous ischemic stroke	41%
Tumoral disease	8,9%
Coronary artery disease	29%
Device (ACP/watchman)	58%/42%

- Old population with numerous comorbidities

Stroke risk factors

Mean CHA_2DS_2-VASc score

4.5 ± 0.1

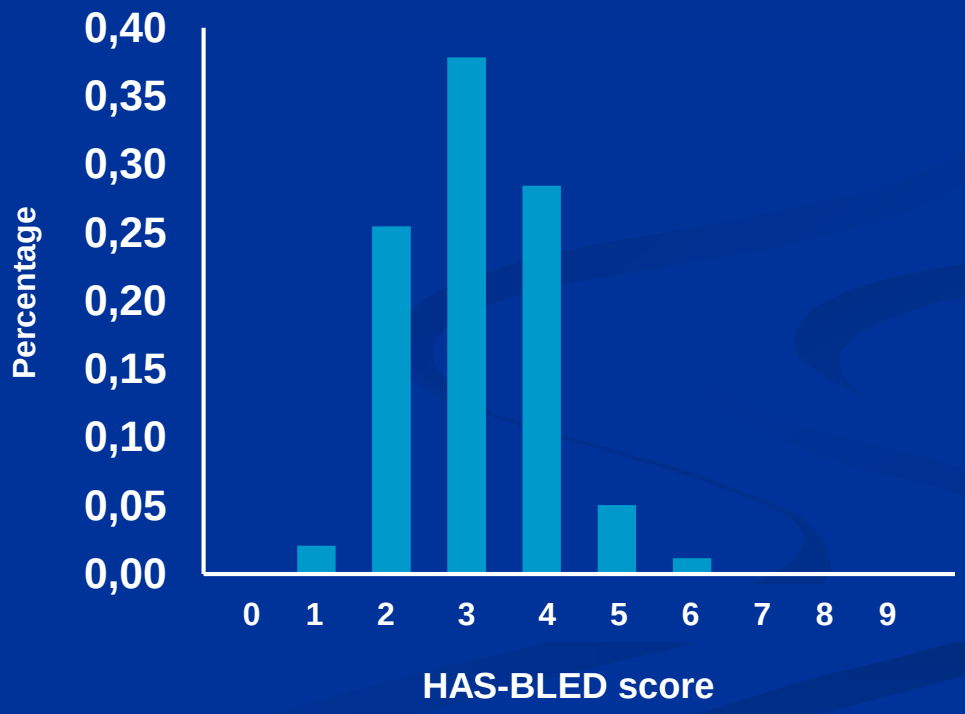


- **Patients with high stroke risk**
- **25% with CHA_2DS_2-VASc < 4**

Bleeding Risk

Mean HAS-BLED score

3.1 ± 0.1



- **93% of patients presented with history of hemorragae**

Results of the procedure

Procedure outcome	n (%)
Successful implantation	420 (96.3)
Successful implantation (requiring two different procedures or more)	9 (2.1)
Implantation failure	
Unsuitable anatomy	4 (0.9)
LAA thrombus	3 (0.6)

- Implant success rate : 98,4%
- Similar to previous publications

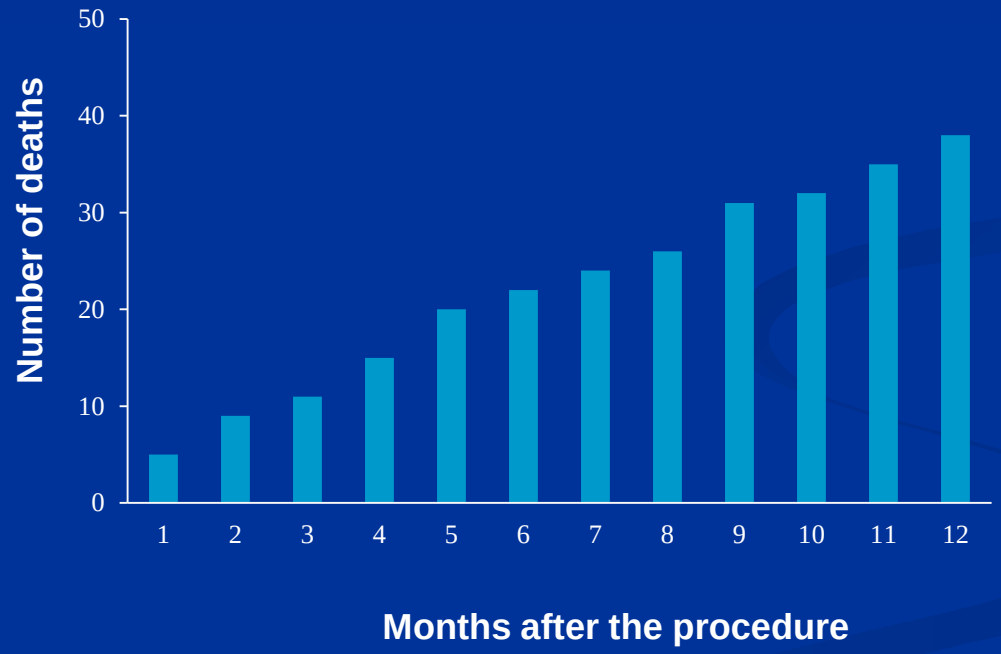
Complications related to the procedure

Procedure or device related complications	n (%)
Device embolization	5 (1.1)
Requiring surgery	3 (0.7)
Snared	2 (0.4)
Ischemic stroke	2 (0.4)
Serious pericardial effusion	8 (1,9)
Air embolism	0 (0)
Adverse reaction to anesthesia	0 (0)
Systemic embolism	0 (0)
Acute coronary syndrome	0 (0)
Other	1 (0.3)

Comparaison vs previous studies

	Protect -AF	Prevail	Tzikas	FLAAC
Embolization	0,6	0,7	0,7	1,1*
Stroke	1,1	0,7	0,8	0,4
Drainage	4,8	1,5	1,4	1,9*

Mortality rate during patient Follow-up



Follow-up 12,7 ± 0.2

Mortality rate : 8,9%

- **This rate is related to numerous associated comorbidity of the population**

Causes of Deaths

Deaths (all causes)	**38 (8.9)**
Death related or possibly related to the device or the procedure	**7 (1.6)**
Device embolization	2 (0.5)
Pericardial effusion	1 (0.2)
Device-related ischemic stroke	1 (0.2)
Procedure related major bleeding (femoral artery, procedure-related esophagus lesion)	2 (0.5)
Post-procedure respiratory insufficiency	1 (0.2)
Ischemic stroke	**1 (0.3)**
Hemorrhagic stroke	**3 (0.7)**
Cardiovascular/unexplained death	**10 (2.3)**
Other major bleeding	**3 (0.7)**
Non cardiovascular comorbidity	**14 (3.3)**

Décès pdt hospitalisation : 0,7%

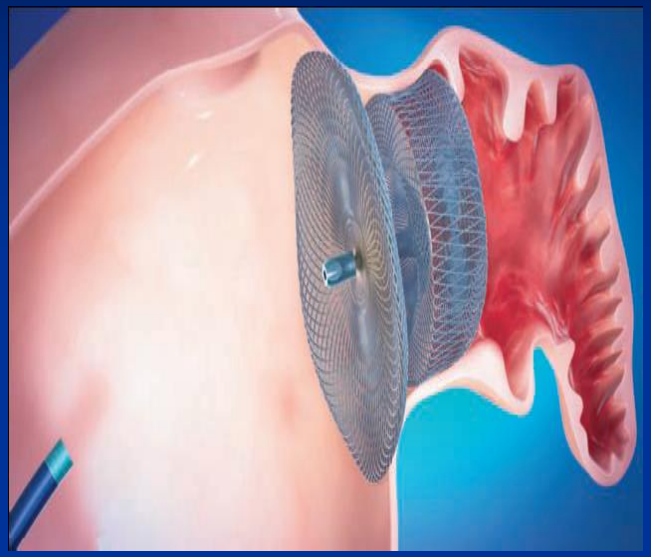
Décès à distance : 0,9%

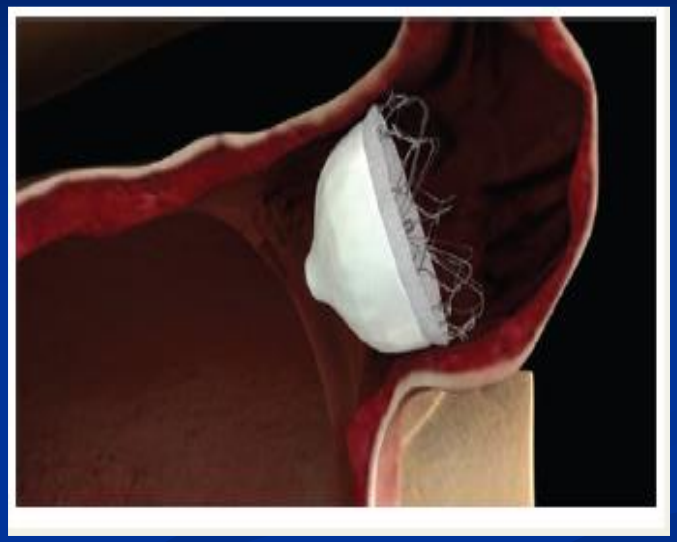
Infection : 8
I Renale : 2

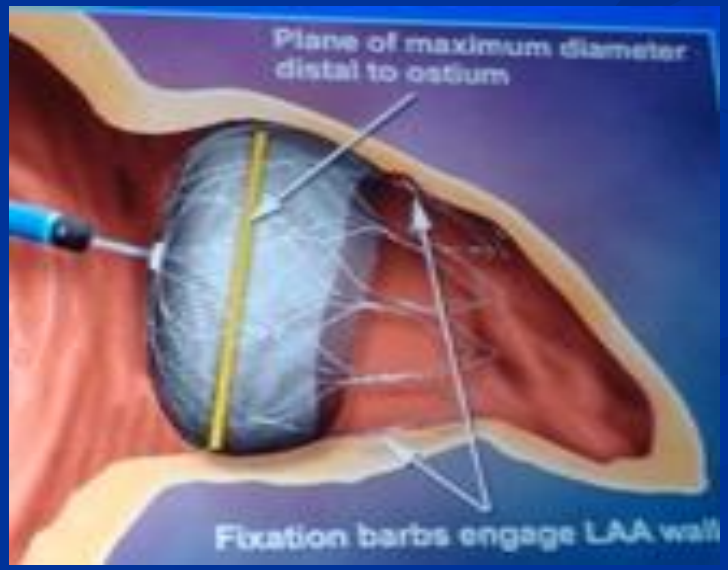
Efficacy
Flaac vs other registries

	PROTECT-AF	ASAP	KEFER	TZIKAS	FLAAC
effectif	463	150	90	1045	436
Type of prosthesis	Watchman	Watchman	ACP	ACP	Watchman ou ACP
Efficacy criteria					
Ischemic Stroke	2,2	1,7	2,1	2,3	2.7
Cardiovascular death	0,7	1,66	3,6	1,2	2.3
Systemic Embolism	0,3	0	0	-	-
Death rate	3	5	6	4,3	8.9

Principle of transcatheter approach







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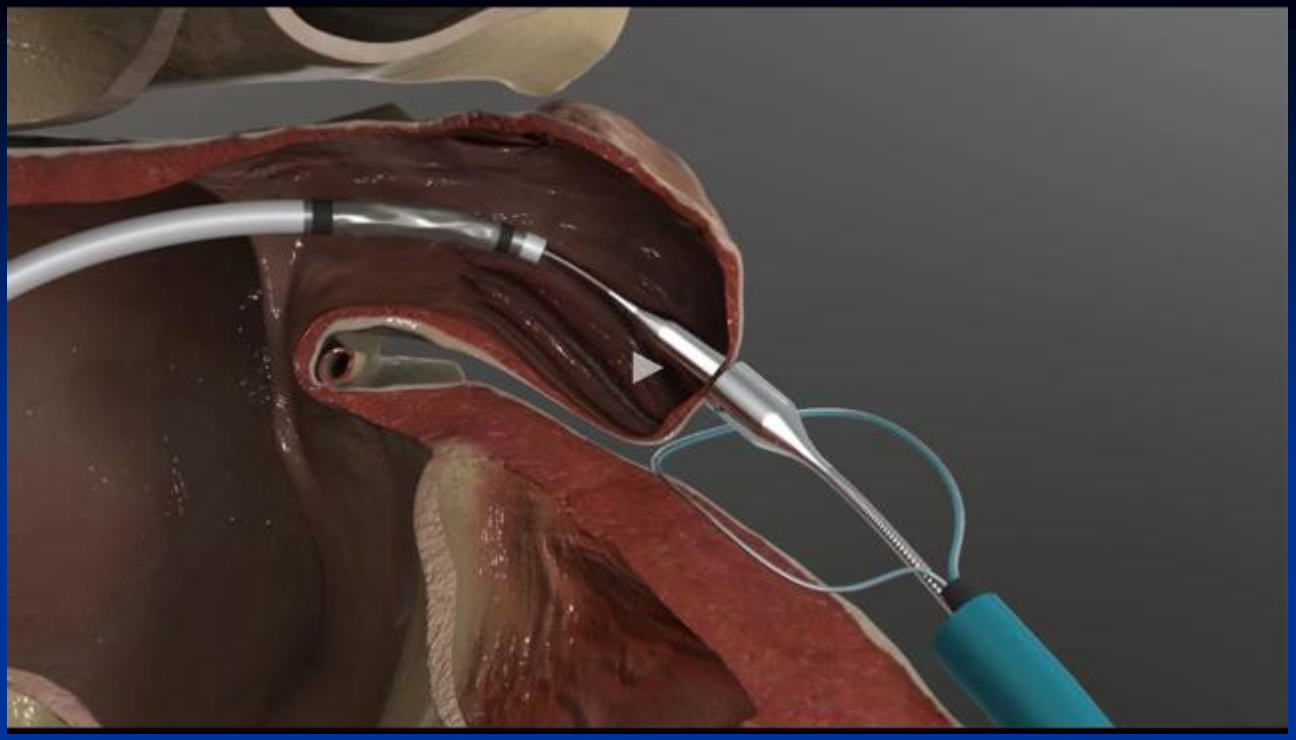

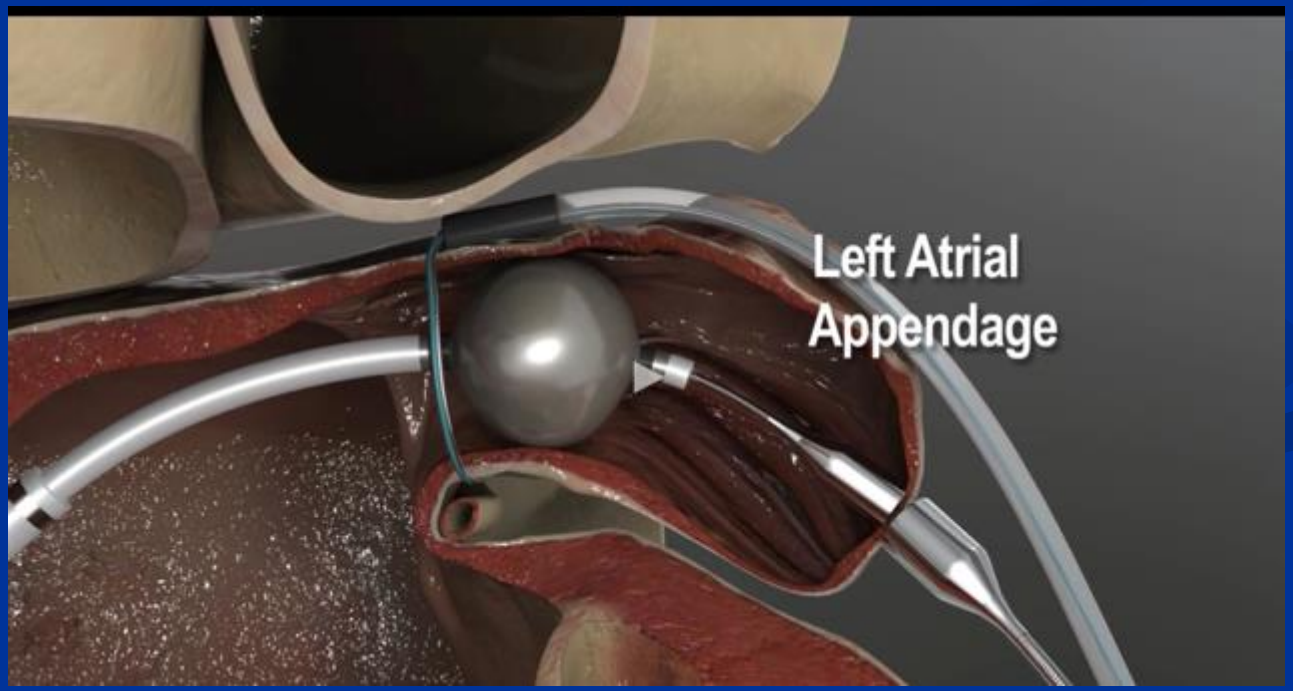

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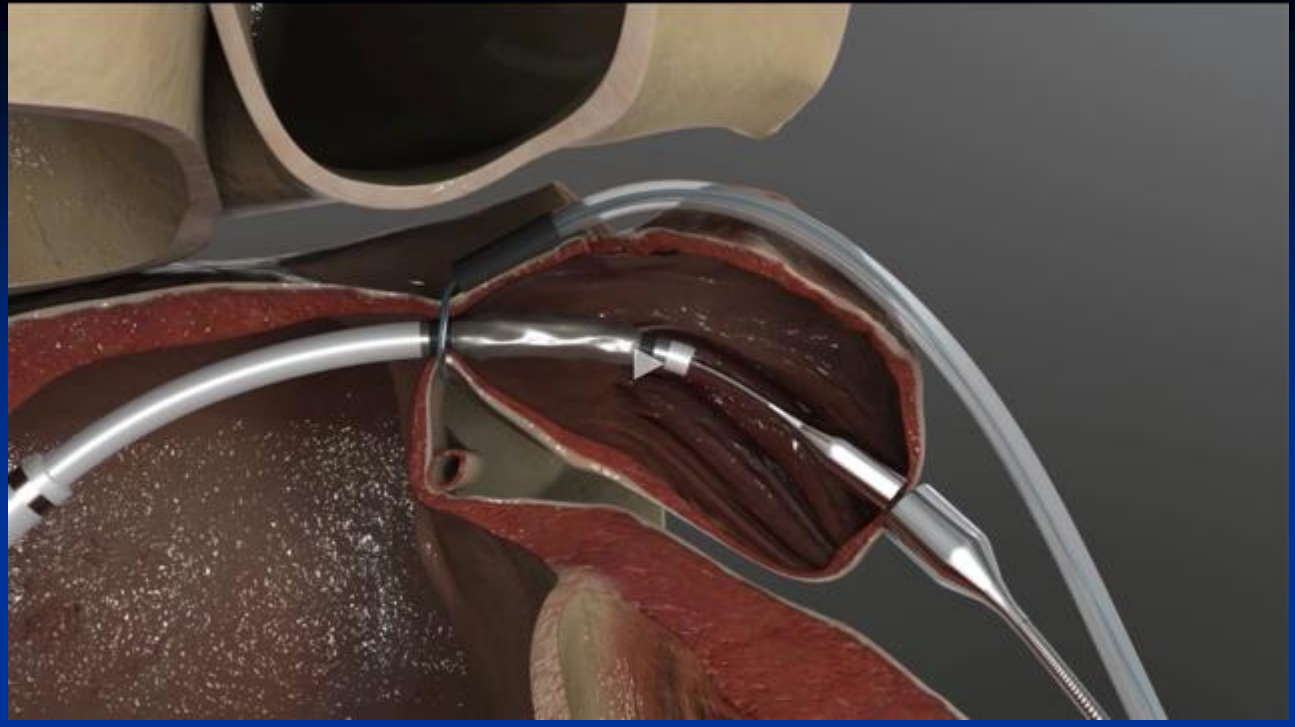
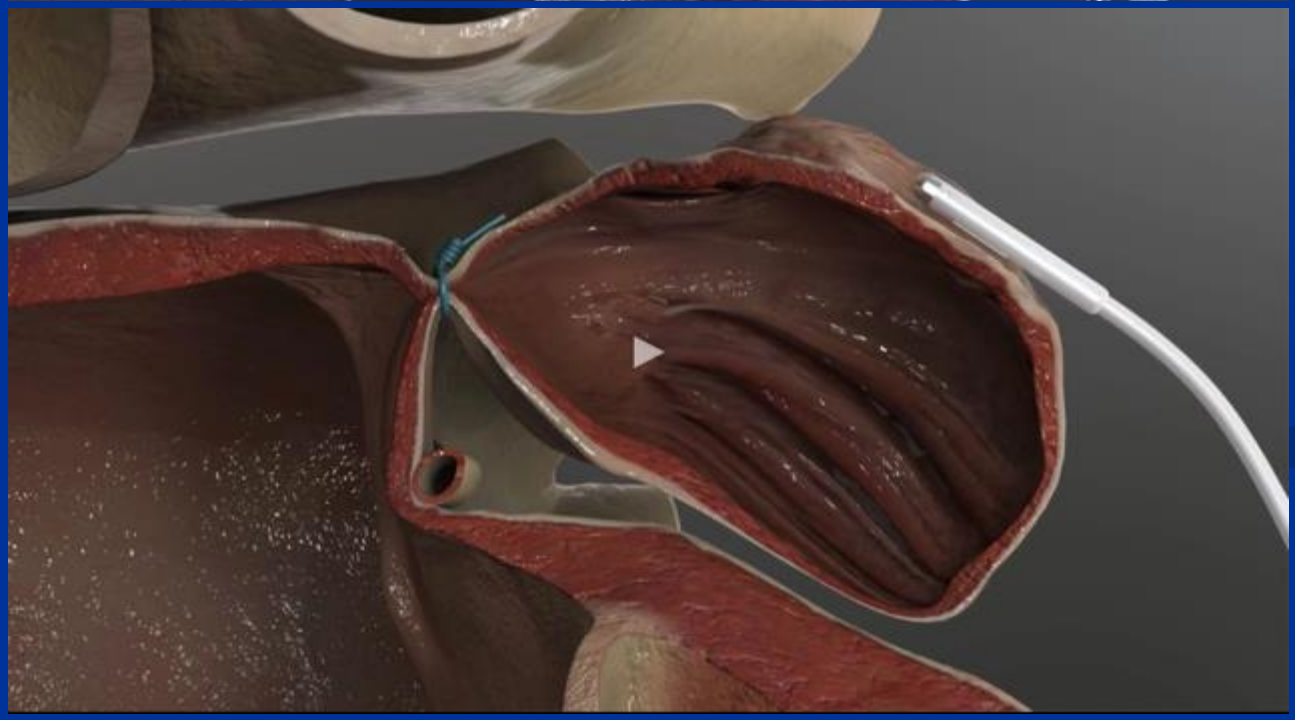


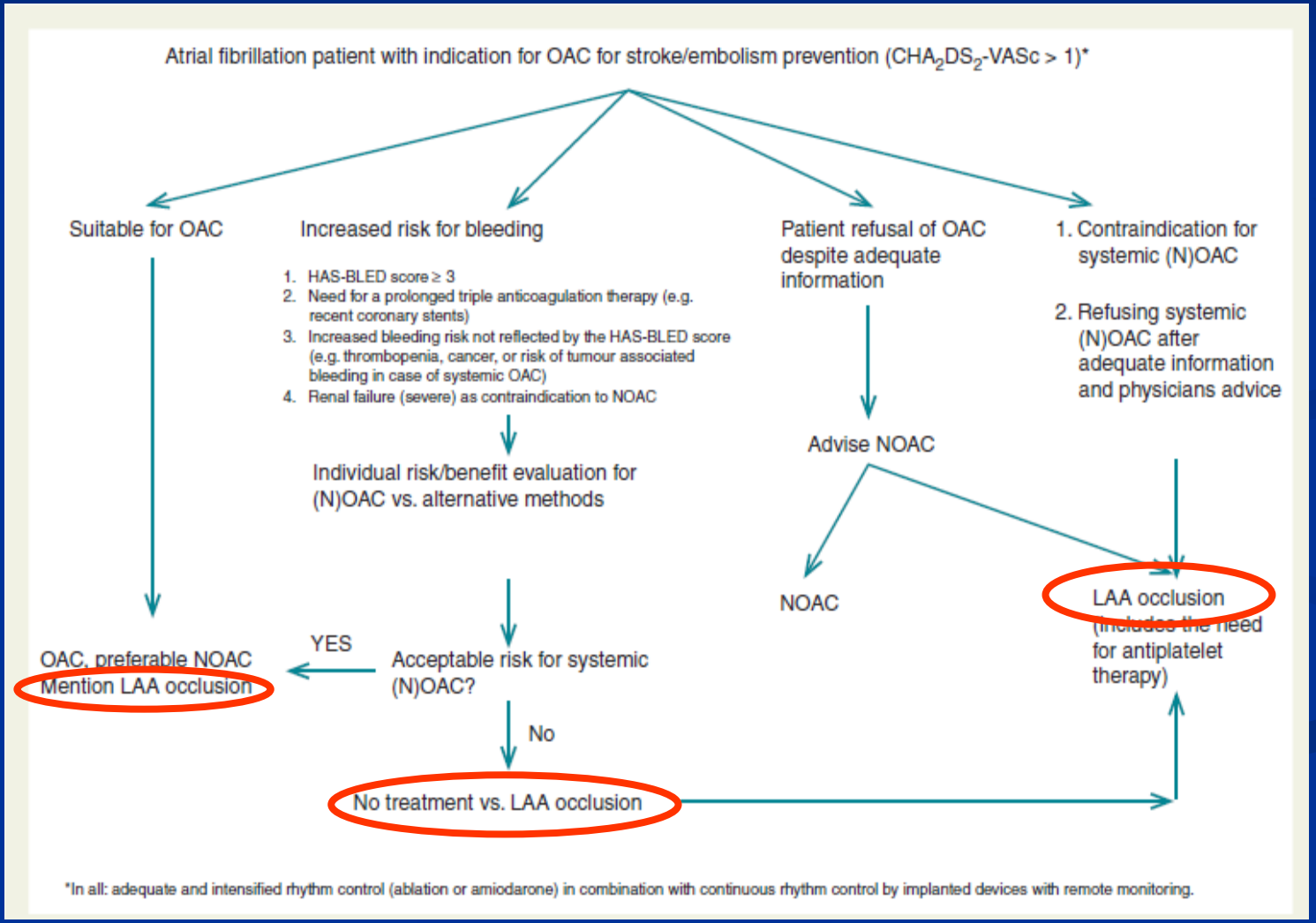


EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion

Bernhard Meier (EAPCI Chairperson) (Switzerland)[1], Yuri Blaauw (The Netherlands)[2], Ahmed A. Khattab (Switzerland)[1], Torsten Lewalter (Germany)[3], Horst Sievert (Germany)[4], Claudio Tondo (Italy)[5], Michael Glikson (EHRA Chairperson) (Israel)[6*]

Document Reviewers: Gregory Y. H. Lip (UK), Jose Lopez-Minguez (Spain), Marco Roffi (Switzerland), Carsten Israel (Germany), Dariusz Dudek (Poland), Irene Savelieva (on behalf of EP-Europace, UK)

Indication de l'implantation



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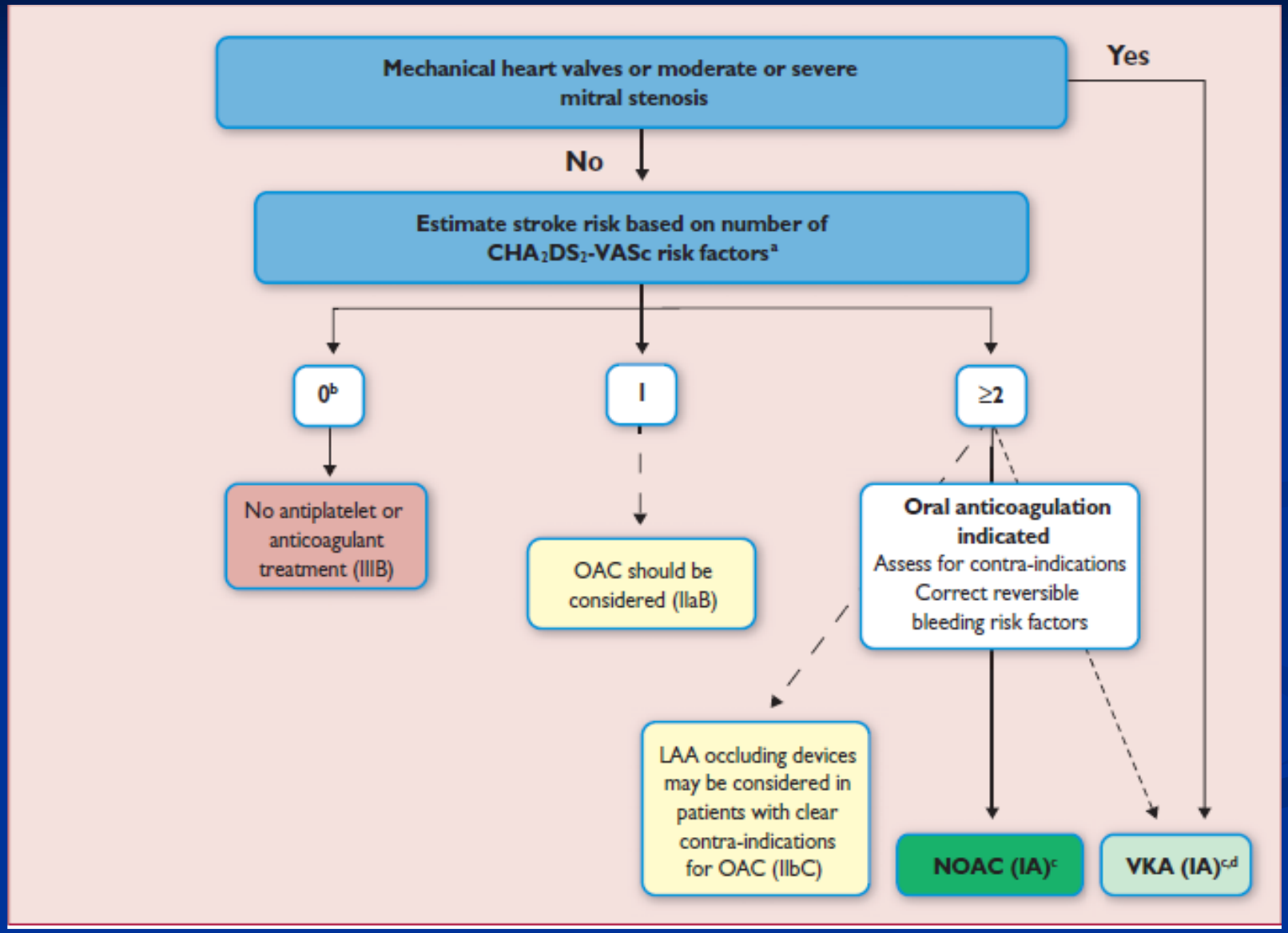
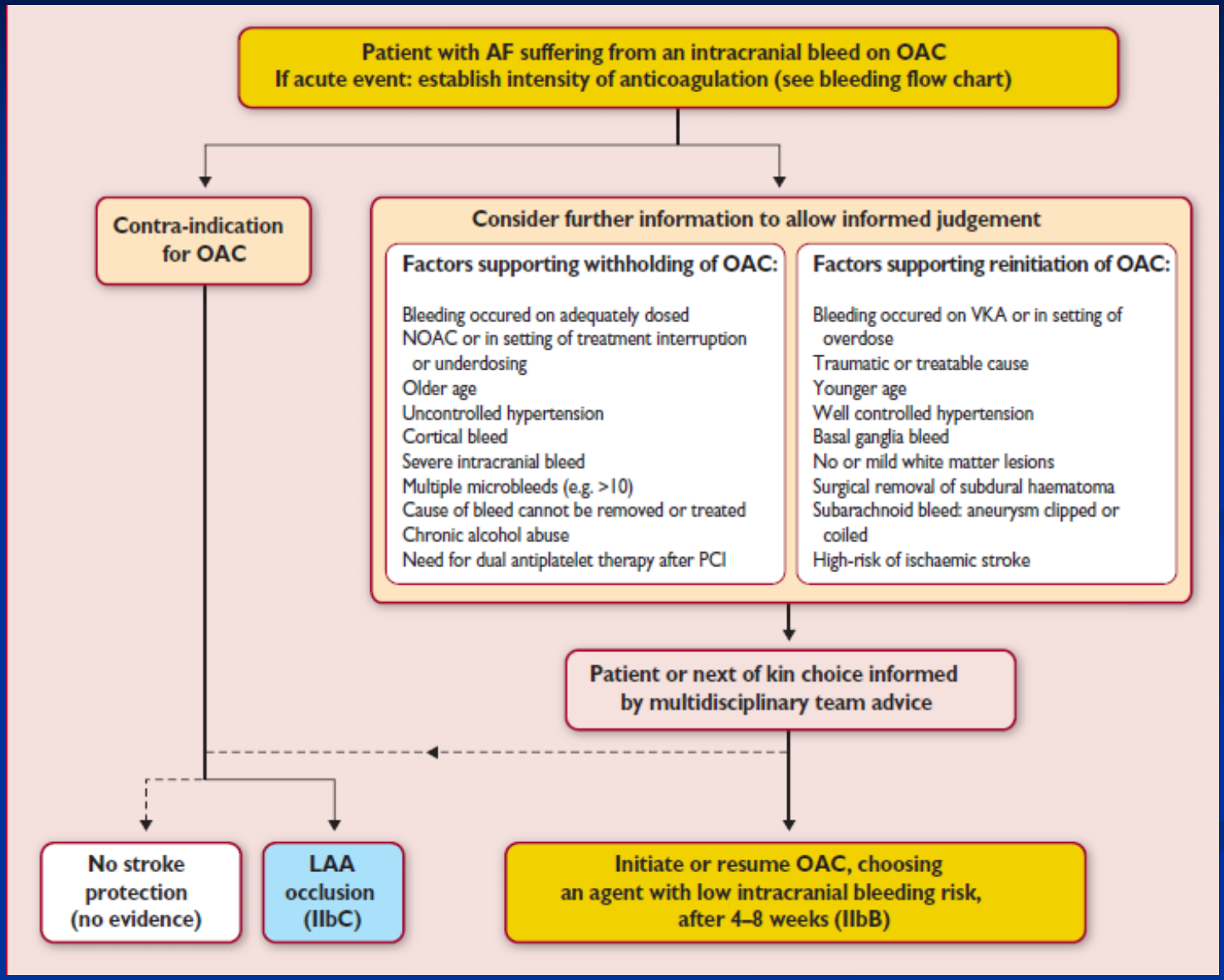

Mechanical heart valves or moderate or severe mitral stenosis
Yes
No
Estimate stroke risk based on number of CHA2DS2-VASc risk factors[a]
0[b]
1
≥2
No antiplatelet or anticoagulant treatment (IIIB)
OAC should be considered (IIaB)
Oral anticoagulation indicated
Assess for contra-indications
Correct reversible bleeding risk factors
LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)
NOAC (IA)[c]
VKA (IA)[c,d]

ESC 2016


Patient with AF suffering from an intracranial bleed on OAC
If acute event: establish intensity of anticoagulation (see bleeding flow chart)
Contra-indication for OAC
Consider further information to allow informed judgement
Factors supporting withholding of OAC:
Bleeding occured on adequately dosed NOAC or in setting of treatment interruption or underdosing
Older age
Uncontrolled hypertension
Cortical bleed
Severe intracranial bleed
Multiple microbleeds (e.g. >10)
Cause of bleed cannot be removed or treated
Chronic alcohol abuse
Need for dual antiplatelet therapy after PCI
Factors supporting reinitiation of OAC:
Bleeding occured on VKA or in setting of overdose
Traumatic or treatable cause
Younger age
Well controlled hypertension
Basal ganglia bleed
No or mild white matter lesions
Surgical removal of subdural haematoma
Subarachnoid bleed: aneurysm clipped or coiled
High-risk of ischaemic stroke
Patient or next of kin choice informed by multidisciplinary team advice
No stroke protection (no evidence)
LAA occlusion (IIbC)
Initiate or resume OAC, choosing an agent with low intracranial bleeding risk, after 4–8 weeks (IIbB)

In France

- Prostheis is reimbursed for patients with non valvular AF and high thromboembolism risk with score $CHA_2DS_2VASc \geq 4$
- And definitive CI for oral anticoagulation

- Stroke recurrence under correct anticoagulaiton is not considered as an indication for LAA occlusion

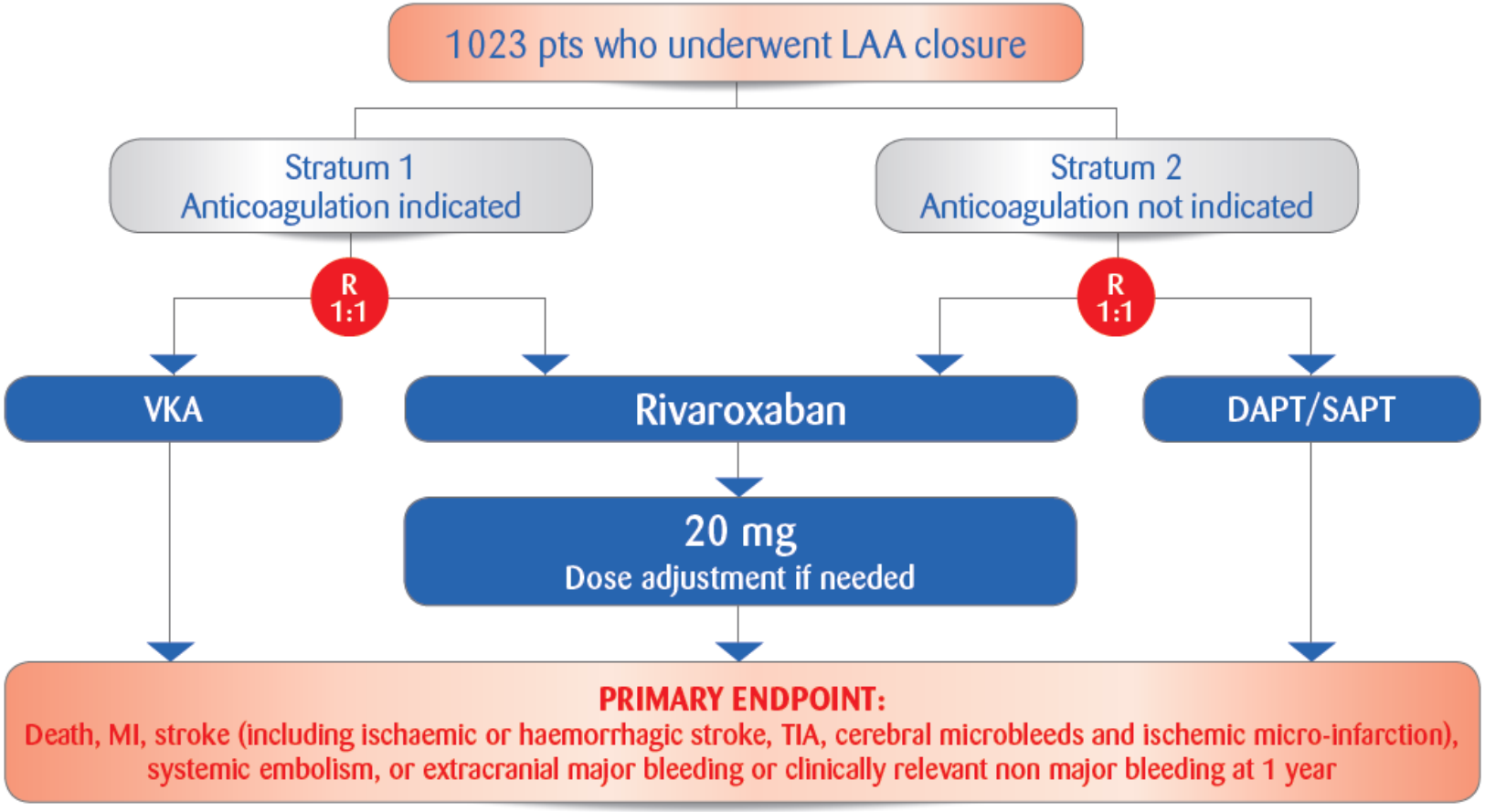
- Need for cardiac surgery in the center

POST INTERVENTION ANTITHROMBOTIC STRATEGY

- 6 weeks with oral anticoagulation if possible
- Otherwise Aspirine+Plavix for 1-6 mois
- Then Aspirine alone or nothing in certain cases
- Suivi avec TTE before dsicharge and CT scan at 3, 6, 12 months
- Place for NACO ?

Anticoagulation with Rivaroxaban versus **D**ual or single antiplatelet therapy to **R**educe **I**schemic and bleeding events in **A**trial fibrillation patients **T**reated with **I**nvasive **C**losure of the left atrial appendage:

The randomized ADRIATIC Study



Design :

- PROBE study design (Prospective Randomised Open, Blinded End-point).
- 80 high volume centers, International

Ongoing Clinical trial

Trial	Expected no. of patients	Intervention	Condition	Study design	Primary end-point
LAAOSIII	4700	LAA occlusion (suture and/or surgical stapler)	AF and cardiac surgery with cardiopulmonary bypass	Randomized	Stroke or systemic arterial embolism
Safety and Efficacy of Left Atrial Appendage Occlusion Devices	150	Device: LARIAT	AF	Observational model: Case control	Effect of LAA occlusion by LARIAT device

Thank you very much for your attention!!!!