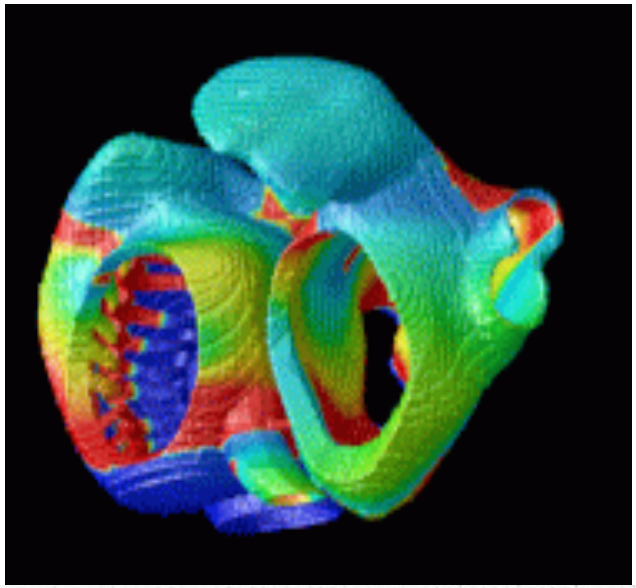
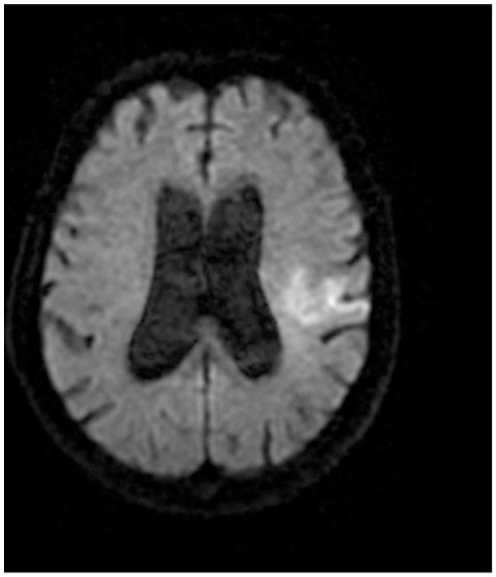
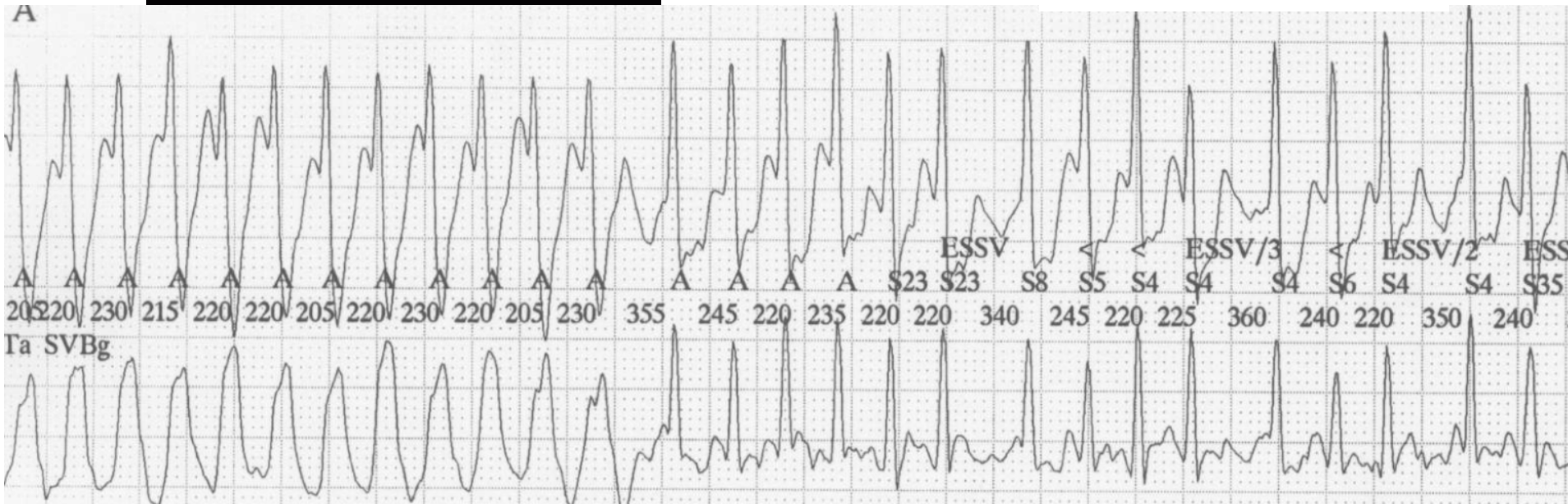
Fibrillation atriale
Une maladie musculaire?







- Man, 75 year old, hypertension (3 anti-hypertension drugs)

- Permanent atrial fibrillation. Pace maker for atrio-ventricular block. Moderate left ventricular dysfonction (LVEF 45%).

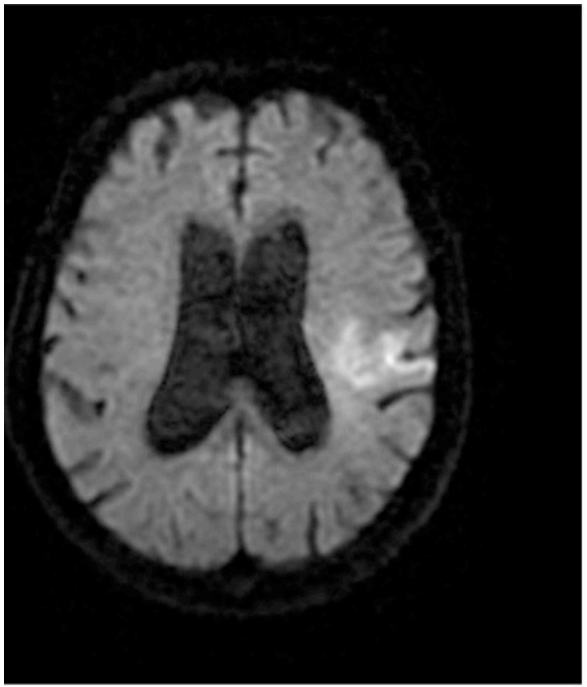
- Anticoagulants? ChadsVasc-2 score : 3
  - Oui ?
  - Non?

- Man, 75 year old, hypertension (3 anti-hypertension drugs)
- Permanent atrial fibrillation. Pace maker for atrio-ventricular block. Moderate left ventricular dysfonction (LVEF 45%).
- Anticoagulants? Chads 2 score : 3
- No stroke after 15 years of follow-up

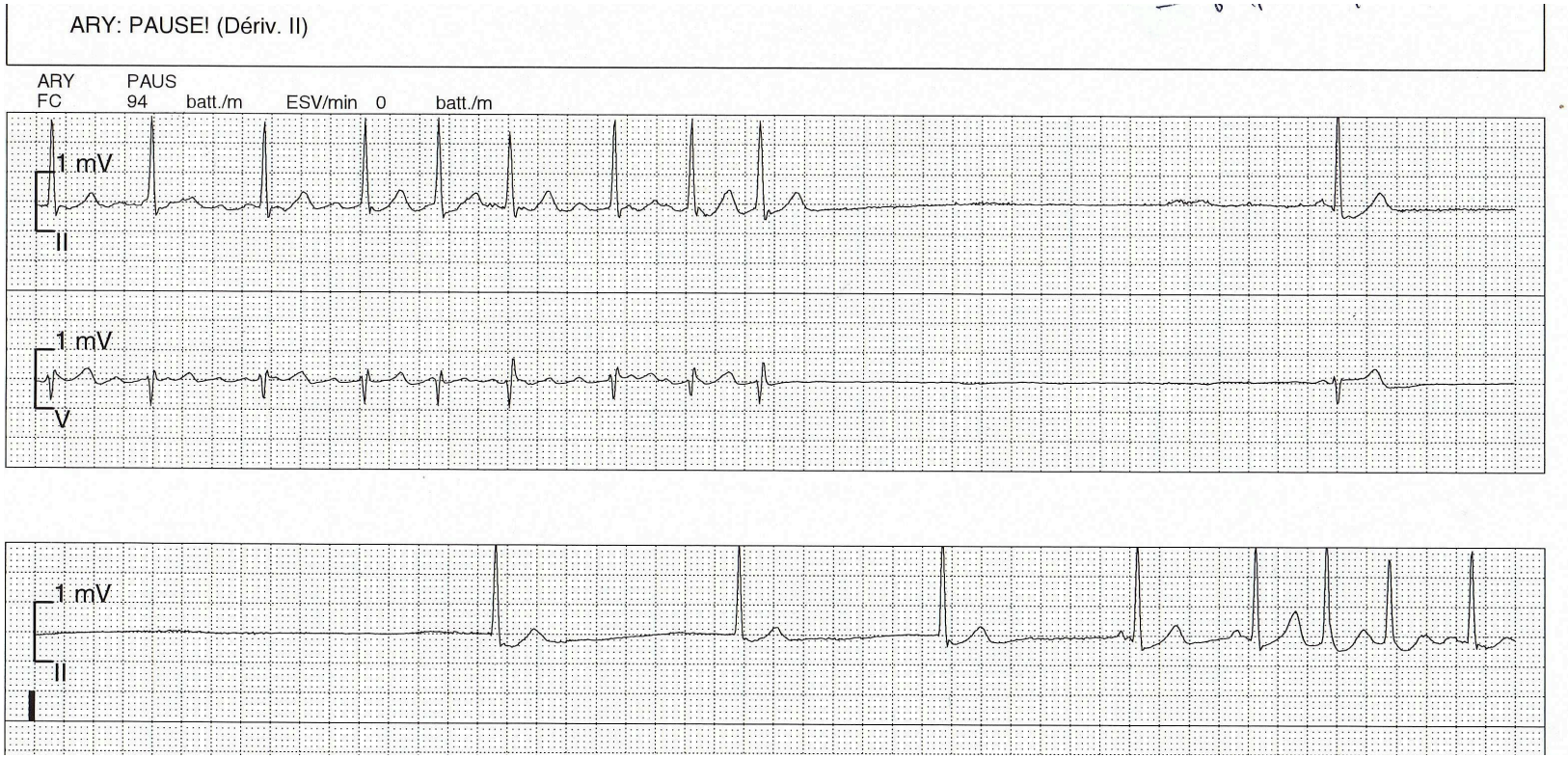
- Boy, 10 years old. Atrial flutter, sinus dysfonction
- SCN5a variant
  - Anticoagulants?
  - Yes?
  - No?

- Boy, 10 years old. Atrial flutter, sinus dysfonction
- SCN5a variant
  - Anticoagulants

Chads Vasc 2 score : 0

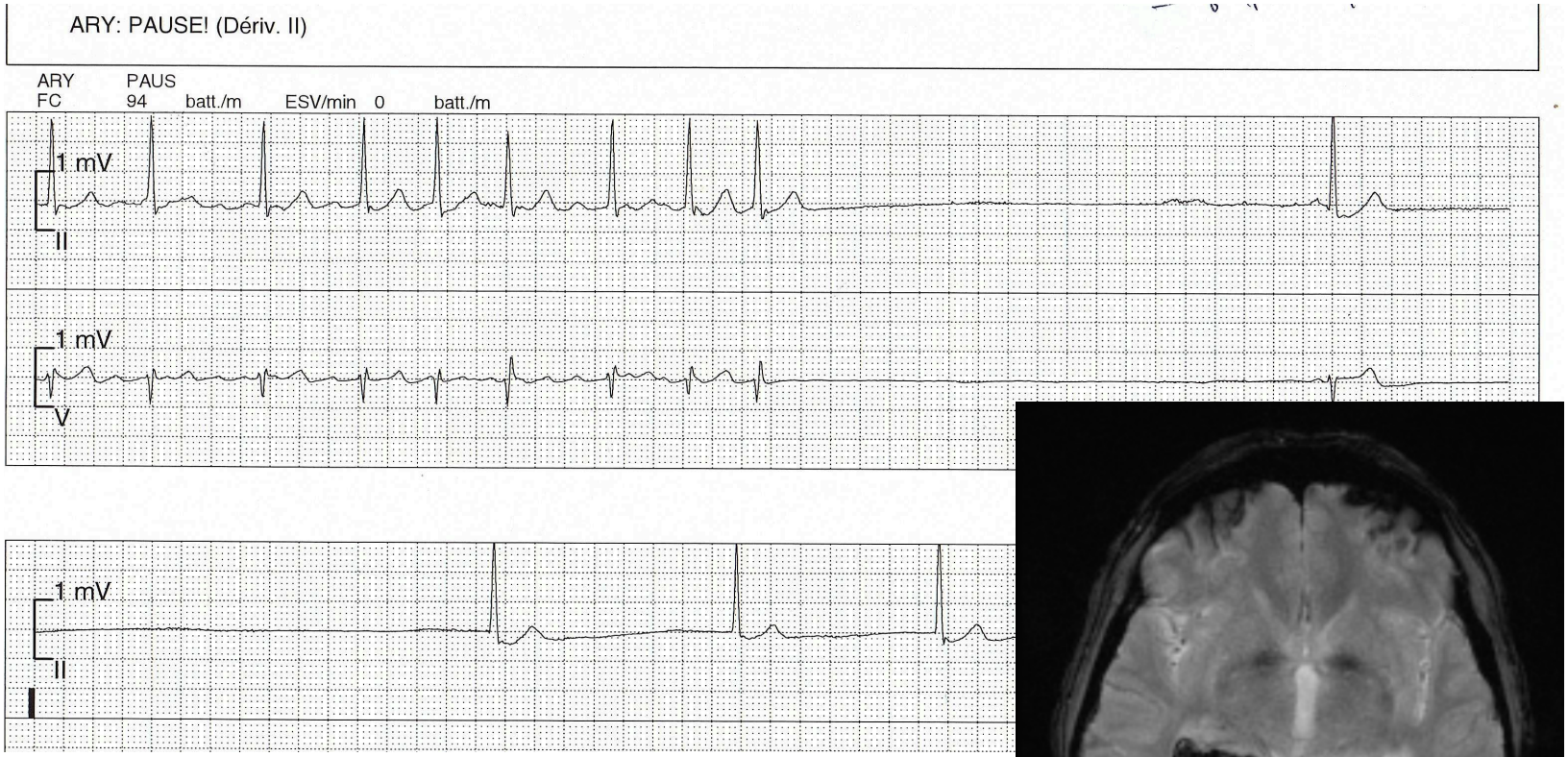


Woman, 60 years old, sinus node dysfunction and atrial fibrillation. Anticoagulants?



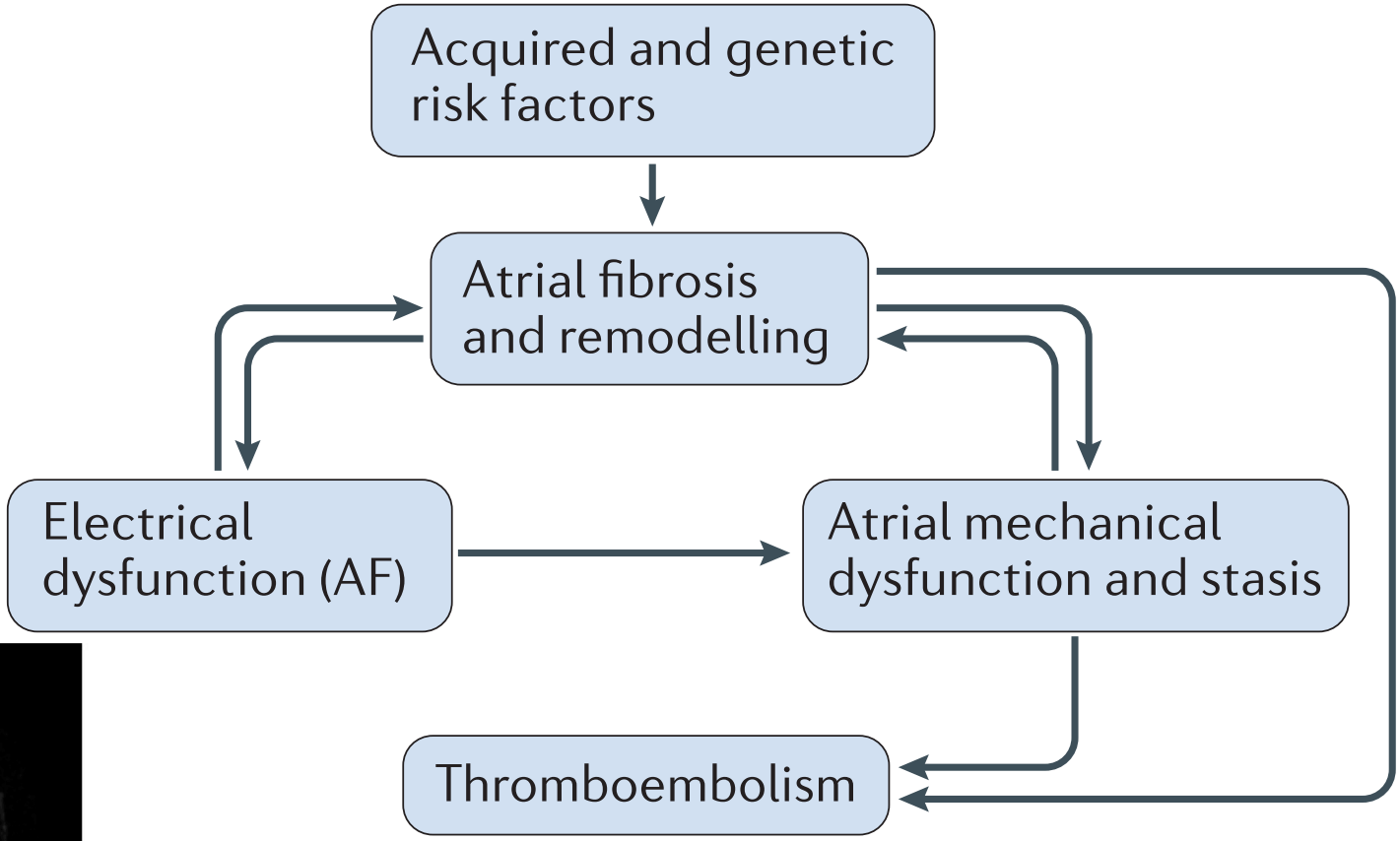
- Anticoagulation Yes?
- No?

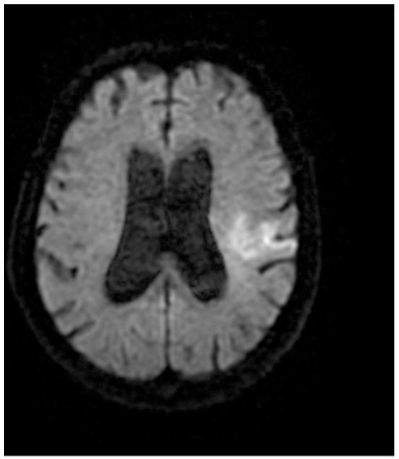
Woman, 60 years old, sinus node dysfunction and atrial fibrillation. Anticoagulants?



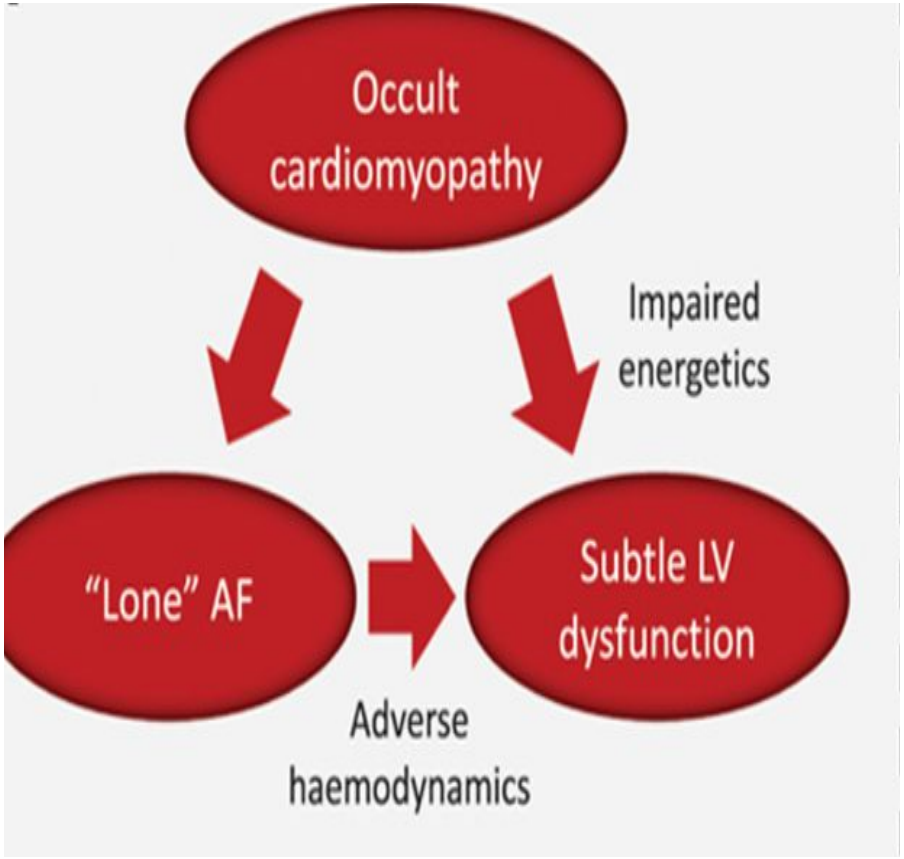
Chads2 score : 0

Myopathie atriale

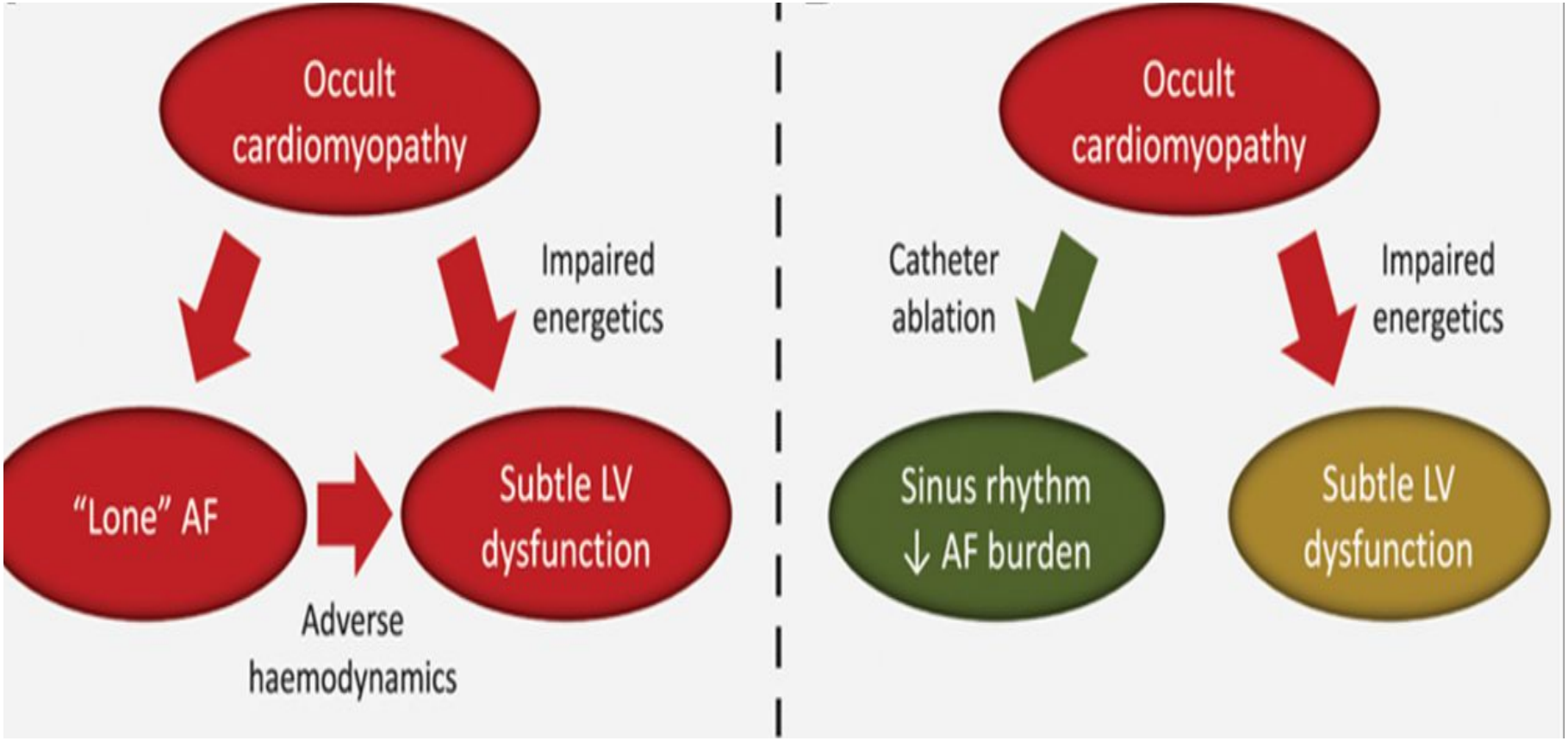




Dysfonction ventriculaire gauche occulte



Dysfonction ventriculaire gauche occulte

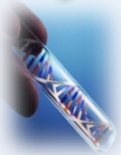


Substrat génétique

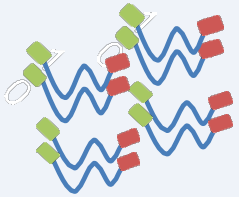
94 PATIENTS

Prélèvement sanguin

PANEL FA 55 GENES

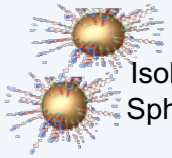


Extraction ADN



1 Création de la banque
Ampliseq™ Library

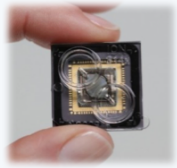
2 Amplification clonale de la banque



Isolate Positive Ion Sphere™ Particles

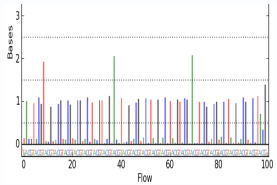
3 Séquençage sur puce

Ion PGM™ Sequencer



Puce de séquençage

4 Analyse données informatiques



Filtres effectués
-**n**= 1
-**Coverture** > 30
-**Pas rs** (reference SNP)/ **rs** / **Frame shift**
-**Faux-sens**
-**PolyPhen-2** (probably damaging, possibly damaging, benign)
-**SIFT** (deleterious, tolerated…)
-**Mutation Taster** (disease causing, polymorphism…)
-**ESP**
-**MAF** < 1%

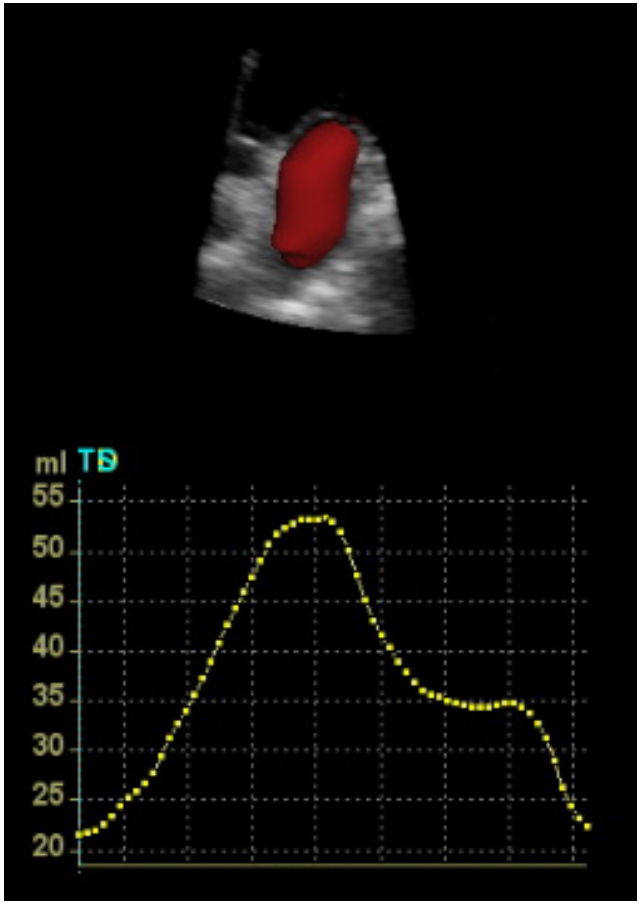
Résultats : 64447 variations (17 variants pathogènes)

Gene	Chr	Exon	Patient	Type FA	Coord. Cdna	Coord. Protéique		dbSNP	PolyPhen-2: score	PolyPhen-2: commentaire	Align GVGD	SIFT	Mutation Taster	1000 Genomes	Validé	ESP	MAF/MinorAllele Count
AKAP9	7	46	6211-1	perm	c.11229G>A	p.Met3743Ile	M3743I	rs143306820	0,998	PROBABLY DAMAGING	Class C0 (GV: 0.00 - GD: 10.12)	Deleterious (score: 0, median: 3.38)	disease causing (p-value: 1)	X	X		0.002/0
ABCC8	11	32	2115-1	parox	c.3941G>A	p.Arg1314His	R1314H	rs372153432	1,000	PROBABLY DAMAGING	Class C25 (GV: 0.00 - GD: 28.82)	Deleterious (score: 0, median: 3.38)	disease causing (p-value: 1)			Eur. Am.: T=0.00% - Afr. Am.: T=0.02%	N/A
DES	2	3	2510-1	persist puis parox	c.665G>A	p.Arg222His	R222H	rs367961979	0,970	PROBABLY DAMAGING	Class C25 (GV: 0.00 - GD: 28.82)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)			Eur. Am.: A=0.02% - Afr. Am.: A=0.00%	N/A
DSG2	18	6	6198-1	perm	c.566C>T	p.Pro189Leu	P189L		1,000	PROBABLY DAMAGING	Class C65 (GV: 0.00 - GD: 97.78)	Deleterious (score: 0, median: 3.57)	disease causing (p-value: 1)				
DSP	6	2	2126-1	parox	c.242G>A	p.Cys81Tyr	C81Y	rs140965835	0,995	PROBABLY DAMAGING	Class C0 (GV: 213.42 - GD: 82.85)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)		X	Eur. Am.: A=0.05% - Afr. Am.: A=0.00%	N/A
DSP	6	23	2235-1	parox	c.3550C>T	p.Arg1184Trp	R1184W		1,000	PROBABLY DAMAGING	Class C65 (GV: 0.00 - GD: 101.29)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)				
DSP	6	24	4464-1	perm	c.7981A>T	p.Ile2661Phe	I2661F		1,000	PROBABLY DAMAGING	Class C0 (GV: 234.72 - GD: 21.28)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)				
DSP	6	24	4464-1	perm	c.7997G>A	p.Gly2666Asp	G2666D		1,000	PROBABLY DAMAGING	Class C0 (GV: 206.04 - GD: 82.83)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)				
FHOD3	18	7	2095-1	parox	c.614T>C	p.Leu205Pro	L205P		1,000	PROBABLY DAMAGING	Class C0 (GV: 144.08 - GD: 0.00)	Deleterious (score: 0.04, median: 3.53)	disease causing (p-value: 1)				
FHOD3	18	8	1885-1	parox	c.776C>T	p.Thr259Met	T259M		1,000	PROBABLY DAMAGING	Class C0 (GV: 215.24 - GD: 59.13)	Deleterious (score: 0, median: 3.52)	disease causing (p-value: 1)				
GATA5	20	3	2300-1	parox	c.616G>A	p.Gly206Ser	G206S		1,000	PROBABLY DAMAGING	Class C55 (GV: 0.00 - GD: 55.27)	Deleterious (score: 0, median: 3.34)	disease causing (p-value: 1)				
JPH2-Int	20	2	4162-1	perm	c.764C>T	p.Ser255Leu	S255L		1,000	PROBABLY DAMAGING	Class C25 (GV: 57.75 - GD: 92.35)	Deleterious (score: 0.01, median: 3.63)					
LTBP2	14	33	2103-1	perm	c.4877C>T	p.Pro1626Leu	P1626L	rs141230498	1,000	PROBABLY DAMAGING	Class C65 (GV: 0.00 - GD: 97.78)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 0.979)		X	Eur. Am.: A=0.00% - Afr. Am.: A=0.05%	N/A
LTBP2	14	35	4641-2	persist	c.5224G>A	p.Gly1742Ser	G1742S		1,000	PROBABLY DAMAGING	Class C55 (GV: 0.00 - GD: 55.27)	Deleterious (score: 0, median: 4.32)	disease causing (p-value: 1)				
MMP9	20	3	2186-1	parox	c.427C>T	p.Arg143Cys	R143C		1,000	PROBABLY DAMAGING	Class C35 (GV: 56.64 - GD: 154.23)	Deleterious (score: 0, median: 2.90)	disease causing (p-value: 1)				
MYOZ1	10	3	1875-1	parox	c.167G>C	p.Gly56Ala	G56A	rs200945452	1,000	PROBABLY DAMAGING	Class C55 (GV: 0.00 - GD: 60.00)	Deleterious (score: 0, median: 3.58)	disease causing (p-value: 1)				N/A
TMEM43	3	5	2691-1	parox	c.424G>A	p.Glu142Lys	E142K	rs145619906	1,000	PROBABLY DAMAGING	Class C15 (GV: 44.60 - GD: 56.87)	Deleterious (score: 0.03, median: 3.37)	disease causing (p-value: 1)	X	X	Eur. Am.: A=0.15% - Afr. Am.: A=0.09%	0.001/0

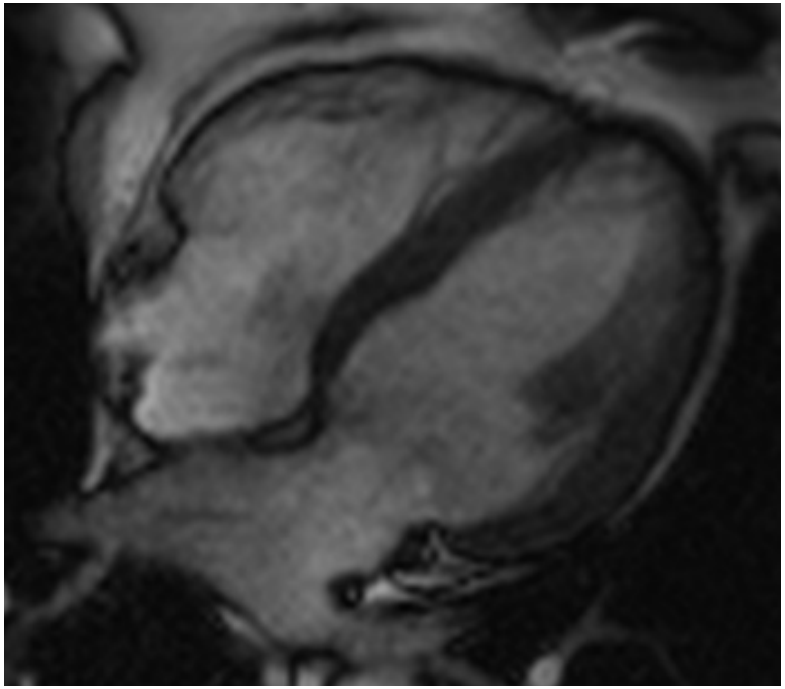
- Confirmation par SANGER et sous-clonage bactérienne
- Séquençage des gènes classiques

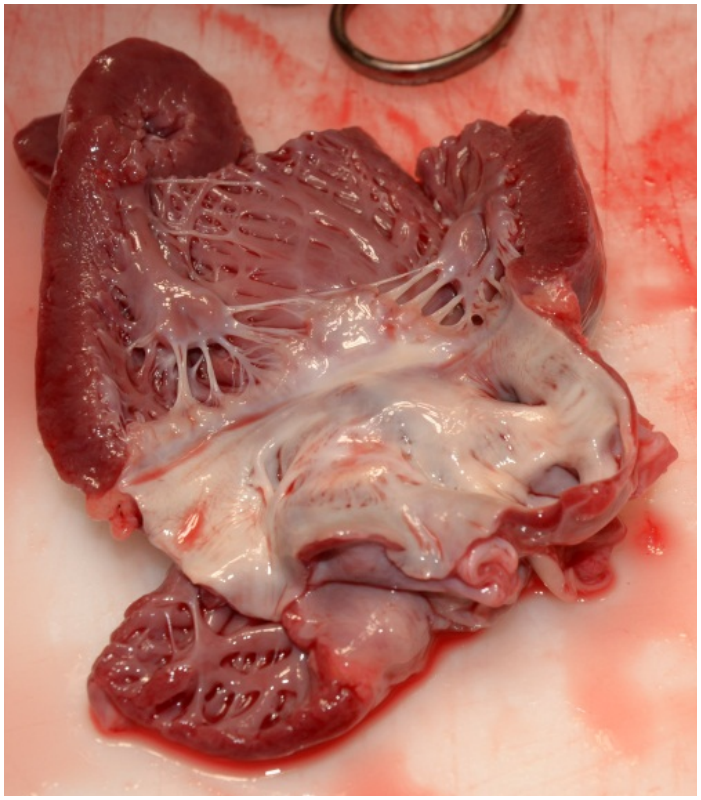
Oreillette gauche

Tableau 1	Paramètres volumiques de la fonction atriale (1)		
Fonction globale; réservoir	FEOG	[(LAmax-LAmin)/LAmax]	
Fonction réservoir	Index d'expansion	[(LAmax-LAmin)/LAmin]	230 ± 150 %
Conduit	Fraction d'éjection passive	[(LAmax-LApre-A)/LAmax]	44 ± 15%
Fonction pompe	Fraction d'éjection active	[(LApre-A-LAmin)/LApre-A]	40 ± 12%



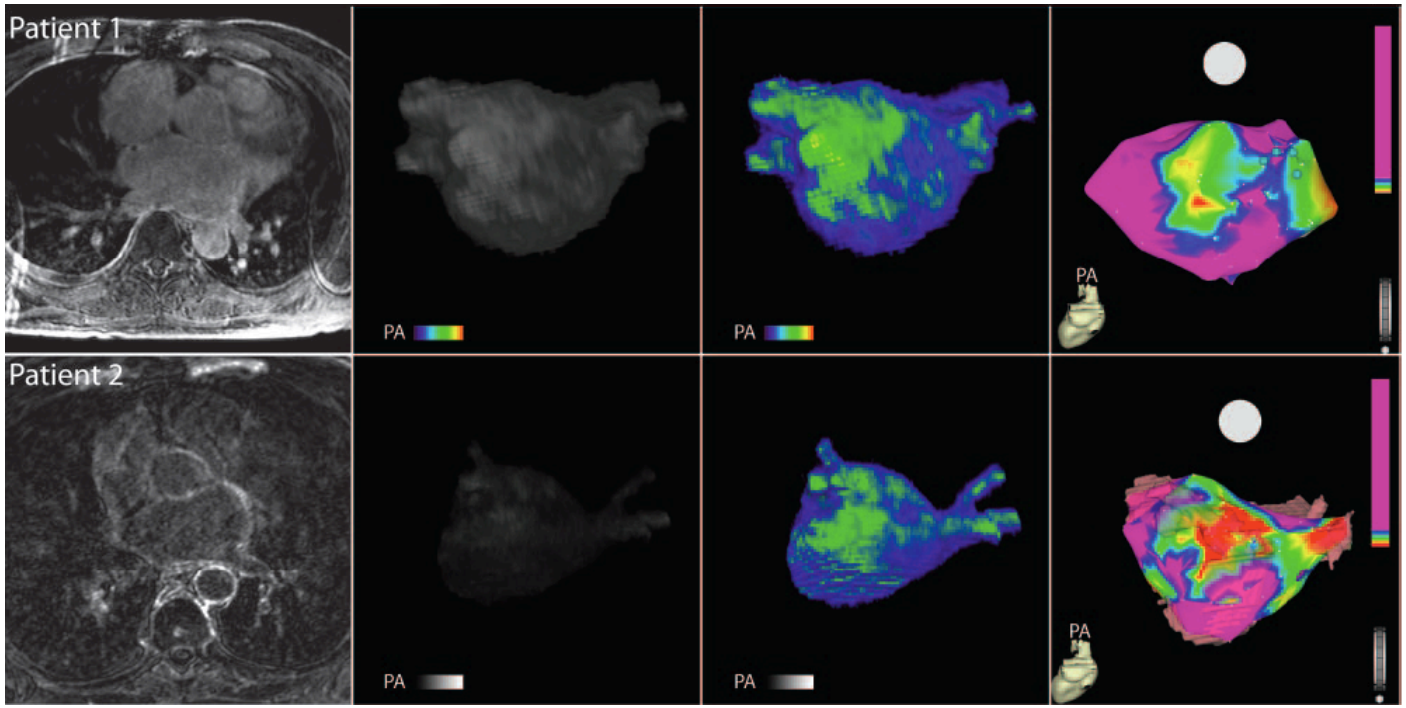
Oreillette gauche





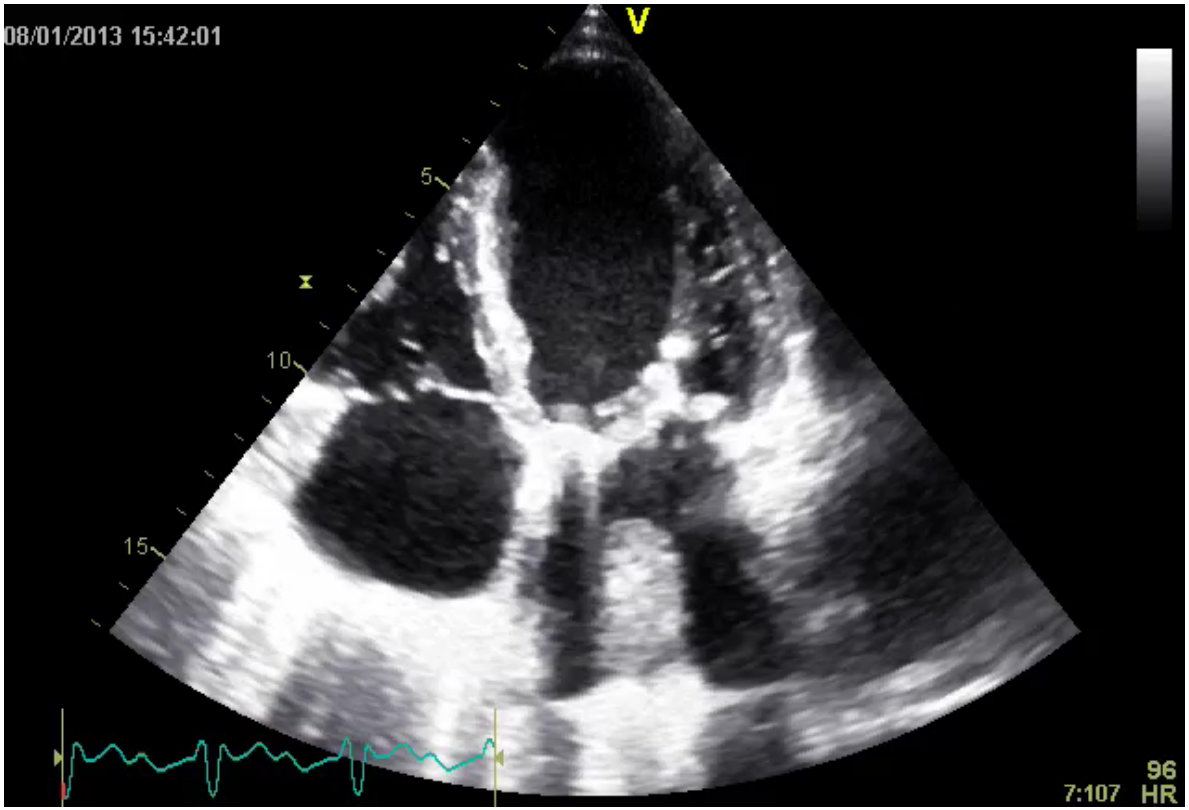
Oreillette gauche

- Le remodelage atrial: La fibrose



1. Oakes, R.S., et al., *Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation.* Circulation, 2009.

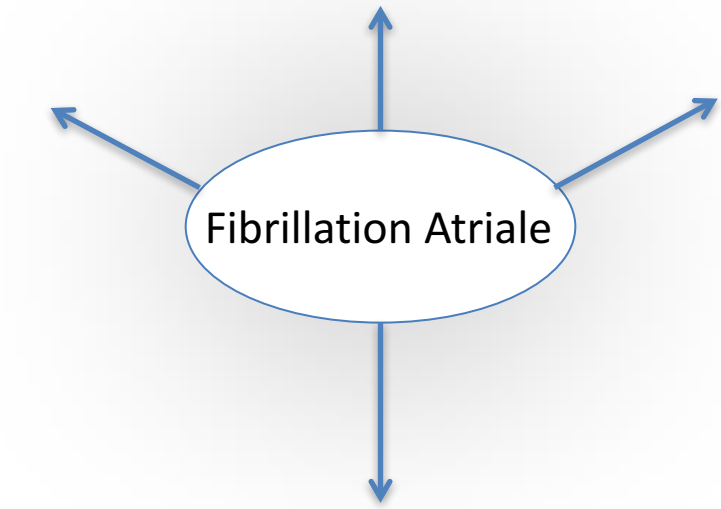
Thrombus intra-atrial



Risque embolique et Fibrillation atriale?

Différents Types
d'AVC ischémiques

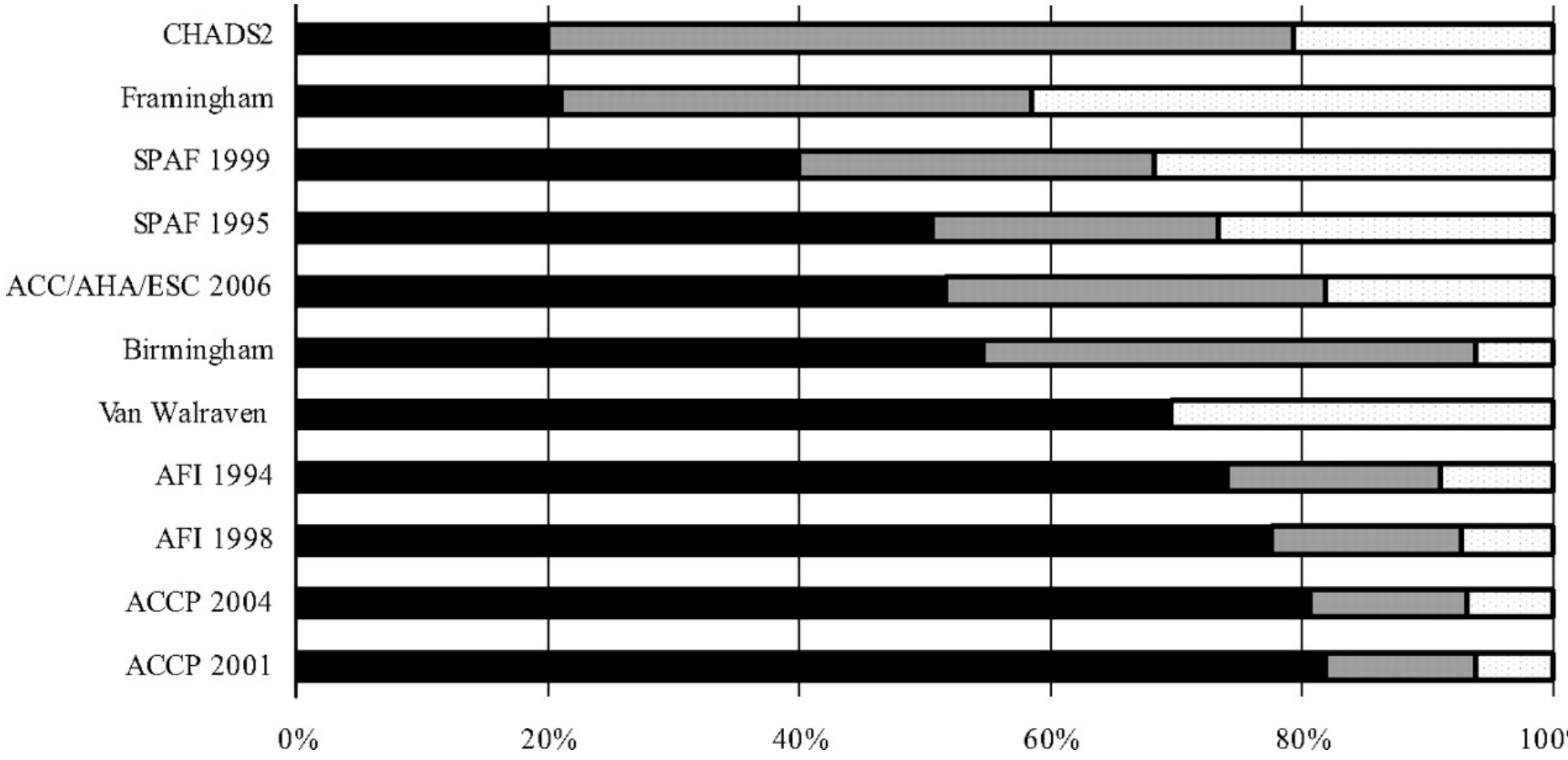
Différents types
électro-cliniques



Différents scores de risque

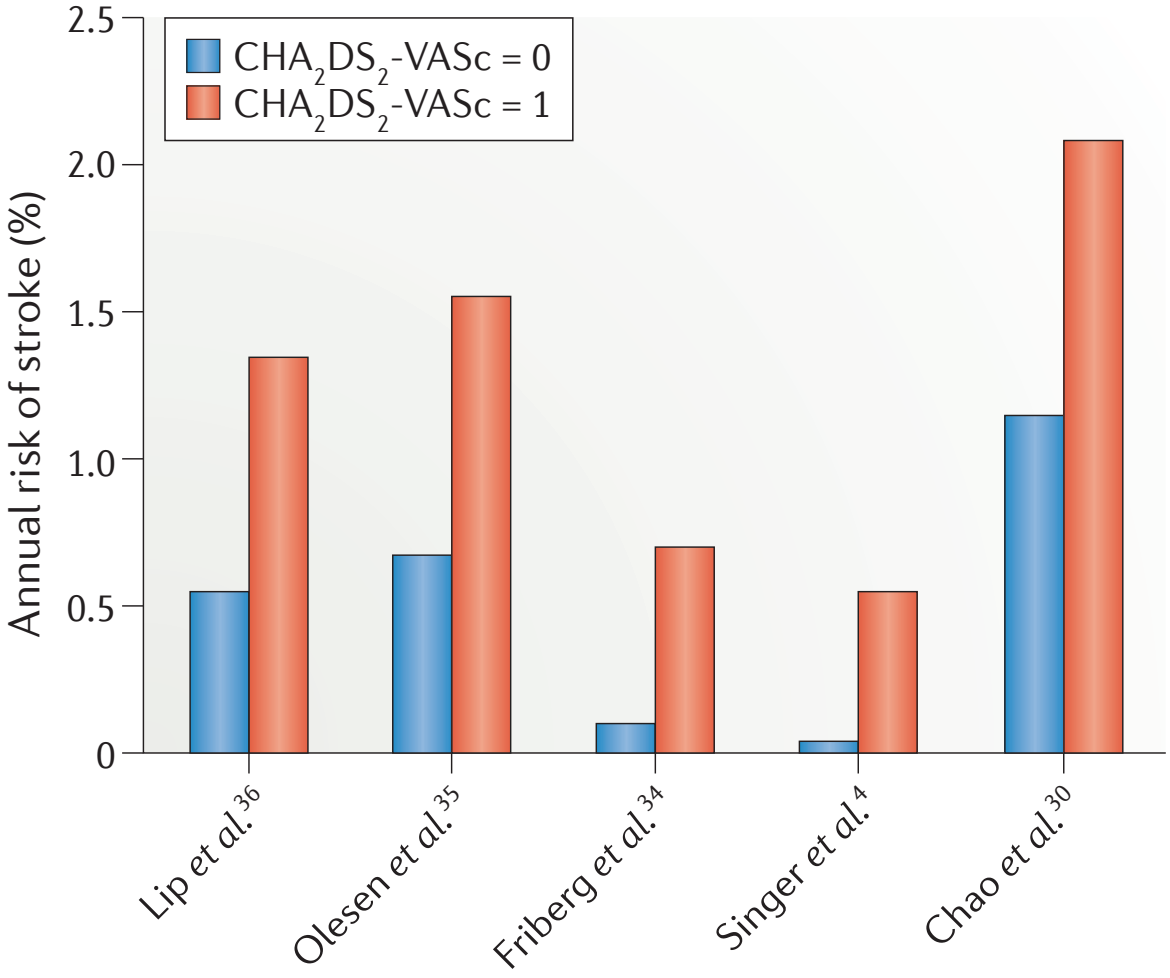
Un même traitement?

Absence de schéma optimal de stratification du risque

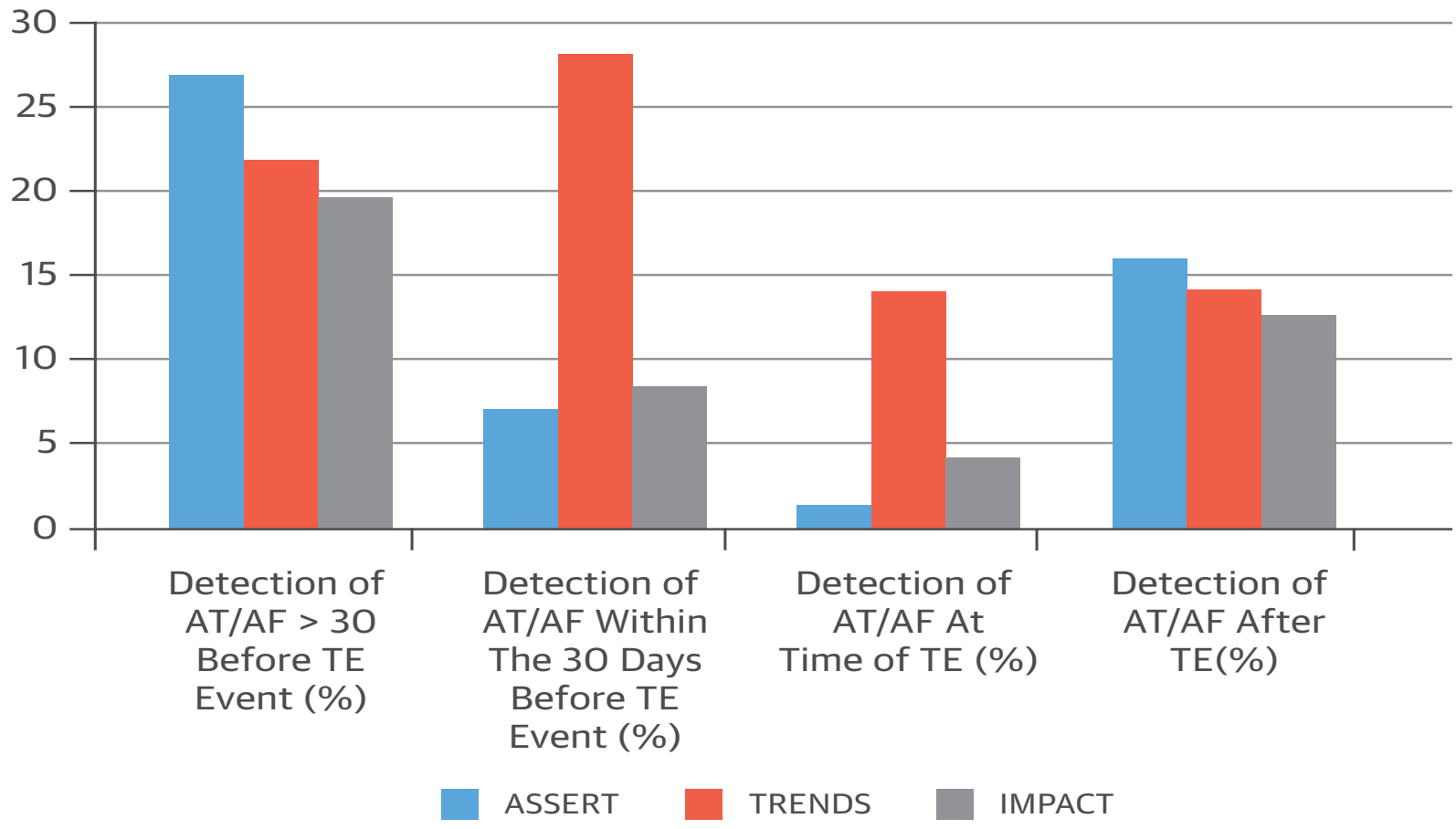


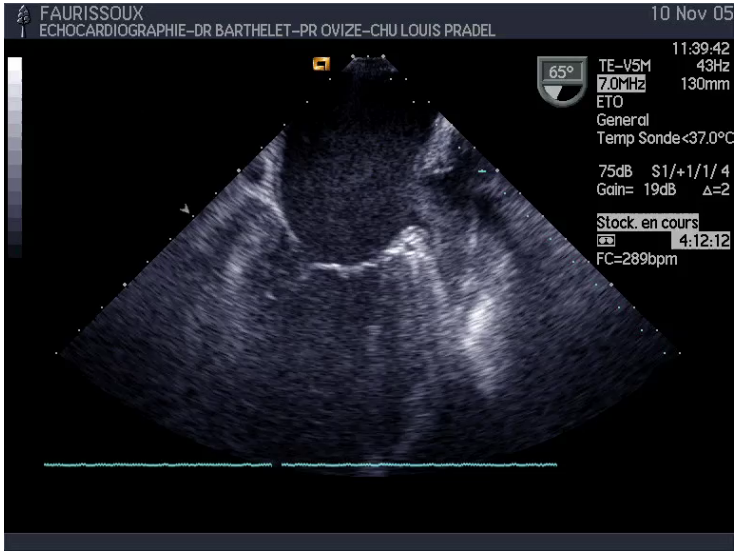
Stroke Risk in Atrial Fibrillation Working Group, Stroke 2008;39:1901-1910

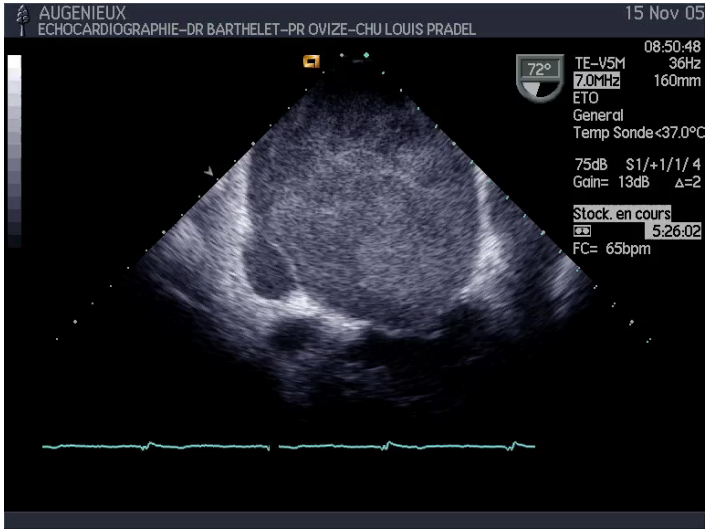
Variabilité du risque d'AVC

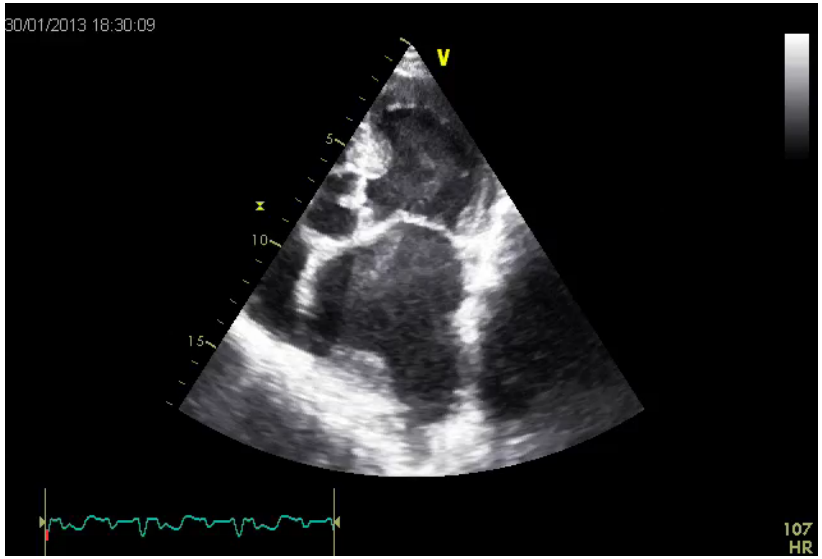


Dissociation temporelle entre FA et AVC

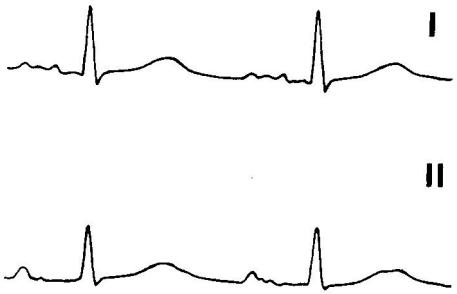


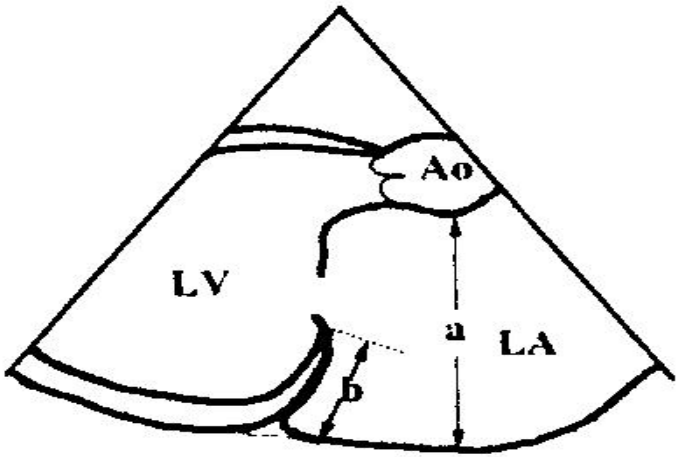

FAURISSOUX
ECHOCARDIOGRAPHIE-DR BARTHELET-PR OVIZE-CHU LOUIS PRADEL
10 Nov 05
11:39:42
65°
TE-V5M
7.0MHz
ETO
General
Temp Sonde<37.0°C
43Hz
130mm
75dB S1/+1/1/ 4
Gain= 19dB Δ=2
Stock. en cours
4:12:12
FC=289bpm

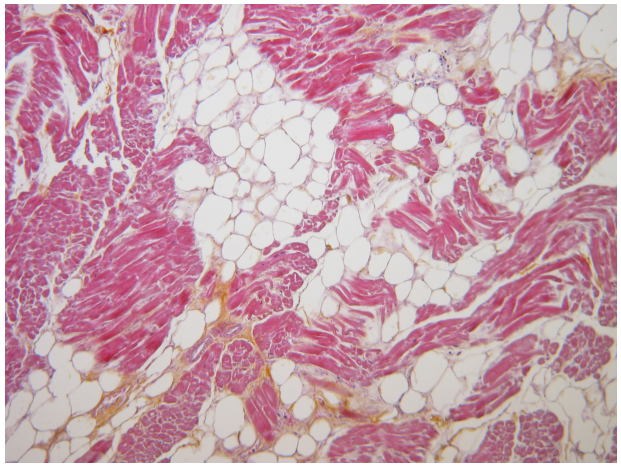

AUGENIEUX
ECHOCARDIOGRAPHIE-DR BARTHELET-PR OVIZE-CHU LOUIS PRADEL
15 Nov 05
08:50:48
72°
TE-V5M
7.0MHz
ETO
General
Temp Sonde<37.0°C
36Hz
160mm
75dB S1/+1/1/ 4
Gain= 13dB Δ=2
Stock. en cours
5:26:02
FC= 65bpm

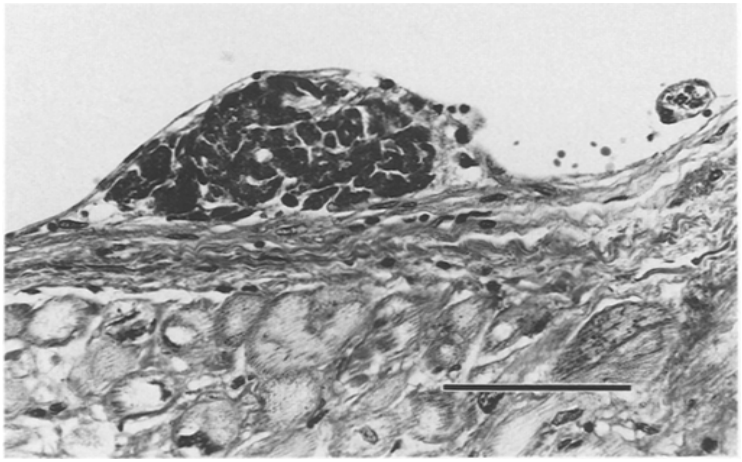

30/01/2013 18:30:09
V
5
10
15
107
HR

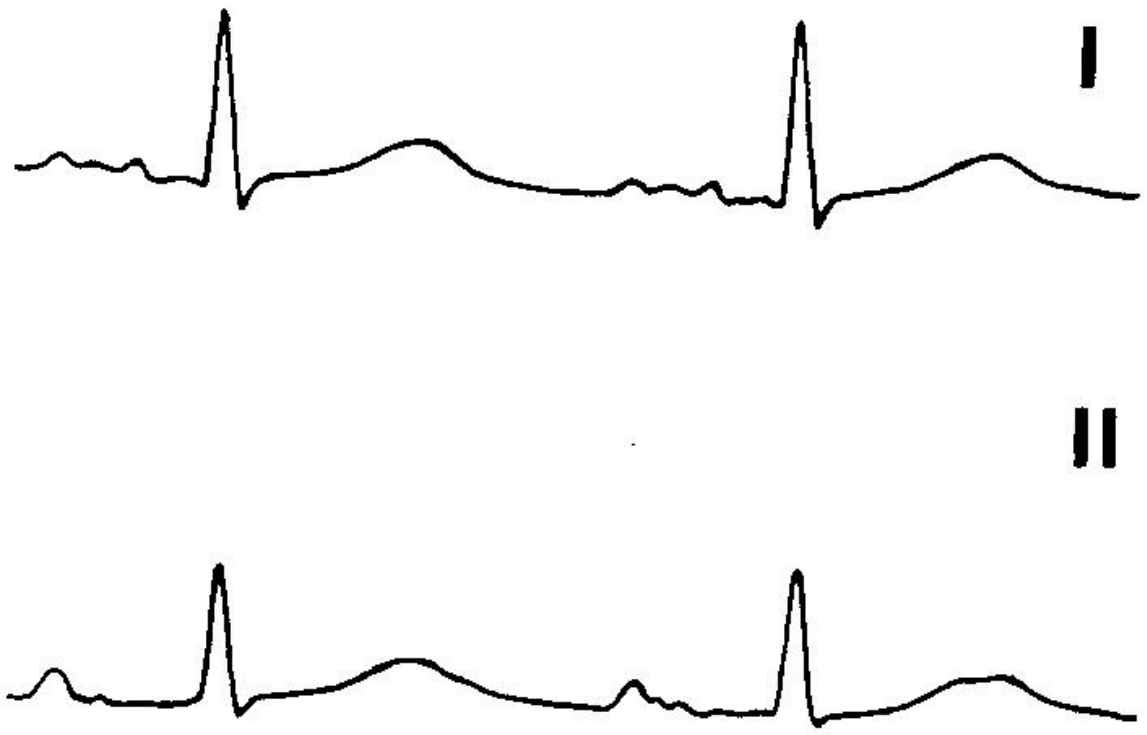
Myopathie atriale


I
II

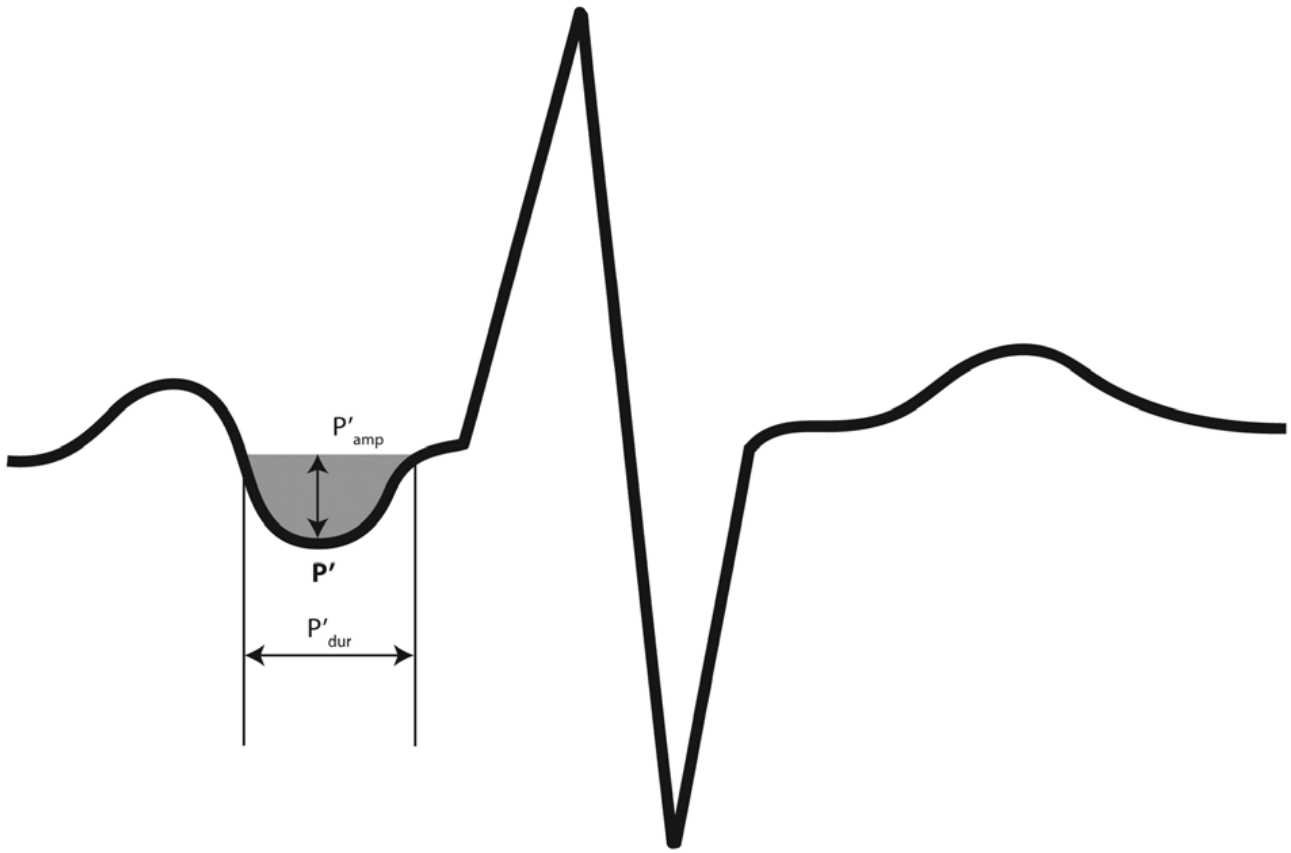

Ao
LV
a
LA
b



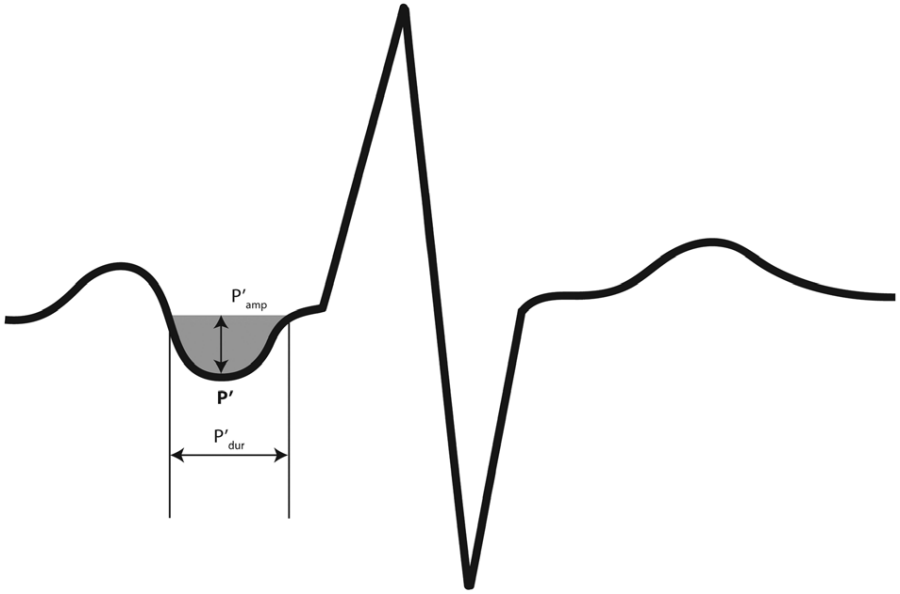


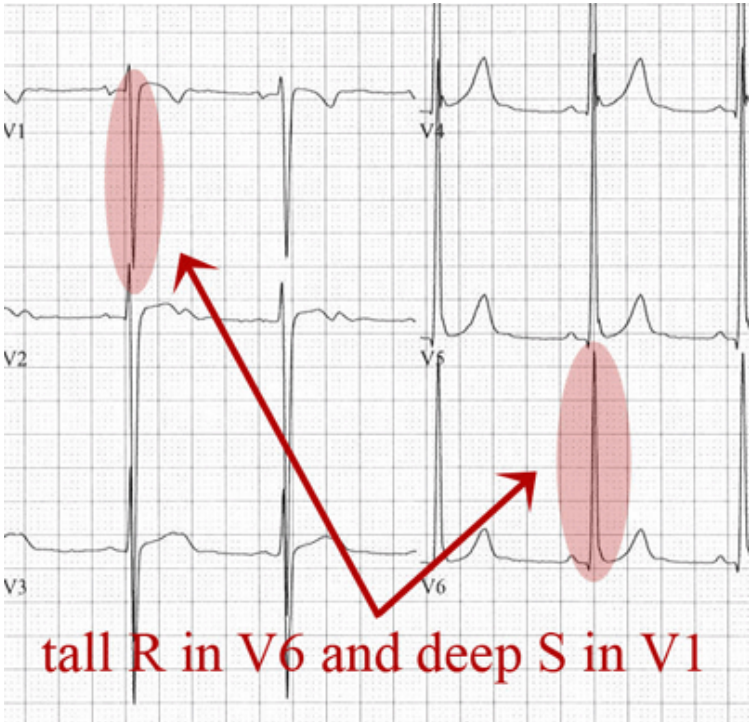

I
II

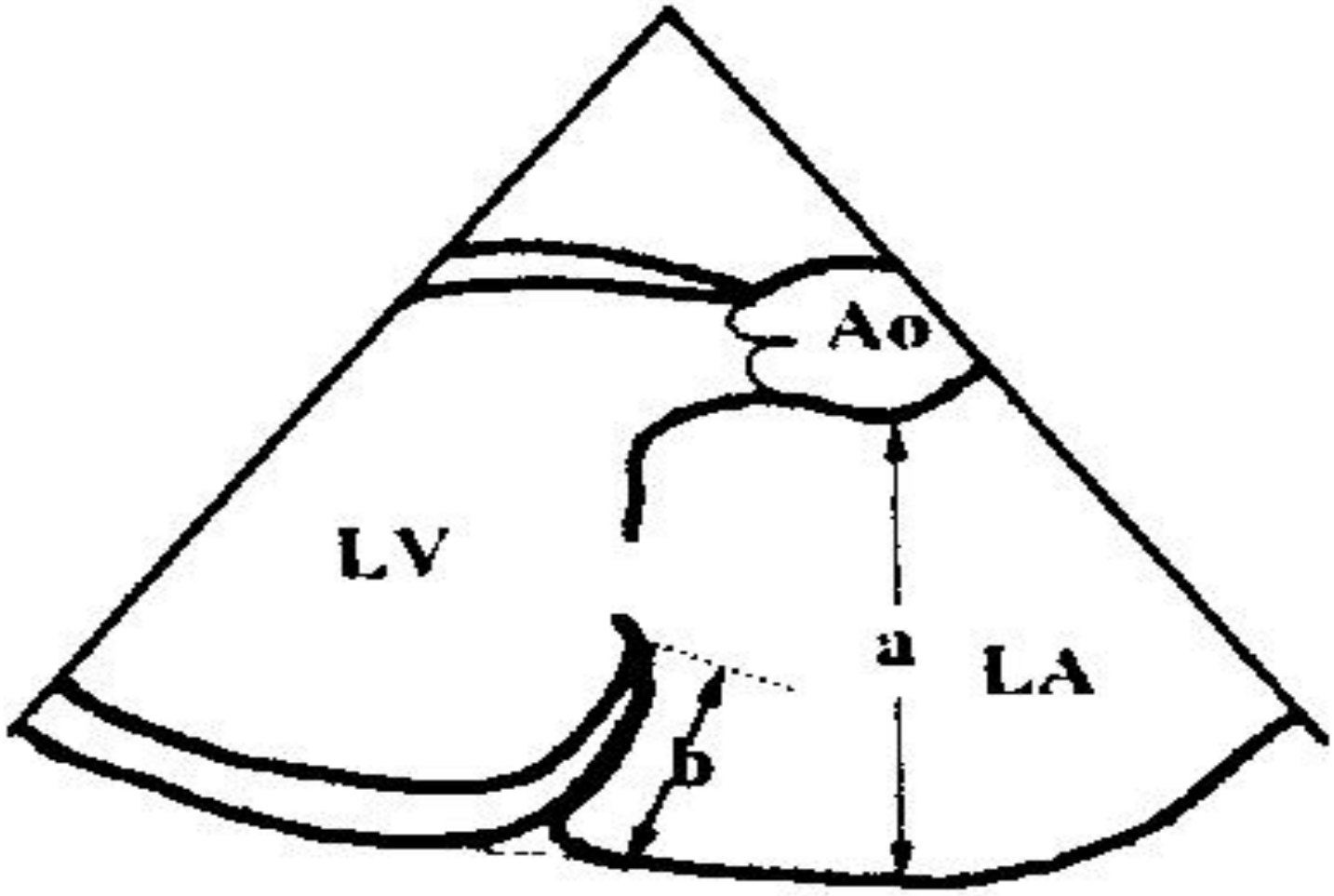
241 patients avec AVC versus 798 patients contrôles à partir d'une cohorte de 3567 patients



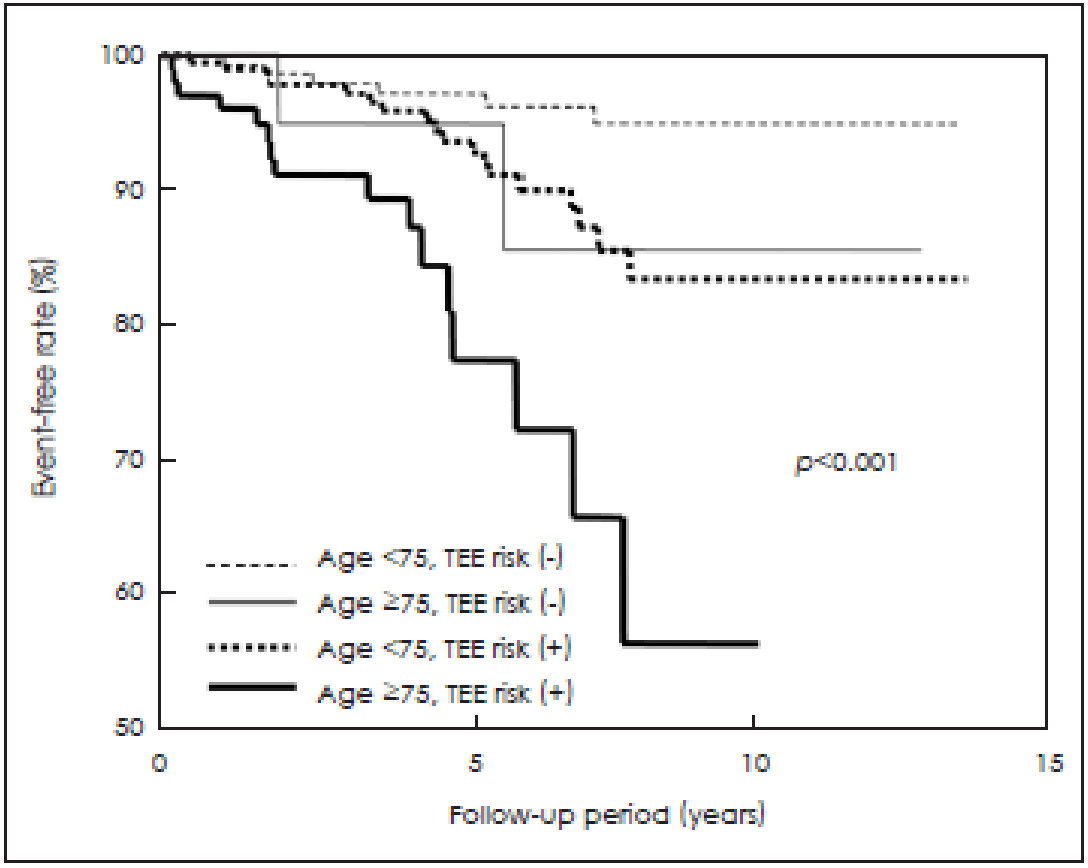
P-wave terminal force in lead V_1

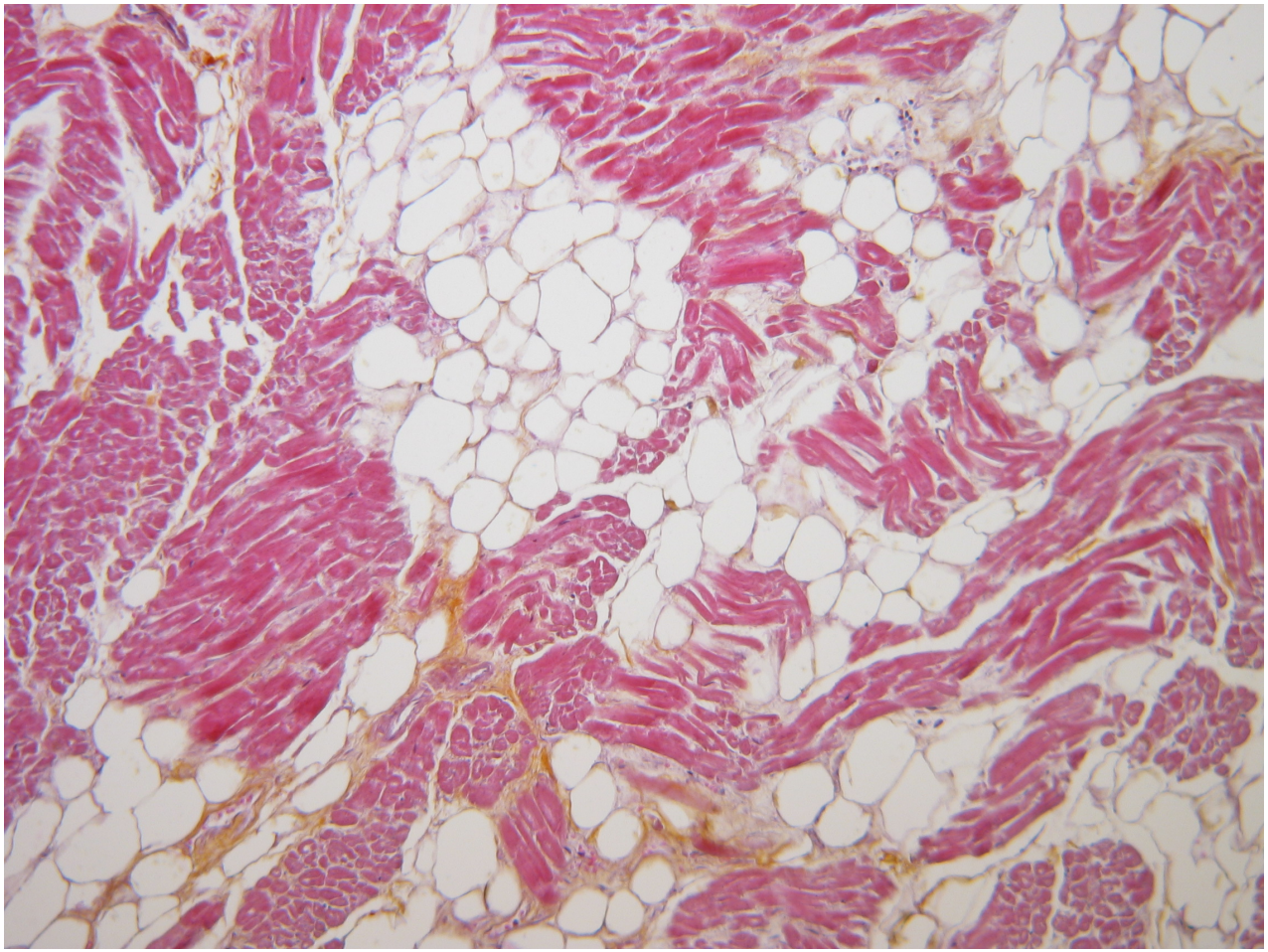




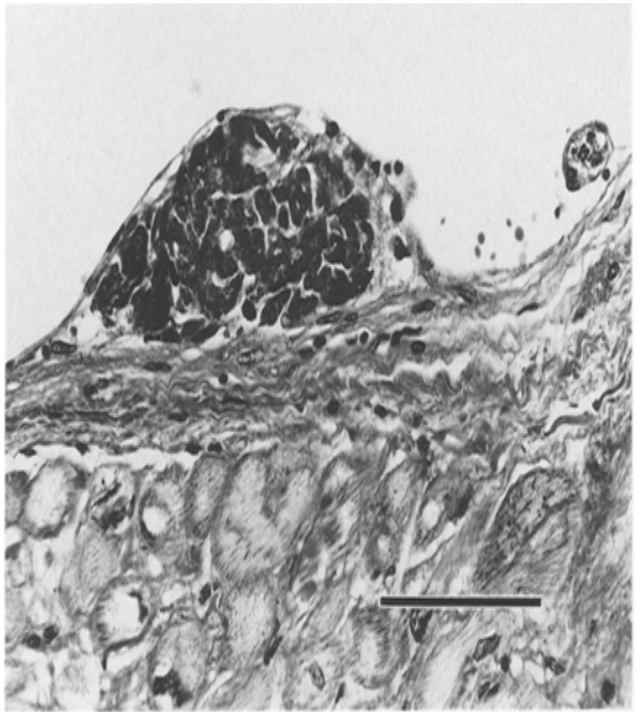

Ao
LV
a
LA
b

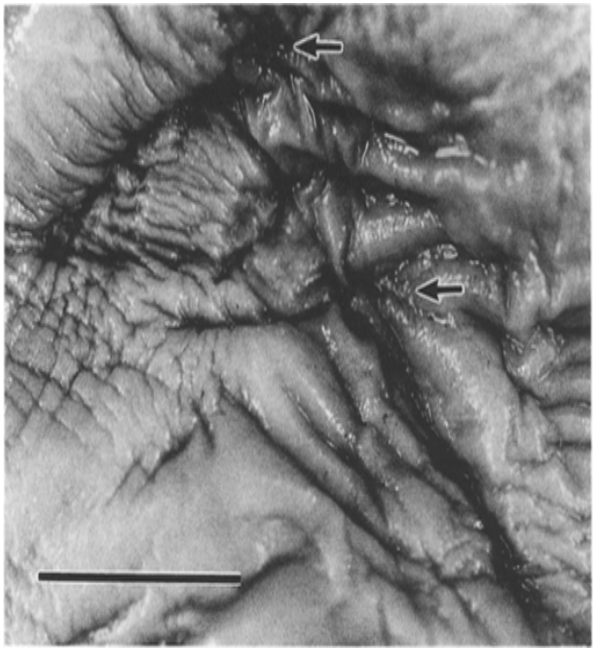
Rôle de l’échocardiographie trans-oesophagienne

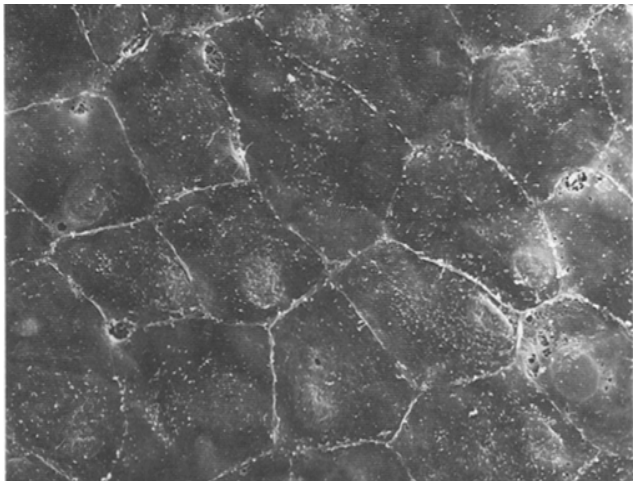




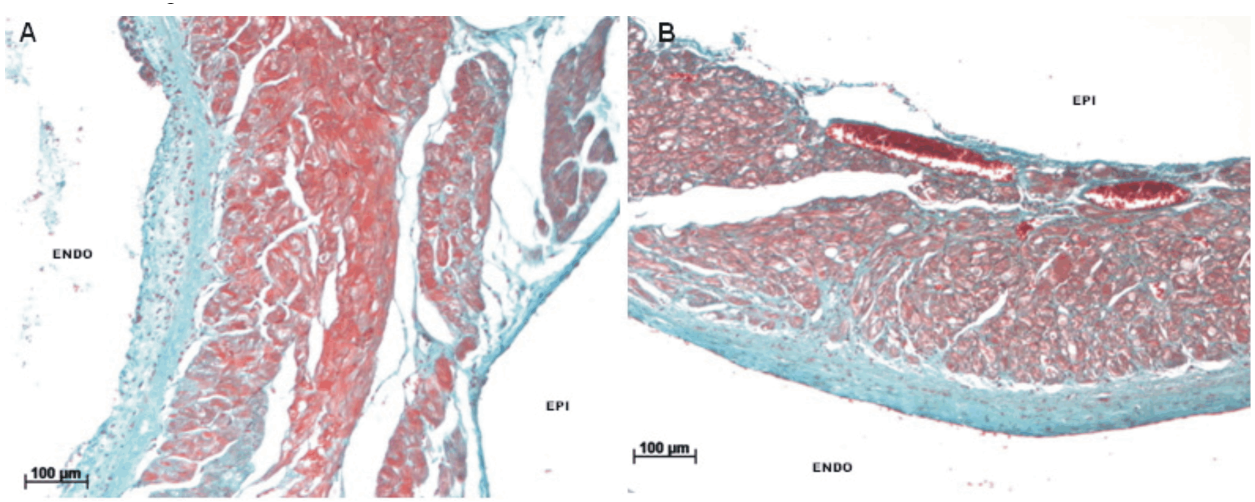
Micro thrombus

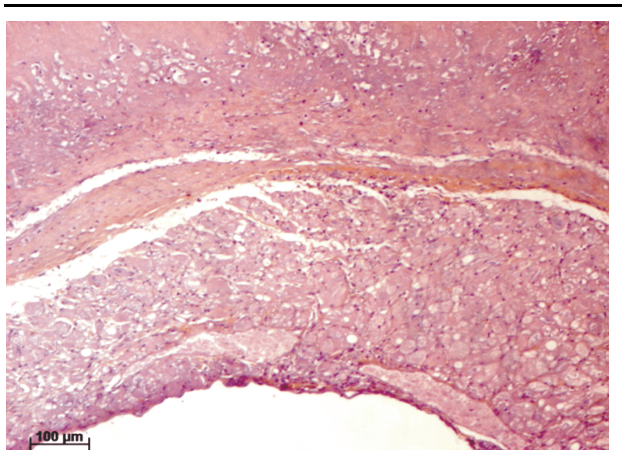




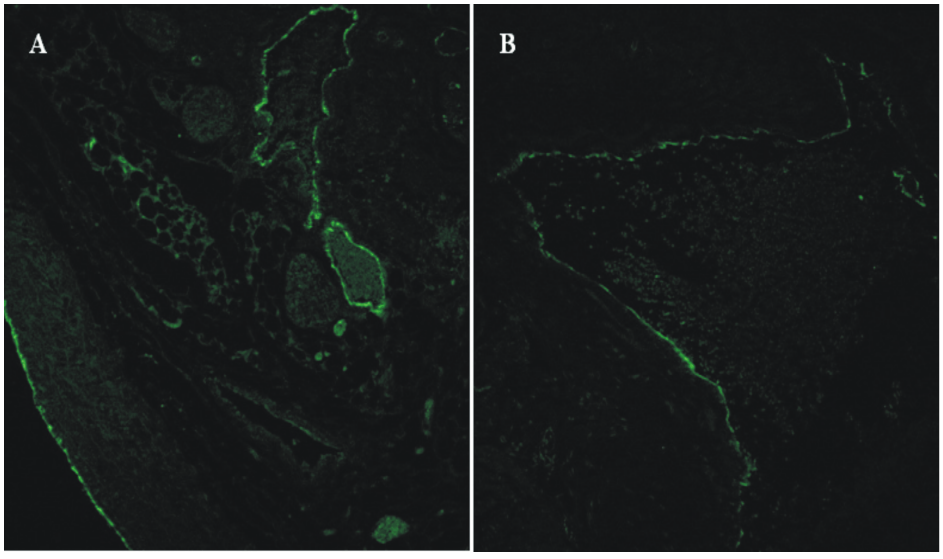


Myopathie atriale : fibrose, Thrombogénicité…



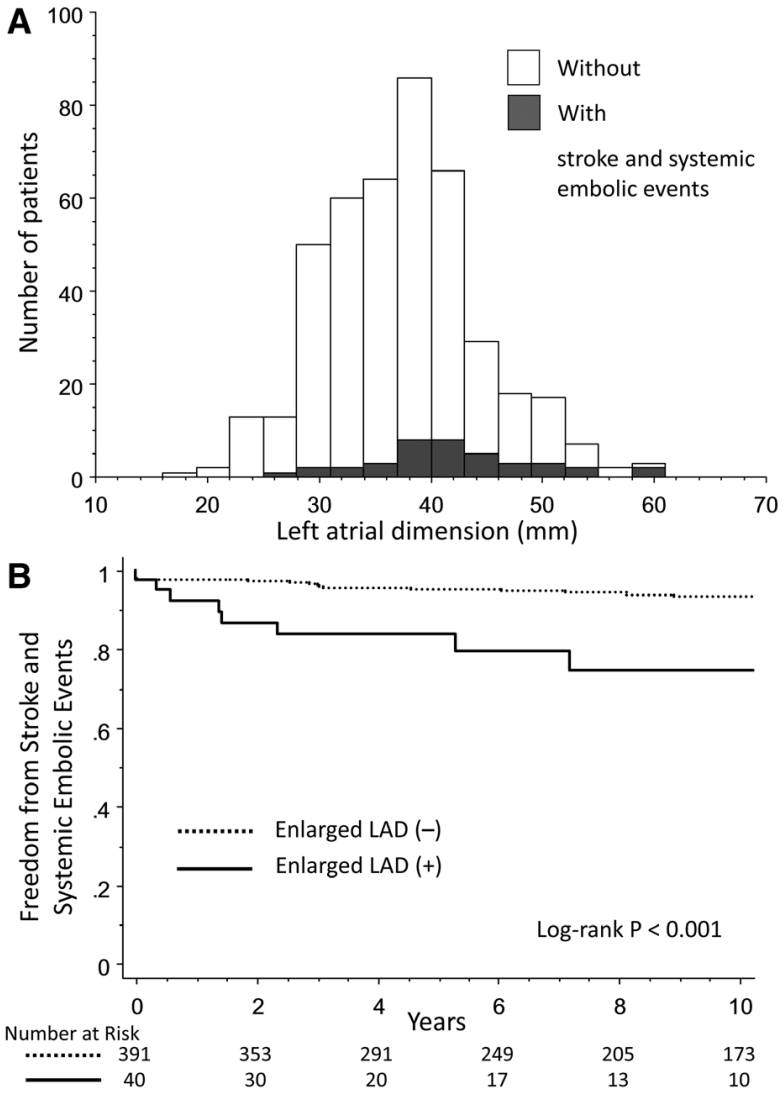


Thrombus mural

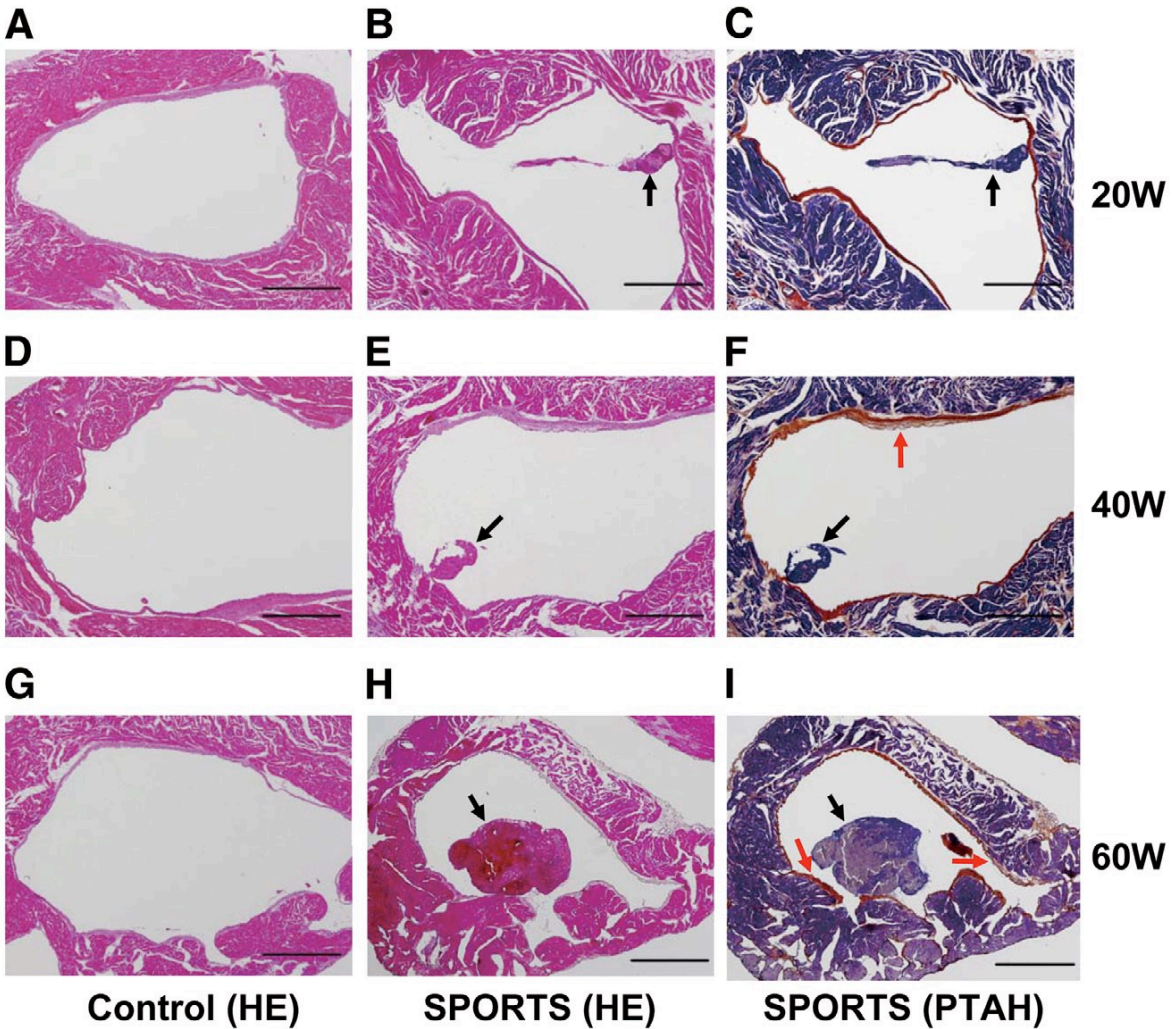


Expression de F vW

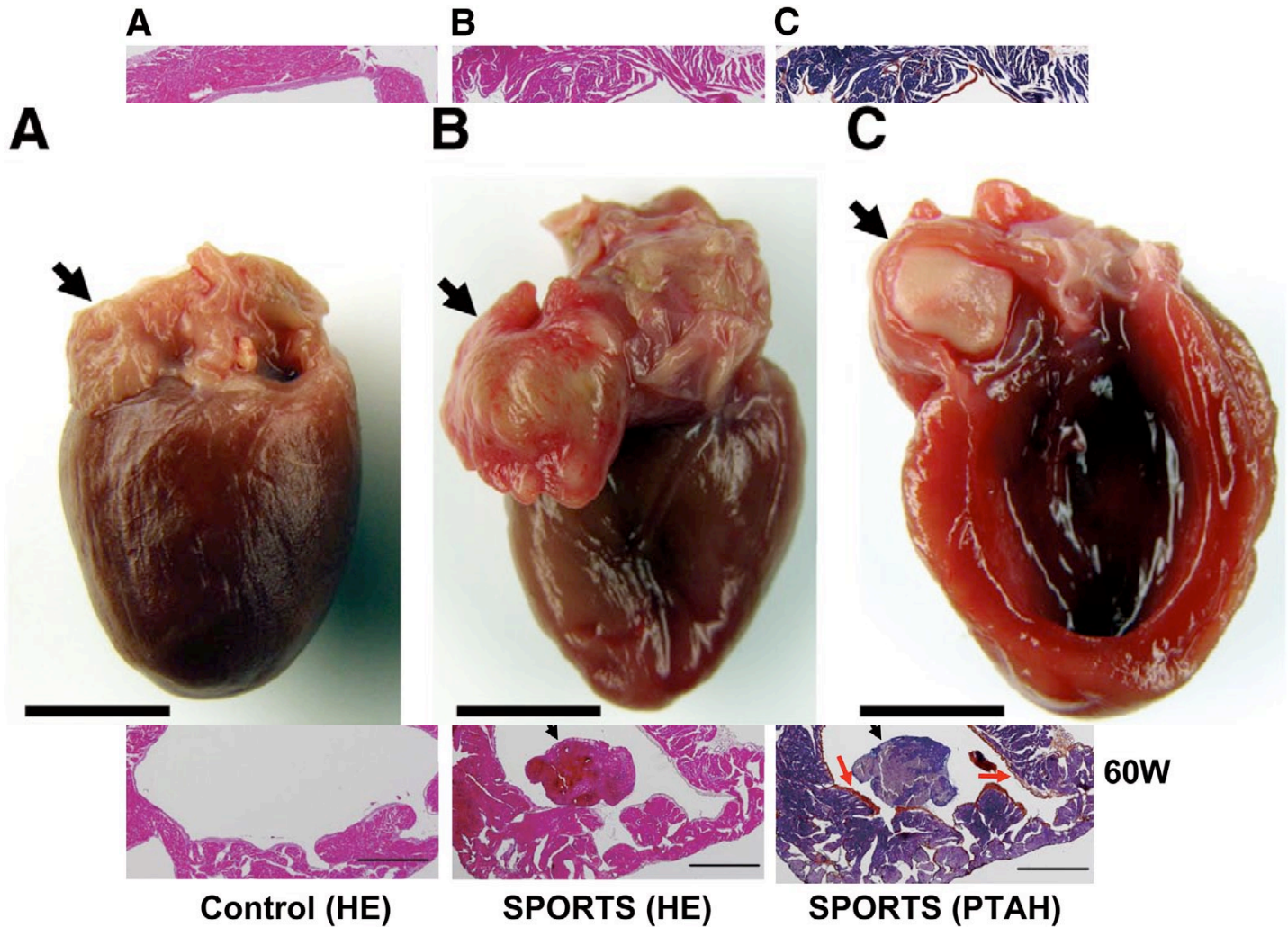
Cardiomyopathie Hypertrophique : AVC 1 % par an
Fibrillation atriale absente dans 50% des cas



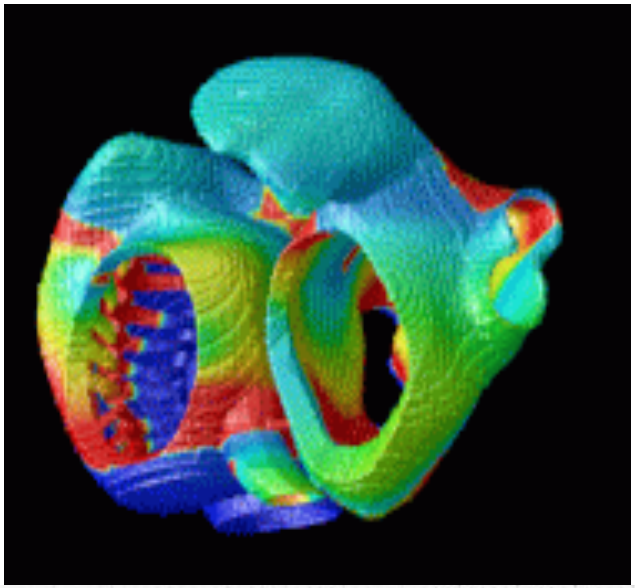
Modèle expérimental de thrombus intra-atrial gauche ***sans*** fibrillation atriale

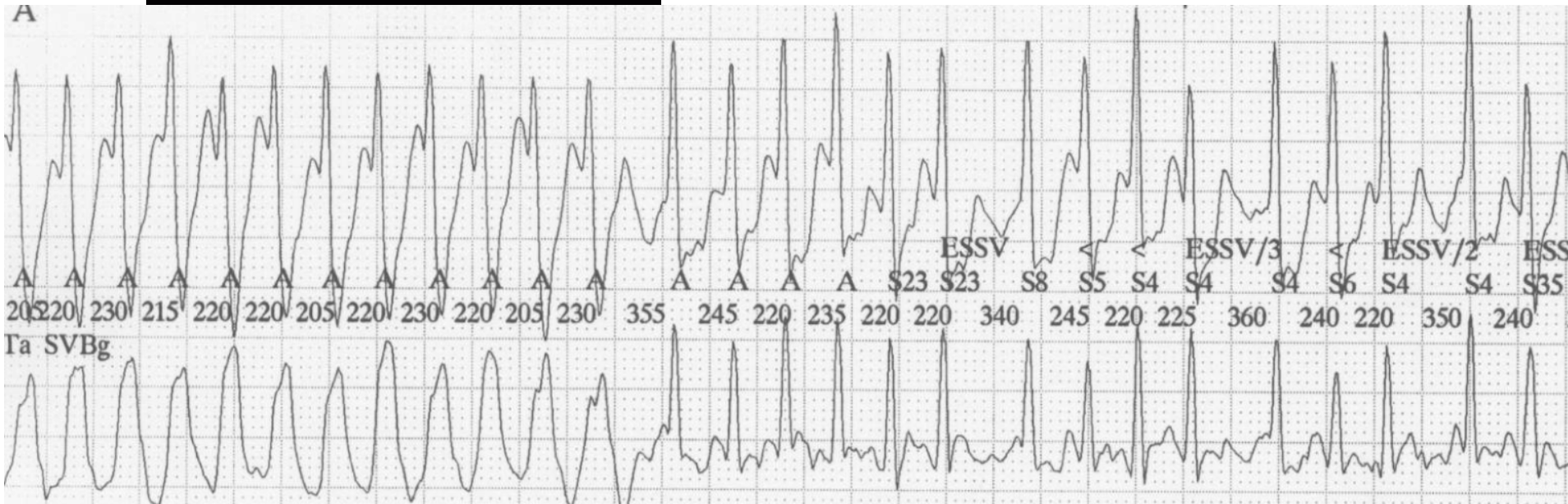


Modèle expérimental de thrombus intra-atrial gauche ***sans*** fibrillation atriale

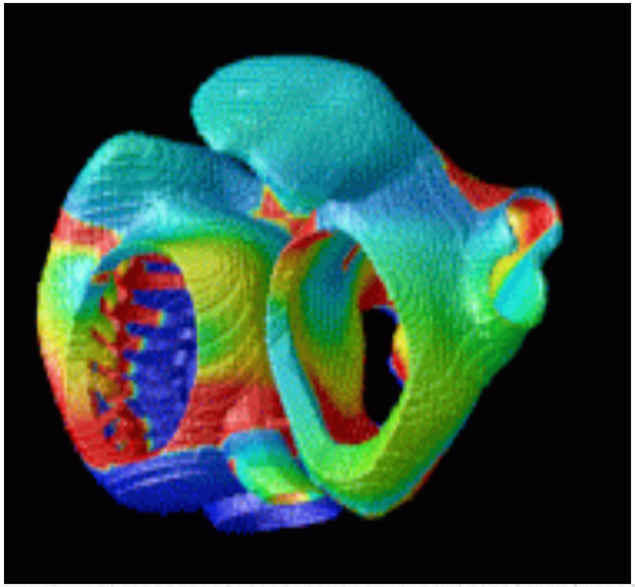


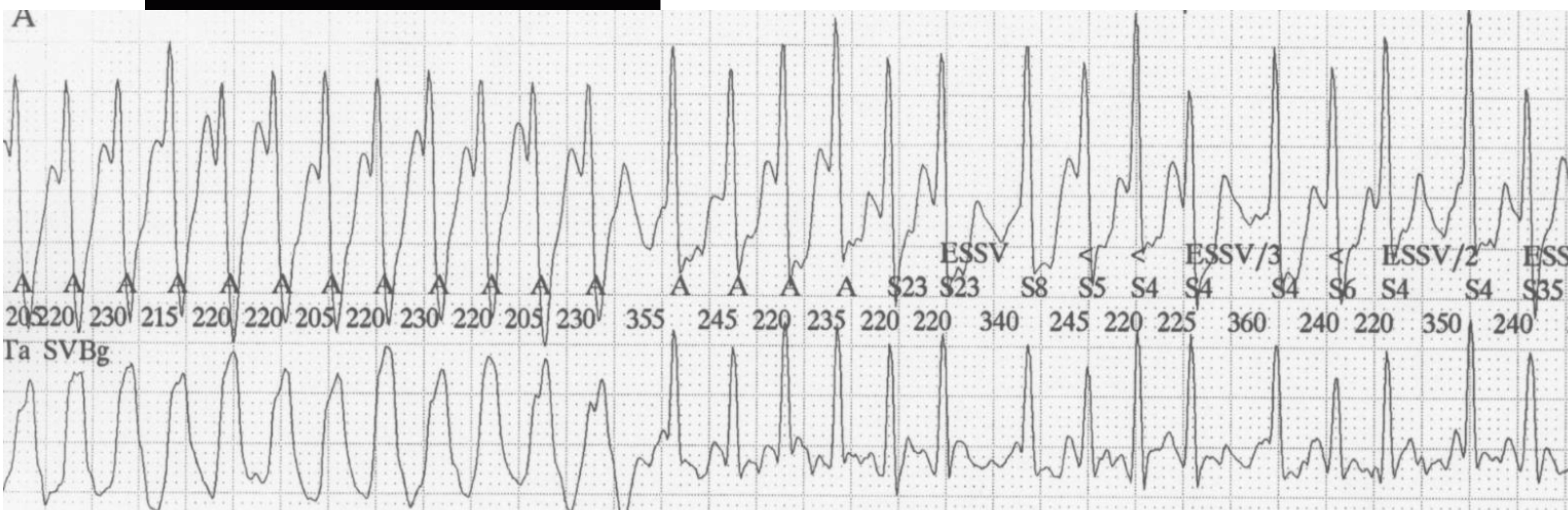
Fibrillation atriale
Une maladie musculaire

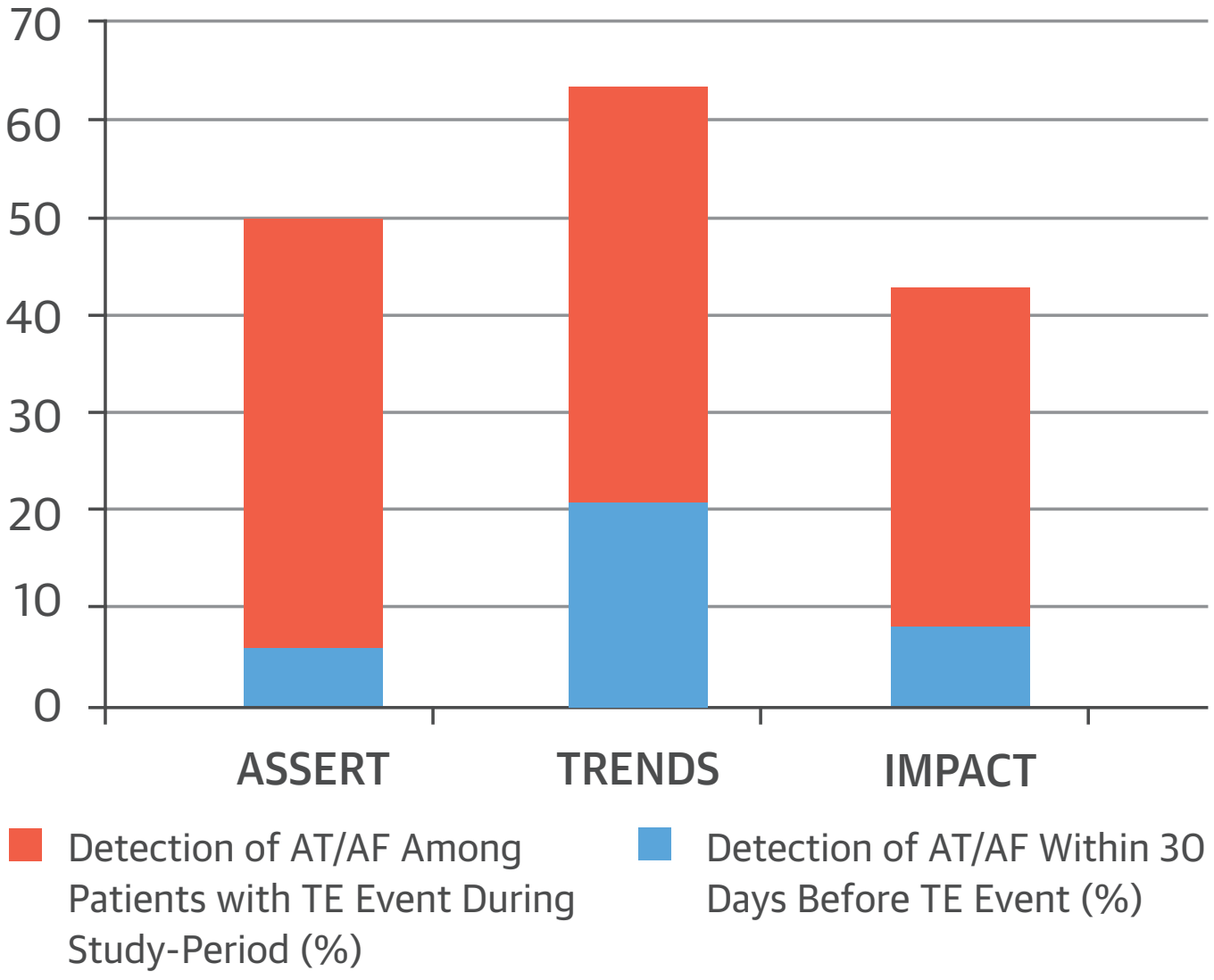




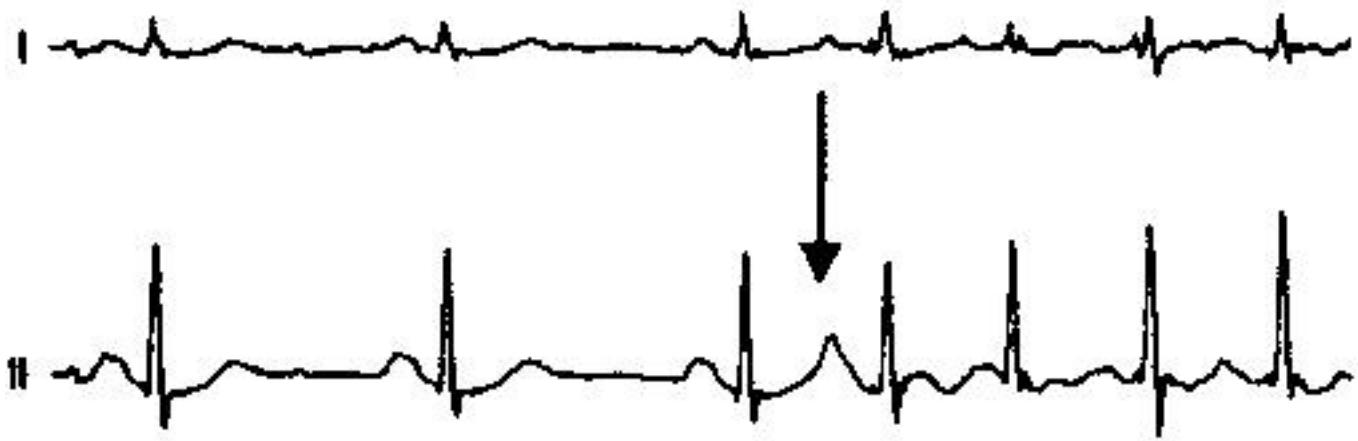
Fibrillation atriale
Une maladie (neuro) musculaire



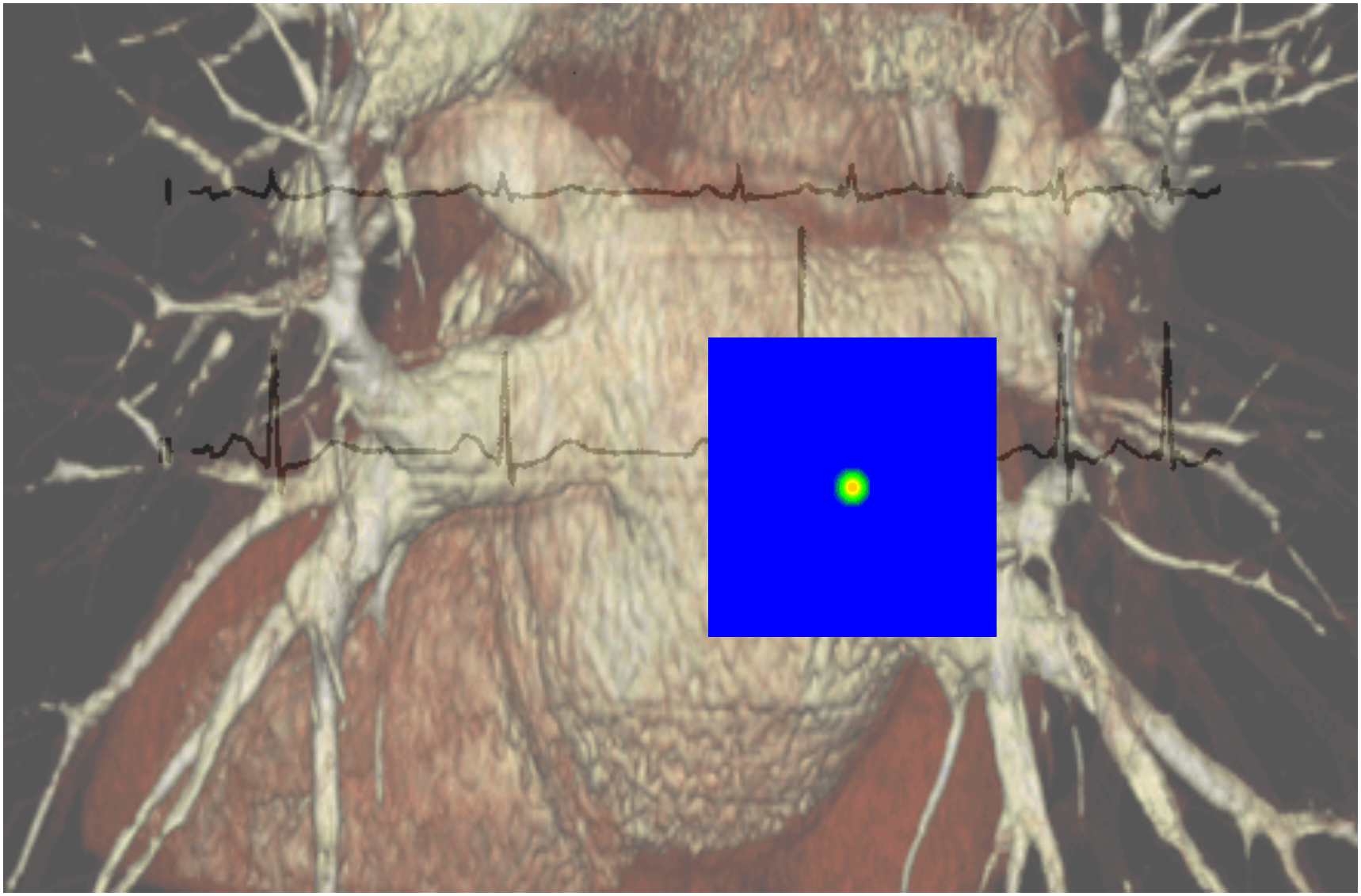



70
60
50
40
30
20
10
0
ASSERT
TRENDS
IMPACT
Detection of AT/AF Among Patients with TE Event During Study-Period (%)
Detection of AT/AF Within 30 Days Before TE Event (%)

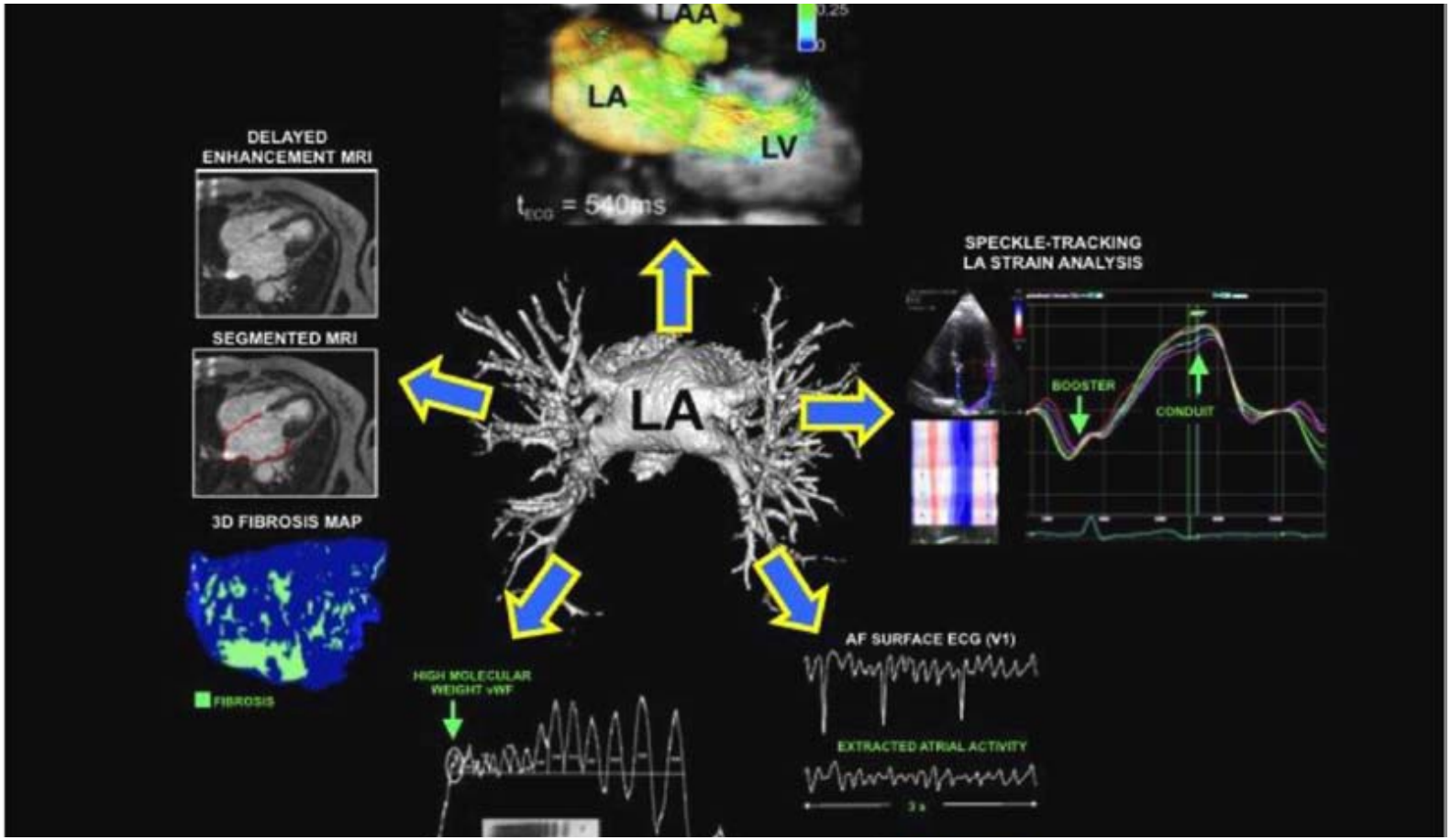
Octagénaire, normotendu



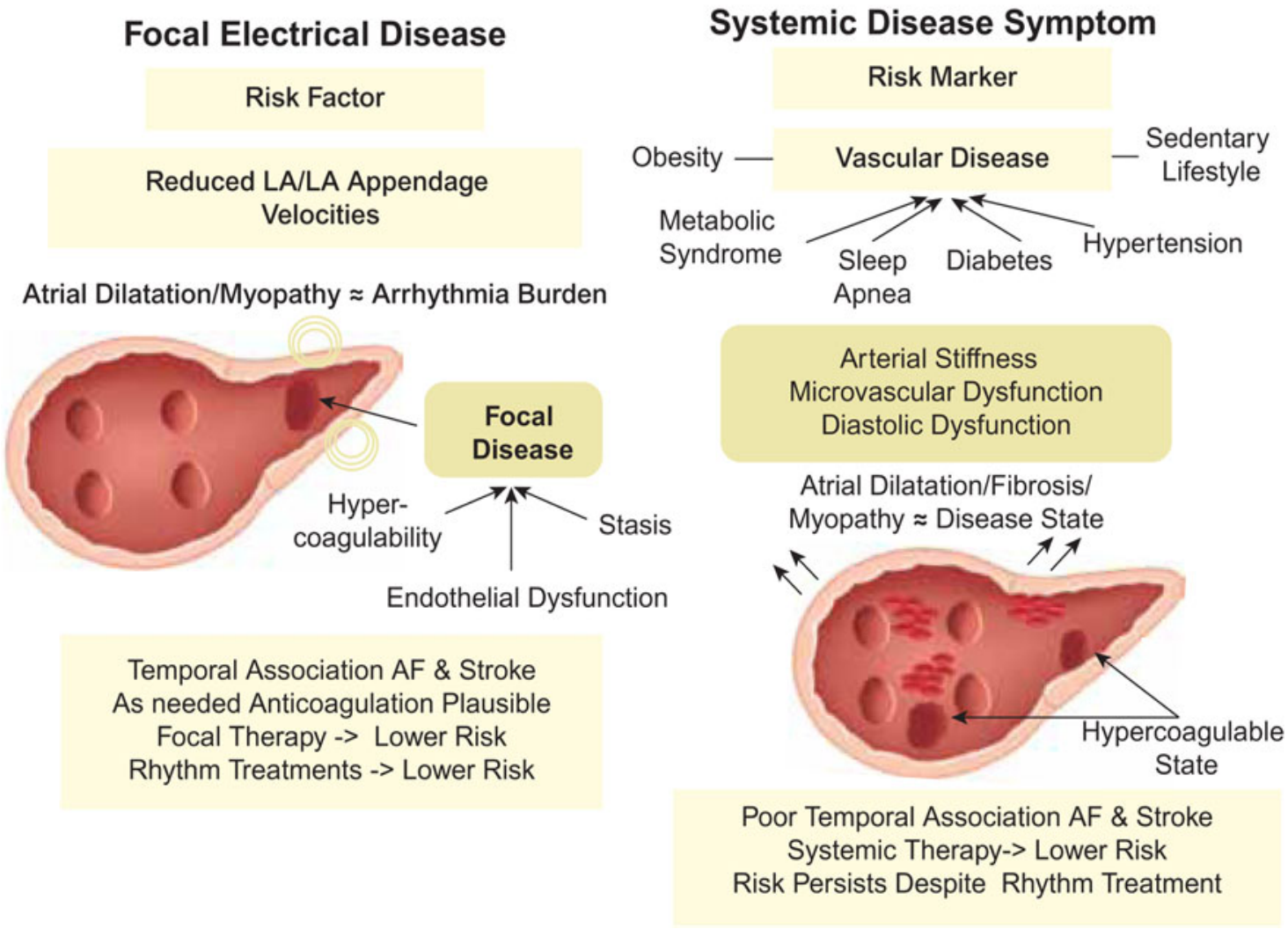
Extra Systole Atriale

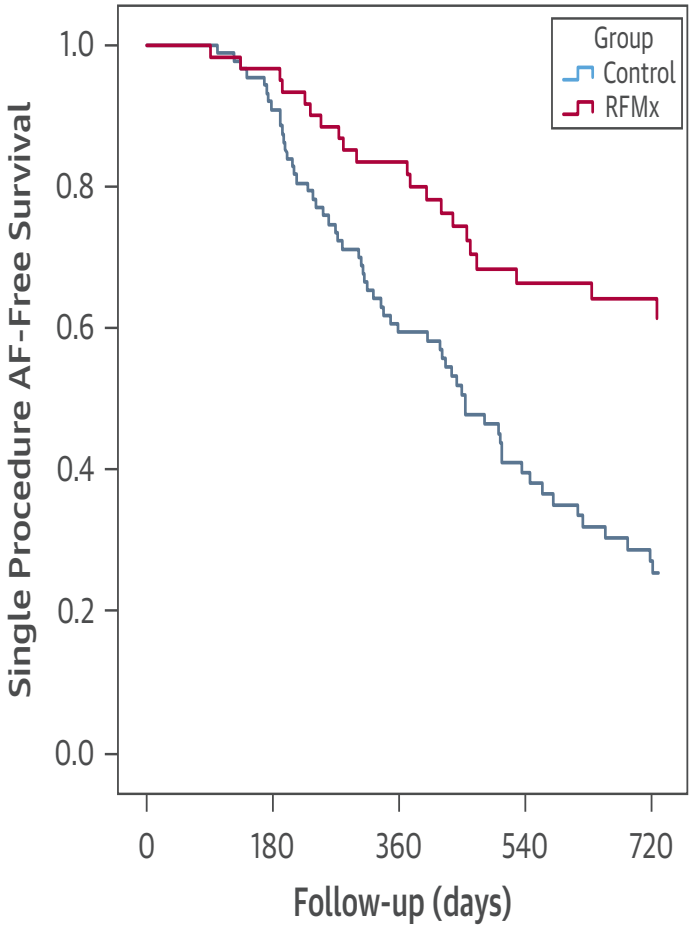


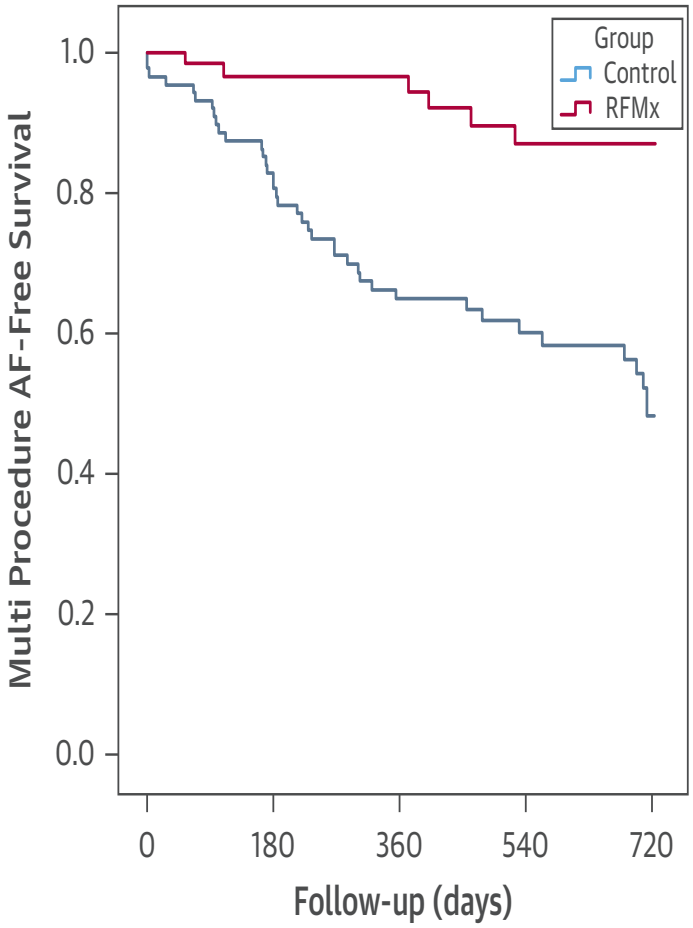
Préciser le substrat
Au-delà du score CHADS2-VASC



Les Fibrillations Atriales

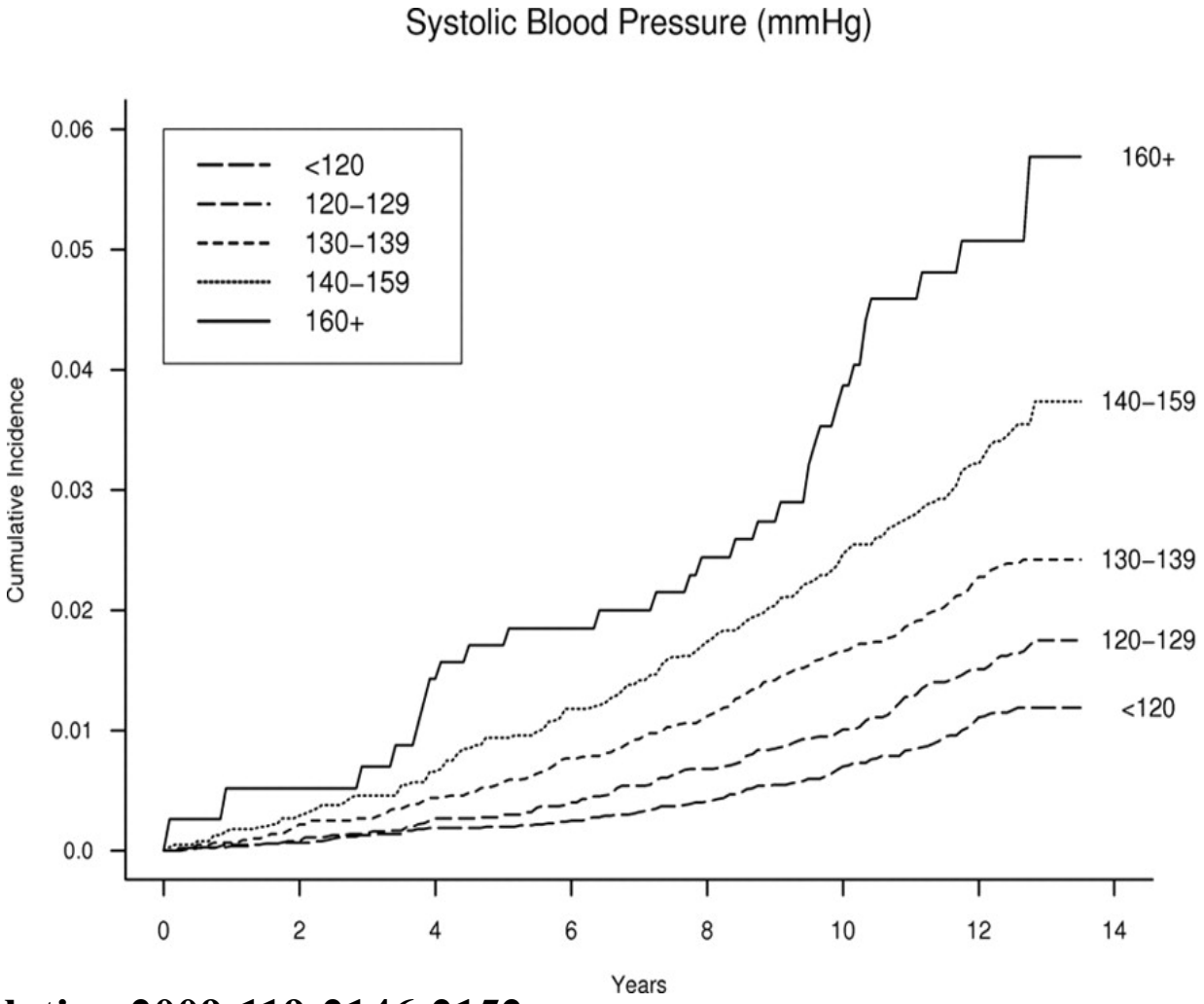






ARREST-AF study

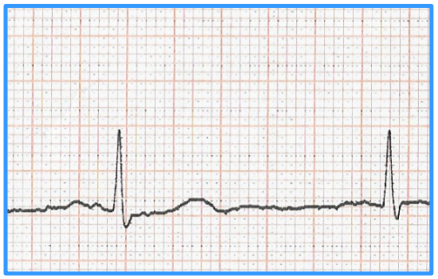
38 876 patients avec fibrillation atriale sans cardiopathie
Rôle de la pression artérielle systolique



Conen, D. et al. Circulation 2009;119:2146-2152

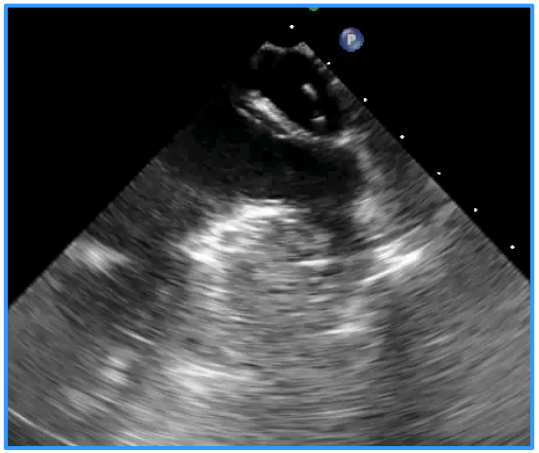
Anticoagulation?

"Dirty" P-waves



Myopathie Atriale

"Sluggish" left atrium



Biomarqueurs
Biologie moléculaire

W. Anné et al. Heart. 2004 Sep; 90(9): 1025–1030.

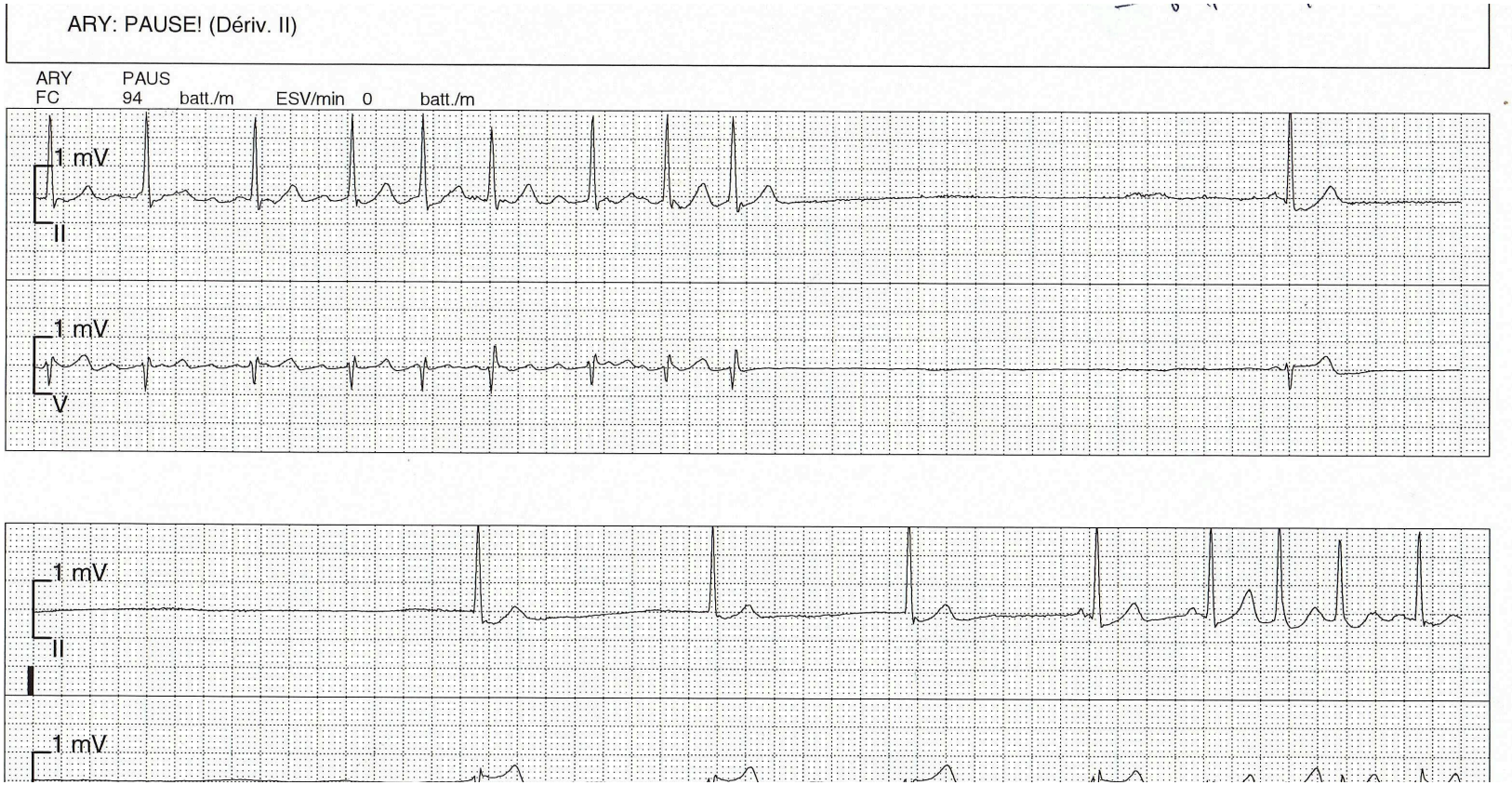
- Homme, 68 ans hypertendu (3 médications anti-hypertensives, statines, IEC, activité physique)

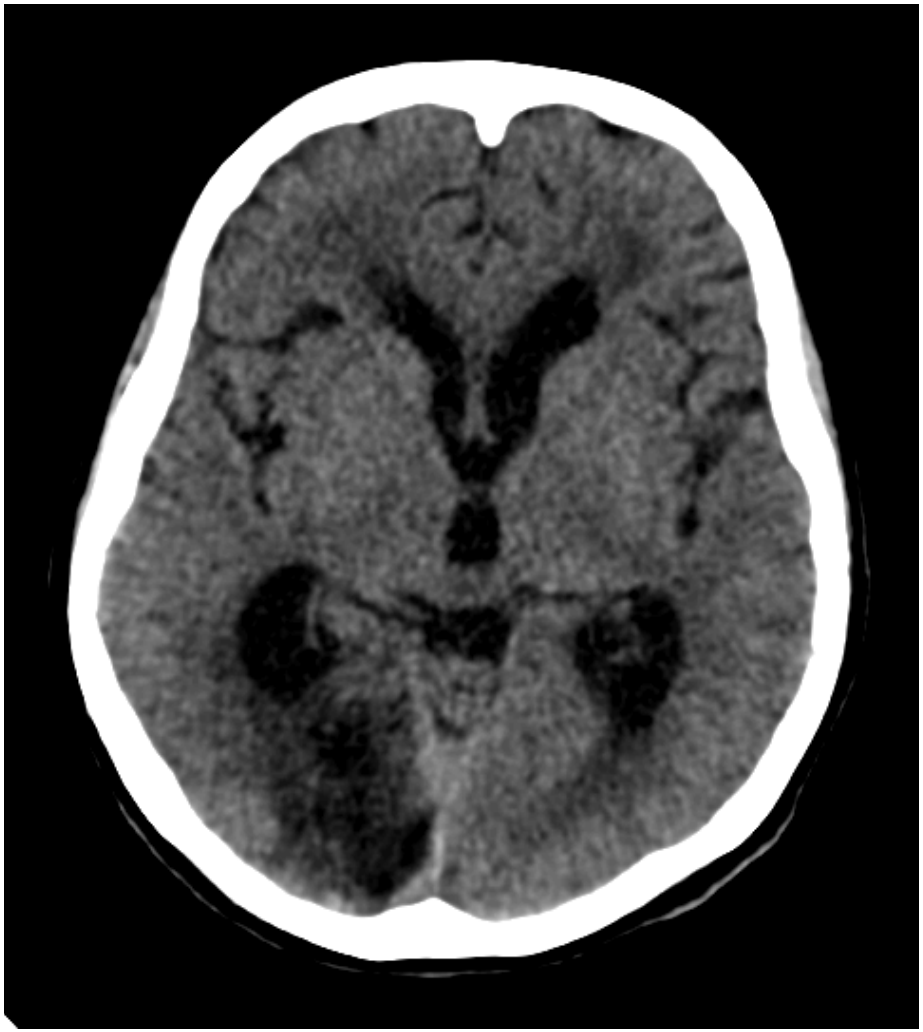
- Fibrillation atriale permanente puis 3 ans après bloc atrio-ventriculaire. PM monochambre.

- Anticoagulants?

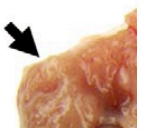
- Garçon, 10 ans. Flutter atrial, dysfonction sinusale
- Variant sur le gène SCN5A
  - Anticoagulation?

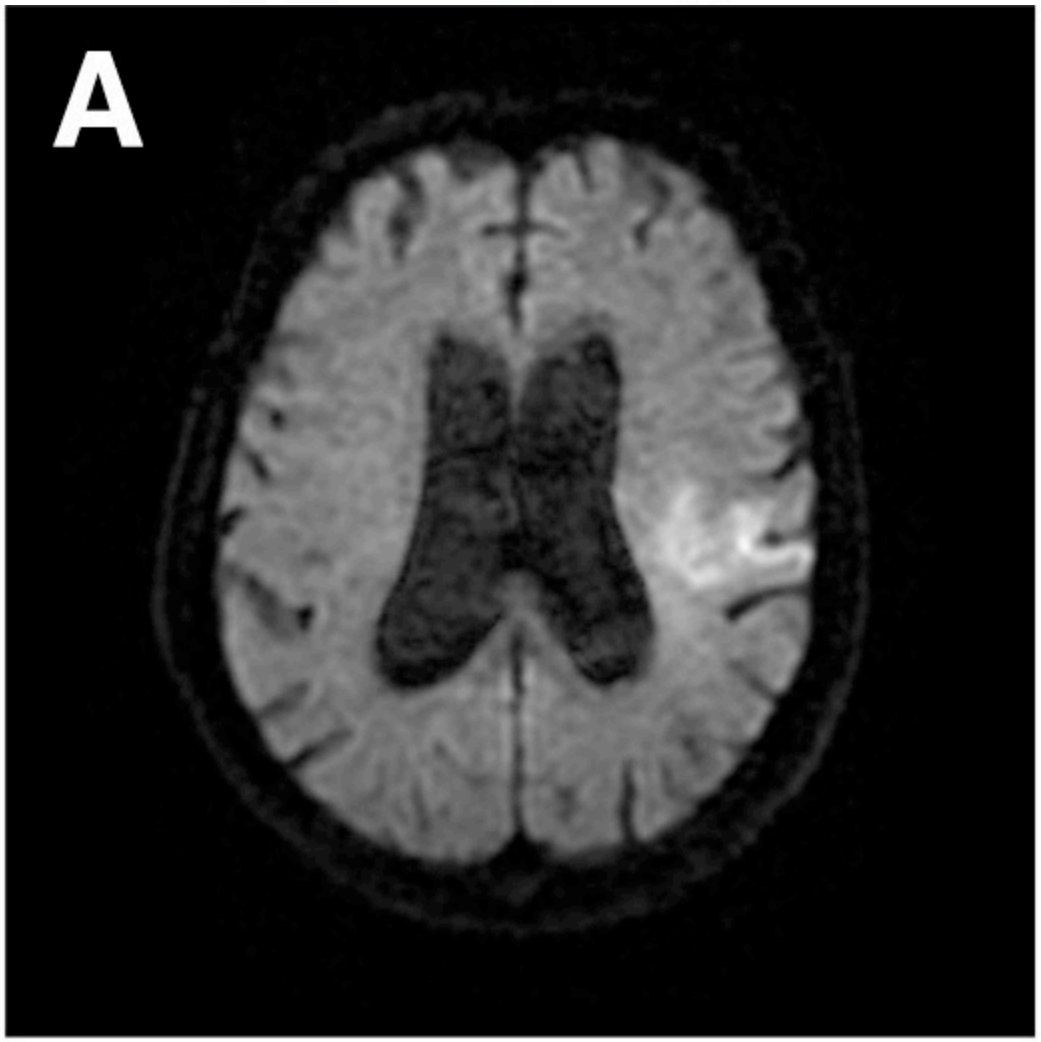
Femme, 60 ans, dysfonction sinusale et fibrillation atriale permanente





A B C





RESEARCH ARTICLE

Open Access

Left atrial volu

otypes

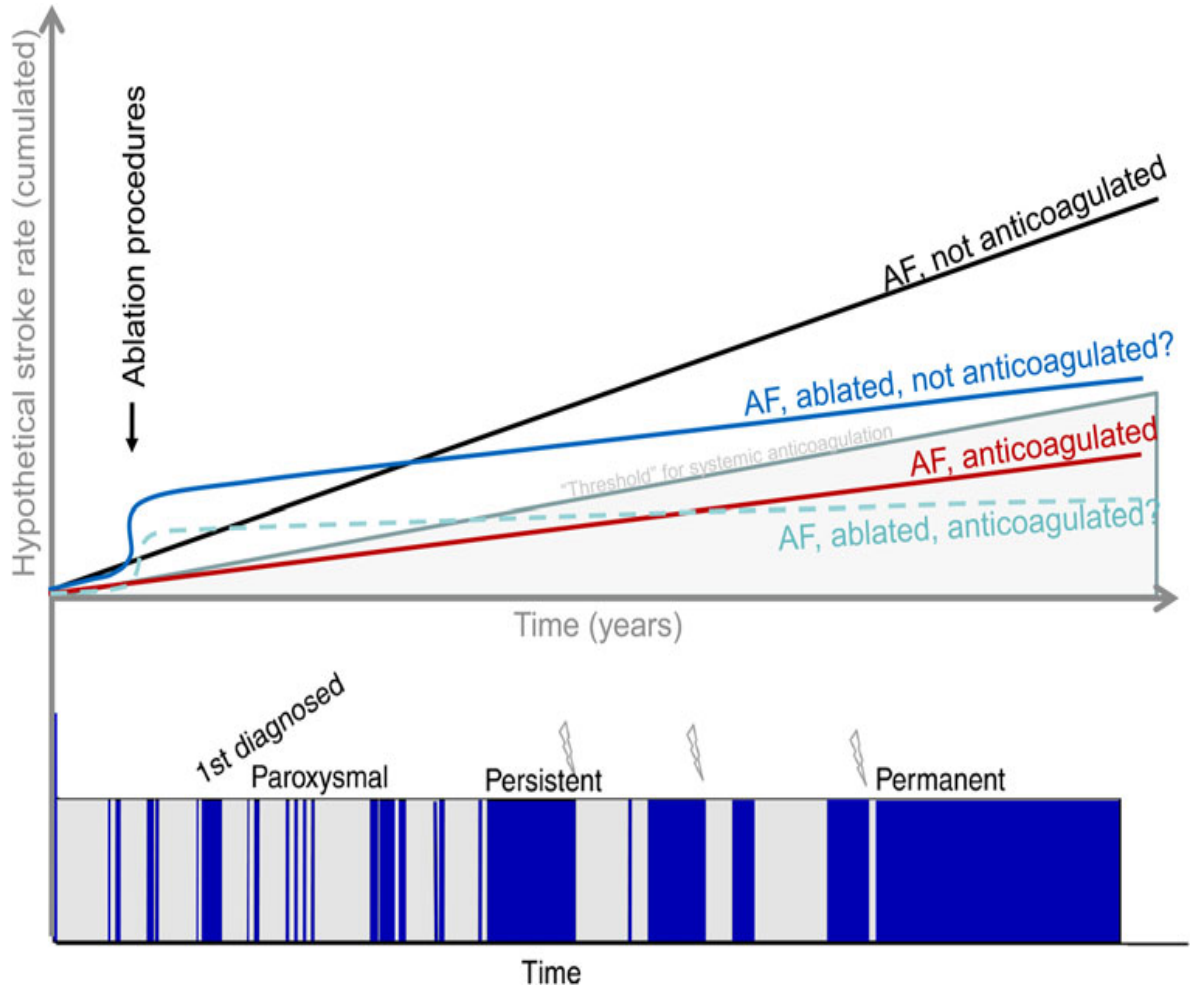
Quratulain Shaikh[1], Bilal Ahmed[2]

Ahmed[4],

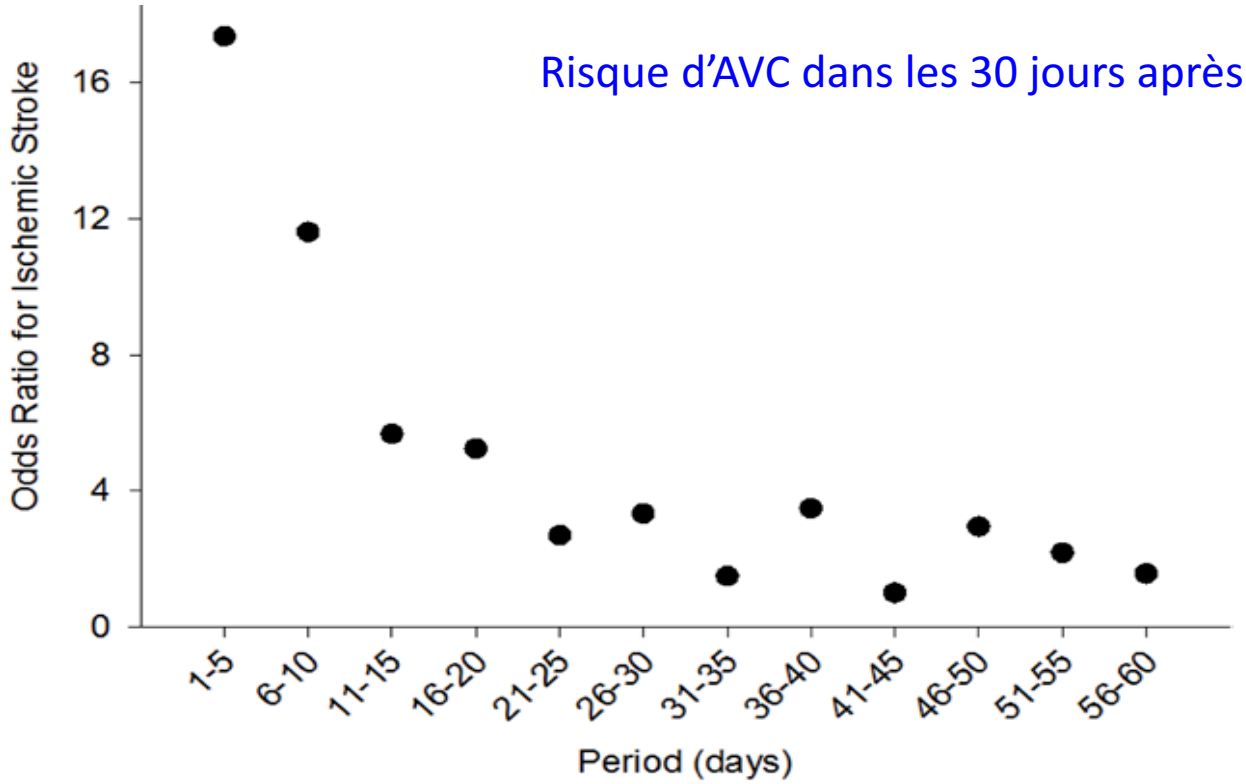
Farzin Majeed[1], Fariha Sadiq Ali[5]

	stroke
LAVi* ml/m²	33.4
LAD# mm	36
LVMiß gm/m²	80.9

Anticoagulation après ablation : Décision probabiliste



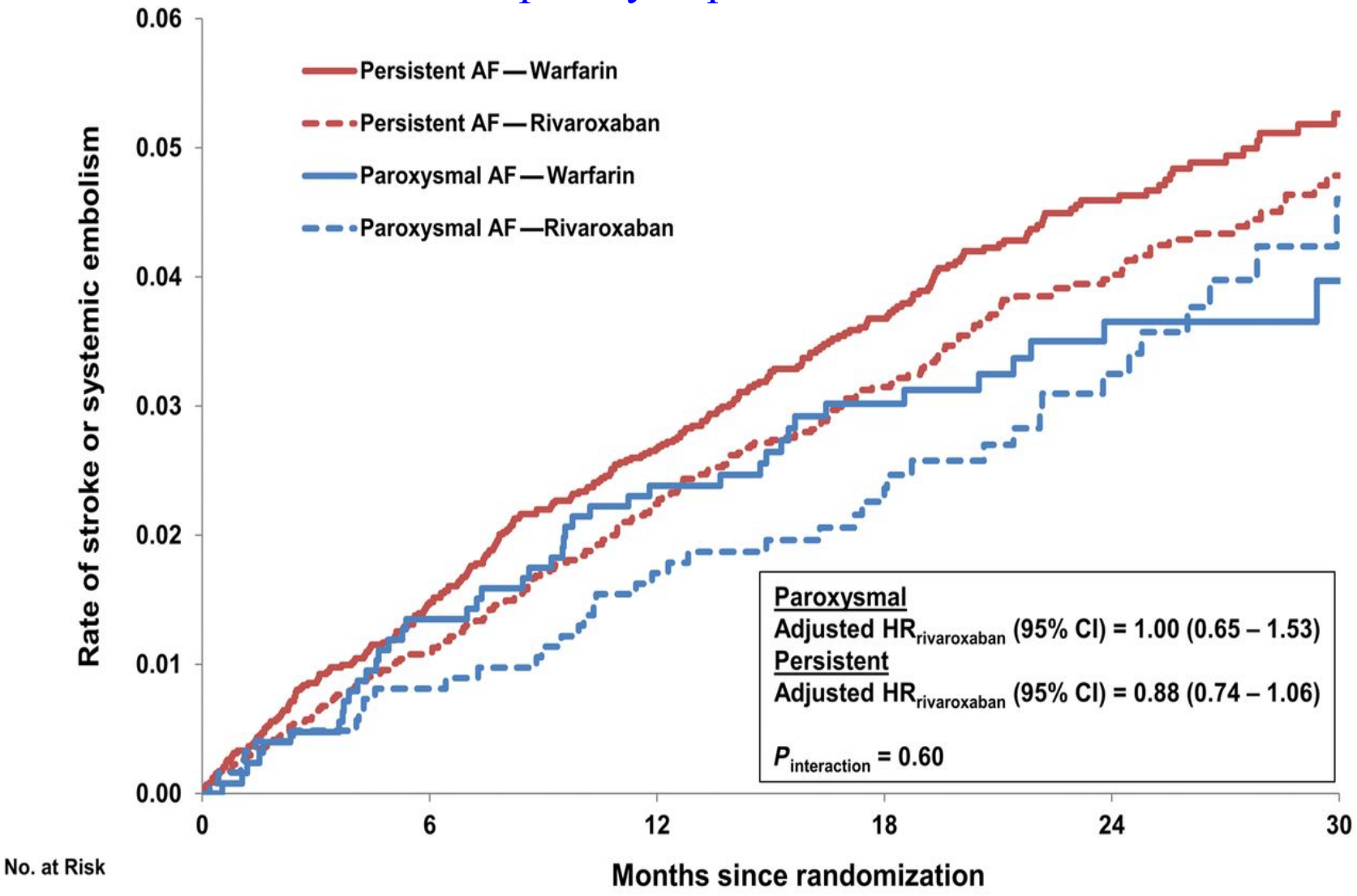
“Charge” de FA



Risque d’AVC dans les 30 jours après FA

Essais en cours : TACTIC AF, OAT Pilot study, CABANA, EAST trial….

ROCKET AF trial
FA paroxystique et embolie cérébrale



38 876 patients avec fibrillation atriale sans cardiopathie
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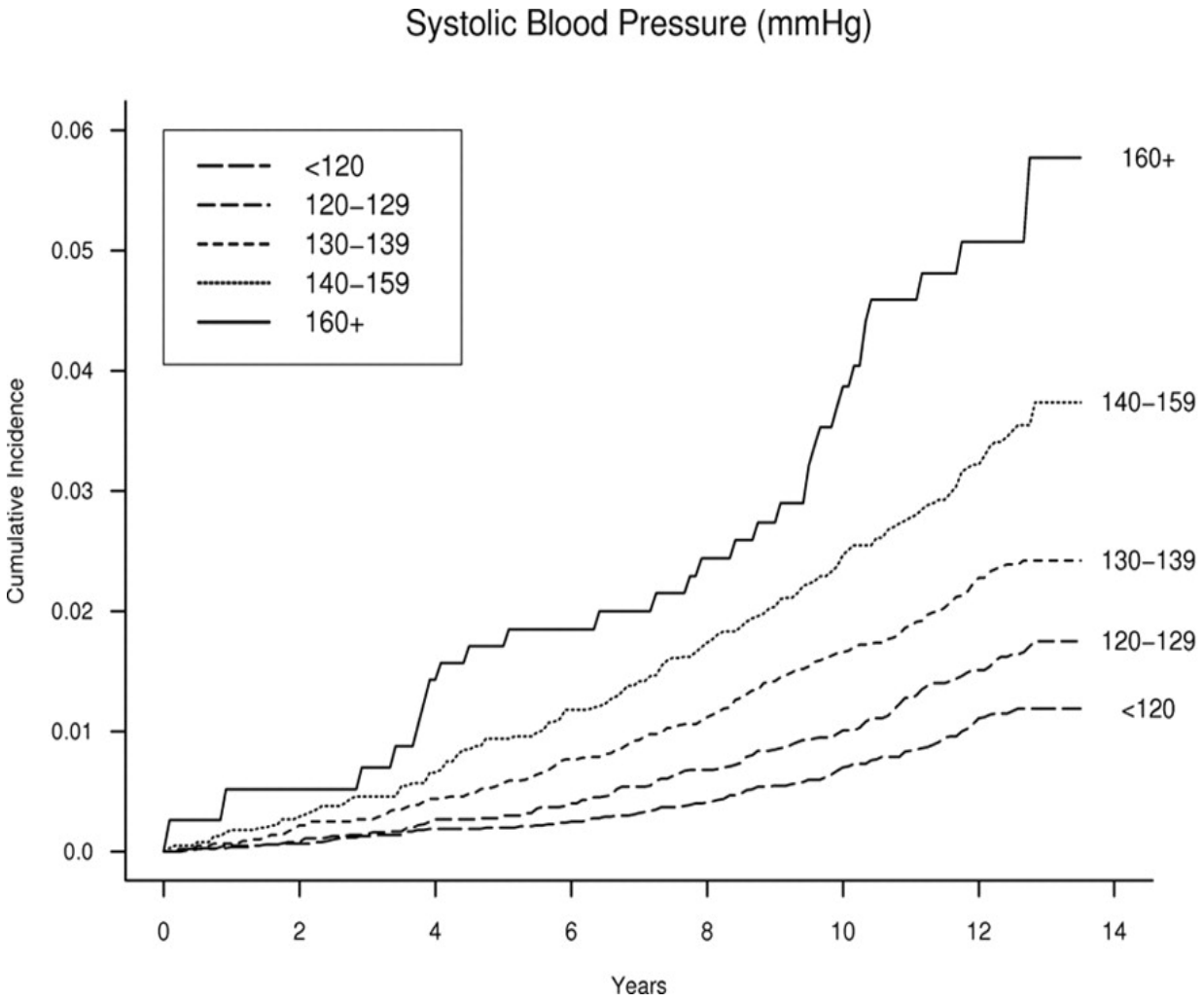


Conen, D. et al. Circulation 2009;119:2146-2152

Le volume atrial seul n'est pas prédicteur de thrombus ou de contraste spontané

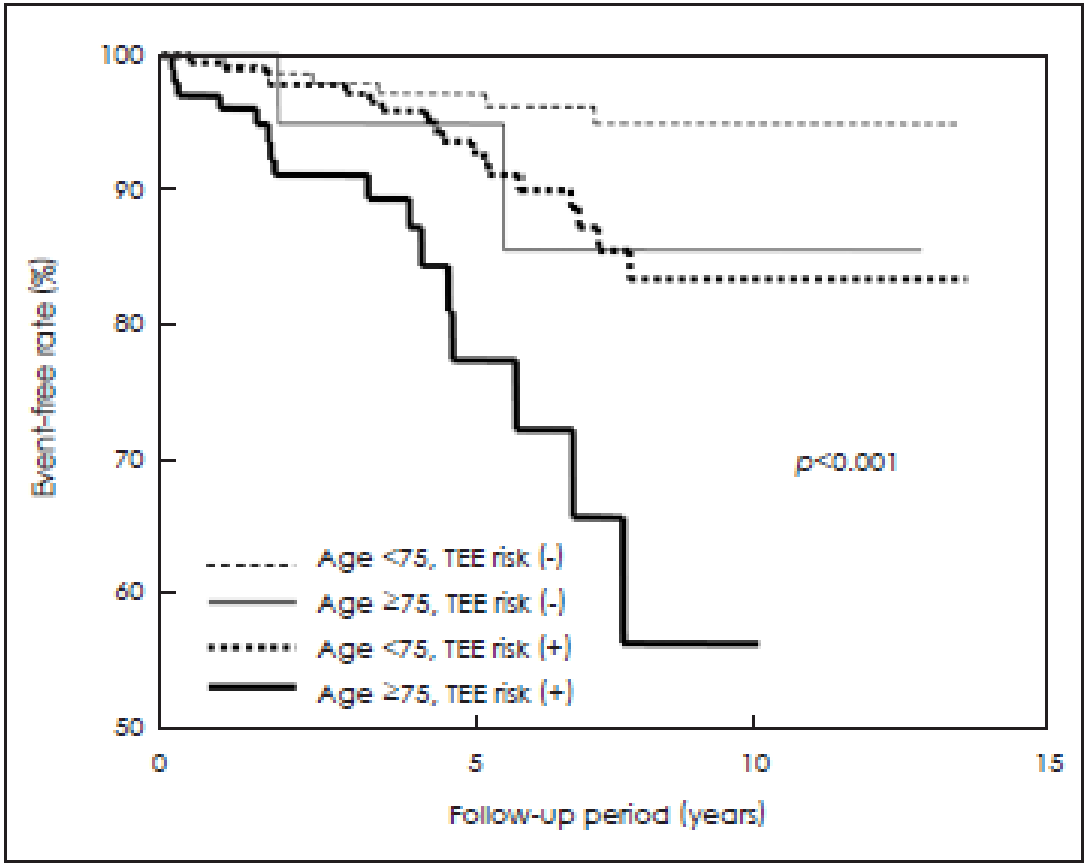
	Univariate analysis			Multivariate analysis				
	OR	95%CI	P	OR	95%CI	P	Wald	Hosr
BMI ≥ 26.9 kg/m^2	0.3	0.1-1.0	0.049	-	-	-	-	
AF episode duration ≥ 1 month	13.3	1.7-106.5	0.003	13.3	1.5-119.6	0.021	5.3	
Indexed LAV ≥ 45.2 mL/m^2	3.4	1.0-11.6	0.044	-	-	-	-	
Av. peak positive strain rate ≤ 1.01 (s^{-1})	6.3	1.9-20.9	0.001	-	-	-	-	
Av. Peak negative strain rate ≥ –1.33 (s^{-1})	21.7	2.7-173.9	<0.001	21.5	2.5-186.1	0.005	7.7	
Av. Peak-to-peak strain rate ≤ 2.02 (s^{-1})	12.1	3.5-42.3	<0.001	-	-	-	-	
SD time-to-peak positive strain ≥ 101.3 ms	3.6	1.1-11.6	0.026	3.8	0.9-15.1	0.062	3.5	
			Constant	0.01	-	0.002	16.2	

Oreillette gauche et Fibrillation atriale Milieu thrombogénique
Rôle du sludge

Clinical and echocardiographic features of patients with $CHADS_2$ score 0 and left atrial or left atrial appendage thrombus or sludge

Age (yrs)	Gender	LVEF (%)	Other Condition	Sludge or Thrombus
44	M	50	Ventricular septal defect repair	Thrombus
47	M	40	Hypertrophic cardiomyopathy	Sludge
53	F	50	Postural orthostatic tachycardia	Thrombus
60	M	55	Mitral valve prolapse*	Thrombus
61	F	55	Breast cancer	Thrombus
72	M	45	Severe atherosclerotic disease	Thrombus

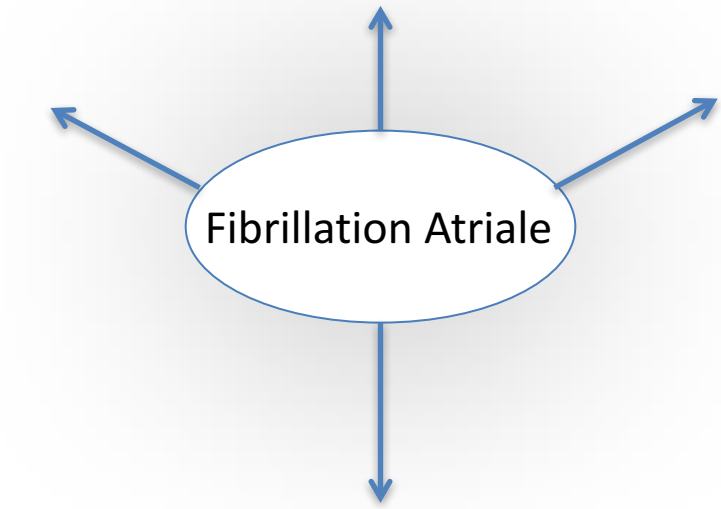
Rôle de l'échocardiographie trans-oesophagienne



Risque embolique et Fibrillation atriale?

Différents Types
d'AVC ischémiques

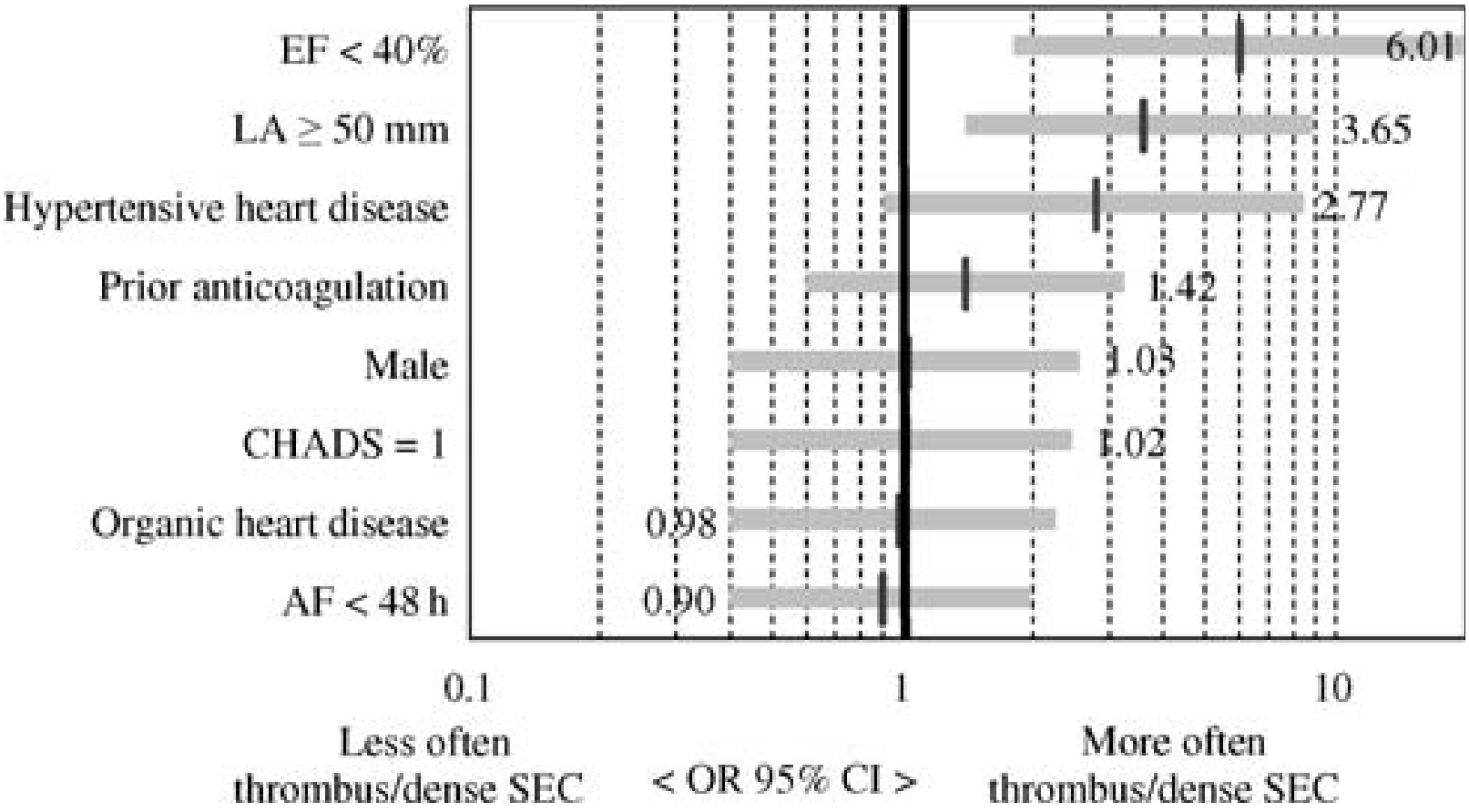
Différents types
électro-cliniques



Différents scores de risque

Un même traitement?

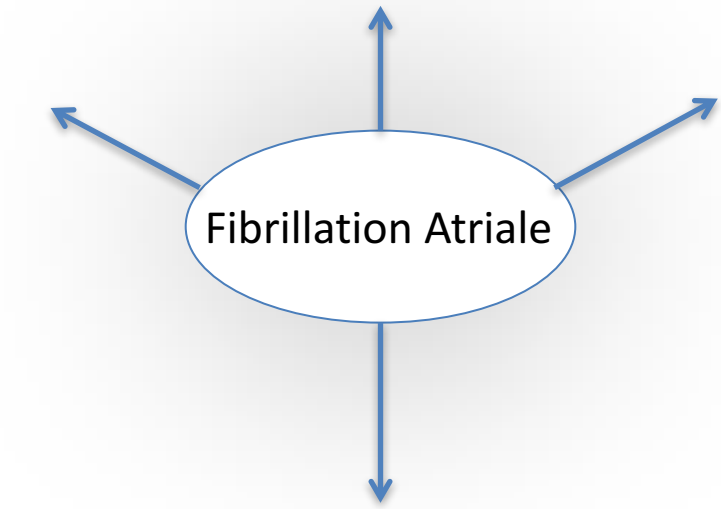
CHADS 2 : 0/1
Contraste spontané : 8%



Risque embolique et Fibrillation atriale?

Différents Types
d'AVC ischémiques

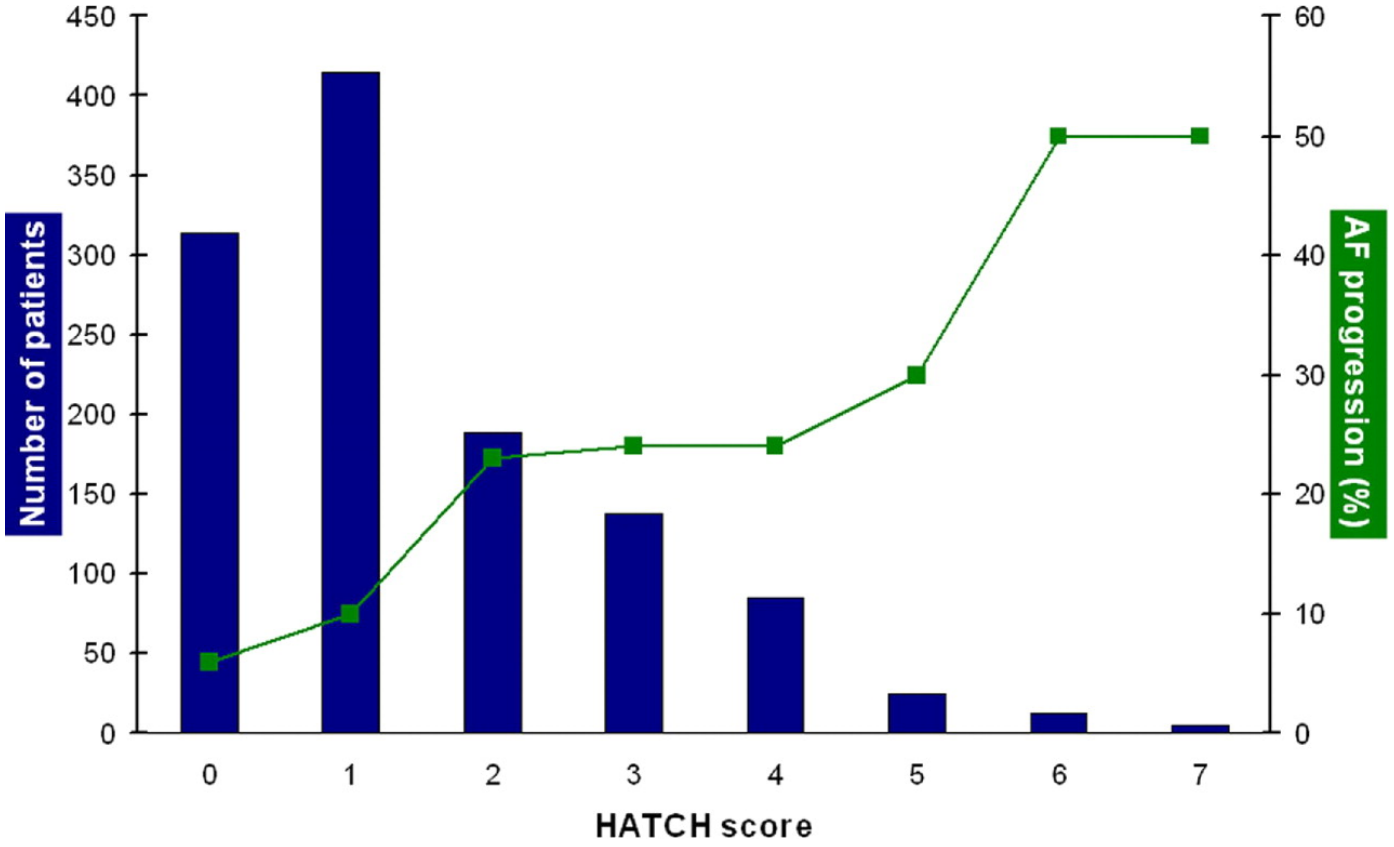
Différents types
électro-cliniques



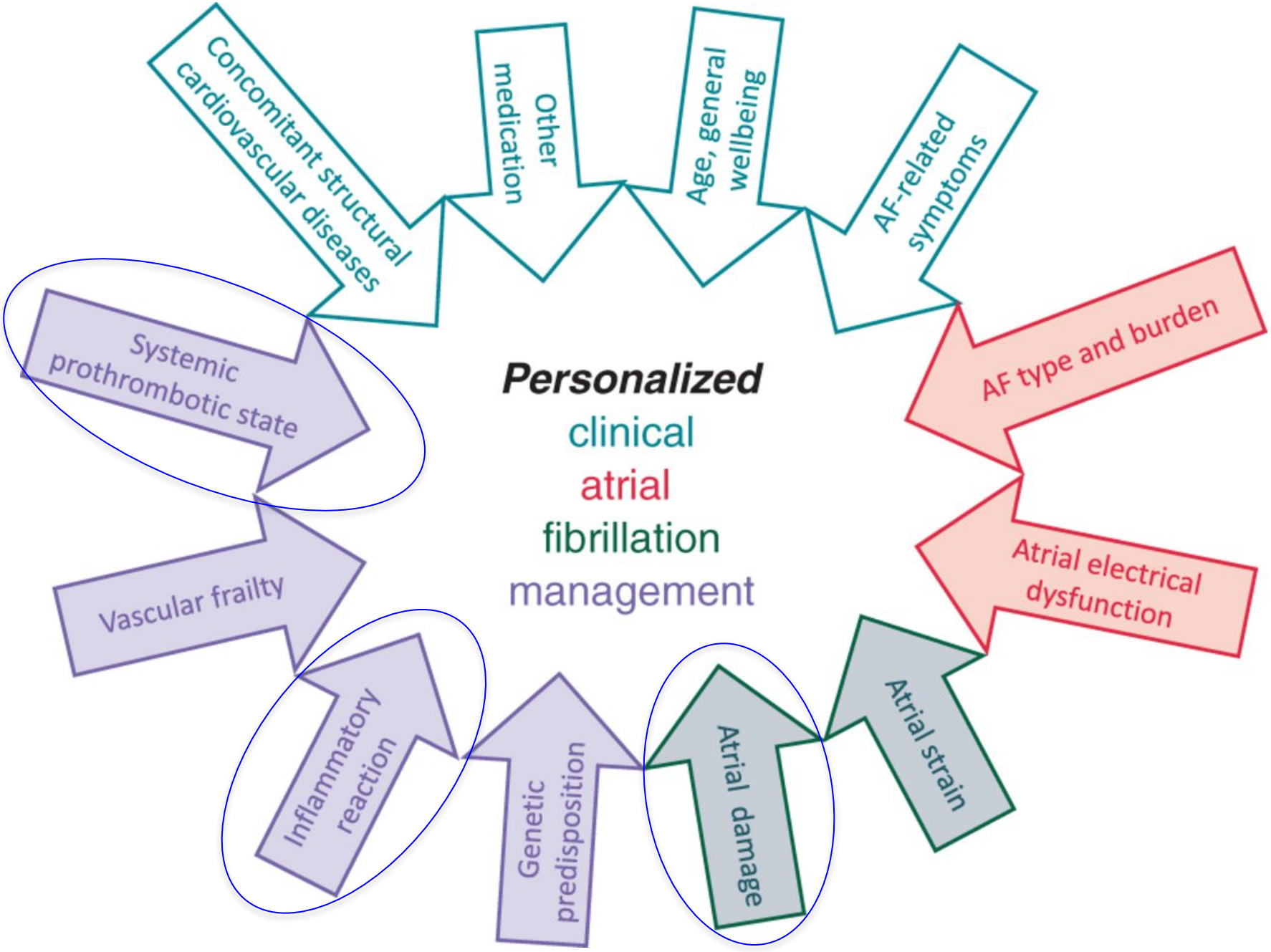
Différents scores de risque

Un même traitement?

HATCH Score et Progression de la fibrillation atriale
5333 patients

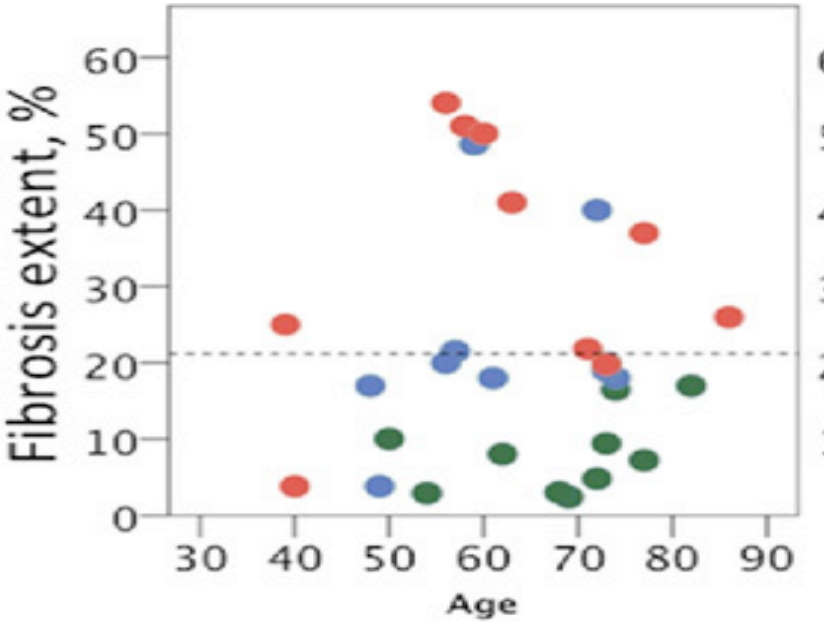


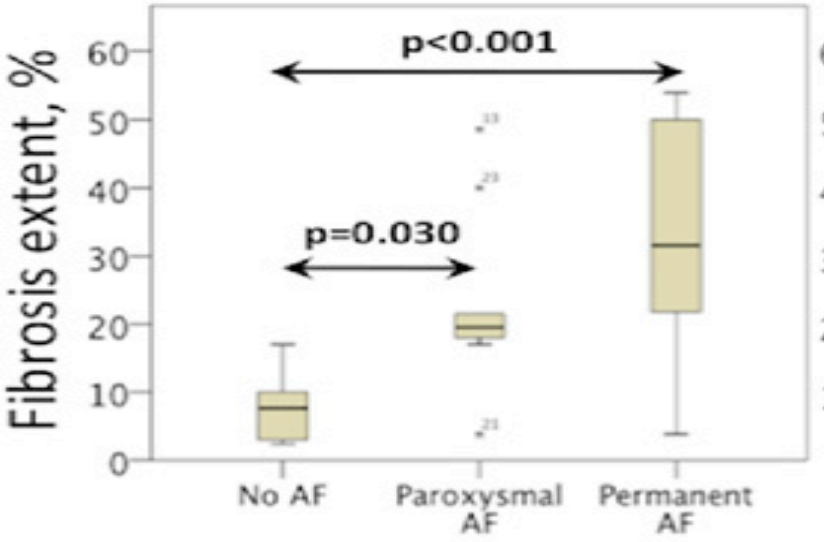
de Vos, C. B. et al. J Am Coll Cardiol 2010;55:725-731



Kirchhof P et al. Europace 2013;15:1540-1556

Mean Values	Cardioembolic stroke	Atherothrombotic stroke	P value
LAVi* ml/m^2	33.4	30	<.00
LAD# mm	36	35	<.05
LVMiß gm/m^2	80.9	76	<.05





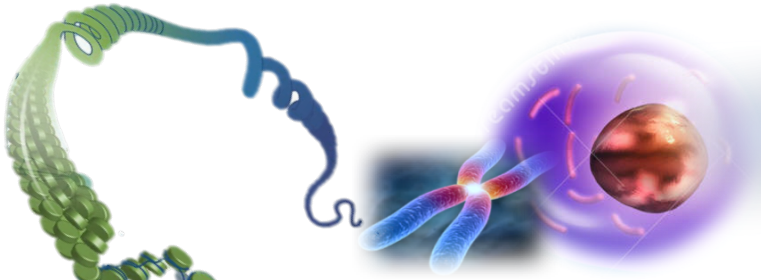
Crista terminalis

Outcome*	Model 1†	Model 2‡
Any ischemic stroke	1.24 (1.07–1.42)	1.21 (1.04–1.39)
Ischemic stroke subtypes		
Cryptogenic or cardioembolic	1.31 (1.10–1.55)	1.28 (1.07–1.53)
Cryptogenic	1.29 (0.99–1.68)	1.25 (0.95–1.65)
Cardioembolic	1.32 (1.07–1.62)	1.30 (1.05–1.62)
Noncardioembolic	1.14 (0.94–1.40)	1.12 (0.92–1.37)
Sensitivity analyses		
Excluding patients with any atrial fibrillation		
Any ischemic stroke		
Cryptogenic or cardioembolic		
Cryptogenic		
Cardioembolic		
Noncardioembolic		

Etudes autopsiques

- ✓ Masawa et al *Virchows Archiv 1993* « Il n'est pas rare de ne pas trouver de thrombus »

- ✓ Dans 81 % des cas œdème et épaississement fibreux de l'endothélium.



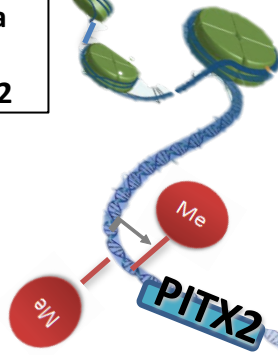
Modifications épigénétiques

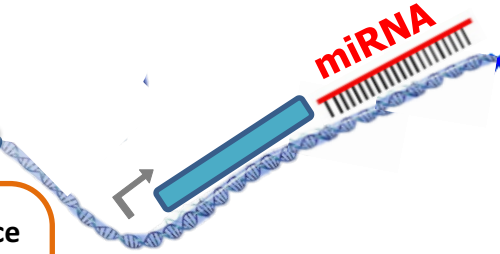
Variations génétiques

Facteurs de risque environnementaux

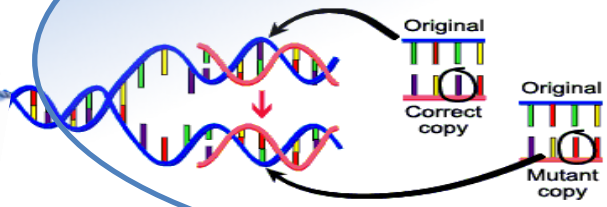
-1623 gènes dérégulés dans l'OG

-Correlation entre la surface OG et l'expression de PITX2





3 Variant ADN



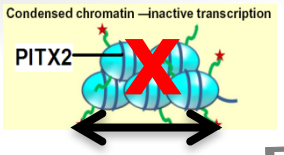
1 La méthylation de la région promotrice de Pitx2 peut induire une down régulation de PITX2

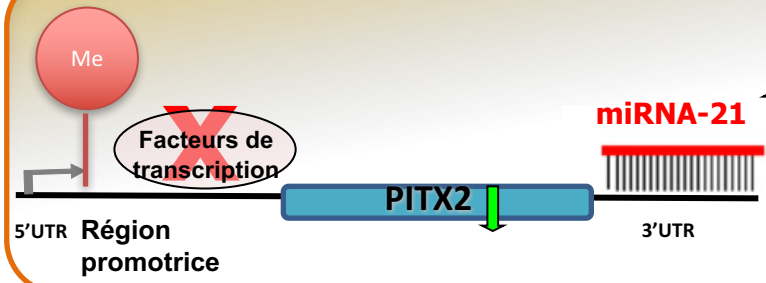
-Etudes supplémentaires pour confirmer l'effet anti-arythmique de la Decitabine chez le rat SHR agé

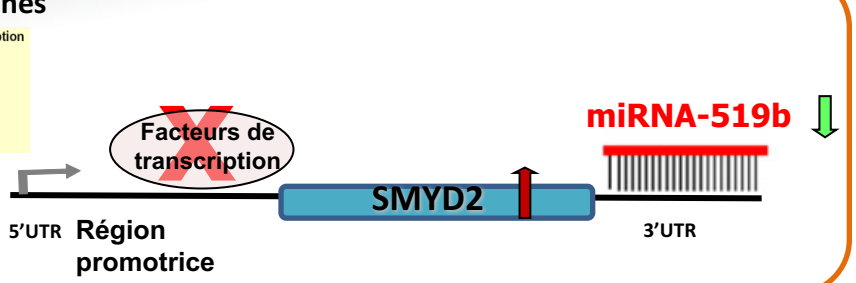
2 -47 miRNAs déregulés dans l'OG

-MiR-21 et miR-519b ciblent PITX2 et SMYD2, respectivement

Méthylation d'histones

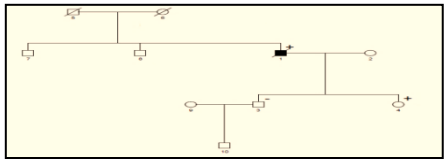






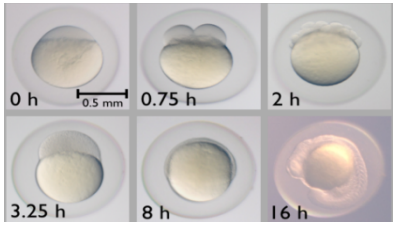
Perspectives

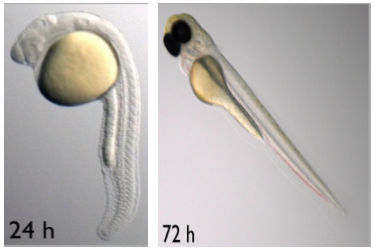
- **Dépistage**



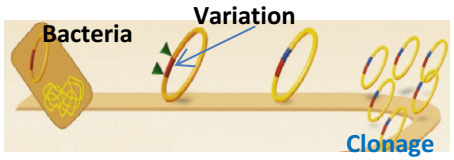
*** Exploration fonctionnelle des variants**

• Modêle animal : Poisson zèbre





•Culture Cellulaire : cardiomyocytes



La ou les fibrillations atriales?