

“Dronedarona, paciente a paciente”

Fibrilación Auricular

¿Un sola enfermedad?

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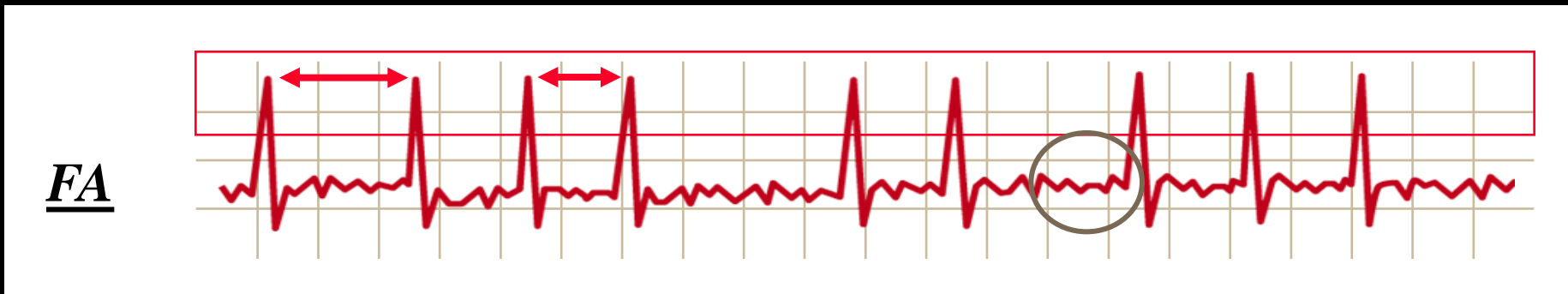
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1. ¿Qué es la FA?
2. Mecanismos y tipos
3. Factores predisponentes
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5. ¿Diferentes “FAs” estudios principales?

**¿Qué es la
FA?**

Definición

- Ondas P reemplazadas por oscilaciones rápidas que varían en amplitud, forma y LC
- Respuesta ventricular irregular



ACC/AHA/ESC 2006 guidelines J Am Coll Cardiol 2006;48:854-906

Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)[†]

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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3.1 Definition

AF is defined as a cardiac arrhythmia with the following characteristics:

- (1) The surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as *arrhythmia absoluta*), i.e. RR intervals that do not follow a repetitive pattern.
- (2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
- (3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and < 200 ms (> 300 bpm).

Duración > 30 seg

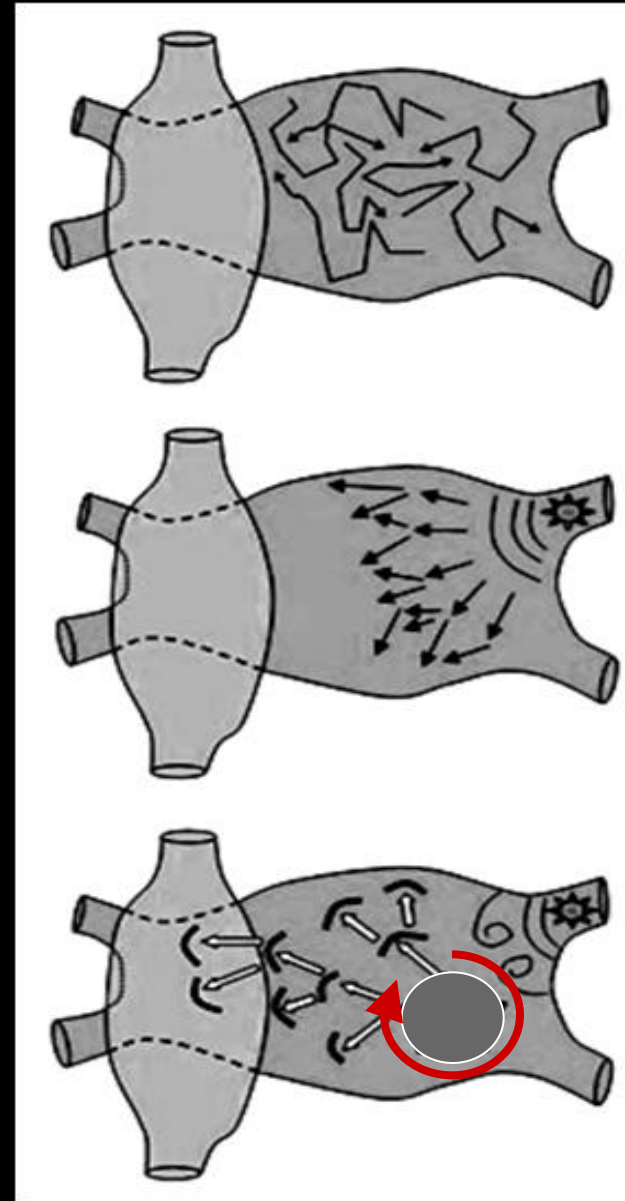
¿Qué es la FA?

- **Definición dice poco**
- **Como diagnosticar FA pero no su mecanismo ni sus tipos**

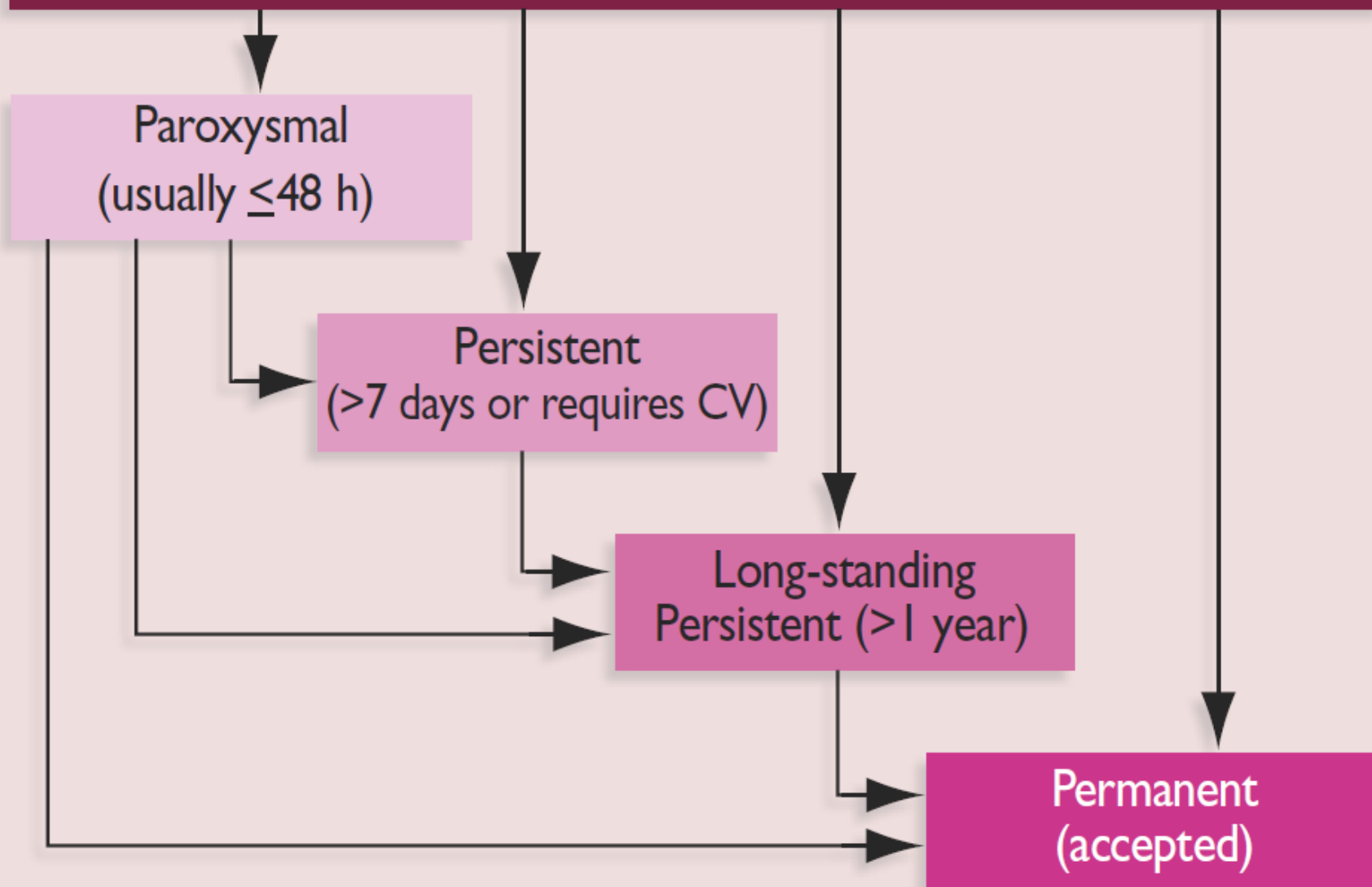
¿Mecanismos y tipos de FA?

¿Mecanismo FA?

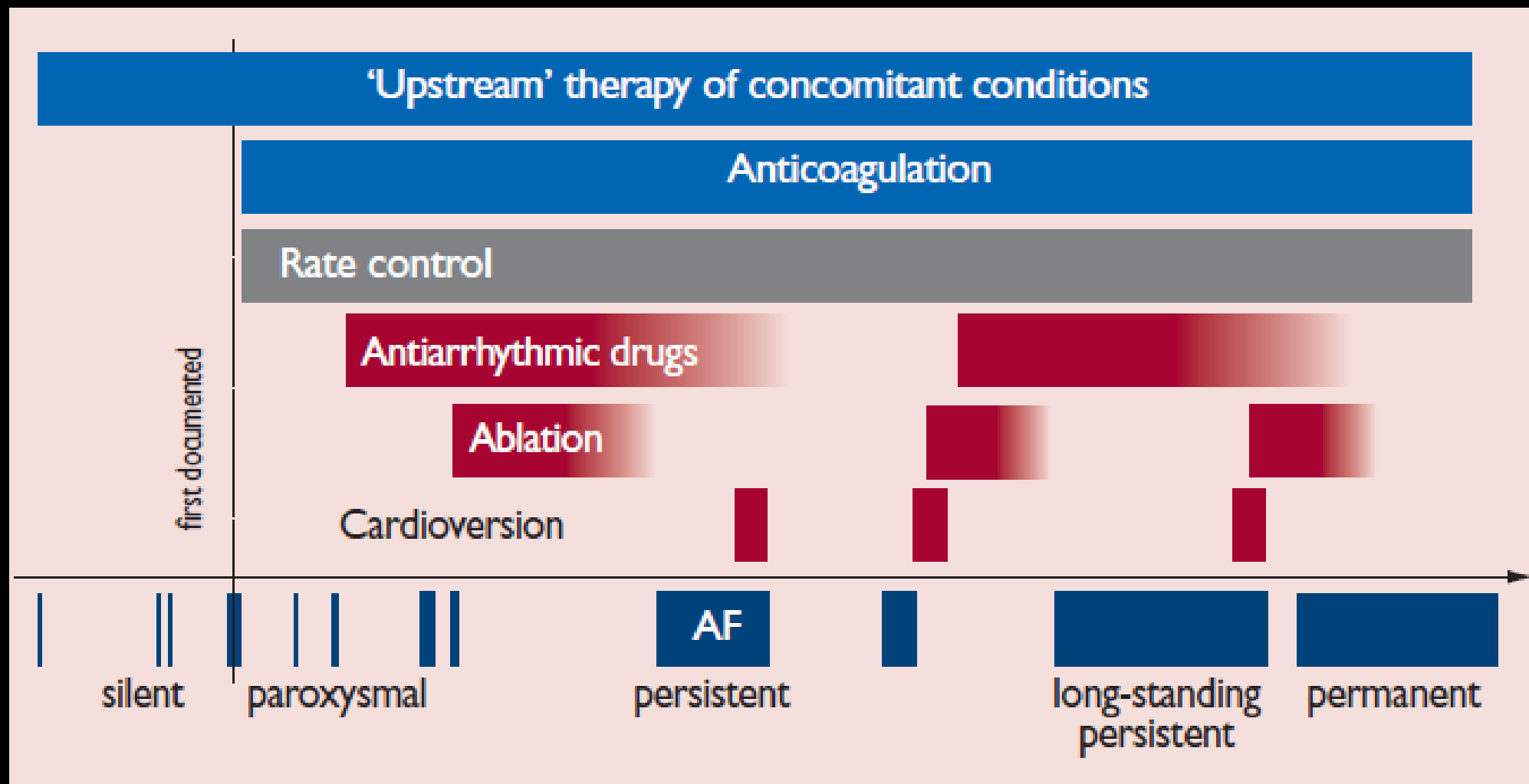
- Rentrada aleatoria (funcional)
- Focal (conduction fibrilatoria)
- Reentrada fija (anatomica)



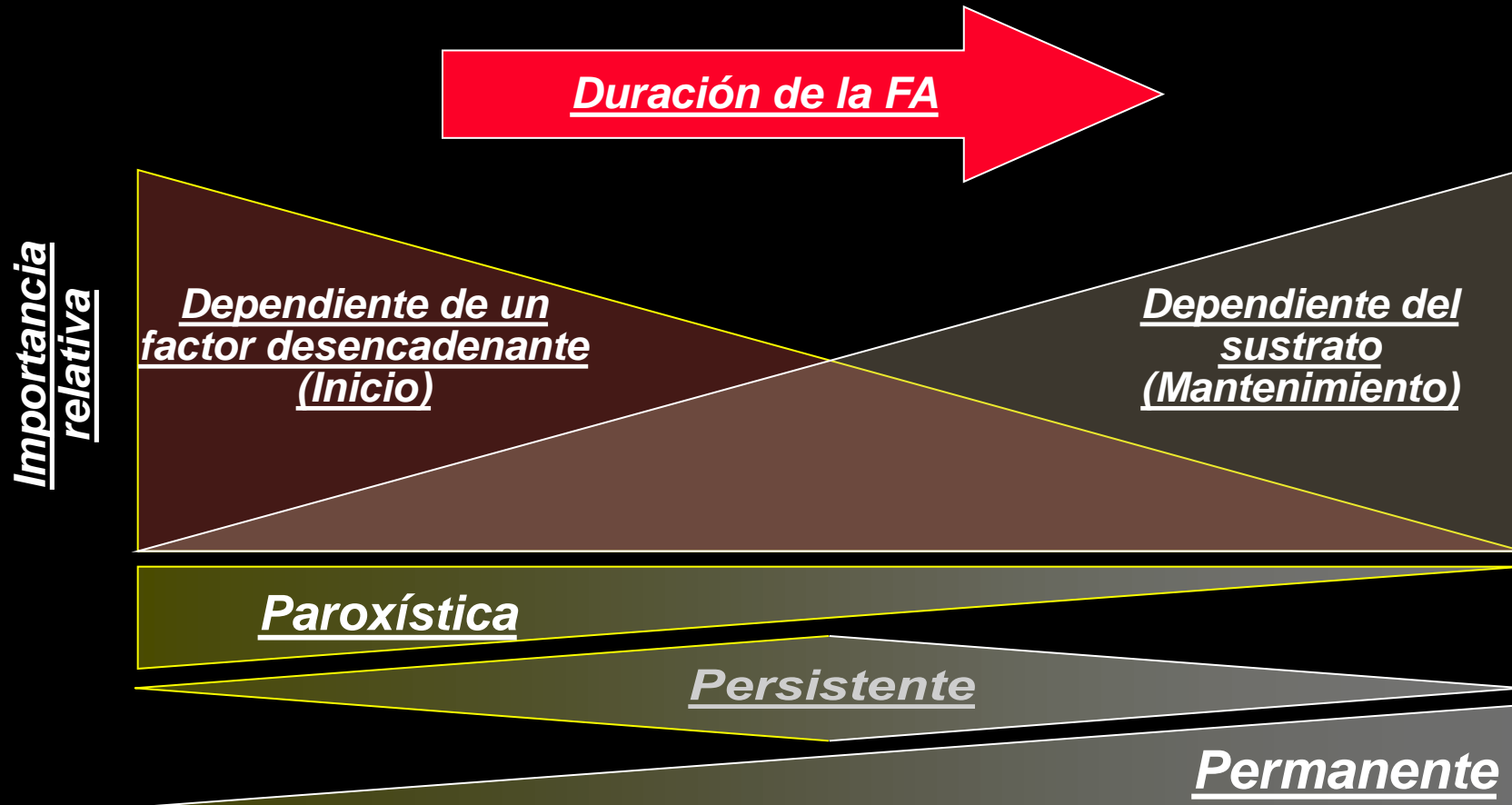
First diagnosed episode of atrial fibrillation



Solo 2-3% permancerán con FA Px



FA: enfermedad progresiva



Factores Clínicos Predisponentes

Antecedentes Familiares

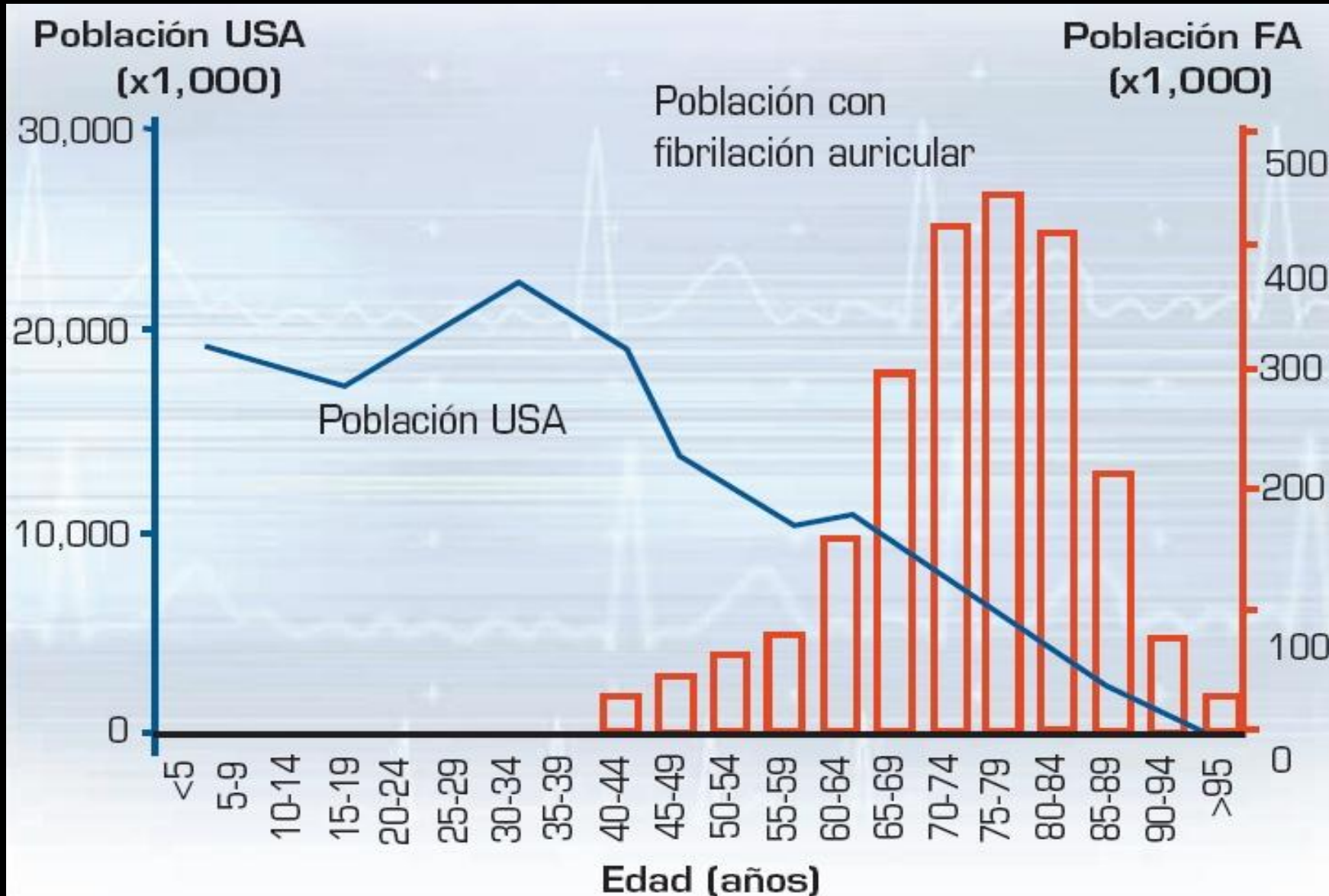
- **Formas hereditarias**
 - ◆ **Locus: 10q22-24,40 y 6q14-16.41**
 - ◆ **Canales: KCNQ1, KCNE2, KCNJ2, KCNA5 y SCN5A**
- **Riesgo FA si progenitor con FA**
 - ◆ **1,8 RR**
 - ◆ **3,2 RR** (**<75 a y no cardiopatía**)
 - ◆ **5 RR** (**<60 a**)

Brugada et al. N Engl J Med 1997

Fox et al. JAMA 2004

Edad

70% pts con FA: 65-85 a



Sexo

<65 a: ♂ > ♀

65-75 a: ♂ = ♀

>75 a: ♂ < ♀ (60% ♀)

Furberg et al. the Cardiovascular Health Study. Am J Cardiol 1994

HTA

- **FR mas frecuente: 70%**
- **Riesgo relativo de 1,5 (ajustado para otros FR)**
- **Incidencia acumulada de FA en 20 años:**
 - ◆ **5,6% si presión de pulso <40 mmHg**
 - ◆ **23,3% si presión de pulso >60 mmHg**
- **Incremento riesgo relativo:**
1,26 x 20 mmHg incremento p. pulso

Otros intrínsecos

- **Cardiopatía estructural**

- ◆ ICC RR: 4,5-5,9
- ◆ Enf Valvular RR: 1,8-3,4

- **DBM:**

- ◆ RR: 1,8
- ◆ Controvertido

- **HTR**

- ◆ 30% ptes con FA

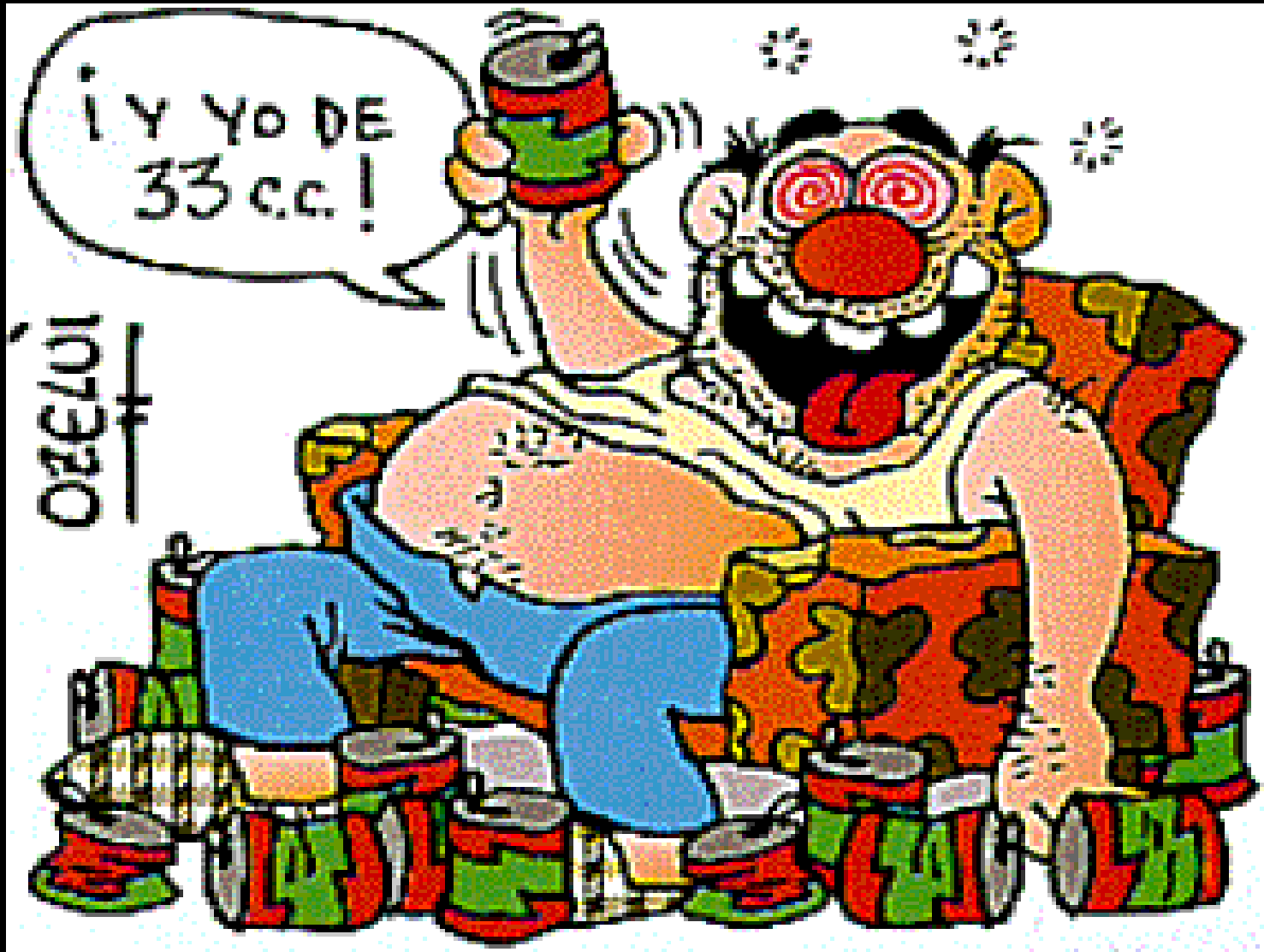
- **S. Apnea Sueño**

- ◆ Asociación (primaria o por FR?)
- ◆ Menos recurrencias FA post CVE con CPAP

Otros extrínsecos

- **Personalidad y estrés**
 - ◆ Asociación debil estrés en ♂ (Framningham)
- **Alcohol**
 - ◆ Consumo >36 g/d -> RR 1,5
 - ◆ 5% FA en ♂: alcohol crónico
 - ◆ Causas: tóxicas y autonómicas
- **Ejercicio físico**
 - ◆ De resistencia elevado -> RR 2-10
 - ◆ Causas: ↑AI, autonómicas y bradicardia

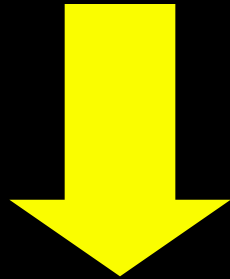
Valentino Rossi Campeón del mundo de motociclismo de 500 cc



Otros Factores Predisponentes

Mecanismos FA: Hechos

- ◆ Inducción mediante estimulación
- ◆ Terminación mediante cardioversión eléctrica

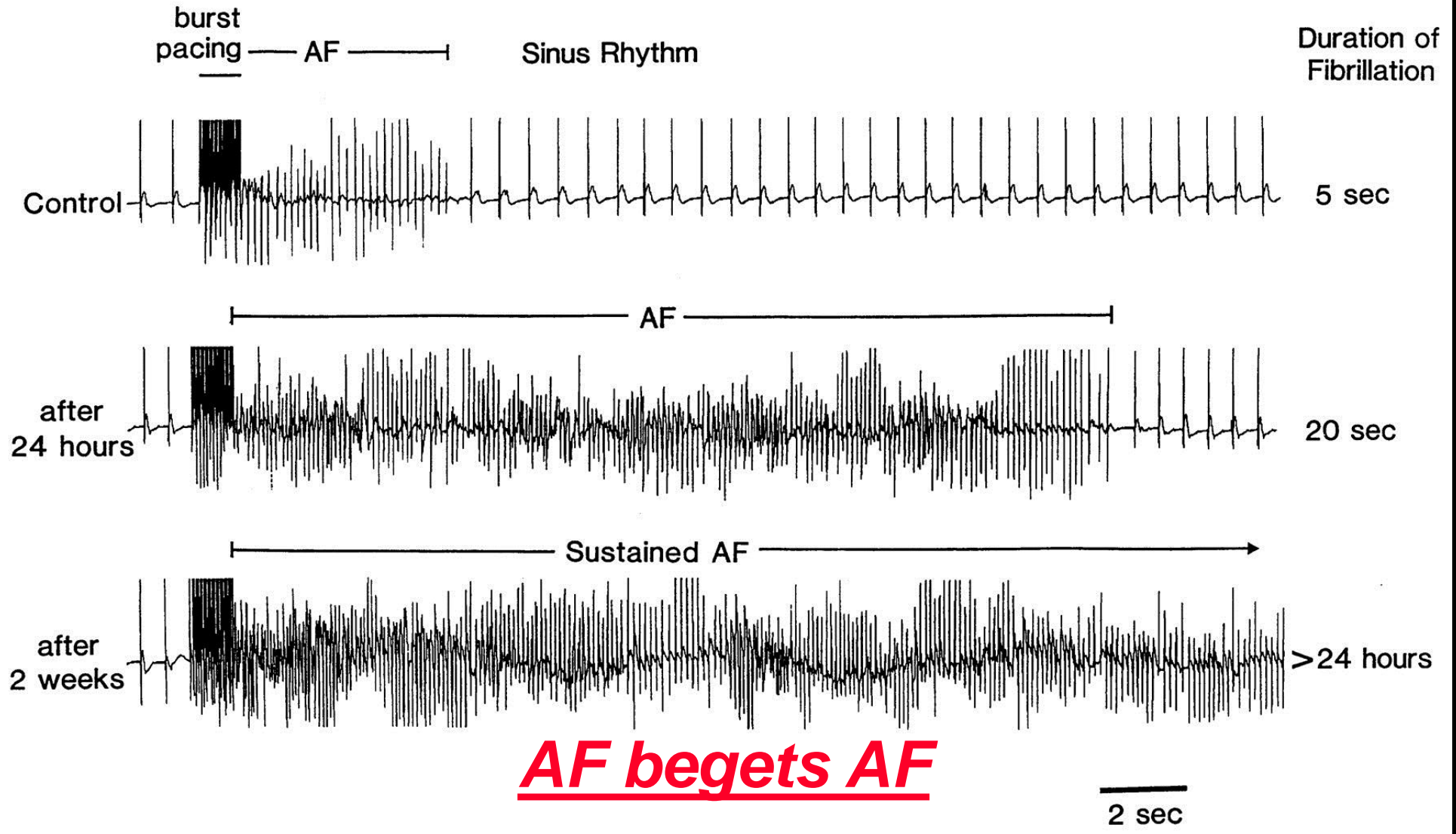


- ◆ REENTRADA: sostenimiento
 - ☞ Funcional → se requiere una masa auricular mínima
 - ☞ Anatomical → asociada con fibrosis

Perpetuación

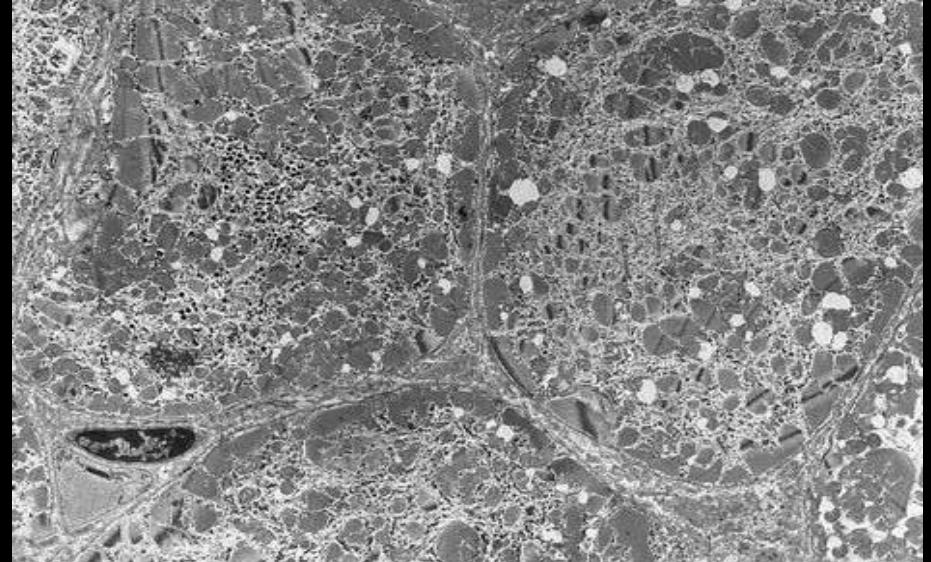
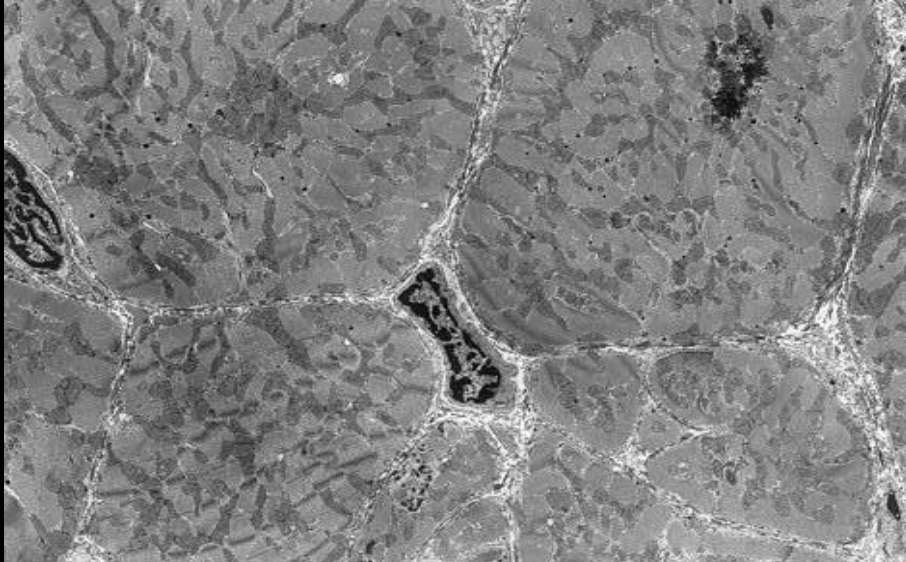
- **Mecanismos: sostenimiento FA**
- **Perpetuación de FA durante años no justificado**
- **Factores adicionales**
 - ◆ **Re-iniciadores:** Ectopia VP
 - ◆ **Estabilización Reentrada:** Remodelado

Remodelado



Wijffels MC et al. Circulation. 1995;92(7):1954-68.

Remodelado Estructural



Morillo CA et al. Circulation. 1995;91(5):1588-95.

Ausma J et al. Circulation. 1997;96(9):3157-63.

Aimé-Sempé C et al. J Am Coll Cardiol. 1999;34(5):1577-86.

Polontchouk L et al. 1: J Am Coll Cardiol. 2001;38(3):883-91.

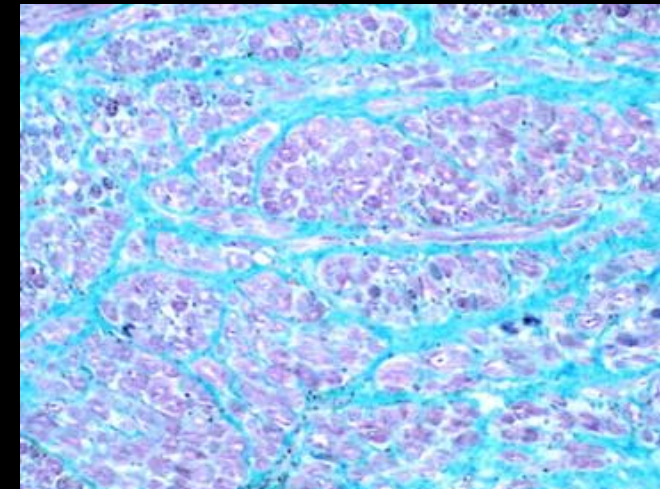
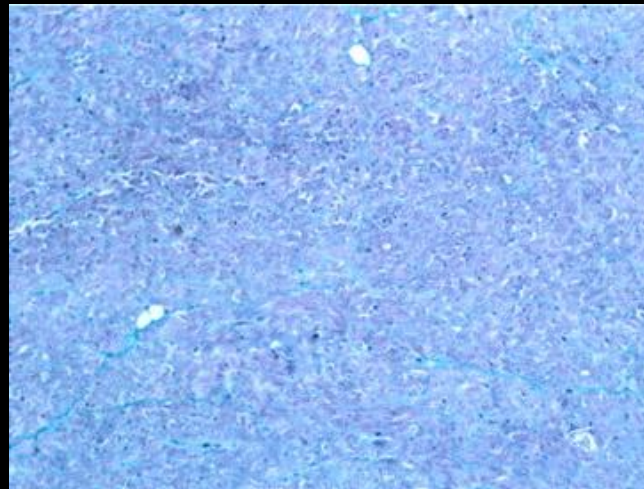
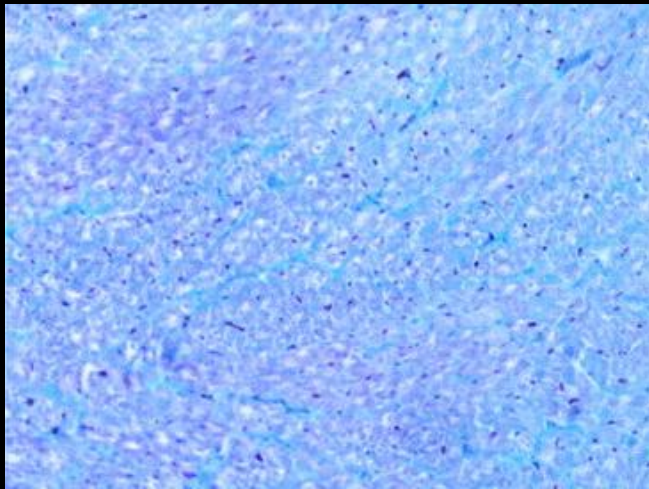
Remodelado Anatómico

Control

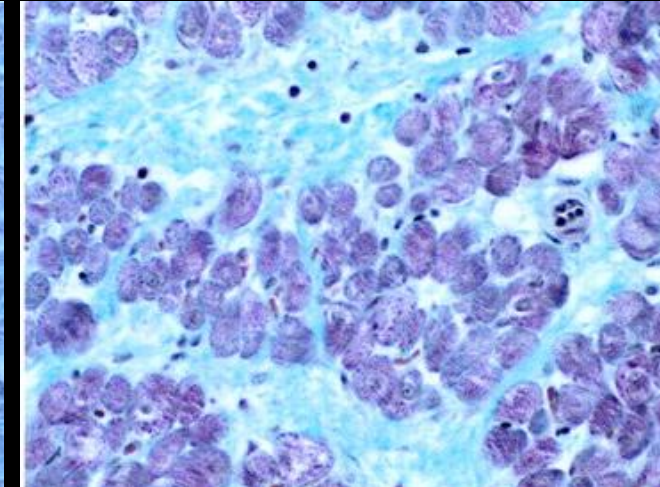
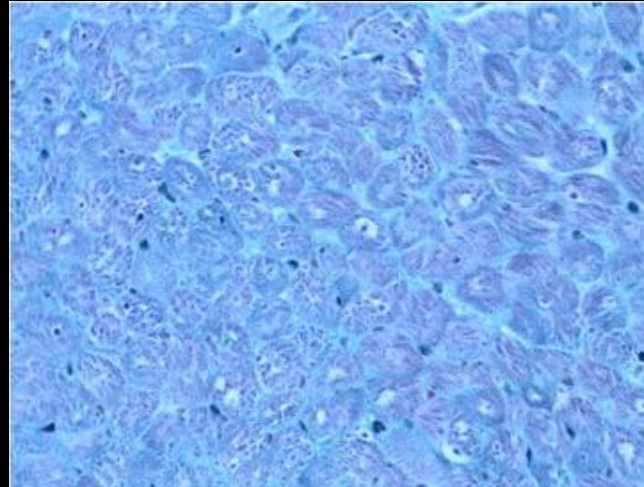
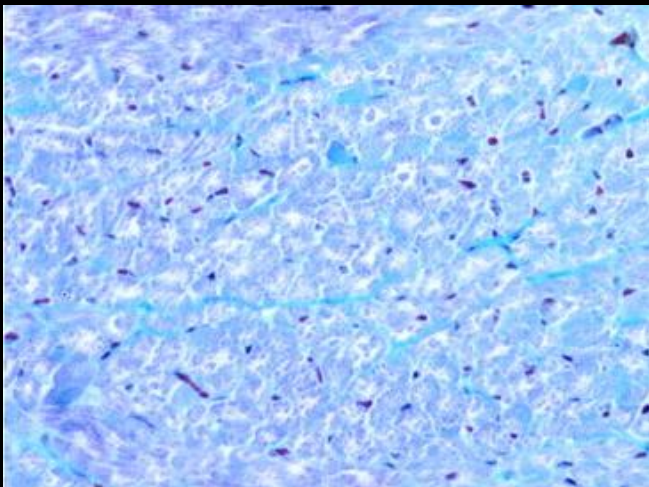
Atrial Pacing

ICC

x500



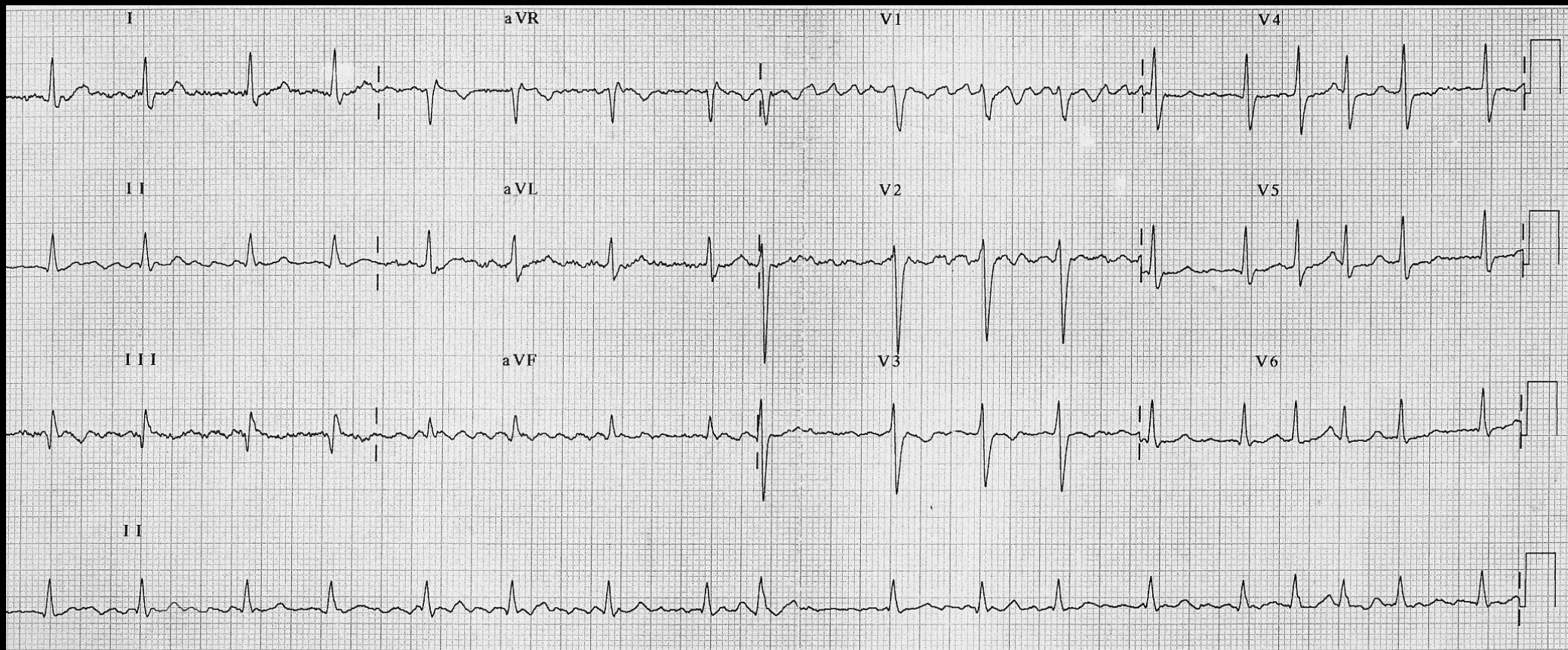
x1250



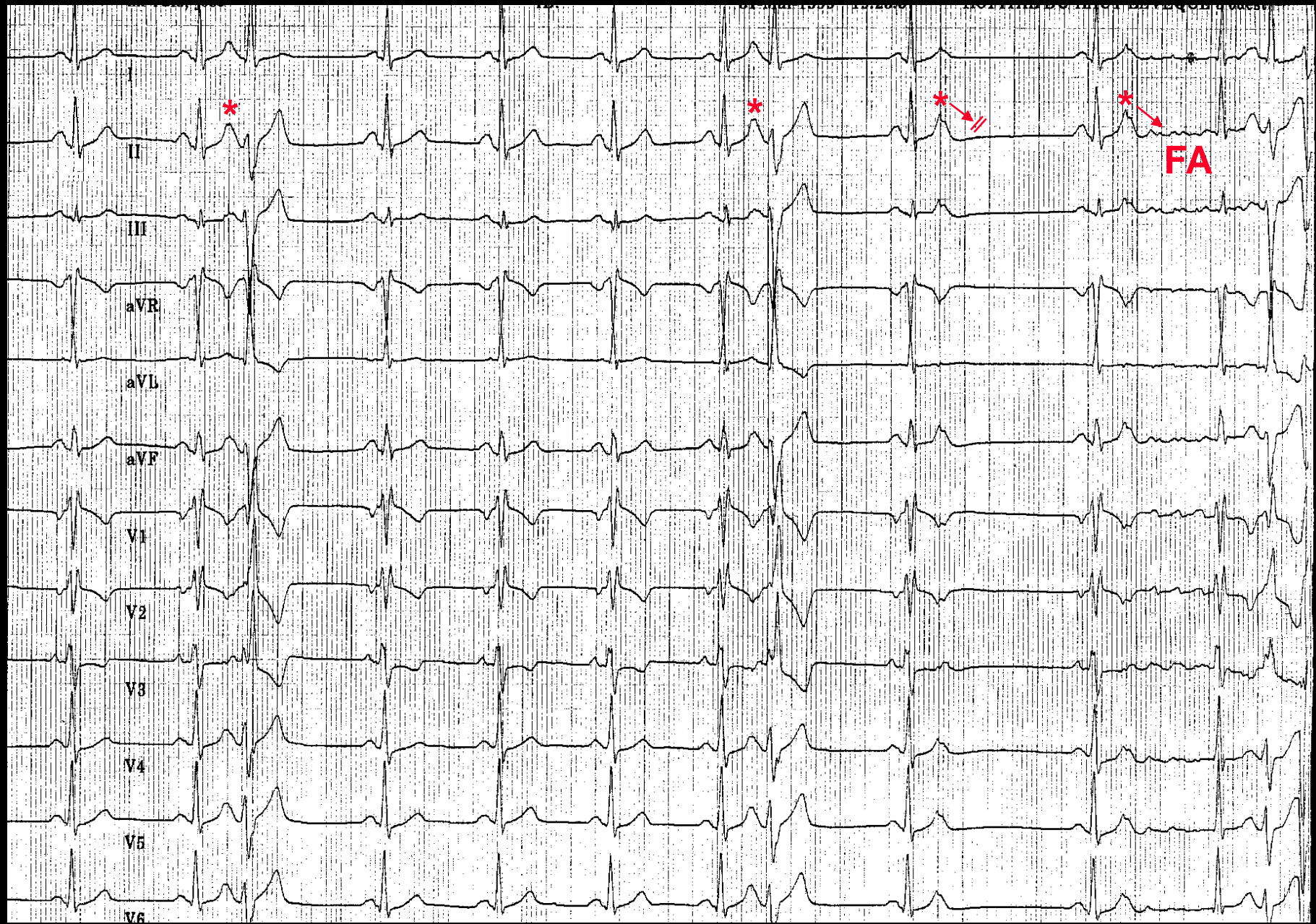
Li D et al. Circulation. 1999;100(1):87-95.

Formas FA

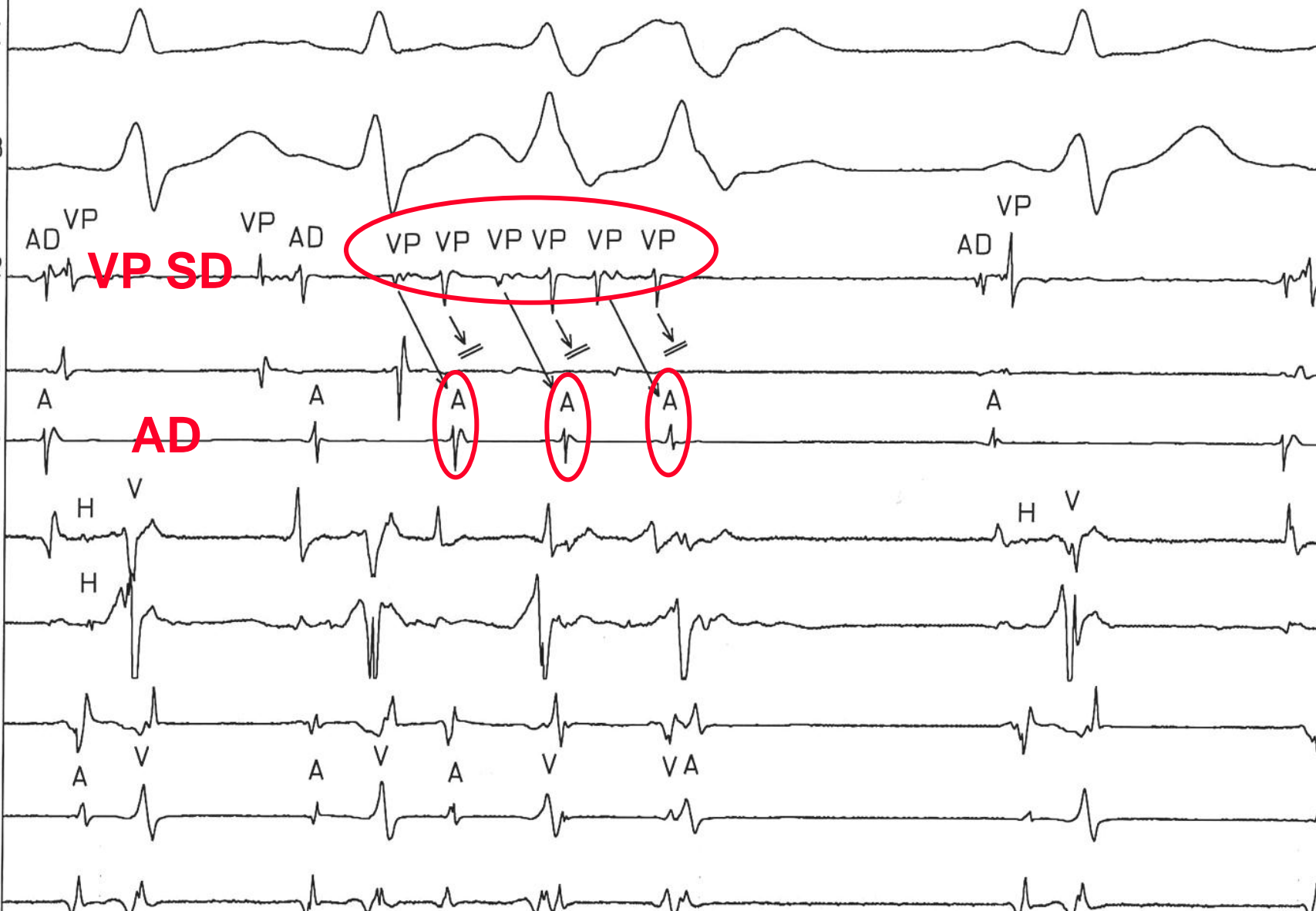
- FA Px y Ps → Iniciadores → VPs
- FA Pm → Mantenedores → Fibrosis atrial

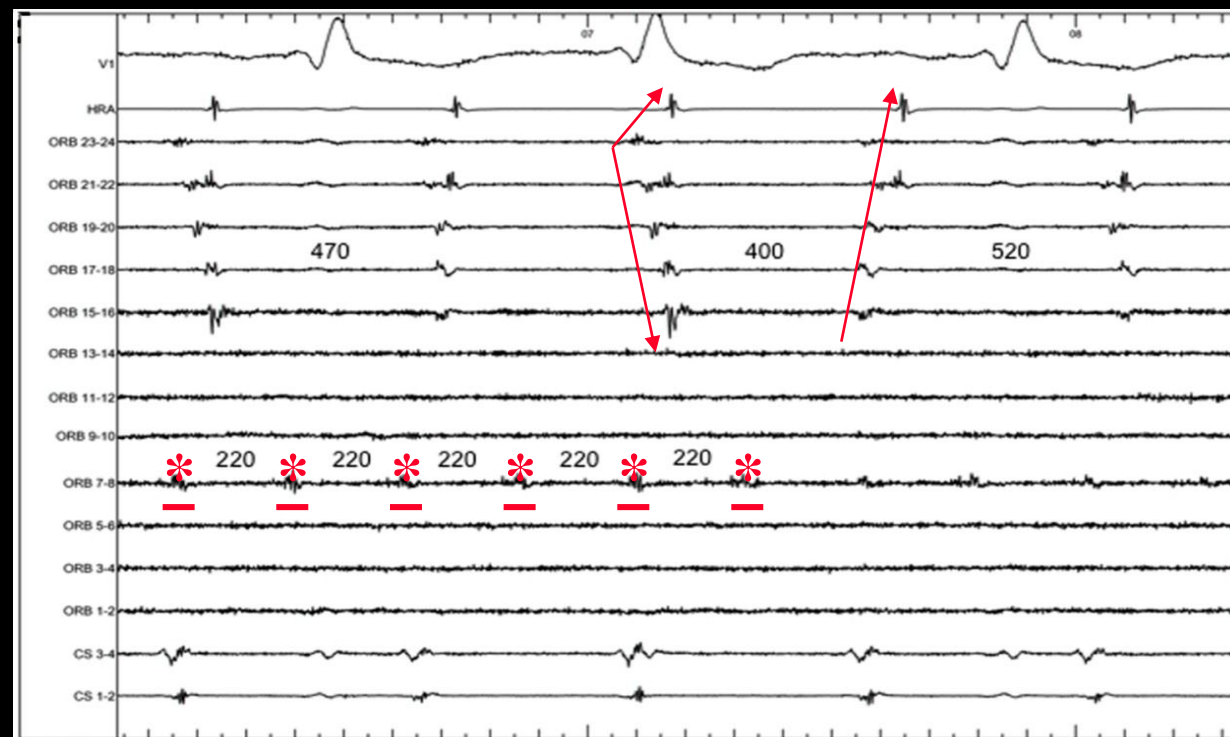
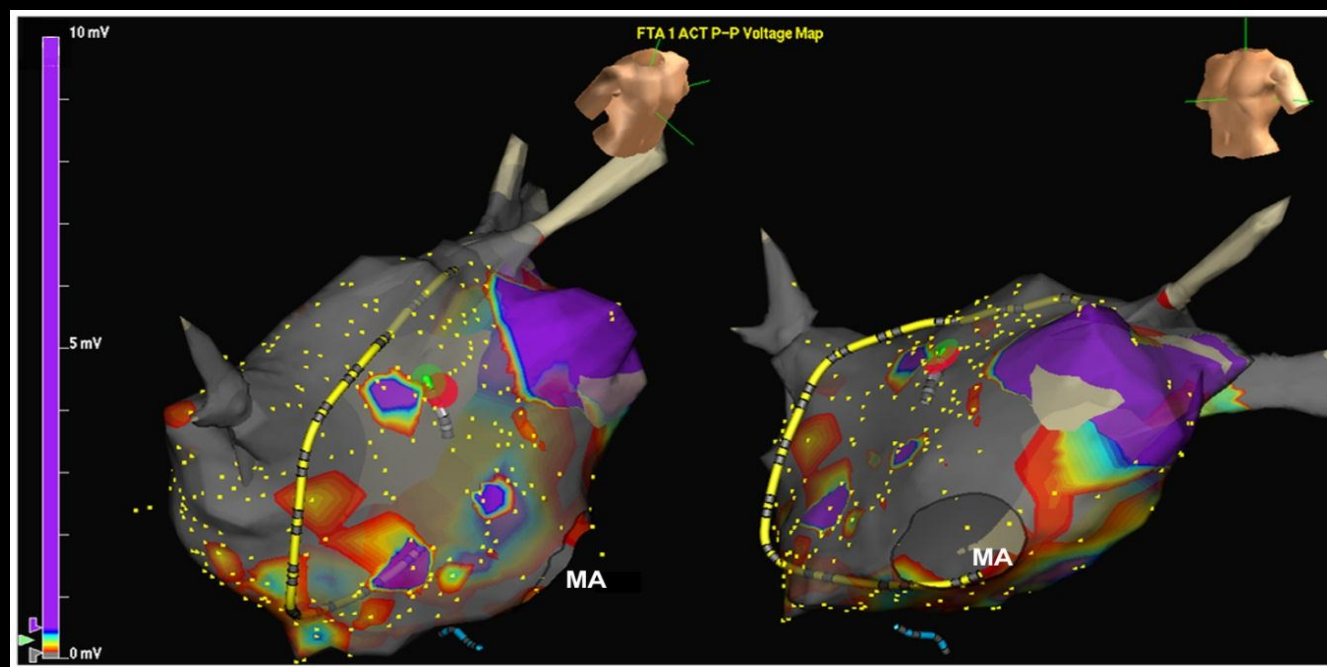




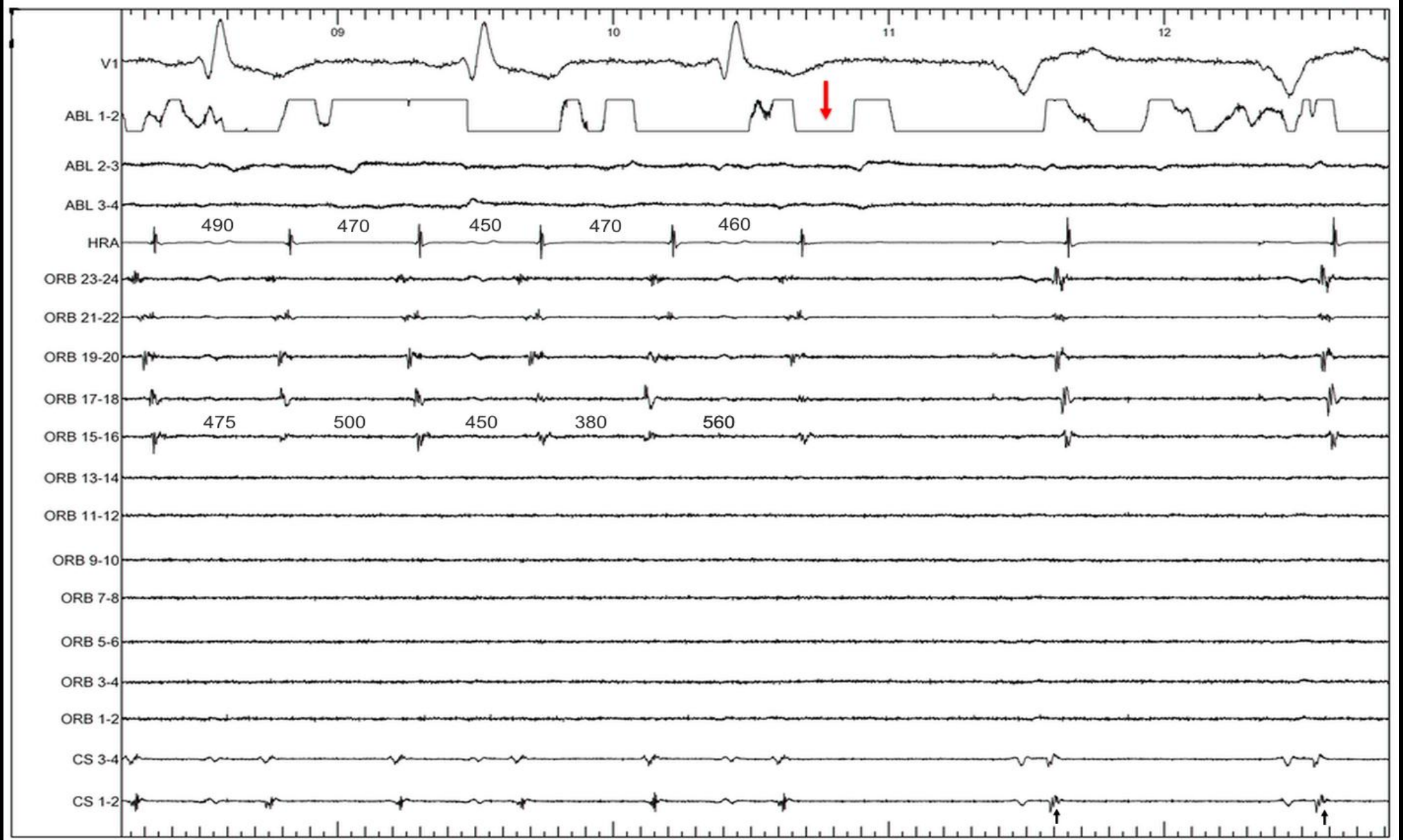


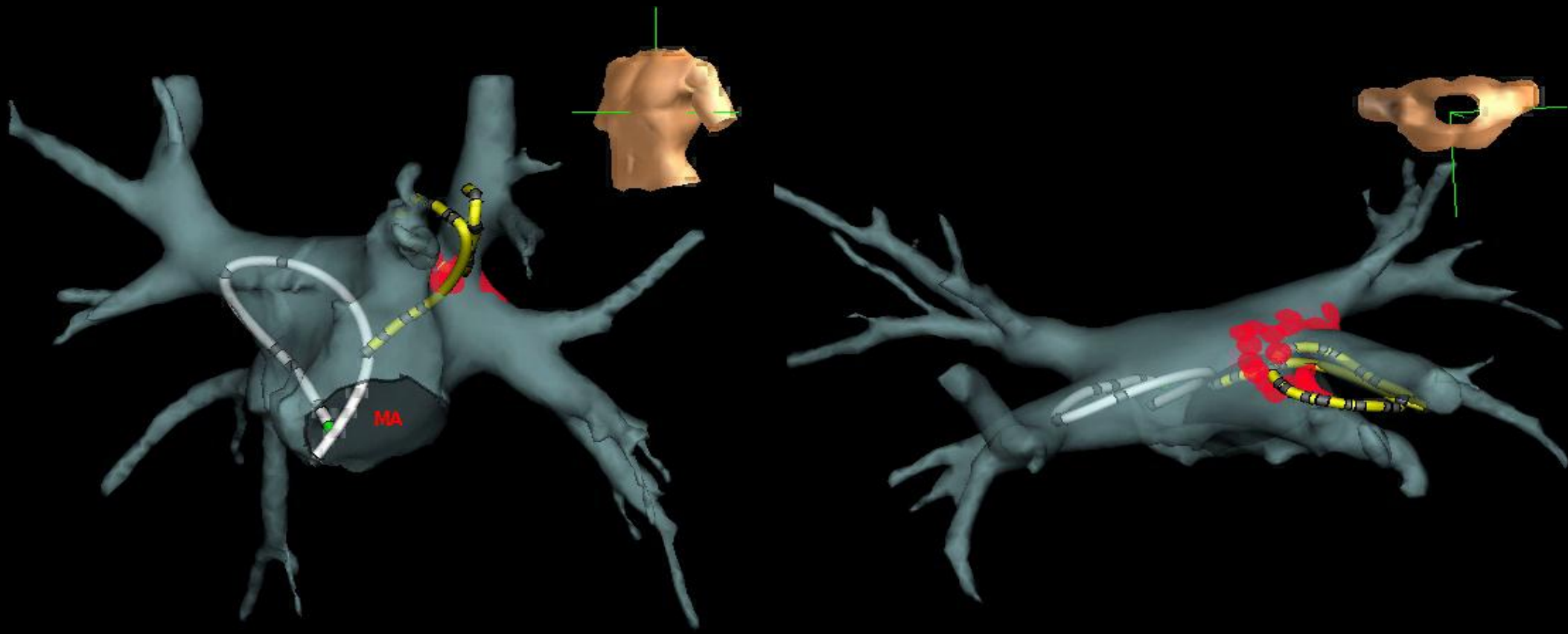
1000 2000





RF



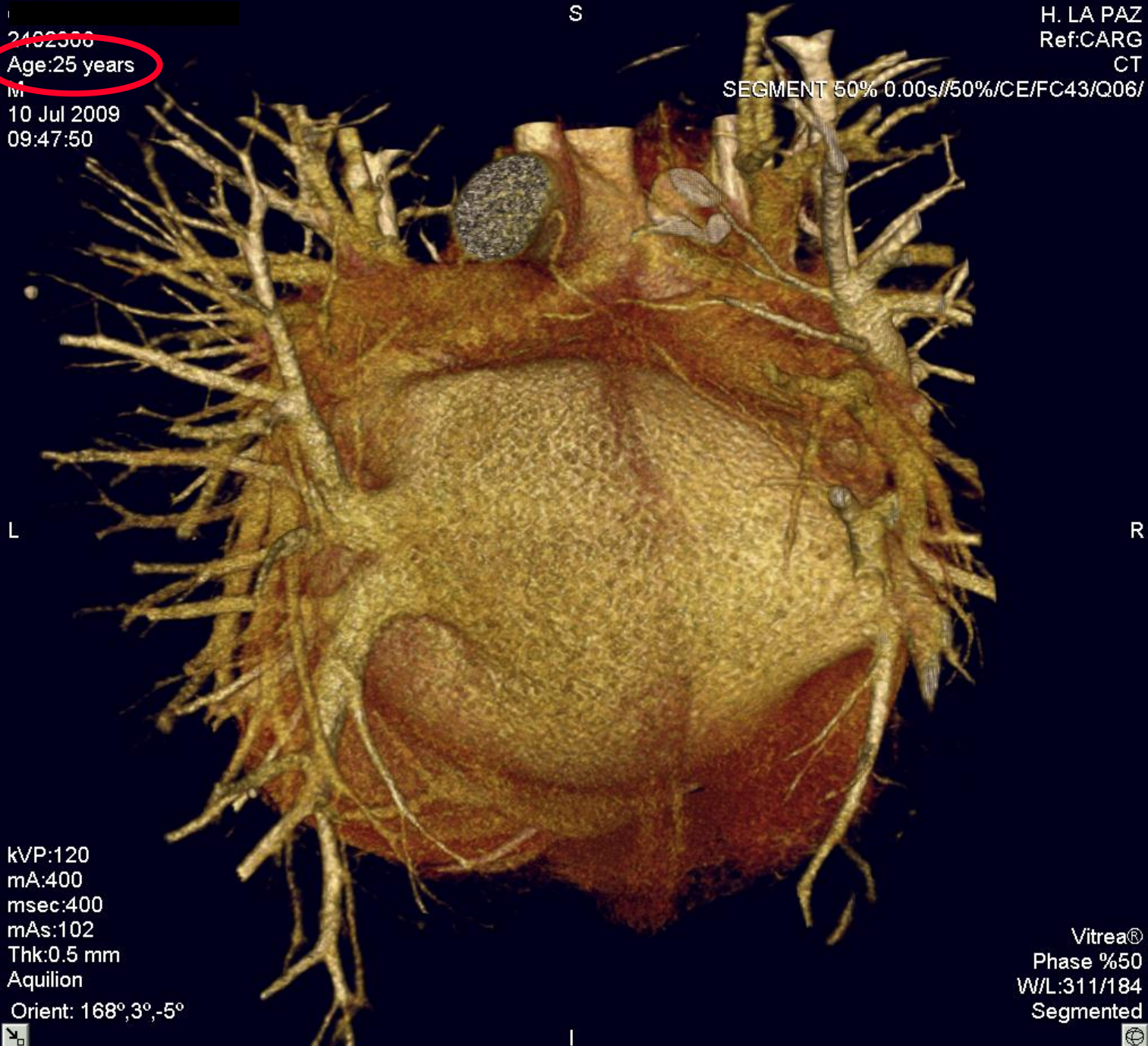


Merino et al. Heart Rhythm 2008

2482308
Age:25 years
M
10 Jul 2009
09:47:50

H. LA PAZ
Ref:CARG
CT

SEGMENT 50% 0.00s//50%/CE/FC43/Q06/



kVP:120
mA:400
msec:400
mAs:102
Thk:0.5 mm
Aquilion
Orient: 168°,3°,-5°

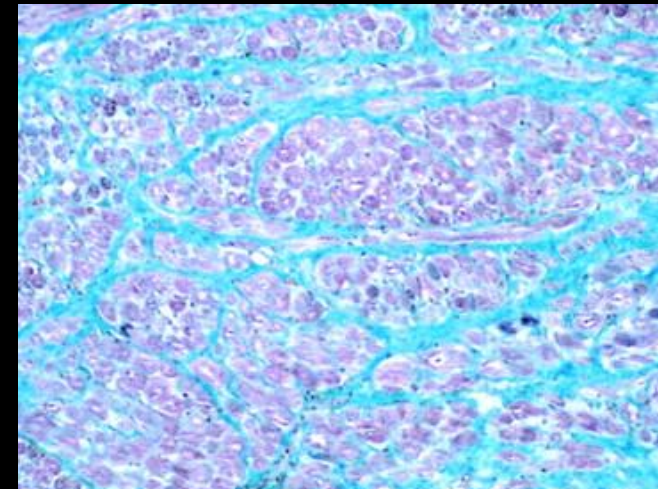
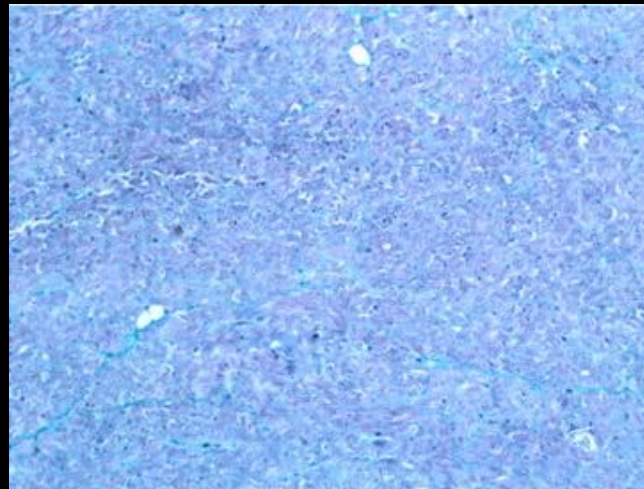
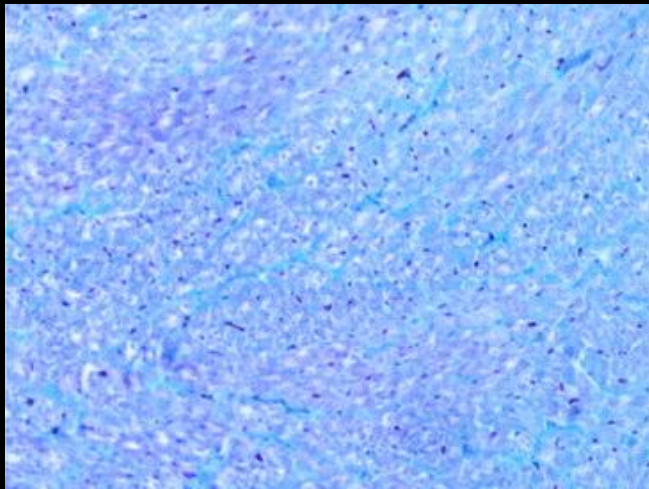
Vitrea®
Phase %50
W/L:311/184
Segmented

Histology

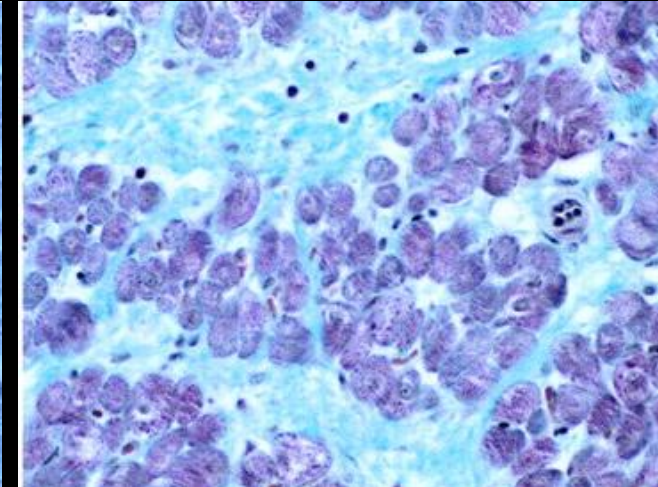
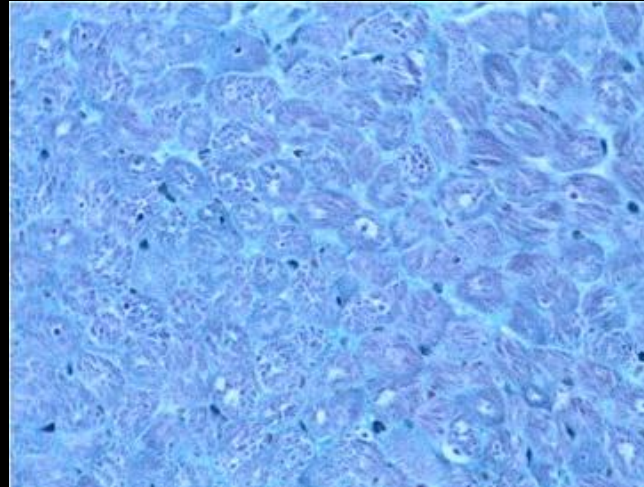
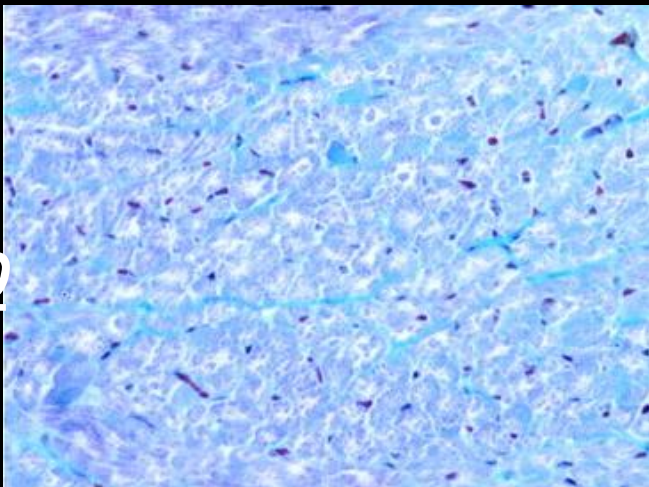
Control

Atrial Pacing

ICC



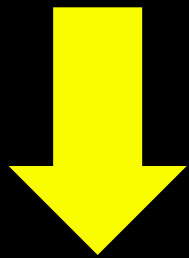
x500



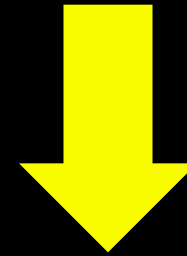
x1250

Li D et al. Circulation. 1999;100(1):87-95.

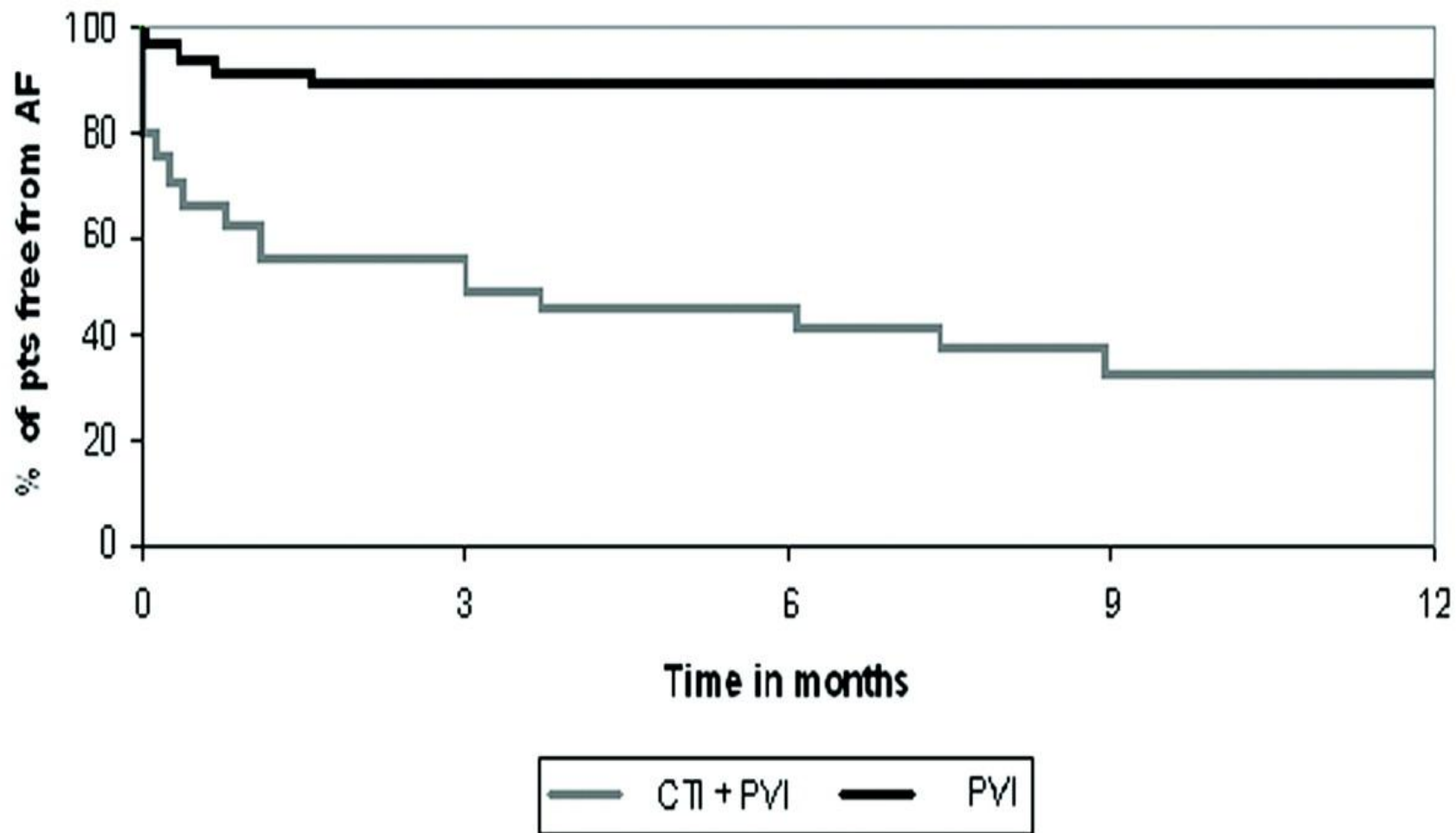
Ptes FA vs FA + FTA



Abl VPs



Abl VPs + ICT



Consecuencias Hemodinámicas y Clínicas

Consecuencias Hemodinámicas de la FA

- **Contribución al GC**
- **Control de FC**
- **Adecuación de FC a demandas metabólicas**
- **Irregularidad**

Hemodynamic Effects of an Irregular Sequence of Ventricular Cycle Lengths During Atrial Fibrillation

DAVID M. CLARK, MD, VANCE J. PLUMB, MD, FACC, ANDREW E. EPSTEIN, MD, FACC,
G. NEAL KAY, MD, FACC

Birmingham, Alabama

Objectives. The aim of this study was to determine the independent hemodynamic effects of an irregular sequence of ventricular cycle lengths in patients with atrial fibrillation (AF).

Background. Atrial fibrillation may reduce cardiac output by several possible mechanisms, including loss of the atrial contribution to left ventricular filling, valvular regurgitation, increased ventricular rate or irregular RR intervals. This study was designed to evaluate the effects of an irregular RR interval, independent of the average ventricular rate, on cardiac hemodynamic data during AF.

Methods. Sixteen patients with AF were studied invasively. During intrinsically conducted AF (mean rate 102 ± 22 beats/min), the right ventricular apex electrogram was recorded onto frequency-modulated (FM) tape. After atrioventricular node ablation, the right ventricular apex was stimulated in three pacing modes in randomized sequence: 1) VVI at 60 beats/min; 2) VVI at

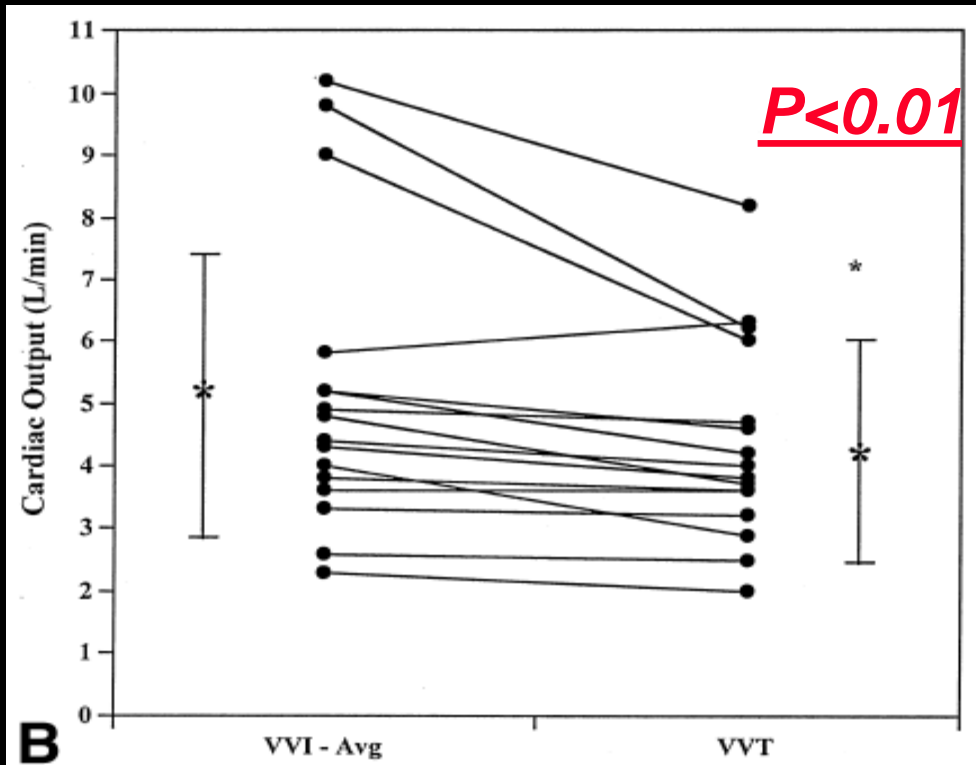
the same average rate as during intrinsically conducted AF (102 ± 22 beats/min); and 3) during VVT pacing in which the pacemaker was triggered by playback of the FM tape recording of the right ventricular apex electrogram previously recorded during intrinsically conducted AF (VVT 102 ± 22 beats/min).

Results. Compared with VVI pacing at the same average rate, an irregular sequence of RR intervals decreased cardiac output (4.4 ± 1.6 vs. 5.2 ± 2.4 liters/min, $p < 0.01$), increased pulmonary capillary wedge pressure (17 ± 7 vs. 14 ± 6 mm Hg, $p < 0.002$) and increased right atrial pressure (10 ± 6 vs. 8 ± 4 mm Hg, $p < 0.05$).

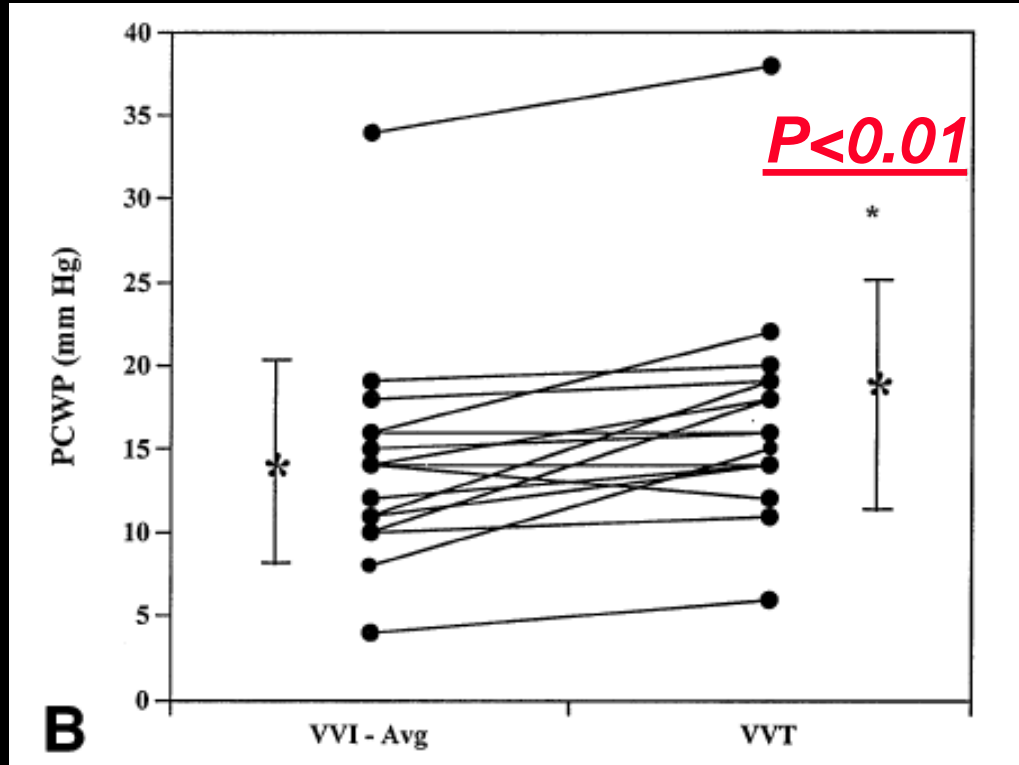
Conclusions. An irregular sequence of RR intervals produces adverse hemodynamic consequences that are independent of heart rate.

(J Am Coll Cardiol 1997;30:1039-45)
©1997 by the American College of Cardiology

Regular vs irregular VVI pacing



CO decrease 0.8 l/min



PCWP increase 3 mmHg

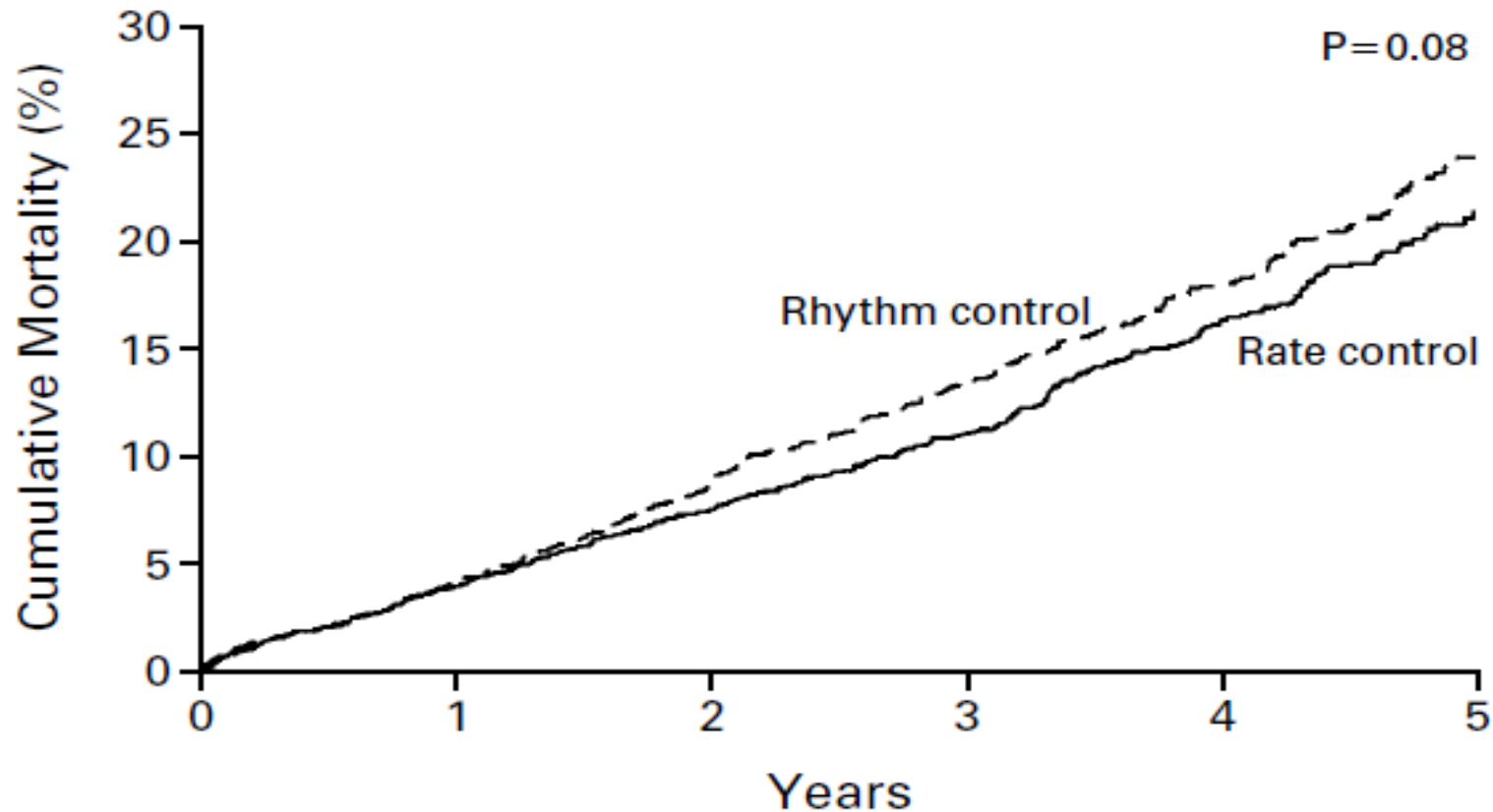
Consecuencias FA

- 15% de motivos de Urgencias Hospital
10% de los ingresos Hospital
(incremento 60% en últimos 20 años)
- Riesgo embolia cerebral x 5
- Riesgo muerte x 2
- Coste 13.500 millones € en Union Europea

¿Es relevante el RS?

The AFFIRM trial

RATE VERSUS RHYTHM CONTROL FOR ATRIAL FIBRILLATION



“Pendulo” del Tto de FA



Control
RS

Control
FC

No todo es lo que parece ...

***“Un coche rojo con
un caballito es un Ferrari”***



AFFIRM Subanalysis

Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

TABLE 3. Covariates Significantly Associated With Survival Results With Echocardiographic Data Excluded

Covariate	P	HR	HR: 99% Confidence Limits	
			Lower	Upper
Age at enrollment*	<0.0001	1.06	1.04	1.08
Coronary artery disease	<0.0001	1.65	1.31	2.07
Congestive heart failure	<0.0001	1.83	1.45	2.32
Diabetes	<0.0001	1.56	1.22	2.00
Stroke or transient ischemic attack	<0.0001	1.54	1.17	2.05
Smoking	<0.0001	1.75	1.29	2.39
First episode of atrial fibrillation	0.0067	1.27	1.01	1.58
Sinus rhythm	<0.0001	0.54	0.42	0.70
Warfarin use	<0.0001	0.47	0.36	0.61
Digoxin use	<0.0001	1.50	1.18	1.89
Rhythm-control drug use	0.0005	1.41	1.10	1.83

SR w/o present AAD is associated with better survival

Conclusions—Warfarin use improves survival. SR is either an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model. Currently available AADs are not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects. If an effective method for maintaining SR with fewer adverse effects were available, it might be beneficial. (*Circulation*. 2004;109:1509-1513.)

Estudio MADIT-II

Table 4

Multivariate Proportional Hazards Regression Model: Risk of All-Cause Mortality in the Conventional Therapy Group for Selected Risk Factors*†

Risk Factor	HR	95% Confidence Interval	p Value
NYHA functional class >II	1.87	1.23-2.86	0.004
Atrial fibrillation‡	1.87	1.05-3.22	0.034
QRS >120 ms	1.65	1.08-2.51	0.020
Age >70 yrs	1.57	1.02-2.41	0.042
BUN >26 mg/dl (and <50 mg/dl)	1.56	1.00-2.42	0.048

**¿Diferentes “FAs”
estudios principales?**



Estudio ATHENA

- **Dronedarona vs Placebo**
- **FA Px/Ps o FTA +**
 - ◆ **>75 años**
 - ◆ **>70 años + 1FR** (ACV, HTA, DBM, FEVI \leq 40%, AI \geq 50 mm)
- **Objetivo:**
Mortalidad y/o hospitalización CV a 1 año

Estudio ATHENA

- N = 4628 pts
- 551 centros 37 países



ORIGINAL ARTICLE

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D., Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D., and Stuart J. Connolly, M.D., for the ATHENA Investigators*

Dronedarona

Primary Outcome

Mortalidad CV o hospitalizaciones

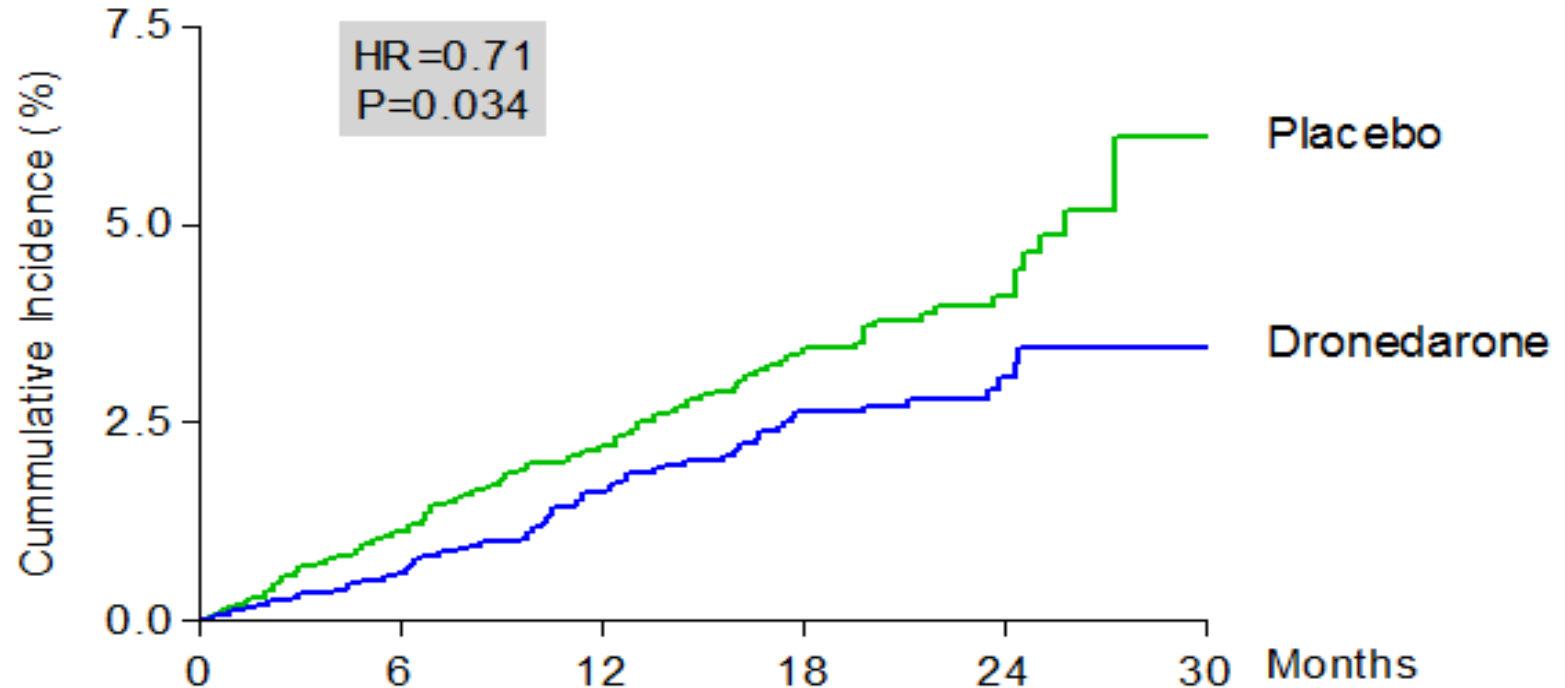


Patients at risk

Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

Dronedarone

CV Mortality

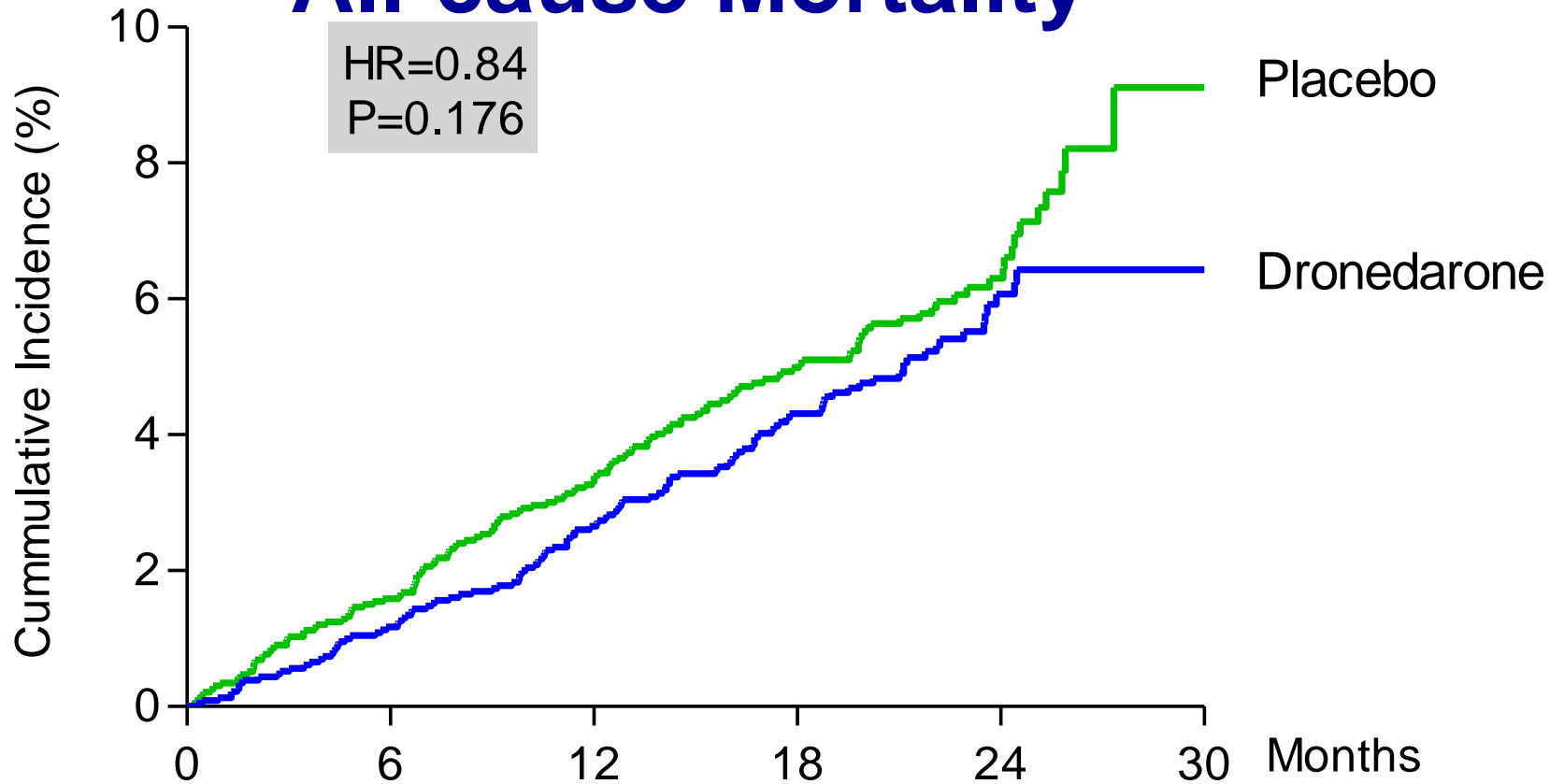


Patients at risk

Placebo	2327	2290	2250	1629	636	7
Dronedarone	2301	2274	2240	1593	615	4

Dronedarone

All-cause Mortality

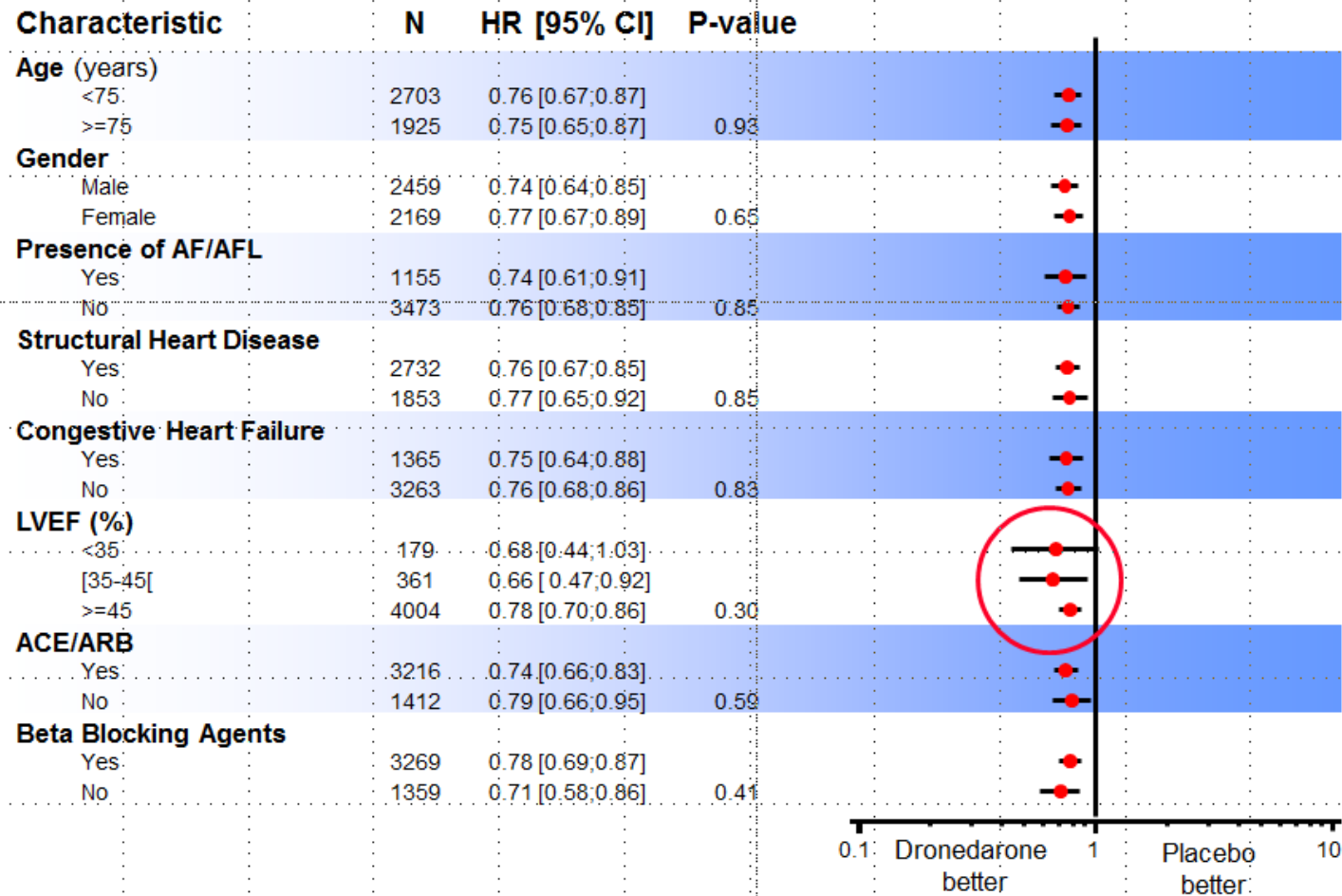


Patients at risk

Placebo	2327	2290	2250	1629	636	7
Dronedarone	2301	2274	2240	1593	615	4

Dronedarona

Hazard Ratios for Primary Outcome in Important Clinical Subgroups



Merino 61



PALLAS

*Permanent Atrial fibrillation outcome Study
using Dronedaronone on top of standard therapy*

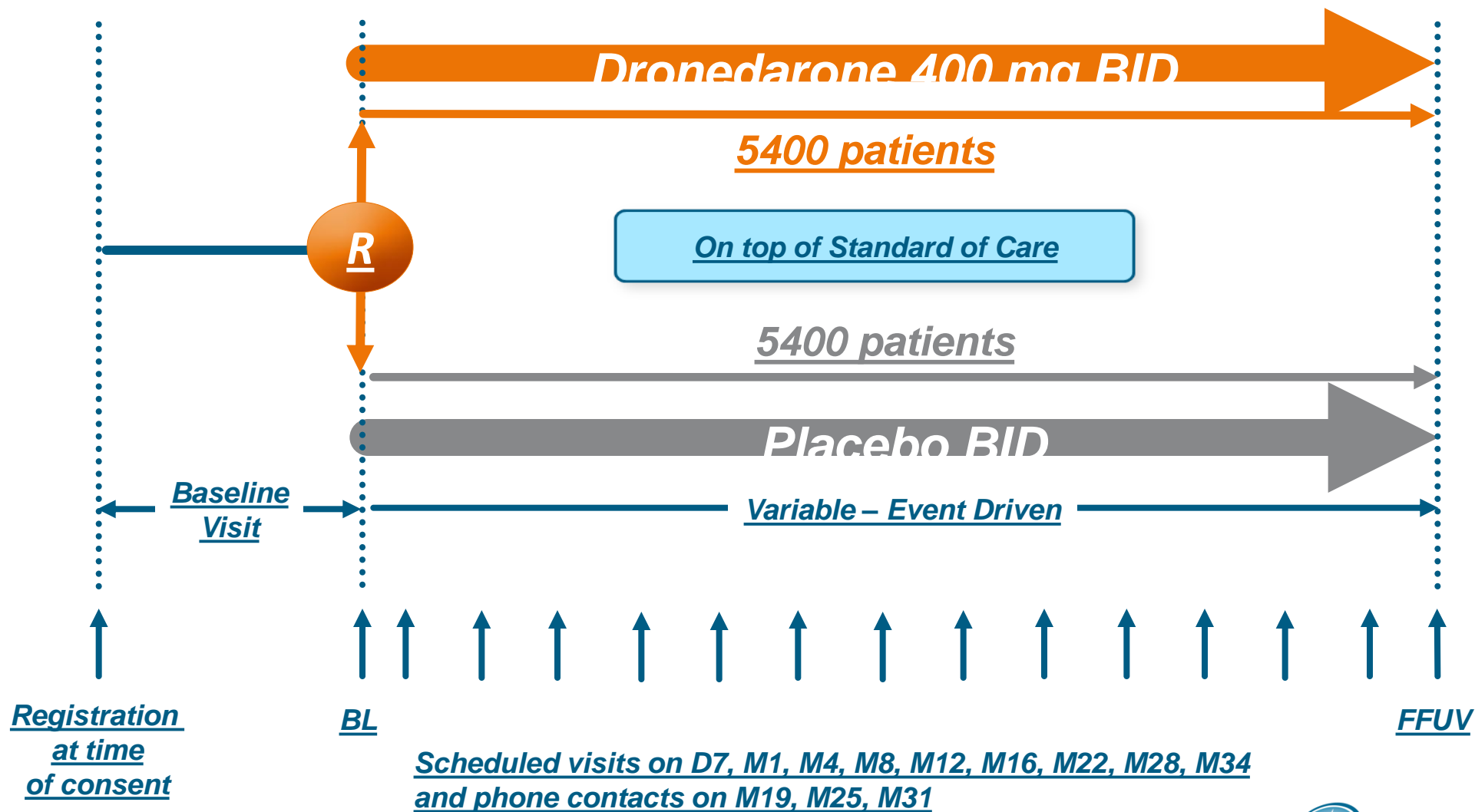
PALLAS: Inclusion criteria

1. Permanent AF
 - > 6 months
(ECG or medical report)

2. ≥ 65 years

3. CV disease
 - CAD, HF, LV EF $\leq 40\%$
 - Stroke
 - Peripheral vascular disease
 - ≥ 75 yo + HT + DBM

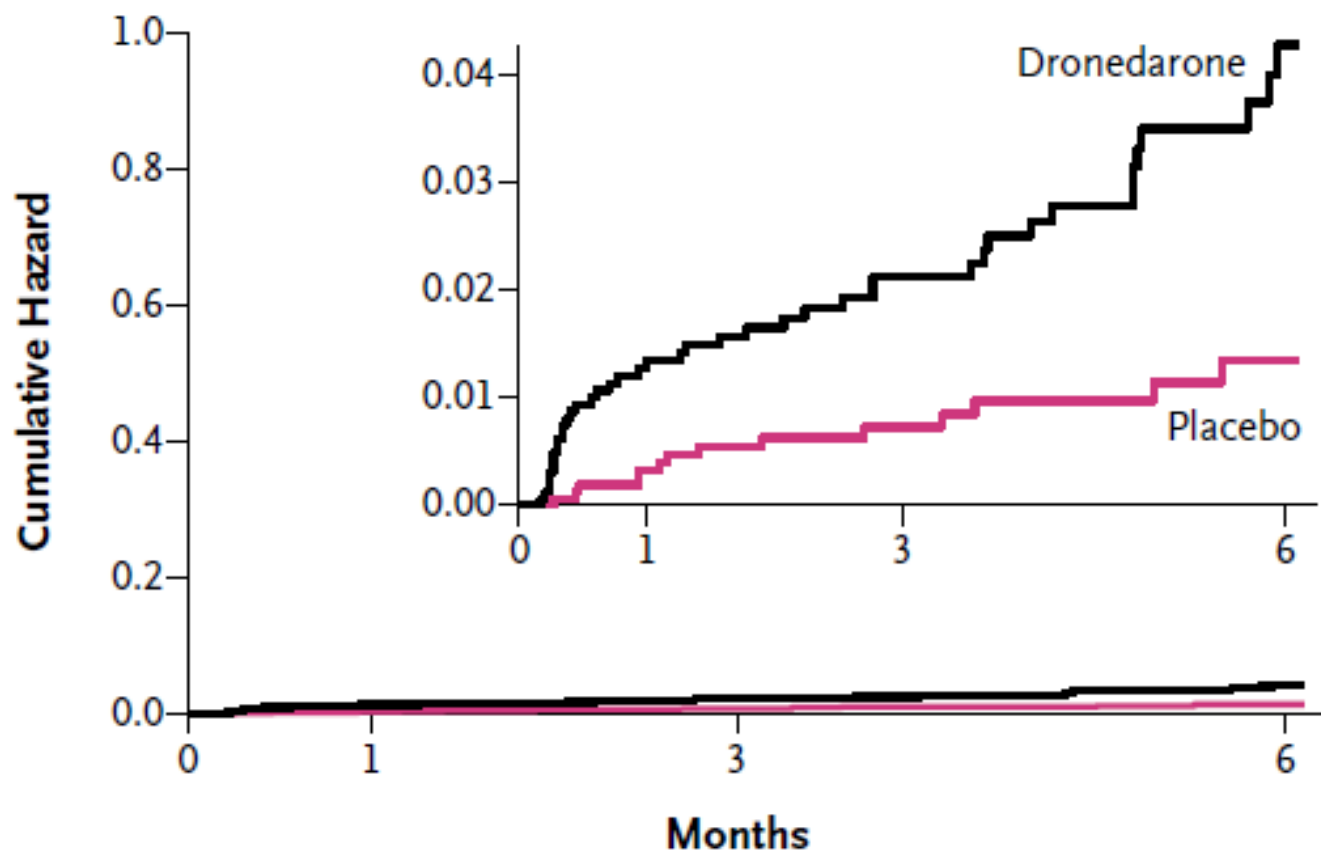
PALLAS: Study design



ORIGINAL ARTICLE

Dronedarone in High-Risk Permanent Atrial Fibrillation

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No. at Risk

Placebo	1617	1445	908	377
Dronedarone	1619	1421	930	353

Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

**¿Cómo se pueden
explicar estas
diferencias?**

Table 1. A Comparison of Demographic and Clinical Characteristics and Outcomes among Patients in Three Studies of Dronedarone.*

Variable	ATHENA	PALLAS	ANDROMEDA
Demographic characteristic			
Mean age (yr)	72	75	72
Female sex (%)	47	35	25
Clinical characteristic (%)			
	Px/Ps: 100%		
Baseline atrial fibrillation	25	100	25
Hypertension	86	83	37
Coronary artery disease	30	41	65
Congestive heart failure class II or III	21	54	97
Treatment (%)			
Beta-blocker	71	74	61
Digoxin	14	33	31
Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker	70	78	86
Oral anticoagulant	60	84	31
Outcome (hazard ratio)†			
Death			
Any cause	0.84	1.94	2.13
Cardiovascular cause	0.71	2.11	2.75
Presumed arrhythmia	0.55	3.26	1.68
Stroke	0.66	2.32	NA
Congestive heart failure‡	0.86	1.89	1.22

Conclusiones

- FA una enfermedad con distintos tipos / fases
- Papel del remodelado
- Elevado morbimortalidad
- Nuevas alternativas farmacológicas:
 - ◆ Eficaces para prevenir FA → asociados con beneficio pronóstico (FA px / ps)
 - ◆ Efectos secundarios → prevalecen cuando no se puede esperar un beneficio clínico (FA pm o No FA)



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