Can long acting antiarrhythmic therapy improve results and compliance ?

Leonardo Calo’

Responsabile U.O.C. Cardiologia
Policlinico Casilino -Roma

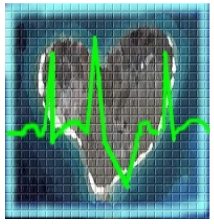


Table 17 Oral antiarrhythmic drugs used for maintaining sinus rhythm after cardioversion

Drug	Dose	Main contra-indications and precautions	Warning signs warranting discontinuation	AV nodal slowing	Suggested ECG monitoring during initiation
Amiodarone	600 mg in divided doses for 4 weeks, 400 mg for 4 weeks, then 200 mg once daily	Caution when using concomitant therapy with QT-prolonging drugs and in patients with SAN or AV node and conduction disease. The dose of VKAs and of digitalis should be reduced. Increased risk of myopathy with statins. Caution in patients with pre-existing liver disease.	QT prolongation >500 ms	10–12 bpm in AF	Baseline, 1 week, 4 weeks
Dronedarone	400 mg twice daily	Contra-indicated in NYHA Class III or IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, or powerful CYP3A4 inhibitors (e.g. verapamil, diltiazem, azole antifungal agents), and when CrCl <30 mg/mL. The dose of digitalis, beta-blockers, and of some statins should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect a decline in renal function. Caution in patients with pre-existing liver disease.	QT prolongation >500 ms	10–12 bpm in AF	Baseline, 1 week.
Flecainide Flecainide slow release	100–150 mg twice daily 200 mg once daily	Contra-indicated if CrCl <50 mg/mL, liver disease, IHD or reduced LV ejection fraction. Caution in the presence of SAN or AV node or conduction disease. CYP2D6 inhibitors (e.g. fluoxetine or tricyclic antidepressants) increase plasma concentration.	QRS duration increases >25% above baseline	None	Baseline, day 1, day 2–3
Propafenone Propafenone SR	150–300 mg three times daily 225–425 mg twice daily	Contra-indicated in IHD or reduced LV ejection fraction. Caution in the presence of SAN or AV node and conduction disease, renal or liver impairment, and asthma. Increases concentration of digitalis and warfarin.	QRS duration increase >25% above baseline	Slight	Baseline, day 1, day 2–3
d,l sotalol	80–160 mg twice daily	Contra-indicated in the presence of significant LV hypertrophy, systolic heart failure, asthma, pre-existing QT prolongation, hypokalaemia, CrCl<50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose.	QT interval >500 ms, QT prolongation by >60 ms upon therapy initiation	Similar to high dose blockers	Baseline, day 1, day 2–3

AF = atrial fibrillation; b.p.m. = beats per minute; CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4; ECG = electrocardiogram; IHD = ischaemic heart disease; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VKA = vitamin K antagonist.

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

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) of the ESC

Endorsed by the European Stroke Organisation (ESO)

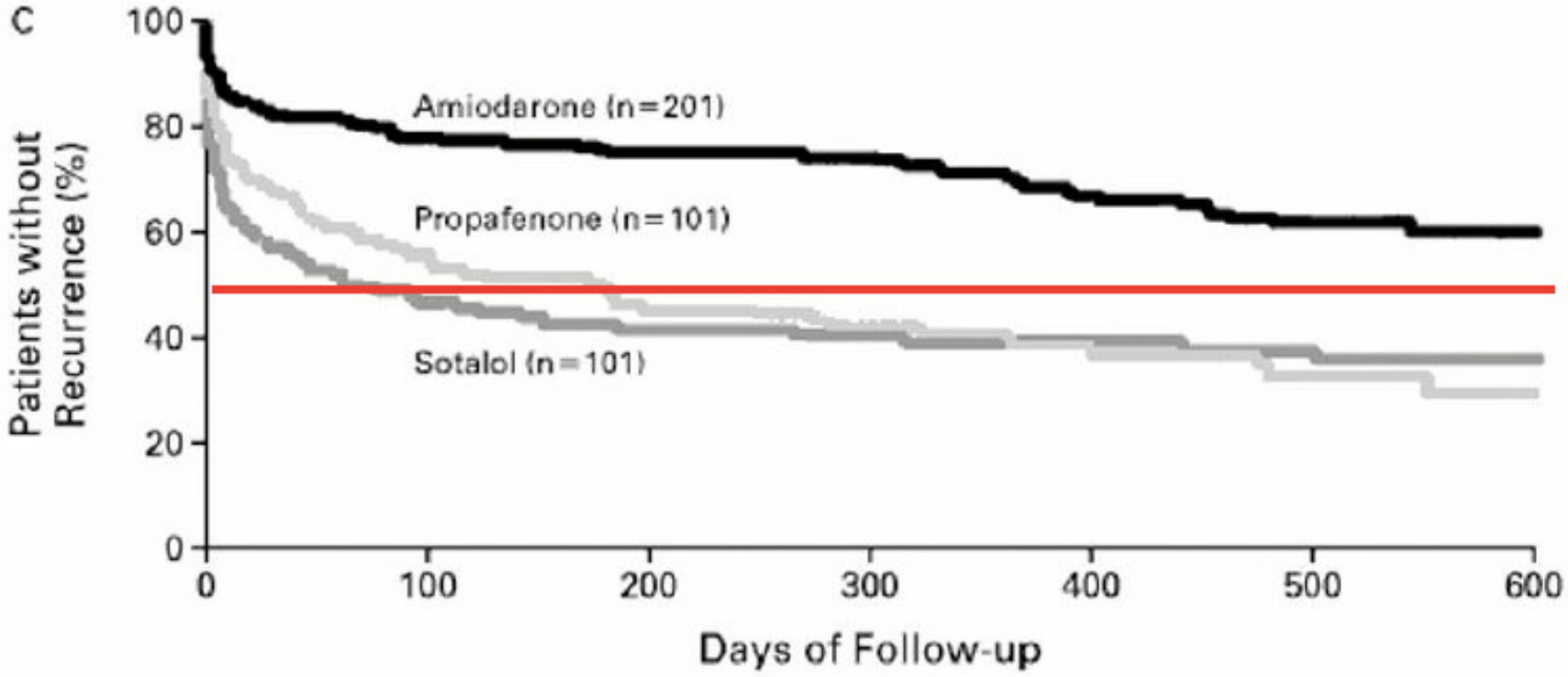
Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany) Stefano Benussi*[1] (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson[1] (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella[1] (Spain), Hans-Christoph Diener[2] (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte[1] (The Netherlands), and Panagiotis Vardas (Greece)

Recommendations for rhythm control therapy

Recommendations	Class[a]	Level[b]	Ref[c]
General recommendations			
Rhythm control therapy is indicated for symptom improvement in patients with AF.	I	B	120, 586, 601
Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy to facilitate maintenance of sinus rhythm.	IIa	B	203, 204, 296, 312
With the exception of AF associated with haemodynamic instability, the choice between electrical and pharmacological cardioversion should be guided by patient and physician preferences.	IIa	C	
Cardioversion of AF			
Electrical cardioversion of AF is recommended in patients with acute haemodynamic instability to restore cardiac output.	I	B	612, 702-704
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy.	I	B	584, 601, 627, 628, 648, 705
Pre-treatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to enhance success of electrical cardioversion and prevent recurrent AF.	IIa	B	248, 584, 633
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant are recommended for pharmacological cardioversion of new-onset AF.	I	A	602–605, 614, 618, 622, 706, 707
In patients with no history of ischaemic or structural heart disease, ibutilide should be considered for pharmacological conversion of AF.	IIa	B	
In selected patients with recent-onset AF and no significant structural or ischaemic heart disease, a single oral dose of flecainide or propafenone (the 'pill in the pocket' approach) should be considered for patient-led cardioversion, following safety assessment.	IIa	B	620, 621
In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF.	I	A	597–601
Vernakalant may be considered as an alternative to amiodarone for pharmacological conversion of AF in patients without hypotension, severe heart failure or severe structural heart disease (especially aortic stenosis).	IIb	B	602–605, 616, 618
Stroke prevention in patients designated for cardioversion of AF			
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa	B	708, 709
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B	648, 708
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B	648, 708
Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours.	IIa	B	648
In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion.	I	B	353, 710
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks.	I	C	
A repeat TOE to ensure thrombus resolution should be considered before cardioversion.	IIa	C	
AAD for the long-term maintenance of sinus rhythm/prevention of recurrent AF			
The choice of AAD needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden.	I	A	41, 580
Dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A	581, 583, 584, 588, 601
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure.	I	A	583, 588
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure.	I	B	596–598
Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.	IIa	C	596–598
Patients on AAD therapy should be periodically evaluated to confirm their eligibility for treatment.	IIa	C	583, 588, 657, 658, 660

Continued

Amiodarone to Prevent Recurrence of AF (CTAF)



Roy et al. New Engl J Med 2000;342:913.

Europace (2011) **13**, 329–345
doi:10.1093/europace/euq450

Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation

Nick Freemantle[1], Carmelo Lafuente-Lafuente[2], Stephen Mitchell[3], Laurent Eckert[4]*, and Matthew Reynolds[5]

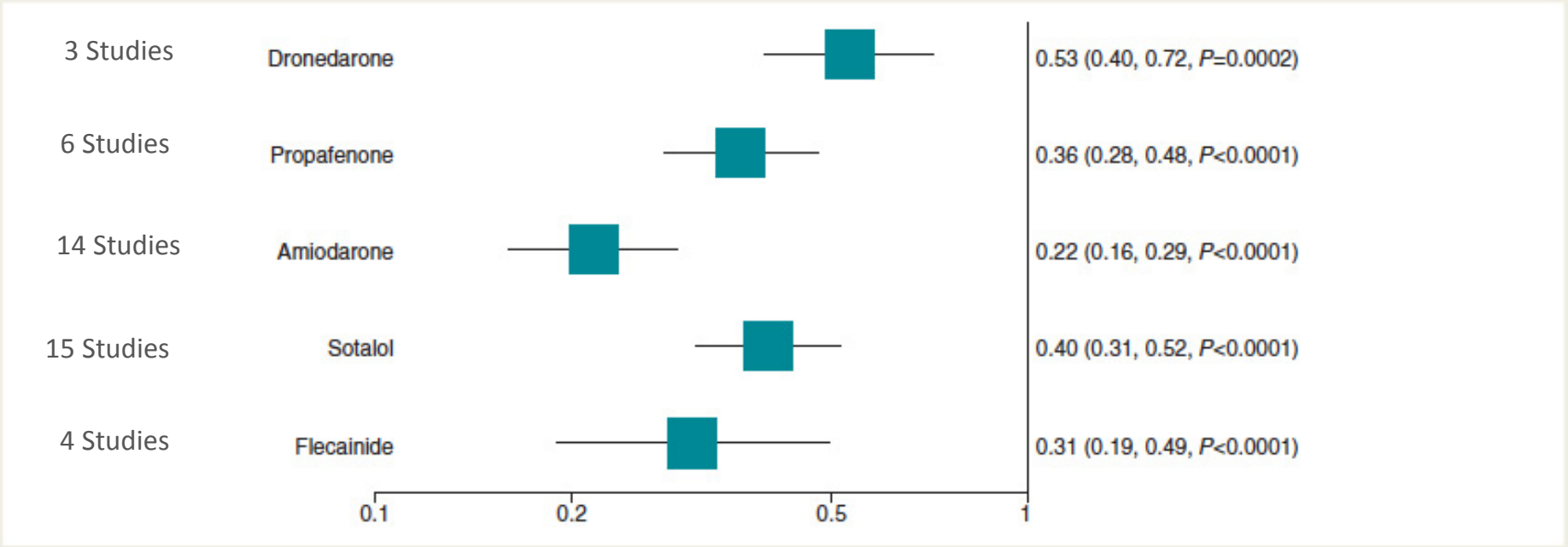
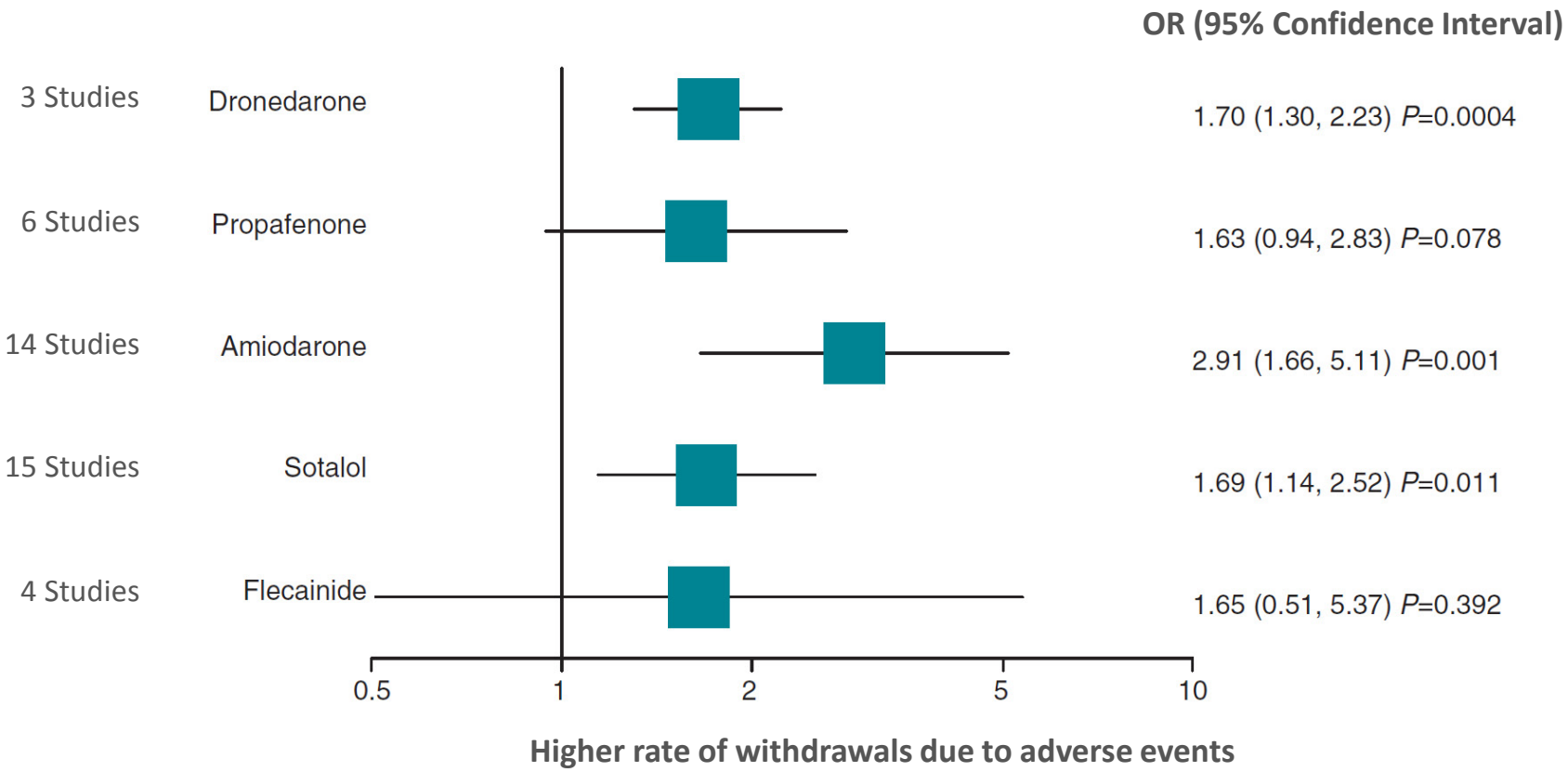


Figure 5 Mixed treatment comparison analysis: effect of anti-arrhythmic drugs on atrial fibrillation recurrence. Odds ratios and 95% confidence intervals. Note—odds ratio lower than 1 describes a lower rate of atrial fibrillation recurrence for the active treatment.

POTENTIAL SIDE EFFECTS

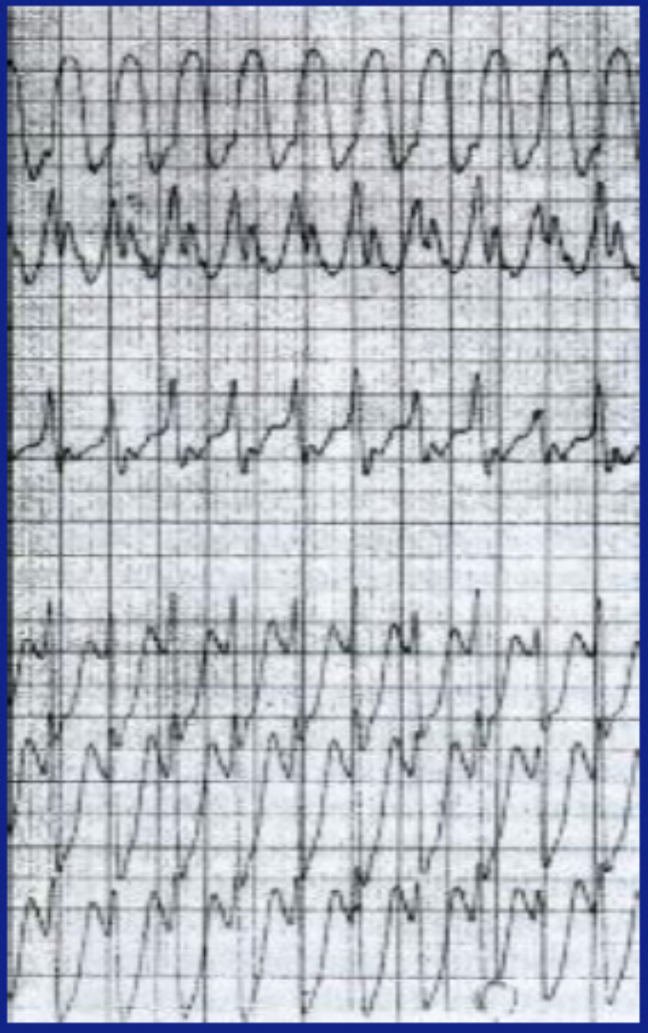
AADs – Withdrawal due to Adverse Events

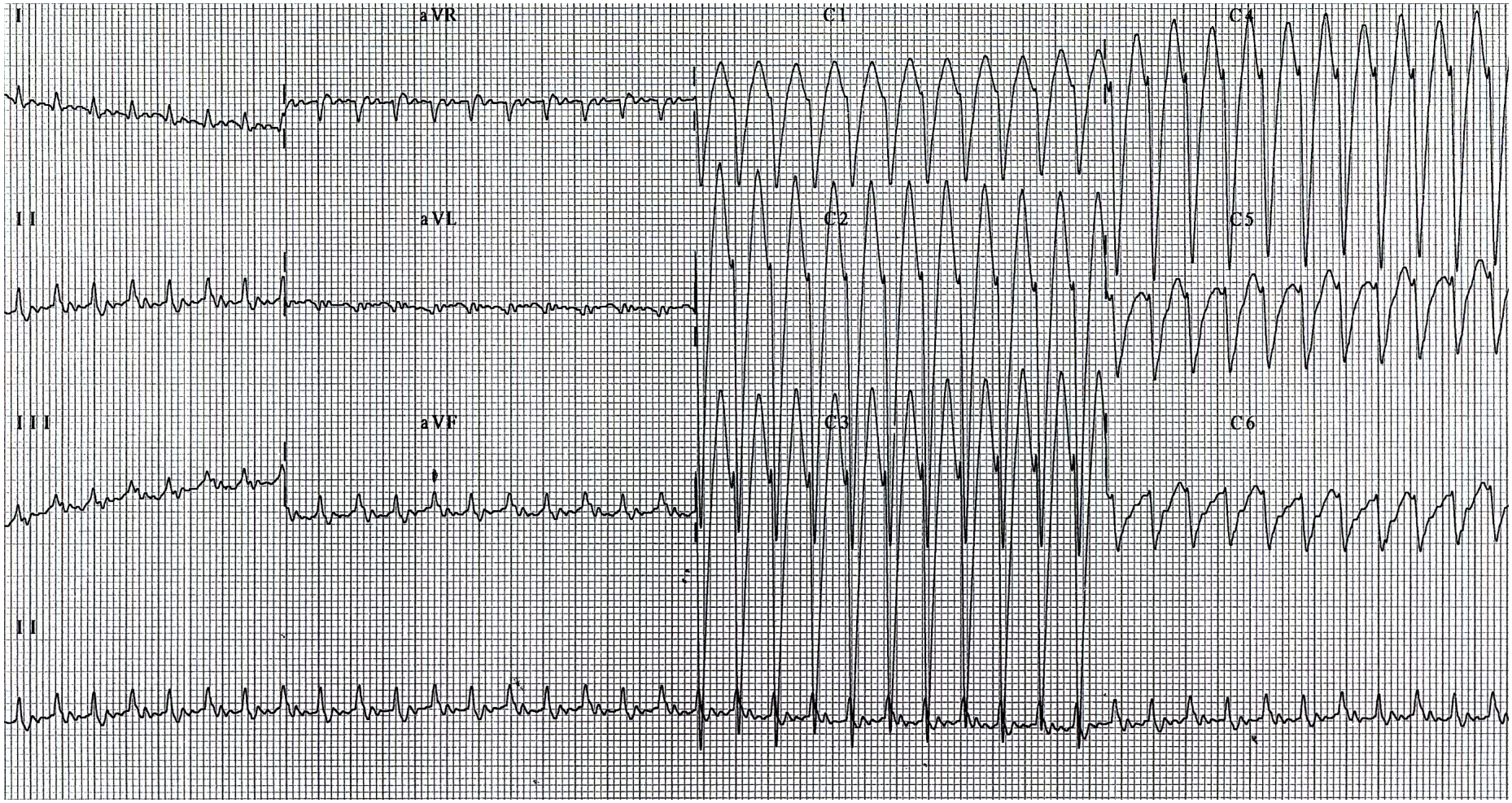
Risk of Drug Discontinuation for Adverse Events

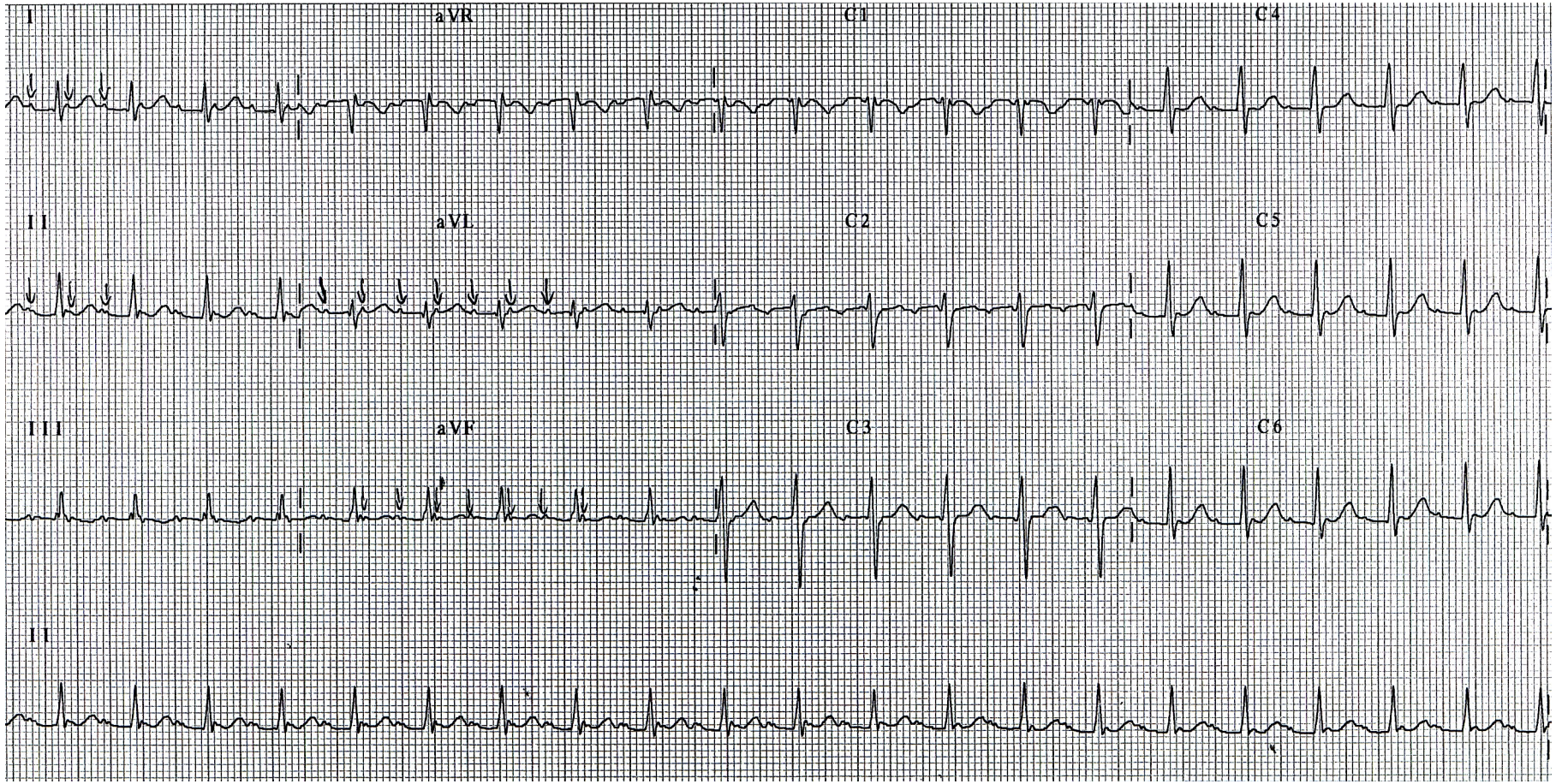


Modified from Freemantle N et al. Europace 2011;13:329-45

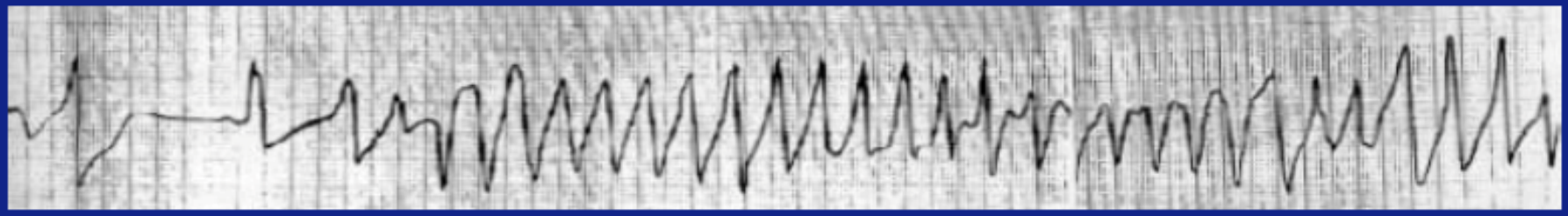
What You Don't Want




I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II


I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II

What You Really Don't Want



Torsione di punta

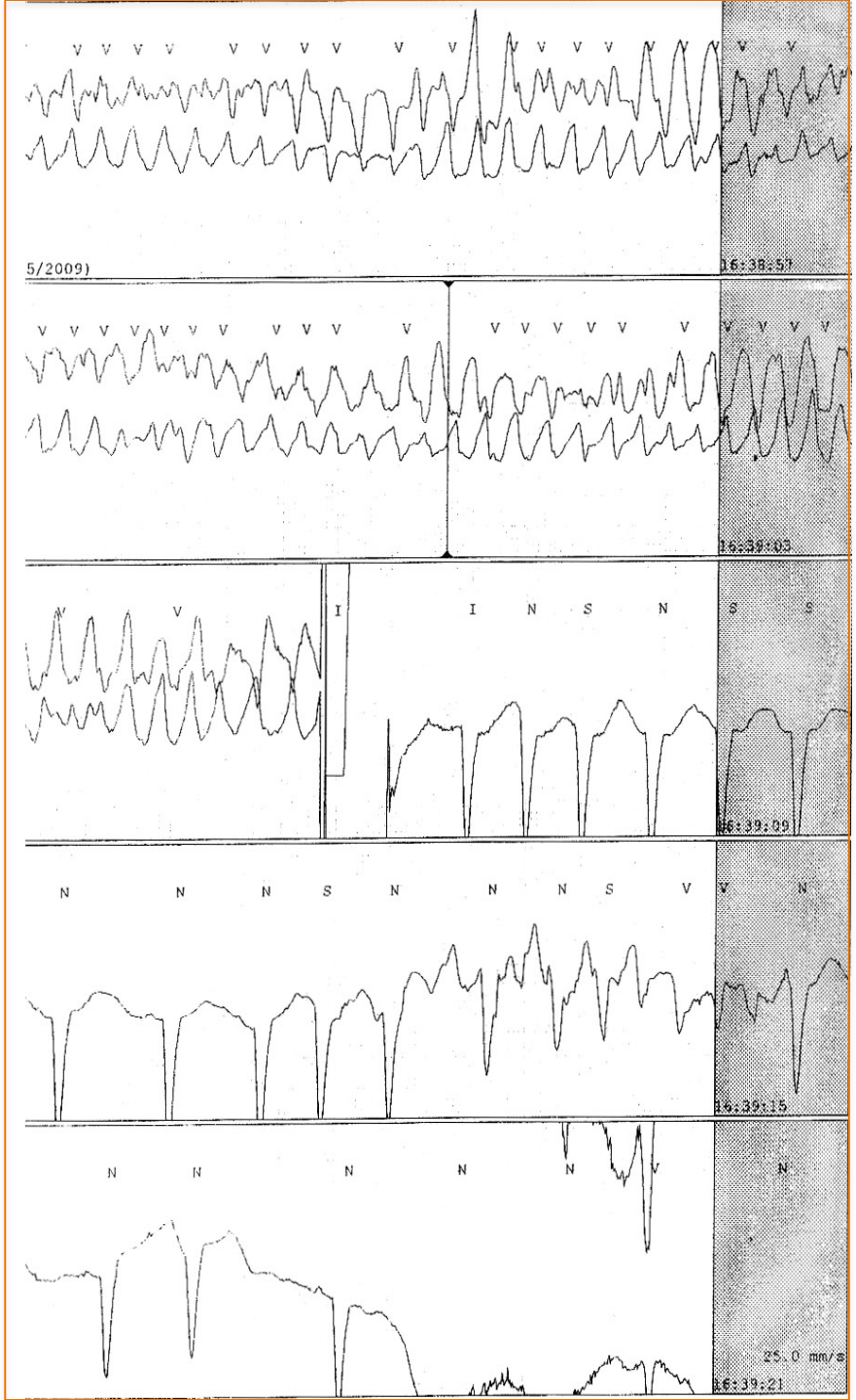

5/2009)
16:38:57
16:39:03
16:39:09
16:39:15
16:39:21
25.0 mm/s

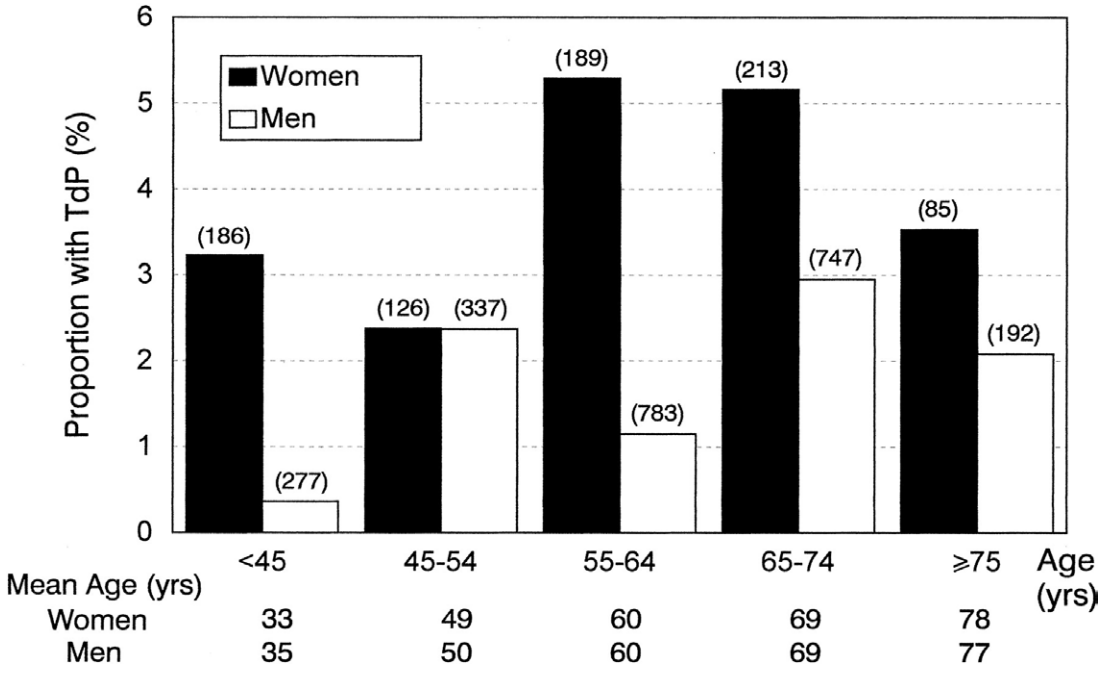
Table 3 **Ventricular proarrythmia risk factors for class 1C antiarrhythmic drugs**

Risk factors
Wide QRS (>120 ms), Brugada ECG sign
Low LVEF, CHF
Structural heart disease, CAD
High rate (use-dependent effect)
High dose
Hypokalaemia
Severe renal failure (creatinine clearance $\leq$ 35 mL/min/1.73 m^2)
Excessive QRS increase (>150% from baseline)

CAD, coronary artery disease; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; ECG, electrocardiogram.

Safety - Minimize Proarrhythmic Risk

- **Women → Avoid Sotalol**



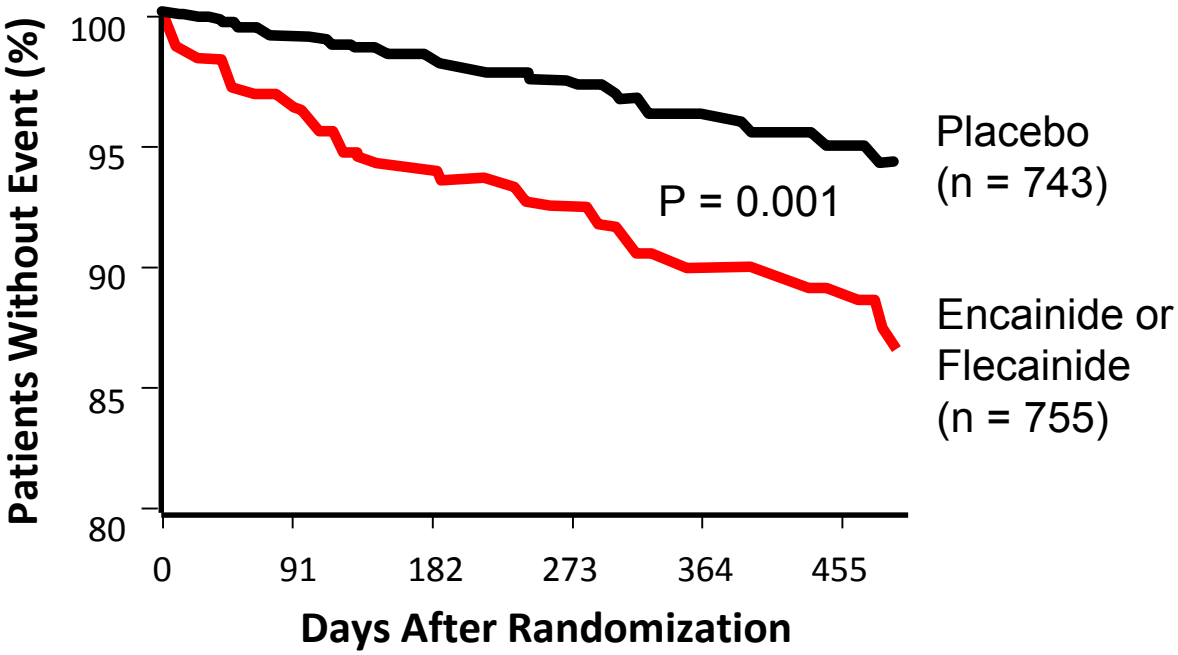
Women x2 Risk of Torsade de Points

Lehmann MH et al. Circulation. 1996;94:2535-2541

Safety - Minimize Proarrhythmic Risk

- **Myocardial Ischemia or scar**

Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial



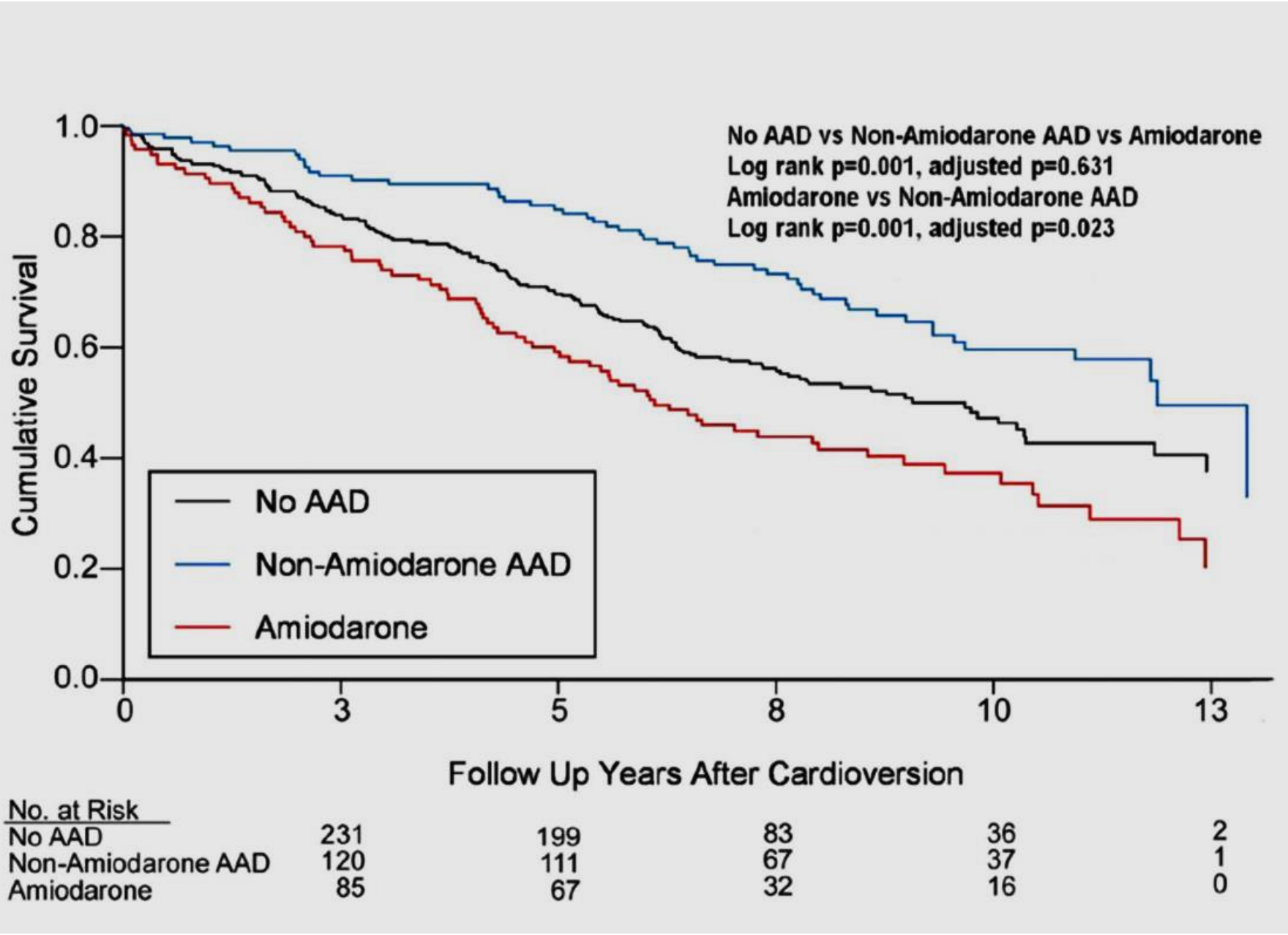
Echt DS. N. Engl J Med. 1991;324:781-788

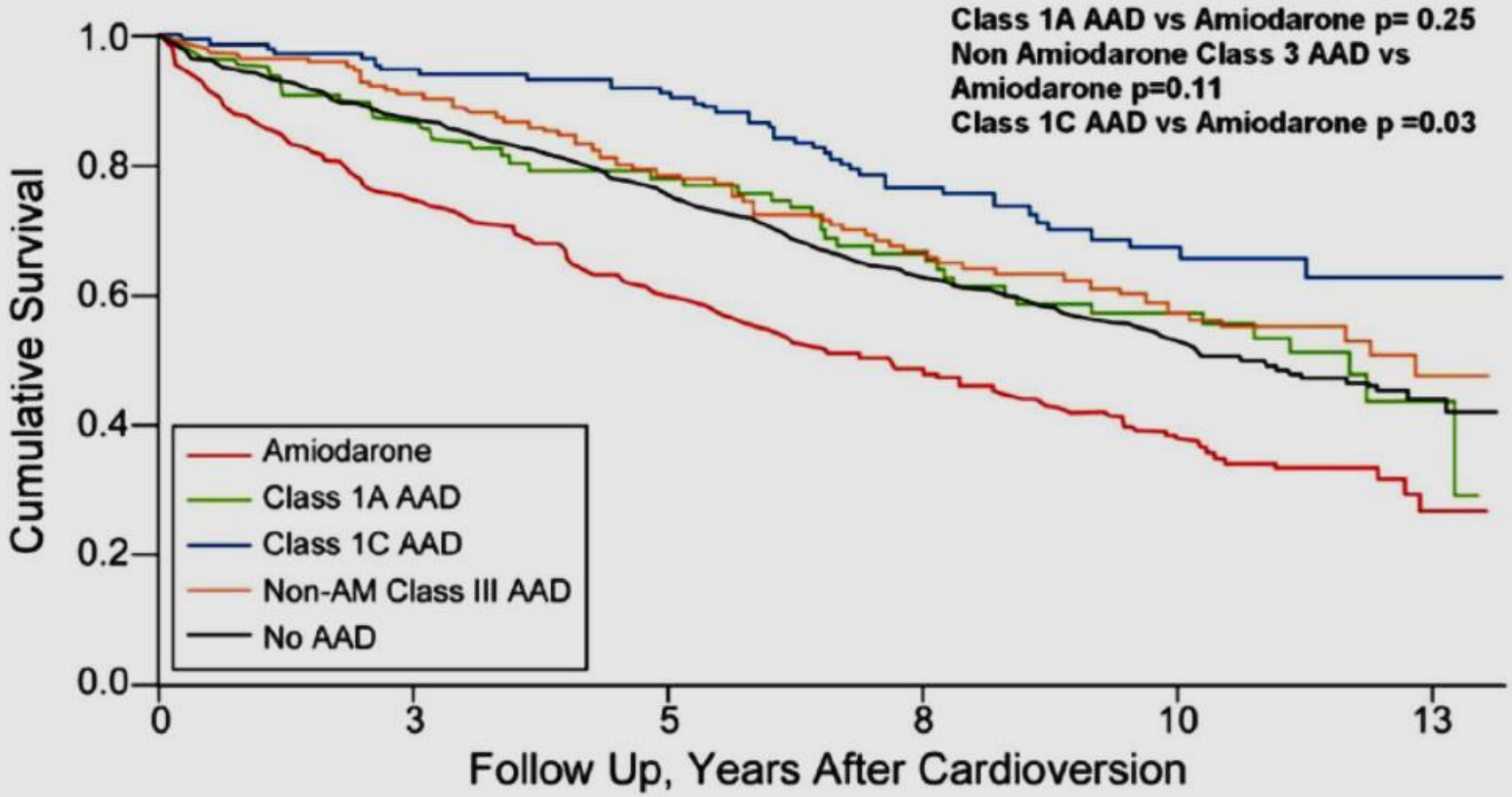
Pacing Clin Electrophysiol. 2014 October ; 37(10): 1338–1348. doi:10.1111/pace.12426.

Left Ventricular Hypertrophy and Antiarrhythmic Drugs In Atrial Fibrillation: Impact On Mortality

Roy Chung, MD, **Penny L. Houghtaling, MS**, **Michael Tchou, MD**, **Mark J. Niebauer, MD, PhD**, **Bruce D. Lindsay, MD**, **Patrick J. Tchou, MD**, and **Mina K. Chung, MD**
The Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH

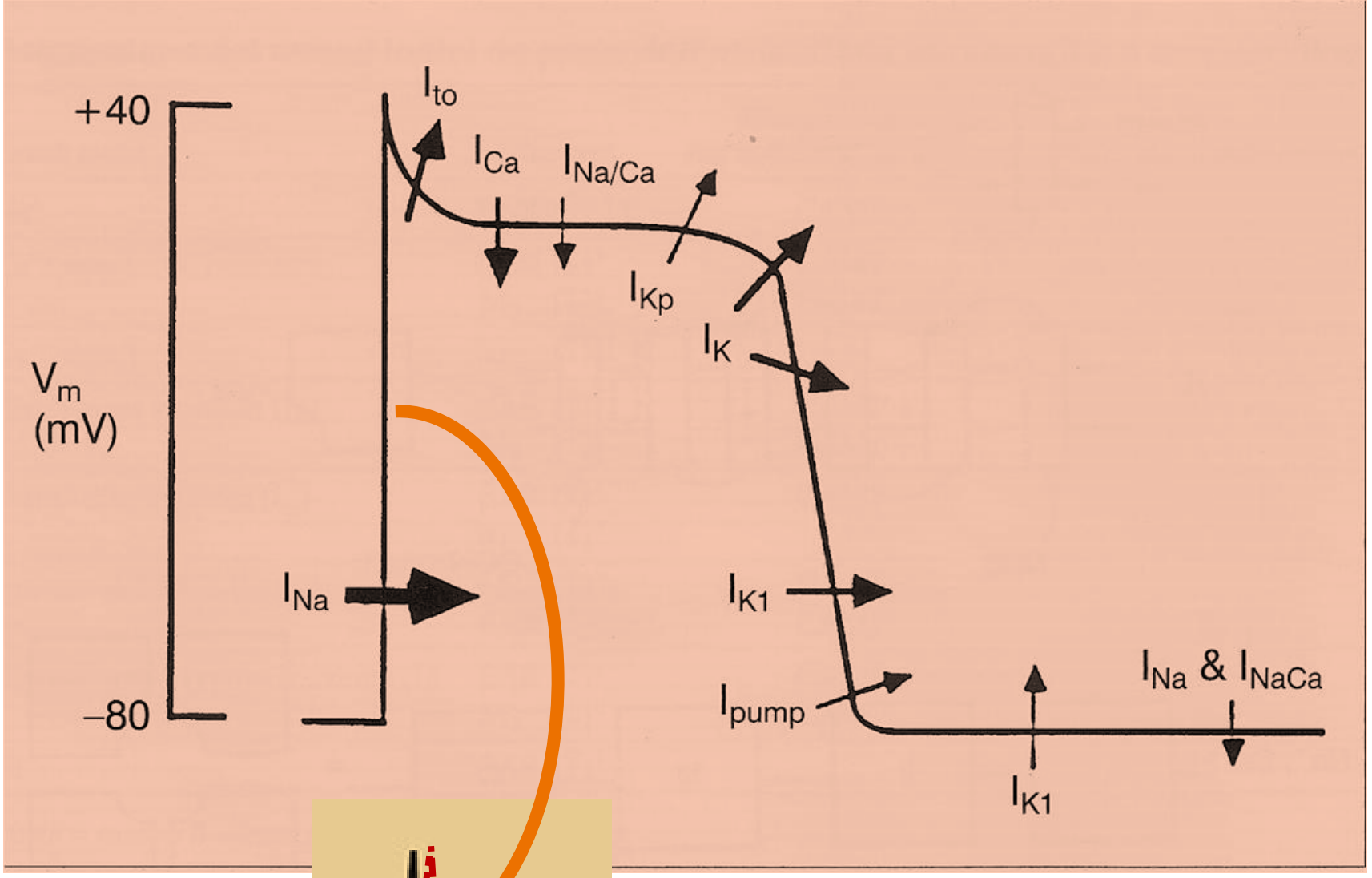
537 patients with
LVH≥1.4cm
mean age was 67.5±11.7
years 76.4% were males
mean LVEF was
48.3±13.3%

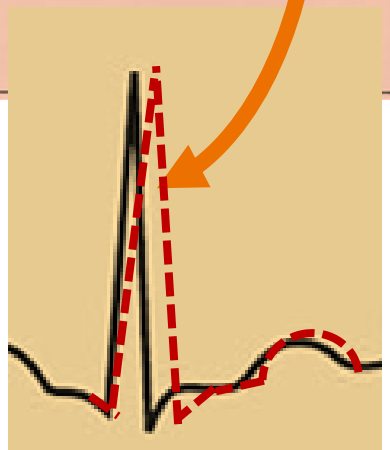

No AAD vs Non-Amiodarone AAD vs Amiodarone
Log rank p=0.001, adjusted p=0.631
Amiodarone vs Non-Amiodarone AAD
Log rank p=0.001, adjusted p=0.023
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
No AAD
Non-Amiodarone AAD
Amiodarone
0
3
5
8
10
13
Follow Up Years After Cardioversion
No. at Risk
No AAD 231 199 83 36 2
Non-Amiodarone AAD 120 111 67 37 1
Amiodarone 85 67 32 16 0



No. at Risk						
Amiodarone	111	80	63	45	42	37
Class 1A AAD	31	25	24	21	21	18
Class 1C AAD	47	45	44	36	32	32
Non-AM Class III AAD	50	43	38	31	27	26
No AAD	288	230	200	156	147	142

FLECAINIDE





Flecainide

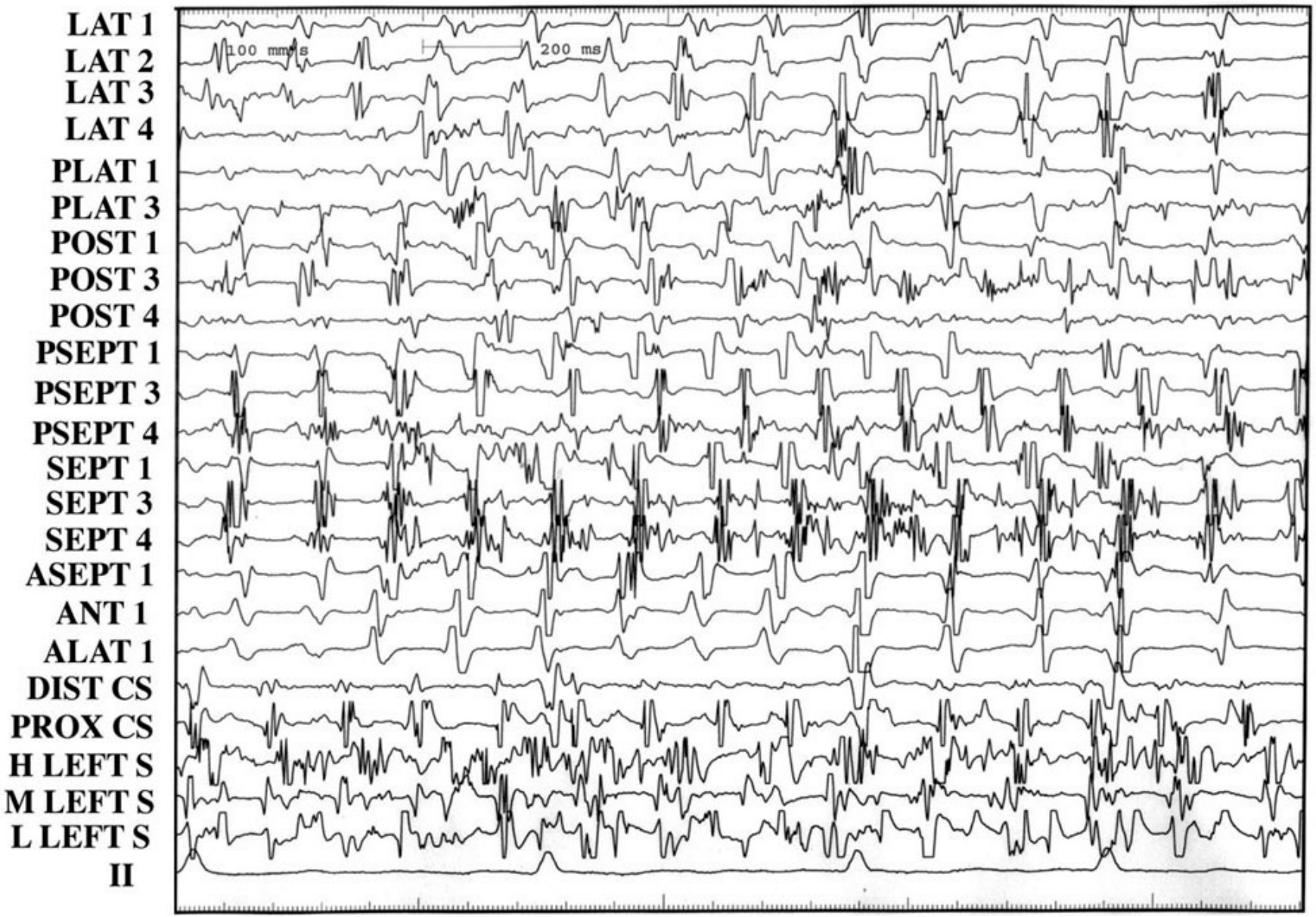
Electrophysiological properties

Flecainide prolongs the PR (17–29%) and QT (4–11%) intervals and the QRS complex (11–27%). Most of the QT prolongation is due to a widening of the QRS complex, so that the JT interval and the rate-corrected QT interval (QTc) remain unchanged or slightly increase (3–8%).

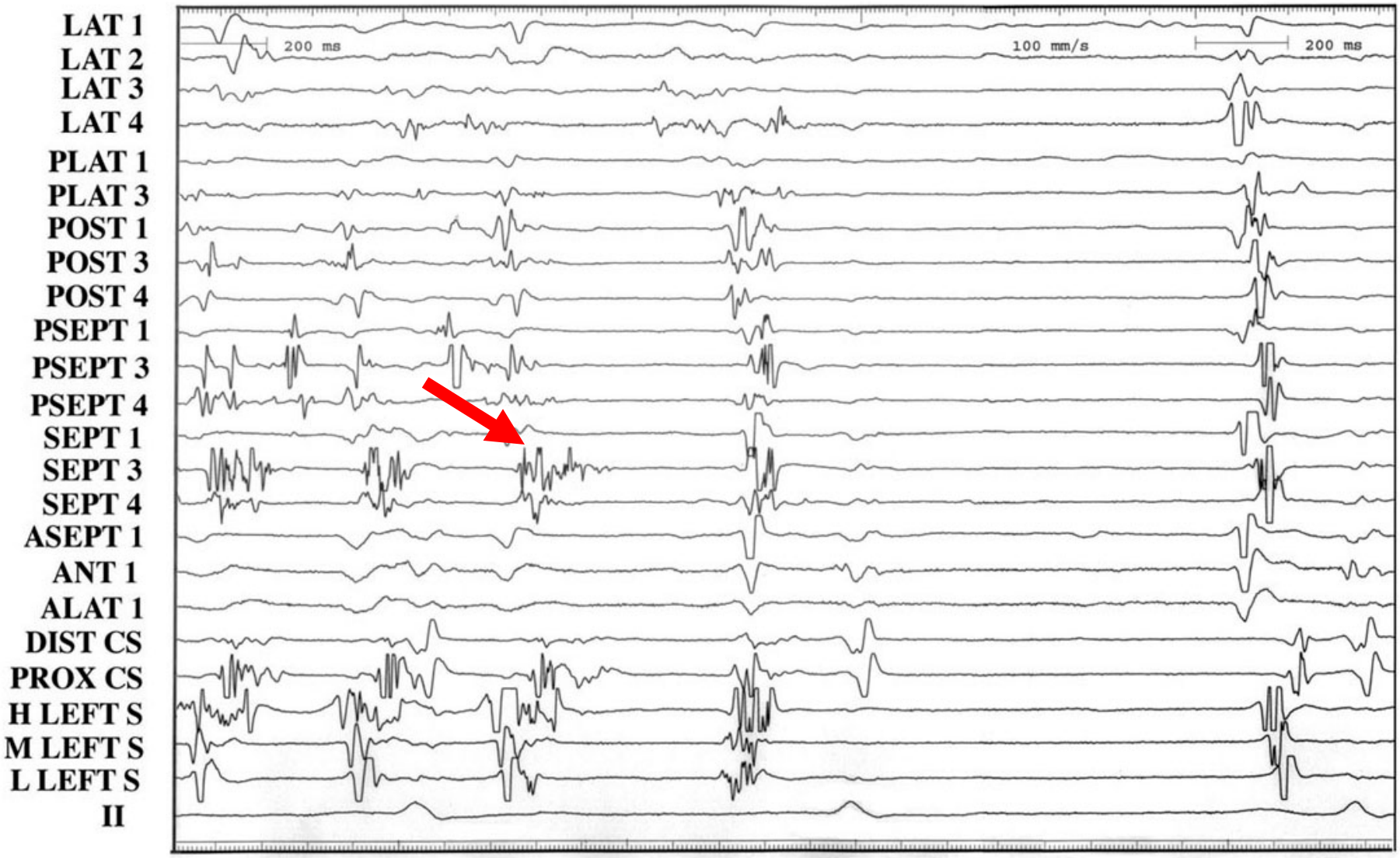
Flecainide also prolongs atrial, AV nodal and ventricular refractoriness, but itseffects on refractoriness are less pronounced than its effects on intracardiac conduction.

Flecainide increases the endocardial pacing threshold; it may therefore be necessary for pacemaker-dependent pts to reprogramme their pacemaker.

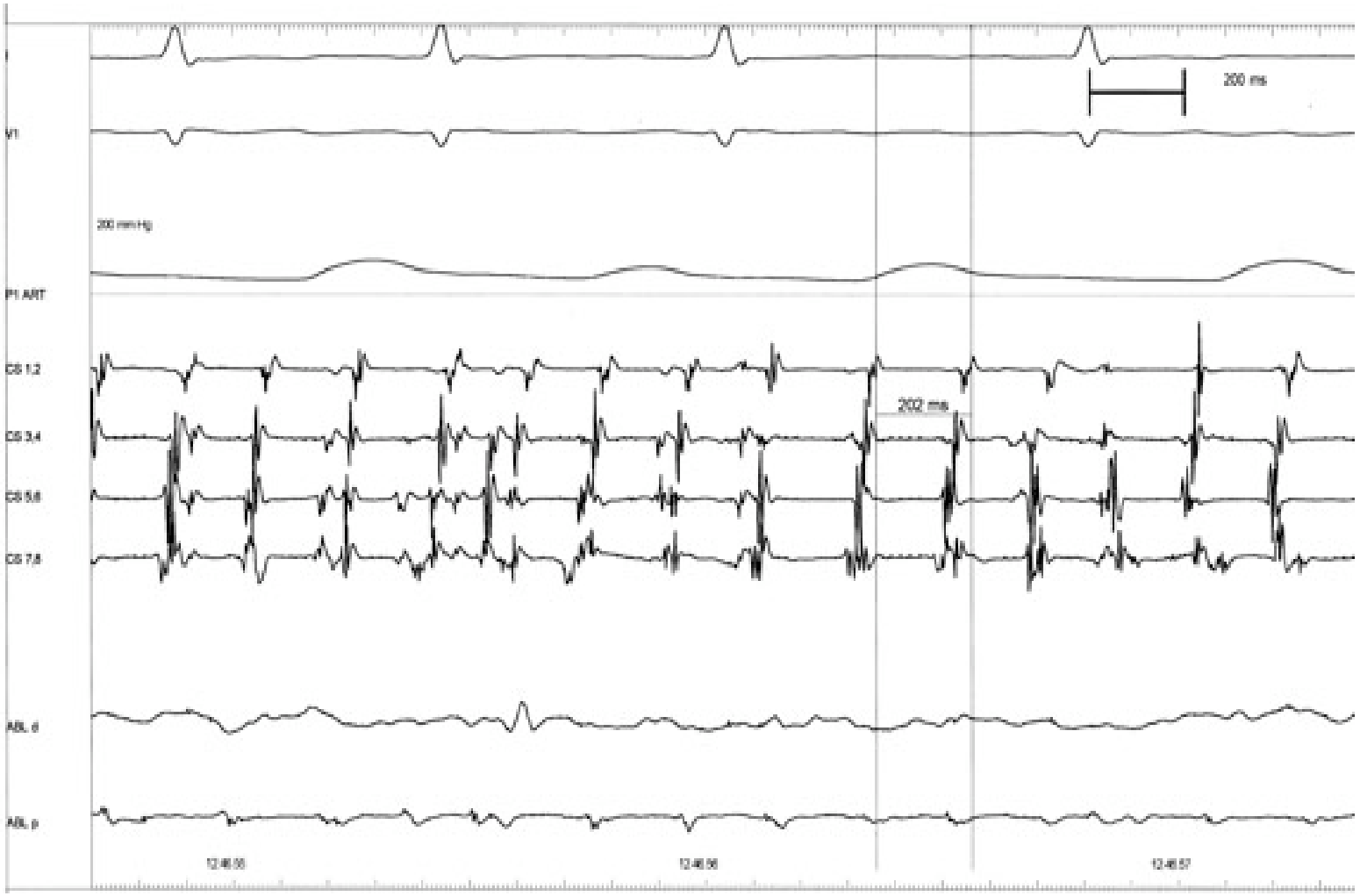
Flecainide does not affect sinus rate, although bradycardia has been occasionally reported. It increases the corrected sinus node recovery time and the sinoatrial conduction time in pts with sinus node dysfunction.

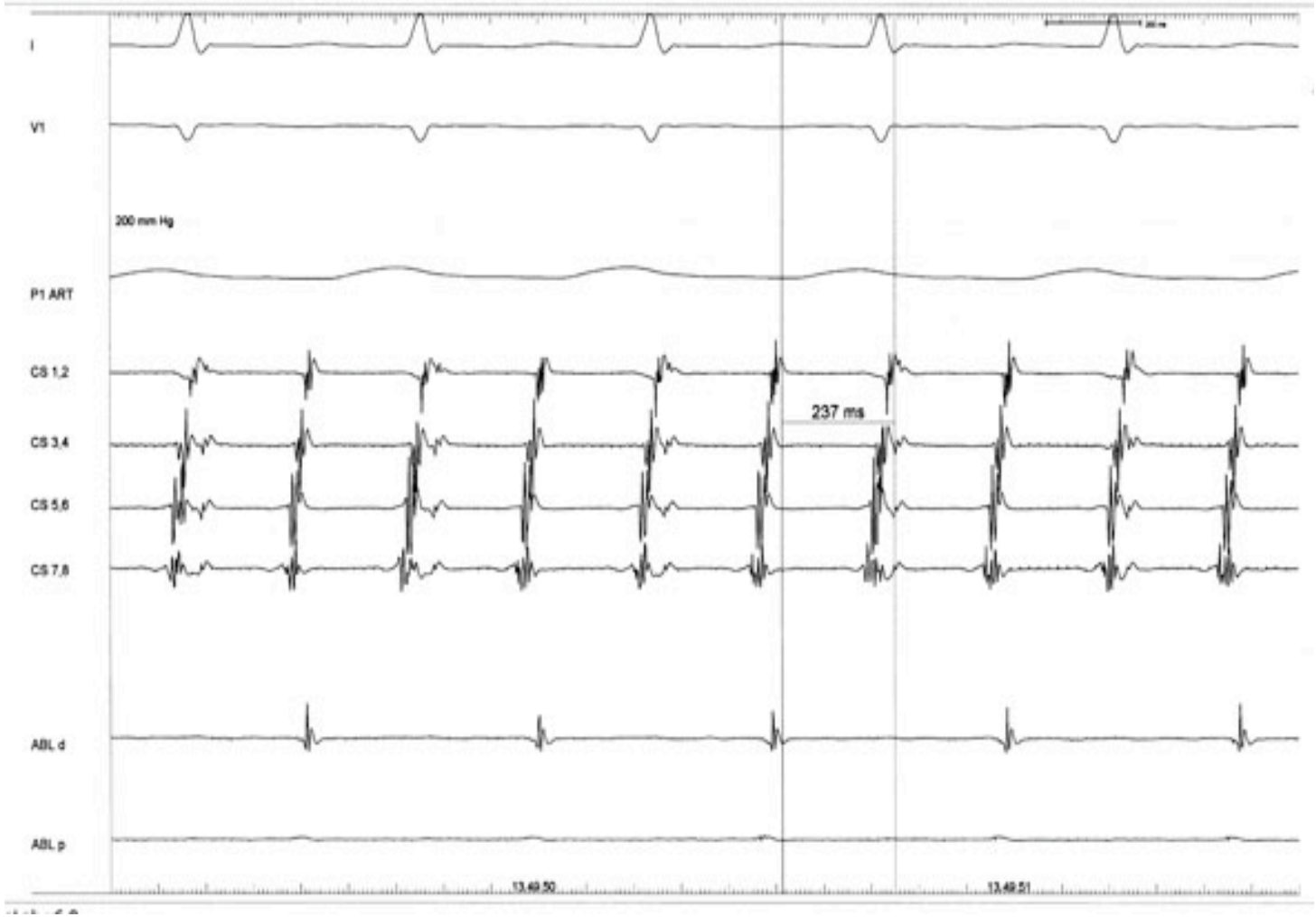


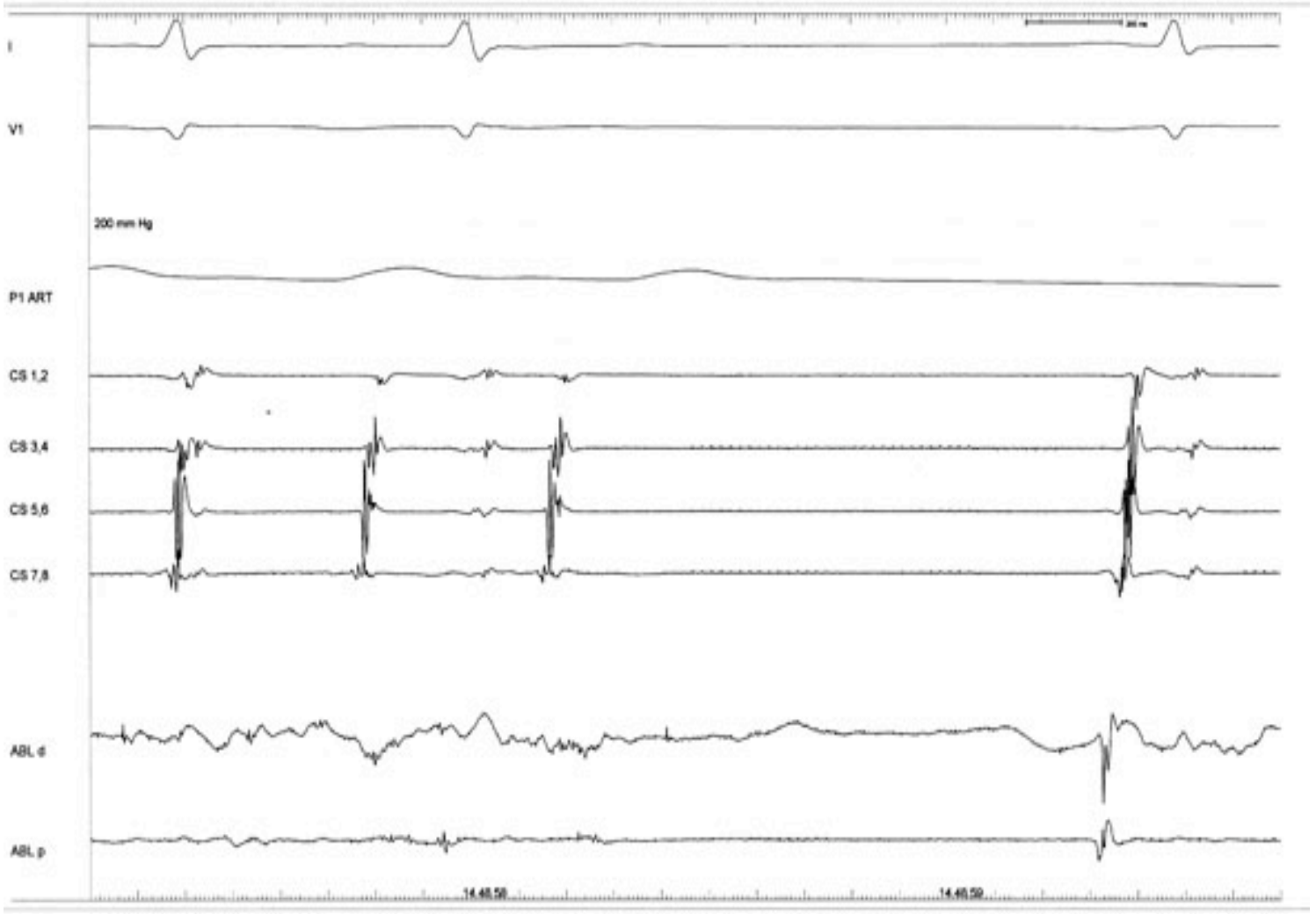
Before Flecainide



After Flecainide 4’45”

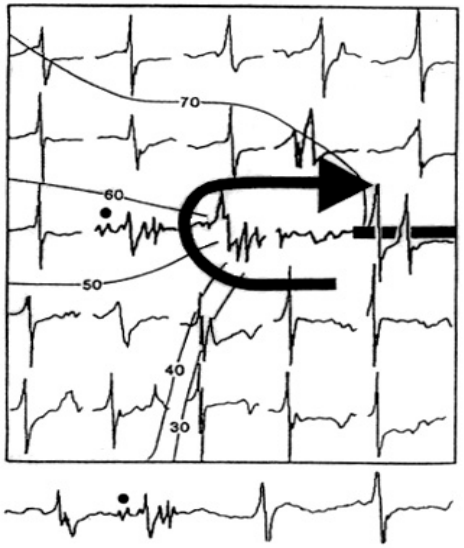

200 ms
V1
200 mm Hg
P1 ART
CS 1,2
CS 3,4
CS 5,6
CS 7,8
202 ms
ABL d
ABL p
12:46:55
12:46:56
12:46:57


I
V1
200 mm Hg
P1 ART
CS 1,2
CS 3,4
CS 5,6
CS 7,8
237 ms
ABL d
ABL p
13:49:50
13:49:51


I
V1
200 mm Hg
P1 ART
CS 1,2
CS 3,4
CS 5,6
CS 7,8
ABL d
ABL p
14:46:58
14:46:59

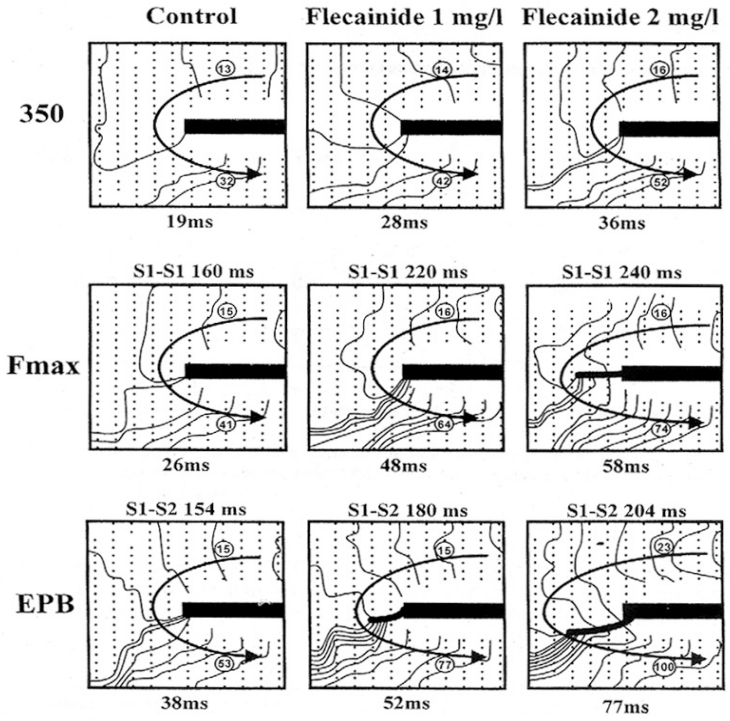
CONCLUSION

Termination of AF by flecainide in humans seems to be characterized by preferential conduction delay in the areas with baseline fragmented electrograms



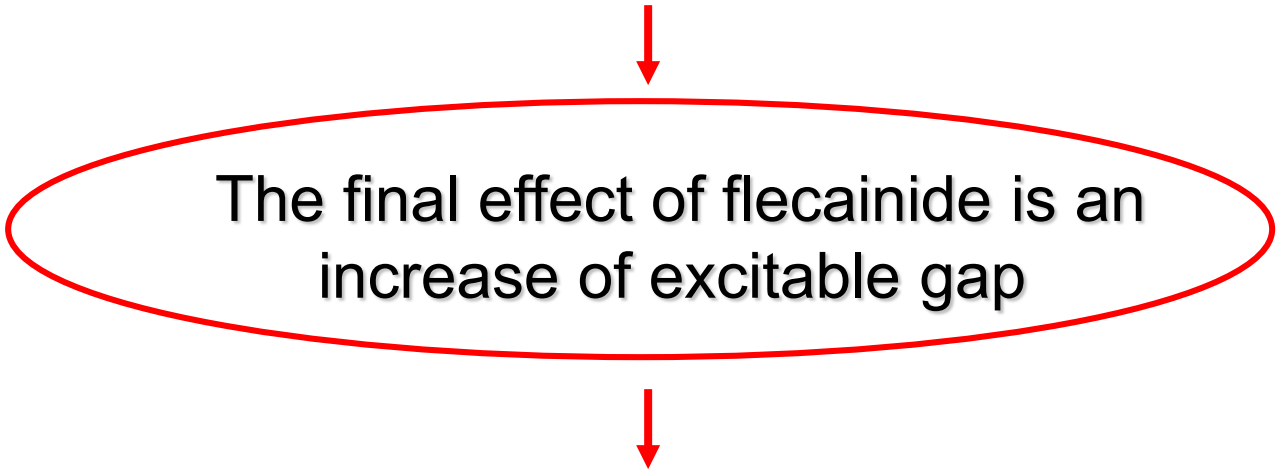
PIVOT POINTS

Our results confirm in human atrial myocardium the data of a recent experimental study (Danse PW et al. JCE 2000)



Flecainide causes a preferential depression of conduction around a pivot point in rabbit ventricular myocardium

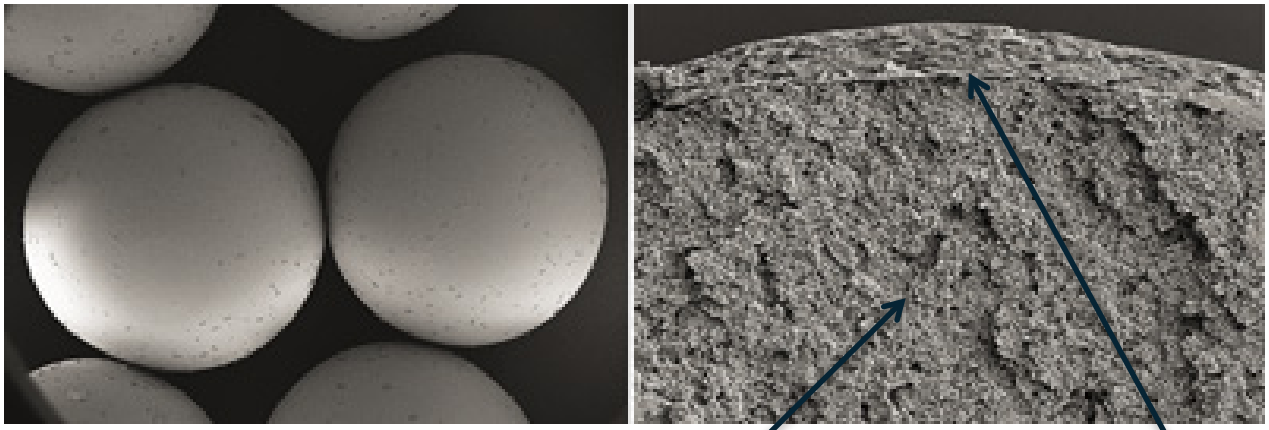
The relevant increase of FF interval by flecainide could be due to the preferential conduction delay at the pivot points rather than to the increase in the atrial ERP



The better recovery of excitability determine a greater fusion of wavelets favouring the termination of AF

FARMACOCINETICA DELLA FLECAINIDE RP

Struttura dei microgranuli alla microscopia elettronica



- Microgranuli rivestiti dal polimero a base di acido metacrilico-metil metacrilato (EUDRAGIT S-100).
- L'emivita di eliminazione (t ½) risulta essere di circa 20 ore.

CARATTERISTICHE FARMACOCINETICHE DELLA FLECAINIDE

Assorbimento

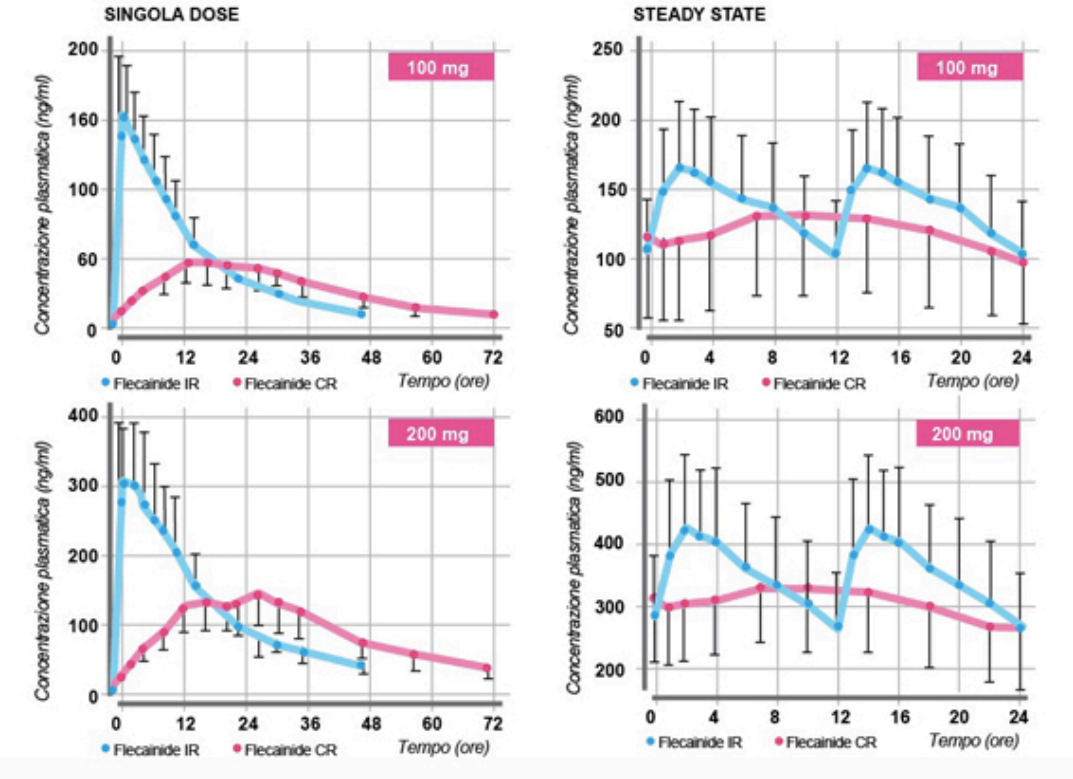
- I livelli di steady-state vengono raggiunte dopo 5 giorni di trattamento con un range di minima oscillazione ed il livellamento dei valori relativi alla concentrazione del picco plasmatico.

- Nessun accumulo a livello plasmatico è stato osservato nel trattamento cronico.

- La **flecainide** non viene sottoposta a un vasto metabolismo di primo passaggio.

- Per evitare che il cibo influisca sull'assorbimento del farmaco, **la flecainide deve essere assunta a stomaco vuoto** o un'ora prima dell'assunzione di cibo.

CARATTERISTICHE FARMACOCINETICHE DELLA FLECAINIDE

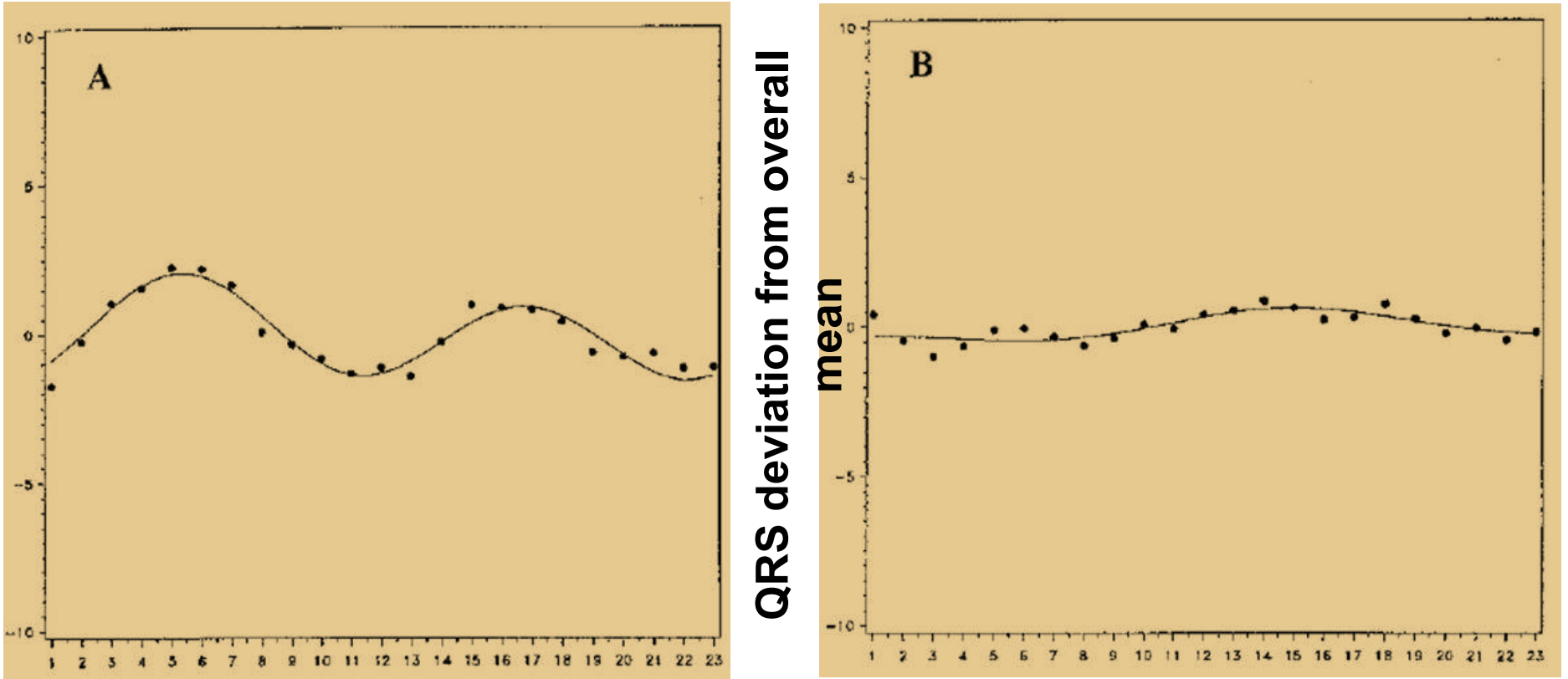


Concentrazioni plasmatiche di **flecainid**e (valori medi e SD) nel tempo per flecainide IR e flecainide CR dopo somministrazione di dose singola o ripetuta di 100 e 200 mg

Circadian variations of QRS duration

Flecainide immediate-release (IR) formulation

Flecainide controlled-release (CR) formulation



Hours from first administration

Philippe Coumel, J Cardiovasc Pharmacol 2003

Metodi

L'EPIFLEC STUDY* era uno studio prospettico, aperto, osservazionale condotto da 151 cardiologi che hanno prescritto:

- (gruppo 1) flecainide LI per 838 pazienti,
- (gruppo 2) flecainide LP a 214 pazienti,
- (gruppo 3) flecainide LI all'inizio – flecainide LP a seguire per 242 pazienti

La posologia utilizzata era compresa tra 100-200 mg/die.

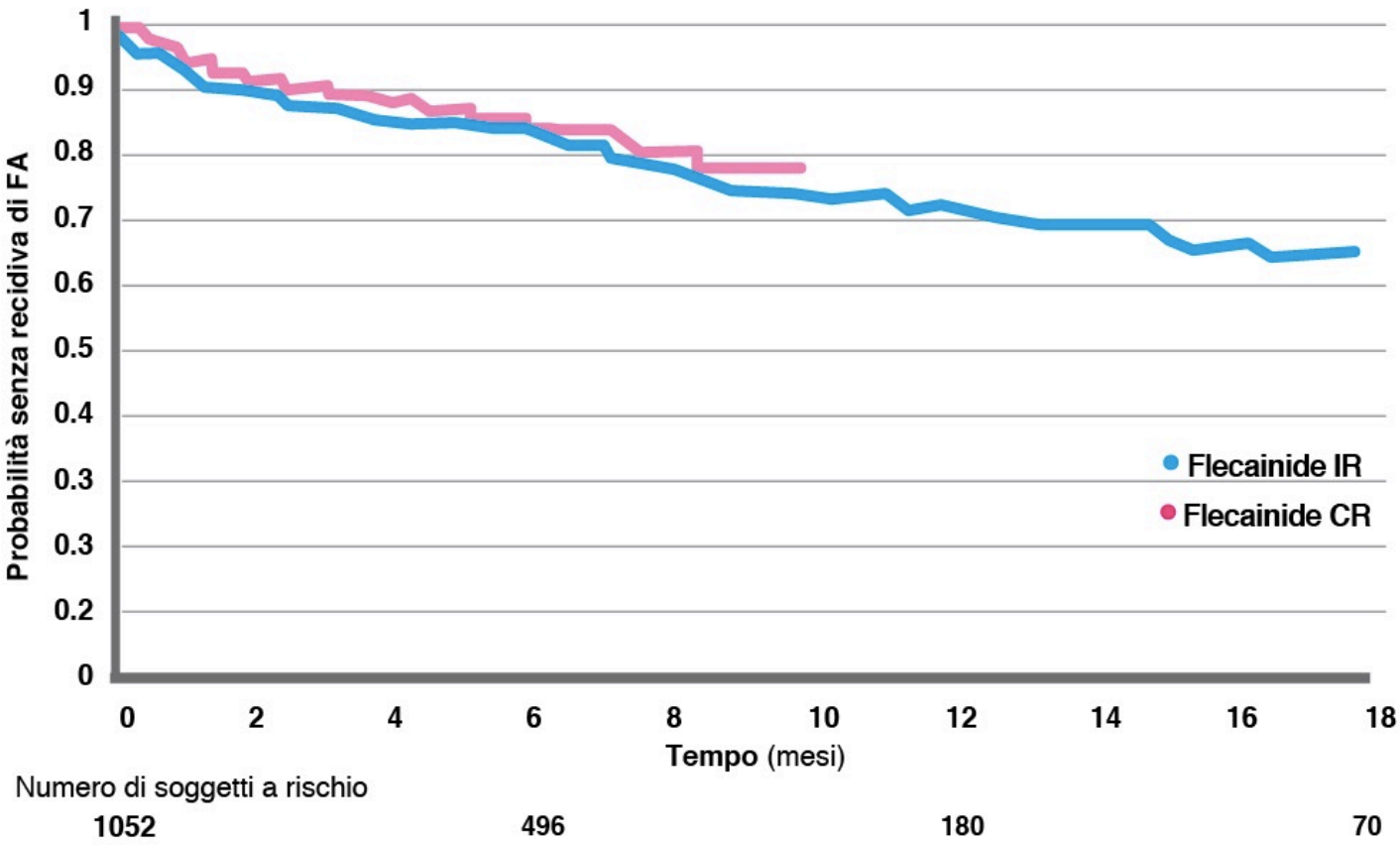
In questi pazienti, AF era o parossistica (35%) o persistente (65%).

Patologie concomitanti sono state osservate nel 80% di questi pazienti (età media 68 anni) con una elevata incidenza (50%) di ipertensione.

La durata media del trattamento è stata di:

- 6,9 +/- 6,7 mesi nel gruppo 1 (LI)
- 6.2 +/- 3.1 mesi nel gruppo 2 (LP)
- 12,7 +/- 5,4 mesi nel gruppo 3 (LI prima – LP dopo)

*Pharmaco-Epidemiological Flecainide study


Probabilità senza recidiva di FA
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.3
0.2
0
0
2
4
6
8
10
12
14
16
18
Tempo (mesi)
Flecainide IR
Flecainide CR
Numero di soggetti a rischio
1052
496
180
70

EPIFLEC STUDY

Eventi avversi cardiovascolari (CV) e non cardiovascolari (eccetto recidive della FA)	**Flecainide IR** (n= 838)	**Flecainide PR** (n= 214)	**Flecainide IR-PR** (n= 242)
Numero di eventi	161	40	44
Numero di pazienti con > 1 evento (%)	135(16)	35(16)	38(16)
Numero di decessi	9	0	0
OSPEDALIZZAZIONI			
Numero di ospedalizzazioni	49	16	4
Numero di pazienti (%)	58(5)	14(7)	3(1)
Numero di eventi CV non letali	87	20	24
Proaritmie	**3**	**1**	**1**
Flutter	**14**	**2**	**5**
Disturbi della conduzione atrio-ventricolare	**5**	**0**	**1**
Bradicardia sintomatica	**8**	**0**	**3**
Extrasistole ventricolare	**3**	**0**	**0**
Ipotensione ortostatica	0	0	1
Sincope	3	0	0
Infarto del miocardio	3	0	0
Bypass o angioplastica aortocoronarica		0	1
Angina instabile	3	0	0
Insufficienza cardiaca	9	2	2
Ictus o TIA	1	3	0
Altre	35	11	11
NUMERO DI EVENTI NON CV NON LETALI	65	20	20

Tipologie individuali di Non-Aderenza

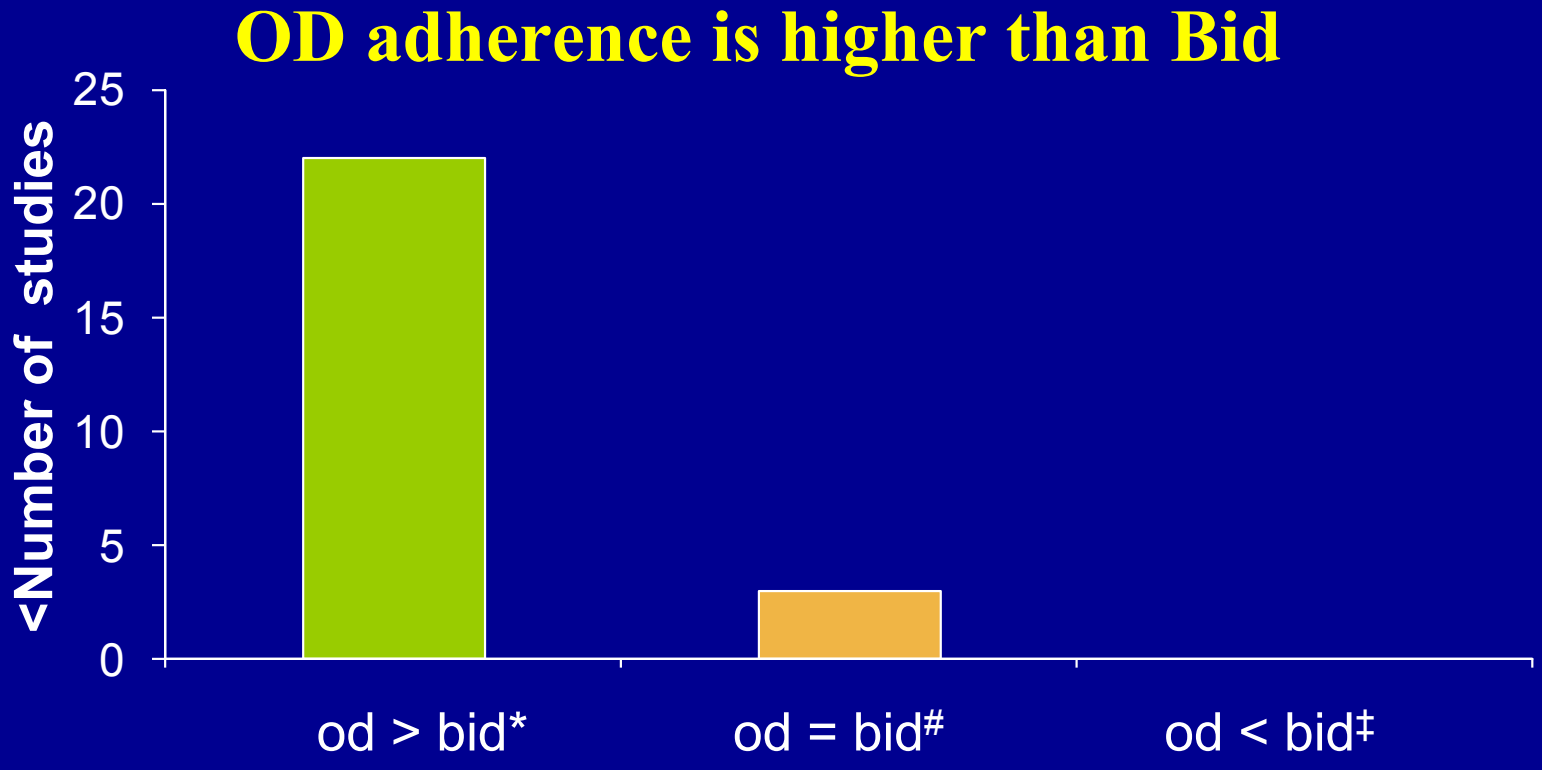
Non-Aderenza intenzionale

- Il paziente decide personalmente (in modo più o meno esplicito e consapevole) di non iniziare, ovvero proseguire, una terapia prescritta dal medico
- Conseguenza diretta: ***mancato inizio o interruzione del trattamento***

Non-Aderenza non-intenzionale

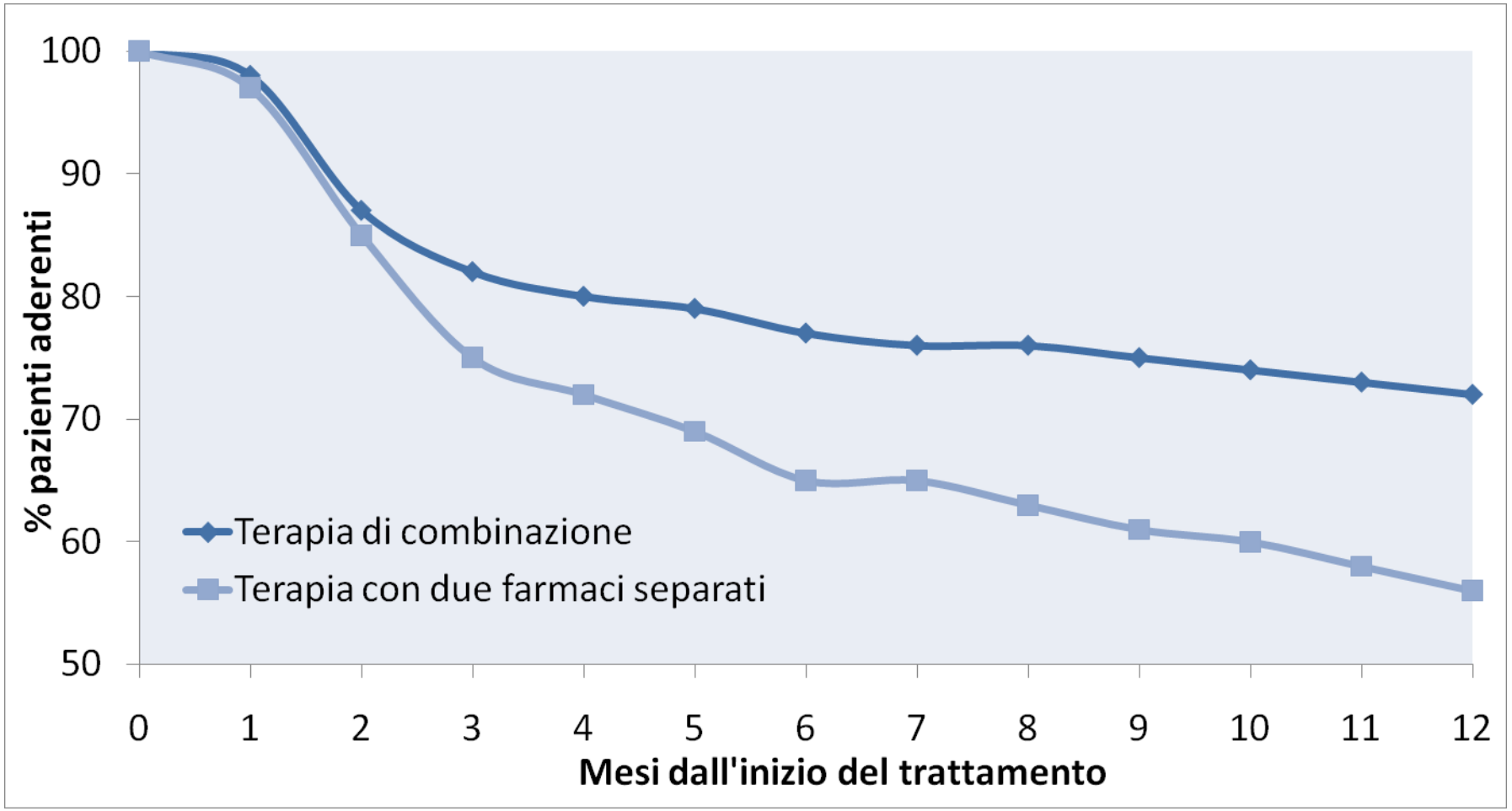
- Il paziente "vorrebbe" essere aderente alle prescrizioni, ma fattori contingenti lo impediscono. Si determina un occasionale o ricorrente "salto" di dose del farmaco
- Conseguenza diretta: ***sottodosaggio del farmaco*** (in genere meno del 70-80% della dose prescritta)

Studies evaluating the therapy adherence



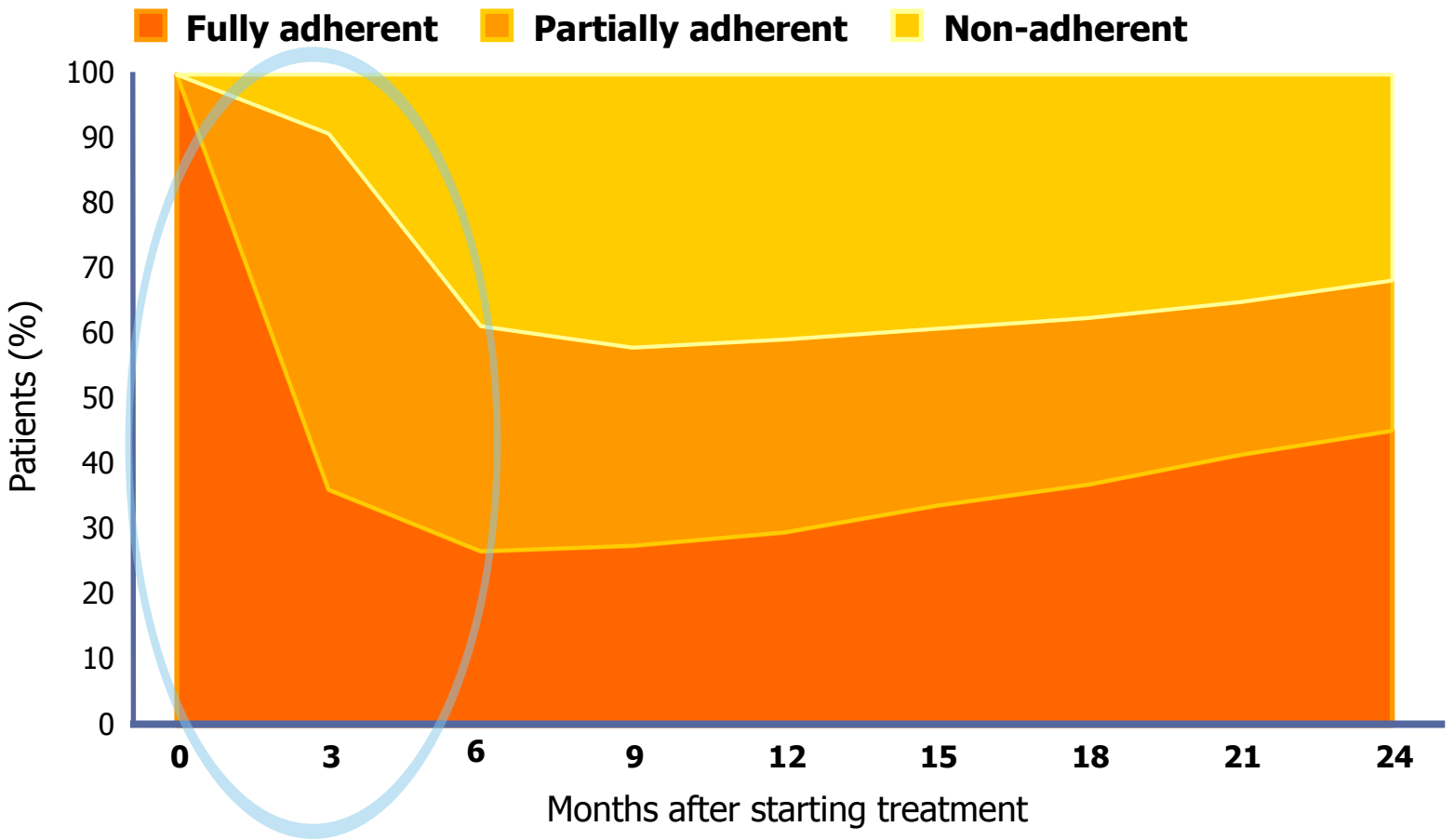
Pubmed; 2001–2011

Uno schema posologico più semplice migliora la continuità della terapia



DEZII CM. MANAG CARE. 2000;9 (SUPPL):S2-S6.

Adherence to Any Antihypertensive Drug



Sturkenboom et al. E*SH*, Milan 2005