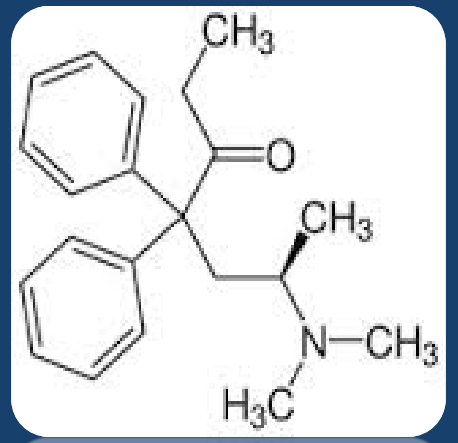
Is there a role for antiarrhythmic treatment in AF patients?



ALESSANDRO CAPUCCI M.D.
Clinica di Cardiologia e Aritmologia
Universita' Politecnica delle Marche
Ancona

DISCLOSURES

- Speaker Fee:
- Abbot, Bayer,Boheringer,Boston Scientific,Meda,Medico, Sanofi-Synthelabo,Sorin.

Therapeutic options for AF

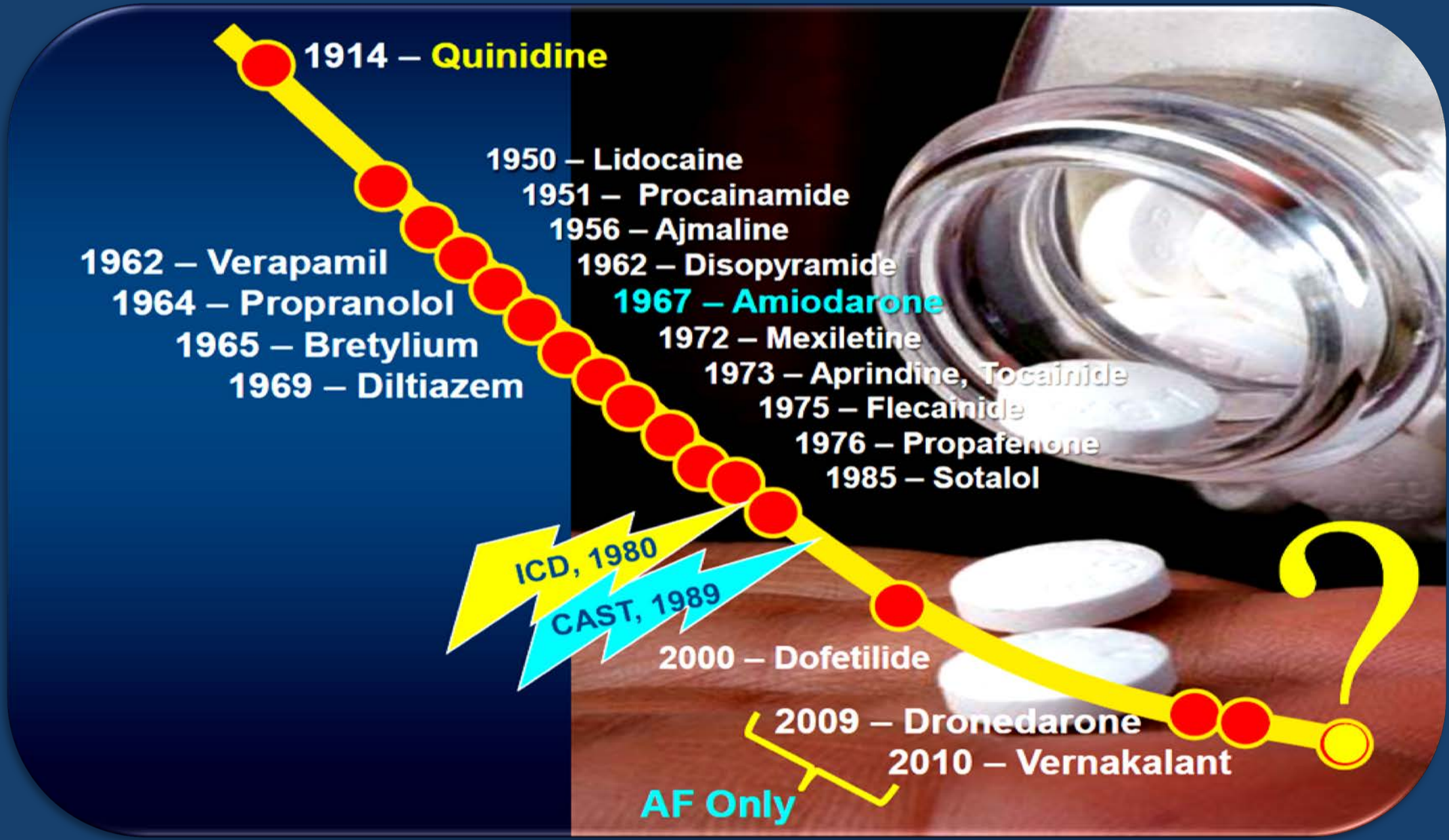
1. Rhythm control
2. Rate control
3. AF ablation
4. AV node ablation
5. Pill in the pocket

DRAFT

Key topics in the management of AF: focus of 2012 update

- Anticoagulation risk stratification
- Use of novel oral anticoagulants (NOACs)
- Left atrial appendage occlusion / excision
- Pharmacological cardioversion (vernakalant)
- **Oral antiarrhythmic therapy (dronedarone and short-term therapy)**
- Left atrial catheter ablation

Camm AJ, et al. Eur Heart J. 2012;33:2719-47.


1914 – Quinidine
1950 – Lidocaine
1951 – Procainamide
1956 – Ajmaline
1962 – Disopyramide
1962 – Verapamil
1964 – Propranolol
1965 – Bretylium
1967 – Amiodarone
1969 – Diltiazem
1972 – Mexiletine
1973 – Aprindine, Tocainide
1975 – Flecainide
1976 – Propafenone
1985 – Sotalol
ICD, 1980
CAST, 1989
2000 – Dofetilide
2009 – Dronedarone
2010 – Vernakalant
AF Only

Classificazione dei farmaci antiaritmici di Vaughan Williams e Harrison (I)

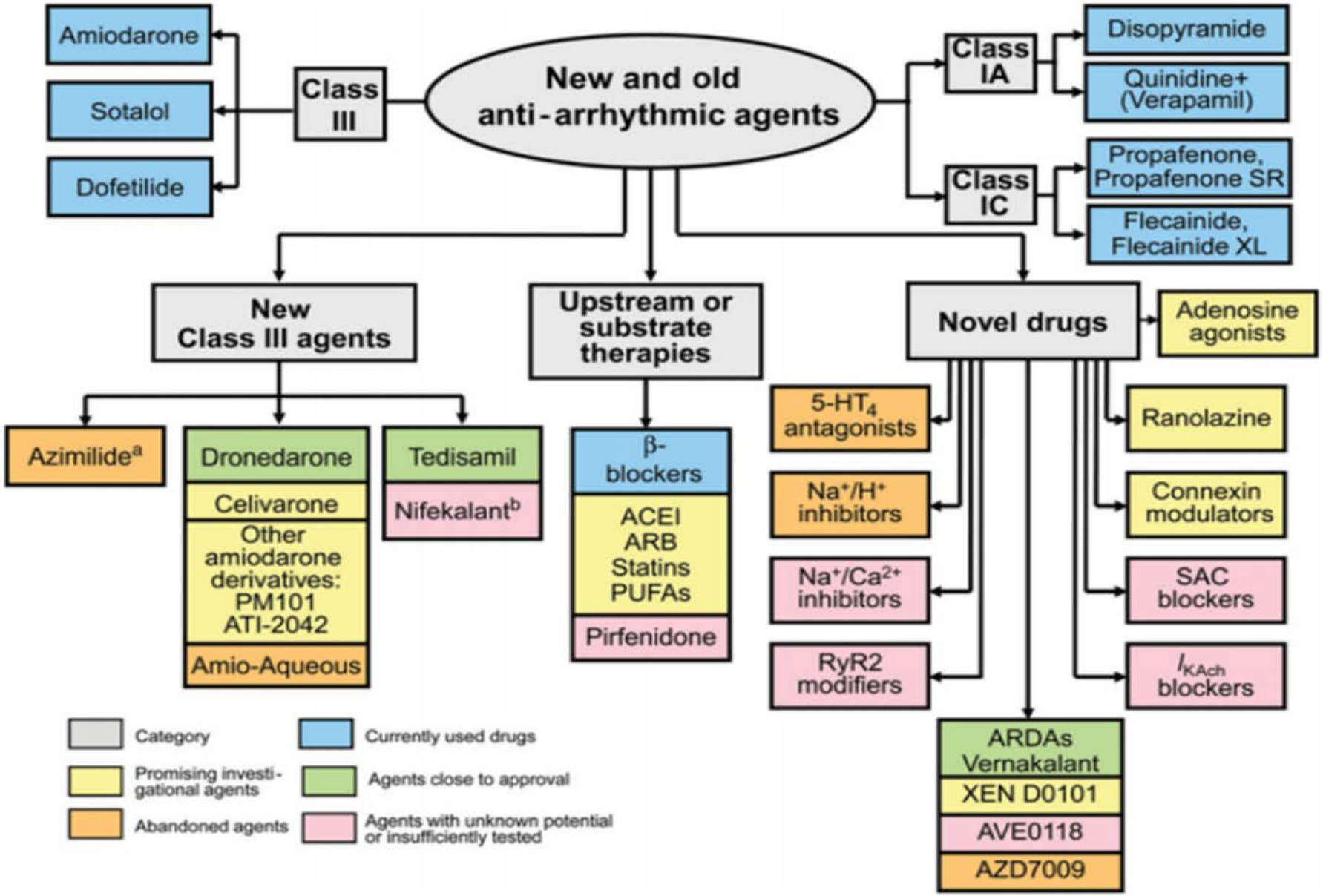
Classe e meccanismo d'azione	*Esempi*
I Bloccanti i canali del Na^+	
IA Blocco dei canali del Na^+: ++ • **Depressione della fase 0: ++** • **Rallentamento della conduzione: ++** **Blocco dei canali del K^+: ++** • **Prolungamento della ripolarizzazione: ++** • **Prolungamento della refrattarietà: ++**	***chinidina, procainamide, disopiramide***
IB Blocco dei canali del Na^+: ++ • **Depressione della fase 0: +** • **Rallentamento della conduzione:** **Tessuto normale: ±** **Tessuto patologico: +** **Blocco dei canali del K^+: -** • **Prolungamento della ripolarizzazione: -** • **Prolungamento della refrattarietà: -**	***lidocaina, difenilidantoina, mexiletina, tocainide***
IB Blocco dei canali del Na^+: ++ • **Depressione della fase 0: +++** • **Rallentamento della conduzione: +++** **Blocco dei canali del K^+: +** • **Prolungamento della ripolarizzazione: +** • **Prolungamento della refrattarietà: +**	***encainide, flecainide, moricizina, propafenone***

Modificato da: Harrison DA. Am J Cardiol 1985; 56: 185-7

Classificazione dei farmaci antiaritmici di Vaughan Williams e Harrison (II)

Classe e meccanismo d'azione	*Esempi*
II Bloccanti i recettori β- adrenergici	***propranololo, acebutololo, atenololo, metoprololo, nadololo,timololo, esmololo***
III Bloccanti i canali del K^+ • **Prolungamento della ripolarizzazione: +++** • **Prolungamento della refrattarietà: +++**	***amiodarone, bretilio, sotalolo***
IV Bloccanti i canali del Ca^{++} • **Riduzione dell'automatismo delle cellule del nodo seno-atriale; rallentamento della conduzione e aumento della rafrattarietà delle cellule del nodo atrio-ventricolare**	***verapamil diltiazem gallopamil***

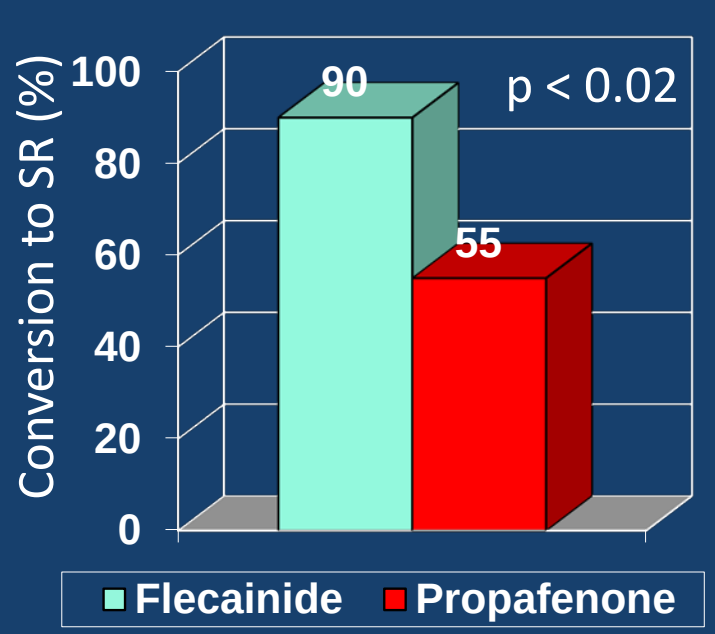
Modificato da: Harrison DA. Am J Cardiol 1985; 56: 185-7

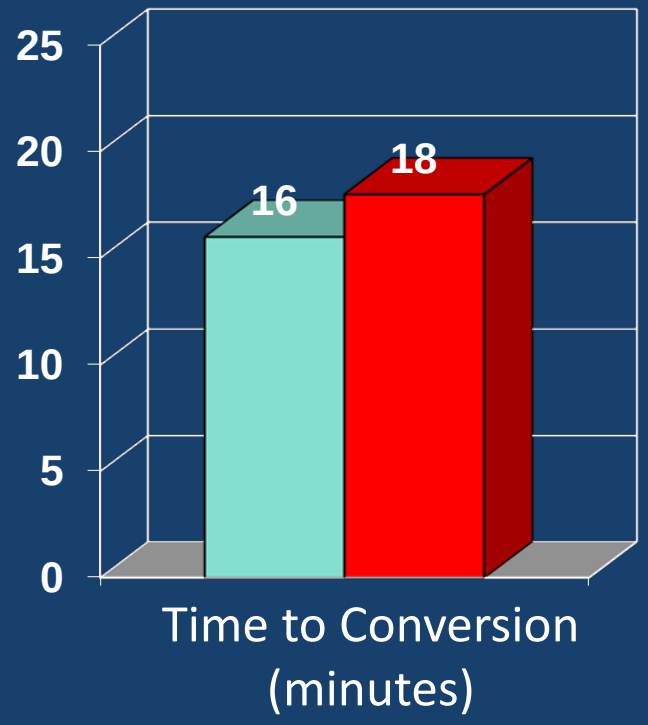

New and old anti-arrhythmic agents
Class III
Amiodarone
Sotalol
Dofetilide
Class IA
Disopyramide
Quinidine+ (Verapamil)
Class IC
Propafenone, Propafenone SR
Flecainide, Flecainide XL
New Class III agents
Azimilide[a]
Dronedarone
Celivarone
Other amiodarone derivatives: PM101 ATI-2042
Amio-Aqueous
Tedisamil
Nifekalant[b]
Upstream or substrate therapies
β-blockers
ACEI ARB Statins PUFAs
Pirfenidone
Novel drugs
Adenosine agonists
5-HT4 antagonists
Na+/H+ inhibitors
Na+/Ca2+ inhibitors
RyR2 modifiers
Ranolazine
Connexin modulators
SAC blockers
IKAch blockers
ARDAs Vernakalant
XEN D0101
AVE0118
AZD7009
Category
Currently used drugs
Promising investi-gational agents
Agents close to approval
Abandoned agents
Agents with unknown potential or insufficiently tested

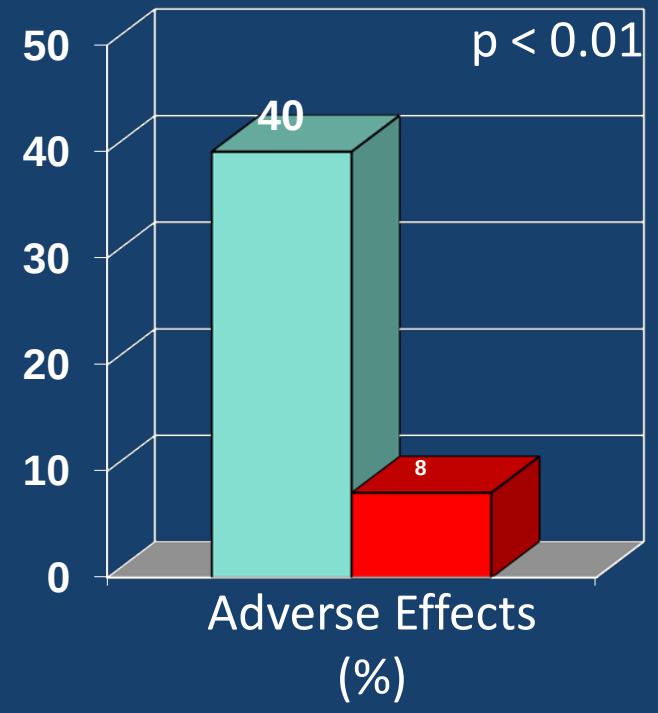
FLECAINIDE E PROPAFENONE

Atrial Fibrillation
Conversion with i.v. 1C Antiarrhythmic Drugs

50 pts with AF / AFL (arrhythmia duration < 24 h in 31 pts)

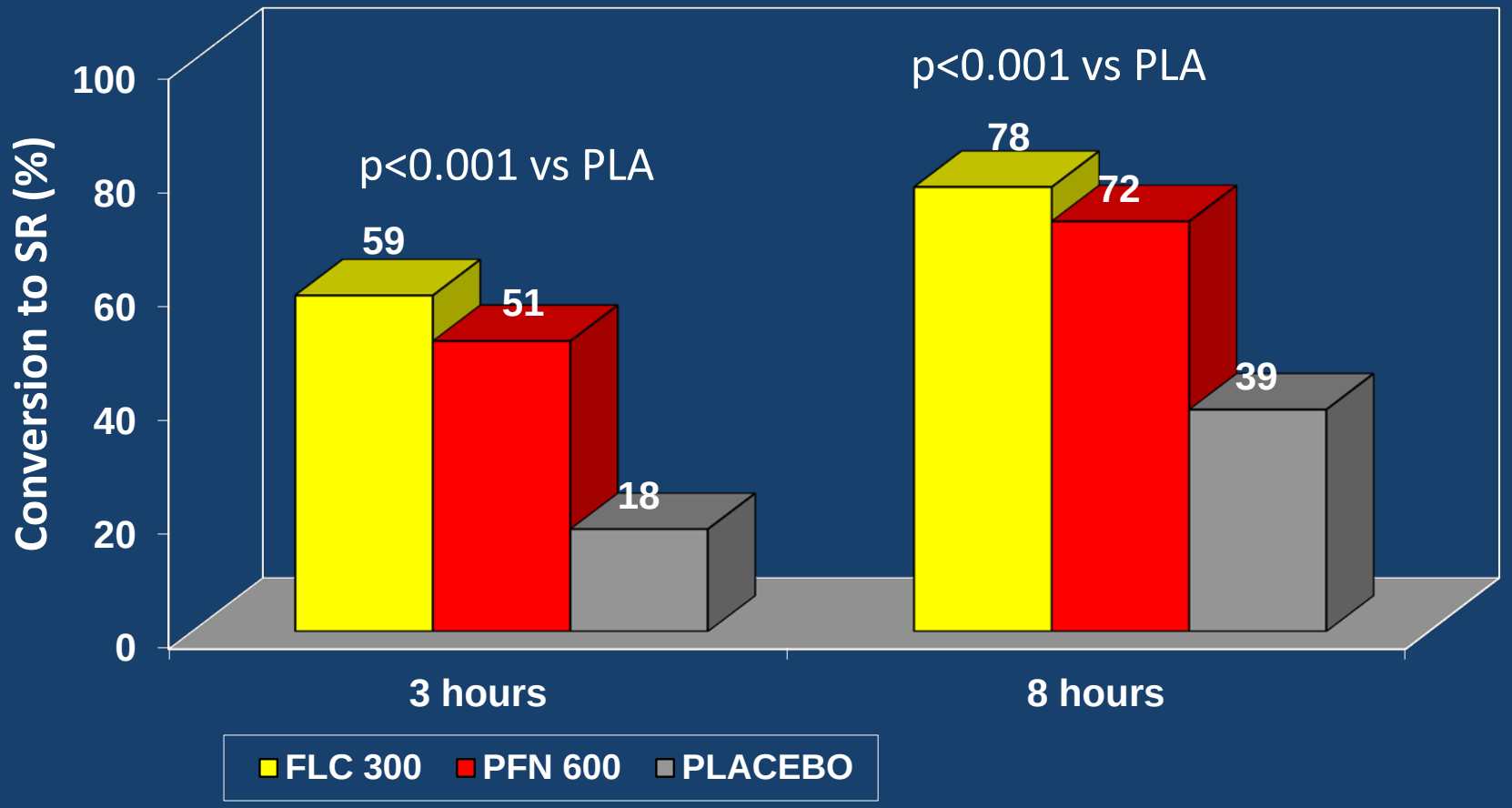






Suttorp M.J. J Am Coll Cardiol 16:1722; 1990

Atrial Fibrillation
Oral Flecainide or Propafenone in Recent Onset AFIB



Capucci A., Am J Cardiol 74: 503; 1994

Recommendations for pharmacological cardioversion

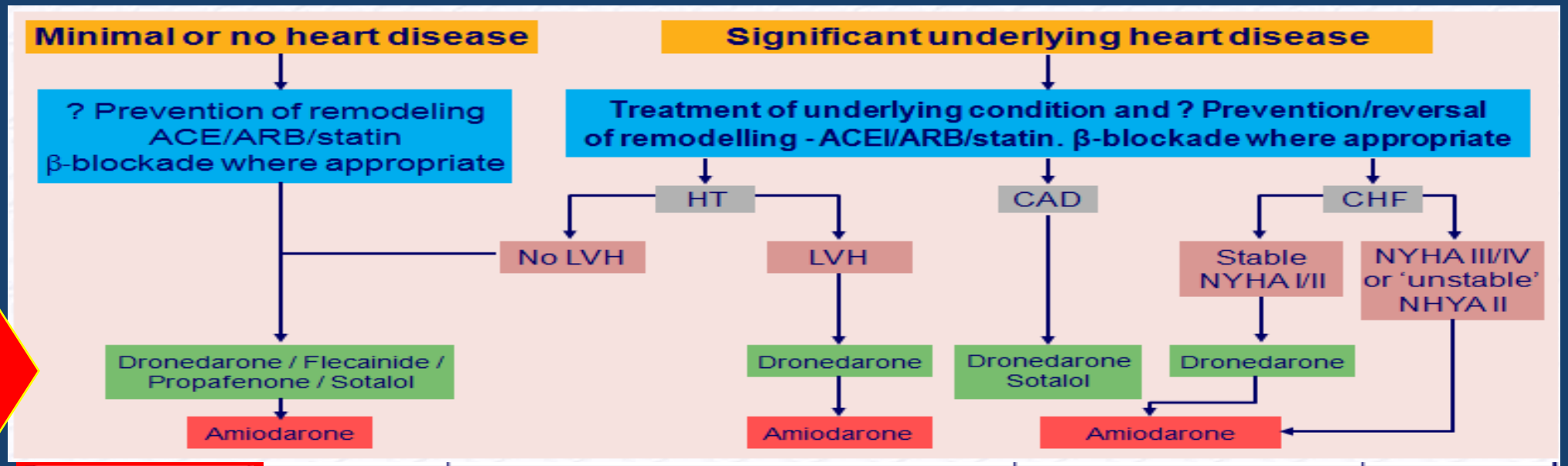
Recommendations	Class[a]	Level[b]	Ref.[c]
When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.	I	A	71–73
In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.	I	A	74–76
In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.	IIa	B	67

ESC Guidelines 2012

Condizioni critiche

- Popolazione di pazienti valutata
- Tipo di FA
- Tempo di trattamento dall’ insorgenza

Atrial Fibrillation
Rhythm control

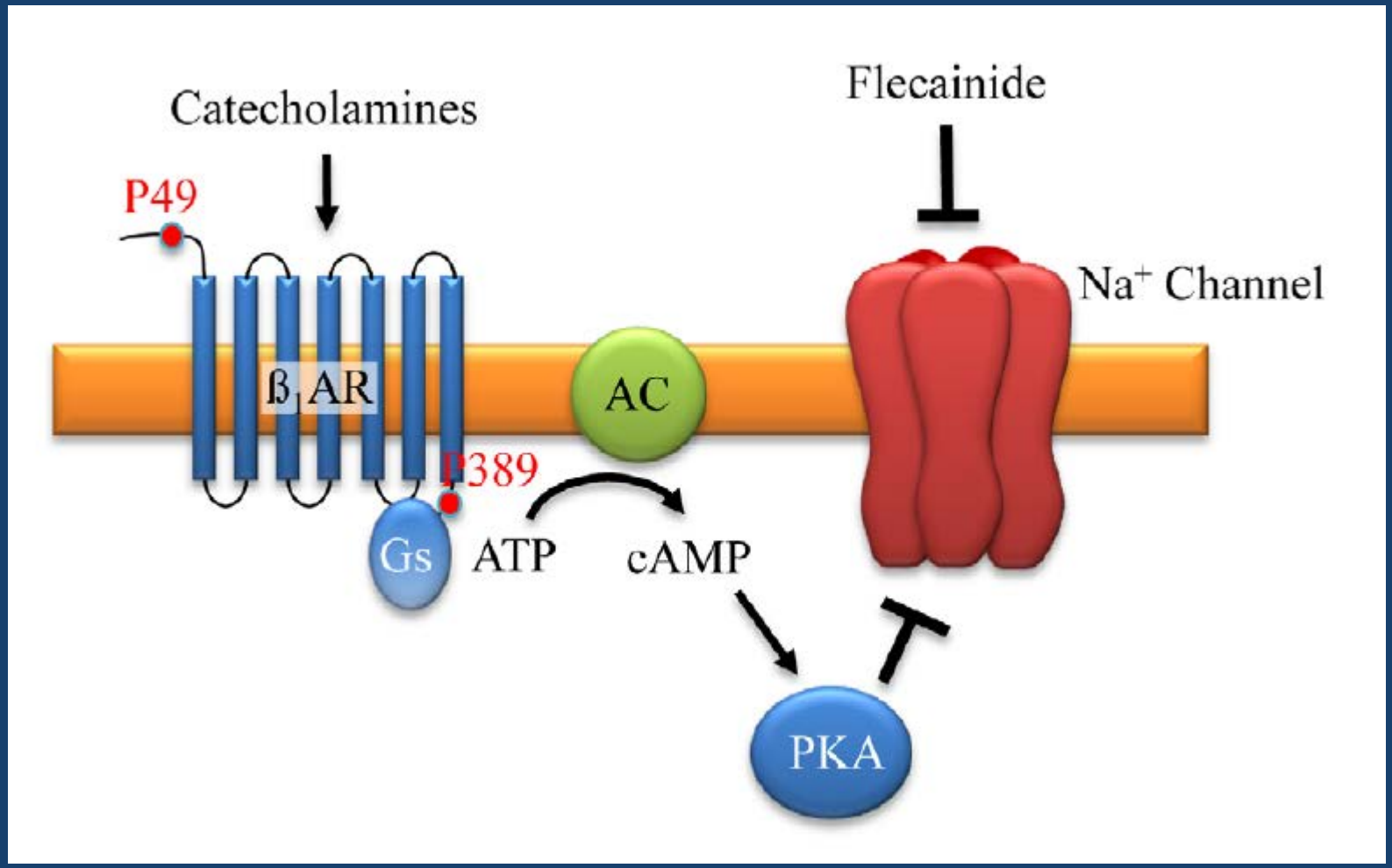


Flecainide	100-200 mg b.i.d.	Contraindicated if creatinine clearance < 50 mg/mL, in coronary artery disease, reduced LV ejection fraction.	QRS duration increase > 25% above baseline	None
Flecanide XL	200 mg o.d.	Caution in the presence of conduction system disease.		
Propafenone	150-300 mg t.i.d.	Contraindicated in coronary artery disease, reduced LV ejection fraction.	QRS duration increase > 25% above baseline	Slight
Propafenone SR	225-425 mg b.i.d.	Caution in the presence of conduction system disease and renal impairment.		

ESC Guidelines 2012

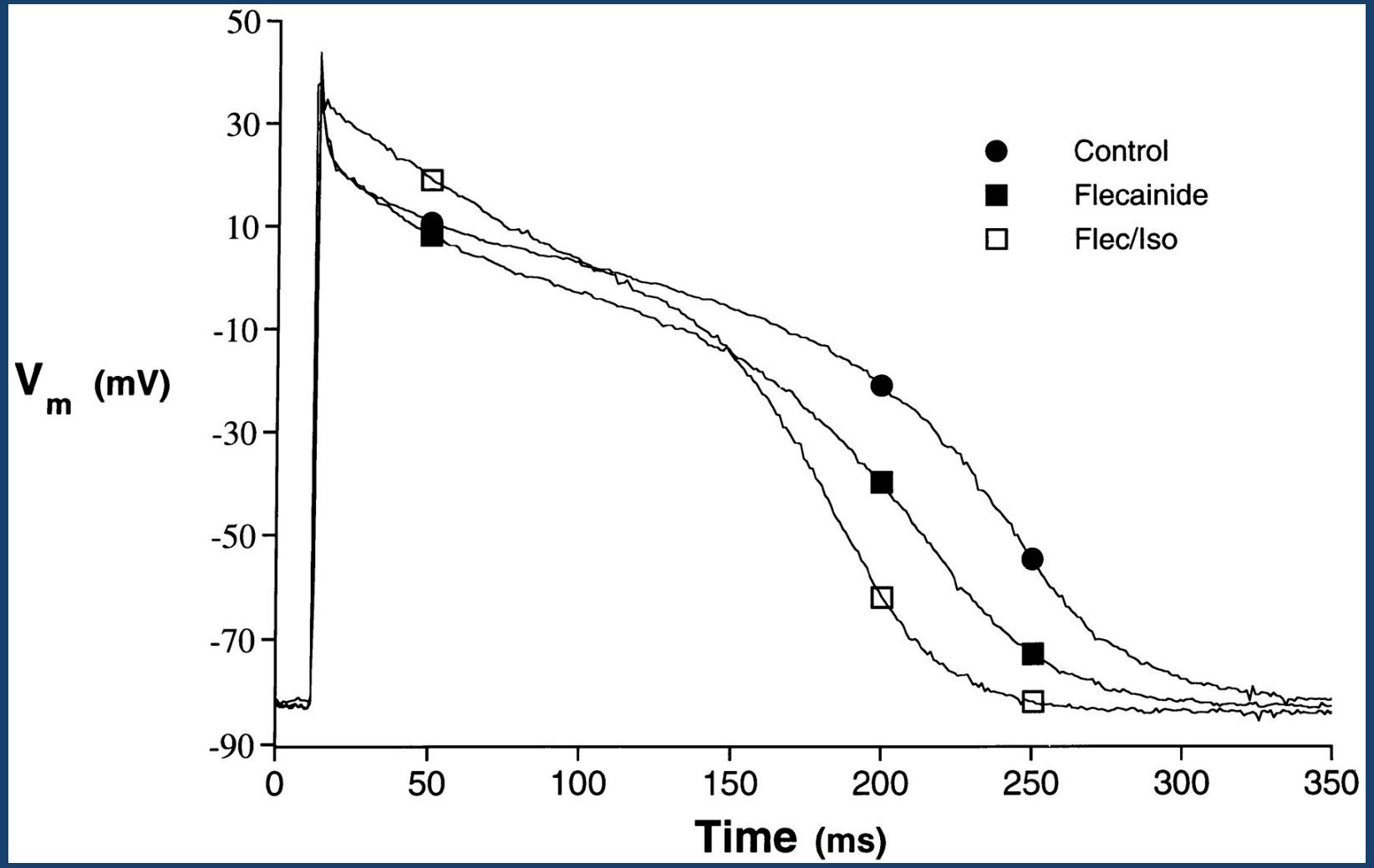
Beta$_1$-Adrenoceptor Polymorphism Predicts Flecainide Action in Patients with Atrial Fibrillation

Amir M. Nia[1☯], Evren Caglayan[1☯], Natig Gassanov[1☯], Tom Zimmermann[1], Orhan Aslan[1], Martin Hellmich[2], Firat Duru[3], Erland Erdmann[1], Stephan Rosenkranz[1], Fikret Er[1*]



Nia et al. PLoS ONE 2009

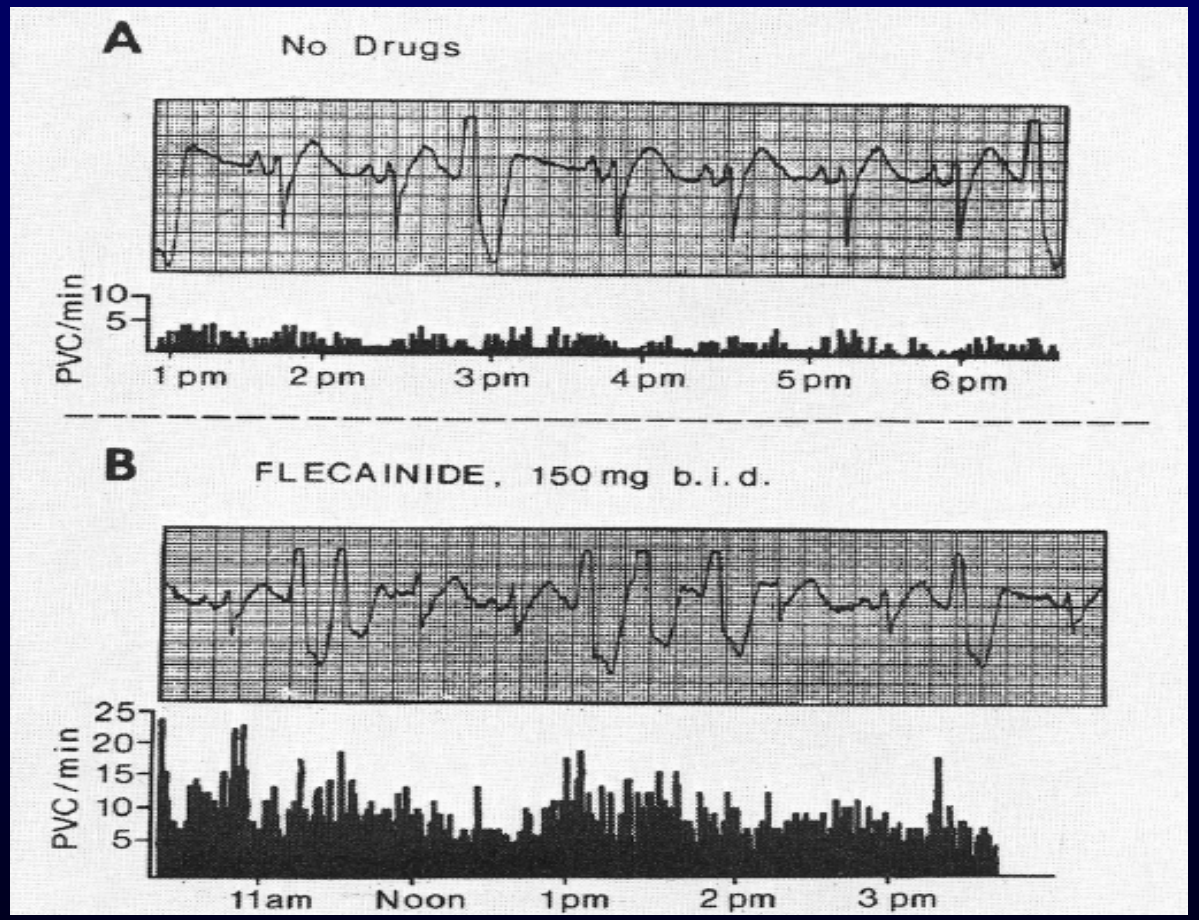
Modification of APD by flecainide and flec+isoproterenol in a single canine Purkinje fiber

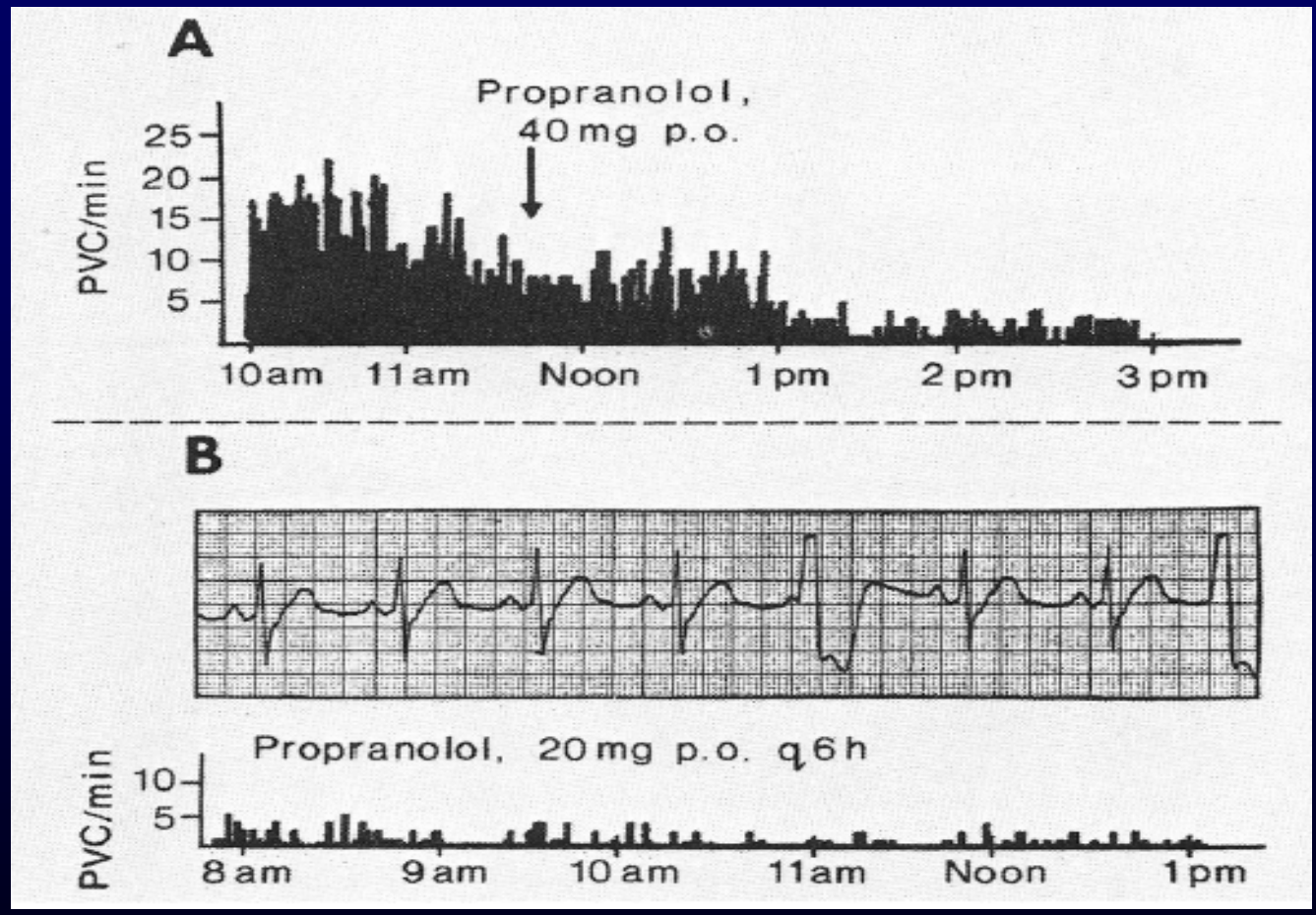


Myerburg et al. Circulation 1997

Reversal of proarrhythmic effects of flecainide acetate and encainide hydrochloride by propranolol.

R J Myerburg, K M Kessler, M M Cox, H Huikuri, E Terracall, A Interian, Jr, P Fernandez and A Castellanos





Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Circulation 1989

Our Study design

- Prospective randomized open trial in patients with persistent atrial fibrillation

Study endpoints

- One year symptomatic atrial fibrillation recurrence rate
- Improvements of quality of life during one year follow-up

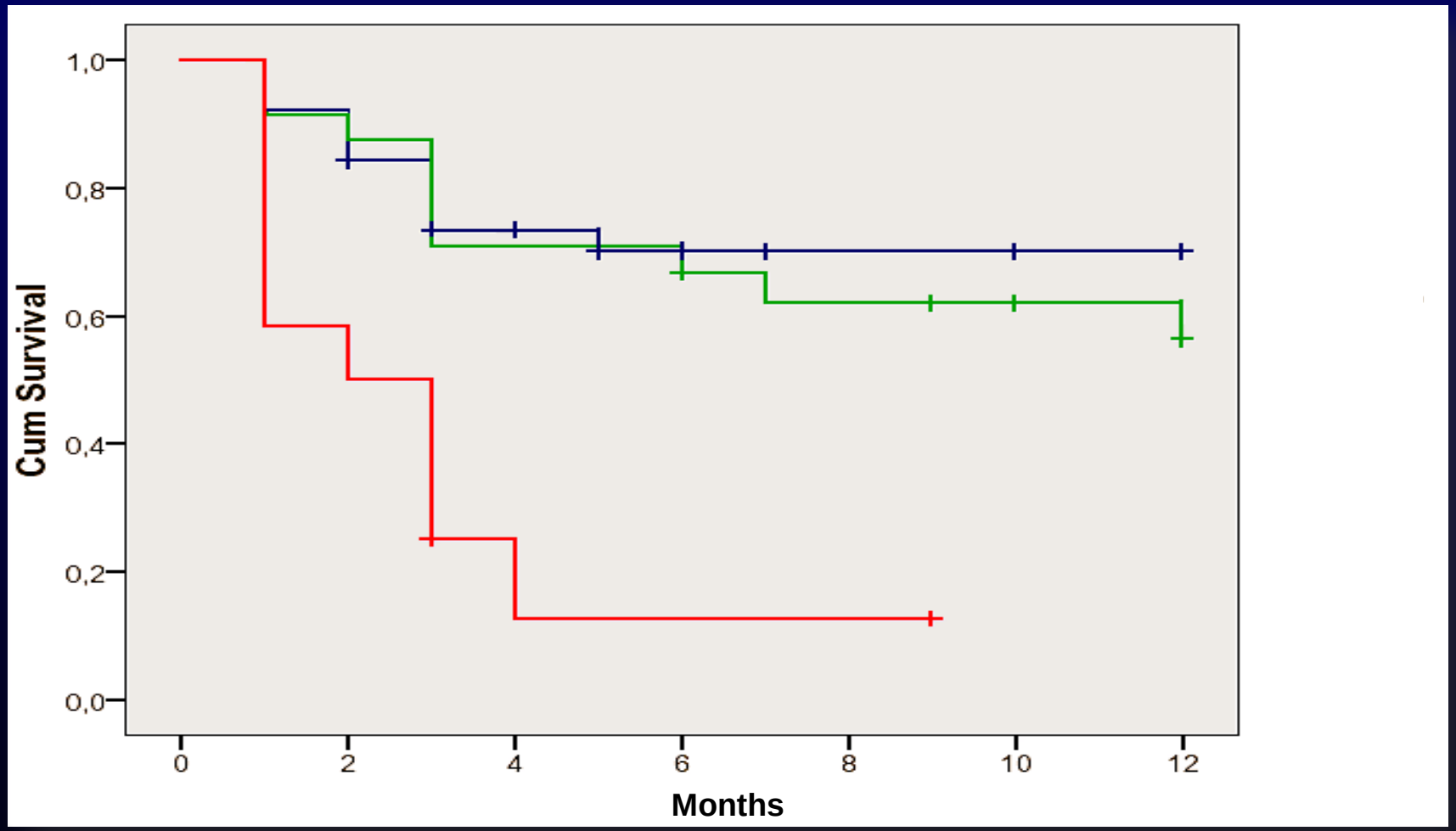
Capucci et al. *In press*

Maximum dose up-tritation

- **1 month:**
  - Group A: Flecainide 50 mg x 2 + Metoprolol 50 mg x 2
  - Group B: Flecainide 50 mg x 2
  - Group C: Metoprolol 50 mg x 2
- **3 months:**
  - Group A: Flecainide 100 + 50 mg + Metoprolol 50 mg x 2
  - Group B: Flecainide 100 + 50 mg
  - Group C: Metoprolol 50 mg x 2
- **6 months:**
  - Group A: Flecainide 100 mg x 2 + Metoprololo 50 mg x 2
  - Group B: Flecainide 100 mg x 2
  - Group C: Metoprololo 100 mg x 2
- **1 year**: end of follow-up

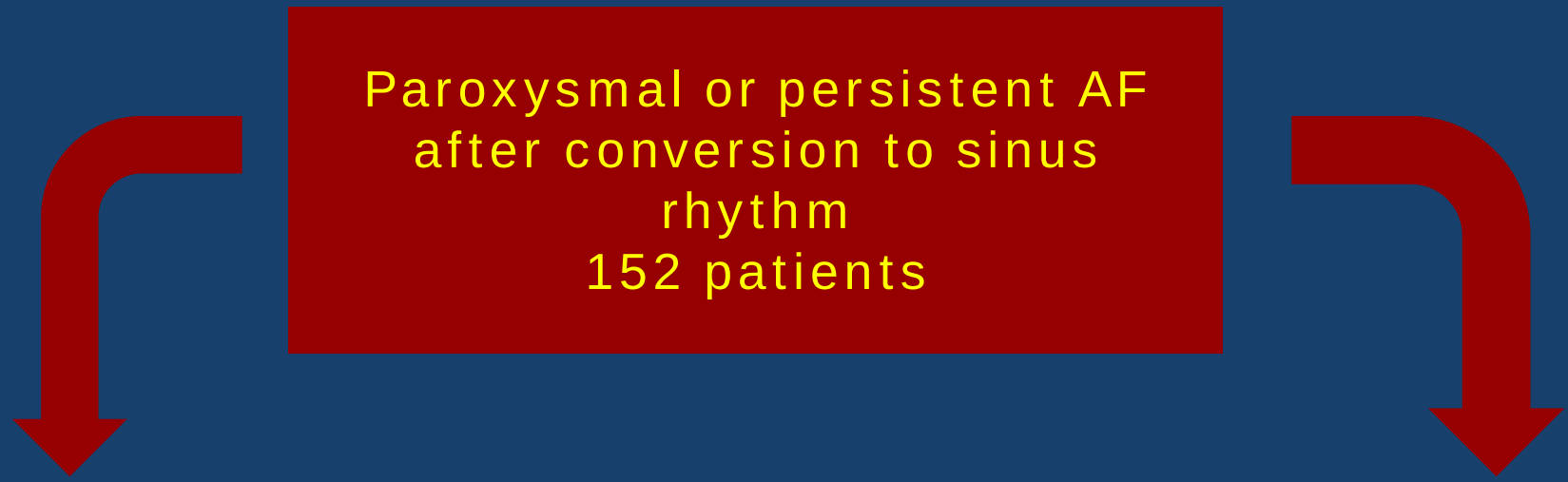
Atrial fibrillation recurrence rate

90% of recurrences are described in the first 6 months



Capucci et al., provisional data

Treatment strategy



Flecainide + metoprolol

80 patients

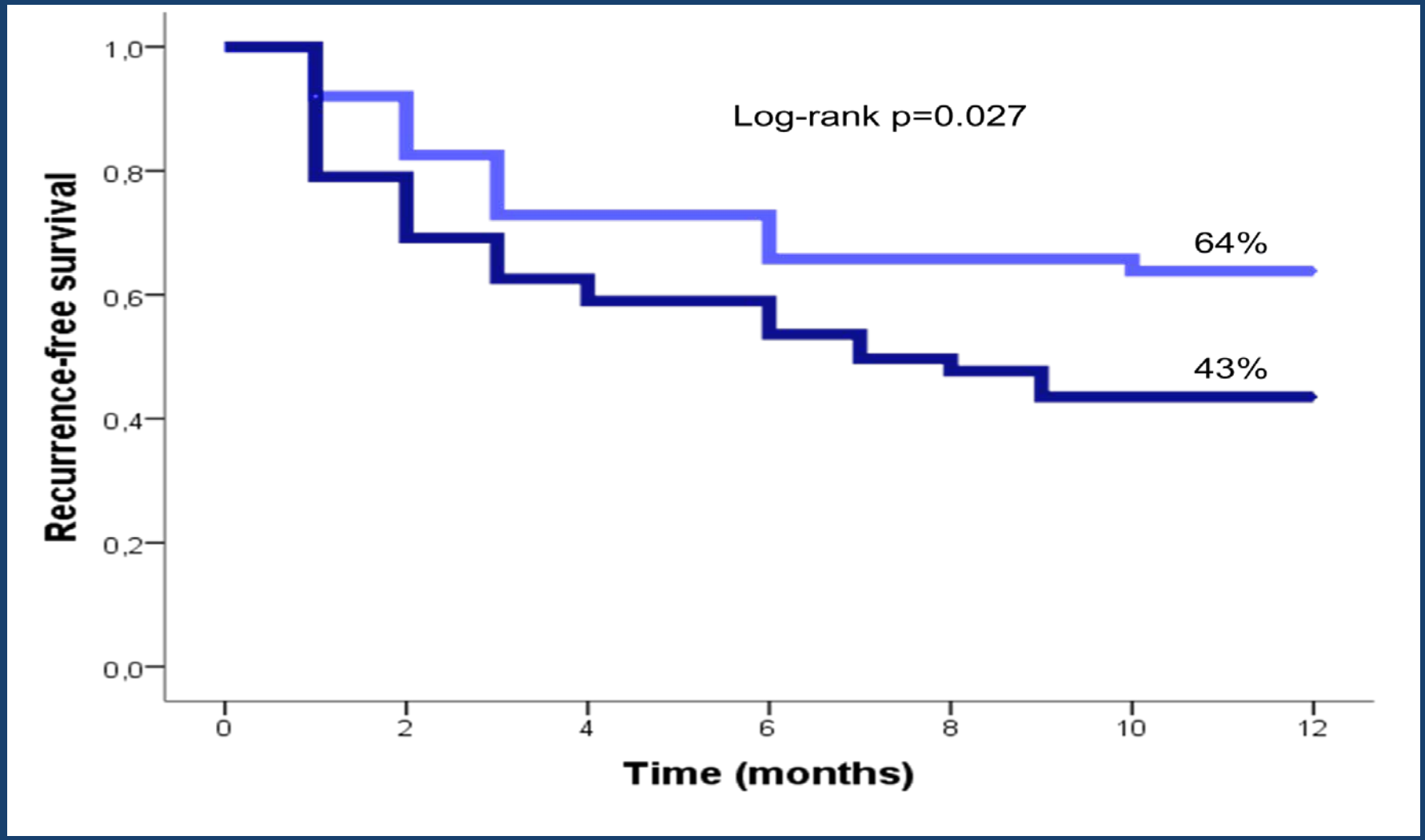
Flecainide

72 patients

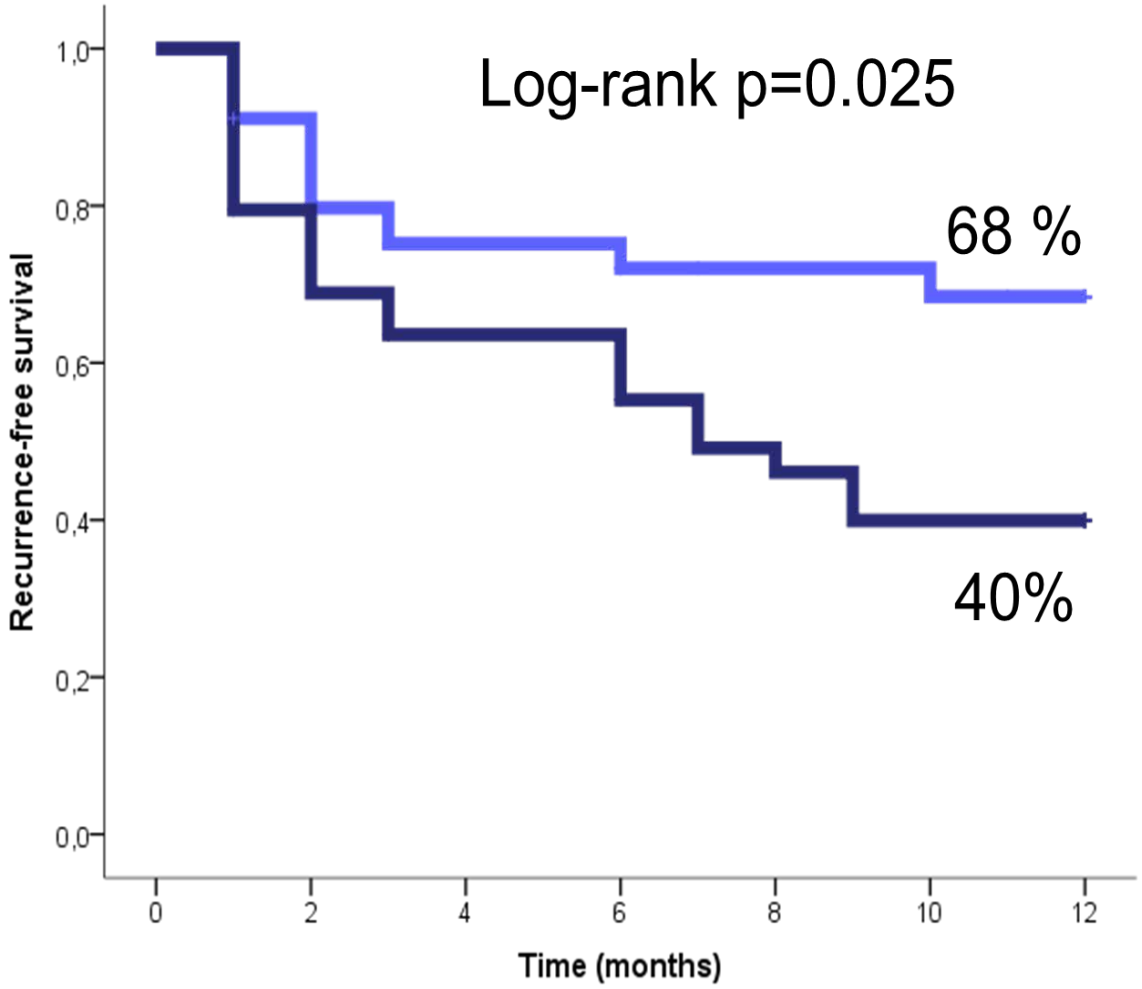
Capucci et al. *In press*

Variable	Combination (n=80)	Flecainide (n=72)	p
Age (years)	66,6±12.9	65,9±11.5	,708
Male gender (%)	55,0	66,7	,152
AF history (%)	25,4	16,7	,214
Hypertension (%)	72,5	64,3	,279
Diabetes (%)	11,3	12,5	,504
Dyslipidemia (%)	51,3	46,4	,553
Smoking Habit (%)	21,1	24,2	,663
eGFR<60 ml/min(%)	14,1	11,5	,665
Obesity (%)	21,1	18,2	,667
COPD (%)	11,1	19,7	,186
CHA2DS2-Vasc	2,4	2,3	,564
LAD (mm)	43.9±4.6	42.9±8.7	.482
LVEDD (mm)	51.4±5.5	50.8±4.8	.553
LVEF	59.4±9.1	60.2±10.5	.512

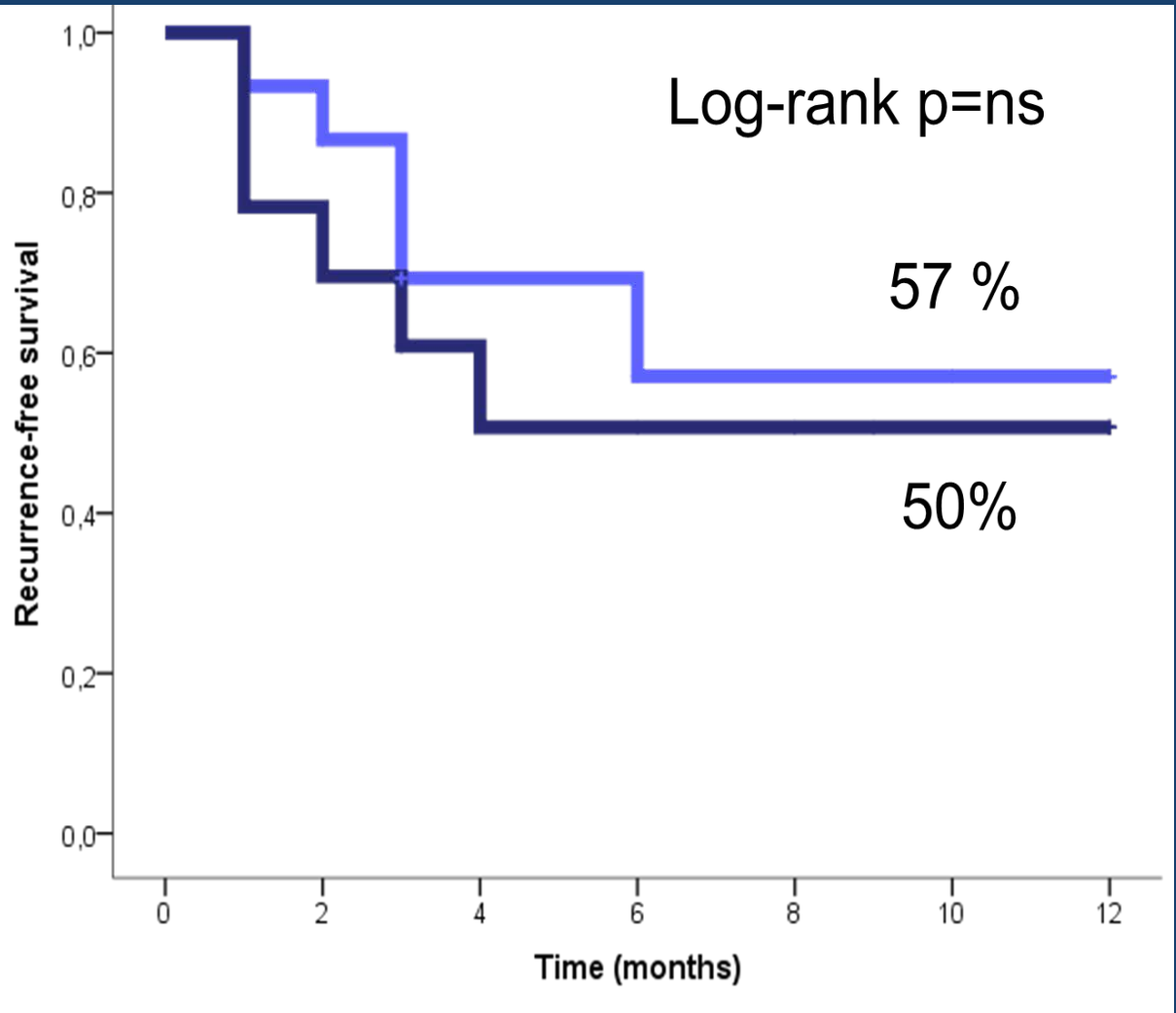
Time free from AF recurrence (n=152)



Persistent AF (n=92)

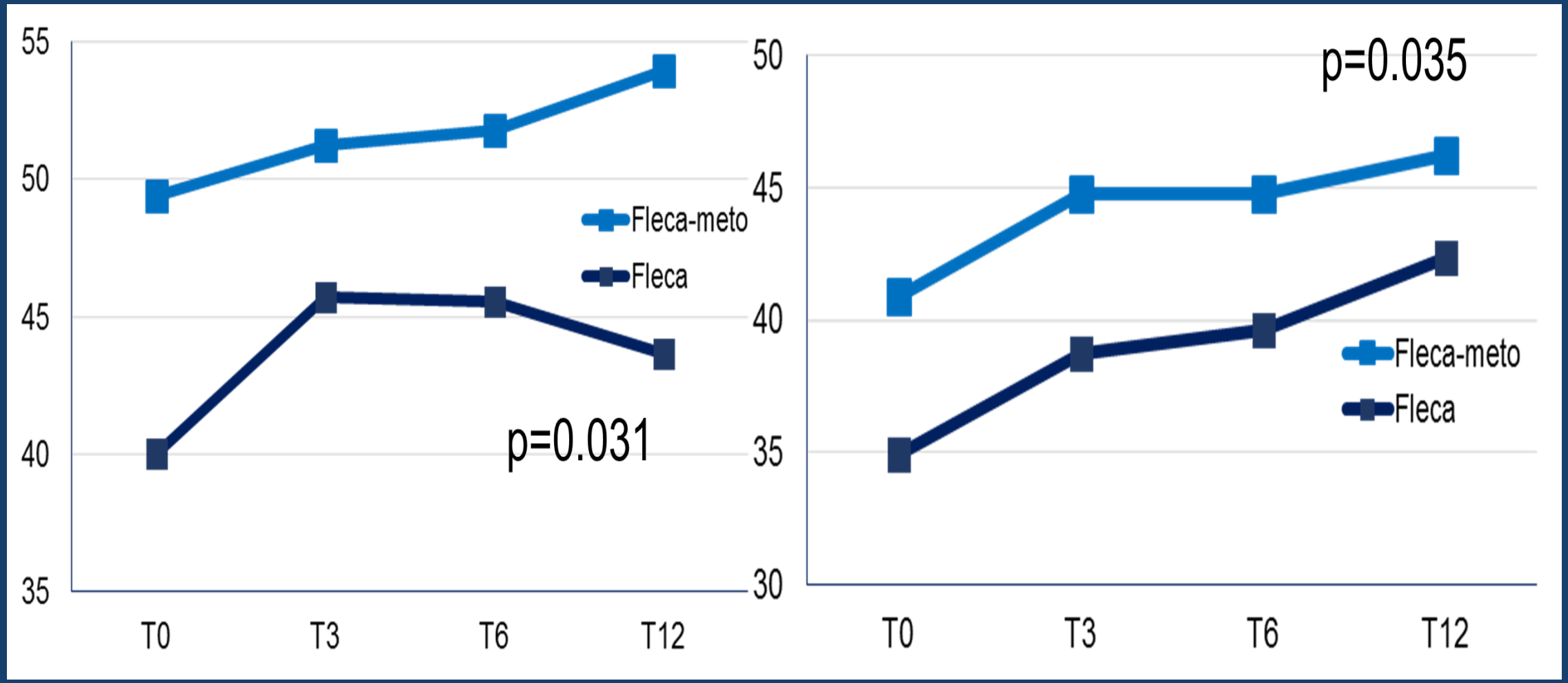


Paroxysmal AF (n=60)

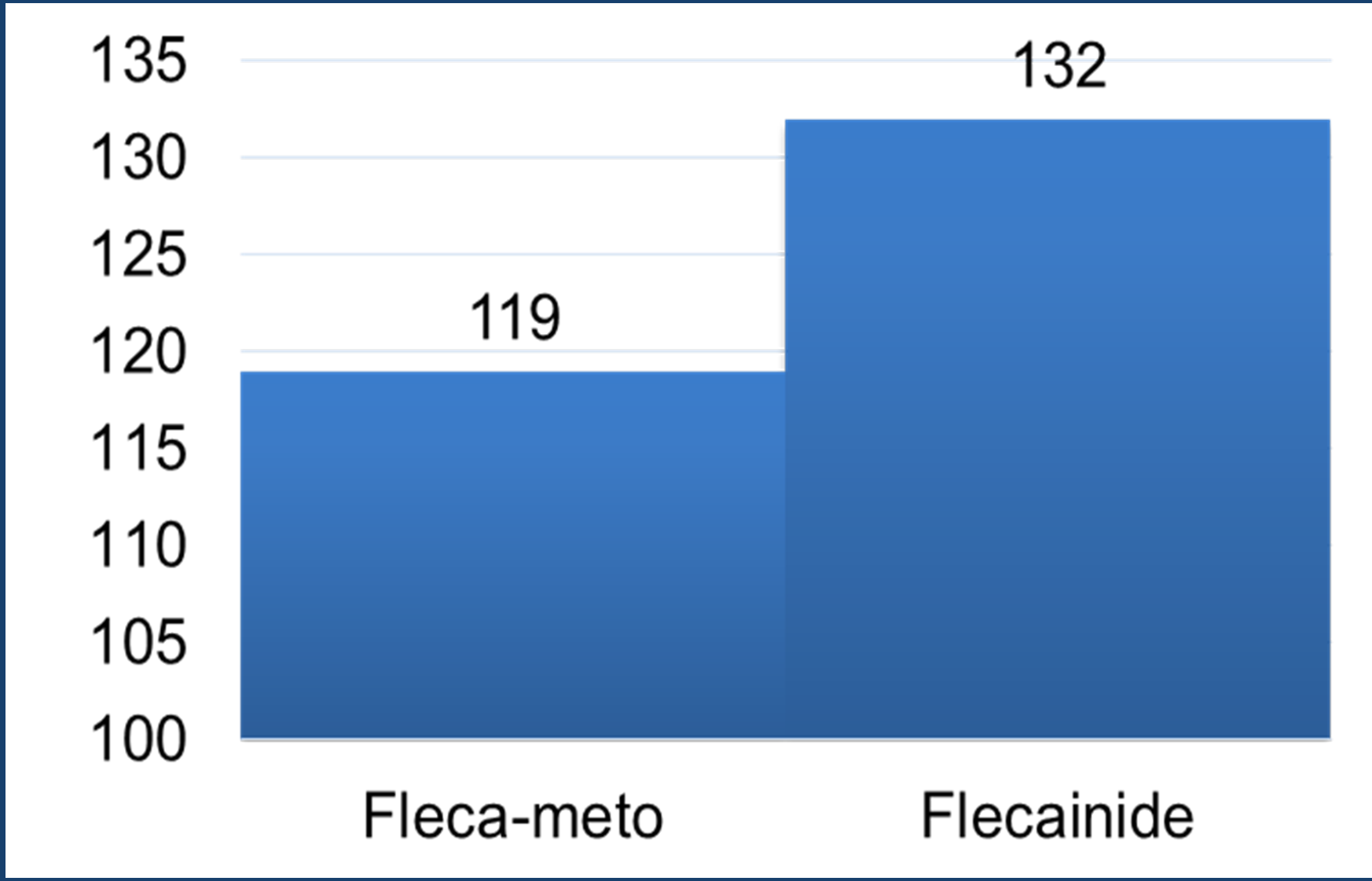


Physical Health

Mental Health



Mean flecainide dose at 1-year

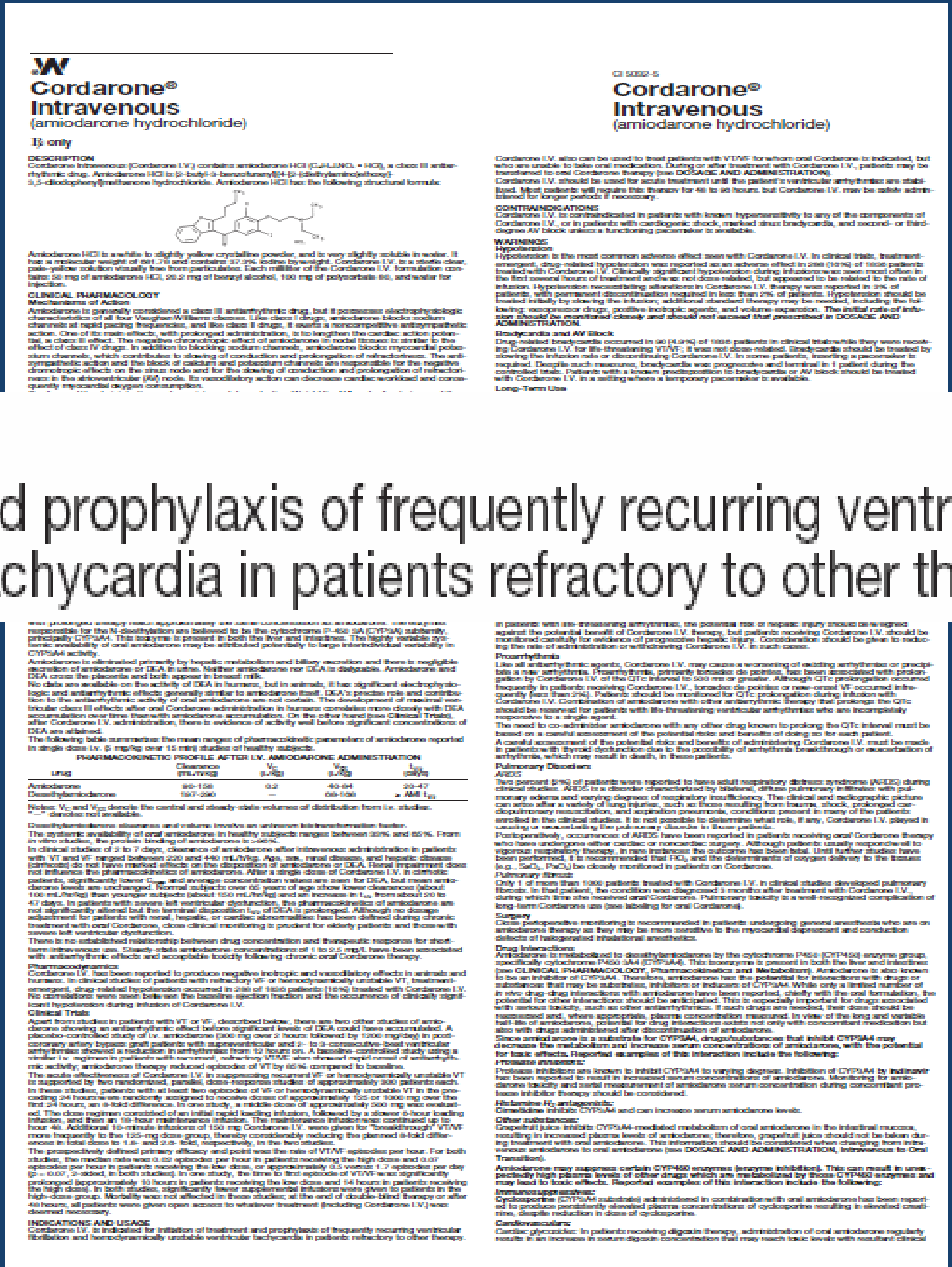


Conclusions

- β1 adrenergic receptors further reduce the action potential duration and enhance the conduction slowing already mediated by flecainide
- β-blockers revert the pro-arrhythmic effect of many IA and IC anti-arrhythmic drugs in vitro
- In a clinical setting, β-blockers have been demonstrated as effective in preventing IC-mediated PVCs
- β-blockers in combination to rhythm control therapy could have the potential to further reduce recurrences while improve quality of life and drug tolerabilty

AMIODARONE

Sebbene l’amiodarone sia approvato dall’FDA solo per il trattamento delle aritmie ventricolari refrattarie



INDICATIONS AND USAGE

Cordarone I.V. is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

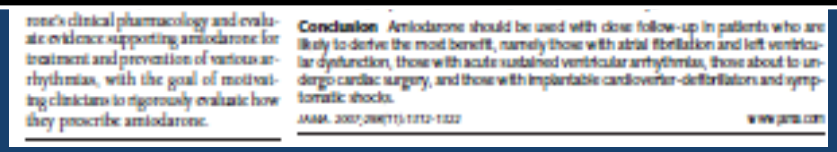
rimane l’antiaritmico più frequentemente prescritto in particolare per FA (nonostante non sia di prima scelta)!!

PRESCRITTO TROPPO SPESSO????

JAMA® Prescribing Amiodarone: An Evidence-Based Review of

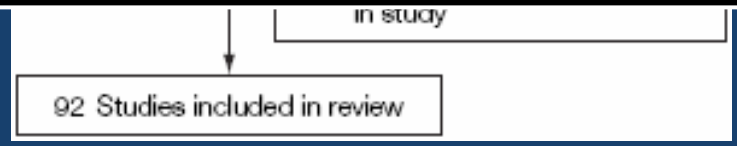
Gli autori, sulla base di queste analisi, hanno concluso che:

- può essere usato con sicurezza nella disfunzione Vsx e insufficienza cardiaca congestizia;
- utile in acuto sia in caso di arresto cardiaco che in caso di TVS;
- sicuro e valido farmaco aggiuntivo in associazione all'ICD per ridurre il numero di shock;
- efficace in associazione ai beta-bloccanti nell' "elettrical storm",
- appropriato come farmaco di prima linea solo nei pz sintomatici con disfunzione Vsx ed insufficienza cardiaca congestizia, dove però il rapporto rischio/beneficio del suo impiego deve essere confrontato con le altre strategie alternative disponibili per trattare la FA;
- nel flutter atriale e nella TPSV è preferibile l'ablazione con catetere; l'amiodarone ha scarsa/nulla efficacia.
- l'uso dell'amiodarone in profilassi va limitato al periodo perioperatorio cardiochirurgico;


tone's clinical pharmacology and evaluate evidence supporting amiodarone for treatment and prevention of various arrhythmias, with the goal of motivating clinicians to rigorously evaluate how they prescribe amiodarone.

Conclusion Amiodarone should be used with close follow-up in patients who are likely to derive the most benefit, namely those with atrial fibrillation and left ventricular dysfunction, those with acute sustained ventricular arrhythmias, those about to undergo cardiac surgery, and those with implantable cardioverter-defibrillators and symptomatic shocks.

JAMA. 2007;298(11):1272-1322 www.jama.com



AF CARDIOVERSION

Recommendations	Class[a]	Level[b]
When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.	I	A
In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.	I	A

ESC Guidelines 2012

AF RHYTHM CONTROL

Recommendations	Class[a]	Level[b]
The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:		
• amiodarone	I	A
• dronedarone	I	A
• flecainide	I	A
• propafenone	I	A
• d,l-sotalol	I	A
Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C).	I	A / C
In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.	I	B
In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.	I	A

ESC Guidelines 2012

AF RATE CONTROL

Recommendations	Class[a]	Level[b]
In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.	I	B
In pre-excitation, preferred drugs are class I antiarrhythmic drugs or amiodarone.	I	C

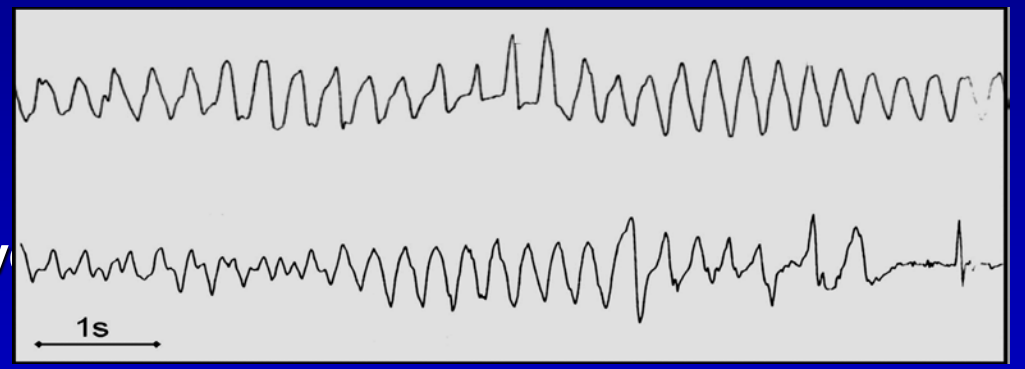
ESC Guidelines 2012

Amiodarone for rate control in patients with AF and CHF

1. Significant long-term toxicity: a second-line treatment (ACC/AHA/ESC Guidelines 2006)

- Useful when other drugs are unsuccessful or contraindicated
- Safety concerns when given in combination with β-blockers and digoxin
  - 25% of the patients developed VAs

    3–48 h after amiodarone loading[1]



2. IV amiodarone is relatively safe and more effectiv control[2]

- In critically ill patients[3]

(1) Schrickel et al. Europace 2006;8:403–407. (2) Hofmann et al. Int J Cardiol 2006;110:27–32. (3) Delle KG et al. Crit Care Med 2001; 29:1149–1153.

Proarrhythmic Effect of Class III Drugs

Effect	Amio	Sotalol	Class III AAD
• Bradycardia	↑↑	↑↑↑	±
• QT/QTc prolongation	↑↑↑	↑↑	↑↑
• QT/QT dispersion			
- Space	↓↓	↓ ± →	± ? ↑
- Time	↓↓	?	?
• EAD in Purkinje or Myocardial fibers	↓↓	↑	↑↑
• EAD reversibility	—	↑	↑↑
• Calcium antagonist Effect	++	—	—
• APD lenght K Dependence	±	↑↑	↑↑
• T3 interaction	++	—	—
• TdP % incidence	< 1	3-4	3-6

Singh BN. Am J Cardiol 1996;78(Suppl4A):41-53

http://crim.sciedupress.com Case Reports in Internal Medicine, 2014, Vol. 1, No. 1

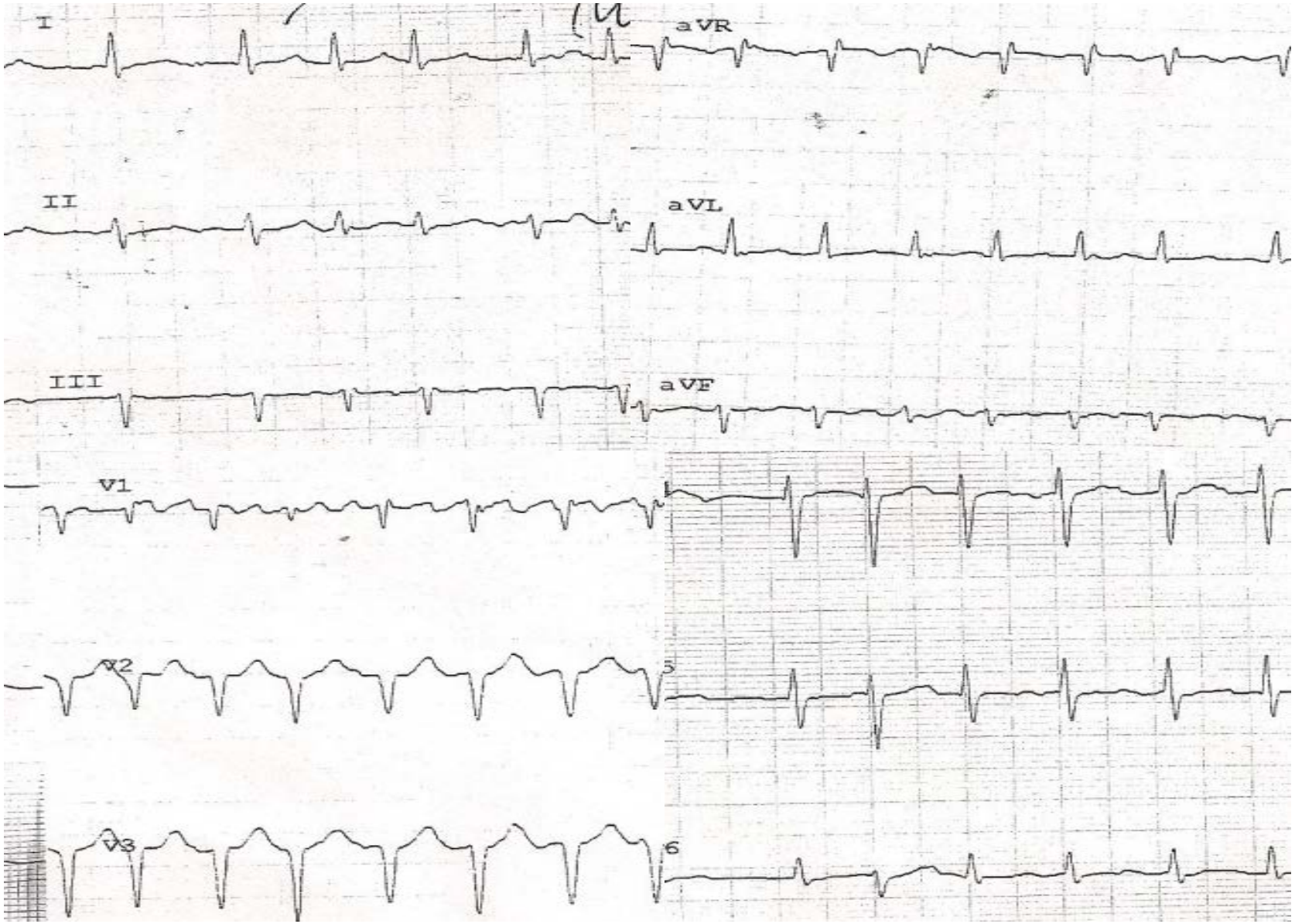
CASE REPORT

Amiodarone and digitalis: An odd couple in a tachycardiomyopathic patient

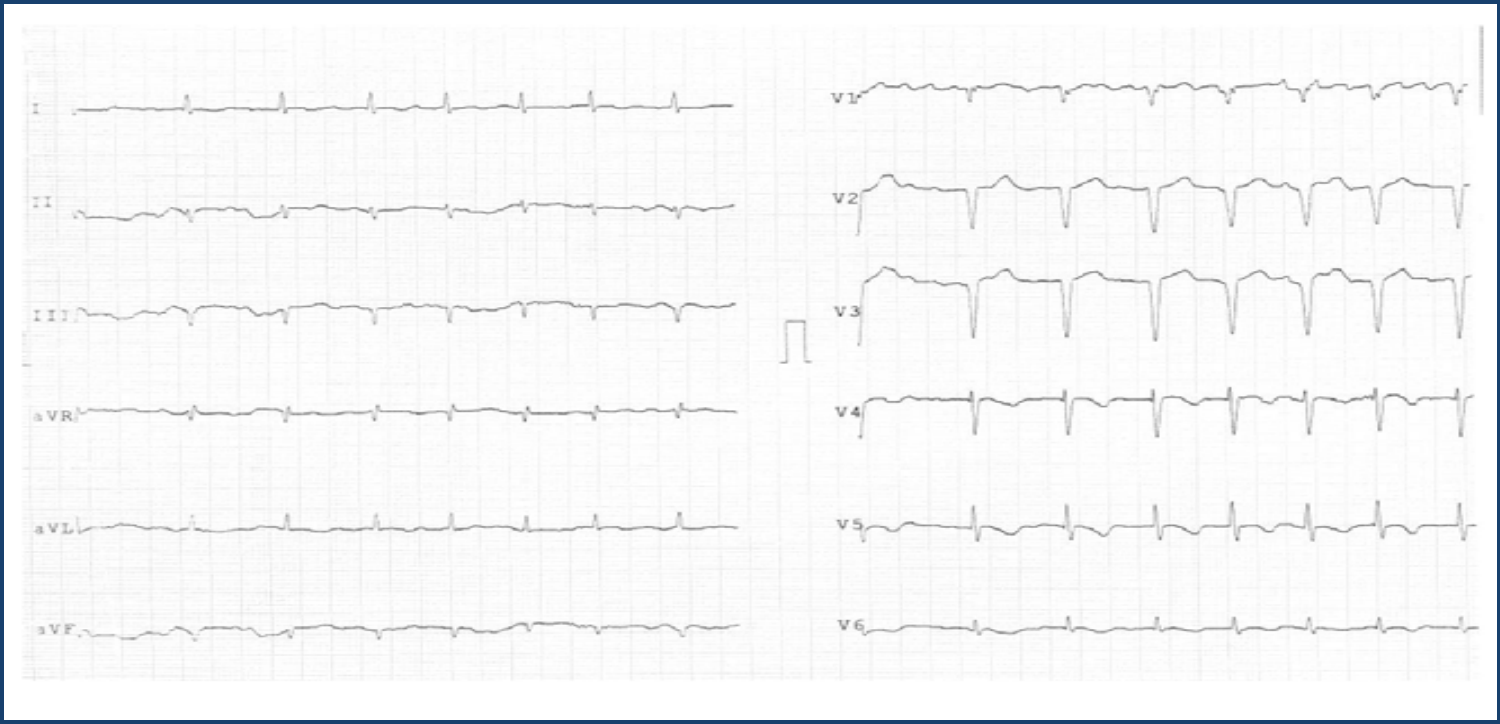
Federico Guerra, Michela Brambatti, Maria Vittoria Matassini, Alessandro Capucci

- 76 yo, F, hypertension, admitted for shortness of breath and fatigue
- Felodipine 5 mg, Ramipril 10 mg daily as antihypertensive therapy
- Clinical Sign and XRay suggestive for HF
- AF at the ECG with minimum and maximum QTc intervals of 450 and 475 ms, respectively. EF 30%

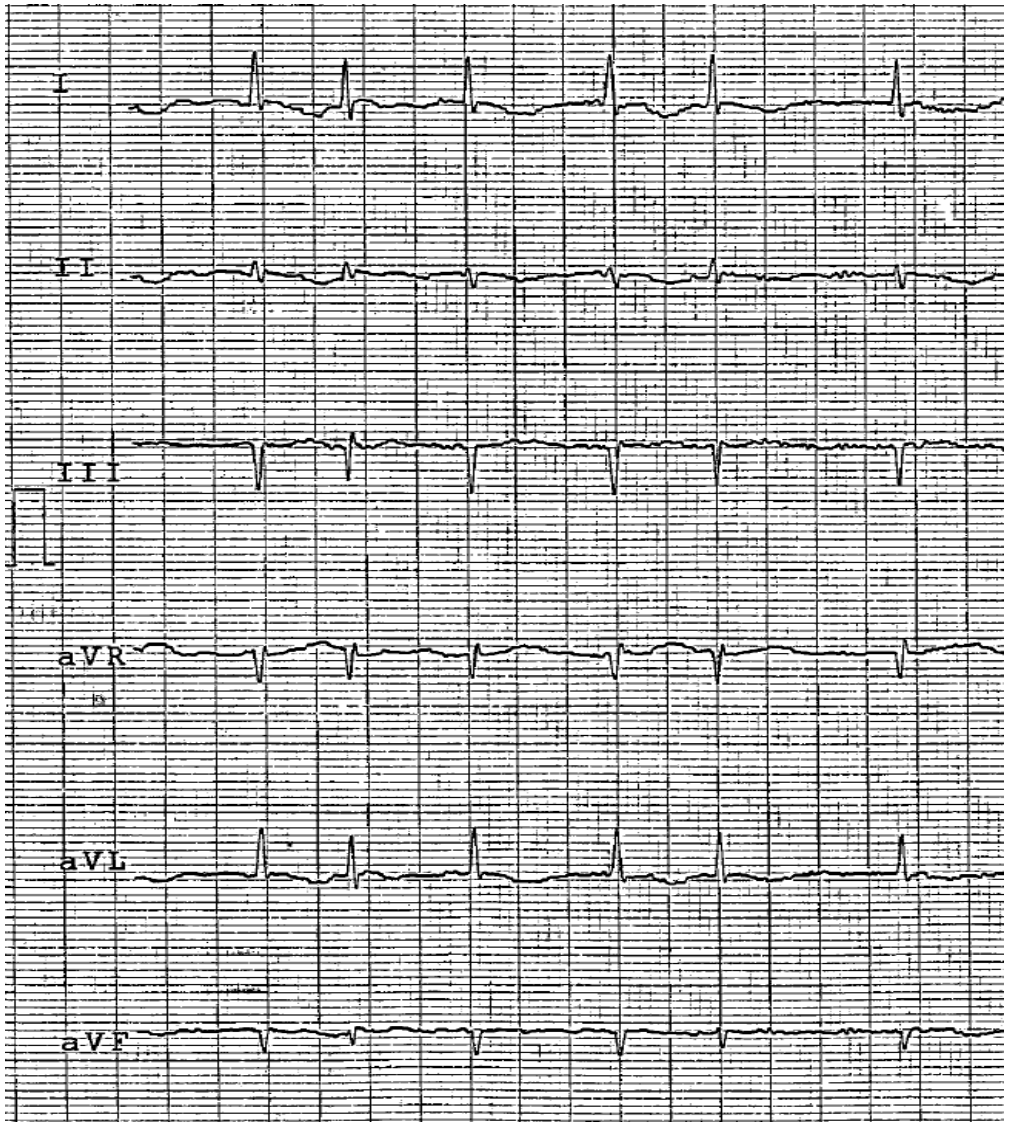
What does the ECG say?

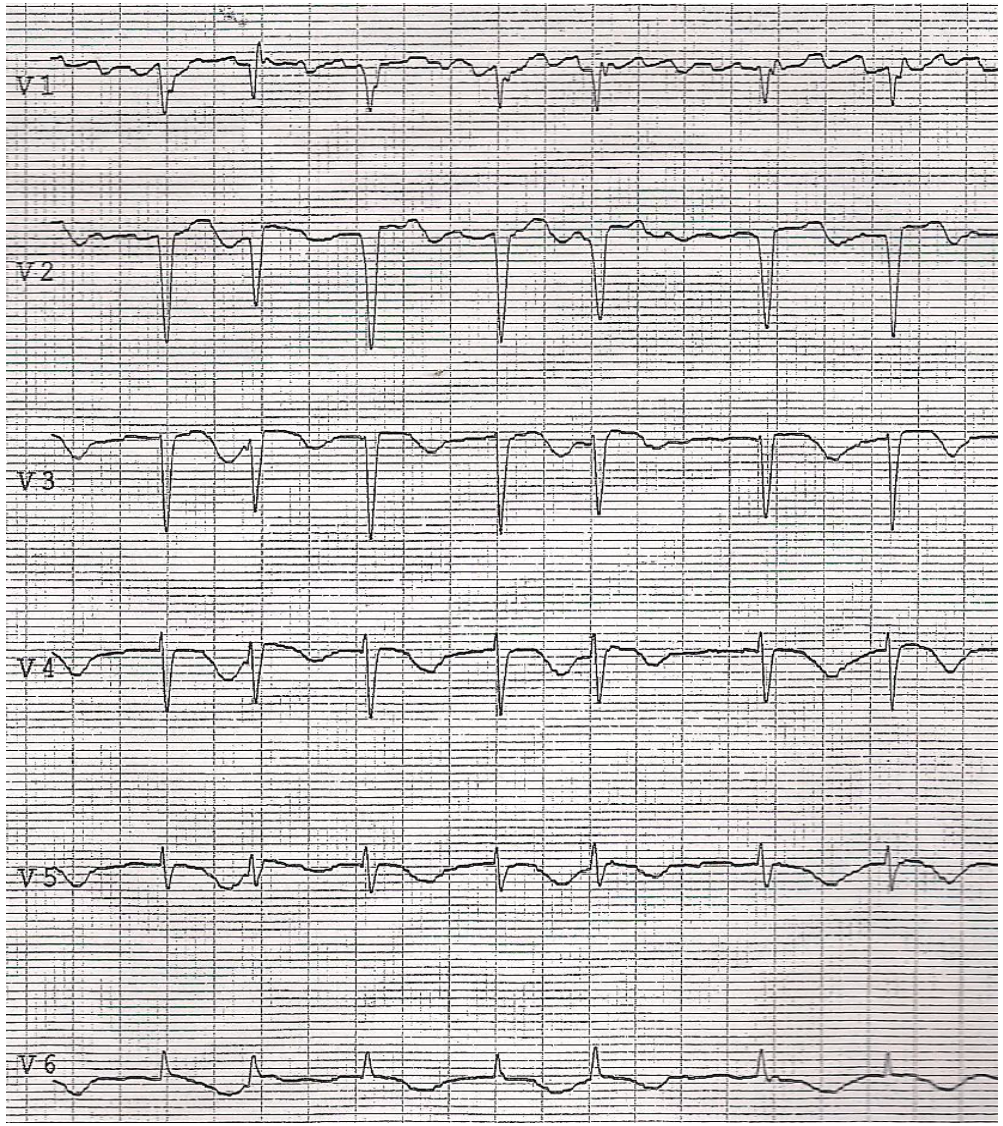


- Treated with furosemide 20 mg IV and digoxin 0.5 mg IV. As AF less than 24 hours, a pharmacological cardioversion was attempted with Amiodarone 300 mg IV bolus followed by a 0.6 mg/minute infusion.
- After 12 hours→ Still AF → STOP amiodarone and DCC was attempted after another 6 hours.

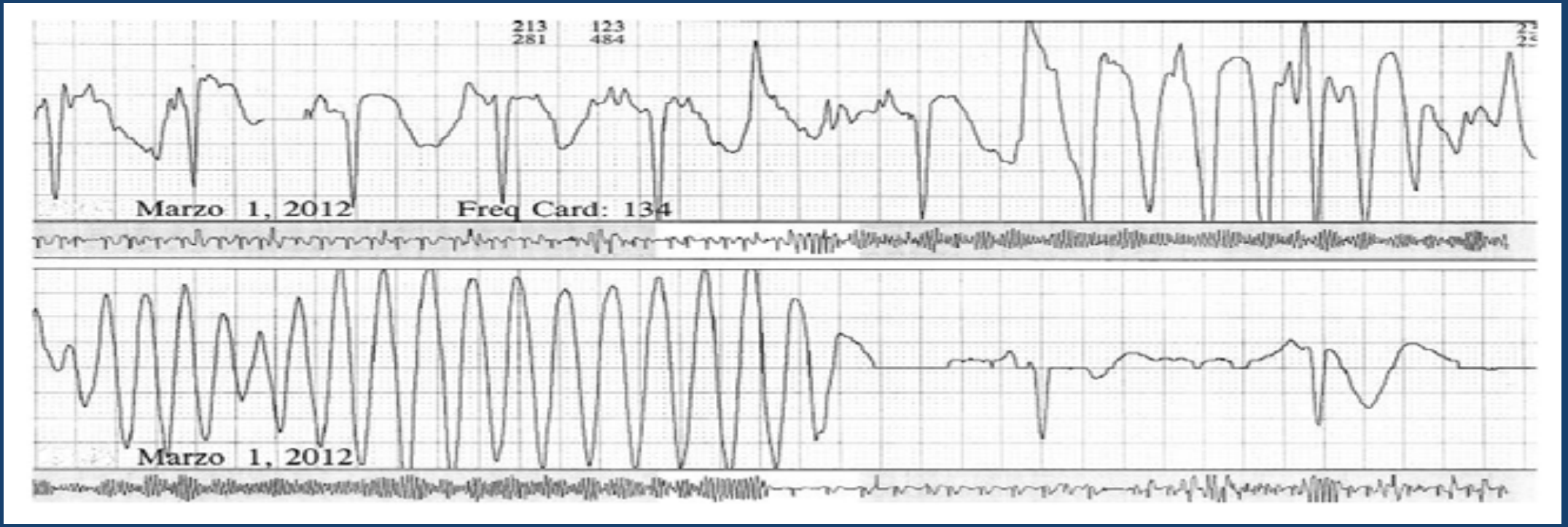


What does the ECG say now?





- 150 J biphasic shock was delivered→SR with frequent premature supraventricular complexes. In order to avoid early AF recurrence, amiodarone infusion (0.6 mg/minute IV) was started again. A few hours later, syncope occurred….



Latest status

- **A temporary pacemaker at 90 bpm was inserted to prevent further bradycardia-related TdP episodes**
- AF recurred a few minutes later
- In the next 7 days, QTc shortened progressively to 420 ms and no further arrhythmic events were recorded
- Coronary angiography performed 2 days later did not show any significant coronary lesions
- **At discharge, the patient's heart rate was normal and stable, thanks to an adequate rate control with beta-blockers, and LVEF improved to 45%**

Key findings and discussion points

- Acute systolic dysfunction may contribute to a small extent to a QT interval prolongation. In our patient, it seems that the combination of tachycardiomyopathy, digitalis and amiodarone may have resulted in triggered activity due to delayed after depolarization and, finally, TdP
- The present case shows that tachycardiomyopathy could predispose to QT prolongation, making amiodarone not safe enough when given to patients with acute ventricular dysfunction and concomitant digitalis therapy
- It is also presumable that dronedarone, as an amiodarone derivate, could have caused the same proarrhythmic effects in the elderly, decompensated PALLAS patients treated with digoxin, as suggested by retrospective adverse event reportings

(*Circulation.* 2004;110:247-252.)

Original Articles

Heart Failure and Sudden Death in Patients With Tachycardia-Induced Cardiomyopathy and Recurrent Tachycardia

Pamela Nerheim, MD; Sally Birger-Botkin, RN; Lubna Piracha, DO; Brian Olshansky, MD

AF: Investigational Antiarrhythmics

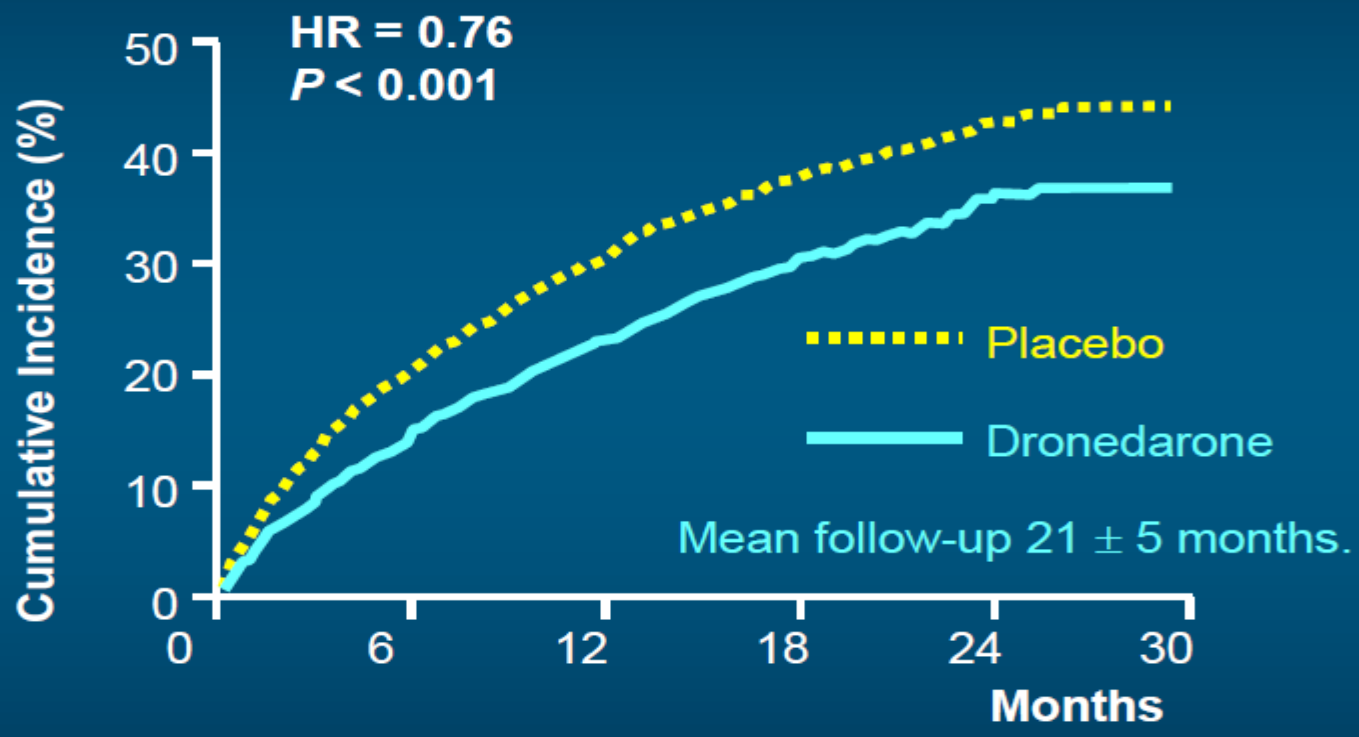
(Ross H, Kowey PR, Naccarelli GV. New Arrhythmia Techologies (Wang); 2005; 1-13)

- Azimilide (I_{Kr}; I_{Ks})
- Dronedarone (I_{Kr}; I_{Ks}; B_1; I_{Ca}; I_{to}; I_{Na})
- SSR149744C (I_{Kr}; I_{Ks}; B_1; I_{Ca}; I_{to}; I_{Na})
- Piboserod (5-HT_4 receptor antagonist)
- Tedisamil (IV) ($I_{Kv1.5}$; $I_{Kv4.3}$; I_{Kr}; I_{to}; I_{KATP}; I_{Na}; I_{Kur})
- RSD-1235 (Atrial-selective K inhibitor-I_{Kur}; I_{to}; I_{Na}; I_{KACH})
- ZP-123 (GAP 486)(Facilitates conduction in gap junction)
- Tecadenoson (CVT-150) (Long-acting IV A-1 adenosine agonist)
- AVE-0118 (Atrial-selective K inhibitor-$I_{Kv1.5}$; $I_{Kv4.3}$; I_{Kur}; I_{to}; I_{KACH})
- AZD7009 (I_{Kr};I_{Kur};I_{Na})
- NIP142 (I_{Kur}; I_{KACH})
- NIP151 (I_{KACH})
- GsMtx4 (SAC blocker)

DRONEDARONE

ATHENA TRIAL- *Primary outcome-*

Time to first cardiovascular hospitalization or death

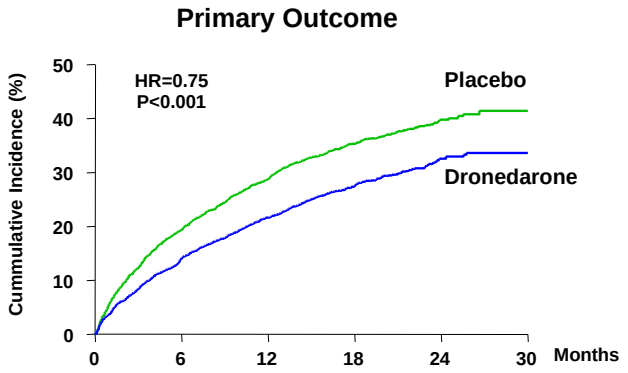


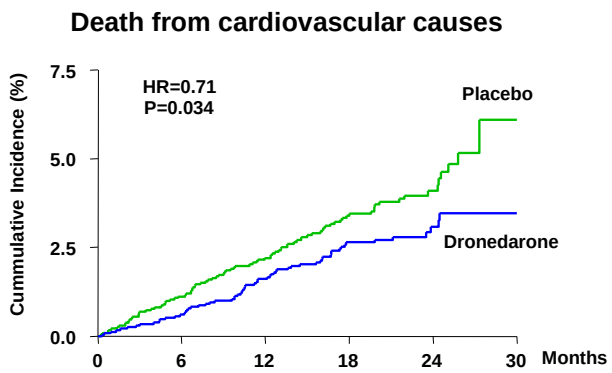
Patients at risk						
Placebo	2327	1858	1625	1072	385	3
Dronedarone	2301	1963	1776	1177	403	2

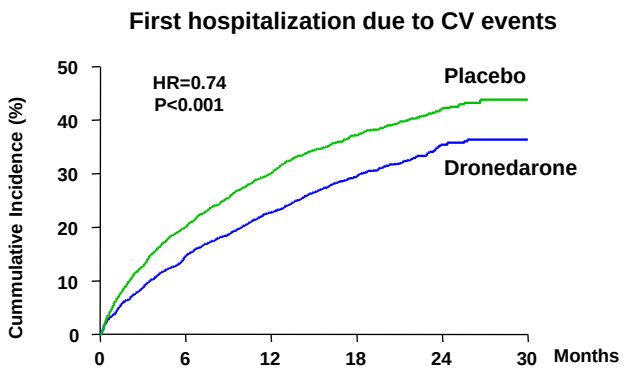
Hohnloser SH et al. ATHENA Investigators. N Engl J Med. 2009 Feb 12;360(7):668-78.

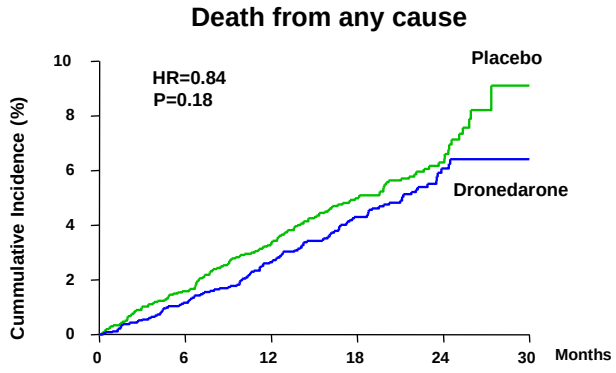
Dronedarone reduced the risk of hospitalization due to CV events or death in patients with AF - ATHENA trial

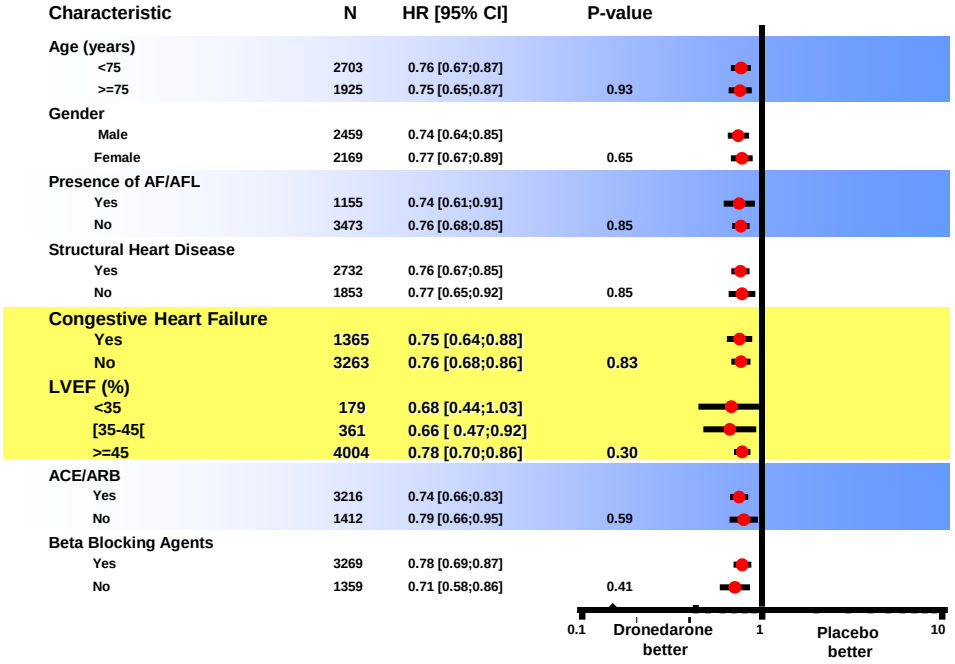
- 4628 patients, 540 with LVEF <45%, NYHA class II-III 21.1%











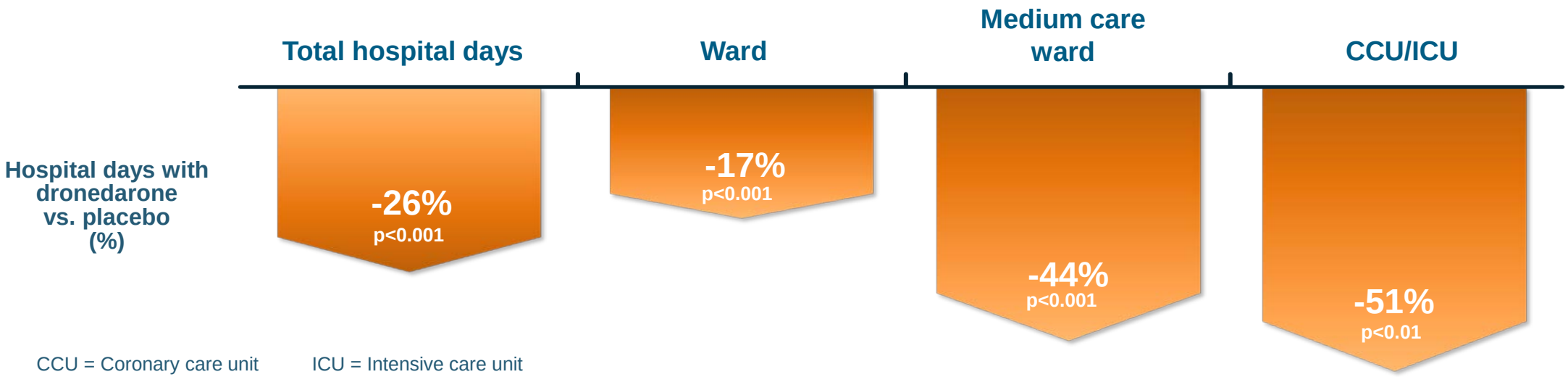
- Primary outcome: first hospitalization due to CV events or death
- Patients with CHF had a benefit similar to that of the entire group

- **Adverse effects**: bradycardia, QT prolongation, diarrhea, nausea, rash and an increase in serum creatinine level. No thyroid- and pulmonary-related events

Hohnloser et al. N Engl J Med 2009;360:666-678

Dronedarone significantly reduced the duration of first AF related hospitalisation

Decrease of the duration of first AF related hospitalisation according to the level of care (Dronedarone vs. placebo*)

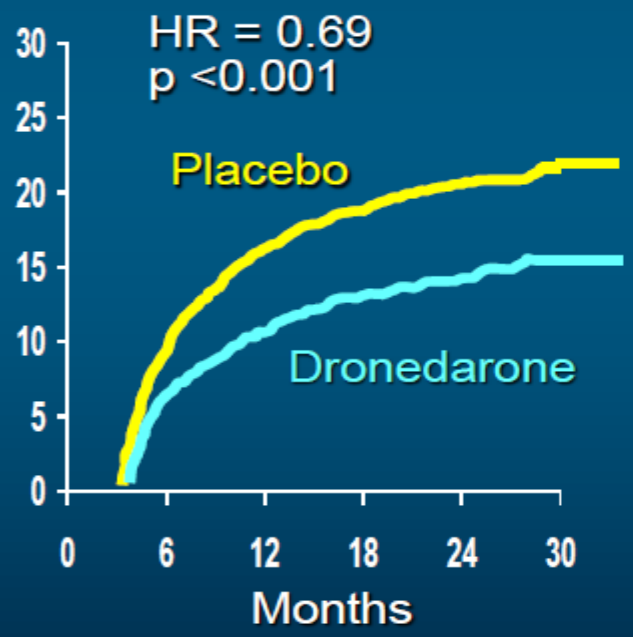


CCU = Coronary care unit ICU = Intensive care unit
* Dronedarone and placebo treatments were additional to standard therapy

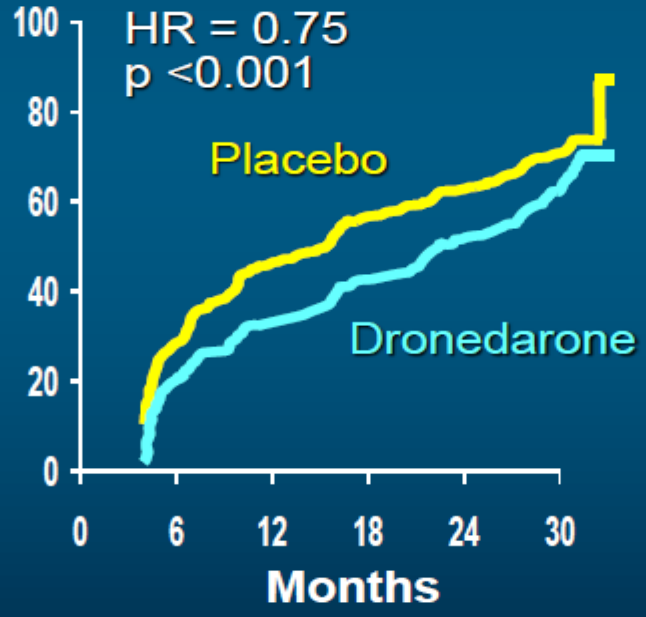
Adapted from Torp-Pedersen C, *et al.* Europace. 2011;13(8):1118-26.

ATHENA TRIAL

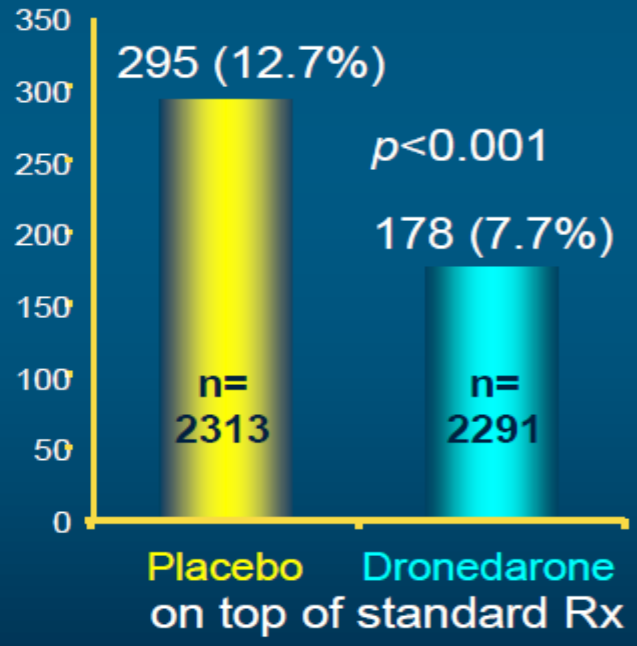
Time to 1st DCV



Time to 1st AF/AFL



No. in Permanent AF



All AF related hospitalization: HR=0.626, 95% CI = [0.54; 0.73]
First AF related hospitalization: HR=0.63, 95% CI = [0.55; 0.72]

Page R, et al. Am J Cardiol 2011

PALLAS

Permanent Atrial fibriLLAtion outcome Study

1^0 Outcomes	Dronedarone (n = 1619)		Placebo (n = 1617)		Dronedarone vs Placebo		
	Events	%/yr	Events	%/yr	HR	95% CI	P value
1^{st} Co-primary (Stroke/MI/SEE/CV Death)	43	8.2	19	3.6	2.29	1.34-3.94	0.002
2^{nd} Co-primary (All Death/Unplanned CV Hospitalization)	127	25.3	67	12.9	1.95	1.45-2.62	<0.001

Connolly S, NEJM, 2011

ATHENA vs PALLAS

PALLAS Risk Factors	ATHENA (Overall)		PALLAS	
	Dronedarone n = 2301 %	Placebo n = 2327 %	Dronedarone (n = 1619) %	Placebo (n = 1617) %
CAD	28.7	31.3	40.9	41.2
Prior Stroke/TIA	7.3	7.1	26.9	28.3
Symptomatic HF	-	-	14.4	14.8
LVEF ≤ 40%	4.2	4.7	21.3	20.7
Peripheral Arterial Disease	-	-	11.6	13.2
Age ≥ 75 with HTN & Diabetes	2.1	2.7	18.2	17.1

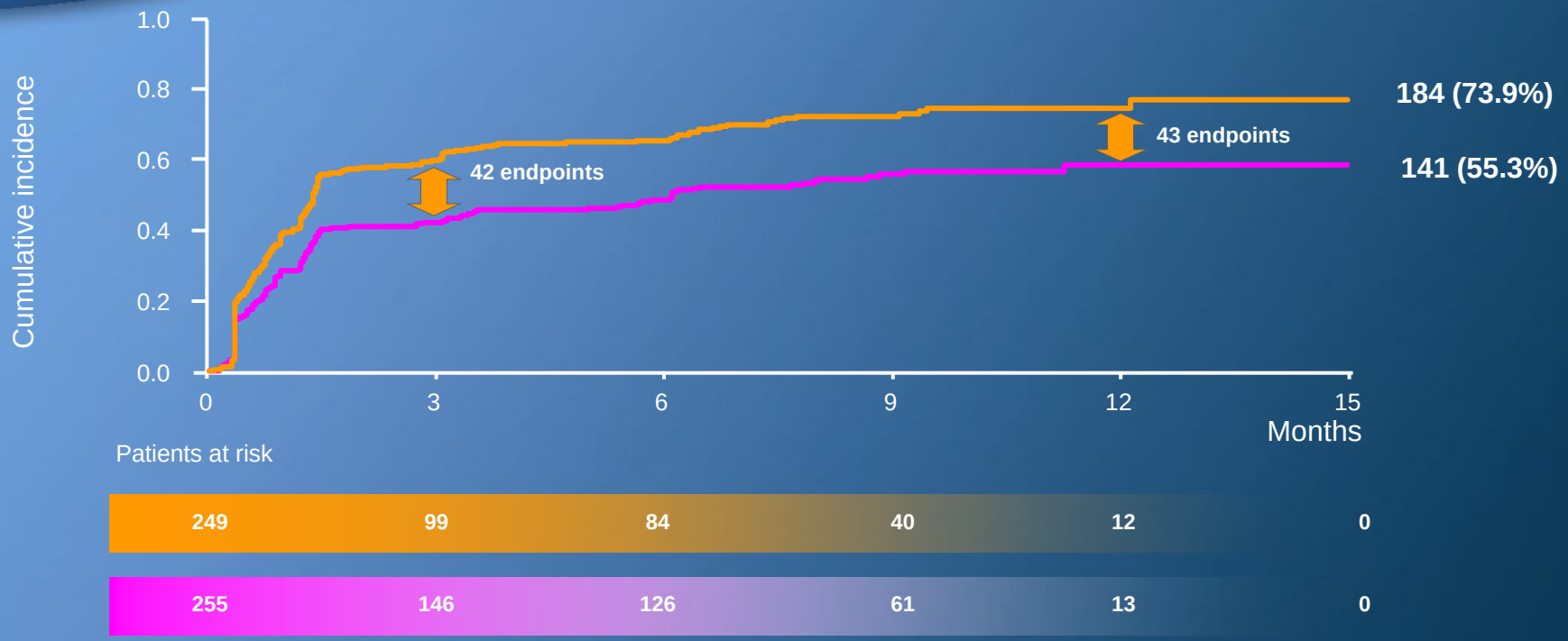
Hohnloser SH, et al. N Engl J Med. 2009;360:668-78

Connolly S. et al. N Engl J Med 2011 Dec 15;365(24):2268-76

Studio Pallas

- Pazienti più severi
- Maggior parte dei casi con morte improvvisa erano in terapia con digitale
- Nessun farmaco antiaritmico presenta indicazioni specifiche al suo impiego nei pazienti con FA permanente.

Primary Endpoint: More AF Events But Less Early Discontinuation With Dronedarone



RRR (95%CI) = 1.589 (1.275;1.98)

p-value <0.001

Dronedarone

Amiodarone

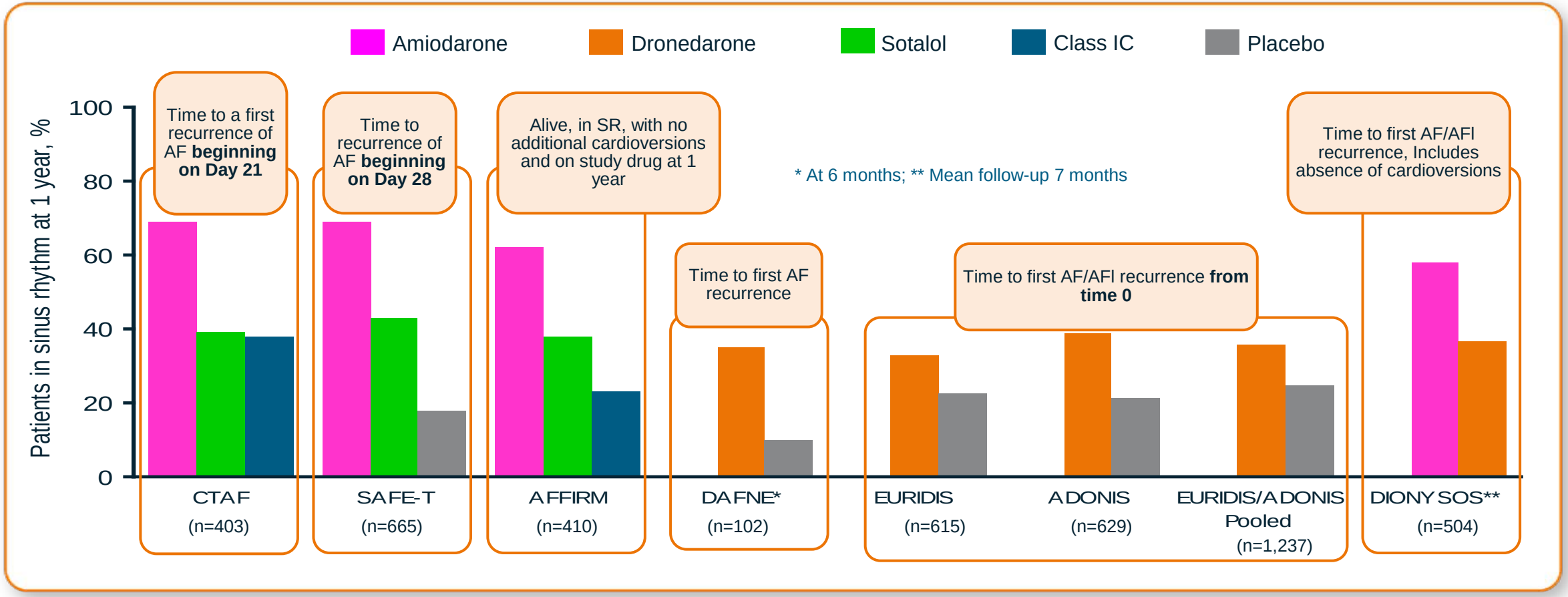
	Dronedarone (n=249)	**Amiodarone** (n=255)
Number of patients with endpoint	**184 (73.9%)**	**141 (55.3%)**
ECG documented AF endpoint	**158 (63.5%)**	**107 (42.0%)**
Documented AF after conversion	91 (36.5%)	62 (24.3%)
Unsucessful electrical cardioversion	29 (11.6%)	16 (6.3%)
No spontaneous conversion and no electrical cardioversion on day 10 to day 28	38 (15.3%)	29 (11.4%)
Premature study drug discontinuation	**26 (10.4%)**	**34 (13.3%)**
Lack of efficacy	1 (0.4%)	0
Intolerance	25 (10.0%)	34 (13.3%)

DIONYSOS:
NUMBER OF PATIENTS WITH AT LEAST 1 HEPATIC TEAE

Hepatic TEAE	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg for 28 days, then 200 mg OD (n=255)
TEAE	22 (8.8%)	14 (5.5%)
SAE	2 (0.8%)	2 (0.8%)
AE + discontinuation	7 (2.8%)	6 (2.4%)
SAE + death	0 (0.0%)	0 (0.0%)

- 2 patients in the dronedarone group:
  - 1 acute hepatic failure, probably due to cardiogenic shock
  - 1 acute hepatic failure in a patients with pancreas neoplasia
- 2 patients in the amiodarone group:
  - 1 colangitis
  - 1 acute cholecystitis

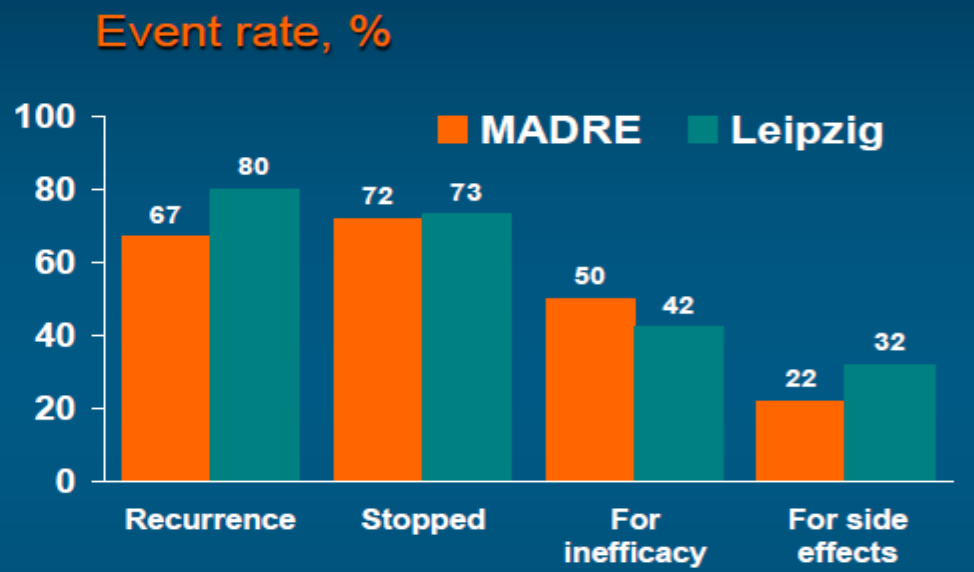
Maintenance of sinus rhythm: Data from various clinical studies

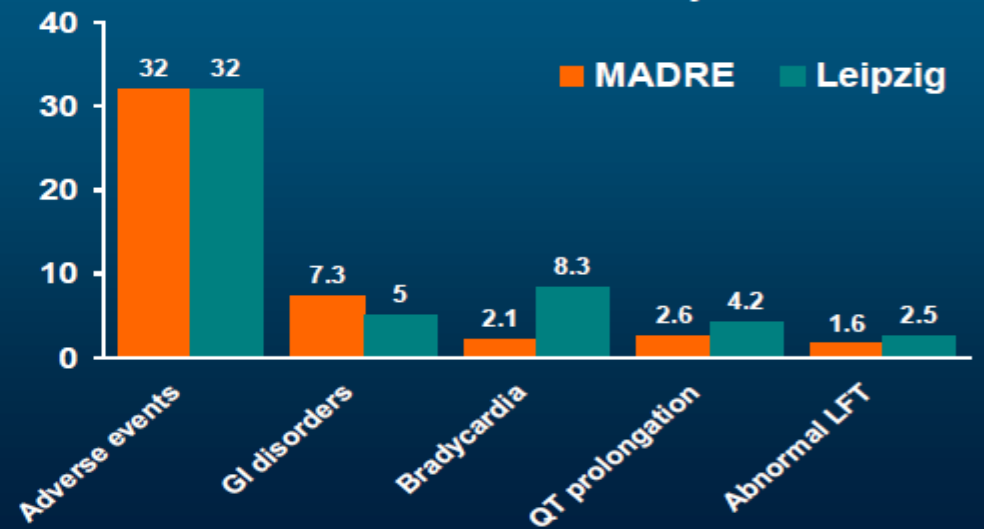


Adapted from:
1. Camm AJ, Savelieva I. Future Prescriber 2009; 10 (1): 24-32.
2. Roy D, et al. N Engl J Med 2000;342:913–20.
3. Singh BN, et al. N Engl J Med 2005;352:1861–72.
4. AFFIRM Investigators. J Am Coll Cardiol 2003;42:20–9.
5. Touboul P, et al. Eur Heart J. 2003;24(16):1481-7.
6. Singh BN, et al. N Engl J Med 2007;357:987-99.
7. Le Heuzey JY, et al. J Cardiovasc Electrophysiol. 2010 1;21(6):597-605.

Post-market Experience: Magdeburg and Leipzig Registries

Registry	Magdeburg (MADRE)	Leipzig
# patients	191	120
Age, yrs	63 ± 10	67 ± 9
PAF, %	63	34
Duration, yrs	3.6 ± 4.1	6.1± 6.8
HTN, %	66	93
CAD, %	22	17
Prior AAD, %	63	19
Prior PVI	0	28
Follow-up, mos	14.3 ± 4.9	6-9





More effective in non-lone AF (62% vs 84%), U-shape relationship with LA size

Said SM, et al. Int J Cardiol 2013;167:2600-4
Said SM, et al. JCP 2013;53:841-5

Recommendations regarding dronedarone	Class[a]	Level[b]
Dronedarone is recommended in patients with recurrent AF as a moderately effective antiarrhythmic agent for the maintenance of sinus rhythm.	I	A
Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.	IIa	B
Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.	III	B
Dronedarone is not recommended in patients with permanent AF	III	B

ESC Guidelines 2012

RASSEGNA

G Ital Cardiol 2012;13(5):326-333

Dronedarone: una reale innovazione o solo una valida seconda scelta? Come districarsi tra linee guida, agenzie regolatorie e pratica clinica quotidiana

Alessandro Capucci[1], Federico Guerra[1], Cesare Antenucci[2], Roberto Antonicelli[3], Paolo Bocconcelli[4], Giuseppe Boriani[5], Paolo Busacca[6], Nino Ciampani[7], Stefano Della Casa[8], Domenico Gabrielli[9], Marcello Galvani[10], Massimo Margheri[11], Francesco Melandri[12], Maria Grazia Modena[13], Gian Piero Perna[14], Pierluigi Pieri[15], Giancarlo Piovaccari[16], Andrea Pozzolini[17], Claudio Rapezzi[18], Giovanni Quinto Villani[19]

Less effective than amiodarone, but similar efficacy when compared to other AADs.

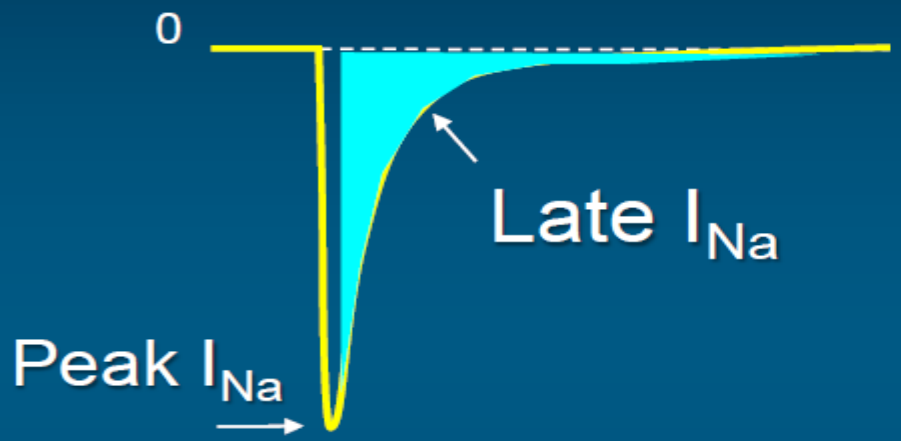
Low risk profile in patients with mild structural cardiopathy and non permanent AF.

Avoid in permanent AF, heart failure NYHA class III and IV, acute heart failure or hepatic or renal failure amiodarone-related.

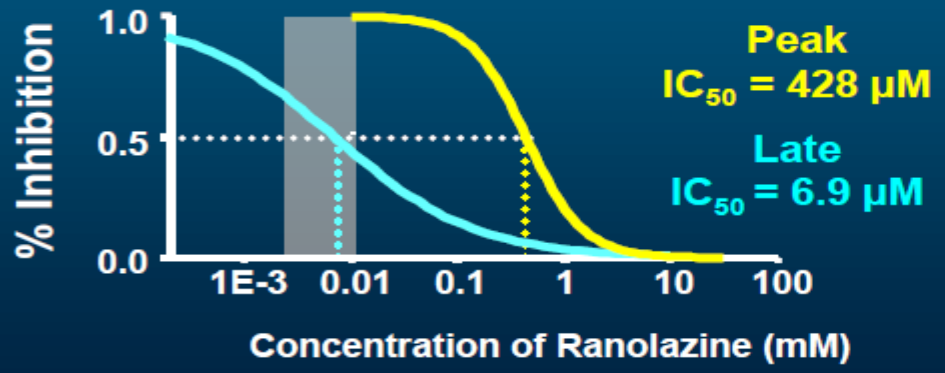
RANOLAZINA

Ranolazine

Sodium Current

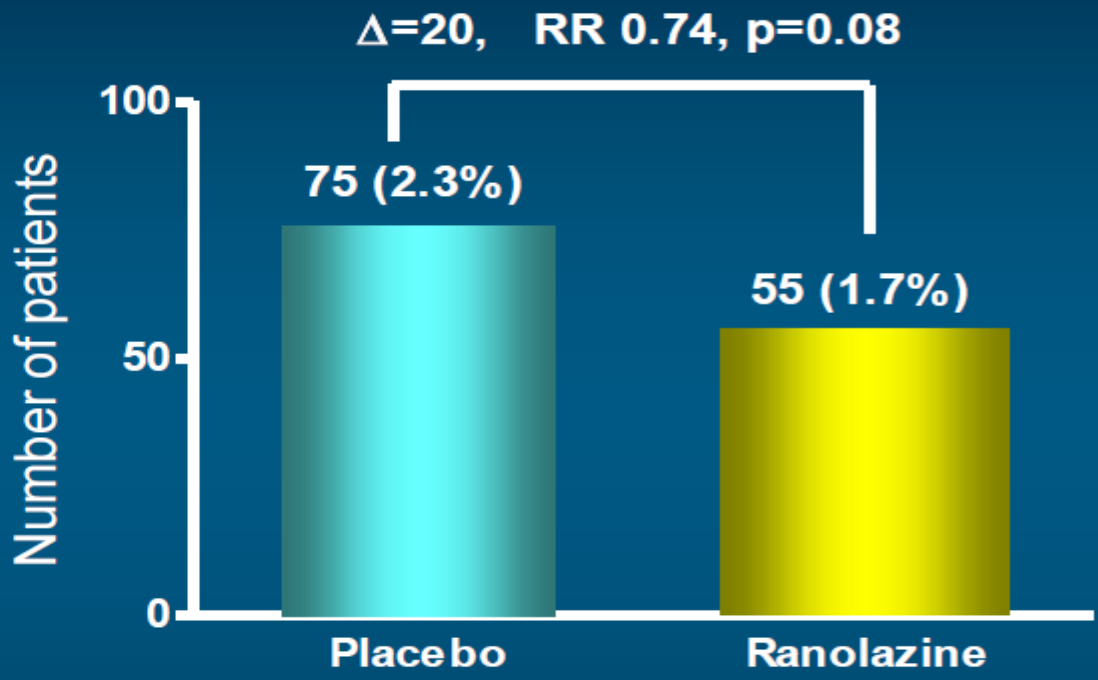


Human Cardiac NaCh in HEK293 Cells



Rajamani S., et al., Eur Heart J. 28(1) 2007

New-Onset Atrial Fibrillation



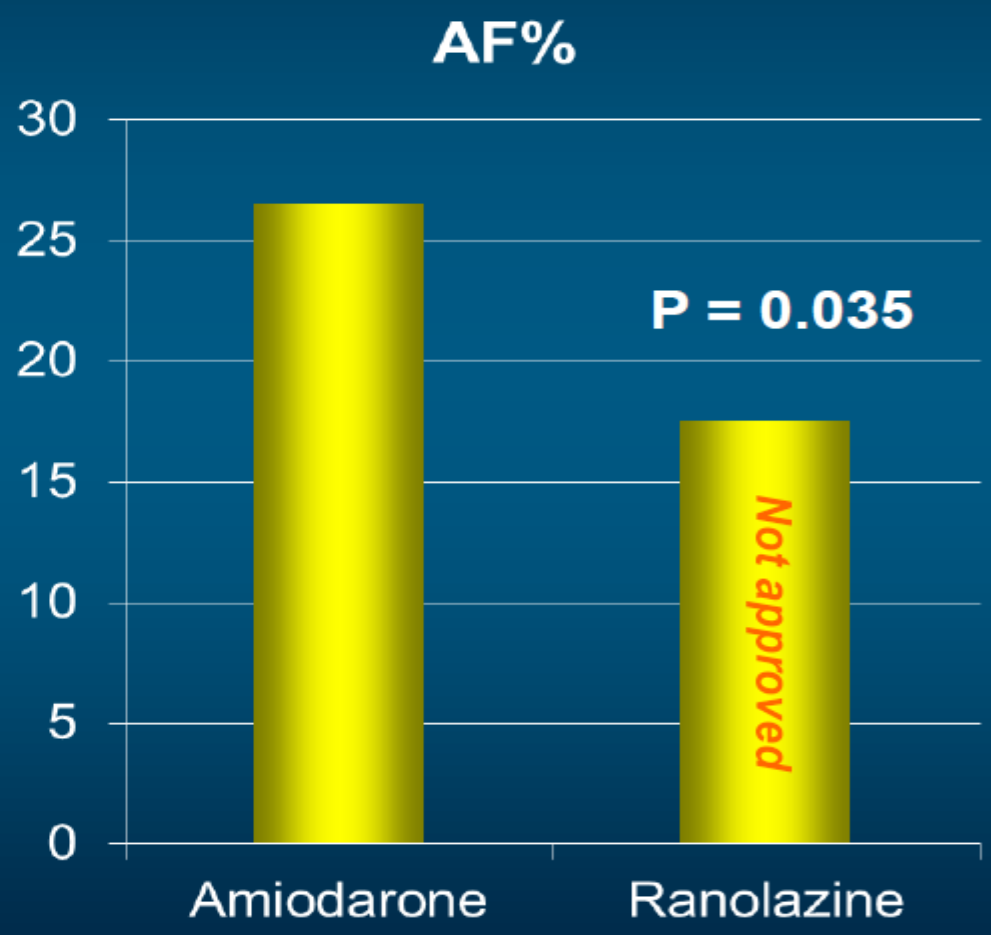
MERLIN TIMI 36

TIMI

Scirica et al. Circulation. 2007;116:1449-1457.

RANOLAZINE VS AMIODARONE

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10–14 days) - N=211 (53.7%)
- Ranolazine (1,500 mg preoperative followed by 1,000 mg twice daily for 10–14 days) - N=182 (46.3%)
- Mean age 65 ± 10 years, 72% male



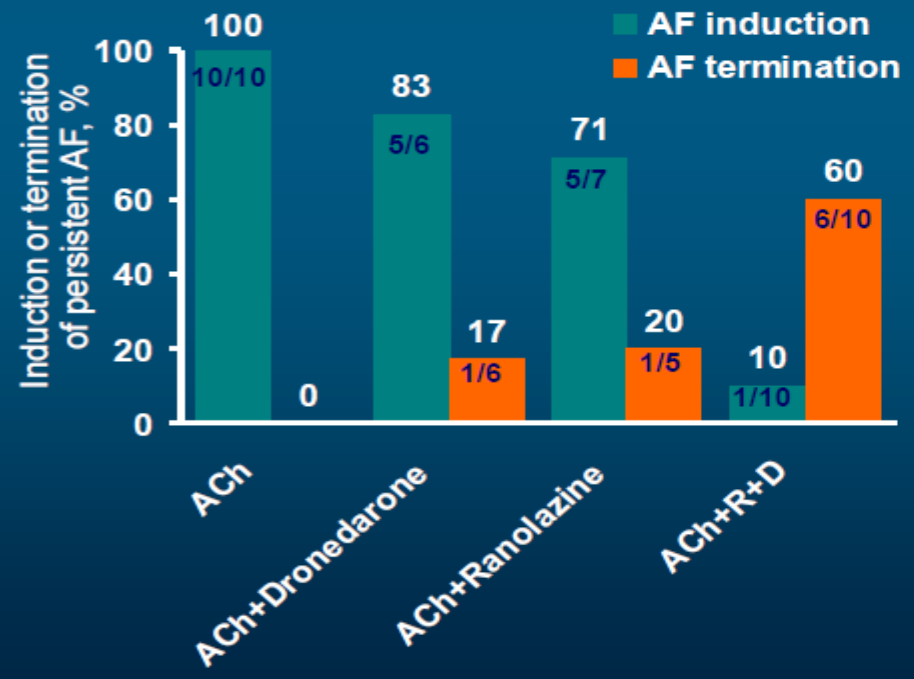
Ranolazine associated independently with a reduction of post-op AF

CABG=coronary artery bypass grafting

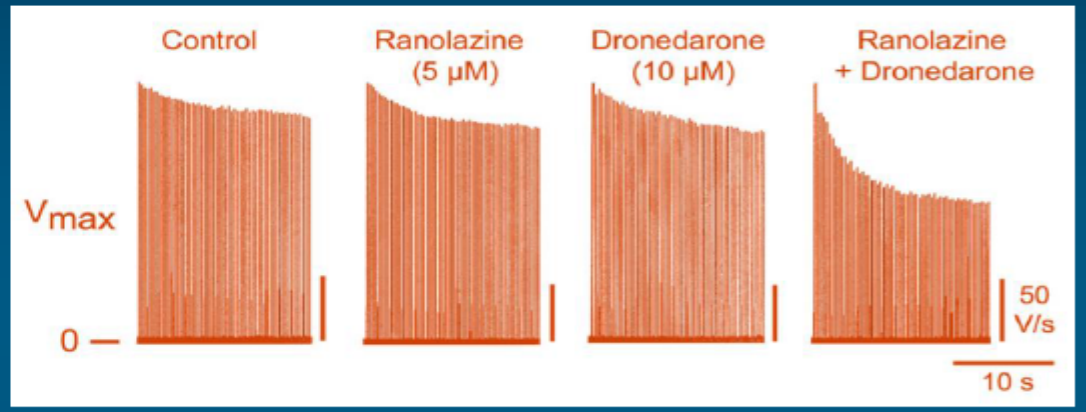
Murdock D, et al. ACC Abstracts 2011, New Orleans, LA, USA

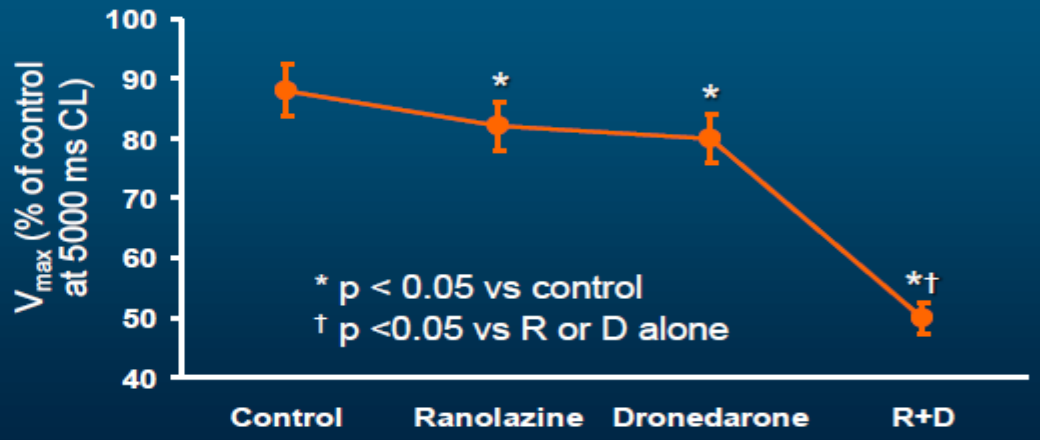
RANOLAZINE + DRONEDARONE

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 μmol/L
- Dronedarone 10 μmol/L



Pulmonary vein preparations

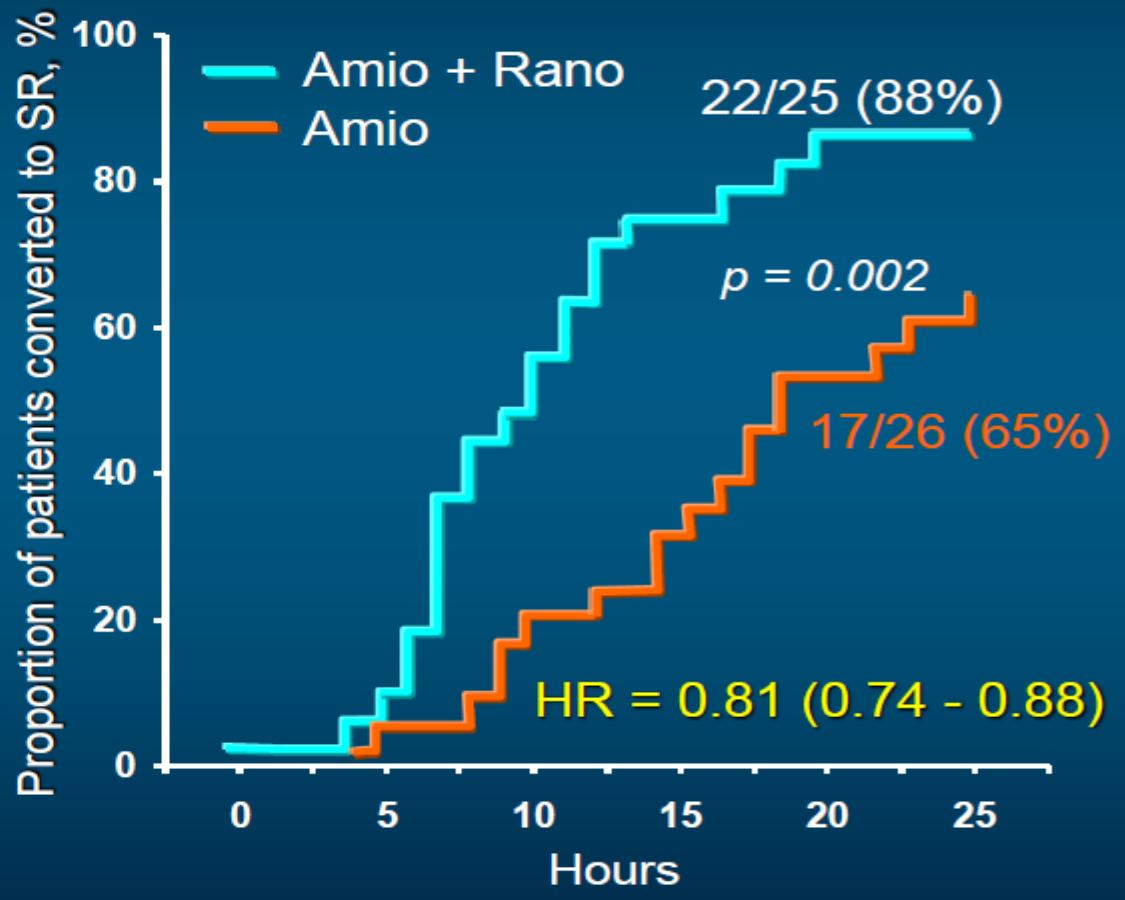




Burashnikov A, et al. J Am Coll Cardiol 2010;56:1216–24

RANOLAZINE + AMIODARONE

- Pilot RCT
- N = 51 with AF < 48 h
- Age 63 ± 8 years, 65% men
- HTN 68–77%, CAD 20–27%
- I.V. amio 5 mg/kg for 1 h followed by infusion of 50 mg/h for 24 h
- I.V. amio + ranolazine 1,500 mg p.o.
- 1° EP: conversion within 24 h



Median time to conversion:
18 h (Amio) vs 10 h (Amio+Rano)

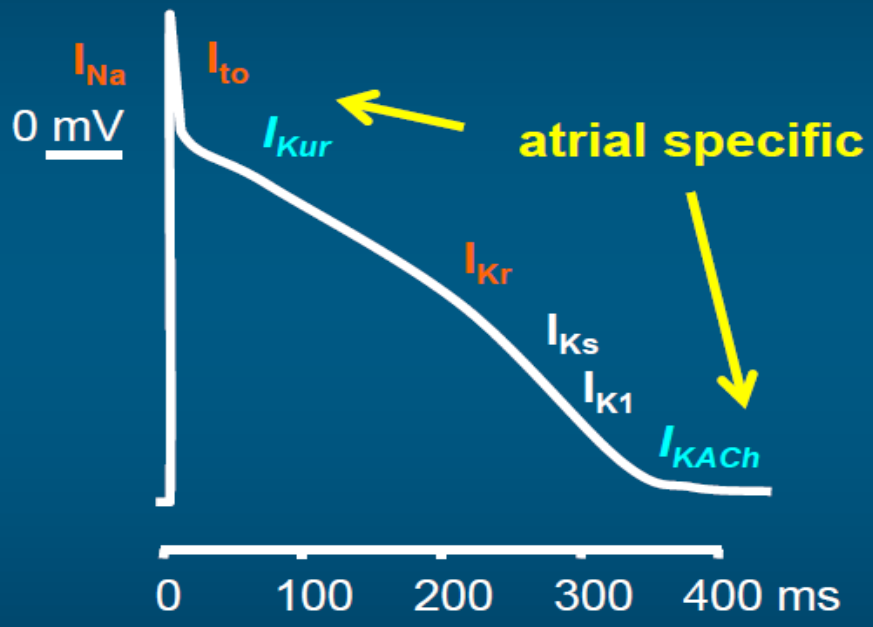
SR=sinus rhythm

Fragakis N, et al. Am J Cardiol 2012;110:673–7

VERNAKALANT

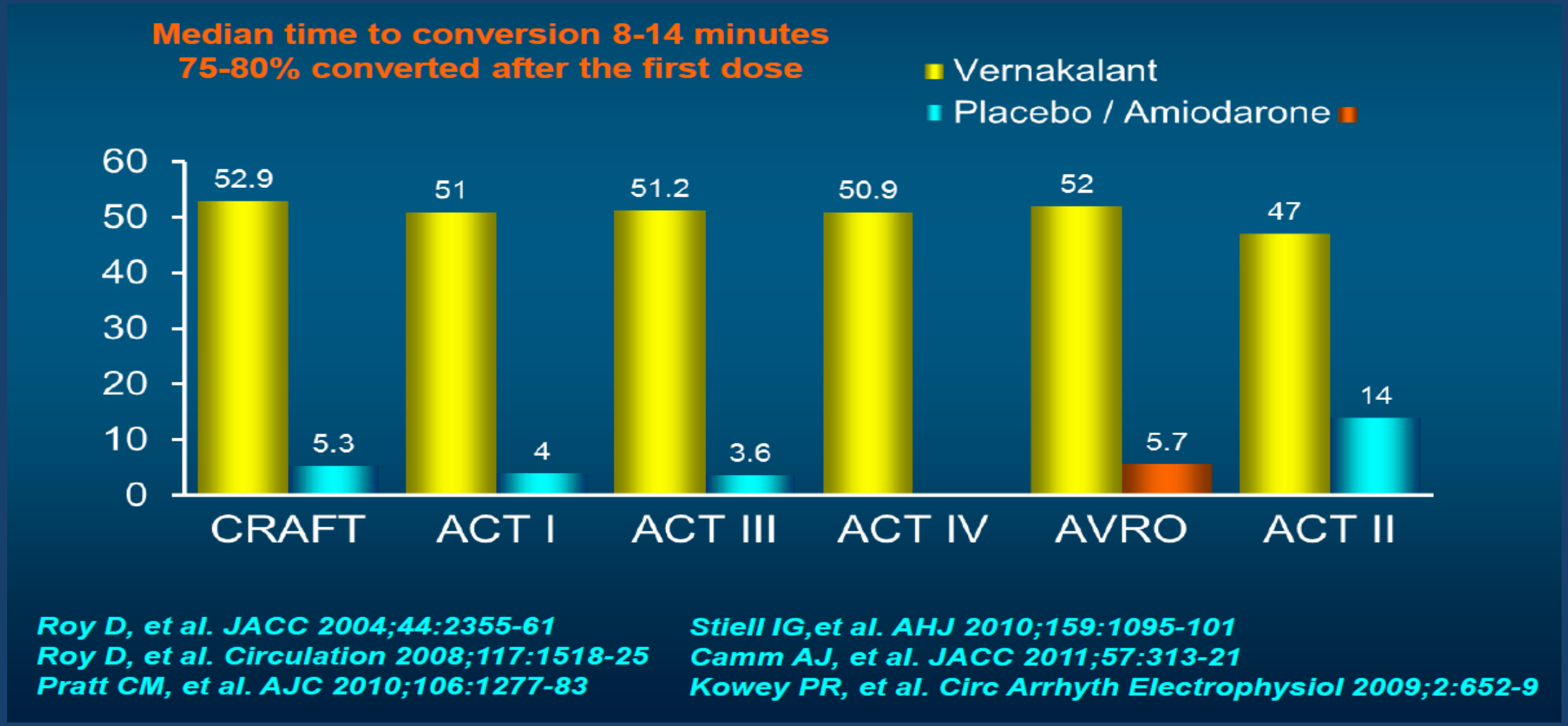
VERNAKALANT

- Unique ion channel-blocking profile
  - Frequency- and voltage-dependent I_{Na} block
  - Early activating K^+ block (IK_{ur}, I_{to})
  - I_{KACh} block
- Rate enhanced decrease in conduction velocity
- Atrial-selective APD/ERP prolongation
- Little effect on ventricular repolarization
- Mean elimination $t_{1/2}$: ~3 hours
- Minimal adverse hemodynamic effects



Astellas FDA 2007 Backgrounder 2007-4327b1-01
Fedida D, et al. J Cardiovasc Electrophysiol 2005;16:1227-38

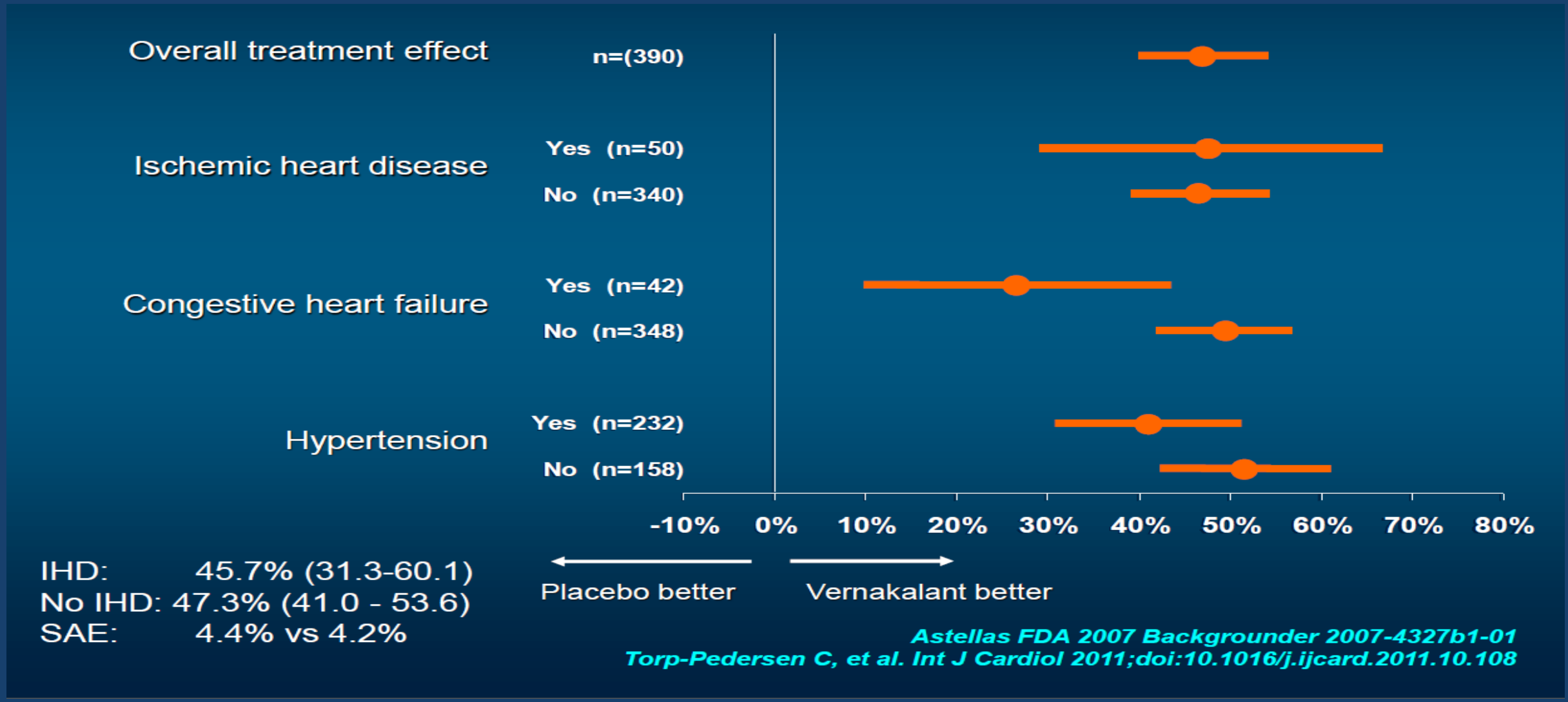
VERNAKALANT – *AF cardioversion-*



Roy D, et al. JACC 2004;44:2355-61
Roy D, et al. Circulation 2008;117:1518-25
Pratt CM, et al. AJC 2010;106:1277-83

Stiell IG,et al. AHJ 2010;159:1095-101
Camm AJ, et al. JACC 2011;57:313-21
Kowey PR, et al. Circ Arrhyth Electrophysiol 2009;2:652-9

ACT I and ACT III studies

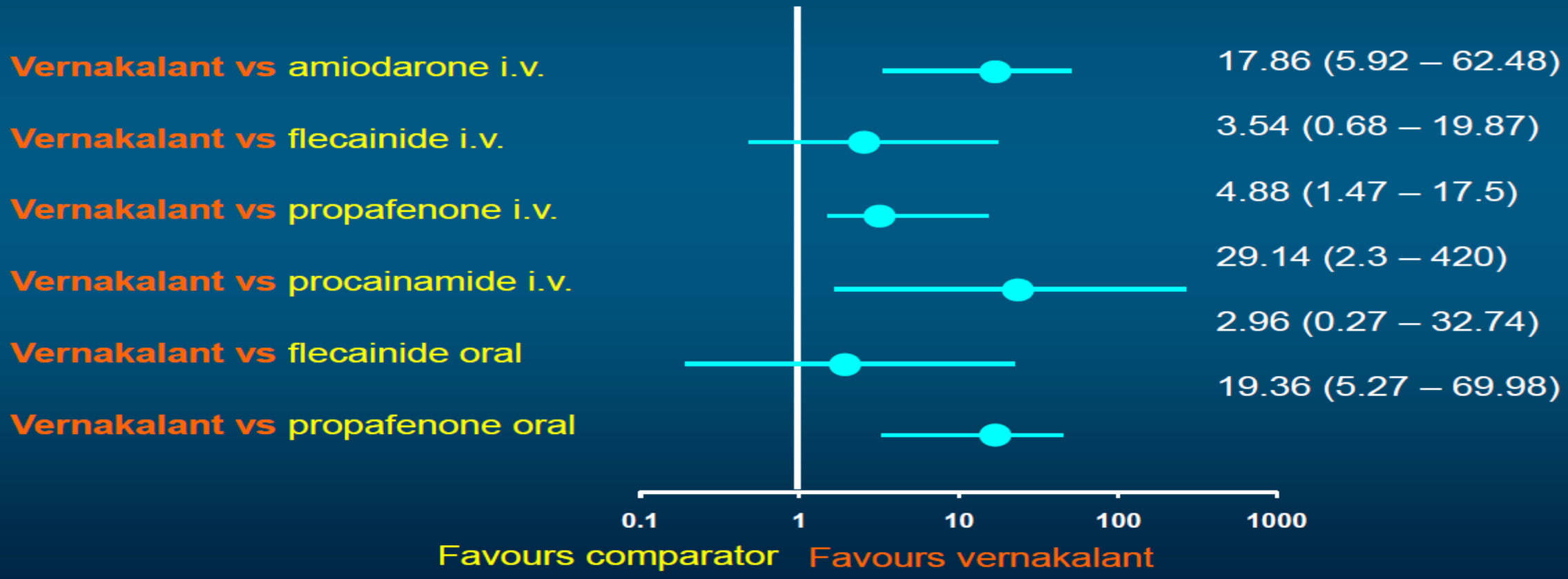


IHD: 45.7% (31.3-60.1)
No IHD: 47.3% (41.0 - 53.6)
SAE: 4.4% vs 4.2%

Astellas FDA 2007 Backgrounder 2007-4327b1-01
Torp-Pedersen C, et al. Int J Cardiol 2011;doi:10.1016/j.ijcard.2011.10.108

VERNAKALANT CARDIOVERSION VS OTHERS AADs

- 22 studies, 2410 patients with "short-duration" AF
- 1° endpoint: conversion within 2 h
- Pair-wise comparison against placebo, Bayesian MTC



Bash LD, et al. CV Drugs Ther 2012;26:167-79

VERNAKALANT- Adverse effects

Adverse effect	Incidence and warnings
Hypotension	Vernakalant vs placebo: 5.8% vs 3.6%, severe 1.2% vs 0.6% Usually transient (15-20 min) **Greater risk in patients with CHF (16.1% vs 4.7%)** Do not use if SBP < 100 mm Hg
Ventricular arrhythmia	6.3% vs 5.3% at 2 h **Patients with CHF had higher incidence of ventricular arrhythmia (7.3% vs 1.6%)** No drug-related torsades
Bradycardia	Predominantly at the time of conversion to SR (1.8%) Responded well to vernakalant discontinuation (0.5%) and/or administration of atropine
Atrial flutter	As a transitional rhythm in 8.6-12.7%, as AE in 1% Majority of patients with AFL continue to convert to SR Electrical cardioversion for the remaining patients No 1:1 atrioventricular conduction
ECG intervals	QTc increased by 20-25 ms QRS increased by 8 ms Do not use if baseline QT > 440 ms
Concomitant Rx	~ 76% received beta-blockers, calcium antagonists, or digoxin ~ 24% AAD within 24 h No difference in conversion rates and adverse effects

Recommendations for pharmacological cardioversion of recent-onset AF		
Recommendations	**Class**	**Level**
When pharmacological cardioversion is preferred and there is no or minimal structural heart disease, intravenous flecainide, propafenone, ibutilide, or vernakalant are recommended.	I	A
In patients with AF ≤7 days and moderate structural heart disease (but without hypotension <100 mm Hg, NYHA class III or IV heart failure, recent [<30 days] ACS, or severe aortic stenosis) intravenous vernakalant may be considered. Vernakalant should be used with caution in patients with NYHA class I–II heart failure.	IIb	B
Intravenous vernakalant may be considered for cardioversion of postoperative AF ≤3 days in patients after cardiac surgery.	IIb	B

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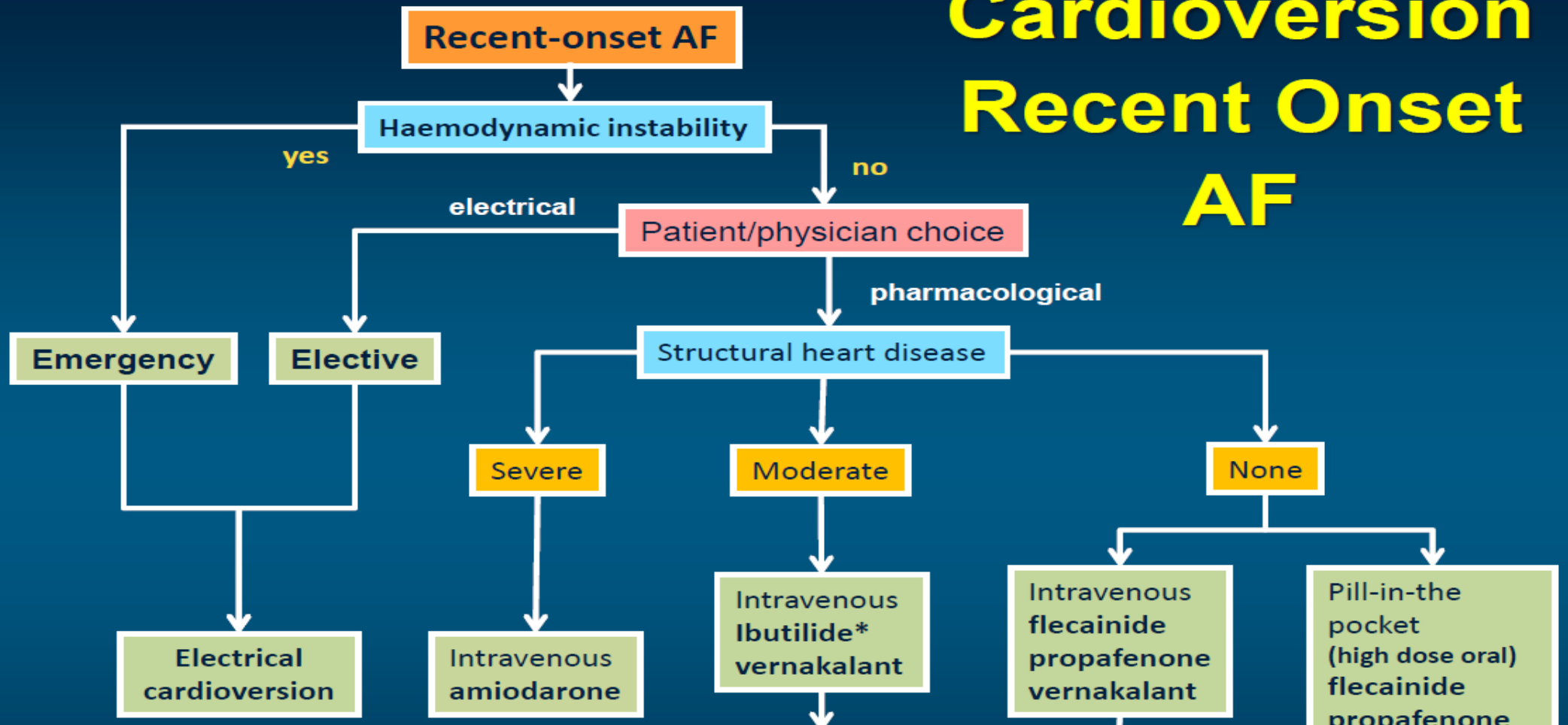
Cardioversion Recent Onset AF



[a]Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.
[b]Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
[c] 'Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.

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CONCLUSION

- AF THERAPY DID NOT HAVE ANY MAJOR SUCCESS % ADVANCE IN THE LAST YEARS DESPITE THE PRESENCE OF FEW NEW AAD AND THE ADVENT OF ABLATION PROCEDURES
- WE LEARNT HOWEVER THAT DIFFERENT AF TYPES AND COMORBIDITIES MAY MAKE AN IMPORTANT DIFFERENCE IN TERM OF THERAPEUTIC EFFICACY AND RESPONCES
- A FULL pros /cons DRUGS AND ABLATION PROCEDURES KNOWLEDGE IS THEREFORE MANDATORY
- AAD MAINTAIN AN IMPORTANT ROLE IN THIS CLINICAL COMPLEX CONTEXT

GRAZIE PER L’ ATTENZIONE