CARDIOVERSIÓN FARMACOLÓGICA EN URGENCIAS… ¿A QUIÉN Y CÓMO?

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CARDIOVERSIÓN FARMACOLÓGICA EN URGENCIAS…

¿A QUIÉN Y CÓMO?

Pharmacological cardioversion

"Many episodes of AF **terminate spontaneously** within the first hours or days.

Pharmacological cardioversion of AF may be **indicated**, by a bolus administration of an antiarrhythmic drug:

- if medically indicated (e.g. in severely compromised patients)
- in patients who remain symptomatic despite adequate rate control
- in patients in whom rhythm control therapy is pursued

The conversion rate with antiarrhythmic drugs is **lower than with DCC**, but does not require conscious sedation or anaesthesia, and may facilitate the choice of antiarrhythmic drug therapy to prevent recurrent AF.

Most patients who undergo pharmacological cardioversion require continuous medical supervision and **ECG monitoring during the drug infusion** and for a period afterwards (usually about half the drug elimination half-life) to detect proarrhythmic events such as ventricular proarrhythmia, sinus node arrest, or atrioventricular block.

Several agents are available for pharmacological cardioversion ."

AF guidelines. ESC. 2010

CARDIOVERSIÓN FARMACOLÓGICA EN URGENCIAS… ¿A QUIÉN Y CÓMO?

-FLECAINIDA: iv/vo

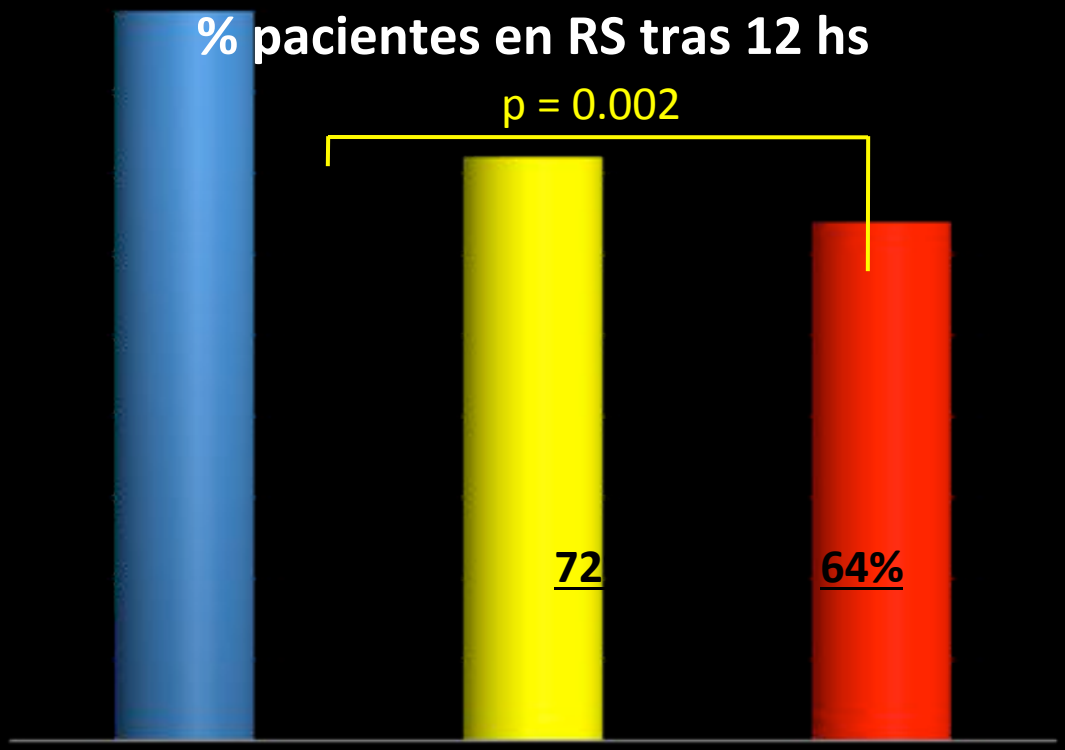
-PROPAFENONA: iv/vo

-AMIODARONA: iv

-VERNAKALANT: iv

Comparison of iv **FLECAINIDE**, **PROPAFENONE** and **AMIODARONE** for conversion of acute AF to sinus rhythm

150 P with acute (≤48h) AF
- **Flecainide** and **propafenone**: 2 mg/kg in 20 min (a second dose of 1 mg/kg in 20 min was given if SR not achieved after 8 h).
- **Amiodarone**: 5 mg/kg in 20 min, followed by a continuous infusion of 50 mg/hour.



The American Journal of Cardiology
Volume 86, Issue 9, 1 Nov 2000, 950-953

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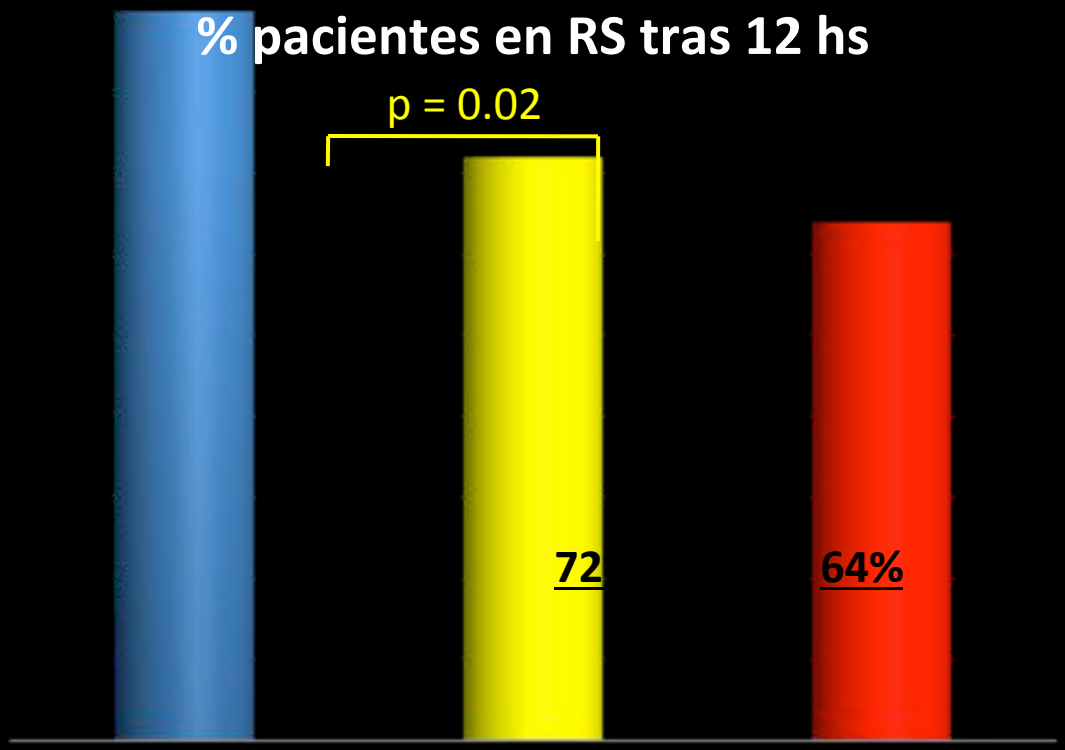

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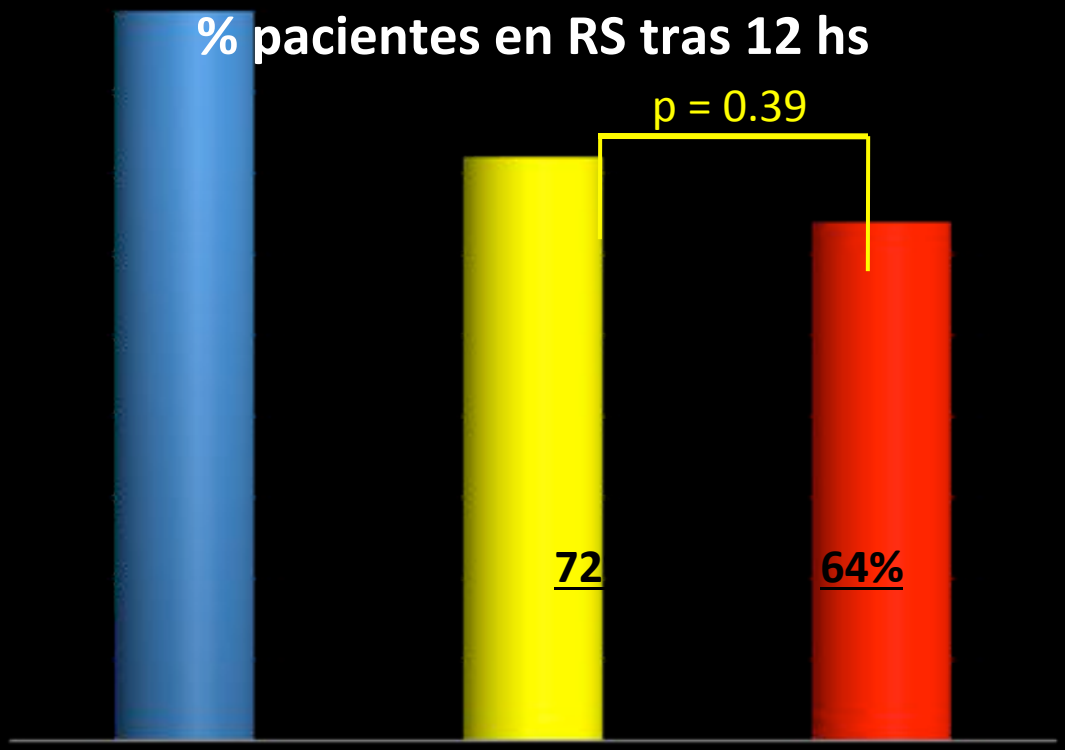

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150 P with acute (≤48h) AF

Medianas de tiempo hasta paso a sinusal:

- Flecainida: 25 min (range 4 to 660). Propafenone: 30 min (range 10 to 660)
- Amiodarone: 333 min (range 15 to 710)

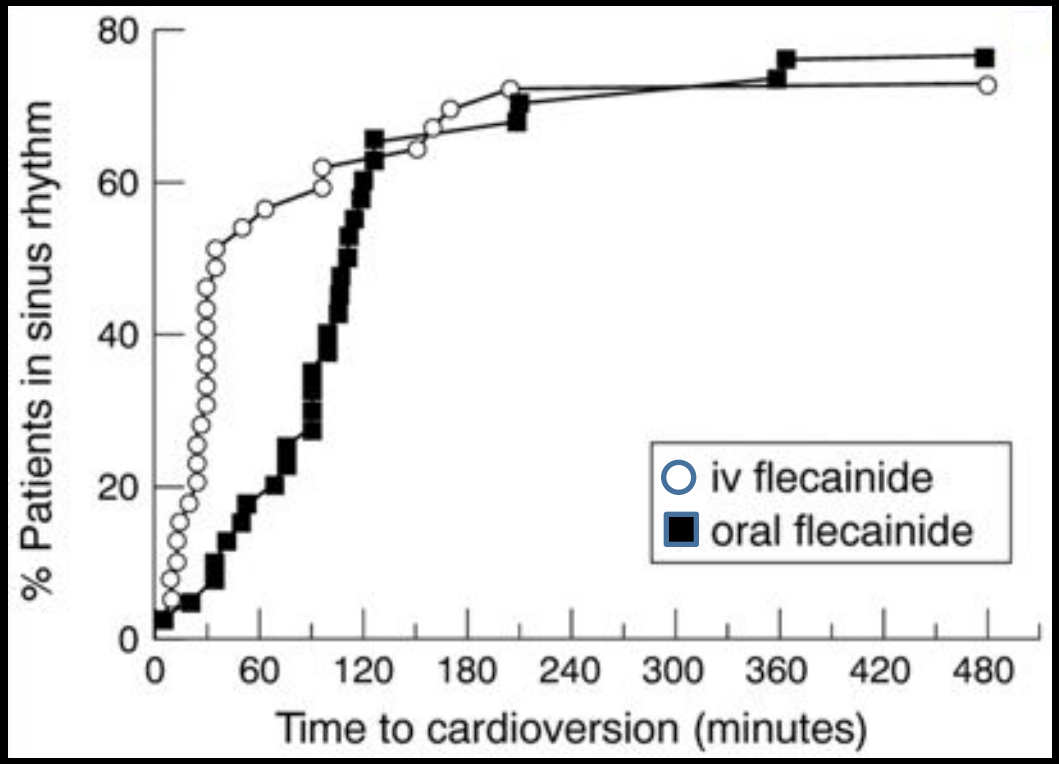
The American Journal of Cardiology
Volume 86, Issue 9, 1 Nov 2000, 950-953

Oral *Vs* iv FLECAINIDE for the cardioversion of acute AF

Acute AF patients (N=79) were given: **iv flecainide** (n = 39; 2 mg/kg –max: 150mg- in 30min) or **oral flecainide** (n = 40; 4mg/kg-max 300mg)

RESULTS: Both forms were well tolerated, with no adverse clinical events.

- The mean time to cardioversion was 110 minutes in the oral group and 52 minutes in the iv group (p = 0.002).
- 2 h after treatment, 68% in the oral group and 64% in the iv group had reverted to SR (p = 0.74).
- 8 h after treatment, 75% in the oral group (75%) and 72% in the iv group had reverted to SR (p = 0.76).



Heart. 2000; 84. 37

LIMITACIONES CON LA FLECAINIDA

"Flecainide should be avoided in patients with underlying heart disease involving abnormal LV function or ischaemia."

ESC. AF Guidelines. 2010

Exclusion criteria were:

- clinical signs of **CHF** (NYHA class >II)
- severely **reduced left ventricular systolic function**
- unstable **angina**, acute **myocardial infarction** within the preceding 6 weeks
- **hypotension** (systolic blood pressure <100 mmHg)
- **recent anti-arrhythmic therapy** (treatment with antiarrhythmic agents of class I or III within the previous 48 h or amiodarone within the previous 6 months)
- any previously documented **atrio-ventricular** or **intraventricular conduction disturbances** of more than first degree atrio-ventricular block or of more than unifascicular block
- **sick sinus syndrome** (unless protected by a permanent pacemaker)
- prolongation of the **QTc >450 ms**
- compromised **renal function** (i.e., serum creatinine >2.5 mg/dl) or **hepatic** insufficiency
- uncorrected **hypokalaemia or hypomagnesaemia**
- **pregnancy** and lactation
- **age** <19 or >90 years

→ Concurrent control of the ventricular rate with digoxin, beta-blockers, or calciumchannel blockers (verapamil, diltiazem) was permitted

… Y A LOS DE ICC, CARDIOPATÍA O IQUÉMICOS?

¿¿ AMIODARONA ??

AMIODARONA para la reversión de FA de inicio reciente (metánalisis) CJEM 2002;4(6):414-420

Conventional and High dose trials

5 randomized, placebo- or rate-controlled trials have evaluated conventional doses of IV amiodarone (<1600 mg/d) in patients with recent-onset AF

…Cowan and coworkers studied patients with recent-onset AF complicating myocardial infarction and found that 24-h conversion rates were no better with amiodarone than digoxin.
…Donovan and cohorts found no difference in conversion rates between amiodarone (7 mg/kg) and placebo after 8 hours.
…Galve conducted the largest trial of conventional IV dosing, in which 100 patients were randomized to amiodarone (5 mg/kg IV over 30 min, followed by 1200 mg IV over 24 hours) or saline placebo. At 24 hours there was no difference in conversion rates.
…The only trial using sequential dosing with conventional IV loading and oral doses of amiodarone found no benefit at 4, 24 or 48 hours compared to digoxin.

→ In summary, conventional doses of amiodarone appear to have no effect on the acute conversion of recent-onset AF to SR.

→ High-dose amiodarone (>1600mg/24h), is more effective than placebo for converting recent-onset AF to normal sinus rhythm. It is important to note that the high-dose amiodarone trials had strict enrollment criteria similar to those for Class Ic agents, and excluded patients with NYHA

CJEM 2002;4(6):414-420

Table 1. Randomized, placebo- or rate-controlled trials of intravenous amiodarone for acute conversion of recent-onset atrial fibrillation

Author, year, ref. no.	Onset	Mean duration	Agent(s)	Total dose (first 24 h)	N	End-point time	Success rate, %	Conversion time
Noc, 1990[33]	≤ 2 d	NR	Amiodarone Verapamil	350 mg	13 11	3 h	A: 77* V: 0	Range 10-175 min
Cowan, 1986[34]	<48 h compli-cating MI	NR	Amiodarone Digoxin	1500 mg	18 16	24 h	A: 83 D: 75	NR
Donovan, 1995[35]	≤ 72 h	11.5 h 8.9 h	Amiodarone Placebo	490 mg	32 32	2 h 6 h	A: 34, PL: 22 A: 59, PL: 56	NR
Galve, 1996[36]	≤ 7 d	25 h 18 h	Amiodarone Placebo	1650 mg	50 50	24 h	A: 68 V: 60	328 min 332 min
Joseph, 2000[37]	<24 h	NR	Sotalol iv, po Amiodarone iv, po Digoxin	1150 mg	40 39 36	4 h 24 h 48 h	S: 40, A: 31, D: 25 S: 80,† A: 69, D: 50 S: 88,† A: 77, D: 58	13.0 h† 18.1 h† 26.9 h
Capucci, 1992[38]	≤ 7 d	28 h 30 h 27 h	Flecainide po Amiodarone Placebo	2150 mg	22 19 21	3 h 6 h 12 h 24 h	F: 68,*‡ A: 16, PL: 29 F: 91,*‡ A: 37, PL: 48 F: 91,* A: 47 F: 95, A: 89	169 min*‡ 217 min 234 min
Hou, 1995[39]	Recent	14 h 4 h	Amiodarone Digoxin	1620 mg	20 19	24 h	A: 95 D: 74	2.5 h 6.5 h
Boriani, 1995[40]	≤ 7 d	29 h 31 h 29 h 30 h	Flecainide po Propafenone po Amiodarone Placebo	2150 mg	69 119 51 121	1 h 3 h 6 h	F: 13, PR: 8, A: 6, PL: 9 F: 57,‡ PR: 45,‡ A: 25, PL: 18 F: 75,‡ PR: 76,‡ A: 57,‡ PL: 37	161 min 181 min 225 min*‡ 181 min
Cotter, 1999[41]	≤ 48 h	NR	Amiodarone Placebo	3000 mg	50 50	8 h 24 h	A: 62, PL: 58 A: 92,‡ PL: 64	NR
Kochiadakis, 1998[42]	≤ 48 h	16 h 18 h	Amiodarone iv, po Placebo	3500 mg	48 49	24 h	A: 83‡ PL: 55	7 h‡ 13 h
Vardas, 2000[43]	Recent, persis-tent and chronic	24 h 28 h	Amiodarone iv, po Placebo	2300 mg	108 100	1 h 24 h 30 d	A: 38,‡ PL: 25 (OR 1.84; 95% CI 1.01-3.33) A: 61,‡ PL: 40 (OR 2.35; 95% CI 1.35-41.1) A: 81,‡ PL: 40 (OR 6.21; 95% CI 3.33-11.57)	NR

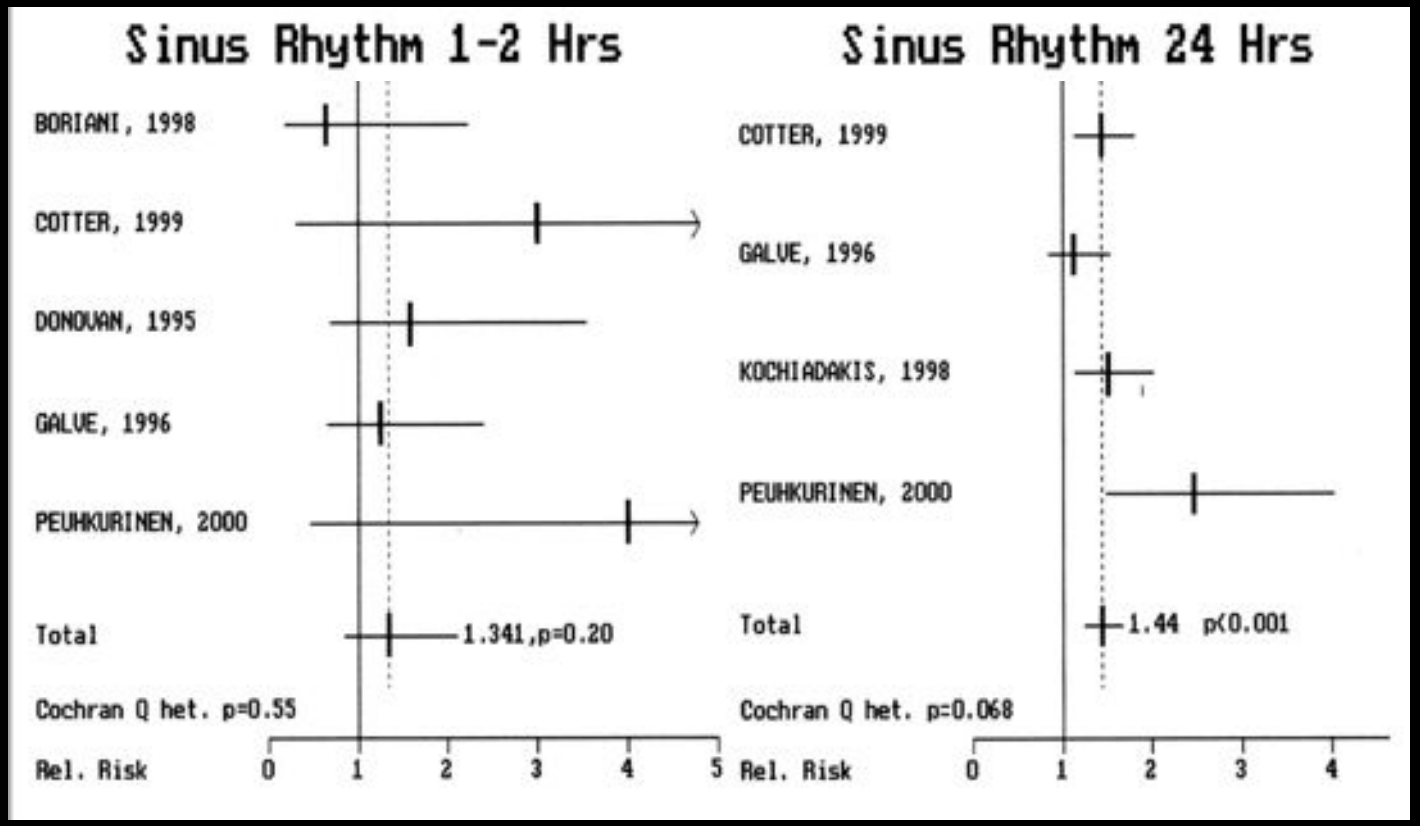
*$p < 0.05$ for comparison between agents; †$p < 0.05$ for comparison v. digoxin; ‡$p < 0.05$ v. placebo
AF = atrial fibrillation; NR = not reported; A = amiodarone; V = verapamil; D = digoxin; PL = placebo; S = Sotalol; iv = intravenous; po = by mouth; F = flecainide; PR = propafenone

AMIODARONA para la reversión de FA de inicio reciente (metánalisis) JACC 2003; 41:255-262

-"Amiodarone is **superior to placebo** for cardioversion of AF, and even though the onset of conversion is delayed, its efficacy is similar **at 24 h** compared with class Ic drugs.

-These results favor amiodarone as a **drug of choice** for patients with recent AF in the setting of **ventricular dysfunction** **and** **ischemic heart disease** in whom class Ic and other, more rapidly acting antiarrhythmic drugs cannot be used".

- Amiodarona Vs Placebo -



… ALGO NUEVO?

VERNAKALANT

Vernakalant

-Nuevo agente antiarrítmico que actúa básicamente en las **aurículas** prolongando la repolarización local y sus periodos refractarios mediante el bloqueo de las corrientes I_{kur} e I_{KACh} (I_{to} y componente tardío I_{Na}).

-Esta atrioselectividad la hace muy útil para tratar la **FA** ,con muy baja proarritmia ventricular, a diferencia de la mayoría de FAA.

-Se ha evaluado su forma **iv** para el ttº de la FA de reciente comienzo y la **oral** para el mantenimiento del RS en pacientes con FA paroxística.

- La aprobación de vernakalant iv para la **reversión de FA <1 semana** se basa en los resultados de varios estudios, algunos aleatorizados, doble ciego y controlados con placebo (CRAFT, ACT I, ACT II y ACT III) y en un ensayo con comparador activo (AVRO).

Vernakalant

- **No** útil en reversión de FA > 1 semana ni en flúter.

- Tras su administración iv , 3 mg/k en 10’ - 15’espera - 2mg/k en 10’, la tasa de **reversión** de FA aguda a los 90’ es del 50-55% y ocurre a los **10-14 min** del inicio.

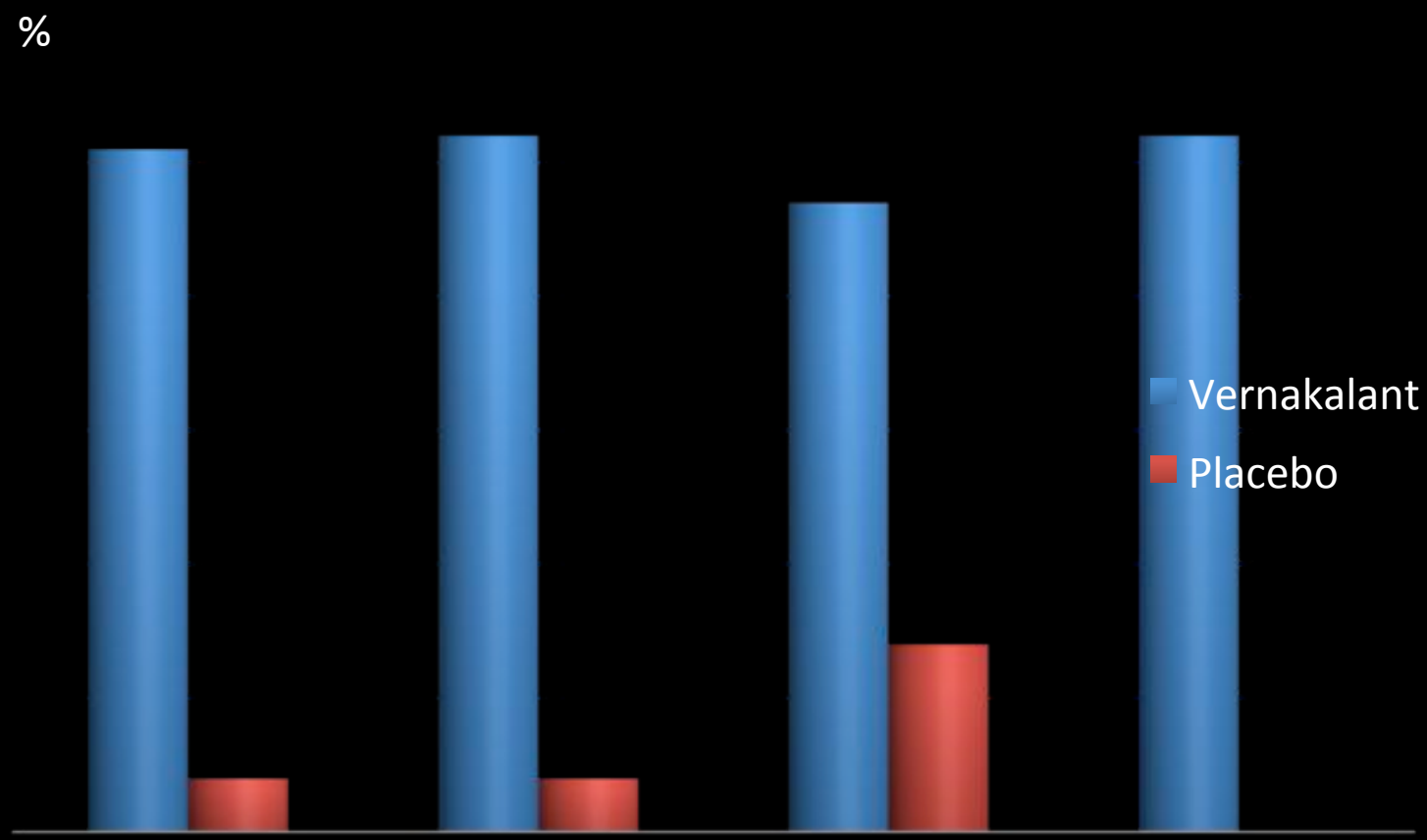
- Tras la 1ª dosis revierten un 40%, tras la 2ª dosis sólo un 20% de ellos responderán.

- Vida media 3 horas (**vigilancia 6h**) con metabolismo hepático. Monitorizar ECG y PA no invasiva.

- **Efectos secundarios** principales: disgeusia, tos y estornudos. Más infrecuentes: hipotensión y raramente TVNS, ambas st en ICC.

Estudios ACT (Atrial Arrhythmia Conversion Trial)

Vernakalant iv para la cardioversión farmacológica de la FA reciente frente a placebo



Tasas de conversión de la FA **a los 90min** en grupos Vernakalant y Placebo para FA de <3d

2008 Drugs Today

Estudio AVRO

Vernakalant iv para la cardioversión farmacológica de la FA <48h frente a Amiodarona

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Heart Rhythm Disorders

CME

A Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation

A. John Camm, MD,* Alessandro Capucci, MD,† Stefan H. Hohnloser, MD,‡ Christian Torp-Pedersen, MD,§ Isabelle C. Van Gelder, MD,‖¶ Brian Mangal, MSc,# Gregory Beatch, PhD,# on behalf of the AVRO Investigators

- **Vernakalant**: 3mg/k en 10min – 15 min – 2mg/k en 10min
- **Amiodarona**: 5 mg/kg de una hora, seguida de una perfusión de 50 mg en 1 hora

2011 JACC

Selection of AVRO participants:

- 232 Men and women between 18 and 85 years with symptomatic recent-onset AF (duration of 3 to 48 h) who:
    1) were eligible for cardioversion,
    2) hemodynamically stable (SBP > 100 but <160 mm Hg and DBP <95 mm Hg),
    3) taking adequate anticoagulation therapy (if recommended by official guidelines).

-**Patients were excluded if**:

-1) uncorrected **QT** > 440 ms; familial long QT syndrome;
-2) previous torsades de pointes (TdP), ventricular fibrillation, or sustained ventricular tachycardia (VT)
-3) symptomatic **bradycardia**,(ventricular rate <50 beats/min) or known sick sinus syndrome;
-4) **QRS** >140 ms.
-5) Patients with a pacemaker
-6) atrial flutter (AFL)
-7) atrial thrombus
-8) **unstable congestive heart failure (CHF)**, NYHA class IV or heart failure requiring inotropes
-9) myocardial infarction, **acute coronary syndrome**, or cardiac surgery **within 30 days** prior to enrollment
-10)cerebrovascular accident within 3 months prior to enrollment
-11) atrioventricular block
-12) **valvular stenosis**
-13) hypertrophic obstructive cardiomyopathy
-14) restrictive cardiomyopathy or constrictive pericarditis
-15) end-stage disease states
-16) previously failed electrical cardioversion
-17) secondary causes of AF
-18) uncorrected electrolyte imbalance
-19) digoxin toxicity
-20) Patients were not permitted to receive class I or III antiarrhythmic drugs from 24 h pre-dose and intravenous or oral amiodarone within 30 or 90 days pre-dose, respectively

AVRO

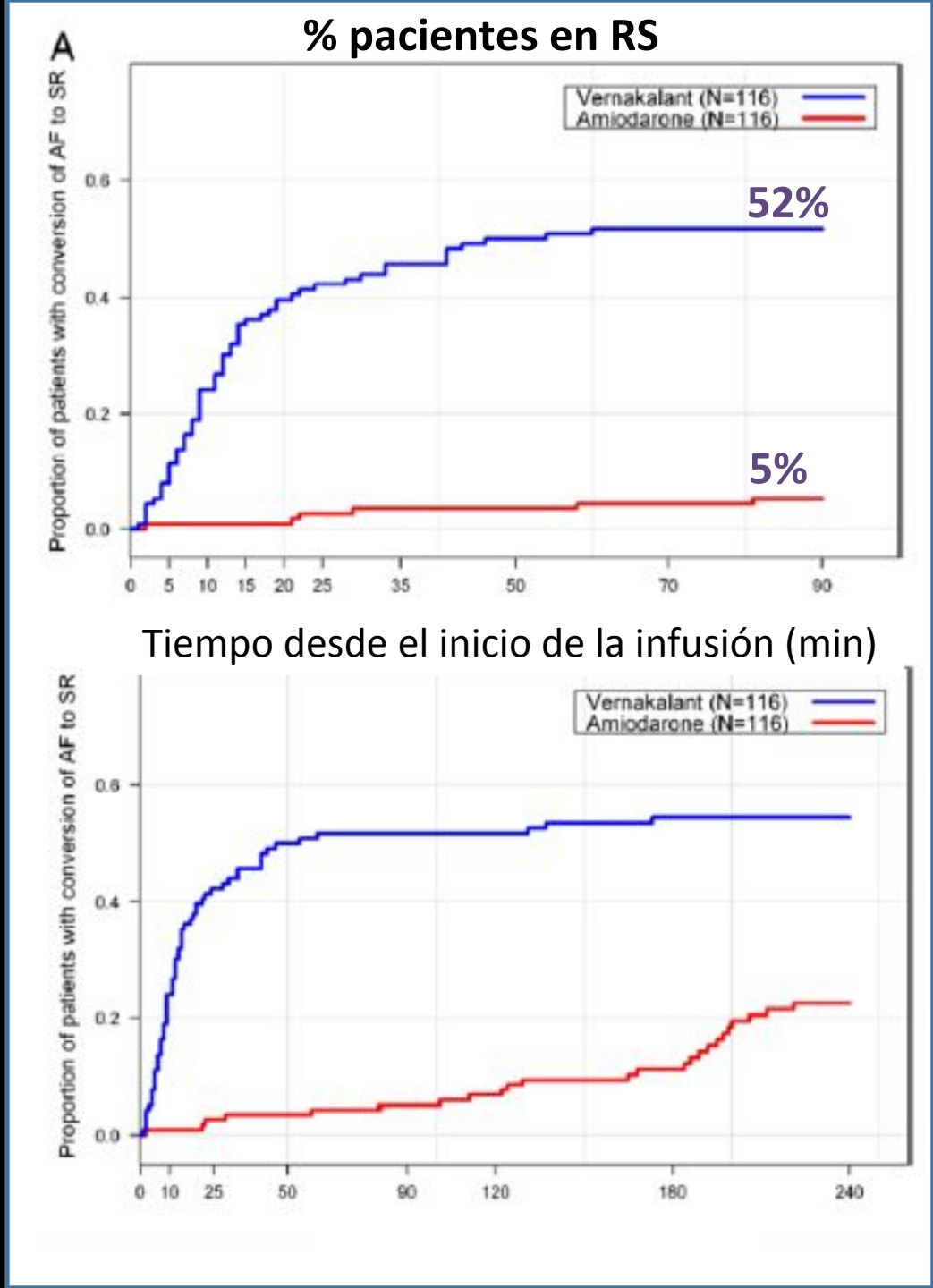
Table 1 Demographic and Baseline Characteristics

	Treatment Group		
	Vernakalant (n = 116)	Amiodarone (n = 116)	Total (n = 232)
Baseline characteristics			
Male, n (%)	75 (64.7)	71 (61.2)	146 (62.9)
White, n (%)	111 (95.7)	111 (95.7)	222 (95.7)
Age (yrs), mean (SD)	63.1 (10.81)	62.2 (11.63)	62.7 (11.21)
No previous episode of AF	34 (29.3)	33 (28.4)	67 (28.9)
1–3 previous episodes of AF	44 (37.9)	40 (34.5)	84 (36.2)
>3 previous episodes of AF*	38 (32.8)	42 (36.2)	80 (34.5)
Median duration of current AF, h (25%, 75% quartiles)	17.7 (9.1, 28.7)	17.9 (9.7, 31.4)	17.7 (9.3, 30.4)
AF duration ≤24 h, n (%)	73 (62.9)	65 (56.0)	138 (59.5)
Medical history, n (%)			
Hypertension	86 (74.1)	80 (69.0)	166 (71.6)
Structural heart disease†	36 (31.0)	45 (38.8)	81 (34.9)
Ischemic heart disease	22 (19.0)	30 (25.9)	52 (22.4)
Myocardial infarction	11 (9.5)	8 (6.9)	19 (8.2)
Valvular heart disease	4 (3.4)	12 (10.3)	16 (6.9)
Heart failure	20 (17.2)	26 (22.4)	46 (19.8)
NYHA functional class I‡	9 (45.0)	12 (46.2)	21 (45.7)
NYHA functional class II‡	11 (55.0)	14 (53.8)	25 (54.3)
LADD (mm), mean (SD)	40.6 (6.77)	41.0 (6.04)	40.8 (6.40)
LADD >50 mm	5 (4.3)	7 (6.0)	12 (5.2)
LVEF (%), mean (SD)	57.6 (7.34)	59.5 (6.97)	58.5 (7.21)
LVEF <50%	15 (12.9)	4 (3.4)	19 (8.2)
Medications used within 7 days, n (%)			
Any rate control§	71 (61.2)	78 (67.2)	149 (64.2)
Beta-blockers	63 (54.3)	76 (65.5)	139 (59.9)
Calcium-channel blockers	10 (8.6)	4 (3.4)	14 (6.0)
Digitalis glycosides	6 (5.2)	10 (8.6)	16 (6.9)

AVRO

Resultados (1)

- Vkt más eficaz en revertir la FA



AVRO

Resultados (2)

- Amiodarona más eficaz para frenar la FA

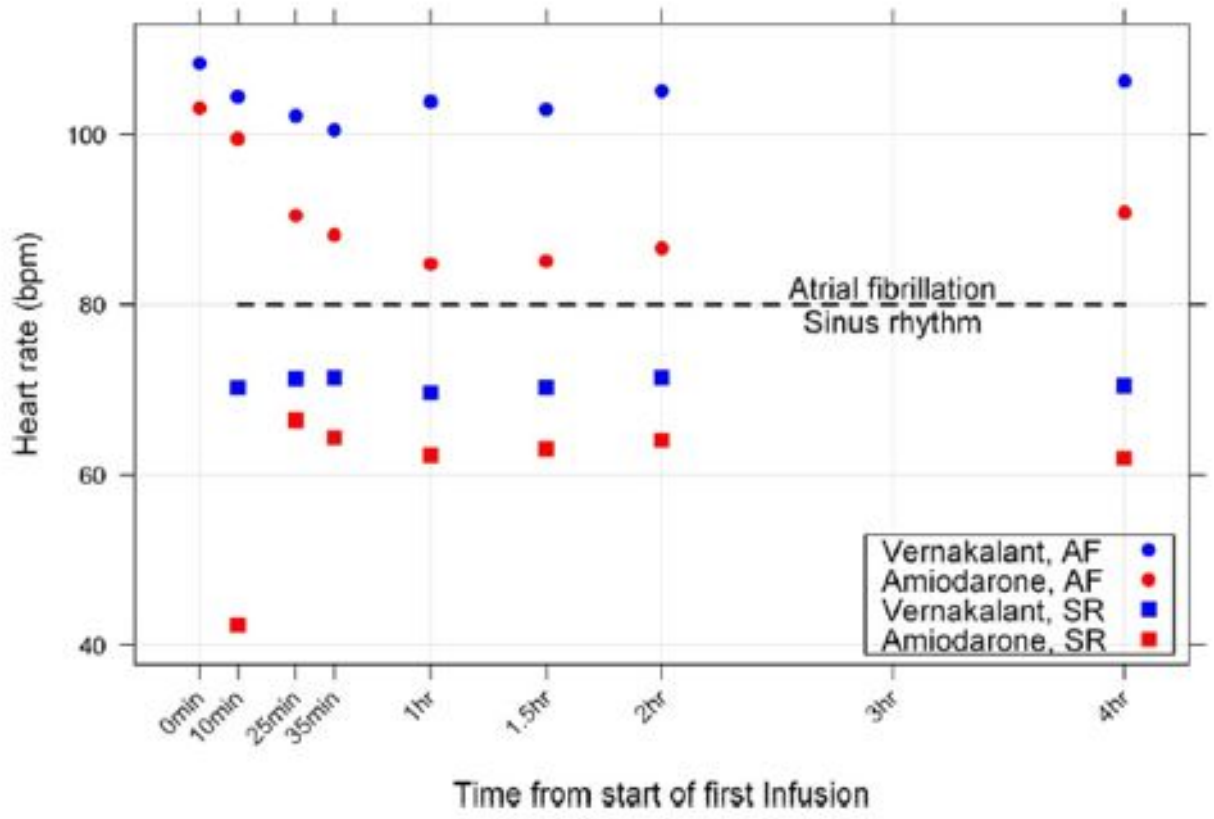


Figure 3 Mean Heart Rate for Patients in AF and for Patients in SR Over 4 h Post-Dose

En ensayos clínicos, las reacciones adversas notificadas con más frecuencia observadas en las primeras 24 horas fueron disgeusia (alteración del gusto) (20,1%), estornudos (14,6%), parestesias (9,7%), naúseas (6%) e hipotensión (5%).

Table 2 Summary of AEs Occurring Within 24 h Post-Dose

	0–2 h Post-Dose		2–24 h Post-Dose	
	Vernakalant (n = 116)	Amiodarone (n = 116)	Vernakalant (n = 116)	Amiodarone (n = 116)
Any treatment-emergent AE*	32 (27.6)	10 (8.6)	21 (18.1)	15 (12.9)
Any related treatment-emergent AE	22 (19.0)	1 (0.9)	4 (3.4)‡	1 (0.9)‡
Common related treatment-emergent AEs†				
Dysgeusia	8 (6.9)	0	0	0
Sneezing	4 (3.4)	0	0	0
Cough	3 (2.6)	0	0	0
Any treatment-emergent SAE	3 (2.6)	1 (0.9)	2 (1.7)	1 (0.9)
Any related treatment-emergent SAE	3 (2.6)	1 (0.9)	0	0
Discontinuations due to AEs	3 (2.6)	1 (0.9)	0	0

Values are patients, n (%). *Treatment-emergent AEs were defined as any AE that began or worsened following the start of study drug infusion. †Common related treatment-emergent AEs were those that occurred in >2 patients in the study. ‡Related treatment-emergent AEs occurring within 2 to 24 h post-dose included bradycardia, supraventricular tachycardia, prolonged electrocardiogram QT, and decreased heart rate in the vernakalant group, and increased blood bilirubin in the amiodarone group.

AE = adverse event; SAE = serious adverse event.

LIMITACIONES CON EL VERNAKALANT

Contraindicado en:

- Síndrome Coronario Agudo dentro de los últimos 30 días
- Estenosis aórtica grave
- Hipotensión (PAs <100 mm Hg)
- ICC en NYHA III o IV
- QT prolongado (>440 msec no corregido)
- Bradicardia grave (<50lpm), disfunción sinusal o BAV de 2º o 3º sin MP
- Pacientes con antiarrítmicos iv de control del ritmo (clase I y III) dentro de las 4 horas previas a la administración, así como en las 4 primeras horas después de la administración

Fármacos aprobados en Europa para cardioversión farmacológica de FA

- Vernakalant (Brinavess®) aprobado en Europa para la reversión rápida de FA a sinusal en adultos con FA < 1 semana y en pacientes postquirúrgicos con FA < 3 días

Table 12 Drugs and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	2 mg/kg i.v. over 10 min, or 200–300 mg p.o.	N/A	Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450–600 mg p.o.		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest	So far only evaluated in clinical trials; recently approved. [68–70]

ESC. 2010