La soluzione “pill in the pocket”nella terapia della FA: un’ efficacia sottovalutata

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PLACE 25 giugno 2026

L' approccio PIP (pill in the pocket) è una strategia efficace e sicura in pazienti **accuratamente selezionati** affetti da **FA parossistica sintomatica.**

AHA/ACC/HRS Practice Guideline

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

ELSEVIER

Check for updates

Canadian Journal of Cardiology 34 (2018) 1371–1392

Society Guidelines

2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Europace (2016) **18**, 1609–1678
doi:10.1093/europace/euw295

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

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**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outpatient Treatment of Recent-Onset Atrial Fibrillation with the "Pill-in-the-Pocket" Approach

Paolo Alboni, M.D., Giovanni L. Botto, M.D., Nicola Baldi, M.D., Mario Luzi, M.D., Vitantonio Russo, M.D., Lorella Gianfranchi, M.D., Paola Marchi, M.D., Massimo Calzolari, M.D., Alberto Solano, M.D., Raffaele Baroffio, M.D., and Germano Gaggioli, M.D.*

From the Divisions of Cardiology, Ospedale Civile, Cento (P.A., L.G.); Ospedale S. Anna, Como (G.L.B., M.L.); Ospedale SS. Annunziata, Taranto (N.B., V.R.); Ospedale del Delta, Lagosanto (P.M.); Arcispedale Santa Maria Nuova, Reggio Emilia (M.C.); Ospedali Riuniti, Lavagna (A.S.); Ospedale Galmarini, Tradate (R.B.); and Ospedale Civile, Sampierdarena (G.G.) — all in Italy. Address reprint requests to Dr. Alboni at the Division of Cardiology, Ospedale Civile, I-44042 Cento, Italy, or at p.alboni@ausl.fe.it.

*Additional study investigators are listed in the Appendix.

N Engl J Med 2004;351:2384-91.

ABSTRACT

BACKGROUND

In-hospital administration of flecainide and propafenone in a single oral loading dose has been shown to be effective and superior to placebo in terminating atrial fibrillation. We evaluated the feasibility and the safety of self-administered oral loading of flecainide and propafenone in terminating atrial fibrillation of recent onset outside the hospital.

METHODS

We administered either flecainide or propafenone orally to restore sinus rhythm in 268 patients with mild heart disease or none who came to the emergency room with atrial fibrillation of recent onset that was hemodynamically well tolerated. Of these patients, 58 (22 percent) were excluded from the study because of treatment failure or side effects. Out-of-hospital self-administration of flecainide or propafenone — the "pill-in-the-pocket" approach — after the onset of heart palpitations was evaluated in the remaining 210 patients (mean age [±SD], 59±11 years).

RESULTS

During a mean follow-up of 15±5 months, 165 patients (79 percent) had a total of 618 episodes of arrhythmia; of those episodes, 569 (92 percent) were treated 36±93 minutes after the onset of symptoms. Treatment was successful in 534 episodes (94 percent); the time to resolution of symptoms was 113±84 minutes. Among the 165 patients with recurrences, the drug was effective during all the arrhythmic episodes in 139 patients (84 percent). Adverse effects were reported during one or more arrhythmic episodes by 12 patients (7 percent), including atrial flutter at a rapid ventricular rate in 1 patient and noncardiac side effects in 11 patients. The numbers of monthly visits to the emergency room and hospitalizations were significantly lower during follow-up than during the year before the target episode ($P<0.001$ for both comparisons).

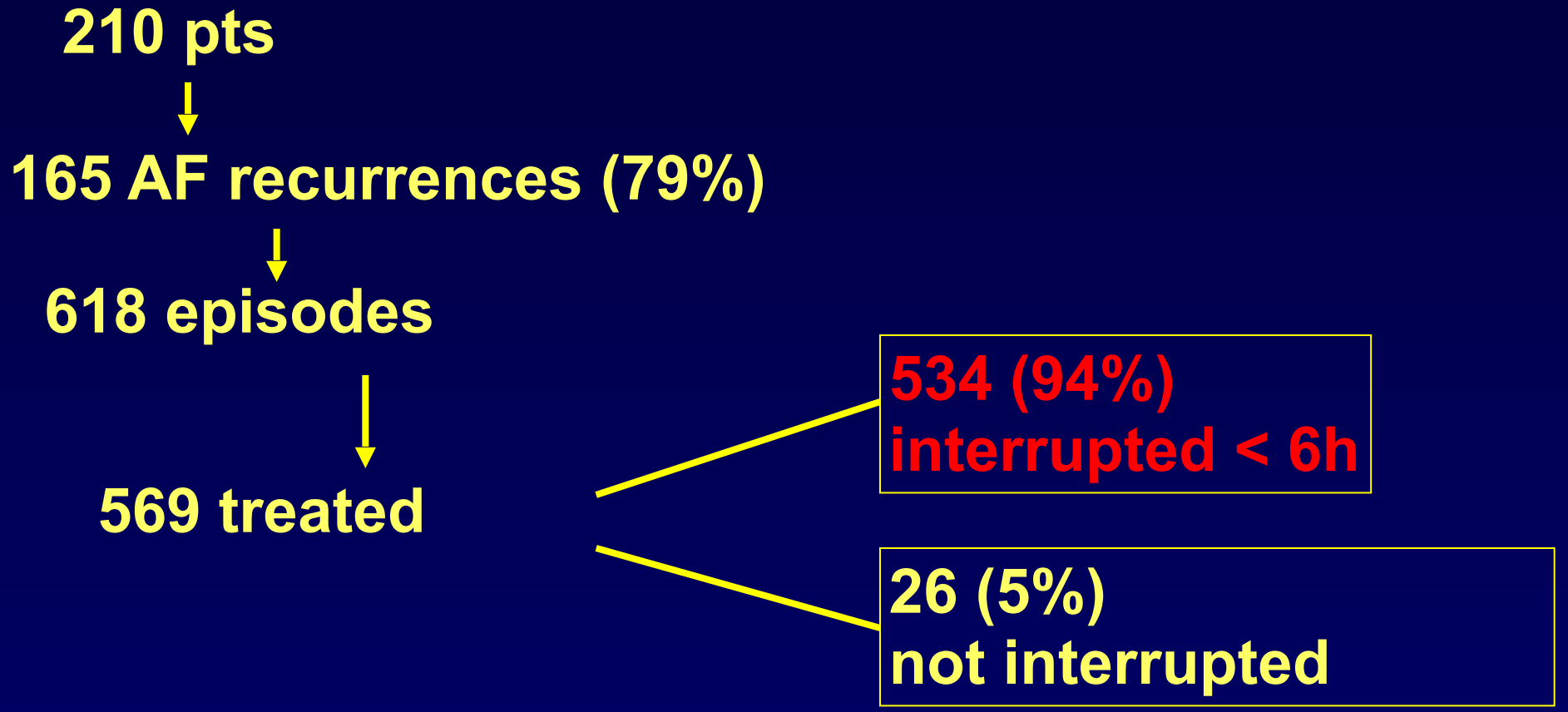
CONCLUSIONS

In a selected, risk-stratified population of patients with recurrent atrial fibrillation, pill-in-the-pocket treatment is feasible and safe, with a high rate of compliance by patients, a low rate of adverse events, and a marked reduction in emergency room visits and hospital admissions.

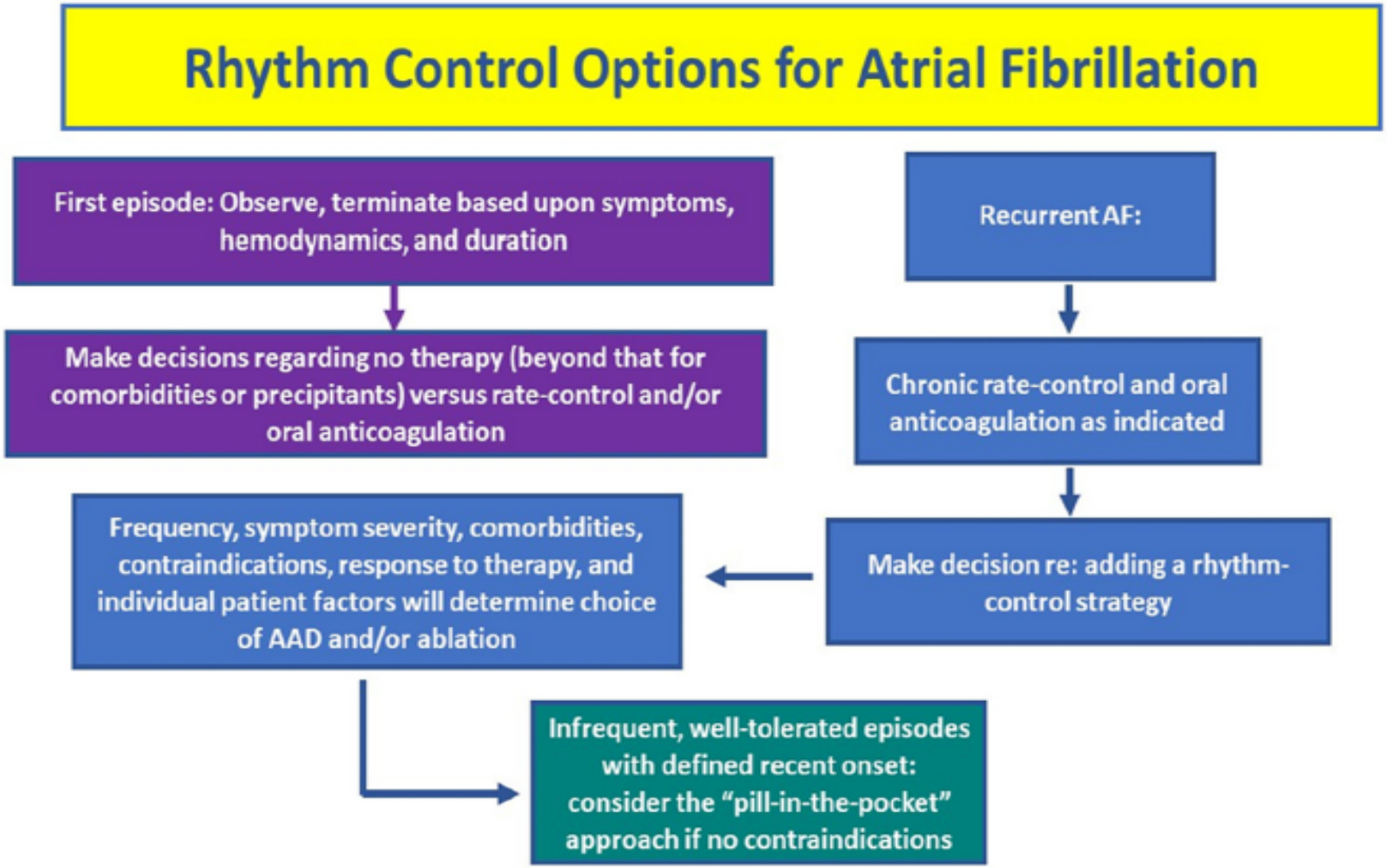
Pill in the pocket 1C approach

(Alboni et al. NEJM 2004)

Follow-up 15±5 mos



TOP Left



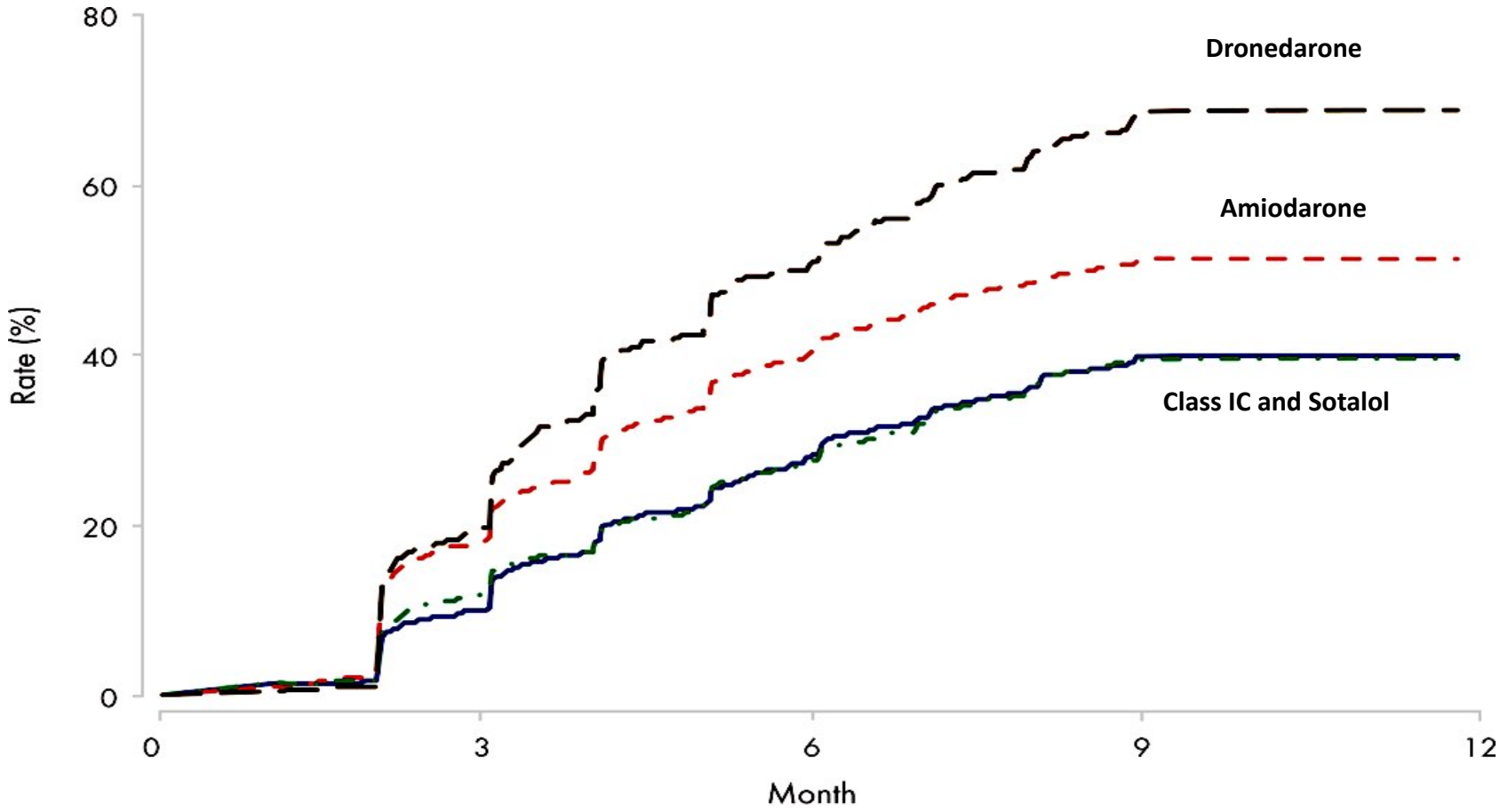
BOTTOM Right

Figure 1. Rhythm control options for atrial fibrillation (AF).

Pitfalls nella terapia di controllo del ritmo

- Discontinuazione nel tempo
- Scarsa aderenza

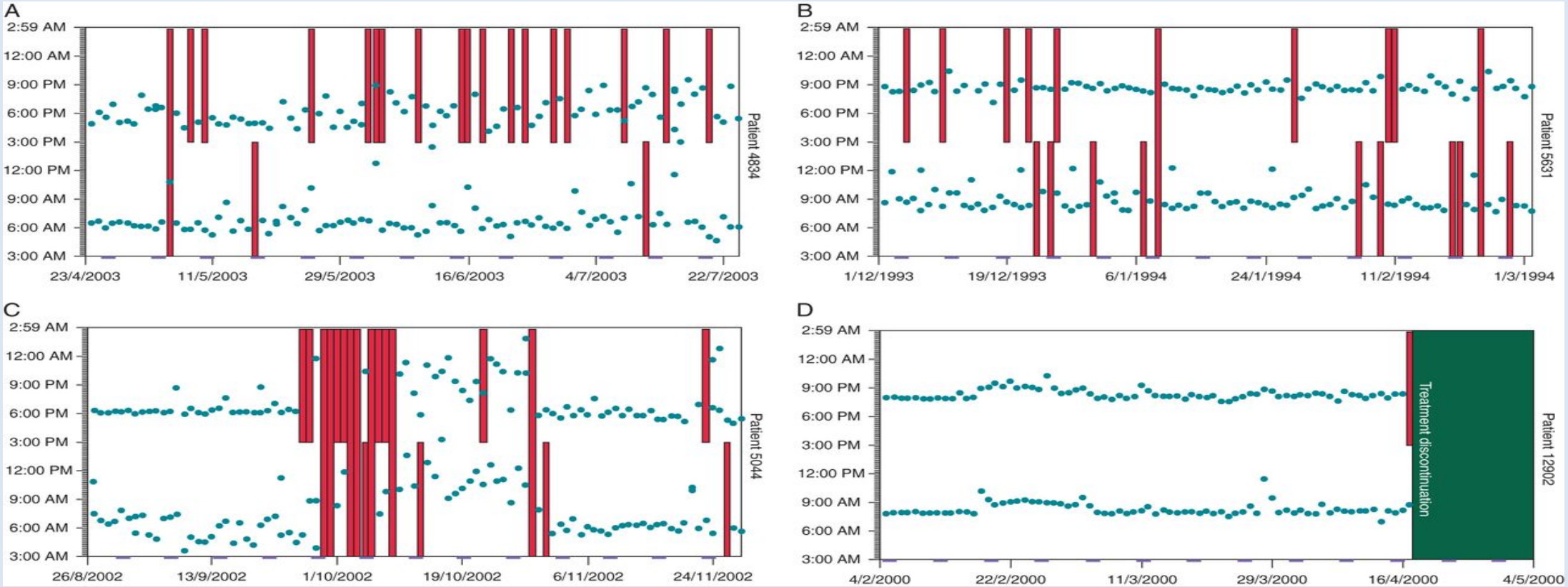
Kaplan Meier rate of discontinuation by initial AAD



8,562 patients <65 y, without SHD. Rates of discontinuation rate was 40% for class IC drugs, 52% for amiodarone, 40% for sotalol, and 69% for dronedarone

LaPointe et al. Circ Cardiovasc Qual Outcomes 2015;8:292-300

Varying patterns of adherence.



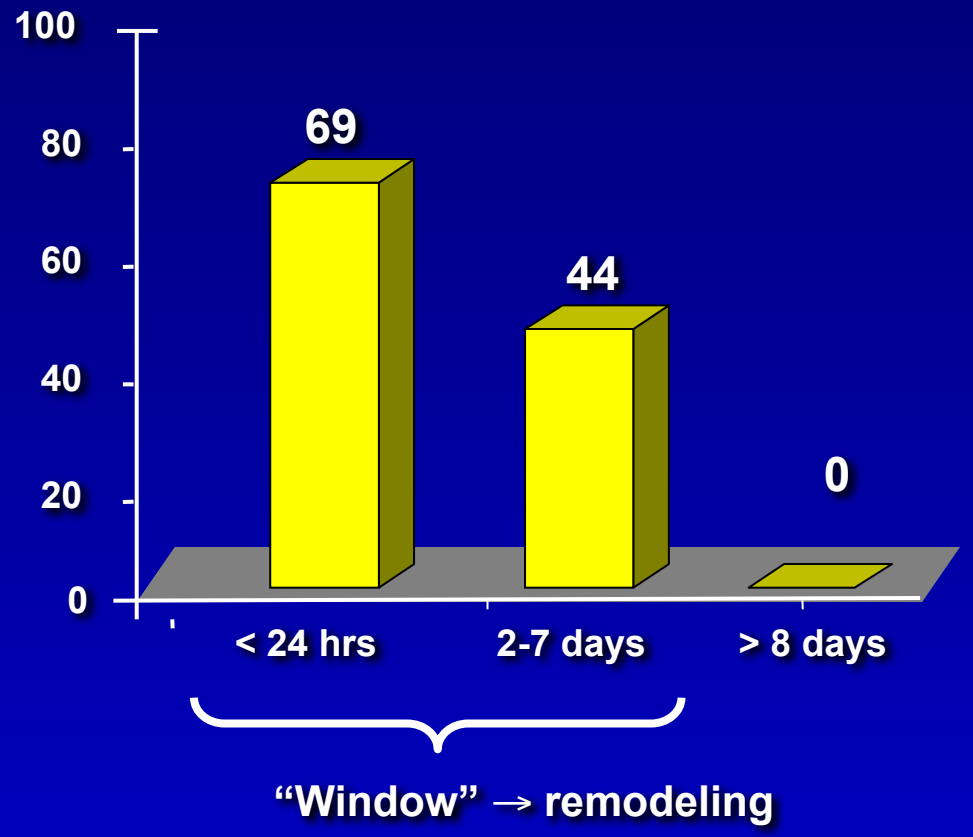
Bernard Vrijens, and Hein Heidbuchel Europace 2015;17:514-523

Europace
European Pacing, Arrhythmias and Cardiac Electrophysiology

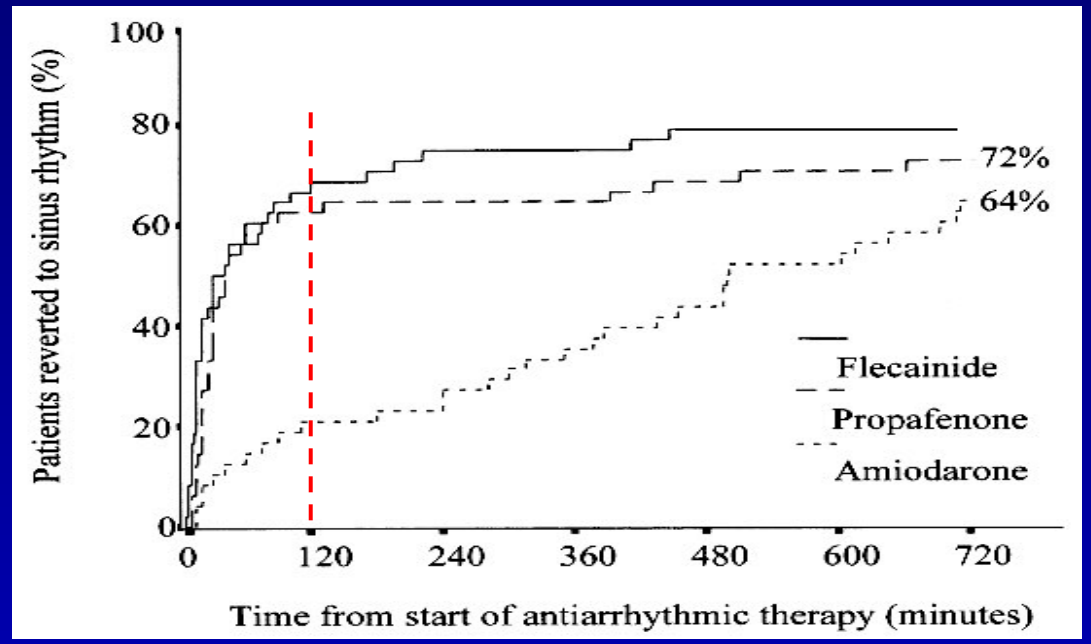
QUANDO PENSARE AL PIP (pill in the pocket)?

Conversion rates of recent-onset AF

AADs are more effective when initiated within 2 days



Cumulative conversion rates (%) of AF (≤ 48 hrs) in relation to the time after infusion



- IC AADs – SR is restored in 60-70% within 2 h
- Amiodarone - slower onset of CV
  - Lower risk of proarrhythmia
  - First choice in patients with HF or CAD

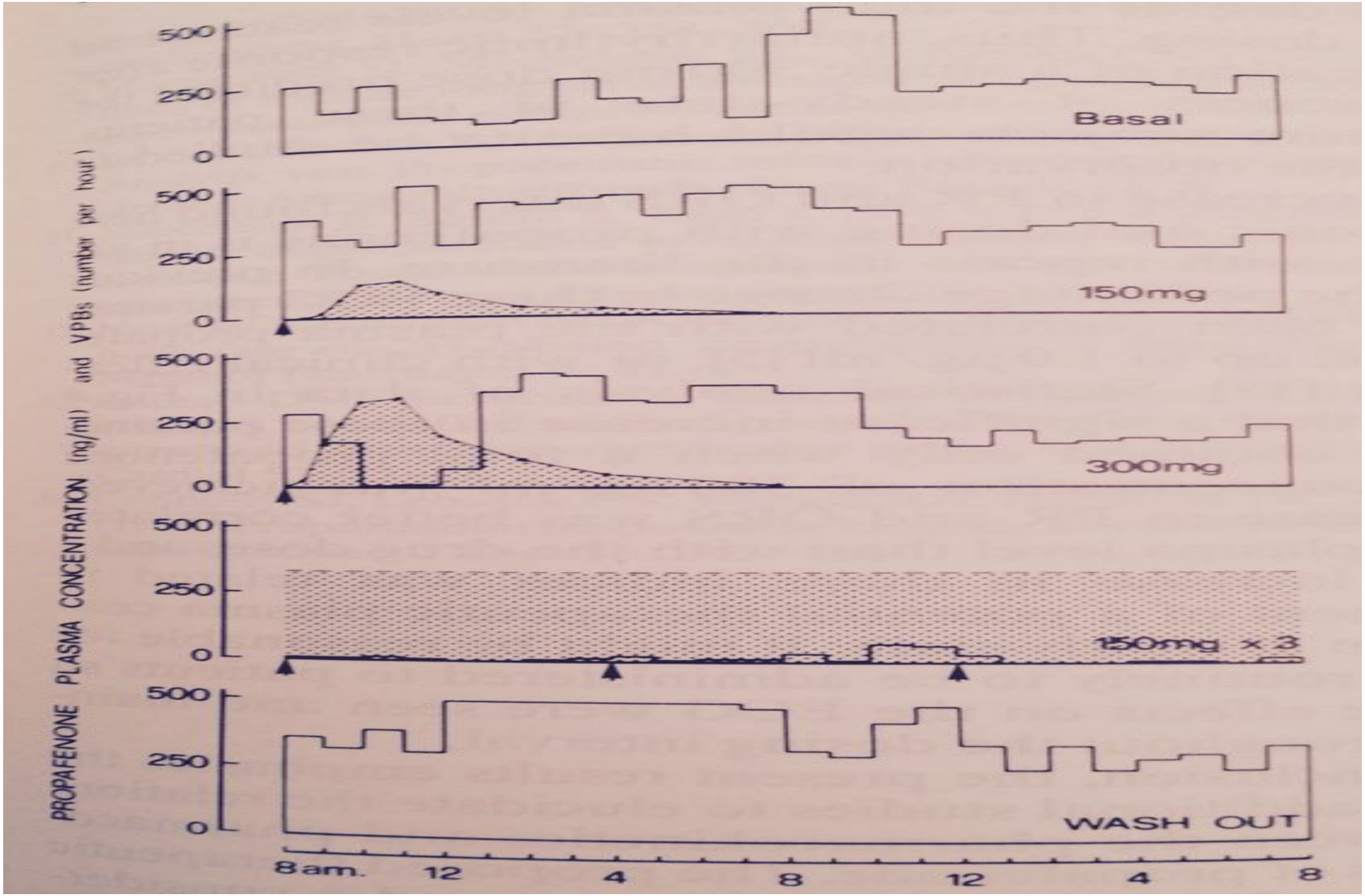
Reisinger J. Am J Cardiol 1998;81:1450

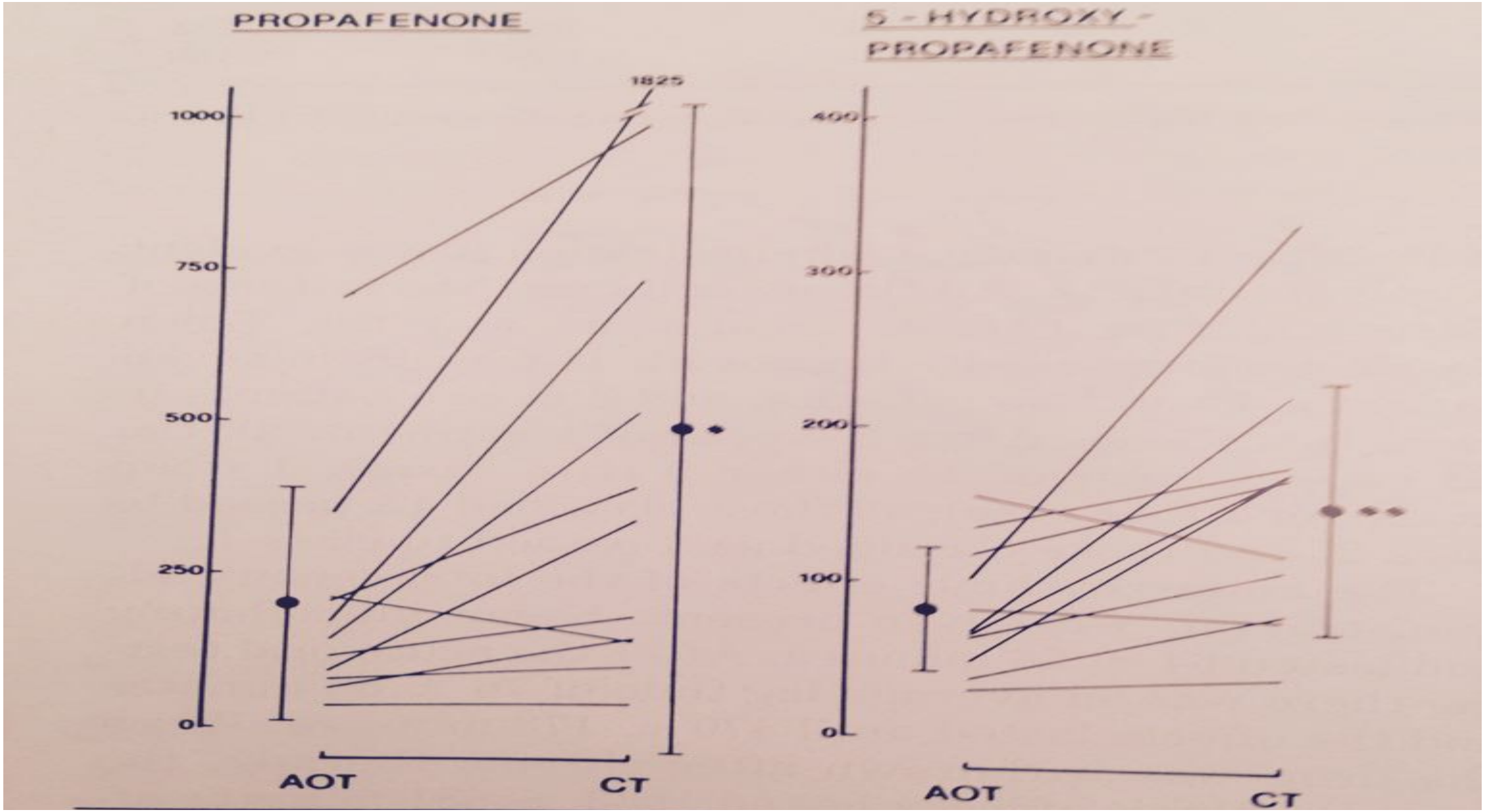
Martinez-Marcos Am J Cardiol 2000;86:950–953

Minimal Effective Concentration Values of Propafenone and 5-Hydroxy-Propafenone In Acute and Chronic Therapy

Alessandro Capucci,[1] Giuseppe Boriani,[1]
Bruno Marchesini,[2] Enrico Strocchi,[2]
Luciana Tomasi,[2] Marco Balducelli,[1]
Lorenzo Frabetti,[1] Ettore Ambrosioni,[2]
Bruno Magnani[1]

[1]Institute of Cardiovascular Diseases and [2]Department of C
Pharmacology and Therapeutics, University of Bologna,
Bologna, Italy.


PROPAFENONE PLASMA CONCENTRATION (ng/ml) and VPBs (number per hour)
500
250
0
Basal
150mg
300mg
150mg x 3
WASH OUT
8 am.
12
4
8
12
4
8


PROPAFENONE
1825
1000
750
500
250
0
AOT
CT
5 - HYDROXY - PROPAFENONE
400
300
200
100
0
AOT
CT

Flecainide prolongs atrial APD and refractoriness at fast rates (Wang et al. Circ Res 1992;71:271-287)

Reverse use-dependence

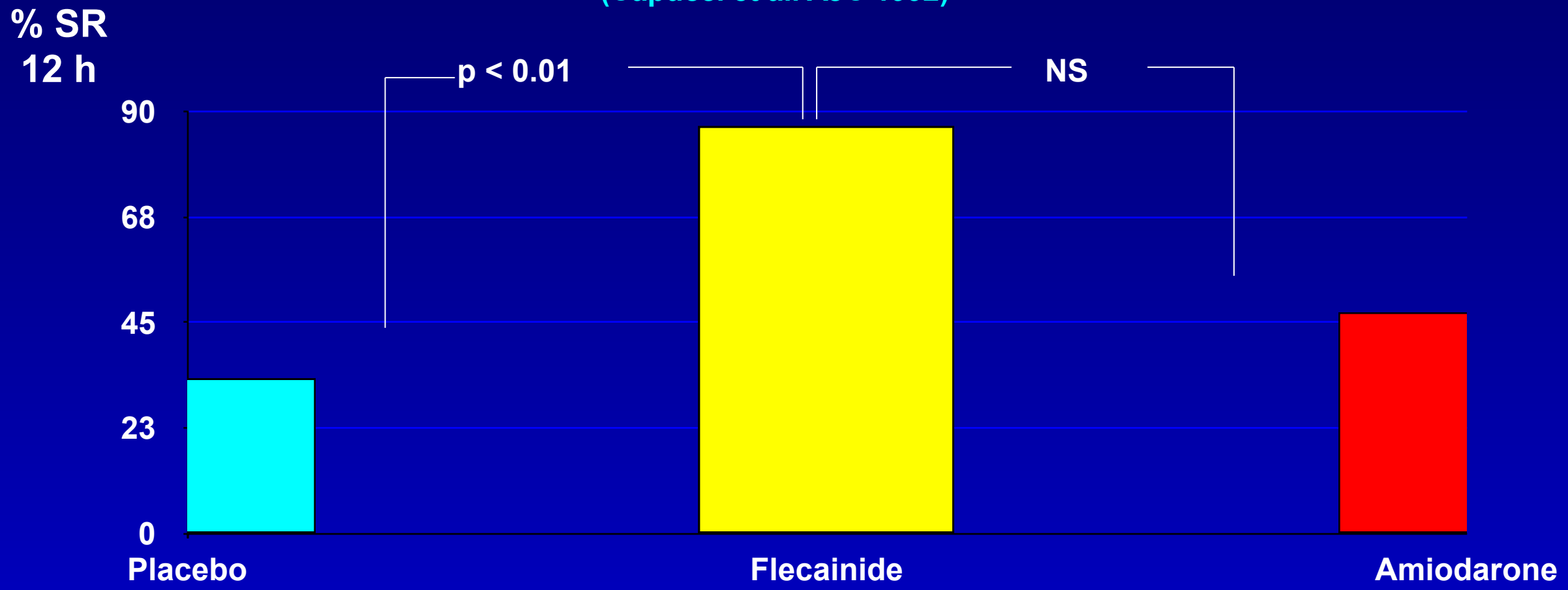
1. Flecainide has no effect on QT interval, but produces a rate-dependent prolongation in atrial APD and refractoriness (exerts a class III effect)
- Slows the recovery kinetics of Na^+ channels at fast rates

"Pill in the Pocket" Antiarrhythmic Drugs for Orally Administered Pharmacologic Cardioversion of Atrial Fibrillation

James A. Reiffel, MD[a,*], and Alessandro Capucci, MD[b]

Oral Flecainide vs i.v. Amiodarone vs Placebo to convert AF to SR

(Capucci et al. AJC 1992)



Conversion of Recent-Onset Atrial Fibrillation by a Single Oral Loading Dose of *Propafenone* or *Flecainide*

Alessandro Capucci, MD, Giuseppe Boriani, MD, Gian Luca Botto, MD, Tiziano Lenzi, MD, Ida Rubino, MD, Camillo Falcone, MD, Giuseppe Trisolino, MD, Stefano Della Casa, MD, Nicola Binetti, MD, Mario Cavazza, MD, Mario Sanguinetti, MD, and Bruno Magnani, MD

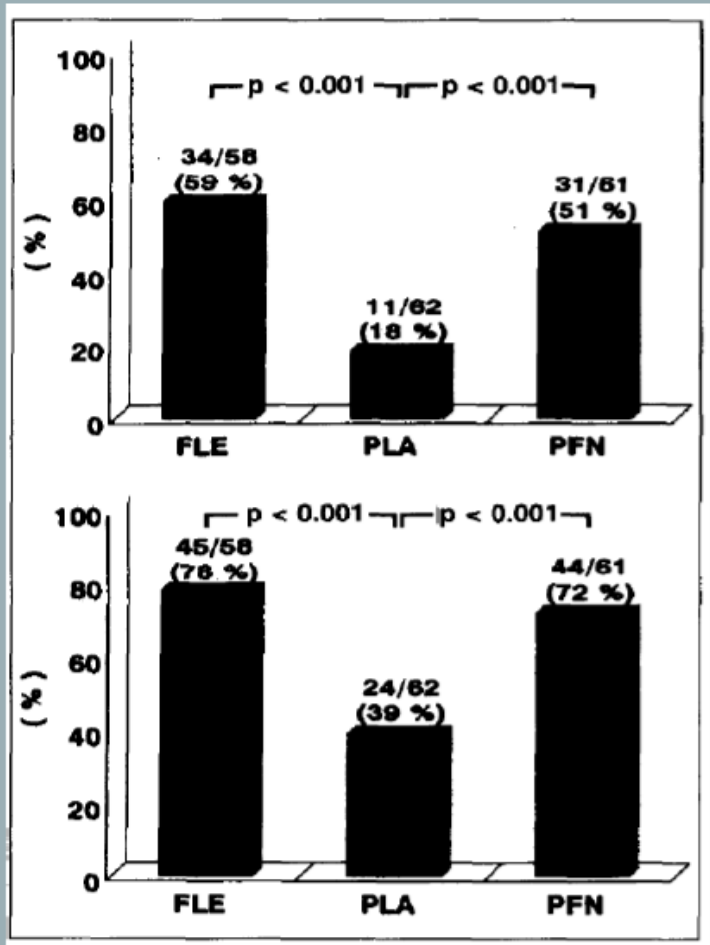
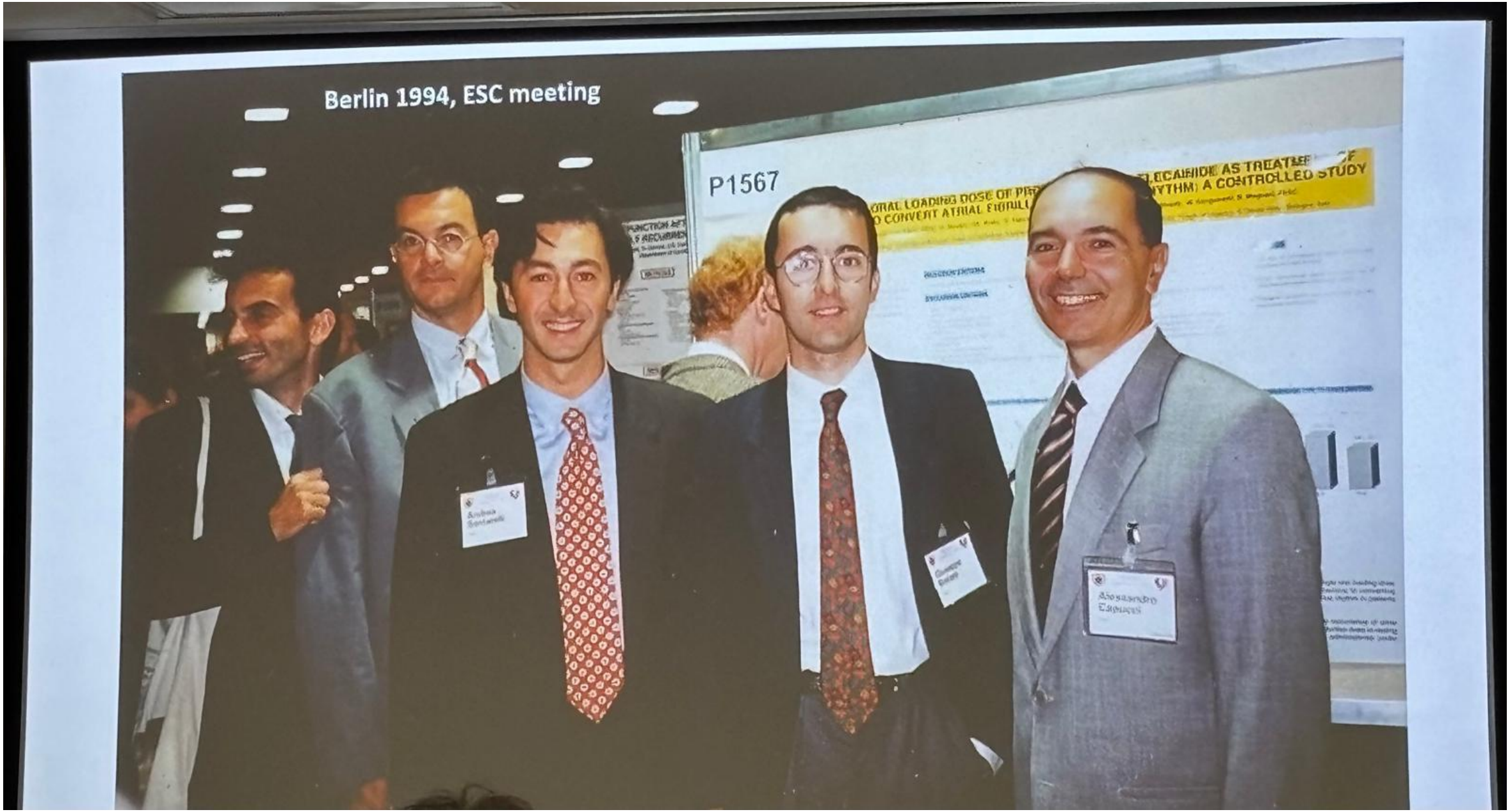


FIGURE 1. Conversion rates from atrial fibrillation to sinus rhythm at 3 hours *(top)* and at 8 hours *(bottom)* for each treatment group. FLE = flecainide; PFN = propafenone; PLA = placebo.

"The present study confirms that acute oral antiarrhythmic drug loading is simple and effective"

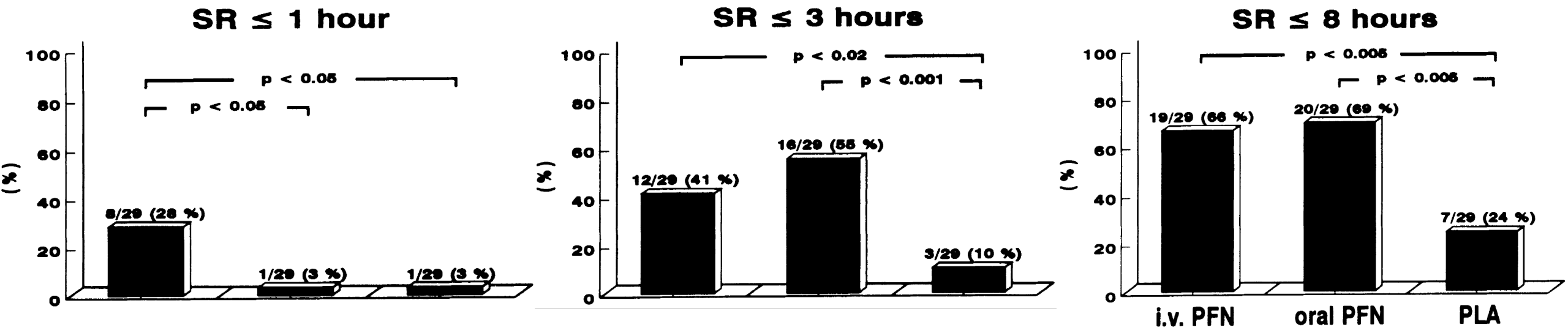
THE AMERICAN JOURNAL OF CARDIOLOGY® VOLUME 74 SEPTEMBER 1, 1994


Berlin 1994, ESC meeting
P1567

Propafenone for Conversion of Recent-Onset Atrial Fibrillation*

A Controlled Comparison Between Oral Loading Dose and Intravenous Administration

Giuseppe Boriani, MD; Alessandro Capucci, MD; Tiziano Lenzi, MD; Mario Sanguinetti, MD; and Bruno Magnani, MD

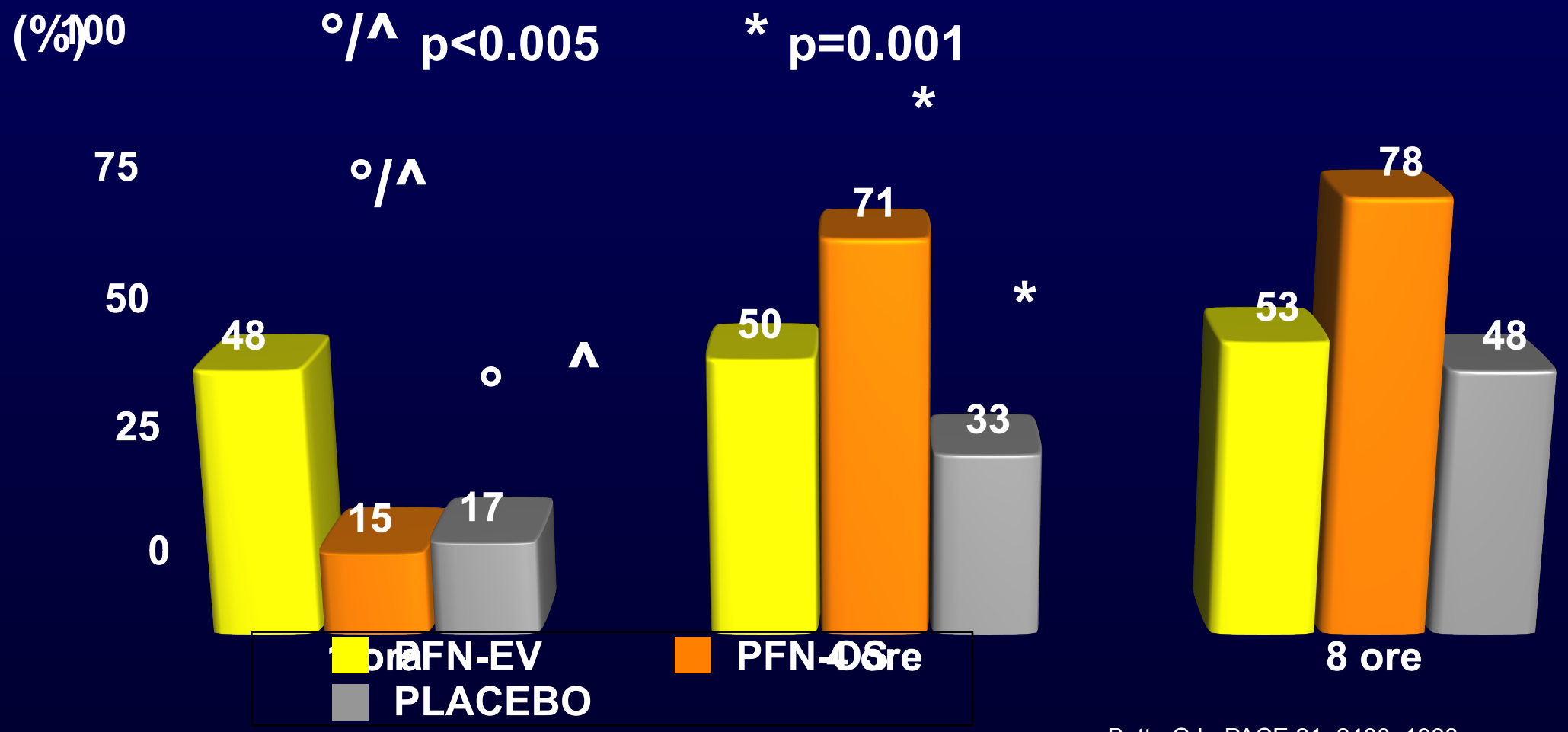


Left column: intravenous propafenone; middle column: oral propafenone; right column: placebo

Boriani G et al. Chest. 1995 Aug;108(2):355-8.

Fibrillazione Atriale

Conversione con Propafenone nella F.A. Recente



Botto G.L. PACE 21: 2480; 1998

Acute Flecainide

- To obtain the maximum benefit i.v. you need a 0.007 mg/kg continuous infusion after the bolus (2 mg/Kg)
- In oral “pill in the pocket” acute administration dosage is related to weight and basal AAD chronic therapy

PAZIENTI SELEZIONATI

- Soggetti senza segni di cardiopatia o con cardiopatia lieve:

- pz con FA idiopatica
- con ipertensione arteriosa senza disfunzione sistolica
- con lieve vizio valvolare

- Criteri di esclusione:

- disfunzione sistolica sinistra FEVS< 50%
- cardiopatia ischemica
- ipertrofia ventricolare severa
- alterazioni della conduzione cardiaca come QRS>120 ms, PR > 200 ms o preeccitazione
- segni clinici o elettrocardiografici di malattia del nodo del seno, bradicardia, o blocco AV avanzato
- ipotensione (P.A.S< 100 mmHg)
- paziente in trattamento antiaritmico profilattico
- storia di intolleranza a flecainide o propafenone

1. CARICO ORALE IN AMBIENTE MONITORIZZATO

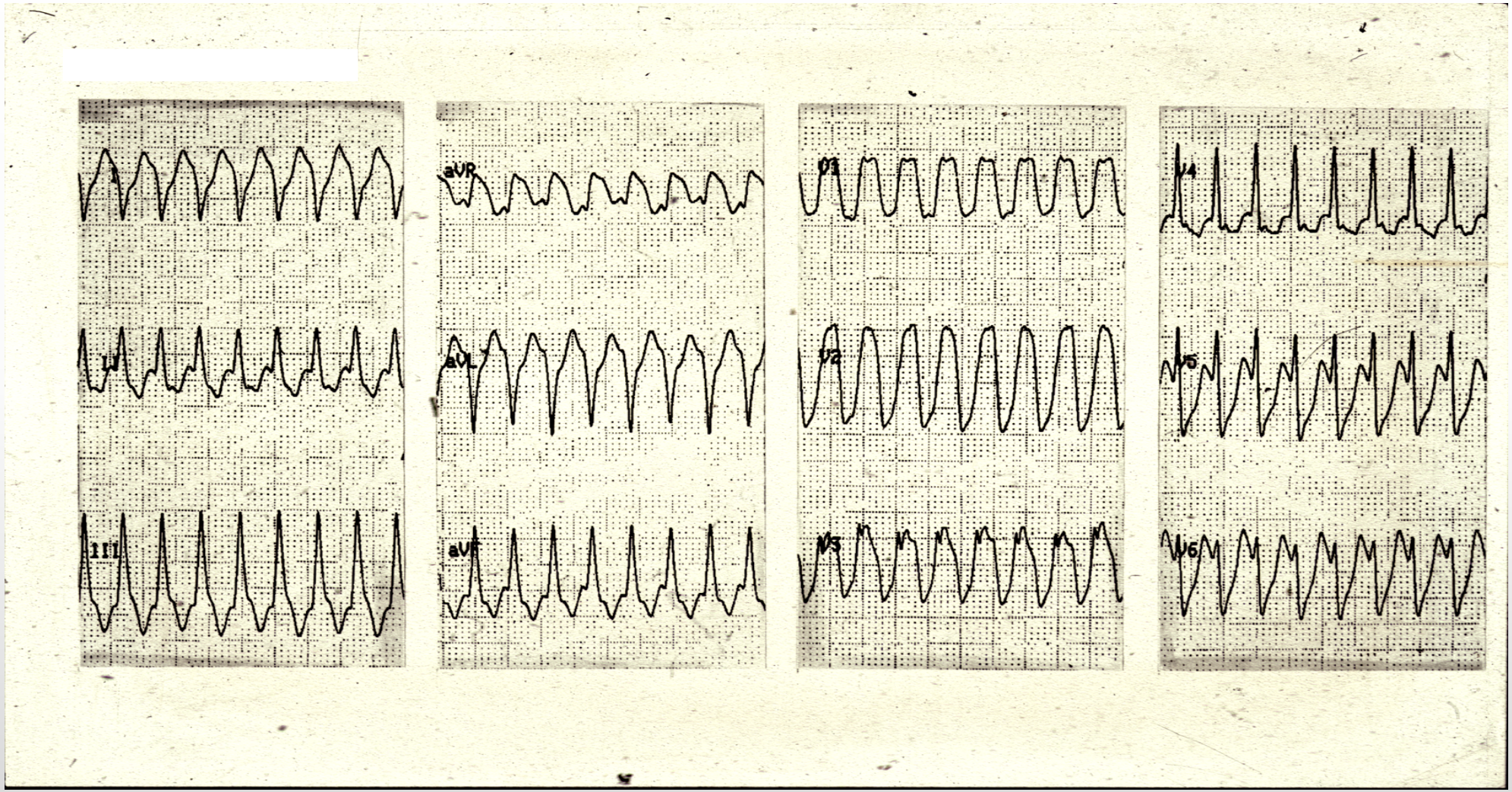
FCm > 70/min. P.A.S> 100 mmHg

Flecainide 200 mg (300 mg se ≥ 70 kg) per os.

Propafenone 450 mg (600 mg se ≥ 70 kg) per os.

Il monitoraggio iniziale può avvenire nel pronto soccorso e richiede:

- Telemetria per 6 ore
- Monitoraggio pressorio ogni 30 minuti


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

Oral Propafenone To Convert Recent-Onset Atrial Fibrillation in Patients with and without Underlying Heart Disease

A Randomized, Controlled Trial

Giuseppe Boriani, MD; Mauro Biffi, MD; Alessandro Capucci, MD; Gian Luca Botto, MD; Tiziana Broffoni, MD; Ida Rubino, MD; Stefano Della Casa, MD; Mario Sanguinetti, MD; and Bruno Magnani, MD

Background: The effectiveness of oral propafenone in converting recent-onset atrial fibrillation to sinus rhythm has been established by controlled trials. However, it is not clear whether the effectiveness of propafenone is affected by the presence or absence of underlying heart disease.

Objectives: To investigate the safety and effectiveness of oral propafenone and the role of underlying heart disease.

Design: Randomized, single-blind, controlled study.

Setting: 3 teaching hospitals.

Patients: 240 hospitalized patients with recent-onset atrial fibrillation.

Intervention: Propafenone (one 600-mg oral dose) or placebo.

Measurements: Conversion rates at 3 and 8 hours.

Results: Propafenone was more effective than placebo for converting atrial fibrillation to sinus rhythm at 3 hours: Fifty-four of 119 patients (45%) receiving propafenone and 22 of 121 patients (18%) receiving placebo had conversion ($P < 0.001$). It was also more effective at 8 hours: Ninety-one of 119 patients (76%) receiving propafenone and 45 of 121 patients (37%) receiving placebo had conversion ($P < 0.001$). Subgroup analysis showed that among patients without heart disease, 78% of those receiving propafenone and 56% of those receiving placebo converted to sinus rhythm within 8 hours ($P = 0.02$). In those with hypertension, the rate was 70% for those receiving propafenone and 27% for those receiving placebo ($P < 0.001$); in patients with structural heart disease, the rate was 81% for those receiving propafenone and 17% for those receiving placebo ($P < 0.001$).

Conclusions: Oral loading of propafenone was more effective than placebo for conversion to sinus rhythm within 8 hours and had a favorable safety profile. The rate of spontaneous conversion to sinus rhythm was higher in patients without structural heart disease; this finding has important implications for the assessment of drug effectiveness in recent-onset atrial fibrillation.

Ann Intern Med. 1997;126:621-625.

Il problema della conversione della FA in un flutter 1:1

"Atrial fibrillation was transformed into atrial flutter with rapid ventricular response in one patient in the placebo group. It is known that such an effect occurs more often with class IC drugs than with other drugs or spontaneously, …."

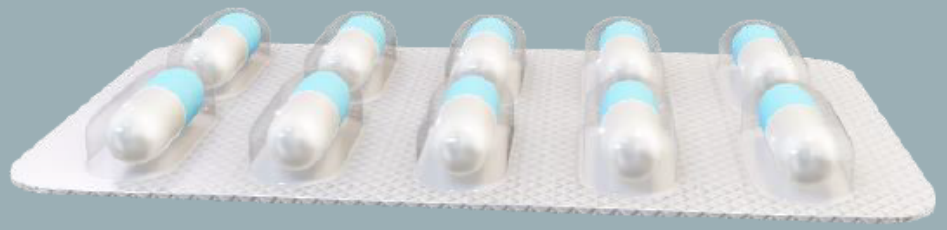
" It is usually adrenergic dependent."

"The occurrence of atrial tachycardia and flutter in the placebo group emphasizes that tachycardia with regular ventricular rhythm may spontaneously develop during atrial fibrillation even when patients are not receiving class IC agents."

Reproducible efficacy of oral loading Propafenone in PAF

(Capucci et al. AJC 2003)

2. ASSUNZIONE DOMICILIARE



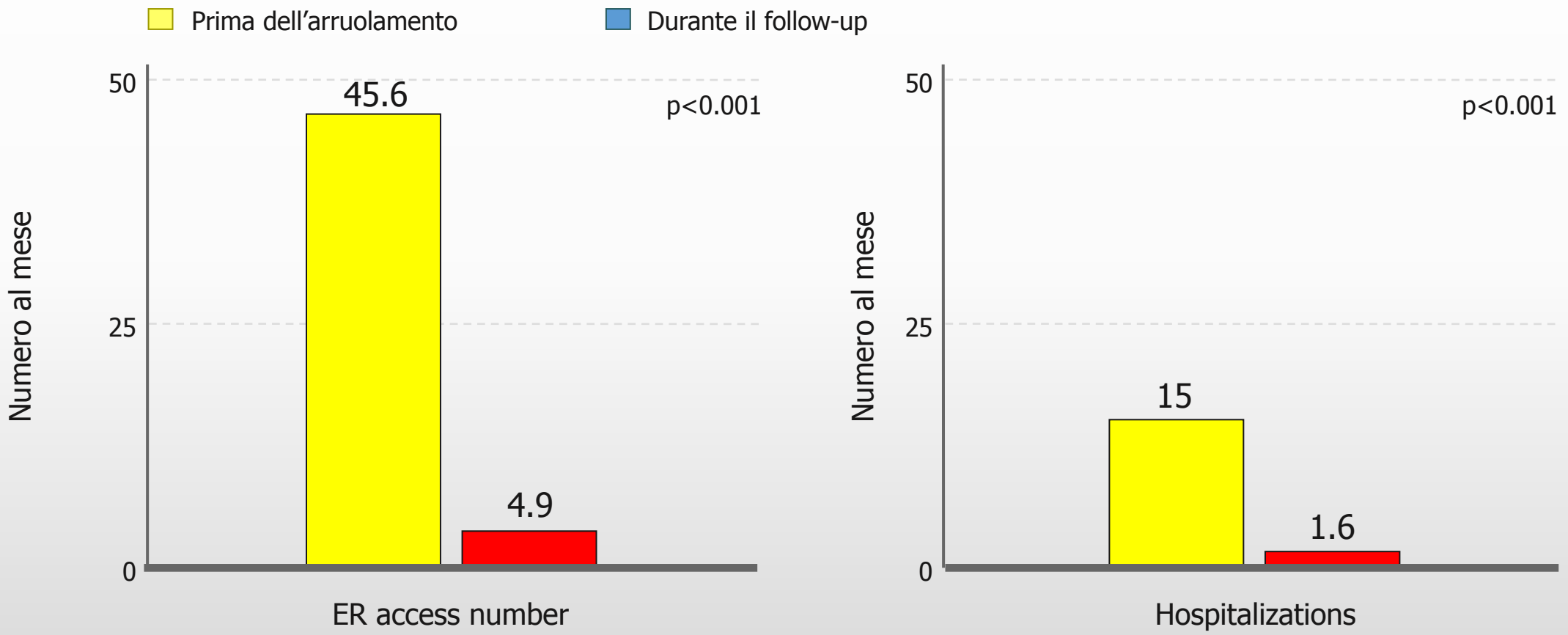
30 minuti prima di assumere l'antiaritmico è consigliato assumere un beta bloccante o un calcio antagonista non diidropiridinico per evitare una elevata risposta ventricolare. (*AHA/ACC/HRS Class IIa, Level B; Can J Cardiol 2018 Nov*)

È raccomandata la posizione supina o la posizione seduta almeno per 4 ore. *(ESC Class IIa, Level C)*

Al paziente deve essere consigliato di recarsi in PS in caso di peggioramento dei sintomi dopo l'assunzione del farmaco o se la FA non si è interrotta dopo 6-8 ore.

Il paziente non deve assumere il farmaco più di una volta nell'arco di 24 ore.

Pill in the pocket: ER drop-down



Alboni P et al. N Engl J Med. 2004;351:2384-91.

Systematic review and cost-effectiveness evaluation of 'pill-in-the-pocket' strategy for paroxysmal atrial fibrillation compared to episodic in-hospital treatment or continuous antiarrhythmic drug therapy

C Martin Saborido,[1] J Hockenhull,[1] A Bagust,[1] A Boland,[1]
R Dickson[1]* and D Todd[2]

	Costs	QALYs	Time in NSR	Relapses
Pill in the pocket	£ 1512	9,21	3220	2422
AADs	£ 2389	9,23	2274	1403
In-hospital CV	£ 2340	9,29	2683	2153

- The pill-in-the-pocket is less effective in preventing recurrences
- Life expectancy adjusted for QoL is similar between both groups
- Pill in the pocket related costs are 40 % lower

Saborido CM et al. Health Technol Assess. 2010;14:1-75.

Caso clinico

- Paziente donna di 95 anni, ipertesa in anamnesi in terapia con Ace – inibitore. Aspirinetta 100 mg per 45% mono-restringimento carotideo. FE 59% in assenza di valvulopatie
- Da 1 anno 9 episodi di FA sintomatici (insorgenti di notte a riposo) con FC media all' insorgenza di 130/min (dispnea e agitazione)
- Flecainide 200 mg in unica dose:passaggio a RS fra 1.5 e 2 ore massimo , stando a riposo. Mai sincopi e /o lipotimie
- **Terapia ipocoagulante?**

Caso clinico 2

- Maschio, 72 anni, LP con regime di vita sedentario
- Fattori di rischio: nessuno.Lieve dilatazione Asn. FE 61%.
- Anamnesi cardiovascolare remota: pregressi episodi di fibrillazione atriale persistente (non passano sua sponte anche dopo 24 ore), profondamente sintomatici con FC 140/min
- Nell' ultimo anno 30 episodi di FA sempre diurni insorti a riposo o in concomitanza con il pasto, mai in rapporto con attività fisica

Caso clinico 2, maschio 72 anni

- Flecainide 300 mg in unica somministrazione prima di coricarsi o appena possibile
- Risultato : sempre in RS al mattino
- **Mai andato in Ospedale per FA**
- Non anticoagulato al momento per Chads-va 1 e brevi FA
- Durata media di FA post assunzione PIP:3-4 h
- **TERAPIA IPOCOAGULANTE? ABLAZIONE FA?**

What is the purpose of pharmacologic cardioversion?

Even though the reported rate of spontaneous conversion is up to 50%, in the first 24 h after the onset of atrial fibrillation, an earlier restoration of sinus rhythm by cardioversion will result in:

- ***early alleviation of patients' symptoms***
- *no need of atrio-ventricular node blocking drugs*
- ***decrease the chances of thromboembolism***
- *prevent tachycardia-related cardiomyopathy*
- *lessen atrial mechanical dysfunction and electrophysiological remodeling*

Ijaz A Khan DOI: http://dx.doi.org/10.1016/j.ehj.2004.06.007 1274-1276

TAKE HOME MESSAGE

Gestione autonoma dei parossismi di FA sintomatici, limitando gli accessi in PS, le ospedalizzazioni e riducendo i costi sanitari.

Sicuro in pazienti senza cardiopatia o con cardiopatia lieve.

Richiede una fase di monitoraggio iniziale.

Efficacia a domicilio riproducibile (non più di una volta nelle 24 ore).

Buona compliance da parte del paziente.

GRAZIE PER L'ATTENZIONE