# Les anti-arythmiques

DIU de rythmologie

Paris, 22 janvier 2008

J-M DAVY - Montpellier

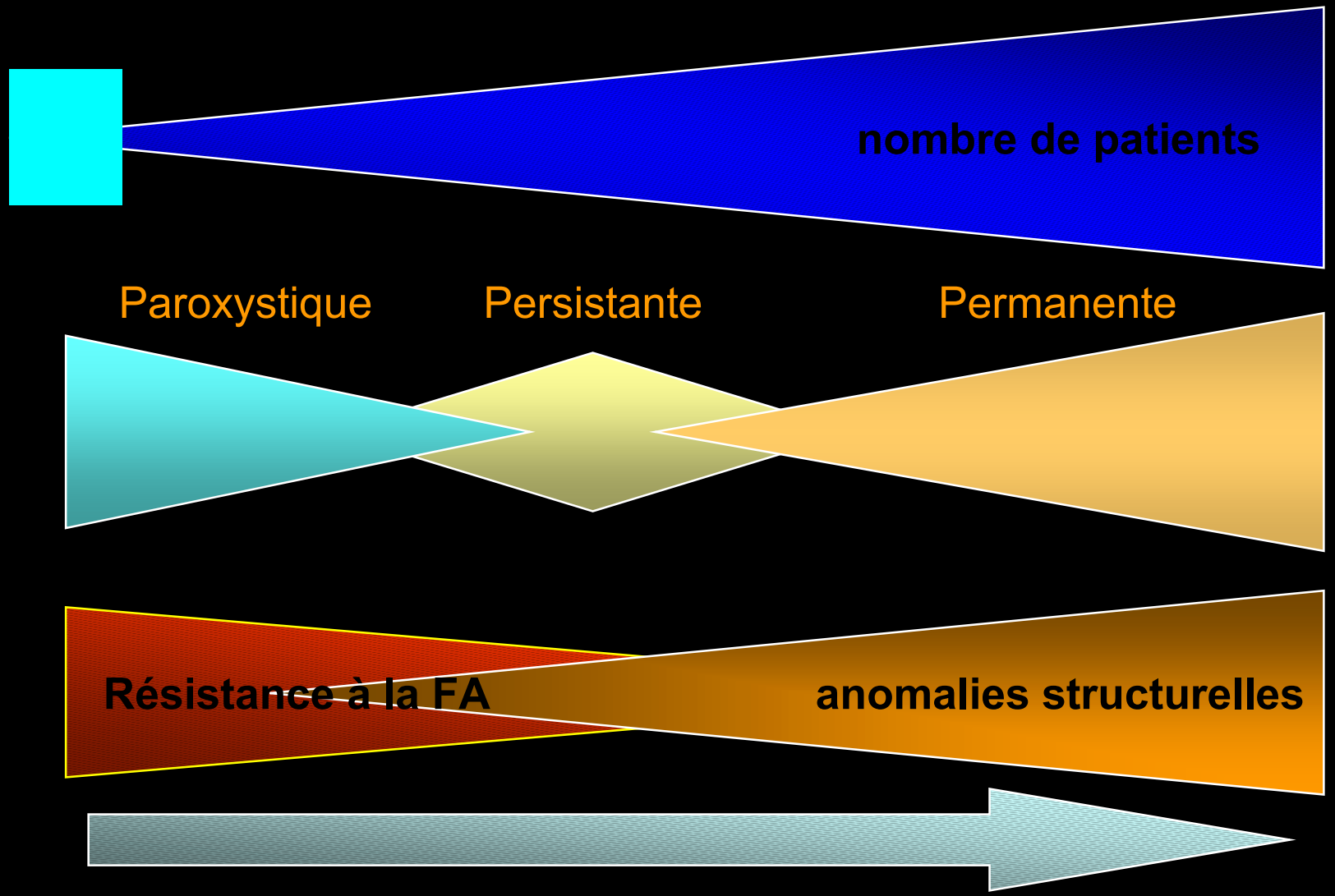
# AA : le défi, les promesses, et les doutes

**Table 26.1** Mechanisms of Arrhythmias

| Level of integration | Key molecular components | Arrhythmogenic mechanism | Prototypical arrhythmias |
|---|---|---|---|
| Myocyte level | | | |
| Impulse initiation | Pacemaker current ($I_f$ or $I_{st}$)<br>T-type calcium channels | Suppression or acceleration of the physiological pacemaker | Sinus tachycardia or sinus bradycardia |
| | Unclear | Abnormal automaticity | Ectopic atrial tachycardia |
| | Na–Ca exchange<br>Ca-activated chloride channel<br>Ca-activated nonspecific cation channel | Triggered diastolic activity (DADs) | Ventricular tachycardia of digitalis toxicity; possibly some reperfusion arrhythmias |
| Excitation | Na channels<br>ATP-sensitive K channels | Conduction slowing or block in atria or ventricles | Ischemic arrhythmias with slow conduction resulting from interstitial K accumulation |
| | L-type Ca channels | Conduction slowing or block in AV node | Iatrogenic AV block caused by calcium channel blocker |
| Repolarization | Voltage-dependent K channels<br>Sodium channels<br>L-type calcium channels<br>Na-Ca exchange | Action potential prolongation (EADs) | Torsade de pointes<br>Polymorphic VT |
| Multicellular level | | | |
| Cell-cell coupling | Connexins | Conduction delay or block caused by cellular uncoupling | Acute ischemic arrhythmias |
| Network properties | Collagen and other extracellular matrix proteins | Reentry<br>Impedance mismatch<br>Discontinuous conduction | Inherited: Wolff–Parkinson–White syndrome<br>Acquired: monomorphic VT around an infarct |

exemple de la FA
exemple de la TV-FV

# l'histoire naturelle de la FA



# l'attitude classique

- maintenir le rythme sinusal aussi longtemps que possible dans la FA paroxystique
- réduire la FA persistante en répétant les cardioversions (3-5)
- accepter et ralentir la FA permanente quand les récidives sont trop fréquentes

# les avancées des années 80

- Développement  des nouveaux médicaments antiarrhythmiques : class IA / IC / III / amiodarone
- utilisation d'autres bloqueurs du noeud AV  : betaB / calciumB / amio ?
- données épidemiologiques : risque embolique / insuffisance cardiaque / mortalité
- concepts physiopathologiques : cardiomyopathie tachycardie-induite

# doutes thérapeutiques des années 90

- mauvaise utilisation des AVK : non la FA idiopathique mais les patients âgés !
- Risques des AA : mortalité et IC
  Coplen , Flaker
- Bénéfice affirmé du contrôle de la fréquence V : comportant parfois l'ablation du noeud et le PMK !

REDUIRE OU RALENTIR ?

1. les AA actuels
2. les AA du futur

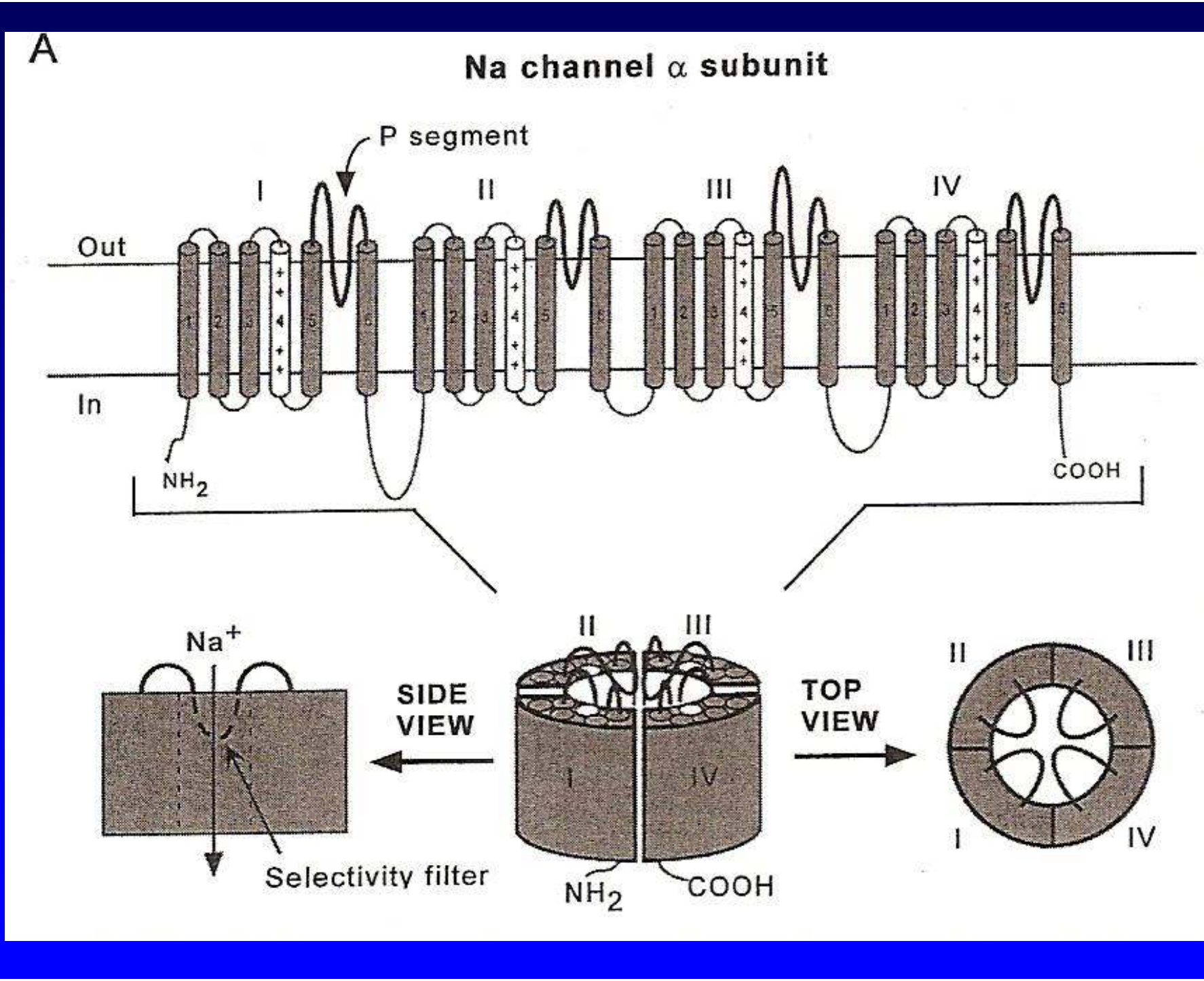
# 1. les AA actuels

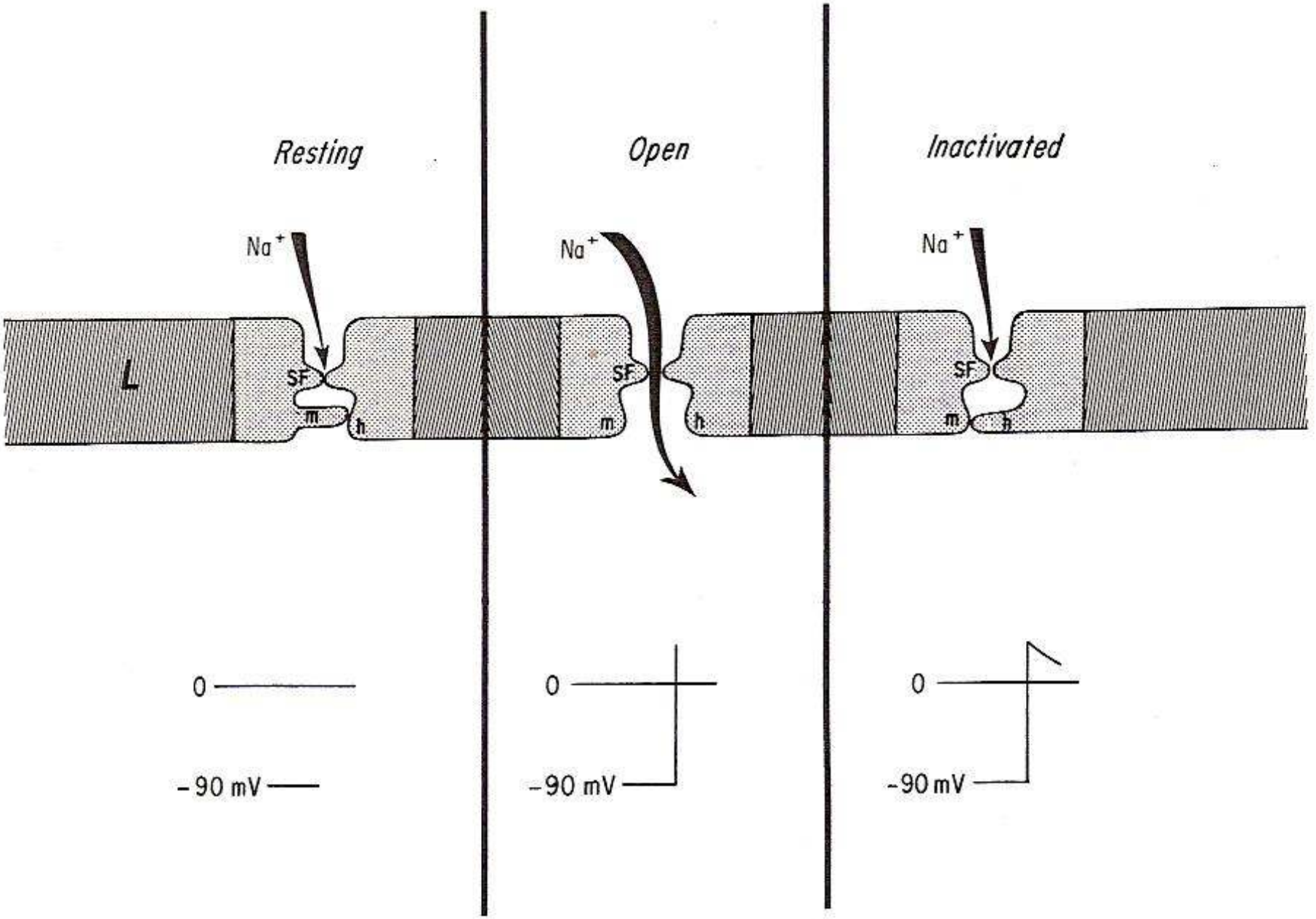
1. Un « poison » du canal ionique
2. AA et fréquence cardiaque
3. Classification des AA
4. Pharmacocinétique des AA

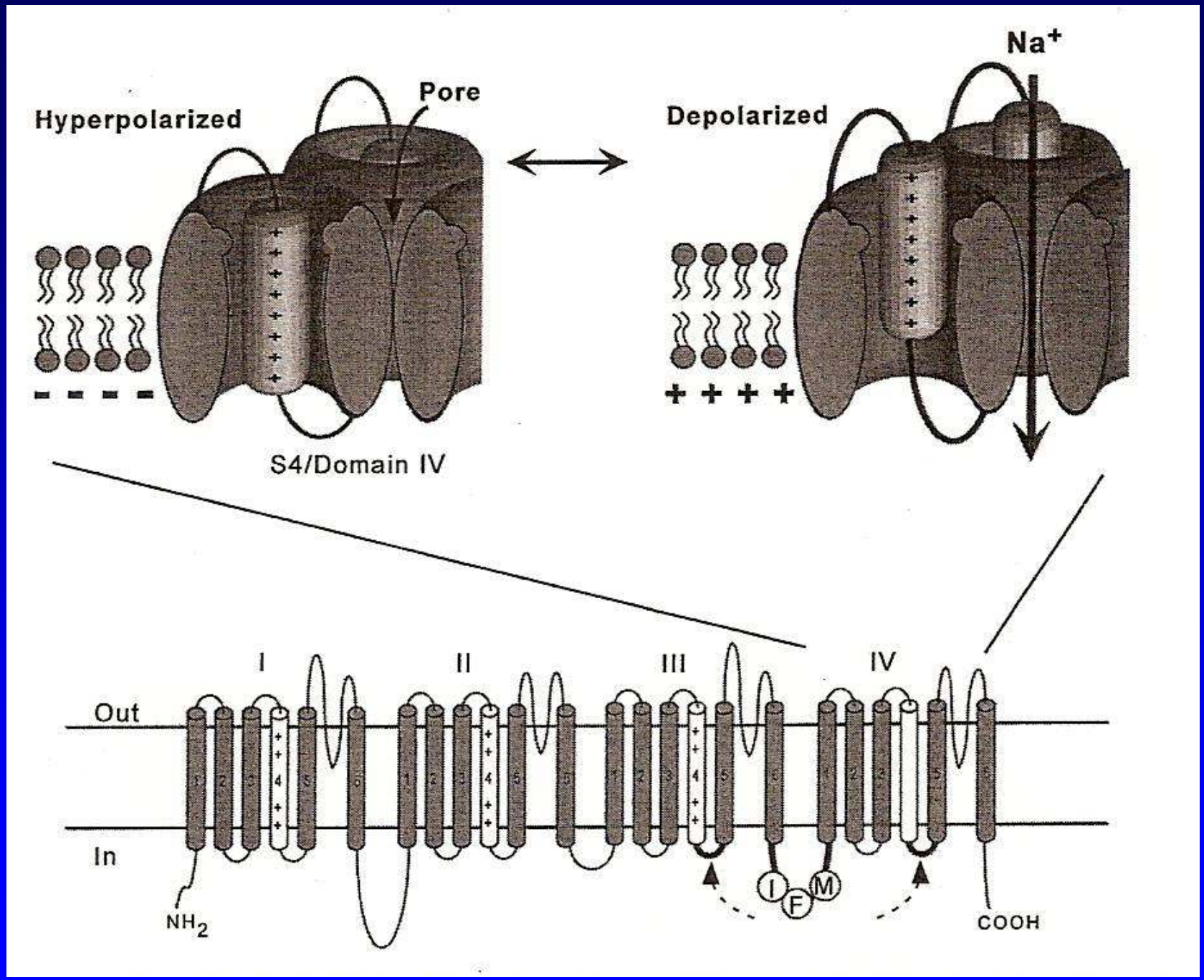
# 1 - Antiarythmiques et canal ionique

## TABLE 8-1. VAUGHAN WILLIAMS ANTIARRHYTHMIC DRUG CLASSIFICATION

| Class | Action | Drug |
|---|---|---|
| I | Sodium channel blockers | |
| Ia | Moderate phase 0 depression | Quinidine |
| | Moderate conduction slowing | Procainamide |
| | Prolongs repolarization | Disopyramide |
| Ib | Minimal phase 0 depression | Lidocaine |
| | Shortens repolarization | Tocainide |
| | | Mexiletine |
| Ic | Marked phase 0 depression | Flecainide |
| | Marked conduction slowing | Propafenone |
| | Slight effect on repolarization | Moricizine |
| II | β blockers | Propranol |
| | | Acebutolol |
| | | Esmolol |
| III | Prolongs repolarization | Bretylium |
| | | Amiodarone |
| | | Sotalol |
| | | Ibutilide |
| | | Dofetilide |
| IV | Calcium channel blockers | Verapamil |
| | | Diltiazem |
| | Purine agonist | Adenosine |
| | Digitalis glycosides | Digoxin |
| | | Digitoxin |


A
Na channel α subunit
P segment
I
II
III
IV
Out
In
NH2
COOH
Na+
SIDE VIEW
Selectivity filter
II
III
I
IV
NH2
COOH
TOP VIEW
II
III
I
IV


Resting
Open
Inactivated
Na+
Na+
Na+
L
SF
m
h
SF
m
h
SF
m
h
0
-90 mV
0
-90 mV
0
-90 mV


Hyperpolarized
Pore
Depolarized
Na+
S4/Domain IV
I
II
III
IV
Out
In
NH2
I
F
M
COOH

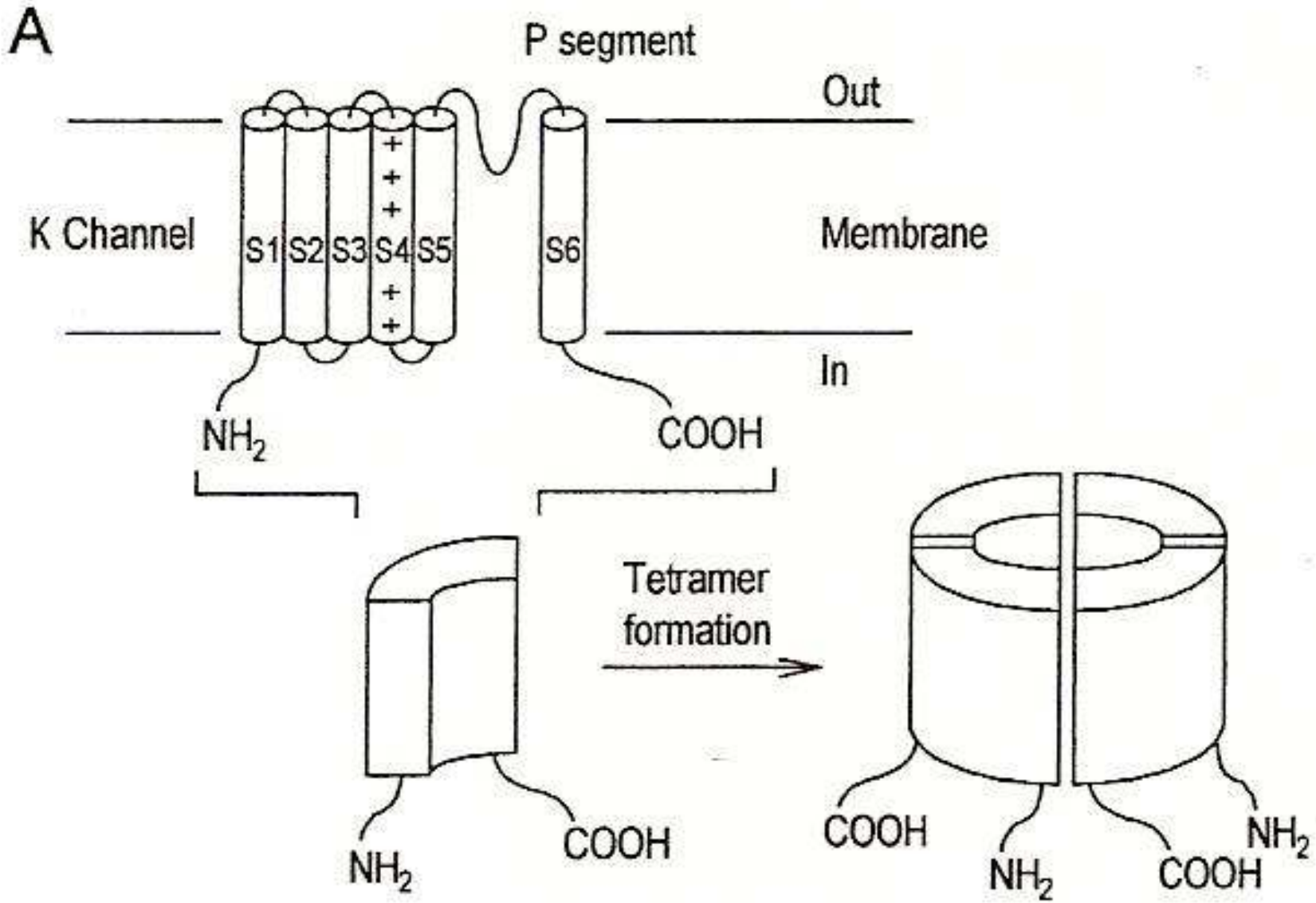

A
P segment
Out
K Channel
S1
S2
S3
S4
S5
S6
Membrane
In
NH2
COOH
Tetramer
formation
NH2
COOH
COOH
NH2
COOH
NH2

**Table 23–1. Effect of Antiarrhythmic Drugs on Major Ionic Currents in Cardiac Purkinje and Ventricular Muscle Fibers**

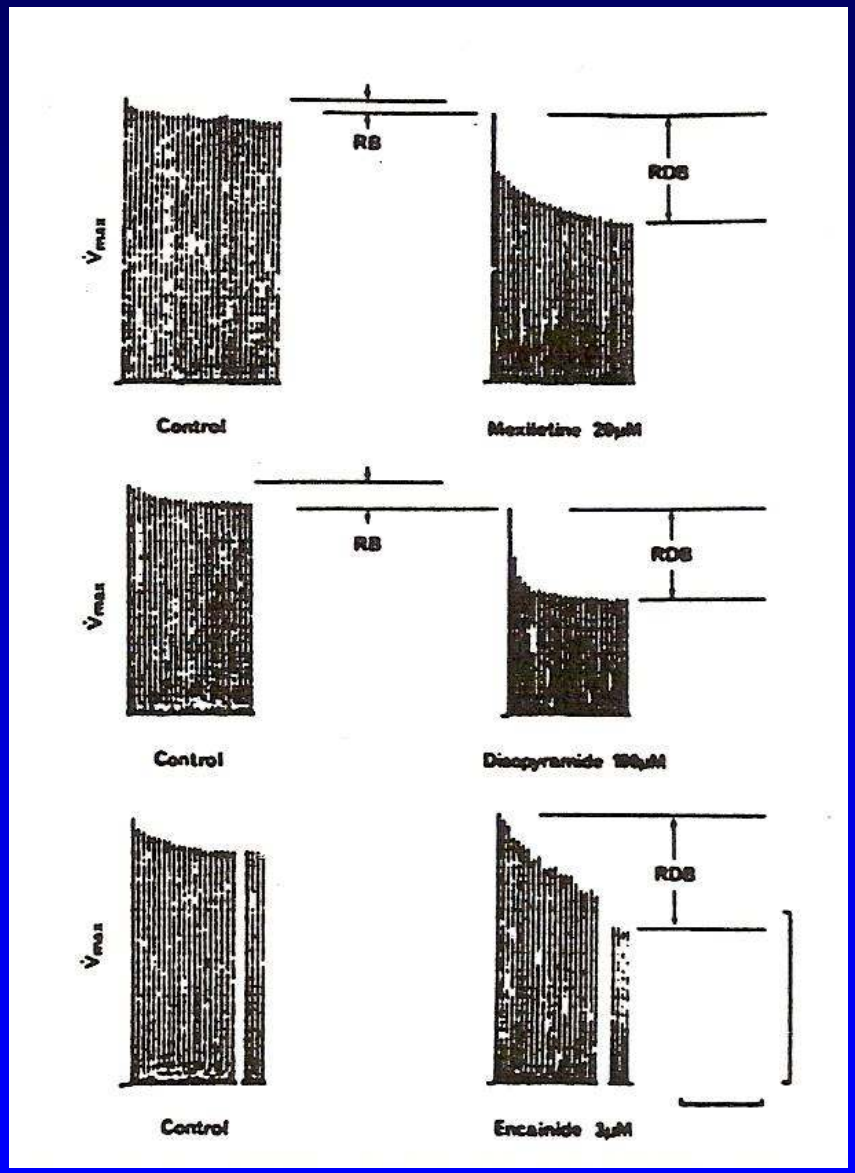
| Drugs | $i_{Na}$ | L-type $i_{Ca}$ | $i_{Kl}$ | $i_K$ | $i_{to}$ | $i_f$ |
|---|---|---|---|---|---|---|
| Class I | | | | | | |
| A | | | | | | |
| Quinidine | ↓ | ↓ | —↓ | ↓ | ↓ | ↓ |
| Procainamide | ↓ | ↓ | — | ↓ | | —↓ |
| Disopyramide | ↓ | ↓ | —↓ | ↓ | ↓ | ↓ |
| B | | | | | | |
| Lidocaine | ↓ | —↓ | —↓ | —↓ | — | ↓ |
| Mexiletine | ↓ | ↓ | — | — | | |
| Diphenylhidantoin | ↓ | | | | | |
| C | | | | | | |
| Flecainide | ↓ | ↓ | ↓ | ↓ | | |
| Encainide | ↓ | | | | | |
| Moricizine | ↓ | ↓ | | | | |
| Lorcainamide | ↓ | | | | | |
| Propafenone | ↓ | ↓ | | | | |
| Class II | | | | | | |
| Propranolol | ↓ | | | | | |
| Metoprolol | — | ↓ | ↓ | | | |
| Class III | | | | | | |
| Amiodarone | ↓ | ↓ | ↓ | ↓ | | |
| Sotalol | | | ↓ | ↓ | ↓ | — |
| Bretylium | | | | ↓ | | |
| Clofilium | | | — | ↓ | ↓ | |
| Class IV | | | | | | |
| Verapamil | ↓ | ↓ | | | | |
| Diltiazem | | ↓ | | | | |

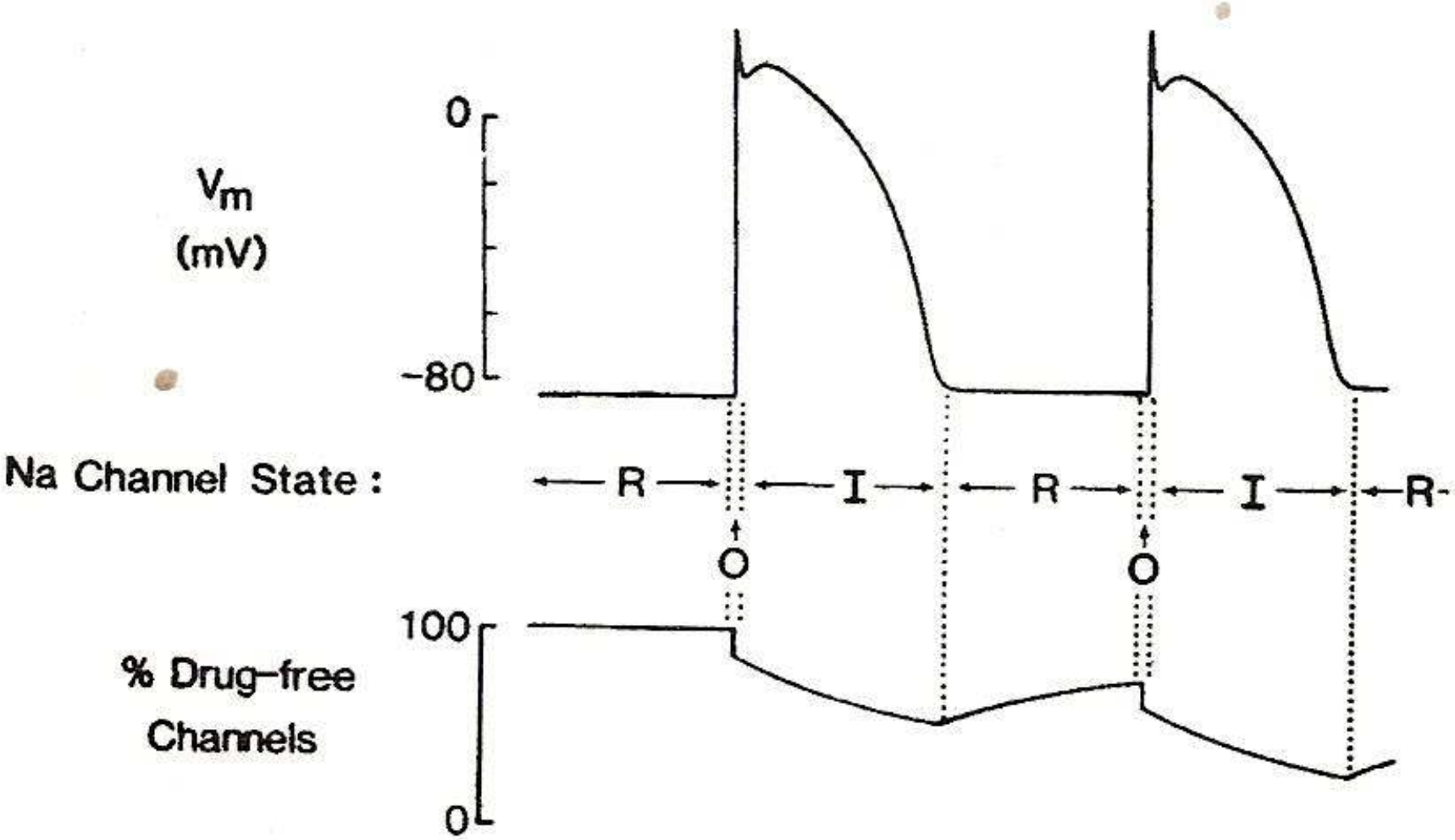
# 2 - AA et fréquence cardiaque

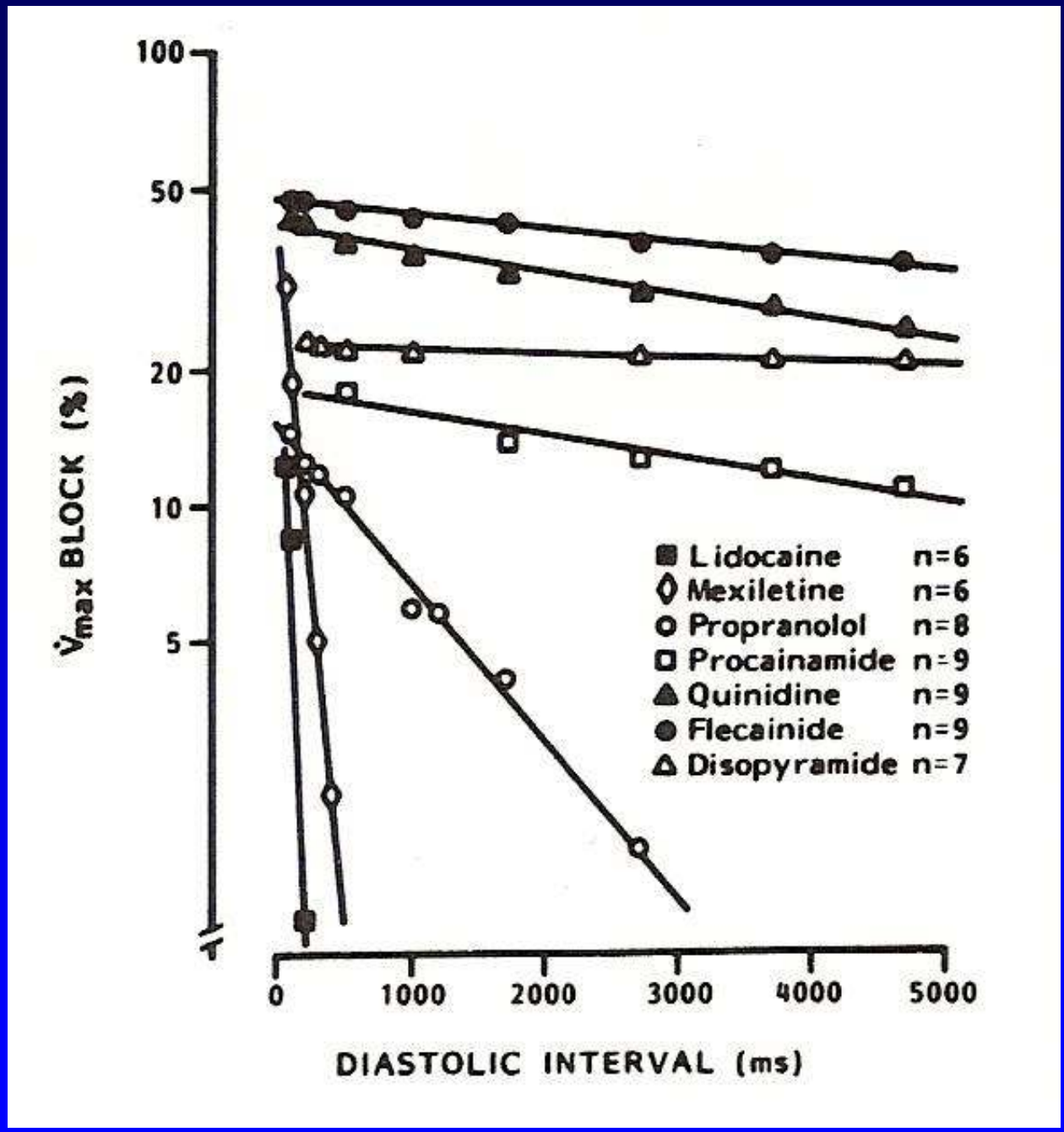
Use dépendance positive des AA de classe I

Use dépendance inverse des AA de classe III purs

# AA de classe I

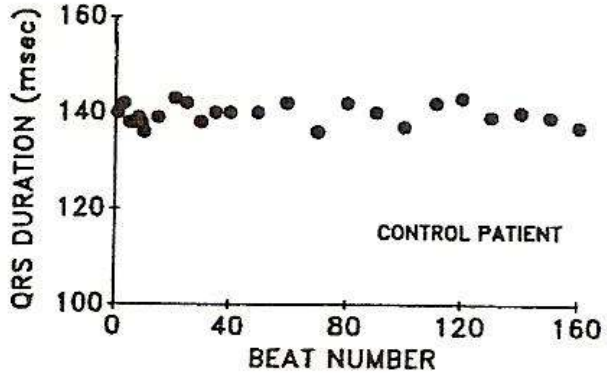

RB
RDB
Control
Mexiletine 20µM
RB
RDB
Control
Disopyramide 100µM
RDB
Control
Encainide 3µM

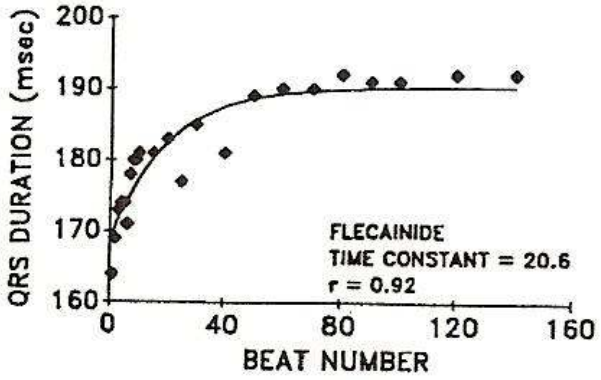

0
$V_m$
(mV)
-80
Na Channel State :
R
I
R
I
R
O
O
100
% Drug-free
Channels
0

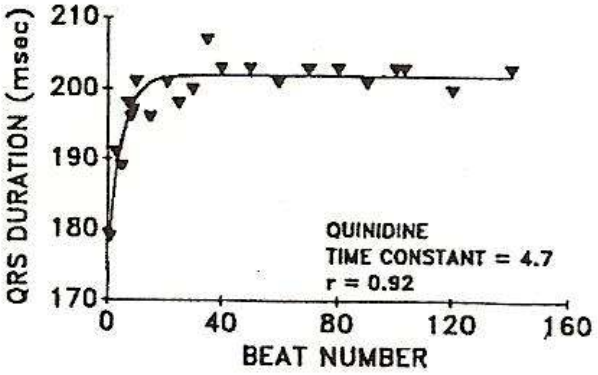

100
50
20
10
5
1
$\dot{V}_{max}$ BLOCK (%)
Lidocaine n=6
Mexiletine n=6
Propranolol n=8
Procainamide n=9
Quinidine n=9
Flecainide n=9
Disopyramide n=7
0
1000
2000
3000
4000
5000
DIASTOLIC INTERVAL (ms)

## REPRESENTATIVE TIME CONSTANTS OF RECOVERY FROM SODIUM CHANNEL BLOCKADE IN PURKINJE FIBERS (SECONDS)

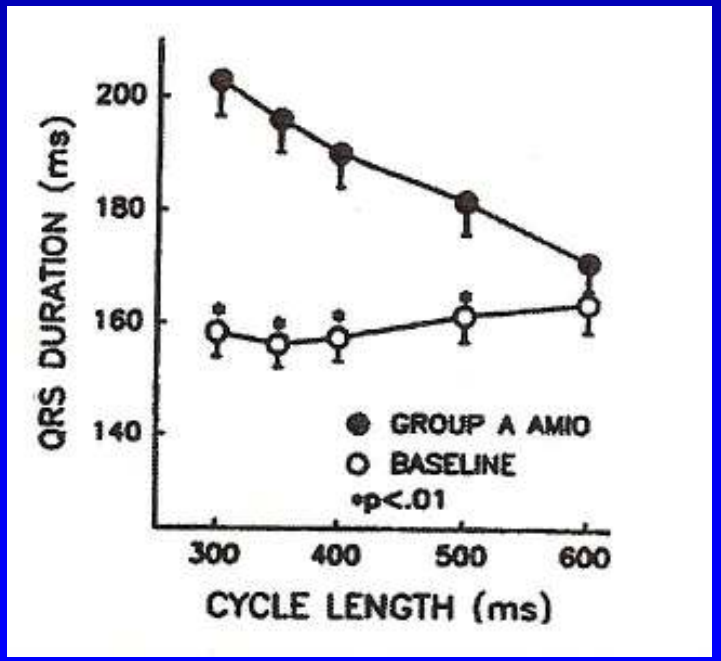
| | |
|---|---|
| Lidocaine[85] | 0.18 |
| Mexiletine[86] | 0.23 |
| Tocainide[87] | 0.55 |
| Phenytoin[88] | 0.71 |
| Procainamide[89] | 2.6 |
| Quinidine[90] | 4.0 |
| Disopyramide[91] | 15.7 |
| Propafenone | 5.4 |
| (5-OH-propf)[92] | 19.3 |
| Moricizine[72] | 17.0 |
| Flecainide[72] | 21.0 |


QRS DURATION (msec)
160
140
120
100
0
40
80
120
160
BEAT NUMBER
CONTROL PATIENT

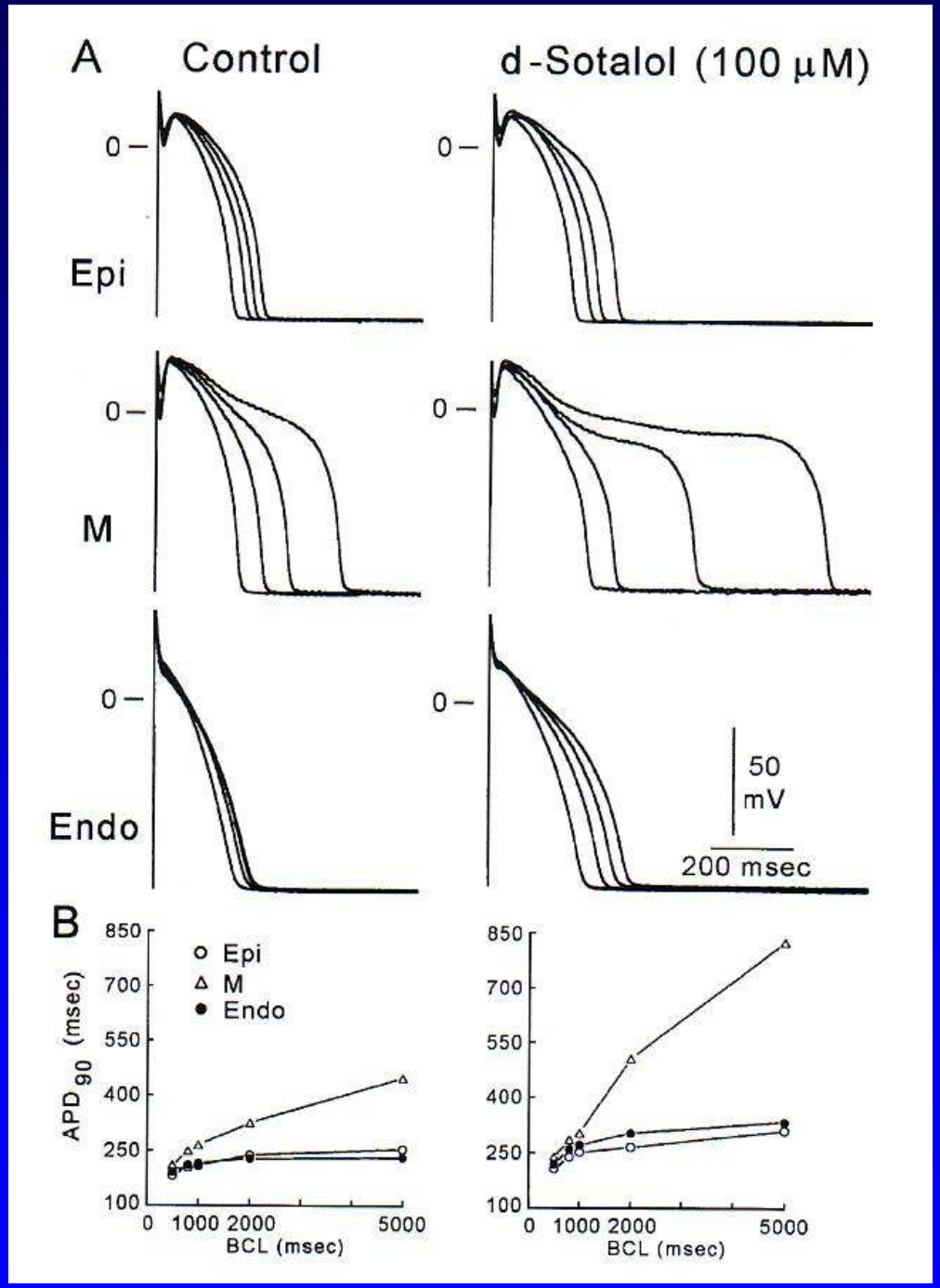

QRS DURATION (msec)
200
190
180
170
160
0
40
80
120
160
BEAT NUMBER
FLECAINIDE
TIME CONSTANT = 20.6
r = 0.92

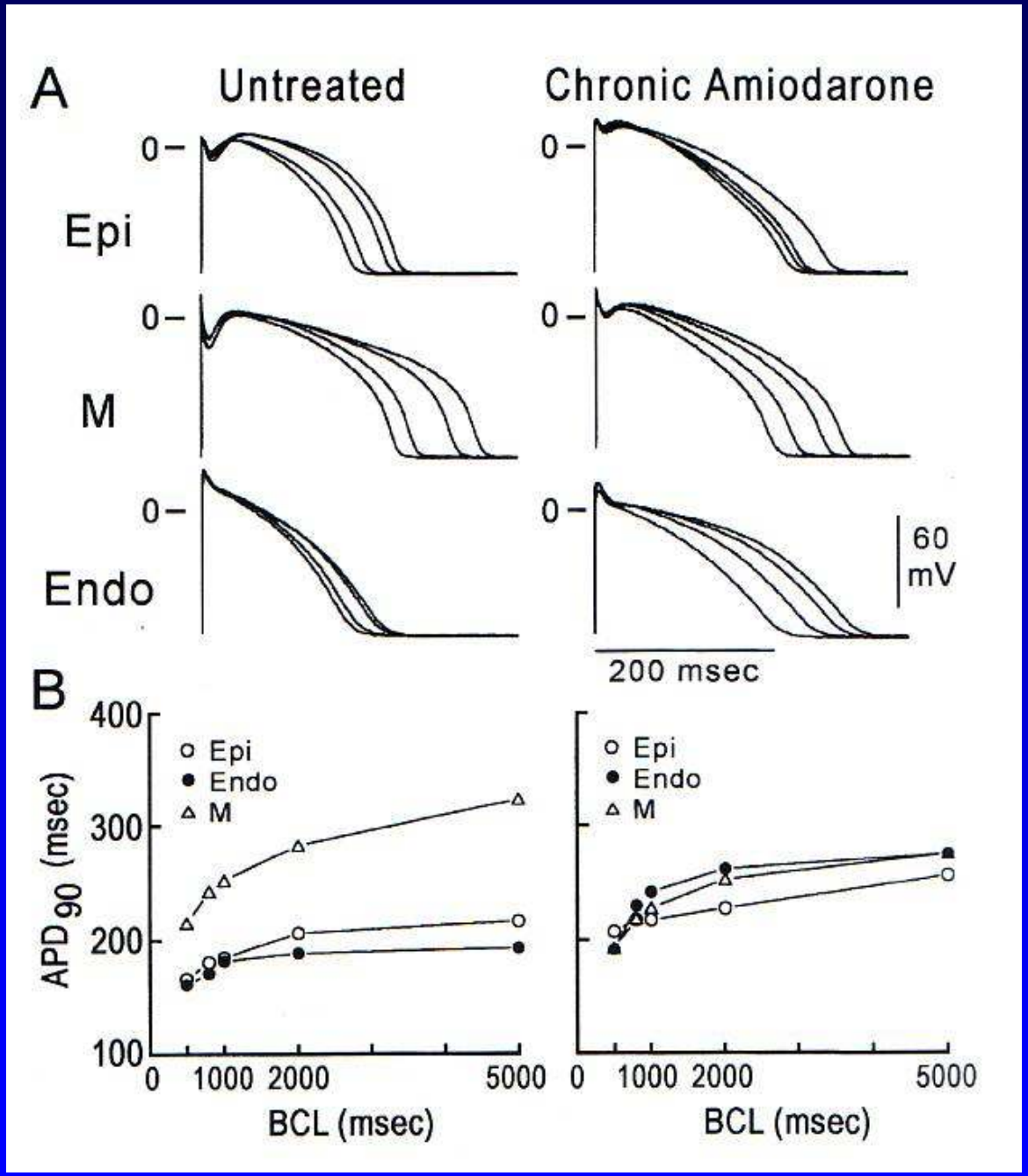

QRS DURATION (msec)
210
200
190
180
170
0
40
80
120
160
BEAT NUMBER
QUINIDINE
TIME CONSTANT = 4.7
r = 0.92

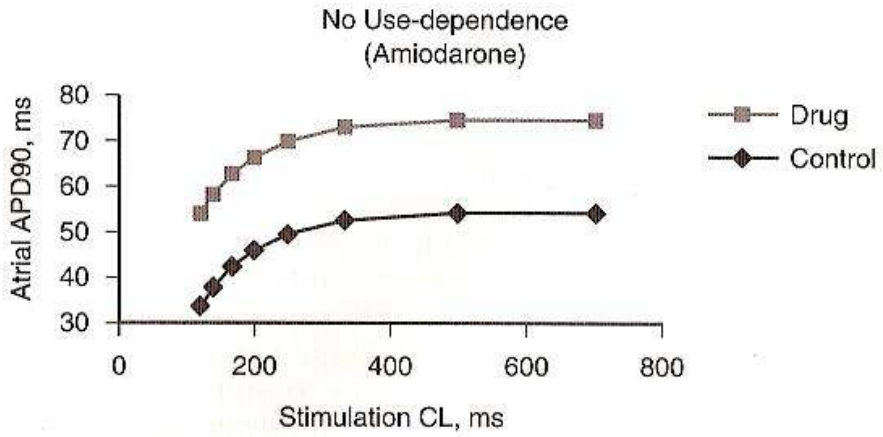
A


QRS DURATION (ms)
200
180
160
140
300
400
500
600
CYCLE LENGTH (ms)
GROUP A AMIO
BASELINE
*p<.01

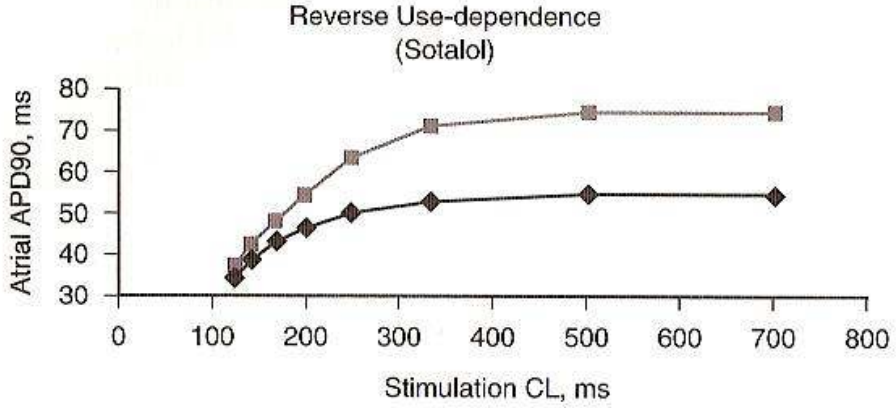
# AA de classe III


A
Control
d-Sotalol (100 μM)
0
Epi
M
Endo
50
mV
200 msec
B
Epi
M
Endo
APD90 (msec)
850
700
550
400
250
100
0
1000
2000
5000
BCL (msec)

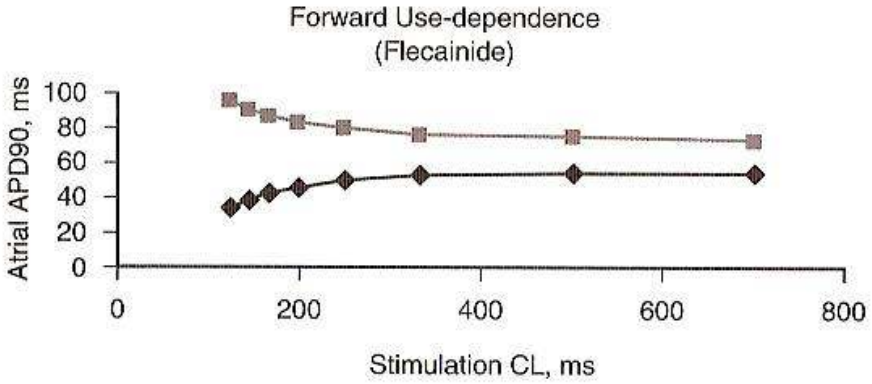

A
Untreated
Chronic Amiodarone
0
Epi
M
Endo
60
mV
200 msec
B
400
300
200
100
APD90 (msec)
Epi
Endo
M
0
1000
2000
5000
BCL (msec)



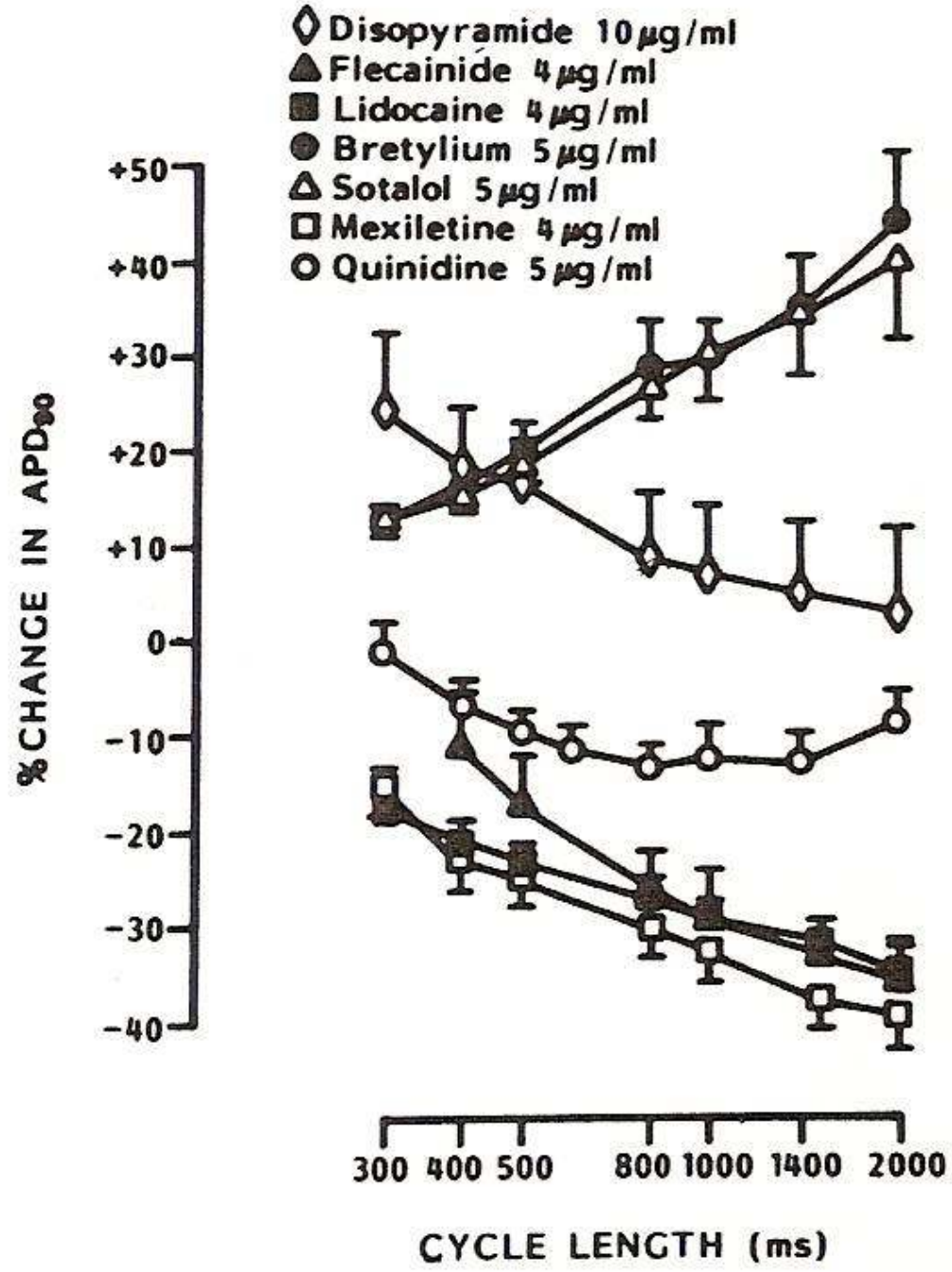

Amiodarone or dronedarone (complex ion-channel effects)




Sotalol, dofetilide, ibutilide, and other $I_{kr}$ blockers




Flecainide or propafenone effects in atrial muscle only block $I_{to}$, $I_{kur}$, and $I_{Kr}$

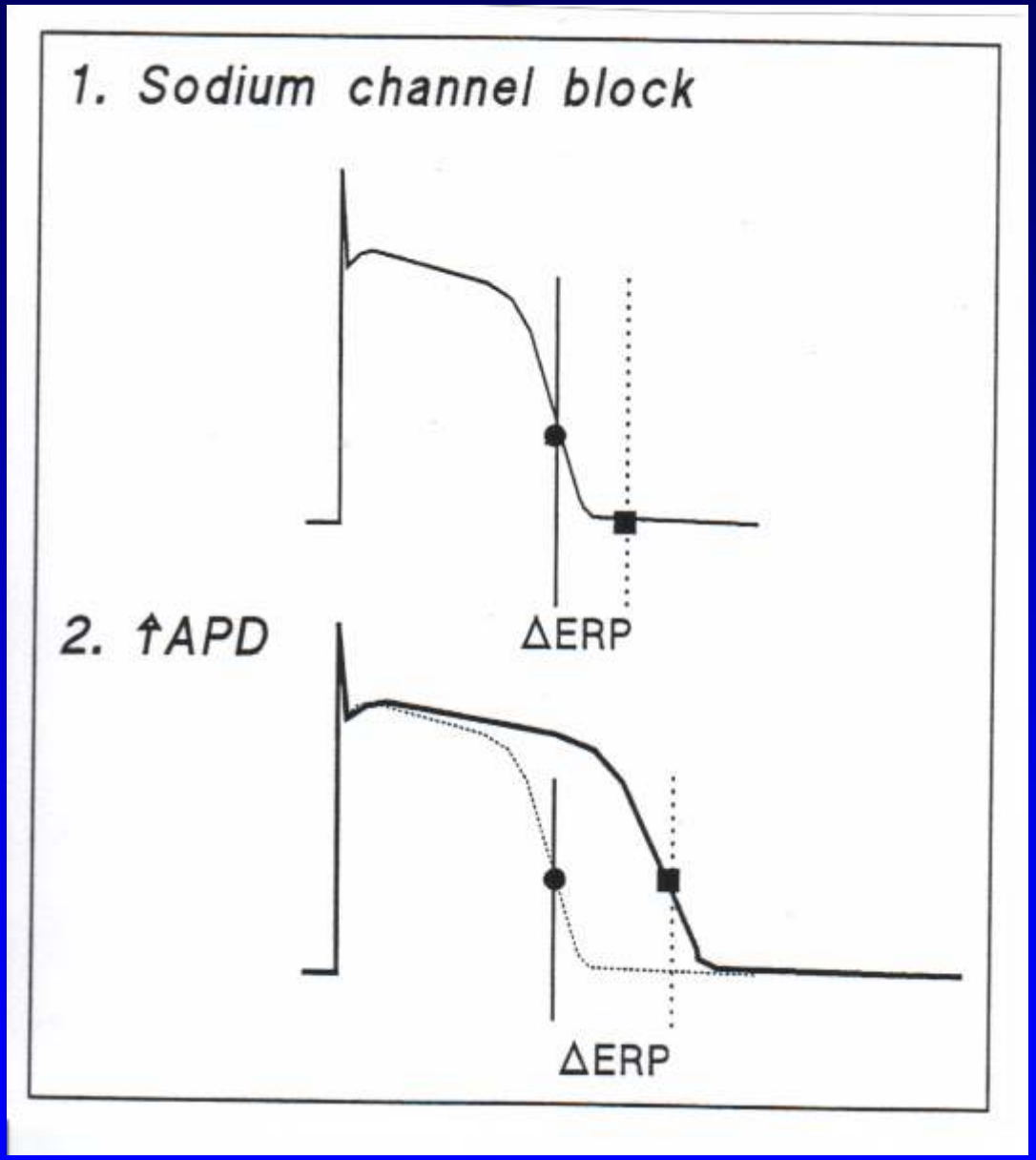

Disopyramide 10 µg/ml
Flecainide 4 µg/ml
Lidocaine 4 µg/ml
Bretylium 5 µg/ml
Sotalol 5 µg/ml
Mexiletine 4 µg/ml
Quinidine 5 µg/ml
+50
+40
+30
+20
+10
0
-10
-20
-30
-40
% CHANGE IN APD90
300 400 500 800 1000 1400 2000
CYCLE LENGTH (ms)

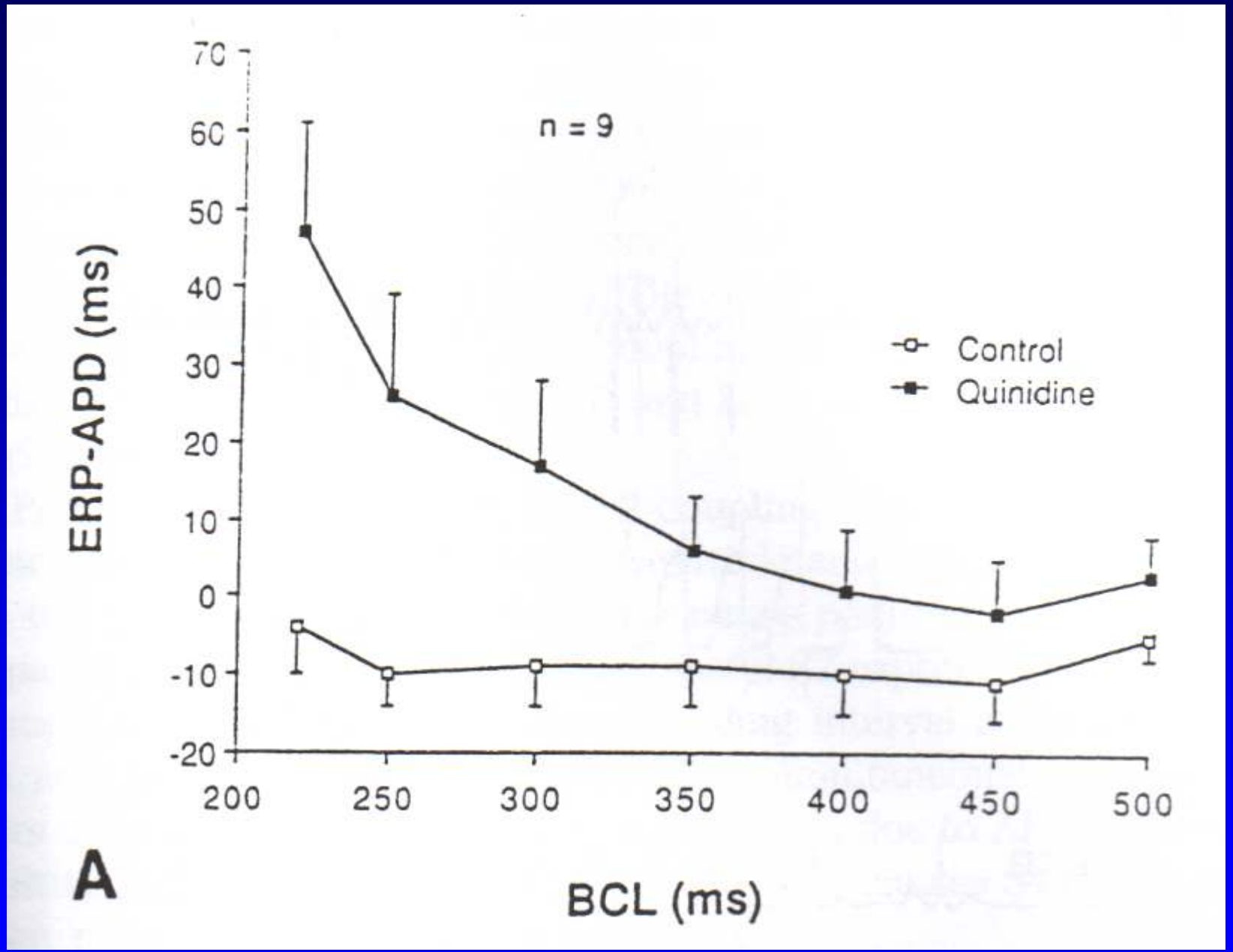
# Classification de HONDEGHEM (1991)

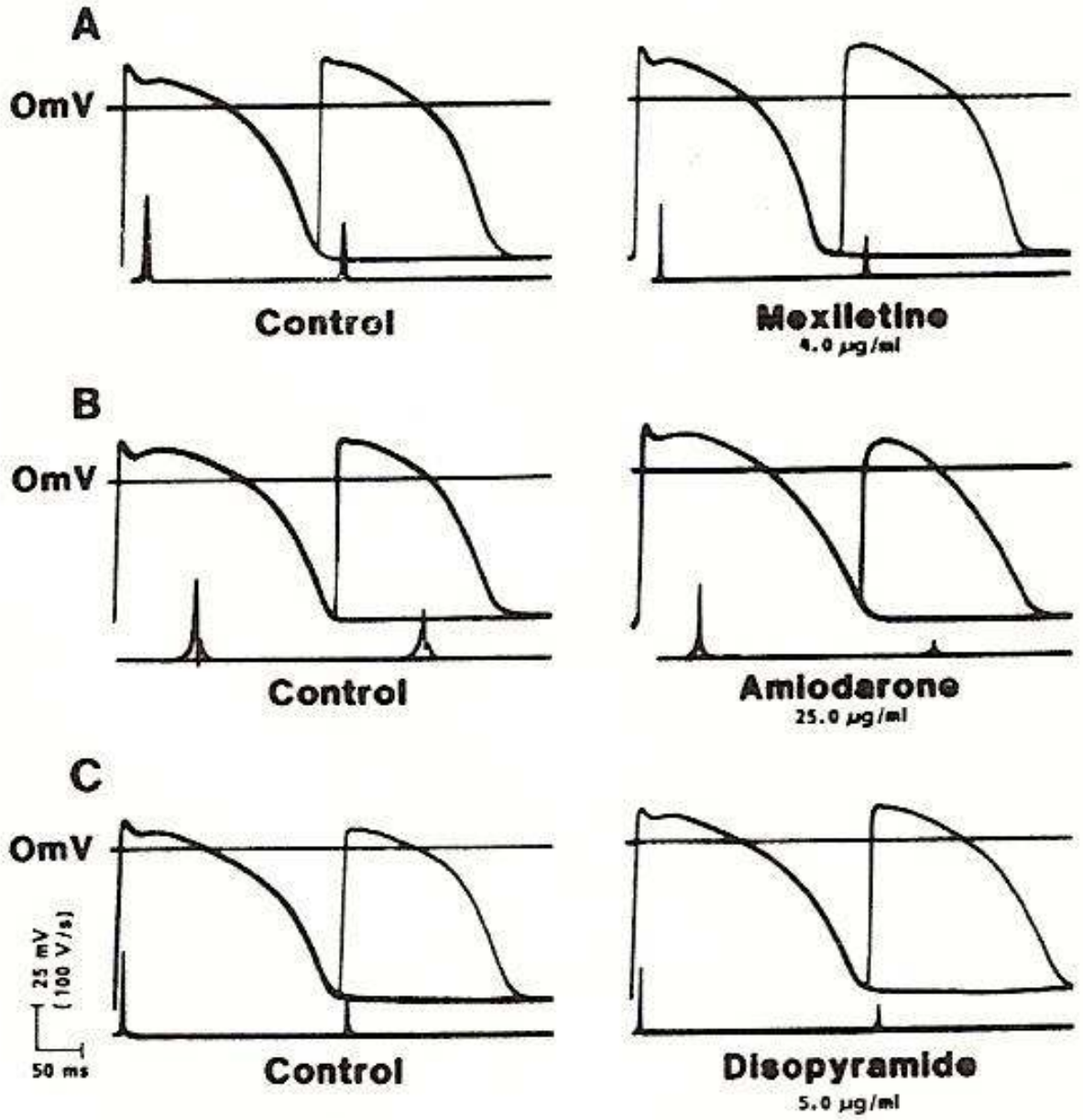
- classe III = prolongation PA/QT
- III B = bradycardie dépendant - "use dependance" inverse
  peu AA et beaucoup pro A
  ex : classe III pur
- III A = accélération dépendant - "use dependance" positive
  très AA = défibrillateur chimique
  ex : ?
- III AB = cycle indépendant - peu de use dependance
  AA et peu pro A
  ex : amiodarone

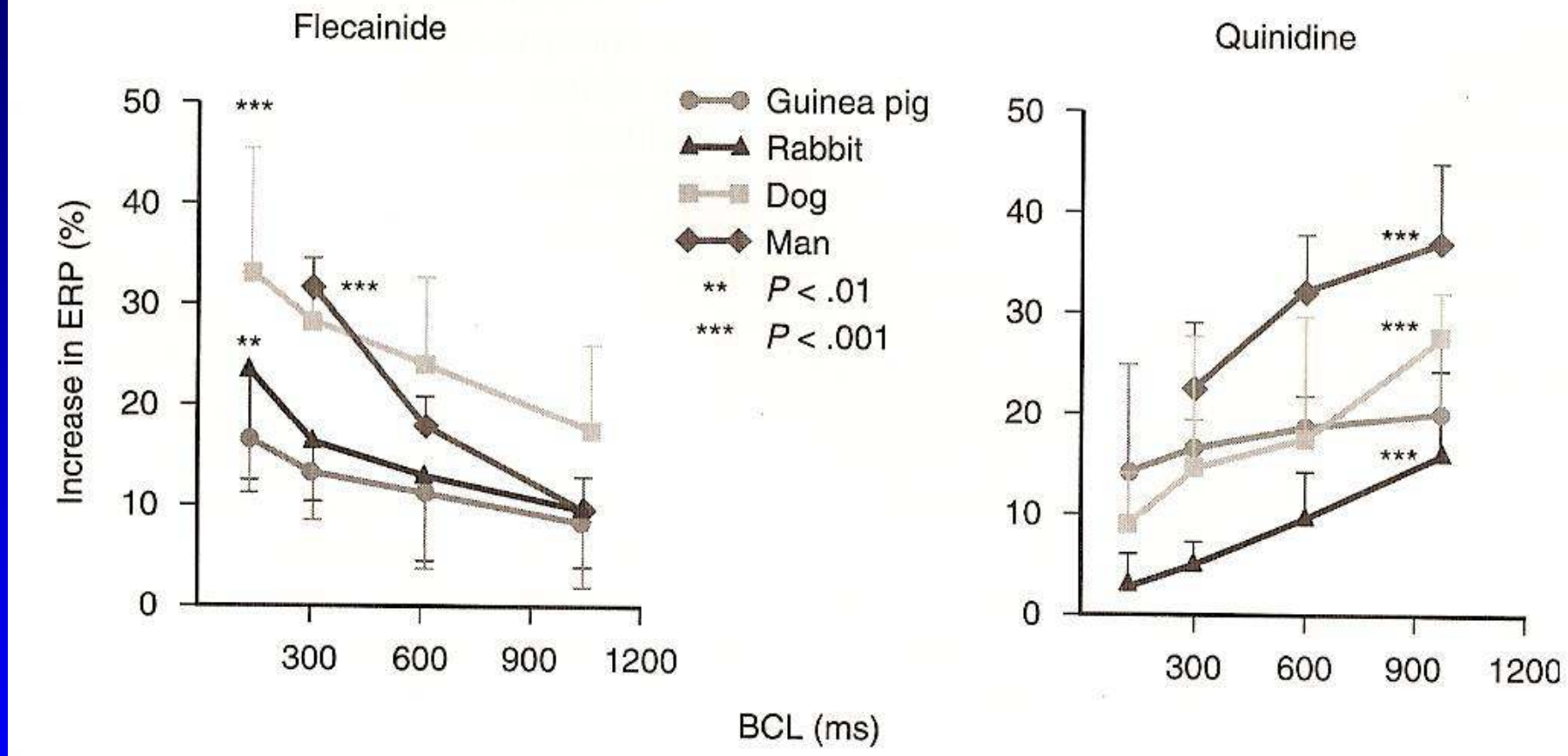
# Classe Ic et réfractorité

Notion de période réfractaire post-dépolarisation


1. Sodium channel block
ΔERP
2. ↑APD
ΔERP


70
60
50
40
30
20
10
0
-10
-20
n = 9
Control
Quinidine
ERP-APD (ms)
200
250
300
350
400
450
500
BCL (ms)
A

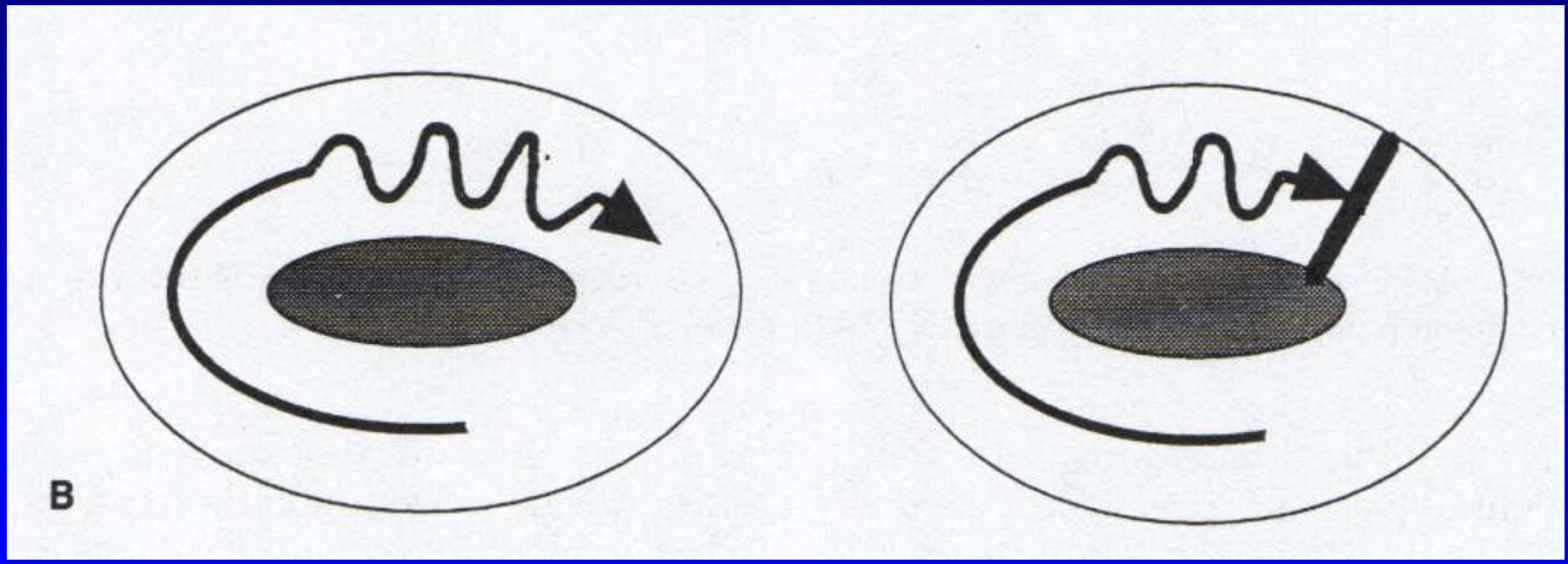

A
0mV
Control
Mexiletine
4.0 µg/ml
B
0mV
Control
Amiodarone
25.0 µg/ml
C
0mV
25 mV
(100 V/s)
50 ms
Control
Disopyramide
5.0 µg/ml


Flecainide
Quinidine
Increase in ERP (%)
50
40
30
20
10
0
300
600
900
1200
BCL (ms)
Guinea pig
Rabbit
Dog
Man
** P < .01
*** P < .001
***
**

# FA et antiarythmiques

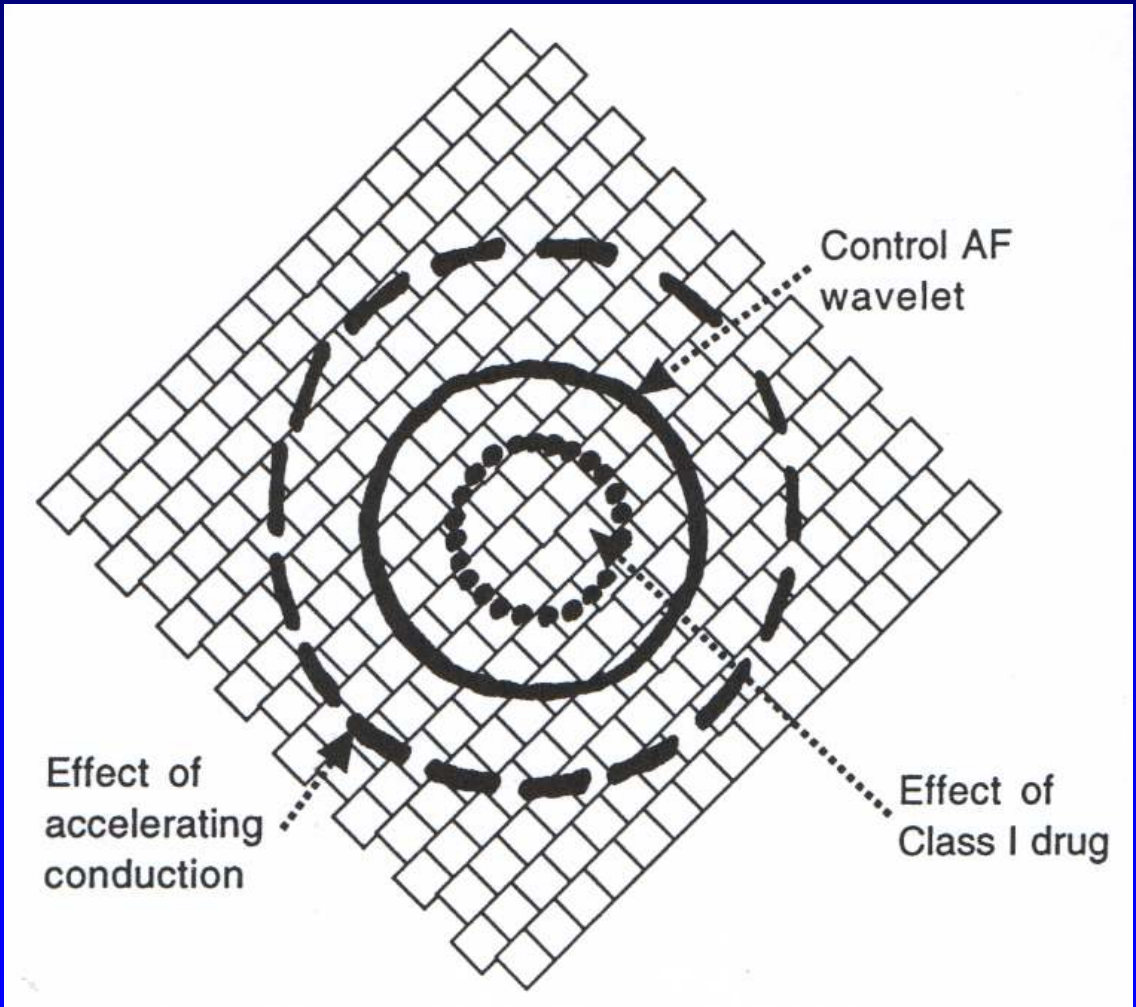
- les AA de classe Ic allongent les PR en FA (PR post dépolarisation) , et malgré un ralentissement de la conduction allongent la LO
  les AA de classe III perdent leurs propriétés d ’allonger les PR et la LO aux cycles rapides en raison de leur use-dépedance inverse

# Réentrée anatomique et conduction




ARRET par diminution de la conduction - FRANZ , 1994

# Réentrée fonctionnelle et conduction

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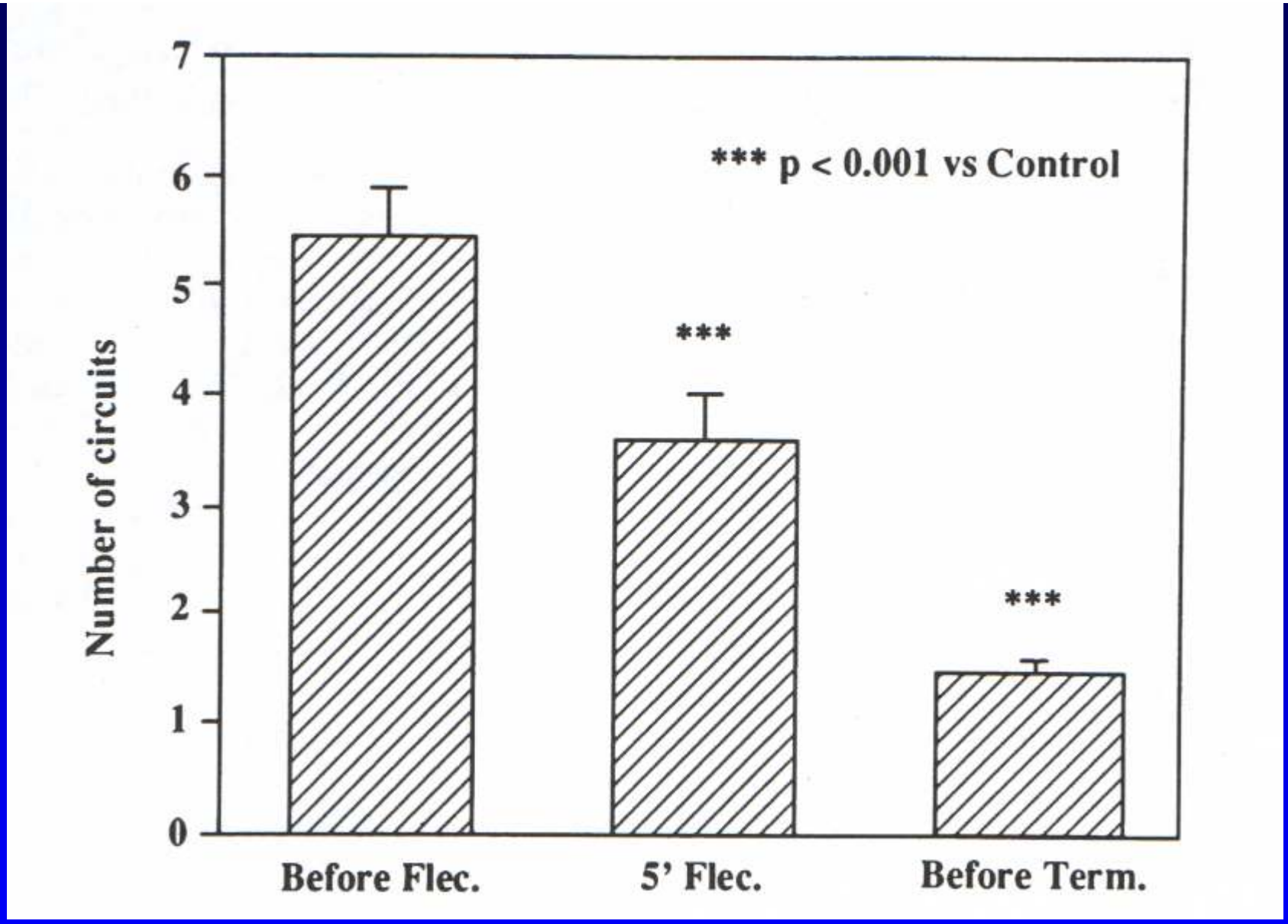
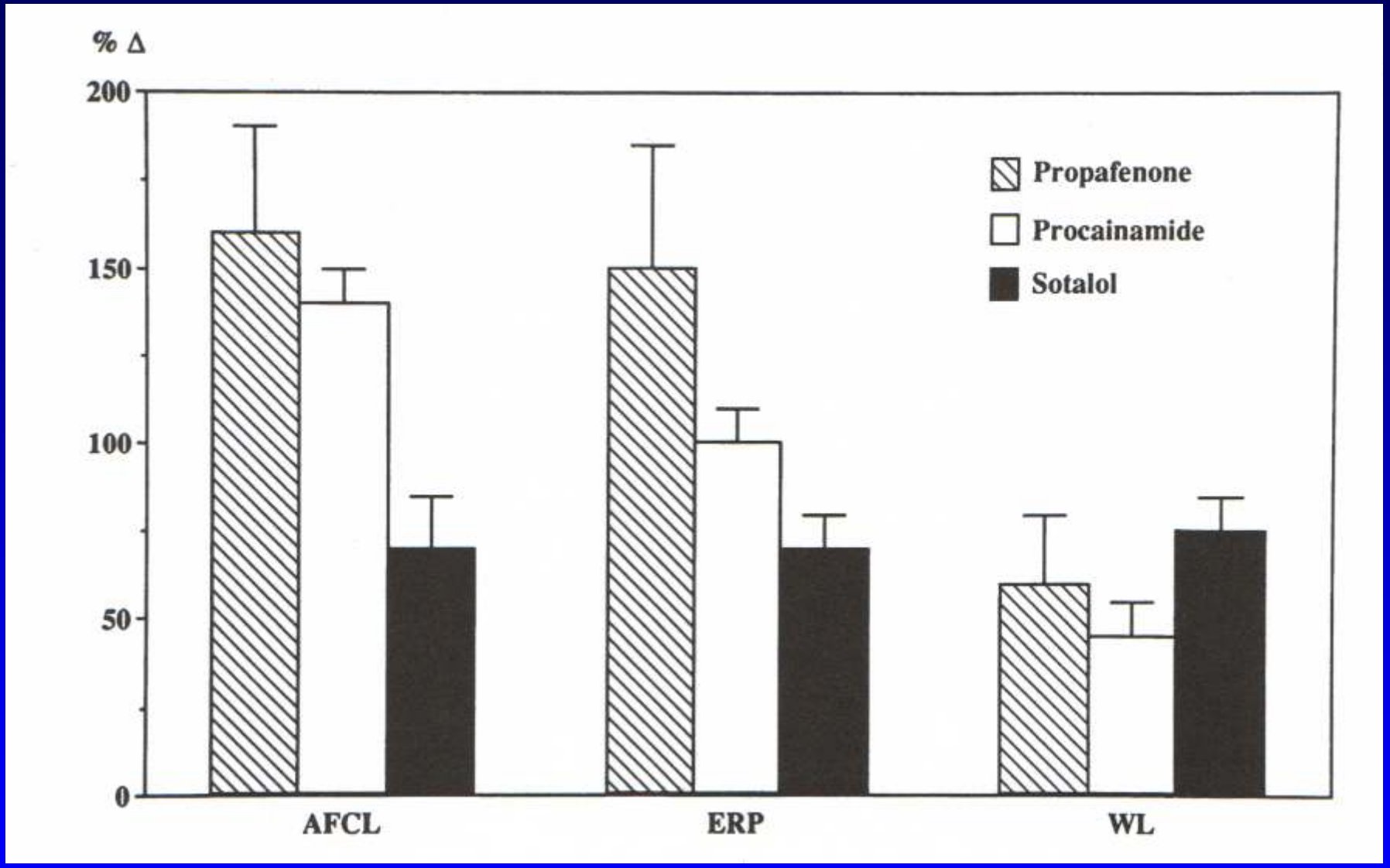
RWF - 1994

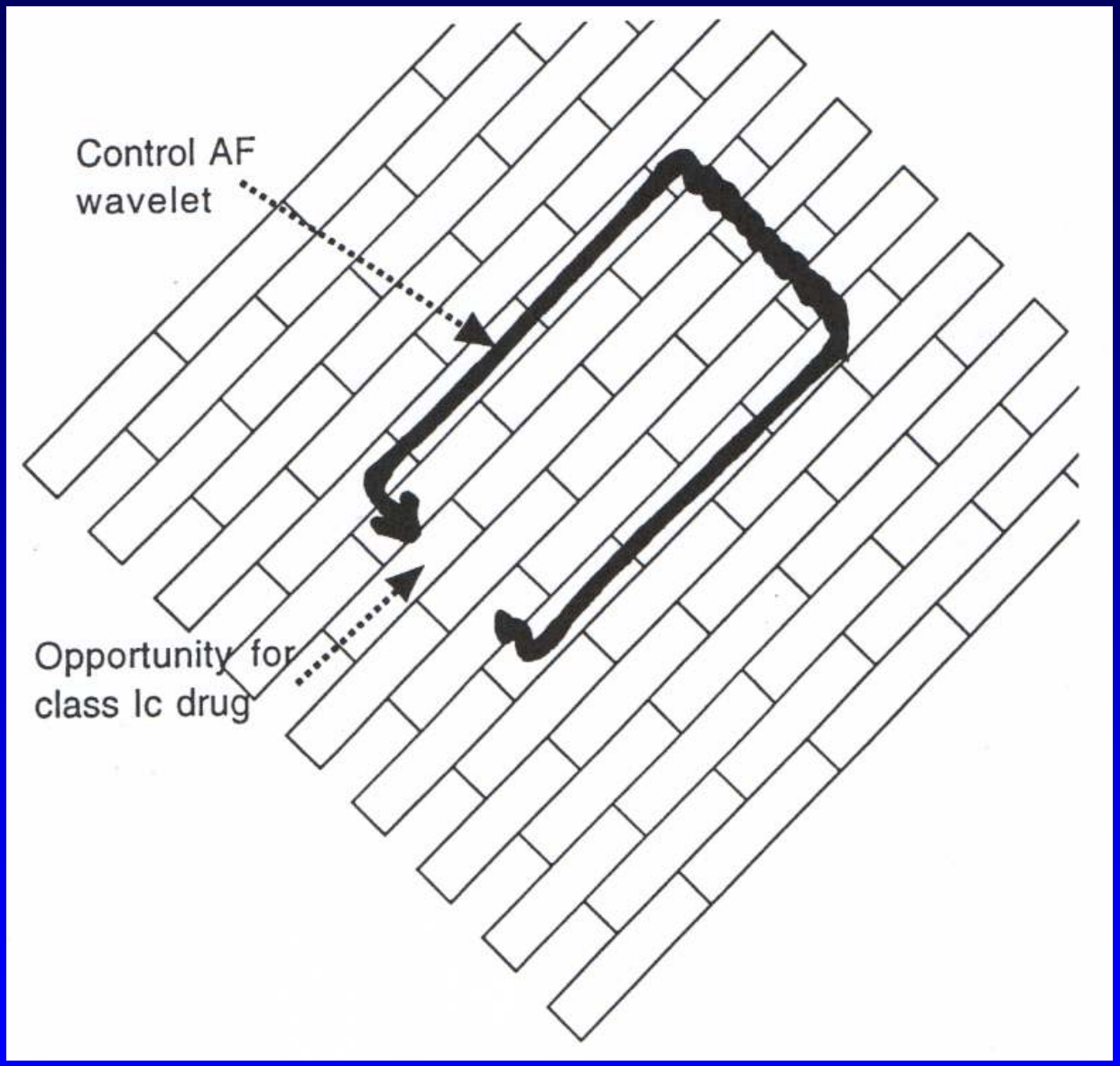
Classe IC et diminution de la conduction




WANG et NATTEL, Circ Res 1992




WANG et NATTEL, Circ 1993

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RWF - 1994

Classe IC et conduction anisotropique -

# 3 - Classification des AA

# Quelle classification ?

- Classification de Vaughan Williams – 1970 :
  - électrophysiologie cellulaire
- Classification de Touboul – 1975 :
  - électrophysiologie clinique
- Classification de Harrison – 1985 :
  - électrophysiologie cellulaire (classe I A, B, et C)
- Classification de Taormina « Sicilian Gambit » - 1991 :
  - des canaux ioniques au système nerveux autonome
- Classification de Hondeghem - 1991:
  - Physiopathologie des arythmies (classe III)

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| Ic | Marked phase 0 depression | Flecainide |
| | Marked conduction slowing | Propafenone |
| | Slight effect on repolarization | Moricizine |
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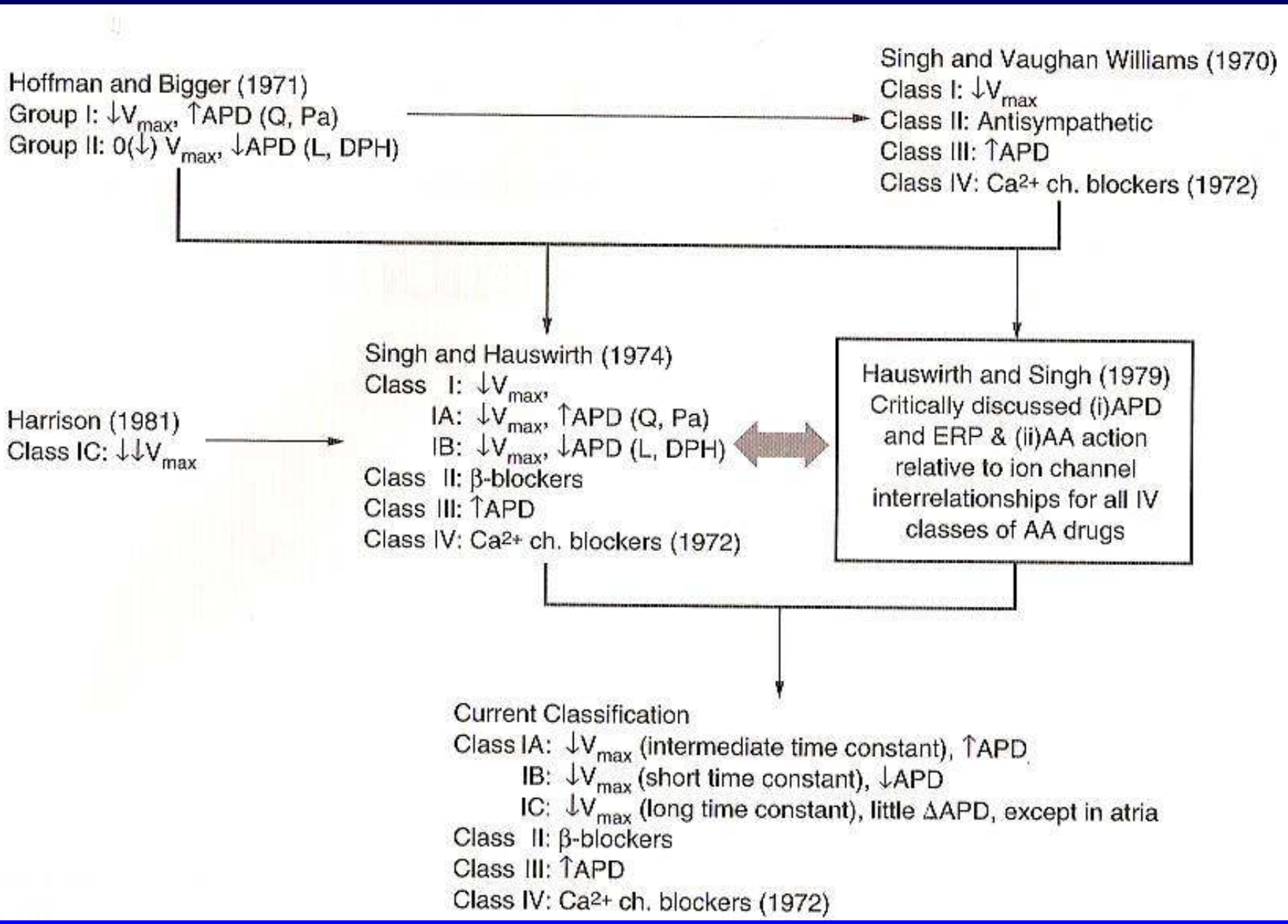
| | | Acebutolol |
| | | Esmolol |
| III | Prolongs repolarization | Bretylium |
| | | Amiodarone |
| | | Sotalol |
| | | Ibutilide |
| | | Dofetilide |
| IV | Calcium channel blockers | Verapamil |
| | | Diltiazem |
| | Purine agonist | Adenosine |
| | Digitalis glycosides | Digoxin |
| | | Digitoxin |


Hoffman and Bigger (1971)
Group I: ↓$V_{max}$, ↑APD (Q, Pa)
Group II: 0(↓) $V_{max}$, ↓APD (L, DPH)
Singh and Vaughan Williams (1970)
Class I: ↓$V_{max}$
Class II: Antisympathetic
Class III: ↑APD
Class IV: $Ca^{2+}$ ch. blockers (1972)
Singh and Hauswirth (1974)
Class I: ↓$V_{max}$,
IA: ↓$V_{max}$, ↑APD (Q, Pa)
IB: ↓$V_{max}$, ↓APD (L, DPH)
Class II: β-blockers
Class III: ↑APD
Class IV: $Ca^{2+}$ ch. blockers (1972)
Harrison (1981)
Class IC: ↓↓$V_{max}$
Hauswirth and Singh (1979)
Critically discussed (i)APD and ERP & (ii)AA action relative to ion channel interrelationships for all IV classes of AA drugs
Current Classification
Class IA: ↓$V_{max}$ (intermediate time constant), ↑APD
IB: ↓$V_{max}$ (short time constant), ↓APD
IC: ↓$V_{max}$ (long time constant), little ΔAPD, except in atria
Class II: β-blockers
Class III: ↑APD
Class IV: $Ca^{2+}$ ch. blockers (1972)

# Les AA usuels en pratique classe I : bloqueurs Na

- Classe I A : QRS ↗ QT ↗
  - SERECOR : hydroquinidine
  - RYTHMODAN : disopyramide
- Classe I B : QRS → QT →
  - MEXITIL : méxilétine
- Classe I C : QRS ↗ QT →
  - FLECAINE : flécaïnidine
  - RYTHMOL : propafénone
  - CIPRALAN : cibenzoline

# Les AA usuels en pratique - 2

- Classe II : Bétabloquants
  - Tous sauf sotalol
- Classe III : PA et QT ↗
  - SOTALEX : DL sotalol
  - CORDARONE : amiodarone
- Classe IV : anticalciques
  - ISOPTINE : vérapamil
  - TILDIEM : diltiazem

# Les AA usuels en pratique - iv

- Classe I C :
  - FLECAINE : flécaïnidine
  - CIPRALAN : cibenzoline
- Classe III :
  - CORVERT : ibutilide
- et les autres …
  - CORDARONE : amiodarone
  - ISOPTINE : vérapamil
  - TILDIEM : diltiazem
  - AVLOCARDYL , ….

# Classification et efficacité

- La classification ne nous aide pas pour prédire la plus grande efficacité :
  - Exemple de l'amiodarone
- La classification nous aide par contre pour prédire l'absence d'efficacité :
  - Exemple du vérapamil
- La classification nous aide par contre pour prédire la (rare) place des associations = 2 AA de classe différente :
  - Exemple de CORDARONE + FLECAINE

# L’efficacité au long cours : le succès de l’amiodarone

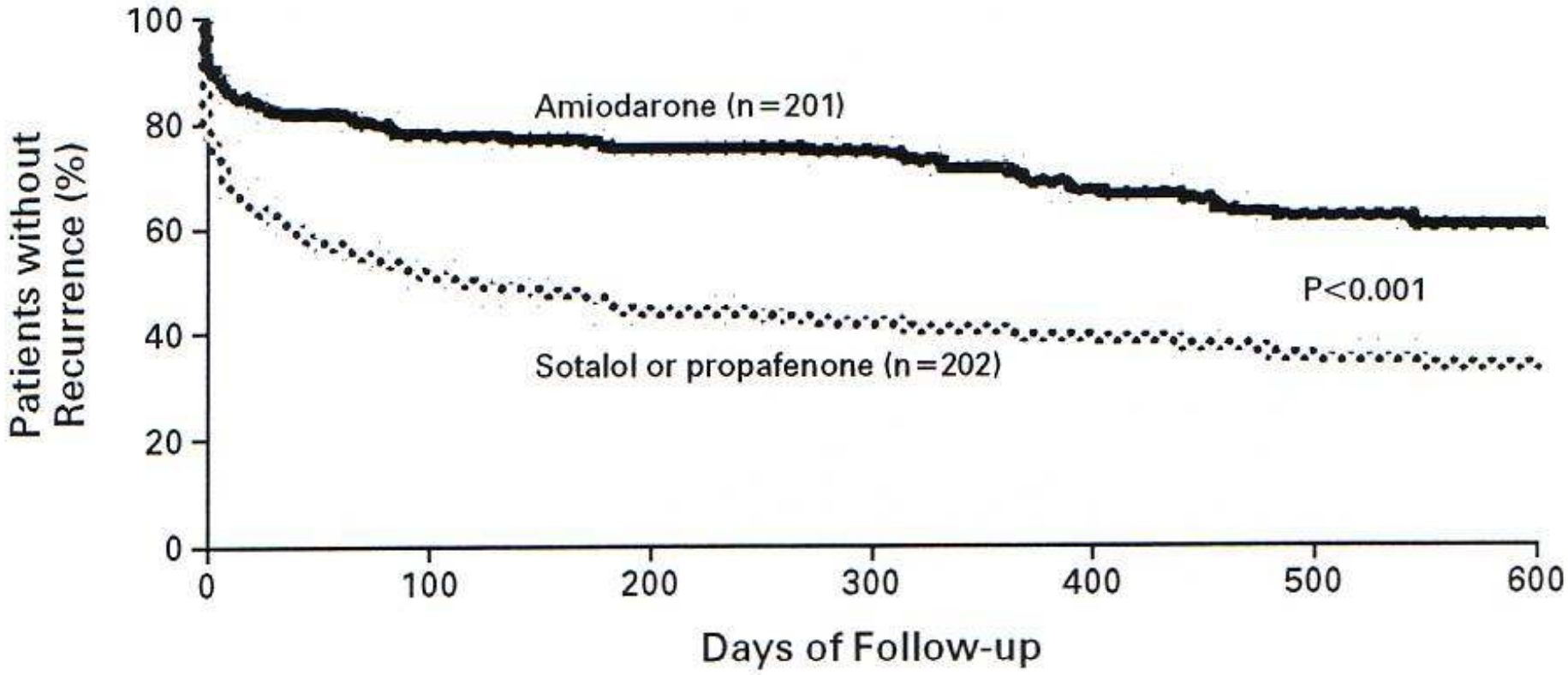
# Étude CTAF – D. Roy, 2000

- 403 patients avec 1 accès de FA de plus de 10 min ces 6 derniers mois
- Ni infarctus récent ni insuffisance cardiaque NYHA III-IV

| Study Drug | Day 21 | 3 Months | 6 Months | 12 Months |
|---|---|---|---|---|
| | milligrams per day | | | |
| Amiodarone | 327±134 | 205±44 | 196±39 | 186±48 |
| Propafenone | 547±139 | 527±111 | 520±122 | 471±121 |
| Sotalol | 230±80 | 231±81 | 219±85 | 224±83 |

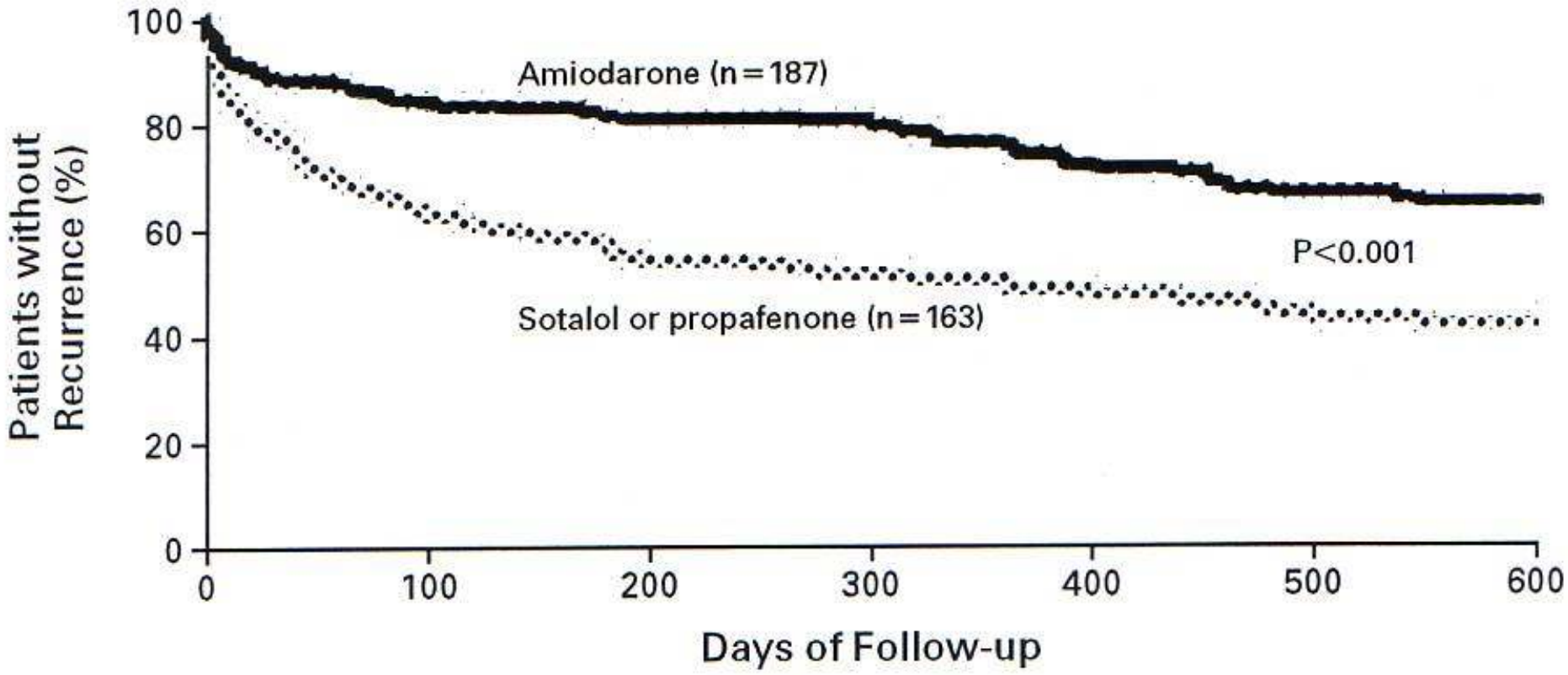
# Étude CTAF – D. Roy, 2000

Tout patient randomisé – RR 0.43 – 69% vs 39% à 1 an



# Étude CTAF – D. Roy, 2000

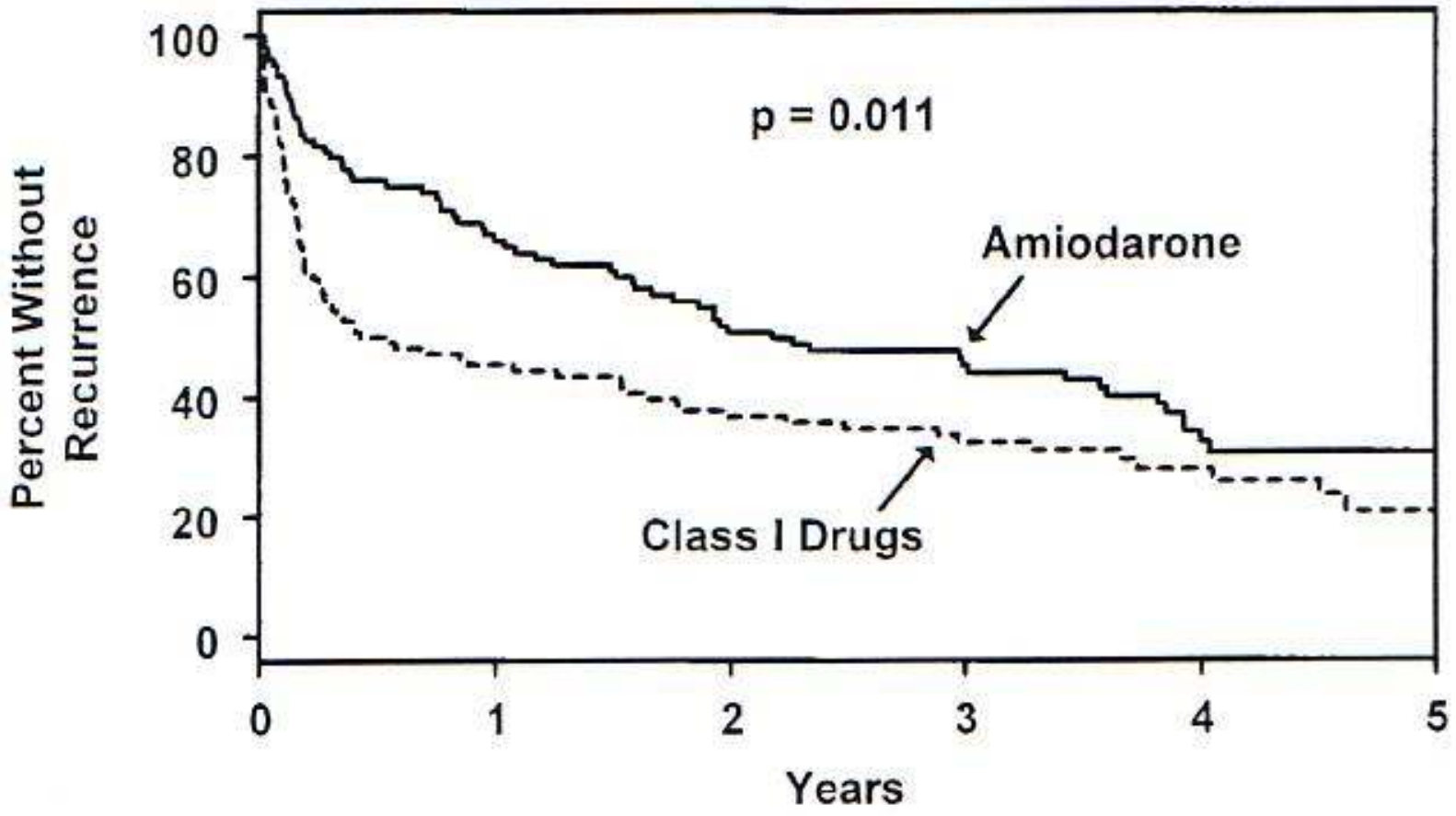
Patient en RS à la randomisation – RR = 0.45



# AFFIRM – 1st AA drug substudy

- 410 patients randomisés pour :
  - amiodarone 200 mg
  - sotalol 240 mg
  - classe IA ou IC : quinidine 600 mg, disopyramide 300 mg, propafénone 450 mg, flécainide 100 mg
- Patient sans récidive : vivant, sous AA, en RS, sans CEE

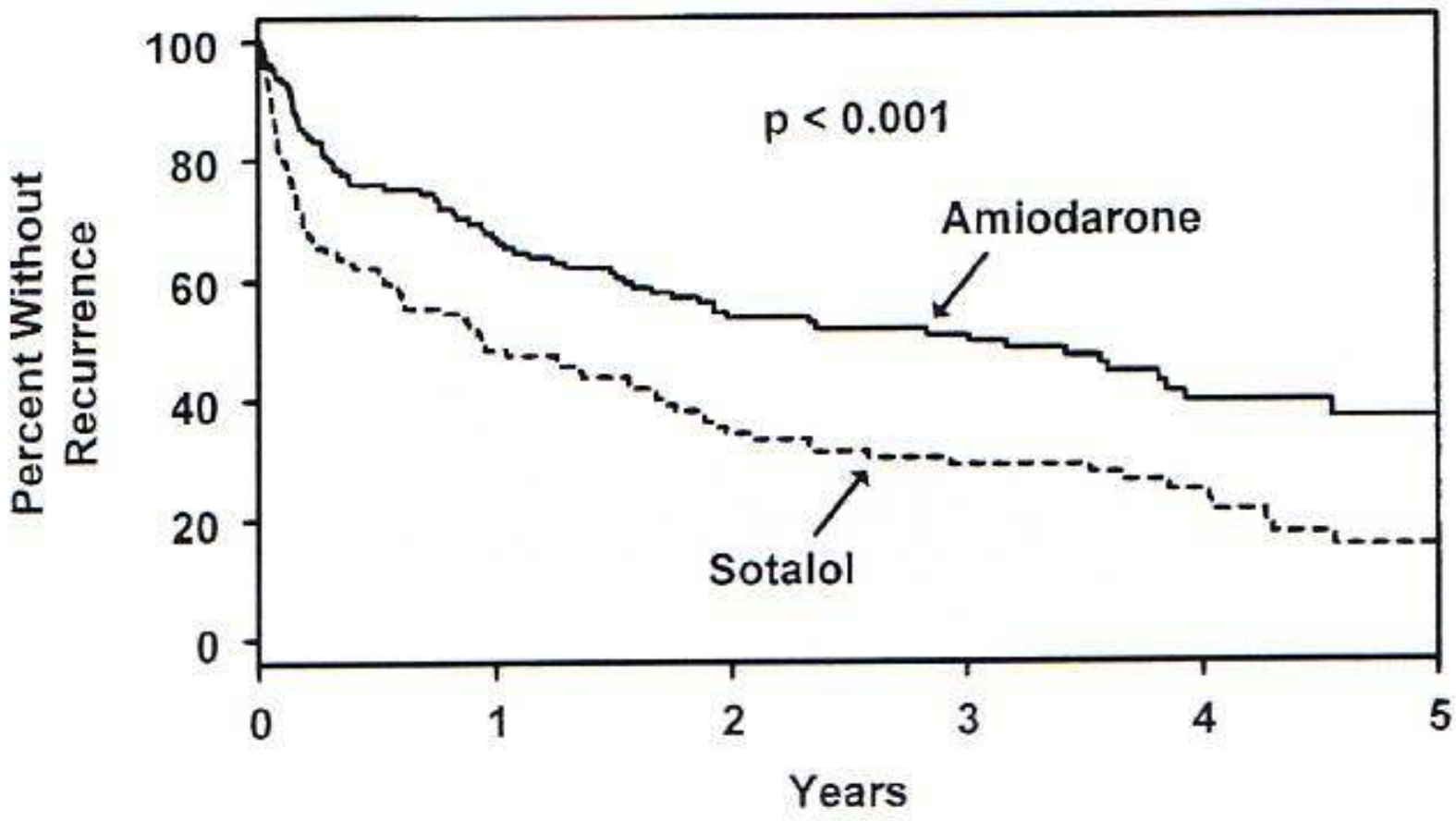
# AFFIRM – 1st AA drug substudy




Number of Recurrences (% Without Recurrence)

| | | | | | | |
|---|---|---|---|---|---|---|
| Amio: | 0 (100%) | 35 (66%) | 50 (51%) | 55 (45%) | 64 (33%) | 65 (31%) |
| Class I: | 0 (100%) | 61 (45%) | 70 (37%) | 74 (33%) | 77 (28%) | 80 (21%) |

# AFFIRM – 1st AA drug substudy

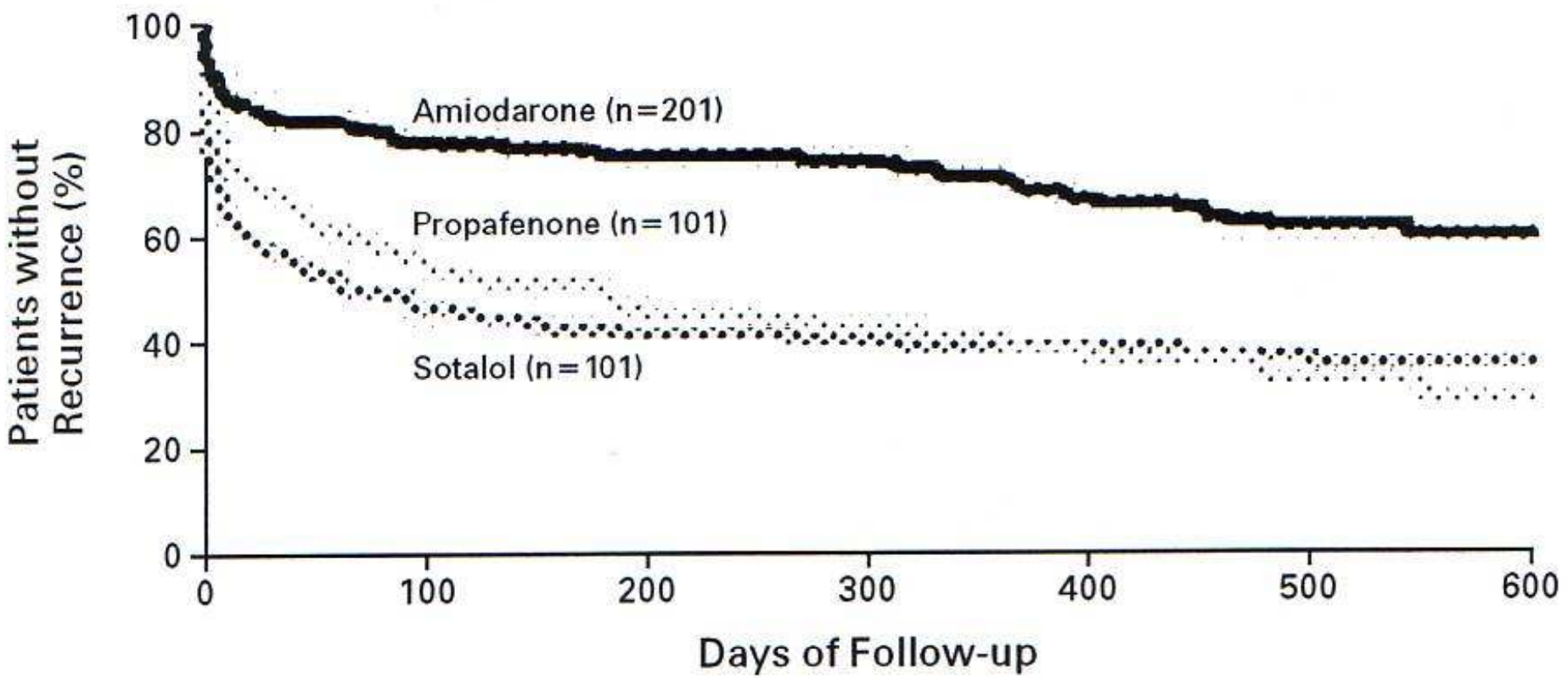



Number of Recurrences (% Without Recurrence)

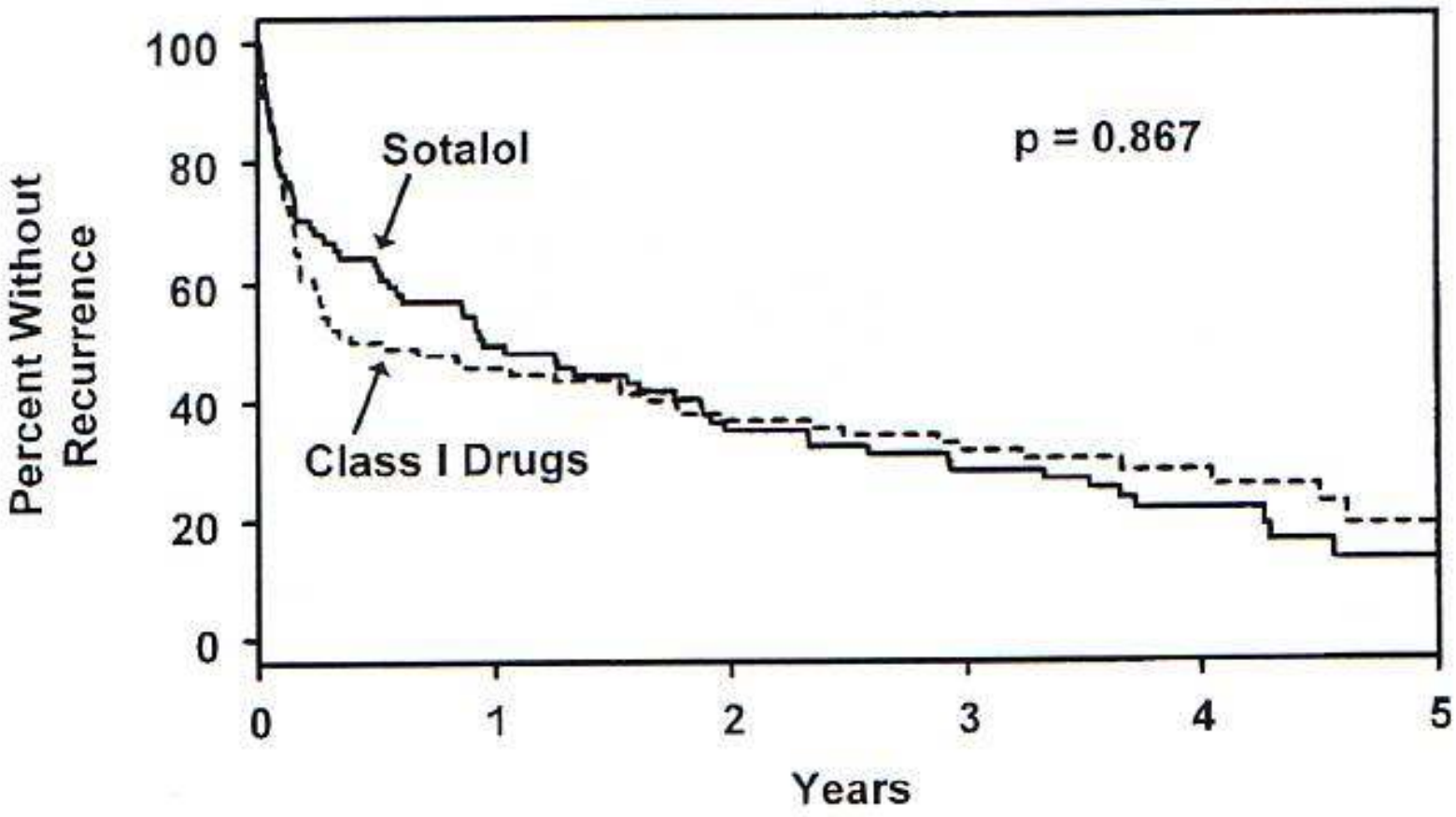
| | | | | | | |
|---|---|---|---|---|---|---|
| Amio: | 0 (100%) | 42 (67%) | 58 (53%) | 61 (50%) | 69 (39%) | 70 (37%) |
| Sotalol: | 0 (100%) | 61 (48%) | 76 (34%) | 81 (29%) | 84 (25%) | 89 (15%) |

# L’efficacité au long cours : l’équivalence des autres AA

# Étude CTAF – D. Roy, 2000



# AFFIRM – 1st AA drug substudy

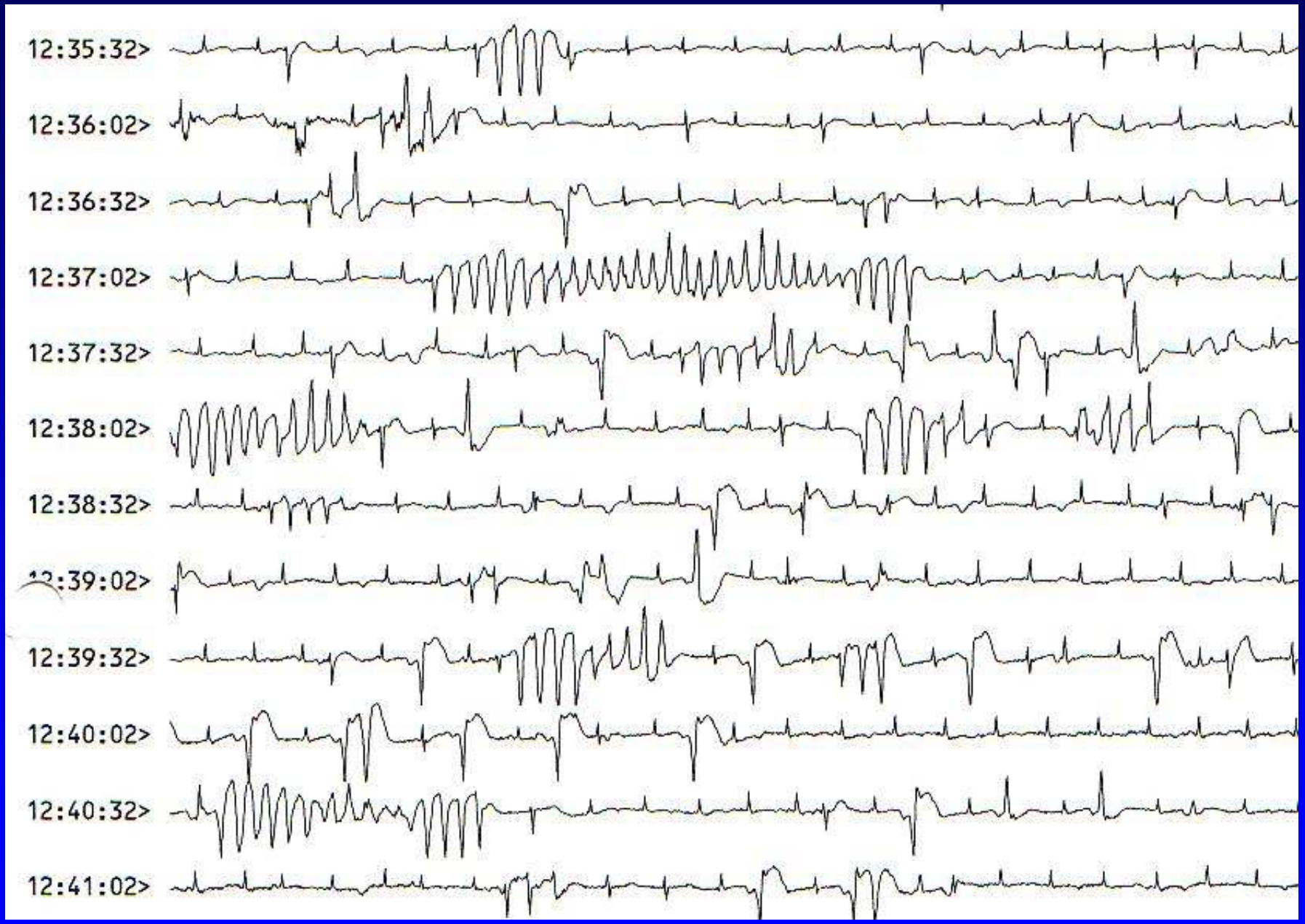



Number of Recurrences (% Without Recurrence)

| | | | | | | |
|---|---|---|---|---|---|---|
| Sotalol: | 0 (100%) | 41 (49%) | 52 (35%) | 57 (28%) | 61 (22%) | 64 (13%) |
| Class I: | 0 (100%) | 50 (46%) | 58 (37%) | 62 (31%) | 64 (28%) | 67 (19%) |

# Les effets II° cardiaques des AA

- Les torsades de pointe : uniquement
  - Les AA de classe I A : tous, dose-indépendant
  - Les AA de classe III : III purs, dose-dépendant
- Les troubles conductifs intra-V et les TV « toxiques » post-IDM :
  - Les AA de classe I A, B et C
- Les effets inotropes négatifs :
  - Tous sauf  amiodarone
- Les troubles conductifs sinusaux et nodaux
  - Toutes les classes I, II, III, IV et digoxine !


12:35:32>
12:36:02>
12:36:32>
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12:37:32>
12:38:02>
12:38:32>
12:39:02>
12:39:32>
12:40:02>
12:40:32>
12:41:02>

# Les effets II° cardiaques des AA

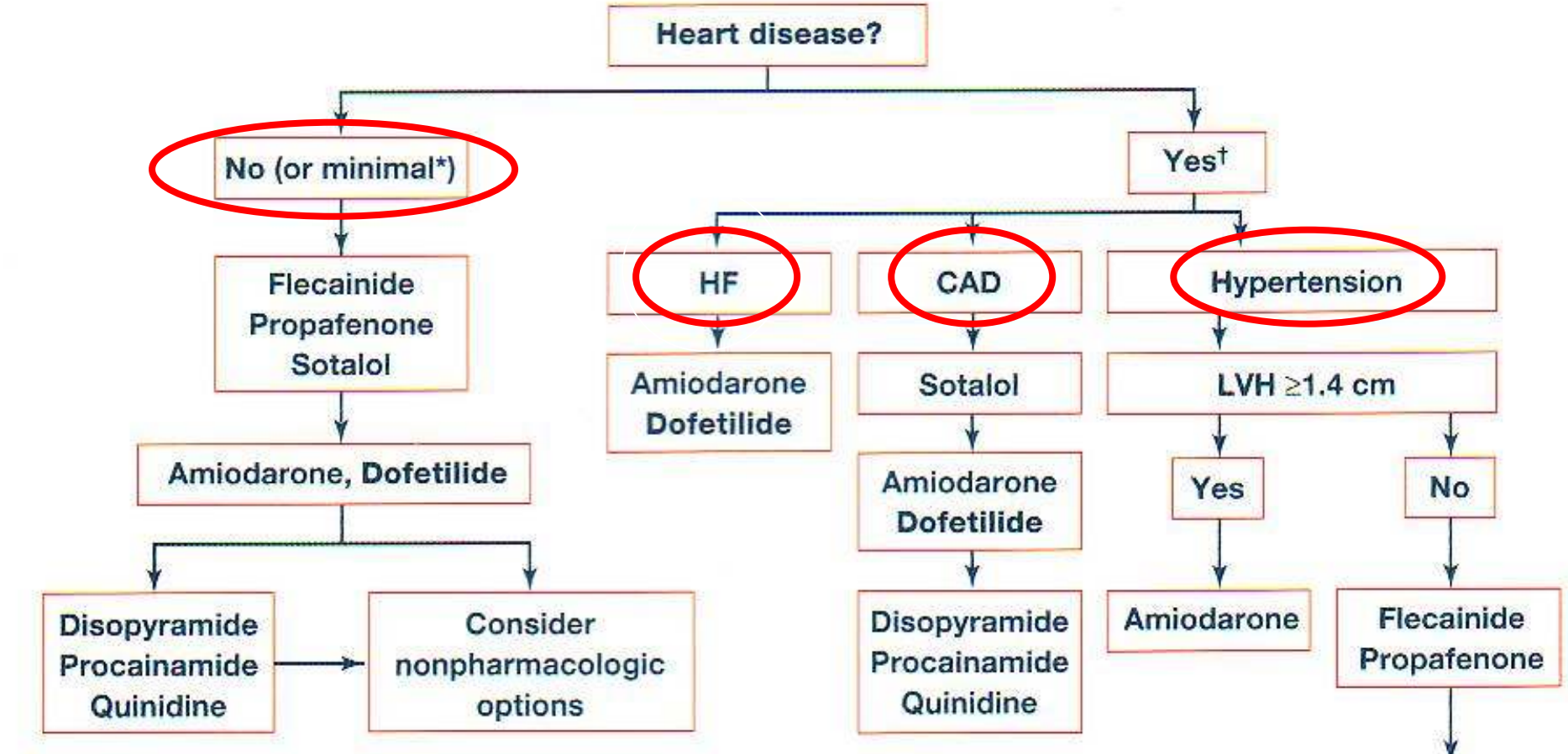
- Amiodarone : seul AA sans
  - Torsade de pointe
  - TV sur IDM ancien
  - BAV infra-nodal en cas de bloc de branche
  - Effet inotrope négatif en cas d'insuffisance cardiaque
  - et grande efficacité !!
- Pourquoi ? :
  - effets multiples I + II + III + IV ??
- Par contre :
  - troubles conductifs sinusaux et nodaux

# effets II° extra-cardiaques des AA

- exemple de l'amiodarone
  - dysthyroïdies
  - thésaurismoses
  - > 30 % après 3 ans de TT !!
- exemples
  - des hypoglycémies sous Cipralan
  - des allergies cutanées sous Quinidine
- A contrario :
  - Effets neuro-sensoriels des AA de classe I
  - Effets atropiniques du Rythmodan

# effets II° extra-cardiaques des AA

- Dans le cas de l'amiodarone :
  - Tous les 6 mois : TSH
  - Tous les 6 mois : Rx des poumons
  - Pas de place pour la surveillance ophtalmo !
- Pour les autres AA :
  - Aucune surveillance extra-cardiaque
- Les effets secondaires extra-cardiaques ne sont pas classe-dépendants et l'essai d'un autre AA est toujours indiqué en cas d'intolérance



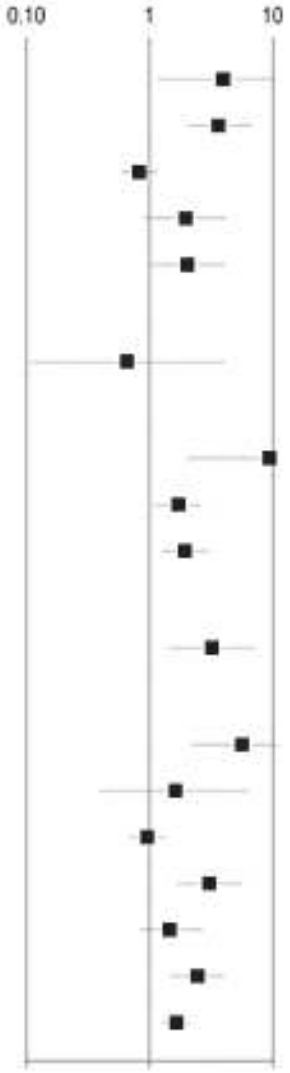

*For adrenergic atrial fibrillation, beta blockers or sotalol is the initial drug of choice.
†Consider nonpharmacologic options to maintain sinus rhythm if drugs fail.
HF=heart failure; CAD=coronary artery disease; LVH=left ventricular hypertrophy.

# Une méta-analyse récente

**Lafuente-Lafuente, C. et al.**
**Arch Intern Med**
**2006;166:719-728.**

# Arrêt pour effets secondaires - 1

| Drugs Studied | No. of Studies | Total No. of Events: Antiarrhythmic | Total No. of Events: Control | Peto OR (95% CI) | P Value |
|---|---|---|---|---|---|
| | | | | Antiarrhythmic vs Control | |
| Class IA | | | | | |
| Disopyramide phosphate | 2 | 9/75 | 2/71 | 3.85 (1.13-13.2) | .03 |
| Quinidine sulfate: higher dose | 5 | 44/233 | 12/209 | 3.58 (2.01-6.40) | <.001 |
| Quinidine: lower dose* | 2 | 181/895 | 77/339 | 0.81 (0.59-1.10) | .18 |
| Quinidine: all studies | 7 | 225/1128 | 89/548 | 1.90 (0.90-4.02)† | .39 |
| All class IA | 8 | 234/1203 | 91/594 | 2.02 (1.00-4.10)† | .05 |
| Class IB | | | | | |
| All: aprindine hydrochloride | 1 | 2/47 | 3/47 | 0.66 (0.11-3.95) | .65 |
| Class IC | | | | | |
| Flecainide acetate | 3 | 7/71 | 0/78 | 9.14 (1.94-42.9) | .005 |
| Propafenone hydrochloride | 5 | 94/720 | 23/378 | 1.69 (1.09-2.62) | .02 |
| All class IC | 9 | 103/843 | 23/466 | 1.93 (1.27-2.93) | .002 |
| Class II | | | | | |
| All: metoprolol tartrate | 1 | 20/197 | 6/197 | 3.16 (1.43-6.99) | .005 |
| Class III | | | | | |
| Amiodarone | 3 | 20/161 | 1/113 | 5.55 (2.24-13.7) | <.001 |
| Dofetilide | 1 | 9/182 | 2/68 | 1.61 (0.41-6.23) | .49 |
| Sotalol hydrochloride: PAFAC, SOPAT* | 2 | 149/647 | 77/339 | 0.95 (0.68-1.33) | .77 |
| Sotalol: rest of studies | 6 | 44/483 | 7/344 | 3.02 (1.65-5.53) | <.001 |
| Sotalol: all studies | 8 | 193/1130 | 84/683 | 1.47 (0.84-2.06)† | .14 |
| Azimilide dihydrochloride + dronedarone | 2 | 68/1042 | 11/537 | 2.46 (1.51-4.01) | <.001 |
| All class III | 14 | 290/2515 | 98/1401 | 1.63 (1.29-2.07) | <.001 |

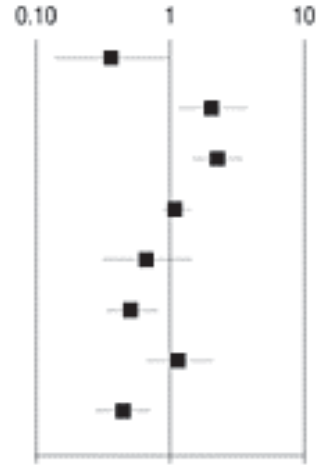



Lafuente-Lafuente, C. et al. Arch Intern Med 2006;166:719-728.

# Arrêt pour effets secondaires - 2

**Comparing 2 Antiarrhythmics**

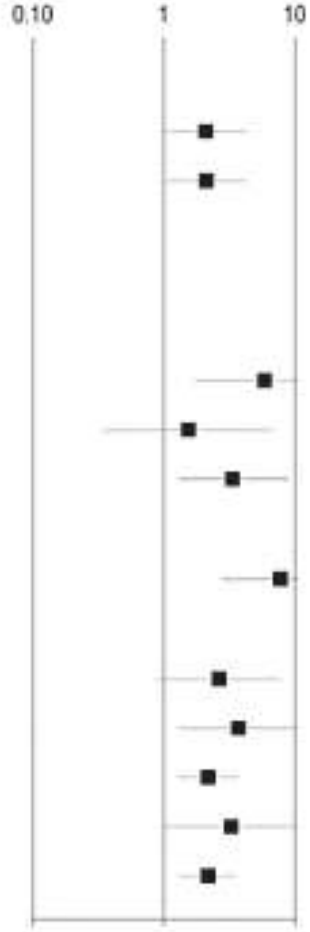
| | | Drug A | Drug B | | |
|---|---|---|---|---|---|
| Disopyramide vs other class I drugs | 2 | 6/60 | 12/53 | 0.37 (0.14-1.03) | .06 |
| Quinidine vs flecainide | 2 | 37/132 | 22/137 | 2.04 (1.14-3.64) | **.02** |
| Other class I drugs | 4 | 64/258 | 34/268 | 2.25 (1.45-3.51) | **<.001** |
| Sotalol | 6 | 230/1109 | 171/869 | 1.12 (0.89-1.40) | .34 |
| Flecainide vs propafenone | 2 | 12/145 | 18/152 | 0.68 (0.32-1.43) | .31 |
| Amiodarone vs class I drugs | 4 | 41/298 | 60/262 | 0.52 (0.34-0.81) | **.004** |
| Sotalol | 2 | 31/219 | 24/196 | 1.18 (0.67-2.07) | .58 |
| Sotalol vs class I except quinidine | 4 | 32/290 | 56/277 | 0.45 (0.28-0.72) | **.002** |




Lafuente-Lafuente, C. et al. Arch Intern Med 2006;166:719-728.

# Effets pro-arythmiques : tachy- ou brady- (1)

| Drugs Studied | No. of Studies | Total No. of Events: Antiarrhythmic | Total No. of Events: Control | Peto OR (95% CI) | P Value |
|---|---|---|---|---|---|
| | | Antiarrhythmic vs Control | | | |
| Class IA | | | | | |
| Disopyramide phosphate | 2 | 0/75 | 0/71 | Not Estimable | NA |
| Quinidine sulfate | 7 | 33/1128 | 6/548 | 2.10 (1.02-4.33) | .04 |
| All class IA | 8 | 33/1203 | 6/594 | 2.06 (1.00-4.26) | .05 |
| Class IB | | | | | |
| All: aprindine hydrochloride | 1 | 0/47 | 0/47 | Not Estimable | NA |
| Class IC | | | | | |
| Flecainide acetate | 3 | 9/71 | 1/78 | 5.97 (1.67-21.3) | .006 |
| Propafenone hydrochloride | 5 | 6/720 | 2/378 | 1.52 (0.33-7.02) | .59 |
| All class IC | 9 | 15/843 | 3/466 | 3.41 (1.28-9.09) | .01 |
| Class II | | | | | |
| All: metoprolol tartrate | 1 | 15/197 | 0/197 | 7.96 (2.84-22.3) | <.001 |
| Class III | | | | | |
| Amiodarone | 4 | 12/428 | 2/245 | 2.65 (0.88-8.00) | .08 |
| Dofetilide | 2 | 16/431 | 1/325 | 3.77 (1.31-10.8) | .01 |
| Sotalol hydrochloride | 9 | 60/1391 | 13/815 | 2.20 (1.31-3.69) | .003 |
| Azimilide dihydrochloride + dronedarone | 2 | 11/1042 | 1/537 | 3.30 (1.01-10.8) | .05 |
| All class III | 16 | 99/3292 | 17/1922 | 2.20 (1.31-3.69) | <.001 |

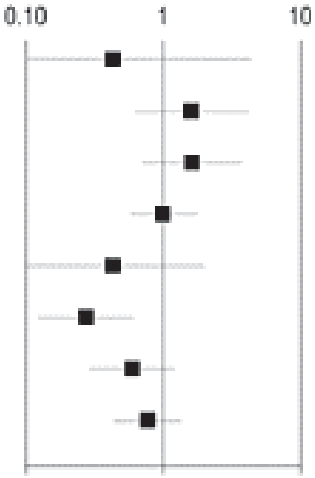



Lafuente-Lafuente, C. et al. Arch Intern Med 2006;166:719-728.

# Effets pro-arythmiques : tachy- ou brady- (2)

**Comparing 2 Antiarrhythmics**

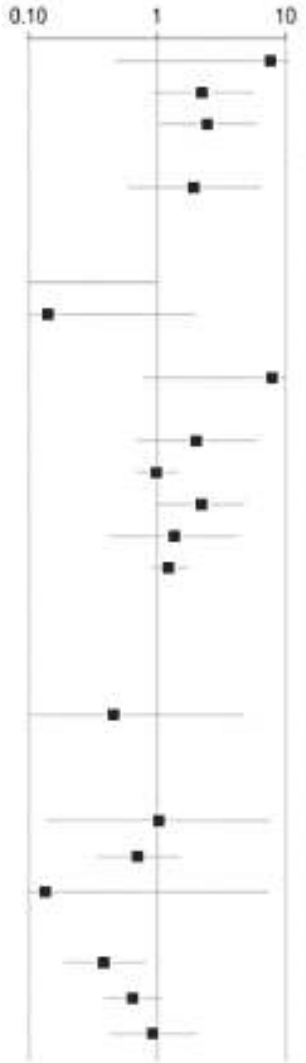
| | | Drug A | Drug B | | |
|---|---|---|---|---|---|
| Disopyramide vs other class I drugs | 2 | 1/60 | 2/53 | 0.43 (0.04-4.25) | .47 |
| Quinidine vs flecainide | 2 | 12/132 | 8/137 | 1.60 (0.64-3.96) | .31 |
| Other class I drugs | 4 | 15/258 | 10/268 | 1.59 (0.71-3.56) | .26 |
| Sotalol | 6 | 32/1109 | 29/869 | 1.00 (0.60-1.68) | >.99 |
| Flecainide vs propafenone | 2 | 2/145 | 5/152 | 0.43 (0.10-1.93) | .27 |
| Amiodarone vs class I drugs | 3 | 8/264 | 23/221 | 0.28 (0.13-0.59) | <.001 |
| Sotalol | 3 | 13/486 | 20/457 | 0.60 (0.30-1.20) | .15 |
| Sotalol vs class I except quinidine | 4 | 26/290 | 31/277 | 0.77 (0.44-1.34) | .35 |




**Lafuente-Lafuente, C. et al. Arch Intern Med 2006;166:719-728.**

# mortalité

| Drugs Studied | No. of Studies | No. of Events/Total: Antiarrhythmic | No. of Events/Total: Control | Peto OR (95% CI) | *P* Value |
|---|---|---|---|---|---|
| **Antiarrhythmic vs Control** | | | | | |
| Class IA | | | | | |
| Disopyramide phosphate | 2 | 2/75 | 0/71 | 7.56 (0.47-1.22) | .16 |
| Quinidine sulfate | 7 | 21/1128 | 4/548 | 2.26 (0.93-5.45) | .07 |
| All class IA | 8 | 23/1203 | 4/594 | **2.39 (1.03-5.59)** | **.04** |
| Class IB | | | | | |
| All: aprindine hydrochloride, bidisomide | 2 | 9/781 | 3/540 | 1.89 (0.59-6.03) | .28 |
| Class IC | | | | | |
| Flecainide acetate | 3 | 0/71 | 0/78 | Not Estimable | NA |
| Propafenone hydrochloride | 5 | 0/720 | 2/378 | 0.05 (0.00-1.02) | .05 |
| All class IC | 9 | 1/843 | 2/466 | 0.14 (0.00-1.88) | .14 |
| Class II | | | | | |
| All: metoprolol tartrate | 1 | 3/197 | 0/197 | 7.47 (0.77-72.20) | .08 |
| Class III | | | | | |
| Amiodarone | 4 | 13/428 | 3/245 | 1.96 (0.68-5.67) | .21 |
| Dofetilide | 2 | 83/431 | 83/325 | 0.97 (0.67-1.40) | .88 |
| Sotalol hydrochloride | 9 | 30/1391 | 5/815 | 2.09 (0.97-4.49) | .06 |
| Azimilide dihydrochloride + dronedarone | 2 | 10/1042 | 4/537 | 1.31 (0.43-3.97) | .63 |
| All class III | 16 | 136/3292 | 95/1922 | 1.19 (0.88-1.61) | .27 |
| **Comparing 2 Antiarrhythmics** | | **Drug A** | **Drug B** | | |
| Disopyramide vs other class I drugs | 2 | 1/60 | 2/53 | 0.46 (0.05-4.52) | .51 |
| Quinidine vs | | | | | |
| Flecainide | 2 | 0/132 | 0/137 | Not Estimable | NA |
| Other class I drugs | 4 | 2/258 | 2/268 | 1.04 (0.14-7.46) | .97 |
| Sotalol | 6 | 13/1109 | 17/869 | 0.71 (0.34-1.46) | .35 |
| Flecainide vs propafenone | 2 | 0/145 | 1/152 | 0.14 (0.00-6.96) | .32 |
| Amiodarone vs | | | | | |
| Class I drugs | 4 | 10/241 | 26/257 | **0.39 (0.19-0.79)** | **.009** |
| Sotalol | 3 | 28/463 | 39/447 | 0.66 (0.40-1.10) | .11 |
| Sotalol vs class I except quinidine | 4 | 15/243 | 17/251 | 0.94 (0.44-1.99) | .87 |



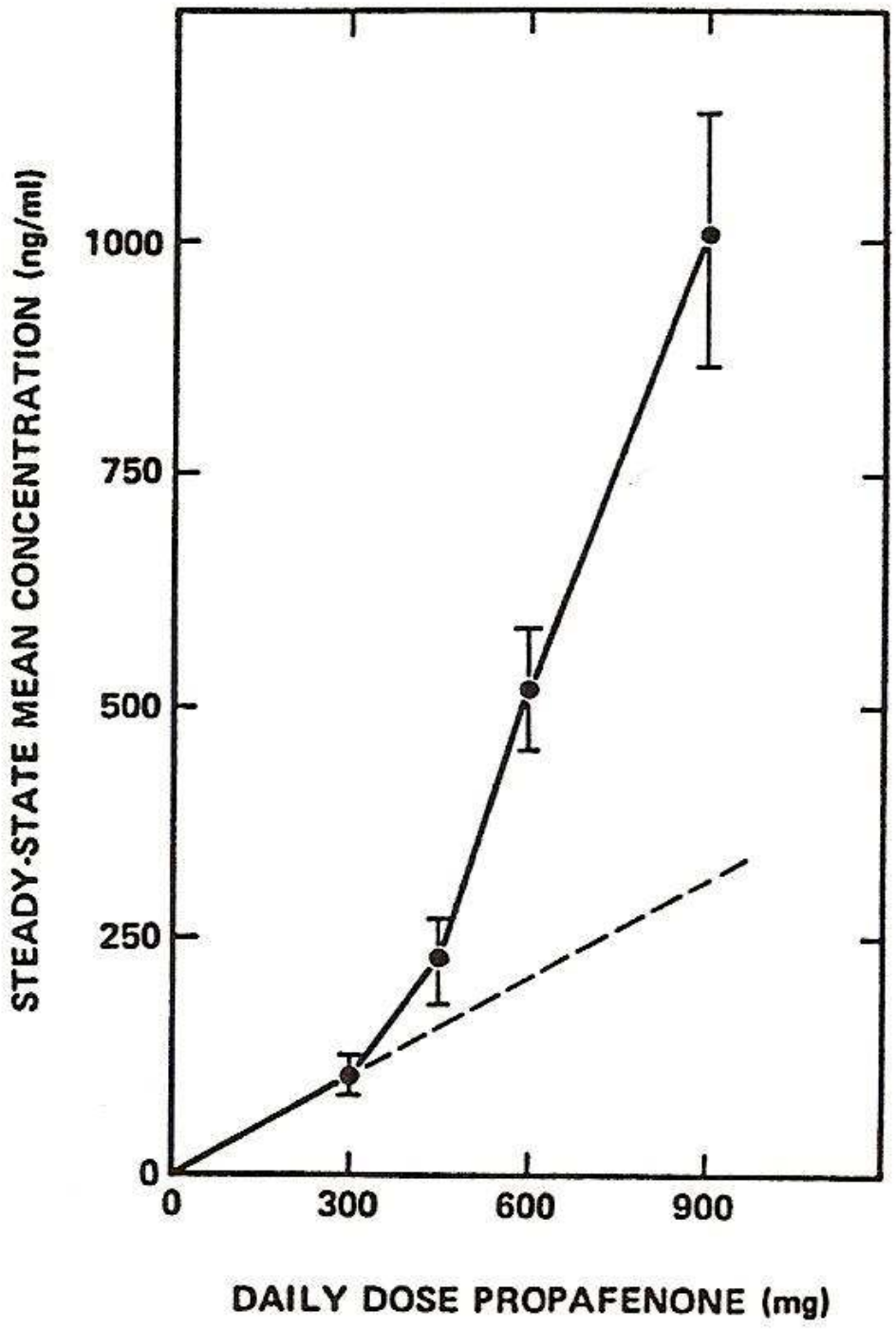
# 4 - AA et pharmacocinétique

## Clinical Pharmacology of Flecainide

| | |
|---|---|
| Dose | Oral 50–150 mg t.i.d. |
| Absorption | Rapid, complete |
| Bioavailability | 95% |
| Peak levels | 3–4 hours |
| Protein binding | 40% |
| Volume of distribution | 10 liters/kg |
| Half-life | 20 hr (11–30) |
| Therapeutic blood levels | 0.2–1.0 μg/mL |
| Metabolism | Hepatic (70%) |
| Metabolites | meta-O-Dealkylated flecainide |
| | Meta-O-Dealkylated lactam flecainide |
| | Probably inactive |

## Clinical Pharmacology of Propafenone

| | |
|---|---|
| Dose | Oral, 150–300 mg t.i.d. |
| Absorption | Rapid, complete |
| Bioavailability | Dose-related 13–55%; (first-pass hepatic clearance) |
| Peak levels | 2–5 hr |
| Protein binding | 90–95% |
| Volume of distribution | 3.0 liter/kg (200–300 liters) |
| Half-life | 6 hr (3–12 hr) in extensive metabolizers; 17 hr (10–32 hr) in poor metabolizers |
| Therapeutic blood levels | Variable |
| Metabolism | Hepatic (99%) (rapid in extensive metabolizers, 90% of patients) |
| Metabolites | 5-Hydroxypropafenone<br>*N*-Depropylpropafenone |


STEADY-STATE MEAN CONCENTRATION (ng/ml)
1000
750
500
250
0
0
300
600
900
DAILY DOSE PROPAFENONE (mg)

## TABLE 8-10. PHARMACOKINETIC PROPERTIES OF SOTALOL

| | |
|---|---|
| Absorption rate | $T_{max}$ 2–3 h |
| Extent of absorption | >90% of dose |
| Extent of bioavailability | ~100% of dose |
| Binding to plasma protein | 0% |
| Approximate volume of distribution | 1.6–2.4 L/kg |
| Elimination | |
| Renal (unchanged) | ~90% |
| Biotransformation | 0% |
| Approximate plasma half-life | 15 (7–18) h |
| Pattern of elimination kinetics | First order |
| Kinetic model applicable | Open two compartment |
| Metabolites | None detected |
| Steady state to dose ratio | Two-fold variation |
| Special features | Accumulation in renal failure, kinetics not affected by liver function |

## Clinical Pharmacology of Amiodarone

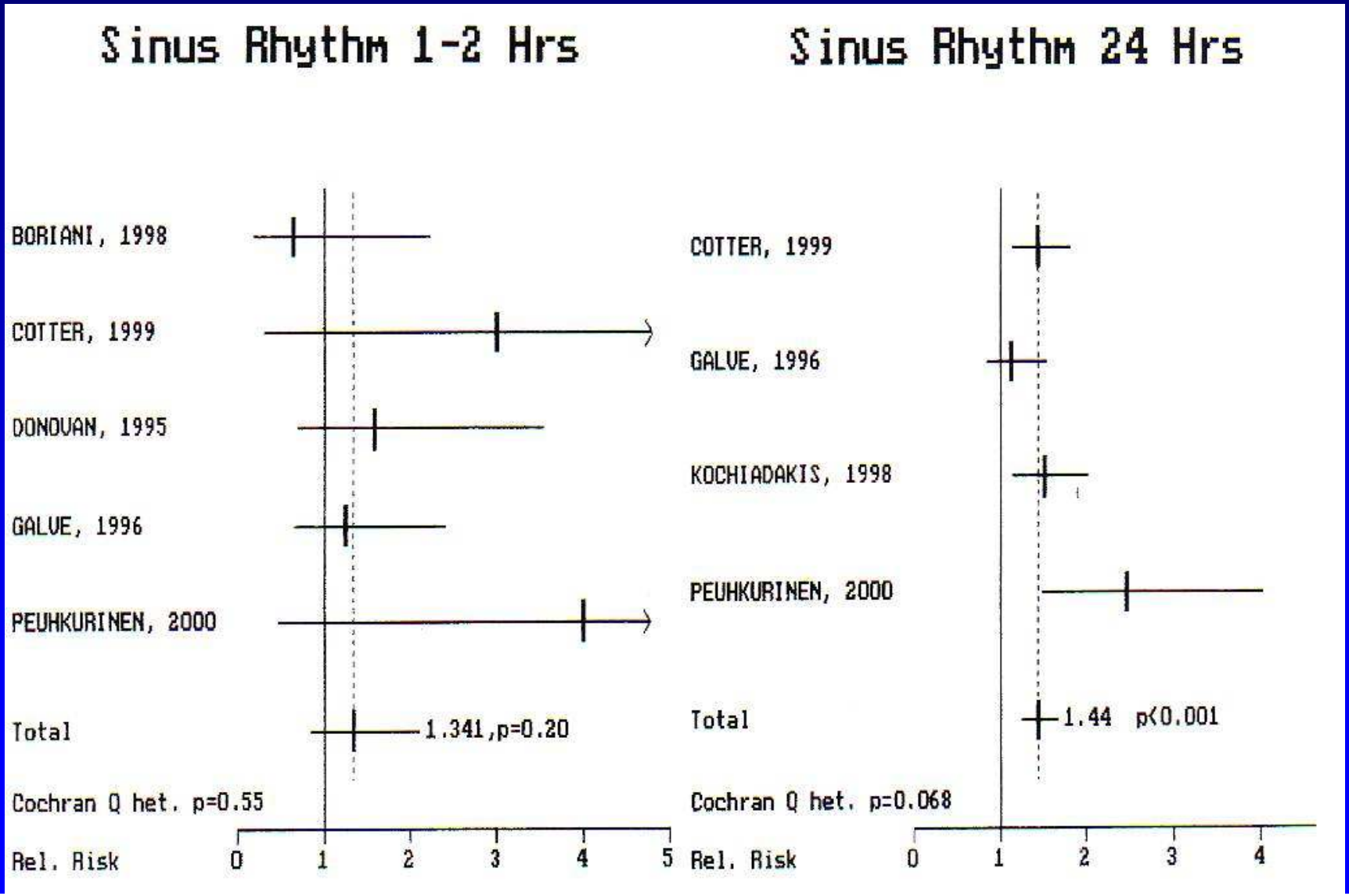
| | |
|---|---|
| Absorption rate | 2–12 hr |
| Extent of absorption | Poor and slow |
| Bioavailability | Variable (22–86%) |
| Peak plasma levels | 4–6 hr |
| Protein binding | 96% |
| Volume of distribution | |
| Acute | 1.3–65.8 L/kg |
| Steady-state | 5.0 L/kg |
| Elimination | Hepatic and intestinal |
| Elimination half-life | |
| Acute | 3–21 hr |
| Chronic | 52.6 d |
| Total body clearance | 0.10–0.77 L/min |
| Metabolites | Mono-*N*-desethylamiodarone |
| | Bis-*N*-desethylamiodarone |
| | Deiodinated metabolites |
| Therapeutic level | 1.0–2.5 μg/mL |

L’efficacité immédiate :
le succès des classes Ic
sur la cardioversion

la place de la pharmacocinétique!

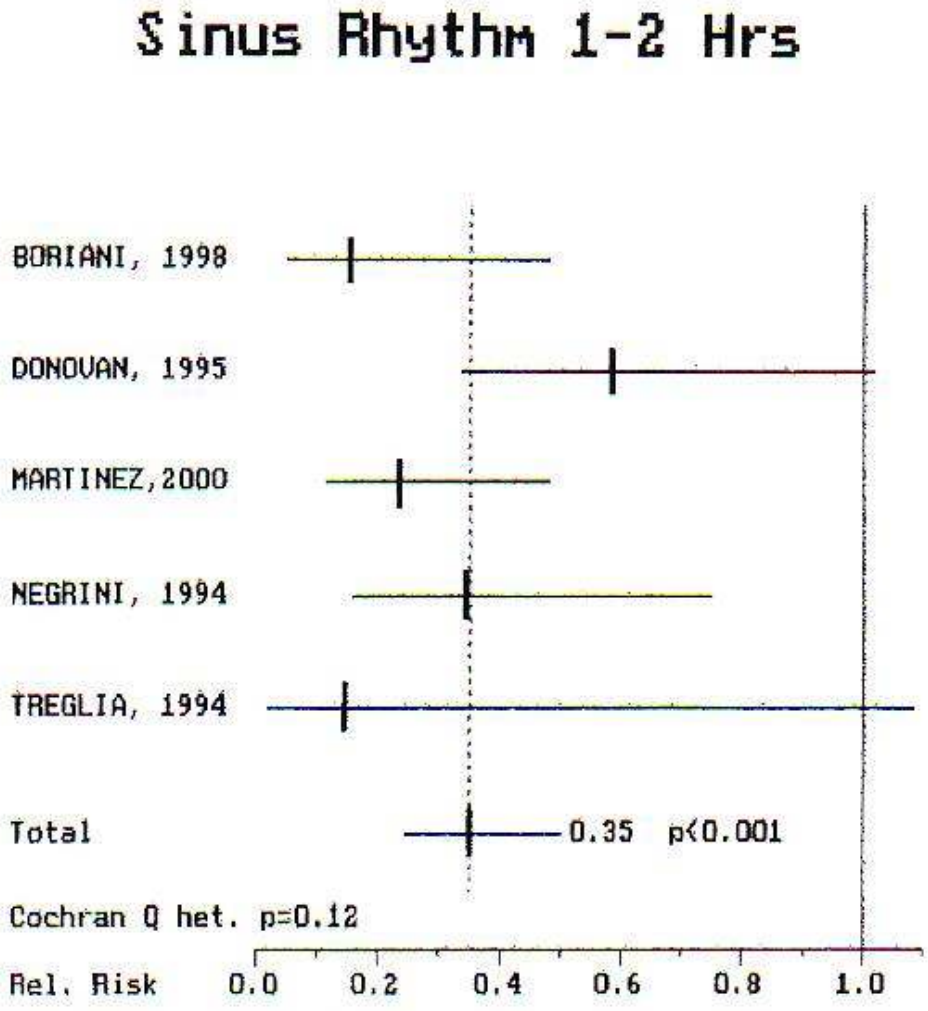
# Méta-analyse de Chevalier – 2003

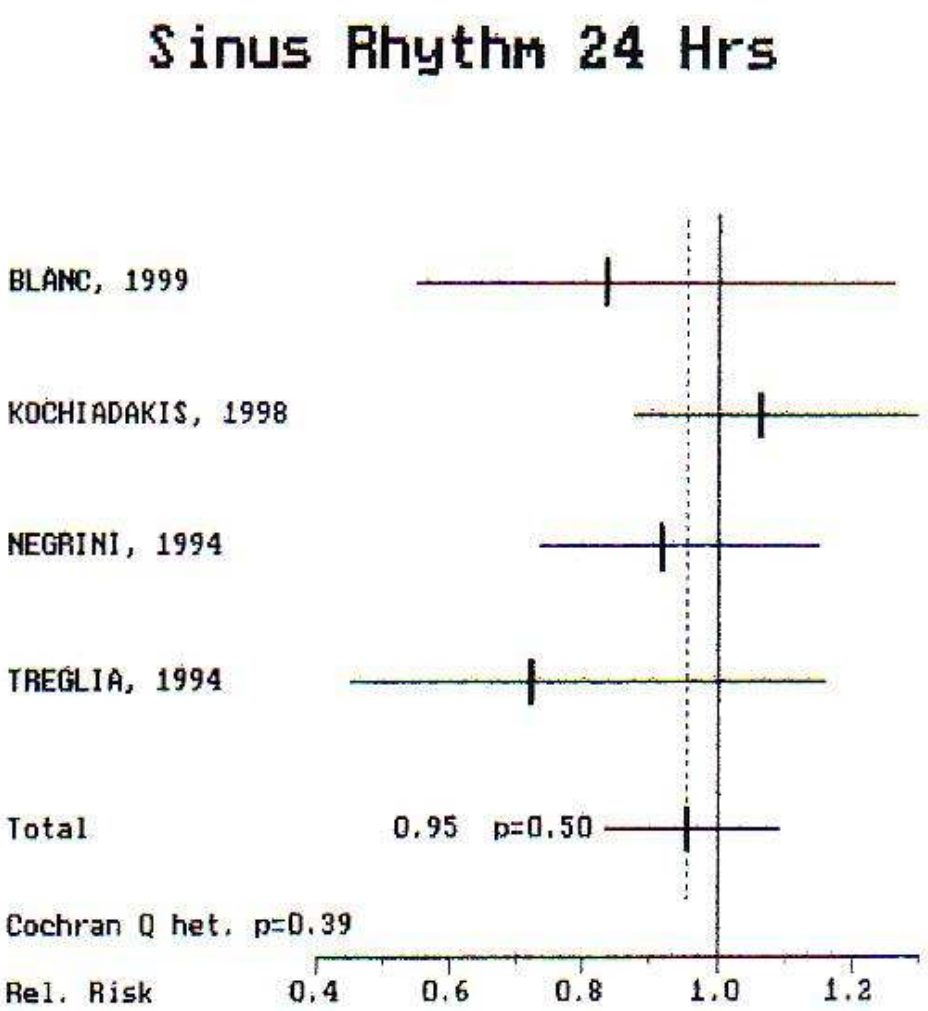
## placebo vs amiodarone : 6 études 595 patients



# Méta-analyse de Chevalier – 2003

## classe Ic vs amiodarone : 7 études 579 patients



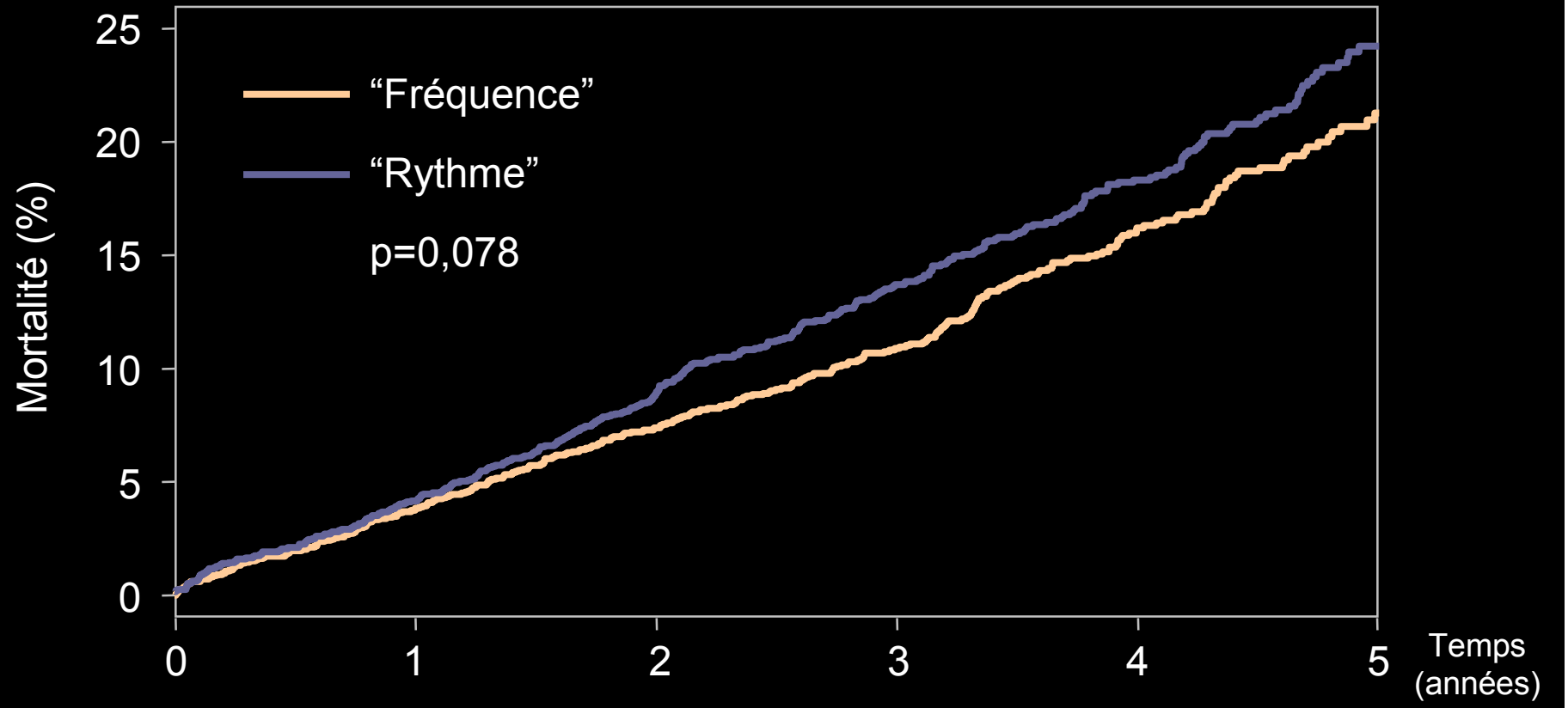
Les AA actuels :

on peut mieux faire …

# La question des années 2000 : réduire ou ralentir

5 études et une méta-analyse

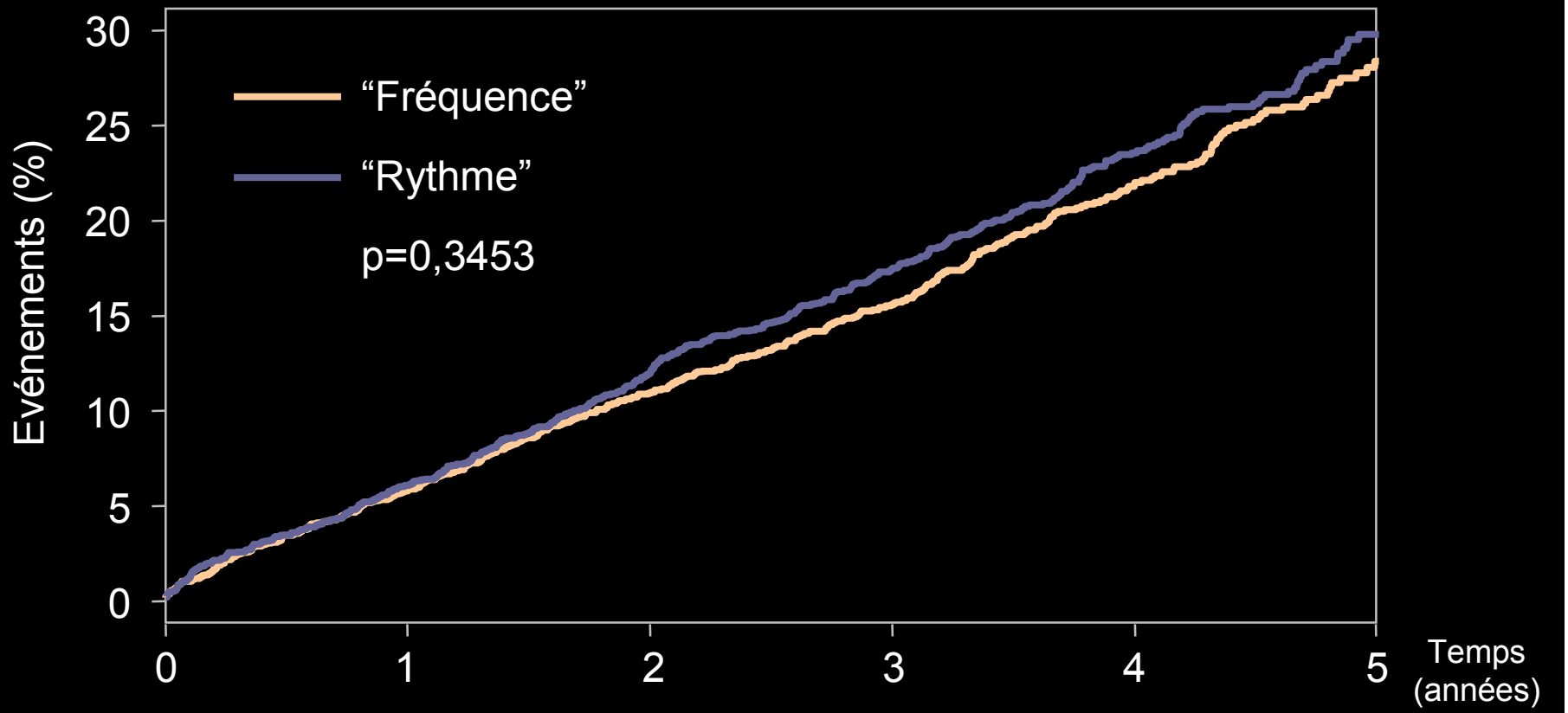
# Critère d'évaluation principal : mortalité totale (toutes étiologies confondues)




| | | | | | | |
|---|---|---|---|---|---|---|
| "Fréquence" n : | 2027,0 | 1926,78 | 1827,148 | 1329,210 | 774,275 | 236,306 |
| "Rythme" n : | 2033,0 | 1932,80 | 1807,175 | 1316,257 | 780,314 | 255,352 |

The AFFIRM investigators N Engl J Med 2002; 347(23): 1825-33.

# Critère composite 2re : décès, AVC invalidants, encéphalopathies anoxiques, saignements majeurs, arrêts cardiaques




| | | | | | | |
|---|---|---|---|---|---|---|
| "Fréquence" n : | 2027 | 1888 | 1760 | 1264 | 722 | 208 |
| "Rythme" n : | 2033 | 1895 | 1746 | 1259 | 719 | 231 |

The AFFIRM investigators N Engl J Med 2002; 347(23): 1825-33.

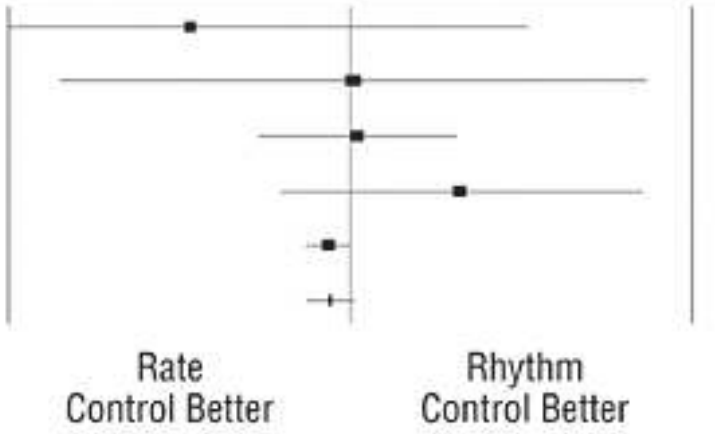
# Méta-analyse des 5 études « réduire / ralentir »

**de Denus, S. et al. Arch Intern Med 2005;165:258-262.**

| Trial | AFFIRM[5,12] | RACE[7] | STAF[6] | PIAF[4,13] | HOT CAFE[8] |
|---|---|---|---|---|---|
| No. of patients | 4060 | 522 | 200 | 252 | 205 |
| Duration of AF before randomization | NA (69.2% had AF ≥2 d for the qualifying episode) | Rate: 337 d (median)<br>Rhythm: 309 d (median) | Rate: 10.4 mo (mean)<br>Rhythm: 13.7 mo (mean) | Rate: 118 d (mean)<br>Rhythm: 103 d (mean) | Rate: 243.2 d (mean)<br>Rhythm: 220.4 d (mean) |
| Follow-up, y | 3.5 (Mean) | 2.3 (Mean) | 1.6 (Mean) | 1 | 1.7 (Mean) |
| AF population | Age ≥65 y or other risk factors for stroke or death; AF likely to be recurrent | Recurrent persistent AF or atrial flutter | Persistent AF with moderate to high risk of recurrence | Persistent, symptomatic AF | Persistent AF |
| Patient details | | | | | |
| Mean age, y | 69.7 | 68 | 65.8 | 60.5 | 60.8 |
| Female, % | 39.3 | 36.6 | 36.5 | 27 | 34.6 |
| HTN, % | 70.8 | 49 | 62.5 | 50 | 64.4 |
| HF, %* | 23.1 | 50 | 55.5 | 16.5 | 62 |
| IHD, % | 38.2 | 27 | 43.5 | 23 | 43.9 |
| Anticoagulation | Rate: required<br>Rhythm: physician discretion if sinus rhythm maintained | Rate: required, except if age <65 y and no cardiac disease<br>Rhythm: physician discretion if sinus rhythm maintained | Both groups: ACCP guidelines | All patients | Rate: ACCP guidelines<br>Rhythm: physician discretion if sinus rhythm maintained |
| AV blocking agents used in the rate control group, % | Digoxin, 70.6<br>β-Blocker, 68.1<br>Diltiazem hydrochloride, 46.1<br>Verapamil hydrochloride,16.8 | NS | β-Blocker, 45<br>Calcium channel blocker,† 22<br>Digoxin, 75 | β-Blocker, 9<br>Digoxin, 70<br>Diltiazem, 100 | β-Blocker, 89.1<br>Calcium channel blocker,† 7.9<br>Digoxin, 42.6 |
| AA agents most frequently used in the rhythm control group, % | Amiodarone hydrochloride, 62.8<br>Sotalol hydrochloride, 41.4<br>Propafenone hydrochloride, 14.5 | Sotalol as initial agent, followed by other agents if necessary | Amiodarone, 42<br>Sotalol, 22<br>Class I, 12 | Amiodarone, 100 | Amiodarone, 56.7<br>Propafenone, 36.5<br>Sotalol, 24.0 |
| Patients in sinus rhythm at end of study, % | | | | | |
| Rhythm | 3 y, 73.3; 5 y, 62.6 | 39 | 38 | 56 | 63.5 |
| Rate | 5 y, 34.6 | 10 | 9 | 10 | NS |
| Trial weight, % | | | | | |
| All-cause mortality | 91.7 | 5.5 | 1.7 | 0.7 | 0.5 |
| Ischemic strokes | 62.5 | NA | 23 | NA | 14.6 |

de Denus, S. et al. Arch Intern Med 2005;165:258-262.

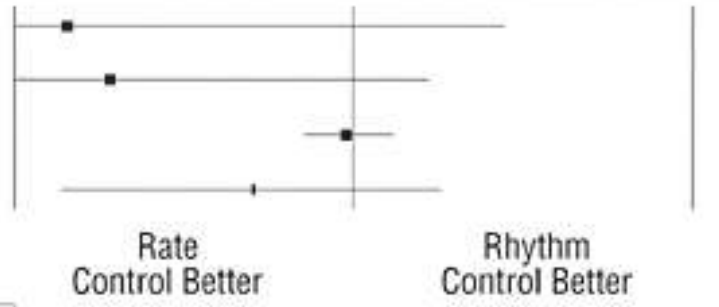
| Trial | Rate | Rhythm |
|---|---|---|
| HOT CAFE[8] | 1/101 | 3/104 |
| PIAF[4,13] | 2/125 | 2/127 |
| RACE[7] | 18/256 | 18/266 |
| STAF[6] | 8/100 | 4/100 |
| AFFIRM[5,12] | 310/2027 | 356/2033 |
| **Combined** | **339/2609** | **383/2630** |
| Percentage | 13.0 | 14.6 |




OR, 0.87 (95% CI; 0.74 - 1.02), *P* = .09

mortalité

| Trials | Rate | Rhythm |
|---|---|---|
| HOT CAFE[8] | 0/101 | 3/104 |
| STAF[6] | 1/100 | 5/100 |
| AFFIRM[5,12] | 77/2027 | 80/2033 |
| **Combined** | **78/2228** | **88/2237** |
| Percentage | 3.5 | 3.9 |




OR, 0.50 (95% CI; 0.14 - 1.83), *P* = .30

AVC AIT

# rôle du rythme sinusal ?

Analyse « sous traitement » de la mortalité

18 covariants :

- 12 paramètres de base cliniques (n= 3677 patients) ou échographiques (n= 2796 patients)
- 6 paramètres temps-dépendant : RS, AVK, digoxine, béta-, Ca-, médicaments AA
- $p < 0,01$

Affirm investigators, Circulation 2004;109:1509

**TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included**

| Covariate | *P* | HR | HR: 99% Confidence Limits Lower | Upper |
|---|---|---|---|---|
| Age at enrollment* | <0.0001 | 1.06 | 1.05 | 1.08 |
| Coronary artery disease | <0.0001 | 1.56 | 1.20 | 2.04 |
| Congestive heart failure | <0.0001 | 1.57 | 1.18 | 2.09 |
| Diabetes | <0.0001 | 1.56 | 1.17 | 2.07 |
| Stroke or transient ischemic attack | <0.0001 | 1.70 | 1.24 | 2.33 |
| Smoking | <0.0001 | 1.78 | 1.25 | 2.53 |
| Left ventricular dysfunction | 0.0065 | 1.36 | 1.02 | 1.81 |
| Mitral regurgitation | 0.0043 | 1.36 | 1.03 | 1.80 |
| Sinus rhythm | <0.0001 | 0.53 | 0.39 | 0.72 |
| Warfarin use | <0.0001 | 0.50 | 0.37 | 0.69 |
| Digoxin use | 0.0007 | 1.42 | 1.09 | 1.86 |
| Rhythm-control drug use | 0.0005 | 1.49 | 1.11 | 2.01 |

Circulation 2004;109:1509

Les études « réduire vs ralentir » :

rien ne vaut le rythme sinusal, mais sans les AA actuels …

# 2. les AA du futur

1 – d'autres bloqueurs des canaux ioniques

2 – des anti-arythmiques agissant sur d'autres échanges ioniques

3 – des traitements anti-arythmiques par des médicaments « non-anti-arythmiques »

# Les nouveaux anti-arythmiques : 3 directions

1 – d'autres bloqueurs des canaux ioniques

# De nouveaux bloqueurs des canaux ioniques

| **“Conventional” agents** | **Mechanism of action** |
|---|---|
| Azimilide | Class III (IKs _ IKr blocker) |
| Tedisamil | Class III (IKr _ Ito blocker) |
| Ersentilide | Class III (IKr blocker) _ _-blocker |
| Trecetilide | Class III (IKr _ INa blocker) |
| Almokalant, terikalant | Class III (IKr blocker) |
| SB237376 | Class III (IKr blocker) |
| ARH050642 | Class III |
| EMD60263 | Class III _ Ca sensitizer |
| HMR1402 | Class III (IKs blocker) |
| HMR1556 | Class III (IKs blocker) |
| L768673 | Class III (IKs blocker) |
| Ambasilide | Ito, IK1, IKAch, IKur, and INa blocker |
| Dronedarone (SR33589) | Class I–IV |
| E0474 | Class I _ III |

dofétilide

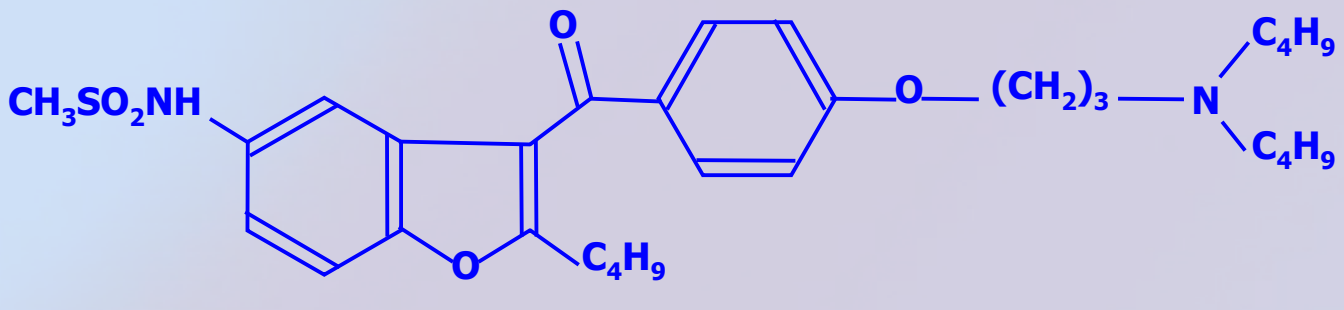
TIKOSYN

azimilide

STEDICOR

# Dronedarone: MULTAQ

- Dronedarone is a new benzofurane derivative




Dronedarone(MW=593)

# Dronedarone: Multifactorial ionic mechanism of action

- Outward currents:

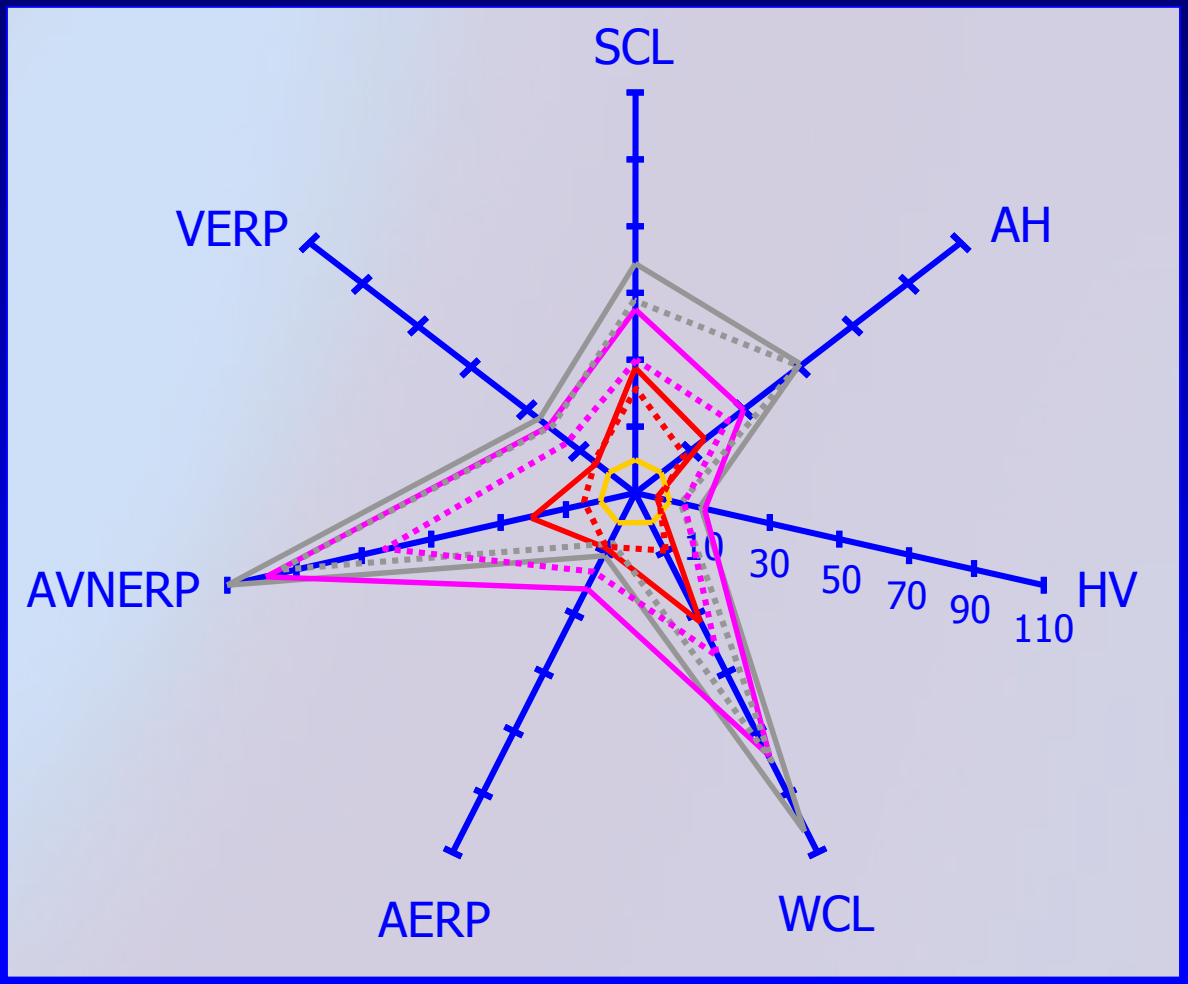
| guinea-pig ($IC_{50}$; µM)[2] | Dronedarone | Amiodarone |
|---|---|---|
| $I_{Kr}$ (ventricle) | 2-3 | 10 |
| $I_{Ks}$ (ventricle) | 10 | 30 |
| $I_{K1}$ (ventricle) | >30 | ≤30 |
| $I_{K(Ach)}$ (atrium) | 0.01 | 1 |

- Inward currents:

| | Dronedarone | Amiodarone |
|---|---|---|
| $I_{Na}$ (human; 3 µM)[1] | -97% | -41% |
| $I_{Ca(L)}$ (guinea-pig; $CI_{50}$, µM)[2] | 0.2 | 10 |

(1) Lalevée et coll. (2003) *J Cardiovasc Electrophysiol* **14**;885-890
(2) Gautier et coll. (2003) *J Cardiovasc Pharmacol* 41:191-202.

# Dronedarone: Electrophysiological effects



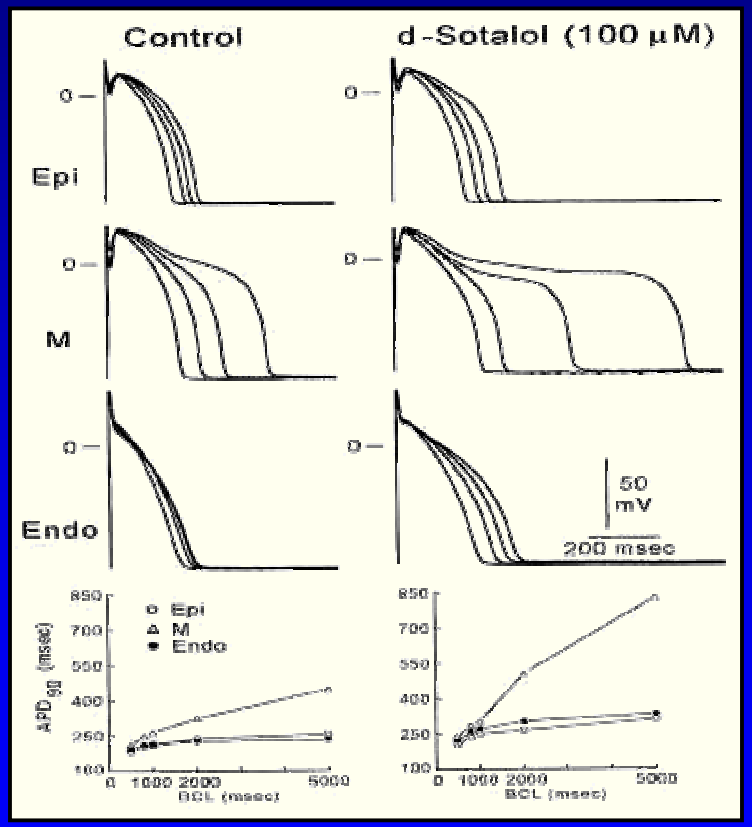

- baseline
- 1 mg/kg IV (+ 50 min)
- + 1 mg/kg IV (+ 50 min)
- 2.5 mg/kg IV (+ 50 min)
- + 2.5 mg/kg IV (+ 50 min)
- 5 mg/kg IV (+ 50 min)
- + 5 mg/kg IV (+ 50 min)

Model: Anesthetized dogs

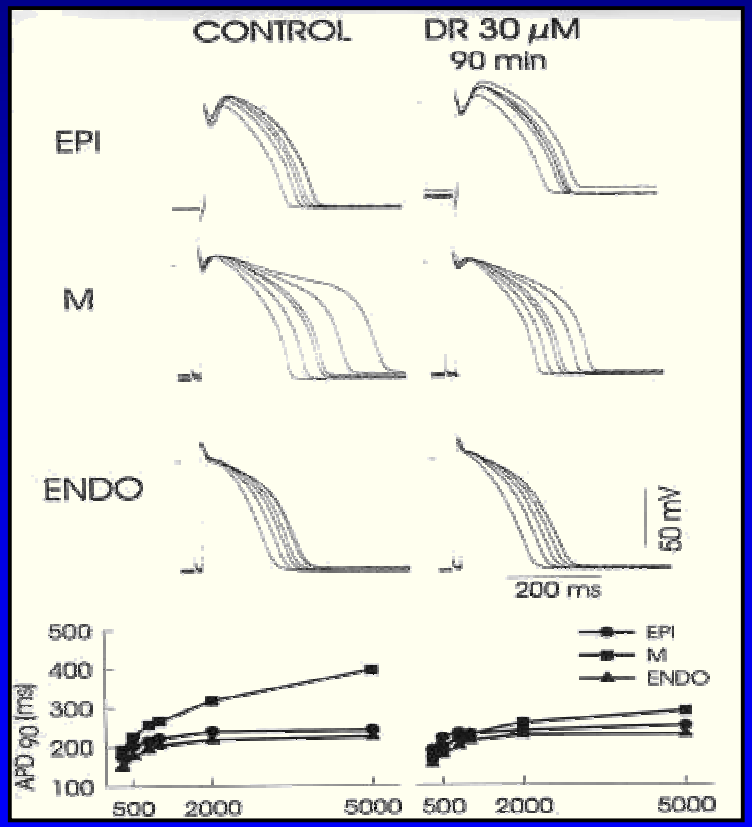
Manning A et al, J Cardiovasc Pharmacol, 1995; 25:

# Dronedarone reduces transmural dispersion of ventricular repolarization

- Effects of d-Sotalol and Dronedarone on transmural repolarization of the dog ventricle



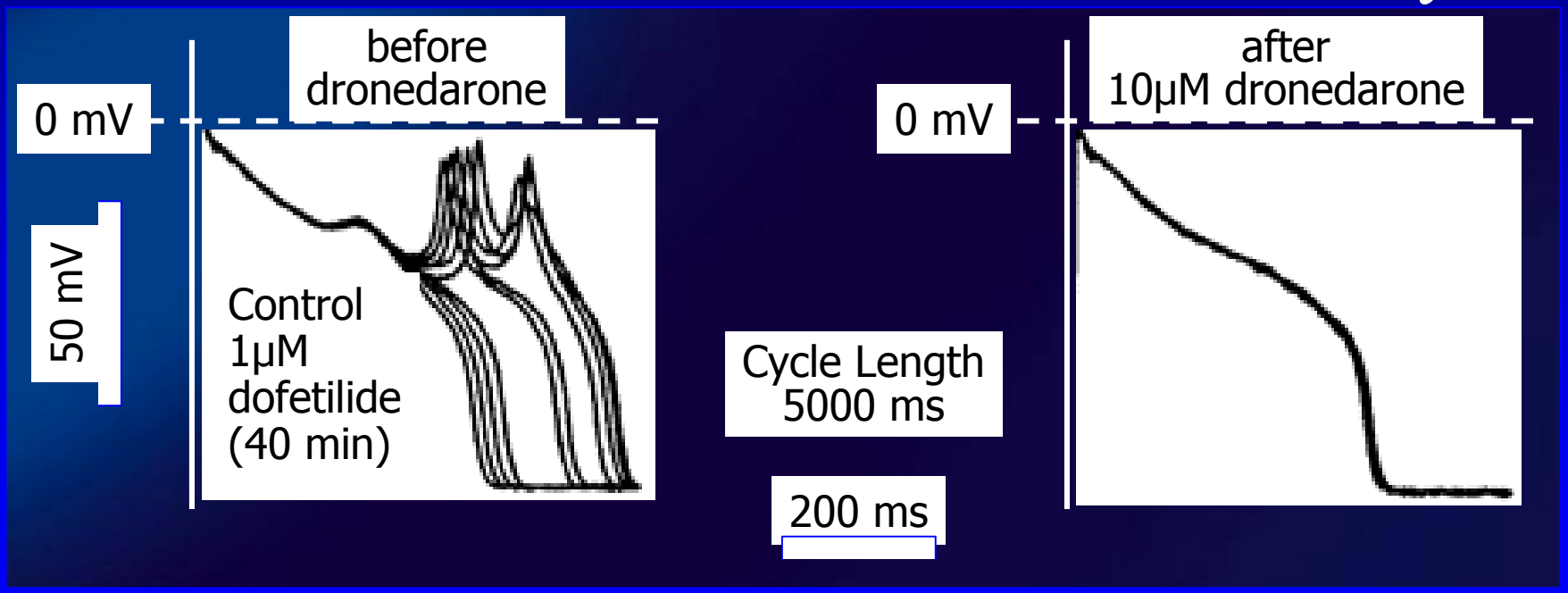

Sicouri et al. J Cardiovasc Pharmacol Ther 1997;2:27




Sicouri Fund Clin Pharmacol 1999;13:72

# Dronedarone: protects from class III drug-induced EADs

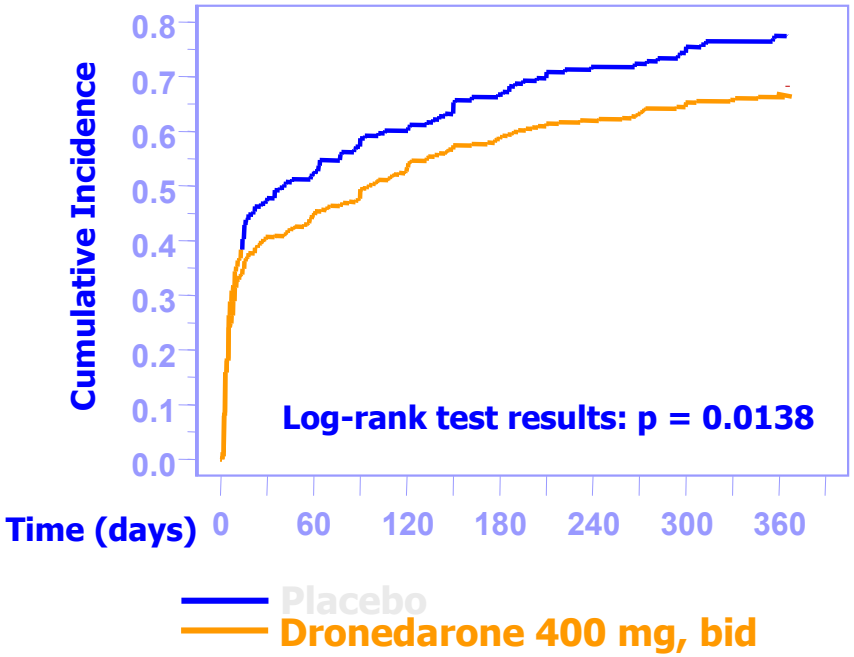
- Effect of Dronedarone on EADs induced by



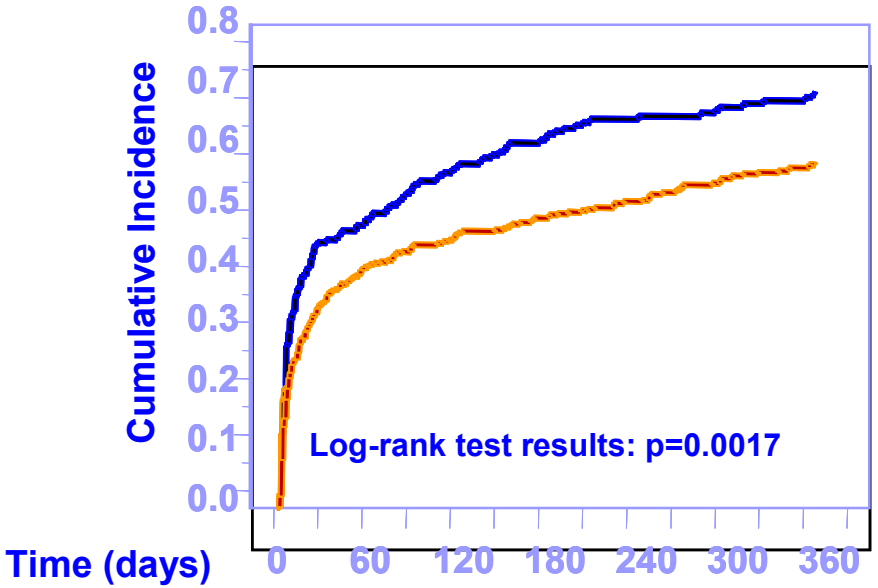

Varro A, et al. Brit J Pharmacol 2001;133:625

# Études « pivot » : EURIDIS et ADONIS
# Objectif primaire : première récidive de FA-flutter

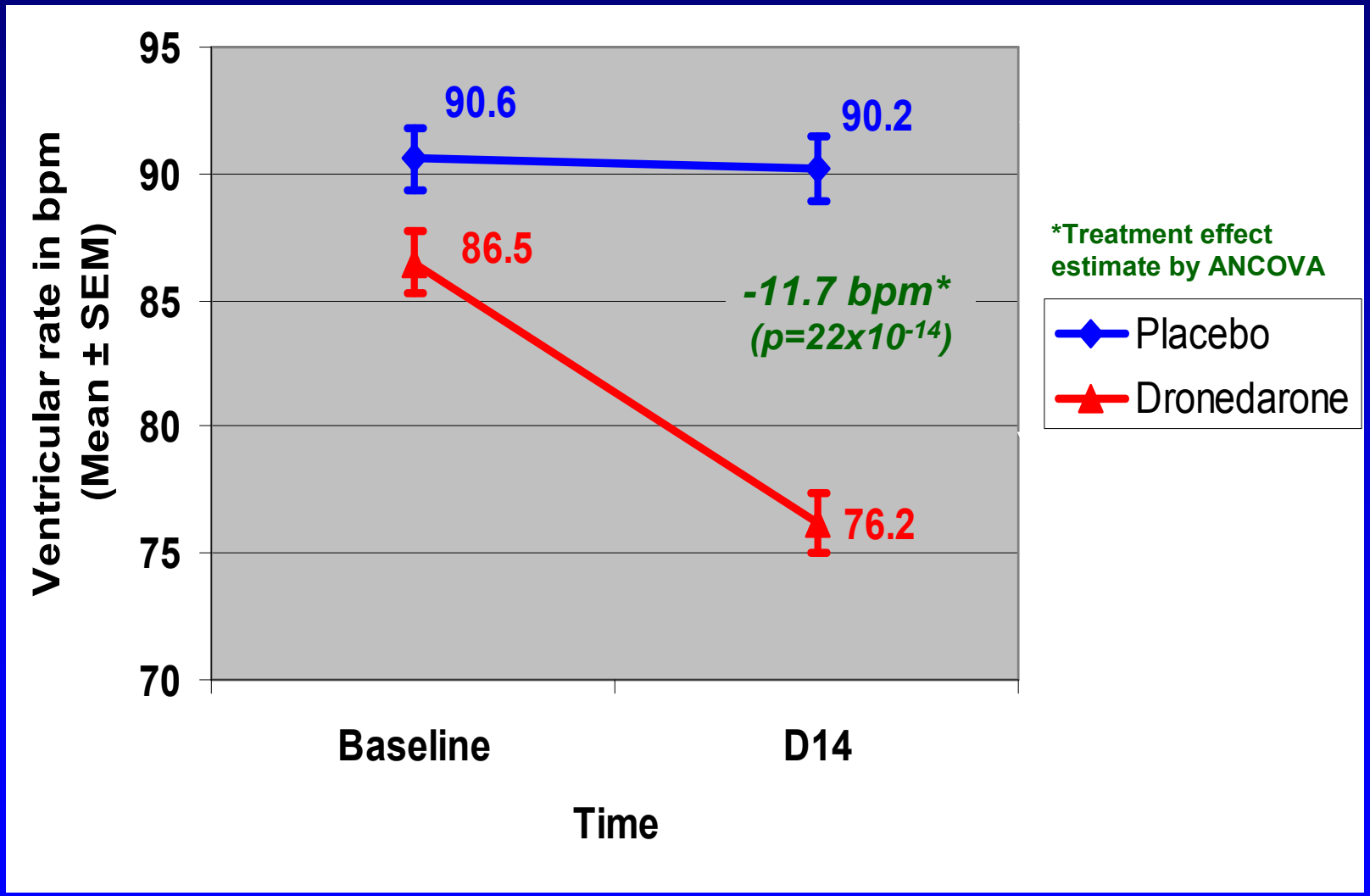
| **EURIDIS** | Placebo (N=201) | Dronedarone 800mg (N=411) |
|---|---|---|
| pts with a recurrence | 155 | 272 |
| Median Time in days | 41 | 96 |
| RR (95% CI) | 0.784 ([0.644;0.955]) | |



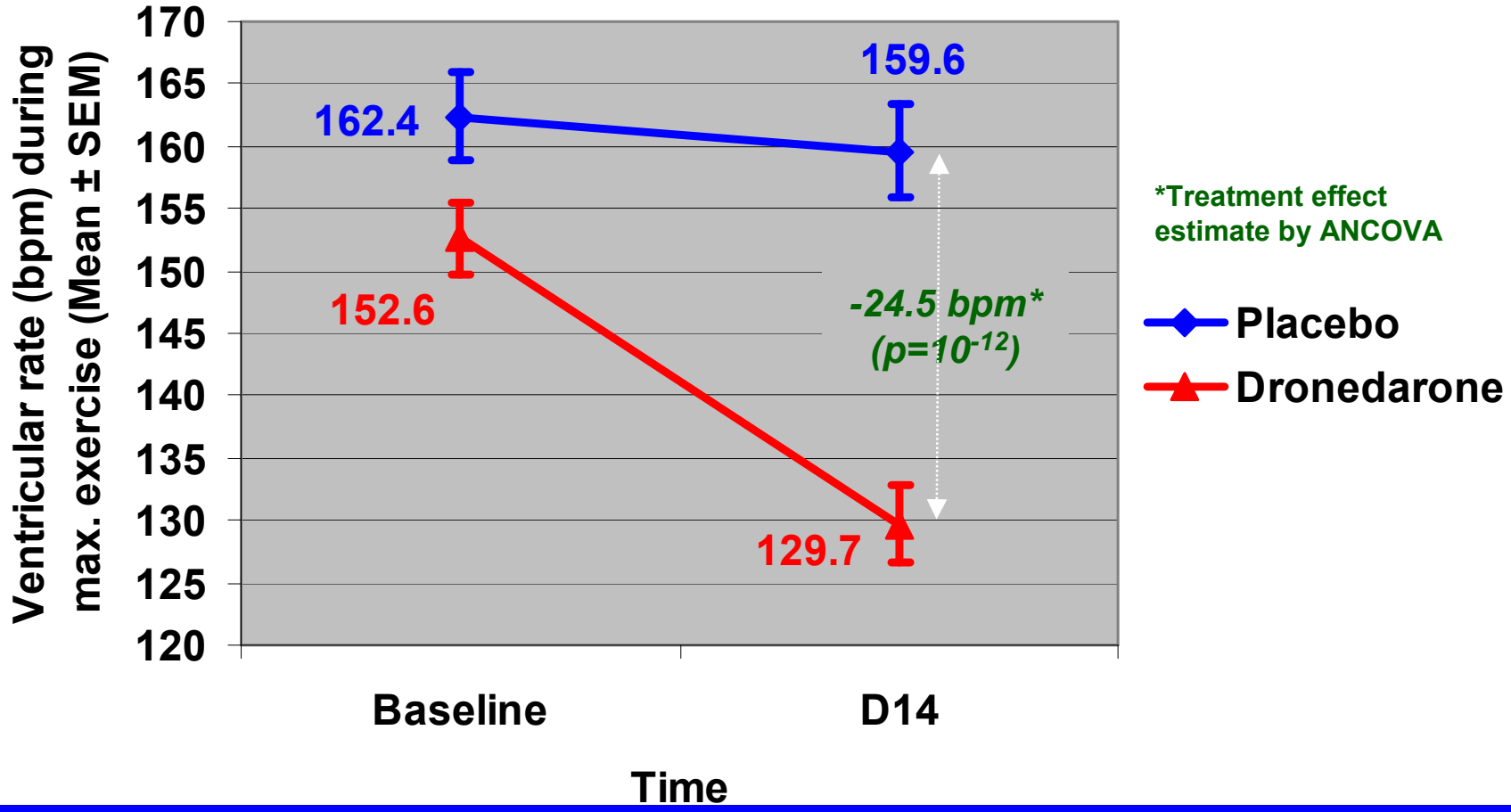

| **ADONIS** | Placebo (N=208) | Dronedarone 800 mg (N=417) |
|---|---|---|
| pts with a recurrence | 146 | 246 |
| Median time in days | 59 | 158 |
| RR (95% CI) | 0.725 ([0.590;0.890]) | |



# Étude ERATO : fréquence ventriculaire en FA permanente – Holter de 24h
# n = 165 patients



# Étude ERATO : fréquence ventriculaire en FA permanente – ECG d'effort



# Les nouveaux anti-arythmiques : 3 directions

2 – des anti-arythmiques agissant sur d'autres échanges ioniques

# anti-arythmiques agissant sur d'autres échanges ioniques

- Modulateurs des connexines
- Inhibiteurs de l'échangeur Na+/H+
- Agoniste de l'adénosine
- Inhibiteur de l'échangeur Na+/Ca+
- Antagonistes des récepteurs 5 HT4
- Bloqueurs des canaux activés par l'étirement : « SAC »

# « nouveaux » anti-arythmiques – Camm, 2005

| Novel agents | Mechanism of action |
|---|---|
| RSD1235, AZD7009, AVE1231 | Atrial repolarization delaying action |
| NIP142 | Class III (IKur and IK,Ach blocker) |
| CP060S | Class IV (Na_/Ca2_ exchange) |
| Tecadenoson | Selective adenosine A1-blocker |
| DTI0009 | Selective adenosine A1-blocker |
| GsMtx4 | Stretch receptor antagonist |
| Abanoquil (UK-52046) | _1A-antagonist |
| Cariporide | Na_/H_ exchange inhibitor |
| E3174 | Angiotensin II antagonist |
| KB-R7943 | Na_/Ca2_ exchange inhibitor |
| AAP10, ZP123 | Connexin modulator |
| KB130015 | Thyroid antagonist |
| Piboserod | 5-HT4 receptor inhibitor |
| ZP123, | AAP10 Connexin modulator |

# Les nouveaux anti-arythmiques : 3 directions

3 – des traitements anti-arythmiques par des médicaments « non-anti-arythmiques »

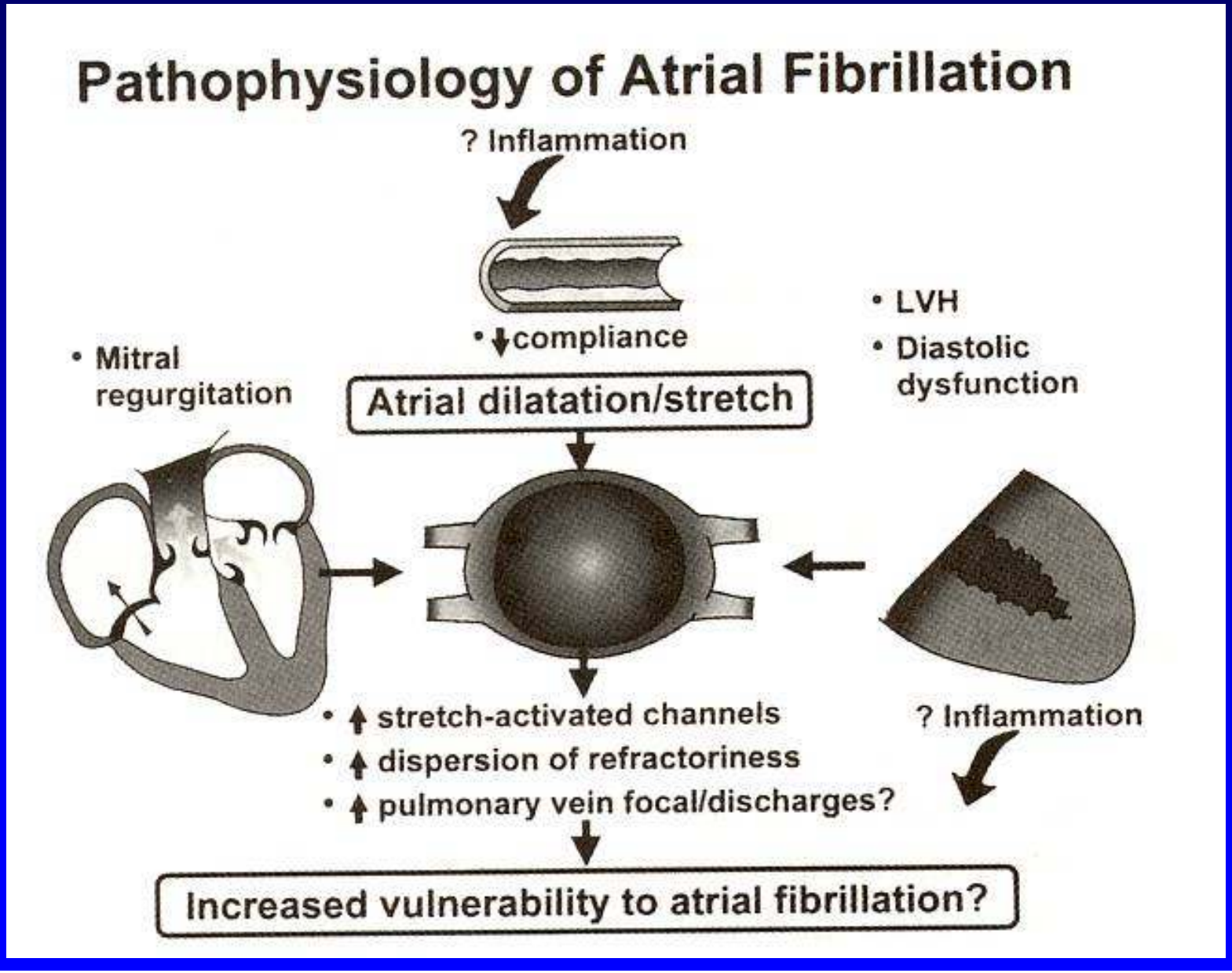
# traitements anti-arythmiques par des médicaments « non-anti-arythmiques »

- Sartans et IEC
- Anti-aldostérones
- Statines
- Corticostéroides
- Oméga-3

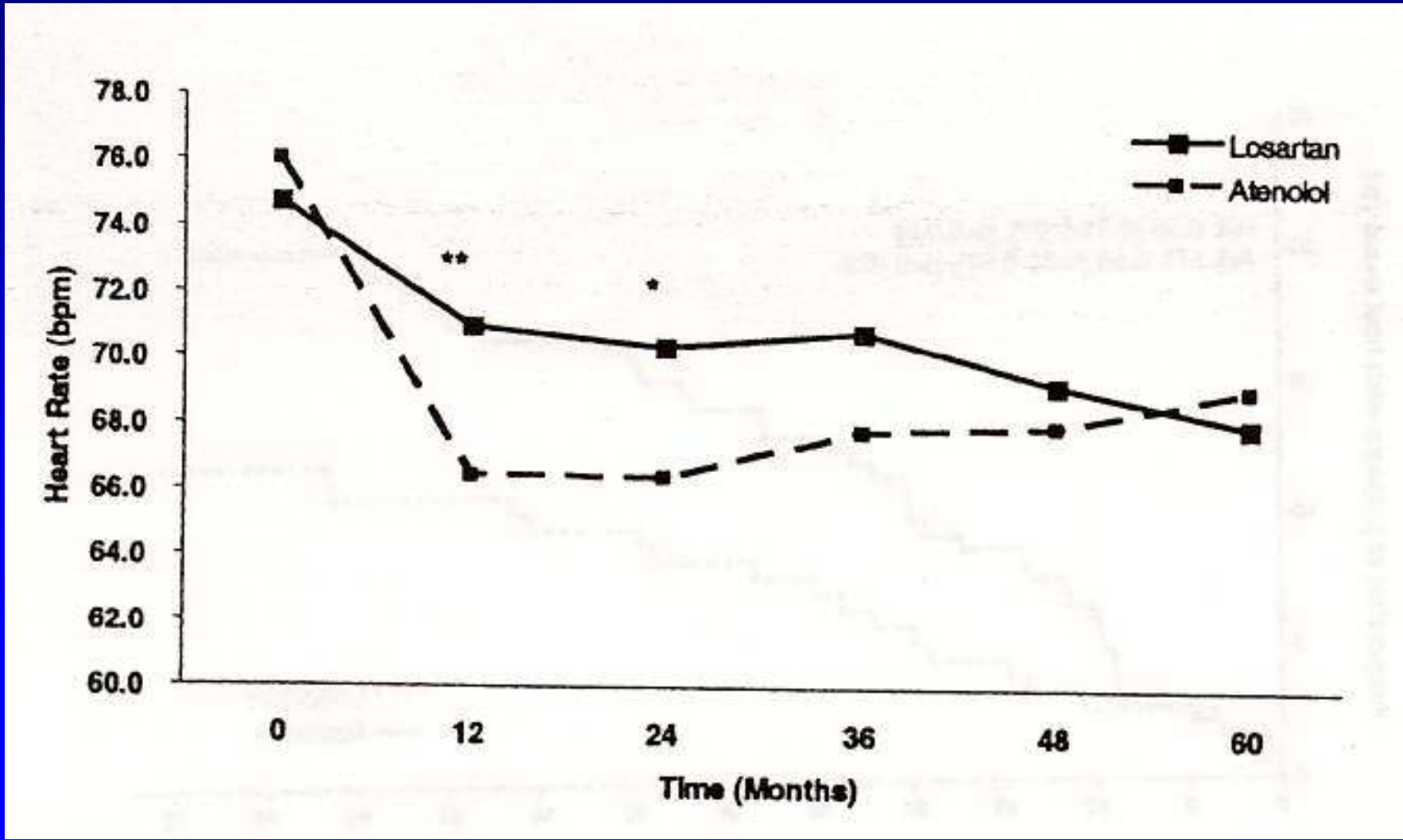
# TT AA par des médicaments « non-anti-arythmiques »

| Medicaments | Cibles possibles | Données actuelles |
|---|---|---|
| IEC et sartans | Hypertension<br>Insuffisance cardiaque<br>Effets directs : fibrose, AA | Données expérimentales<br>Etudes rétrospectives<br>Etudes prospectives limitées<br>Méta-analyse<br>Une étude en cours : ACTIVE |
| Anti-aldostérones | Hypertension<br>Insuffisance cardiaque<br>Effets directs : fibrose, AA | Données cliniques : reduction de la mort subite<br>Observations cliniques : CEE et aldostéronémie |
| Statines | Insuffisance coronaire<br>Maladie athéromateuse<br>Effets directs : anti-inflammatoires, anti-oxydants | Données expérimentales<br>Etudes cliniques rétrospectives<br>Etudes de registres |
| Corticostéroïdes | Effets anti-inflammatoires | Données expérimentales<br>Etudes prospectives limitées |
| Oméga-3 et huiles de poisson | Effets hypolipémiants<br>Effets anti-arythmiques directs | Données expérimentales<br>Données cliniques : TV et FV<br>Etudes discordantes |

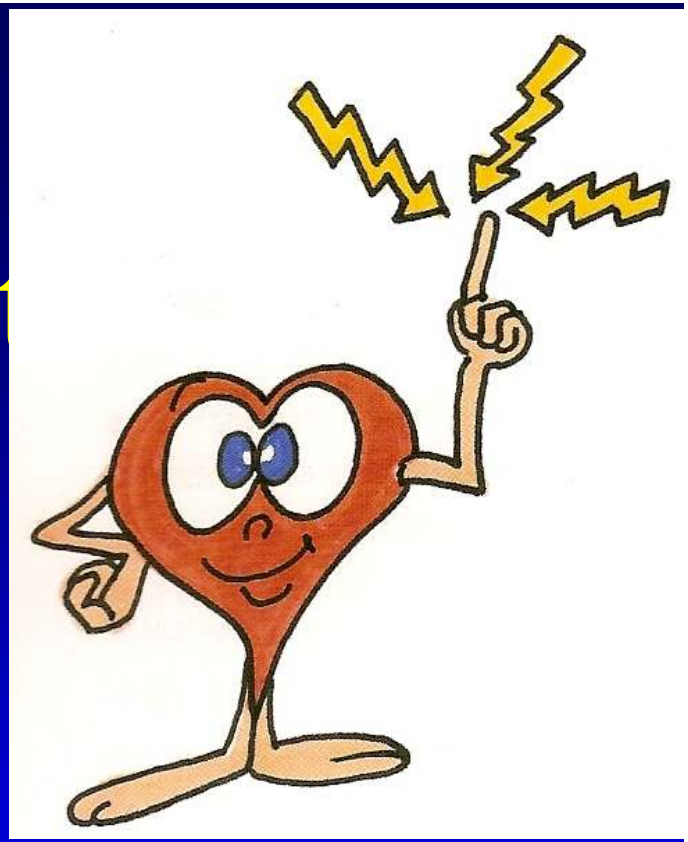
# Gersh, 2005

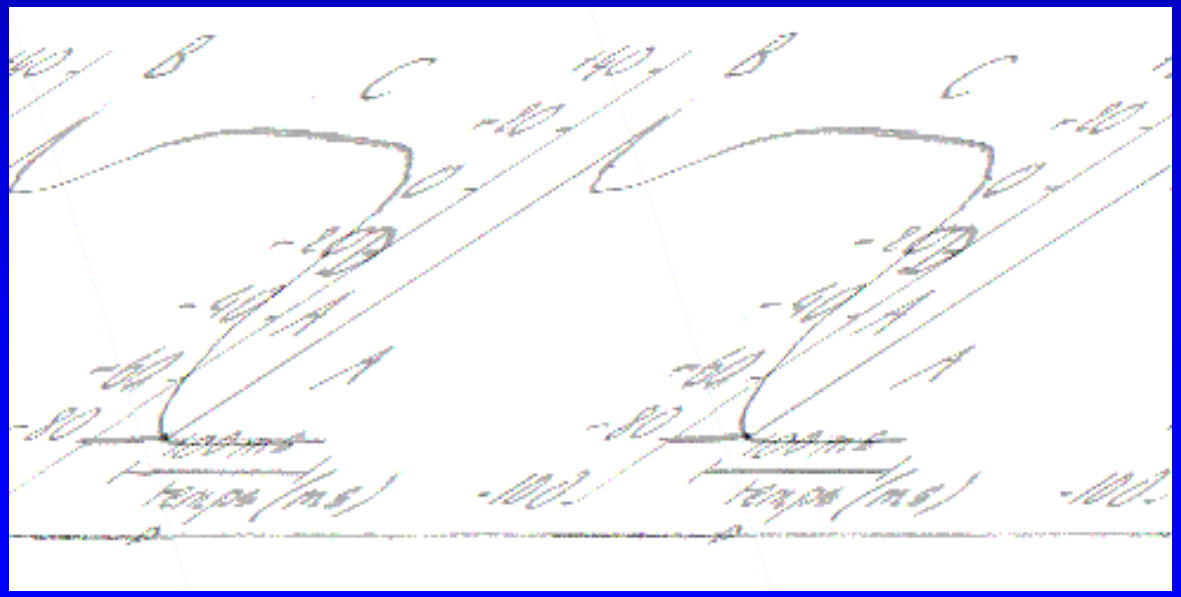

Pathophysiology of Atrial Fibrillation
? Inflammation
• ↓compliance
• Mitral regurgitation
Atrial dilatation/stretch
• LVH
• Diastolic dysfunction
• ↑ stretch-activated channels
• ↑ dispersion of refractoriness
• ↑ pulmonary vein focal/discharges?
? Inflammation
Increased vulnerability to atrial fibrillation?

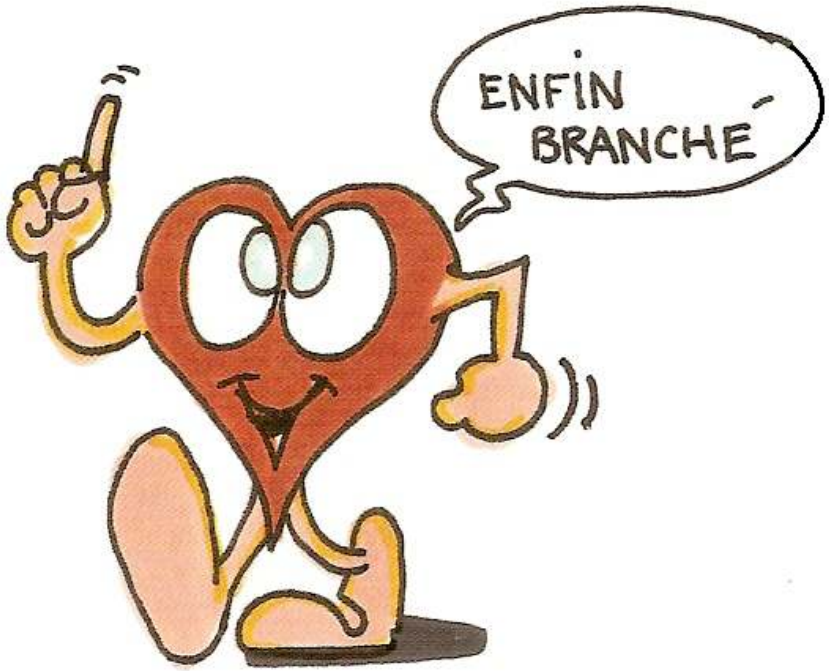
# Wachtell , 2005



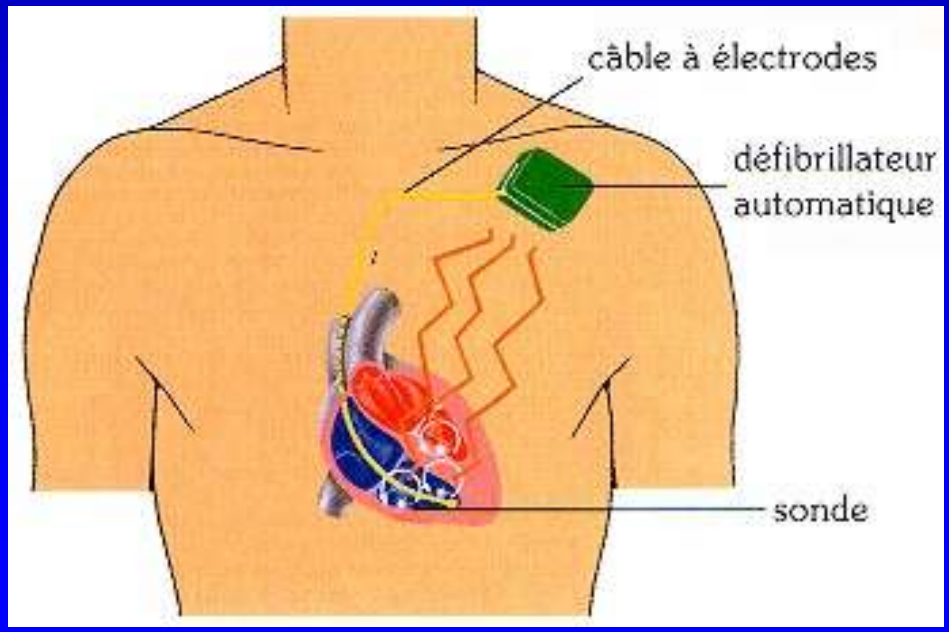
# Potentiel d’act








# Défibrillation interne



# La thérapie cellulaire : un TT AA du futur ?