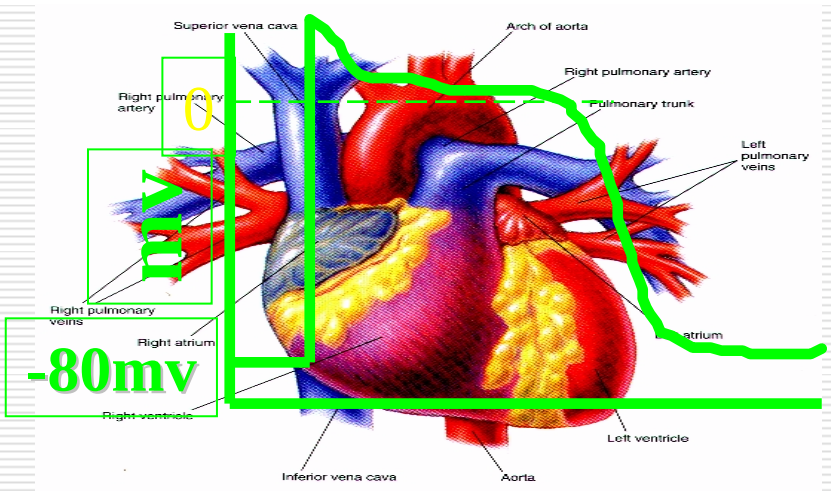
# תרופות אנטיאריתמיות

# Antiarrhythmic Drugs




קורס למתמחים, קיסריה נובמבר 2010


Prof. Amos Katz
Cardiology Department

פרופ עמוס כץ
המערך הקרדיולוגי

אוניברסיטת בן-גוריון בנגב
Ben-Gurion University of the Negev

מדינת ישראל
משרד הבריאות

המרכז הרפואי ע"ש ברזילי, אשקלון
THE BARZILAI MEDICAL CENTER ASHKELON

affiliated to the Faculty of Health Sciences
Ben-Gurion University of The Negev

מסונף לפקולטה למדעי הבריאות
אוניברסיטת בן-גוריון בנגב

# נושאי הוראה

- Pharmacology
  - Pharmacodynamics
  - Pharmacokinetics
  - Use Dependency
- Classification
  - Vaughn Williams
  - Sicilian Gambit
- Adverse effects:
  - Cardiovascular
    - Proarrhythmia
    - Exacerbation of CHF
  - Noncardiovascular
- Special Situation
  - ICD / PM
  - AF Model
  - Brugada syndrome
  - Pregnancy

# Pharmacodynamics Principles

The effect of the drug on the patients

# כללי

- AA drugs cross the cell membrane and interact with receptors in the membrane channels when the latter are in the
  - Rested
  - Activated
  - Inactivated
- Different association and dissociation rate constants
  - Voltage and time dependent
- When the drug is bound to a receptor ionic channel can not conduct, even in the activated

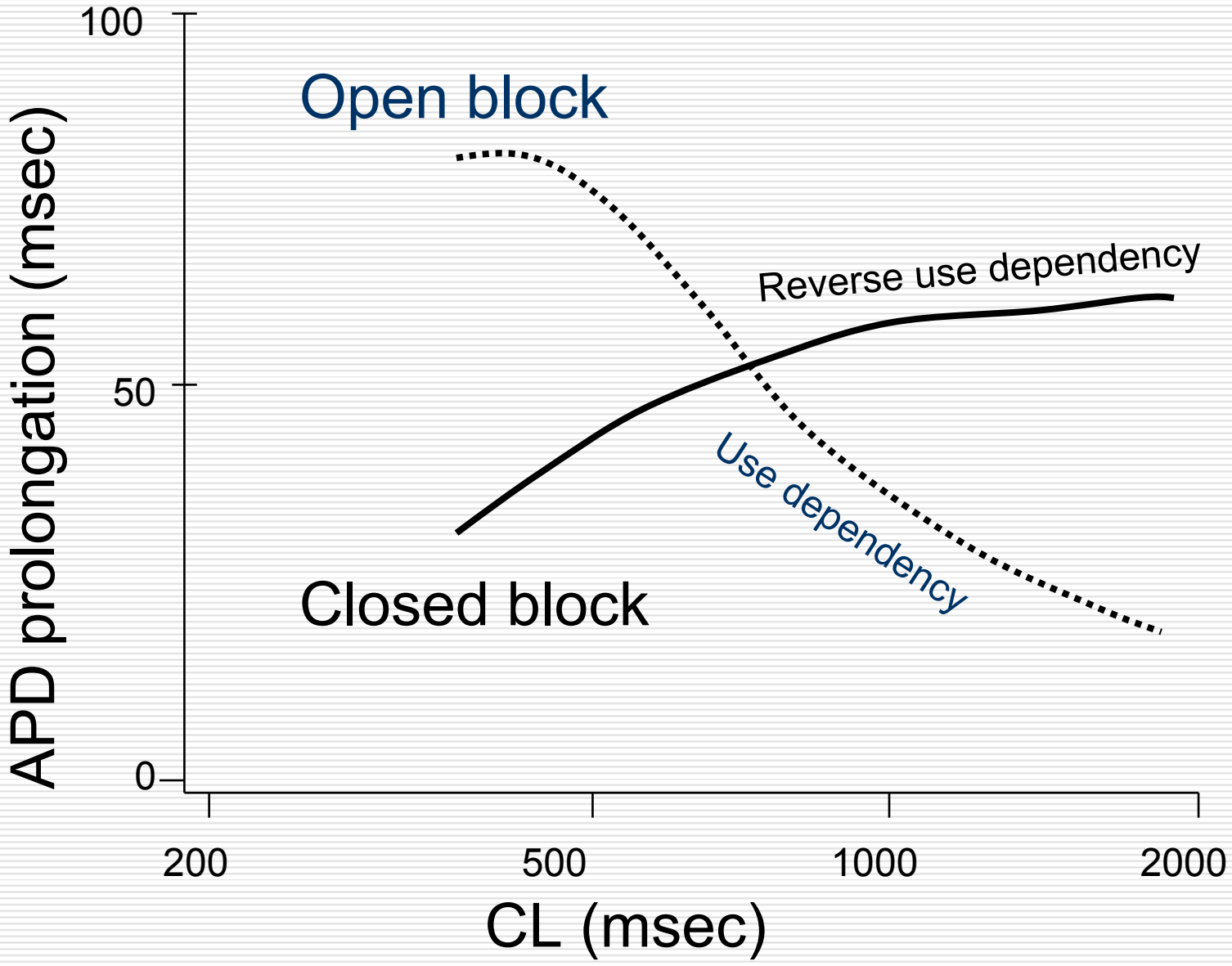
# USE-DEPENDENCE

- **AA that** exert inhibitory effects on the upstroke of the action potential
  - At rapid rates of stimulation
  - After longer periods of stimulation
- Depression of V·max, is greater after the channel has been "used" (i.e., after action potential depolarization)
- Interaction of the AA with
  - Open
  - Inactive
- Little interaction with the resting channels
- class IB exhibit fast kinetics
- class IC drugs have slow kinetics
- class IA drugs – intermediate
- With increased diastole time - slower rate
  - a greater proportion of receptors become drug free

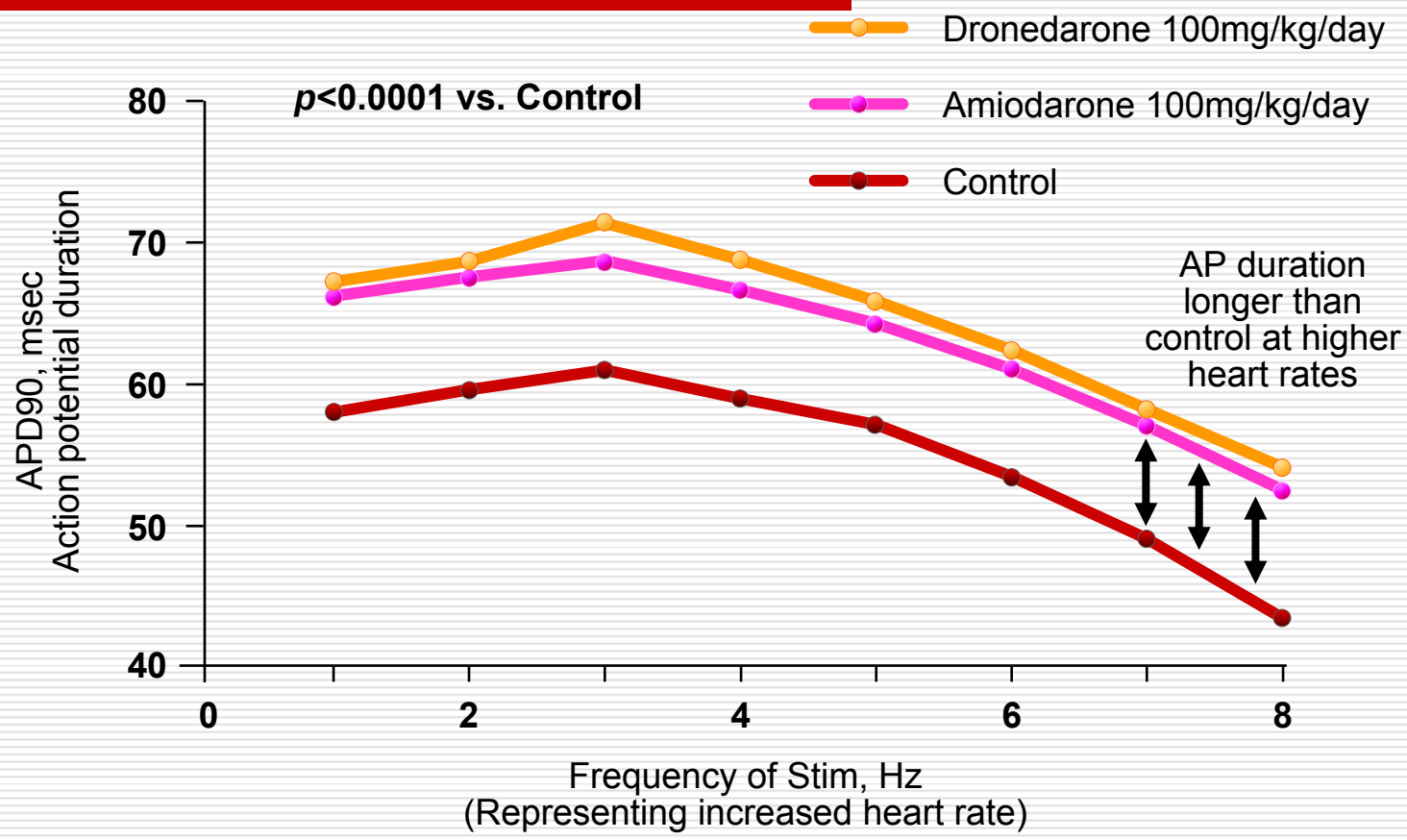
# REVERSE USE-DEPENDENCE

- Exert greater effects at slow rates than at fast rates
- Particularly true for drugs that lengthen repolarization
- The QT interval becomes prolonged more at slow than fast rates
- This effect is opposite to what the ideal antiarrhythmic - precipitating torsades de pointes.

# Use Dependency



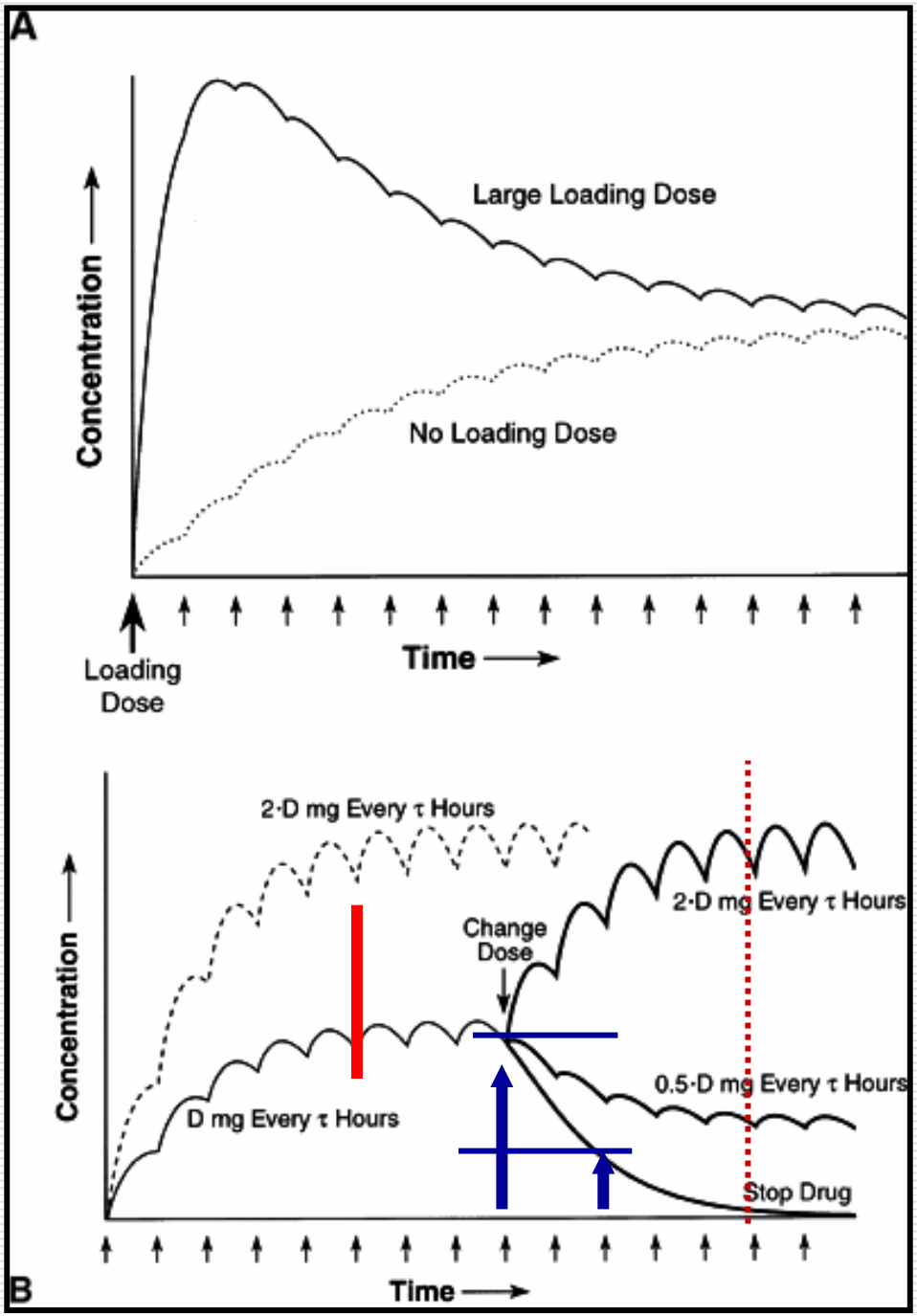
# Dronedarone a non reverse-use dependent effect on action potential duration




On rabbit atrial APD90 (Action Potential Duration at 90% repolarisation).
Sun W, *et al. J Cardiovasc Pharmacol.* May 2002;39(5):677-684.

# Pharmacokinetics Principles

Absorption, Distribution, Elimination


A
Concentration
Large Loading Dose
No Loading Dose
Loading Dose
Time
B
Concentration
2·D mg Every τ Hours
Change Dose
2·D mg Every τ Hours
0.5·D mg Every τ Hours
D mg Every τ Hours
Stop Drug
Time

# CLACIFICATION

# סווג של תרופות אנטיאריתמיות

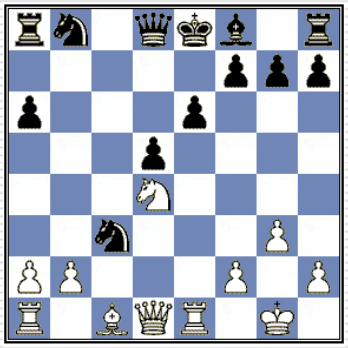
## Vaughn Williams

- Class I – Na Channel blockers
  - Ia
  - I b
  - I c
- Class II - Beta Blockers
- Class III – K channel blockers
- Class IV – Ca Channel blockers

- Digoxin
- Adenosine

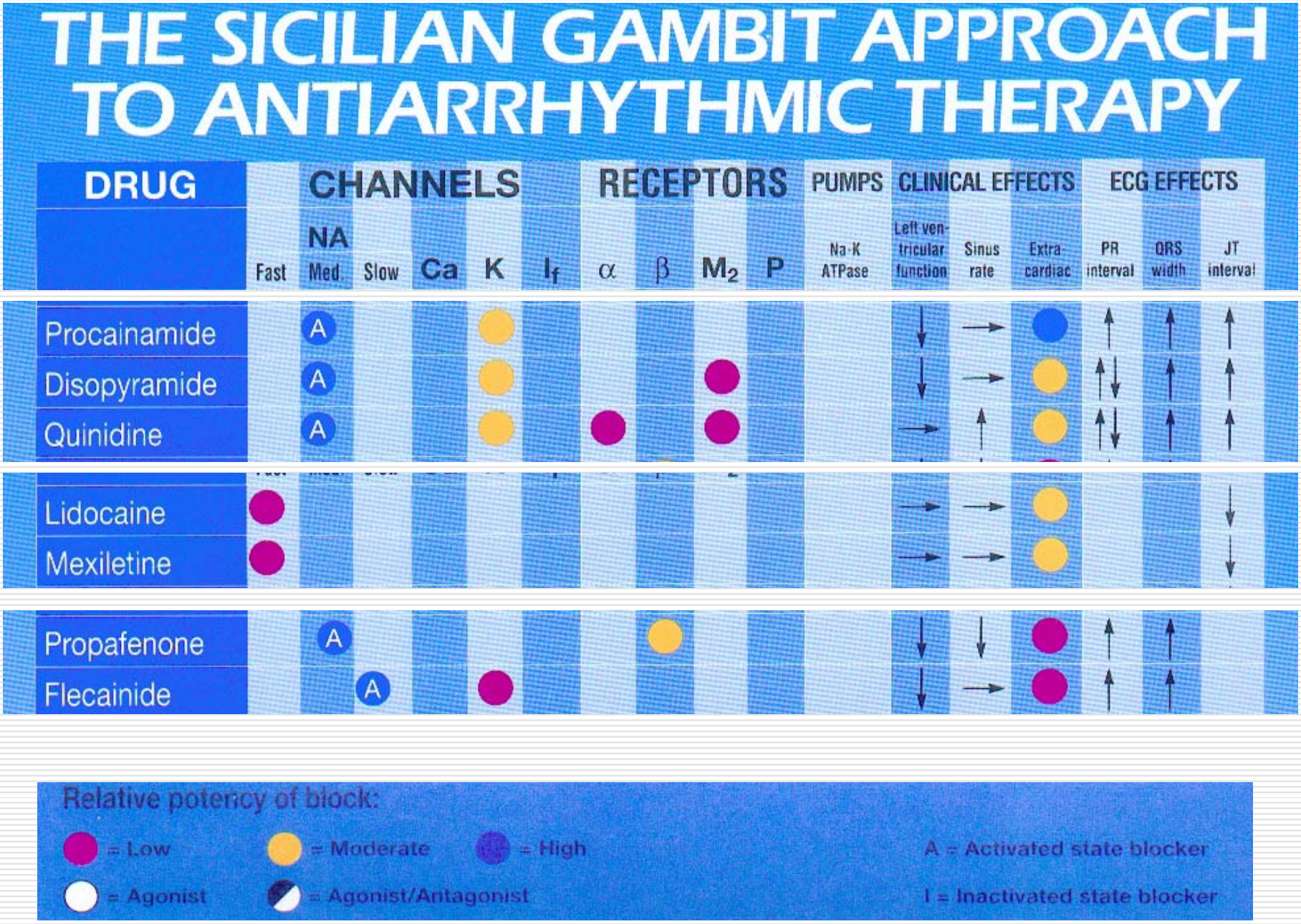
# The Sicilian Gambit

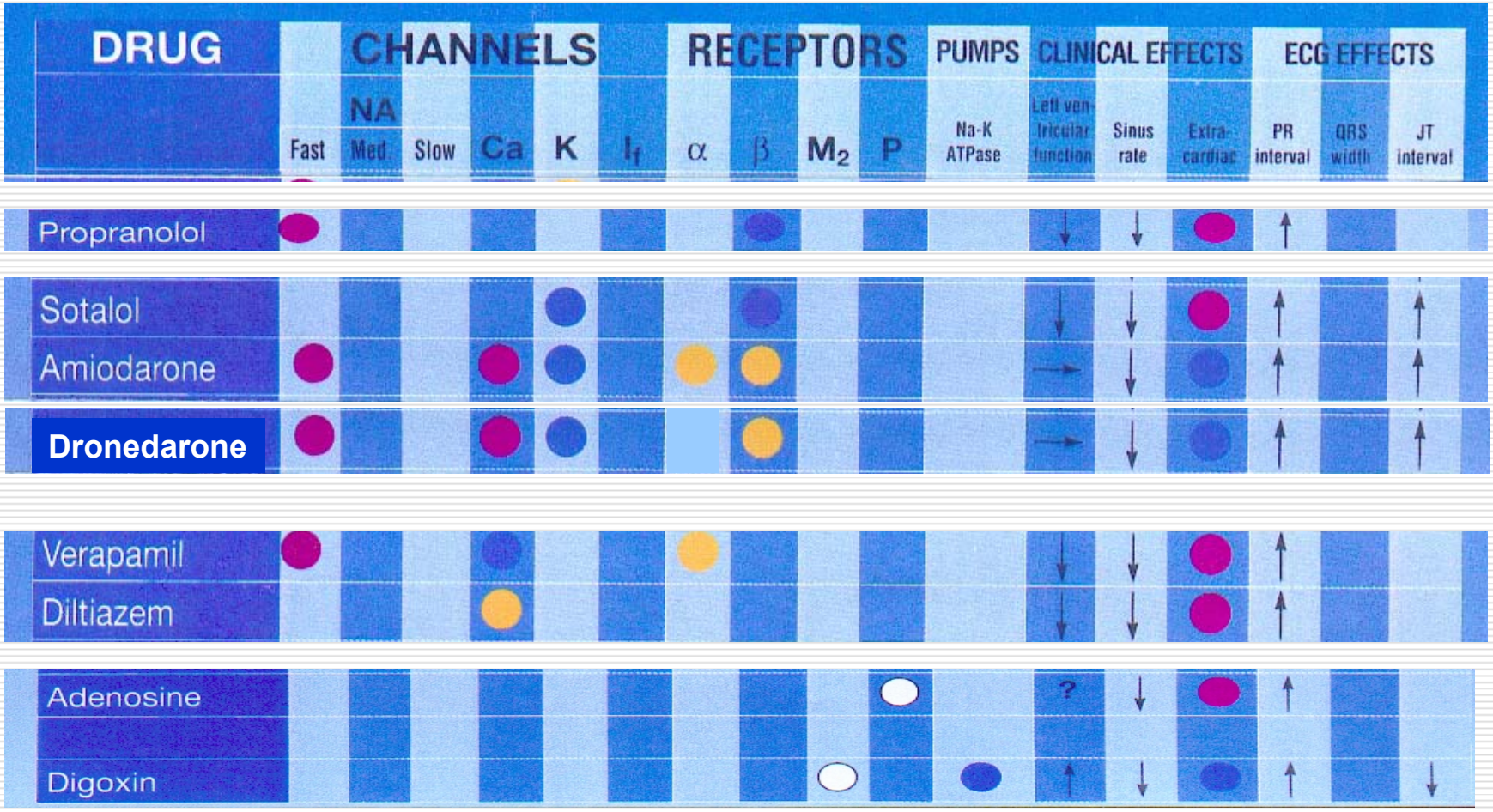
A New Approach to the Classification of Antiarrhythmic Drugs Based on Their Action on Arrhythmogenic Mechanisms

Circulation 1991;84:1831

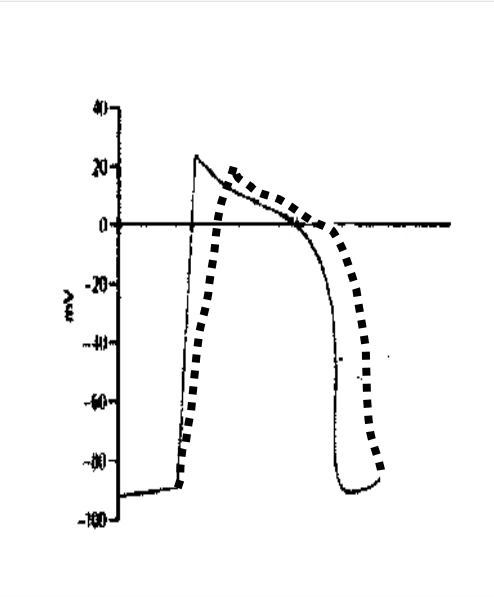
# THE SICILIAN GAMBIT APPROACH TO ANTIARRHYTHMIC THERAPY



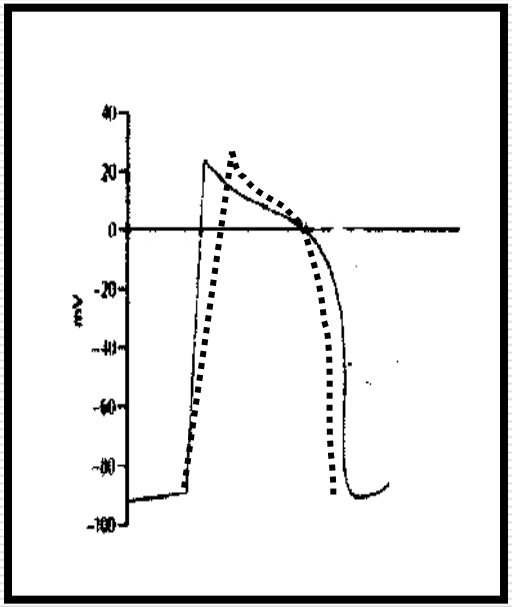

DRUG
CHANNELS
RECEPTORS
PUMPS
CLINICAL EFFECTS
ECG EFFECTS
NA
Fast
Med
Slow
Ca
K
$I_f$
α
β
$M_2$
P
Na-K ATPase
Left ventricular function
Sinus rate
Extracardiac
PR interval
QRS width
JT interval
Propranolol
Sotalol
Amiodarone
Dronedarone
Verapamil
Diltiazem
Adenosine
Digoxin
?
Relative potency of block:
= Low
= Moderate
= High
= Agonist
= Agonist/Antagonist
A = Activated state blocker
I = Inactivated state blocker

# Mechanisms of Action of Antiarrhythmic Drugs
# Class I

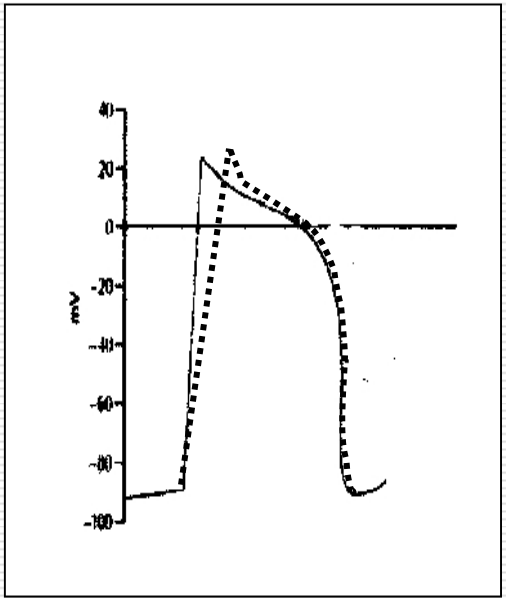
a



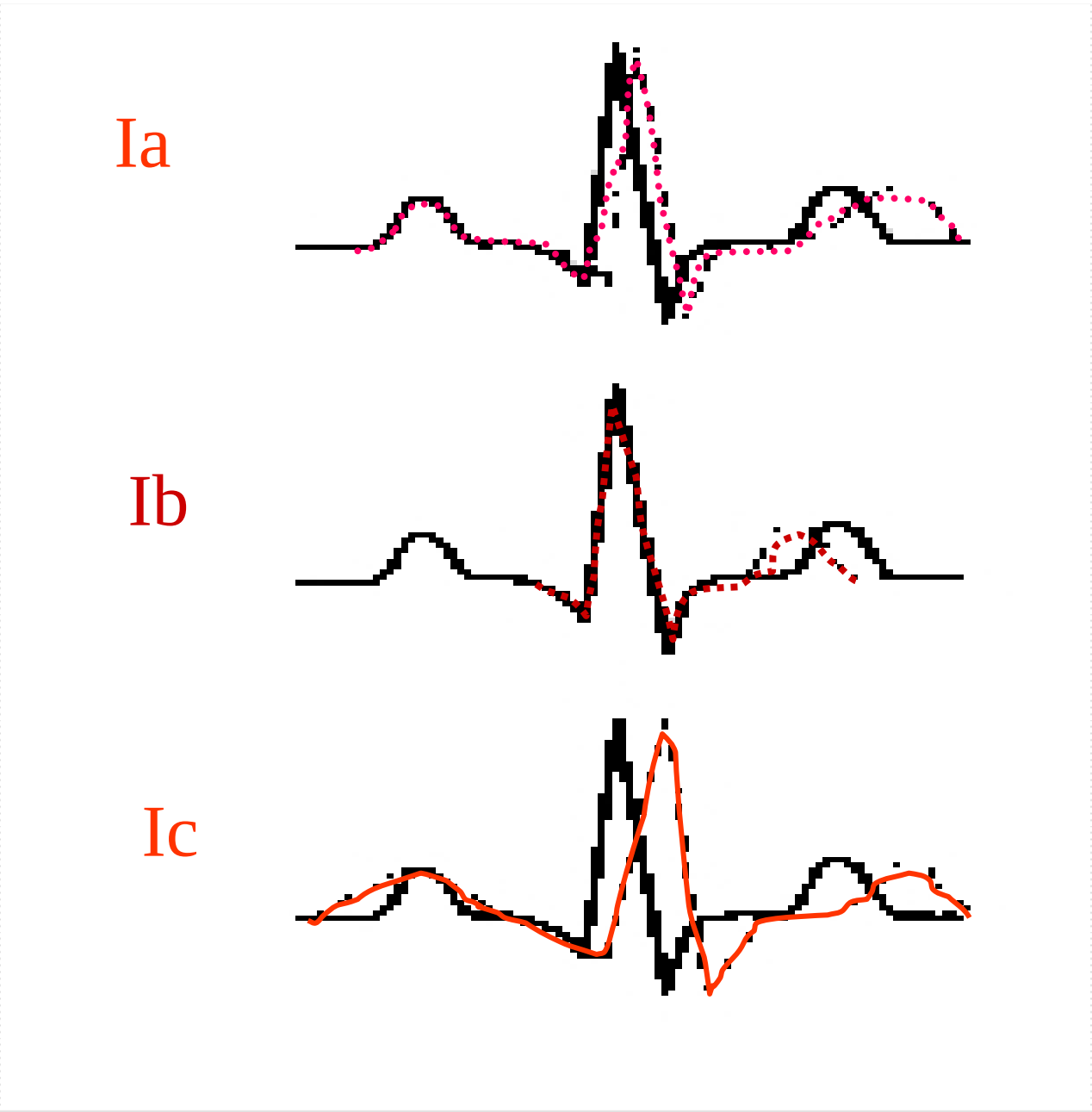
b



c



**C > A > B**

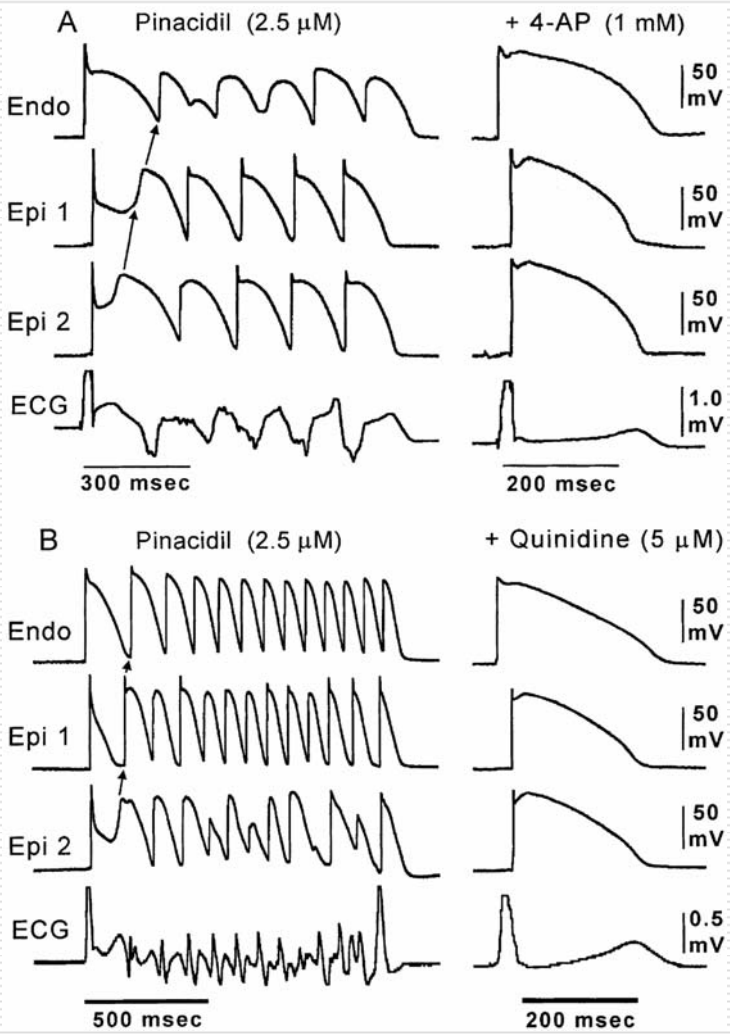

Ia
Ib
Ic

# Quinidine

Quinidine: a valuable medication joins the list
of ‘endangered species Sami Viskin Europace 2007

- Brugada syndrome
- congenital short QT syndrome
- Idiopathic VF
- *AF?*
- *ICD?*

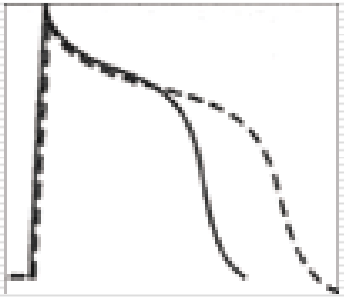
# Effects of Ito blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in arterially perfused RV wedge preparation




**Yan, G.-X. et al. Circulation 1999;100:1660-1666**

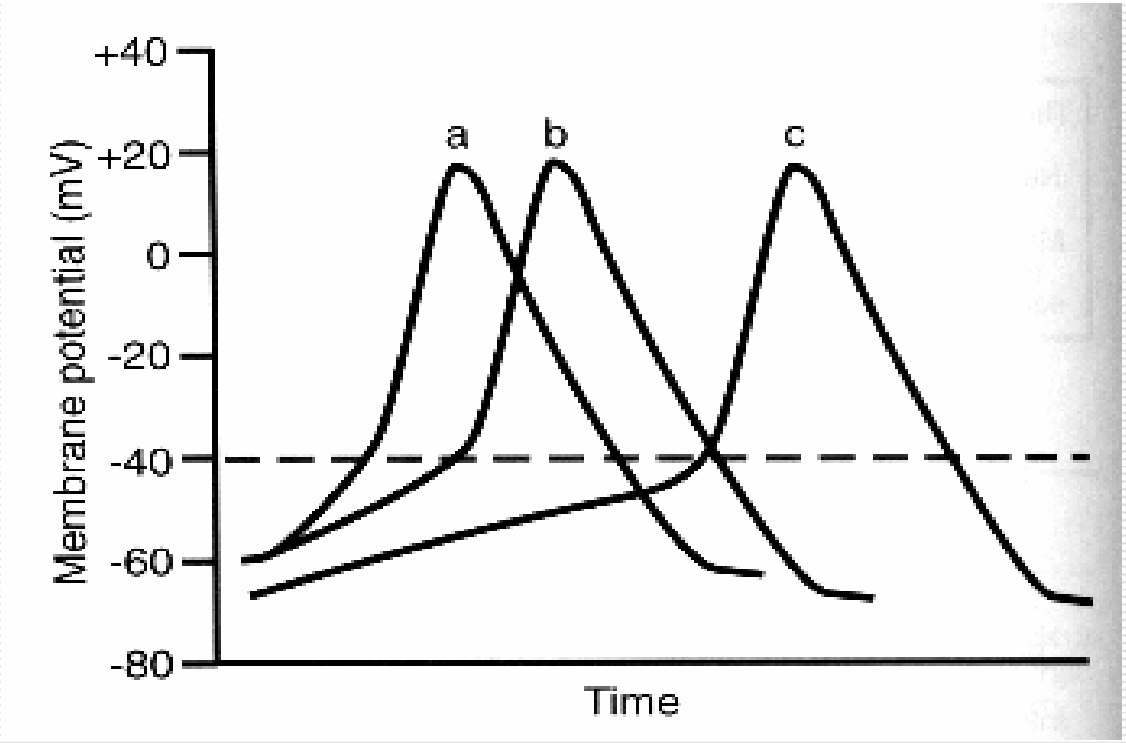
# Lidocaine

- **Slows conduction: blocks the fast $Na^+$ channels**
  - **rapid heart rate**
  - **high $K^+$, ischemia**

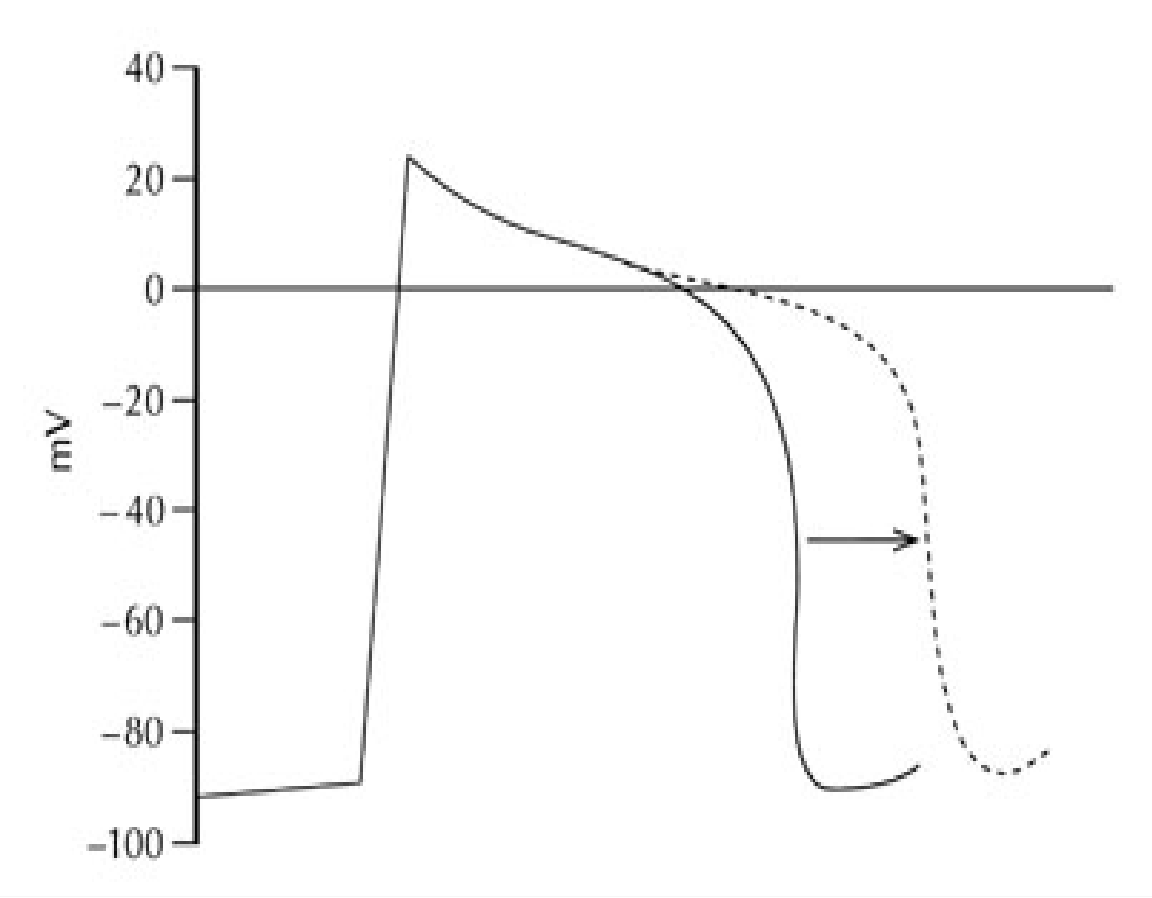


- **Decreases refractoriness**
- **Blocks $Na^+$ entry during the plateau phase of AP.**
- **APs of longer duration have greater "window currents".**
- **Therefore, APs of greater duration are preferentially shortened.**

# Mechanisms of Action of Antiarrhythmic Drugs Class II



# Mechanisms of Action of Antiarrhythmic Drugs
# Class III



# Class III

## Drugs that prolong repolarization

# Amiodarone

Sotalol

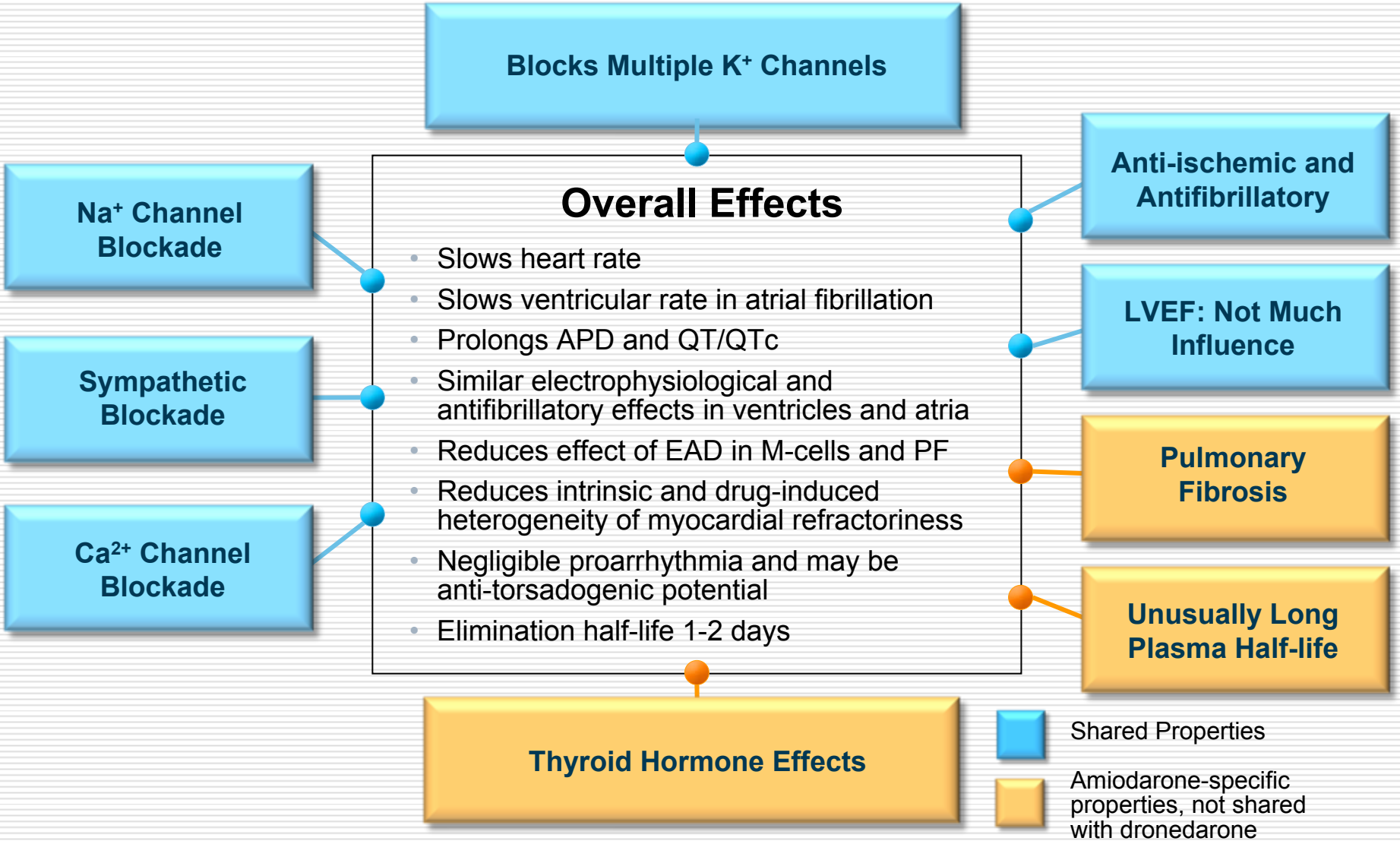
*Dofetilide*

*Ibutilide*

Azimelide

**Dronedarone**

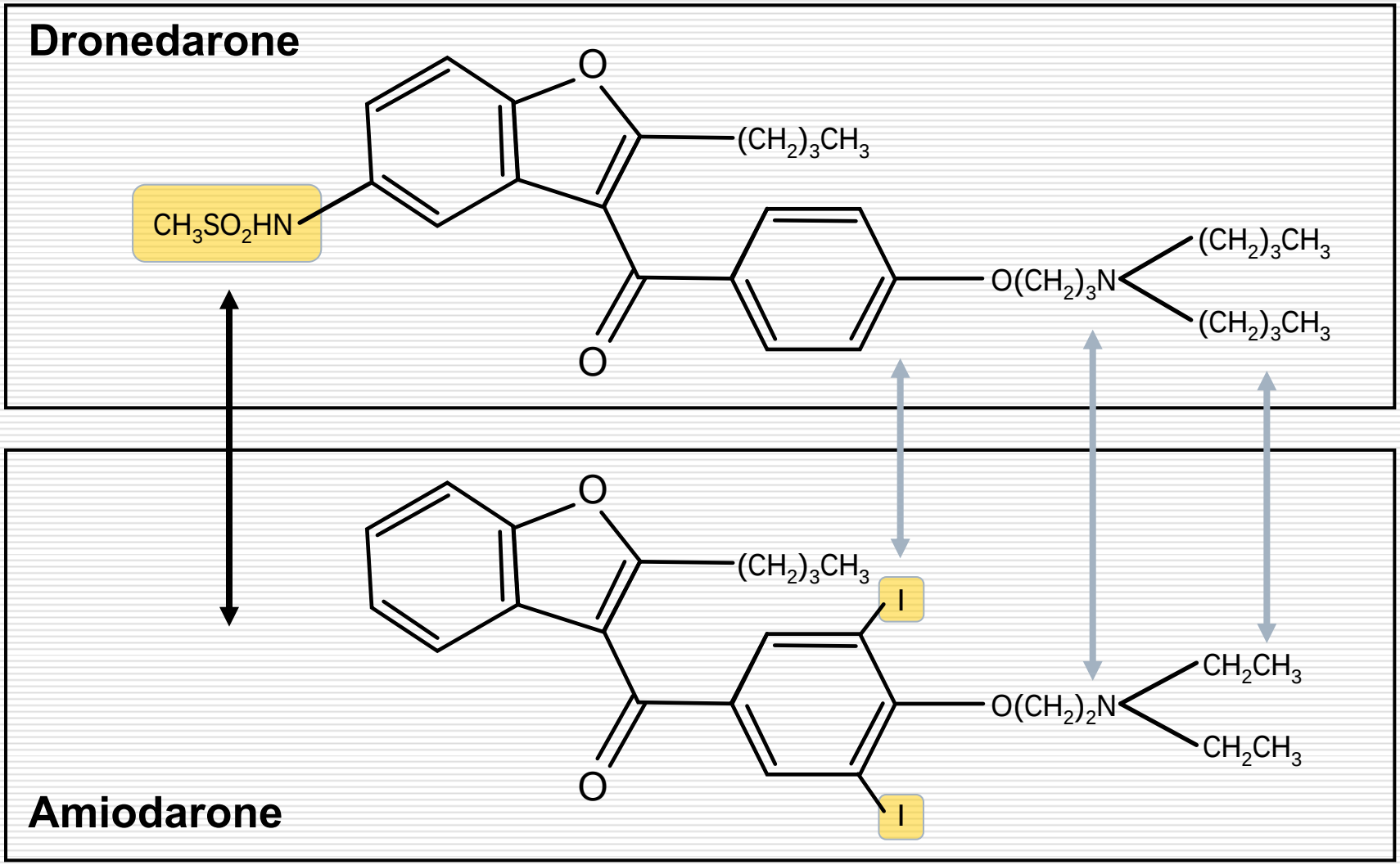
# Dronedarone Displays Important Differences to Amiodarone





Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-26.
Kathofer *et al. Cardiovasc Drug Rev* 2005;23(3):217-30.

# Dronedarone has Key Structural Differences to Amiodarone




Kathofer *et al. Cardiovasc Drug Rev.* 2005;23(3):217-30.

# Dronedarone is a Multichannel Blocker

- Dronedarone Possesses Electrophysiologic Characteristics of all Four Vaughan Williams Classes
  - Outward currents
    - Ikr: rapidly activating delayed rectifier potassium current (ventricle)
    - Iks: slowly activating delayed rectifier potassium current (ventricle)
    - Ito: transient outward current
    - Ik(Ach): muscarinic receptor-operated K+ current (atrium)
  - Inward currents
    - Fast sodium currents
    - Calcium channel antagonist

Gautier P, *et al. J Cardiovasc Pharmacol.* 2003;41(2):191-202.
Doggrell SA, Hancox JC, *Expert Opin Investig Drugs* 2004;13:415-426.

# Dronedarone possesses a very low proarrhythmic profile

- Dronedarone induces a homogenous effect on ventricular repolarisation
- Dronedarone effect on action potential duration shows no reverse-use dependency
- Dronedarone suppresses early after-depolarisation induces by pure class III agents

Sicouri S, *Fund Clin Pharmacol.* 1999;13:72.
Sun W, et al. J Cardiovasc Pharmacol. May 2002;39(5):677-684.
Varro A, et al. Brit J Pharmacol. 2001;133:625-634.

# Dronedarone Clinical Trial

## Atrial Fibrillation

- 2a DAFNE
- 2b EURIDIS/ADONIS
- 2c ERATO
- 3a ATHENA
- 3b ATHENA Post-hoc Analysis

## LV Dysfunction

- ACT2401
- 2d ANDROMEDA

# ANDROMEDA

**ANtiarrhythmic trial with DROnaderone in Moderate to severe CHF Evaluating morbidity DecreAse**

# Increased Mortality after Dronedarone Therapy for Severe Heart Failure

Lars Køber, M.D., Christian Torp-Pedersen, M.D., John J.V. McMurray, M.D., Ole Gøtzsche, M.D., Samuel Lévy, M.D., Harry Crijns, M.D., Jan Amlie, M.D., and Jan Carlsen, M.D., for the Dronedarone Study Group*

N Engl J Med 2008;358:2678-87.

# Efficacy Vs.

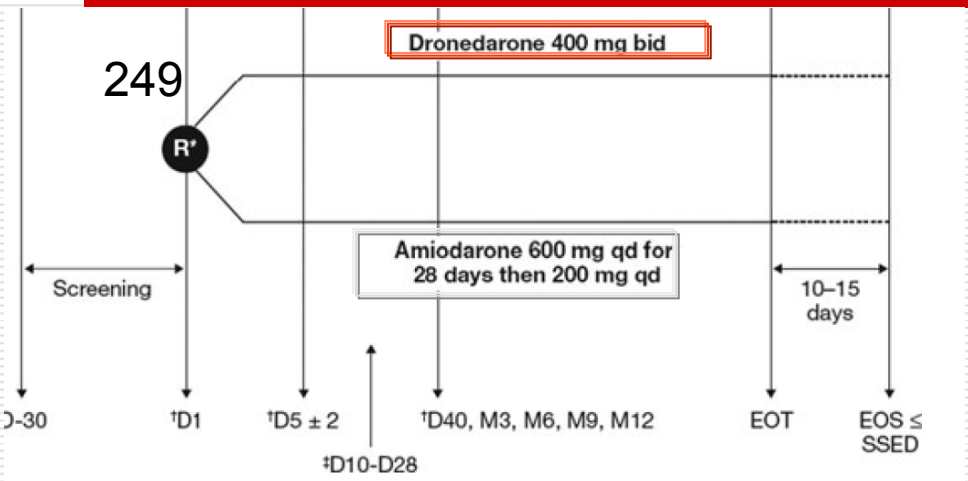
# Amiodarone?

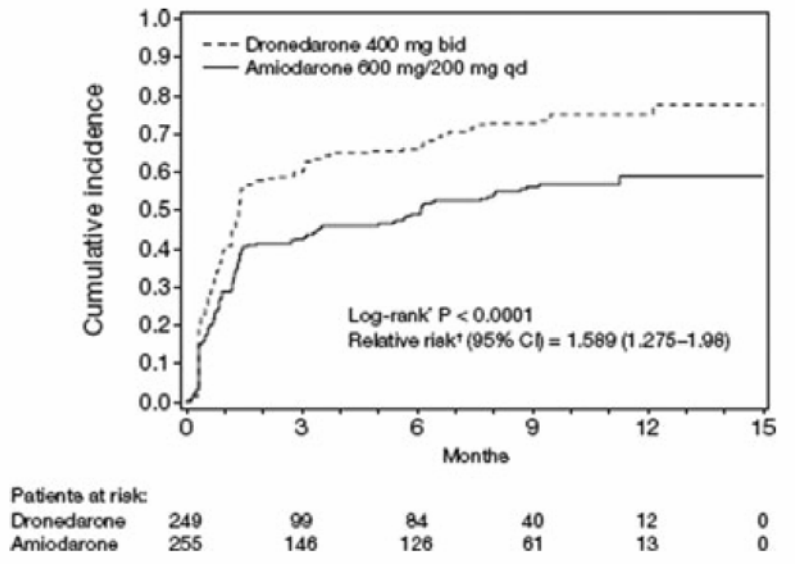
# A Short-Term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation: The DIONYSOS Study

JEAN-YVES LE HEUZEY, M.D.,* GAETANO M. DE FERRARI, M.D.,† DAVID RADZIK, M.D.,‡ MASSIMO SANTINI, M.D.,§ JUNREN ZHU, M.D.,¶ and JEAN-MARC DAVY, M.D.#

## DIONYSOS

***Cardiovasc Electrophysiol, 2010***




- **Mean duration 7 months.**
- **AF recurrence with dronedarone-63.5% compared with amiodarone 42.0%**
- **Premature drug discontinuation dronedarone 10.4% vs Amiodarone 13.3%**
- **Dronedarone had a better safety profile**
  - thyroid
  - neurologic events
  - lack of interaction with oral anticoagulants.

## Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

(J Am Coll Cardiol 2009;54:1089-95)

Jonathan P. Piccini, MD, MHS, Vic Hasselblad, PHD, Eric D. Peterson, MD, MPH,

- **Meta-analysis randomized studies**
  - Amiodarone (A) vs. placebo (4)
  - Dronedarone (D) vs placbo (4).
  - Amiodarone vs. Dronedarone (1)

Conclusions:

- Dronedarone is less effective than amiodarone for the maintenance of sinus rhythm
- Dronedarone has fewer adverse effects
  - For every 1,000 patients treated with dronedarone instead of amiodarone
    - ~ 228 more recurrences of AF
    - 9.6 fewer deaths
    - 62 fewer adverse events requiring discontinuation of drug.

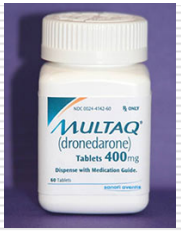
# Dronedarone - MULTAQ

**FDA Approved Indication:**

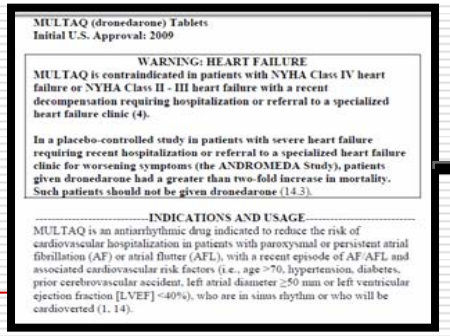
to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter (AFL) with a recent episode of AF/AFL and associated cardiovascular risk factors

- -age > 70,
- -hypertension,
- -diabetes,
- -prior cerebrovascular accident,
- -left atrial diameter ≥ 50 mm
- -left ventricular ejection fraction (LVEF < 40%),

who are in sinus rhythm or who will be cardioverted




# Black Box Warning



MULTAQ (dronedarone) Tablets
Initial U.S. Approval: 2009

**WARNING: HEART FAILURE**

**MULTAQ is contraindicated in patients with NYHA Class IV heart failure or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic (4).**

**In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone (14.3).**

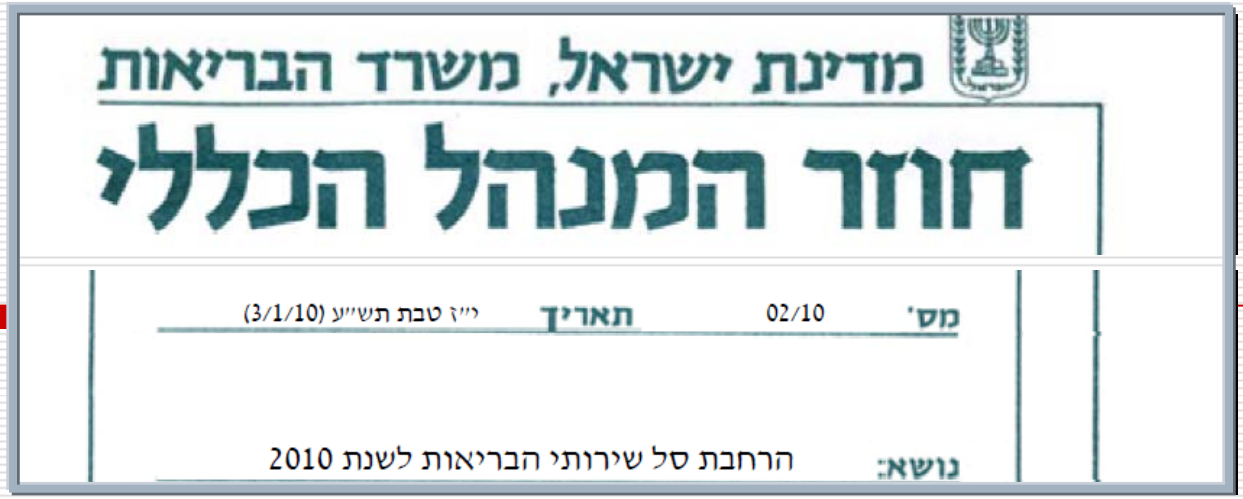
**INDICATIONS AND USAGE**

MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted (1, 14).

- **מולטאק** אינה מתאימה לחולי אי-ספיקת לב חמורה או בלתי-יציבה (NYHA FC III IV)

- **קראטינין-** צפויה עליה של עד כ-10%-15%ברמות הקראטינין בכ- 5% מהחולים, המבטאת הפרעה בהפרשה טובולרית ולא הפרעה גלומרולרית,שיעור הסינון הכלייתי ( ;GFR) אינו נפגע.
עלייה זו מתייצבת תוך מספר ימים ולכן מומלץ למדוד את רמות הקראטינין כשבוע לאחר תחילת הטיפול ולהתייחס לרמת הקראטינין כרמת הבסיס החדשה.

- **CYP3A4**: מולטאק עוברת מטבוליזם כבדי ב- CYP 3A4. יש לנקוט זהירות בטיפול עם תרופות נוספות אחרות העוברות מטבוליזם באותו ציטוכרום.



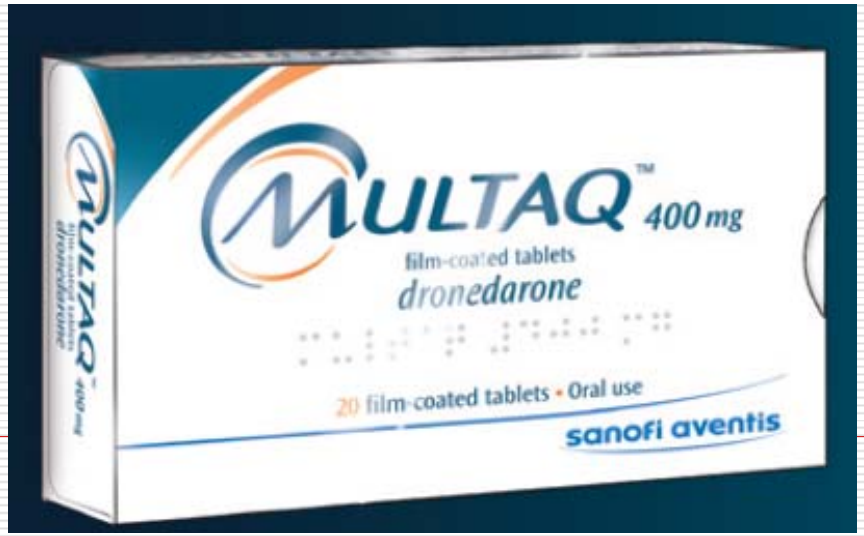
מדינת ישראל, משרד הבריאות

# חוזר המנהל הכללי

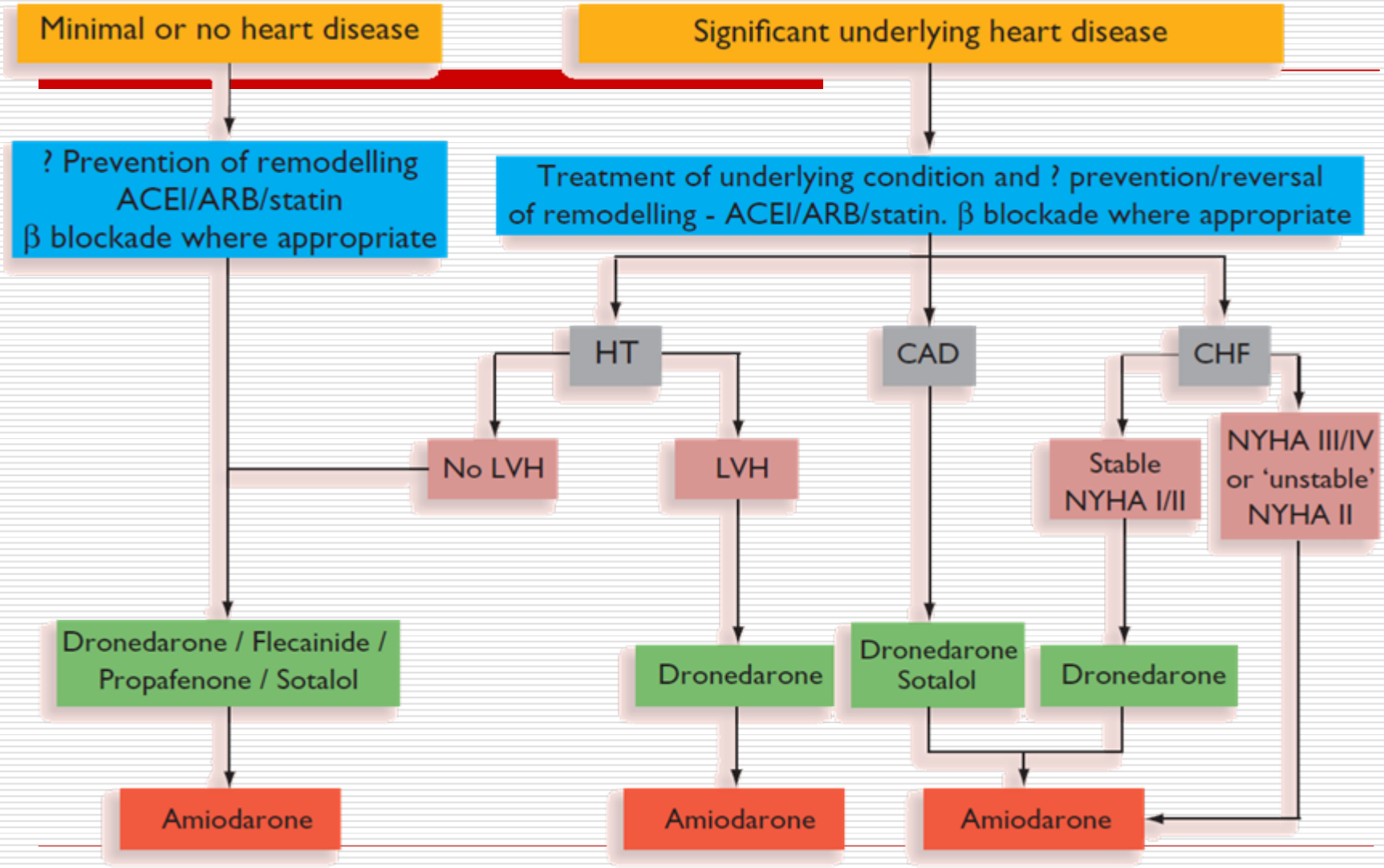
מס' 02/10 תאריך י"ז טבת תש"ע (3/1/10)

נושא: הרחבת סל שירותי הבריאות לשנת 2010

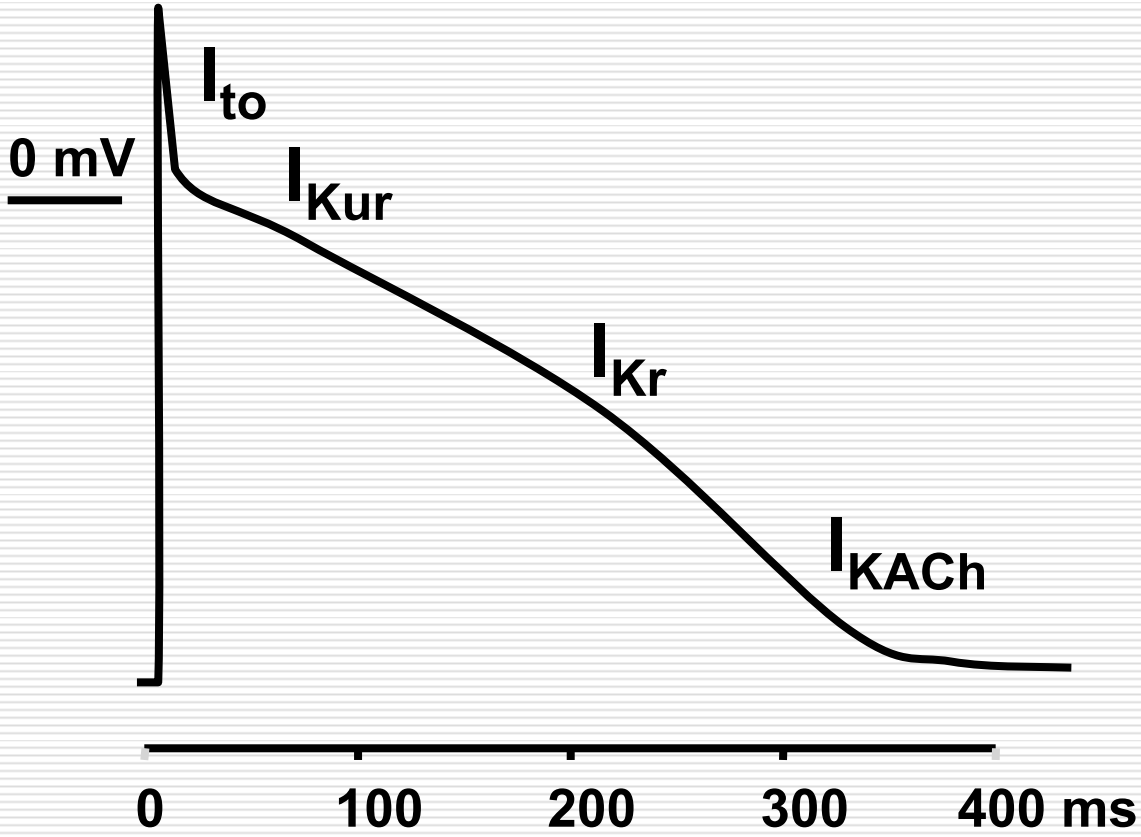
| | | |
|---|---|---|
| Dronedarone | Multaq | טיפול בפרפור עליות ורפרוף עליות בחולים שפיתחו תופעות לוואי משמעותיות לטיפול ב-Amiodarone |



# Choice of AAD - Underlying Pathology



# Vernakalant Blocks K+ Channels Important in Atrial Repolarization




| Current | $IC_{50}$ (μM) |
|---|---|
| $I_{to}$ | 5-30 |
| $I_{Kur}$ | 3-13 |
| $I_{KACh}$ | 10 |
| $I_{Kr}$ | 7-21 |
| $I_{Ks}$ | > 100 |
| $I_{K1}$ | > 100 |

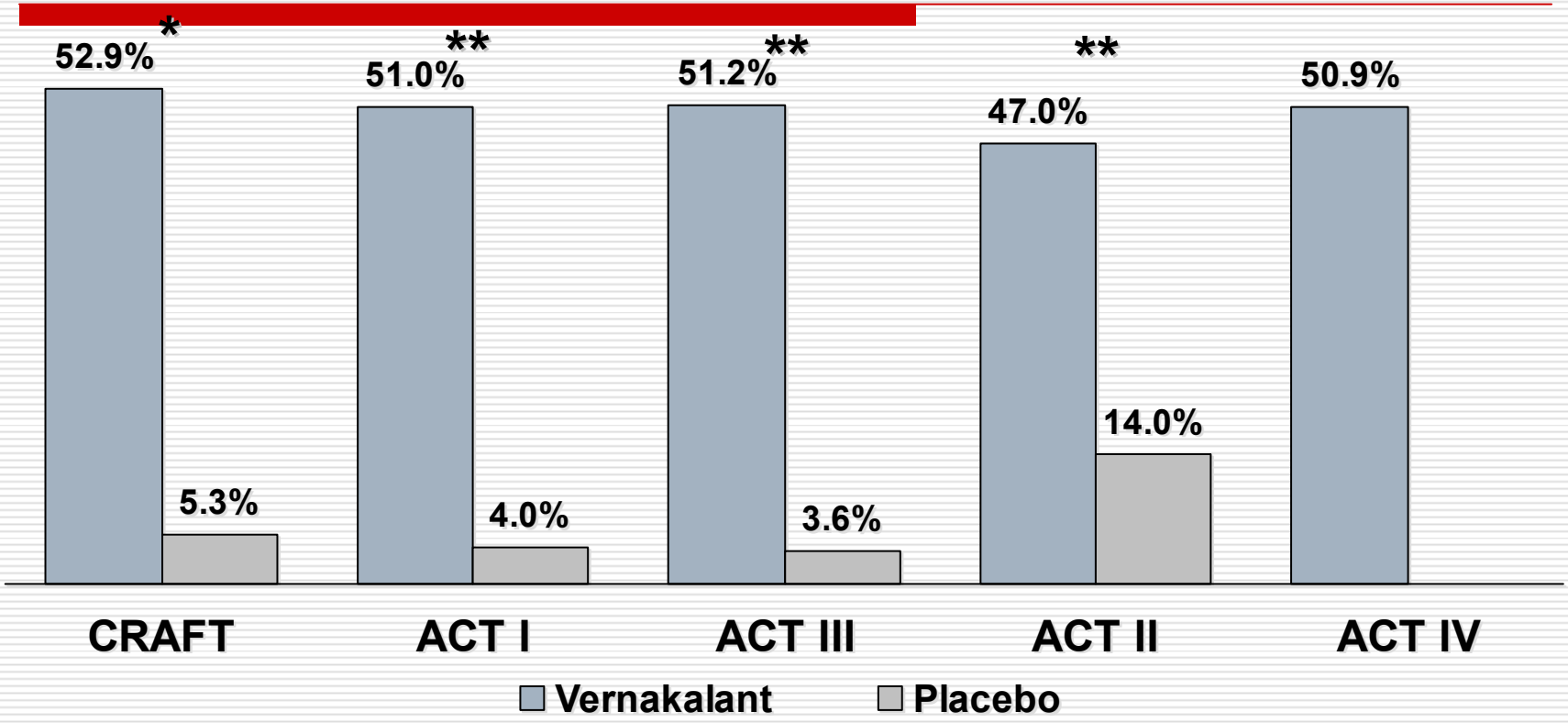
Fedida et al. J Cardiovasc Electrophysiol 2005

# Vernakalant Mechanism of Action

***Summary***

- Multiple ion channel blocker $I_K$, $I_{Na}$
- Activity potentiated in atria during AF
- Converts AF rapidly and suppresses torsade de pointes in animal models
- Pharmacologic effects consistent with ion channel blocking profile

# Vernakalant Consistent Conversion Rates *All Patients*



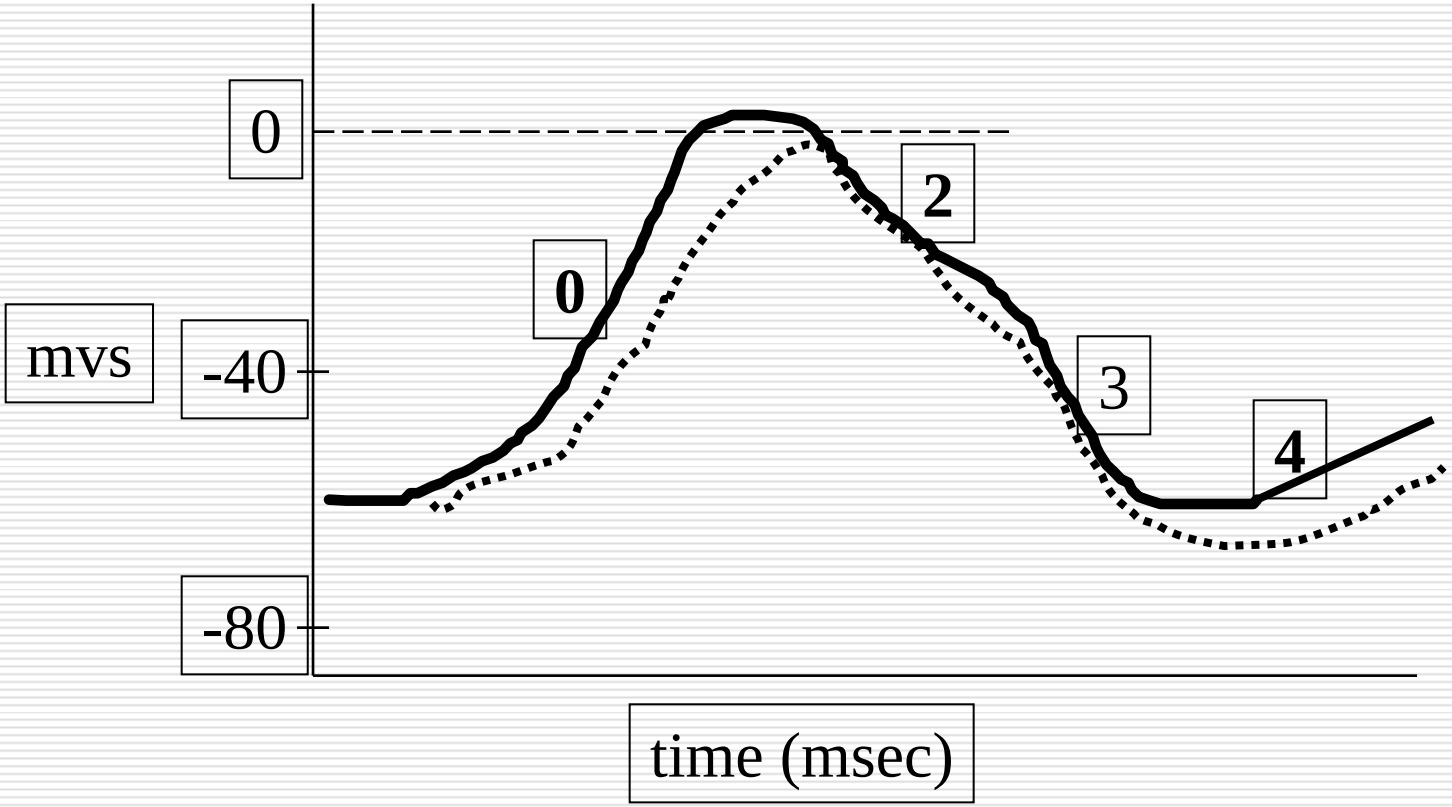

**CRAFT:** Dosing was 2+3 mg/kg; data represents % converted at 60 min post last dose; AF duration 3-72 hours
**ACT I, III** & IV: AF <7 days
**ACT II:** Post CABG and valvular AF study; AF duration 3-72 hours
**ACT IV**: A placebo group was not included in the ACT IV study

* P=0.0015
** P≤0.0001

# Class IV

Verapamil
Diltiazem

# Mechanisms of Action of Antiarrhythmic Drugs Class IV




*RECALL*: **INWARD Ca++ CURRENT CAUSES DEPOLARIZATION**

# Therapeutic Uses

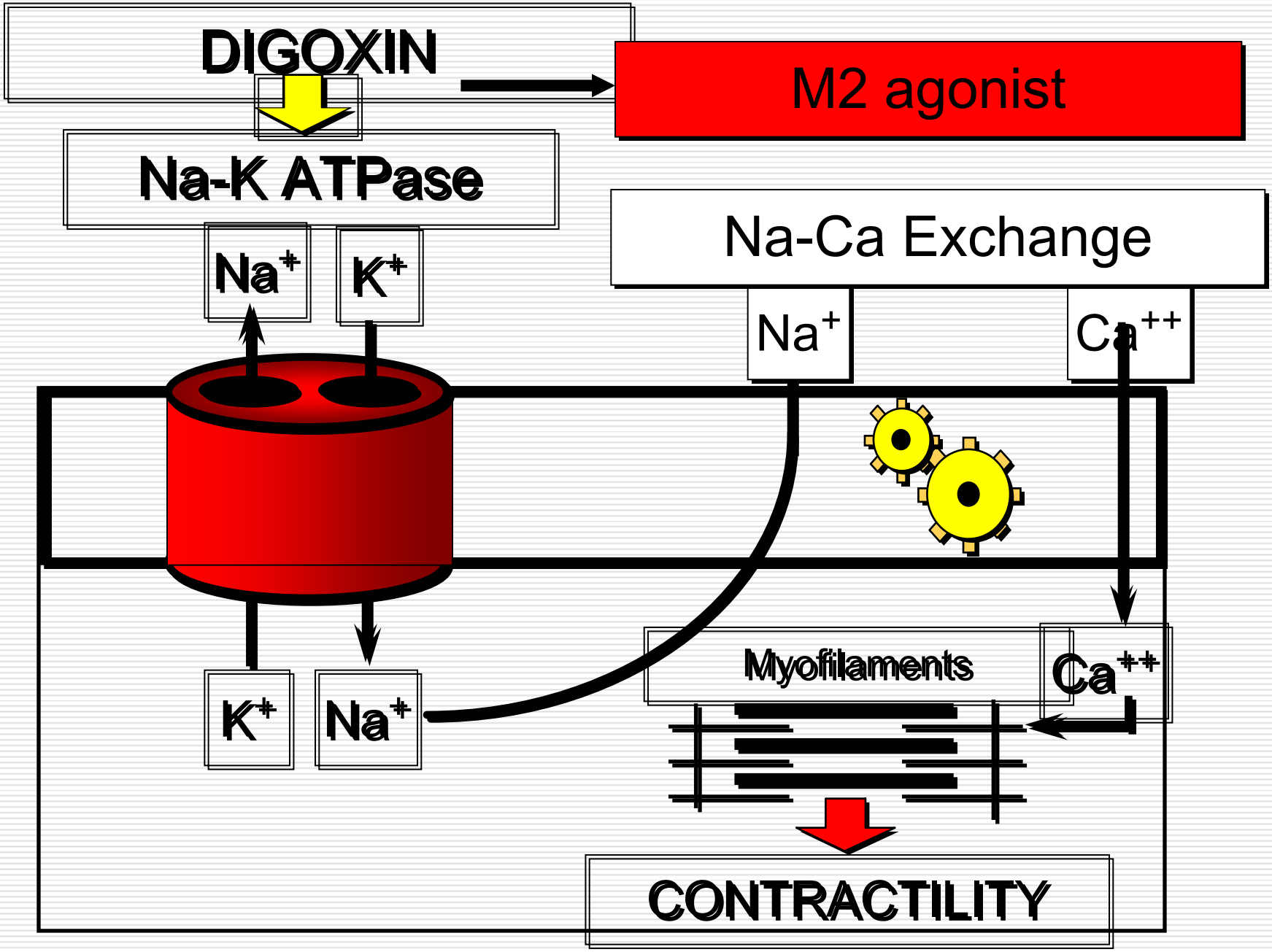
- Treatment and prophylaxis of SVT
- Slows ventricular rate in AFib and flutter
- Electropharmacological Actions
  - Atrial Fibrillation
- Idiopathic Ventricular Tachycardia (verapamil)

# Adenosine

- Interacts with A1 receptors present on the extracellular surface of cardiac cells
- Direct effects mediated through the guanine nucleotide
  - Activating K+ channels (IK Ach, IK Ado) acetylcholine like
  - Increase in K+ conductance shortens atrial APD
  - Decreases atrial contractility
  - In the sinus and AV nodes
- Indirect
  - Antagonizes catecholamine-stimulated adenylate cyclase to decrease c amp
  - decrease ICa-L and the pacemaker current If in sinus node cells
    - slows the sinus rate -> reflex increase in sinus rate
  - N region of the AV node, conduction is depressed
    - Prolongation of the AH interval results, often with transient first-, second-, or third-degree AV node block
    - Delay in AV nodal conduction is rate dependent

# Adenosine

**SVT:**
**- AVNRT**
**- AVRT**
**VT: -**
**AT: -**


DIGOXIN
M2 agonist
Na-K ATPase
Na-Ca Exchange
Na+
K+
Na+
Ca++
K+
Na+
Myofilaments
Ca++
CONTRACTILITY

# Digoxin

- Autonomic nervous system
  - Enhancing both central and peripheral vagal tone
  - Slowing the sinus node discharge rate
  - Shortening atrial refractoriness
  - Prolonging AV nodal refractoriness
- Denervated hearts little effect

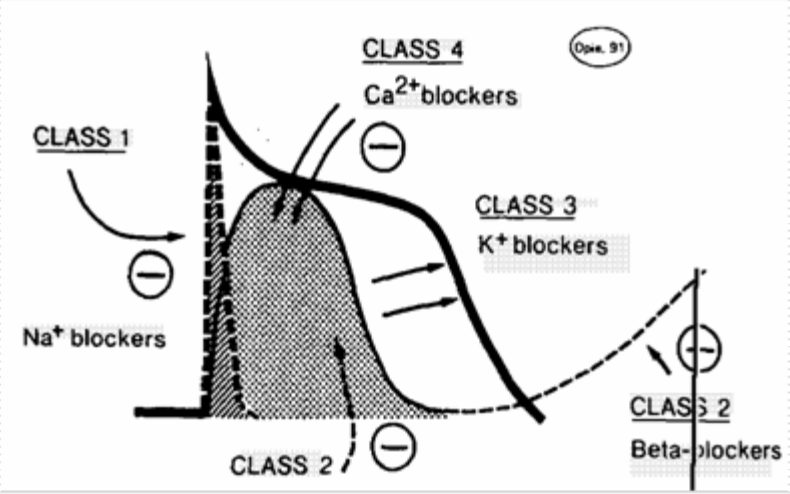
# Ranolazine

Noval anti anginal agent with Antiarrhythmic properties:

Ion channel effect similar to chronic amiodarone Rx

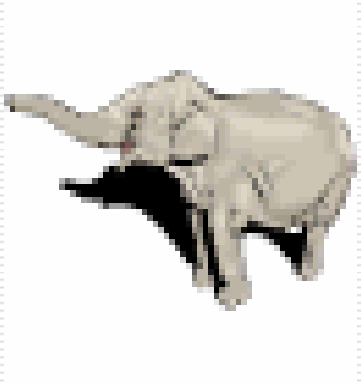
Reduced

- $I_{kr}$
- $I_{ks}$
- Late $I_{Na}$
- $I_{Ca}$
- Suppress EAD & TdP




MERILIN TIMI 36

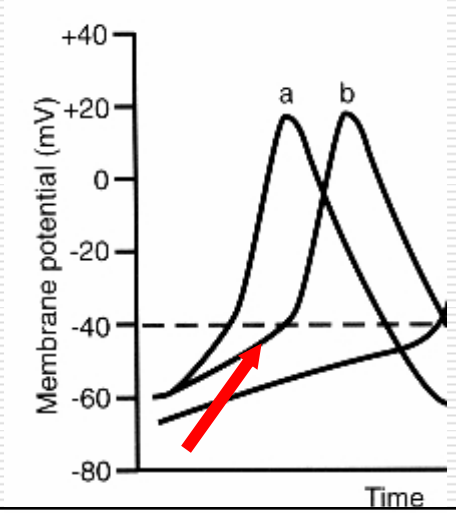
# לכל יצור הומאוטרמי מספר נתון של פעימות לב



**המאיט – מאריך ימיו**

**הממהר – מקצר ימיו**

**Sinoatrial $I_f$ current blocker a new target for heart rate reduction**




# Ivabradine = Corlan

**BEAUTIFUL, SHIFT**

**ההתוויה המאושרת ע"י משרד הבריאות הישראלי כמו גם במדינות אחרות היא:**

Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contra-indication or intolerance for beta-blockers

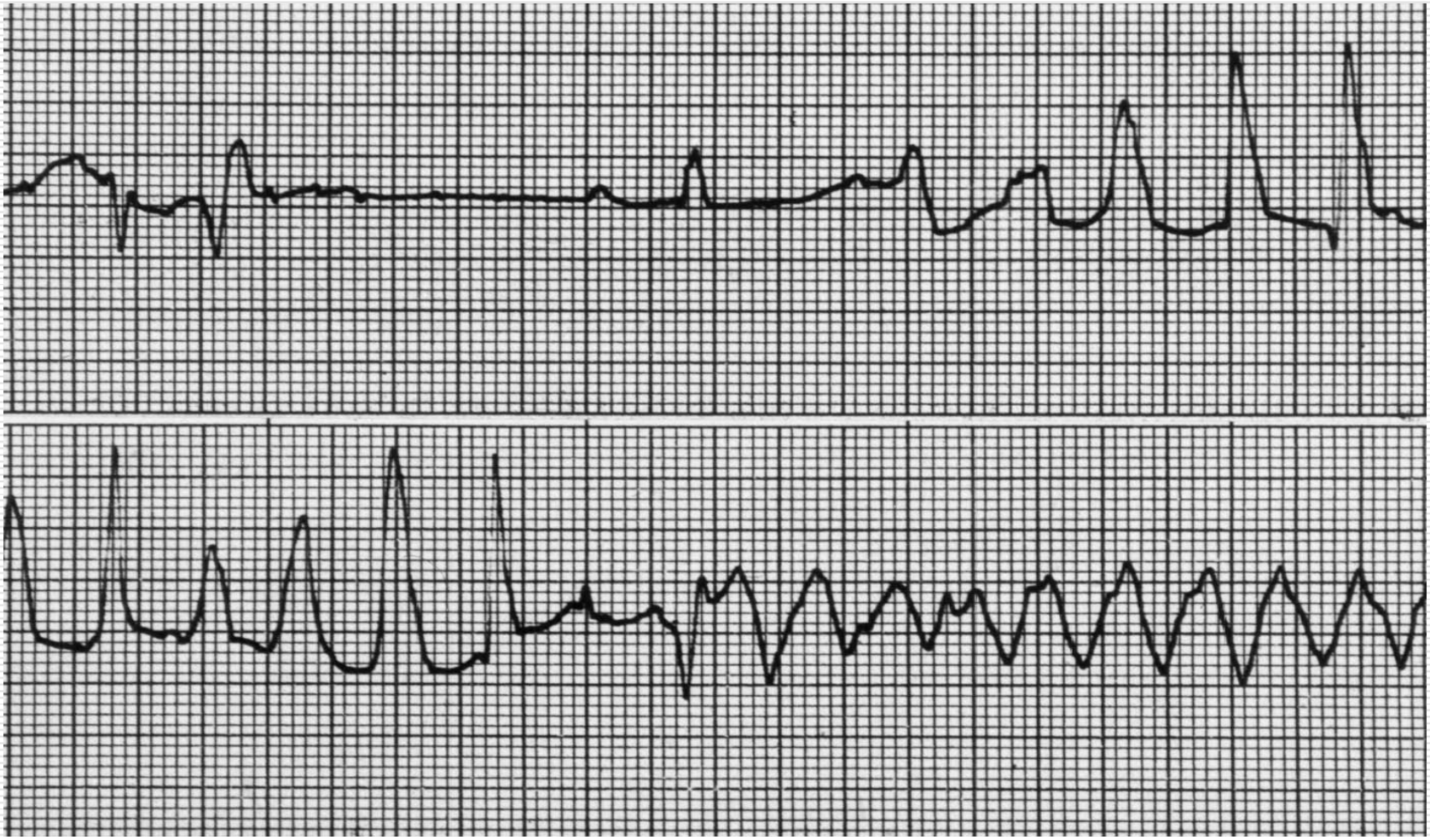
# Pharmacokinetics of Antiarrhythmic Drugs

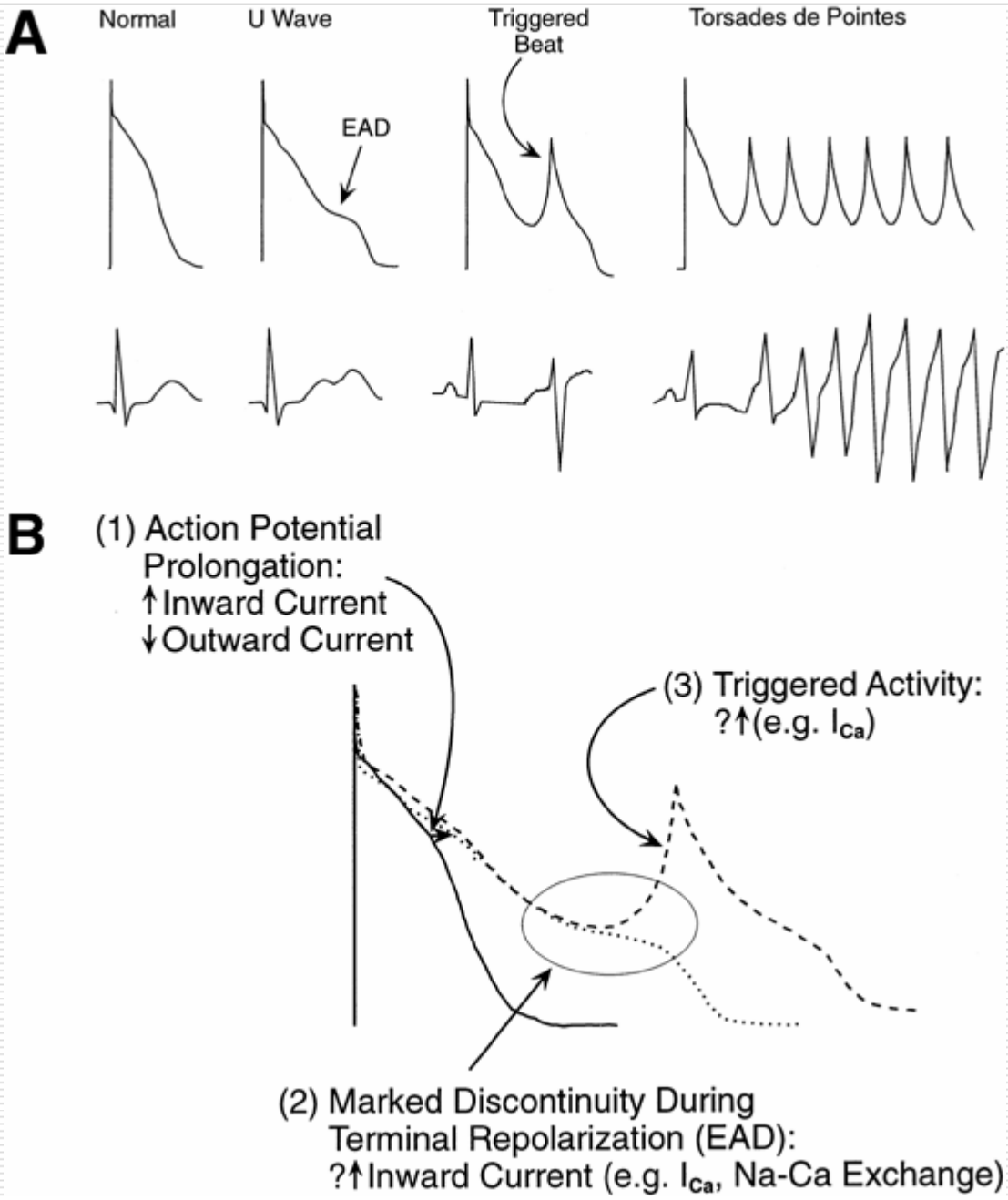
| Drug | Bioavilability. % | Protein Binding % | Time to peak hr | Elimination ½ T hr | Elimination route |
|---|---|---|---|---|---|
| Quinidine | 70-85 | 70-95 | 1-4 | 6-8 | Liver |
| Procainamide | 70-95 | 15-20 | 0.5-1.5 | 3-5 | Liver & Kidney |
| Disopyramide | 85 | variable | 2 | 4-8 | Liver & Kidney |
| Lidocaine | - | 50-80 | - | 1-4 | Liver |
| Mexiletine | 90 | 70 | 2-4 | 8-16 | Liver |
| Flecainide | 95 | 30-40 | 2-4 | 12-27 | Liver & Kidney |
| Propafenone | 5-50 | 95 | 2-3 | 2-4 | Liver |
| Amiodarone | 35-65 | 96 | 3-7 | 30-100 d | Liver |
| Sotalol | 100 | 0 | 2-4 | 7-18 | Kidney |

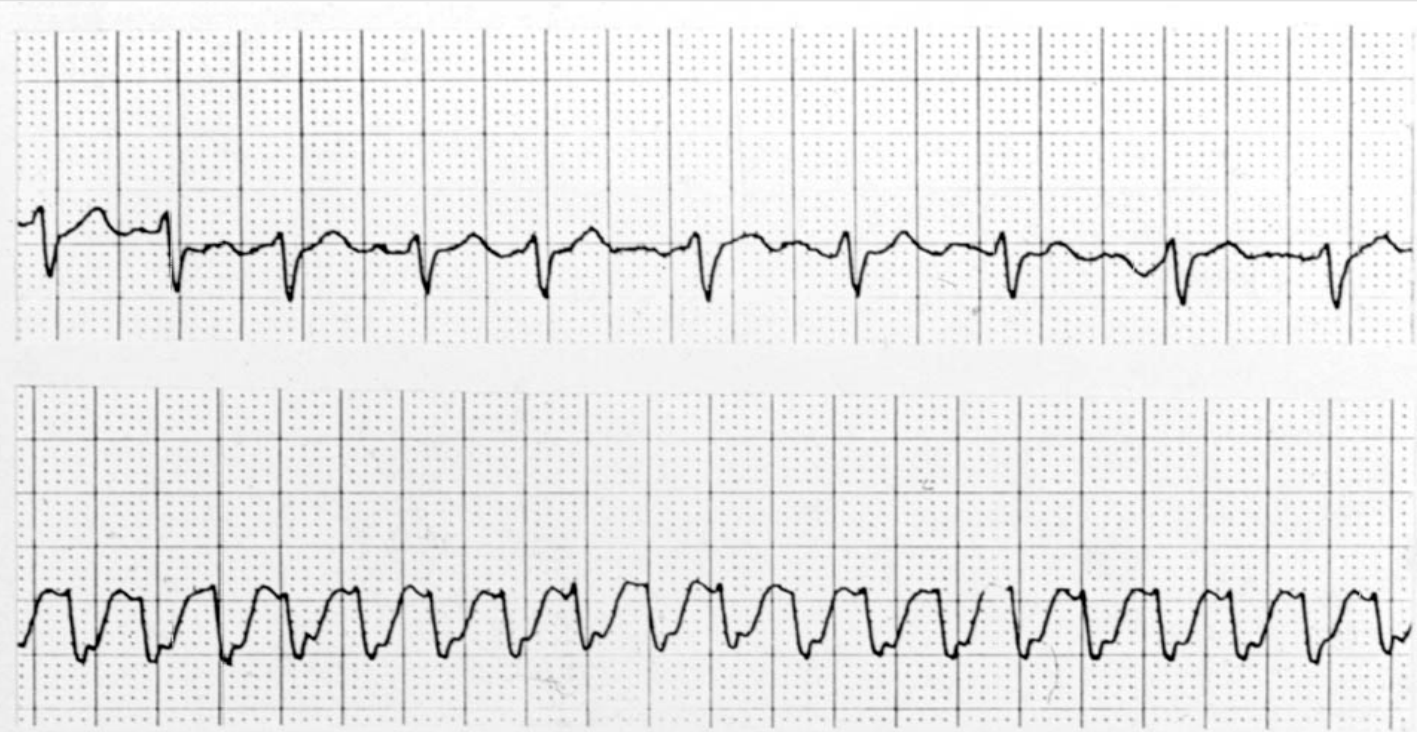
# Proarrhythmia

# Types of Proarrhythmia During Treatment With Various Antiarrhythmic Drugs for AF or Atrial Flutter According to the Vaughan Williams Classification

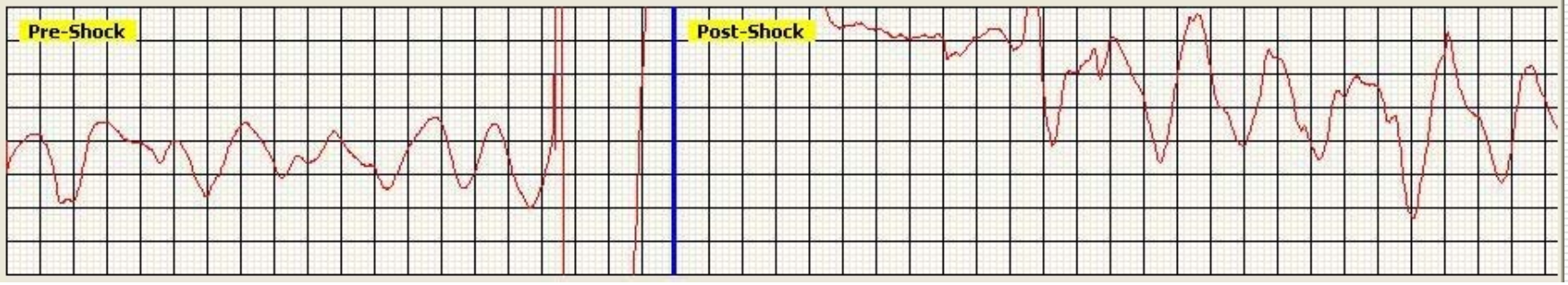
| |
|---|
| **Ventricular proarrhythmia** |
| Torsades de pointes (VW types IA and III drugs*) |
| Sustained monomorphic ventricular tachycardia (usually VW type IC drugs) |
| Sustained polymorphic ventricular tachycardia/VF without long QT (VW types IA, IC, and III drugs) |
| **Atrial proarrhythmia** |
| Provocation of recurrence (probably VW types IA, IC, and III drugs) |
| Conversion of AF to flutter (usually VW type IC drugs) |
| Increase of defibrillation threshold (a potential problem with VW type IC drugs) |
| **Abnormalities of conduction or impulse formation** |
| Acceleration of ventricular rate during AF (VW types IA and IC drugs) |
| Accelerated conduction over accessory pathway (digoxin, intravenous verapamil, or diltiazem†) |
| Sinus node dysfunction, atrioventricular block (almost all drugs) |

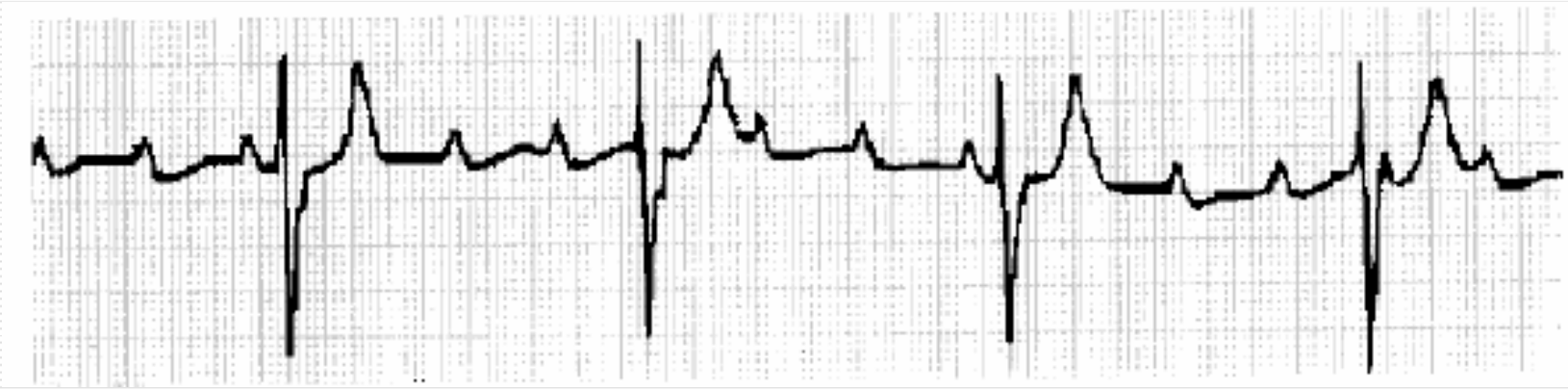



A
Normal
U Wave
Triggered Beat
Torsades de Pointes
EAD
B
(1) Action Potential Prolongation:
↑Inward Current
↓Outward Current
(3) Triggered Activity:
?↑(e.g. $I_{Ca}$)
(2) Marked Discontinuity During Terminal Repolarization (EAD):
?↑Inward Current (e.g. $I_{Ca}$, Na-Ca Exchange)



| | |
|---|---|
| Date: | 27/08/2005 |
| Time: | 06:26:16 |
| Event Description: | Shock #1 Sel=200J Del=201J |
| Heart Rate: | --- |
| Lead Fault: | --- |
| Energy Selected: | 200J |
| Energy Delivered: | 201J |
| Gain Setting: | |
| Paddle Type: | Hands-Free Pads |
| Frequency Response: | Monitor 1 to 40 Hz. |



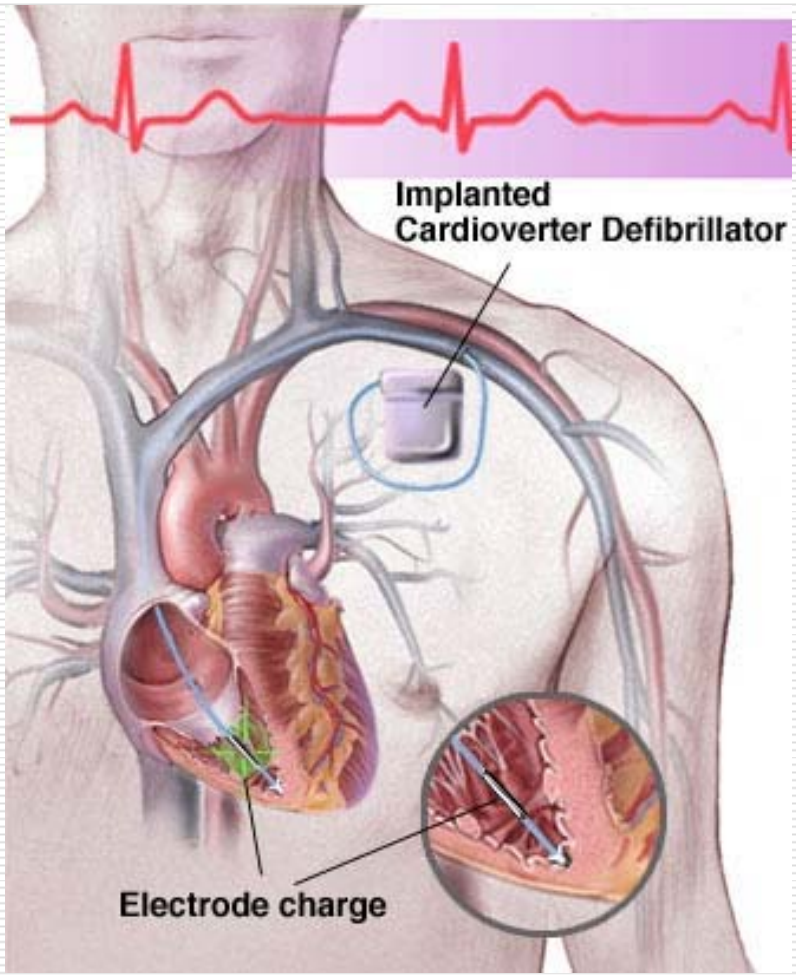


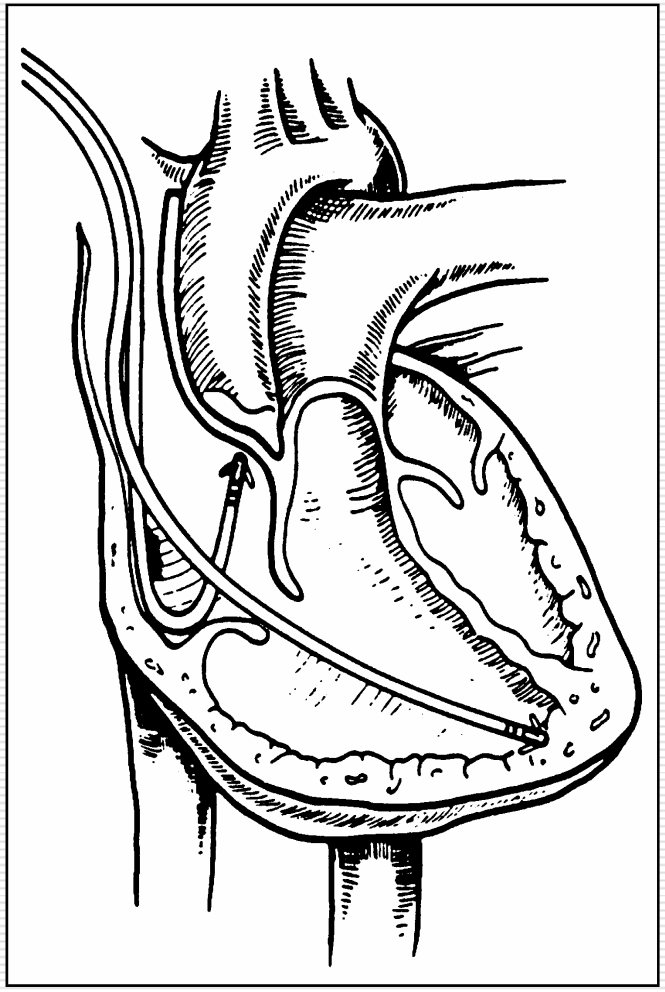
# התחלת טיפול: אמבולטורי או באישפוז?

- אין קונצנזוס
  - AHA: חולים עם EF נמוך - באישפוז
  - לב תקין, QT תקין אמבולטורי
- התחלה אמבולטורית - מינון נמוך
  - מעקב QT
  - מעקב א.ק.ג
- מודאג? באשפוז
- סיכון גבוה: EF ירוד, CHF, סיכון ל TdP
  נשים, K, Mg אנטיביוטיקה, אנטיהיסטמיניקה

# אפקט על ספי קיצוב ודפיברילציה

# אפקט על ספי קיצוב ודפיברילציה



| Drug | Pacing | Defibrillation |
|---|---|---|
| Quinidine | מעלה בריכוז גבוה | עשוי לעלות בריכוז גבוה |
| Procainamide | מעלה בריכוז גבוה | ללא אפקט |
| Disopyramide | מעלה בריכוז טוקסי | ? |
| Lidocaine | ( 0 או +) | מעלה |
| Mexiletine | ( 0 או +) | ( 0 או +) * |
| Flecainide | מעלה | ( 0 או +) |
| Propafenone | מעלה | ( 0 או +) |
| Amiodarone | 0 | מעלה |
| Sotalol | 0 | מוריד |

# אינטראקציה
# התאמה למחלות רקע לא CV

# שינוי מינון במחלות שונות או עם תרופות אחרות

| | Disease | | | Drug | | | |
|---|---|---|---|---|---|---|---|
| Drug | Heart Failure | Renal | Hepatic | Digoxin | Warfarin | Cimetidine | Phenytoin or Phenobarbital |
| Amiodarone | . . . | . . . | ↓ Dosage | ↑↑ Serum digoxin level | ↑↑ Protime | . . . | . . . |
| Bretylium | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Digoxin | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Diltiazem hydrochloride | ↓ Dosage | . . . | ↓ Dosage | ±↑ Serum digoxin level | . . . | ↓ Dosage | . . . |
| Disopyramide | Avoid | ↓ Dosage | ±↓ Dosage | . . . | . . . | . . . | ↑ Dosage |
| Flecainide | Avoid | ↓ Dosage | . . . | ↑ Serum digoxin level | . . . | ±↓ Dosage | . . . |
| Ibutilide | . . . | . . . | . . . | . . . | . . . | . . . | . . . |
| Lidocaine | ↓ Dosage | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Mexiletine hydrochloride | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | ↑ Dosage |
| Moricizine | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Phenytoin | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Procainamide hydrochloride | ±↓ Dosage | ↓ Dosage | . . . | . . . | . . . | ↓ Dosage | . . . |
| Propafenone hydrochloride | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | ↑ Protime | ±↓ Dosage | . . . |
| Quinidine | . . . | . . . | ↓ Dosage | ↑↑ Serum digoxin level | ±↓ Warfarin dosage | ↓ Dosage | ↑ Dosage |
| Sotalol hydrochloride | Cautious use | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Tocainide | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Verapamil | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | . . . | ↓ Dosage | ±↑ Dosage (phenobarbital) |

# שינוי מינון במחלות שונות או עם תרופות אחרות

| | Disease | | | Drug | | | |
|---|---|---|---|---|---|---|---|
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| Bretylium | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Digoxin | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Diltiazem hydrochloride | ↓ Dosage | . . . | ↓ Dosage | ±↑ Serum digoxin level | . . . | ↓ Dosage | . . . |
| Disopyramide | Avoid | ↓ Dosage | ±↓ Dosage | . . . | . . . | . . . | ↑ Dosage |
| Flecainide | Avoid | ↓ Dosage | . . . | ↑ Serum digoxin level | . . . | ±↓ Dosage | . . . |
| Ibutilide | . . . | . . . | . . . | . . . | . . . | . . . | . . . |
| Lidocaine | ↓ Dosage | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Mexiletine hydrochloride | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | ↑ Dosage |
| Moricizine | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Phenytoin | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Procainamide hydrochloride | ±↓ Dosage | ↓ Dosage | . . . | . . . | . . . | ↓ Dosage | . . . |
| Propafenone hydrochloride | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | ↑ Protime | ±↓ Dosage | . . . |
| Quinidine | . . . | . . . | ↓ Dosage | ↑↑ Serum digoxin level | ±↓ Warfarin dosage | ↓ Dosage | ↑ Dosage |
| Sotalol hydrochloride | Cautious use | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Tocainide | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
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# שינוי מינון במחלות שונות או עם תרופות אחרות

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| Bretylium | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Digoxin | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Diltiazem hydrochloride | ↓ Dosage | . . . | ↓ Dosage | ±↑ Serum digoxin level | . . . | ↓ Dosage | . . . |
| Disopyramide | Avoid | ↓ Dosage | ±↓ Dosage | . . . | . . . | . . . | ↑ Dosage |
| Flecainide | Avoid | ↓ Dosage | . . . | ↑ Serum digoxin level | . . . | ±↓ Dosage | . . . |
| Ibutilide | . . . | . . . | . . . | . . . | . . . | . . . | . . . |
| Lidocaine | ↓ Dosage | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Mexiletine hydrochloride | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | ↑ Dosage |
| Moricizine | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Phenytoin | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Procainamide hydrochloride | ±↓ Dosage | ↓ Dosage | . . . | . . . | . . . | ↓ Dosage | . . . |
| Propafenone hydrochloride | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | ↑ Protime | ±↓ Dosage | . . . |
| Quinidine | . . . | . . . | ↓ Dosage | ↑↑ Serum digoxin level | ±↓ Warfarin dosage | ↓ Dosage | ↑ Dosage |
| Sotalol hydrochloride | Cautious use | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Tocainide | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Verapamil | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | . . . | ↓ Dosage | ±↑ Dosage (phenobarbital) |

# שינוי מינון במחלות שונות או עם תרופות אחרות

| | Disease | | | Drug | | | |
|---|---|---|---|---|---|---|---|
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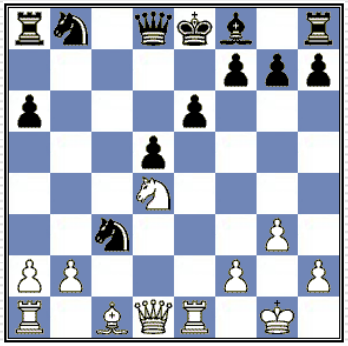
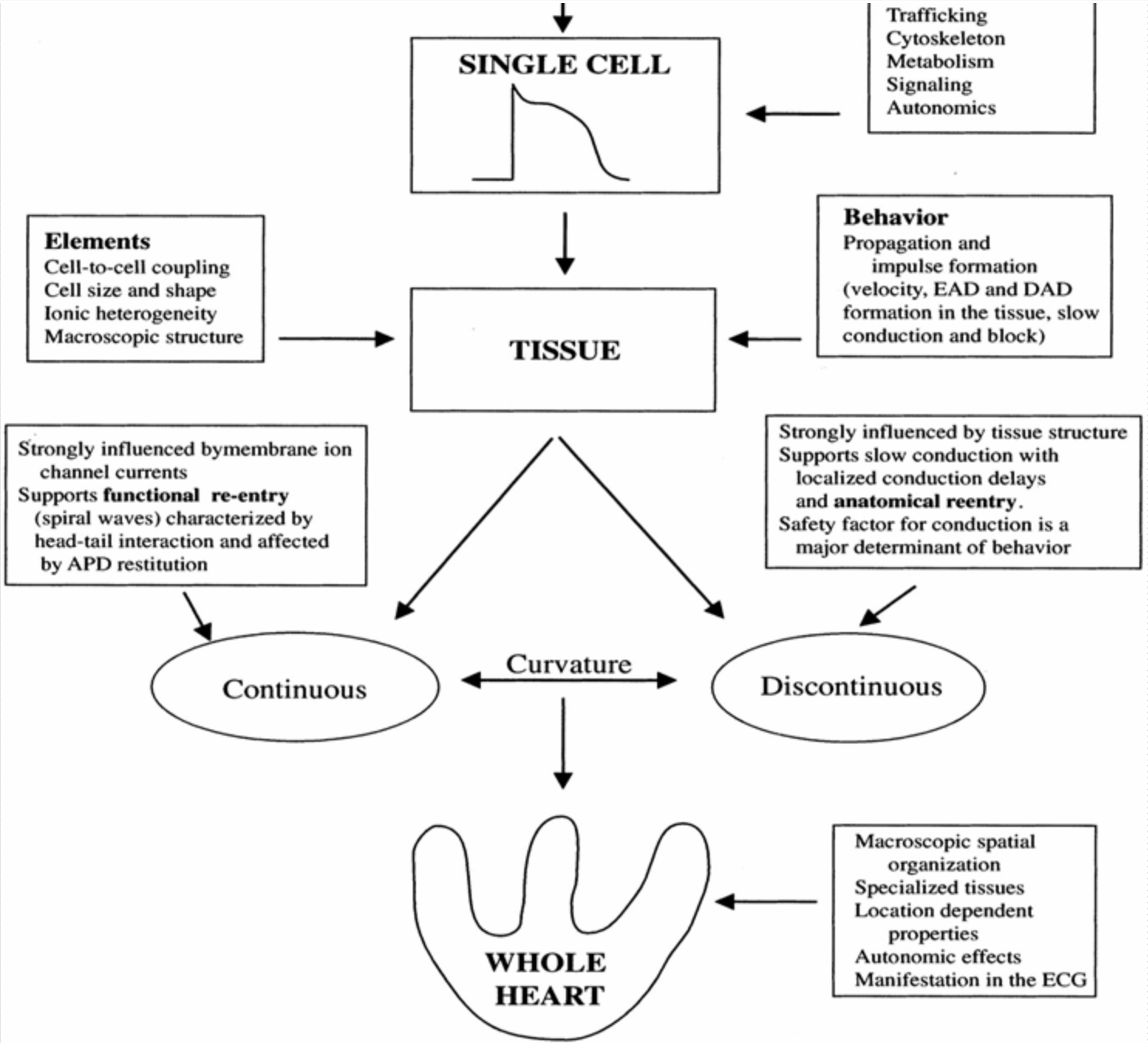
| Bretylium | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Digoxin | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Diltiazem hydrochloride | ↓ Dosage | . . . | ↓ Dosage | ±↑ Serum digoxin level | . . . | ↓ Dosage | . . . |
| Disopyramide | Avoid | ↓ Dosage | ±↓ Dosage | . . . | . . . | . . . | ↑ Dosage |
| Flecainide | Avoid | ↓ Dosage | . . . | ↑ Serum digoxin level | . . . | ±↓ Dosage | . . . |
| Ibutilide | . . . | . . . | . . . | . . . | . . . | . . . | . . . |
| Lidocaine | ↓ Dosage | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Mexiletine hydrochloride | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | ↑ Dosage |
| Moricizine | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Phenytoin | . . . | . . . | ↓ Dosage | . . . | . . . | ↓ Dosage | . . . |
| Procainamide hydrochloride | ±↓ Dosage | ↓ Dosage | . . . | . . . | . . . | ↓ Dosage | . . . |
| Propafenone hydrochloride | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | ↑ Protime | ±↓ Dosage | . . . |
| Quinidine | . . . | . . . | ↓ Dosage | ↑↑ Serum digoxin level | ±↓ Warfarin dosage | ↓ Dosage | ↑ Dosage |
| Sotalol hydrochloride | Cautious use | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Tocainide | . . . | ↓ Dosage | . . . | . . . | . . . | . . . | . . . |
| Verapamil | Cautious use | . . . | ↓ Dosage | ↑ Serum digoxin level | . . . | ↓ Dosage | ±↑ Dosage (phenobarbital) |

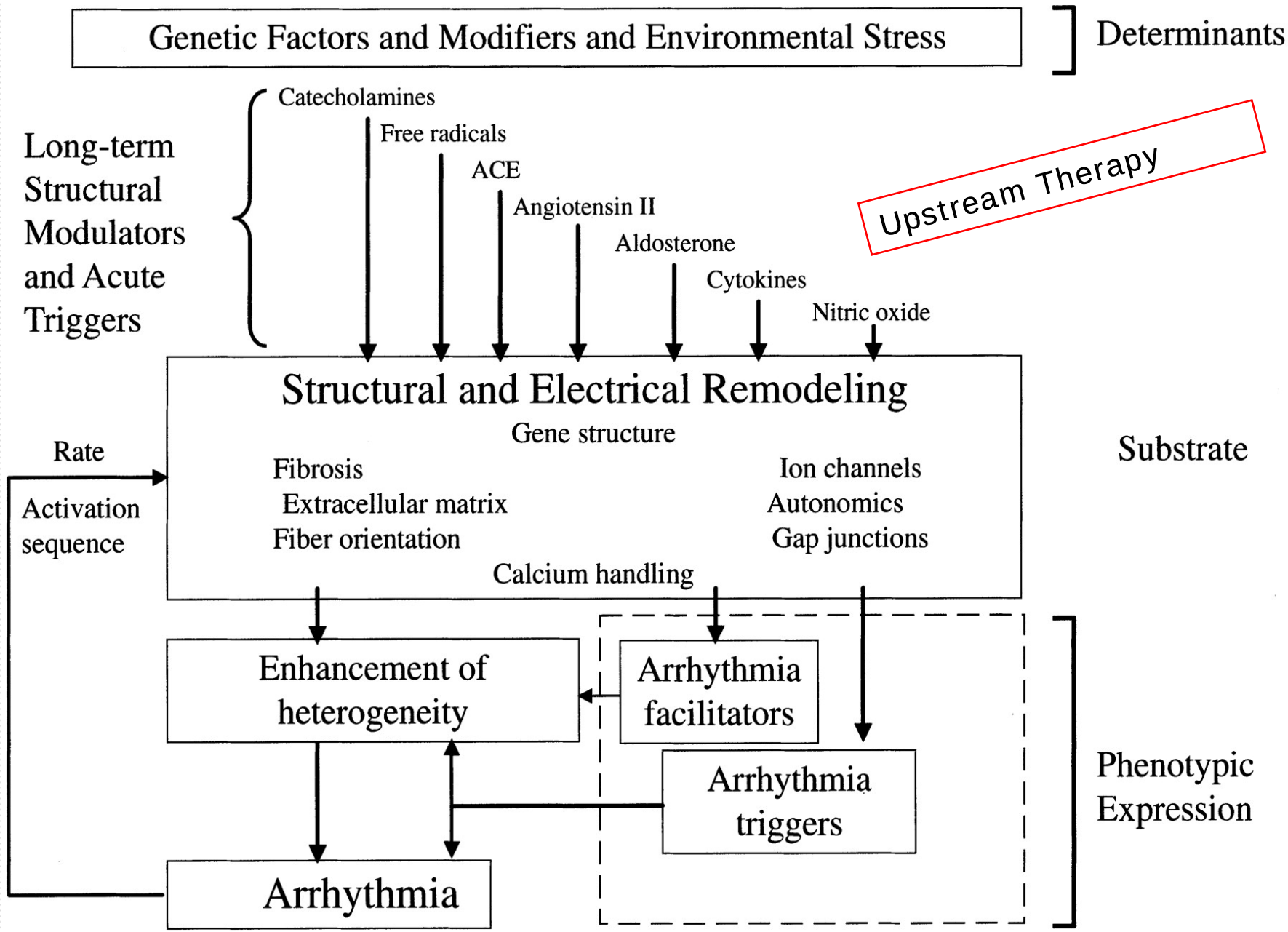
# New Approach to Antiarrhythmic Therapy

## Members of the Sicilian Gambit

Circulation 2001;104:2865


SINGLE CELL
Trafficking
Cytoskeleton
Metabolism
Signaling
Autonomics
Elements
Cell-to-cell coupling
Cell size and shape
Ionic heterogeneity
Macroscopic structure
TISSUE
Behavior
Propagation and impulse formation (velocity, EAD and DAD formation in the tissue, slow conduction and block)
Strongly influenced bymembrane ion channel currents
Supports functional re-entry (spiral waves) characterized by head-tail interaction and affected by APD restitution
Strongly influenced by tissue structure
Supports slow conduction with localized conduction delays and anatomical reentry.
Safety factor for conduction is a major determinant of behavior
Continuous
Curvature
Discontinuous
WHOLE HEART
Macroscopic spatial organization
Specialized tissues
Location dependent properties
Autonomic effects
Manifestation in the ECG


Genetic Factors and Modifiers and Environmental Stress
Determinants
Long-term Structural Modulators and Acute Triggers
Catecholamines
Free radicals
ACE
Angiotensin II
Aldosterone
Cytokines
Nitric oxide
Upstream Therapy
Structural and Electrical Remodeling
Gene structure
Fibrosis
Extracellular matrix
Fiber orientation
Ion channels
Autonomics
Gap junctions
Calcium handling
Substrate
Rate
Activation sequence
Enhancement of heterogeneity
Arrhythmia facilitators
Arrhythmia triggers
Arrhythmia
Phenotypic Expression

European Heart Journal
doi:10.1093/eurheartj/ehq278

ESC GUIDELINES

# Guidelines for the management of atrial fibrillation

**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)†**

**Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)**

2010

European Heart Journal

http://eurheartj.oxfordjournals.org/

**ACC/AHA/ESC PRACTICE GUIDELINES**

# ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

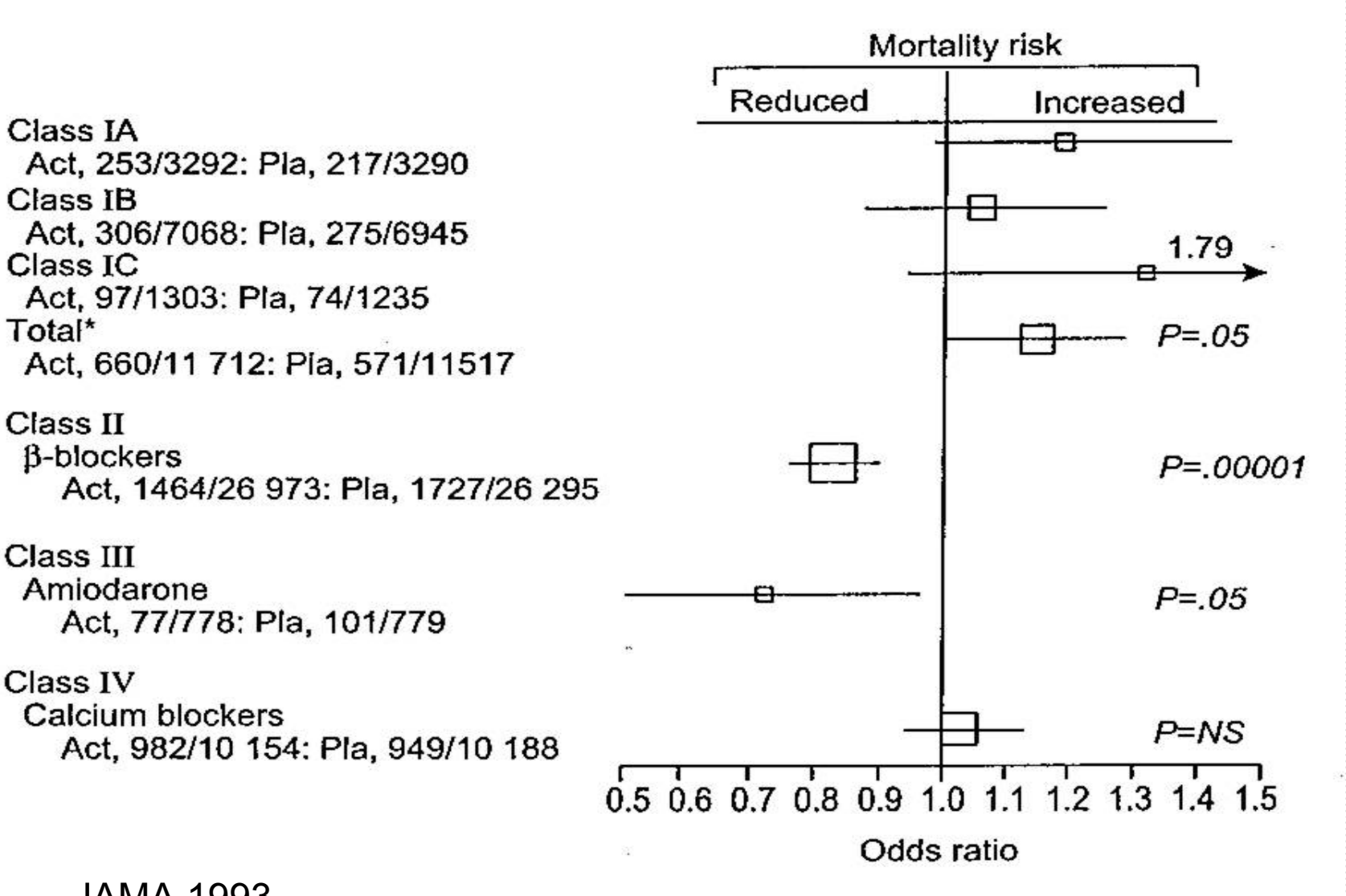
A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death)

*Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society*


**WRITING COMMITTEE MEMBERS**

Douglas P. Zipes, MD, MACC, FAHA, FESC, *Co-Chair*
A. John Camm, MD, FACC, FAHA, FESC, *Co-Chair*

# השפעת תרופות אנטיאריתמיות על תמותה




JAMA 1993

# 6. THERAPIES FOR VENTRICULAR ARRHYTHMIAS

## *6.2. Drug Therapy*

- AA drugs have not been shown to be effective for primary prevention (exception of BB)
- AA may be effective as adjunctive therapy under special circumstances
- Potential adverse side effects

### *6.3.1.2. Amiodarone and Sotalol*

- Both sotalol and amiodarone have also been shown to reduce the frequency of ICD shock therapy

# Brugada Syndrome

**Class IIb**

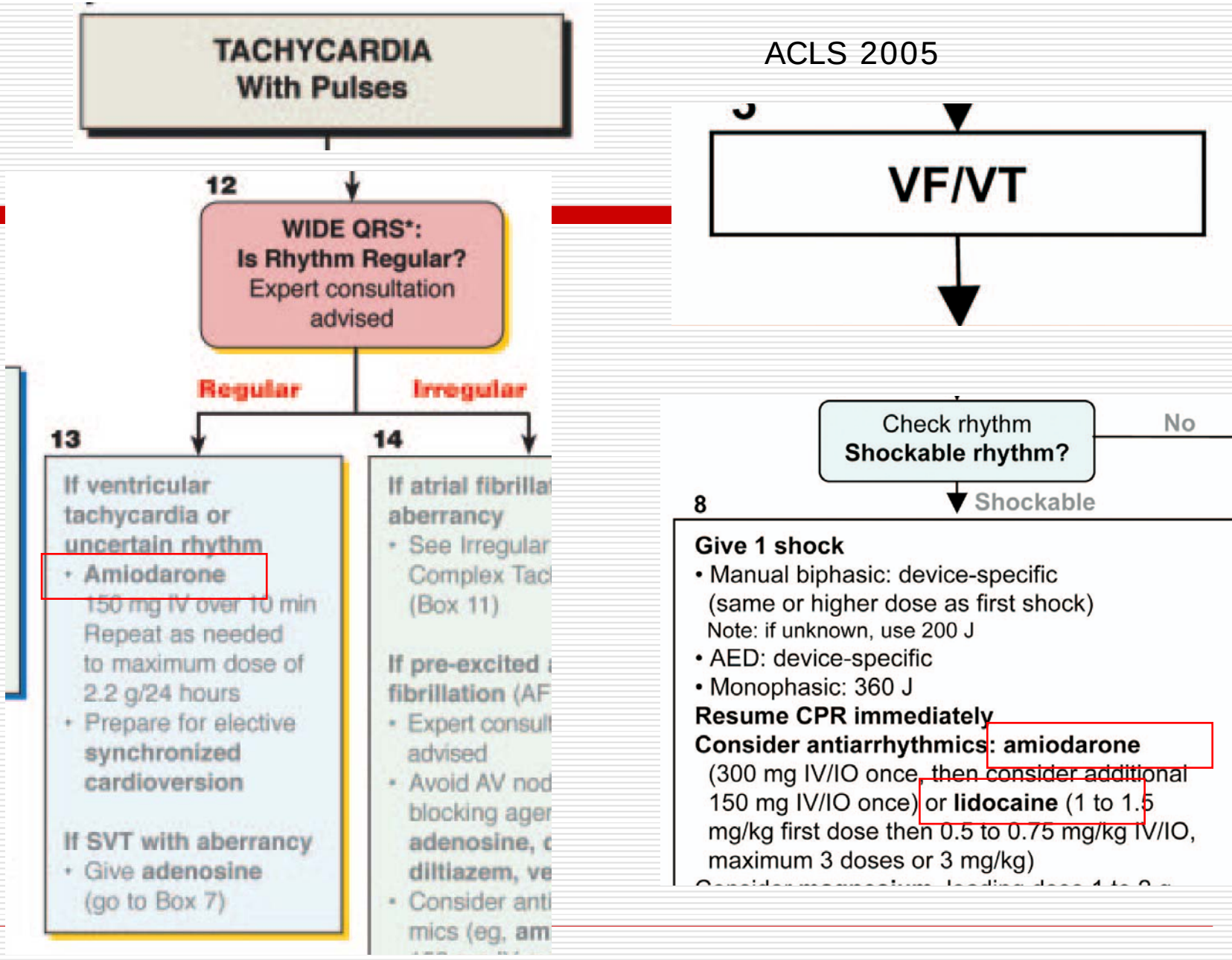
1. **EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation with or without a mutation in the *SCN5A* gene. *(Level of Evidence: C)***
2. **Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. *(Level of Evidence: C)***

# 7.1.1. Arrhythmias Associated With Acute Coronary Syndromes

*7.1.1.3. Unstable Sustained Ventricular Tachycardia*

For recurrent VT, if VT is monomorphic and the EF is normal, either procainamide, sotalol, amiodarone, or lidocaine can be used. Alternately, if the EF is low, amiodarone or lidocaine is recommended (amiodarone 150 mg intravenously over 10 min or lidocaine 0.5 to 0.75 mg/kg intrave-

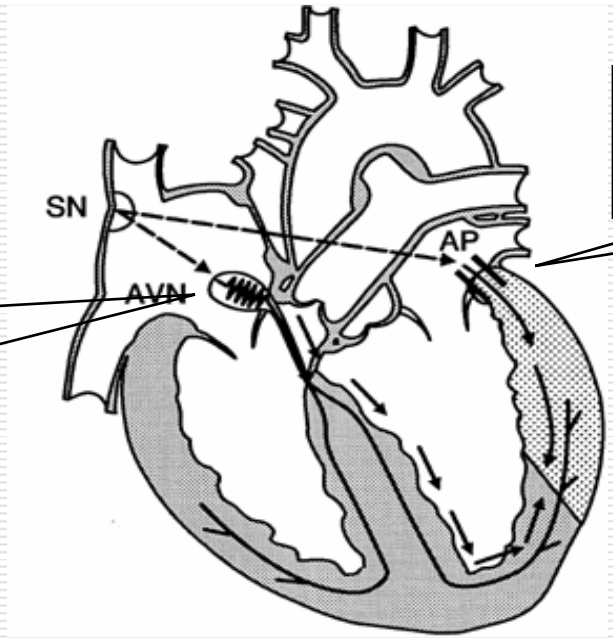
ACLS 2005


TACHYCARDIA
With Pulses
12
WIDE QRS*:
Is Rhythm Regular?
Expert consultation advised
Regular
Irregular
13
If ventricular tachycardia or uncertain rhythm
• Amiodarone
150 mg IV over 10 min
Repeat as needed to maximum dose of 2.2 g/24 hours
• Prepare for elective synchronized cardioversion
If SVT with aberrancy
• Give adenosine
(go to Box 7)
14
If atrial fibrilla
aberrancy
• See Irregular
Complex Tac
(Box 11)
If pre-excited
fibrillation (AF
• Expert consult
advised
• Avoid AV nod
blocking ager
adenosine, c
diltiazem, ve
• Consider anti
mics (eg, am
VF/VT
Check rhythm
Shockable rhythm?
No
Shockable
8
Give 1 shock
• Manual biphasic: device-specific
(same or higher dose as first shock)
Note: if unknown, use 200 J
• AED: device-specific
• Monophasic: 360 J
Resume CPR immediately
Consider antiarrhythmics: amiodarone
(300 mg IV/IO once, then consider additional 150 mg IV/IO once) or lidocaine (1 to 1.5 mg/kg first dose then 0.5 to 0.75 mg/kg IV/IO, maximum 3 doses or 3 mg/kg)

**Pharmacologic Agents for Prophylactic Treatment of Supraventricular Tachycardia (SVT).***

| Drug | Usual Maintenance Dose | Major Side Effects | Cautions, Contraindications |
|---|---|---|---|
| **SVT without preexcitation** | | | |
| Beta-blockers† | | Hypotension, heart block, bradycardia | Asthma, congestive heart failure |
| Metoprolol | 50–200 mg daily | | |
| Bisoprolol | 2.5–10 mg daily | | |
| Atenolol | 50–100 mg daily | | |
| Propranolol‡§ | 80–240 mg daily | | |
| Calcium-channel blockers | | Hypotension, heart block, negative inotropic effect | Congestive heart failure |
| Diltiazem‡ | 180–360 mg daily | | |
| Verapamil‡ | 120–480 mg daily | Interaction with digoxin, constipation | |
| Digoxin | 0.125–0.375 mg daily | Toxic effects of digitalis, bradycardia | Serum levels should be monitored |
| **SVT with preexcitation and SVT refractory to atrioventricular-node–blocking agents** | | | |
| First-line agents | | | |
| Class IC drugs | | Ventricular tachycardia, enhanced atrioventricular nodal conduction, negative inotropic effect | Ischemic and structural heart disease |
| Flecainide | 100–300 mg daily | In addition to above-mentioned side effects of class IC drugs, interaction with digoxin | |
| Propafenone‡ | 450–900 mg daily | | Drug accumulation in 5–10% of patients with cytochrome P-450 2D6 deficiency |
| **Alternative agents** | | | |
| Amiodarone | 200 mg daily | Skin discoloration, hypothyroidism or hyperthyroidism, gastrointestinal upset, hepatotoxic effects, corneal deposits, tremor, optic neuropathy, pulmonary toxicity | Interaction with oral anticoagulants |
| Sotalol | 160–320 mg daily | Hypotension, heart block, bradycardia, torsades de pointes (latter is dose-dependent; increased risk in women, in patients with left ventricular hypertrophy, and in those with low potassium plasma levels) | Asthma, congestive heart failure; dose reduction in elderly patients and those with renal failure; most studied and used antiarrhythmic drug during pregnancy (class B) |

# WPW




תרופות המשפיעות
על AP

תרופות המשפיעות
על AVN

תרופות המשפיעות
על AVN ועל AP

## Pharmacologic Agents for Short-Term Treatment of Supraventricular Tachycardia (SVT).*

**SVT and atrial fibrillation with preexcitation and SVT refractory to drugs listed above**

| | | |
|---|---|---|
| Procainamide | 30 mg/min continuous infusion to a maximal dose of 17 mg/kg (maintenance infusion of 2–4 mg/min) | Hypotension, widening of QRS complex, torsades de pointes |
| Flecainide | 2 mg/kg over a 10-min period | Negative inotropic effect, rapidly conducting atrial flutter, widening of QRS complex |
| Propafenone | 2 mg/kg over a 10-min period | |
| Ibutilide | If ≥60 kg: 1 mg over a 10-min period<br>If <60 kg: 0.01 mg/kg over a 10-min period<br>Repeat once if no response after 10 additional min | Prolongation of QT interval, torsades de pointes |

**Amiodarone**

# תרופות אנטיאריתמיות בהריון

**Table 4.** Definitions of U.S. FDA Classification (Use in Pregnancy Setting

| FDA Classification | Definition |
|---|---|
| Category A | Controlled studies show no risk. Adequate well-controlled studies in pregnant women have failed to demonstrate risk to the fetus. |
| Category B | No evidence of risk in humans. Either animal studies show risk, but human studies do not, or, if no adequate human studies have been done, animal findings are negative. |
| Category C | Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or are lacking as well. However, potential benefits may justify the potential risk |
| Category D | Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits of the drug may be acceptable when they outweigh the potential risk. |
| Category X | Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing report, have shown fetal risk that clearly outweighs any possible benefits to the patients. |

FDA indicates Food and Drug Administration.

- חלק מן התרופות נכנסו לשימוש בשל העדר דיווחים על תופעות לוואי
- D - Amiodarone
- D - Atenolol
- B - Sotalol
- C - אחרים

**Recommendations for Treatment Strategies for Supraventricular Tachycardia During Pregnancy**

| Treatment Strategy | Recommendation | Classification | Level of Evidence |
|---|---|---|---|
| **Acute conversion of PSVT** | Vagal maneuver | I | C |
| | Adenosine | I | C |
| | DC cardioversion | I | C |
| | Metoprolol, propranolol | IIa | C |
| | Verapamil | IIb | C |
| **Prophylactic therapy** | Digoxin | I | C |
| | Metoprolol* | I | B |
| | Propranolol* | IIa | B |
| | Sotalol,* flecainide† | IIa | C |
| | Procainamide | IIb | B |
| | Quinidine, propafenone,† verapamil | IIb | C |
| | Catheter ablation | IIb | C |
| | Atenolol‡ | III | B |
| | Amiodarone | III | C |

# Antiarrhythmic Drugs:
# Agents with occasionally beneficial side-effects

## תרופות אנטיאריתמיות הינן תרופות בעלות תופעות לוואי אלקטרופיזיולוגיים

## אשר לעיתים גם מועילים