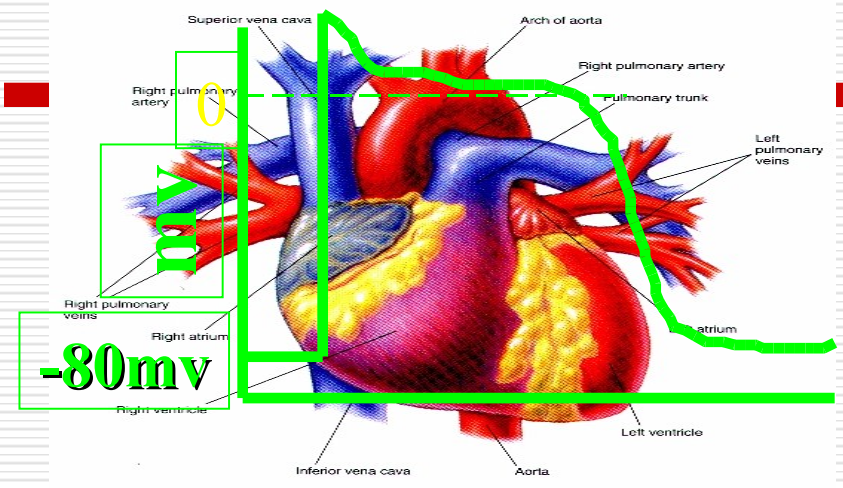
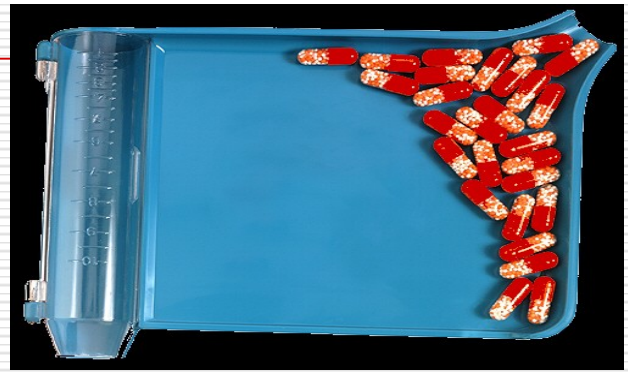
תרופות אנטיאריתמיות

Antiarrhythmic Drugs





קורס למתמחים, קיסריה 11.2008

Prof. Amos Katz

פרופ עמוס כץ

Cardiology Depart

המערך הקרדיולו

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
- Vaughn Williams classification
  - Ion Channel blockers
- Adverse effects:
  - Cardiovascular
    - Proarrhythmia
    - Exacerbation of CHF
  - Noncardiovascular
- AF Model
- Special Situation
  - ICD
  - PM
  - 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

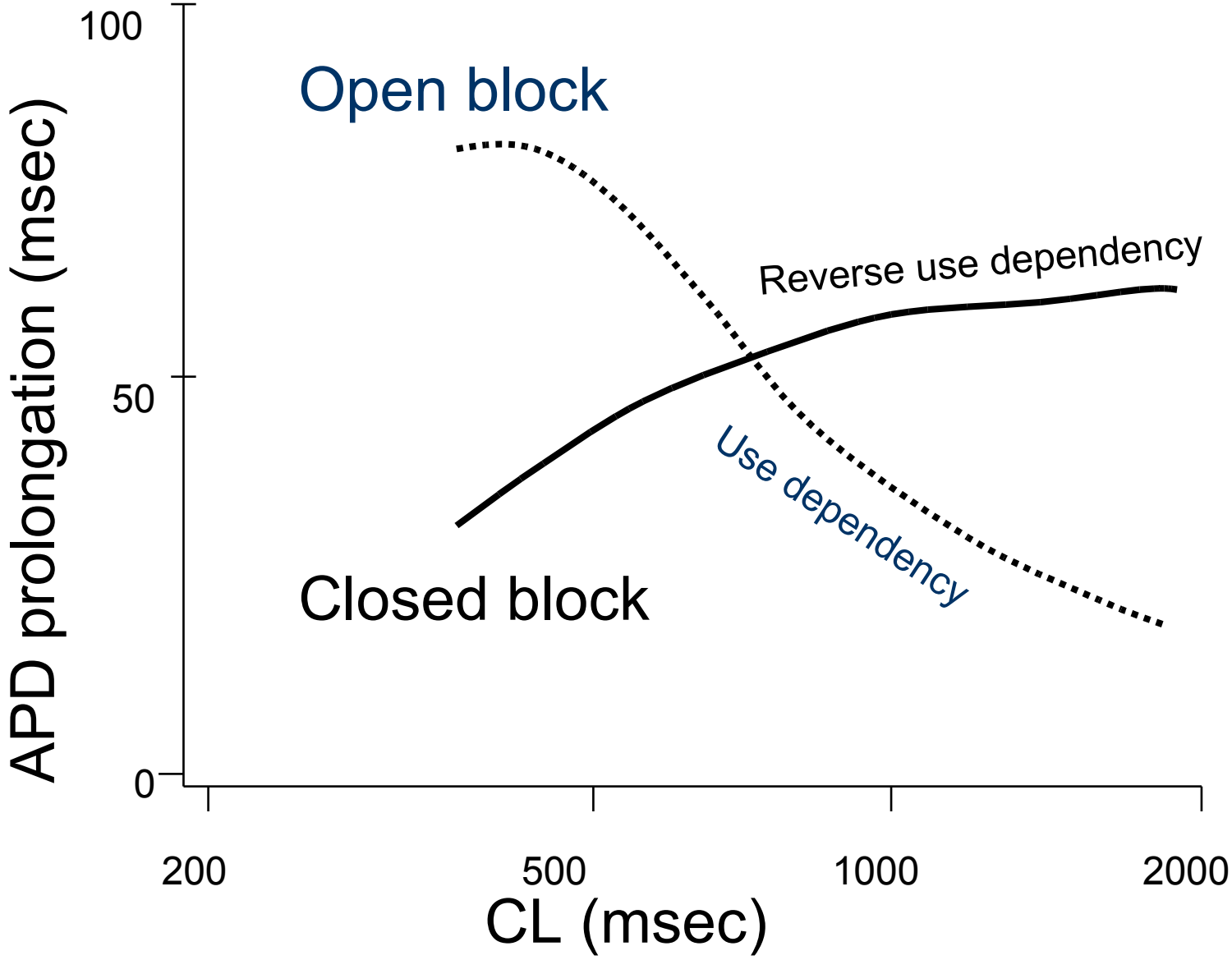
USE-DEPENDENCE

- **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 time diastole - slower rate
  - a greater proportion of receptors become drug free

REVERSE USE-DEPENDENCE

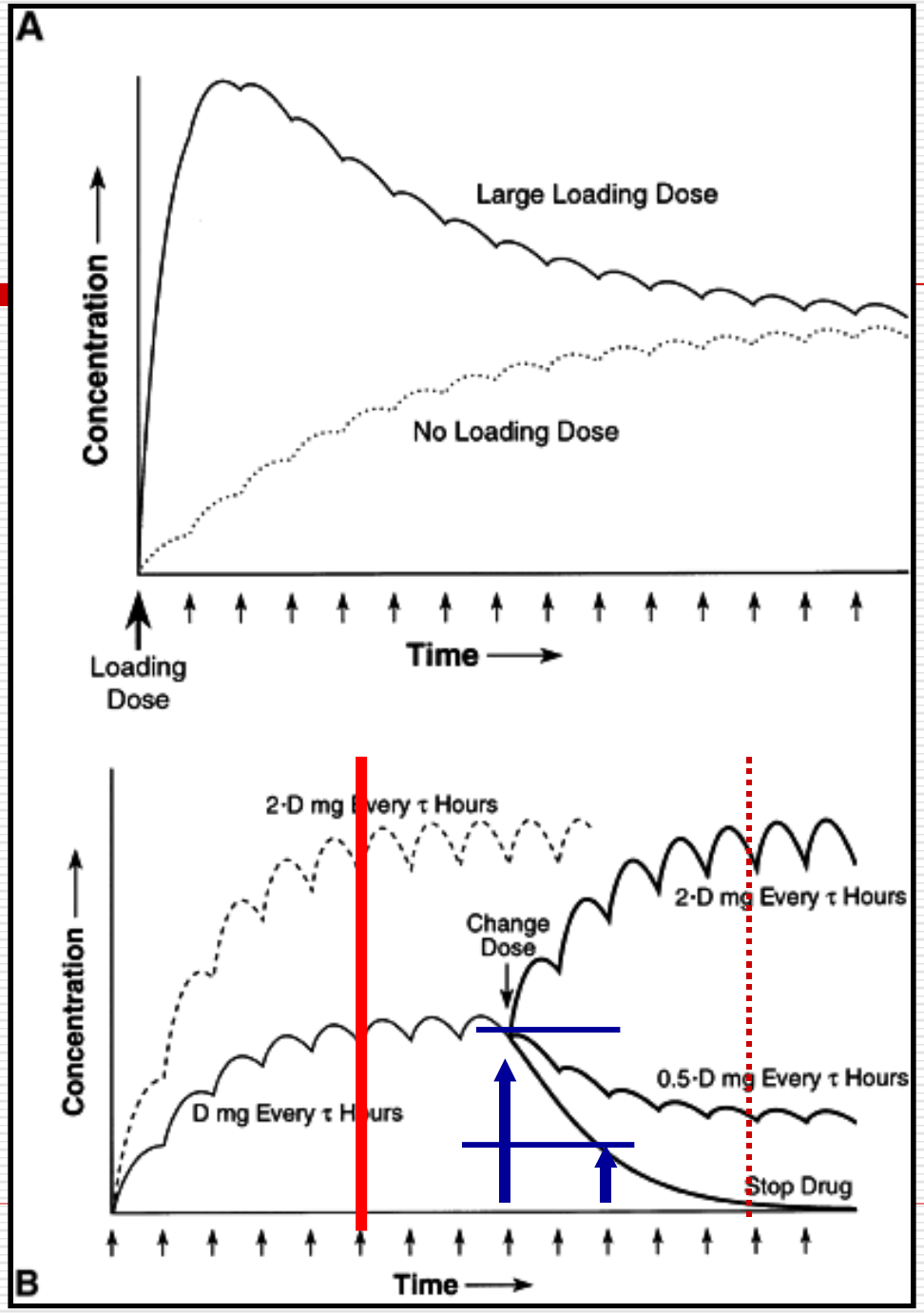
- Exert greater effects at slow rates than at fast rates
- Particularly true for drugs that lengthen repolarization
- The QT interval becomes prolonged more at slow than fast rates
- This effect is opposite to what the ideal antiarrhythmic - precipitating torsades de pointes.

Use Dependency

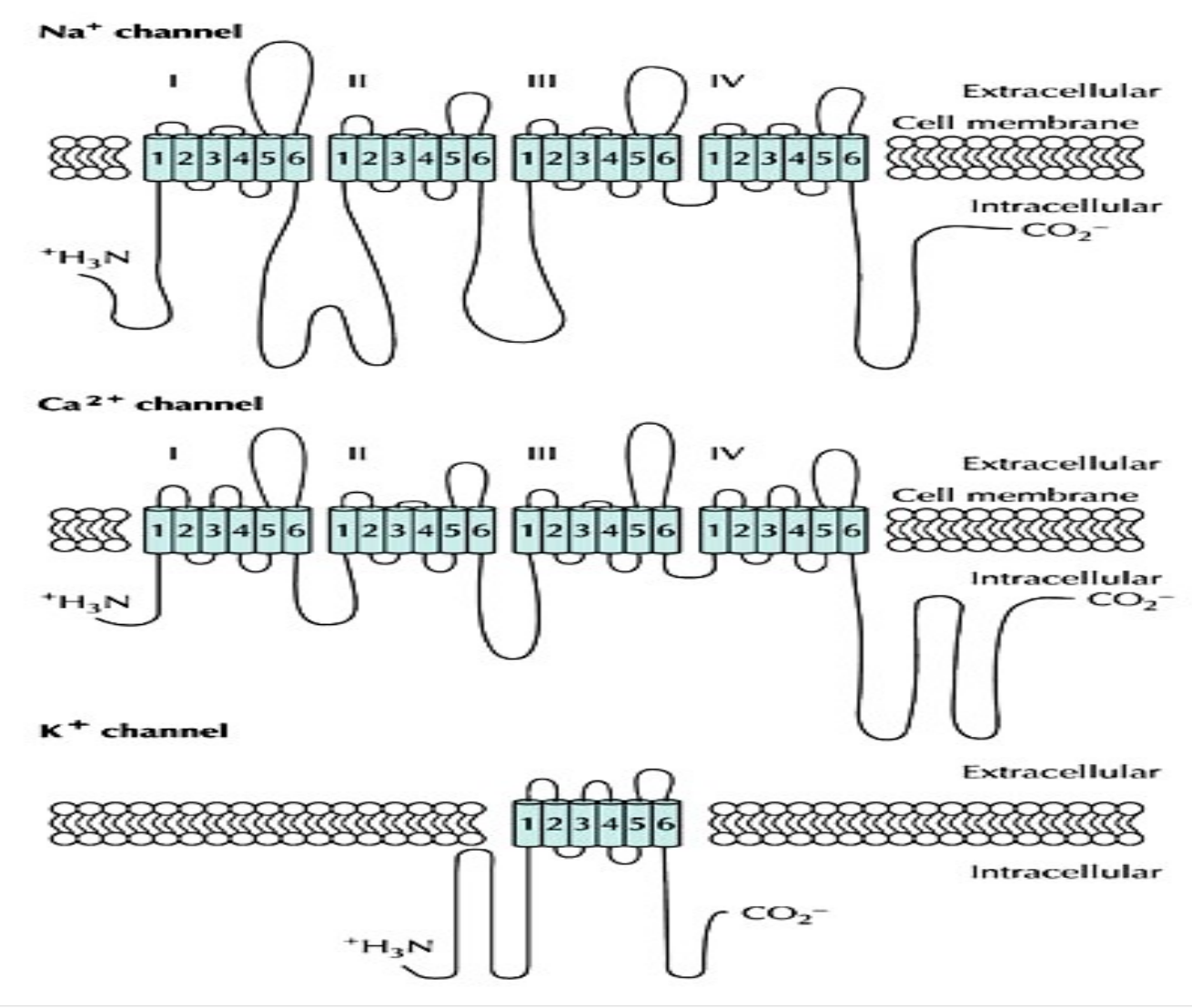


Pharmacokinetics Principles

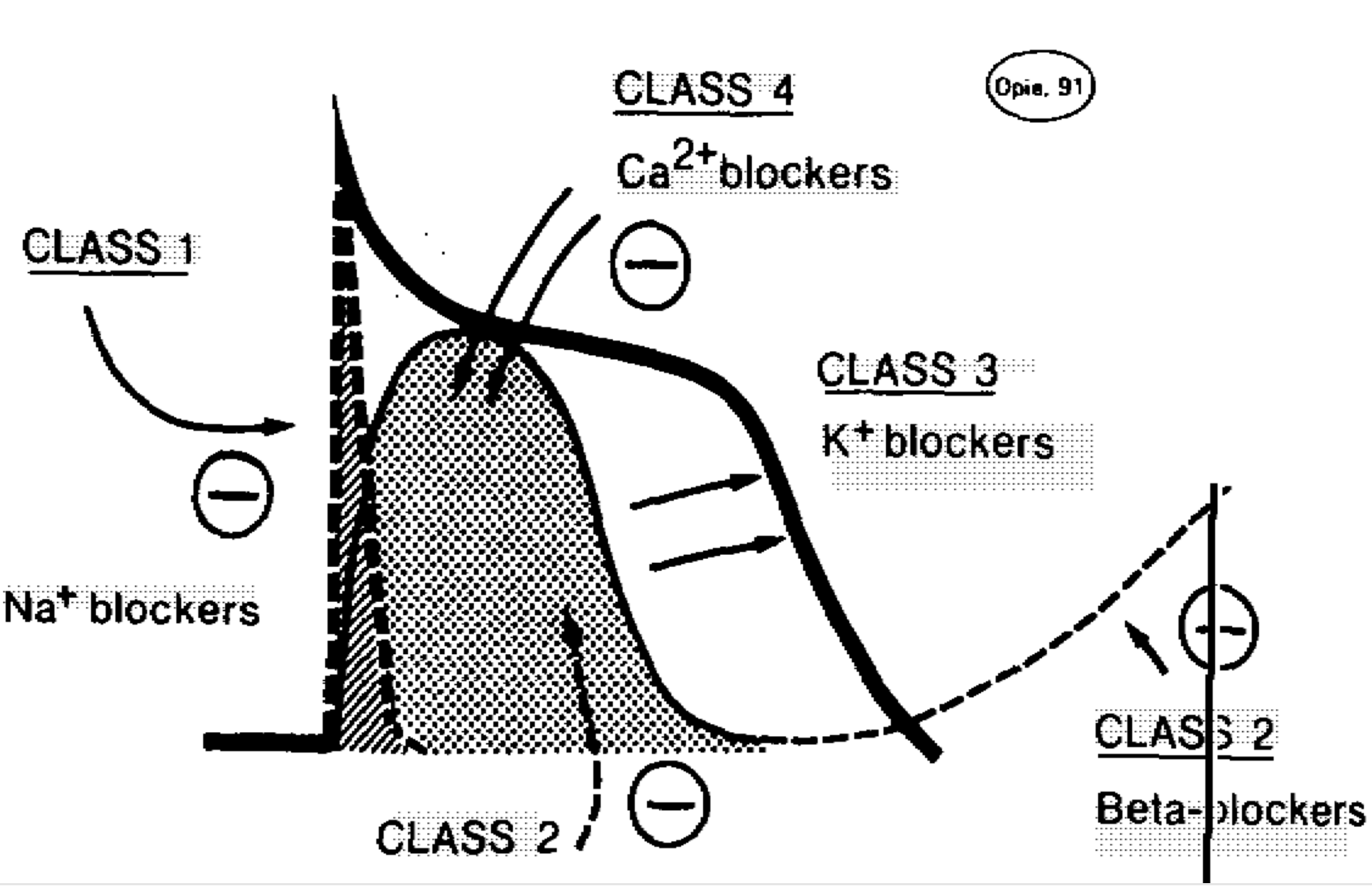
Absorption, Distribution, Elimination


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

Ion Channel Concepts



Antiarrhythmic Mechanisms of Action



סווג של תרופות אנטיאריתמיות

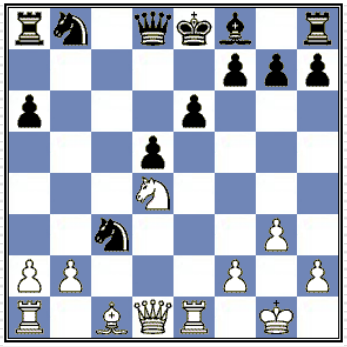
Vaughn Williams

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

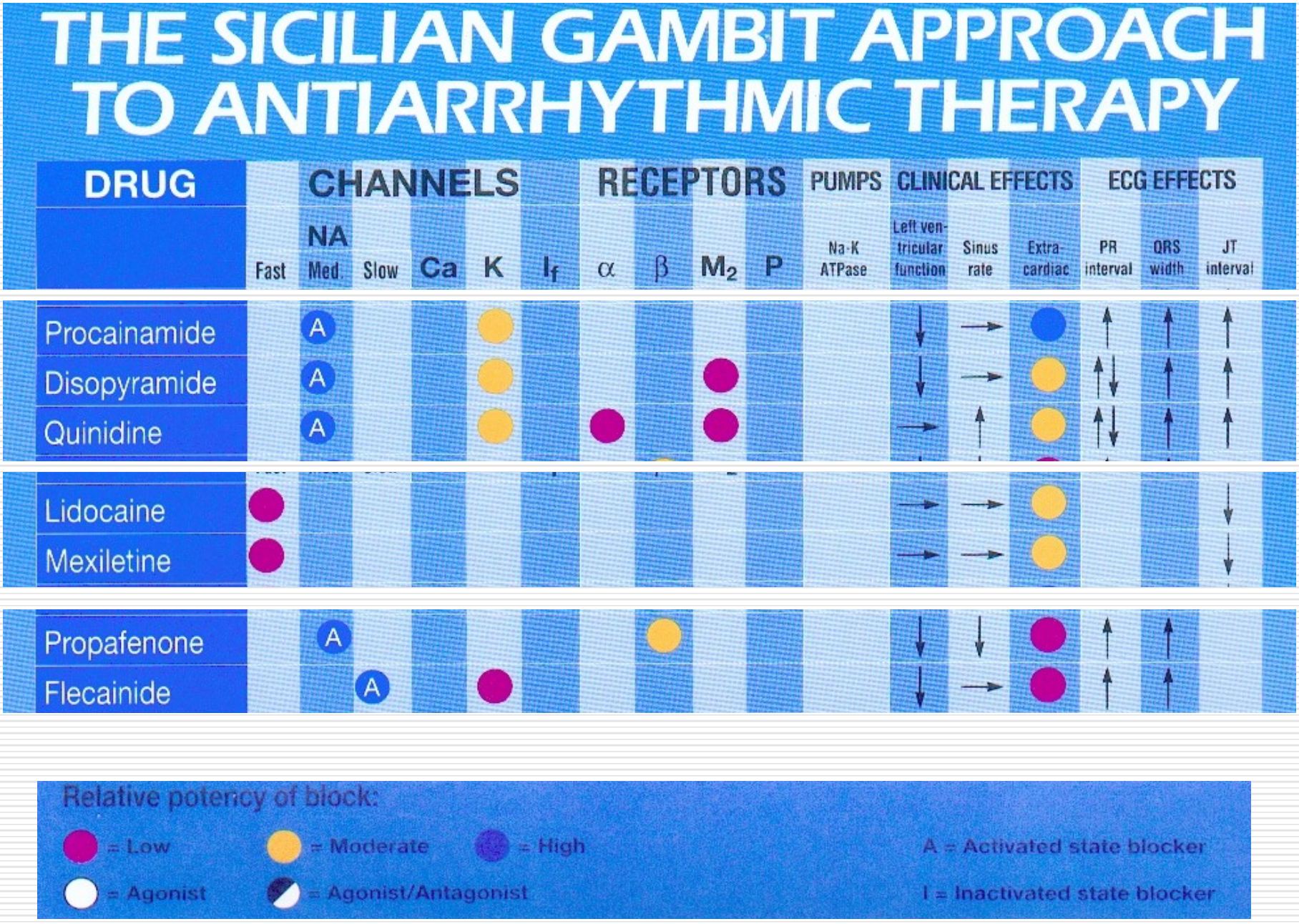
- Digoxin
- Adenosine

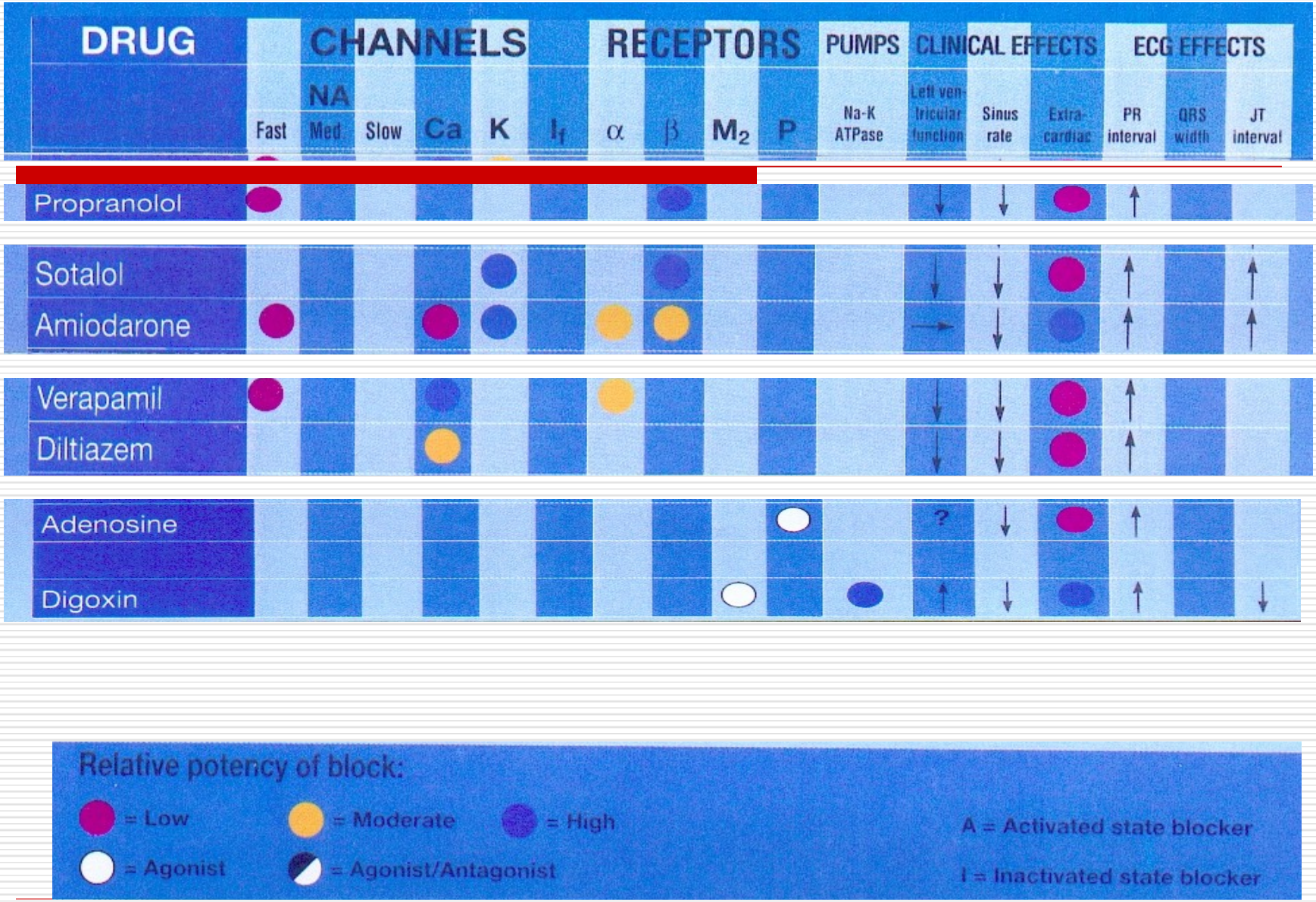
The Sicilian Gambit

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
Procainamide
Disopyramide
Quinidine
Lidocaine
Mexiletine
Propafenone
Flecainide
A
Relative potency of block:
= Low
= Moderate
= High
= Agonist
= Agonist/Antagonist
A = Activated state blocker
I = Inactivated state blocker


DRUG
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Extracardiac
PR interval
QRS width
JT interval
Propranolol
Sotalol
Amiodarone
Verapamil
Diltiazem
Adenosine
Digoxin
?
Relative potency of block:
= Low
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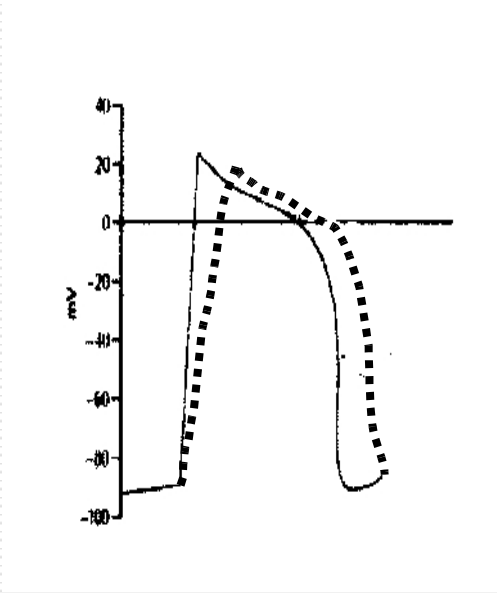
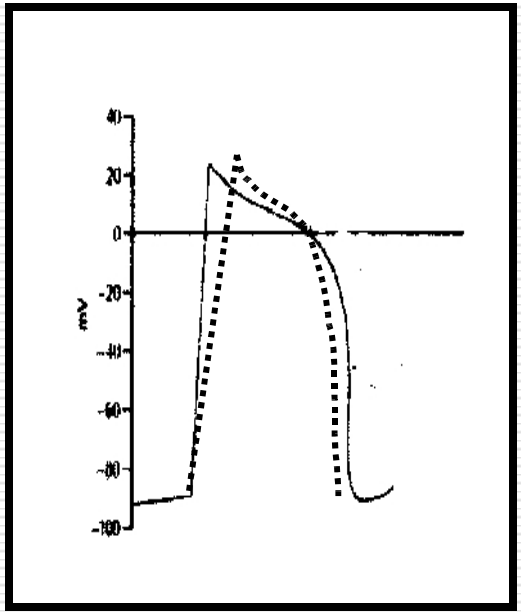
Mechanisms of Action of Antiarrhythmic Drugs Class I

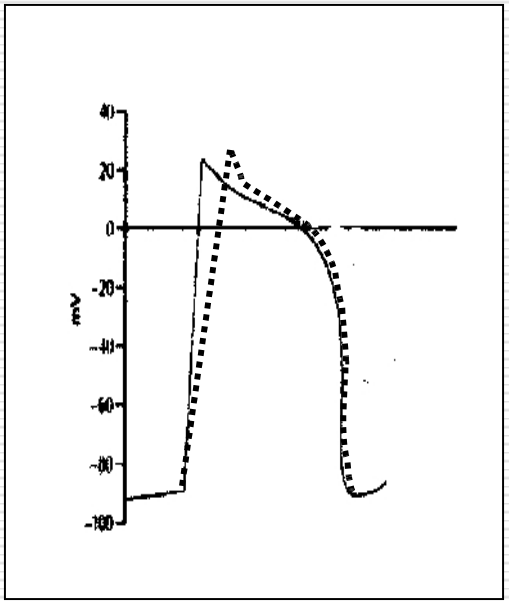
a



b

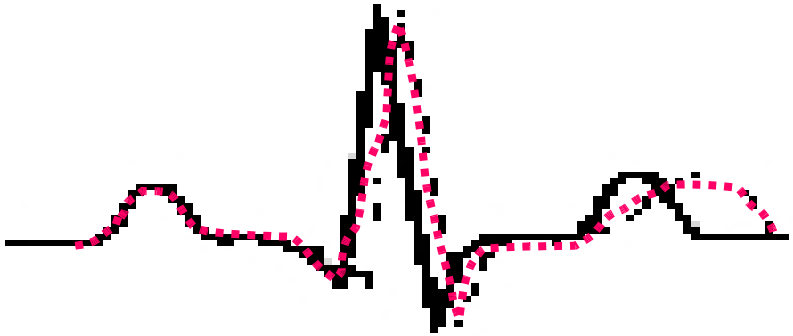


c

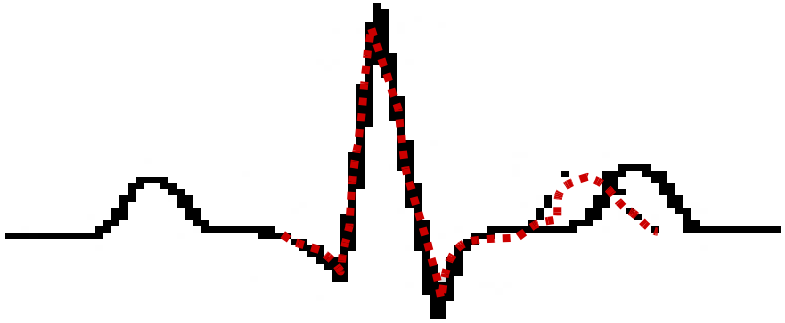


C > A > B

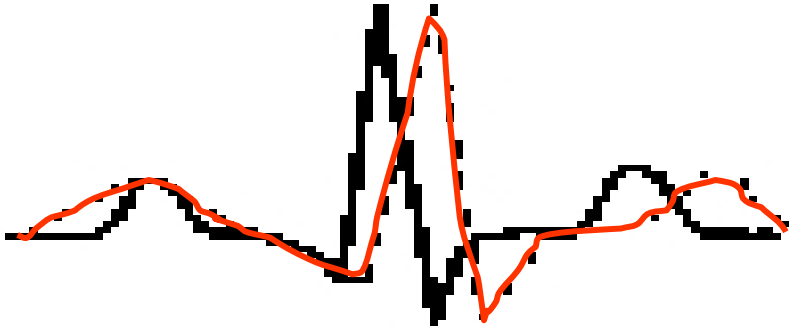
Ia



Ib



Ic

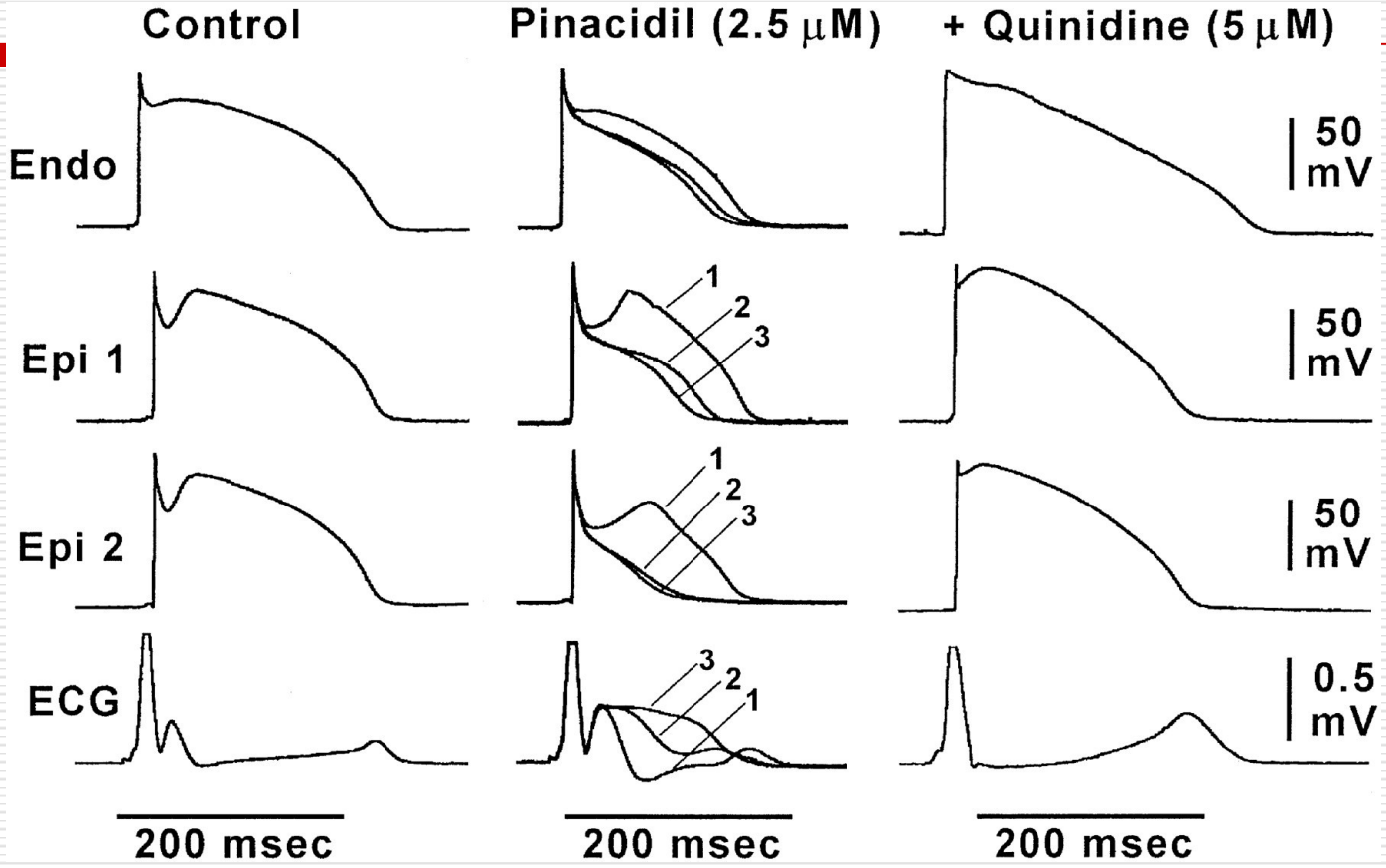


Quinidine

Quinidine: a valuable medication joins the list of 'endangered species Sami ViskinEuropace 2007

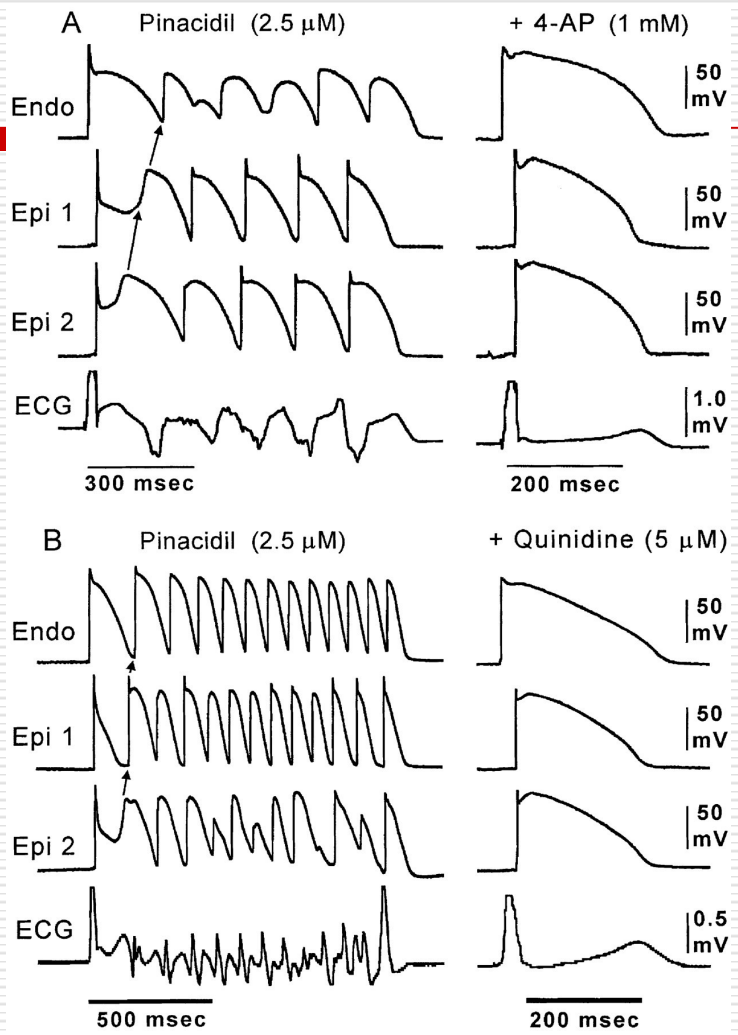
- Brugada syndrome
- congenital short QT syndrome
- Idiopathic VF
- *AF?*
- *ICD?*

Effect of quinidine on pinacidil-induced ST-segment elevation



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

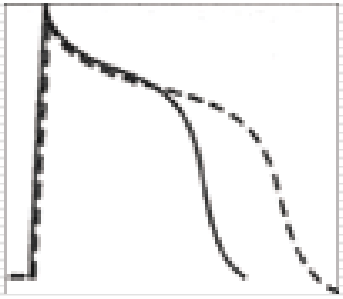
Effects of Ito blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in arterially perfused RV wedge preparation



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

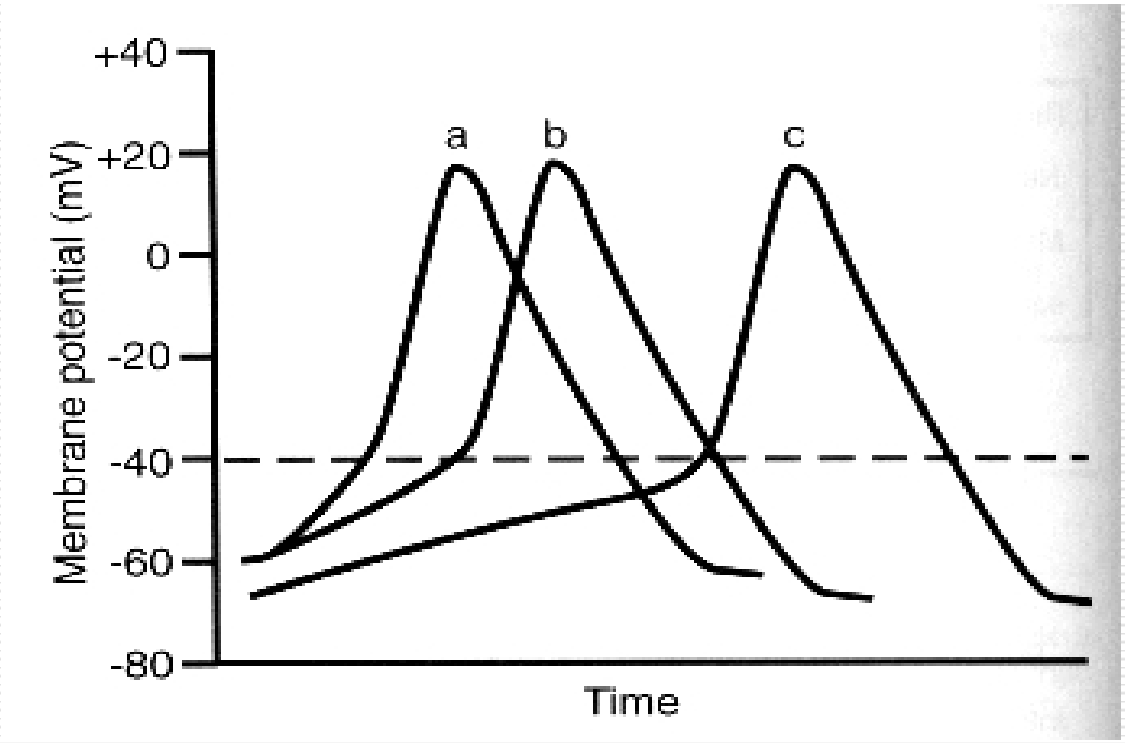
Lidocaine

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

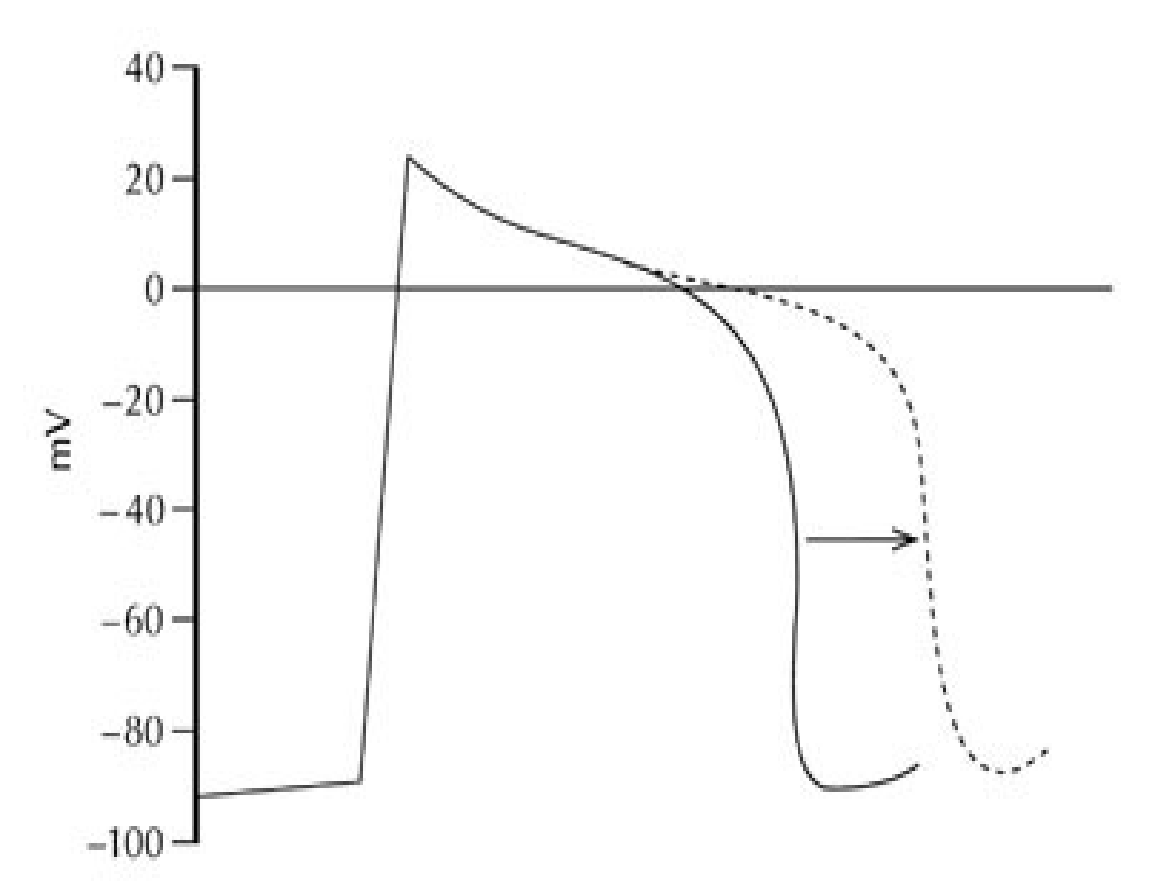


- **Decreases refractoriness**
- **Blocks Na^+ entry during the plateau phase of AP.**
- **APs of longer duration have greater "window currents".**
- **Therefore, APs of greater duration are preferentially shortened.**

Mechanisms of Action of Antiarrhythmic Drugs Class II



Mechanisms of Action of Antiarrhythmic Drugs Class III



Class III

Drugs that prolong repolarization

Amiodarone

Sotalol

Bretylium

Dofetilide

Ibutilide

Azimelide

Dronedarone

Amiodarone: a multifactorial approach

K^+ channel blockade

Na^+ channel blockade

Phospholipase inhibition

Overall Effect

- Slows the heart, lowers MVO_2
- Maintains cardiac output
- Inhibits ventricular tachycardia
- Negligible proarrhythmic activity
- Minimises effects of early depolarisation
- No negative inotropicity
- Prolonged therapeutic effect

Sympathetic blockade

No effect on LV function

Ca^{++} channel blockade

Unusually long plasma half life

Thyroid hormone inhibition

"…amiodarone may be effective because of, rather than in spite of, its pharmacological complexity."

Nadamanee,1992

New Class III

- Dofetilide
- Ibutilide
- Azimelide
- Dronedarone
- **- noniodinated benzofuran no iodine**
- **- inhibiting the potassium currents I(Kr), I(Ks), I(KI), I(KACh), I(sus), I Na L-Ca, antiadrenergic properties.**

The NEW ENGLAND JOURNAL of MEDICINE N Engl J Med 2008;358:2678-87.

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*

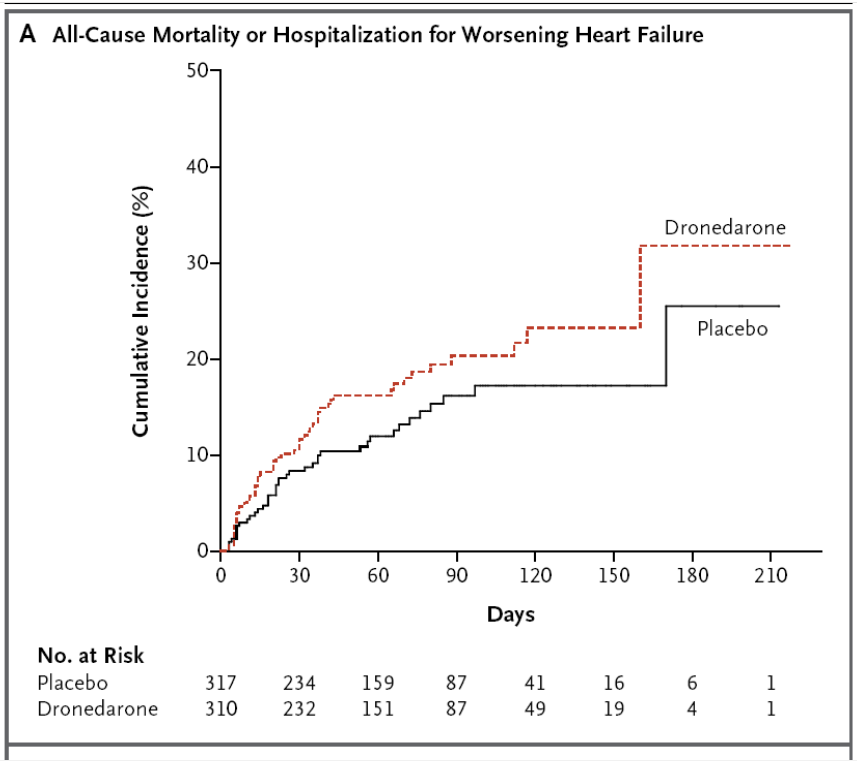
ANDROMEDA

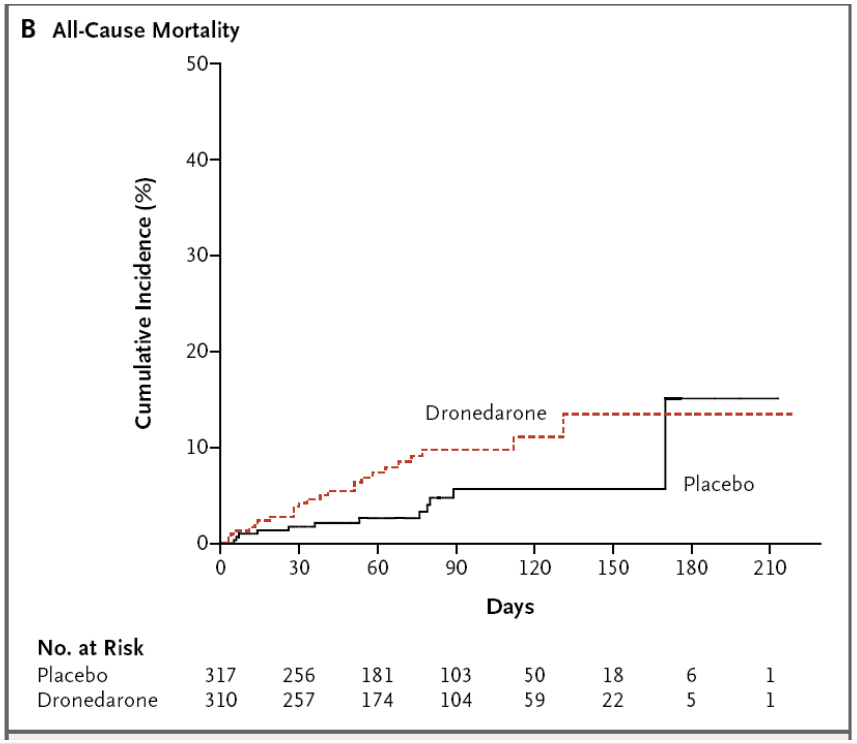
- Multicenter double-blind
- Patients hospitalized with CHF and severe LVD receive 400 mg of dronedarone X2 or placebo.
- Pprimary end point was the composite of death or hospitalization for HF for heart failure.
- 627 patients
- Prematurely terminated
- During a median follow-up of 2 months,
- 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; [CI], 1.07 to 4.25; P = 0.03).
- Excess mortality was predominantly related to worsening of HF

Conclusions

In patients with severe HF and LV systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of heart failure

ANDROMEDA


A All-Cause Mortality or Hospitalization for Worsening Heart Failure
Cumulative Incidence (%)
50
40
30
20
10
0
Dronedarone
Placebo
0
30
60
90
120
150
180
210
Days
No. at Risk
Placebo 317 234 159 87 41 16 6 1
Dronedarone 310 232 151 87 49 19 4 1


B All-Cause Mortality
Cumulative Incidence (%)
50
40
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0
Dronedarone
Placebo
0
30
60
90
120
150
180
210
Days
No. at Risk
Placebo 317 256 181 103 50 18 6 1
Dronedarone 310 257 174 104 59 22 5 1

ATHENA

- A Trial with dronedarone to prevent Hospitalization or dEath in patieNts with Atrial fibrillation/flutter
- Tested the hypothesis that dronedarone, a multichannel blocking antiarrhthymic drug would prolong time to first cardiovascular hospitalization or death in moderate- to high-risk elderly patients with AF
- Prospective, multicenter placebo controlled, minimum follow-up of 1 year

ClinicalTrials.gov Identifier: NCT00174785

Hohnloser SH. *J Cardiovasc Electrophysiol*. 2008;19:69-73

ATHENA: Inclusion criteria

- Paroxysmal or persistent AF:
  - Patients ≥ 75 years or 70-74 years with 1 or more of the following:
    - Hypertension (antihypertensive drugs of at least 2 different classes)
    - Prior CVA (stroke or TIA) or systemic embolism
    - Diabetes
    - Left atrium diameter ≥50 mm by echocardiography
    - LVEF < 0.40 by 2D-echo

ClinicalTrials.gov Identifier: NCT00174785

Hohnloser SH. *J Cardiovasc Electrophysiol*. 2008;19:69-73.

ATHENA

- Unique primary endpoint:
  - Time to first CV hospitalization or all-cause mortality
- Secondary endpoint
  - All cause mortality
  - Cardiovascular death
  - Cardiovascular hospitalization
- >500 international centers
- 4628 patients randomized
- Largest antiarrhythmic drug trial in patients with AF ever conducted

ClinicalTrials.gov Identifier: NCT00174785

Hohnloser SH. *J Cardiovasc Electrophysiol*. 2008;19:69-73.

ATHENA

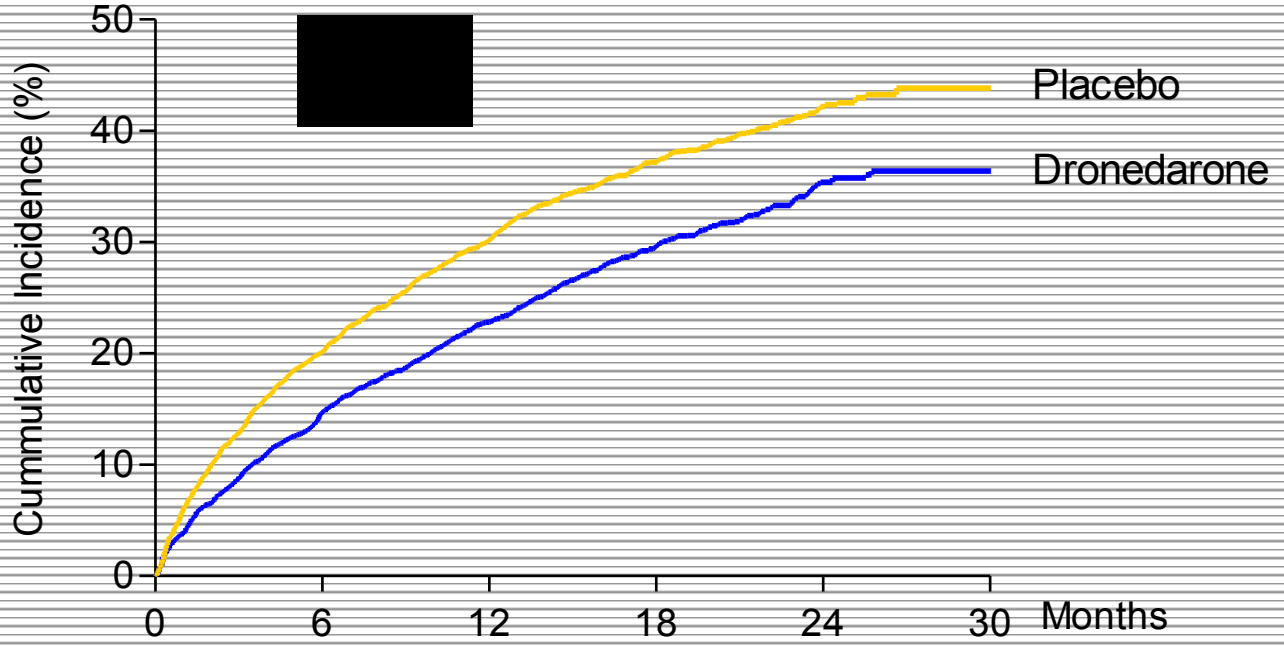
- Population
  - Typical elderly AF population at risk for hospitalization
  - Mean age 72 years
  - 47% female
  - 2/3 structural heart disease
  - 1/3 evidence of coronary heart disease
  - 21% CHF NYHA class II/III, IV HF excluded
  - 12% patients LVEF < 45%
  - 70% on effective baseline medication

ClinicalTrials.gov Identifier: NCT00174785

Hohnloser SH. *J Cardiovasc Electrophysiol*. 2008;19:69-73.

ATHENA: Primary Outcome

Time to first cardiovascular hospitalization or death



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

Mean follow-up 21 ± 5 months

Hohnloser SH. Heart Rhythm Society 2008 Scientific Sessions; May 15, 2008; San Francisco, CA.

New Class III

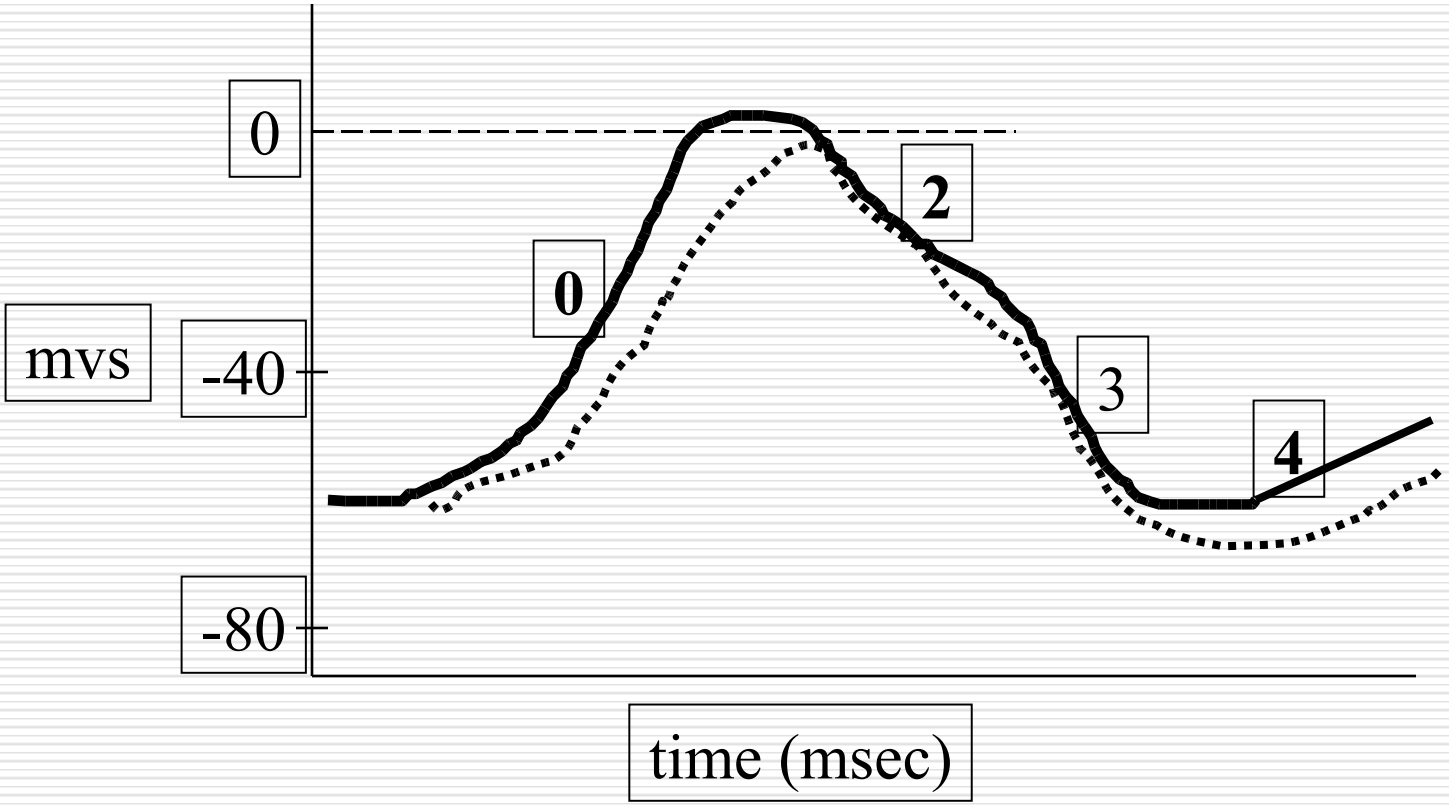
Dronedarone **Son of Amiodarone EURIDIS, ADONIS, ANDROMEDA, ATHENA**

- **Not for CHF**
- **No amiodarone like toxicity; thyroid or pulmonary problems**
- **For normal or moderate hearts**

Class IV

Verapamil
Diltiazem

Mechanisms of Action of Antiarrhythmic Drugs Class IV



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

Therapeutic Uses

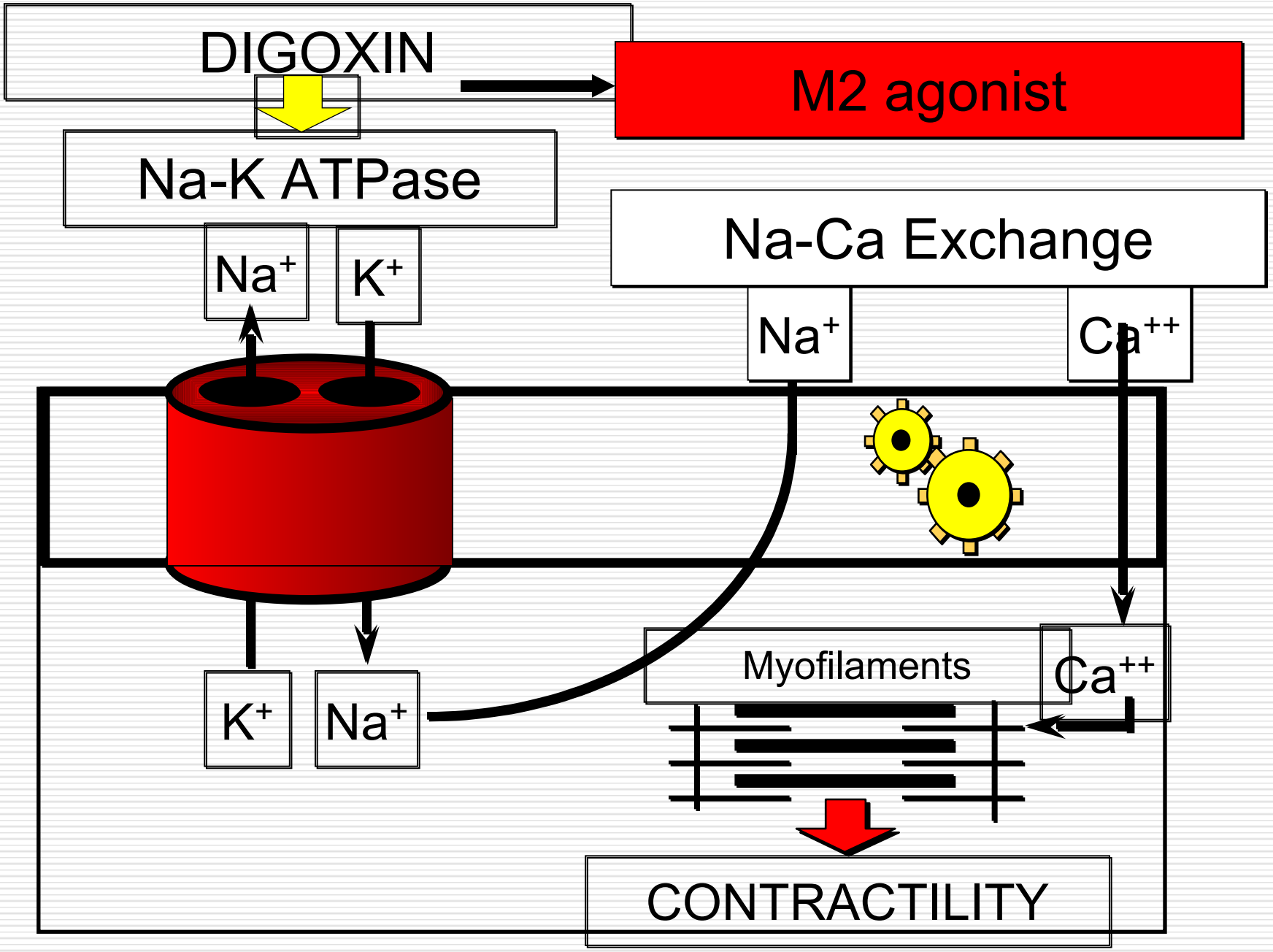
- Treatment and prophylaxis of SVT
- Slows ventricular rate in AFib and flutter
- Electropharmacological Actions
  - Atrial Fibrillation
- Idiopathic Ventricular Tachycardia (verapamil)

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

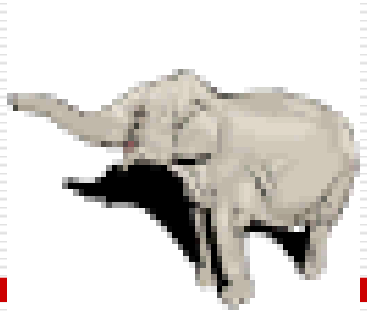
SVT:
- AVNRT
- AVRT
VT: -
- :AT

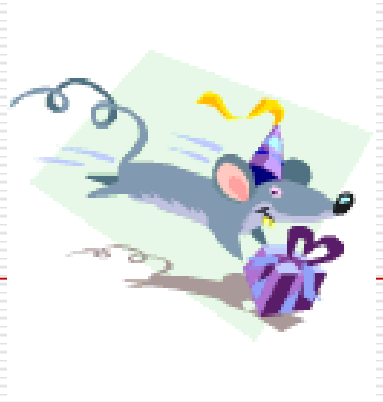

DIGOXIN
M2 agonist
Na-K ATPase
Na-Ca Exchange
Na+
K+
Na+
Ca++
Myofilaments
Ca++
K+
Na+
CONTRACTILITY

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

לכל יצור הומאוטרמי מספר נתון של פעימות לב



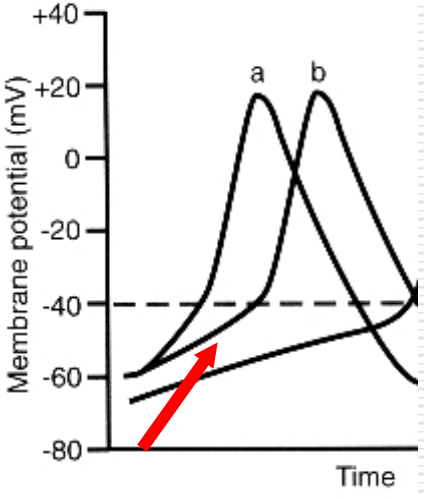


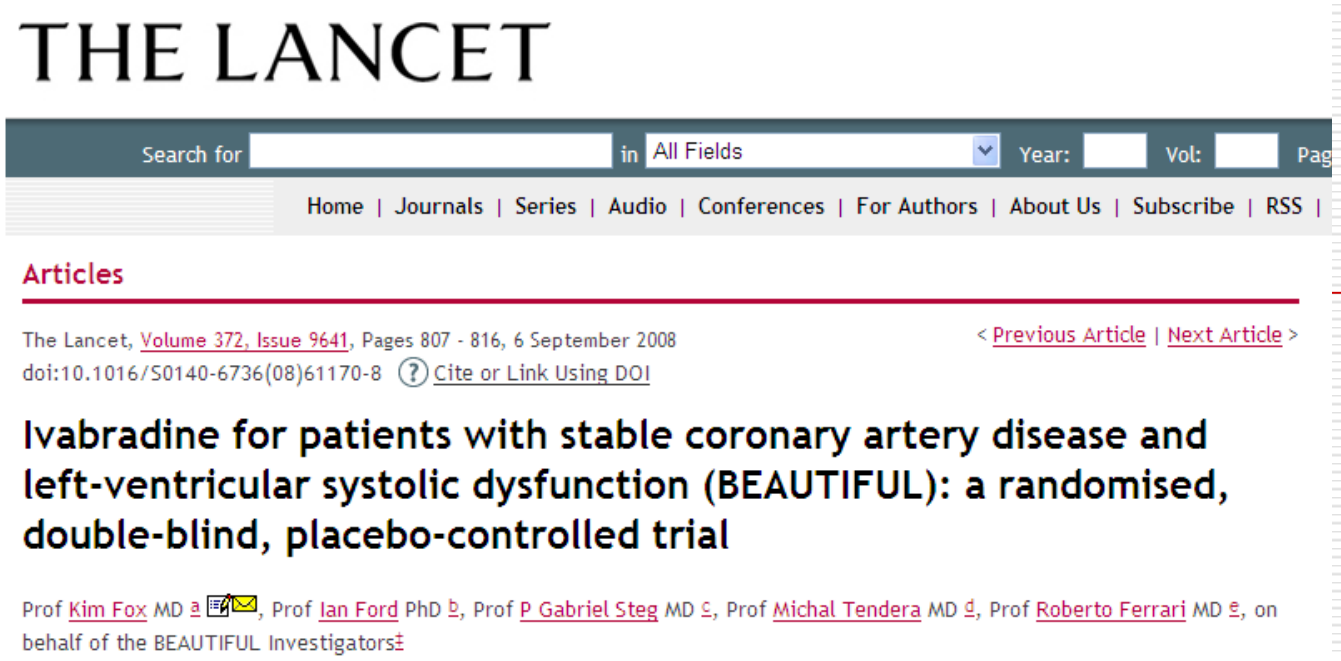
הממהר – מקצר ימיו

המאיט – מאריך ימיו

Sinoatrial I_f current blocker a new target for heart rate reduction

Ivabradine = Proclan





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Articles

The Lancet, Volume 372, Issue 9641, Pages 807 - 816, 6 September 2008
doi:10.1016/S0140-6736(08)61170-8 Cite or Link Using DOI

< Previous Article | Next Article >

Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial

Prof Kim Fox MD [a], Prof Ian Ford PhD [b], Prof P Gabriel Steg MD [c], Prof Michal Tendera MD [d], Prof Roberto Ferrari MD [e], on behalf of the BEAUTIFUL Investigators‡

- Reduction in heart rate with ivabradine does not improve cardiac outcomes in all patients with stable coronary artery disease and left-ventricular systolic dysfunction, but could be used to reduce the incidence of coronary artery disease outcomes in a subgroup of patients who have heart rates of 70 bpm or greater.

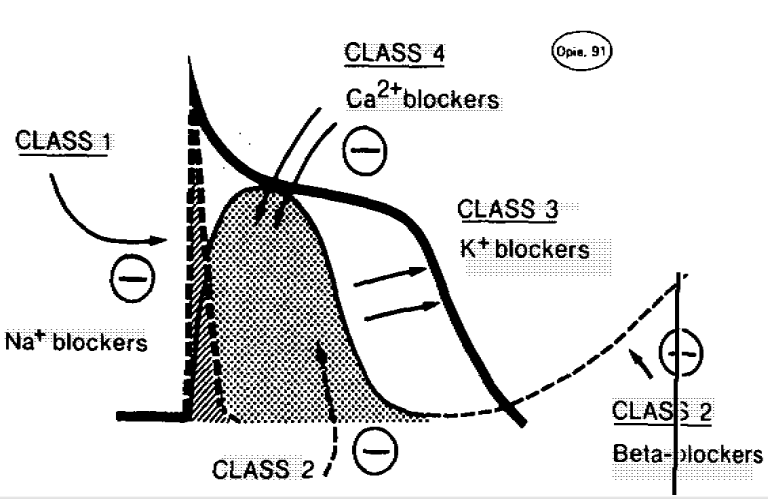
Ranolazine

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



MERLIN TIMI-36:
Antianginal agent ranolazine shown to be antiarrhythmic

Primary arrhythmia end points

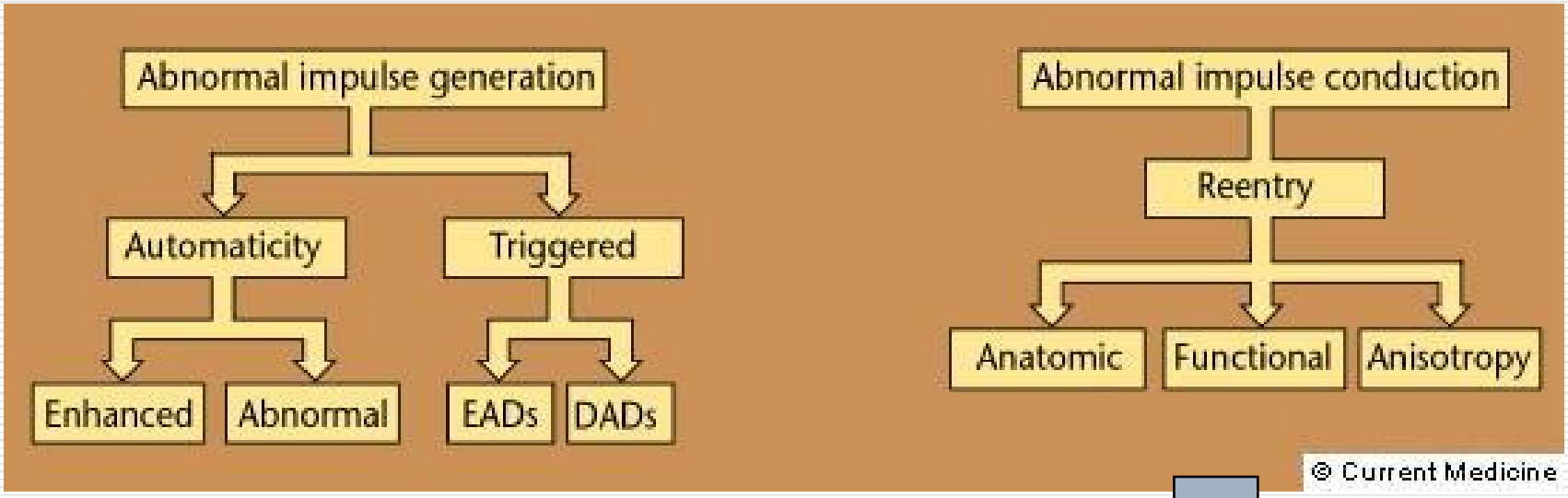
Arrhythmic end point	Ranolazine (%)	Placebo (%)	p
Ventricular tachycardia ≥3 beats	52.0	60.6	<0.001
Ventricular tachycardia ≥8 beats	5.3	8.3	<0.001
Supraventricular tachycardia ≥ 4 beats	44.7	55.0	<0.001
New-onset atrial fibrillation	1.7	2.4	0.08
Bradycardia <45 beat per minute, complete heart block, or pause ≥2.5 sec	39.8	46.6	<0.001
Pause ≥3 sec	3.1	4.3	0.01

To download table as a slide, click on slide logo below

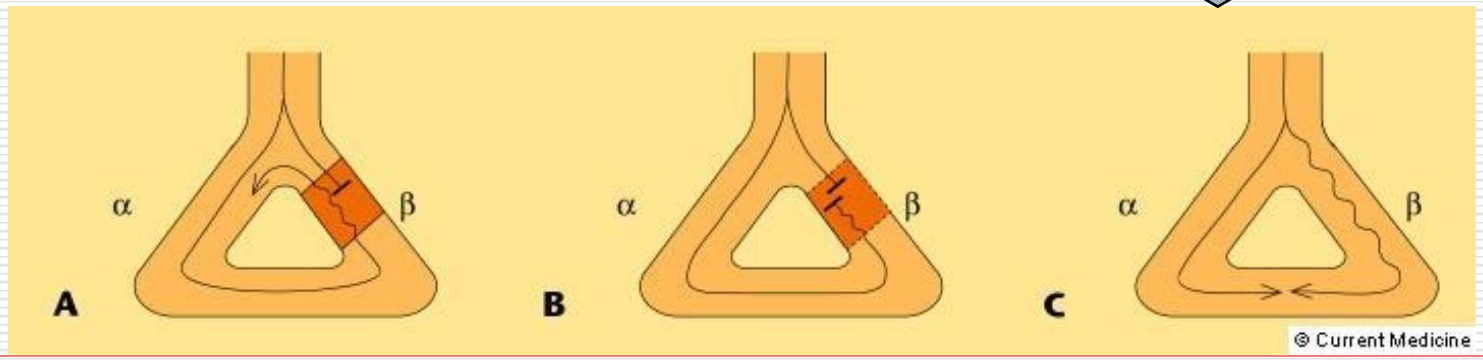
A subgroup analysis looking at high-risk patients, including those with heart failure and those with QT intervals exceeding 450 ms, also showed the drug to be effective as an antiarrhythmic. Among those with ejection fractions <40% and those with a baseline QT interval >450 ms, there was a significant 47% reduction in the incidence of ventricular tachycardia lasting eight beats or longer. The incidence of sudden cardiac death was not significantly different between the two study groups at one year.

Scirica B. European Society of Cardiology Congress 2007; September 5, 2007; Vienna, Austria.

Mechanism of arrhythmias



↑ refractoriness ↓ conduction



33–2 Classification of Drug Actions on Arrhythmias Based on Modification of Vulnerable Parameter

Mechanism	Arrhythmia	Vulnerable Parameter (Effect)	Drugs (Effect)
Automaticity			
Enhanced Normal	Inappropriate sinus tachycardia	Phase 4 depolarization (decrease)	Beta-adrenergic blocking agents
	Some idiopathic ventricular tachycardias		Na^+ channel blocking agents
Abnormal	Atrial tachycardia	Maximum diastolic potential (hyperpolarization)	Muscarinic receptor subtype 2 (M_2) agonists
		Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents
			M_2 agonists
	Accelerated idioventricular rhythms	Phase 4 depolarization (decrease)	Ca^{2+} or Na^+ channel blocking agents
Triggered Activity			
EAD	Torsades de pointes	Action potential duration (shorten)	Beta-adrenergic agonists; vagolytic agents (increase rate)
		EAD (suppress)	Ca^{2+} channel blocking agents; Mg^{2+}; beta-adrenergic blocking agents
DAD	Digitalis-induced arrhythmias	Calcium overload (unload)	Ca^{2+} channel blocking agents
		DAD (suppress)	Na^+ channel blocking agents
	Right ventricular outflow tract ventricular tachycardia	Calcium overload (unload)	Beta-adrenergic blocking agents
		DAD (suppress)	Ca^{2+} channel blocking agents; adenosine
Na Channel Dependent Reentry			
Long excitable gap	Typical atrial flutter	Conduction and excitability (depress)	Types IA, IC Na^+ channel blocking agents
	Circus movement tachycardia in Wolff-Parkinson-White syndrome (WPW)	Conduction and excitability (depress)	Types IA, IC Na^+ channel blocking agents
	Sustained uniform ventricular tachycardia	Conduction and excitability (depress)	Na^+ channel blocking agents
Short excitable gap	Atypical atrial flutter	Refractory period (prolong)	K^+ channel blocking agents
	Atrial fibrillation	Refractory period (prolong)	K^+ channel blocking agents
	Circus movement tachycardia in WPW	Refractory period (prolong)	Amiodarone, sotalol
	Polymorphic and uniform ventricular tachycardia	Refractory period (prolong)	Type IA Na^+ channel blocking agents
	Bundle branch reentry	Refractory period (prolong)	Type IA Na^+ channel blocking agents; amiodarone
	Ventricular fibrillation	Refractory period (prolong)	
Ca Channel Dependent Reentry			
	Atrioventricular nodal reentrant tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Circus movement tachycardia in WPW	Conduction and excitability (depress)	Ca^{2+} channel blocking agents
	Verapamil-sensitive ventricular tachycardia	Conduction and excitability (depress)	Ca^{2+} channel blocking agents

TABLE 33–4 Clinical Usage Information for Antiarrhythmic Agents

Drug	Usual Dosage Ranges: Intravenous (mg) *Loading*	Usual Dosage Ranges: Intravenous (mg) *Maintenance*	Usual Dosage Ranges: Oral (mg) *Loading*	Usual Dosage Ranges: Oral (mg) *Maintenance*	Time to Peak Plasma Concentration (Oral) (hr)	Effective Serum or Plasma Concentration (µg/ml)	Half-Life (hr)	Bioavailability (%)	Major Route of Elimination	Pregnancy Class
Quinidine	6 to 10 mg/kg at 0.3 to 0.5 mg/kg/min	–	800 to 1000	300 to 600 q6hr	1.5 to 3.0	3 to 6	5 to 9	60 to 80	Liver	C
Procainamide	6 to 13 mg/kg at 0.2 to 0.5 mg/kg/min	2 to 6 mg/min	500 to 1000	250 to 1000 q4-6hr	1	4 to 10	3 to 5	70 to 85	Kidneys	C
Disopyramide	1 to 2 mg/kg over 15 to 45 min*	1 mg/kg/hr		100 to 300 q6-8hr	1 to 2	2 to 5	8 to 9	80 to 90	Kidneys	C
Lidocaine	1 to 3 mg/kg at 20 to 50 mg/min	1 to 4 mg/min	N/A	N/A	N/A	1 to 5	1 to 2	N/A	Liver	B
Mexiletine	500 mg*	0.5 to 1.0 gm/24 hr	400 to 600	150 to 300 q8-12hr	2 to 4	0.75 to 2	10 to 17	90	Liver	C
Phenytoin	100 mg q5min for ≤1000 mg		1000	100 to 400 q12-24hr	8 to 12	10 to 20	18 to 36	50 to 70	Liver	D
Flecainide	2 mg/kg*	100 to 200 q12hr		50 to 200 q12hr	3 to 4	0.2 to 1.0	20	95	Liver	C
Propafenone	1 to 2 mg/kg		600 to 900	150 to 300 q8-12hr	1 to 3	0.2 to 3.0	5 to 8	25 to 75	Liver	C
Moricizine	N/A	N/A	300	100 to 400 q8hr	1 to 3	0.1	2	40	Liver	B
Propranolol	0.25 to 0.5 mg q5min to ≤0.20 mg/kg			10 to 200 q6-8hr	4	1 to 2.5	3 to 6	35 to 65	Liver	C

Braunvald's Heart Disease 8th edition chapter 33

TABLE 33–4 Clinical Usage Information for Antiarrhythmic Agents—cont'd

Drug	Usual Dosage Ranges: Intravenous (mg) *Loading*	Usual Dosage Ranges: Intravenous (mg) *Maintenance*	Usual Dosage Ranges: Oral (mg) *Loading*	Usual Dosage Ranges: Oral (mg) *Maintenance*	Time to Peak Plasma Concentration (Oral) (hr)	Effective Serum or Plasma Concentration (µg/ml)	Half-Life (hr)	Bioavailability (%)	Major Route of Elimination	Pregnancy Class
Amiodarone	15 mg/min for 10 min, 1 mg/min for 3 hr, 0.5 mg/min thereafter	1 mg/min	800 to 1600 qd for 7-14 days	200 to 600 qd		0.5 to 1.5	56 days	25	Kidneys	D
Bretylium	5 to 10 mg/kg at 1 to 2 mg/kg/min	0.5 to 2 mg/min	N/A	4 mg/kg/day	2 to 4	0.04 to 0.90	8 to 14	20 to 50	Liver	C
Sotalol	10 mg over 1 to 2 min			80 to 320 q12hr	2.5 to 4	2.5	12	90 to 100	Kidneys	B
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	N/A	N/A	6		Kidneys	C
Dofetilide	2- to 5-µg/kg infusion	N/A	N/A	0.125 to 0.5 q12hr			7 to 13	90	Kidneys	C
Azimilide	N/A	N/A	N/A	100 to 200 qd		200 to 1000		90 to 100	Kidneys	–
Verapamil	5 to 10 mg over 1 to 2 min	0.005 mg/kg/min		80 to 120 q6-8hr	1 to 2	0.10 to 0.15	3 to 8	10 to 35	Liver	C
Adenosine	6 to 18 mg (rapidly)	N/A	N/A	N/A	N/A					C
Digoxin	0.5 to 1.0 mg	0.125 to 0.25 qd	0.5 to 1.0	0.125 to 0.25 qd	2 to 6	0.0008 to 0.002	36 to 48	60 to 80	Kidneys	C

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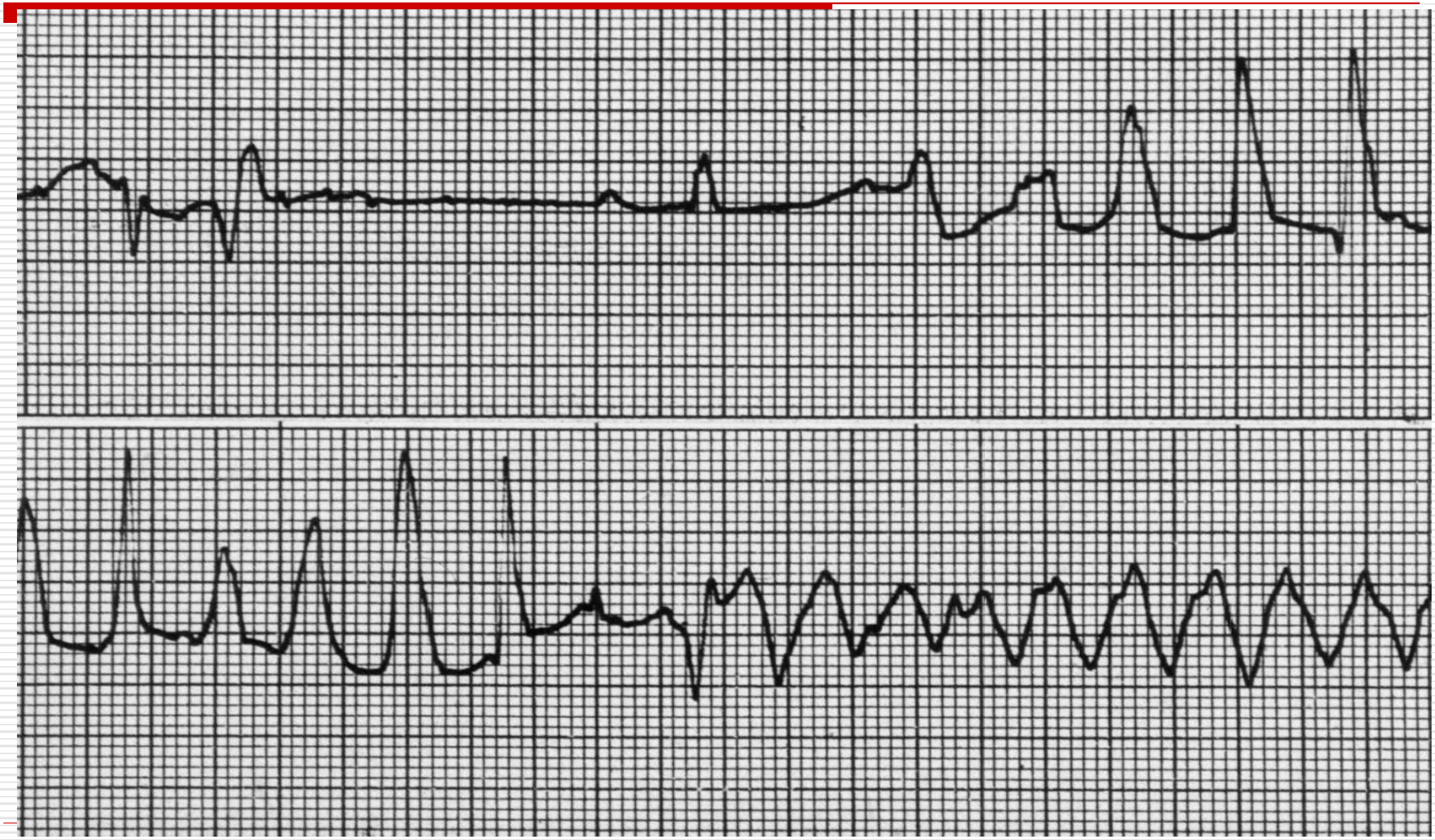
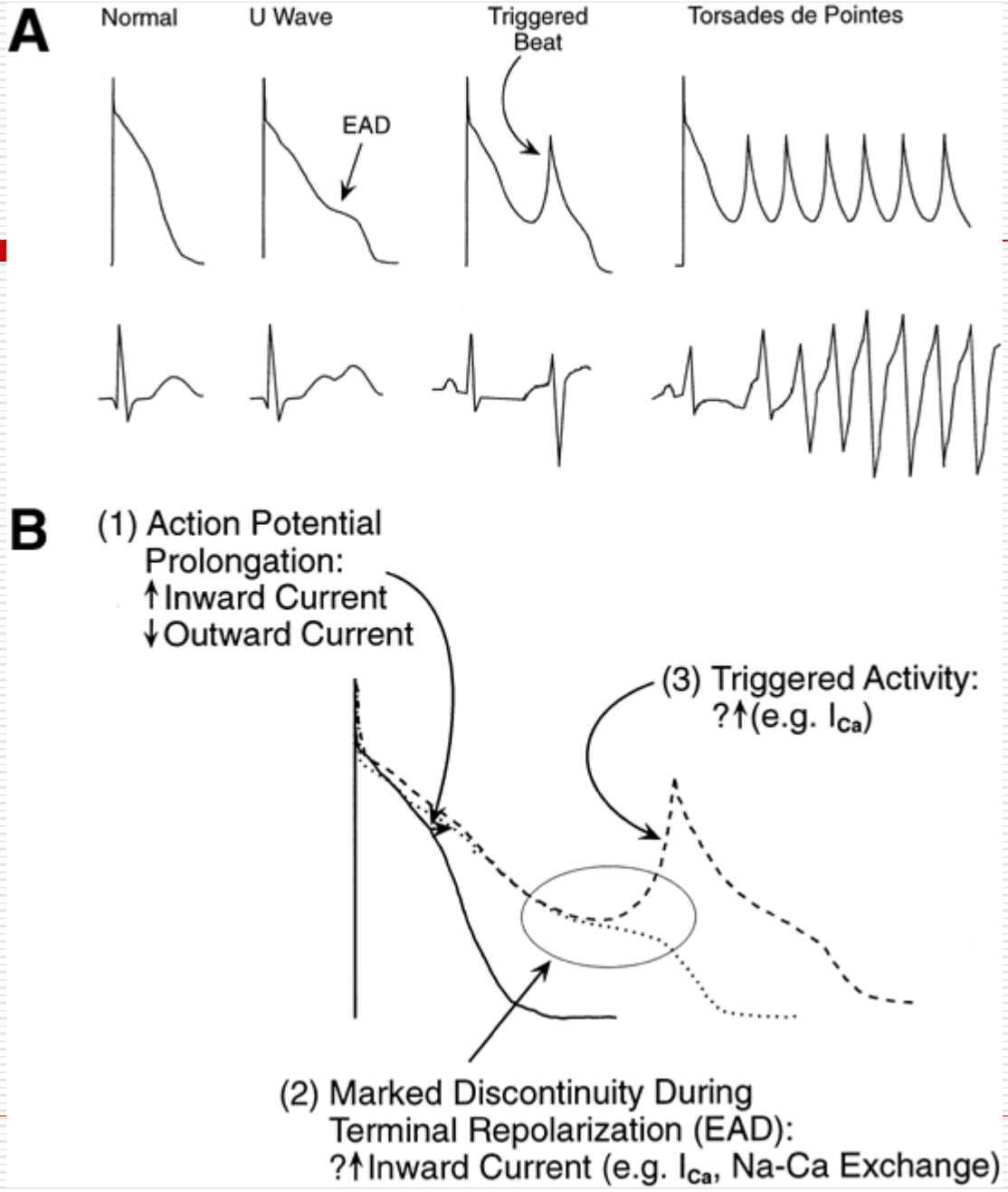
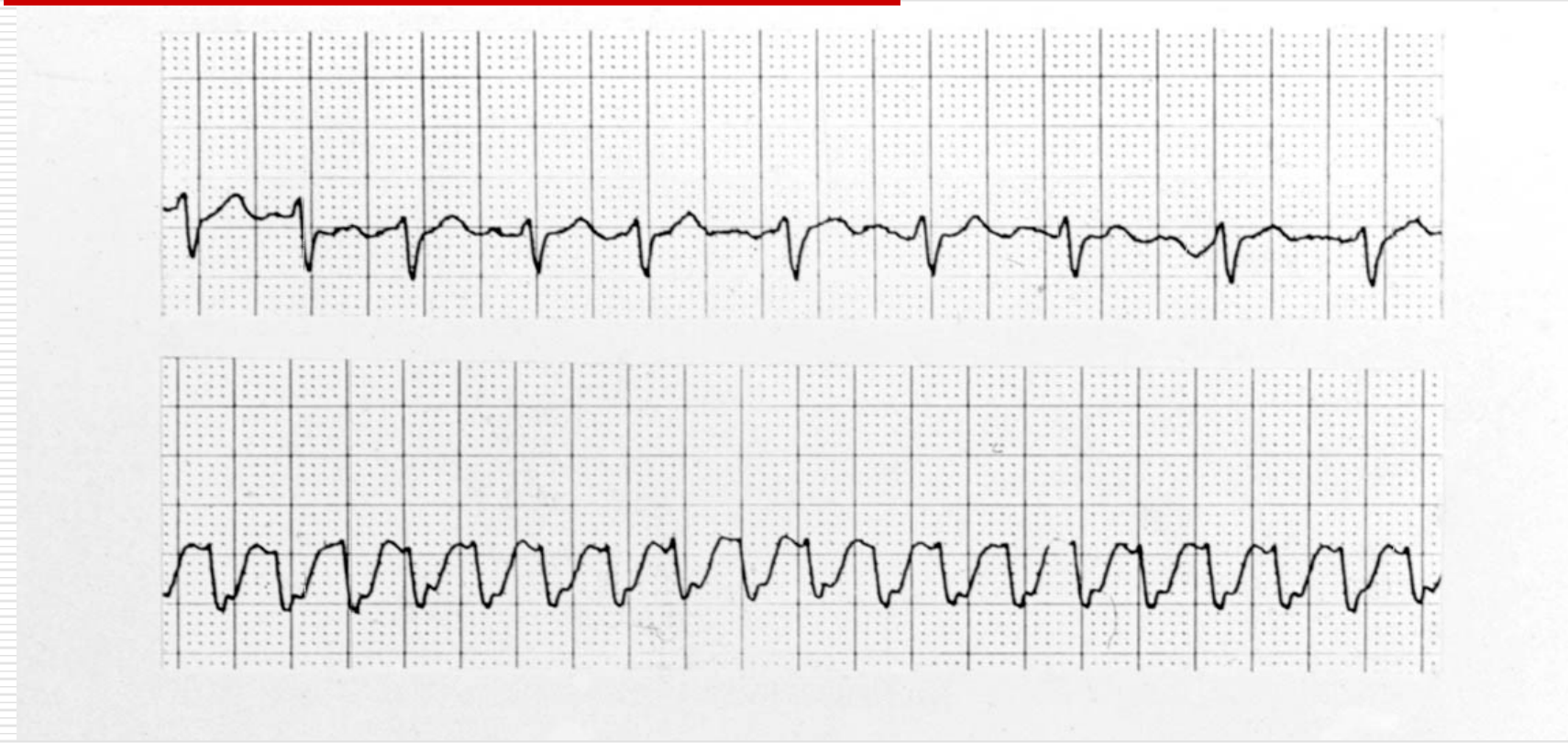
Proarrhythmia

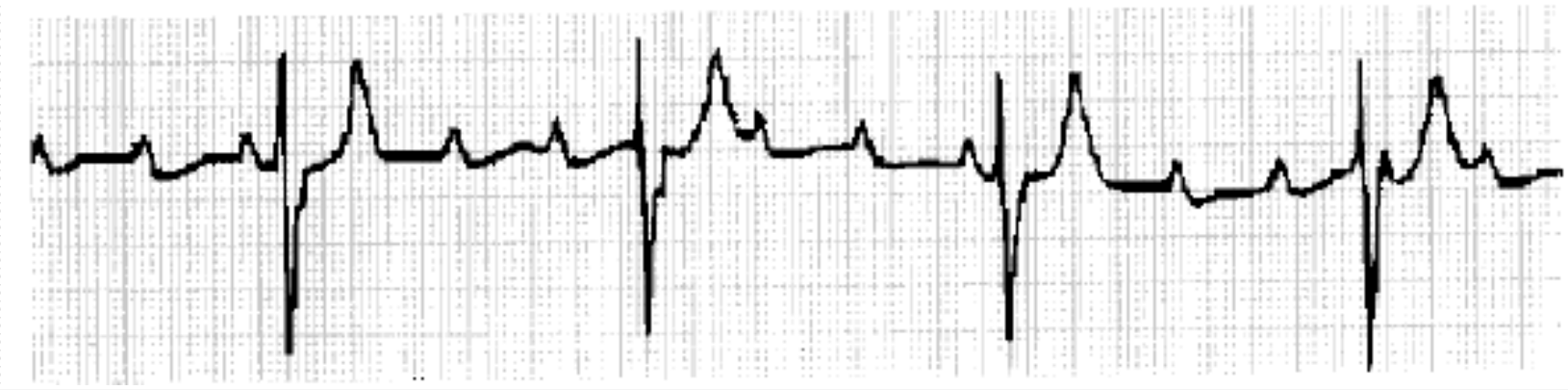
Types of Proarrhythmia During Treatment With Various Antiarrhythmic Drugs for AF or Atrial Flutter According to the Vaughan Williams Classification

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
EAD
Triggered Beat
Torsades de Pointes
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)





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

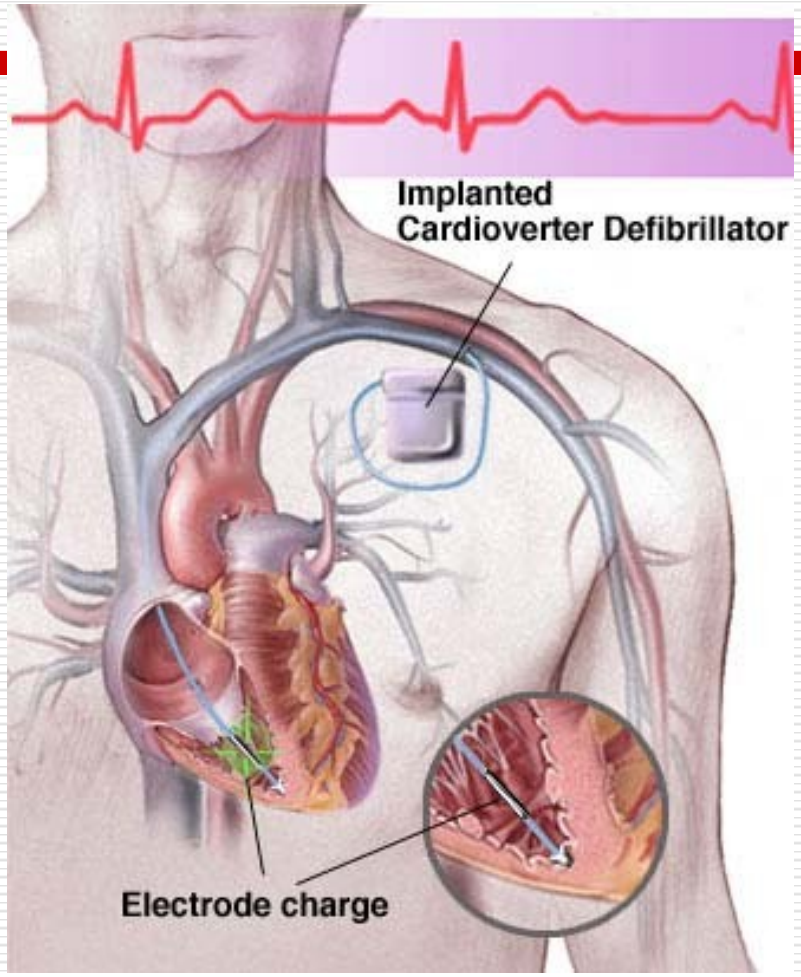
אפקט על ספי קיצוב ודפיברילציה

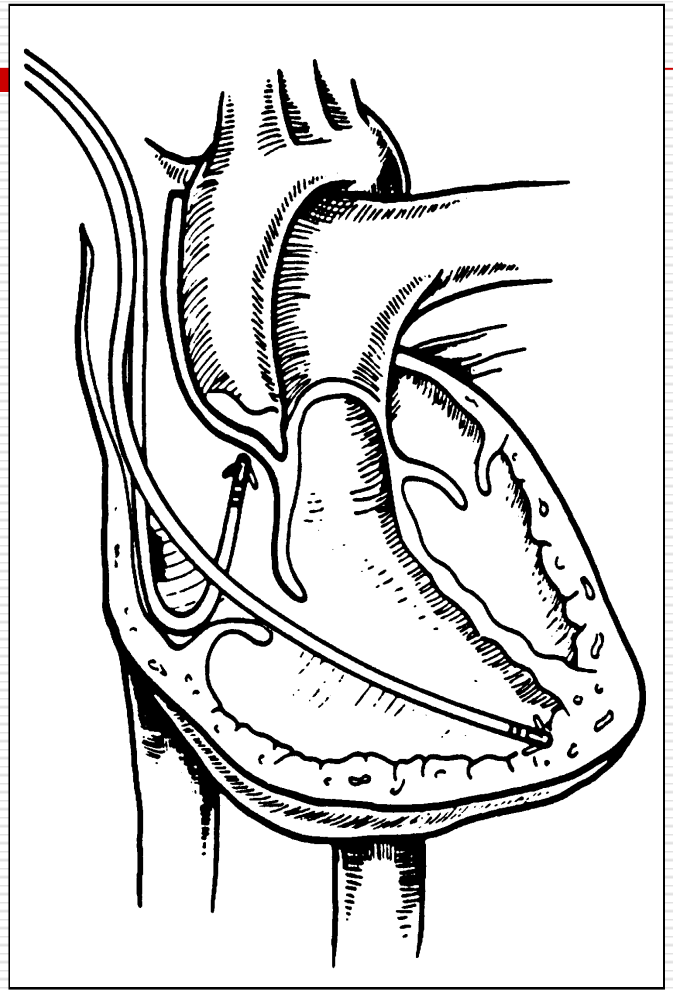
Rate of Device Discharges and Therapies

Trial	Discharge Rate, % of Patients	Comments
CABG-Patch	50% at 1 year; 57% at 2 years	
MADIT I	±60% at 2 years	43.9% of patients received 142 therapies over 27 months (shocks 17.6%)
MADIT II	7.9% of patients per year	13.4% of patients received 701 device therapies (shocks 59% of therapies)
DEFINITE	7.4% of patients per year	41 patients; 91 shocks
SCD-HeFT	7.5% of patients per year	Appropriate shocks: 5.1% of patients per year

***Circulation*. 2007;115:1170-1176**

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

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			
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			
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)

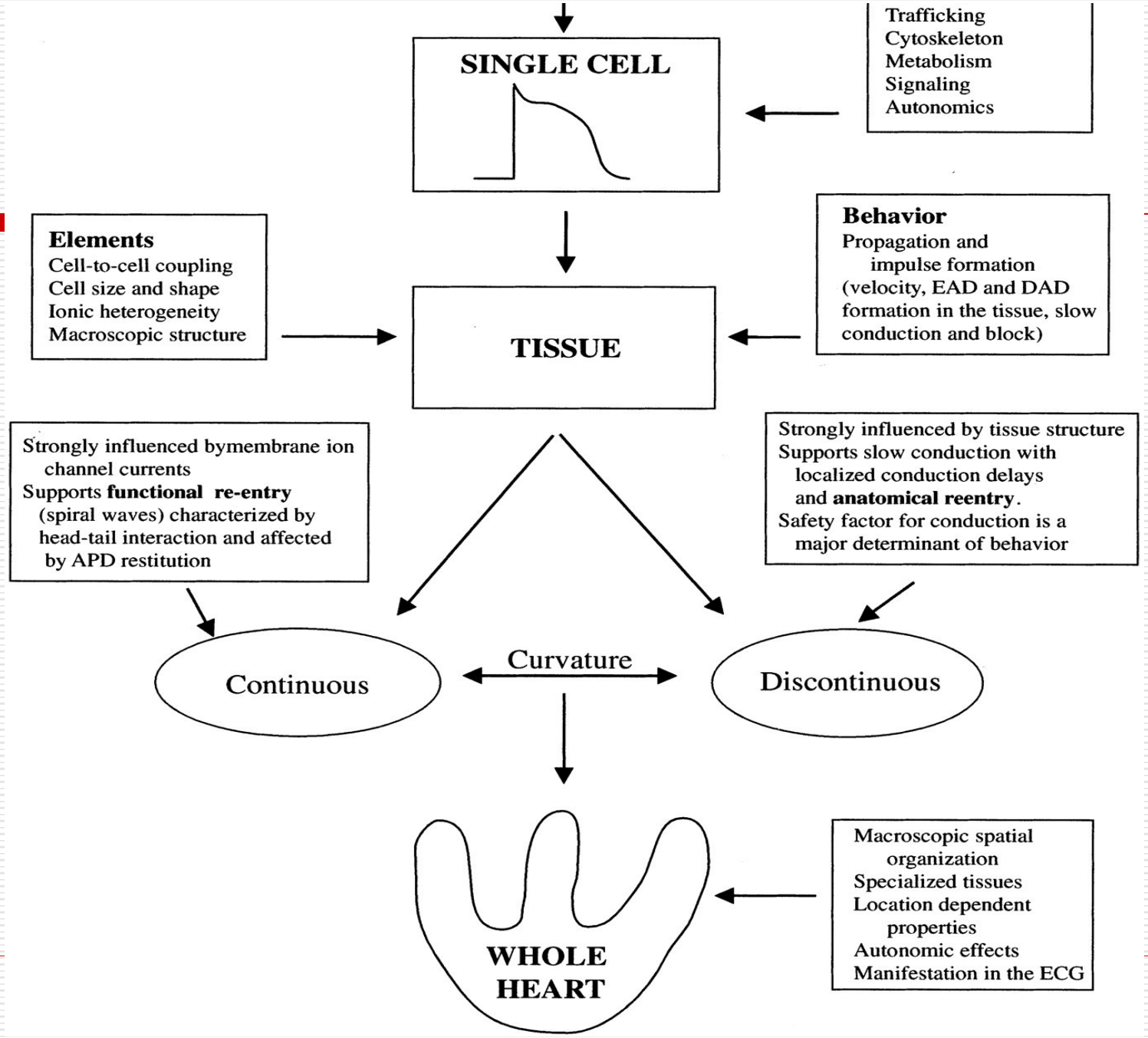
שינוי מינון במחלות שונות או עם תרופות אחרות

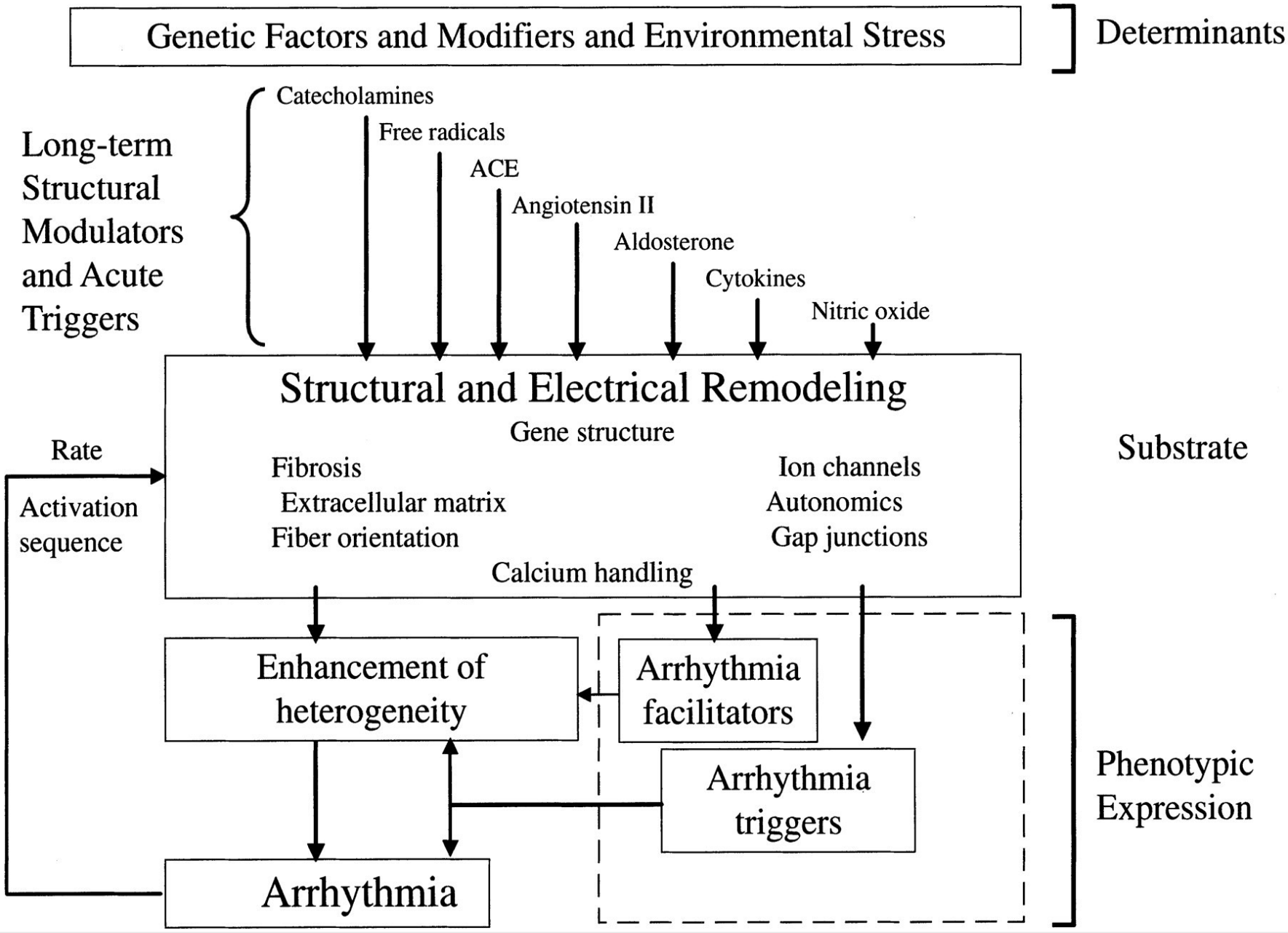
	Disease			Drug			
Drug	Heart Failure	Renal	Hepatic	Digoxin	Warfarin	Cimetidine	Phenytoin or Phenobarbital
Amiodarone	. . .	. . .	↓ Dosage	↑↑ Serum digoxin level	↑↑ Protime	. . .	. . .
Bretylium	. . .	↓ Dosage	. . .	. . .	. . .	. . .	. . .
Digoxin	. . .	↓ Dosage	. . .	. . .	. . .	. . .	. . .
Diltiazem 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)

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
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

ACC/AHA/ESC Practice Guidelines

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation)

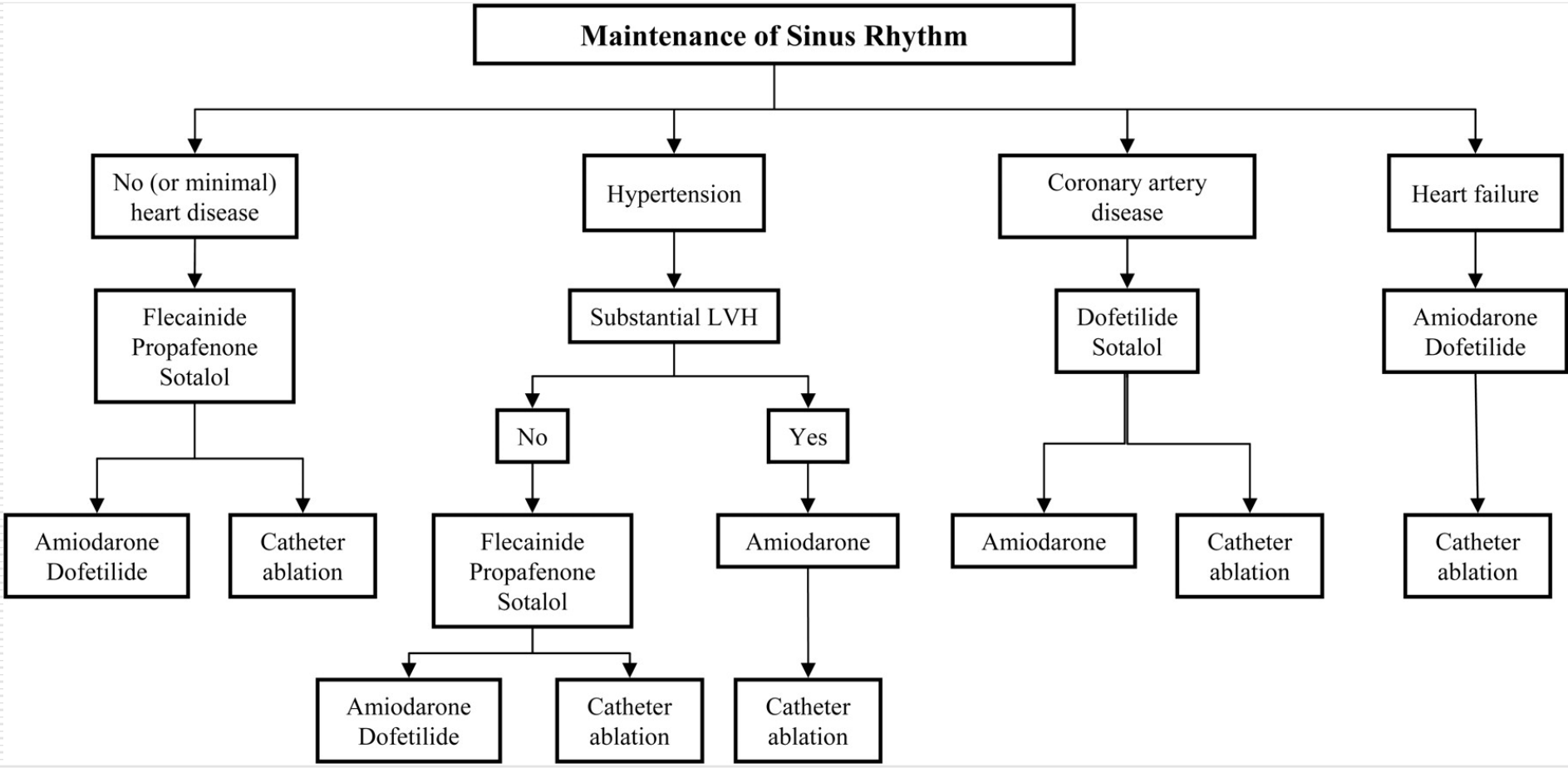
Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

WRITING COMMITTEE MEMBERS

Recommended Doses of Drugs Proven Effective for Pharmacological Cardioversion of Atrial Fibrillation

Drug*	Route of Administration	Dosage†	Potential Adverse Effects
Amiodarone	Oral	Inpatient: 1.2 to 1.8 g per day in divided dose until 10 g total, then 200 to 400 mg per day maintenance or 30 mg/kg as single dose Outpatient: 600 to 800 mg per day divided dose until 10 g total, then 200 to 400 mg per day maintenance	Hypotension, bradycardia, QT prolongation, torsades de pointes (rare), GI upset, constipation, phlebitis (IV)
	Intravenous/oral	5 to 7 mg/kg over 30 to 60 min, then 1.2 to 1.8 g per day continuous IV or in divided oral doses until 10 g total, then 200 to 400 mg per day maintenance	
Dofetilide	Oral	Creatinine Clearance (mL/min) / Dose (mcg BID) More than 60 / 500 40 to 60 / 250 20 to 40 / 125 Less than 20 / Contraindicated	QT prolongation, torsades de pointes; adjust dose for renal function, body size, and age
Flecainide	Oral	200 to 300 mg‡	Hypotension, atrial flutter with high ventricular rate
	Intravenous	1.5 to 3.0 mg/kg over 10 to 20 min‡	
Ibutilide	Intravenous	1 mg over 10 min; repeat 1 mg when necessary	QT prolongation, torsades de pointes
Propafenone	Oral	600 mg	Hypotension, atrial flutter with high ventricular rate
	Intravenous	1.5 to 2.0 mg/kg over 10 to 20 min‡	
Quinidine§	Oral	0.75 to 1.5 g in divided doses over 6 to 12 h, usually with a rate-slowing drug	QT prolongation, torsades de pointes, GI upset, hypotension

Antiarrhythmic Drug Therapy to Maintain Sinus in pts with Recurrent Paroxysmal or Persistent Atrial Fibrillation



ACC/AHA/ESC PRACTICE GUIDELINES

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

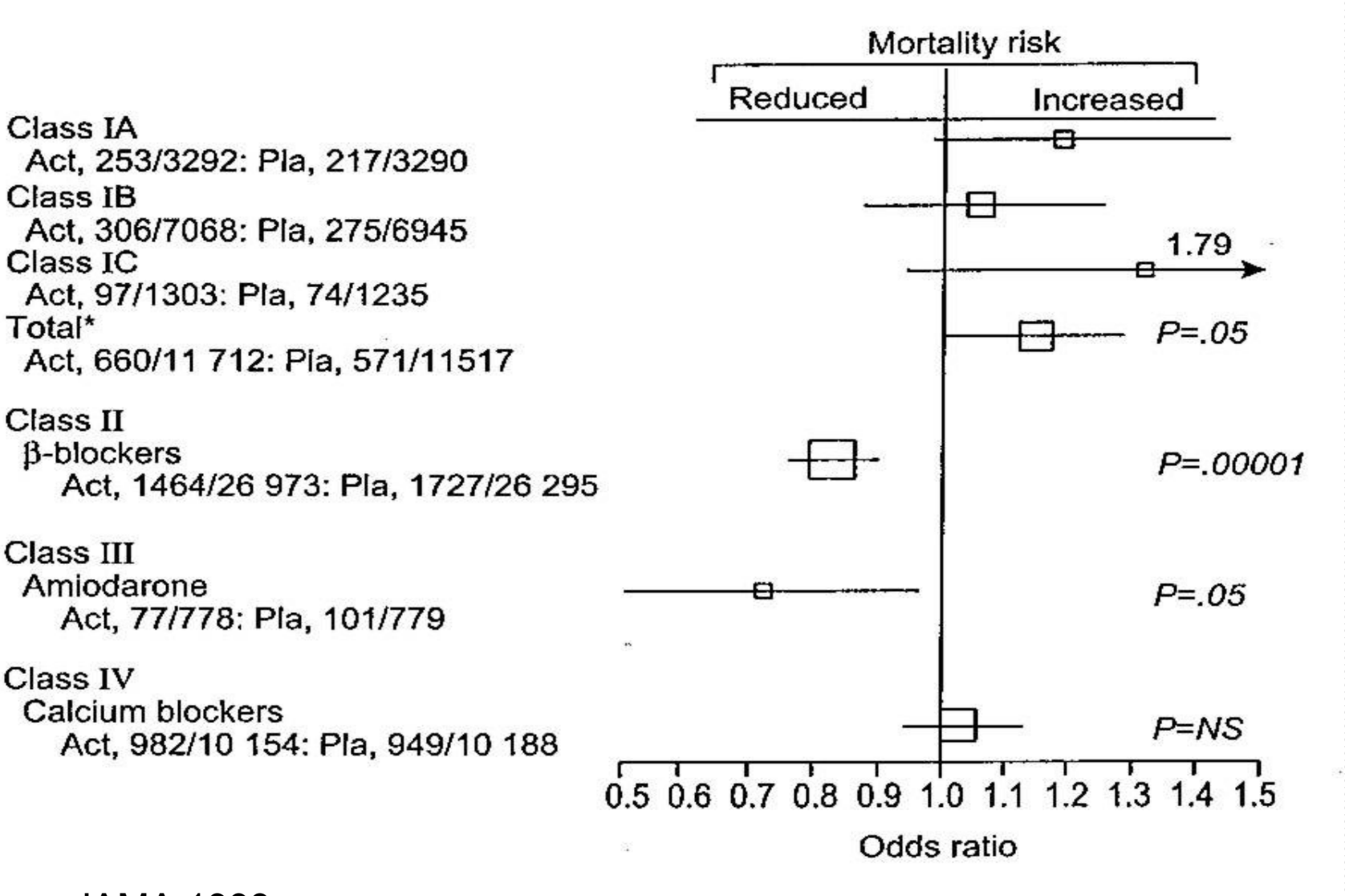
A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death)

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

THERAPIES FOR VENTRICULAR ARRHYTHMIAS

- With the exception of BB, AA no rule in the prevention of SCD
- May be effective as adjunctive therapy
  - Amiodarone
  - Sotalol
  - Quinidine

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

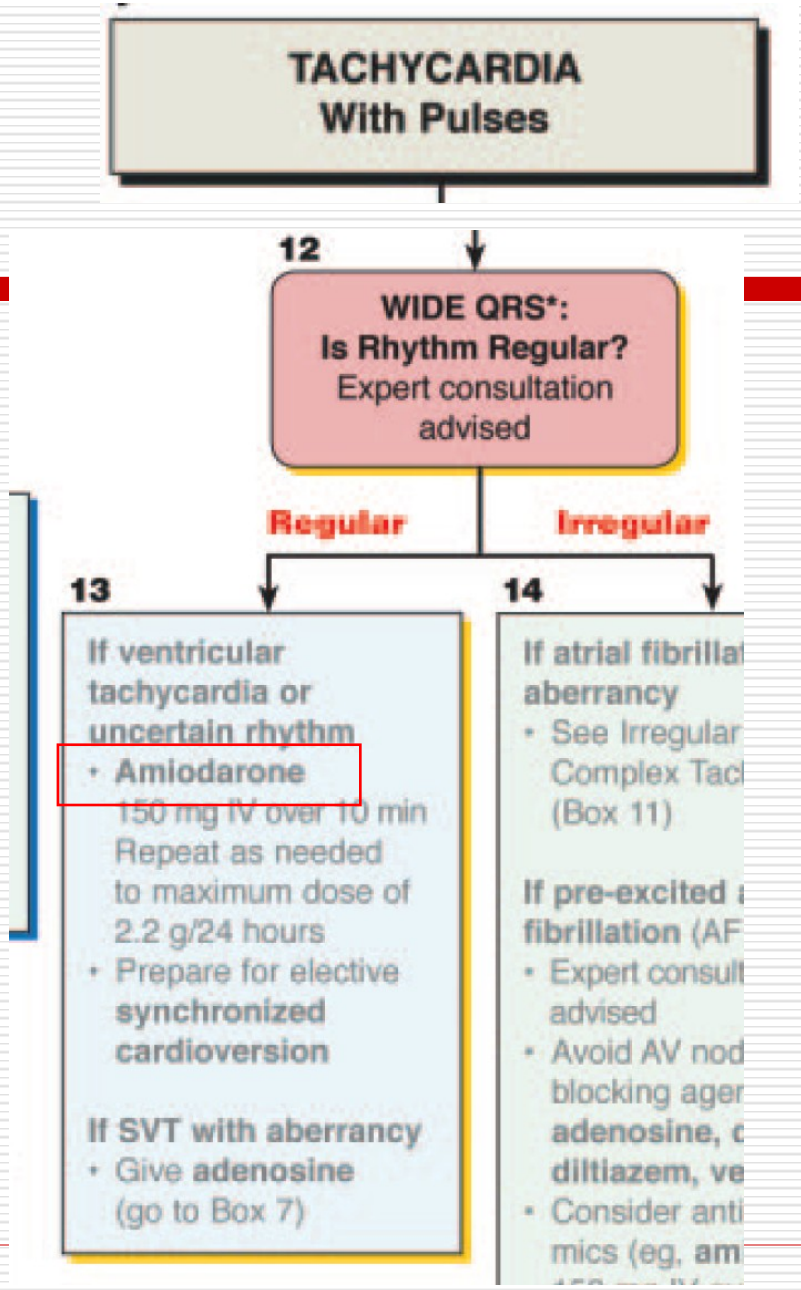
1. **EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation with or without a mutation in the *SCN5A* gene. *(Level of Evidence: C)***
2. **Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada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

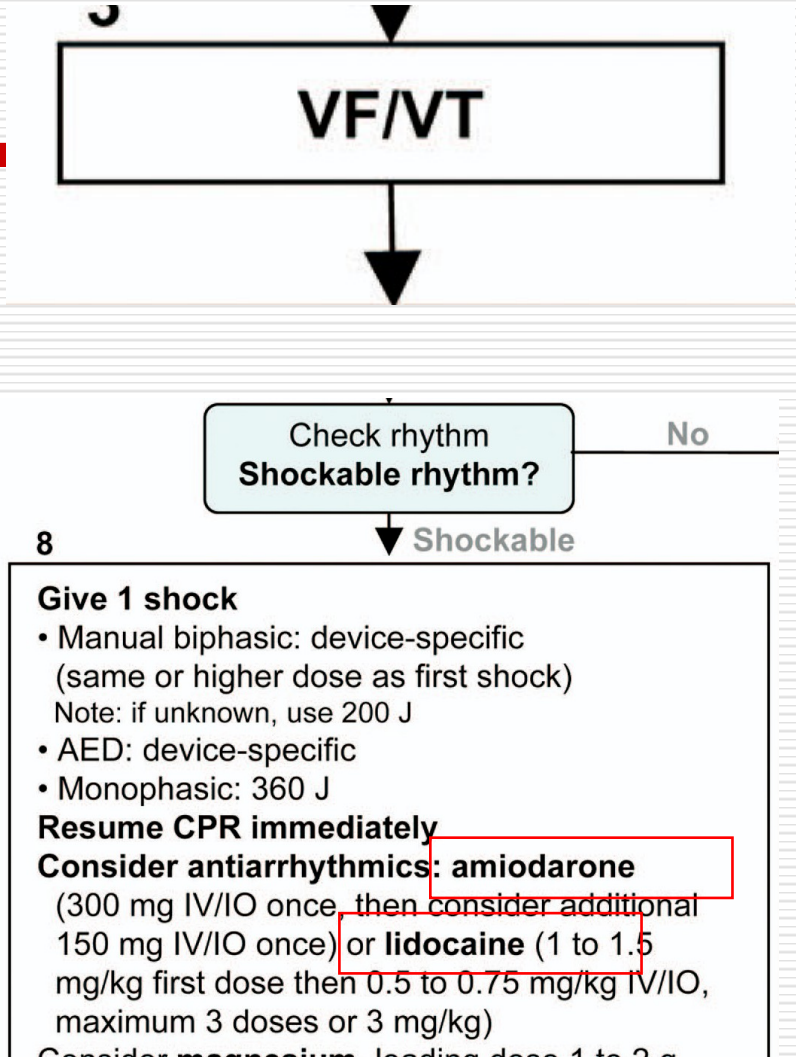
7.1.1. Arrhythmias Associated With Acute Coronary Syndromes

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)

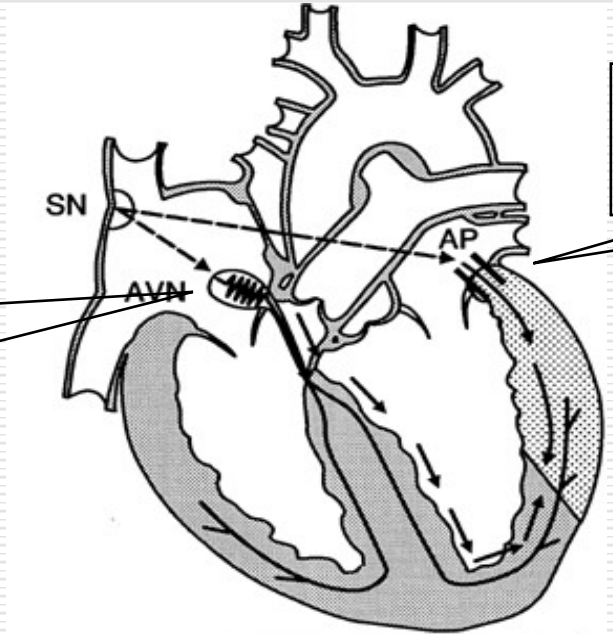
Pharmacologic Agents for Short-Term Treatment of Supraventricular Tachycardia (SVT).*

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 If <60 kg: 0.01 mg/kg over a 10-min period Repeat once if no response after 10 additional min	Prolongation of QT interval, torsades de pointes

Amiodarone

WPW



תרופות המשפיעות
על AP

תרופות המשפיעות
על AVN

תרופות המשפיעות
על AVN ועל AP

Table 4. 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)

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
- Amiodarone - D
- D Atenolol -
- Sotalol - B
- אחרים - C

TABLE 33–4 Clinical Usage Information for Antiarrhythmic Agents

Drug	Usual Dosage Ranges: Intravenous (mg) *Loading*	Usual Dosage Ranges: Intravenous (mg) *Maintenance*	Usual Dosage Ranges: Oral (mg) *Loading*	Usual Dosage Ranges: Oral (mg) *Maintenance*	Time to Peak Plasma Concentration (Oral) (hr)	Effective Serum or Plasma Concentration (µg/ml)	Half-Life (hr)	Bioavailability (%)	Major Route of Elimination	Pregnancy Class
Quinidine	6 to 10 mg/kg at 0.3 to 0.5 mg/kg/min	–	800 to 1000	300 to 600 q6hr	1.5 to 3.0	3 to 6	5 to 9	60 to 80	Liver	C
Procainamide	6 to 13 mg/kg at 0.2 to 0.5 mg/kg/min	2 to 6 mg/min	500 to 1000	250 to 1000 q4-6hr	1	4 to 10	3 to 5	70 to 85	Kidneys	C
Disopyramide	1 to 2 mg/kg over 15 to 45 min*	1 mg/kg/hr		100 to 300 q6-8hr	1 to 2	2 to 5	8 to 9	80 to 90	Kidneys	C
Lidocaine	1 to 3 mg/kg at 20 to 50 mg/min	1 to 4 mg/min	N/A	N/A	N/A	1 to 5	1 to 2	N/A	Liver	B
Mexiletine	500 mg*	0.5 to 1.0 gm/24 hr	400 to 600	150 to 300 q8-12hr	2 to 4	0.75 to 2	10 to 17	90	Liver	C
Phenytoin	100 mg q5min for ≤1000 mg		1000	100 to 400 q12-24hr	8 to 12	10 to 20	18 to 36	50 to 70	Liver	D
Flecainide	2 mg/kg*	100 to 200 q12hr		50 to 200 q12hr	3 to 4	0.2 to 1.0	20	95	Liver	C
Propafenone	1 to 2 mg/kg		600 to 900	150 to 300 q8-12hr	1 to 3	0.2 to 3.0	5 to 8	25 to 75	Liver	C
Moricizine	N/A	N/A	300	100 to 400 q8hr	1 to 3	0.1	2	40	Liver	B
Propranolol	0.25 to 0.5 mg q5min to ≤0.20 mg/kg			10 to 200 q6-8hr	4	1 to 2.5	3 to 6	35 to 65	Liver	C

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TABLE 33–4 Clinical Usage Information for Antiarrhythmic Agents—cont'd

Drug	Usual Dosage Ranges: Intravenous (mg) *Loading*	Usual Dosage Ranges: Intravenous (mg) *Maintenance*	Usual Dosage Ranges: Oral (mg) *Loading*	Usual Dosage Ranges: Oral (mg) *Maintenance*	Time to Peak Plasma Concentration (Oral) (hr)	Effective Serum or Plasma Concentration (µg/ml)	Half-Life (hr)	Bioavailability (%)	Major Route of Elimination	Pregnancy Class
Amiodarone	15 mg/min for 10 min, 1 mg/min for 3 hr, 0.5 mg/min thereafter	1 mg/min	800 to 1600 qd for 7-14 days	200 to 600 qd		0.5 to 1.5	56 days	25	Kidneys	D
Bretylium	5 to 10 mg/kg at 1 to 2 mg/kg/min	0.5 to 2 mg/min	N/A	4 mg/kg/day	2 to 4	0.04 to 0.90	8 to 14	20 to 50	Liver	C
Sotalol	10 mg over 1 to 2 min			80 to 320 q12hr	2.5 to 4	2.5	12	90 to 100	Kidneys	B
Ibutilide	1 mg over 10 min	N/A	N/A	N/A	N/A	N/A	6		Kidneys	C
Dofetilide	2- to 5-µg/kg infusion	N/A	N/A	0.125 to 0.5 q12hr			7 to 13	90	Kidneys	C
Azimilide	N/A	N/A	N/A	100 to 200 qd		200 to 1000		90 to 100	Kidneys	–
Verapamil	5 to 10 mg over 1 to 2 min	0.005 mg/kg/min		80 to 120 q6-8hr	1 to 2	0.10 to 0.15	3 to 8	10 to 35	Liver	C
Adenosine	6 to 18 mg (rapidly)	N/A	N/A	N/A	N/A					C
Digoxin	0.5 to 1.0 mg	0.125 to 0.25 qd	0.5 to 1.0	0.125 to 0.25 qd	2 to 6	0.0008 to 0.002	36 to 48	60 to 80	Kidneys	C

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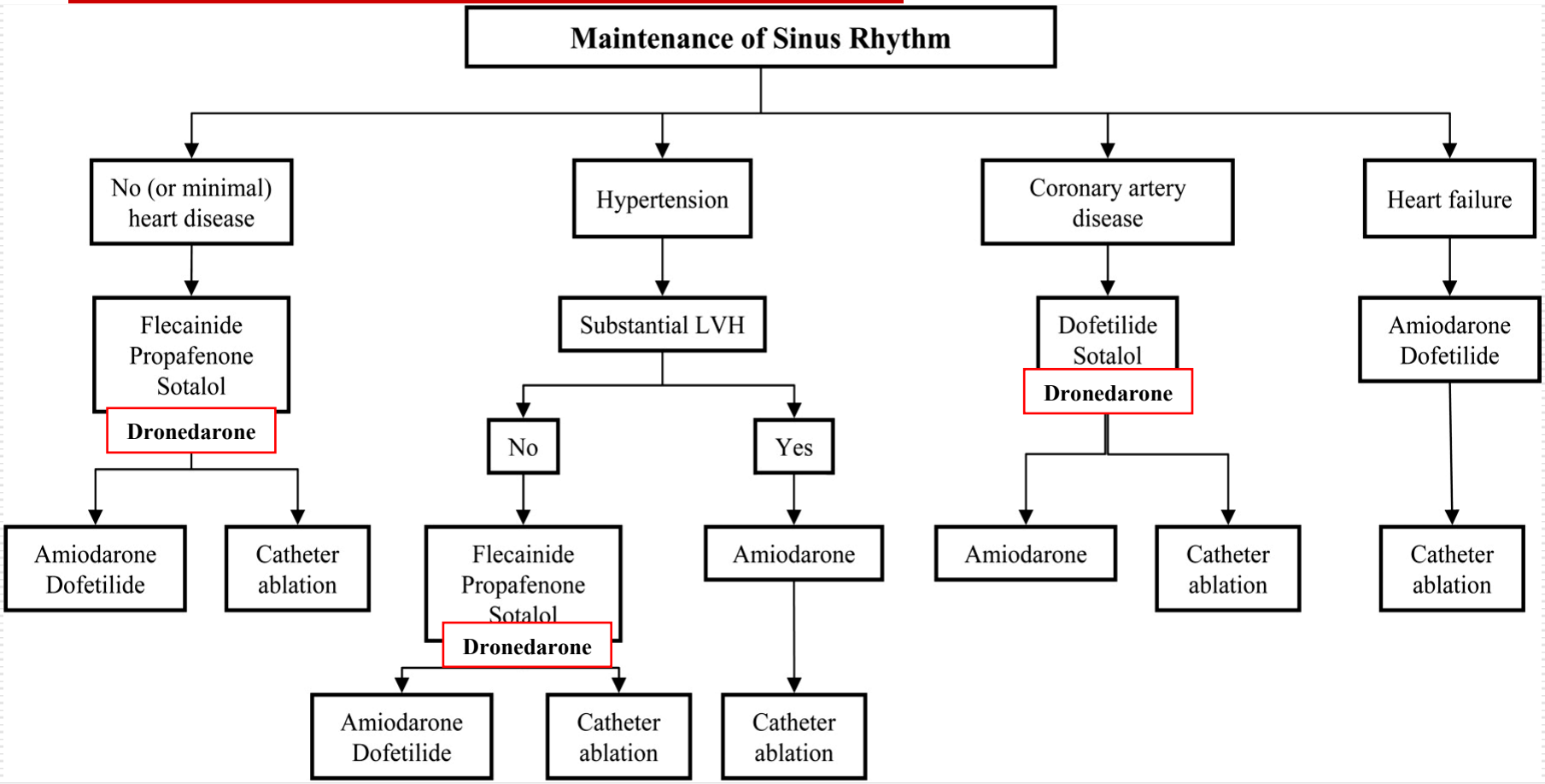
Recommendations for Treatment Strategies for Supraventricular Tachycardia During Pregnancy

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 drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation

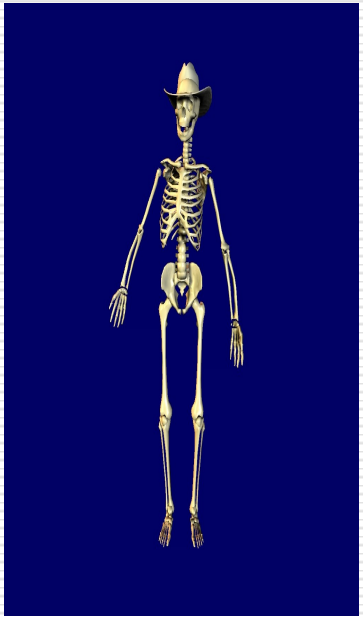


Antiarrhythmic Drugs:

Agents with occasionally beneficial side-effects

~~תרופות אנטיארית'מיות: רוב התרופות~~

בעלות אפקטים אלקטרופיזיולוגיים



אשר לעיתים גם מועילים