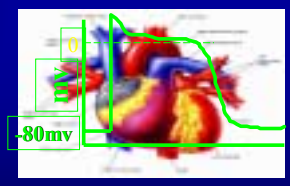
תרופות אנטיאריתמיות
Antiarrhythmic Drugs



קורס למתמחים, קיסריה 10.2004

פרופ' עמוס כץ
מרכז רפואי אוניברסיטאי סורוקה
באר שבע

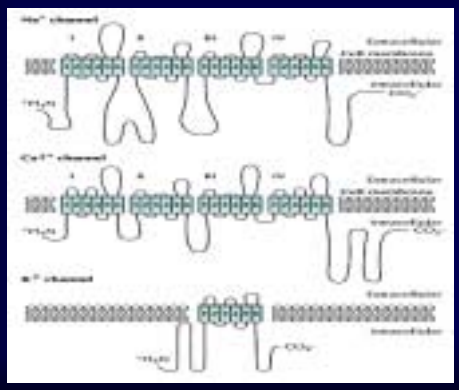
מילות מפתח

- Pharmacodynamics
- Pharmacokinetics
- Use Dependency
- Vaughn Williams classification
- Ion Channel blockers
- Adverse effects:
  - Cardiovascular
    - Proarrhythmia: (a) Torsade de Pointes; (b) atrial flutter with 1:1 AV conduction; (c) exacerbation of sustained VT (d) increased incidence of SCD (e) bradyarrhythmias
    - Exacerbation of CHF
  - Noncardiovascular adverse effects

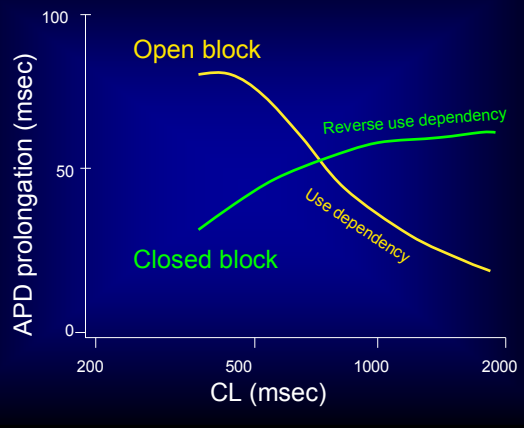
Pharmacodynamics Principles

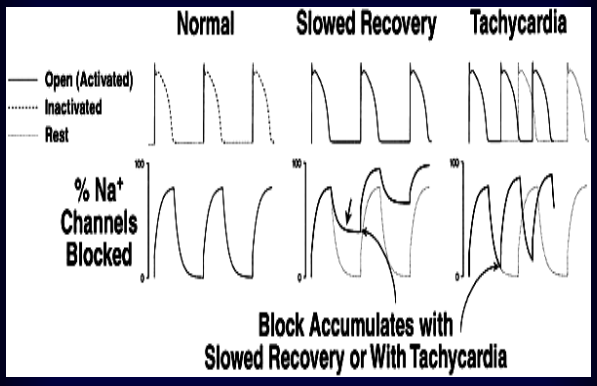
The effect of the drug on the patients

Ion Channel Concepts



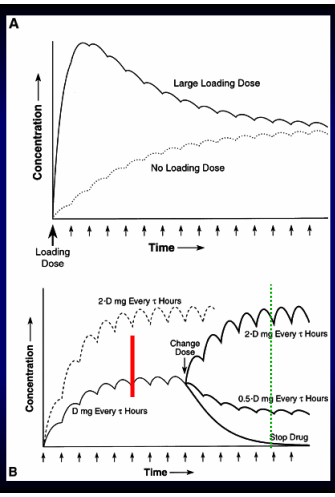
Use Dependency

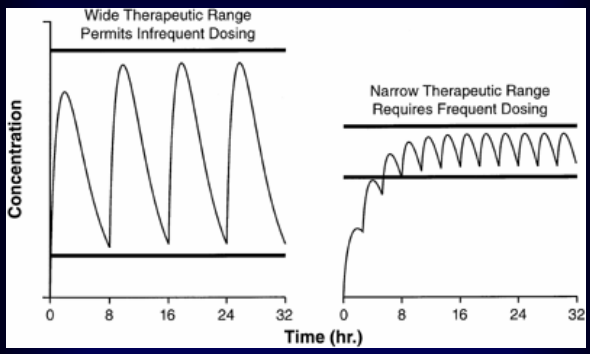


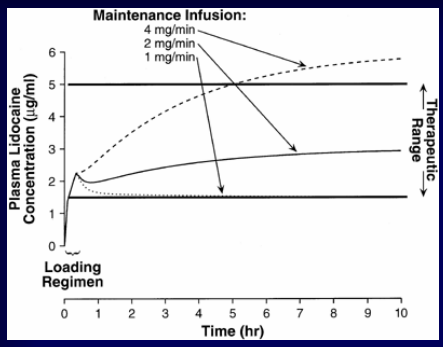


Pharmacokinetics Principles

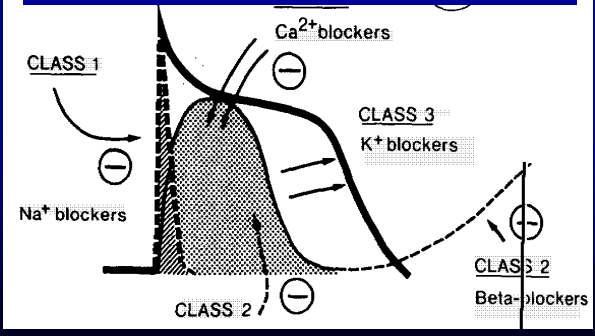
Absorption, Distribution, Elimination







Antiarrhythmic Mechanisms of Action



סווג של תרופות אנטיאריתמיות

Vaughn Williams

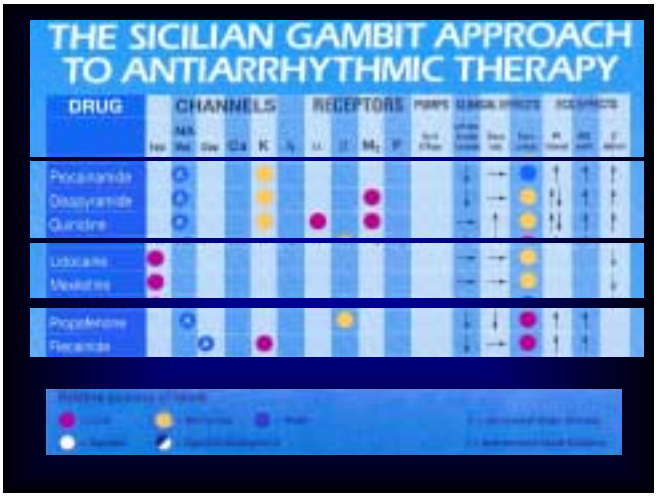
- Class I – Na Channel blockers
  - Ia
  - I b
  - I c
- Class II - Beta Blockers
- Class III – K channel blockers
- Class IV – Ca Channel blockers

- Digoxin
- Adenosine

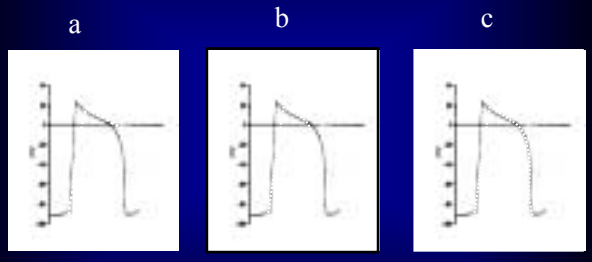
The Sicilian Gambit

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

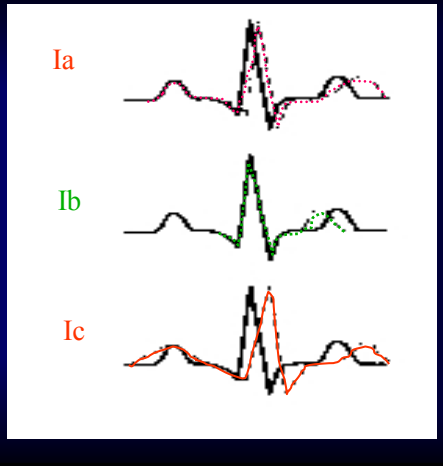
Circulation 1991;84:1831



Mechanisms of Action of Antiarrhythmic Drugs Class I



C > A > B



Pharmacologic Actions of Class I Antiarrhythmic Drugs

Drug	Na^+ channel block $\tau_{recovery}$ (sec)	State dependence	APD	Relative Rate Dependence
Quinidine	3.0	O	↑	Moderate
Lidocaine	0.1	I > O	↓	High
Flecainide	11.0	O	↑ (X)	Low

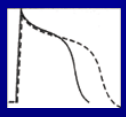
Quinidine

Brugada Syndrome
(Ito)

Idiopathic VF

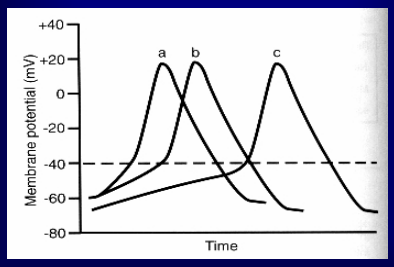
Lidocaine

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

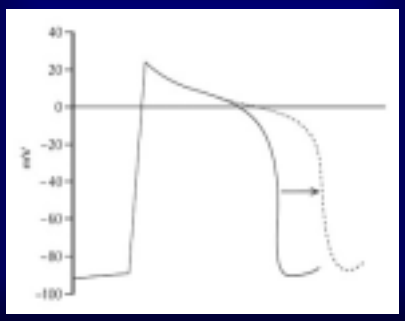


- Decreases refractoriness
- Blocks Na^+ entry during the plateau phase of AP.
- APs of longer duration have greater "window currents".
- Therefore, APs of greater duration are preferentially shortened.

Mechanisms of Action of Antiarrhythmic Drugs Class II



Mechanisms of Action of Antiarrhythmic Drugs Class III

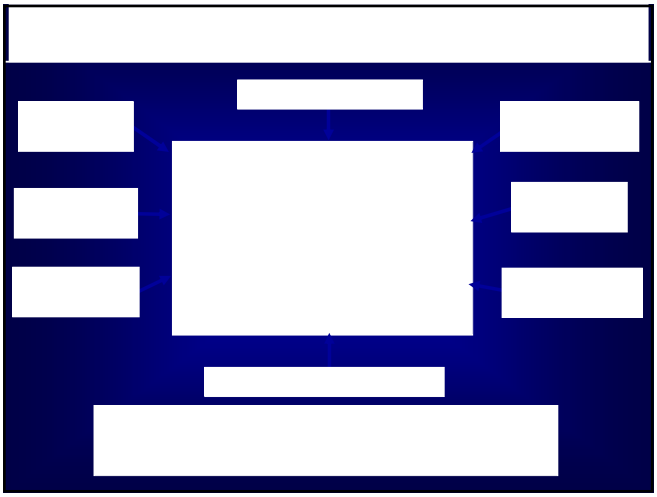


Class III

Drugs that prolong repolarization

Amiodarone

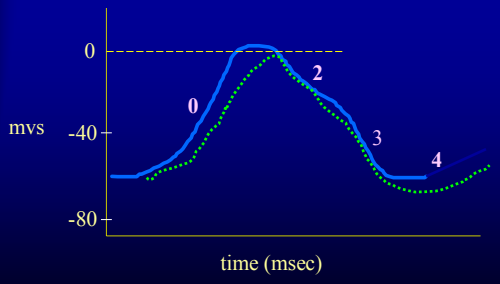
Bretylium
Dofetilide
Ibutilide
Azimelide



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

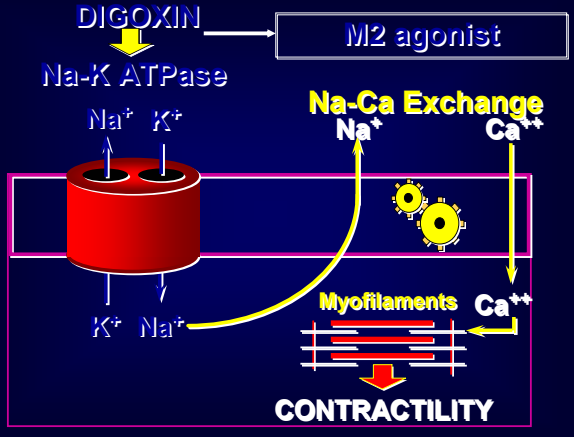
An autocoid whose actions are mediated by specific receptors on the plasma membrane of virtually every cell.

Receptors: -
VT: -
AT: -

Pharmacologic Actions of Adenosine

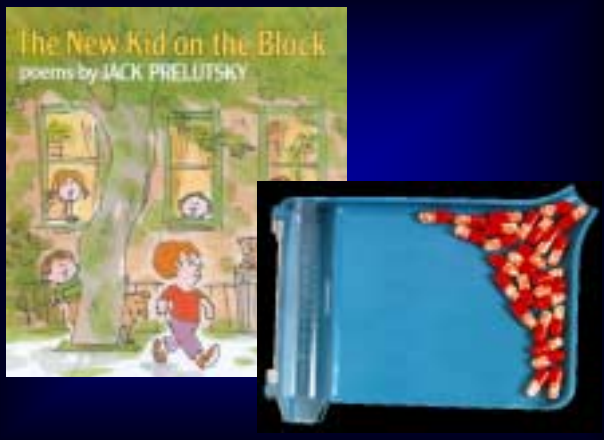
Drug	Na^+ channel block: τ (sec)	Na^+ channel block: State Dependence	↑ APD	Ca^{2+} channel block	Other
Adenosine				4	4 Adenosine receptor activation 4 Activates outward K^+ current

Adenosine slows conduction through the AV node by decreasing conduction velocity



Pharmacokinetics of Antiarrhythmic Drugs

Drug	Bioavailability. %	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



לכל יצור הומאוטרמי מספר נתון של פעימות לב

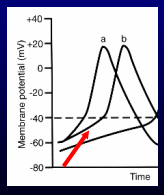
המאיט – מאריך ימיו

הממהר – מקצר ימיו

Sinoatrial I_f current blocker a new target for heart rate reduction

(EHJ sep 2003) - Ivabradine

= Proclan

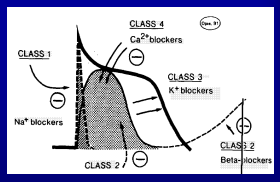


Ranolazine

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



Class III

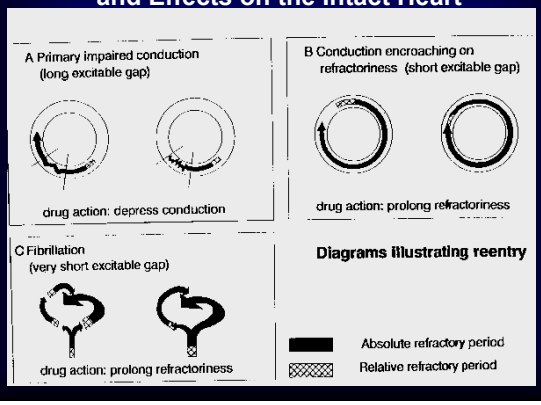
- Dofetilide
- Ibutilide
- Azimelide
- Dronedarone **Son of amiodarone**

EURIDIS, ADONIS:

- **no cardiac toxicity**
- **no excess of chf or TdP**
- **no amiodarone like toxicity; thyroid or pulmonary problems**

No wonder drug

Mechanisms of Action of Antiarrhythmic Drugs and Effects on the Intact Heart

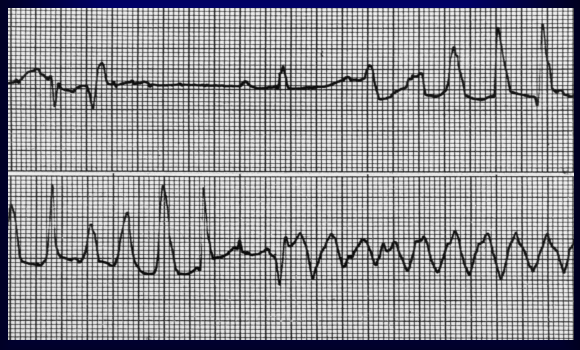


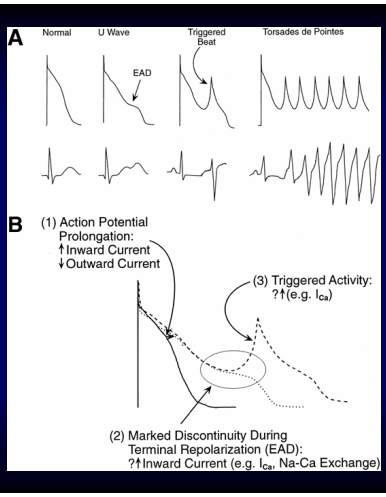
Proarrhythmia

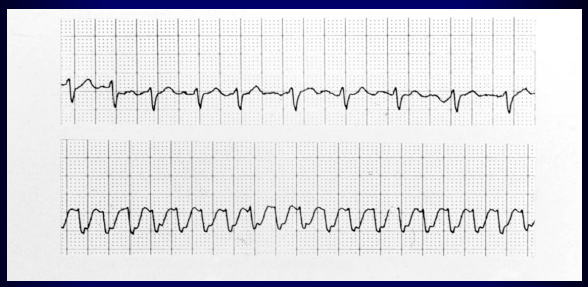
Antiarrhythmic Drugs:
Agents with occasionally beneficial side-effects

תרופות אנטיאריתמיות הינן תרופות בעלות אפקטים אלקטרופיזיולוגיים

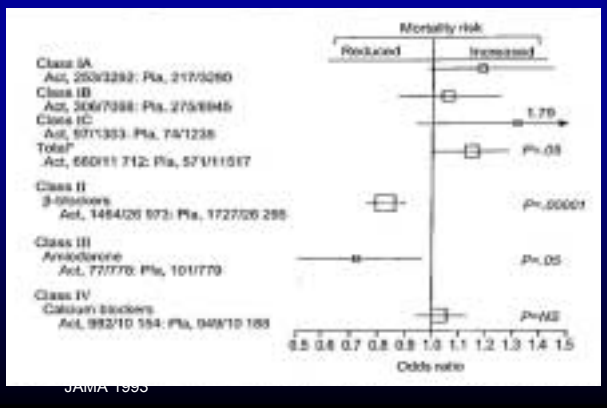
אשר לעיתים גם מועילים



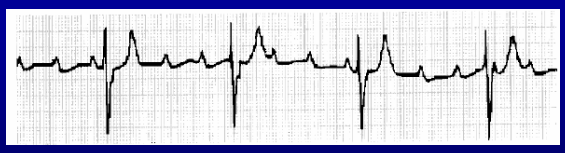




השפעת תרופות אנטיאריתמיות על תמותה



JAMA 1993

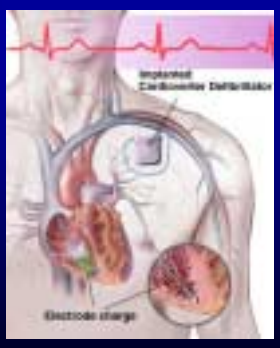


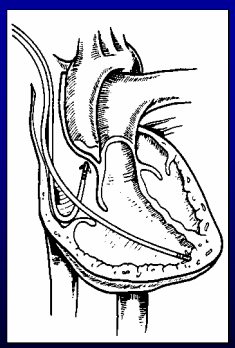
אפקט על ספי קיצוב ודפיברילציה

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





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

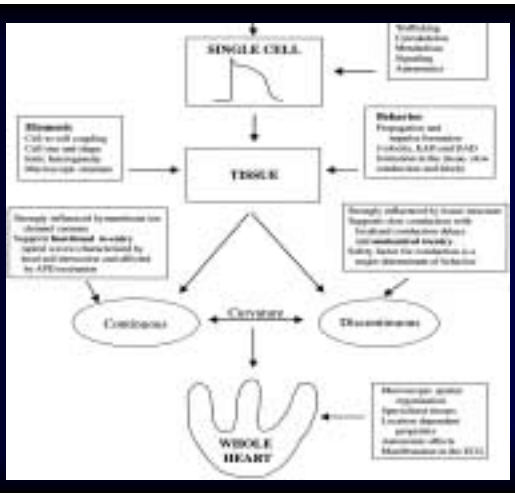
אינטראקציה

Drug	Digoxin	Warfarin INR
Quinidine	מעלה	מעלה
Procainamide	ללא אפקט	ללא אפקט
Disopyramide	ללא אפקט	?
Lidocaine	ללא אפקט	ללא אפקט
Mexiletine	ללא אפקט	ללא אפקט
Flecainide	מעלה	ללא אפקט
Propafenone	מעלה	מעלה
Amiodarone	מעלה	מעלה
Sotalol	ללא אפקט	ללא אפקט

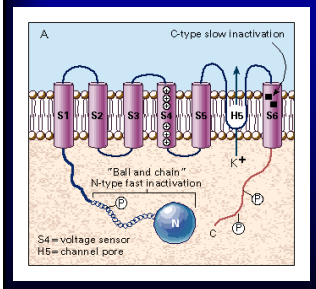
New Approach to Antiarrhythmic Therapy

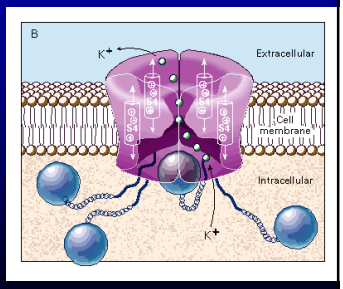
Members of the Sicilian Gambit

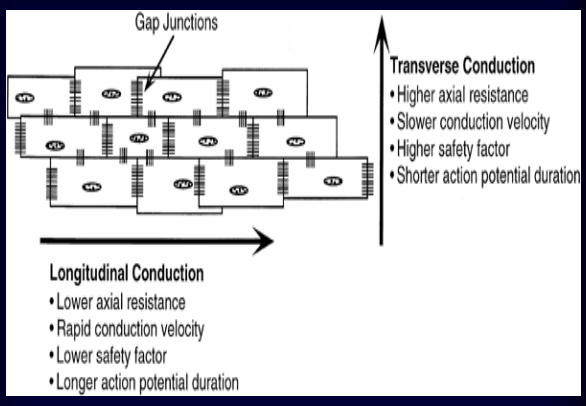
Circulation 2001;104:2865

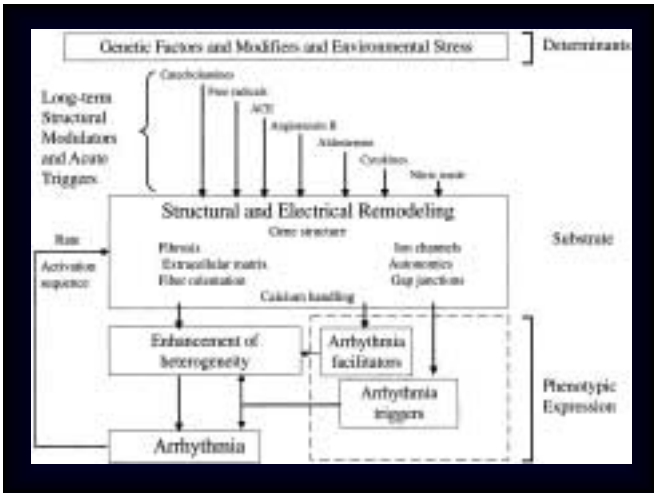


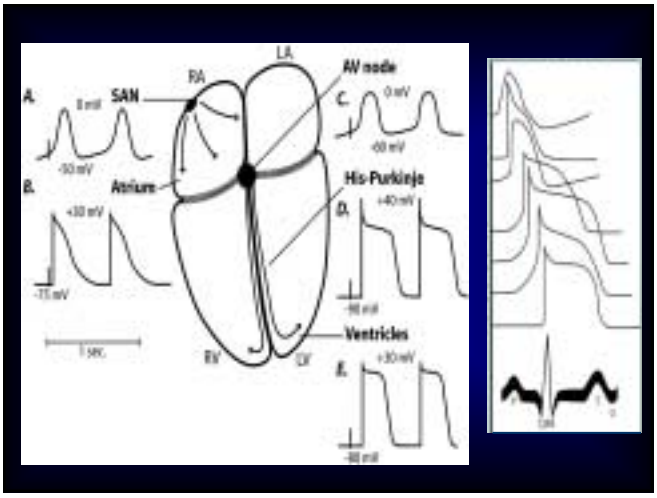
Inactivation of the A-type channels by ball-and-chain and other mechanism



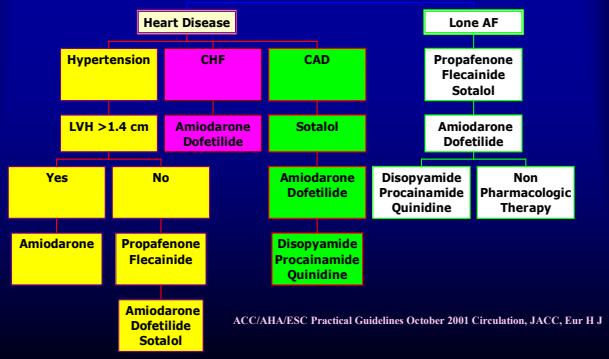








Antiarrhythmic Drug Therapy to Maintain Sinus in pts with Recurrent Paroxysmal or Persistent Atrial Fibrillation



ACC/AHA/ESC Practical Guidelines October 2001 Circulation, JACC, Eur H J

WPW

תרופות המשפיעות על AVN

תרופות המשפיעות על AP

תרופות המשפיעות על AVN ועל AP

Recommendations for Acute Management of Hemodynamically Stable and Regular Tachycardia

ECG	Recommendation*	Classification	Level of Evidence	References
Narrow QRS-complex tachycardia (SVT)	Vagal maneuvers	I	B	
	Adenosine	I	A	(4,69,90)
	Verapamil, diltiazem	I	A	(91)
	Beta blockers	IIb	C	(92,93)
	Amiodarone	IIb	C	(94)
	Digoxin	IIb	C	
Wide QRS-complex tachycardia				
•SVT and BBB	See above			
•Pre-excited SVT/AF†	Flecainide‡	I	B	(95)
	Ibutilide‡	I	B	(96)
	Procainamide‡	I	B	
	DC cardioversion	I	C	
•Wide QRS-complex tachycardia of unknown origin	Procainamide‡	I	B	(84,97)
	Sotalol‡	I	B	(85)
	Amiodarone	I	B	(25,86)
	DC cardioversion	I	B	(98)
	Lidocaine	IIb	B	(85,97)
	Adenosine§	IIb	C	(99)
	Beta blockers¶	III	C	(98)
	Verapamil**	III	B	(73)
Wide QRS-complex tachycardia of unknown origin in patients with poor LV function	Amiodarone	I	B	(25,86)
	DC cardioversion, lidocaine	I	B	(98)

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer

מקרים מיוחדים

- טיפול אנטיאריתמי בתסמונת Brugada
- טיפול אנטיאריתמי VT אידיופטי
- טיפול אנטיאריתמי בהריון

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

The order in which treatment recommendations appear in this table within each class of recommendation does not necessarily reflect a preferred sequence of administration. Please refer to text for details. For pertinent drug dosing information, please refer to the ACC/AHA/ESC Guidelines on the Management of Patients With Atrial Fibrillation.

*Beta-blocking agents should not be taken in the first trimester, if possible.

†Consider AV-nodal–blocking agents in conjunction with flecainide and propafenone for certain tachycardias (see Section V).

‡Atenolol is categorized in class C (drug classification for use during pregnancy) by legal authorities in some European countries.

AV indicates atrioventricular; DC, direct current; PSVT, parosysmal supraventricular tachycardia.

Antiarrhythmic Drugs

Generic Name	Electrocardiographic Effects: PR Interval	QRS Duration	QT Interval	Usefullness in Arrhythmias: Supra-Ventricular	Ventricular	Half-Life	Dosage
Amiodarone	↑↑	↑	↑↑↑	+++	+++	Weeks	200-400 mg/d
Bretylium	0	0	0	0	+	4 h	5 mg/kg IV Bolus
Disopyramide	↑↓[1]	↑↑	↑↑	+	+++	6-8 h	600-900 mg/d
Flecainide	↑	↑↑↑	0	++	++++	20 h	200-300 mg/d
Ibutilide	↑	0	↑↑↑	+++	--4	1-1.5 h	1 mg IV Over 10 min may Repeat x1
Lidocaine	0	0	0	0[3]	+++	1 h	1-4 mg/min after 100 mg Bolus
Mexiletine	0	0	0	0[3]	+++	8 h	450-750 mg/d
Moricizine	↑	↑↑	0	0	+++	2-6 h[2]	600-900 mg/d
Procainamide	↑↓	↑↑	↑↑	+	+++	3-4 h	2000-6000 mg/d
Propafenone	↑	↑↑↑	0	++	+++	7 h	450-900 mg/d
Quinidine	↑↓	↑↑	↑↑	+	+++	6 h	972-1944 mg/d of Gluconate
Sotalol	↑↑	0	↑↑↑	+++	+++	7 h	160-640 mg/d*

1. Anticholinergic effect and direct depressant action.
2. Half-life of active metabolites much longer.
3. May be effective in atrial arrhythmias caused by digitalis.
4. No studies published as yet.
* 320 mg/d for atrial fibrillation