Drugs for Dysrhythmias

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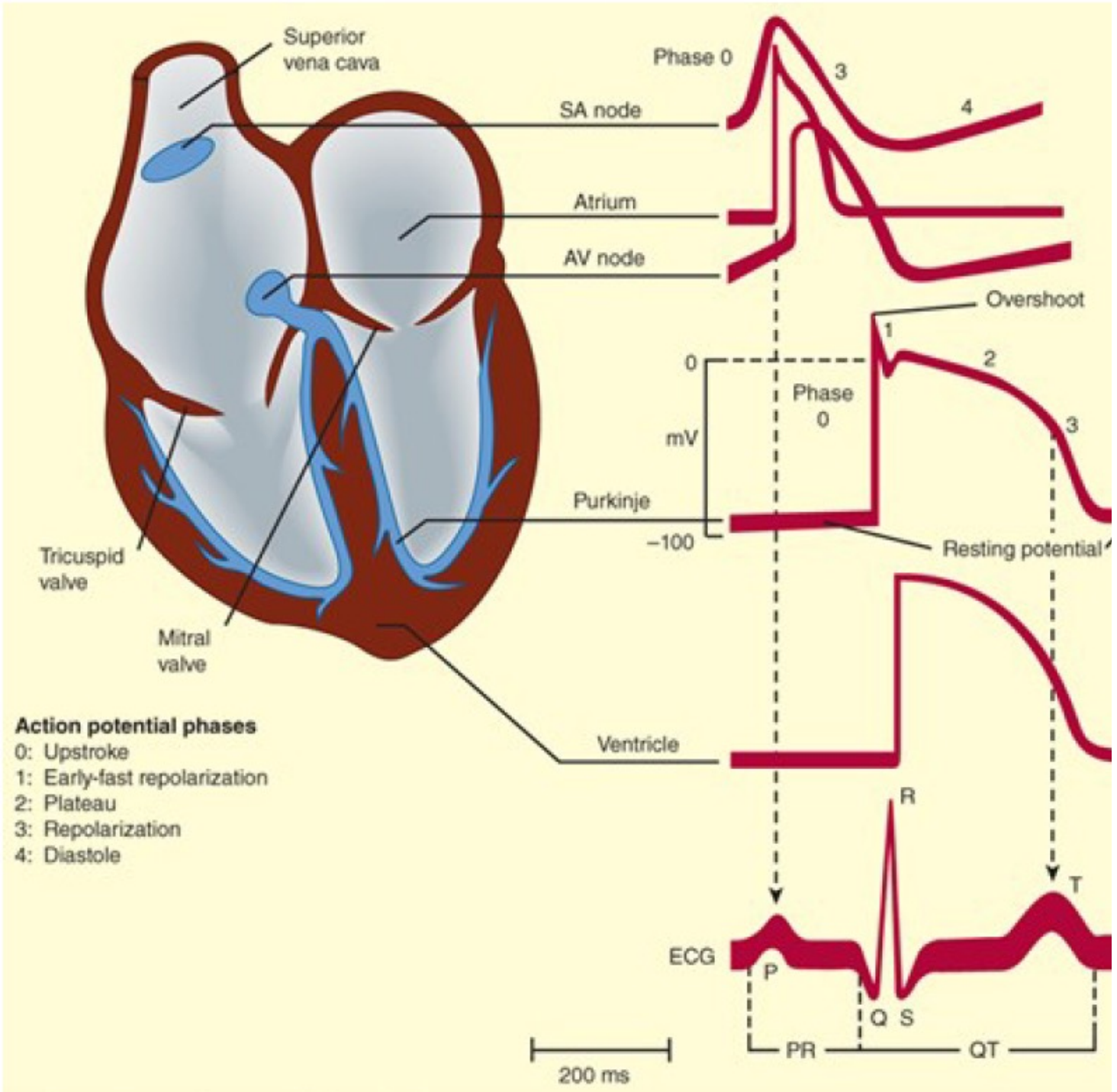
Objectives

1. Identify clinical uses for antiarrhythmics.
2. Explain the mechanism of action of class I (sodium channel blockers), class II (beta blockers), class III (potassium channel blockers), class IV (calcium channel blockers), and miscellaneous antiarrhythmics and relate this to underlying pathophysiology and clinical usefulness of each agent
3. Explain the effects class I (sodium channel blockers), class II (beta blockers), class III (potassium channel blockers), class IV (calcium channel blockers), and miscellaneous antiarrhythmics on the phases of cardiac action potentials.
4. State adverse effects and contraindications to class I (sodium channel blockers), class II (beta blockers), class III (potassium channel blockers), class IV (calcium channel blockers), and miscellaneous antiarrhythmics.
5. Describe the clinically important drug interactions of class I (sodium channel blockers), class II (beta blockers), class III (potassium channel blockers), class IV (calcium channel blockers), and miscellaneous antiarrhythmics.

Cardiac Conduction and Action Potentials

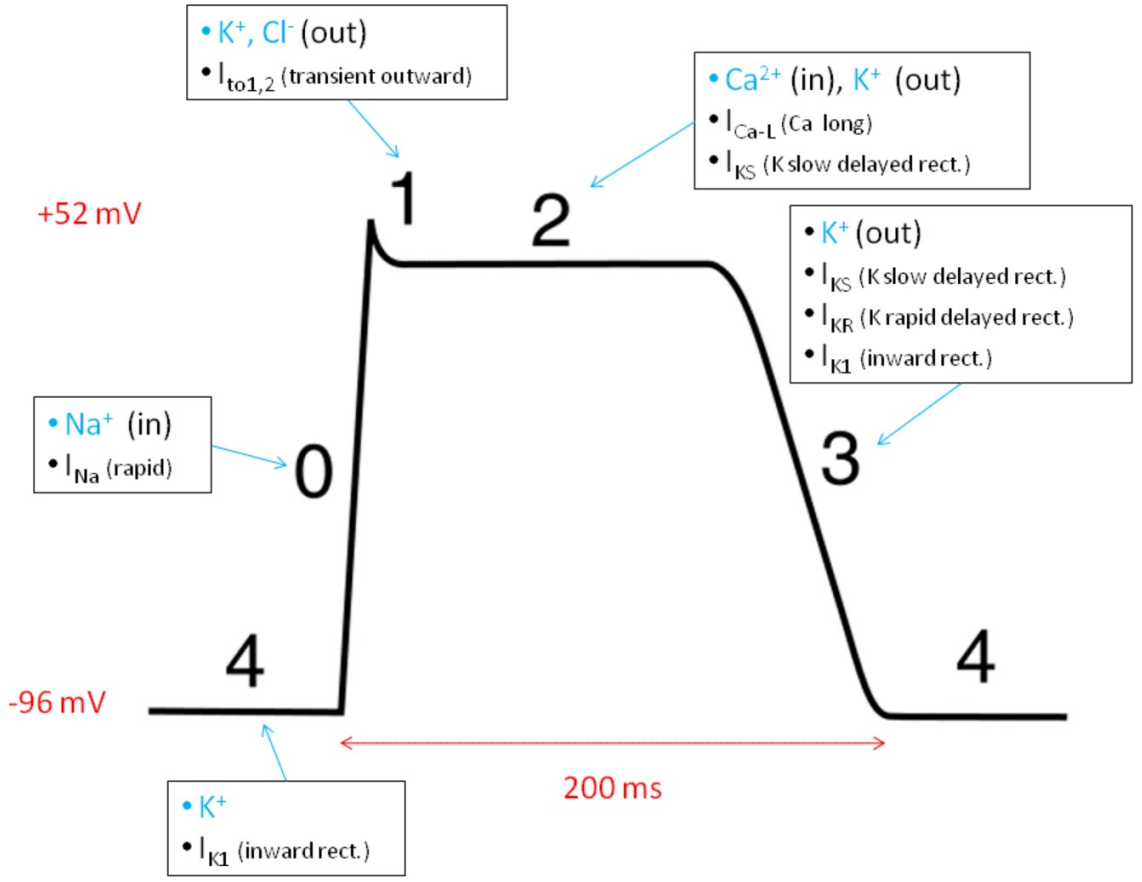
- Flow of ions across cell membranes generates currents
- Ion responds through transporters
  - Currents
  - Concentration gradients



- Source: Bertam G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, 15th Ed.

Myocardial Action Potential

- Phase 0: Rapid Depolarization
  - Cell receives impulse
  - Rapid Na entry
  - Depolarization
- Phase 1: Early Repolarization
  - Na channels inactivated
  - Partial repolarization

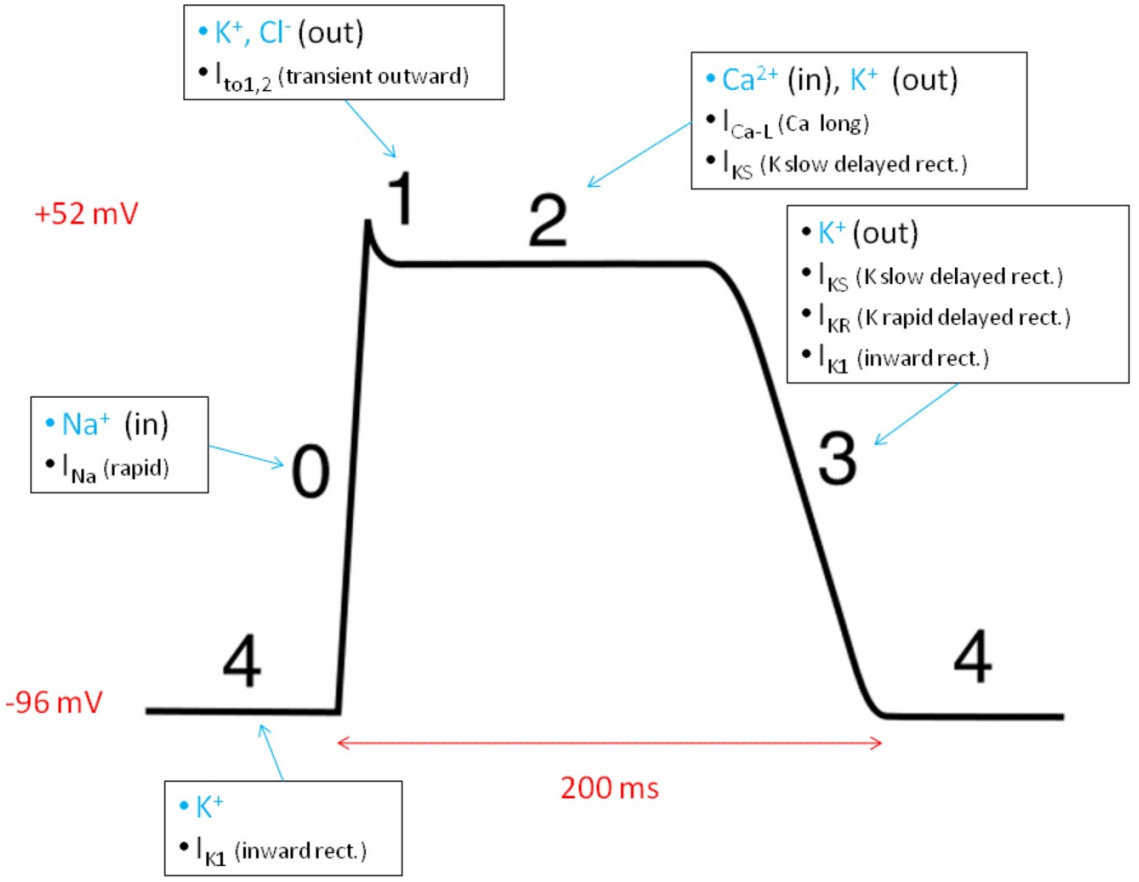


Source: Bertam G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, 15th Ed.

Picture: https://en.wikipedia.org/wiki/Cardiac_action_potential#/media/File:Action_potential_ventr_myocyte.gif

Myocardial Action Potential

- Phase 2: Plateau Phase
  - Ca+ re-entry
  - Absolute refractory period
- Phase 3: Late & Rapid Repolarization
  - Rapid K+ exit
  - Relative refractory period
- Phase 4: Resting Membrane Potential (diastolic depolarization)
  - Threshold potential



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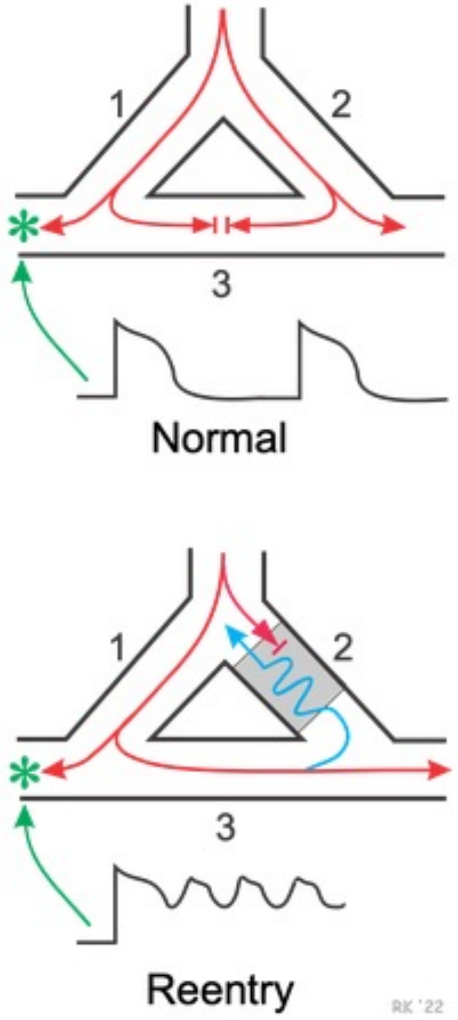
Mechanism of arrythmias

- Abnormal impulses
  1. Altered automaticity
     - Sympathetic
     - Parasympathetic
  2. Enhanced automaticity
  3. Triggered automaticity
- Abnormal impulse conduction
  1. Normal conduction
  2. Reentry
  3. Conduction block
  4. Accessory pathway



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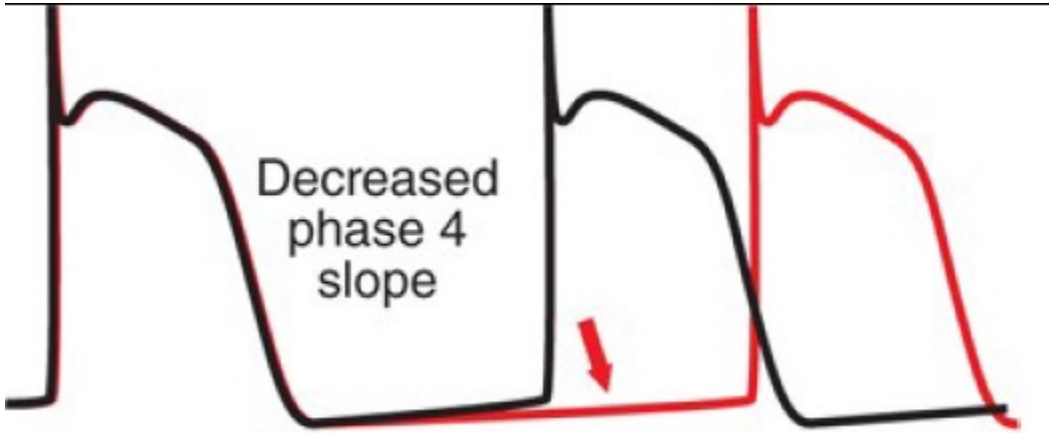
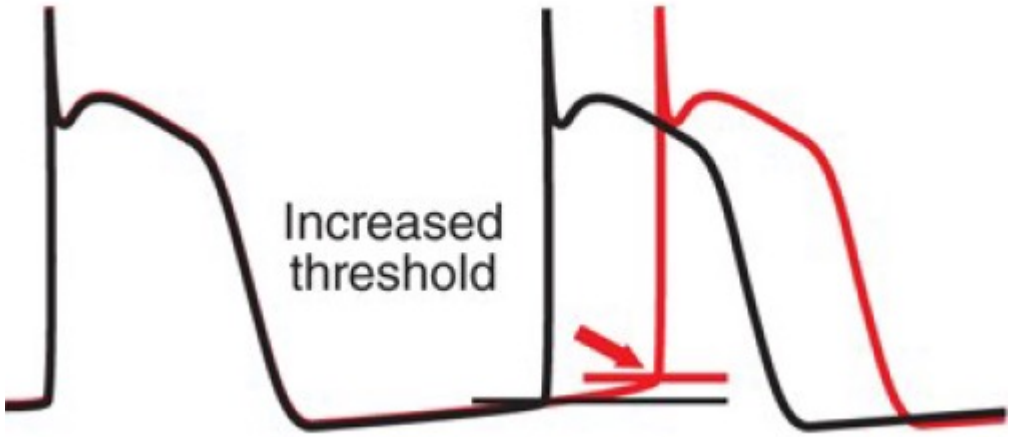
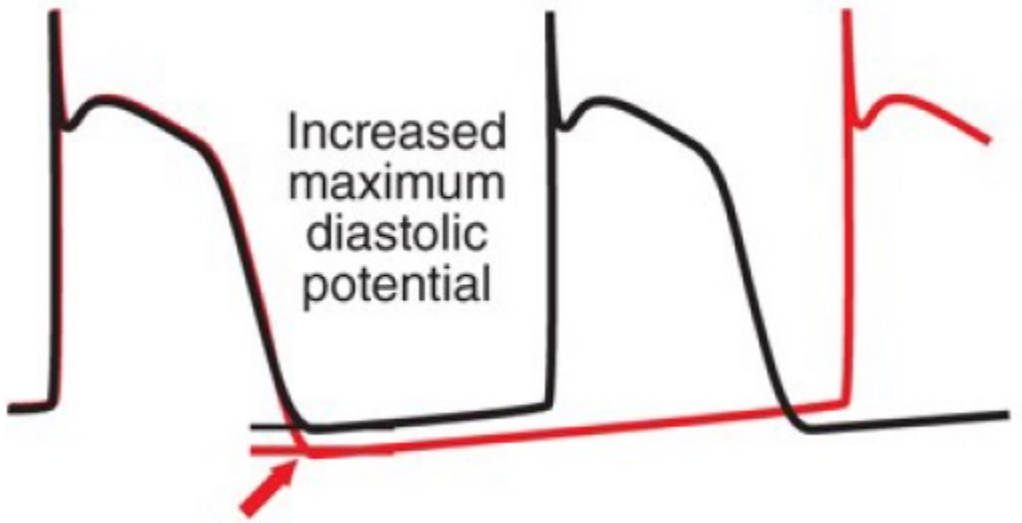
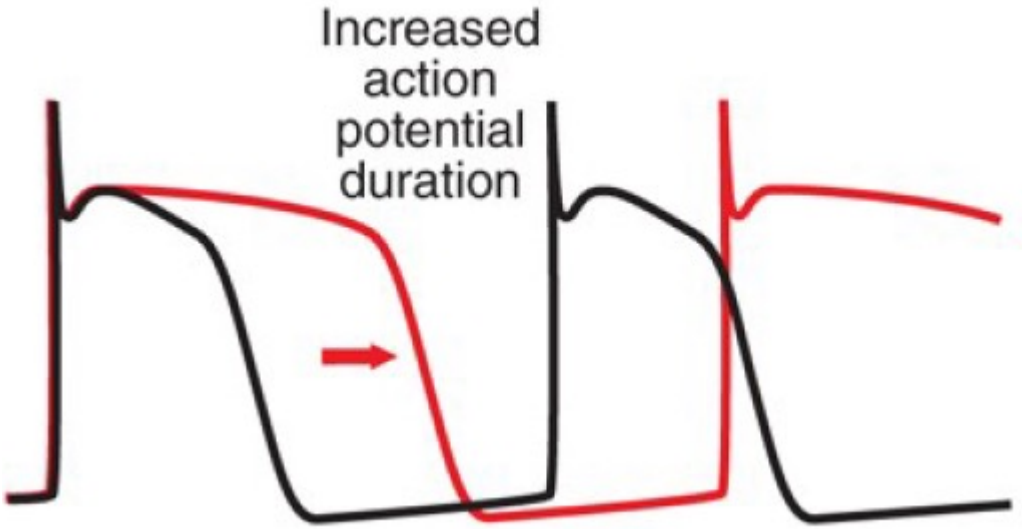
https://www.cvphysiology.com/Arrhythmias/A008c

Antiarrhythmic Drugs Effects









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Classification

Vaughan Williams Classification

Ia	Quinidine, procainamide, and disopyramide	Sodium channel blockade
Ib	Lidocaine and mexilitine	
Ic	Flecainide and propafenone	
II	Propranolol, esmolol, sotalol	Beta-adrenergic blockade
III	Dofetilide, sotalol, and amiodarone	Potassium channel blockade
IV	Verapamil and diltiazem	Calcium channel blockade

Class 1a

- Block fast Na Channels
- Intermediate kinetics
- Depresses phase 0 depolarization (↓ conduction velocity)
- Prolongs action potential and refractoriness
- Useful for SVT, VT, symptomatic premature ventricular beats, & prevention of V-fib
- No longer recommended for routine treatment of a-fib

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Class 1b

- Block fast Na Channels
- Rapid kinetics (<0.5 sec Na channel recovery)
- Increase refractory period
- Little effect on accessory pathways and SN and AV nodes (Calcium dependent action potentials
- Ineffective for supraventricular tachycardias
- Useful for VT & V-Fib

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Class 1c

- Block fast Na Channels
- Slow on/off (Slowed conduction at normal ♥rate)
- Profoundly slow conduction velocity
- Unable to propagate
- Refractoriness unaltered
- Useful for VT & V-Fib (risk of proarrhythmia), refractory SVT

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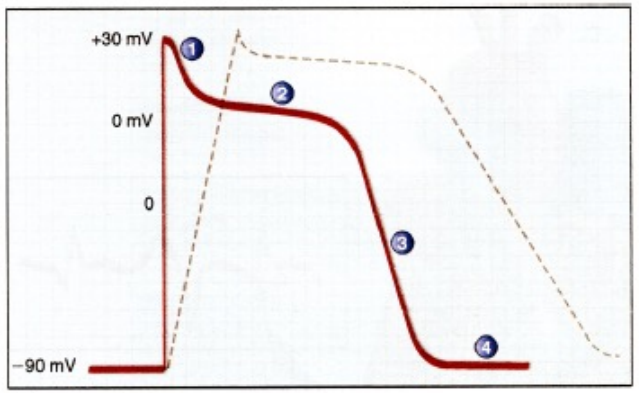
Differences with Class 1 Antiarrhythmics

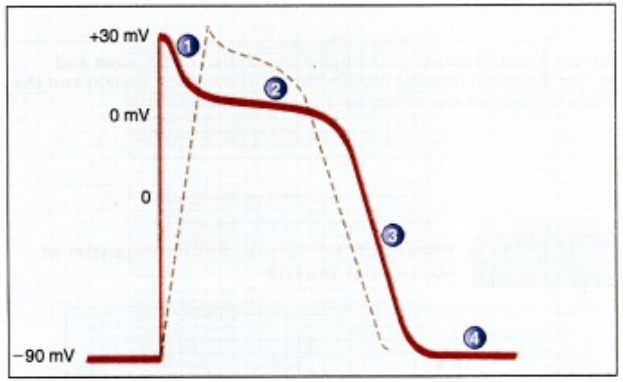
Class 1A



(a)

Produce a moderate decrease in conduction (Phase 0) and prolong the refractory period (Phases 1-3). Also slow the efflux of K^+ ions during repolarization. {dashed line}

Class 1B



(b)

Produce a mild decrease in conduction and shorten the refractory period.
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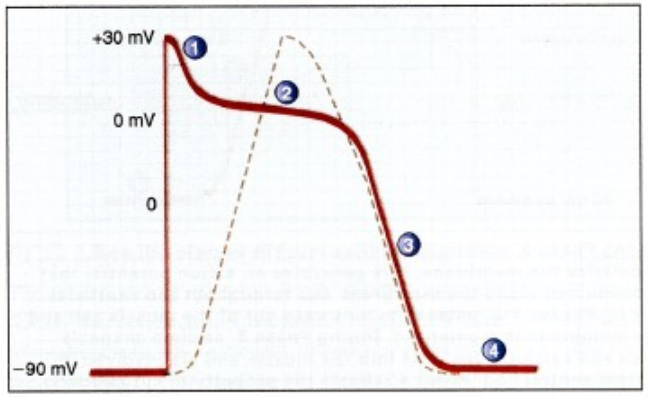
Class 1C



(c)

Produce a marked decrease in conduction but does not prolong the refractory period.
{dashed line}

SE Class I Antiarrhythmics
(all: ventricular proarrhythmias)

- Quinidine: diarrhea (30-40%), vision changes, dizziness
- Procainamide: drug induced Lupus (~50%), hypotension, active metabolite accumulates in renal failure (TdP)
- Disopyramide: anticholinergic SE (~70%), strong negative inotrope
- Flecainide: precipitate CHF, blurred vision, dizziness, headache
- Propafenone: dizziness (25%), GI upset (25%), bronchospasm (blockade of beta-adrenergic receptors), strong negative inotrope
- Lidocaine: confusion, dizziness, seizures

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Class II: Beta-adrenergic blockade

- Mechanism of action: Beta adrenergic receptor blockade in SA and AV nodes
  - Reduction of heart rate
  - Increase av nodal conduction time
  - Prolong AV nodal refractoriness
- Propranolol: Additional Na^+ blocking effects at high doses
- Good for acute and chronic control of supraventricular arrhythmias avoid for pts with accessory pathways
- Side effects: bronchospasm, fatigue, hypotension, hypoglycemia masking, worsening of heart failure

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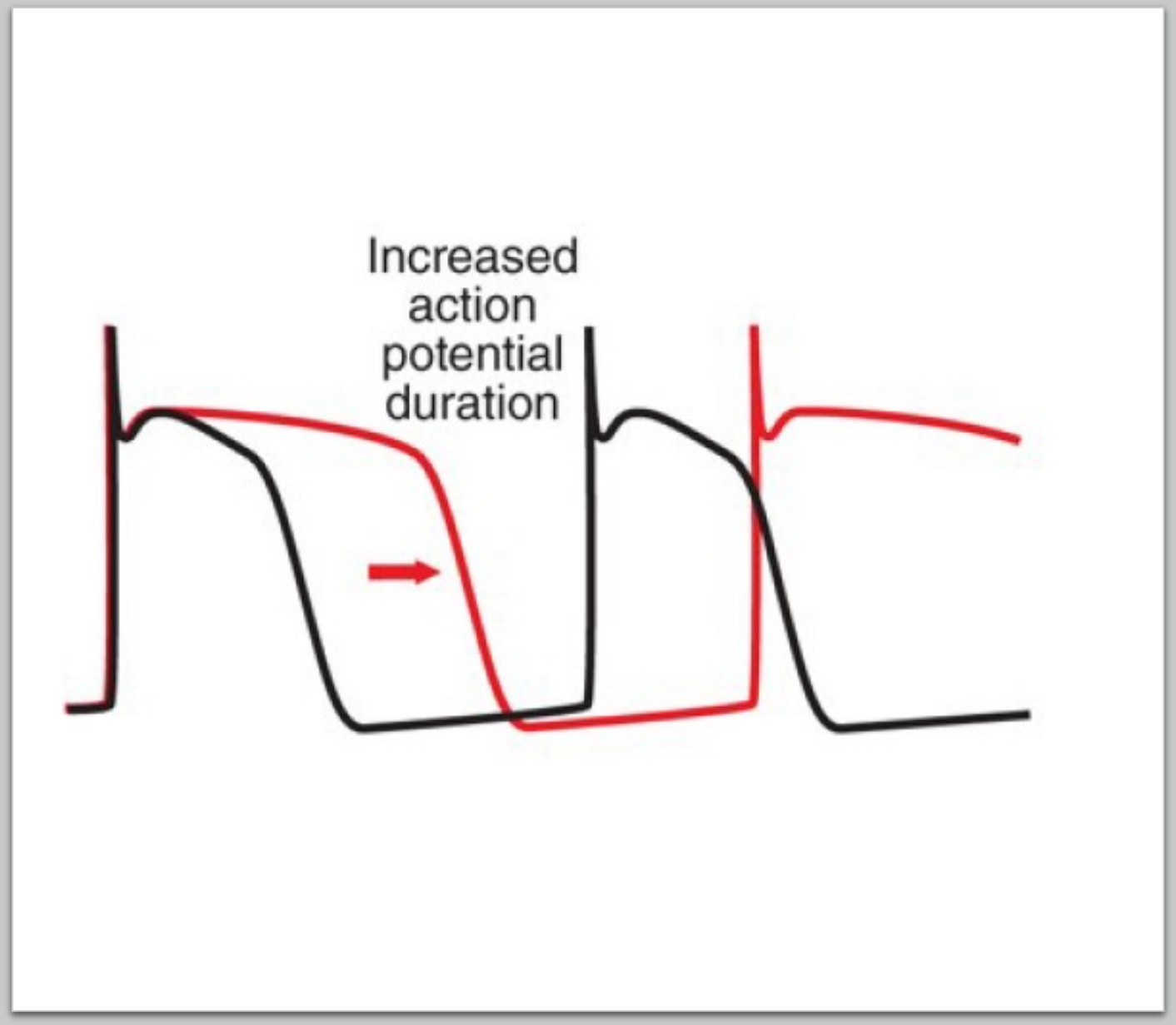
Class III Antiarrhythmics

- Amiodarone, sotalol (additional class II effects), dofetilide
- K^+ channel blockade
  - Prolong phase 2
  - Prolong repolarization
- Used for most supraventricular and ventricular arrhythmias. Major anti-arrhythmic effect is
- prolongation of the refractory period (increase in the duration of the QT interval).
- Decreases heart rate and AV conduction: PR and QRS. Intervals are prolonged.



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Amiodarone

Mechanism of Action

Class	Mechanism	IV		PO	
I	Sodium Blocker	--	+	+	++
II	Beta-Blocker	++	++	++	++
III	Potassium Blocker	--	+	++	++++
IV	Calcium Blocker	+	+	+	+
		minutes-hours	hours-days	days-weeks	weeks-months

Amiodarone: Adverse effects

- Acute
  - Cardiac: bradycardia, hypotension, and QT prolongation
  - Gastrointestinal: nausea and constipation
  - Administration: phlebitis (IV only)
- Chronic
  - Cardiac: bradycardia, AV block, and QT prolongation
  - Pulmonary: fibrosis
  - Ophthalmic: corneal microdeposits, blurred vision, and optic neuropathy/neuritis
  - Gastrointestinal: nausea and hepatitis
  - Thyroid: hypo- and hyperthyroidism
  - Skin: bruising, photosensitivity, and blue-gray discoloration
  - Musculature: myopathy

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Class III Adverse Effects

- Sotalol: Torsades, QT prolongations, ventricular arrhythmias, Beta adrenergic receptor blockade effects (hypotension, fatigue, bronchospasm)
- Dofetilide: Torsades and excessive prolongation of QT interval

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Class IV: Calcium Channel Blocker

- Calcium channel blockers decrease entry of calcium into cells whose electrophysiologic action depends on the influx of calcium through the slow-type calcium channels.
- Depolarization of SA and AV nodal cells is highly dependent on the influx of calcium ions.
- Slow depolarization, decrease the heart rate, & AV nodal conduction is slowed
- Combined effects is to reduce ventricular rate during fast supraventricular arrhythmias.
- Another, not necessarily a desired effect of calcium channel blockers is to interfere with calcium entry into cardiac and smooth muscles affecting contraction. May precipitate heart failure in patients with CHF
- Calcium channel blockers are divided into two groups
  - **Dihydropyridines-**Only block calcium in smooth muscle to cause arterial vasodilation and are mainly used in the treatment of angina pectoris and hypertension.
  - **Nondihydropyridines-** verapamil and diltiazem.
- Adverse effects: Headache, dizziness, constipation, hypotension, bradycardia and heart block
- Avoid in WPW and accessory pathway

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Digoxin

- Mechanism: augment vagal tone – leading to the inhibition of Ca currents in the AV node
  - Prolong refractory period
  - Reduced AV nodal conduction and rate
- Narrow therapeutic window
- Interactions:
  - Greater risk with hypokalemia
  - P-glycoprotein
- Avoid with WPW

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Digoxin: Adverse Effects

- Cardiac toxicities
  - ventricular arrhythmias
  - heart block
  - bradycardia
- Gastrointestinal toxicities
  - anorexia
  - nausea
  - vomiting
  - abdominal pain
- CNS toxicities
  - confusion
  - agitation
  - delirium
  - vision changes
- Risk factors for digoxin toxicity
  - hypokalemia
  - hypomagnesemia
  - hypercalcemia
  - hypothyroidism
  - interacting medications
  - renal insufficiency

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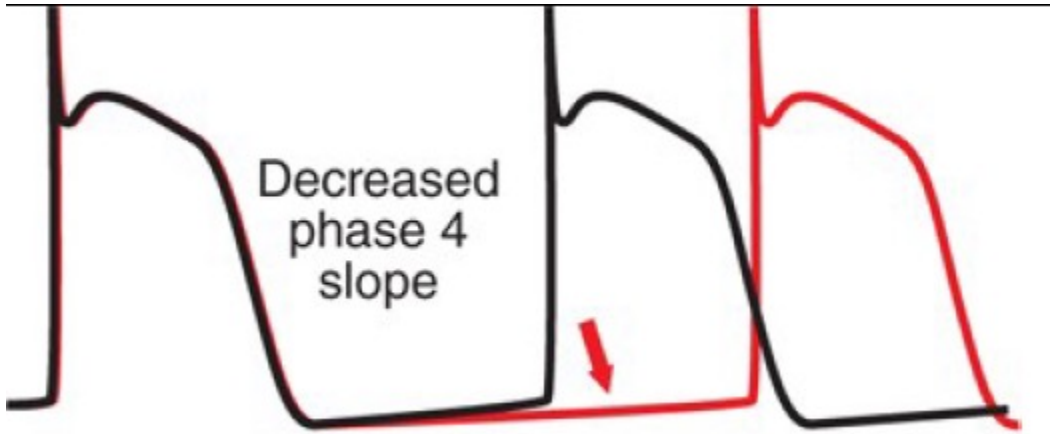
Adenosine

- Mechanism: Activation of G protein coupled adenosine receptors
  - Activates K current in atrium, SA, and AV nodes
  - Shortening of action potential duration, hyperpolarization leading to decreased automaticity
- Adverse effects:
  - Asystole (transient
  - Flushing
  - Chest pressure
  - Bronchospasm
- Half-life: < 10 seconds



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Atropine

- Mechanism: Block muscarinic receptors in AV node
  - Reduce AV nodal block
  - Increased heart rate
- Adverse effects:
  - Cardiac: prolonged p wave, shortened PR segment, prolonged QT, widening of QRS
  - Arrhythmias
  - Anticholinergic symptoms

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Drug Interactions

- Interactions and impacts can vary
- Many antiarrhythmics have active metabolites
- Utilize drug information databases: Lexicomp, Micromedex, Crediblemeds

Enzymatic Interactions 3A4: Propafenone, amiodarone, dofetilide 2D6: Propafenone, amiodarone, flecainide	Gut excretion by Transporters P-Glycoprotein Substrates: Digoxin, diltiazem, verapamil, carvedilol, anticoagulants Inhibitors: amiodarone, carvedilol, diltiazem, verapamil, propafenone	QTc Prolongation Class IA, III

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Common Atrial Arrhythmias Mechanism and Treatment

Arrhythmia	Mechanism	Therapy considerations
Premature depolarizations	Unknown	None
Atrial fibrillation	Disorganized reentry, continual AV node stimulation	Control AV node response: AV nodal blockade Maintain normal conduction: K^+ or Na^+ blockade
Atrial flutter	Reentrant circuit in atrium	AV nodal blockade
Atrial tachycardia	Enhanced automaticity or reentry	Adenosine AV nodal blockade
AV nodal reentrant tachycardia	Reentrant circuit near or in AV node	Adenosine AV nodal blockade and Flecainide/Propafenone
Arrhythmia with WPW	Reentry	Adenosine (acute) K^+ or Na^+ blockade (chronic)
Afib with accessory pathway (WPW)	Accessory pathway	Procainamide (acute) K^+ or Na^+ blockade (chronic)

AV nodal blockade: BB, CCB, increased vagal tone unless specific agent specified.

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Common Atrial Arrhythmias Mechanism and Treatment

Arrhythmia	Mechanism	Treatment
VT with history of MI	Reentry near the healed myocardium	Acute: Amiodarone, Lidocaine, Procainamide Chronic: Amiodarone, K^+ or Na^+ blockade
VT without structural heart disease	Delayed after depolarization triggered by sympathetic stimulation	Acute: Adenosine, CCB, BB Chronic: CCB, BB
Ventricular fibrillation	Disorganized reentry	Acute: Defibrillation, amiodarone, lidocaine Chronic: ICD, Amiodarone, K^+ or Na^+ blockade
Torsades de pointtes	Early after depolarization triggered activity	Acute: Magnesium Chronic: BB

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